BASIC PRINCIPLES OF ORGANIC CHEMISTRY

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Basic Principles of Organic Chemistry

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Preface

No period in the history of organic chemistry has been as dynamic and productive of research accomplishment as the twelve years between the completion of the first and present editions of this textbook. New reagents, new reactions, and extraordinary syntheses have been manifold. New techniques and new instruments for analysis and determination of structures, improved methods for theoretical calculations, as well as new junctures with physical, inorganic, and biochemistry, have made organic chemistry an enormously vital discipline. But along with this "best of times," there is a "worst of times" coming from the recognition that many widely used organic compounds are more toxic than previously suspected. Some are carcinogenic; some may be destroying the ozone layer in the upper atmosphere, which protects all life from the sun's strong ultraviolet radiation; others are concentrated and persist in living tissue to as yet unknown effect. Nonetheless, our society has come to depend on synthetic organic chemicals, and we may ponder the fact that in just a few years the petroleum that makes so many useful organic compounds easily available will be in very short supply throughout the world. It has been a real challenge for us to try to cover the elements of modern organic chemistry with sufficient breadth to anticipate the interests and needs of the future chemists, biologists, physicians, medical scientists, and engineers, who constitute the majority of those who study the subject, and, at the same time, give a balanced view of both its current accomplishments and difficulties.

Our attempt has resulted in a large book that may appear unwieldy. Between editions, we often received suggestions from professors to write a book "covering just the material I need in my course," but no two ever seemed to agree on what "the" material should be. Perhaps the discipline has now progressed in breadth and complexity that no simple short text can suffice, any more than the old-fashioned grocery store can compete with the supermarket to supply the diverse needs of a modern community. To a degree, our book has a parallel to a supermarket because not only do we cover many subjects, we cover the important ones in detail. There is no intention on our part to supply just the right amount of material for some particular course of study. Instead, we intend to provide a broad enough range of topics to accommodate almost any desired emphasis or approach to the subject. More on our objectives with regard to different possible approaches to the study of organic chemistry is given in the latter part of Section 1-5 (p. 24). This book makes a substantial break with tradition in the matter of organic nomenclature. It was difficult to decide to do this because changes in this area are very hard to achieve, perhaps for the reason that they threaten the viability of what already is published and, indeed, even our customary forms of verbal communication. One of the authors remembers vividly the protests of his thesis supervisor to the idea of acquiescing to the admonition of a manuscript reviewer who felt that "crotyl chloride" and "methylvinylcarbinyl chloride" represented just too much of a mixing of nomenclature systems for isomeric compounds. "But we've used those names in nineteen earlier papers!" Nonetheless, organic chemists and organic chemistry will surely be better off to name these same compounds systematically as 1-chloro-2-butene and 3-chloro-1-butene.

Use of systematic nomenclature is a bit like energy conservation - we all recognize it is necessary, but we would just as soon the start be made after we are dead. The phenomenal growth of organic chemistry during the past decade and the switch by the indexes of Chemical Abstracts to use much more systematic nomenclature suggests that the right time is now. The approach we will take in this book to the nomenclature problem is described in more detail in Chapter 3 (pp. 49-5 1). As in the earlier edition, considerable attention is given to the application of the principles of thermodynamics, quantum mechanics, kinetics, and spectroscopy to understanding and correlating the myriad of seemingly unrelated facts of organic chemistry. Much of this material could be appropriately categorized as belonging to a "Department of Fuller Explanation," and rightly so because it represents a real attempt to achieve a genuine understanding of difficult points of fact and theory. Examples include rather detailed discussions of the properties of solvents, the differences between resonance and molecular-orbital treatments of valence, ionization strengths of acids, the origin of spin-spin splitting and kinetic effects in nuclear magnetic resonance spectra, reaction mechanisms, photosynthesis, carbohydrate metabolism, peptide-sequence determinations and peptide syntheses, enzyme action, and reactions of transition-metal compounds. It will not be possible to cover many of these topics in the usual one-year course, but many options are possible, as well as opportunities for individual studies.

Many individuals contributed to the progress and content of this edition. Special thanks are due for the suggestions of the reviewers, in particular to Professor George E. Hall of Mount Holyoke College, who read and commented not only on the whole of the first draft but also a much-revised second draft. Helpful suggestions also were received from Professors Robert E. Ireland, Robert G. Bergman, W. A. Goddard III, and John H. Richards of the California Institute of Technology, Jerome Berson of Yale University, Ernst Berliner of Bryn Mawr College, Emil T. Kaiser of the University of Chicago, J. E. Guillet of the University of

Toronto, and Dr. John Thirtle of Eastman Kodak. The students at both Caltech and the University of California at Irvine participated in class-testing the first draft and contributed significantly to the final draft. We owe them much for their patience and helpful suggestions. Over the years, many teachers and students have taken time to send us their comments regarding the first edition, and many of these suggestions have been very helpful in preparing the second edition. Also, we are indebted to our respective colleagues for providing the encouragement that makes an endeavor of this kind possible. The revised drafts were prepared in part while one of us was on leave at Stanford University and the other at the University of Hawaii. We are very appreciative of the substantial assistance and hospitality provided by these universities.

The manuscript and its interminable revisions were typed with skill and patience by Ms. Rose Meldrum. Our thanks also go to Ms. Margaret Swingle. It was a pleasure to work with Mr. Georg Klatt who did the final artwork, and Ms. Mary Forkner who was the production supervisor. The index was prepared with a HP9830 calculator system, and it would never have been possible to alphabetize and edit the 7500 entries without the help of equipment loaned by Mr. Stanley Kurzet of Infotek Systems. Special thanks are due to Drs. James L. Hall and Jean D. Lassila (as well as Ms. Patricia Sullivan) for their seemingly tireless efforts and continual contributions through the various stages of editing and proofreading. Finally, the patience of our families during the several years that it has taken to write and produce this book is worthy of very particular mention and appreciation. As before, we will be pleased to receive corrections and suggestions from our readers for further improvement of later editions.

-John D. Roberts Marjorie C. Caserio May 15,1977

CHAPTER OVERVIEW

1: Introduction to Organic Chemistry

The learning about and learning how to use organic chemistry is not a straightforward process, wherein one step leads to another in a simple, logical way like Euclidean geometry. A more realistic analogy would be to consider yourself thrust into and required to deal successfully with a sizable group of strangers speaking a new and complex language. In such a situation, one has to make many decisions- how much of the language to learn at the outset? Which people are the best to interact with first? Which will be the most important to know in the long run? How well does one have to know each person? How much does one have to know about the history of the group to understand their interactions? These are difficult questions, and a period of confusion, if not anxiety, is expected in any attempt to complete a task of this kind in a set, brief period of time. Clearly, it would be difficult to learn all at once the language, the people, and the interactions between them. Nonetheless, this is pretty much what is expected of you in learning organic chemistry.

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1.2: A Bit of History
1.3: What Preparation Should You Have?
1.4: Why Is Organic Chemistry Special?
1.5: The Breadth of Organic Chemistry
1.6: Some Philosophical Observations
1.E: Introduction to Organic Chemistry (Exercises)

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1.1: Prelude to Organic Chemistry

You now are starting the study of organic chemistry, which is the chemistry of compounds of carbon. In this introductory chapter, we will tell you something of the background and history of organic chemistry, something of the problems and the rewards involved, and something of our philosophy of what is important for you to learn so that you will have a reasonable working knowledge of the subject, whether you are just interested in chemistry or plan for a career as a chemist, an engineer, a physician, a biologist, and so on. The subject is very large; more than two million organic compounds have been isolated or prepared and characterized, yet the number of guiding principles is relatively small. You certainly will not learn everything about organic chemistry from this book, but with a good knowledge of the guiding principles, you will be able later to find out what you need to know either from the chemical literature, or directly by experiment in the laboratory.

Unfortunately, learning about and learning how to use organic chemistry is not a straightforward process, wherein one step leads to another in a simple, logical way like Euclidean geometry. A more realistic analogy would be to consider yourself thrust into and required to deal successfully with a sizable group of strangers speaking a new and complex language. In such a situation, one has to make many decisions- how much of the language to learn at the outset? Which people are the best to interact with first? Which will be the most important to know in the long run? How well does one have to know each person? How much does one have to know about the history of the group to understand their interactions? These are difficult questions, and a period of confusion, if not anxiety, is expected in any attempt to complete a task of this kind in a set, brief period of time. Clearly, it would be difficult to learn all at once the language, the people, and the interactions between them. Nonetheless, this is pretty much what is expected of you in learning organic chemistry.

A number of approaches have been devised to help you become familiar with and use organic chemistry. In terms of our analogy, one way is to learn the language, then the relationships between the people, and finally, well prepared, to proceed to interact with the people singly and then in groups. Such an approach may be logical in concept, but is not to everyone's taste as a way to learn. Many of us do better with an interactive approach, where language, relationships, and people are worked out more or less in concert, with attendant misunderstandings and ambiguities.

What we will try to do is to introduce some of the important basic concepts and the elements of the language of organic chemistry, then show how these are used in connection with various classes of compounds. The initial round will be a fairly extensive one and you should not expect to be able to master everything at once. This will take practice and we will provide opportunity for practice.

One of the appealing yet bothersome features of modern organic chemistry is its extraordinary vitality. Unlike Euclidean geometry or classical mechanics, it is evolving rapidly and many of the concepts introduced in this book are either new or have been drastically modified in the past ten years. Every issue of the current chemical journals has material of such basic interest that one would like to include it in an introductory course. Truly, those who write organic textbooks write on water, with no hope of producing *the* definitive book. Things just change too fast. Despite this, one of the great ideas of modern civilization, namely that organic compounds can be described in terms of more or less simple three-dimensional molecular structures with atoms held together by chemical bonds, has persisted for more than one hundred years and seems unlikely to be superseded, no matter how much it is refined and modified.

1.1.1: Contributors and Attributions

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1.2: A Bit of History

You may not be much interested in the way that organic chemistry developed, but if you skip to the next section without reading further, you will miss some of the flavor of a truly great achievement - of how a few highly creative chemists were able, with the aid of a few simple tools, to determine the structures of molecules, far too small and too elusive to be seen individually with the finest optical microscope, manifesting themselves only by the collective behavior of at least millions of millions at once.

Try to visualize the problems confronting the organic chemist of 100 years ago. You will have no more than reasonably pure samples of organic compounds, the common laboratory chemicals of today, glassware, balances, thermometers, means of measuring densities, and a few optical instruments. You also will have a relatively embryonic theory that there are molecules in those bottles and that one compound differs from another because its molecules have different members or kinds of atoms and different arrangements of bonds. Your task will be to determine what kinds and what numbers of atoms they contain, that is, to determine their *molecular formulas*. Obviously, a compound with formula C_2H_6O and one with $C_2H_6O_2$ are not the same compound. But suppose two compounds from different sources both are C_2H_6O. To decide whether these are the *same or different* you could smell them (far better to *sniff* than to inhale), taste them (emphatically not recommended), see if they have the same appearance and viscosity (if liquids), or use more sophisticated criteria: boiling point, melting point, density, or refractive index. Other possibilities would be to see if they both have the same solubility in water or other solvents and whether they give the same reaction products with various reagents. Of course, all this gets a bit tough when the compounds are not pure and no good ways are available to purify them, but that is part of the job. Think about how you might proceed.

In retrospect it is surprising that in less than fifty years an enormous, even if incomplete, edifice of structural organic chemistry was constructed on the basis of the results of chemical reactions without determination of a single bond distance, and with no electronic theory as a guide. Interestingly, all of the subsequent developments of the quantum mechanical theory of chemical bonds has not altered this edifice in significant ways. Indeed, for a long time, a goal of molecular quantum mechanics was simply to be able to corroborate that when an organic chemist draws a single line between two carbon atoms to show that they are bonded, he in fact knows what he is doing. And that when he draws two (or three) bonds between the carbons to indicate a double (or triple) bond, quantum mechanics supports this also as a valid idea.

Furthermore, when modern tools for determining organic structures that involve actually measuring the distances between the atoms became available, these provided great convenience, but no great surprises. To be sure, a few structures turned out to be incorrect because they were based on faulty or inadequate experimental evidence. But, on the whole, the modern three-dimensional representations of molecules that accord with actual measurements of bond distances and angles are in no important respect different from the widely used three-dimensional ball-and-stick models of organic molecules, and these, in essentially their present form, date from at least as far back as E. Paterno, in 1869.

How was all of this achieved? Not by any very simple process. The essence of some of the important ideas follow, but it should be clear that what actually took place was far from straightforward. A diverse group of people was involved; many firmly committed to, if not having a vested interest in, earlier working hypotheses or *paradigms* that had served as useful bases for earlier experimentation, but were coming apart at the seams because they could not accommodate the new facts that kept emerging. As is usual in human endeavors, espousal of new and better ideas did not come equally quickly to all those used to thinking in particular ways. To illustrate, at least one famous chemist, Berthelot, still used HO as the formula for water twenty-five years after it seemed clear that H_2O was a better choice.

1.2.1: Determination of Molecular Formulas

Before structures of molecules could be established, there had to be a means of establishing molecular formulas and for this purpose the key concept was Avogadro's hypothesis, which can be stated in the form "equal volumes of gases at the same temperature and pressure contain the same number of molecules." Avogadro's hypothesis allowed assignment of *relative* molecular weights from measurements of gas densities. Then, with analytical techniques that permit determination of the weight percentages of the various elements in a compound, it became possible to set up a self-consistent set of relative atomic weights.[1] From these and the relative molecular weights, one can assign molecular formulas. For example, if one finds that a compound contains 22.0% carbon (atomic weight $= 12.00$), 4.6% hydrogen (atomic weight $= 1.008$), and 73.4% bromine (atomic weight $= 79.90$), then the ratios of the numbers of atoms are $(22.0/12.00) : (4.6/1.008) : (73.4/79.90) = 1.83 : 4.56 : 0.92$. Dividing each of the last set of

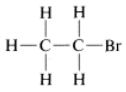
numbers by the smallest (0.92) gives $1.99 : 4.96 : 1 \cong 2 : 5 : 1$, which suggests a molecular formula of C_2H_5Br or a multiple thereof. If we know that hydrogen gas is H_2 and has a molecular weight of $2 \times 1.008 = 2.016$, we can compare the weight of a given volume of hydrogen with the weight of the same volume of our unknown in the gas phase at the same temperature and pressure. If the experimental ratio of these weights turns out to be 54, then the molecular weight of the unknown would be $2.016 \times 54 = 109$ and the formula C_2H_5Br would be correct.

1.2.2: Valence

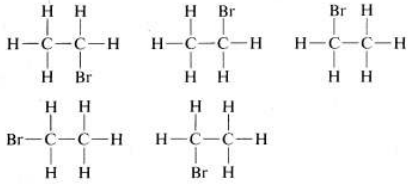
If we assume that the molecule is held together by chemical bonds, without knowing more, we could write numerous structures such as $H-H-H-H-H-C-C-Br, H-C-Br-H-H-C-H-H$, and so on. However, if we also know of the existence of stable H_2, but not H_3; of stable Br_2, but not of Br_3; and of stable CH_3Br, CH_2Br_2, $CHBr_3$, and CBr_4, but not of CH_4Br, $CHBr$, CBr, and so on, a pattern of what is called *valence* emerges. It will be seen that the above formulas all are consistent if hydrogen atoms and bromine atoms form just *one* bond (are univalent) while carbon atoms form *four* bonds (are tetravalent). This may seem almost naively simple today, but a considerable period of doubt and uncertainty preceded the acceptance of the idea of definite valences for the elements that emerged about 1852.

1.2.3: Structural Formulas

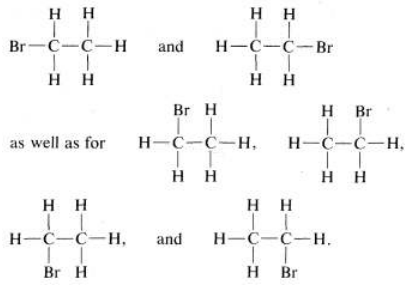
If we accept hydrogen and bromine as being univalent and carbon as tetravalent, we can write



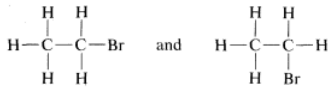
as a structural formula for C_2H_5Br.[2] However, we also might have written



There is a serious problem as to whether these formulas represent the *same* or *different* compounds. All that was known in the early days was that every purified sample of C_2H_5Br, no matter how prepared, had a boiling point of $38°C$ and density of $1.460\ \mathrm{g\ ml^{-1}}$. Furthermore, all looked the same, all smelled the same, and all underwent the same chemical reactions. There was no evidence that C_2H_5Br was a mixture or that more than one compound of this formula could be prepared. One might conclude, therefore, that all of the structural formulas above represent a single substance even though they superficially, at least, look different. Indeed, because $H-Br$ and $Br-H$ are two different ways of *writing* a formula for the same substance, we suspect that the same is true for



There are, though, two of these structures that could be different from one another, namely

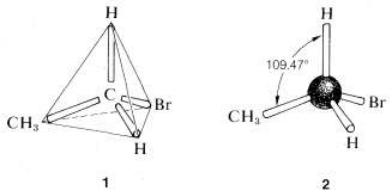


In the first of these, CH_3- is located opposite the $Br-$ and the $H-$'s on the carbon with the Br also are opposite one another. In the second formula, CH_3- and $Br-$ are located *next* to each other as are the $H-$'s on the same carbon. We therefore have a problem as

to whether these two different formulas also represent different compounds.

1.2.4: Tetrahedral Carbon

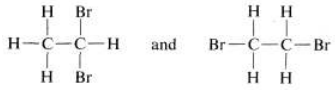
A brilliant solution to the problem posed in the preceding section came in 1874 when J. H. van't Hoff proposed that all four valences of carbon are equivalent and directed to the corners of a regular tetrahedron.[3] If we redraw the structures for C_2H_5Br as 1, we see that there is only *one* possible arrangement and, contrary to the impression we got from our earlier structural formulas, the bromine is *equivalently* located with respect to each of the hydrogens on the same carbon.



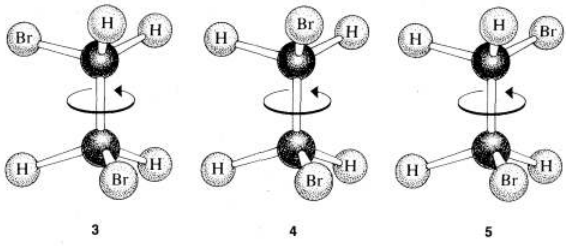
A convenient way of representing organic molecules in three dimensions, which shows the tetrahedral relationships of the atoms very clearly, uses the so-called ball-and-stick models. The sticks that represent the bonds or valences form the tetrahedral angles of 109.47°.

1.2.5: The Question of Rotational Isomers

The tetrahedral carbon does not solve all problems without additional postulates. For example, there are two different compounds known with the *same* formula $C_2H_4Br_2$. These substances, which we call **isomers**, can be reasonably written as



However, ball-and-stick models suggest further possibilities for the second structure, for example 3, 4, and 5:

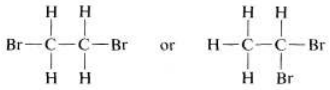


This is a problem apparently first clearly recognized by Paterno, in 1869. We call these rotational (or conformational) isomers, because one is converted to another by rotation of the halves of the molecule with respect to one another, with the $C-C$ bond acting as an axle. If this is not clear, you should make a ball-and-stick model and see what rotation around the $C-C$ bond does to the relationships between the atoms on the carbons.

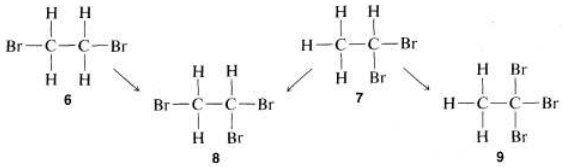
The difficulty presented by these possibilities finally was circumvented by a brilliant suggestion by van't Hoff of "free rotation," which holds that isomers corresponding to different rotational angles, such as 3, 4, and 5, do not have separate stable existence, but are interconverted by rotation around the $C-C$ bond so rapidly that they are indistinguishable from one another. Thus there is only *one* isomer corresponding to the different possible rotational angles and a total of only *two* isomers of formula $C_2H_4Br_2$. As we shall see, the idea of free rotation required extensive modification some 50 years after it was first proposed, but it was an extremely important paradigm, which, as often happens, became so deeply rooted as to become essentially an article of faith for later organic chemists. Free rotation will be discussed in more detail in Chapters 5 and 27.

1.2.6: The Substitution Method for Proof of Structure

The problem of determining whether a particular isomer of $C_2H_4Br_2$ is



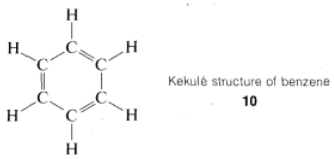
could be solved today in a few minutes by spectroscopic means, as will be explained in Chapter 9. However, at the time structure theory was being developed, the structure had to be deduced on the basis of chemical reactions, which could include either how the compound was formed or what it could be converted to. A virtually unassailable proof of structure, where it is applicable, is to determine how many different *substitution* products each of a given group of isomers can give. For the $C_2H_4Br_2$ pair of isomers, *substitution of a bromine for a hydrogen* will be seen to give only *one* possibility with one compound and *two* with the other:



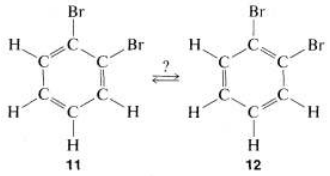
Therefore, if we have two bottles, one containing one $C_2H_4Br_2$ isomer and one the other and run the substitution test, the compound that gives only one product is 6 and the one that gives a mixture of two products is 7. Further, it will be seen that the test, besides telling which isomer is 6 and which is 7, establishes the structures of the two possible $C_2H_3Br_3$ isomers, 8 and 9. Thus only 8 can be formed from both of the different $C_2H_4Br_2$ isomers whereas 9 is formed from only one of them.

1.2.7: The Benzene Problem

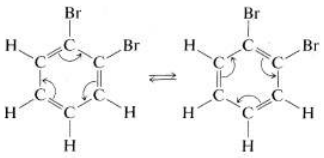
There were already many interconversion reactions of organic compounds known at the time that valence theory, structural formulas, and the concept of the tetrahedral carbon came into general use. As a result, it did not take long before much of organic chemistry could be fitted into a concordant whole. One difficult problem was posed by the structures of a group of substitution products of benzene, C_6H_6, called "aromatic compounds," which for a long time defied explanation. Benzene itself had been prepared first by Michael Faraday, in 1825. An ingenious solution for the benzene structure was provided by A. Kekule, in 1866, wherein he suggested (apparently as the result of a hallucinatory perception) that the six carbons were connected in a hexagonal ring with alternating single and double carbon-to-carbon bonds, and with each carbon connected to a single hydrogen, 10:



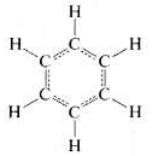
This concept was controversial, to say the least, mainly on two counts. Benzene did not behave as expected, as judged by the behavior of other compounds with carbon-to-carbon double bonds and also because there should be two different dibromo substitution products of benzene with the bromine on adjacent carbons (11 and 12) but only one such compound could be isolated.



Kekule explained the second objection away by maintaining that 11 and 12 were in rapid equilibrium through concerted bond shifts, in something like the same manner as the free-rotation hypothesis mentioned previously:



However, the first objection could not be dismissed so easily and quite a number of alternative structures were proposed over the ensuing years. The controversy was not really resolved until it was established that benzene is a regular planar hexagon, which means that all of its $C-C$ bonds have the same length, in best accord with a structure written not with double, not with single, but with 1.5 bonds between the carbons, as in 13:

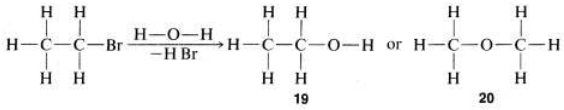


13

This. in turn, generated a massive further theoretical controversy over just how 13 should be interpreted, which, for a time, even became a part of "Cold-War" politics![4] We shall examine experimental and theoretical aspects of the benzene structure in some detail later. It is interesting that more than 100 years after Kekule's proposal the final story on the benzene structure is yet to be told.[5]

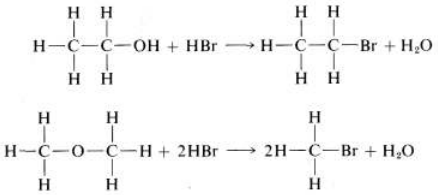
1.2.8: Proof of Structure through Reactions

The combination of valence theory and the substitution method as described in Section 1-1F gives, for many compounds, quite unequivocal proofs of structure. Use of chemical transformations for proofs of structure depends on the applicability of a simple guiding principle, often called the "**principle of least structural change**." As we shall see later, many exceptions are known and care is required to keep from making serious errors. With this caution, let us see how the principle may be applied. The compound C_2H_5Br discussed in Section 1-1A reacts slowly with water to give a product of formula C_2H_6O. The normal valence of oxygen is two, and we can write two, and only two, different structures, 19 and 20, for C_2H_6O:



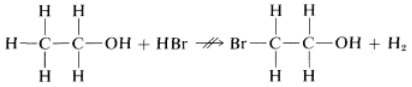
19 20

The principle of least structural change favors 19 as the product, because the reaction to form it is a simple replacement of bromine bonded to carbon by $-OH$, whereas formation of 20 would entail a much more drastic rearrangement of bonds. The argument is really a subtle one, involving an assessment of the reasonableness of various possible reactions. On the whole, however, it works rather well and, in the specific case of the C_2H_6O isomers, is strongly supported by the fact that treatment of 19 with strong hydrobromic acid (HBr) converts it back to C_2H_5Br. In contrast, the isomer of structure 20 reacts with HBr to form two molecules of CH_3Br:



In each case, $C-O$ bonds are broken and $C-Br$ bonds are formed.

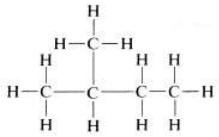
We could conceive of many other possible reactions of C_2H_6O with HBr, for example



which, as indicated by $\not\rightarrow$, does *not* occur, but hardly can be ruled out by the principle of least structural change itself. Showing how the probability of such alternative reactions can be evaluated will be a very large part of our later discussions.

1.2.9: Reactivity, Saturation, Unsaturation, and Reaction Mechanisms

The substitution method and the interconversion reactions discussed for proof of structure possibly may give you erroneous ideas about the reactions and reactivity of organic compounds. We certainly do not wish to imply that it is a simple, straightforward process to make all of the possible substitution products of a compound such as

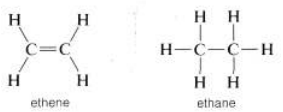


In fact, as will be shown later, direct substitution of bromine for hydrogen with compounds such as this does not occur readily, and when it does occur, the four possible substitution products indeed are formed, but in far from equal amounts because there are *differences in reactivity* for substitution at the different positions. Actually, some of the substitution products are formed only in very small quantities. Fortunately, this does not destroy the validity of the substitution method but does make it more difficult to apply. If direct substitution fails, some (or all) of the possible substitution products may have to be produced by indirect means. Nonetheless, you must understand that the success of the substitution method depends on determination of the total number of possible isomers - it does *not* depend on how the isomers are prepared.

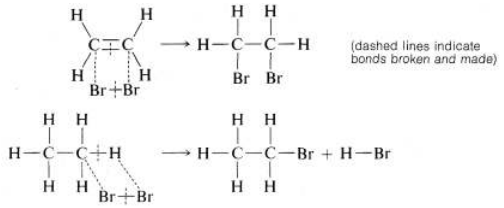
Later, you will hear a lot about compounds or reagents being "reactive" and "unreactive." You may be exasperated by the loose way that these terms are used by organic chemists to characterize how fast various chemical changes occur. Many familiar inorganic reactions, such as the neutralization of hydrochloric acid with sodium hydroxide solution, are extremely fast at ordinary temperatures. But the same is not often true of reactions of organic compounds. For example, C_2H_5Br treated in two different ways is converted to gaseous compounds, one having the formula C_2H_6 and the other C_2H_4. The C_2H_4 compound, **ethene**, reacts *very quickly* with bromine to give $C_2H_4Br_2$, but the C_2H_6 compound, **ethane**, does not react with bromine except at high temperatures or when exposed to sunlight (or similar intense light). The reaction products then are HBr and C_2H_5Br, and later, HBr and $C_2H_4Br_2$, $C_2H_3Br_3$, and so on.

We clearly can characterize C_2H_4 as "reactive" and C_2H_6 as "unreactive" toward bromine. The early organic chemists also used the terms "unsaturated" and "saturated" for this behavior, and these terms are still in wide use today. But we need to distinguish between "unsaturated" and "reactive," and between "saturated" and "unreactive," because these pairs of terms are not synonymous. The equations for the reactions of ethene and ethane with bromine are different in that ethene *adds* bromine, $C_2H_4 + Br_2 \rightarrow C_2H_4Br_2$, whereas ethane *substitutes* bromine, $C_2H_6 + Br_2 \rightarrow C_2H_5Br + HBr$.

You should reserve the term "unsaturated" for compounds that can, at least potentially, react by *addition*, and "saturated' for compounds that can only be expected to react by *substitution*. The difference between addition and substitution became much clearer with the development of the structure theory that called for carbon to be tetravalent and hydrogen univalent. Ethene then was assigned a structure with a carbon-to-carbon *double* bond, and ethane a structure with a carbon-to-carbon *single* bond:



Addition of bromine to ethene subsequently was formulated as breaking one of the carbon-carbon bonds of the double bond and attaching bromine to these valences. Substitution was written similarly but here bromine and a $C-H$ bond are involved:

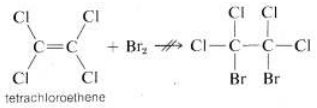


We will see later that the way in which these reactions actually occur is much more complicated than these simple equations indicate. In fact, such equations are regarded best as chemical accounting operations. The number of bonds is shown correctly for

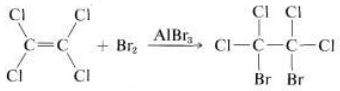
both the reactants and the products, and there is an indication of which bonds break and which bonds are formed in the overall process. However, do not make the mistake of assuming that no other bonds are broken or made in intermediate stages of the reaction.

Much of what comes later in this book will be concerned with what we know, or can find out, about the **mechanisms** of such reactions - a reaction mechanism being the actual sequence of events by which the reactants become converted to the products. Such information is of extraordinary value in defining and understanding the range of applicability of given reactions for practical preparations of desired compounds.

The distinction we have made between "unsaturated" and "reactive" is best illustrated by a definite example. Ethene is "unsaturated" (and "reactive") toward bromine, but tetrachloroethene, C_2Cl_4, will not add bromine at all under the same conditions and is clearly "unreactive." But is it also "saturated"?



The answer is definitely no, because if we add a small amount of aluminum bromide, $AlBr_3$, to a mixture of tetrachloroethene and bromine, addition does occur, although sluggishly:



Obviously, tetrachloroethene is "unsaturated" in the sense it can undergo addition, even if it is unreactive to bromine in the absence of aluminum bromide.

The aluminum bromide functions in the addition of bromine to tetrachloroethene as a **catalyst**, which is something that facilitates the conversion of reactants to products. The study of the nature and uses of catalysts will concern us throughout this book. Catalysis is our principal means of controlling organic reactions to help form the product we want in the shortest possible time.

[1]We will finesse here the long and important struggle of getting a truly self-consistent table of atomic weights. If you are interested in the complex history of this problem and the clear solution to it proposed by S. Cannizzaro in 1860, there are many accounts available in books on the history of chemistry. One example is J. R. Partington, *A History of Chemistry*, Vol. IV, Macmillan, London, 1964. Relative atomic weights now are based on $^{12}C = 12$ (exactly).

[2]Formulas such as this appear to have been used first by Crum Brown, in 1864, after the originators of structural formulas, A. Kekule and A. Couper (1858), came up with rather awkward, impractical representations. It seems incredible today that even the drawing of these formulas was severely criticized for many years. The pot was kept boiling mainly by H. Kolbe, a productive German chemist with a gift for colorful invective and the advantage of a podium provided by being editor of an influential chemical journal.

[3]The name of J. A. Le Bel also is associated with this particular idea, but the record shows that Le Bel actually opposed the tetrahedral formulations, although, simultaneously with van't Hoff, he made a related very important contribution, as will be discussed in Chapter 5.

[4]The "resonance theory," to be discussed in detail in Chapters 6 and 21, was characterized in 1949 as a physically and ideologically inadmissible theory formulated by "decadent bourgeois scientists." See L. R. Graham, *Science and Philosophy in the Soviet Union*, Vintage Books, New York, 1973, Chapter VIII, for an interesting account of this controversy.

[5]Modern organic chemistry should not be regarded at all as a settled science, free of controversy. To be sure, personal attacks of the kind indulged in by Kolbe and others often are not published, but profound and indeed acrimonious differences of scientific interpretation exist and can persist for many years.

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1.3: What Preparation Should You Have?

We have tried to give you a taste of the beginnings of organic chemistry and a few of the important principles that brought order out of the confusion that existed as to the nature of organic compounds. Before moving on to other matters, it may be well to give you some ideas of what kind of preparation will be helpful to you in learning about organic chemistry from this textbook.

The most important thing you can bring is a strong desire to master the subject. We hope you already have some knowledge of general chemistry and that you already will have had experience with simple inorganic compounds. That you will know, for example, that elemental bromine is Br_2 and a noxious, dark red-brown, corrosive liquid; that sulfuric acid is H_2SO_4, a syrupy colorless liquid that reacts with water with the evolution of considerable heat and is a strong acid; that sodium hydroxide is $NaOH$, a colorless solid that dissolves in water to give a strongly alkaline solution. It is important to know the characteristics of acids and bases, how to write simple, balanced chemical reactions, such as $2H_2 + O_2 \rightarrow 2H_2O$, and $2NaOH + H_2SO_4 \rightarrow Na_2SO_4 + 2H_2O$, what the concept of a mole of a chemical substance is, and to be somewhat familiar with the periodic table of the elements as well as with the metric system, at least insofar as grams, liters, and degrees centigrade are concerned. Among other things, you also should understand the basic ideas of the differences between salts and covalent compounds, as well as between gases, liquids, and solids; what a solution is; the laws of conservation of mass and energy; the elements of how to derive the Lewis electron structures of simple molecules such as $H:\ddot{\underset{\cdot\cdot}{O}}:H$ = water; that $PV = nRT$; and how to calculate molecular formulas from percentage compositions and molecular weights. We shall use no mathematics more advanced than simple algebra but we do expect that you can use logarithms and are able to carry through the following conversions forward and backward:

$$\log_{10} 510,000 = \log_{10}\left(5.1 \times 10^5\right) = 5.708$$

The above is an incomplete list, given to illustrate the level of preparation we are presuming in this text. If you find very much of this list partly or wholly unfamiliar, you don't have to give up, but have a good general chemistry textbook available for study and reference - and use it! Some useful general chemistry books are listed at the end of the chapter. A four-place table of logarithms will be necessary; a set of ball-and-stick models and a chemical handbook will be very helpful, as would be a small electronic calculator or slide rule to carry out the simple arithmetic required for many of the exercises.

In the next section, we review some general chemistry regarding saltlike and covalent compounds that will be of special relevance to our later discussions.

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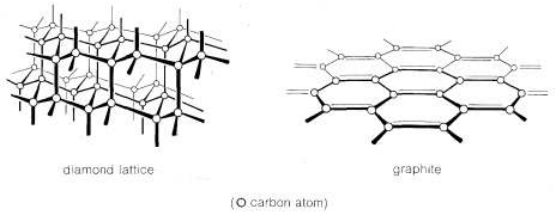
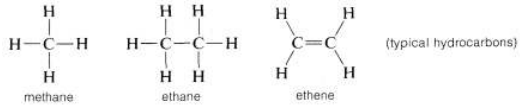
1.4: Why Is Organic Chemistry Special?

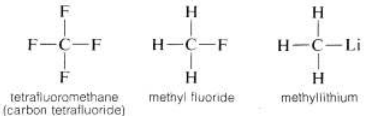
Let us consider some of the factors that make so much of chemistry center on a single element, carbon. One very important feature is that carbon-carbon bonds are strong, so long chains or rings of carbon atoms bonded to one another are possible. Diamond and graphite are two familiar examples, the diamond lattice being a three-dimensional network of carbon atoms, whereas graphite actually more closely resembles a planar network. The lubricating properties of graphite actually are related to its structure, which permits the planes to slide one past the other.



But carbon is not unique in forming bonds to itself because other elements such as boron, silicon, and phosphorus form strong bonds *in the elementary state*. The uniqueness of carbon stems more from the fact that it forms strong carbon-carbon bonds that also are strong when in combination with other elements. For example, the combination of hydrogen with carbon affords a remarkable variety of carbon hydrides, or **hydrocarbons** as they usually are called. In contrast, none of the other second-row elements except boron gives a very extensive system of stable hydrides, and most of the boron hydrides are much more reactive than hydrocarbons, especially to water and air.

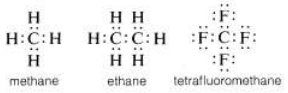


Carbon forms bonds not only with itself and with hydrogen but also with many other elements, including strongly electron-attracting elements such as fluorine and strongly electropositive metals such as lithium:



Why is carbon so versatile in its ability to bond to very different kinds of elements? The special properties of carbon can be attributed to its being a relatively small atom with four valence electrons. To form simple saltlike compounds such as sodium chloride, $Na^{\oplus}Cl^{\ominus}$, carbon would have to either lose the four valence electrons to an element such as fluorine and be converted to a quadripositive ion, $C^{4\oplus}$, or acquire four electrons from an element such as lithium and form a quadrinegative ion, $C^{4\ominus}$. Gain of four electrons would be energetically very unfavorable because of mutual repulsion between the electrons.

Customarily, carbon completes its valence-shell octet by *sharing* electrons with other atoms. In compounds with shared electron bonds (or covalent bonds) such as methane, ethane, or tetrafluoromethane, each of the bonded atoms including carbon has its valence shell filled, as shown in the following electron-pair or Lewis[6] structures:



In this way, repulsions between electrons associated with completion of the valence shell of carbon are compensated by the electron-attracting powers of the positively charged nuclei of the atoms to which the carbon is bonded.

However, the electrons of a covalent bond are not necessarily shared equally by the bonded atoms, especially when the affinities of the atoms for electrons are very different. Thus, carbon-fluorine and carbon-lithium bonds, although they are not ionic, are polarized such that the electrons are associated more with the atom of higher electron affinity. This is usually the atom with the higher effective nuclear charge.

$\overset{\delta\oplus}{C} : \overset{\delta\ominus}{F}$ $\qquad$ $\overset{\delta\ominus}{C} : \overset{\delta\oplus}{Li}$ $\qquad$ ($\delta\oplus$, $\delta\ominus$ denote partial ionic bonds)

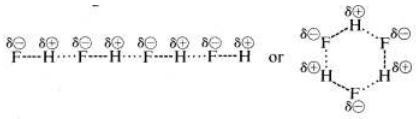
We see then a gradation from purely ionic to purely covalent bonding in different molecules, and this is manifest in their chemical and physical properties. Consider, for instance, the hydrides of the elements in the second horizontal row of the periodic table. Their melting and boiling points,[7] where known, are given below.

	LiH	BeH_2	BH_3	CH_4	NH_3	H_2O	HF
mp, °C	680	(decomposes at 125)	–	−182	−78	0	−83.7
bp, °C	–		–	−161	−33	100	+19.7

Lithium hydride can be regarded as a saltlike *ionic* compound, $\overset{\oplus}{Li}\ \ :\overset{\ominus}{H}$. Electrostatic attractions between oppositely charged ions in the crystal lattice are strong, thereby causing lithium hydride to be a high-melting, nonvolatile solid like sodium chloride, lithium fluoride, and so on.

Methane, CH_4, is at the other extreme. It boils at $-161°$, which is about $800°$ lower even than the melting point of lithium hydride. Because carbon and hydrogen have about the same electron-attracting power, $C-H$ bonds have little ionic character, and methane may be characterized as a *nonpolar* substance. As a result, there is relatively little electrostatic attraction between methane molecules and this allows them to "escape" more easily from each other as gaseous molecules - hence the low boiling point.

Hydrogen fluoride has a boiling point some $200°$ higher than that of methane. The bonding electron pair of HF is drawn more toward fluorine than to hydrogen so the bond may be formulated as $\overset{\delta\oplus}{H}$ ---- $\overset{\delta\ominus}{F}$. In liquid hydrogen fluoride, the molecules tend to aggregate through what is called **hydrogen bonding** in chains and rings arranged so the positive hydrogen on one molecule attracts a negative fluorine on the next:

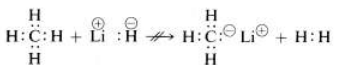


When liquid hydrogen fluoride is vaporized, the temperature must be raised sufficiently to overcome these intermolecular electrostatic attractions; hence the boiling point is high compared to liquid methane. Hydrogen fluoride is best characterized as a *polar*, but not ionic, substance. Although the $O-H$ and $N-H$ bonds of water and ammonia have somewhat less ionic character than the $H-F$ bonds of hydrogen fluoride, these substances also are relatively polar in nature and also associate through hydrogen bonding in the same way as does hydrogen fluoride.

The chemical properties of lithium hydride, methane, and hydrogen fluoride are in accord with the above formulations. Thus, when the bond to the hydrogen is broken, we might expect it to break in the sense $Li^{\oplus} \vdots : H^{\ominus}$ for lithium hydride, and $\overset{\delta\oplus}{H} \vdots : \ddot{F} :^{\delta\ominus}$ for hydrogen fluoride so that the electron pair goes with the atom of highest electron affinity. This is indeed the case as the following reaction indicates:

$$Li^{\oplus} \vdots : H^{\ominus} \ + \ H \vdots : \ddot{F} : \ \longrightarrow Li^{\oplus} : \ddot{F} :^{\oplus} + H : H$$

Methane, with its relatively nonpolar bonds, is inert to almost all reagents that could remove hydrogen as $H^{\oplus}$ or $H :^{\ominus}$ except under anything but extreme conditions. As would be expected, methyl cations $CH_3^{\oplus}$ and methyl anions $CH_3 :^{\ominus}$ are very difficult to generate and are extremely reactive. For this reason, the following reactions are not observed:



From the foregoing you may anticipate that the chemistry of carbon compounds will be largely the chemistry of covalent compounds and will not at all resemble the chemistry of inorganic salts such as sodium chloride. You also may anticipate that the major differences in chemical and physical properties of organic compounds will arise from the nature of the *other* elements

bonded to carbon. Thus methane is not expected to, nor does it have, the same chemistry as other one-carbon compounds such as methyllithium, CH_3Li, or methyl fluoride, CH_3F.

[6]G. N. Lewis (1876-1946), the renowned U.S. chemist, was the first to grasp the significance of the electron-pair in molecular structure. He laid the foundation for modern theory of structure and bonding in his treatise on *Valence and the Structure of Atoms and Molecules* (1923).

[7]Throughout this text all temperatures not otherwise designated should be understood to be in ^oC; absolute temperatures will be shown as ^oK.

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1.5: The Breadth of Organic Chemistry

Organic chemistry originally was defined as the chemistry of those substances formed by living matter and, for quite a while, there was a firm belief that it would never be possible to prepare organic compounds in the laboratory outside of a living system. However, after the discovery by Wohler, in 1828, that a supposedly typical organic compound, urea, could be prepared by heating an inorganic salt, ammonium cyanate, this definition gradually lost significance and organic chemistry now is broadly defined as the chemistry of carbon-containing compounds. Nonetheless, the designation "organic" is still very pertinent because the chemistry of organic compounds is also the chemistry of living organisms.

Each of us and every other living organism is comprised of, and endlessly manufactures, organic compounds. Further, all organisms consume organic compounds as raw materials, except for those plants that use photosynthesis or related processes to synthesize their own from carbon dioxide. To understand every important aspect of this chemistry, be it the details of photosynthesis, digestion, reproduction, muscle action, memory or even the thought process itself, is a primary goal of science and it should be recognized that only through application of organic chemistry will this goal be achieved.

Modern civilization consumes vast quantities of organic compounds. Coal, petroleum, and natural gas are primary sources of carbon compounds for use in production of energy and as starting materials for the preparation of plastics, synthetic fibers, dyes, agricultural chemicals, pesticides, fertilizers, detergents, rubbers and other elastomers, paints and other surface coatings, medicines and drugs, perfumes and flavors, antioxidants and other preservatives, as well as asphalts, lubricants, and solvents that are derived from petroleum.

Much has been done and you soon may infer from the breadth of the material that we will cover that most everything worth doing already has been done. However, many unsolved scientific problems remain and others have not even been thought of but, in addition, there are many technical and social problems to which answers are badly needed. Some of these include problems of pollution of the environment, energy sources, overpopulation and food production, insect control, medicine, drug action, and improved utilization of natural resources.

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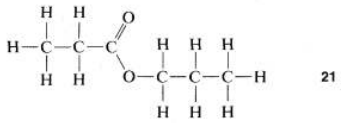
1.6: Some Philosophical Observations

As you proceed with your study of organic chemistry, you may well feel confused as to what it is you are actually dealing with. On the one hand, there will be exhortations to remember how organic chemistry pervades our everyday life. And yet, on the other hand, you also will be exhorted to think about organic compounds in terms of abstract structural formulas representing molecules when there is absolutely no way at all to deal with molecules as single entities. Especially if you are not studying organic compounds in the laboratory concurrently, you may come to confuse the abstraction of formulas and ball-and-stick models of the molecules with the reality of organic compounds, and this would be most undesirable. At each stage of the way, you should try to make, or at least visualize, a juncture between a structural formula and an actual substance in a bottle. This will not be easy - it takes time to reach the level of experience that a practicing organic chemist has so that he can tell you with some certainty that the structural formula 21 represents in actuality, a limpid, colorless liquid with a pleasant odor, slightly soluble in water, boiling somewhere about 100°.



21

A useful method for developing this sort of feeling for the relationship between structures and actual compounds is to check your perception of particular substances with their properties as given in a chemical handbook.

One, perhaps comforting, thought for you at this time is that differences between the chemical behaviors of relatively similar organic compounds usually are ascribed to just three important and different kinds of effects - two of which have root in common experience. One, called *steric hindrance*, is a manifestation of experience that two solid objects cannot occupy the same space at once. Another is the *electrical effect*, which boils down to a familiar catechism that like electrical charges repel each other and unlike charges attract each other. The remaining important effect, the one that has no basis in common experience, derives from quantum mechanics. The *quantum mechanical effect* explains why benzene is unusually stable, how and why many reactions occur in special ways and, probably most important of all, the ways that organic compounds interact with electromagnetic radiation of all kinds - from radio waves to x rays.

We shall try to give as clear explanations as possible of the quantum mechanical effects, but some of it will just have to be accepted as fact that we cannot ourselves experience directly nor understand intuitively. For example, when a grindstone rotates, so far as our experience goes, it can have an infinitely variable rate of rotation and, consequently, infinitely variable rotation (angular) momentum. However, molecules in the gas phase have only *specific* rotation rates and corresponding *specific* rotational momentum values. No measurement technique can detect in-between values of these quantities. Molecules are "quantized rotators." About all you can do is try to accept this fact, and if you try long enough, you may be able to substitute familiarity for understanding and be happy with that.

All of us have some concepts we use continually (even perhaps unconsciously) about energy and work. Thermodynamics makes these concepts quantitative and provides very useful information about what might be called the potential for any process to occur, be it production of electricity from a battery, water running uphill, photosynthesis, or formation of nitrogen oxides in combustion of gasoline. In the past, most organic chemists seldom tried to apply thermodynamics to the reactions in which they were interested. Much of this was due to the paucity of thermodynamic data for more than a few organic compounds, but some was because organic chemists often liked to think of themselves as artistic types with little use for quantitative data on their reactions (which may have meant that they didn't really know about thermodynamics and were afraid to ask).

Times have changed. Extensive thermochemical data are now available, the procedures are well understood, and the results both useful and interesting. We shall make considerable use of thermodynamics in our exposition of organic chemistry. We believe it will greatly improve your understanding of why some reactions go and others do not.

Finally, you should recognize that you almost surely will have some problems with the following chapters in making decisions as to how much time and emphasis you should put on the various concepts, principles, facts, and so on, that we will present for you. As best we can, we try to help you by pointing out that this idea, fact, and so on, is "especially important," or words to that effect. Also, we have tried to underscore important information by indicating the breadth of its application to other scientific disciplines as

well as to technology. In addition, we have caused considerable material to be set in smaller type and indented. Such material includes extensions of basic ideas and departments of fuller explanation. In many places, the exposition is more complete than it needs to be for you at the particular location in the book. However, you will have need for the extra material later and it will be easier to locate and easier to refresh your memory on what came before, if it is one place. We will try to indicate clearly what you should learn immediately and what you will want to come back for later.

The problem is, no matter what we think is important, you or your professor will have your own judgments about relevance. And because it is quite impossible to write an individual text for your particular interests and needs, we have tried to accommodate a range of interests and needs through providing a rather rich buffet of knowledge about modern organic chemistry. Hopefully, all you will need is here, but there is surely much more, too. So, to avoid intellectual indigestion, we suggest you not try to learn everything as it comes, but rather try hardest to understand the basic ideas and concepts to which we give the greatest emphasis. As you proceed further, the really important facts, nomenclature, and so on (the kind of material that basically requires memorization), will emerge as that which, in your own course of study, you will find you use over and over again. In hope that you may wish either to learn more about particular topics or perhaps gain better understanding through exposure to a different perspective on how they can be presented, we have provided supplementary reading lists at the end of each chapter.

Our text contains many exercises. You will encounter some in the middle of the chapters arranged to be closely allied to the subject at hand. Others will be in the form of supplementary exercises at the end of the chapters. Many of the exercises will be drill; many others will extend and enlarge upon the text. The more difficult problems are marked with a star (*).

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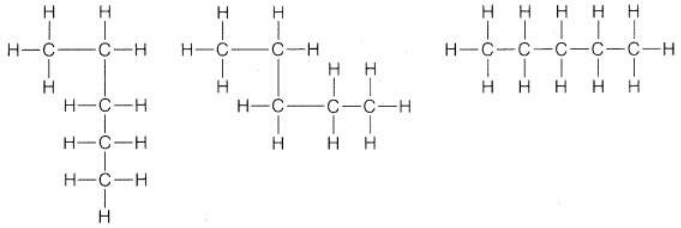
1.E: Introduction to Organic Chemistry (Exercises)

Exercise 1-1 How many *different* isomers are there of $C_{H2}Br_4$? (Assume free-rotating tetrahedral carbon and univalent hydrogen and bromine.) How could one determine which of these isomers is which by the substitution method?

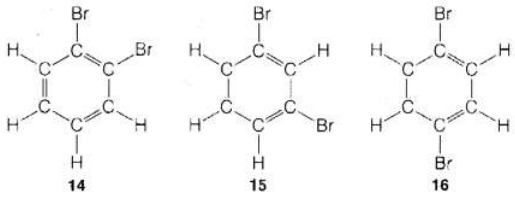
Exercise 1-2 A compound of formula $C_3H_6Br_2$ is found to give only a *single* substance, $C_3H_5Br_3$, on further substitution. What is the structure of the $C_3H_6Br_2$ isomer and of its substitution product?

Exercise 1-3 A compound of formula C_5H_{12} gives only a *single* monobromo substitution product of formula $C_5H_{11}Br$. What is the structure of this C_5H_{12} isomer? (Notice that carbon can form both continuous chains and branched chains. Also notice that structures such as the following represent the *same* isomer because the bonds to carbon are tetrahedral and are free to rotate.)



Exercise 1-4 A gaseous compound of formula C_2H_4 reacts with liquid bromine (Br_2) to give a single $C_2H_4Br_2$ compound. The $C_2H_4Br_2$ so formed gives only *one* $C_2H_3Br_3$ substitution product. Deduce the structure of C_2H_4 and the bromo compounds derived from it. (This was a key problem for the early organic chemists.)

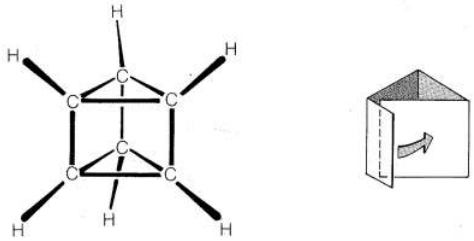
Exercise 1-5 Three different dibromobenzenes are known, here represented by just one of the Kekulé structures, 14, 15, and 16:



14 15 16

Show how the substitution method described in Section 1-1F could be used to determine which isomer is which and, in addition, establish the structures of the various possible tribromobenzenes of formula $C_6H_3Br_3$.

Exercise 1-6 The German chemist Ladenburg, in 1868, suggested the prismatic formula 17 for benzene:



17 18

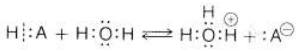
Assuming the C–C bonds of the prism all are the same length, determine how many mono-, di-, and tribromine-substituted isomers are possible for 17. Compare the results with those expected for benzene with structure 13. If you have molecular models of the ball-and-stick type, these will be very helpful. A simple alternative model for 17 would be a piece of stiff paper folded and fastened as in 18 to give a prism with three equal square faces.

Exercise 1-7 The compound C_2H_5Br reacts slowly with the compound CH_4O to yield a single substance of formula C_3H_8O. Assuming normal valences throughout, write structural formulas for CH_4O and the *three different* possible structural (not rotational) isomers of C_3H_8O and show how the principle of least structural change favors one of them as the reaction product. What would you expect to be formed from each of these three C_3H_8O isomers with strong hydrobromic acid?

Exercise 1-8 There are a large number of known isomers of C_5H_{10}, and some of these are typically unsaturated, like ethene, while others are saturated, like ethane. One of the saturated isomers on bromine substitution gives only *one* compound of formula C_5H_9Br. Work out a structure for this isomer of C_5H_{10} and its monobromo substitution product.

Exercise 1-9 Lithium hydride could be written as either $Li^{\oplus}:H^{\ominus}$ or $H^{\oplus}:Li^{\ominus}$ depending on whether lithium or hydrogen is more electron-attracting. Explain why hydrogen is actually more electron-attracting, making the correct structure $Li^{\oplus}:H^{\ominus}$.

Exercise 1-10 An acid (HA) can be defined as a substance that donates a proton to a base, for example water. The proton-donation reaction usually is an equilibrium reaction and is written as



Predict which member of each of the following pairs of compounds would be the stronger acid. Give your reasons.

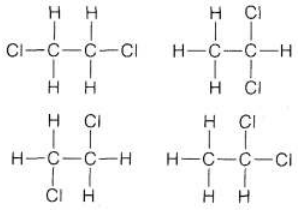
a. LiH, HF
b. NH_3, H_2O
c. H_2O_2, H_2O
d. CH_4, CF_3H

Exercise 1-11 (This problem is in the nature of review of elementary inorganic chemistry and may require reference to a general chemistry book.) Write Lewis structures for each of the following compounds. Use distinct, correctly placed dots for the electrons. Mark all atoms that are not neutral with charges of the proper sign.

a. ammonia, NH_3
b. ammonium bromide, NH_4Br
c. hydrogen cyanide, HCN
d. ozone ($\angle O{-}O{-}O = 120^{o}$)
e. carbon dioxide, CO_2
f. hydrogen peroxide, $HOOH$
g. hydroxylamine, $HONH_2$
h. nitric acid, HNO_3
i. hydrogen sulfide, H_2S
j. boron trifluoride, BF_3

Exercise 1-12 Use ball-and-stick models or suitable three-dimensional drawings to determine which members of the following sets of formulas represent identical compounds, provided "free rotation" is considered to be possible around all *single* bonds (except when these bonds are present in a cyclic structure):

a.



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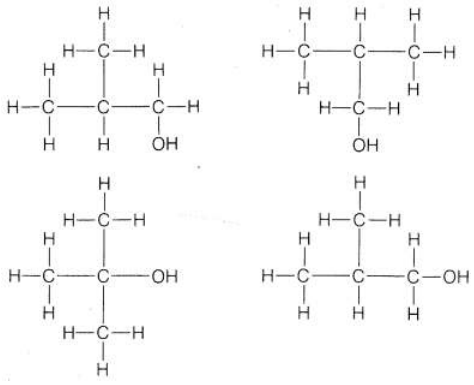
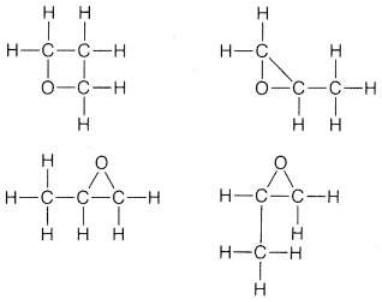
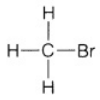


b.

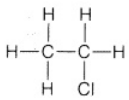


c.

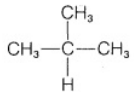
Exercise 1-13 Write structures for all of the *different* monobromo substitution products (of Br for H) you would expect for each of the following compounds.



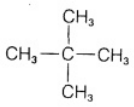
a.



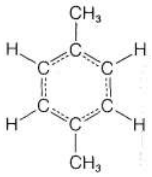
b.



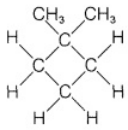
c.



d.



e.



f.

Exercise 1-14 There are two isomers of C_3H_6 with normal carbon and hydrogen valences. Each adds bromine - one rapidly and the other very sluggishly - to give *different* isomers of $C_3H_6Br_2$. The $C_3H_6Br_2$ derived from the C_3H_6 isomer that reacts sluggishly with bromine can give just *two* different $C_3H_5Br_3$ isomers on further bromine substitution, whereas the other $C_3H_6Br_2$ compound can give *three* different $C_3H_5Br_3$ isomers on further substitution. What are the structures of the C_3H_6 isomers and their $C_3H_6Br_2$ addition products?

Exercise 1-15* (Remember that here and elsewhere, * denotes a more difficult exercise.) The vast majority of organic substances are compounds of carbon with hydrogen, oxygen, nitrogen, or the halogens. Carbon and hydrogen can be determined in combustible compounds by burning a weighed sample in a stream of oxygen (Figure 1-1) and absorbing the resulting water and carbon dioxide in tubes containing anhydrous magnesium perchlorate and soda lime, respectively. The gain in weight of these tubes corresponds to the weights of the water and the carbon dioxide formed.

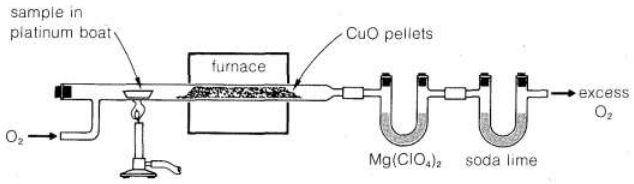


Figure 1-1: *Schematic representation of a combustion train for determination of carbon and hydrogen in combustible substances.*

The molecular weight of a moderately volatile substance can be determined by the historically important **Victor Meyer procedure**, by which the volume of gas produced by vaporization of a weighed sample of an unknown is measured at a given temperature (Figure 1-2). The relationship $PV = nRT$ is used here, in which P is the pressure in mm of mercury, V is the volume in mL, T is the absolute temperature in $^{\circ}\mathrm{K}$ $[= 273.15 + T\,(^{\circ}\mathrm{C})]$, n is the number of moles, and R is the gas constant $= 62,400$ in the units of $(\mathrm{mm\ Hg} \times \mathrm{mL}) / (\mathrm{mol} \times {}^{\circ}\mathrm{K})$. The number of moles, n, equals m/M in which m is the weight of the sample and M is the gross molecular weight. An example of the use of the Victor Meyer method follows.

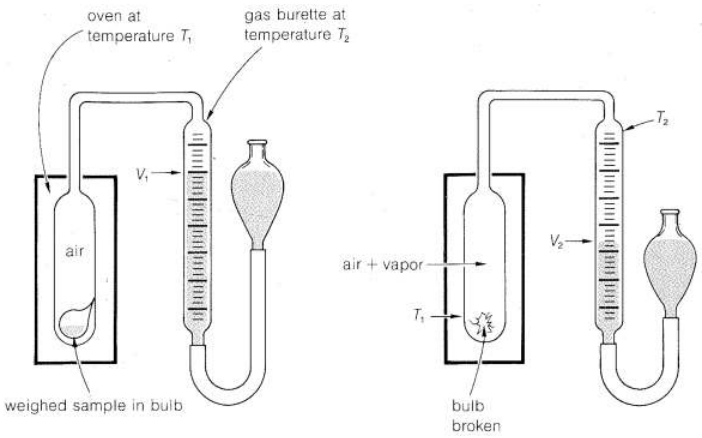


Figure 1-2: *Schematic diagram of a Victor Meyer apparatus for determination of the vapor density of a substance that is volatile at the oven temperature T_1. The air displaced from the heated chamber by the volatilization of the sample in the bulb is measured in the gas burette at temperature T_2 as the difference in the burette readings V_2 and V_1.*

A 0.005372-g sample of a liquid carbon-hydrogen-oxygen compound on combustion gave $0.01222\ \mathrm{g}$ of CO_2 and $0.00499\ \mathrm{g}$ of H_2O. In the Victor Meyer method, $0.0343\ \mathrm{g}$ of the compound expelled a quantity of air at 100° $(373^{\circ}\mathrm{K})$ which, when collected at 27° $(300^{\circ}\mathrm{K})$ and $728\ \mathrm{mm\ Hg}$, amounted to $15.2\ \mathrm{mL}$.

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Show how these results lead to the empirical and molecular formula of C_3H_6O. Write at least five isomers that correspond to this formula with univalent H, divalent O, and tetravalent C.

Exercise 1-16 Determine the molecular formula of a compound of molecular weight 80 and elemental percentage composition by weight of $C = 45.00$, $H = 7.50$, and $F = 47.45$. Write structures for all the possible isomers having this formula. (See Exercise 1-15 for a description of how percentage composition is determined by combustion experiments.)

Exercise 1-17 Why is the boiling point of water (100°) substantially higher than the boiling point of methane (-161°)?

Exercise 1-18 Dimethylmercury, $CH_3-Hg-CH_3$, is a volatile compound of bp 96°, whereas mercuric fluoride $F-Hg-F$ is a high-melting solid having mp 570°. Explain what differences in bonding in the two substances are expected that can account for the great differences in physical properties.

Exercise 1-19* There are four possible isomers of C_4H_9Br. Let us call two of these *A* and *B*. Both *A* and *B* react with water to give the *same* isomer of $C_4H_{10}O$ and this isomer of $C_4H_{10}O$ reacts with strong HBr to give back only *A*. Substitution of *A* with bromine gives only *one* of the possible $C_4H_8Br_2$ isomers. Substitution of *B* with bromine gives three different $C_4H_8Br_2$ isomers, and one of these is identical with the $C_4H_8Br_2$ from the substitution of *A*. Write structural formulas for *A* and *B*, and the isomers of $C_4H_8Br_2$ formed from them with bromine, and for the isomers of $C_4H_{10}O$ expected to be formed from them with water. Indicate in which reaction the principle of least structural change breaks down.

1.E.1: Contributors

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CHAPTER OVERVIEW

2: Structural Organic Chemistry

In this chapter, we first briefly review the most important types of covalent bonds encountered in organic substances and the ways in which these bonds are represented in structural formulas. Next we consider the sizes and shapes of organic molecules and how structural formulas written in two dimensions can be translated into three-dimensional models that show the relative positions of the atoms in space. We also discuss models that reflect the relative sizes of the atoms and the way in which the atoms may interfere with each other when in close quarters (steric hindrance). Then we go on to further important aspects of structure-the functional group concept and position isomerism. Our aim is to have you become more familiar with the various kinds of organic compounds and begin to see how the practicing organic chemist visualizes molecules and correlates the diverse kinds of structures that he has to deal with in his work.

2.1: Structural Formulas

2.2: The Sizes and Shapes of Organic Molecules

2.3: Classification by Functional Groups

2.4: Isomerization in Organic Compounds

2.E: Structural Organic Chemistry (Exercises)

2.1: Contributors and Attributions

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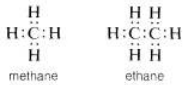
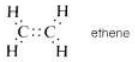
2.1: Structural Formulas

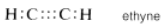
The building block of structural organic chemistry is the tetravalent carbon atom. With few exceptions, carbon compounds can be formulated with four covalent bonds to each carbon, regardless of whether the combination is with carbon or some other element. The two-electron bond, which is illustrated by the carbon-hydrogen bonds in methane or ethane and the carbon-carbon bond in ethane, is called a **single bond**. In these and many related substances, each carbon is attached to four other atoms:



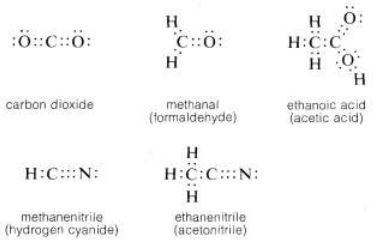
There exist, however, compounds such as ethene (ethylene), C_2H_4, in which two electrons from each of the carbon atoms are mutually shared, thereby producing *two* two-electron bonds, an arrangement which is called a **double bond**. Each carbon in ethene is attached to only three other atoms:



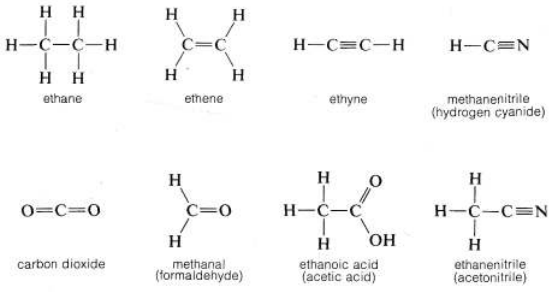
Similarly, in ethyne (acetylene), C_2H_2, three electrons from each carbon atom are mutually shared, producing *three* two-electron bonds, called a **triple bond**, in which each carbon is attached to only two other atoms:



Of course, in all cases each carbon has a full octet of electrons. Carbon also forms double and triple bonds with several other elements that can exhibit a covalence of two or three. The carbon-oxygen (or carbonyl) double bond appears in carbon dioxide and many important organic compounds such as methanal (formaldehyde) and ethanoic acid (acetic acid). Similarly, a carbon-nitrogen triple bond appears in methanenitrile (hydrogen cyanide) and ethanenitrile (acetonitrile).

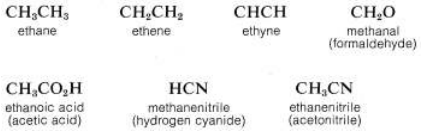


By convention, a single straight line connecting the atomic symbols is used to represent a single (two-electron) bond, two such lines to represent a double (four-electron) bond, and three lines a triple (six-electron) bond. Representations of compounds by these symbols are called **structural formulas**; some examples are

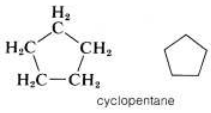


A point worth noting is that structural formulas usually do not indicate the *nonbonding* electron pairs. This is perhaps unfortunate because they play as much a part in the chemistry of organic molecules as do the bonding electrons and their omission may lead the unwary reader to overlook them. However, when it is important to represent them, this can be done best with pairs of dots, although a few authors use lines:

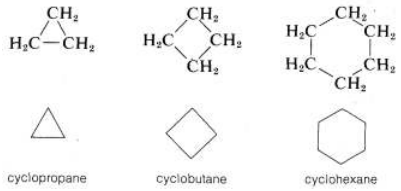
To save space and time in the representation of organic structures, it is common practice to use "condensed formulas" in which the bonds are not shown explicitly. In using condensed formulas, normal atomic valences are understood throughout. Examples of condensed formulas are



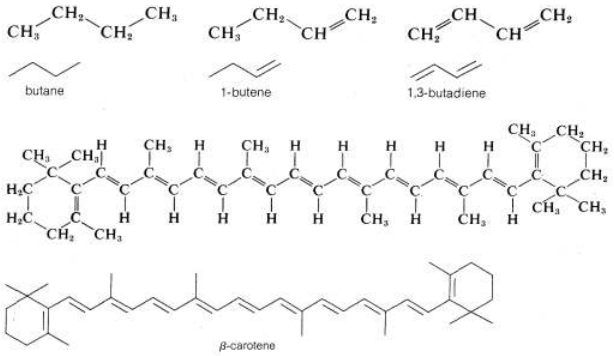
Another type of abbreviation that often is used, particularly for ring compounds, dispenses with the symbols for carbon and hydrogen atoms and leaves only the lines in a structural formula. For instance, cyclopentane, C_5H_{10}, often is represented as a regular pentagon in which it is understood that each apex represents a carbon atom with the requisite number of hydrogens to satisfy the tetravalence of carbon:



Likewise, cyclopropane, C_3H_6; cyclobutane, C_4H_8; and cyclohexane, C_6H_{12}, are drawn as regular polygons:



Although this type of line drawing is employed most commonly for cyclic structures, its use for open chain (acyclic) structures is becoming increasingly widespread. There is no special merit to this abbreviation for simple structures such as butane, C_4H_{10}; 1-butene, C_4H_8; or 1,3-butadiene, C_4H_6, but it is of value in representing more complex molecules such as β-carotene, $C_{40}H_{56}$:



Line structures also can be modified to represent the three-dimensional *shapes* of molecules, and the way that this is done will be discussed in detail in Chapter 5. At the onset of you study of organic chemistry, you should write out the formulas rather completely until you are thoroughly familiar with what these abbreviations stand for.

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2.2: The Sizes and Shapes of Organic Molecules

The size and shape of molecules are as much a part of molecular structure as is the order in which the component atoms are bonded. Contrary to the impression you may get from structural formulas, complex molecules are not flat and formless, but have well-defined spatial arrangements that are determined by the lengths and directional character of their chemical bonds. It is not easy to visualize the possible arrangements of the bonds in space and it is very helpful to have some kind of mechanical model that reflects the molecular geometry, including at least an approximation to the relative lengths of the bonds. "Ball-and-stick" models such as the ones used by Paterno (Section 1-1D) fill this purpose admirably.

2.2.1: Bond Angles and Ball-and-Stick Models

It is well established that the normal carbon atom forms its four single bonds in compounds of the type CX_4 so that the four attached atoms lie at the corners of a regular tetrahedron. The bond angles $X-C-X$ are 109.5^{o} and this value is the "normal" valence angle of carbon. For many purposes, ball-and-stick models of organic compounds give useful information about the spatial relationships of the atoms, and for CX_4 the angles between sticks are set at 109.5^{o} (Figure 2-1). Organic molecules strongly resist deformation forces that alter their valence angles from normal values. Therefore ball-and-stick models correspond better to the behavior of actual molecules if the connectors representing single bonds are made to be rather stiff.

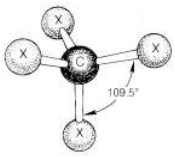


Figure 2-1: Ball-and-stick model of CX_4

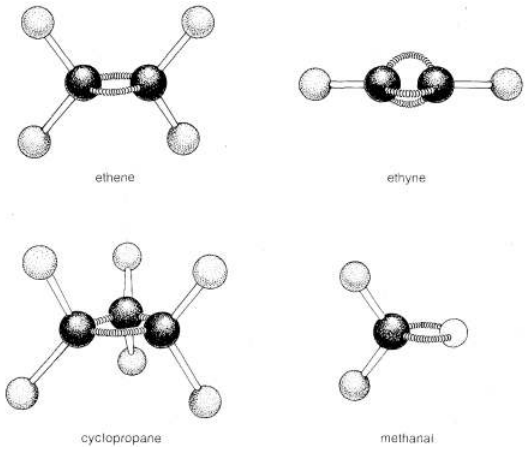


Figure 2-2: Ball-and-stick models of some simple organic molecules

Whereas methane, CH_4, is tetrahedral, ethene, C_2H_4, is not. According to the best available physical measurements, all six atoms of ethene lie in a single plane and the $H-C-H$ bond angles are 117.3^{o}. Methanal (formaldehyde) also is a planar molecule with an $H-C-H$ bond angle of 118°.

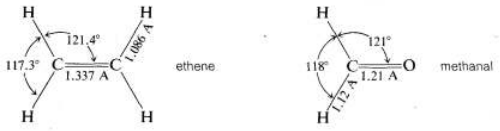


Figure 2-2), but the $H-C-H$ angles are inaccurate because they are 109.5^{o} rather than the observed 117° to 118°.

Ethyne, C_2H_2, has been established experimentally to be a linear molecule; that is, the $H-C-C$ bond angle is 180°:

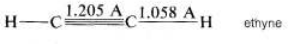


Figure 2-2.

Structural units that have $C-C-C$ valence angles substantially less than the tetrahedral value include double and triple bonds, and small rings such as cyclopropane. Several bent bonds are required to construct models of compounds containing these units. Interestingly, such compounds are much less stable and more reactive than otherwise similar molecules for which models can be constructed with straight sticks at tetrahedral angles.

2.2.2: Bond Lengths and Space-Filling Models

The length of a chemical bond is the average distance between the nuclei of two bonded atoms, regardless of where the bonding electrons happen to be. The customary unit of length is the angstrom[1] ($\mathrm{A} = 10^{-10}\ \mathrm{m}$), and measurements often can be made with an accuracy of $0.001\ \mathrm{A}$ by using the techniques of molecular spectroscopy, x-ray diffraction (for crystalline solids), and electron diffraction (for volatile compounds). Bond lengths vary considerably with structure and depend on the identity of both atoms, the type of bonding (single, double, or triple), and the nature of other atoms or groups bonded to the two atoms in question. These effects are apparent in the data of Table 2-1, which lists the bond lengths in several simple organic compounds. Multiple bonds, double or triple, clearly are shorter than single bonds, and it can be stated as a general observation that the more bonding electrons in a given bond, the shorter (and stronger) the bond. The lengths of single $C-C$ bonds also vary significantly depending on what other atoms or groups are attached to the carbons. Thus Table 2-1 shows that single $C-C$ bonds become progressively shorter as the number of multiple bonds or electronegative atoms attached to the carbons increases.

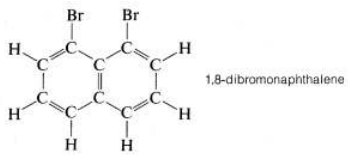
Although molecular models cannot represent the subtle variations in bond lengths and bond angles that actual molecules exhibit, most kinds of commercially available molecular models do attempt to reproduce relative bond lengths with some degree of reality. In the ball-and-stick type, the sticks usually come in various lengths to simulate different kinds of bonds; $C-H$ bonds typically are scaled to represent $1.1\ \mathrm{A}$, $C-C$ bonds to be $1.54\ \mathrm{A}$, and $C=C$ and $C\equiv C$ to be correspondingly shorter. In some model sets the bonds can be cut to any desired length.

While the ball-and-stick models of molecules are very useful for visualizing the relative positions of the atoms in space, they are unsatisfactory whenever we also want to show how large the atoms are. Actually, atomic radii are so large relative to the lengths of chemical bonds that when a model of a molecule such as methyl chloride is constructed with atomic radii and bond lengths, both to scale, the bonds connecting the atoms are not clearly evident. None-

Compound	Formula	Bond length, A C—C	C=C	C≡C	C—H	C—Cl
ethane	$CH_3—CH_3$	1.534			1.093	
ethene	$H_2C=CH_2$		1.339		1.086	
ethyne	$HC\equiv CH$			1.205	1.058	
butane	$CH_3—CH_2—CH_2—CH_3$	1.539			1.100	
2-butene	$CH_3—CH=CH—CH_3$	1.520	1.339			
2-butyne	$CH_3—C\equiv C—CH_3$	1.47		1.20	1.09	
1,3-butadiene	$CH_2=CH—CH=CH_2$	1.483	1.337		1.08[b]	
1-buten-3-yne	$CH\equiv C—CH=CH_2$	1.448	1.34	1.20	1.07[b]	
chloroethane	$CH_3—CH_2Cl$	1.595			1.101[c]	1.779
1,1-dichloroethane	$CH_3—CHCl_2$	1.55				1.79
1,1,1-trichloroethane	$CH_3—CCl_3$	1.54			1.09	1.76
hexachloroethane	$CCl_3—CCl_3$	1.49				1.76

[a]From "Tables of Interatomic Distances and Configuration in Molecules and Ions," *Special Publication Nos. 11 and 18*, The Chemical Society, London, 1958 and 1965.
[b]Refers to C—H of terminal CH_2 group.
[c]Refers to C—H of CH_2Cl group.

Figure 2-3 shows how the CPK models can indicate intense molecular crowding, as between the bromines in 1,8-dibromonaphthalene, a close relative of 1,2-dibromobenzene mentioned in Section 1-1G:



1,8-dibromonaphthalene

As we shall see, such crowding has many chemical consequences.

Ideally, a model should reflect not only the size and shape of the molecule it represents but also the flexibility of the molecule. By this we mean that

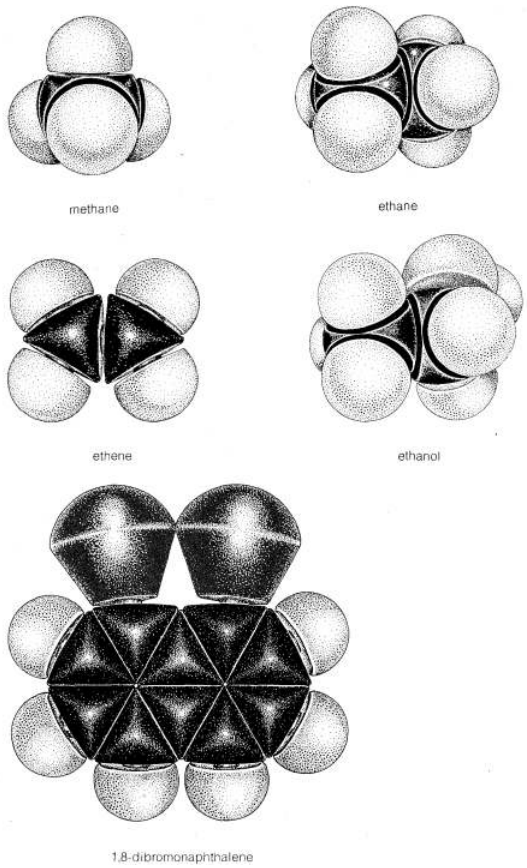


Figure 2-3: CPK space-filling models of organic compounds

it should simulate the type of motions available to the molecule, particularly bond rotation. For example, it is known that rotation normally occurs about single bonds in open-chain compounds but is restricted about double bonds. Motions of this kind are demonstrated easily with ball-and-stick models, but are not at all obvious with the space-filling type. For this reason, ball-and-stick models or their equivalent are more generally useful than the space-filling models for visualizing structures and the positions of the atoms relative to one another.

[1]The angstrom unit likely will be replaced eventually by the nanometer ($1\ \mathrm{nm} = 10^{-9}\ \mathrm{m} = 10\ \mathrm{A}$).

2.2.3: Contributors and Attributions

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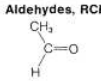
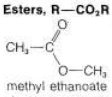
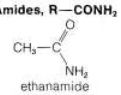
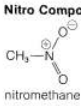
2.3: Classification by Functional Groups

There are a number of recurring types of structural features in organic compounds that commonly are known as **functional groups**. In fact, a traditional approach to the subject of organic chemistry involves the classification of compounds according to their functional groups. Thus the structural features $C=C$, $C\equiv C$, $C=O$, OH, NH_2, and $C\equiv N$ are the functional groups of alkenes, alkynes, carbonyl compounds, alcohols, amines, and nitriles, respectively. It will be helpful to look at the structural features of some of the major types of organic compounds even though the details of their chemistry will not be discussed until later chapters. Examples of the structures arranged in accord with their functional groups are given in Table 2-2. The examples chosen are representative of compounds containing carbon and hydrogen (**hydrocarbons**) as well as compounds containing halogens, oxygen, nitrogen, and sulfur. We do not expect you to memorize this table. In time you will become familiar with all of the types of structures in it.

In Table 2-2 we generally have used **systematic names** as first-choice names because these names emphasize the relationships between the compounds and ease the burden fo the beginning student in having to remember many special names. We have little hope that systematic names such as methanal, 2-propanone, and ethanoic acid soon will replace the commonly used nonsystematic names formaldehyde, acetone, and acetic acid. But there is no question that every organic chemist knows what compounds the names methanal, 2-propanone, and ethanoic acid represent, so the beginner can communicate with these names and later become familiar with and use the special names. We will have more to say on this subject in Chapter 3.

Table 2-2
Types and Examples of Organic Compounds Arranged According to Functional Groups

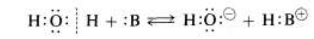
Hydrocarbons, R—H[a]				
Alkanes $CH_3CH_2CH_3$ propane	Alkenes $CH_3CH{=}CH_2$ propene	Alkynes $CH_3C{\equiv}CH$ propyne	Cycloalkanes cyclohexane	Arenes benzene
Alcohols, R—OH $CH_3CH_2{-}OH$ ethanol (ethyl alcohol)	**Ethers, R—O—R** $CH_3CH_2{-}O{-}CH_2CH_3$ ethoxyethane (diethyl ether)	**Halides, R—X** $CH_3CH_2{-}Br$ bromoethane (ethyl bromide)	**Aldehydes, RCHO**  ethanal (acetaldehyde)	**Ketones, R_2CO** 2-propanone (acetone)
Carboxylic Acids, R—CO_2H ethanoic acid (acetic acid)	**Esters, R—CO_2R**  methyl ethanoate (methyl acetate)	**Amides, R—$CONH_2$**  ethanamide (acetamide)		
Amines, R—NH_2 $CH_3CH_2{-}NH_2$ ethanamine (ethylamine)	**Nitro Compounds, R—NO_2**  nitromethane	**Nitriles, RC≡N** $CH_3C{\equiv}N$ ethanenitrile (acetonitrile)	**Thiols, RSH** $CH_3CH_2{-}SH$ ethanethiol	

[a]The symbol R represents a hydrocarbon group.

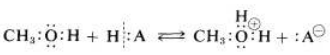
2.3.1: How Are Functional-Group Classifications Useful?

One of the main reasons for classifying compounds by their functional groups is that it also classifies their chemical behavior. By this we mean that the reactions of compounds and, to some extent, their physical properties are influenced profoundly by the nature of the functional groups present. Indeed, many organic reactions involve transformations of the functional group that do not affect the rest of the molecule. For instance, alcohols, $R-OH$, can be transformed into a number of other compounds, such as organic halides, $R-Cl$ or $R-Br$; ethers, $R-O-R$; and amines, $R-NH_2$ without changing the structure of the hydrocarbon group R. Furthermore, any compound possessing a particular functional group may be expected to exhibit reactions characteristic of that group and, to some extent at least, of inorganic compounds with similar functional groups.

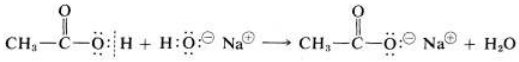
A good example of the use of the functional-group concept is for acid-base properties. Alcohols, ROH, are structurally related to water, HOH, in that both possess a hydroxyl function. We may then expect the chemistry of alcohols to be similar to that of water. In fact, both are weak *acids* because the OH group has a reactive proton that it can donate to a sufficiently strongly basic substance, written as $:B$ here:



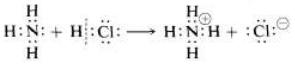
Water and alcohols both are weak *bases* because the oxygens of their OH groups have unshared electron pairs to use in bonding with a proton donated by an acid, HA:

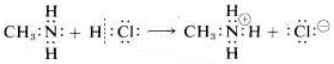


We can carry the analogy further to include carboxylic acids, RCO_2H, which also have a hydroxyl function. They also should possess acidic and basic properties. They do have these properties and they are, in fact, stronger acids than either water or alcohols and form salts with bases:



Amines, RNH_2, are structurally related to ammonia, NH_3, and we therefore may predict that they will have similar properties. A property of ammonia that you probably will have encountered earlier is that it acts as a base and forms salts with acids. Amines behave likewise:



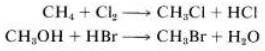


It is with logic of this kind - inferring chemical behavior from structural analogies - that much of organic chemistry can be understood. There are other logical classification schemes, however, and one of these depends more on *types* of reactions than on functional groups.

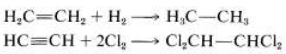
2.3.2: Classifications by Reaction Types

The rationale of classification by reaction types is that different functional groups may show the same kinds of reactions. Thus, as we have just seen, alcohols, carboxylic acids, and amines all can accept a proton from a suitably strong acid. Fortunately, there are very few different types of organic reactions - at least as far as the overall result that they produce. The most important are acid-base, substitution, addition, elimination, and rearrangement reactions. Some examples of these are given below, and you should understand that these are descriptive of the overall chemical change and nothing is implied as to *how* or *why* the reaction occurs (also see Section 1-1I).

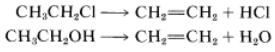
Substitution of one atom or group of atoms for another:



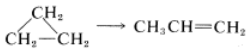
Addition, usually to a double or triple bond:



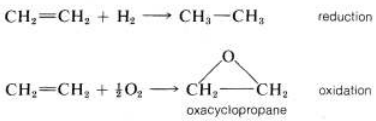
Elimination, which is the reverse of addition:



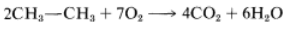
Rearrangement where one structure is converted to an isomeric structure:



Certain reactions commonly are described as either *oxidation* or *reduction* reactions and most simply can be thought of as reactions that result in changes in the oxygen or hydrogen content of a molecule by direct or indirect reactions with oxygen or hydrogen, respectively. They frequently fall into one of the categories already mentioned. Reduction of ethene to ethane is clearly *addition*, as is oxidation of ethene to oxacyclopropane:



Reactions that lead to substantial degradation of molecules into smaller fragments are more difficult to classify. An example is the combustion of ethane to carbon dioxide and water. All of the chemical bonds in the reactants are broken in this reaction. It seems pointless to try to classify this as anything but a complete combustion or oxidation reaction:



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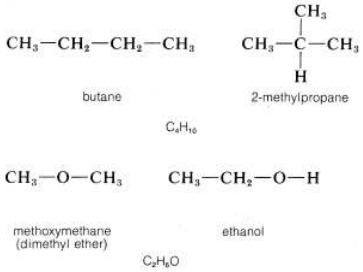
2.4: Isomerization in Organic Compounds

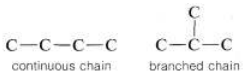
More than one stable substance can correspond to a given molecular formula. Examples are butane and 2-methylpropane (isobutane), each of which has the molecular formula C_4H_{10}. Similarly, methoxymethane (dimethyl ether) and ethanol have the same formula, C_2H_6O:



Compounds having the same number and kinds of atoms are called **isomers**.[2] Whereas only one stable substance is known corresponding to the formula CH_4, thirty-five stable isomers have been prepared of the formula C_9H_{20}. From this one may begin to sense the rich variety of organic chemistry, which leads to many problems - in telling one compound from another, in determining structures, and also in finding suitable names for compounds. In the rest of this chapter we will describe one type of isomer - the position isomer - and in later chapters we will discuss another type of isomer - the stereoisomer - and the experimental approaches that are used to establish the purity, identity, structure, and stereochemistry of organic compounds.

2.4.1: Position Isomers

Compounds having the same number and kind of atoms but having different bonding arrangements between the atoms are called **position isomers**. Butane and 2-methylpropane are examples of position isomers. The atoms are connected differently in the two structures because the carbon chain in butane is a straight or continuous chain, whereas in 2-methylpropane it is branched:



Therefore these two molecules are structurally different and, accordingly, do not have the same chemical and physical properties. They cannot be converted one into the other without breaking and remaking $C-C$ and $C-H$ bonds. Methoxymethane and ethanol are also position isomers because the oxygen clearly is connected differently in the two molecules:

The term *position isomer* means the same as *constitutional isomer*. The designation *structural isomer* also is used, but this term is taken by some to include both position isomers and stereoisomers; that is, "structure" can mean both the way in which atoms are connected and their different arrangements in space.

The number of position isomers possible for a given formula rapidly increases with the increasing number of carbon atoms, as can be seen from the number of theoretically possible structures of formula C_nH_{2n+2} up to $n = 10$ given in Table 2-3. In 1946, it was reported that all of the 75 compounds with values of $n = 1$ to $n = 9$ had been prepared in the laboratory. Before we can begin to discuss the chemistry of these compounds it is necessary to know how

Table 2-3
Alkanes (C_nH_{2n+2})

No. of carbons (n)	Name	No. of isomers
1	methane	1
2	ethane	1
3	propane	1
4	butane	2
5	pentane	3
6	hexane	5
7	heptane	9
8	octane	18
9	nonane	35
10	decane	75
20	eicosane	366,319
30	triacontane	4.11×10^9

to name them; without convenient and systematic rules for nomenclature that are adopted universally, catastrophic confusion would result. We shall tackle this problem in the next chapter.

[2]The prefix *iso* is from the Greek word meaning the same or alike.

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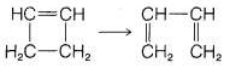
2.E: Structural Organic Chemistry (Exercises)

Exercise 2-1 Draw the Lewis electron-pair structure of 2-propanone (acetone) clearly showing the bonding and nonbonding electron pairs in the valence shell of each atom. Draw structural formulas for other compounds having the composition C_3H_6O that possess

a. an aldehyde function.
b. an ether function in a ring.
c. an alcohol function and a double bond.
d. an alcohol function and a ring.

Exercise 2-2 Classify each of the following reactions as a substitution, addition, elimination, rearrangement, oxidation-reduction, or acid-base proton-transfer reaction:

a. $CH_3COOH + CH_3NH_2 \rightarrow CH_3C\overset{\ominus}{O}O + CH_3\overset{\oplus}{N}H_3$
b. $C_6H_6 + Br_2 \rightarrow C_6H_5Br + HBr$
c. $CH_2{=}CH_2 + H_2O_2 \rightarrow HOCH_2CH_2OH$
d. $CH_3COOCH_3 + NH_3 \rightarrow CH_3CONH_2 + CH_3OH$
e. $CH_2{=}CH{-}CH_2{-}CH{=}CH_2 \rightarrow CH_3{-}CH{=}CH{-}CH{=}CH_2$
f. 
g. $ClCH_2CH_2Cl + KOH \rightarrow CH_2{=}CHCl + KCl + H_2O$
h. $CH_3C\equiv\overset{\ominus}{C}{:}\,\overset{\oplus}{N}a + CH_3OH \rightarrow CH_3C\equiv CH + \overset{\oplus}{N}a\overset{\ominus}{O}CH_3$
i. $CH_3Cl + \overset{\oplus}{N}a\overset{\ominus}{O}CH_3 \rightarrow CH_3OCH_3 + \overset{\oplus}{N}a\overset{\ominus}{C}l$

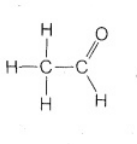
Exercise 2-3 Write a balanced equation for the complete combustion of benzene, C_6H_6, to CO_2 and H_2O, and for the incomplete combustion of benzene to CO and H_2O.

Exercise 2-4 How many grams of bromine will react by addition with (a) $20\ g$ of ethene (b) $20\ g$ of ethyne?

Exercise 2-5 Write balanced equations for the reactions of (a) metallic sodium with water, (b) metallic sodium with methanol, (c) sodium hydride with water, and (d) sodium hydride with ethanol.

Exercise 2-6 Write balanced equations for the reactions of (a) ammonia with sulfuric acid, (b) $CH_3CH_2NH_2$ with sulfuric acid, (c) sodium hydroxide with ammonium chloride, and (d) sodium hydroxide with $CH_3CH_2\overset{\oplus}{N}H_3\overset{\ominus}{C}l$.

Exercise 2-7 Draw structural formulas of the type



representing each of the required number of isomers for the following formulas. Be sure to use the normal valences for all of the atoms. Table 2-2 will be helpful to indicate possible structural types of various isomers.

a. C_5H_{12} (three)
b. $C_3H_4Br_2$ (four)
c. C_2H_4O (three)
d. C_4H_8 (four)
e. C_3H_9N (four)
f. C_3H_5Cl (at least three)
g. C_6H_6 (at least five; more than 100 can be written!)
h. $C_2H_4O_2$ (at least four)

i. C_3H_4O (at least three)
j. C_2H_3N (at least three)

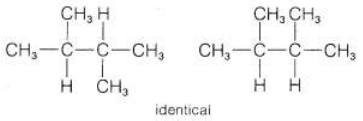
Exercise 2-8 Draw Lewis electron-pair structures for the following substances whose structural formulas are given. Use distinct, correctly placed dots for the electrons and show both the bonding and nonbonding pairs. Mark all atoms that are not neutral with charges of the proper sign.

a. propane, $CH_3CH_2CH_3$
b. methylcyclopropane, $(CH_2)_2CHCH_3$
c. propadiene, $CH_2{=}C{=}CH_2$
d. propyne, $HC \equiv CCH_3$
e. benzene, C_6H_6
f. tetrafluoroethene, $F_2C{=}CF_2$
g. methoxymethane, CH_3OCH_3
h. ethanal, CH_3CHO
i. ethanoic acid, CH_3CO_2H
j. benzenamine, $C_6H_5NH_2$
k. nitromethane, CH_3NO_2
l. benzenecarbonitrile, $C_6H_5C \equiv N$

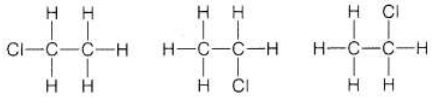
Exercise 2-9 Write an expanded structural formula with a line for each bond for each of the following substances which are represented by a condensed formula:

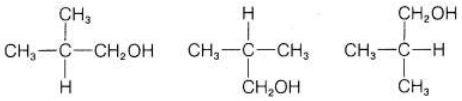
a. $CH_3CH(CH_3)_2$
b. CH_3CCCH_3
c. $(CH_2)_4$
d. CH_2CHCCH
e. $CH_3CONHCH_3$
f. $CH_3CO_2C_2H_5$
g. CH_2CHCHO
h. $C_6H_5NO_2$
i. C_2H_5CN
j. $(CH_3O)_2CO$

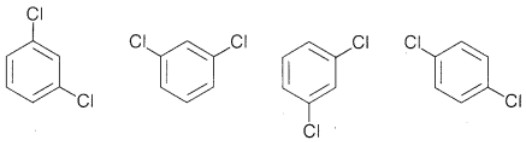
Exercise 2-10 Free rotation generally occurs around C–C *single* bonds (see Section 1-1E). Thus the following structural formulas are of the same compound, 2,3-dimethylbutane, because rotation about the central C–C bond makes the structures identical:

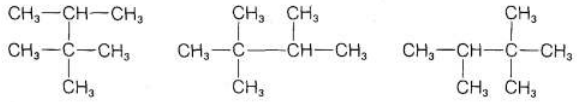


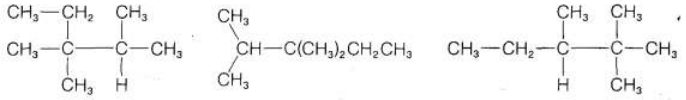
For the following structural formulas, determine which represent the same compound and which do not.

a.


b.


c.


d. 

e. 

Exercise 2-11 Write all the structural formulas you can for the different covalent isomers of the following molecular formulas. All the atoms should have their normal valences (i.e., monovalent for hydrogen and halogens, divalent for oxygen, trivalent for nitrogen, and tetravalent for carbon).

a. C_3H_6 (two)
b. C_3H_4 (three)
c. C_2H_4O (three)
d. C_2H_4ClF (two)
e. C_3H_9N (four)
f. C_4H_9Cl (four)

Exercise 2-12 With reference to Table 2-2 in necessary, draw structural formulas that satisfy the following descriptions:

a. three position isomers of $C_2H_4O_2$ with a carbonyl group $(-C{=}O)$.
b. four position isomers of $C_4H_{10}O$ with a hydroxyl group $(-OH)$.
c. a compound of formula C_5H_{12} that would have all its hydrogens located in chemically *identical* positions. (Chemically identical means that if one were to substitute a bromine for any one of the hydrogens, the same monobromo compound would be formed.)
d. a compound of formula C_3H_7ON with two chemically different methyl groups and an amide function.
e. two compounds of formula C_4H_8O, one of which is an aldehyde, the other a ketone.
f. two compounds of formula $C_3H_6O_2$, one of which is a carboxylic acid, the other a carboxylic ester.
g. two compounds of formula C_3H_4O, both with $C{=}O$ groups.
h. a compound of formula $C_9H_{12}N_2$ in which all the hydrogens are located in chemically identical positions and both nitrogens are present as nitrile functions.

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CHAPTER OVERVIEW

3: Organic Nomenclature

A chemical nomenclature is a set of rules to generate systematic names for chemical compounds. The nomenclature used most frequently worldwide is the one created and developed by the International Union of Pure and Applied Chemistry (IUPAC). The primary function of chemical nomenclature is to ensure that a spoken or written chemical name leaves no ambiguity concerning which chemical compound the name refers to: each chemical name should refer to a single substance.

3.1: Prelude to Organic Nomenclature
3.2: Alkanes
3.3: Cycloalkanes
3.4: Alkenes, Cycloalkenes, and Alkadienes
3.5: Alkynes
3.6: Arenes
3.E: Organic Nomenclature (Exercises)

Thumbnail: A chemical nomenclature is a set of rules to generate systematic names for chemical compounds. The nomenclature used most frequently worldwide is the one created and developed by the International Union of Pure and Applied Chemistry (IUPAC).

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3.1: Prelude to Organic Nomenclature

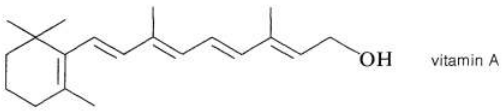
Organic chemists, regardless of what languages they speak, can communicate with one another about their chemical work simply by writing equations and structural formulas. But this is a slow process if the molecules are complicated, and is not well suited for conversation (try describing a structural formula of a complex molecule to someone). For more rapid and efficient communication we need to have names for compounds, and we should have every reason to hope that, after 100 years, the names now in use would be clear, unambiguous, easy to pronounce, easy to spell and to remember, as well as being amenable to arrangement in alphabetical order. But, even more, we should hope that the names of organic compounds would contain enough information so we could generate the proper structures from them, and conversely, if we know the structures then the system would have simple enough rules that we could construct universally recognized and accepted names.

Unfortunately, these splendid ideals have not yet been realized. A good part of the problem is that people are resistant to change and especially resistant to changes in *names*. To give an example, the carboxylic acid, $CH_3{-}CO_2H$, commonly is known as "acetic acid". The name arises from the Latin word *acetum*, for sour wine or vinegar, and acetic acid is the principal constituent, besides, water, of vinegar. A similarly common compound is called "acetone" and, in the ideal world, acetone should be structurally related to acetic acid. But acetone is $CH_3{-}CO{-}CH_3$, and the name arises only because acetone is formed by strong heating of the calcium salt of acetic acid, $(CH_3{-}CO_2)_2Ca \rightarrow CH_3{-}CO{-}CH_3 + CaCO_3$, a reaction that is of no current importance whatsoever. Better nomenclature systems use names based on the *name of the hydrocarbon with the same number of carbons in the longest continuous chain in the molecule*. On this basis, CH_3CO_2H is related to *ethane* and is called *ethanoic acid*, whereas $CH_3{-}CO{-}CH_3$ with three carbons is related to *propane* and called 2-*propanone*.

As far as possible, we shall use these names as our first choices, because organic chemistry is growing too fast to sustain the present chaos of nonsystematic nomenclatures in current use. You might well ask why nonsystematic names persist for so long. The reasons are complex and variable. Alchemists intentionally used abstruse names and symbolism to disguise what they really were working with. Chemical industry, especially in the drug area, has practiced much the same thing in using unintelligible trade names and codes for proprietary products. Obviously, everyone who handles or sells chemicals is not a chemist, and to the nonchemist, a short nonsystematic name will make more sense than a longer systematic name. A salesman who markets tons of "acrolein", $CH_2{=}CH{-}CH{=}O$, has little reason to adopt the systematic name, 2-propenal.

People probably persist in using nicknames for chemicals for much the same reason that they use nicknames for people. Nicknames are less formal, usually shorter, and imply familiarity with the subject. Another cogent reason to resist dramatic changes in chemical nomenclature is that it would make the current and earlier literature archaic or even unintelligible. Universal adoption tomorrow of a nomenclature system different from the one we use here would render this book instantly obsolete. As a result, changes usually are made in small steps and may not be really effective until a generation or more passes. (Consider in this context the efforts to convert monetary systems and weights and measures to the decimal system.)

Ideally, every organic substance should have a completely descriptive, systematic name to permit only one structural formula to be written for it. This ideal has been approached closely in some of the current nomenclature systems but, unfortunately, truly systematic nomenclature for very complicated compounds is often hopeless for conversational or routine scriptorial purposes. As a result, we will at times resort to using (common) trivial names, especially if it is impractical to do otherwise. Clearly, the description *9-(2,6,6-trimethyl-1-cyclohexenyl)-3,7-dimethyl-2,4,6,8-nonatetraen-1-ol* has phonetic disadvantages as a handy name for vitamin A:



vitamin A

A very important consideration for becoming more familiar with the systematic names is their increasing use in indexing systems. When organic chemists dealt with relatively few compounds, it was possible to accommodate a wide variety of special nomenclature customs. However, the rapid growth of knowledge in the past twenty years, which probably has doubled the number of organic compounds, has also enormously increased the burden on those who dedicate themselves to making this knowledge easily available to others by indexing the current literature. A natural reaction is to discard common names in favor of more systematic ones and to develop numerical designations suitable for computer processing. The difference in sizes of the *Chemical*

Abstracts[1] indexes for the years 1907-1916 and for the current year should be convincing as to the need for having systematic names become more widely used and important. But the fact remains that the naming systems used in indexing are not always the same as those used in practice, and we are left with the necessity of having to know both.

Learning the nomenclature of organic compounds has many of the elements of learning a language, be it Latin or Fortran. Fortunately, like a language it does not have to be learned all at once. One can become familiar with naming of simple hydrocarbons, then study their chemistry (avoiding that part which involves compounds with as yet unlearned names), proceed to the naming of alkenes, study their chemistry, and so on. This is a very simple and natural way but can be inconvenient in a textbook if one wants to review the nomenclature of more than one class of compounds at a time.

In this chapter, we consolidate the nomenclature of a number of classes of compounds - an undertaking that may not seem very logical to someone who will soon be troubled enough with the chemistry of these compounds let alone their names. We recommend, however, a thorough study now of alkane and haloalkane nomenclature (Section 3-1) followed by a more cursory examination of the rest of the chapter. Then, as unfamiliar names arise, you can quickly review the basic rules for alkanes and proceed to the new class you have encountered. The idea is to have many of the important rules in one place. Nomenclature rules for other types of compounds are given in Chapter 7.

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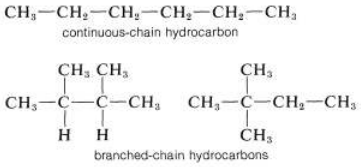
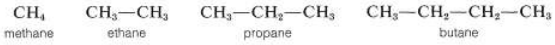
3.2: Alkanes

The most definitive set of organic nomenclature rules currently in use were evolved through several international conferences and are known as the **International Union of Pure and Applied Chemistry Rules** (IUPAC rules). We first shall describe this system for naming the hydrocarbons known as **alkanes** - the so-called saturated **paraffin** hydrocarbons that have no double or triple bonds, or rings, and conform to the general formula C_nH_{2n+2}.

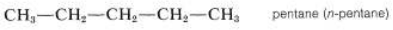
The alkanes are classified as "continuous chain" (that is, "**unbranched**") if all the carbon atoms in the chain are linked to no more than two other carbons; or "**branched** chain" if one or more carbon atoms are linked to more than two other carbons:



The first four continuous-chain hydrocarbons have nonsystematic names:

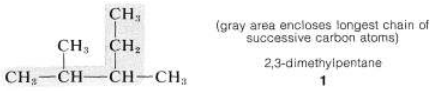


The higher members, beginning with pentane, are named systematically with a numerical prefix (pent-, hex-, hept-, etc., to denote the number of carbon atoms) and with the ending *-ane* to classify the compound as a paraffin hydrocarbon, as in Table 3-1. To specify a continuous-chain hydrocarbon, the prefix *n-* (for normal) sometimes is used. However, in the absence of any qualifying prefix, the hydrocarbon is considered to be "normal" or unbranched and we shall not use this prefix henceforth. You should memorize the names up to $C_{10}H_{22}$.



The possibility of having branched-chain hydrocarbons that are structural isomers of the continuous-chain hydrocarbons begins with butane ($n = 4$). The IUPAC rules for the systematic naming of these hydrocarbons follow.

1. The *longest* continuous chain of carbon atoms is taken as the parent hydrocarbon and is the framework on which the various substituent groups are attached. Thus the hydrocarbon **1** is a substituted pentane rather than a substituted butane because the longest chain has five carbons:



2. The substituent groups attached to the main chain are named by replacing the ending *-ane* of the alkane by *-yl*. We then have the *alkyl groups*

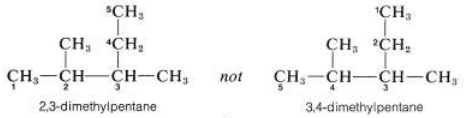
Table 3-1
The Normal Alkanes, C_nH_{2n+2}

n	Name	Formula	*n*	Name	Formula
1	methane	CH_4	11	undecane	$CH_3(CH_2)_9CH_3$
2	ethane	CH_3CH_3	12	dodecane	$CH_3(CH_2)_{10}CH_3$
3	propane	$CH_3CH_2CH_3$	13	tridecane	$CH_3(CH_2)_{11}CH_3$
4	butane	$CH_3(CH_2)_2CH_3$	14	tetradecane	$CH_3(CH_2)_{12}CH_3$
5	pentane	$CH_3(CH_2)_3CH_3$	15	pentadecane	$CH_3(CH_2)_{13}CH_3$
6	hexane	$CH_3(CH_2)_4CH_3$	20	eicosane	$CH_3(CH_2)_{18}CH_3$
7	heptane	$CH_3(CH_2)_5CH_3$	30	triacontane	$CH_3(CH_2)_{28}CH_3$
8	octane	$CH_3(CH_2)_6CH_3$	40	tetracontane	$CH_3(CH_2)_{38}CH_3$
9	nonane	$CH_3(CH_2)_7CH_3$	50	pentacontane	$CH_3(CH_2)_{48}CH_3$
10	decane	$CH_3(CH_2)_8CH_3$	100	hectane	$CH_3(CH_2)_{98}CH_3$

(or *alkyl radicals*, the simplest examples being the methyl (CH_3-) and ethyl (CH_3CH_3-) groups.

3. The parent hydrocarbon then is numbered starting from the end of the chain, and the substituent groups are assigned numbers corresponding to their positions on the chain. The direction of numbering is chosen to give the lowest numbers to

the side-chain substituents.[2] Thus hydrocarbon 1 is 2,3-dimethylpentane rather than 3,4-dimethylpentane. The prefix di- signifies that there are *two* identical substituents:



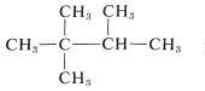
1

The prefixes used to designate the number of substituents follow up to ten.

1 mono-	6 hexa-
2 di-	7 hepta-
3 tri-	8 octa-
4 tetra-	9 nona-
5 penta-	10 deca-

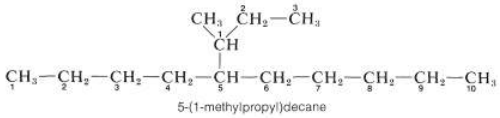
Mono- is not used to designate a single substituent in systematic nomenclature, but may be used in conversation for emphasis.

4. Where there are two identical substituents at one position as in 2, numbers are supplied for each, and the prefix, di-, tri-, and so on, is included to signify the number of groups of the same kind:



2

5. Branched-chain substituent groups are given appropriate names by a simple extension of the system used for branched-chain hydrocarbons. The longest chain of the substituent is numbered *starting with the carbon attached directly to the parent hydrocarbon chain*. Parentheses are used to separate the numbering of the substituent and of the main hydrocarbon chain:



Additional examples of alkyl substituents and their names are listed in Table 3-2. These are further classified according to whether they are primary, secondary, or tertiary. An alkyl group is described as **primary** if the carbon at the point of attachment is bonded to only *one* other carbon, as **secondary** if bonded to *two* other carbons, and **tertiary** if bonded to *three* other carbons. Thus if R is any hydrocarbon radical, the different kinds of alkyl groups are

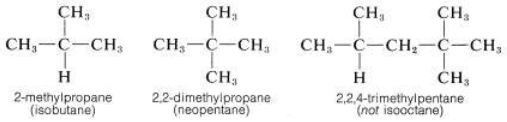
Confusion can arise here because we often refer to specific carbons rather than whole alkyl groups as **primary**, **secondary**, and so on. In this context, a carbon is **primary** if it is bonded to *one* other carbon, **secondary** if bonded to *two*, **tertiary** if bonded to *three*, and **quaternary** if bonded to *four*. Thus, either carbon of ethane is primary, the $C2$ carbon in propane, $CH_3CH_2CH_3$, is secondary, and the $C2$ carbon of 2,2-dimethylpropane, $(CH_3)_4C$, is quaternary.

The situation with regard to naming alkyl substituents has been muddied considerably by the fact that the IUPAC rules allow use of trivial names for a few alkyl groups. Thus *sec*-butyl sometimes is used in place of 1-methylpropyl, and *tert*-butyl in place of 1,1-dimethylethyl These and other examples are included in parentheses in Table 3-2. Further odd-ball but less official customs are the prefix *iso*, which is reserved for substituents with two methyl groups at the end of an otherwise straight chain (e.g., isopropyl), and the prefix *neo*,

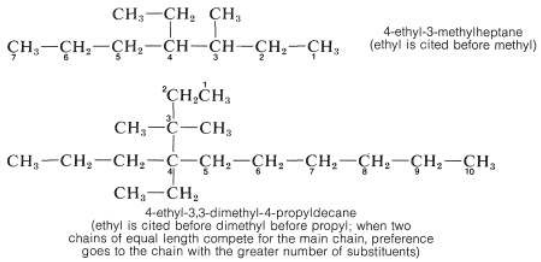
Table 3-2
Typical Alkyl Groups (C_nH_{2n+1})

Primary (RCH_2—)		
CH_3— methyl	CH_3CH_2— ethyl	$CH_3CH_2CH_2$— propyl
$CH_3CH_2CH_2CH_2$— butyl	$(CH_3)_2CHCH_2$— 2-methylpropyl (isobutyl)	$(CH_3)_3CCH_2$— 2,2-dimethylpropyl (neopentyl)
Secondary (R_2CH—)		
$(CH_3)_2CH$— 1-methylethyl (isopropyl)	$CH_3CH_2CH(CH_3)$— 1-methylpropyl (*sec*-butyl)	
Tertiary (R_3C—)		
$(CH_3)_3C$— 1,1-dimethylethyl (*tert*-butyl)	$CH_3CH_2C(CH_3)_2$— 1,1-dimethylpropyl (*tert*-pentyl)	

which is used to denote three methyl groups at the end of a chain (e.g., neopentyl, which is more properly called 2,2-dimethylpropyl). Also in common use are the names *isobutane* and *neopentane* for the hydrocarbons 2-methyl-propane and 2,2-dimethylpropane, respectively There is no ambiguity involved in the use of *iso* and *neo* prefixes here, but the practice of using the name "isooctane" for 2,2,4-trimethylpentane is erroneous. Fortunately, use of these special names is declining.

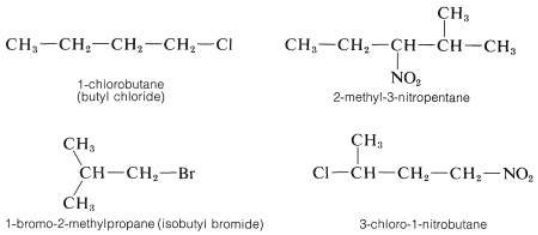


6. When there are two or more different substituents present, the question arises as to what order they should be cited in naming the compound. The system adopted by IUPAC and long practiced by *Chemical Abstracts* cites them in alphabetical order without regard for whether there is a multiplying prefix such as di- or tri-. Examples are given below.



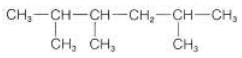
When a hydrocarbon is substituted with other than alkyl groups a new problem arises, which can be illustrated by CH_3CH_2Cl This substance can be called either chloroethane or ethyl chloride, and both names are used in conversation and in print almost interchangeably. In the IUPAC system, halogens, nitro groups, and a few other monovalent groups are considered to be *substituent groups on hydrocarbons* and are named as haloalkanes, nitroalkanes, and so on.

The alphabetical order of precedence is preferred for substituents of different types when two or more are attached to a hydrocarbon chain because this makes indexing and using indexes more straightforward:



The rest of this chapter is devoted to names of compounds we will not discuss for several chapters ahead and you may wish to stop at this point and return later as necessary. However, you should test your knowledge of alkane nomenclature by doing Exercises 3-1, 3-2, 3-3, 3-9, 3-10, and 3-11.

[2]Confusion is possible when the numbering from each end is similar. The rule is that when the series of substituent locants are compared term by term, the "lowest" series has the lowest number at the *first* point of difference. The compound



is 2,3,5-trimethylhexane, *not* 2,4,5-trimethylhexane.

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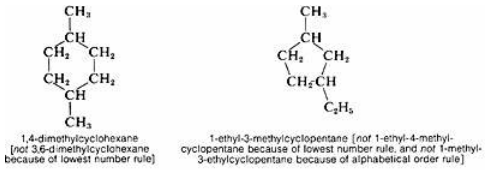
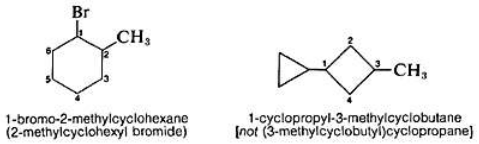
3.3: Cycloalkanes

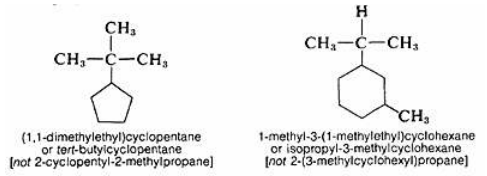
The cycloalkanes with one ring have the general formula C_nH_{2n}, and are named by adding the prefix cyclo- to the name of the corresponding continuous-chain alkane having the same number of carbon atoms as the ring. Substituents are assigned numbers consistent with their position in such a way as to give the lowest numbers possible for the substituent positions:



The substituent groups derived from cycloalkanes by removing one hydrogen are named by replacing the ending *-ane* of the hydrocarbon with *-yl* to give cycloalkyl. Thus cyclohex*ane* becomes cyclohex*yl*, cyclopentane becomes cyclopentyl, and so on. Remember, the numbering of the cycloalkyl substituent starts at the position of attachment, and larger rings take precedence over smaller rings:



When a cycloalkane has an alkyl substituent, the compound could be called either an alkylcycloalkane or a cycloalkylalkane. The alkylcycloalkane name is the proper one in naming alkyl substituted cycloalkanes.



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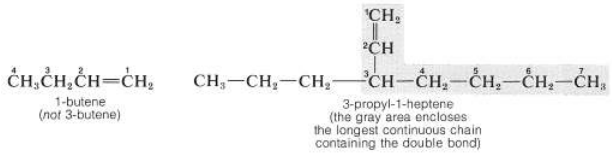
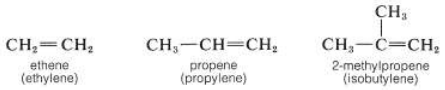
3.4: Alkenes, Cycloalkenes, and Alkadienes

The open-chain hydrocarbons with one double bond have the general formula C_nH_{2n} and are called *alkenes*. The carbon-carbon double bond often is called an "olefinic linkage" and the alkenes designated as **olefins** (oil-formers). These terms arose because the gaseous lower-molecular-weight alkenes yield "oily" products on treatment with chlorine or bromine. The term "unsaturated" hydrocarbon also is used - again because these substances normally react with bromine and chlorine and are hence "unsaturated" with reference to reagents of this type (also see Section 1-1I).

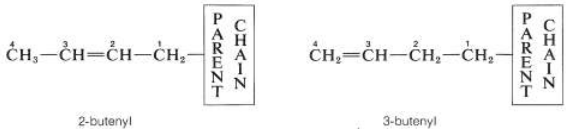
According to the IUPAC system for naming alkenes, the longest continuous chain containing the double bond is given the name of the corresponding alkane with the ending *-ane* changed to *-ene*. This chain then is numbered so that the position of the *first* carbon of the double bond is indicated by the lowest possible number:



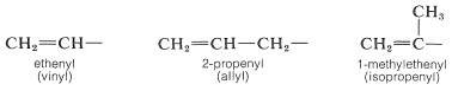
A few very common alkenes also are called "alkylenes" by appending the suffix *-ene* to the name of the hydrocarbon radical with the same carbon skeleton. Examples are shown below with their alkylene names in parentheses. We shall continue to use the IUPAC names whenever possible.



The hydrocarbon groups derived from alkenes have the suffix *-enyl*, as in alkenyl, and numbering of the group starts with the carbon atom attached to the main chain:

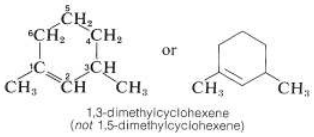


A few alkenyl groups have trivial names that commonly are used in place of systematic names. These are vinyl, allyl, and isopropenyl. And again we shall avoid using these names, except parenthetically:



Also, hydrogen atoms that are bonded directly to the unsaturated carbon atoms of a double bond often are called *vinyl hydrogens*, although the term *alkenic hydrogens* is more accurate and therefore preferable.

Cycloalkenes are named by the system used for the open-chain alkenes, except that *numbering always is started at one of the carbons of the double bond* and continued around the ring *through* the double bond so as to keep the index numbers as small as possible:

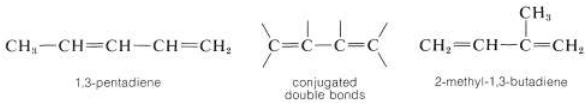


When a hydrocarbon group is double-bonded to a single carbon of a cycloalkane ring, the suffix *-ylidene*, as in alkylidene, is used:

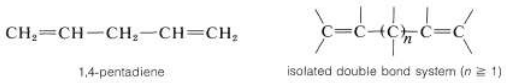
Many compounds contain two or more double bonds and are known as alkadienes, alkatrienes, alkatetraenes, and so on, the suffix denoting the number of double bonds. The location of each double bond is specified by appropriate numbers, as illustrated below:

A further classification is used for the relationships of the double bonds to each other. Thus 1,2-alkadienes and similar substances are said to have **cumulated** double bonds:

1,3-Alkadienes and other compounds with alternating double and single bonds are said to have **conjugated** double bonds:



Compounds with double bonds that are neither cumulated nor conjugated are classified as having **isolated** double-bond systems:



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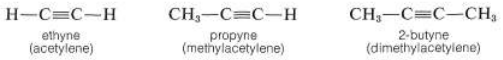
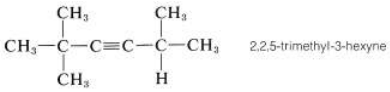
3.5: Alkynes

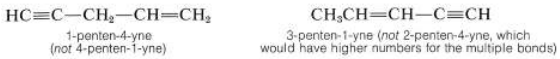
A number of hydrocarbons, called **alkynes** or **acetylenes**, have triple bonds between carbon atoms.[3] They conform to the general formula C_nH_{2n-2} for one triple bond. The IUPAC system for naming alkynes employs the ending *-yne* instead of the *-ane* used for naming of the corresponding saturated hydrocarbon:



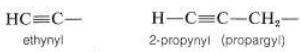
The numbering system for locating the triple bond and substituent groups is analogous to that used for the corresponding alkenes:



Hydrocarbons with more than one triple bond are called **alkadiynes**, **alkatriynes**, and so on, according to the number of triple bonds Hydrocarbons with both double and triple bonds are called **alkenynes** (*not* alkynenes). The chain always should be numbered to give the multiple bonds the lowest possible numbers, and when there is a choice, double bonds are given lower numbers than triple bonds. For example,



The hydrocarbon substituents derived from alkynes are called **alkynyl** groups:



[3]Alkyne rhymes with "mine" and "thine."

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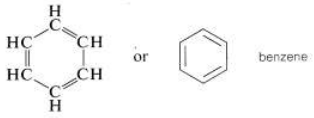
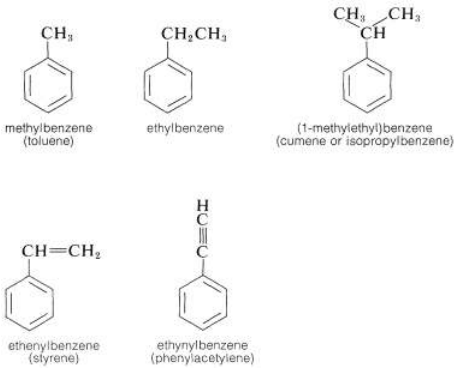
3.6: Arenes

The so-called aromatic hydrocarbons, or **arenes**, are cyclic unsaturated compounds that have such strikingly different chemical properties from conjugated alkenes (polyenes) that it is convenient to consider them as a separate class of hydrocarbon. The simplest member is benzene, C_6H_6, which frequently is represented as a cyclic conjugated molecule of three single and three double carbon-carbon bonds. Actually, all the carbon-carbon bonds are equivalent (see Chapter 1) but it is convenient to represent the structure in the manner shown:



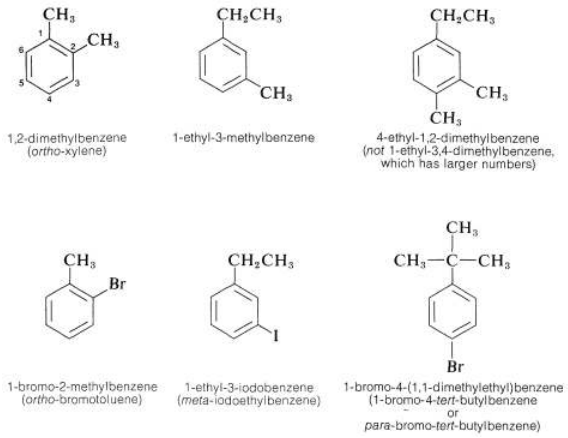
A variety of substituted benzenes are known that have one or more of the hydrogen atoms of the ring replaced with other atoms or groups. In almost all of these compounds the special properties associated with the benzene nucleus are retained. A few examples of "benzenoid" hydrocarbons follow, and it will be noticed that the hydrocarbon substituents include alkyl, alkenyl, and alkynyl groups. Many have trivial names indicated in parentheses:



The hydrocarbon group from benzene itself (C_6H_5-) is called a *phenyl* group and often is abbreviated as Ph or less preferably by the symbol ϕ. Generally, aryl groups are abbreviated as Ar, in contrast to alkyl groups for which we use R. Thus CH_3Ar is a methyl-substituted arene, whereas RC_6H_5 is an alkyl-substituted benzene.

When there are two or more substituents on a benzene ring, position isomerism arises. Thus there are three possible isomeric disubstituted benzene derivatives according to whether the substituents have the 1,2, 1,3, or 1,4 relationship. The isomers commonly are designated as *ortho*, *meta*, and *para* (or *o*, *m*, and *p*) for the 1,2-, 1,3-, and 1,4-isomers, respectively. The actual symmetry of the benzene ring is such that only *one* 1,2-disubstitution product is found, despite the fact that two would be predicted if benzene had the 1,3,5-cyclohexatriene structure:

When the benzene ring carries different substituents we shall cite them in alphabetical order (disregarding multiplying prefixes) and assign their positions on the ring with the lowest possible numbers. Examples are



The IUPAC nomenclature system for other types of compounds is given in Chapter 7 and is based on the fundamental rules described in this chapter.

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3.E: Organic Nomenclature (Exercises)

Exercise 3-1 Draw structural formulas corresponding to the following names:

a. 2,7,8-trimethyldecane
b. 2,3,4-trimethyl-4-propylheptane
c. 5-(1,1-dimethylpropyl)nonane
d. 4-(chloromethyl)-5-(1-nitroethyl)decane

Exercise 3-2 Give the IUPAC name for each of the following structures:

a. $(CH_3)_2CHCH(CH_3)CH_2CH(CH_3)_2$
b. $CH_3CH_2CH_2CH(CH_3)CH(CH_2CH_3)CH_2CH_2CH_3$
c. $CH_3CH_2CH(CH_2CH_2CH_3)CH_2CH(CH_3)_2$
d. $CH_3CH(CH_3)CH(CH_3)CH(CH_3)CH(CH_3)_2$

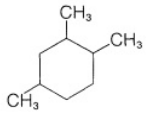
Exercise 3-3 The following are *improper* IUPAC names. Determine what is incorrect or ambiguous about the name and give the correct name.

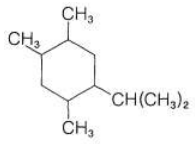
a. 2-methyl-3-propylpentane
b. 3-methyl-3-chloropentane
c. 2,3,3,7,7-pentamethyloctane
d. 3-(1,1-dimethylethyl)pentane

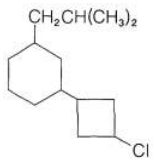
Exercise 3-4 Write structural formulas for each of the following:

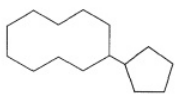
a. (2,2-dimethylpropyl)cyclopentane
b. 1,2,3-tri(chloromethyl)cyclopropane
c. 1,4-dicyclohexylcyclooctane
d. 1-(1-methylcyclopropyl)-1,2,2,3,3-pentamethylcyclopropane

Exercise 3-5 Give the IUPAC name for each of the following:

a.


b.


c.


d.


Exercise 3-6 Write structural formulas corresponding to the following IUPAC names:

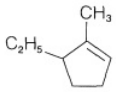
a. 1,3,6-trimethylcyclohexene
b. 1,2,3,3-tetrachlorocyclopropene

c. 2,5-dimethyl-1,5-hexadiene

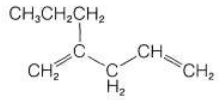
d. 3-methylidenecyclohexane

Exercise 3-7 Give the IUPAC name for each of the following:

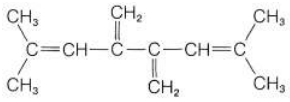
a.



b.



c.



d.

Exercise 3-8 Draw structures for the following compounds:

a. 1,3-hexadien-5-yne

b. 1-cyclodecen-4-yne

c. 5-ethynyl-1,3,6-heptatriene

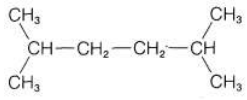
d. 3-methylidenecyclooctyne

Exercise 3-9 There are nine heptane isomers of formula C_7H_{16}. Write structural formulas for each. Name each by the IUPAC system. (In working a problem such as this, proceed systematically by constructing first the heptane, then all the possible hexanes, the pentanes, and so on. Should you inadvertently duplicate a structure, this will become apparent when you name it; duplicate names usually are easier to spot than duplicate structures.)

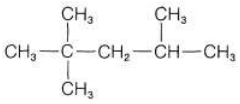
Exercise 3-10 Write structural formulas for the eight position isomers of $C_5H_{11}Cl$. Name each as a chloroalkane.

Exercise 3-11 Name each of the following hydrocarbons by the IUPAC system:

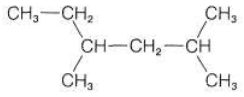
a.



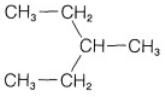
b.



c.

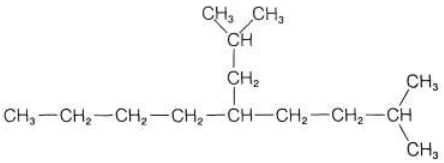


d.



e. $(CH_3{-}CH_2{-}CH_2{-})_4{-}C$

f.



Exercise 3-12 Draw the structure of 1,1-dimethyl-3-(1-methyethyl)cyclohexane four times. In the first structure circle all the primary carbons; in the second, circle all the secondary carbons; in the third, circle the tertiary carbons; in the fourth, circle the quaternary carbons.

Exercise 3-13 Draw the possible *primary* alkyl or alkenyl groups of formulas:

a. C_5H_{11} (four)
b. C_5H_9 (eight)

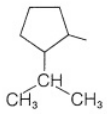
Exercise 3-14 Write structural formulas for the following substituent groups:

a. chloromethyl
b. 1-chloroethyl
c. 3-methylbutyl
d. 1,2-dimethylpropyl
e. 1-methyl-2-propenyl
f. 2-methyl-1-propenyl
g. 1-buten-3-ynyl
h. 2-methylcyclohexyl
i. 2-cyclohexenyl
j. phenylmethyl
k. *para*-nitrophenyl
l. 2,4-dichlorophenyl
m. propylidene

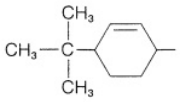
Exercise 3-15 Name the following substituent groups by the IUPAC system and indicate whether they are primary, secondary, tertiary, or aryl groups:

a. $BrCH_2CH_2CH_2-$
b. $(CH_3CH_2)_3C-$
c. $CH_3C \equiv CCH_2-$

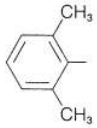
d.



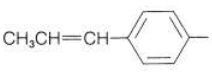
e.



f.



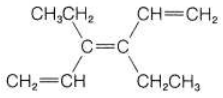
g.

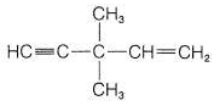


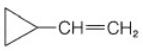
Exercise 3-16 Write structural formulas for each of the following substances:

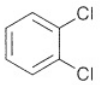
a. 1-octene
b. 1,4-hexadiene
c. 1,2-dimethylcyclobutane
d. 1,2-cyclononadiene
e. 3-chloro-3-methyl-1-butyne
f. cyclooctyne
g. 2-chloro-1,3-butadiene
h. 3-methyl-2-hexen-4-yne
i. (1,1-dimethylethyl)benzene
j. (1-methylpropyl)benzene
k. *meta*-nitrotoluene
l. 1-phenyl-1-methylcyclohexane
m. (phenylmethyl)cyclohexane

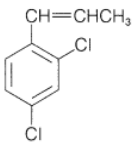
Exercise 3-17 Name each of the following substances by the IUPAC system:

a. $(CH_3)_2C{=}CHCH_3$
b. $Cl_2C{=}C(CH_3)_2$
c. $(CH_3)_2C{=}C{=}CHBr$
d. 

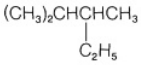
e. 

f.
g. 

h.
i. 

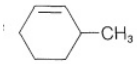
j. 

Exercise 3-18 Decide whether the following structures are named correctly according to the IUPAC rules. If a name is incorrect or ambiguous, assign the correct name:



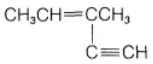
a. 1-ethyl-2-methylbutane

b. $Cl_2CHCHCl_2$ tetrachloroethane

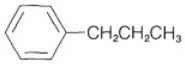


c. 1-methyl-2-cyclohexene

d. $CH_2{=}CHCH_2Cl$ 1-chloro-2-propene



e. 2-ethynyl-2-butene



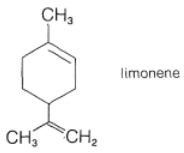
f. phenylpropane

g. dinitrobenzene

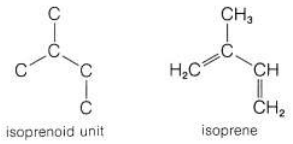
h. $(CH_3)_2CHCH_2CH_3$ isopentane

Exercise 3-19

a. The major component in the oil obtained from pressing the rinds of oranges and lemons is a hydrocarbon called limonene. It is obtained in commercial quantities from citrus rind and is sold as a flavoring and perfume agent. Name limonene by the IUPAC system.



b. The carbon skeleton of limonene is made up of branched five-carbon repeating segments called **isoprene** (or **isoprenoid**) units. Furthermore, limonene has the formula $C_{10}H_{16}$, which corresponds to two C_5H_8 isoprene molecules linked together.



What is the IUPAC name for isoprene? Indicate the isoprene units in the limonene structure by drawing a dotted line through each of the bonds that joins one isoprene unit to the other.

c. Like limonene, β-carotene and vitamin A have carbon skeletons made up of isoprenoid units. These compounds belong to a class of naturally occurring compounds called **terpenes**. Mark off the isoprenoid units in β-carotene and vitamin A as you did for limonene.

Exercise 3-20 If you have access to the 1967-71 Eighth Collective Subject Index of *Chemical Abstracts*, locate the page number in the index where each of the compounds shown in Exercise 2-8 occurs and give the name used. Notice that past *Chemical Abstracts* indexes do *not* use completely systematic nomenclature, especially for compounds with only a few carbons, but these indexes will be made completely systematic in the future.

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CHAPTER OVERVIEW

4: Alkanes

Alkanes are the simplest organic molecules, consisting of only carbon and hydrogen and with only single bonds between carbon atoms. Alkanes are used as the basis for naming the majority of organic compounds (their nomenclature). Alkanes have the general formula C_nH_{2n+2}.

4.1: Prelude to Alkanes
4.2: Physical Properties of Alkanes and The Concept of Homology
4.3: Chemical Reactions of Alkanes. Combustion of Alkanes
4.4: Combustion. Heats of Reaction. Bond Energies
4.5: Halogenation of Alkanes. Energies and Rates of Reactions
4.6: Practical Halogenations and Problems of Selectivity
4.7: Nitration of Alkanes
4.E: Alkanes (Exercises)

Thumbnail: Structure of propane.

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4.1: Prelude to Alkanes

Although this chapter is concerned with the chemistry of only one class of compounds, saturated hydrocarbons or alkanes, several fundamental principles are developed that we shall use extensively in later chapters. The study of some of these principles has been associated traditionally more with physical chemistry than with organic chemistry. We include them here, at the beginning of out discussion of organic reactions, because they provide a sound basis for understanding the key questions concerning the practical use of organic reactions. Is the equilibrium point of a given reaction far enough toward the desired products to be useful? Can conditions be found in which the reaction will take place at a practical rate? How can unwanted side reactions be suppressed?

Initially, we will be concerned with the physical properties of alkanes and how these properties can be correlated by the important concept of homology. This will be followed by a brief survey of the occurrence and uses of hydrocarbons, with special reference to the petroleum industry. Chemical reactions of alkanes then will be discussed, with special emphasis on combustion and substitution reactions, These reactions are employed to illustrate how we can predict and use energy changes - particularly ΔH, the heat evolved or absorbed by a reacting system, which often can be estimated from bond energies. Then we consider some of the problems involved in predicting reaction rates in the context of a specific reaction, the chlorination of methane. The example is complex, but it has the virtue that we are able to break the overall reaction into quite simple steps.

Before proceeding further, it will be well to reiterate what an alkane is, lest you be confused as to the difference between alkanes and alkenes. **Alkanes** are compounds of carbon and hydrogen only, without double bonds, triple bonds, or rings. They all conform to the general formula $\mathrm{C}_n\mathrm{H}_{2n+2}$ and sometimes are called **paraffin** hydrocarbons, open-chain saturated hydrocarbons, or **acyclic** hydrocarbons. The nomenclature of alkanes has been discussed in Chapter 3, and you may find it well to review Section 3-1 before proceeding.

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4.2: Physical Properties of Alkanes and The Concept of Homology

The series of straight-chain alkanes, in which n is the number of carbons in the chain, shows a remarkably smooth gradation of physical properties (see Table 4-1 and Figure 4-1). As n increases, each additional CH_2 group contributes a fairly constant increment to the boiling point and density, and to a lesser extent to the melting point. This makes it possible to estimate the properties of an unknown member of the series from those of its neighbors. For example, the boiling points of hexane and heptane are 69° and 98°, respectively. Thus a difference in structure of one CH_2 group for these compounds makes a difference in boiling point of 29°; we would predict the boiling point of the next higher member, octane, to be $98^o + 29^o = 127^o$, which is close to the actual boiling point of 126°.

Table 4-1
Physical Properties of Alkanes, $CH_3(CH_2)_{n-1}H$

n	Name	Bp, °C (760 mm)	Mp, °C	Density at 20°, d_4^{20}, g ml^{-1}
1	methane	−161.5	−183	0.424[a]
2	ethane	−88.6	−172	0.546[a]
3	propane	−42.1	−188	0.501[b]
4	butane	−0.5	−135	0.579[b]
5	pentane	36.1	−130	0.626
6	hexane	68.7	−95	0.659
7	heptane	98.4	−91	0.684
8	octane	125.7	−57	0.703
9	nonane	150.8	−54	0.718
10	decane	174.1	−30	0.730
11	undecane	195.9	−26	0.740
12	dodecane	216.3	−10	0.749
15	pentadecane	270.6	10	0.769
20	eicosane	342.7	37	0.786[c]
30	triacontane	446.4	66	0.810[c]

[a]At the boiling point. [b]Under pressure. [c]For the supercooled liquid.

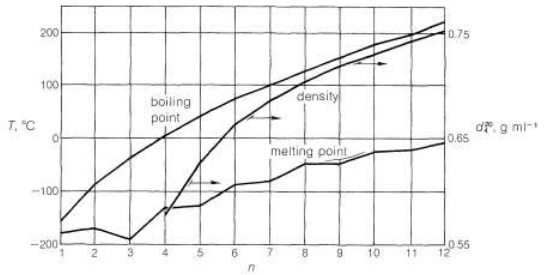

Figure 4-1: Dependence on n of melting points, boiling points, and densities (d_4^{20}) of continuous-chain alkanes, $CH_3\,(CH_2)_{n-1}\,H$

Members of a group of compounds, such as the alkanes, that have similar chemical structures and graded physical properties, and which differ from one another by the number of atoms in the structural backbone, are said to constitute a *homologous series*. When used to forecast the properties of unknown members of the series, the concept of *homology* works most satisfactorily for the higher-molecular-weight members because the introduction of additional CH_2 groups makes a smaller relative change in the overall composition of such molecules. This is better seen from Figure 4-2, which shows

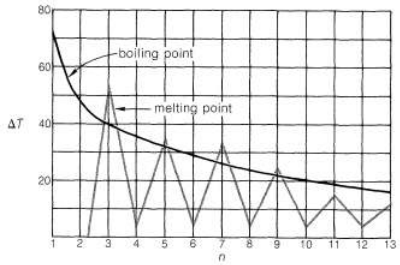

Figure 4-2: Dependence of ΔT (difference in boiling and melting points between consecutive members of the series of continuous-chain alkanes) on n (number of carbon atoms)

how ΔT, the differences in boiling points and melting points between consecutive members of the homologous series of continuous-chain alkanes, changes with the number of carbons, n.

Branched-chain alkanes do not exhibit the same smooth gradation of physical properties as do the continuous-chain alkanes. Usually there is too great a variation in molecular structure for regularities to be apparent. Nevertheless, in any one set of isomeric hydrocarbons, volatility increases with increased branching. This can be seen from the data in Table 4-2, which lists the physical properties of the five hexane isomers. The most striking feature of the data is the 19° difference between the boiling points of hexane and 2,2-dimethylbutane.

Table 4-2
Physical Properties of Hexane Isomers

Isomer	Structure	Bp, °C	Mp, °C	Density at 20°, d_4^{20}, g ml^{-1}
hexane	$CH_3(CH_2)_4CH_3$	68.7	−94	0.659
3-methylpentane	$CH_3CH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2CH_3$	63.3	−118	0.664
2-methylpentane	$CH_3\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2CH_2CH_3$	60.3	−154	0.653
2,3-dimethylbutane	$CH_3\underset{\displaystyle CH_3}{\underset{\vert}{C}}H-\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_3$	58.0	−129	0.661
2,2-dimethylbutane	$CH_3\underset{\displaystyle CH_3}{\underset{\vert}{\overset{\displaystyle CH_3}{\overset{\vert}{C}}}}CH_2CH_3$	49.7	−98	0.649

Figure 4-1 for alkanes. This generally will be true, except when the number of carbons is small and when the hydrocarbon chain has polar substituents. To explain briefly, consider compounds such as alcohols, ROH, which have polar $\overset{\delta\ominus}{O}\text{- - -}\overset{\delta\oplus}{H}$ groups. As we indicated in Section 1-3, polarity causes molecules to associate with one another, which decreases their volatility, raises melting points, increases solubility in polar liquids, and decreases solubility in nonpolar liquids. This explains why methanol, CH_3OH, is much less volatile and much more water-soluble than methane, CH_4. But we find that the water-solubility of alcohols falls off rapidly with the length of the carbon chain, certainly faster than expected for a simple homologous series effect. Whereas methanol, CH_3OH, and ethanol, CH_3CH_2OH, are completely soluble in water, butanol, $CH_3CH_2CH_2CH_2OH$, is only slightly soluble. This illustrates the conflicting properties conferred on molecules by polar groups compare to nonpolar hydrocarbon groups, and points up that large changes in physical properties can be expected in the early part of a homologous series until the hydrocarbon chain is sufficiently long, usually six or more carbons, so that the hydrocarbon parts dominate over the polar parts of the molecules.

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4.3: Chemical Reactions of Alkanes. Combustion of Alkanes

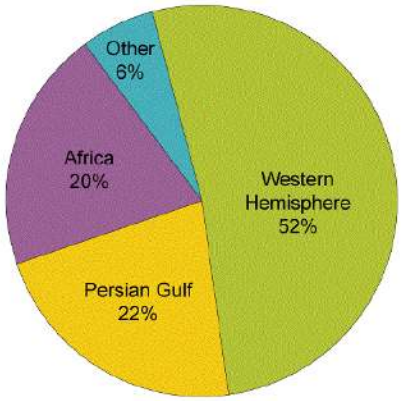
As a class, alkanes generally are unreactive. The names saturated hydrocarbon, or "paraffin," which literally means "not enough affinity" [L. *par*(*um*), not enough, + *affins*, affinity], arise because their chemical "affinity" for most common reagents may be regarded as "saturated" or satisfied. Thus none of the $C-H$ or $C-C$ bonds in a typical saturated hydrocarbon, for example ethane, are attacked at ordinary temperatures by a strong acid, such as sulfuric acid (H_2SO_4), or by an oxidizing agent, such as bromine (in the dark), oxygen, or potassium permanganate ($KMnO_4$). Under ordinary conditions, ethane is similarly stable to reducing agents such as hydrogen, even in the presence of catalysts such as platinum, palladium, or nickel.

However, all saturated hydrocarbons are attacked by oxygen at elevated temperatures and, if oxygen is in excess, complete combustion to carbon dioxide and water occurs. Vast quantities of hydrocarbons from petroleum are utilized as fuels for the production of heat and power by combustion, although it is becoming quite clear that few of the nations of the world are going to continue to satisfy their needs (or desires) for energy through the use of petroleum the way it has been possible in the past.

Petroleums differ considerably in composition depending on their source. However, a representative petroleum[1] on distillation yields the following fractions:

1. *Gas* fraction, boiling up to 40°, contains normal and branched alkanes from C_1 to C_5. Natural gas is mainly methane and ethane. "Bottled" gas (liquefied petroleum gas) is mainly propane and butane.
2. *Gasoline*, boiling point from 40° to 180°, contains mostly hydrocarbons from C_6 to C_{10}. Over 100 compounds have been identified in gasoline, and these include continuous-chain and branched alkanes, cycloalkanes, and alkylbenzenes (arenes). The branched alkanes make better gasoline than their continuous-chain isomers because they give less "knock" in high-compression gasoline engines.
3. *Kerosine*, boiling point 180° to 230°, contains hydrocarbons from C_{11} to C_{12}. Much of this fraction is utilized as jet engine fuels or is "cracked" to simpler alkanes (and alkenes).
4. *Light gas oil*, boiling point 230° to 305°, C_{13} to C_{17}, is utilized as diesel and furnace fuels.
5. *Heavy gas oil and light lubricating distillate*, boiling point 305° to 405°, C_{18} to C_{25}.
6. *Lubricants*, boiling point 405° to 515°, C_{26} to C_{38}, familiarly encountered as paraffin was and petroleum jelly (Vaseline).
7. The distillation residues known as *asphalts*.

The way in which petroleum is refined and the uses for it depend very much on supply and demand, which always are changing. However, the situation for the United States in 1974 is summarized in Figure 4-3, which shows roughly how much of one barrel of oil (160 liters) is used for specific purposes.



Source: U.S. Energy Information Administration, *Petroleum Supply Monthly* (February 2012), preliminary data.

Figure 4-3: Sources and uses of petroleum in the United States in 2011.

In the past three decades, petroleum technology has outpaced coal technology, and we now are reliant on petroleum as the major source of fuels and chemicals. Faced with dwindling oil reserves, however, it is inevitable that coal again will become a major source of raw materials. When coal is heated at high temperatures in the absence of air, it carbonizes to *coke* and gives off a gaseous mixture of compounds. Some of these gases condense to a black viscous oil (*coal tar*), others produce an aqueous condensate called *ammoniacal liquors*, and some remain gaseous (*coal gas*). The residue is coke, which is used both as a fuel and

as a source of carbon for the production of steel. The major component in coal gas is methane. Coal tar is an incredible mixture of compounds, mostly hydrocarbons, a substantial number of which are arenes. Coal and coal tar can be utilized to produce alkanes, but the technology involved is more complex and costly than petroleum refining. It seems inevitable that the cost of hydrocarbon fuel will continue to rise as supply problems become more difficult. And there is yet no answer to what will happen when the world's limited quantities of petroleum and coal are exhausted.

[1]See F. D. Rossini, "Hydrocarbons in Petroleum," *J. Chem. Educ.* **37**, 554 (1960).

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4.4: Combustion. Heats of Reaction. Bond Energies

All hydrocarbons are attacked by oxygen at elevated temperatures and, if oxygen is in excess, complete combustion occurs to carbon dioxide and water:

\[CH_4 + 2O_2 \rightarrow CO_Edit2 + 2H_2O\]

The heat evolved in this process - the heat of the combustion reaction, ΔH - is a measure of the amount of energy stored in the $C-C$ and $C-H$ bonds of the hydrocarbon compared to the energy stored in the products, carbon dioxide and water. It can be measured experimentally with considerable accuracy and generally is reported as ΔH^0 the amount of heat (in kilocalories)[2] liberated on complete combustion of one mole of hydrocarbon when the reactants and the products are in standard states, and at the same temperature, usually 25°.[3] Not all chemical reactions that occur spontaneously liberate heat - some actually absorb heat. By convention, ΔH^0 is given a *negative* sign when heat is evolved (**exothermic reaction**) and a *positive* sign when heat is absorbed (**endothermic reaction**). The heat evolved or absorbed also is called the **enthalpy** change.

For the combustion of $1\ \text{mol}$ of methane at 15°, we find by experiment (corrected from constant volume to constant pressure, if necessary) that the reaction is exothermic by $212.8\ \text{kcal}$. This statement can be expressed as follows:

$$CH_4(g) + 2O_2(g) \rightarrow CO_2(g) + 2H_2O(l) \tag{4.4.1}$$

with $\Delta H^o = -212.8\, kcal$.

The symbol (g) denotes that the reactants and products are in the gaseous state except for the water, which is liquid (l). If we wish to have ΔH^0 with gaseous water $H_2O\ (g)$ as the product we have to make a correction for the heat of vaporization of water ($10.5\ \text{kcal mol}^{-1}$ at 25°):

$$\begin{array}{lll} CH_4(g) + 2O_2(g) \longrightarrow CO_2(g) + 2H_2O(l) & \Delta H^0 = -212.8 \text{ kcal} \\ 2H_2O(l) \longrightarrow 2H_2O(g) & \Delta H^0 = +2 \times 10.5 \text{ kcal} \\ \hline CH_4(g) + 2O_2(g) \longrightarrow CO_2(g) + 2H_2O(g) & \Delta H^0 = -191.8 \text{ kcal} \end{array}$$

The task of measuring the heats of all chemical reactions is a formidable one and about as practical as counting grains of sand on the beach. However, it is of practical interest to be able to estimate heats of reaction, and this can be done quite simply with the aid of bond energies. The necessary bond energies are given in Table 4-3, and it is important to notice that they apply only to *complete dissociation of gaseous substances to gaseous atoms at* $25^\circ C$. Also, they do not apply, without suitable corrections, to many compounds, such as benzene, that have more than one double bond. This limitation will be discussed in Chapters 6 and 21.

To calculate ΔH^0 for the combustion of one mole of methane, first we break bonds as follows, using $98.7\ \text{kcal mol}^{-1}$ for the energy of each of the

https://chem.libretexts.org/@go/page/22172

Table 4-3
Bond Energies (kcal mole^{-1} at 25°C)[a]

Diatomic Molecules					
H—H	104.2	F—F	37.5	H—F	135.9
O=O	118.9	Cl—Cl	58.1	H—Cl	103.1
N≡N	226.8	Br—Br	46.4	H—Br	87.4
C=O[b]	257.3	I—I	36.5	H—I	71.4

Polyatomic Molecules					
C—H	98.7	C—C	82.6	C—F	116
N—H	93.4	C=C	145.8	C—Cl	81
O—H	110.6	C≡C	199.6	C—Br	68
S—H	83	C—N	72.8	C—I	51
P—H	76	C=N	147	C—S	65
N—N	39	C≡N	212.6	C=S[c]	128
N=N	100	C—O	85.5	N—F	65
O—O	35	C=O[d]	192.0	N—Cl	46
S—S	54	C=O[e]	166	O—F	45
N—O	53	C=O[f]	176	O—Cl	52
N=O	145	C=O[g]	179	O—Br	48

[a]The bond energies for diatomic molecules in this table are from the extensive and up-to-date compilation of J. A. Kerr, M. J. Parsonage, and A. F. Trotman-Dickenson in the *Handbook of Chemistry and Physics*, 55th ed., CRC Press, 1975, pp. F-204 to F-208; those for polyatomic molecules are from L. Pauling, *The Nature of the Chemical Bond*, 3rd ed., Cornell University Press, Ithaca, N.Y., 1960.
[b]Carbon monoxide. [c]For carbon disulfide. [d]For carbon dioxide. [e]For formaldehyde. [f]Other aldehydes. [g]Ketones.

$C-H$ bonds,

$$H:\underset{\cdot\cdot}{\overset{H}{\overset{\cdot\cdot}{C}}}:H(g) \longrightarrow \cdot\dot{C}\cdot\,(g) + 4H\cdot\,(g) \qquad \Delta H^0 = +4 \times 98.7 \text{ kcal} = +394.8 \text{ kcal}$$

and then $118.9\ \text{kcal mol}^{-1}$ for the energy of the double bond in oxygen:

$$2\,:\ddot{O}::\ddot{O}:\,(g) \longrightarrow 4\,:\ddot{\underset{\cdot\cdot}{O}}\,(g) \qquad \Delta H^0 = +2 \times 118.9 \text{ kcal} = +237.8 \text{ kcal}$$

Then we make bonds, using $192\ \text{kcal mol}^{-1}$ for each $O=C$ bond in carbon dioxide,

$$\cdot\dot{C}\cdot\,(g) + 2\,:\ddot{\underset{\cdot\cdot}{O}}\,(g) \longrightarrow :\ddot{O}::C::\ddot{O}:\,(g) \qquad \Delta H^0 = -2 \times 192.0 \text{ kcal} = -384.0 \text{ kcal}$$

and $110.6\ \text{kcal mol}^{-1}$ for each of the $H-O$ bonds in water:

$$2\,:\ddot{\underset{\cdot\cdot}{O}}\,(g) + 4H\cdot\,(g) \rightarrow 2H:\ddot{\underset{\cdot\cdot}{O}}:H\,(g) \qquad \Delta H^0 = -4 \times 110.6 \text{ kcal} = -442.4 \text{ kcal}$$

The net sum of these ΔH^0 values is $394.8 + 237.8 - 384.0 - 442.4 = -193.8$ kcal, which is reasonably close to the value of -191.8 kcal for the heat of combustion of one mole of methane determined experimentally.

The same type of procedure can be used to estimate ΔH^0 values for many other kinds of reactions of organic compounds in the vapor phase at 25°. Moreover, if appropriate heats of vaporization are available, it is straightforward to compute ΔH^0 for vapor-phase reactions of substances which are normally liquids or solids at 25°. The special problems that arise when solutions and ionic substances are involved are considered in Chapters 8 and 11.

It is important to recognize that the bond energies listed in Table 4-3 for all molecules other than diatomic molecules are *average* values. That the $C-H$ bond energy is stated to be 98.7 kcal does not mean that, if the hydrogens of methane were detached one by one, 98.7 kcal would have to be put in at each step. Actually, the experimental evidence is in accord with quite different energies for the separate dissociation steps:

$$\begin{aligned}
&CH_4 \longrightarrow CH_3\cdot + H\cdot && \Delta H^\circ = 104 \text{ kcal}\\
&CH_3\cdot \longrightarrow \cdot CH_2\cdot + H\cdot && \Delta H^\circ = 111 \text{ kcal}\\
&\cdot CH_2\cdot \longrightarrow \cdot\dot{C}H + H\cdot && \Delta H^\circ = 101 \text{ kcal}\\
&\cdot\dot{C}H \longrightarrow \cdot\dot{C}\cdot\,(g) + H\cdot && \Delta H^\circ = 81 \text{ kcal}\\
&\overline{\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad}\\
&CH_4 \longrightarrow \cdot\dot{C}\cdot\,(g) + 4\,H\cdot && \Delta H^\circ = 397 \text{ kcal at } 25^\circ
\end{aligned}$$

The moral is that we should try to avoid using the bond energies in Table 4-3 as a measure of ΔH^0 for the dissociation of just one bond in a polyatomic molecule. For this we need what are called *bond-dissociation energies*, some of which are given in Table 4-6. The values given have been selected to emphasize how structure influences bond energy. Thus, $C-H$ bond energies in alkanes decrease in the order primary $>$ secondary $>$ tertiary; likewise, $C-H$ bonds decrease in strength along the series $C\equiv C-H > C=C-H > C-C-H$.

How accurate are ΔH^0 values calculated from bond energies? Generally quite good provided nonbonded interactions between the atoms are small and the bond angles and distances are close to the normal values (Section 2-2B). A few examples of calculated and experimental heats of combustion of some hydrocarbons are given in Table 4-4. Negative discrepancies represent heats of combustion *smaller* than expected from the average bond energies and positive values correspond to *larger* than expected heats of combustion.

Table 4-4
Calculated and Experimental Heats of Combustion of Gaseous Hydrocarbons at 25°C

Hydrocarbon	ΔH^0 of combustion, calculated from bond energies, kcal mole^{-1}	ΔH^0 of combustion, experimental values,[a] kcal mole^{-1}	Discrepancy, kcal mole^{-1}
CH_4	−193.8	−191.8	−2.0
$CH_3-CH_2-CH_2-CH_3$	−634.4	−635.1	+0.7
$CH_3-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_3$	−634.4	−633.1	−1.3
$CH_3(CH_2)_6CH_3$	−1221.8	−1223.0	+1.2
$CH_3-\overset{\displaystyle CH_3}{\overset{\vert}{\underset{\displaystyle CH_3}{\underset{\vert}{C}}}}-\overset{\displaystyle CH_3}{\overset{\vert}{\underset{\displaystyle CH_3}{\underset{\vert}{C}}}}-CH_3$	−1221.8	−1218.9	−2.9
	−440.6	−468.3	+27.7
	−881.1	−881.8	+0.7

[a]Based on the individual heats of formation compiled by D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, *The Chemical Thermodynamics of Organic Compounds*, John Wiley and Sons, Inc., New York, 1969.

Comparing isomers in Table 4-4, we see that 2-methylpropane and 2,2,3,3-tetramethylbutane give off less heat when burned than do butane and octane, and this is a rather general characteristic result of chain branching.

Cyclopropane has a ΔH^0 of combustion of 27.7 kcal mol^{-1} *greater* than expected from bond energies, and this clearly is associated with the abnormal $C-C-C$ bond angles in the ring. These matters will be discussed in detail in Chapter 12. For cyclohexane, which has normal bond angles, the heat of combustion is close to the calculated value.

[2]In this book we use kilocalories in place of the presently recommended (SI) joules for units of energy. As of the date of writing, it is not clear just how general the use of the joule will become among chemists. To convert calories to joules (or kcal to kJ), multiply by 4.184.

[3]You may wonder how a reaction, such as combustion of methane, can occur at 25°. The fact is that the reaction can be carried out at any desired temperature. The important thing is that the ΔH^0 value we are talking about here is the heat liberated or absorbed when you start with the reactants at 25° and finish with the products at 25°. As long as ΔH^0 is defined this way, it does not matter at what temperature the reaction actually occurs. Standard states for gases are 1 atm partial pressure. Standard states for liquids or solids usually are the pure liquid or solid at 1 atm external pressure.

4.4.1: Contributors and Attributions

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4.5: Halogenation of Alkanes. Energies and Rates of Reactions

The economies of the highly industrialized nations of the world are based in large part on energy and chemicals produced from petroleum. Although the most important and versatile intermediates for conversion of petroleum to chemicals are compounds with double or triple bonds, it also is possible to prepare many valuable substances by *substitution reactions of alkanes*. In such substitutions, a hydrogen is removed from a carbon chain and another atom or group of atoms becomes attached in its place.

A simple example of a substitution reaction is the formation of chloromethane and chlorine:

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl \tag{4.5.1}$$

The equation for the reaction is simple, the ingredients are cheap, and the product is useful. However, if we want to decide in advance whether such a reaction is actually feasible, we have to know more. Particularly, we have to know whether the reaction proceeds in the direction it is written and, if so, whether conditions can be found under which it proceeds at a convenient rate. Obviously, if one were to mix methane and chlorine and find that, at most, only 1% conversion to the desired product occurred and that the 1% conversion could be achieved only after a day or so of strong heating, this reaction would be both too unfavorable and too slow for an industrial process.

One way of visualizing the problems involved is with energy diagrams, which show the energy in terms of some arbitrary **reaction coordinate** that is a measure of progress between the initial and final states (Figure 4-4). Diagrams such as Figure 4-4 may not be familiar to you, and a mechanical analogy may be helpful to provide better understanding of the very important ideas involved. Consider a two-level box containing a number of tennis balls. An analog to an energetically favorable reaction would be to have all of the balls

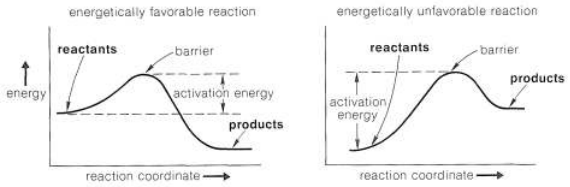
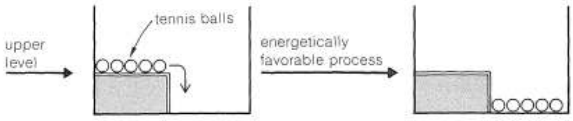


Figure 4-4: Schematic energy diagrams for reactions that are energetically favorable and unfavorable when proceeding from left to right along the reaction coordinate

on the upper level where any disturbance would cause them to roll down to the lower level under the influence of gravity, thereby losing energy.



If the upper level is modified and a low fence added to hold the balls in place, it will be just as energetically favorable as when the fence is not there for the balls to be at the lower level. The difference is that the process will not occur *spontaneously* without some major disturbance. We can say there is an **energy barrier** to occurrence of the favorable process.

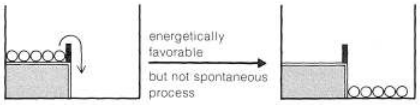
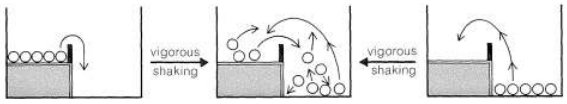


Figure 4-4 where we show an energy barrier to the spontaneous conversion of reactants to products for an energetically favorable chemical reaction.

Now, if we shake the box hard enough, the balls on the upper level can acquire enough energy to bounce over the barrier and drop to the lower level. The balls then can be said to acquire enough **activation energy** to surmount the barrier. At the molecular level, the activation energy must be acquired either by collisions between molecules as the result of their thermal motions, or from some external agency, to permit the reactants to get over the barrier and be transformed into products. We shortly will discuss this more, but first we wish to illustrate another important concept with our mechanical analogy, that of **equilibrium** and **equilibration**.

With gentle shaking of our two-level box, all of the balls on the upper level are expected to wind up on the lower level. There will not be enough activation to have them go from the lower to the upper level. In this circumstance, we can say that the balls are not equilibrated between the lower and upper levels. However, if we shake the box *vigorously* and *continuously*, no matter whether we start with all of the balls on the lower or upper level, an *equilibrium* will be set up with, on the average, most of the balls in the energetically more favorable lower level, but some in the upper level as well.



To maintain a constant average fraction of the balls at each level with vigorous and continued shaking, the *rate* at which balls go from the upper to the lower level must be equal to the *rate* that they go in the opposite direction. The balls now will be *equilibrated* between the two levels. At equilibrium, the fraction of the balls on each of the two levels is wholly independent of the height of the barrier, just as long as the activation (shaking) is sufficient to permit the balls to go *both* ways.

The diagrams of Figure 4-4 are to be interpreted in the same general way. If thermal agitation of the molecules is sufficient, then equilibrium can be expected to be established between the reactants and the products, whether the overall reaction is energetically favorable (left side of Figure 4-4) or energetically unfavorable (right side of Figure 4-4). But as with our analogy, when equilibrium is established we expect the major portion of the molecules to be in the more favorable energy state.

What happens when methane is mixed with chlorine? No measurable reaction occurs when the gases are mixed and kept in the dark at room temperature. Clearly, either the reaction is energetically unfavorable or the energy barrier is high. The answer as to which becomes clear when the mixture is heated to temperatures in excess of 300° or when exposed to strong violet or ultraviolet light, whereby a rapid or even explosive reaction takes place. Therefore the reaction is energetically favorable, but the activation energy is greater than can be attained by thermal agitation alone at room temperature. Heat or light therefore must initiate a pathway for the reactants to be converted to products that has a low barrier or activation energy.

Could we have predicted the results of this experiment ahead of time? First, we must recognize that there really are several questions here. Could we have decided whether the reaction was energetically favorable? That the dark reaction would be slow at room temperature? That light would cause the reaction to be fast? We consider these and some related questions in detail because they are *important* questions and the answers to them are relevant in one way or another to the study of *all* reactions in organic chemistry.

4.5.1: The Question of the Equilibrium Constant

Presumably, methane could react with chlorine to give chloromethane and hydrogen chloride, or chloromethane could react with hydrogen chloride to give methane and chlorine. If conditions were found for which both reactions proceeded at a finite rate, equilibrium finally would be established when the rates of the reactions in each direction became equal:

$$\mathrm{CH_4 + Cl_2 \rightleftharpoons CH_3Cl + HCl} \tag{4.5.2}$$

At equilibrium, the relationship among the amounts of reactants and products is given by the equilibrium constant expression

$$K_{eq} = \frac{[CH_3Cl][HCl]}{[CH_4][Cl_2]} \tag{4.5.3}$$

in which K_{eq} is the equilibrium constant.

The quantities within the brackets of Equation 4.5.3 denote either concentrations for liquid reactants or partial pressures for gaseous substances. If the equilibrium constant K_{eq} is *greater than* 1, then on mixing equal volumes of each of the participant substances (all are gases above -24°), reaction to the *right* will be initially faster than reaction to the left, until equilibrium is established; at this point there will be more chloromethane and hydrogen chloride present than methane and chlorine. However, if the equilibrium constant were *less than* 1, the reaction initially would proceed faster to the *left* and, at equilibrium, there would be more methane and chlorine present than chloromethane and hydrogen chloride.[4] For methane chlorination, we know from experiment that the reaction goes to the right and that K_{eq} is much greater than unity. Naturally, it would be helpful in planning other organic preparations to be able to estimate K_{eq} in advance.

It is a common experience to associate chemical reactions with equilibrium constants greater than one with the evolution of heat, in other words, with negative ΔH^0 values. There are, in fact, many striking examples. Formation of chloromethane and hydrogen chloride from methane and chlorine has a K_{eq} of 10^{18} and ΔH^0 of -24 kcal per mole of CH_3Cl formed at 25°. Combustion of hydrogen with oxygen to give water has a K_{eq} of 10^{40} and $\Delta H^0 = -57$ kcal per mole of water formed at 25°. However, this correlation between K_{eq} and ΔH^0 is neither universal nor rigorous. Reactions are known that absorb heat (are endothermic) and yet have $K_{eq} > 1$. Other reactions have large ΔH^0 values and equilibrium constants much less than 1.

The problem is that the energy change that correlates with K_{eq} is not ΔH^0 but ΔG^0 (the so-called change of "**standard Gibbs energy**")[5], and if we know ΔG^0, we can calculate K_{eq} by the equation

$$\Delta G^o = -2.303RT \log_{10} K_{eq} \tag{4.5.4}$$

in which R is the gas constant and T is the absolute temperature in degrees Kelvin. For our calculations, we shall use R as 1.987 cal deg^{-1} mol^{-1} and you should not forget to convert ΔG^0 to cal.

Tables of ΔG^0 values for formation of particular compounds (at various temperatures and states) from the elements are available in handbooks and the literature. With these, we can calculate equilibrium constants quite accurately. For example, handbooks give the following data, which are useful for methane chlorination:

$$\begin{aligned}
\text{C}(s) + 2\text{H}_2(g) &\longrightarrow \text{CH}_4(g) && \Delta G^0 = -12.1 \text{ kcal } (25^\circ)\\
\text{C}(s) + \tfrac{3}{2}\text{H}_2(g) + \tfrac{1}{2}\text{Cl}_2(g) &\longrightarrow \text{CH}_3\text{Cl}(g) && \Delta G^0 = -14.0 \text{ kcal } (25^\circ)\\
\tfrac{1}{2}\text{H}_2(g) + \tfrac{1}{2}\text{Cl}_2(g) &\longrightarrow \text{HCl}(g) && \Delta G^0 = -22.8 \text{ kcal } (25^\circ)
\end{aligned}$$

Combining these with proper regard for sign gives

$$\begin{aligned}
\text{CH}_4(g) &\longrightarrow \text{C}(s) + 2\text{H}_2(g) && \Delta G^0 = +12.1 \text{ kcal}\\
\text{C}(s) + \tfrac{3}{2}\text{H}_2(g) + \tfrac{1}{2}\text{Cl}_2(g) &\longrightarrow \text{CH}_3\text{Cl}(g) && \Delta G^0 = -14 \text{ kcal}\\
\tfrac{1}{2}\text{H}_2(g) + \tfrac{1}{2}\text{Cl}_2(g) &\longrightarrow \text{HCl}(g) && \Delta G^0 = -22.8 \text{ kcal}\\
\hline
\text{CH}_4(g) + \text{Cl}_2(g) &\longrightarrow \text{CH}_3\text{Cl}(g) + \text{HCl}(g) && \Delta G^0 = -24.7 \text{ kcal } (25^\circ)
\end{aligned}$$

and $\log K_{eq} = -(-24.7 \times 1000) / (2.303 \times 1.987 \times 298.2)$, so $K_{eq} = 1.3 \times 10^{18}$. Unfortunately, insufficient ΔG^0 values for formation reactions are available to make this a widely applicable method for calculating K_{eq} values.

The situation is not wholly hopeless, because there is a relationship between ΔG^0 and ΔH^0 that also involves T and another quantity, ΔS^0, the standard **entropy change** of the process:

$$\Delta G^o = \Delta H^o - T\Delta S^o \tag{4.5.5}$$

This equation shows that ΔG^0 and ΔH^0 are equal when ΔS^0 is zero. Therefore the sign and magnitude of $T\Delta S^0$ determine how well K_{eq} correlates with ΔH^0. Now, we have to give attention to whether we can estimate $T\Delta S^0$ values well enough to decide whether the ΔH^0 of a given reaction (calculated from bond energies or other information) will give a good or poor measure of ΔG^0.

4.5.2: Entropy and Molecular Disorder

To decide whether we need to worry about ΔS^0 with regard to any particular reaction, we have to have some idea what physical meaning entropy has. To be very detailed about this subject is beyond the scope of this book, but you should try to understand the physical basis of entropy, because if you do, then you will be able to predict at least qualitatively whether ΔH^0 will be about the same or very different from ΔG^0. Essentially, the entropy of a chemical system is a measure of its *molecular disorder* or *randomness*. Other things being the same, the more random the system is, the more favorable the system is.

Different kinds of molecules have different degrees of translational, vibrational, and rotational freedom and, hence, different average degrees of molecular disorder or randomness. Now, if for a chemical reaction the degree of molecular disorder is different for the products than for the reactants, there will be a change in entropy and $\Delta S^0 \neq 0$.

A spectacular example of the effect of molecular disorder in contributing to the difference between ΔH^0 and ΔG^0 is afforded by the formation of liquid nonane, C_9H_{20}, from solid carbon and hydrogen gas at 25°:

$$9\,\text{C}\,(\text{s}) + 10\,\text{H}_2\,(\text{g}) \;\rightarrow \text{C}_{91020}\,(\text{l}) \tag{4.5.6}$$

with $\Delta H^o = -54.7\,kcal$ and $\Delta S^o = 5.0\,kcal$.

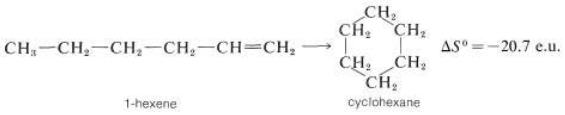
Equations 4.5.4 and 4.5.5 can be rearranged to calculate ΔS^0 and K_{eq} from ΔH^0 and ΔG^0:

and

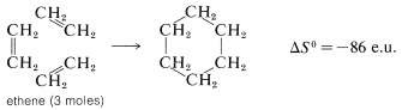
$$K_{eq} = 10^{-\Delta G^o/2.303\,RT} = 10^{-5.900/(2.303\times 1.987\times 298.2)} = 4.7\times 10^{-5} \tag{4.5.7}$$

These ΔH^0, ΔS^0, and K_{eq} values can be compared to those for $H_2 + \frac{1}{2}O_2 \longrightarrow H_2O$, for which ΔH^0 is -57 kcal, ΔS^0 is 8.6 e.u., and K_{eq} is 10^{40}. Obviously, there is something *unfavorable* about the entropy change from carbon and hydrogen to nonane. The important thing is that there is a great *difference* in the constraints on the atoms on each side of the equation. In particular, hydrogen molecules in the gaseous state have great translational freedom and a high degree of disorder, the greater part of which is lost when the hydrogen atoms become attached to a chain of carbons. This makes for a large *negative* ΔS^0, which corresponds to a *decrease* in K_{eq}. The differences in constraints of the carbons are less important. Solid carbon has an ordered, rigid structure with little freedom of motion of the individual carbon atoms. These carbons are less constrained in nonane, and this would tend to make ΔS^0 more positive and ΔG^0 more negative, corresponding to an increase in K_{eq} (Equations 4.5.4 and 4.5.5). However, this is a *small* effect on ΔS^0 compared to the enormous difference in the degree of disorder of hydrogen between hydrogen gas and hydrogen bound to carbon in nonane.

Negative entropy effects usually are observed in ring-closure reactions such as the formation of cyclohexane from 1-hexene, which occur with substantial loss of rotational freedom (disorder) about the $C-C$ bonds:



There is an even greater loss in entropy on forming cyclohexane from ethene because substantially more freedom is lost in orienting three ethene molecules to form a ring:



For simple reactions, with the same number of molecules on each side of the equation, with no ring formation or other unusual changes in the constraints between the products and reactants, ΔS^0 usually is relatively small. In general, for such processes, we know from experience that K_{eq} *usually is greater than 1 if* ΔH^0 *is more negative than* -15 kcal *and usually is less than 1 for* ΔH^0 *more positive than* $+15$ kcal. We can use this as a "rule of thumb" to predict whether K_{eq} should be greater or less than unity for vapor-phase reactions involving simple molecules. Some idea of the degree of success to be expected from this rule may be inferred from the examples in Table 4-5, which also contains a further comparison of some experimental ΔH^0 values with those calculated from bond energies.

Table 4-5
Comparison of Calculated and Experimental ΔH^0 Values and Equilibrium Constants for Some Simple Reactions[a,b]

Reaction	Expt. ΔH^0	Calc. ΔH^0	K_{eq}
$CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl$	−23.8	−25	1×10^{18}
$C(s) + 2H_2 \longrightarrow CH_4$	−17.9	−15[c]	8.0×10^{8}
$3C(s) + 4H_2 \longrightarrow C_3H_8$ (propane)	−24.8	−24[c]	1.3×10^{4}
$6C(s) + 7H_2 \longrightarrow C_6H_{14}$ (hexane)	−40.0	−38[c]	0.9
$9C(s) + 10H_2 \longrightarrow C_9H_{20}$ (nonane)	−54.7	−51[c]	4.7×10^{-5}
1-hexene ⟶ cyclohexane	−19.5	−19.4	6.0×10^{9}
$\frac{1}{2}H_2 + \frac{1}{2}Cl_2 \longrightarrow HCl$	−22.0	−22[d]	5.0×10^{16}
$\frac{3}{2}H_2 + \frac{1}{2}N_2 \longrightarrow NH_3$	−11.0	−11	8.2×10^{2}
$CO + H_2O \longrightarrow CO_2 + H_2$	−9.9	−10	1×10^{5}
$CH_3OH + HCl \longrightarrow CH_3Cl + H_2O$	−7.3	−3	1.8×10^{8}

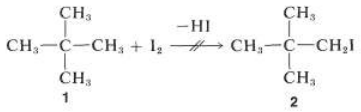
[a] All participants in the gaseous state at 298.2°K unless otherwise stated, and at constant pressure.

[b] Thermochemical values have been taken mostly from *Selected Values of Chemical Thermodynamic Properties* by F. D. Rossini, et al. (Circular of the National Bureau of Standards 500, Washington, D.C., 1952) and *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds* by F. D. Rossini, et al. (American Petroleum Institute Research Project 44, Carnegie Press, Pittsburgh, 1953).

[c] Calculated using $\Delta H^0 = 171.3$ kcal per mole for $C(s) \longrightarrow C(g)$, at 25°.

[d] Not an independent value because the bond energy for product was calculated from the experimental ΔH^0.

Suppose ΔG^0 is positive, what hope do we have of obtaining a useful conversion to a desired product? There is no simple straightforward and general answer to this question. When the reaction is reversible the classic procedure of removing one or more of the products to prevent equilibrium from being established has many applications in organic chemistry, as will be seen later. When this approach is inapplicable, a change in reagents is necessary. Thus, iodine does not give a useful conversion with 2,2-dimethylpropane, 1, to give 1-iodo-2,2-dimethylpropane, 2, because the position of equilibrium is too far to the left ($K_{eq} \cong 10^{-5}$):



Alternative routes with favorable ΔG^0 values are required. Development of ways to make indirectly, by efficient processes, what cannot be made directly is one of the most interesting and challenging activities of organic chemists.

4.5.3: Why Do Methane and Chlorine Fail to React in the Dark at 25°?

To reach an understanding of why methane and chlorine do not react in the dark, we must consider the details of *how* the reaction occurs - that is, the *reaction mechanism*. The simplest mechanism would be for a chlorine molecule to collide with a methane molecule in such a way as to have chloromethane and hydrogen chloride formed directly as a result of a *concerted* breaking of the $Cl-Cl$ and $C-H$ bonds and making of the $C-Cl$ and $H-Cl$ bonds (see Figure 4-5). The failure to react indicates that there must be an energy barrier too high for this mechanism to operate. Why should this be so?

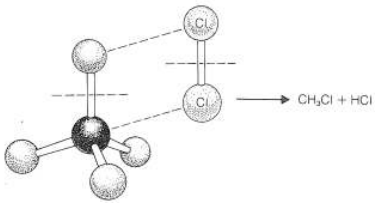


Figure 4-5: Four-center collision of chlorine with methane as visualized with ball-and-stick models

First, this mechanism involves a very precisely oriented "four-center" collision between chlorine and methane that would have a low probability of occurrence (i.e., a large decrease in entropy because a precise orientation means high molecular ordering). Second, it requires pushing a chlorine molecule sufficiently deeply into a methane molecule so one of the chlorine atoms comes close enough to the carbon to form a bond and yield chloromethane.

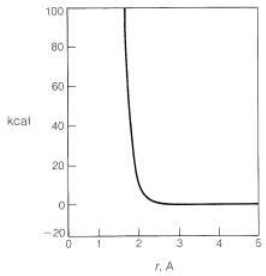


Figure 4-6: Graph of the potential energy of pairs of neon atoms as a function of the internuclear distance. The energy values are per mole of neon atoms.

Generally, to bring nonbonded atoms to near-bonding distances (1.2 A to 1.8 A) requires a large expenditure of energy, as can be seen in Figure 4-6. Interatomic repulsive forces increase rapidly at short distances, and pushing a chlorine molecule into a methane molecule to attain distances similar to the 1.77-A carbon-chlorine bond distance in chloromethane would require a considerable amount of compression (see Figure 4-7). Valuable information

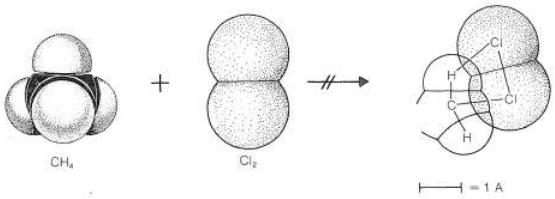


Figure 4-7: Models showing the degree of atomic compression required to bring a chlorine molecule to within bonding distance of carbon and hydrogen of methane

about interatomic repulsions can be obtained with space-filling models of the CPK type (Section 2-2), which have radii scaled to correspond to actual atomic interference radii, that is, the interatomic distance at the point where curves of the type of Figure 4-6 start to rise steeply. With such models, the degree of atomic compression required to bring the nonbonded atoms to within near-bonding distance is more evident than with the ball-and-stick models. It may be noted that four-center reactions of the type postulated in Figure 4-5 are encountered only rarely.

If the concerted four-center mechanism for formation of chloromethane and hydrogen chloride from chlorine and methane is discarded, all the remaining possibilities are *stepwise reaction mechanisms*. A slow stepwise reaction is dynamically analogous to the flow of sand through a succession of funnels with different stem diameters. The funnel with the smallest stem will be the most important bottleneck and, if its stem diameter is much smaller than the others, it alone will determine the flow rate. Generally, a multistep chemical reaction will have a slow rate-determining step (analogous to the funnel with the small stem) and other relatively *fast steps*, which may occur either before or after the slow step.

A possible set of steps for the chlorination of methane follows:

$$\text{(1)}\quad Cl_2 \xrightarrow{\text{slow}} 2:\ddot{\underset{\cdot\cdot}{Cl}}\cdot$$

$$\text{(2)}\quad CH_4 \xrightarrow{\text{slow}} CH_3\cdot + H\cdot$$

$$\text{(3)}\quad :\ddot{\underset{\cdot\cdot}{Cl}}\cdot + CH_3\cdot \xrightarrow{\text{fast}} CH_3Cl$$

$$\text{(4)}\quad :\ddot{\underset{\cdot\cdot}{Cl}}\cdot + H\cdot \xrightarrow{\text{fast}} HCl$$

Reactions (1) and (2) involve dissociation of chlorine into chlorine atoms and the breaking of a $C-H$ bond of methane to give a methyl radical and a hydrogen atom. The methyl radical, like chlorine and hydrogen atoms, has one election not involved in bonding. Atoms and radicals usually are highly reactive, so formation of chloromethane and hydrogen chloride should proceed readily by Reactions (3) and (4). The crux then will be whether Steps (1) and (2) are reasonable under the reaction conditions.

In the absence of some *external stimulus*, only collisions due to the usual thermal motions of the molecules can provide the energy needed to break the bonds. At temperatures below 100°, it is very rare indeed that the thermal agitation alone can supply sufficient energy to break any significant number of bonds stronger than 30 to 35 kcal mol^{-1}.

The $Cl-Cl$ bond energy from Table 4-3 is 58.1 kcal, which is much too great to allow bond breaking from thermal agitation at 25° in accord with Reaction (1). For Reaction (2) it is not advisable to use the 98.7 kcal $C-H$ bond energy from Table 4-3 because this is one fourth of the energy required to break all four $C-H$ bonds (Section 4-3). More specific **bond-dissociation energies** are given in Table 4-5, and it will be seen that to break one $C-H$ bond of methane requires 104 kcal at 25°, which again is too much to be gained by thermal agitation. Therefore we can conclude that Reactions (1)-(4) can not be an important mechanism for chlorination of methane at room temperature.

One might ask whether dissociation into ions would provide viable mechanisms for methane chlorination. Part of the answer certainly is: Not in the vapor phase, as the following thermochemical data show:

$$Cl_2 \longrightarrow :\ddot{\underset{\cdot\cdot}{Cl}}^{\oplus} + :\ddot{\underset{\cdot\cdot}{Cl}}:^{\ominus} \qquad \Delta H^{\circ} = 270 \text{ kcal}$$

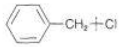
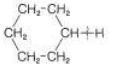
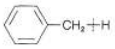
$$CH_4 \longrightarrow CH_3:^{\ominus} + H^{\oplus} \qquad \Delta H^{\circ} \cong 400 \text{ kcal}$$

Ionic dissociation simply does not occur at ordinarily accessible temperatures by collisions between molecules in the vapor state. What is needed for formation of ions is either a highly energetic external stimulus, such as bombardment with fast-moving electrons, or an ionizing solvent that will assist ionization. Both of these processes will be discussed later. The point here is that ionic dissociation is not a viable step for the vapor-phase chlorination of methane.

4.5.4: Why Does Light Induce the Chlorination of Methane?

First, we should make clear that the light does more than provide energy merely to lift the molecules of methane and chlorine over the barrier of Figure 4-4. This is evident from the fact that very little light is needed, far less than one light photon per molecule of chloromethane produced. The light could activate either methane or chlorine, or both. However, methane is colorless and chlorine is yellow-green. This indicates that chlorine, not methane, interacts with visible light. A photon of near-ultraviolet light, such as is absorbed by chlorine gas, provides more than enough energy to split the molecule into two chlorine atoms:

Table 4-6
Bond-Dissociation Energies at 25°

Compound	Bond energy (kcal mole^{-1})[a]	Compound	Bond energy (kcal mole^{-1})[a]
CH_3–H	104	H_3C–CH_3	88
CH_3CH_2–H	98	$CH_3\overset{O}{\overset{\|}{C}}$–$CH_3$	77
$(CH_3)_2CH$–H	95	H_3C–F	109
$(CH_3)_3C$–H	92	H_3C–Cl	84
CH_2=CH–H	108	CCl_3–Cl	73
HC≡C–H	128	H_3C=CH–Cl	89
	101	H_2C=$CHCH_2$–Cl	71
	97		95
	95		69
	96	H_3C–Br	70
		CCl_3–Br	54
		H_3C–I	56
		HC≡CH ⟶ 2CH	230
		H_2C=CH_2 ⟶ $2CH_2$	173
	110	HO–H	119
		CH_3O–H	102
CH_2=CH–CH_2–H	89	HS–H	90
	85	CH_3S–H	88
Cl_3C–H	96	HO–OH	51
$CH_3\overset{O}{\overset{\|}{C}}$–H	86	$(CH_3)_2CO$–$OC(CH_3)_3$	37

[a]These values are mostly from the compilations of K. W. Egger and A. T. Cocks, *Helv. chim. Acta* **56,** 1516 (1973), and J. A. Kerr, M. J. Parsonage, and A. F. Trotman-Dickenson, *Handbook of Chemistry and Physics*, 55th ed., CRC Publishing Co., 1975, F-213 to F-216.

Once produced, a chlorine atom can remove a hydrogen atom from a methane molecule and form a methyl radical and a hydrogen chloride molecule. The bond-dissociation energies of CH_4 (104 kcal) and HCl (103.1 kcal) suggest that this reaction is endothermic by about 1 kcal:

Figure 4-8). The methyl radical resulting from the attack of atomic chlorine on a hydrogen of methane then can remove a chlorine atom from molecular chlorine and form chloromethane and a new chlorine atom:

Use of bond-dissociation energies gives a calculated ΔH^0 of -26 kcal for this reaction, which is certainly large enough, by our rule of thumb, to predict that K_{eq} will be greater than 1. Attack of a methyl radical on molecular chlorine is expected to require somewhat more oriented collision than for a chlorine atom reacting with methane (the chlorine molecule probably should be endwise, not sidewise, to the radical) but the interatomic repulsion probably should not be much different.

The net result of $CH_4 + Cl\cdot \longrightarrow CH_3\cdot + HCl$ and $CH_3\cdot + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$ is formation of chloromethane and hydrogen chloride from methane and chlorine. Notice that the chlorine atom consumed in the first step is replaced by another one in the second step. This kind of sequence of reactions is called a **chain reaction** because, in principle, one atom can induce the reaction of an infinite number of molecules through operation of a "chain" or cycle of reactions. In our example, chlorine atoms formed by the action of light on

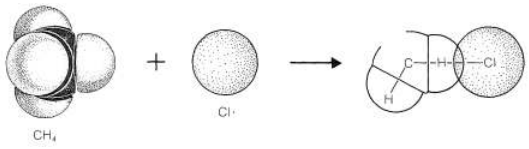


Figure 4-7.

Cl_2 can induce the chlorination of methane by the **chain-propagating steps**:

$$CH_4 + Cl\cdot \longrightarrow HCl + CH_3\cdot$$
$$CH_3\cdot + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$$

In practice, chain reactions are limited by so-called **termination** processes. In our example, chlorine atoms or methyl radicals are destroyed by reacting with one another, as shown in the following equations:

$$CH_3\cdot + :\ddot{Cl}\cdot \longrightarrow CH_3Cl$$
$$2\,CH_3\cdot \longrightarrow CH_3CH_3$$
$$2:\ddot{Cl}\cdot \longrightarrow Cl_2$$

Chain reactions may be considered to involve three phases: First, **chain initiation** must occur, which for methane chlorination is activation and conversion of chlorine molecules to chlorine atoms by light. Second, **chain-propagation** steps convert reactants to products with no net consumption of atoms or radicals. The propagation reactions occur in competition with **chain-terminating** steps, which result in destruction of atoms or radicals. Putting everything together, we can write:

$$Cl_2 \xrightarrow{\text{light}} 2:\ddot{Cl}\cdot \qquad \text{chain initiation}$$
$$CH_4 + :\ddot{Cl}\cdot \longrightarrow CH_3\cdot + HCl$$
$$CH_3\cdot + Cl_2 \longrightarrow CH_3Cl + :\ddot{Cl}\cdot \qquad \text{chain propagation}$$
$$CH_3\cdot + :\ddot{Cl}\cdot \longrightarrow CH_3Cl$$
$$:\ddot{Cl}\cdot + :\ddot{Cl}\cdot \longrightarrow Cl_2$$
$$CH_3\cdot + CH_3\cdot \longrightarrow CH_3CH_3 \qquad \text{chain termination}$$

The chain-termination reactions are expected to be exceedingly fast because atoms and radicals have electrons in unfilled shells that normally are bonding. As a result, bond formation can begin as soon as the atoms or radicals approach one another closely, without need for other bonds to begin to break. The evidence is strong that bond-forming reactions between atoms and radicals usually are **diffusion-controlled**, that there is almost no barrier or activation energy required, and the rates of combination are simply the rates at which encounters between radicals or atoms occur.

If the rates of combination of radicals or atoms are so fast, you might well wonder how chain propagation ever could compete. Of course, competition will be possible if the propagation reactions themselves are fast, but another important consideration is the fact that the *atom or radical concentrations are very low*. Suppose that the concentration of $Cl\cdot$ is 10^{-11} M and the CH_4 concentration 1 M. The probability of encounters between two $Cl\cdot$ atoms will be proportional to $10^{-11} \times 10^{-11}$, and between CH_4 and $Cl\cdot$ atoms it will be $10^{-11} \times 1$. Thus, other things being the same, $CH_4 + Cl\cdot \longrightarrow CH_3\cdot + HCl$ (propagation) would be favored over $2Cl\cdot \longrightarrow Cl_2$ (termination) by a factor of 10^{11}. Under favorable conditions, the methane-chlorination chain may go through 100 to 10,000 cycles before termination occurs by radical or atom combination. Consequently the efficiency (or **quantum yield**) of the reaction is very high in terms of the amount of chlorination that occurs relative to the amount of the light absorbed.

The overall rates of chain reactions usually are slowed very much by substances that can combine with atoms or radicals and convert them into species incapable of participating in the chain-propagation steps. Such substances are called **radical traps**, or **inhibitors**. Oxygen acts as an inhibitor in the chlorination of methane by rapidly combining with a methyl radical to form the comparatively stable (less reactive) peroxymethyl radical, $CH_3OO\cdot$. This effectively terminates the chain:

$$CH_3\cdot + O_2 \longrightarrow CH_3OO\cdot \qquad \text{inhibition}$$

4.5.5: Can We Predict Whether Reactions Will Be Fast or Slow?

To a considerable degree, we can predict *relative* reactivities, provided we use common sense to limit our efforts to reasonable situations. In the preceding section, we argued that reactions in which atoms or radicals combine can well be expected to be extremely fast because each entity has a potentially bonding electron in an outer unfilled shell, and bringing these together to form a bond does not require that other bonds be broken:

$$Cl\cdot + \cdot Cl \xrightarrow{\text{fast}} Cl{:}Cl$$

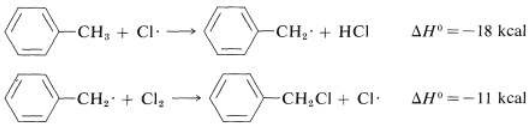
Figure 4-6). As CH_4 and $Cl\cdot$ get closer together, the new bond starts to form and the old bond starts to break. At the top of the barrier, the hydrogen will be bonded partly to chlorine and partly to carbon, $[Cl - - - H - - - CH_3]$, and this we call the activated complex or transition state. The concept of the transition state is an important one, which we will use repeatedly later in connection with many other kinds of reactions. The value of the concept lies in the fact that the reacting system, when it reaches the top of the barrier, can be though of as a chemical entity with a particular, even if not well-defined, structure and definite thermodynamic properties.

The difference between the average energy of the reactants and the energy of the transition state is called the *activation energy* (Figure 4-4). We expect this energy to be smaller (lower barrier) if a weak bond is being broken and a strong bond is being made. The perceptive reader will notice that we are suggesting a parallel between reaction rate and ΔH^0 because ΔH^0 depends on the difference in strengths of the bonds being broken and formed. Yet previously (Section 4-4A), we pointed out that the energy barrier for a reaction need bear no relationship to how energetically feasible the reaction is, and this is indeed true for complex reactions involving many steps. But our intuitive parallel between rate and ΔH^0 usually works quite well for the rates of *individual* steps. This is borne out by experimental data on rates of removal of a hydrogen atom from methane by atoms or radicals ($X\cdot$), such as $F\cdot$, $Cl\cdot$, $Br\cdot$, $HO\cdot$, $H_2N\cdot$, which generally parallel the strength of the new bond formed:

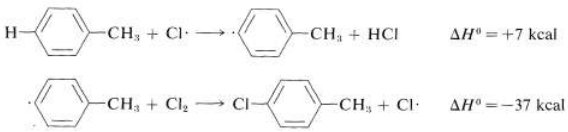
$$CH_4 + X\cdot \longrightarrow CH_3\cdot + HX$$

Similarly, if we look at the $H - C$ bond-dissociation energies of the hydrocarbons shown in Table 4-6, we would infer that $Cl\cdot$ would remove a hydrogen most rapidly from the carbon forming the weakest $C - H$ bond and, again, this is very much in accord with experience. For example, the chlorination of methylbenzene (toluene) in sunlight leads to the substitution of a methyl hydrogen rather than a ring hydrogen for the reason that the methyl $C - H$ bonds are weaker and are attacked more rapidly than the ring $C - H$ bonds. This can be seen explicitly in the ΔH^0 values for the chain-propagation steps calculated from the bond-dissociation energies of Table 4-6.

Methyl substitution (observed):



Ring substitution (not observed):



The ΔH^0 of ring-hydrogen abstraction is unfavorable by $+7$ kcal because of the high $C - H$ bond energy (110 kcal). Thus this step is not observed. It is too slow in comparison with the more favorable reaction at the methyl group even though the second propagation step is energetically favorable by -37 kcal and presumably would occur very rapidly. Use of bond-dissociation energies to predict relative reaction rates becomes much less valid when we try to compare different kinds of reactions. To illustrate, ethane might react with $F\cdot$ to give fluoromethane or hydrogen fluoride:

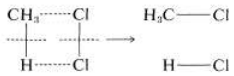
$$CH_3—CH_3 + F\cdot \longrightarrow CH_3\cdot + CH_3F \qquad \Delta H^0 = -20 \text{ kcal}$$
$$CH_3—CH_3 + F\cdot \longrightarrow CH_3CH_2\cdot + HF \qquad \Delta H^0 = -38 \text{ kcal}$$

It is not a good idea to try to predict the relative rates of these two reactions on the basis of their overall ΔH^0 values because the nature of the bonds made and broken is too different.

4.5.6: How Should We Go about Formulating a Reaction Mechanism?

Faced with proposing a mechanism for a reaction that involves overall making or breaking of more than two bonds, the beginner almost invariably tries to concoct a process wherein, with a *single* step, all of the right bonds break and all of the right bonds form. Such mechanisms, called **concerted mechanisms**, have three disadvantages. First, they are almost impossible to prove correct. Second, prediction of the relative rates of reactions involving concerted mechanisms is especially difficult. Third, concerted mechanisms have a certain sterility in that one has no control over what happens while they are taking place, except an overall control of rate by regulating concentrations, temperature, pressure, choice of solvents, and so on.

To illustrate, suppose that methane chlorination appeared to proceed by way of a one-step concerted mechanism:



At the instant of reaction, the reactant molecules in effect would disappear into a dark closet and later emerge as product molecules. There is no way to prove experimentally that all of the bonds were made and formed simultaneously. All one could do would be to use the most searching possible tests to probe for the existence of discrete steps. If these tests fail, the reaction still would not be *proved* concerted because other, still more searching tests might be developed later that would give a different answer. The fact is, once you accept that a particular reaction is concerted, you, in effect, accept the proposition that further work on its *mechanism* is futile, no matter how important you might feel that other studies would be regarding the factors affecting the reaction rate.

The experienced practitioner in reaction mechanisms accepts a concerted mechanism for a reaction involving the breaking and making of more than two bonds as a last resort. He first will try to analyze the overall transformation in terms of discrete steps that are individually simple enough surely to be concerted and that also involves energetically reasonable intermediates.

Such an analysis of a reaction in terms of discrete mechanistic steps offers many possibilities for experimental studies, especially in development of procedures for detecting the existence, even if highly transitory, of the proposed intermediates. We shall give many examples of the fruitfulness of this kind of approach in subsequent discussions.

[4]If calculations based on chemical equilibrium constants are unfamiliar to you, we suggest you study one of the general chemistry texts listed for supplemental reading at the end of Chapter 1.

[5]Many books and references use ΔF^0 instead of ΔG^0. The difference between standard Gibbs energy ΔG^0 and the Gibbs energy ΔG is that ΔG^0 is defined as the value of the free energy when all of the participants are in standard states. The free energy for ΔG for a reaction $\mathrm{A} + \mathrm{B} + \cdots \longrightarrow \mathrm{X} + \mathrm{Y} + \cdots$ is equal to $\Delta G^0 - 2.303RT \log \frac{[\mathrm{X}][\mathrm{Y}]\cdots}{[\mathrm{A}][\mathrm{B}]\cdots}$ where the products, $[\mathrm{X}], [\mathrm{Y}]\cdots$, and the reactants, $[\mathrm{A}], [\mathrm{B}]\cdots$, do not have to be in standard states. We shall use only ΔG^0 in this book.

[6]The entropy unit $\mathrm{e.u.}$ has the dimensions calorie per degree or $\mathrm{cal\ deg^{-1}}$.

4.5.7: Contributors and Attributions

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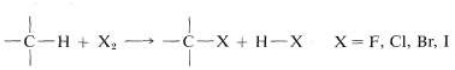
4.6: Practical Halogenations and Problems of Selectivity

Given the knowledge that a particular reaction will proceed at a suitable rate, a host of practical considerations are necessary for satisfactory operation. These considerations include interference by possible side reactions that give products other than those desired, the ease of separation of the desired product from the reaction mixture, and costs of materials, apparatus, and labor. We shall consider these problems in connection with the important synthetic reactions discussed in this book.

The chlorination of saturated hydrocarbons can be induced by light, but also can be carried out at temperatures of about 300° in the dark. Under such circumstances the mechanism is similar to that of light-induced chlorination, except that the chlorine atoms are formed by thermal dissociation of chlorine molecules. Solid carbon surfaces catalyze thermal chlorination, possibly by aiding in the cleavage of the chlorine molecules.

Direct monohalogenation of saturated hydrocarbons works satisfactorily only with chlorine and bromine. For the general reaction



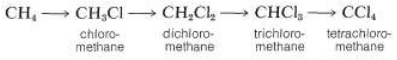
the calculated ΔH^{0} value is negative and very large for fluorine, negative and moderate for chlorine and bromine, and positive for iodine (see Table 4-7). With fluorine, the reaction evolves so much heat that it may be difficult to control, and products from cleavage of carbon-carbon as well as of carbon-hydrogen bonds may be obtained. The only successful, direct fluorination procedure for hydrocarbons involves diffusion of minute amounts of fluorine mixed with helium into liquid or solid hydrocarbons at low temperatures, typically -78° (Dry Ice temperature). As fluorination proceeds, the concentration of fluorine can be increased. The process is best suited for preparation of completely fluorinated compounds, and it has been possible to obtain in this way amounts of $(CF_3)_4C$ and $(CF_3)_3C-C(CF_3)_3$ from 2,2-dimethylpropane and 2,2,3,3-tetramethylbutane corresponding to 10-15% yields based on the fluorine used.

Bromine generally is much less reactive toward hydrocarbons than chlorine is, both at high temperatures and with activation by light. Nonetheless, it usually is possible to brominate saturated hydrocarbons successfully. Iodine is unreactive.

Table 4-7: Calculated Heat of Reaction for Halogenation fo Hydrocarbons

Halogen (X)	ΔH^{o} (kcal/mole)[a]
F	-116
Cl	-27
Br	-10
I	13
[a]Calculated from the bond energies of Table 4-3.	

The chlorination of methane does not have to stop with the formation of chloromethane (methyl chloride). It is usual when chlorinating methane to obtain some of the higher chlorination products: dichloromethane (methylene chloride), trichloromethane (chloroform), and tetrachloromethane (carbon tetrachloride):

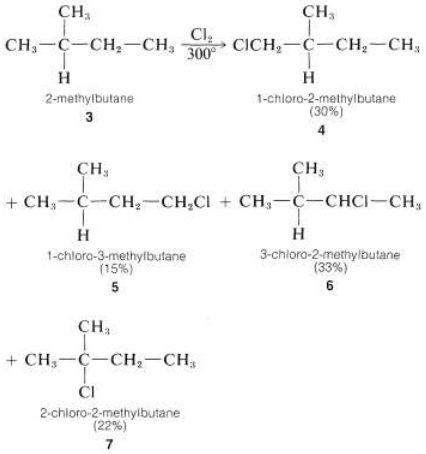


In practice, one can control the degree of substitution to a considerable extent by controlling the methane-chlorine ratio. For example, for monochlorination to predominate, a high methane-chlorine ratio is necessary such that the chlorine atoms react with CH_4 and not with CH_3Cl.

4.6.1: Selectivity in Alkane Halogenation

For propane and higher hydrocarbons for which more than one monosubstitution product is generally possible, difficult separation problems bay arise when a particular product is desired. For example, the chlorination of 2-methylbutane 3 at 300° gives all four

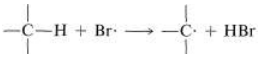
possible monosubstitution products, 4, 5, 6, and 7:

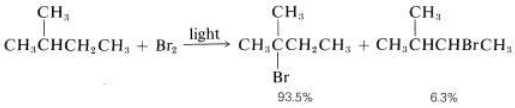


On a purely statistical basis, we may expect the ratio of products from 3 to correlate with the number of available hydrogens at the various positions of substitution. That is, 4, 5, 6, and 7 would be formed in the ratio 6:3:2:1 (50%:25%:17%:8%). However, as can be seen from Table 4-6, the strengths of hydrogen bonds to primary, secondary, and tertiary carbons are not the same and, from the argument given in Section 4-4E we would expect the weaker $C-H$ bonds to be preferentially attacked by $Cl\cdot$. The proportion of 7 formed is about three times that expected on a statistical basis which is in accord with our expectation that the tertiary $C-H$ bond of 2-methylbutane should be the weakest of the $C-H$ bonds. (See Table 4-6.)

The factors governing selectivity in halogenation of alkanes follow:

1. The rates at which the various $C-H$ bonds of 2-methylbutane are broken by attack of chlorine atoms approach 1:1:1 as the temperature is raised above 300°. At higher temperatures both chlorine atoms and hydrocarbons become more reactive because of increases in their thermal energies. Ultimately, temperatures are attained where a chlorine atom essentially removes the first hydrogen with which it collides regardless of position on the hydrocarbon chain. In such circumstances, the composition of monochlorination products will correspond to that expected from simple statistics.

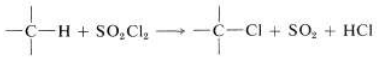
2. Bromine atoms are far more selective than chlorine atoms. This is not unexpected because  is endothermic, whereas corresponding reactions with a chlorine atoms usually are exothermic (data from Table 4-6). Bromine removes only those hydrogens that are relatively weakly bonded to a carbon atom. As predicted, attack of $Br\cdot$ on 2-methylbutane leads mostly to 2-bromo-2-methylbutane, some secondary bromide, and essentially no primary bromides:



3. The selectivity of chlorination reactions carried on in *solution* is increased markedly in the presence of benzene or alkyl-substituted benzenes because benzene and other arenes form loose complexes with chlorine atoms. This substantially cuts down chlorine-atom reactivity, thereby making the chlorine atoms behave more like bromine atoms.

4.6.2: Chemical Initiation of Radical-Chain Substitution

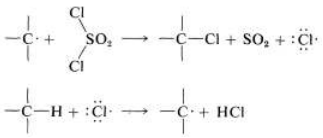
It is possible to achieve chlorination of alkanes using sulfuryl chloride (SO_2Cl_2, bp 69°) in place of chlorine:



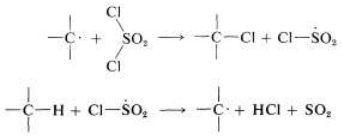
The reaction has a radical-chain mechanism and the chains can be initiated by light or by chemicals, usually peroxides, $ROOR$. Chemical initiation requires an *initiator* with a weak bond that dissociates at temperatures between 40-80°. Peroxides are good examples. The $O-O$ bond is very weak (30-50 kcal) and on heating dissociates to alkoxyl radicals, $RO\cdot$, which are reactive enough

to generate the chain-propagating radicals from the reactants. The exact sequence of chemical initiation is not always known, but a plausible route in the present case would have $RO\cdot$ abstract hydrogen from the alkane:

The propagation steps that would follow are



Chlorination with sulfuryl chloride of alkanes with more than one kind of hydrogen gives a mixture of alkyl chlorides resembling that obtained with chlorine itself. However, in some circumstances the mixture of chlorides is not the same mixture obtained with chlorine itself and when this is true, the hydrogen-abstraction step probably involves $\cdot SO_2Cl$ rather than $Cl\cdot$. The alternative propagation steps then are



Different product ratios are expected from $Cl\cdot$ and $ClSO_2\cdot$ for the same reason that $Cl\cdot$ and $Br\cdot$ lead to different product ratios (Section 4-5A). Other reagents that sometimes are useful halogenating agents in radical-chain reactions include

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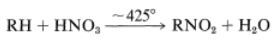
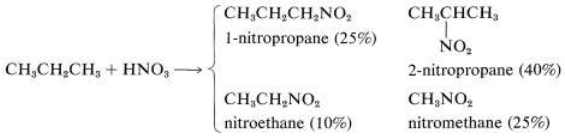
4.7: Nitration of Alkanes

Another reaction of commercial importance is the nitration of alkanes to give nitroparaffins. Such reactions usually are carried out in the vapor phase at elevated temperatures using nitric acid (HNO_3) or nitrogen tetroxide (N_2O_4) as the nitrating agent:



All available evidence points to a radical mechanism for nitration, but many aspects of the reaction are not fully understood. Mixtures are obtained; nitration of propane gives not only 1- and 2-nitropropanes but nitroethane and nitromethane:



In commercial practice, the yield and product distribution in nitration of alkanes is controlled as far as possible by the judicious addition of catalysts (e.g., oxygen and halogens), which are believed to raise the concentration of alkyl radicals. The products are separated from the mixtures by fractional distillation.

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4.E: Alkanes (Exercises)

Exercise 4-1 Use the data of Tables 4-1 and 4-2 to estimate the boiling points of tetradecane, heptadecane, 2-methylhexane, and 2,2-dimethylpentane.

Exercise 4-2 Write detailed structures and predict which compound in each pair would have (1) the lower boiling point and (2) the higher water solubility.

a. $H_2NCH_2CH_2NH_2$, $H_3CCH_2CH_2CH_3$
b. CH_3OCH_3, CH_3CH_2OH
c. $CH_3CH_2CH_2CH_2OH$, $(CH_3)_2COH$
d. CH_3CO_2H, HCO_2CH_3
e. $CH_3(CH_2)_6CO_2H$, $CH_3(CH_2)_7CO_2H$

Exercise 4-3 The heat of combustion of 1 mole of liquid decane to give carbon dioxide and liquid water is $1620.1\ \text{kcal}$. The heat of vaporization of decane at 25° is $11.7\ \text{kcal mol}^{-1}$. Calculate the heat of combustion that would be observed for all the participants in the vapor phase.

Exercise 4-4 Kilogram for kilogram, would the combustion of gaseous methane or of liquid decane (to CO_2 and liquid water) give more heat?

Exercise 4-5 Use the bond-energy table (4-3) to calculate ΔH^0 for the following reactions in the vapor phase at 25°:

a. $CH_3CH_2CH_3 + 5O_2 \rightarrow 3CO_2 + 4H_2O$
b. $CH_4 + \frac{3}{2}O_2 \rightarrow CO + 2H_2O$
c. $CO + 3H_2 \rightarrow CH_4 + H_2O$

Exercise 4-6 Calculate ΔH^0 for $C\,(s) \rightarrow C\,(g)$ from the heat of combustion of 1 gram-atom of carbon to CO_2 as $94.05\ \text{kcal}$, and the bond energies in Table 4-3.

Exercise 4-7 The dissociation $HO{-}H \rightarrow HO\cdot + H\cdot$ for gaseous water at 25° has ΔH^0 equal to $+119.9\ \text{kcal}$. What is ΔH^0 for dissociation of the $O{-}H$ bond of $HO\cdot$?

Exercise 4-8 Methane reacts slowly with bromine atoms and it has been established that ΔH^0 for the following reaction is $17\ \text{kcal mol}^{-1}$ of CH_4:

$$CH_4 + Br\cdot \rightarrow CH_3\cdot + HBr \quad \Delta H^0 = +17\ \text{kcal} \tag{4.E.1}$$

a. Calculate the $C{-}H$ bond strength of CH_4 from this result and any other required bond energies you choose to employ.

b. The heat of the following reaction in the vapor state is $192\ \text{kcal mol}^{-1}$ of CH_4:

$$CH_4 + 2O_2 \rightarrow CO_2 + 2H_2O\,(g) \quad \Delta H^0 = -192\ \text{kcal} \tag{4.E.2}$$

From ΔH^0 and any other required bond energies in Table 4-3, compute a second $C{-}H$ bond-energy value for methane.

c. Consider whether the two $C{-}H$ bond-energy values obtained in Parts **a** and **b** should be the same in theory and experiment, provided that the experimental error is small.

Exercise 4-9 Calculate the pressures of each of the participants at *equilibrium* in the reaction $CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$ when CH_4 and Cl_2 are mixed, each at one atmosphere pressure. Assume that $K_{eq} = 10^{18}$.

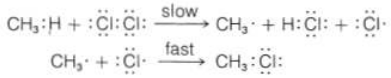
Exercise 4-10

a. Calculate ΔH^0 from bond energies for the conversion of 1-hexene to cyclohexane at 25° and from this, with ΔS^0 as $-20.7\ \text{e.u. mol}^{-1}$, calculate the equilibrium constant K_{eq} from Equation 4-2. For comparison, calculate the equilibrium constant that would be expected if the degrees of disorder of the reactants and the products were equal (i.e., $\Delta S^0 = 0$).

b. How large can ΔS^0 be at 25° for a reaction before our $\pm 15\ \text{kcal}$ rule starts to give incorrect answers?

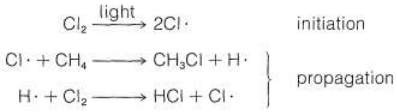
Exercise 4-11 Knowing that the equilibrium constant K_{eq} for formation of nonane from solid carbon and hydrogen gas is 4.7×10^{-5}, explain why liquid nonane does not forthwith decompose into its elements.

Exercise 4-12 A possible mechanism for the reaction of chlorine with methane would be to have collisions by which a chlorine molecule removes a hydrogen according to the following scheme:



Use appropriate bond energies to assess the likelihood of this reaction mechanism. What about the possibility of a similar mechanism with elemental fluorine and methane?

Exercise 4-13 Calculate ΔH^0 for each of the propagation steps of methane chlorination by a mechanism of the type



Compare the relative energetic feasibilities of these chain-propagation steps with those of other possible mechanisms.

Exercise 4-14 Show how the data in Table 4-6 might be extrapolated to predict the principal product to be expected from the vapor-phase, light-induced monochlorination of 1,1-dimethylcyclopropane.

Exercise 4-15* Use the data given in Section 4-5A for the percentages of the monochlorides formed in the vapor-phase chlorination of 2-methylbutane at 300° and take into account the statistical factors for the different numbers and kinds of hydrogens in answering the following:

a. From the ratio of 1-chloro-2-methylbutane to 1-chloro-3-methylbutane formed, what can you say about the $\mathrm{C{-}H}$ bond strengths at the $\mathrm{CH_3}$ carbons?

b. Calculate the ratio of rates of attack of $\mathrm{Cl\cdot}$ on the *individual* hydrogens attached to primary ($\mathrm{C_1}$ and $\mathrm{C_4}$), secondary ($\mathrm{C_3}$), and tertiary ($\mathrm{C_2}$) carbons of 2-methylbutane. Check these ratios by showing they are consistent with the composition of the overall chlorination product.

c. Use your relative rate ratios from Part **b** to calculate the ratios of isomers to be expected in the thermal (300°) monochlorination of (a) propane, (b) 2-methylpropane, and (c) 2,2-dimethylbutane. Show your method in detail.

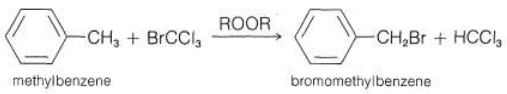
Exercise 4-16

a. Write equations to show reasonable radical-chain initiation, propagation, and termination steps in the monobromination of 2-methylbutane shown in Section 4-5A. Explain clearly why the products of chain termination are obtained in trace amounts only.

b. Use bond energies of Tables 4-3 and 4-6 and bond-dissociation energies of $63\ \mathrm{kcal}$ for tertiary $\mathrm{C{-}Br}$ and $68\ \mathrm{kcal}$ for secondary $\mathrm{C{-}Br}$ bonds to estimate ΔH^0 for each of the propagation steps leading to the two observed products. Which propagation step in the formation of 2-bromo-2-methylbutane is expected to be the slow step?

c. Calculate the relative rates of attack of bromine atoms at the tertiary $\mathrm{C{-}H}$ *versus* the secondary $\mathrm{C{-}H}$ bonds from the product composition in the bromination of 2-methylbutane. Are the relative rates qualitatively consistent with what you would expect based on the ΔH^0 data?

Exercise 4-17* The peroxide-induced bromination of methylbenzene with bromotrichloromethane gives bromomethylbenzene and trichloromethane:



Write initiation, propagation, and termination steps for this radical-chain reaction. Estimate a ΔH^0 for the overall reaction using the bond-dissociation energies of Table 4-6. Would you expect bromotrichloromethane to be a selective or nonselective brominating agent? Explain.

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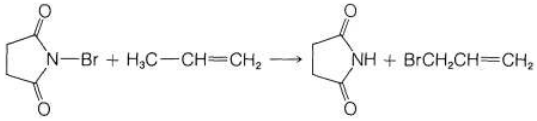
Exercise 4-18* *tert*-Butyl hypochlorite is a useful chlorinating agent. On irradiation, or with chemical initiators, this reagent with methylbenzene gives chloromethylbenzene:

Write a possible mechanism for the reaction, showing the propagation steps with $(CH_3)_3CO\cdot$ as the chain-propagating radical. Use the bond-dissociation energies of Table 4-6 to determine whether your mechanism is energetically and kinetically feasible. Assume the $O-Cl$ bond-dissociation energy of *tert*-butyl hypochlorite is $61\ \text{kcal mol}^{-1}$.

Exercise 4-19*

a. N-Bromosuccinimide (NBS) is an excellent brominating reagent and is used widely to prepare bromoalkenes from alkenes (**Wohl-Ziegler** reaction):



The reaction is initiated with chemical initiators (peroxides) and is as selective as bromination with molecular bromine. Write plausible propagation steps (three of them) for this reaction, given the fact that the actual brominating agent appears to be molecular bromine that is generated from NBS by HBr.

b. What products would you expect to be formed on bromination of 2-methylbutane with N-bromosuccinimide?

Exercise 4-20 Calculate ΔH^0 for the following reactions in the vapor state at 25°, using the bond energies of Table 4-3:

a. $2CH_4 + 7Cl_2 \rightarrow CCl_3{-}CCl_3 + 8HCl$
b. $CH_3CH_3 + \frac{7}{2}O_2 \rightarrow 2CO_2 + 3H_2O$
c. $CH_3CH_3 + H_2 \rightarrow 2CH_4$
d. $CH_3CH_3 + Br_2 \rightarrow 2CH_3Br$
e. $CH_4 + 2Cl_2 \rightarrow C\,(g) + 4HCl$

Exercise 4-21

a. Would ΔH^0 for Exercise 4-20e be greater, or less if C (solid) were the reaction product? Explain.

b. What are the implications of the heats of reaction determined in Exercise 4-20c and d with regard to the "saturated" character of ethane?

Exercise 4-22 A $C-F$ bond energy can be computed from thermochemical studies of the vapor-phase reaction

$$CH_4 + 4F_2 \rightarrow CF_4 + 4HF \quad \Delta H^0 = -460\ \text{kcal} \tag{4.E.3}$$

Show how the ΔH^0 value for this reaction may be used to calculate the energy of the $C-F$ bond if all the other bond energies are known.

Exercise 4-23 The heat of combustion of liquid benzene to give carbon dioxide and liquid water is $780.96\ \text{kcal mol}^{-1}$. The heat required to vaporize one mole of benzene is 8.2 kcal and one mole of water 10.5 kcal. Calculate the heat of combustion of benzene from the bond energies given in Table 4-3 and determine the extent to which benzene is *more*, or *less*, stable than expected from bond energies shown.

Exercise 4-24 Suppose we assume the following bond energies (kcal):

$\equiv C-H$	120	$C \equiv C$	230
$=C-H$	104	$C=C$	167
$-C-H$	98	$C-C$	88

(4.E.4)

What corresponding values would we have to assign to $C-Br$ bonds if the ΔH^0 values calculated for the reactions $HC \equiv CH + Br_2 \rightarrow BrHC{=}CHBr$ and $BrHC{=}CHBr + Br_2 \rightarrow CHBr_2CHBr_2$ are to be exactly the same as those calculated using only the bond energies

from Table 4-3? Show your reasoning.

Exercise 4-25 Explain why there is an increasingly poor correlation between ΔH^0 and the equilibrium constant K_{eq} for the formation of methane, propane, hexane, and nonane from solid carbon and hydrogen gas (Table 4-5).

Exercise 4-26 The ΔH^0 values for formation of cyclohexane from 1-hexene and of hydrogen chloride from hydrogen and chlorine differ by less than $3\ \text{kcal mol}^{-1}$ but the respective equilibrium constants are different by a factor of 10^7. Explain.

Exercise 4-27* The entropy change ΔS^0 for the formation of chloroethane by chlorination of ethane is $+0.5$ e.u., and for the formation of chloroethane by combination of hydrogen chloride with ethene ΔS^0 is -31 e.u. Explain.

$$\begin{aligned} &CH_3{-}CH_3 + Cl_2 \rightarrow CH_3CH_2Cl + HCl \quad \Delta S^0 = +0.5\ \text{e.u.} \\ &CH_2{=}CH_2 + HCl \rightarrow CH_3CH_2Cl \qquad\quad \Delta S^0 = -31\ \text{e.u.} \end{aligned} \tag{4.E.5}$$

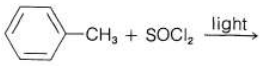
Exercise 4-28 Investigate the energies (ΔH^0) of possible chain mechanisms for the light-induced monobromination of methane and compare with those for chlorination. What are the prospects for iodination of methane?

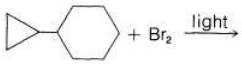
Exercise 4-29 The heat of combustion of cyclopropane, $(CH_2)_3$, to give carbon dioxide and liquid water is $499.8\ \text{kcal mol}^{-1}$. Show how this value, assuming normal C–H bond strengths, can be used to calculate the average C–C bond energy of cyclopropane.

Exercise 4-30 Write a mechanism analogous to that usually written for methane chlorination that would lead to production of hexachloroethane as in Exercise 4-20a. (This reaction is used for commercial production of hexachloroethane.)

Exercise 4-31 With reference to the data in Table 4-6, draw the structure(s) of the *major* organic product(s) to be expected from hydrogen abstraction in the following reactions:

a. $(CH_3)_3CH + Br_2 \xrightarrow{\text{light}}$

b. 

c. 

Exercise 4-32 Use the data in Table 4-6 to predict the products of the following reactions. Indicate any ambiguities that you encounter as the result of insufficient data.

a. $CH_2{=}CHCH_3 + Cl\cdot \rightarrow$

b. $CCl_3Br{+}CH_3CH_2\cdot \rightarrow$

c. $CH_3SH{+}CH_3CH_2\cdot \rightarrow$

d. $H_2O_2 \xrightarrow{\text{heat}}$

Exercise 4-33* The oxidation of hydrocarbons by atmospheric oxygen to give hydroperoxides is called **autoxidation**:

$$RH + O_2 \rightarrow ROOH \tag{4.E.6}$$

It is a detrimental reaction because it leads to the deterioration of organic compounds exposed to air (e.g., rubber cracking). Furthermore, the product, ROOH, in common with virtually all organic compounds with $-O{-}O-$ bonds, has the potential of undergoing rapid decomposition on heating, which in fact may occur with explosive violence.

The mechanism of autoxidation is a radical-chain process that is initiated by formation of a hydrocarbon radical, R·.

a. Write the propagation steps for this reaction, using R· or ROO· as the chain-propagating radical. How do you expect that **antioxidants** added to materials such as rubber act to help protect them from autoxidation (see Section 4-4D).

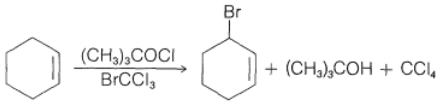
b. Use the data of Table 4-6 to determine the most favorable products of autoxidation of cyclohexene and methylbenzene $(C_6H_5CH_3)$.

c. It is extremely hazardous to store some organic chemicals for long periods of time in unsealed containers exposed to air and light. Aldehydes and ethers are particularly dangerous chemicals to store in this way. Explain why this should be so.

Exercise 4-34* The first step in preparing the very useful elastomer Hypalon involves treating a mixture of long-chain alkanes, $H(CH_2)_nH$, where $n = 50\text{-}200$, with sulfuryl chloride (SO_2Cl_2) in the presence of substances that can initiate radical-chain chlorination, as described in Section 4-5B. The product molecules contain many $C-Cl$ bonds and a few $C-SO_2-Cl$ bonds, the latter of which are subsequently used in a curing step to improve the physical properties. How can the chain mechanism for chlorination with SO_2Cl_2 be modified to account for the formation of $C-SO_2-Cl$ bonds?

Exercise 4-35* Explain why the product distribution in the chlorination of propane by sulfuryl chloride is expected to differ according to whether the hydrogen-abstraction step is accomplished by $Cl\cdot$ or $\cdot SO_2Cl$.

Exercise 4-36* *tert*-Butyl hypobromite is a radical brominating agent that is similar to *tert*-butyl hypochlorite (Exercise 4-18*), but is less easily prepared than the hypochlorite. A good substitute, provided radical bromination is possible, is a mixture of $BrCCl_3$ and $ce(CH_3)_3COCl$. Thus, bromination of cyclohexene results if a high ratio of bromotrichloromethane to hypochlorite is used.



Suggest how this reaction is initiated and propagated, and explain why it is necessary to have an excess of bromotrichloromethane.

Exercise 4-37* Use the data of Table 4-6 and tin-hydrogen and tin-chlorine bond energies of 80 kcal and 120 kcal, respectively, to determine the overall feasibility of the following reaction:

a. Assume the reaction proceeds by a radical-chain mechanism and work out energetically feasible initiation and propagation steps.

b. Draw energy diagrams like those shown in Figure 4-4 that correspond to each of the propagation steps. Indicate clearly on your diagrams which step would be expected to have the highest activation energy (that is, be the slower step), which point on your curves corresponds to the transition state, and which energy differences correspond to the energy change (ΔG^0) in that step of the reaction (assume $T\Delta S^0 = 0$).

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CHAPTER OVERVIEW

5: Stereoisomerism of Organic Molecules

By now you should be familiar with *position isomers* wherein compounds of the same molecular formula differ because substituents, chain branches, and so on, are not at the same positions in the molecules. 1-Chloropropane and 2-chloropropane are straightforward examples of position isomers. A much more subtle form of isomerism is present when two *different* compounds have the *same* molecular formulas, the *same* substituent and chain-branching positions, and, indeed, even have the *same* names by all of the nomenclature rules we have given you so far. *Such isomers are different because their molecules have different arrangements of the atoms in space*. These are **stereoisomers** and this type of isomerism, called **stereoisomerism**, is of enormous importance to all areas of organic chemistry and biochemistry.

5.1: Prelude to Stereoisomerism
5.2: Configurational Isomers
5.3: Conformational Isomers
5.4: Representation of Organic Structure
5.5: The D, L Convention for Designating Stereochemical Configurations
5.6: Molecules with More Than One Chiral Center. Diastereomers
5.7: Some Examples of the Importance of Stereoisomerism to Biology. Biological Stereospeciflcity
5.E: Stereoisomerism of Organic Molecules (Exercises)

5.1: Contributors and Attributions

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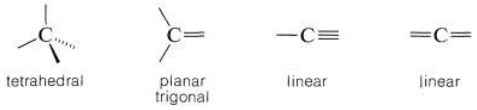
5.1: Prelude to Stereoisomerism

By now you should be familiar with *position isomers* wherein compounds of the same molecular formula differ because substituents, chain branches, and so on, are not at the same positions in the molecules. 1-Chloropropane and 2-chloropropane are straightforward examples of position isomers. A much more subtle form of isomerism is present when two *different* compounds have the *same* molecular formulas, the *same* substituent and chain-branching positions, and, indeed, even have the *same* names by all of the nomenclature rules we have given you so far. *Such isomers are different because their molecules have different arrangements of the atoms in space*. These are **stereoisomers** and this type of isomerism, called **stereoisomerism**, is of enormous importance to all areas of organic chemistry and biochemistry.

To understand stereoisomerism of carbon compounds, we must understand the ways in which the bonds to carbon atoms are arranged in space. As shown in Section 2-2A, this depends on whether the carbon atoms form single, double, or triple bonds to another atom. Thus, four single bonds to a carbon form a tetrahedral arrangement; two single bonds and one double bond to a carbon give a planar array with bond angles near 120°, while one single bond and one triple bond (or two double bonds) to a carbon are arranged linearly:



Finally, if you have not studied the material already, you may wish to return to the last part of Chapter 3 and become acquainted with the nomenclature of cycloalkanes, alkenes, cycloalkenes, and alkynes (Sections 3-2 to 3-4).

5.1.1: Contributors and Attributions

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5.2: Configurational Isomers

5.2.1: Geometric Isomerism

We have defined isomers in a very general way as nonidentical molecules that possess the same number and kind of atoms. However, there are several ways in which isomers can be nonidentical. Among the alkenes, 1- and 2-butene are position isomers, because in these compounds the double bond has a different position in the carbon chain:

Most, but not all alkenes, have stereoisomers that are not identical because of different *spatial* arrangements of the component atoms. Thus there are two stereoisomers of 2-butene that differ in the geometric arrangement of the groups attached to the double bond. In one isomer, both methyl groups are on the *same* side of the double bond (*cis*-2-butene) and in the other, the methyl groups are on *opposite* sides of the double bond (*trans*-2-butene):

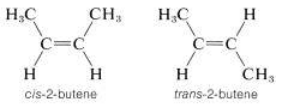


Figure 5-1, and the rigidity of the double bond is simulated in the model by a pair of stiff springs or bent sticks connecting the two carbons of the double bond.

It should be clear to you that there will be no cis-trans isomers of alkenes in which one end of the double bond carries identical groups. Thus we don not expect there to be cis-trans isomers of 1-butene or 2-methylpropene, and

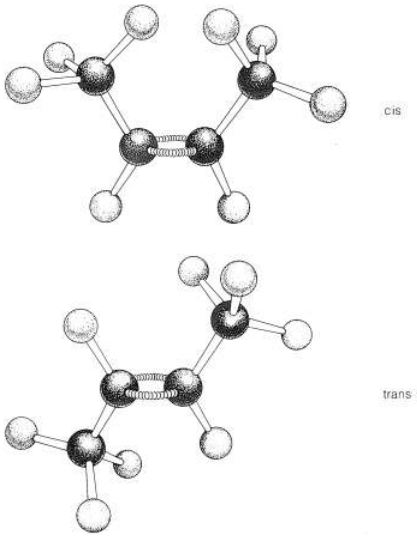
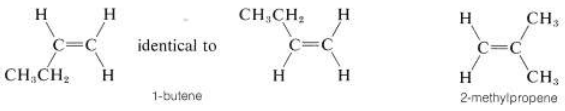


Figure 5-1: Ball-and-stick models of cis- and trans-2-butene

indeed none are known:



You may wish to verify this by making ball-and-stick models of these substances.

Ring formation also confers rigidity on molecular structure such that rotation about the ring bonds is prevented. As a result, stereoisomerism of the cis-trans type is possible. For example, 1,2-dimethylcyclopropane exists in two forms that differ in the arrangement of the two methyl groups with

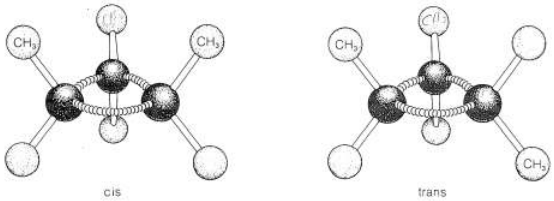
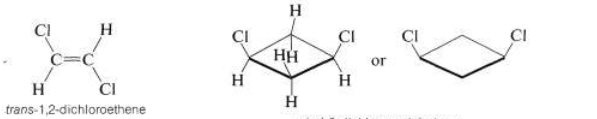


Figure 5-2: Ball-and-stick models of cis and trans isomers of 1,2-dimethylcyclopropane

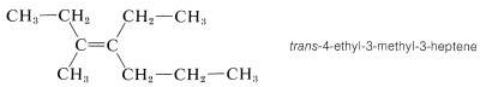
respect to the ring. In the cis isomer, the methyl groups both are situated above (or below) the plane of the ring and in the trans isomer they are situated one above and one below, as shown in Figure 5-2. Interconversion of these isomers does not occur without breaking one or more chemical bonds.

Stereoisomers that do not interconvert rapidly under normal conditions, and therefore are stable enough to be separated, specifically are called **configurational isomers**. Thus *cis*- and *trans*-2-butene are configurational isomers, as are *cis*- and *trans*-1,2-dimethylcyclopropane. The terms *cis-trans isomerism* or *geometric isomerism* commonly are used to describe **configurational isomerism** in compounds with double bonds and rings. When referring to the *configuration* of a particular isomer, we mean to specify its geometry. For instance, the isomer of 1,2-dichloroethene shown below has the trans configuration; the isomer of 1,3-dichlorocyclobutane has the cis configuration:



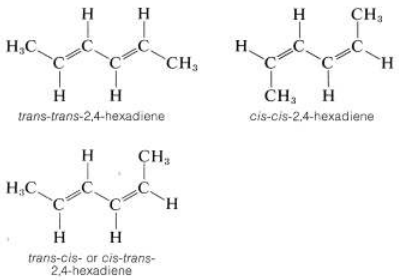
(These structures are drawn in perspective; the ring carbons are shown to be in a horizontal plane and the attached atoms are above or below this plane. If not all of the attached hydrogens are explicitly shown, as in the structure at right, their presence is understood.)

Cis-trans isomerism is encountered very frequently. By one convention, *the configuration of a complex alkene is taken to correspond to the configuration of the longest continuous chain as it passes through the double bond*. Thus the following compound is *trans*-4-ethyl-3-methyl-3-heptene, despite the fact that two identical groups are cis with respect to each other, because the longest continuous chain is trans as it passes through the double bond:

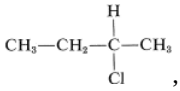


Notice that cis-trans isomerism is not possible at a carbon-carbon triple bond, as for 2-butyne, because the bonding arrangement at the triply bonded carbons is linear:

Many compounds have more than one double bond and each may have the potential for the cis or trans arrangement. For example, 2,4-hexadiene has *three* different configurations, which are designated as trans-trans, cis-cis, and trans-cis. Because the two ends of this molecule are identically substituted, the trans-cis becomes identical with cis-trans:



5.2.2: Chirality

The most important type of stereoisomerism is that which arises when molecules possess two structures that are not identical and also are mirror images of one another. This is not a difficult or unfamiliar concept. Many things around us, such as our hands, and pairs of shoes, are not identical and also are mirror images of one another. In the same way, nonidentical molecules exist in which the only distinction between them is that one is the mirror image of the other. A common statement is that such isomers are mirror images of one another, but these images are *not* "superimposable." A simple example of this type of stereoisomerism is 2-chlorobutane,  , which can exist in two spatial configurations, 1 and 2, that correspond to reflections of each other. These isomers are specifically called **enantiomers**.

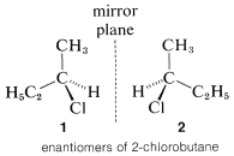


Figure 5-3. If you put CH_3 and CH_3 together, and C_2H_5 and C_2H_5 together, you find that Cl and Cl are on opposite sides, and H and H are on opposite sides. No matter how you turn the models around, they cannot be superimposed unless you break bonds at the number 2 carbon and interchange the positions of any two atoms or groups.

Compounds that lack **reflection symmetry** - meaning that they are *not* identical with their mirror images - are said to be **chiral** (pronounced "ki-rall", rhymes with spiral). This term is derived from the Greek word $\chi\epsilon\iota\rho$ = hand; and "handedness" or **chirality** is a property of **dissymmetric** molecules such that *two* configurational isomers are possible that are nonidentical mirror images. Compounds that possess reflection symmetry - meaning that they are identical with their mirror images - are said to be **achiral**. Enantiomers are not possible for achiral compounds. An **enantiomeric pair** is a pair of substances whose molecules are *nonidentical* mirror images.

The pressing question at this point is how can we tell whether a substances will be chiral or achiral. The most common origin of chirality in molecules, and the one originally recognized by van't Hoff and Le Bel, is the presence of one or more atoms, usually carbon atoms, each of which forms coplanar bonds to *four different atoms or groups*. This is the case for 2-chlorobutane, because the second tetrahedral carbon along the chain is bonded to four different groups: hydrogen, chlorine, methyl, and ethyl. Therefore there is a pair of enantiomers, 1 and 2. Another example is 2-bromo-2-chloro-1,1,1-trifluoroethane, which is a widely used inhalation anaesthetic. The four different groups in this case are hydrogen, chlorine, bromine, and trifluoromethyl; the pair of enantiomers is shown in Structures 3 and 4:

The atom that carries the four different substituents in 1 and 2, or 3 and 4, is called a **chiral atoms** or **chiral center**. The latter is the more general term because, as we shall see later (Section 13-5A), dissymmetry in molecules need not be centered at an atom.[1]

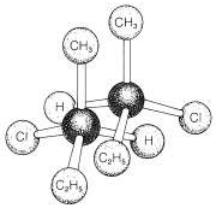
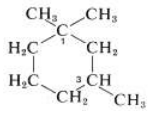


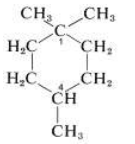
Figure 5-3: Use of ball-and-stick models to show nonidentity of the enantiomers of 2-chlorobutane, 1 and 2

In evaluating a chemical structure for chirality, you should look for carbons carrying four *different* attached groups. There may be more than one chiral carbon, and you should be alert to the fact that structural differences in the attached groups do not necessarily show up at the first, or even the second, position along a chain. As an example, consider the chirality of 1,1,3-trimethylcyclohexane,



1,1,3-trimethylcyclohexane

Carbons $C2$, $C4$, $C5$, and $C6$ are clearly achiral because each is connected to two identical groups, which for these atoms are hydrogens. The same is true for $C1$ because it is connected to two CH_3 groups. You might conclude that $C3$ also is an achiral position because it is connected to two CH_2 groups. But this would be wrong. If you look farther, you will see that the groups attached to $C3$ actually are different and are H, CH_3, $-CH_2CH_2CH_2-$, and $-CH_2C(CH_3)_2$. Therefore 1,1,3-trimethylcyclohexane has a chiral center at $C3$. In contrast, the 1,1,4-isomer has no chiral centers because the groups attached to the ring at $C4$ are identical:



1,1,4-trimethylcyclohexane

Several other terms that we shall use frequently in addition to chirality are **racemic mixture**, **resolution**, and **racemization**. A mixture of *equal* amounts of both enantiomers is a **racemic mixture**; separation of a racemic mixture into its component enantiomers is a **resolution**, and the conversion of either enantiomer into equal parts of both is called **racemization**.

5.2.3: Optical Activity

Until recently, the phenomenon of chirality has been better known as **optical isomerism**, and configurational isomers that are enantiomers were referred to as **optical antipodes**. The reasons for this are mainly historical. It was discovered early in the nineteenth century that many compounds, whether solid, liquid, or gas, have the property of rotating the plane of polarization of polarized light and can be said to be "**optically active**." A satisfactory explanation of the origin of optical activity came much later and developed in its modern form from the classic researches of Louis Pasteur, and from the concept of the three-dimensional carbon atoms expressed independently by J. H. van't Hoff and J. A. Le Bel.[2]

Pasteur's contribution to stereochemistry came as a result of his studies of the shapes of crystals of tartaric acid, $HO_2C-CHOH-CHOH-CO_2H$, and its salts. Tartaric acid, a by-product of wine production, was known to be optically active, and Pasteur showed that it, and nineteen different salts of it, all formed crystals that were *not* identical with their mirror images. A different substance known as "racemic acid," for which we can write the same condensed formula, $HO_2C-CHOH-CHOH-CO_2H$, was known to be optically *inactive*, and Pasteur expected that when he crystallized this acid or its salts he would obtain crystals that would be identical with their mirror images. However, crystallization of the sodium ammonium salt of racemic acid from water at temperatures below 28° gave crystals of *two* different shapes and these shapes were mirror images of one another. Pasteur carefully picked apart the two kinds of crystals and showed that one of them was identical with the corresponding salt of tartaric acid, except that it rotated the plane of polarization of polarized light in the opposite direction. This separation of racemic acid into two optically active forms now is called a "resolution of racemic acid."

On the basis of his discoveries, Pasteur postulated that "optical isomerism" had to be related to the molecular dissymmetry of substances such that nonidentical mirror-image forms could exist. However, it remained for van' t Hoff and Le Bel to provide, almost simultaneously, a satisfactory explanation at the molecular level. In his first published work on tetrahedral carbon van't Hoff said "...it appears more and more that the present constitutional formulae are incapable of explaining certain cases of isomerism; the reason for this is perhaps the fact that we need a more definite statement about the actual positions of the atoms."[3] He goes on to discuss the consequences of the tetrahedral arrangements of atoms about carbon, explicitly in connection with optical isomerism and geometric, or cis-trans, isomerism.

It is not easy for the chemist of today to appreciate fully the contributions of these early chemists because we have long accepted the tetrahedral carbon as an experimentally established fact. At the time the concept was enunciated, however, even the existence of atoms and molecules was questioned openly by many scientists, and to ascribe "shapes" to what in the first place seemed like metaphysical conceptions was too much for many to accept.

5.2.4: Properties of Enantiomers

Optical activity is an experimentally useful property and usually is measured as the angle of rotation (α) of the plane of polarization of polarized light passing through solutions of the substances under investigation (Figure 5-4). Where measurable optical activity is present, it is found that one enantiomer rotates the plane of polarization in one direction, whereas the other causes the plane to rotate *equally* but in the opposite direction. With reference to the plane of incident light, the enantiomer that rotates the plane to the right is called *dextrorotatory* and is symbolized by either *d* or (+); the enantiomer that rotates the plane to the left is *levorotatory*, symbolized by *l* or (−). A racemic mixture then can be designated as *dl* or (±), and will have no net optical rotation. It is very important to know that *d*, *l*, (+), or (−) do not designate configurations. Thus, although (+)-2-butanol actually has configuration 5 and (−)-2-butanol has configuration 6, there is no simple way to predict that a particular sign of rotation will be associated with a particular configuration. Methods used in assigning the true configurations to enantiomers will be discussed later.

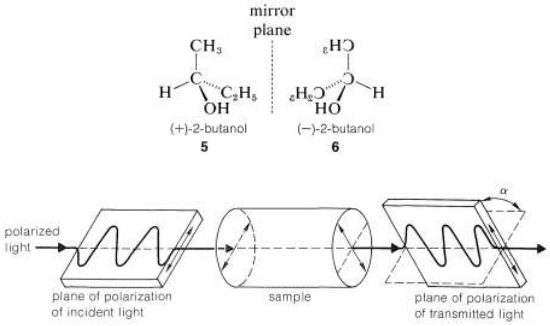


Figure 5-4: Schematic representation of the rotation of the plane of polarization of polarized light by an optically active compound. Plane-polarized light is different from ordinary light in that its electrical component vibrates in a plane rather than in all directions. The angle α is the angle between the plane of polarization of light entering the sample and the plane of polarization of the emerging light.

A very important point to keep in mind about any pair of enantiomers is that they will have identical chemical and physical properties, except for the signs of their optical rotations, with one important proviso: All of the properties to be compared must be determined using achiral reagents in a solvent made up of achiral molecules or, in short, in an *achiral environment*. Thus the melting and boiling points (but not the optical rotations) of 5 and 6 will be identical in an achiral environment. How a chiral environment or chiral reagents influence the properties of substances such as 5 and 6 will be considered in Chapter 19.

[1]In the older literature, chiral centers often are called **asymmetric centers** and you may be confused by the difference between *asymmetric* and *dissymmetric*. Both asymmetric and dissymmetric molecules (or objects) are chiral. An asymmetric object has no symmetry at all and looks different from all angles of view. Formulas 3 and 4 represent asymmetric molecules. A dissymmetric molecule is chiral, but looks the same from more than one angle of view. A helical spring is dissymmetric - it looks the same from each end. We will encounter dissymmetric molecules later.

[2]The tetrahedral carbon was first proposed by E. Paterno in 1869 (see Section1-1E), but he apparently did not recognize its implications for chirality. These implications were recognized first by van't Hoff and Le Bel, with van't Hoff proceeding on the basis of bonds to carbon being directed to the corners of a regular tetrahedron. Le Bel was opposed to such a rigid formulation of the bonds to carbon.

[3]An interesting account and references to van't Hoff's early work can be found in "The Reception of J. H. van't Hoff's Theory of the Asymmetric Carbon" by H. A. M. Snelders, *J. Chem. Educ.* **51**, 2 (1974). A century has passed since van't Hoff first published his theory, which he did before he obtained his doctoral degree from the University of Utrecht. van't Hoff was the first recipient of the Nobel Prize in chemistry (1901) for his later work in thermodynamics and chemical kinetics.

5.2.5: Contributors and Attributions

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5.3: Conformational Isomers

When using ball-and-stick models, if one allows the sticks to rotate in the holes, it will be found that for ethane, $CH_3 - CH_3$, an infinite number of different atomic orientations are possible, depending on the angular relationship (the so-called *torsional* angle) between the hydrogens on each carbon. Two extreme orientations or **conformations** are shown in Figure 5-5. In end-on views of the models, the *eclipsed* conformation is seen to have the hydrogens on the forward carbon directly in front of those on the back carbon. The *staggered* conformation has each of the hydrogens on the forward carbon set between each of the hydrogens on the back carbon. It has not been possible to obtain separate samples of ethane that correspond to these or intermediate orientations because actual ethane molecules appear to have essentially "free rotation" about the single bond joining the carbons. Free, or at least rapid, rotation is possible around all $C - C$ *single* bonds, except when the carbons are part of a ring as in cyclopropane or cyclohexane.

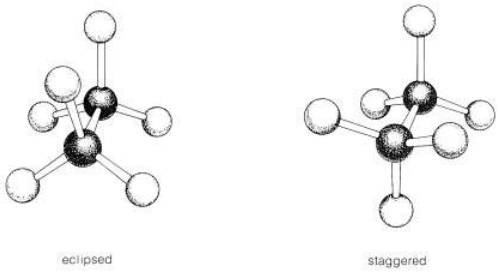

Figure 5-5: Two rotational conformations of ethane

For ethane and its derivatives, the staggered conformations are more stable than the eclipsed conformations. The reason for this in ethane is not wholly clear, but doubtless depends on the fact that, in the staggered conformation, the $C - H$ bonding electrons are as far away from one another as possible and give the least interelectronic repulsion. With groups larger than hydrogen atoms substituted on ethane carbons, space-filling models usually show less interference (**steric hindrance**) for staggered conformations than for eclipsed conformations.

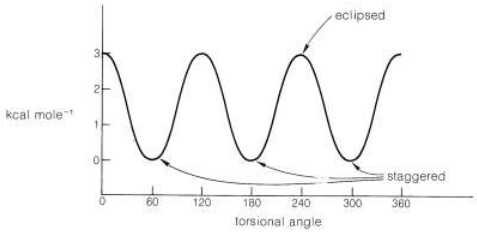

Figure 5-6: Potential-energy curve for rotation about the $C - C$ bond in ethane

The energy difference between eclipsed and staggered ethane is approximately $3\ \text{kcal mol}^{-1}$.[4] This is shown in Figure 5-6 as the height of the peaks (eclipsed forms) separating the valleys (staggered forms) on a curve showing the potential energy of ethane as the methyl groups rotate with respect to each other through 360°. Rotation then is not strictly "free" because there is a 3-kcal mol^{-1} energy barrier to overcome on eclipsing the hydrogens. Even so, the barrier is low enough that rotation is very rapid at room temperature, occurring on the order of 10^{10} times per second.

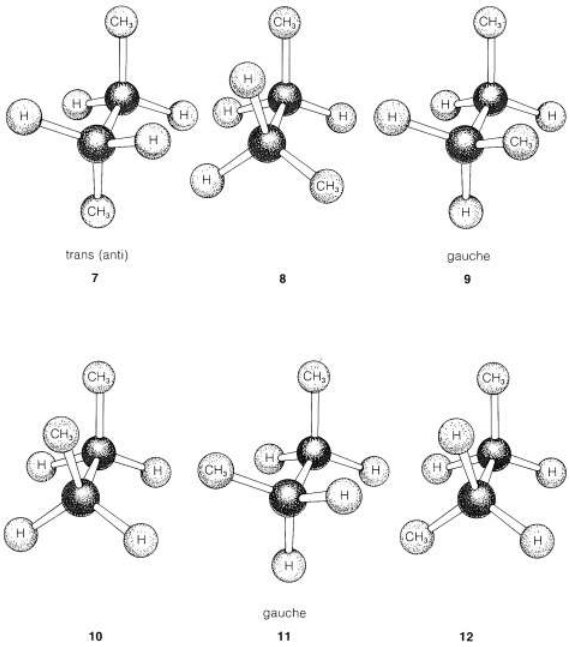

Figure 5-7: Six rotational conformations about the 2,3 $C-C$ bond of butane. The forward groups are shown here as rotating counterclockwise with respect to the rear groups.

In butane, $CH_3CH_2CH_2CH_3$, a 360° rotation about the central $C-C$ bond allows the molecule to pass through three different eclipsed arrangements (8, 10, 12), and three different staggered arrangements (7, 9, 11), as shown in Figure 5-7. Experiment shows that butane favors the staggered form 7 in which the methyl groups are farthest apart. This form is called the *anti* (or *trans*) conformation (sometimes **conformer**), and 63% of the molecules of butane exist in this form at room temperature. The other two staggered forms 9 and 11 are called *gauche* (*syn* or *skew*) conformations and have a torsional angle of 60° between the two methyl groups. Forms 9 and 11 actually are nonidentical mirror images, but bond rotation is so rapid that the separate enantiomeric conformations cannot be isolated. The populations of the two gauche forms are equal at room temperature (18.5% of each) so any optical rotation caused by one form is exactly canceled by an opposite rotation caused by the other.

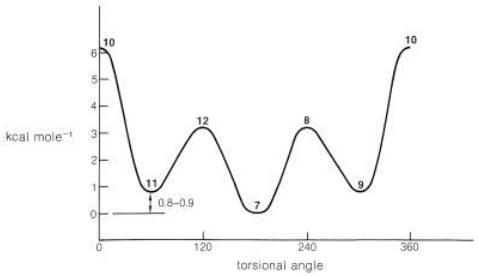

Figure 5-8: Conformational energies and rotational barriers in butane, the difference in energy between the anti and gauche forms is 0.8-0.9 kcal mol^{-1}. The energies are relative to conformation 7 as zero.

The populations of the eclipsed forms of butane, like the eclipsed forms of ethane, are small and represent energy maxima for the molecule as rotation occurs about the central $C-C$ bond. The energy differences between the butane conformations are represented diagrammatically in Figure 5-8. The valleys correspond to staggered forms and the energy difference between the anti and gauche forms is 0.8-0.9 kcal mol^{-1}.

Pioneering work in the field of conformational analysis was contributed by O. Hassel (Norway) and D. R. H. Barton (Britain), for which they shared the Nobel Prize in chemistry in 1969. Hassel's work involved the physical determination of preferred conformations of small molecules, whereas Barton was the first to show the general importance of conformation to chemical reactivity. Study of conformations and conformational equilibria has direct application to explaining the extraordinary specificity exhibited by compounds of biological importance. The compounds of living systems are tailor-made to perform highly specific or even unique functions by virtue of their particular configurations and conformations.

[4]This is by no means a trivial amount of energy - the difference in energy between the staggered and eclipsed forms of $1\ \mathrm{mol}$ ($30\ \mathrm{g}$) of ethane being enough to heat $30\ \mathrm{g}$ of water from 0° to 100°.

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5.4: Representation of Organic Structure

Many problems in organic chemistry require consideration of structures in three dimensions, and it is very helpful to use molecular models to visualize the relative positions of the atoms in space. Unfortunately, we are forced to communicate three-dimensional concepts by means of drawings in two dimensions, and not all of us are equally gifted in making or visualizing such drawings. Obviously, communication by means of drawings, such as those in Figure 5-5 and 5-7, would be impractically difficult and time consuming, thus some form of abbreviation is necessary.

5.4.1: Conformational Drawings

Two styles of abbreviating the eclipsed and staggered conformations of ethane are shown in Figure 5-9; in each, the junction of lines representing bonds is assumed to be a carbon atom. Using the "sawhorse" convention, we always consider that we are viewing the molecule slightly from above and from the right, and it is understood that the central $C-C$ bond is perpendicular to the plane of the paper. With the "Newman" convention, we view the molecule directly down the $C-C$ bond axis so the carbon in front hides the carbon behind. The circle is only a visual aid to help distinguish the bonds of the back carbon from those of the front carbon. The rear atoms in the eclipsed conformation are drawn slightly offset from a truly eclipsed view so the bonds to them can be seen.

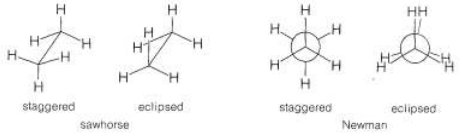


Figure 5-9: Conventions for showing the staggered and eclipsed conformations of ethane

The staggered conformations of butane are shown in Figure 5-10 in both the sawhorse and Newman conventions. There is little to choose between the two conventions for simple ethane derivatives, but the sawhorse convention is strongly favored for representing the conformations of ring compounds such as cyclohexane. The resemblance between the gauche forms of butane and the most stable conformation of cyclohexane is strikingly apparent in the sawhorse representations of both, as shown in Figure 5-10. Notice that the ring carbons of cyclohexane do not lie in one plane and that all the bond angles are tetrahedral. The conformations of this interesting and important molecule are discussed in detail in Chapter 12.

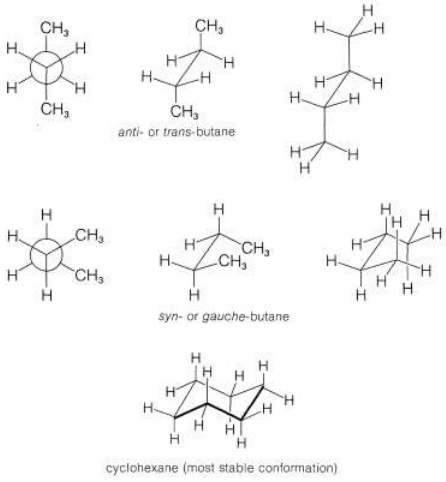
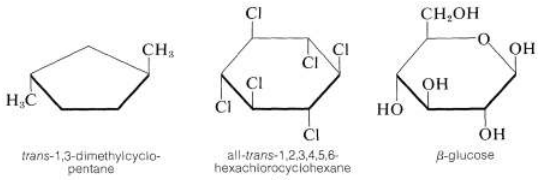


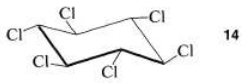
Figure 5-10: Sawhorse and Newman conventions for showing the staggered conformations of butane. Only one gauche form is shown. Cyclohexane is shown to emphasize the resemblance of its stable conformation to the gauche conformation of butane.

Despite the usefulness of the sawhorse-type drawing, cyclic molecules often are drawn with planar rings and distorted bond angles even though the rings actually may not be planar. The reason for this is partly that planar rings are easier to draw and partly to emphasize the configuration of attached groups, irrespective of the conformation. Typical examples follow:



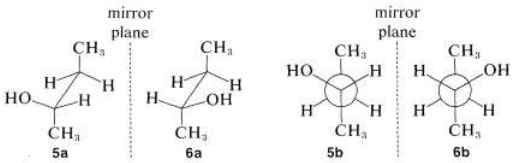
13

Generally we shall avoid such drawings and suggest that it is much better to learn to draw molecules in as nearly correct perspective as possible. Once the sawhorse representation of cyclohexane is mastered, it is almost as easy to drawn 14 as 13, and 14 is much more informative about the shape of the molecule:



14

We have indicated how the enantiomers of 2-butanol differ by drawing their strutures 5 and 6 (Section 5-1D) in perspective to show the tetrahedral configuration of substituents at the chiral carbon. This configuration also can be represented by the sawhorse or Newman formulas using any one of the several possible staggered conformations such as $5a$ and $6a$ or $5b$ and $6b$:



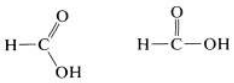
5a 6a 5b 6b

These drawings are clear but can be cumbersome, particularly for more complex molecules, and we shortly shall describe other means of representing the configurations of chiral molecules.

5.4.2: Planar Structures

Planar molecules such as benzene, ethene, and methanal are best drawn in the plane of the paper with bond angles of about 120°. When it is desired to draw them as viewed on edge (out of plane) care must be taken to provide proper perspective. The forward bonds can be drawn with slightly heavier lines; a tapered bond indicates direction, the wide end pointing toward the viewer and the narrow end away from the viewer (Figure 5-11). Barred lines are used here to indicate a rear or receding bond (many writers use dashed lines, but these may be confused with other uses of dashed lines, as for partial bonds).

However, you will find other representations of planar carbons with rather grossly distorted bond angles. For example, methanoic acid is planar with nearly 120° bond angles, but often is drawn with $H-C-O$ angles of 90° and 180°:



methanoic acid (formic acid)

The distorted structures commonly are used to save space and, regretfully, we have to use them very frequently for this reason.

5.4.3: Projection Formulas

The sawhorse or Newman representations of 2-butanol, $5a$ and $5b$ and $6a$ and $6b$, are excellent for showing the arrangements of the atoms in conformations, but are needlessly complex for representing the stereochemical *configuration*. **Fischer projection formulas** are widely used to show configurations and are quite straightforward, once one gets the idea of what they represent..

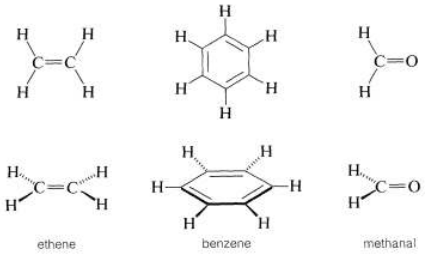


Figure 5-11: Front and side views of planar molecules showing some conventions used to indicate perspective

The projection formulas of 2-butanol are $5c$ and $6c$:

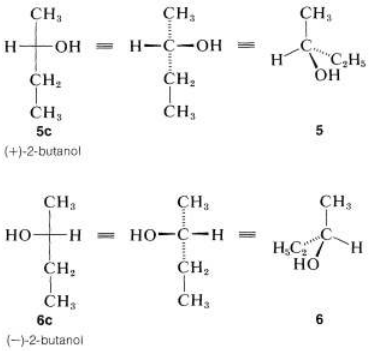


Figure 5-12.

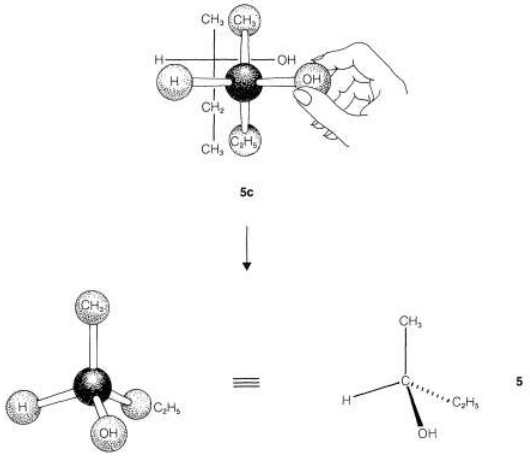


Figure 5-12: Procedure for relating a projection formula to a configurational drawing with the aid of a ball-and-stick model. Assemble the ball-and-stick model over the projection formula (here $5c$) so that the groups are arranged by the convention of the formula (horizontal bonds out, vertical bonds back), then turn the model so the appropriate groups, here CH_3 and H, are parallel to the plane of the paper and make the perspective drawing agree with the model. The reverse procedure translates the perspective drawing into the projection formula.

5.4.4: Contributors and Attributions

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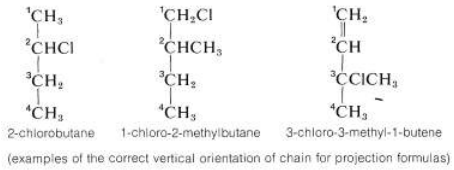
5.5: The D, L Convention for Designating Stereochemical Configurations

We pointed out in Chapter 3 the importance of using systematic names for compounds such that the name uniquely describes the structure. It is equally important to be able to unambiguously describe the configuration of a compound. The convention that is used to designate the configurations of chiral carbons of naturally occurring compounds is called the D, L system. To use it, we view the molecule of interest according to the following rules:

1. The main carbon chain is oriented vertically with the *lowest* numbered carbon at the *top*. The numbering used for this purpose must follow the IUPAC rules:

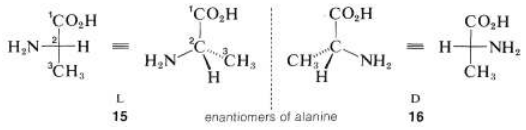


(examples of the correct vertical orientation of chain for projection formulas)

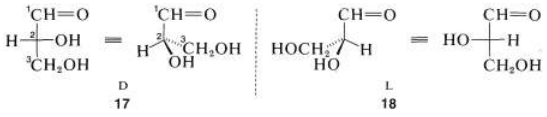
2. Next, the structure must be arranged at the particular chiral carbon whose configuration is to be assigned so the horizontal bonds to that carbon extend toward you and the vertical bonds extend away from you. This arrangement will be seen to be precisely the same as the convention of projection formulas such as $5c$ and $6c$ (Section 5-3C).

3. Now the relative positions of the substituents on the horizontal bonds at the chiral centers are examined. If the main substituent is the *left* of the main chain, the L configuration is assigned; if this substituent is on the *right*, the D configuration is assigned.

For example, the two configurations of the amino acid, alanine, would be represented in perspective or projection as 15 and 16. The carboxyl carbon is $C1$ and is placed at the top. The substituents at the chiral carbon connected to the horizontal bonds are amino ($-NH_2$) and hydrogen. The amino substituent is taken to be the main substituent; when this is on the *left* the acid has the L configuration, and when it is on the *right*, the D configuration. All of the amino acids that occur in natural proteins have been shown to have the L configuration.



Glyceraldehyde, $CH_2OHCHOHCHO$, which has one chiral carbon bonded to an aldehyde function, hydrogen, hydroxyl, and hydroxymethyl (CH_2OH), is of special interest as the simplest chiral prototype of sugars (carbohydrates). Perspective views and Fischer projections of the D and L forms correspond to 17 and 18, respectively, where the carbon of the aldehyde function ($-CH=O$) is $C1$:



The D, L system of designating configuration only can be applied when there *is* a main chain, and when we can make an unambiguous choice of the main substituent groups. Try, for instance, to assign D and L configurations to enantiomers of bromochlorofluoromethane. An excellent set of rules has been worked out for such cases that leads to unambiguous configurational assignments by what is called the R, S **convention**. We discuss the R, S system in detail in Chapter 19 and, if you wish, you can turn to it now. However, for the next several chapters, assigning configurations is much less important to us than knowing what kinds of stereoisomers are possible.

5.5.1: Contributors and Attributions

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5.6: Molecules with More Than One Chiral Center. Diastereomers

We have seen examples of molecules with one chiral center that exist in two mirror-image configurations, which we call enantiomers. What happens when there is more than one chiral center? How many stereoisomers should we expect? Consider the stereoisomers of the important amino acid, threonine, (2-amino-3-hydroxybutanoic acid). For this substance, if we write all of the possible configurations of its *two* chiral carbons, we have *four* different projection formulas, 19-22, corresponding to four different stereoisomers:

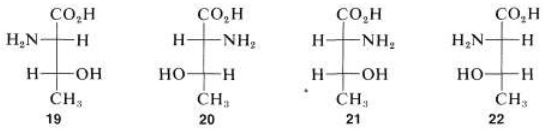


Figure 5-12) and by putting the model over 20-22 verify that none of these projections have the configurations of both chiral carbons the same as your model of 19.

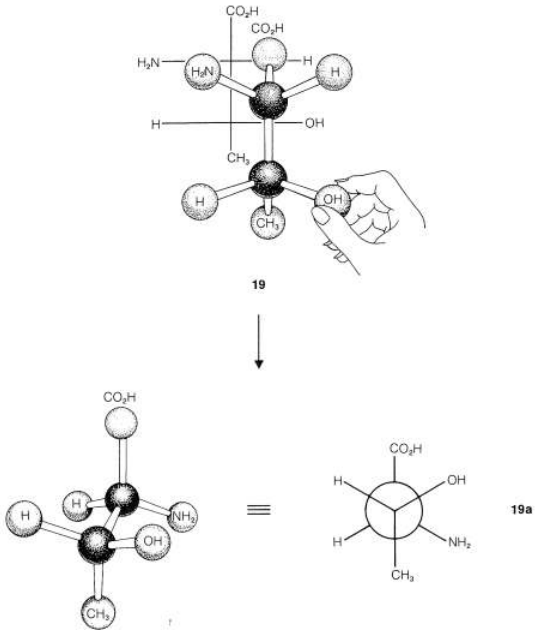
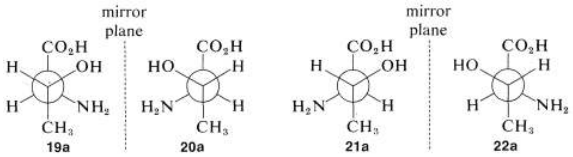


Figure 5-12, except that configurations at each of two atoms are involved. Next, the model is turned and rotated around the center $C-C$ bond to put the methyl and carboxyl groups anti to one another. The Newman formula is then drawn to correspond to the ball-and-stick model.

Because each chiral center added to a chain doubles the number of possible configurations, we expect eight different stereoisomers with three chiral carbons, sixteen with four, and so on, the simple rule the is 2^n possible different stereoisomers for n chiral centers. As we shall see later, this rule has to be modified in some special cases.

What is the relationship between stereoisomers 19-22? This will be clearer if we translate each of the projection formulas into a three-dimensional representation, as shown in Figure 5-13. You will be helped greatly if you work through the sequence yourself with a ball-and-stick model. Drawn as Newman projections, 19-22 come out as shown in 19a-22a:



It should be clear (and, if it isn't, ball-and-stick models will be invaluable) that 19a and (20a\) are mirror images of one another and that 21a and 22a are similarly mirror images.[5] What about other combinations such as 19a and 21a or 20a and 22a? If you look at the pairs closely you will find that they are not mirror images and are not identical. Such substances, related to each other in this way

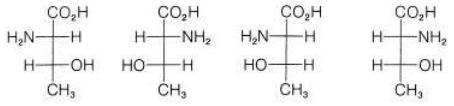
and which can be converted one into the other only by changing the configurations at one or more chiral centers, are called **diastereomers**.

The difference between enantiomers and diastereomers is more than just geometry. Diastereomers have substantially different chemical and physical properties, whereas enantiomers have identical physical properties (apart from their optical rotations). This is illustrated in Table 5-1 for the threonine stereoisomers. The reason for the difference in physical properties between diastereomers can be seen very simply for a substance with two chiral centers by noting that a right shoe on a right foot (D, D) is a mirror image, or has the same physical properties, as a left shoe on a left foot (L, L), but is not a mirror image, nor does it have the same physical properties, as a left show on a right foot (L, D), or a right shoe on a left foot (D, L).

5.6.1: Meso Compounds (Achiral Diastereomers)

All of the threonine stereoisomers 19-22 are chiral substances; that is, they are not identical with their mirror images. However, it is important to recognize that not all diastereomers are chiral. To illustrate this point, we return to the tartaric acids mentioned previously in connection is Pasteur's discoveries (Section 5-1C).

Table 5-1
Reported Physical Properties of the Stereoisomers of Threonine, 2-Amino-3-hydroxybutanoic Acid



Common name:	L-threonine[a]	D-threonine	L-allothreonine	D-allothreonine
Mp, °C:	251–253	251–252	268–272	269–272
Specific rotation, $[\alpha]_\lambda^{25}$ in H_3O^+[b]:	−28.5°	+28.5°	+9.6°	−9.1°

[a]This is the naturally occurring stereoisomer and is an important constituent of many proteins.
[b]The specific rotation $[\alpha]_\lambda^{25}$ is obtained from a measured rotation α of the plane of polarization of polarized light (see Figure 5-4) by the equation $[\alpha]_\lambda^t = 100\alpha/lc$, in which l is the length of the sample in decimeters, c is the concentration in g per 100 ml, t is the temperature, and λ the wavelength of the light (D stands for sodium D light); see Section 19-2.

Proceeding as we did for threonine, we can write four projection formulas for tartaric acid, 2,3-dihydroxybutanedioic acid, as shown by 23-26:

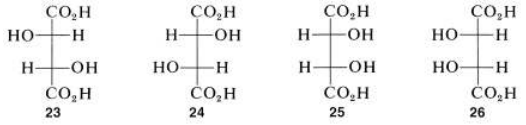
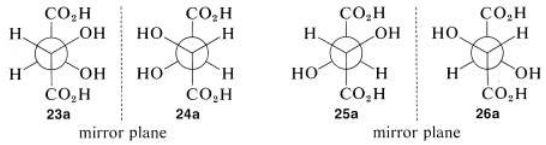
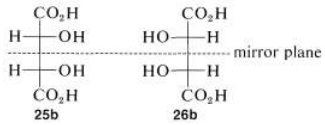


Figure 5-13.)

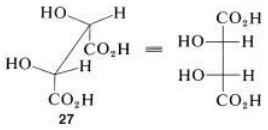


There are two pairs of mirror images 23a and 24a, as well as 25a and 26a. However, what will not be so immediately clear, but what you *must* verify for yourself is that 25a and 26a are, in fact, identical. This means that 25a and 26a are representations of a *single* achiral substance, identical with its mirror image. *Substances that have chiral centers but are themselves achiral are called meso compounds*.

The condition that makes possible the existence of meso compounds is an appropriate degree of molecular symmetry. There are several kinds of such molecular symmetry. In the case of projection formulas 25 (or 26) there is a **plane of symmetry**, which means that a plane can be placed through the molecule such that *one half of the molecule is a mirror image of the other half*. The mirror plane for *meso*-tartaric acid can be seen easily from its projection formulas 25b and 26b. These two formulas are superimposable if one is rotated 180° in the plane of the paper.



The Newman representations $25a$ and $26a$ of *meso*-tartaric acid does *not* have a mirror plane. Why is it different from the Fischer projections in this respect? The reason is that the projection formulas represent a particular *eclipsed* conformation 27 of *meso*-tartaric acid that does have a mirror plane:



Therefore, if you are confronted with a particular sawhorse or Newman formula and you have to decide whether it represents a *meso* compound, the best procedure is to make a ball-and-stick model of the conformation and then rotate around the bonds to see if it can be brought into a conformation (staggered or eclipsed) that has a plane of symmetry (such as 27) or is identical with its mirror image.

As expected from our previous discussions diastereomers of tartaric acid have different physical properties (Table 5-2).

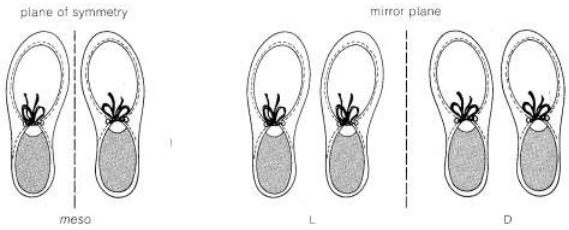
If you find yourself confused about the D, L and *meso* forms of tartaric acid, a simple analogy may help keep matters straight. Consider three sets of shoes. A right shoe beside a left shoe is a meso combination with a plane of symmetry. A left shoe next to a left shoe is not identical with, but is

Table 5-2
Physical Properties of Tartaric Acids

Tartaric acid	$[\alpha]_D^{20}$ in H_2O	Melting point, °C	Density, g ml^{-1}	Solubility in H_2O, g/100 ml at 25°
meso	–	140	1.666	120[19°]
(–)	−11.98°	170	1.760	147
(+)	+11.98°	170	1.760	147
(±)[a]	–	205	1.788	25

[a]Racemic acid (Section 5-1C) has a higher melting point and lower solubility than either of its constituents, (+)- or (–)-tartaric acid. This is a result of how the molecules fit together in the crystals. Apparently a stronger crystal is made by mixing the D and L molecules than can be made from either alone.

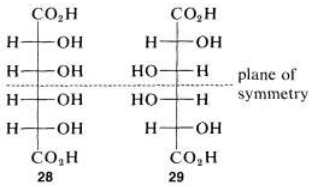
the mirror image of, a right shoe next to a right shoe. None of the three combinations are identical. Each right or left shoe corresponds to a right or left configuration of a tartaric acid carbon so the three sets correspond to *meso*-, L-, and D-tartaric acid, respectively.



There is another symmetry test for meso configurations that is applicable to staggered conformations and can be illustrated with the tartaric acids. If you make models of $25a$ and $26a$ you will find that they are mirror images *and* identical but, as we have said, they have no plane of symmetry. In this conformation, the molecules do have a **center of symmetry**. Thus a line drawn at any angle through the midpoint of the central $C-C$ bond of $25a$ (or $26a$) has an identical environment on each side of the midpoint. Another way of putting it is that each half of the molecule is the *photographic image* (i.e., reverse) of the other half. For a molecule with chiral centers, if its projection formula has a plane of symmetry or if we can find a rotational conformation with either a plane or center of symmetry, then it will be meso and achiral.

The idea that for every n chiral centers there can be 2^n different configurations will be true only if none of the configurations has sufficient symmetry to be identical with its mirror image. For every meso form there will be one less pair of enantiomers and one

less total number of possible configurations than is theoretically possible according to the number of chiral centers. At most, one meso compounds is possible for structures with four chiral centers. An example is offered by the meso forms of tetrahydroxyhexanedioic acid which, with four chiral atoms, have configurations 28 and 29:



[5]The same information can be obtained from projection formulas. You can see that projections 19 and 20 are mirror images and that 20, 21, or 22 can not be superimposed on 19. However, in some situations confusion can result in making such comparisons and it is important to be able to translate the projection formulas into ball-and-stick models or perspective drawings.

5.6.2: Contributors and Attributions

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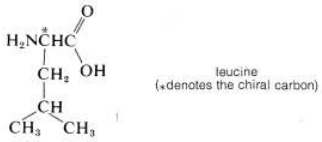
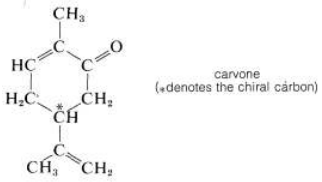
5.7: Some Examples of the Importance of Stereoisomerism to Biology. Biological Stereospecifl city

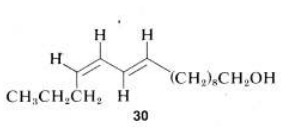
Symmetrical reagents do not differentiate between the members of a pair of enantiomers for the same reason that an ordinary sock fits equally well on a right foot as on a left foot. However, asymmetric or chiral reagents can differentiate between enantiomers, especially by having at least some difference in reactivity toward them. A good analogy is the comparison between the ease of putting a left shoe on a left foot and a left shoe on a right foot. The difference may not be very pronounced for simple compounds with only one or two chiral centers, but generally the larger and more complex that chiral reagent becomes, the greater is its selectivity or power to discriminate between enantiomers and diastereomers as well. The property of being able to discriminate between diastereomers is called *stereospecificity*, and this is an especially important characteristic of biological systems.

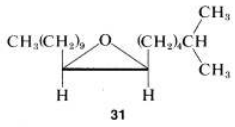
For example, our ability to taste and smell is regulated by chiral molecules in our mouths and noses that act as receptors to "sense" foreign substances. We can anticipate, then, that enantiomers may interact differently with the receptor molecules and induce different sensations. This appears to be the case. The two enantiomers of the amino acid, leucine, for example, have different tastes - one is bitter, whereas the other is sweet. Enantiomers also can smell different, as is known from the odors of the two carvones. One has the odor of caraway and the other of spearmint.



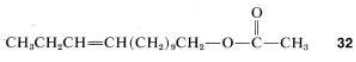


Some animals, and especially insects, rely on what amounts to a "sense-of-smell" for communication with others of their species. Substances synthesized by a particular species, and used to send messages in this way, are called **pheromones**. Many of these substances have rather simple molecular structures because they must be reasonably volatile and yet they are remarkably specific in the response they induce. When stereoisomerism is possible, usually only one isomer is effective. The sex attractant of the silkworm moth *Bombyx mori* has been identified as *trans*-10-*cis*-12-hexadecaden-1-ol, 30, familiarly known as "bombykol," and that of the gypsy moth is 2-methyl-*cis*-7-epoxy-octadecane, 31, or "disparlure":


30


31

There is hope that insect sex lures can be used to disrupt the mating pattern of insects and thereby control insect population. This approach to pest control has important advantages over conventional insecticides in that the chemical lures are specific for a particular species; also they are effective in remarkably low concentrations and are relatively nontoxic. There are problems, however, not the least of which is the isolation and identification of the sex attractant that is produced by the insects only in minute quantities. Also, synergistic effects are known to operate in several insect species such that not one but several pheromones act in concert to attract the opposite sex. Two notable pests, the European corn borer and the red-banded leaf roller, both use *cis*-11-tetradecenyl ethanoate, 32, as the primary sex attractant, but the pure cis isomer is ineffective unless a small amount of trans isomer also is present. The optimum amount appears to be between 4% and 7% of the trans isomer.


32

We shall discuss many other examples of biological stereospecificity in later chapters.

5.7.1: Contributors and Attributions

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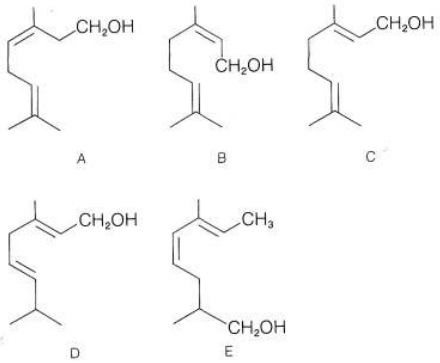
5.E: Stereoisomerism of Organic Molecules (Exercises)

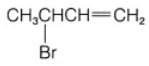
Exercise 5-1 Draw structures showing the configuration of the following compounds. You may wish to review the nomenclature of alkenes, given in Section 3-3.

a. *trans*-3-methyl-3-hexene
b. 2-chloro-*cis*-2,*trans*-heptadiene
c. (*cis*-1-propenyl)cyclobutane
d. *trans*-1,2-di-(*cis*-1-propenyl)cyclobutane

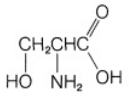
Exercise 5-2 Geraniol is a naturally occurring compound found in certain grasses and is used in perfumes to simulate the odor of roses. The IUPAC name for this compound is 3,7-dimethyl-*trans*-2,6-octadien-1-ol (where "-1-ol" signifies that there is an OH group on the lowest-numbered carbon of the chain). Select the correct structure from among the following:

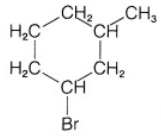


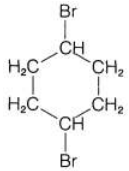
Exercise 5-3 Identify the chiral carbon atoms by an asterisk (*) in each of the following structures. If no chiral carbons are present, write *achiral*.

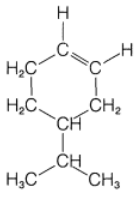
a. 

b. $CH_3CH_2CBr{=}CH_2$

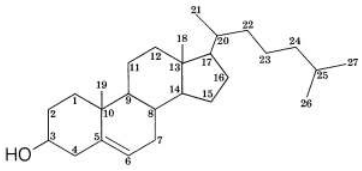
c. 

d. 

e. 

f. 

Exercise 5-4 How many chiral centers are evident in the structure of cholesterol? Identify them by the number of the carbon atom.



cholesterol

Exercise 5-5 The work of the German chemist Wislicenus on hydroxypropanoic acids was influential in the development of van't Hoff's ideas on stereoisomerism. By 1869, Wislicenus had established that there are three isomeric hydroxypropanoic acids, let us call them A, B, and C, of partial structure $C_2H_4(OH)(CO_2H)$. Isomer A was isolated from sour milk and Isomer B from a meat extract. Both A and B had the same physical properties, except for optical rotation, wherein A was levorotatory and B was dextrorotatory. Isomer C was not optically active and had considerably different physical and chemical properties from A or B. Work out structures A, B, and C in as much detail as you can from the information given.

Exercise 5-6 Examine the structures of β-carotene and vitamin A shown in Section 2-1 and Section 3-0 and determine the configuration at each of the double bonds in the chain attached to the ring(s). Are these substances chiral or achiral?

Exercise 5-7 Draw the staggered conformations of each of the following compounds using the indicated convention:

a. 2,3-dimethylbutane (sawhorse)
b. 1,2-dibromo-1,1,2,2-tetrafluoroethane (Newman)
c. the *d*,*l* isomers of 1-chloro-1-fluoroethane (Newman)

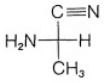
Exercise 5-8 Draw the conformation of 2,2,5,5-tetramethylhexane that you expect to be of lowest energy.

Exercise 5-9 Draw a staggered conformation in both the sawhorse and Newman representations that corresponds to the *configurations* shown in the projection formulas a-c.

a.

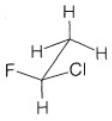
b.

c.

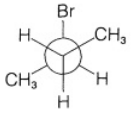


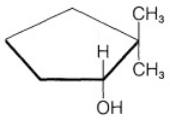
Exercise 5-10 Draw projection formulas that correspond to the specific *configurations* shown in the following structures:

a.

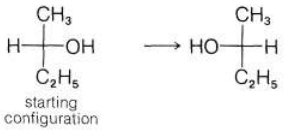


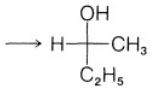
b.

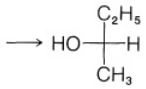


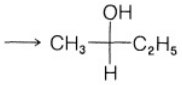
c.* 

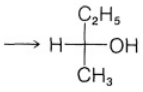
Exercise 5-11 This exercise can clarify for you the constraints on manipulating projection formulas. You will be helped by checking the configuration with models, as in Figure 5-12. The idea is to determine what effect there is, if any, on the configuration represented by the formula by making various changes in the projection. Your answer for each part should be that the operation changes, or does not change, the configuration.

a. interchange of substituents across the horizontal bond: 

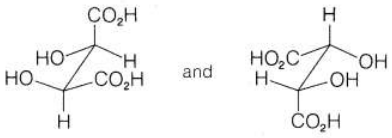
b. interchange of other substituents: 

c. 180° rotation in plane of paper: 

d. 90° rotation in plane of paper: 

e. end-over-end flip *outside* plane of paper: 

Exercise 5-12 Analysis of the crystals of a particular tartaric acid show them to be made up of equal amounts of the following conformations:



Use ball-and-stick models to determine the relationship between these two conformations and also whether this tartaric acid is *meso*-tartaric acid, an optically active tartaric acid, or racemic acid. Give your reasoning.

Exercise 5-13 Write structures for all the configurations possible for 2,4-dibromopentane. Which stereoisomers are enantiomers? Which are diastereomers? What combination of isomers would give a racemic mixture? Which isomer is achiral?

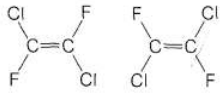
Exercise 5-14 From the compounds listed select all those that may have achiral meso configurations and draw the configurations for each of them.

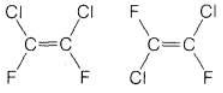
a. 1,2-dichlorocyclopropane
b. 1,4-dichlorocyclohexane
c. 1,3-dichlorocyclohexane
d. 2,3-dichloropentane

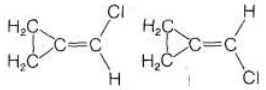
e. 2,3,4-trichloropentane

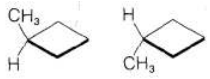
f. 2,3,4,5-tetrachlorohexane

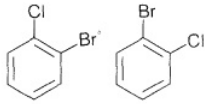
Exercise 5-15 Look carefully at each pair of structures shown below and decide whether they are identical. If you are uncertain, use molecular models.

a. 

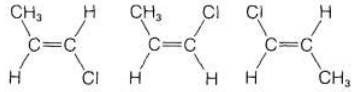
b. 

c. 

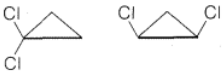
d. 

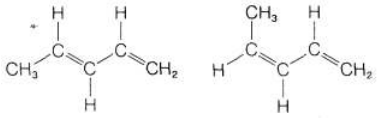
e. 

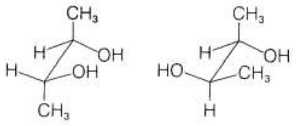
f. Cl—C ≡ C—Br Br—C ≡ C—Cl

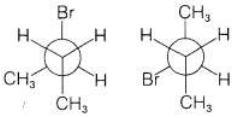
g. 

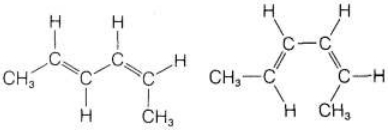
Exercise 5-16 The two structures shown in each of the following pairs are isomers. Determine whether they are position, configurational, or conformational isomers. Use of models will be very helpful.

a. 

b. 

c. 

d. 

e. 

Exercise 5-17 Which of the following compounds could exist as cis-trans configurational isomers?

a. 1,2-dibromoethane
b. 2,3-dibromopropene
c. dibromoethyne
d. 1,3-dibromopropene

Exercise 5-18 Which of the following compounds can exist as (1) a pair of enantiomers, (2) a pair of cis-trans isomers, and (3) as a cis pair of enantiomers and a trans pair of enantiomers?

a. 3-chloro-1-butyne
b. 4-chloro-1-butyne
c. 1-chloro-1,3-butadiene
d. 2-chloro-1,3-butadiene
e. 4-chloro-2-pentene
f. 5-chloro-2-pentene

Exercise 5-19 Write structures showing the specified configurations for each of the following compounds. Make your drawings as clear as possible so there is no ambiguity as to structure or configuration:

a. *cis*-1,2-diphenylethene
b. *trans*-2-chloro-2-butene
c. *trans*-1-propenylbenzene
d. *trans*-*trans*-2,4-heptadiene
e. *cis*-*cis*-2,4-heptadiene
f. *trans*-*cis*-2,4-heptadiene
g. *cis*-*trans*-2,4-heptadiene
h. *cis*-1-*tert*-butyl-4-methylcyclohexane

Exercise 5-20 Write structural formulas showing configuration for all of the possible cis-trans isomers of the following compounds:

a. 1,2,3-trimethylcyclopropane
b. 1,3-dichlorocyclopentane
c. 3-methyl-2,4-hexadiene
d. 1-(3-methylcyclobutyl)-3-methylcyclobutane

Exercise 5-21 Would you expect *cis*- or *trans*-1,2-dimethylcyclopropane to be the more stable? Explain.

Exercise 5-22 Draw suitable formulas for all of the position and configurational isomers possible (include optical isomers but not conformational isomers) for the following compounds of molecular formula:

a. C_3H_5Cl (five)
b. C_5H_{10} (thirteen)
c. C_4H_7Cl (nineteen)

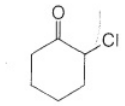
Exercise 5-23 Show how the sawhorse and Newman conventions can be used to represent the *different* possible *staggered* conformations of the following substances:

a. chloroethane
b. 1,2-dichloro-1-fluoroethane
c. 1,2-dichloroethane
d. 2,3-dimethylbutane

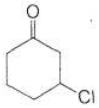
Exercise 5-24 Determine which of the following compounds are chiral and which are achiral. Indicate each chiral atom with an asterisk (*), noting that more than one may be present in some examples.

a. 2,3-dimethylpentane
b. 2,3-dimethyl-2-pentene
c. 2-bromo-3-chlorobutane

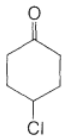
d.



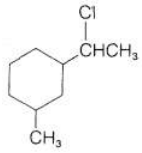
e.



f.



g.



Exercise 5-25 Write structures that fit the following descriptions:

a. An achiral isomer of dimethylcyclohexane that has the methyl groups on different carbons.

b. All the chiral isomers of formula $C_5H_{12}O$.

c. A compound of formula C_4H_5Cl that has just one double bond and is chiral.

d.* The conformation of 2,5-dimethylhexane you would anticipate to be the most stable.

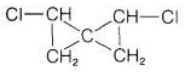
Exercise 5-26 If you have a set of molecular models with which you can make or use bent bonds for double bonds, construct each of the following molecules and determine if stereoisomerism is possible and, if so, identify the type of stereoisomers.

a. $ClCH{=}C{=}CHCl$

b. $ClCH{=}C{=}C{=}CHCl$

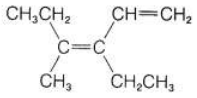
c.

d.*



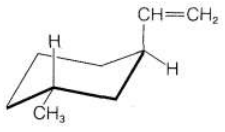
Exercise 5-27 Designate the configuration of the compounds whose structures are drawn below using the cis-trans terminology.

a.

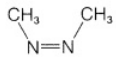


b.

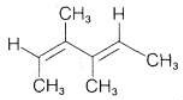
c.



d.



e.

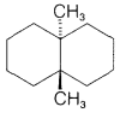


Exercise 5-28 Draw sawhorse formulas as in Figure 5-10 for the following cyclohexane derivatives:

a. 1,1,3,3-tetramethylcyclohexane

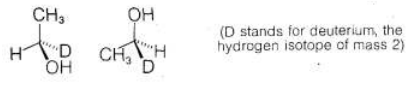
b. *cis*-1,2-dimethylcyclohexane

c.

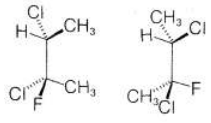


Exercise 5-29 Determine the relationship between the pairs of compounds written as perspective formulas as being enantiomers, diastereomers, conformational isomers, cis-trans isomers, or some combination of these. Models will be very helpful.

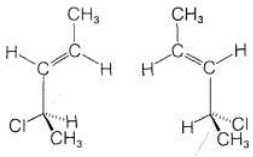
a.



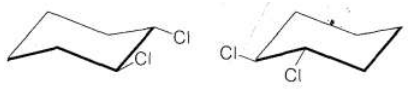
b.



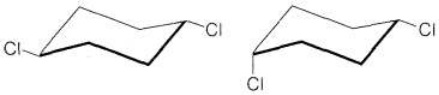
c.



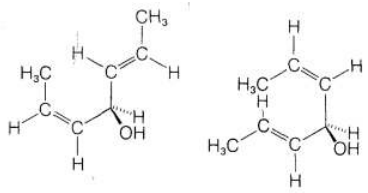
d.



e.



f.



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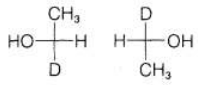
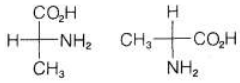
Exercise 5-30 This is a problem similar to 5-29, except that the structures are written mostly as projection formulas of the Fischer or Newman type. Determine the relationship between the pairs of compounds as one of the following: identical, position isomers, enantiomers, diastereomers, conformational isomers, or cis-trans isomers. (D stands for deuterium, the hydrogen isotope of mass 2.)

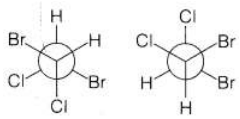
a.



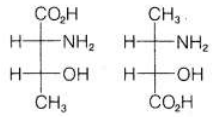
b.



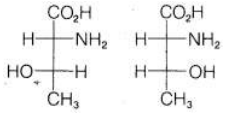
c.



d.



e.



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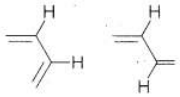
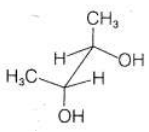


Exercise 5-31 Draw structures for all the possible configurational isomers of the following compounds. In Part a, D stands for deuterium, the hydrogen isotope of mass 2.

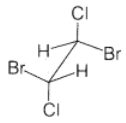
a. ethene-1,2-D_2 (1,2-dideuterioethene)
b. 3-phenoxy-1-butene
c. 4-iodo-2-pentene
d. 2-chloro-3-phenylbutane
e. 2,3-diphenylbutane
f. 3-chlorocyclohexene
g. 3-chlorocyclooctene (use models)
h. 4-chloromethylcyclohexane
i. 3-chloromethylcyclohexane
j. 1-methyl-4-(1-propenyl)cyclohexane
k. 1-methyl-3-(1-propenyl)cyclohexane

Exercise 5-32 Determine which of the following conformations is identical with its mirror image (models will be very helpful). For the purpose of this part of the problem, assume that the compounds are locked in the conformations shown. For Parts a-d, determine which of these substances becomes achiral on free rotation.

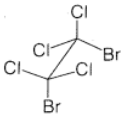
a.



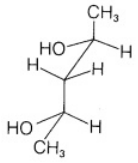
b.



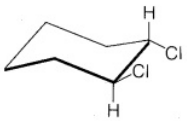
c.



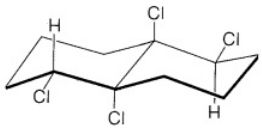
d.



e.



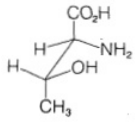
f.



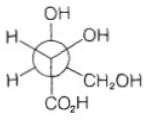
Exercise 5-33 Redraw the perspective drawings a, b, and c as Fischer projection formulas, leaving the configuration at the chiral centers unchanged. Similarly, redraw d and e in perspective, using a staggered sawhorse representation for e.

a.

b.

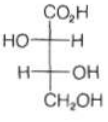


c.



d.

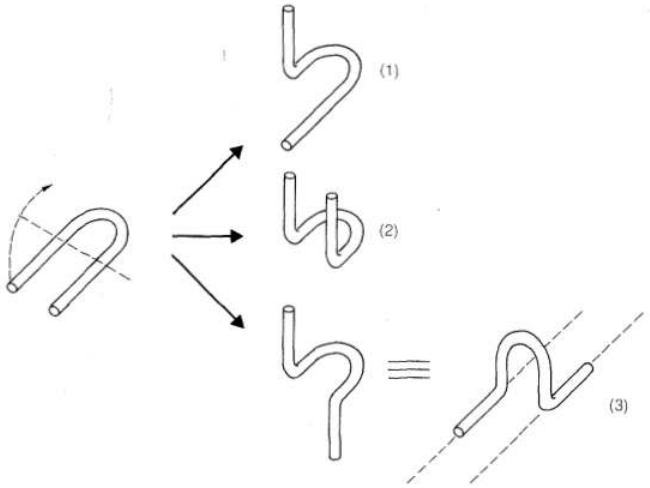
e.



Exercise 5-34 Use the D,L system to designate the configuration at each chiral center in Structures a-e in Exercise 5-33.

Exercise 5-35 This problem is designed to illustrate chirality, asymmetry, and dissymmetry with simple models or common objects.

a. Bend three pieces of wire into a hair-pin shape with *equal* legs. Now take one piece and make a 90° bend in one of the legs in the middle to give (1). Bend up both legs equally of another piece to give (2), and one up and the other down to give (3). Determine whether (1), (2), and (3) are chiral or achiral, and asymmetric, dissymmetric, or symmetric. (See footnote [1], Section 5-1B)



b. Classify each of the following as chiral, achiral, asymmetric, dissymmetric, or symmetric: a cup, a shirt, a bicycle, a tennis racket, an automobile, a penny, a pair of scissors, a flat spiral (4), and a conical spring (5). Indicate any ambiguities that may be involved.

Exercise 5-36 The structures of some biochemically interesting compounds are shown below. Mark the chiral carbons in each and calculate by the 2^{n} rule how many stereoisomers might be expected. Explain why only *one* pair of enantiomers is known for camphor (ball-and-stick models will be very helpful here). How many different stereoisomers would you expect actually could be prepared of the quinine and codeine structures?

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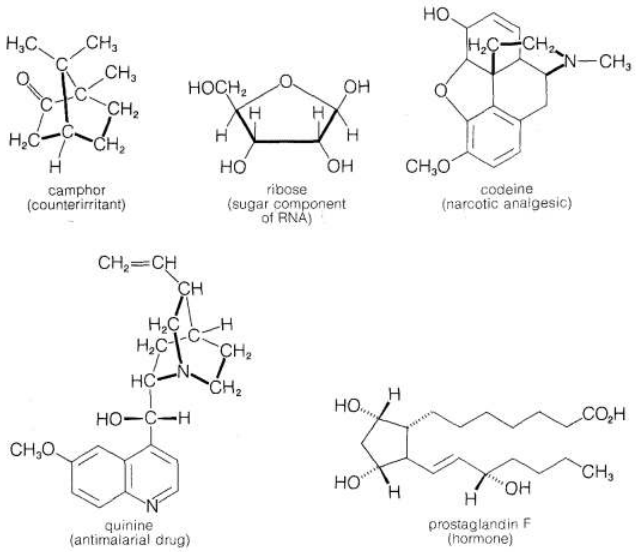

5.E.1: Contributors

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CHAPTER OVERVIEW

6: Bonding in Organic Molecules

In previous chapters, we have shown how you can use ball-and-stick models to predict the general arrangements in space of organic molecules. The sticks correspond to chemical bonds, which we represent in structural formulas as lines, or in Lewis structures as pairs of dots denoting shared pairs of electrons. Remembering that electrons and nuclei are charged particles, and that it is electrical forces of attraction and repulsion between the electrons and nuclei that determine the bonding, perhaps we should be surprised that such simple mechanical models provide so much useful information. What we will try to do in this chapter is to show you how the modern electronic theory of chemical bonding provides strong support for the use of ball-and-stick models for many organic molecules, and also where it indicates that the models need to be modified or cannot properly represent the structural arrangements.

6.1: Prelude to Bonding
6.2: Hydrogenlike Atomic Orbitals
6.3: Bond Formation Using Atomic Orbitals
6.4: Electron Repulsion and Bond Angles. Orbital Hybridization
6.5: Atomic-Orbital Models
6.6: Resonance
6.7: Advanced Quantum Theory of Organic Molecules
6.E: Bonding in Organic Molecules (Exercises)

6.1: Contributors and Attributions

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6.1: Prelude to Bonding

In previous chapters, we have shown how you can use ball-and-stick models to predict the general arrangements in space of organic molecules. The sticks correspond to chemical bonds, which we represent in structural formulas as lines, or in Lewis structures as pairs of dots denoting shared pairs of electrons. Remembering that electrons and nuclei are charged particles, and that it is electrical forces of attraction and repulsion between the electrons and nuclei that determine the bonding, perhaps we should be surprised that such simple mechanical models provide so much useful information. What we will try to do in this chapter is to show you how the modern electronic theory of chemical bonding provides strong support for the use of ball-and-stick models for many organic molecules, and also where it indicates that the models need to be modified or cannot properly represent the structural arrangements.

There are several qualitative approaches to bonding in polyatomic molecules, but we shall discuss here the most widely used and currently popular approach. This approach involves setting up appropriate atomic orbitals for the atoms and considering that each bond arises from the attractive electrical forces of two or more nuclei for a pair of electrons in overlapping atomic orbitals, with each orbital on a different atom. The geometry of the bonds is assumed to be determined by the geometry of the orbitals and by the repulsive forces between the electrons. In the course of showing how this approach can be applied, we shall discuss ways of formulating bonding and geometries for several important kinds of organic compounds. Finally, we will show you some of the results currently being obtained by sophisticated quantum-mechanical calculations, which provide strong support for our qualitative formulations.

6.1.1: Contributors and Attributions

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6.2: Hydrogenlike Atomic Orbitals

With the modern concept of a hydrogen atom we do not visualize the orbital electron traversing a simple planetary orbit. Rather, we speak of an atomic orbital, in which there is only a *probability* of finding the electron in a particular volume a given distance and direction from the nucleus. The boundaries of such an orbital are not distinct because there always remains a finite, even if small, probability of finding the electron relatively far from the nucleus.

There are several discrete atomic orbitals available to the electron of a hydrogen atom. These orbitals differ in energy, size, and shape, and *exact* mathematical descriptions for each are possible. Following is a qualitative description of the nature of some of the hydrogen atomic orbitals.

The most stable or **ground state** of a hydrogen atom is designated $1s$.[1] In the $1s$ state the electron is, on the average, closest to the nucleus (i.e., it is the state with the smallest atomic orbital). *The $1s$ orbital is spherically symmetrical*. This means that the probability of finding the electron at a given distance r from the nucleus is independent of the direction from the nucleus. We shall represent the $1s$ orbital as a sphere centered on the nucleus with a radius such that the probability of finding the electron within the boundary surface is high (0.80 to 0.95); see Figure 6-1. This may seem arbitrary, but an orbital representation that would have a probability of 1 for finding the electron within the boundary surface would have an infinite radius. The reason is that there is a finite, even if small, probability of finding the electron at *any* given distance from the nucleus. The boundary surfaces we choose turn out to have sizes consistent with the distances between the nuclei of bonded atoms.

The $2s$ orbital is very much like the $1s$ orbital except that it is larger and therefore more diffuse, and it has a higher energy. For principal quantum number 2, there are also three orbitals of equal energies called $2p$ orbitals, which have different geometry than the s orbitals. These are shown in Figure

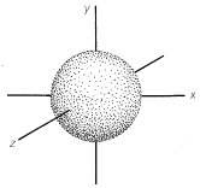


Figure 6-1: Representation of the hydrogen $1s$ orbital

6-2, in which we see that the respective axes passing through the tangent spheres of the three p orbitals lie at right angles to one another. The p orbitals are *not* spherically symmetrical.

The $3s$ and $3p$ states are similar to the $2s$ and $2p$ states but are of higher energy. The $3d$, $4d$, $4f$, ⋯, orbitals have still higher energies and quite different geometries; they are not important for bonding in most organic substances, at least for carbon compounds with hydrogen and elements in the first main row (Li-Ne) of the periodic table. The sequence of orbital energies is shown in Figure 6-3.

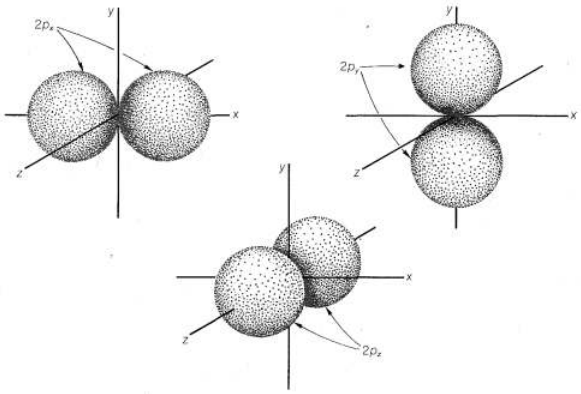


Figure 6-2: The shapes and orientations of the three $2p$ orbitals of a hydrogen atom. Notice that p orbitals have two lobes, one on each side of the nucleus.

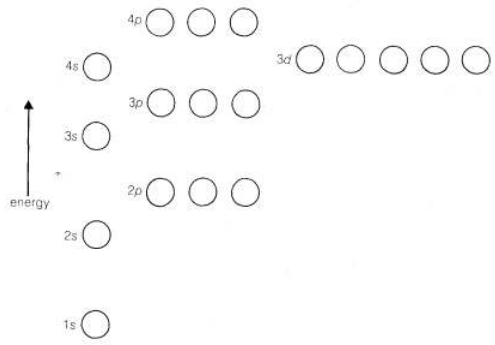


Figure 6-3: Schematic diagram of the relative energies of the hydrogen-like atomic orbitals

The famous **Pauli exclusion principle** states that no more than two elections can occupy a given orbital and then only if they differ with respect to a property of electrons called **electron spin**. An electron can have only one of two possible orientations of electron spin, as may be symbolized by ↑ and ↓. Two electrons with "paired" spins often are represented as ↑↓. Such a pair of electrons can occupy a *single* orbital. The symbols ↑↑ (or ↓↓) represent two **unpaired** electrons, which may *not* go into a single orbital.

If we assume that all atomic nuclei have orbitals like those of the hydrogen atom, we can see how atoms more complex than hydrogen can be built up by adding electrons to the orbitals in accord with the Pauli exclusion principle. The lowest-energy states will be those in which the electrons are added to the lowest-energy orbitals. For example, the electronic configuration of the lowest-energy state of a carbon atom is shown in Figure 6-4, which also shows the relative energies of the $1s$ through $4p$ atomic orbitals. The orbitals of lowest energy are populated with the proper number of electrons to balance the nuclear charge of $+6$ for carbon and to preserve the Pauli condition of no more than two paired electrons per orbital. However, the two highest-energy electrons are put into *different* $2p$ orbitals with unpaired spins in accordance with **Hund's rule**. The rationale of Hund's rule depends on the fact that electrons come closer together. Now, suppose there are two electrons that can go into two different orbitals of the same energy (so-called **degenerate orbitals**). Hund's rule tells us that the repulsion energy between these electrons will be less if they have unpaired spins (↑↑). Why is this so? Because if they have unpaired

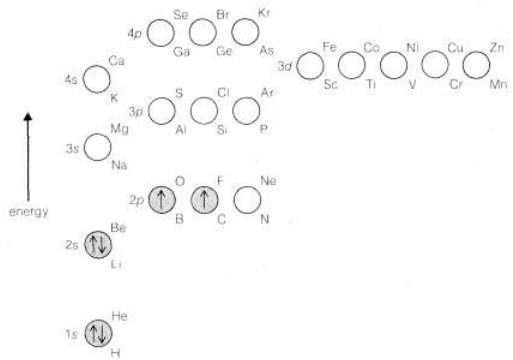
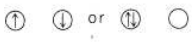


Figure 6-4: Diagram showing the most stable electronic configuration, $(1s)^2\,(2s)^2\,(2p_x)^1\,(2p_y)^1$, of a carbon atom. Addition of more electrons in accord with Hund's rule gives the electronic configuration of the other atoms indicated by the atomic symbols.

spins they cannot be in the *same* orbital at the *same* time. Therefore they will not be able to approach each other as closely as they would if they could be in the same orbital at the same time. For this reason the **electronic configuration**

is expected to be more stable than the configuration



if both orbitals have the *same* energy.

States such as the one shown in Figure 6-4 for carbon are built up through the following steps. Helium has two paired electrons in the $1s$ orbital; its configuration can be written as $(1s)^2$, the superscript outside the parentheses denoting two paired electrons in the $1s$ orbital. For lithium, we expect $Li\ (1s)^2\,(2s)^1$ to be the ground state, in which the $1s$ electrons must be paired according to the exclusion principle. Continuing in this way, we can derive the electronic configurations for the elements in the first three rows of the periodic table, as shown in Table 6-1. These configurations conform to the

Table 6-1
Electronic Configurations of Ground States of Atoms

H $(1s)^1$	Li $(1s)^2(2s)^1$	Na $(1s)^2(2s)^2(2p)^6(3s)^1$
	Be $(1s)^2(2s)^2$	Mg [Ne] $(3s)^2$
	B $(1s)^2(2s)^2(2p)^1$	Al [Ne] $(3s)^2(3p)^1$
	C $(1s)^2(2s)^2(2p)^2$	Si [Ne] $(3s)^2(3p)^2$
	N $(1s)^2(2s)^2(2p)^3$	P [Ne] $(3s)^2(3p)^3$
	O $(1s)^2(2s)^2(2p)^4$	S [Ne] $(3s)^2(3p)^4$
	F $(1s)^2(2s)^2(2p)^5$	Cl [Ne] $(3s)^2(3p)^5$
He $(1s)^2$	Ne $(1s)^2(2s)^2(2p)^6$	Ar [Ne] $(3s)^2(3p)^6$

Figure 6-4.

[1]The index number refers to the principal quantum number and corresponds to the "K shell" designation often used for the electron of the normal hydrogen atom. The principal quantum number 2 corresponds to the L shell, 2 to the M shell, and so on. The notation s (also p, d, f to come later) has been carried over from the early days of atomic spectroscopy and was derived from descriptions of spectroscopic lines as "sharp", "principal", "diffuse", and "fundamental," which once were used to identify transitions from particular atomic states.

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6.3: Bond Formation Using Atomic Orbitals

In writing the conventional Lewis structures for molecules, we assume that a covalent chemical bond between two atoms involves sharing a pair of elections, one from each atom. Figure 6-5 shows how atomic orbitals can be considered to be used in bond formation. Here, we postulate that a *single* bond is formed by the pulling together of two atomic nuclei by attractive forces exerted by the nuclei for the two paired electrons in overlapping atomic orbitals.

Because *two* atomic orbitals can hold a maximum of *four* electrons, it is reasonable to ask why it is that two rather than one, three, or four electrons normally are involved in a bond. The answer is that two overlapping atomic

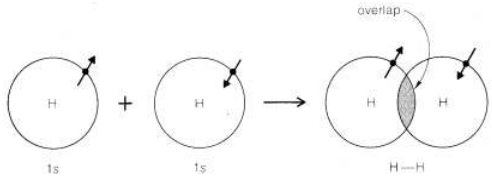

Figure 6-5: Representation of the formation of an $H-H$ bond by sharing of electrons in overlapping orbitals

orbitals can be considered to combine to give one low-energy **bonding molecular orbital** and one high-energy **antibonding molecular orbital** (see the top part of Figure 6-6(a)).[2] Orbitals that overlap as shown in Figure 6-6(a) are said to overlap in the sigma manner,[3] and the bonding orbital is called a **sigma orbital** (σ); the antibonding orbital is called a σ^* **orbital** (read "sigma star"). Two paired electrons suffice to fill the σ orbital. Any additional electrons must go into the high-energy σ^* orbital and contribute not to bonding but to repulsion between the atoms.

The hydrogen molecule-ion, $H_2^{\oplus}$, can be regarded as having one electron in a σ orbital. It has been studied in the vapor state by spectroscopic means and found to have a dissociation energy to $H^{\oplus}$ and $H\cdot$ of $61\ \text{kcal mol}^{-1}$ compared to the $104.2\ \text{kcal mol}^{-1}$ bond energy for H_2. Several possible combinations of two hydrogen orbitals and from one to four electrons are shown in Figure 6-6(b).

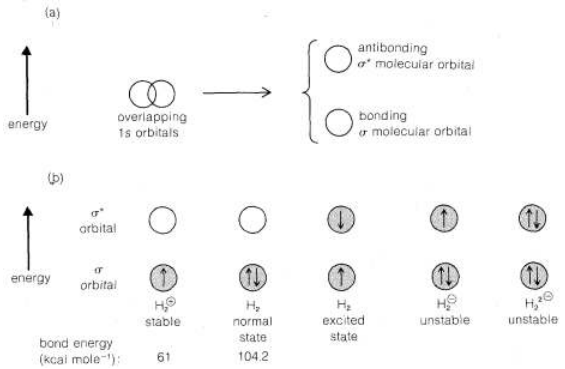

Figure 6-6: (a) Schematic representation of formation of bonding (σ) and antibonding (σ^*) molecular orbitals by overlap of two atomic $1s$ orbitals. (b) Some of the various electronic configurations that are possible with these orbitals

[2]More about the difference between bonding and antibonding orbitals is given in Section 21-2. For now we will say that the property of orbitals that leads to bonding or antibonding is a property analogous to *phase*. An *in-phase* combination of two orbitals is bonding, and an *out-of-phase* combination is antibonding.

[3]The designation sigma (σ) denotes that orbital overlap and electron density are greatest along the internuclear axis.

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6.4: Electron Repulsion and Bond Angles. Orbital Hybridization

In predicting bond angles in small molecules, we find we can do a great deal with the simple idea that *unlike* charges produce *attractive* forces while *like* charges produce *repulsive* forces. We will have electron-nuclear attractions, electron-electron repulsions, and nucleus-nucleus repulsions. Let us first consider the case of a molecule with just *two* electron-pair bonds, as might be expected to be formed by combination of beryllium and hydrogen to give beryllium hydride, $H:Be:H$. The problem will be how to formulate the bonds and how to predict what the $H-Be-H$ angle, θ, will be:

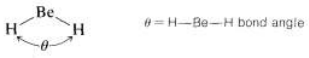
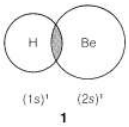
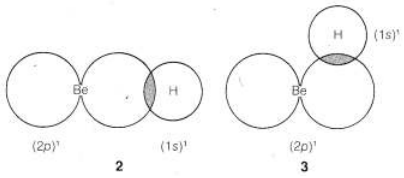


Figure 6-5):



We might formulate a second σ bond involving the $2p$ orbital, but a new problem arises as to where the hydrogen should be located relative to the beryllium orbital. Is it as in 2, 3, or some other way?



The Be and H nuclei will be farther apart in 2 than they will be in 3 or any other similar arrangement, so there will be less *internuclear repulsion* with 2. We therefore expect the hydrogen to locate along a line going through the greatest extension of the $2p$ orbital.

According to this simple picture, beryllium hydride should have two different types of $H-Be$ bonds - one as in 1 and the other as in 2. This is intuitively unreasonable for such a simple compound. Furthermore, the $H-Be-H$ bond angle is unspecified by this picture because the $2s$ Be orbital is spherically symmetrical and could form bonds equally well in any direction.

However, if we forget about the orbitals and only consider the possible repulsions between the electron pairs, and between the hydrogen nuclei, we can see that these repulsions will be minimized when the $H-Be-H$ bond angle is 180°. Thus arrangement 5 should be more favorable than 4, with a $H-Be-H$ angle less than 180°:

Unfortunately, we cannot check this particular bond angle by experiment because BeH_2 is unstable and reacts with itself to give a high-molecular-weight solid. However, a number of other compounds, such as $(CH_3)_2Be$, $BeCl_2$, $(CH_3)_2Hg$, HgF_2, and $(CH_3)_2Zn$, are known to have σ bonds involving $(s)^1(p)^1$ valence states. Measurements of the bond angles at the metal of these substances in the vapor state has shown them to be uniformly 180°.

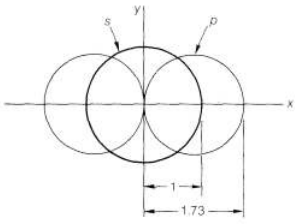


Figure 6-7: Representation of the relative sizes of $2s$ and $2p$ orbitals

How are the s and p orbitals deployed in this kind of bonding? It turns out that *stronger bonds are formed when the degree of overlap of the orbitals is high*. The degree of overlap will depend on the sizes of the orbital and, particularly, on how far out they

extend from the nucleus. Figure 6-7 shows how far $2s$ and $2p$ orbitals extend relative to one another. Bonding with these orbitals as in 1 and 2 does not utilize the overlapping power of the orbitals to the fullest extent. With 1 we have overlap that uses only part of the $2s$ orbital, and with 2, only a part of the $2p$ orbital. Molecules such as BeH_2 can be formulated with *better overlap* and *equivalent bonds* with the aid of the concept of **orbital hybridization**. This concept, published independently by L. Pauling and J. C. Slater in 1931, involves determining which (if any) combinations of s and p orbitals may overlap better and make more effective bonds than do the individual s and p orbitals. The mathematical procedure for orbital hybridization predicts that an s and a p orbital of one atom can form two stronger covalent bonds if they combine to form two new orbitals called sp-**hybridized orbitals** (Figure 6-8). Each sp-hybrid orbital has an overlapping power of 1.93, compared to the pure s orbital taken as unity and a pure p orbital as 1.73. Bond angles of 180° are expected for bonds to an atom using sp-hybrid orbitals and, of course, this also is the angle we expect on the basis of our consideration of minimum electron-pair and internuclear repulsions. Henceforth, we will proceed on the basis that molecules of the type $X:M:X$ may form sp-hybrid bonds.

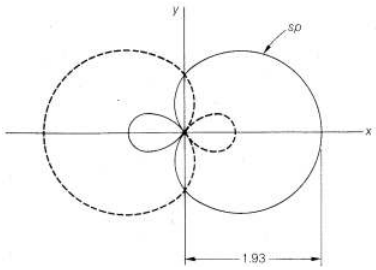


Figure 6-8: Diagram of two sp hybrid orbitals composed of an s orbital and a p orbital. One of the orbitals (solid line) has its greatest extension in the plus x direction, while the other orbital (dotted line) has its greatest extension in the minus x direction. Bonds utilizing both of these sp orbitals would form at an angle of 180°.

On the basis of repulsion between electron pairs and between nuclei, molecules such as BH_3, $B(CH_3)_3$, BF_3, and $AlCl_3$, in which the central atom forms *three* covalent bonds using the valence-state electronic configuration

$(s)^1\,(p_x)^1\,(p_y)^1$, are expected to be planar with bond angles of 120°. For example,

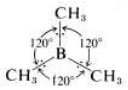


Figure 6-9). These sp^2 orbitals have their axes in a common plane and are at 120° to one another. The predicted overlapping power is 1.99.

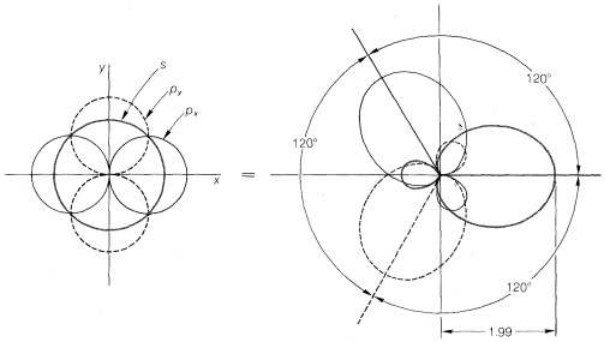


Figure 6-9: Diagram of three sp^2 hybrid orbitals made from an s orbital, a p_x orbital, and a p_y orbital. Each orbital is shown with a different kind of line.

With atoms such as carbon and silicon, the valence-state electronic configuration to form *four* covalent bonds has to be $(s)^1\,(p_x)^1\,(p_y)^1\,(p_z)^1$. Repulsion between the electron pairs and between the attached nuclei will be minimized by formation of a tetrahedral arrangement of the bonds. the same geometry is predicted from hybridization one one s and three p orbitals, which gives four sp^3-**hybrid orbitals** directed at angles of 109.5^o to each other. The predicted relative overlapping power of sp^3-hybrid orbitals is 2.00 (Figure 6-10).

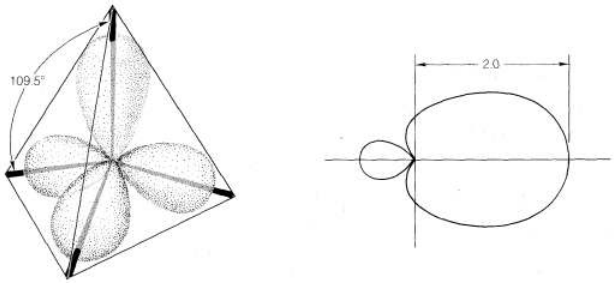


Figure 6-10: Diagram of the sp^3 hybrid orbitals

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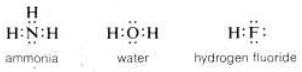
6.5: Atomic-Orbital Models

6.5.1: Alkanes

Saturated compounds such as the alkanes and their derivatives, which have normal tetrahedral angles for the bonds to carbon, can be formulated readily in terms of atomic orbitals with sp^3 σ bonds to carbon. An example is shown in Figure 6-11, which also shows how an atomic-orbital model can be drawn in abbreviated style. The lines in this drawing correspond to bonds and are labeled as sp^3 with sp^3 (the overlapping orbitals of the $C-C$ bond) or as sp^3 with s (the overlapping orbitals of the $C-H$ bonds).

6.5.2: Atoms with Unshared Electron Pairs

Many important molecules such as ammonia, water, and hydrogen fluoride have atoms with unshared pairs of electrons:



If we formulate each of these molecules in such a way to minimize repulsions between like charges, a basically tetrahedral arrangement will be expected because this will place the nuclei (and electron pairs) as widely separated as possible.

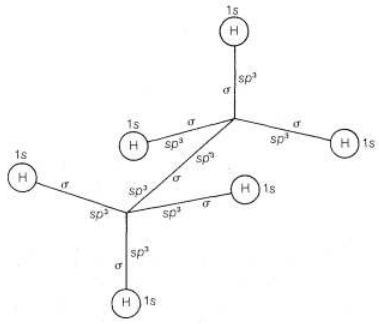
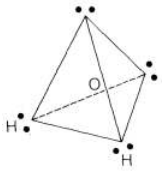


Figure 6-11: Abbreviated atomic-orbital model of ethane showing only the orbitals of the outer-shell electrons

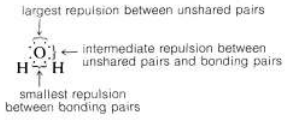
The water molecule could be formulated this way, as in 6, with the oxygen at the center of the tetrahedron:



6

The simple picture predicts that the $H-O-H$ bond angle should be tetrahedral, 109.5°. But actually it is 104.5°.

There are two schools of thought as to why the angle is 104.5°. One idea is that the repulsion model is too simple and has to be modified to take into account that the repulsion is more severe between pairs of unshared electrons than between electrons in bonding orbitals on the same atom. This is because when a bond is formed between *two* nuclei, the attraction of the nuclei for the electrons shrinks the orbitals available to the bonding electrons, thereby reducing their electrostatic repulsion with other pairs. The degree of repulsion between electron pairs diminishes in the sequence: unshared pairs *vs*. unshared pairs $>$ unshared pairs *vs*. bonding pairs $>$ bonding pairs *vs*. bonding pairs. From this, we expect that in water the $H-O-H$ angle will be *less* than tetrahedral, because the larger repulsion between the two unshared pairs will tend to push the bonding pairs closer together.



A similar, but smaller, effect is expected for ammonia because now the repulsion is only between the one unshared pair and bonding pairs. The ammonia $H-N-H$ angle is 107.3°, which is only slightly smaller than the tetrahedral value of 109.5°.

The alternative point of view of why the bond angle of water is 104.5° starts with the premise that, in the simplest approximation, the angle should be 90°! To see how this comes about let us compare $H:Be:H$ with $H:\ddot{O}:H$. You will recall that to form two bonds to Be, we had to promote an electron and change the electronic configuration to the valence configuration, $(2s)^1\,(2p)^1$. The situation with H_2O is different in that the oxygen ground state and valence state are the same, $(2s)^2\,(2p_x)^1\,(2p_y)^1\,(2p_z)^1$. This means we could form two *equivalent* bonds to oxygen using the $2p_y$ and $2p_z$ orbitals at an angle of 90° (Figure 6-12).

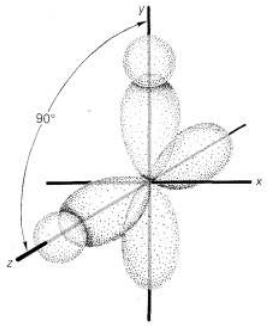


Figure 6-12: Overlap of the hydrogen $1s$ orbitals with $2p_y$ and $2p_z$ orbitals centered on oxygen. The p orbitals are represented here with distorted shapes to make the drawing clearer.

Now, to explain why the $H-O-H$ bond angles are 104.5° instead of 90°, we can say that the repulsion between the hydrogen nuclei is expected to widen the bond angle. An argument in favor of this formulation is provided by the bond angle in H_2S, which is 92.2°. This is much closer to the 90° expected for p-bond orbitals and the hydrogens in H_2S would not be expected to repel each other as much as in H_2O because sulfur is a larger atom than oxygen.

Both ways of formulating the orbitals used in the bonding of water molecules are in current use. Arguments can be advanced in favor of both. Highly sophisticated quantum-mechanical calculations, which we will say more about later, suggest that oxygen in water molecules uses orbitals that are 18% s and 82% p in its bonds ($sp^{4.5}$), and furthermore, that the unshared pairs are in *equivalent hybrid* orbitals [*not* one pair as $(2s)^2$ and the other as $(2p)^2$]. Each of the unshared electron-pair orbitals of oxygen in water is calculated to be about 40% s and 60% p ($sp^{1.5}$).

The results are hardly clearcut, but the bonding orbitals are considerably closer to sp^3 (25% s and 75% p) than they are to 100% p. We recommend that the bonding orbitals of nitrogen and oxygen be considered to be sp^3 and the unshared pairs designated simply as $(n)^2$. An abbreviated atomic orbital model of methanol, CH_3OH, made on this basis is shown in Figure 6-13.

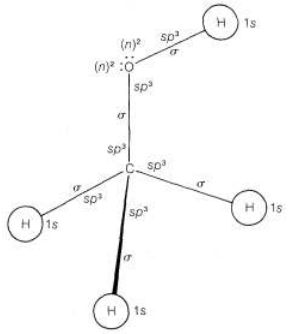


Figure 6-13: Abbreviated atomic-orbital model of methanol, CH_3OH, showing the orbitals of the outer-shell electrons only

6.5.3: Compounds with Double Bonds

Recall from Chapter 2 that bond angles in compounds with carbon-carbon double bonds such as ethene are closer to 120° than to the normal tetrahedral value of 109.5°. There are several way sin which a carbon-carbon double bond can be formulated in terms of atomic-orbital models. One very popular approach is to consider that ethene has two sp^2-hybridized carbons that form one carbon-carbon σ bond and four carbon-hydrogen σ bonds by overlap of the six sp^2 orbitals, as shown in Figure 6-14. The remaining carbon-carbon bond is formulated as arising from *sidewise* overlap of the two p orbitals, one on each carbon, that are not utilized in making the sp^2 hybrids. Sidewise overlap of p orbitals is called π **overlap** to distinguish it from the endwise σ **overlap** of the type we have discussed previously (Figure 6-15). The resulting π **bond** differs from the σ **bond** in that electron density is concentrated in the regions above and below the bond axis rather than along the bond axis.

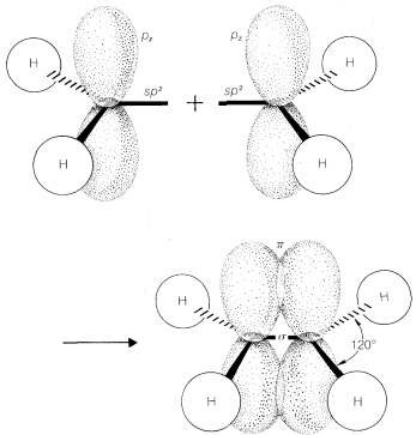


Figure 6-14: The σ-π formulation of ethene

Formulations of ethene in this way suggests that it should be a planar molecule with $H-C-H$ angles of 120°. Ethene is indeed planar, but its $H-C-H$ angles are found to be 117°, rather than the 120° predicted for sp^2 bonds. An explanation of this discrepancy using further electron-repulsion arguments will be discussed later in the chapter.

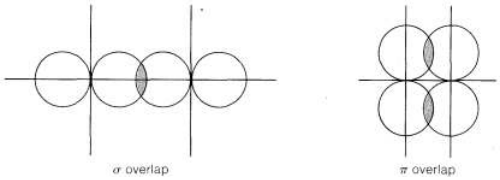


Figure 6-15: Schematic representation of σ overlap and π overlap of p orbitals

The simple elegance of the σ-π model of ethene should not be taken as proving that there actually are two different kinds of bonds between the carbons. The σ-π representation of double bonds is not really unique. Given sp^2 hybridization of the carbons so there are sp^2-σ bonds to the hydrogens, it is possible to take the sp^2 and p orbitals used for the σ and π bonds, rehybridize them, and so derive a new set of overlapping orbitals for the double bond. These orbitals are called τ (**tau**) **bonding orbitals** and can be represented by two banana-shaped orbitals between the carbons (Figure 6-16). The result is two completely equivalent $C-C$ bonds. The τ model has the advantage of offering a striking parallel to ball-and-stick models, whereas the σ-π model is of particular value as a basis for quantitative calculations, as will be discussed in Chapter 21.

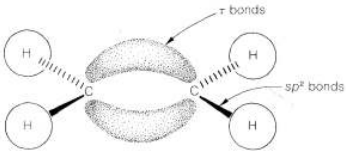


Figure 6-16: Formulation of ethene with τ bonds. Each τ orbital is considered to contain an electron pair.

Using the σ-π model of double bonds, we conclude that the twisted configuration shown in Figure 6-17 should not be very stable. Here the p orbitals are not in position to overlap effectively in the π manner. The favored configuration is expected to have the axes of the p-π orbitals parallel. Because considerable energy would have to be expended to break the p-π double bond and to permit rotation about the remaining sp^2-σ bond, restricted rotation and stable cis-trans isomers are expected. Similar conclusions can be reached on the basis of the τ model of the double bond.

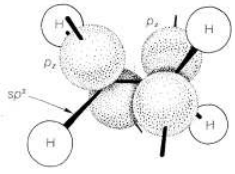


Figure 6-17: Orientation of p orbitals in twisted configuration of ethene

6.5.4: Compounds with Triple Bonds

Ethyne, C_2H_2, is an organic compound that usually is formulated with sp hybrid bonds. The carbon-hydrogen framework is built up through σ overlap of two sp-hybrid orbitals, one from each carbon atom, to form a $C-C$ bond, and σ overlap of the remaining sp orbitals with the s orbital of two hydrogens to form $C-H$ bonds. The remaining *two* carbon-carbon bonds result through sidewise π overlap of the pure p orbitals, as shown in Figure 6-18. This model fits well with the properties of the ethyne molecule being linear (bond angles of 180°. Also, the $C-H$ bonds in ethyne are different from those in ethene or ethane, as judged by their $C-H$ stretching and bending frequencies in the

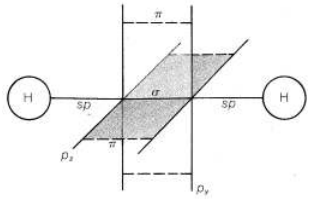


Figure 6-18: The σ-π formulation of ethyne

infrared (Chapter 9), their bond energies, (Table 4-6), and their acidities (Section 11-8). These differences in properties are in keeping with the different states of hybridization of the carbon orbitals that we have postulated for ethane, ethene, and ethyne.

6.5.5: More on Hybrid Bond Orbitals and Molecular Geometry

A summary of the directional character of the s-p hybrid atomic orbitals discussed so far is given in Table 6-2. By referring to this table, it usually is possible to deduce the nature of the bonding orbitals for most organic compounds from the molecular geometry, if this is known, Thus a tetrahedral molecule AX_4 with four attached ligands uses sp^3 hybrid orbitals localized on atom A; a planar triangular molecule AX_3 with three attached ligands at angles of 120° is sp^2 hybridized at atom A; a linear molecule AX_2 with two ligands is sp hybridized at A.

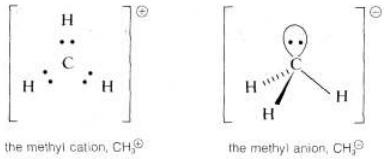
Table 6-2
The s and p Character of the σ Bonding Orbitals of Atom A Expected for Molecules of the Type AX_n With Particular Molecular Shapes and Bond Angles

n in AX_n	Example	Valence electronic configuration of A	Bond angle	Shape	Bond orbital
4	CH_4	$(s)^1(p)^3$	109.5°	tetrahedral	sp^3
3	BF_3	$(s)^1(p)^2$	120°	triangular	sp^2
3	$:NH_3$	$(s)^2(p)^3$	$<109.5°$	pyramidal	$\sim sp^3$
2	$:\ddot{O}H_2$	$(s)^2(p)^4$	$<109.5°$	angular	$\sim sp^3$
2	$BeCl_2$	$(s)^1(p)^1$	180°	linear	sp

Applying the converse of these rules, one should be able to predict molecular geometry by making reasonable assumptions as to the state of hybridization for each atom in the molecule. Obviously in doing this we have to take account of unshared electron pairs. Prediction is easy if unshared pairs are absent. Thus, four attached ligands, as in CH_4, CCl_4, or $BF_4^{\ominus}$, imply sp^3 hybridization at the central atom and therefore a tetrahedral arrangement of ligands. Three ligands, as bonded to carbon in $CH_3^{\oplus}$ or to boron in BF_3, imply sp^2 hybridization for the central atom and a planar triangular arrangement if ligands. Two ligands, as in CO_2, imply sp hybridization and linear geometry.

In many of our later discussions of organic reactions, we will be concerned with cationic, radical, and anionic carbon species that are substitution products of $CH_3^{\oplus}$, $CH_3\cdot$, and $CH_3\ :^{\ominus}$. Because of the importance of these entities, you should know how to formulate them and related substances, such as $^{\ominus}:\ddot{N}H_2$, with atomic orbitals. Perhaps the most straightforward way is to start from CH_4 and see what changes in the $C-H$ bonds we would expect as the result of the hypothetical processes: $CH_4 \rightarrow CH_3\ :^{\ominus} + H^{\oplus}$, $CH_4 \rightarrow CH_3^{\oplus} + H\ :^{\ominus}$, and $CH_4 \rightarrow CH_3\cdot + H\cdot$.

Methane is tetrahedral with sp^3 carbon bonding orbitals. Removal of $H^{\oplus}$ gives $CH_3\ :^{\ominus}$, which corresponds in electronic structure to $H_3N:$ and, for the same reasons, should have a pyramidal shape with nearly tetrahedral $H-C-H$ angles. Removal of $H\ :^{\ominus}$ from CH_4 to give $CH_3^{\oplus}$ with *six* bonding electrons, suggests a change to sp^2 bonding orbitals for the carbon and planar geometry with $H-C-H$ angles of 120°.

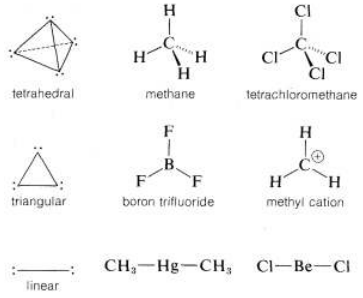


The radical, $CH_3\cdot$ presents a special problem. We can think of it as being formed by the loss of $H\cdot$ from CH_4, by adding an electron to *planar* $CH_3^{\oplus}$, or by removing an electron from pyramidal $CH_3:^{\ominus}$. We can formulate $CH_3\cdot$ with Sp^2 orbitals for the $C-H$ bonds and the extra electron in a p orbital, or with sp^3 orbitals for the $C-H$ bonds and the extra electron in an sp^3 orbital:

The actual structure of $CH_3\cdot$ has the hydrogens and carbons in a plane (left). Therefore it appears that the repulsions between the bonding electron pairs is greater than the repulsions between the extra electron and the bonding pairs. The actual structure corresponds to the one in which the bonding pairs are as far apart as possible.

6.5.6: More on Interelectronic Repulsion and Bond Angles

Molecules of the type AX_4, which have four identical ligands on the central atom and no unshared electrons on A (e.g., CH_4 and CCl_4), are expected to be, and are, tetrahedral. By the same reasoning, three electron pairs around one atom should seek a planar arrangement with 120° angles to minimize electron repulsion; accordingly, species of the type AX_3, which have no unshared pairs on A (e.g., BF_3 and $CH_3^{\oplus}$), have this geometry. With only two electron pairs, the preferred arrangement is linear.



The bond angles of compounds with multiple bonds can be explained similarly. For example, in ethene the four electrons of the double bond occupy the region in space between the two carbon nuclei. The situation at either carbon is rather like the AX_3 case, except that one of the ligands now has a double complement of bonding electrons:

Therefore the carbon orbitals are expected to be directed in one plane to give bond angles that deviate somewhat from 120° because of the high density of electrons in the multiple bond. Thus the $H-C-H$ angle shrinks to 117°, whereas the $H-C=C$ angles open up to 122°, because repulsion between electrons in the $H-C=C$ bonds is greater than between electrons in the $H-C-H$ bonds.

Electron-attracting power (or **electronegativity**) of the ligands also is important in determining bond angles. Thus for compounds of the type CH_3X, in which X is a more electron-attracting group than carbon, the $C-X$ bond is polarized in the sense $H_3\overset{\delta\oplus}{C}--\overset{\delta\ominus}{X}$, and the carbon then should have some of the character of $CH_3^{\oplus}$. Thus the $H-C-H$ angles are expected to be greater than 109.5°, as in fact they are. In chloromethane, for example, the $H-C-H$ angle is 111°.

Also, we can explain on the basis of electron repulsions why the bond angle in phosphine, $:PH_3$ (93°), is less than that in ammonia, $:NH_3$ (107.3°), and the bond angle in $H:\ddot{S}:H$ (92.2°) is less than that in $H:\ddot{O}$ (104.5°). The important point is that phosphorus and sulfur are larger atoms than nitrogen and oxygen. This means than the $H-S-H$ and $H-P-H$ bond angles can be about 90°

without bringing the hydrogens and the bonding pairs as close together as they are in H_2O and NH_3 where the bond angles are near to the tetrahedral value.

6.5.7: Contributors and Attributions

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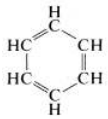
6.6: Resonance

6.6.1: An Atomic-Orbital Model of Benzene

Until now, we have discussed bonding only in terms of electron pair associated with two nuclei. These we may call *localized* electrons. In fact, bonding electrons can be associated with more than two nuclei, and there is a measure of stability to be gained by this because the degree of bonding increases when the electrons can distribute themselves over a greater volume. This effect often is called *electron delocalization* or *resonance*. It is important only if the component atomic orbitals overlap significantly, and this will depend in large part on the molecular geometry.

The classic example of resonance is provided by the π bonding of benzene. This compound was shown in Chapter 1 to have the molecular formula C_6H_6, to be planar, and hexagonal with bond angles of 120°, and to possess six equivalent $C-C$ bonds and six equivalent $C-H$ bonds. Benzene usually is written with a structural formula proposed by Kekulé:



Kekulé structure for benzene

Figure 6-20. Because the π electrons are perfectly paired all around the ring, it is better to consider that the six electrons of benzene form a continuous π bond above and below the carbons of the ring. As mentioned previously, delocalization of the electrons indistinguishably over all six centers (as in benzene) corresponds to a more stable electron distribution than any in which the electrons are considered to be localized in pairs between adjacent carbons.

That benzene is more stable than a single Kekulé, or 1,3,5-cyclohexatriene, structure can be gauged by comparing the experimental heat of combustion

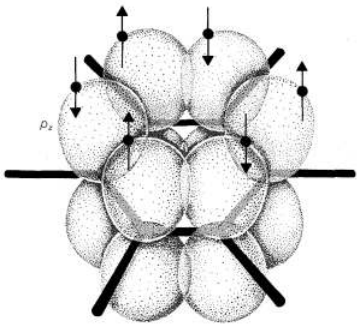


Figure 6-19: Atomic-orbital model of benzene showing the arrangements of the p_z orbitals on each of the carbons

of benzene with the calculated value based on the average bond energies of Table 4-3:

$$\mathrm{C_6H_6\,(g) + \tfrac{15}{2}\,O_2 \longrightarrow 6\,CO_2\,(g) + 3\,H_2O\,(g)} \tag{6.6.1}$$

with

$$\begin{aligned} \Delta H^0_{\text{exp}} &= -789\text{kcal} \\ \Delta H^0_{\text{calc}} &= -827\text{kcal} \end{aligned} \tag{6.6.2}$$

About 38 kcal *less* energy is released on combustion than calculated. Benzene, therefore, is $38\ \text{kcal mol}^{-1}$ *more stable* than the cyclohexatriene structure predicts.

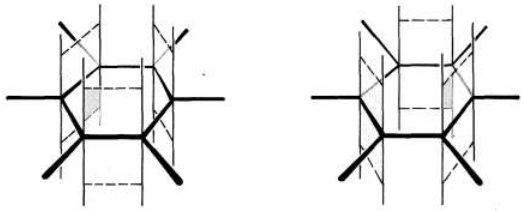
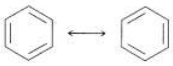


Figure 6-20: Alternative ways of forming π bonds in benzene through pairing of electrons in p orbitals on adjacent carbons

6.6.2: Representation of Resonance

Atomic-orbital models, like that shown for benzene, are useful descriptions of bonding from which to evaluate the potential for electron delocalization. But they are cumbersome to draw routinely. We need a simpler representation of electron delocalization.

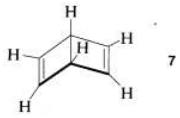
The method that commonly is used is to draw a set of structures, each of which represents a reasonable way in which the electrons (usually in p orbitals) could be paired. If more than one such structure can be written, the actual molecule, ion, or radical will have properties corresponding to some hybrid of these structures. A double-headed arrow $\leftrightarrow$ is written between the structures that we consider to contribute to the hybrid. For example, the two Kekulé forms are two possible electron-pairing schemes or **valence-bond structures** that could contribute to the resonance hybrid of benzene:



It is very important to know what attributes a reasonable set of valence-bond structures has to have to contribute to a hybrid structure. It is equally important to understand what is and what is not implied in writing a set of structures. Therefore we shall emphasize the main points to remember in the rest of this section.

1. The members of a set of structures, as the two Kekulé structures for benzene, have no individual reality. They are hypothetical structures representing different electron-pairing schemes. We are not to think of benzene as a 50:50 mixture of equilibrating Kekulé forms.

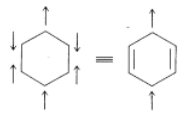
2. To be reasonable, all structures in a set representing a resonance hybrid must have exactly the same locations of the atoms in space. For example, formula 7 does *not* represent a valid member of the set of valence-bond structures of benzene, because the atoms of 7 have different positions from those of benzene (e.g., 7 is not planar):



7

Structure 7 actually represents a known C_6H_6 isomer that has a very different chemistry from that of benzene.

3. All members of the set must have the same number of paired or unpaired electrons. For the normal state of benzene, the six π electrons have three of one spin and three of the other. Structures such as 8, with four electrons of one spin and two of the other, are not valid contributors to the ground state of benzene:



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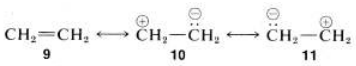
4. The importance of resonance in any given case will depend on the energies of the contributing structures. The lower and more nearly equivalent the members of the set are in energy, the more important resonance becomes. That is to say, *electron stabilization is greatest when there are two or more structures of lowest energy* (as for the two Kekulé structures of benzene). As a corollary, the structure of a molecule is least likely to be satisfactorily represented by a conventional structural formula when two (or more) energetically equivalent, low-energy structures may be written.

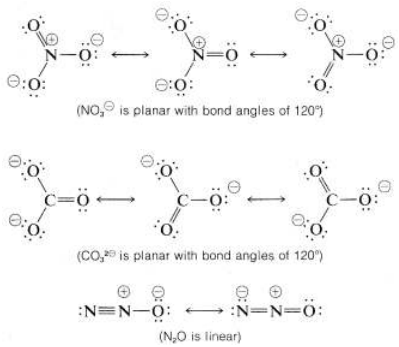
5. If there is only *one* low-energy structure in the set then, to a first approximation, the resonance hybrid may be assigned properties like those expected for that structure. As an example, we show three possible pairing schemes for ethene, 9, 10, and 11:



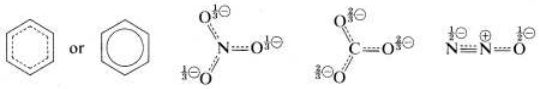
9 10 11

Although 10 and 11 are equivalent, they are much higher in energy than 9 (see discussion in Section 4-4C). Therefore they do not contribute substantially to the structure of ethene that is best represented by 9.

Resonance is by no means restricted to organic molecules. The following sets of valence-bond structures represent the hybrid structures of nitrate ion, $NO_3^{\ominus}$, carbonate ion $CO_3^{2\ominus}$, and nitrous oxide, N_2O. These are only representative examples. We suggest that you check these structures carefully to verify that each member of a set conforms to the general rules for resonance summarized above.



A shorthand notation of hybrid structures frequently is used in which the delocalized π-bonding is shown as a broken line. For benzene, an inscribed circle also is used to indicate continuous π bonding:



6.6.3: Resonance and Reactivity

Electron delocalization is an important factor in the reactivity (or lack of it) of organic molecules. As an example, recall from Chapter 4 that the bond energies of various types of $C-H$ bonds differ considerably (see Table 4-6). In particular, the methyl $C-H$ bond in propene is about 9 kcal *weaker* than the methyl $C-H$ bond of ethane or propane, and this difference can be explained by the use of the resonance concept. The following bond dissociations are involved:

$$CH_2{=}CH{-}CH_3 \longrightarrow CH_2{=}CH{-}\dot{C}H_2 + H\cdot \qquad \Delta H^0 = 89 \text{ kcal}$$
$$CH_3{-}CH_2{-}CH_3 \longrightarrow CH_3{-}CH_2{-}\dot{C}H_2 + H\cdot \qquad \Delta H^0 = 98 \text{ kcal}$$

Figure 6-21 as atomic-orbital and valence-bond structures. Consequently, the 2-propenyl radical is a resonance hybrid of two structures and is more stable than either one is expected to be. No such electron

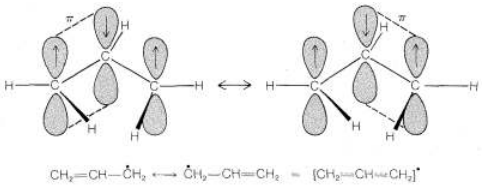


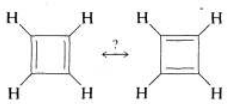
Figure 6-21: Atomic-orbital model, valence-bond structures, and resonance-hybrid formula for the 2-propenyl radical

delocalization is possible for the propyl radical, propane, or propene. Accordingly, the methyl $C-H$ bond strength in propene is less than in propane because of stabilization of the 2-propenyl radical.

The foregoing discussion adds further to our understanding of the selectivity observed in the halogenation reactions discussed in Chapter 4. When propene is chlorinated in sunlight, the product is 3-chloropropene, and we may explain this on the basis that the radical-chain reaction involves propagation steps in which a chlorine atom attacks the hydrogen corresponding to the *weakest* $C-H$ bond:

$$CH_2{=}CH{-}CH_3 + Cl\cdot \longrightarrow CH_2{=}CH{-}\dot{C}H_2 + HCl$$
$$CH_2{=}CH{-}\dot{C}H_2 + Cl_2 \longrightarrow CH_2{=}CH{-}CH_2Cl + Cl\cdot$$

The resonance theory is very useful in accounting for, and in many cases predicting, the behavior of substances with π bonds. However, it is not omnipotent. One example where it fails is cyclobutadiene, for which we can write two equivalent valence-bond structures corresponding to the Kekulé structures for benzene:



Despite this, cyclobutadiene is an extremely unstable substance, reacting with itself almost instantly at temperatures above -250°. For better understanding of this and some related problems, we provide a more detailed discussion of electron delocalization in Chapter 21.

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6.7: Advanced Quantum Theory of Organic Molecules

In recent years, great progress has been made in quantum-mechanical calculations of the properties of small organic molecules by so-called *ab initio* methods, which means calculations from basic physical theory using only fundamental constants, without calibration from known molecular constants. Calculations that are calibrated by one or more known properties and then used to compute other properties are called "semiempirical" calculations.

It should be made clear that there is no single, unique *ab initio* method. Rather, there is a multitude of approaches, all directed toward obtaining useful approximations to mathematical problems for which no solution in closed form is known or foreseeable. The calculations are formidable, because account must be taken of several factors: the attractive forces between the electrons and the nuclei, the interelectronic repulsions between individual electrons, the internuclear repulsions, and the electron spins.

The success of any given *ab initio* method usually is judged by how well it reproduces known molecular properties with considerable premium for use of tolerable amounts of computer time. Unfortunately, many *ab initio* calculations do not start from a readily visualized physical model and hence give numbers that, although agreeing well with experiment, cannot be used to enhance one's qualitative understanding of chemical bonding. To be sure, this should not be regarded as a necessary condition for making calculations. But it also must be recognized that the whole qualitative orbital and hybridization approach to chemical bonding presented in this chapter was evolved from mathematical models used as starting points for early *ab initio* and semiempirical calculations.

> *The success of any given ab initio method is judged by how well it reproduces known molecular properties.*

The efforts of many chemical theorists now are being directed to making calculations that could lead to useful new qualitative concepts of bonding capable of increasing our ability to predict the properties of complex molecules. One very successful *ab initio* procedure, called the "generalized valence-bond" (GVB) method, avoids specific hybridization assignments for the orbitals and calculates an optimum set of orbitals to give the most stable possible electronic configuration for the specified positions of the atomic nuclei. Each chemical bond in the GVB method involves two electrons with paired spins in two more or less localized atomic orbitals, one on each atom. Thus the bonds correspond rather closely to the qualitative formulations used previously in this chapter, for example Figure 6-14.

> *The "generalized valence-bond" (GVB) method, avoids specific hybridization assignments for the orbitals and calculates an optimum set of orbitals to give the most stable possible electronic configuration for the specified positions of the atomic nuclei.*

Electron-amplitude contour diagrams of the GVB orbitals for ethene are shown in Figure 6-22. Let us be clear about what these contour lines represent. They are lines of *equal electron amplitude* analogous to topological maps for which contour lines are equal-altitude lines. The electron amplitudes shown are those calculated *in the planes containing the nuclei* whose positions are shown with crosses. In general, the amplitudes decrease with distance from the nucleus. The regions of *equal-electron amplitude* for s-like orbitals (middle-right of Figure 6-22) surround the nuclei as a set of concentric shells corresponding to the surfaces of the layers of an onion (Figure 6-23). With the sp^2-like orbitals, the amplitude is zero at the nucleus of the atom to which the orbital belongs.

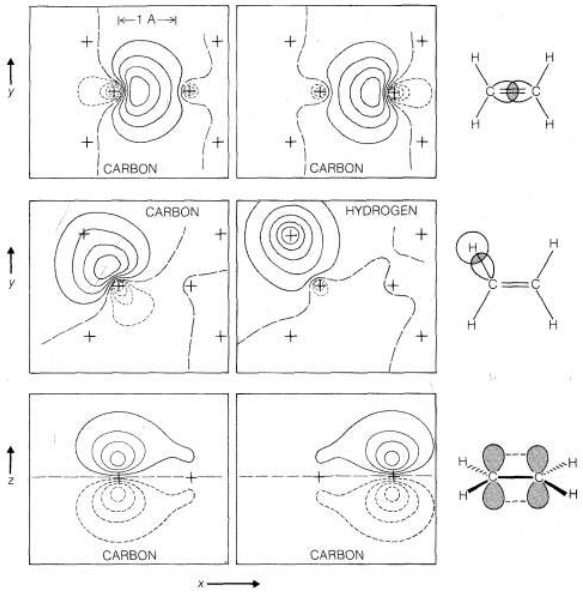

Figure 6-22: Generalized valence-bond orbitals calculated for ethene by the ab initio method. The nuclei are located in the x,y plane of the coordinate system at the positions indicated by crosses. The long dashes correspond to locations of change of phase. The dotted lines are contour lines of electron amplitude of opposite phase to the solid lines. Top shows both σ-bonding carbon orbitals (almost sp^2), middle-left is the carbon orbital and middle-right the hydrogen orbital of one of the $C-H$ bonds, and bottom represents a side view of the π orbitals in perpendicular section to the x,y plane. (Drawings furnished by Dr. W. A. Goddard, III.)

The physical significance of *electron amplitude* is that its square corresponds to the *electron density*, a matter that we will discuss further in Chapter 21. The amplitude can be either positive or negative, but its square (the electron density) is positive, and this is the physical property that can be measured by appropriate experiments.

Looking down on ethene, we see at the top of Figure 6-22 two identical $C-C$ σ-bonding orbitals, one on each carbon, directed toward each other. The long dashed lines divide the space around the atom into regions of opposite orbital phase (solid is positive and dotted is negative). The contours for one of the $C-H$ bonding orbitals are in the middle of the figure, and you will see that the orbital centered on the hydrogen is very much like an s orbital, while the one on the carbon is a hybrid orbital with considerable p character. There are three other similar sets of orbitals for the other ethene $C-H$ bonds.

When we look at the molecule edgewise, perpendicular to the $C-C$ σ bond, we see the contours of the individual, essentially p-type, orbitals for π bonding. Ethyne shows two sets of these orbitals, as expected.

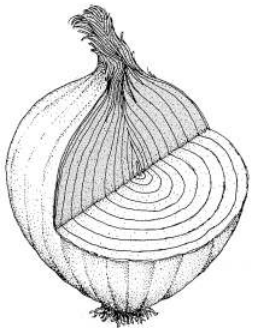

Figure 6-22.

What is the difference between the GVB orbitals and the ordinary hybrid orbitals we have discussed previously in this chapter? Consider the sp^2-like orbitals (upper part of Figure 6-22) and the sp^2 hybrids shown in Figure 6-9. The important point is that the sp^2 hybrid in Figure 6-9 is an atomic orbital calculated for a *single electron on a single atom* alone in space. The GVB orbital is much more physically realistic, because it is an orbital derived for a molecule with all of the nuclei and other electrons present. Nonetheless, the general shape of the GVB sp^2-like orbitals will be seen to correspond rather closely to the simple sp^2 orbital in Figure 6-9. This should give us confidence in the qualitative use of our simple atomic-orbital models.

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6.E: Bonding in Organic Molecules (Exercises)

Exercise 6-1 Write the ground-state configuration for a helium atom with two *unpaired* electrons ($\mathrm{He}\ \uparrow\uparrow$) that is in accord with the Pauli principle. Give your reasoning.

Exercise 6-2 Formulate the electronic configuration of $\mathrm{He_2}$ and $\mathrm{He_2^+}$ in a manner similar to Figure 6-6(b). The ion $\mathrm{He_2^+}$ has been detected spectroscopically; suggest a reason why this ion is more stable than $\mathrm{H_2^+}$.

Exercise 6-3 Write electronic configurations, as in Figure 6-6, for three different *excited* states of $\mathrm{H_2}$, all of which agree with the Pauli principle. Arrange them in order of expected stability. Show your reasoning.

Exercise 6-4 Indicate the probable hybridization of the σ-bonding orbitals on the atoms labeled with a star for each of the following molecules.

a. hydrogen cyanide, $\mathrm{H-\overset{*}{C}\equiv N}$

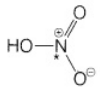
b. carbon disulfide, $\mathrm{S\overset{*}{C}=S}$

c. methanimine, $\mathrm{H_2\overset{*}{C}=NH}$

d. phosphonium ion, $\mathrm{^{\oplus}\overset{*}{P}H_4}$

e. dichloromethane, $\mathrm{\overset{*}{C}H_2Cl_2}$

f. nitric acid,



g. $\mathrm{H_2\overset{*}{C}^{2+}}$

h.* $\mathrm{H_2\overset{*}{C}:}$

Exercise 6-5 Examine the following structures and predict the most likely geometry, using concepts of orbital hybridization. State whether the molecule should be planar or nonplanar, and list the approximate values expected for the bond angles.

a. $\mathrm{SiCl_4}$

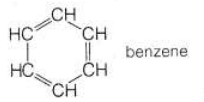
b. $\mathrm{HCOO^{\ominus}}$

c. $\mathrm{CH_3-C\ \equiv CH}$

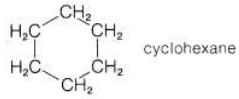
d. $\mathrm{F_2C=C=CF_2}$

e. $\mathrm{(CH_3)_3O^{\oplus}}$

f.



g.



Exercise 6-6 The $\mathrm{P-H}$ bond distance in $\mathrm{PH_3}$ is 1.42 Å and the $\mathrm{N-H}$ bond distance in $\mathrm{NH_3}$ is 1.01 Å. Use the bond angle of 93° for $\mathrm{PH_3}$ and 107.3° for $\mathrm{NH_3}$ and calculate the distance between the hydrogens for each molecule. Would you expect the repulsion between the hydrogen nuclei in $\mathrm{PH_3}$ to be more, or less, than in $\mathrm{NH_3}$?

Exercise 6-7 Write electron-pair structures including bonding and unshared pairs for each of the following compounds. Predict the preferred shape of the molecule as linear, angular, planar and triangular, tetrahedral, or pyramidal.

a. $\mathrm{^{\oplus}NO_2}$

b. $\mathrm{CS_2}$

c. $\mathrm{O=C=C=O}$

d. $\mathrm{H_2C=NH}$

e. $\mathrm{HN=NH}$

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f. CH_3^-

g. $ClNO$

h. NH_2

i. BH_4^-

Exercise 6-8* Use electron-repulsion arguments to explain the following:

a. The $H-N-H$ bond angle in NH_4^+ is larger than in NH_3.

b. The $H-N-H$ bond angle in NH_3 (107.3^o) is larger than the $F-N-F$ bond angles in NF_3 (102.1^o).

c. The $Cl-C-Cl$ angle in $Cl_2C=O$ (phosgene, 111.3^o) is less than the $H-C-H$ angle in $H_2C=O$ (methanal, 118°).

d. The $H-C-H$ angle in methanal (118°) is greater than the $H-C-H$ angle in ethene (116.7^o).

Exercise 6-9 Set up atomic-orbital models to represent the hybrid structures of NO_3^-, CO_3^{2-}, and N_2O.

Exercise 6-10 Set up an atomic orbital model of each of the following structures with normal values for the bond angles. Evaluate each model for potential resonance (electron delocalization). If resonance appears to you to be possible, draw a set of reasonable valence-bond structures for each hybrid.

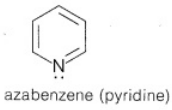
a. $CH_2=CH-\overset{\oplus}{C}H_2$

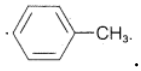
b. $CH_2=CH-CH_2-\overset{\oplus}{C}H_2$

c. $CH_3-\overset{\oplus}{C}H_2$

d. $CH_3C\overset{\ominus}{O}O$

e.

f. 

Exercise 6-11* Draw valence-bond structures for the phenylmethyl radical, $C_6H_5CH_2\cdot$, and the 4-methylphenyl radical,  . Explain why the methyl $C-H$ bonds of methylbenzene (toluene) are weaker than the ring $C-H$ bonds (see Table 4-6).

Exercise 6-12 Suggest why the molecule Be_2 apparently is so unstable that it has not been observed. Explain why Be with an outer-shell electronic configuration of $(2s)^2$ forms $BeCl_2$, whereas He with the configuration $(1s)^2$ does not form $HeCl_2$.

Exercise 6-13 Indicate the hybridization expected at each *carbon* in the following:

a. $CH_3CH_2CH_3$

b. $CH_3CH=CH_2$

c. $HC\equiv C-CH=O$

d. $CH_3-CH=O$

e. $CH_2=C=CH_2$

Exercise 6-14 Draw atomic-orbital models for each of the following substances. Each drawing should be large and clear with all bonds labeled as either σ or π, as shown in the abbreviated formalism of Figures 6-13 and 6-18. Indicate the values expected for the bond angles and whether the molecule or ion should be planar or nonplanar.

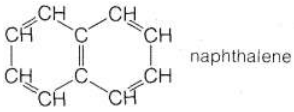
a. BF_3

b. $CH_3\overset{\oplus}{N}H_3$

c. $CH_2=\overset{\oplus}{N}H_2$

d. $CH_2{=}CH{-}C\equiv CH$

e.



Exercise 6-15 Write electron-pair structures for each of the following. Include both bonding and nonbonding pairs and predict the preferred shape of the molecule or ion as linear, triangular (planar), angular, tetrahedral, or pyramidal.

a. CO_2
b. $N\equiv C{-}O^{\ominus}$
c. $CH_2{=}C{=}O$
d. $CH_3{}^+$
e. $F_2C{=}CH_2$
f. $CH_3C\equiv N$
g. SiF_4
h. $HCOOH$
i. $H_3O^{\oplus}$
j. CH_3SH
k.* SO_3

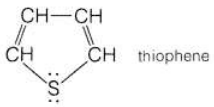
Exercise 6-16 Draw an atomic-orbital model for each of the compounds listed in Exercise 6-15 that is consistent with the geometry deduced for each.

Exercise 6-17 Draw an atomic-orbital picture of 1,3-dichloropropadiene, $ClCH{=}C{=}CHCl$. Examine the structure carefully and predict how many stereoisomers are possible for this structure. What kind of stereoisomers are these?

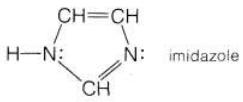
Exercise 6-18 Draw an atomic-orbital picture of 1,4-dichlorobutatriene, $ClCH{=}C{=}C{=}CHCl$. Examine your diagram carefully and predict the number and kind of stereoisomers possible for this structure.

Exercise 6-19* If methanal, $H_2C{=}O$, were protonated to give $H_2C{=}\overset{\oplus}{O}H$, would you expect the $C{=}\overset{\oplus}{O}{-}H$ angle to be closer to 180°, 120°, 109°, or 90°? Explain.

Exercise 6-20* Draw atomic-orbital models for thiophene and imidazole that are consistent with their being planar compounds with six π-electron systems associated with five atomic nuclei.

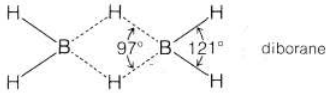


thiophene



imidazole

Exercise 6-21* The boron orbitals in diborane, B_2H_6, overlap with hydrogen $1s$ orbitals in such a way to produce a structure having four ordinary $B{-}H$ bonds, each of which is an electron-pair bond associating two nuclei. The remaining two hydrogens each are bonded to *both* boron nuclei through an electron-pair bond associated with *three* atomic nuclei. This type of bond is referred to as a **three-center bond**.



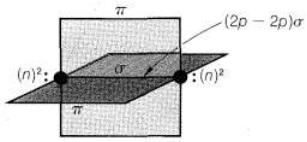
diborane

a. Would you expect diborane to be planar or nonplanar? Explain, using electron-repulsion arguments.

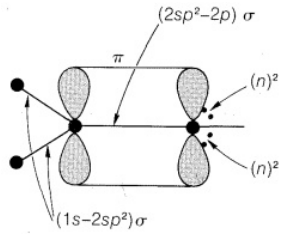
b. Make an atomic-orbital diagram for diborane.

c. Explain why the terminal $H{-}B{-}H$ angle is larger than the internal $H{-}B{-}H$ angle.

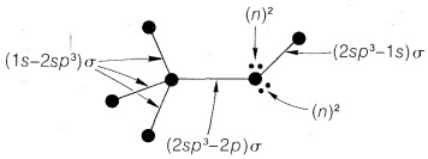
Exercise 6-22 Inspect each of the following orbital diagrams. The nuclei are represented as filled circles, and all bonding and nonbonding orbitals are labeled. The objective of the question is to identify the compound represented by each diagram, based on the number and type of bonding and nonbonding electrons, the type of orbitals, and the charge (if any) associated with each nucleus.



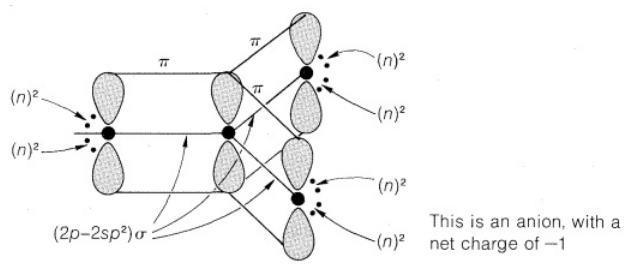
a.



b.



c.



d.

6.E.1: Contributors

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CHAPTER OVERVIEW

7: Other Compounds than Hydrocarbons

We begin our study of compounds with a range of functional groups other than hydrocarbons and consider the nomenclature of organic compounds of oxygen, nitrogen, and halogens. Many of the principles you have learned in connection with naming hydrocarbons will have direct application to these compounds. We will use systematic nomenclature to obtain first-choice names, but we also will indicate common usage, at least parenthetically.

7.1: General Approaches to Naming Organic Compounds
7.2: Alcohols and Phenols- ROH, ArOH
7.3: Ethers, ROR'
7.4: Aldehydes
7.5: Ketones, RCOR'
7.6: Carboxylic Acids
7.7: Acyl Groups, RCO-
7.8: Amines
7.9: Nitriles, RCN
7.10: The Use of Greek Letters to Denote Substituent Positions
7.11: Single- or Multiple-Word Names
7.E: Other Compounds than Hydrocarbons (Exercises)

7.1: Contributors and Attributions

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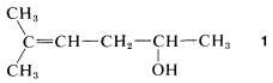
7.1: General Approaches to Naming Organic Compounds

There are two aspects to consider: how to derive the name from the structure, and how to derive the structure from the name. We will discuss each by example.

7.1.1: Naming a Compound of Known Structure

You first should decide what type of compound it is. The decision usually is straightforward for hydrocarbons, which will fall in one or the other of the categories alkanes, alkenes, alkynes, arenes, cycloalkanes, and so on. But when the compound has more than one functional group it is not always obvious which is the parent function. For example, Compound 1 could be named as an *alkene* (because of the double-bond function) or as an *alcohol* (because of the OH function):



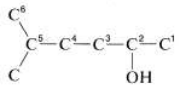
1

There are no simple rules to follow that dictate which is the parent function, and we suggest that the *order of precedence of functional groups* set by *Chemical Abstracts* be used whenever possible (see Table 7-1). By this system, the OH group takes precedence over hydrocarbons, and Compound 1 therefore is named as an *alcohol*, not as an alkene.

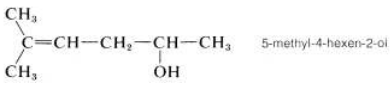
Having decided on the main classification, our next step is to identify the *longest* chain that *includes the main functional group*. Then this chain is numbered, starting at the end that gives the *main function* the *lowest* possible number. The remaining groups, functional or nonfunctional, are taken as substituents and are assigned numbers according to their position along the chain. Thus for Compound 1:

1. The longest continuous carbon chain carrying the OH group is a six-carbon unit. The prefix for a six-carbon hydrocarbon is *hex-*.

2. The chain is numbered so the OH group is at $C2$, the lowest possible number. Therefore the IUPAC suffix is -2-ol, in which *ol* signifies alcohol (see Section 7-2).

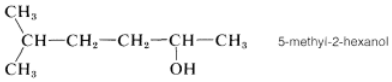


3. The remaining functions are *methyl* (at $C5$) and *-en(e)* (at $C4$). The complete name is



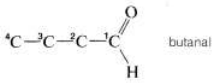
(Notice that the final *e* is dropped from the suffix -ene when followed by another suffix beginning with a vowel.)

One further point of possible confusion is where to locate the numerical symbol for the main functional group in the name. For instance, if the double bond in 1 were *absent*, we could name the compound either 5-methylhexan-2-ol or 5-methyl-2-hexanol. The rule is to *not* divide the name unnecessarily. Thus 5-methyl-2-hexanol would be correct and 5-methylhexan-2-ol would be incorrect:

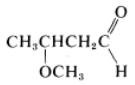


7.1.2: Translating a Name into its Chemical Structure

1. The first step is to identify the parent function, which usually is determined from the suffix or word at the *end* of the name. Suppose, for example, that a structure is to be written for a compound having the name 3-methoxybutanal. The suffix *-al* is the IUPAC suffix for aldehyde; therefore the compound is an aldehyde and the function is $-CHO$.

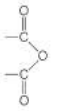


3. The rest of the name, which generally precedes the parent name, describes the substituent and its position on the parent chain. In our example, *3-methoxy* means a CH_3O- group at $C3$. Thus the complete structure of 3-methoxybutanal is



The foregoing examples illustrate that naming compounds from structures or deducing structures from names requires knowledge of both the parent names and the substituent names of the important types of functional and nonfunctional groups. This information is summarized in the following sections and in Table 7-1.

Table 7-1
Classification of Compounds in Order of Decreasing Priority for Citation as Principal Function

Class	Formula	Principal name (suffix)[a]	Substituent name (prefix)
onium	$R_4N^{\oplus}$ $R_4P^{\oplus}$ $R_3O^{\oplus}$ $R_3S^{\oplus}$ $R_2X^{\oplus}$	-onium -ammonium -phosphonium -oxonium -sulfonium -halonium	
carboxylic acids		-oic acid -carboxylic acid	carboxy
carboxylic anhydrides		-oic anhydride -carboxylic anhydride	
carboxylic esters		-oate -carboxylate	R-oxycarbonyl
acyl halides		-oyl halide -carbonyl halide	halomethanoyl, halocarbonyl (haloformyl)
amides		-amide -carboxamide	amido carbamoyl
nitriles		-nitrile -carbonitrile	cyano
aldehydes		-al -carbaldehyde	methanoyl (formyl) oxo (either aldehyde or ketone)

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ketones		-one	oxo
alcohols[a]	—OH	-ol	hydroxy
phenols[a]	—OH	-ol	hydroxy
thiols	—SH	-thiol	mercapto, sulfhydryl
amines	$—NH_2$	-amine	amino
imines	=NH	-imine	imino
hydrocarbons	—H	-ene, -yne, -ane	
ethers[c]	—OR		R-oxy
sulfides[c]	—SR		R-thio
halides[c]	F, Cl, Br, I		halo
nitro[c]			nitro
nitroso[c]	—N=O		nitroso
azides[c]			azido
diazo[c]			diazo

[a]The reason for giving multiple suffixes for some groups will become clearer later. The basic idea is that we use pentan*oic* acid for $CH_3CH_2CH_2CH_2CO_2H$ but cyclobutane*carboxylic* acid for . In the first case, the $—CO_2H$ carbon is part of the chain, but it is not in the second.
[b]Alcohols and phenols differ in the nature of the hydrocarbon group; for alcohols, ROH, R is alkyl or cycloalkyl; for phenols, ArOH, Ar is an aryl group.
[c]These groups should be cited only as prefixes; they are regarded as substituents on the hydrocarbon chains.

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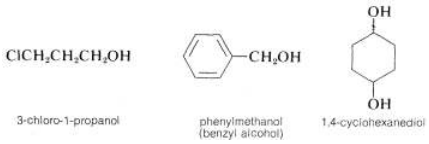
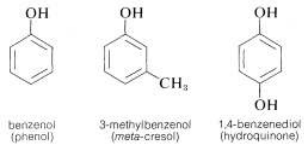
7.2: Alcohols and Phenols- ROH, ArOH

1. By the IUPAC system, the suffix -ol for OH is added to the name of the parent hydrocarbon. Notice that *alkane* + *-ol* becomes *alkanol*, with the *e* omitted:



2. The substituent name for the OH group is *hydroxy* and should be used whenever the OH group is not the parent function (see Table 7-1). Notice how the precedence rules apply - hydroxy below carboxylic acid and hydroxy below ketone:

3. Many trivial names persist, particularly for aromatic, or arene alcohols (phenols):



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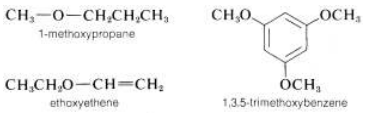
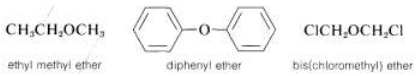
7.3: Ethers, ROR'

The substituent name for the $RO-$ function is *alkoxy*, and it is correct to name $R-O-R'$ compounds as alkoxy derivatives of hydrocarbons:



In the common nomenclature for *ethers*, each of the R groups in $R-O-R'$ is named as a separate word, except when the groups are identical, in which case the prefix *di* or *bis* may be used (*di* is used for simple groups, *bis* for substituted groups):



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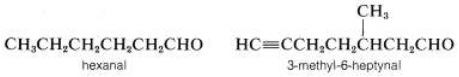
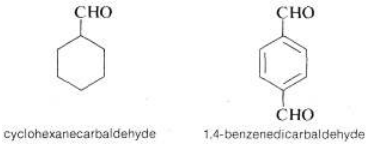
7.4: Aldehydes

1. The suffix *-al* is appended to the name of the hydrocarbon corresponding to the longest carbon chain that *includes* the aldehyde carbon. Remember that *alkane* + *-al* becomes *alkanal* with the *e* omitted, and because the *al* function is necessarily at $C1$, the -1- is redundant and is omitted:

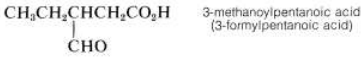


Dialdehydes are named as *-dials*. Thus $OHCCH_2CH_2CH_2CH_2CHO$ is hexanedial.

2. The simplest aldehyde is methanal, $HCHO$, which is familiarly known as formaldehyde. However, when aldehydes are named as derivatives of methanal, they usually are called *carbaldehydes*, and the suffix "carbaldehyde" refers to the $-CHO$ group. This system is used where the hydrocarbon group is not a chain, but a ring, and the CHO group can be thought of as a one-carbon chain:

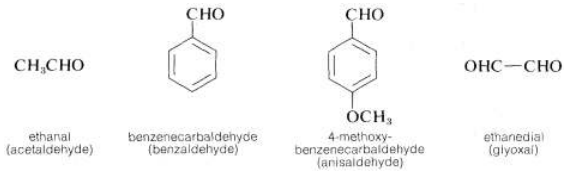


3. When the $-CHO$ group is a substituent on the parent chain or ring and it ranks below another functional group, it properly is designated by the prefix *methanoyl*. However, the prefix *formyl* also is used:



(The naming of acids will be discussed more in detail in Section 7-6.)

4. Trivial names are used for many simple aldehydes, some of which are shown below in parentheses:



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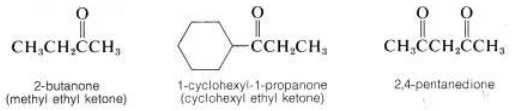
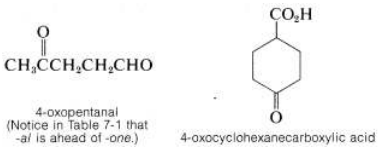
7.5: Ketones, RCOR'

The IUPAC system employs the suffix *-one* added to the prefix identifying the longest carbon chain of $RCOR'$ that includes the carbonyl group. The chain is numbered to give the carbonyl group. The chain is numbered to give the carbonyl group the lowest possible number. In the examples given, the names in parentheses correspond to a less systematic nomenclature of ketones by which the R groups each are named separately:



When the doubly bonded oxygen is regarded as a substituent along the parent chain or ring, it is called an *oxo* group, $=O$,



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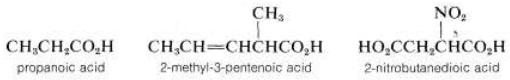
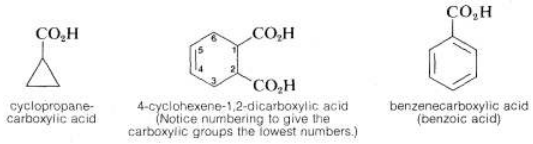
7.6: Carboxylic Acids

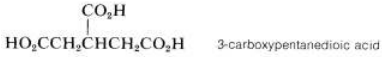
By the IUPAC system, the suffix *-oic* is added to the prefix identifying the hydrocarbon chain that *includes* the carboxyl carbon:



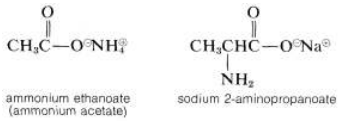
Situations arise when it is necessary to consider the parent as a one-carbon chain. In such circumstances, RCO_2H becomes a *substituted carboxylic acid*. This variation is met most frequently when R is a cycloalkyl or aryl group:



The substituent name for $-CO_2H$ is *carboxy*:



For salts of carboxylic acids, the *-oic* suffix of the acid becomes *-oate* with the counter ion named as a separate word:



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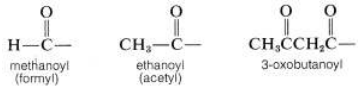
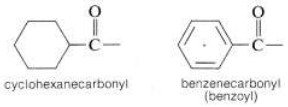
7.7: Acyl Groups, RCO-

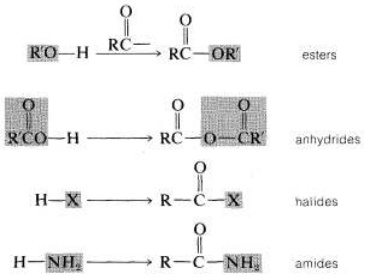
1. The function is called an *acyl* group and in specific cases in named by adding the suffix *-oyl* to the appropriate hydrocarbon prefix. That is, *alkane-* + *-oyl* becomes *alkanoyl*:



Acyl groups also may be called alkanecarbonyl or *cycloalkanecarbonyl* groups:



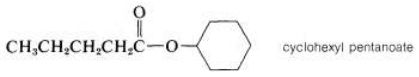
2. When an acyl group replaces the hydrogen of alcohols, carboxylic acids, hydrogen halides, ammonia or amines, we have the acyl compounds known as esters, anhydrides, halides, and amides, respectively.



Each of these types of compounds are named as follows.Image

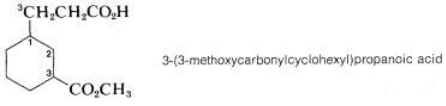
7.7.1: Carboxylic Esters, RCO_2R'

1. The name of the parent carboxylic acid (alkanoic) is changed to alkano*ate* and is preceded, as in a separate word, by the name of the ester alkyl group R':



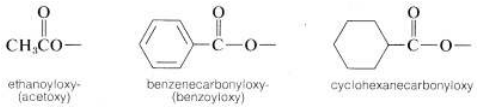
2. When appropriate, esters also are named as carboxylates:

3. When it is necessary to name the $-CO_2R'$ function as a substituent, it becomes *alkoxycarbonyl*, . (Notice that this is structurally different from .)



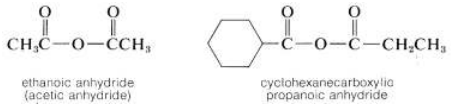
Notice the use of parentheses to separate the numbering of $C3$ of the cyclohexane ring from the numbering of the chain.

4. It also may be necessary at times to name the $R'CO_2-$ group as a substituent, in which case it becomes *acyloxy-* or R'-carbonyloxy-. For example,



7.7.2: Carboxylic Anhydrides, $RCOOCOR'$

Symmetrical anhydrides ($R = R'$) are named after the parent acid; unsymmetrical or "mixed" anhydrides ($R \neq R'$) cite each of the parent acids:

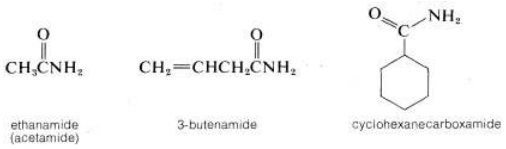


7.7.3: Acyl Halides, $RCOX$

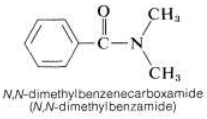
The acyl group, $RCO-$, and the halogen (as halide) are cited separately:

7.7.4: Amides, $RCONH_2$

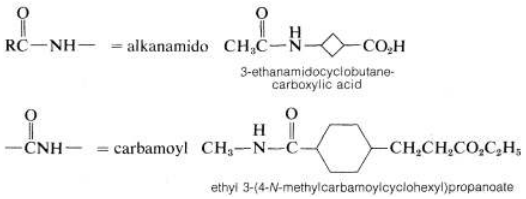
1. The suffix *amide* is appended to the name of the hydrocarbon corresponding to the carbon chain that includes the carbonyl group. That is, *alkan(e)* + *amide* = *alkanamide*. A one-carbon chain is a *carboxamide*:



2. When the amide nitrogen is substituted with lower-ranking groups than the acyl group, the substituents are designated as prefixes. The letter *N* is used to show that the substitution is on nitrogen:



3. Names for amides as substituents include the following:



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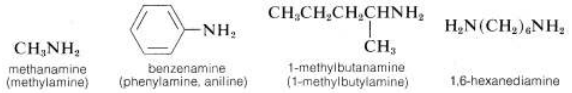
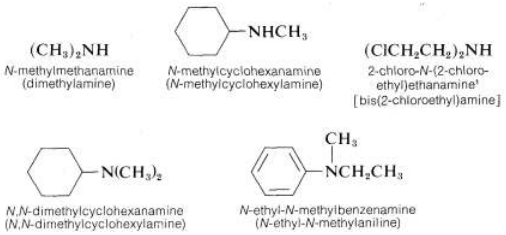
7.8: Amines

The word "amine" is derived from *ammonia*, and the class of compounds known as amines therefore are commonly named as substituted ammonias. In this system, **primary** amines (RNH_2), having only one substituent on nitrogen, are named with the substituent as a prefix. More systematic nomenclature appends *-amine* to the longest chain, as for alcohols:



Secondary (R_2NH) and **tertiary** amines (R_3N), which have two and three substituents on nitrogen, commonly are named as *N*-substituted amines. As for substituted amides, *N* is included to indicate that the substituent is on the nitrogen atom unless there is no ambiguity as to where the substituent is located. Systematic nomenclature of secondary and tertiary amines is related to the systematic ether nomenclature discussed in Section 7-3:



As a substituent, the $-NH_2$ group is called *amino*. N-Substituted amino groups are named accordingly:

[1]Alphabetical order puts *chloro-* ahead of *chloroethyl-*.

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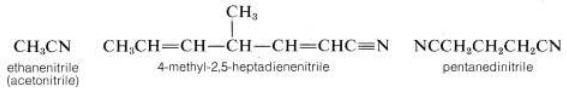
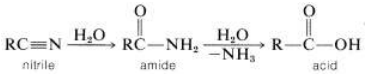
7.9: Nitriles, RCN

1. Compounds with the $\equiv N$ function are named by adding the suffix *nitrile* to the main-chain hydrocarbon that includes the carbon linked to the nitrile ($\equiv N$) function. The chain is numbered so the CN carbon is $C1$:

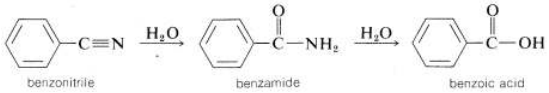


2. Compounds of the type RCN have to be called *carbonitriles* when R is a cycloalkane or similar group:

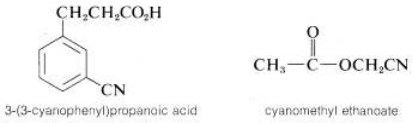
3. Nitriles can be regarded as derivatives of carboxylic acids because the acid, RCO_2H, usually can be obtained from the nitrile, RCN:



A common system of naming nitriles takes the name of the corresponding carboxylic acid and changes the suffix *-oic* to *-onitrile*:



4. The substituent name for $-CN$ is *cyano*. For example,



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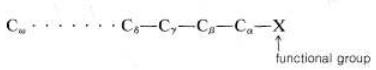
7.10: The Use of Greek Letters to Denote Substituent Positions

In the older literature, considerable use is made of the Greek letters α, β, γ, and so on, to designate successive positions along a hydrocarbon chain. The carbon *directly attached* to the principal function group is denoted as α, the second carbon is β, and so on down the chain:



The *omega* (ω) position is sometimes used to designate the last position along the chain regardless of its length. Thus ω-bromohexanoic acid is 6-bromohexanoic acid. In general, the use of Greek letters in the naming of compounds is to be avoided. Because the usage is widespread, cognizance of the system is important, but systematic naming and numbering systems should be used whenever possible.

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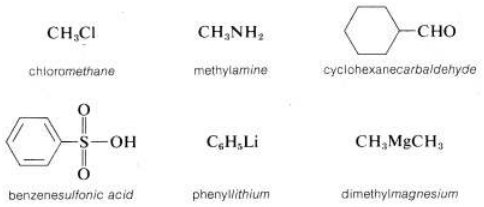
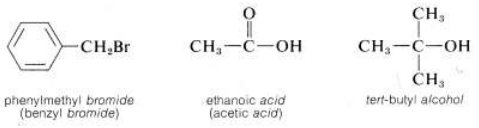
7.11: Single- or Multiple-Word Names

A troublesome point in naming chemical compounds concerns the rules governing when a compound is to be written as a *single* word (as *methylamine*) or as *two or more* words (as *methyl chloride*). To solve this problem, you must determine whether the principle or parent function is an element or a compounds in its own right; if it is either one, then the name is written as a single word.

The following examples should help to clarify the system. In each name, the part of the name that denotes the parent compound[2] is italicized:



However, if the parent function cannot be constructed as being a real compound, the name is correctly written as two or more words. For example, CH_3Cl could be named as a *chloride*, in which case we use two words, methyl chloride, to describe it. A chloride, or any halide, is a class of compound, not a specific compound. To identify a specific halide, the adjective that describes the halide is written as a separate word preceding the class name. Examples follow in which the class name is italicized.[3]



[2]The parent compounds designated here as *amine*, *carbaldehyde*, and *sulfonic acid* are properly ammonia, methanal, and sulfurous acid (HSO_3H) when no substituent groups are attached.

[3]These word-separated names sometimes are called **radicofunctional** names.

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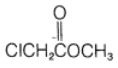
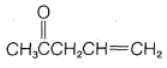
7.E: Other Compounds than Hydrocarbons (Exercises)

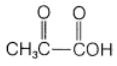
Exercise 7-1 Use Table 7-1 to classify each of the following compounds according to its *principal* functional group:

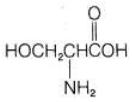
a. 

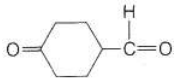
b. $H_2NCH_2CH_2OH$

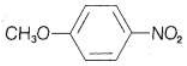
c. $N \equiv CCH_2CH_2OH$

d. 

e. 

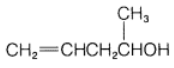
f. 

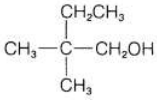
g. 

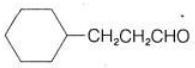
h. 

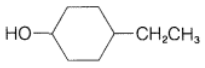
Exercise 7-2 Translate each of the following structures into the proper IUPAC name. Take cognizance of the order of precedence in Table 7-1 and use alphabetical order in citing substituent groups.

a. $CH_3CH_2CH_2OH$

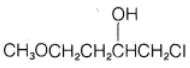
b. 

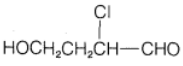
c. 

d. 

e. 

f. $CH_2{=}CH{-}C \equiv C{-}CH_2OH$

g. 

h. 

Exercise 7-3 Translate each of the following names into the appropriate structural formulas. Show the stereochemistry when that is indicated.

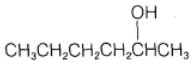
a. cyclopropanol

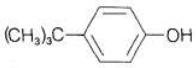
b. 2,2-dimethyl-1-pentanol

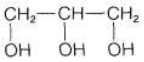
c. dicyclohexylmethanol

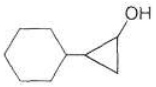
d. *cis*-2-buten-1-ol
e. tetramethoxymethane
f. *cis*-3-methyl-2-pentenal
g. *trans*-2-methylcyclohexanol
h. *meso*-2,3-butanediol

Exercise 7-4 Write systematic names for each of the following compounds:

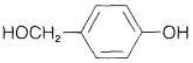
a. 

b. 

c. 

d. 

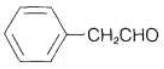
e.

f. 

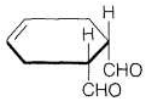
Exercise 7-5 Write structures corresponding to the following names:

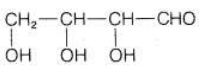
a. methyl phenyl ether
b. 2-methoxyethanol
c. 2-chloromethoxyethanol
d. bis(2,2-difluoropropyl) ether
e. 1,4-di-*tert*-butoxybenzene
f. *cis*-1-propenyloxybenzene

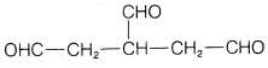
Exercise 7-6 Write appropriate names for each of the following structures. Indicate the stereochemistry where this is specified.

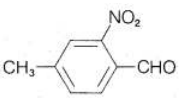
a. 

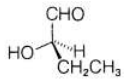
b. $HC \equiv C-CHO$

c. 

d. 

e. 

f. 

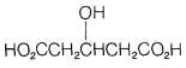
g. 

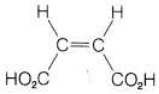
Exercise 7-7 Write appropriate structures corresponding to the following names. Show stereochemistry where specified.

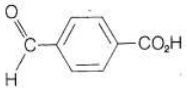
a. 3-methyl-2-butanone
b. 1-cyclopropyl-2-propen-1-one
c. 2-oxopropanal
d. ethenol (vinyl alcohol)
e. *D*-2-hydroxy-3-pentanone
f. *cis*-2,4-dimethylcyclobutanone

Exercise 7-8 Write systematic names for each of the following structures:

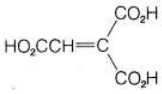
a. $(CH_3)_3CCH_2CO_2H$

b. 

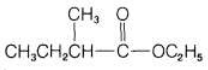
c. 

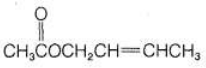
d. 

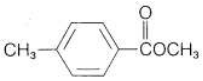
e. $(CH_2{=}CH{-}CO_2)_2Ca$

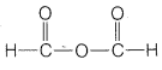
f. 

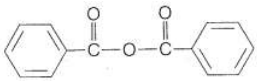
Exercise 7-9 Give the systematic names for each of the following compounds:

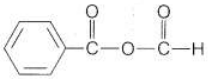
a. 

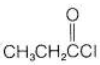
b. 

c. 

d. 

e. 

f. 

g. 

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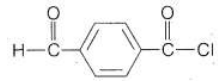
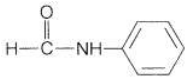
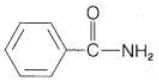
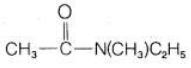
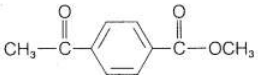
h. 

i. 

j. 

k. 

l. 

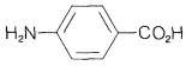
Exercise 7-10 Write appropriate structures for each of the following compounds. Show stereochemistry where specified.

a. N-methylmethanamide
b. propanoic anhydride
c. *D*-2-methylbutyl ethanoate
d. methyl 2-methanoylpropanoate
e. 3-ethanamidobenzenecarboxylic acid
f. *D*-1-methylpropyl-*L*-2-hydroxypropanoate

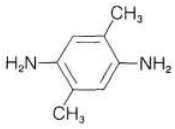
Exercise 7-11 Determine the systematic names for the following compounds:

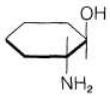
a. $CH_2{=}CHCH_2CH_2NH_2$

b. $CH_3CH_2CH_2N(CH_3)_2$

c. 

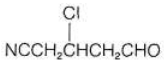
d. $CH_3CONHCH_2CH_2NH_2$

e. 

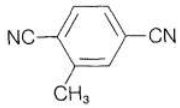
f. 

Exercise 7-12 Determine the systematic names for each of the following compounds:

a. $(CH_3)_2CHCH_2CN$

b. 

c. $NCCH_2CH_2CH_2CH_2CN$

d. 

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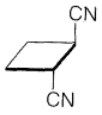
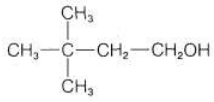
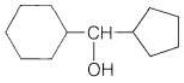
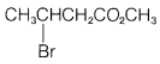
e. 

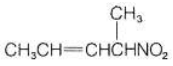
Exercise 7-13 Name each of the following compounds using systematic nomenclature:

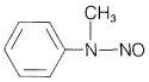
a. 

b. 

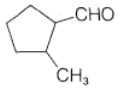
c. 

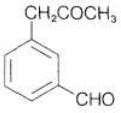
d. $BrCH_2CH_2OCH{=}CH_2$

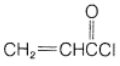
e. 

f. 

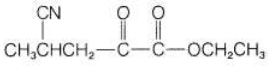
g.

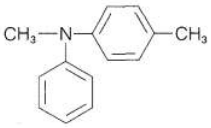
h. 

i. 

j. 

k. $CH \equiv CCH_2CN$

l. 

m. 

Exercise 7-14 Write structural formulas for each of the following substances:

a. 2-methyl-3-buten-2-ol
b. 2,3-dibromopropanoic acid
c. methyl cyclohexanecarboxylate
d. 2-hexanal
e. *trans*-3-ethenyl-2-hepten-6-ynal
f. 4-chloro-2-cyclohexenecarbaldehyde
g. (4-methanoylphenyl)ethanoic acid
h. 4-pentyn-2-one

i. cyclopentanecarbonyl chloride
j. *cis*-2-methyl-2-butenyl benzenecarboxylate
k. 3-nitrobenzenamine
l. butanedioic anhydride
m. 2-butenamide
n. heptanenitrile
o. 3-methylamino-2-oxopentanoic acid
p. phenoxyethanamide
q. N-butylphenylmethanamine
r. N-butyl-N-methylbenzenamine

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CHAPTER OVERVIEW

8: Nucleophilic Substitution and Elimination Reactions

Nucleophilic substitution is a fundamental class of reactions in which an electron rich nucleophile selectively bonds with or attacks the positive or partially positive charge of an atom or a group of atoms to replace a so-called leaving group.

8.1: Prelude to Nucleophilic Substitution and Elimination Reactions
8.2: Classification of Reagents as Electrophiles and Nucleophiles. Acids and Bases
8.3: Thermochemistry of Substitution Reactions
8.4: General Considerations of Substitution Reactions
8.5: Mechanisms of Nucleophilic Substitution Reactions
8.6: Stereochemistry of \(S_N2\) Reactions
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8.8: Structural and Solvent Effects in \(S_N\) Reactions
8.9: The E2 Reaction
8.10: The E1 Reaction
8.11: Elimination Reactions
8.E: Nucleophilic Substitution and Elimination Reactions (Exercises)

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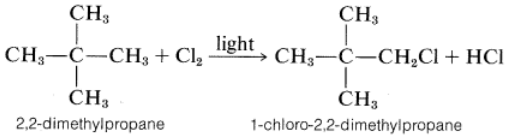
8.1: Prelude to Nucleophilic Substitution and Elimination Reactions

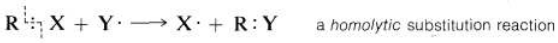
Substitution reactions involve the replacement of one atom or group (X) by another (Y):

$$RX + Y \rightarrow RY + X \tag{8.1.1}$$

We already have described one very important type of substitution reaction, the halogenation of alkanes (Section 4-4), in which a hydrogen atom is replaced by a halogen atom (X = H, Y = halogen). The chlorination of 2,2-dimethylpropane is an example:



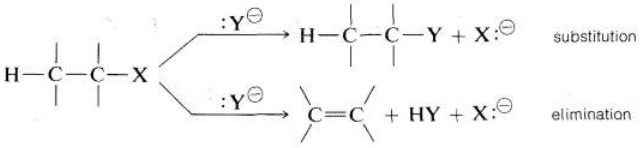
Reactions of this type proceed by radical-chain mechanisms in which the bonds are broken and formed by atoms or radicals as reactive intermediates. This mode of bond-breaking, in which one electron goes with R and the other with X, is called **homolytic** bond cleavage:



There are a large number of reactions, usually occurring in solution, that do *not* involve atoms or radicals but rather involve ions. They occur by **heterolytic** cleavage as opposed to homolytic cleavage of electron-pair bonds. In heterolytic bond cleavage, the electron pair can be considered to go with one or the other of the groups R and X when the bond is broken. As one example, Y is a group such that it has an unshared electron pair and also is a negative ion. A heterolytic substitution reaction in which the R:X bonding pair goes with X would lead to RY and $:X^{\ominus}$,

A specific substitution reaction of this type is that of chloromethane with hydroxide ion to form methanol:

In this chapter, we shall discuss substitution reactions that proceed by ionic or polar mechanisms in which the bonds cleave heterolytically. We also will discuss the mechanistically related **elimination** reactions that result in the formation of carbon-carbon multiple bonds:



These reactions often are influenced profoundly by seemingly minor variations in the structure of the reactants, in the solvent, or in the temperature. It is our purpose to show how these reactions can be understood and how they can be used to prepare other useful organic compounds. But first it will be helpful to introduce the concepts of **nucleophilic** and **electrophilic** reagents, and to consider the ΔH values for heterolytic bond breaking.

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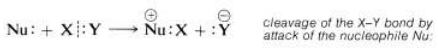
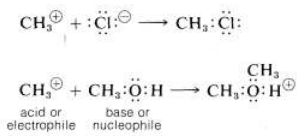
8.2: Classification of Reagents as Electrophiles and Nucleophiles. Acids and Bases

To understand ionic reactions, we need to be able to recognize whether a particular reagent will act to *acquire an electron pair* or to *donate an electron pair*. Reagents that acquire an electron pair in chemical reactions are said to be **electrophilic** ("electron-loving"). We can picture this in a general way as a heterolytic bond breaking of compound $X:Y$ by an electrophile E such that E becomes bonded to Y by the electron pair of the XY bond. Thus

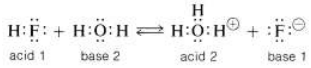
Reagents that donate an electron pair in chemical reactions are said to be **nucleophilic** ("nucleus loving"). Thus the $X:Y$ bond also can be considered to be broken by the nucleophile $Nu:$, which donates its electron pair to X while Y leaves as $Y:^{\ominus}$ with the electrons of the $X:Y$ bond:



Thus, by definition, electrophiles are electron-pair acceptors and nucleophiles are electron-pair donors. These definitions correspond closely to definitions used in the generalized theory of acids and bases proposed by G. N. Lewis (1923). According to Lewis, an acid is any substance that can accept an electron pair, and a base is any substance that can donated an electron pair to form a covalent bond. Therefore acids must be electrophiles and bases must be nucleophiles. For example, the methyl cation may be regarded as a **Lewis acid**, or an electrophile, because it *accepts* electrons from reagents such as chloride ion or methanol. In turn, because chloride ion and methanol donate electrons to the methyl cation they are classified as **Lewis bases**, or nucleophiles:

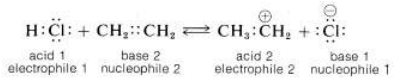


The generalized Lewis concept of acids and bases also includes common proton-transfer reactions.[1] Thus water acts as a base because one of the electron pairs on oxygen can abstract a proton from a reagent such as hydrogen fluoride:



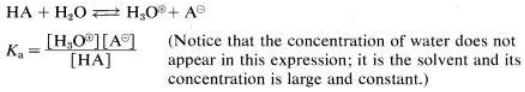
Alternatively, the hydronium ion ($H_3O^{\oplus}$) is an acid because it can accept electrons from another reagent (e.g., fluoride ion) by donating a proton.

A proton donor can be classified as an electrophile and a proton acceptor as a nucleophile. For example, hydrogen chloride can transfer a proton to ethene to form the ethyl cation. Therefore hydrogen chloride functions as the electrophile, or acid, and ethene functions as the nucleophile, or base:



What then is the difference between an acid and an electrophile, or between a base and nucleophile? No great difference until we try to use the terms in a *quantitative* sense. For example, if we refer to acid strength, or acidity, this means the position of *equilibrium* in an acid-base reaction. The equilibrium constant K_a for the dissociation of an acid HA, or the pK_a, is a quantitative measure of acid strength. The larger the value of K_a or the smaller the pK_a, the stronger the acid.

A summary of the relationships between K_a and pK_a follow, where the quantities in brackets are concentrations:



or

$$-\log K_a = -\log [H_3O^{\oplus}] + \log \frac{[HA]}{[A^{\ominus}]}$$

By definition, $-\log K_a = pK_a$ and $-\log [H_3O^{\oplus}] = pH$; hence

$$pK_a = pH + \log \frac{[HA]}{[A^{\ominus}]}$$

or

$$pK_a = pH + \log \frac{[\text{undissociated acid}]}{[\text{anion of the acid}]}$$

(This sometimes is referred to as the Henderson-Hasselbalch equation.)

However, in referring to the strength of reagents as electrophiles or nucleophiles we usually are not referring to chemical equilibria but to *reaction rates*. A good nucleophile is a reagent that reacts rapidly with a particular electrophile. In contrast, a poor nucleophile reacts only slowly with the same electrophile. Consequently, it should not then be taken for granted that there is a parallel between the acidity or basicity of a reagent and its reactivity as an electrophile or nucleophile. For instance, it is incorrect to assume that the strengths of a series of bases, $B:$, in aqueous solution will *necessarily* parallel their nucleophilicities toward a carbon electrophile, such as methyl chloride:

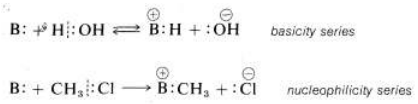
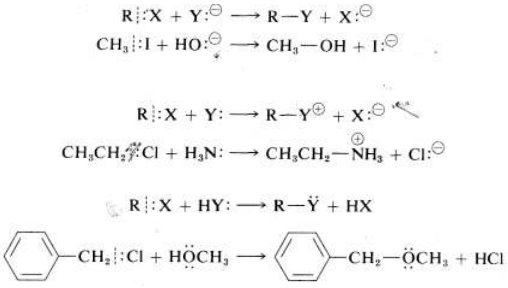
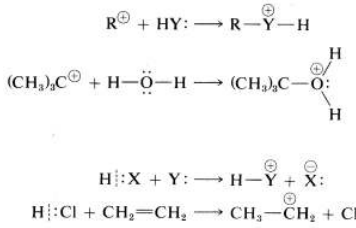


Figure 4-4). Even so, it turns out that most strong bases are good nucleophiles and that most strong proton acids are good electrophiles. We will see that the converse may not be true. Good nucleophiles are not always strong bases [examples are $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$, and $(CH_3)_2S$] and good electrophiles are not always strong acids by either the Bronsted-Lowry or Lewis definitions (examples are $HOBr$, Br_2, Cl_2, I_2).

In what follows we will be concerned with the rates of ionic reactions under *nonequilibrium* conditions. We shall use the term *nucleophilic* repeatedly and we want you to understand that a nucleophile is any neutral or charged reagent that supplies a pair of electrons, either bonding or nonbonding, to form a new covalent bond. In substitution reactions the nucleophile usually is an anion, $Y:^{\ominus}$, or a neutral molecule, $Y:$ or $HY:$. The operation of each of these is illustrated in the following equations for reactions of the general compound RX and some specific examples:



An *electrophile* is any neutral or charged reagent that accepts an electron pair (from a nucleophile) to form a new bond. In the preceding substitution reactions, the electrophile is RX. The electrophile in other reactions may be a carbon cation or a proton donor, as in the following examples:



[1]The concept of an acid as a **proton donor** and a base as a **proton acceptor** is due to Bronsted and Lowry (1923). Previous to this time, acids and bases generally were defined as substances that functioned by forming $H^{\oplus}$ or $OH^{\ominus}$ in water solutions. The

Bronsted-Lowry concept was important because it liberated acid-base phenomena from the confines of water-containing solvents by focusing attention on *proton transfers* rather than the formation of $H^{\oplus}$ or $OH^{\ominus}$. The Lewis concept of generalized acids and bases further broadened the picture by showing the relationship between proton transfers and reactions where an electron-pair acceptor is transferred from one electron-pair donor to another.

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8.3: Thermochemistry of Substitution Reactions

Ionic or polar reactions of alkyl halides rarely are observed in the vapor phase because the energy required to dissociate a carbon-halogen bond heterolytically is almost prohibitively high. For example, while the heat of dissociation of chloromethane to a methyl radical and a chlorine atom is $84\ \text{kcal mol}^{-1}$ (Table 4-6), dissociation to a methyl cation and a chloride ion requires about $227\ \text{kcal mol}^{-1}$:

$$CH_3{:}Cl(g) \longrightarrow CH_3\cdot(g) + Cl\cdot(g) \qquad \Delta H^0 = +84\ \text{kcal}$$

$$CH_3{:}Cl(g) \longrightarrow CH_3^{\oplus}(g) + Cl^{\ominus}(g) \qquad \Delta H^0 = +227\ \text{kcal}$$

However, the heat of ionic dissociation of methyl chloride in aqueous solution is estimated to be $63\ \text{kcal}$, and while this reaction is still substantially endothermic, it requires about $227 - 63 = 164\ \text{kcal}$ *less* energy than in the gas phase:

$$CH_3{:}Cl(aq) \longrightarrow CH_3^{\oplus}(aq) + Cl^{\ominus}(aq) \qquad \Delta H^0 = +63\ \text{kcal}$$

The reason is that ions are much more stable in water than in the gas phase; for example, the transfer of a chloride ion from the gas to water is exothermic by $-85\ \text{kcal}$. The ΔH^0 value for the corresponding transfer of a methyl cation, $CH_3^{\oplus}$, is not known with certainty, but is about $-80\ \text{kcal}$. These ionic **solvation energies** are clearly large. In contrast, the ΔH^0 for solution of methyl chloride in water is small (about $1\ \text{kcal}$). We can use these data to calculate the heat of ionic dissociation of chloromethane in water:

	$CH_3Cl(g) \longrightarrow CH_3^{\oplus}(g) + Cl^{\ominus}(g)$	$\Delta H^0 = +227\ \text{kcal}$[2]
	$CH_3Cl(aq) \longrightarrow CH_3Cl(g)$	$\Delta H^0 = +1\ \text{kcal}$
	$CH_3^{\oplus}(g) \longrightarrow CH_3^{\oplus}(aq)$	$\Delta H^0 = -80\ \text{kcal}$
	$Cl^{\ominus}(g) \longrightarrow Cl^{\ominus}(aq)$	$\Delta H^0 = -85\ \text{kcal}$
net:	$CH_3Cl(aq) \longrightarrow CH_3^{\oplus}(aq) + Cl^{\ominus}(aq)$	$\Delta H^0 = +63\ \text{kcal}$

Thermochemical data for the solvation of ions as used in the preceding calculations are difficult to measure and even to estimate. Therefore this kind of calculation of ΔH^0 for ionic reactions involving organic molecules in solution usually cannot be made. As a result, we have considerably fewer possibilities to assess the thermodynamic feasibility of the individual steps of polar reactions in solution than we do of vapor-phase radical processes. Bond energies are not of much use in predicting or explaining reactivity in ionic reactions unless we have some information that can be used to translate gas-phase ΔH^0 values to solution ΔH^0 values.

[2]Calculated from the following data:

$CH_3Cl(g) \longrightarrow CH_3\cdot(g) + Cl\cdot(g)$	$\Delta H^0 = +84\ \text{kcal}$	bond-dissociation energy
$CH_3\cdot(g) \longrightarrow CH_3^{\oplus}(g) + e^{\ominus}$	$\Delta H^0 = +226.7\ \text{kcal}$	ionization potential from mass spectral studies
$Cl\cdot(g) + e^{\ominus} \longrightarrow Cl^{\ominus}(g)$	$\Delta H^0 = -83.2\ \text{kcal}$	electron affinity from mass spectral studies
	$\Delta H^0 = +227\ \text{kcal}$	

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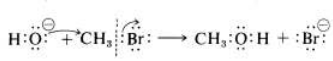
8.4: General Considerations of Substitution Reactions

We now wish to discuss displacements by *nucleophilic* reagents (Y :) on alkyl derivatives (RX). These are *ionic* or *polar* reactions involving attack by a nucleophile at *carbon*. A typical example is the reaction of hydroxide ion with bromomethane to displace bromide ion:



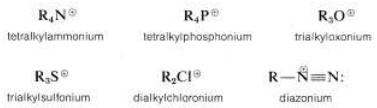
The electron pair of the $C-O$ bond can be regarded as having been donated by the hydroxide ion, while the electron pair of the $C-Br$ bond departs with the leaving bromide ion. The name for this type of reaction is abbreviated S_N, S for substitution and N for nucleophilic.

Reactions of this type are very useful. They can lead to compounds in which the new bond to carbon in the alkyl group, R is to chlorine, bromine, iodine, oxygen, sulfur, carbon, nitrogen, or phosphorus, depending on the nature of the nucleophile used.

Nucleophilic substitutions are especially important for alkyl halides, but they should not be considered to be confined to alkyl halides. Many other alkyl derivatives such as alcohols, ethers, esters, and "onium ions"[3] also can undergo S_N reactions if conditions are appropriate. The scope of S_N reactions is so broad that it is impossible to include all the various alkyl compounds and nucleophiles that react in this manner. Rather we shall approach the subject here through consideration of the mechanisms of S_N reactions, and then develop the scope of the reactions in later chapters.

The mechanism of an S_N reaction and the reactivity of a given alkyl compound RX toward a nucleophile Y depend upon the nature of R, X, and Y, and upon the nature of the solvent. For an S_N reaction to occur at a reasonable rate, it is very important to select a solvent that will dissolve both the alkyl compound and the nucleophilic reagent; considerable assistance may be required from both the solvent and the nucleophile to break what usually is a slightly polar $C-X$ bond. However, the solvents that best dissolve slightly polar organic compounds seldom will dissolve the common, rather highly polar, nucleophilic agents such as $NaBr$, $NaCN$, and H_2O. In practice, relatively polar solvents, or solvent mixtures, such as 2-propanone (acetone), aqueous 2-propanone, ethanol, aqueous 1,4-dioxacyclohexane (dioxane), and so on, provide the best compromise for reactions between alkyl compounds and saltlike nucleophilic reagents. The importance of the solvent in stabilizing ions can be evaluated from the estimated thermochemistry of ionic reactions discussed in Section 8-2.

[3]Examples of -onium cations are



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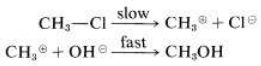
8.5: Mechanisms of Nucleophilic Substitution Reactions

Two simple mechanisms can be written for the reaction of chloromethane with hydroxide ion in aqueous solution that differ in the *timing* of bond breaking relative to bond making. In the first mechanism, A, the overall reaction is the result of two steps, the first of which involves a *slow* dissociation of chloromethane to solvated methyl carbocation[4] and solvated chloride ion. The second step involves a *fast* reaction between the carbocation and hydroxide ion (or water) to yield methanol.

Mechanism A:



or

In the second mechanism, B, the reaction proceeds in a single step. Attack of hydroxide ion at carbon occurs simultaneously with the loss of chloride ion; that is, the carbon-oxygen bond is formed as the carbon-chlorine bond is broken:

Mechanism B:

Both of these mechanisms are important in the displacement reactions of alkyl compounds, although chloromethane appears to react *only* by Mechanism B. Now we will discuss the criteria for distinguishing between the concerted and stepwise mechanisms.

8.5.1: Kinetics of Substitution Mechanisms

Of the two mechanisms, A requires that the reaction rate be determined solely by the rate of the first step (cf. earlier discussion in Section 4-4C). This means that the rate at which methanol is formed (measured in moles per unit volume per unit time) will depend on the chloromethane concentration, but *not* on the hydroxide ion concentration, because hydroxide ion is not utilized except in a *fast secondary* reaction. In contrast, Mechanism B requires the rate to depend on the concentrations of both reagents because the slow step involves collisions between hydroxide ions and chloromethane molecules.

$$v = k_A[CH_3Cl] \tag{8.5.1}$$

$$v = k_B[CH_3Cl][OH^-] \tag{8.5.2}$$

More precisely, the reaction rate (ν) may be expressed in terms of Equation 8.5.1 for Mechanism A and Equation 8.5.2 for Mechanism B:

Customarily, ν is expressed in moles of product formed per liter of solution per unit of time (most frequently in seconds). The concentration terms $[CH_3Cl]$ and $[OH^{\ominus}]$ are then in units of moles per liter, and the proportionality constant k (called the specific rate constant) has the units of sec^{-1} for Mechanism A and $\mathrm{mol}^{-1} \times \mathrm{L} \times \mathrm{sec}^{-1}$ for Mechanism B.

It is important to recognize the difference between *the order of a reaction with respect to a specific reactant* and the *overall order of a reaction*. The order of a reaction with respect to a *particular* reactant is the power to which the concentration of *that reactant* must be raised to have direct proportionality between concentration and reaction rate. According to Equation 8.5.2 the rate of the chloromethane-hydroxide ion reaction is *first order* with respect to chloromethane and *first order* with respect to hydroxide ion. In Equation 8.5.1 the rate is *first order* with respect to chloromethane and *zero order* with respect to hydroxide ion because $[OH^{\ominus}]^0 = 1$. The *overall order* of reaction is the *sum* of the orders of the respective reactants. Thus Equations 8.5.1 and 8.5.2 express the rates of overall *first-order* and *second-order* reactions, respectively.

We can use the overall reaction order to distinguish between the two possible mechanisms, A and B. Experimentally, the rate of formation of methanol is found to be proportional to the concentrations *both* of chloromethane and of hydroxide ion. Therefore the reaction rate is second order overall and is expressed correctly by Equation 8.5.2. This means that the mechanism of the reaction is

the single-step process B. Such reactions generally are classified as **bimolecular nucleophilic substitutions**, often designated S_N2, S for substitution, N for nucleophilic, and 2 for bimolecular, because there are *two* reactant molecules in the transition state. To summarize: For an S_N2 reaction,

- rate:

$$v = k[RX][Y] \tag{8.5.3}$$

- mechanism:

The stepwise Mechanism A is a **unimolecular nucleophilic substitution** and accordingly is designated S_N1. The numeral 1 (or 2) used in these designations does *not* refer to the kinetic order of the reaction, but refers to the number of molecules (not including solvent molecules) that make up the transition state. Thus for S_N1,

- rate:

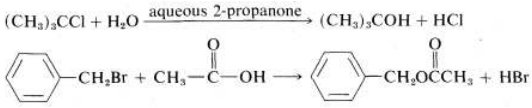
$$v = k[RX] \tag{8.5.4}$$

- mechanism:

or

8.5.2: Solvolysis

Many S_N reactions are carried out using the solvent as the nucleophilic agent. They are called solvolysis reactions and involve solvents such as water, ethanol, ethanoic acid, and methanoic acid. Two examples are



In these examples, solvolysis is necessarily a first-order reaction, because normally the solvent is in such great excess that its concentration does not change appreciably during reaction, and hence its contribution to the rate does not change. However, that the *overall* rate is first order does not mean the reaction necessarily proceeds by an S_N1 mechanism, particularly in solvents such as water, alcohols, or amines, which are reasonably good nucleophilic agents. The solvent can act as the displacing agent in an S_N2 reaction.

To distinguish between S_N1 and S_N2 mechanisms *of solvolysis* requires other criteria, notably stereochemistry (Sections 8-5 and 8-6), and the effect of added nucleophiles on the rate and nature of the reaction products. For example, it often is possible to distinguish between S_N1 and S_N2 solvolysis by adding to the reaction mixture a relatively small concentration of a substance that is expected to be a more powerful nucleophile than the solvent. If the reaction is strictly S_N1, the rate at which RX disappears should remain essentially unchanged because it reacts only as fast as $R^{\oplus}$ forms, and the rate of this step is not changed by addition of the nucleophile, even if the nucleophile reacts with $R^{\oplus}$. However, if the reaction is S_N2, the rate of disappearance of RX should *increase* because RX reacts with the nucleophile in an S_N2 reaction and now the rate depends on both the nature and the concentration of the nucleophile.

[4]Many organic chemists, and indeed the previous versions of this book, use the term "carbonium ion" for species of this kind. However, there is well-established usage of the *-onium* suffix, for ammonium, oxonium, chloronium, and so on, to denote positively charged atoms with *filled* valence shells. In the interest of greater uniformity of nomenclature we shall use "carbocation" for carbon positive ions that have unfilled valence shells (6 electrons).

8.5.3: Contributors and Attributions

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8.6: Stereochemistry of S_N2 Reactions

There are two simple ways in which the S_N2 reaction of methyl chloride could occur with hydroxide ion. These differ in the direction of approach of the reagents (Figure 8-1). The hydroxide ion could attack chloromethane at the **front side** of the carbon where the chlorine is attached or, alternatively, the hydroxide ion could approach the carbon on the side opposite from the chlorine in what is called the **back-side** approach. In either case, the making of the $C-O$ bond is essentially *simultaneous* with the breaking of the $C-Cl$ bond. The difference is that for the back-side mechanism the carbon and the attached hydrogens become planar in the transition state.

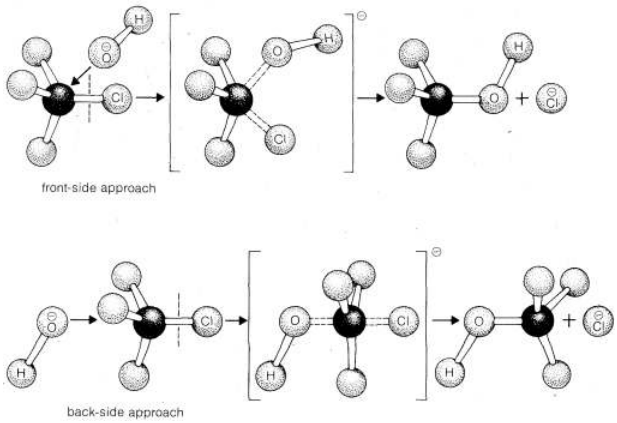


Figure 8.1: Back-side (inverting) and front-side (noninverting) approach of hydroxide ion on methyl chloride, as visualized with ball-and-stick models

The stereochemical consequences of front- and back-side displacements are different. With cyclic compounds, the two types of displacement lead to *different* products. For example, an S_N2 reaction between *cis*-3-methylcyclopentyl chloride and hydroxide ion would give the cis alcohol by front-side approach but the trans alcohol by back-side approach. The actual product is the trans alcohol, from which we know that reaction occurs by back-side displacement:

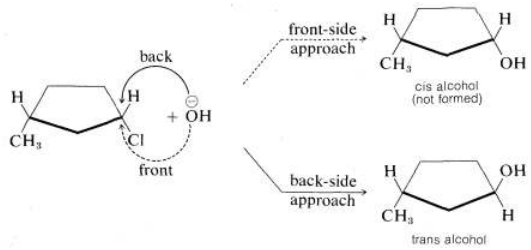


Figure 8-2, demonstrates that front-side displacement of chloride by hydroxide ion will give an enantiomer of 2-butanol of the same configuration as the original chloride, whereas back-side displacement will give the alcohol of the opposite, or *inverted*, configuration. Experiments using either of the two enantiomers show that hydroxide ion attacks 2-chlorobutane exclusively by back-side

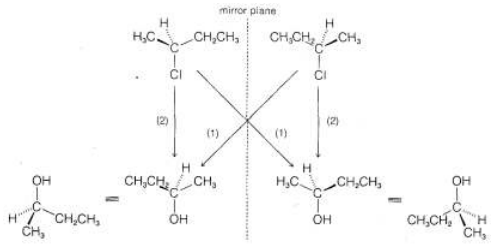
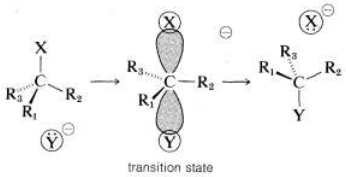


Figure 8.2: Stereochemistry of displacement of 2-chlorobutane with hydroxide by (1) front-side attack (not observed) and (2) back-side attack

displacement to give 2-butanol with the inverted configuration. Similar studies of a wide variety of displacements have established that S_N2 reactions invariably proceed with inversion of configuration via back-side attack. This stereochemical course commonly is known as the **Walden inversion**.[5] An orbital picture of the transition state of an S_N2 reaction that leads to inversion of configuration follows:



[5]The first documented observation that optically active compounds could react to give products having the opposite configuration was made by P. Walden, in 1895. The implications were not understood, however, until the mechanisms of nucleophilic substitution were elucidated in the 1930's, largely through the work of E. D. Hughes and C. K. Ingold, who established that S_N2 substitutions give products of inverted configuration.

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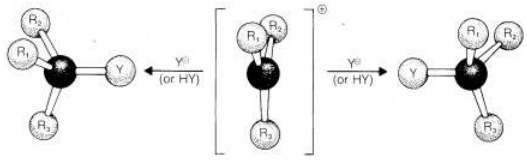
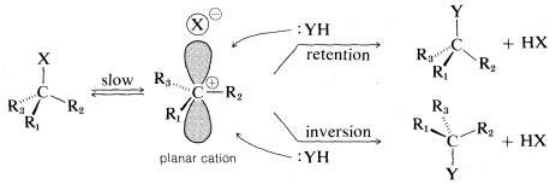
8.7: Stereochemistry of S_N1 Reactions

When an S_N1 reaction is carried out starting with a single pure enantiomer, such as *D*-2-chlorobutane, the product usually is a mixture of the enantiomeric substitution products with a slight predominance of that isomer which corresponds to inversion. Theoretically, a carbocation is expected to be most stable in the planar configuration (Section 6-4E) and hence should lead to exactly equal amounts of the two enantiomers, regardless of the chiral configuration of the starting material (Figure 8-3). However, the extent of configuration change that actually results in an S_N1 reaction depends upon the degree of "shielding" of the front side of the reacting carbon by the leaving group and its associated solvent molecules. If the leaving group does not get away from the carbocation before the product-determining step takes place, there will be some preference for nucleophilic attack at the *back side* of the carbon, which results in a predominance of the product of *inverted* configuration.



Other things being equal, the amount of inversion decreases as the stability of the carbocation intermediate increases, because the more stable the ion the longer is its lifetime, and the more chance it has of getting away from the leaving anion and becoming a relatively "free" ion. The solvent usually has a large influence on the stereochemical results of S_N1 reactions because the stability and lifetime of the carbocations depend upon the nature of the solvent (Section 8-7F).

An orbital picture of S_N1 ionization leading to a racemic product may be drawn as follows:



It should be clear that *complete* racemization is unlikely to be observed if $X^{\ominus}$ stays in close proximity to the side of the positive carbon that it originally departed from. We can say that $X^{\ominus}$ "shields" the front side, thereby favoring a predominance of inversion. If $X^{\ominus}$ gets far away before $:YH$ comes in, then there should be no favoritism for one or the other of the possible substitutions.

If $X^{\ominus}$ and the carbocation, $R^{\oplus}$, stay in close proximity, as is likely to be the case in a solvent that does not promote ionic dissociation, then a more or less "tight" ion pair is formed, $R^{\oplus} \cdots X^{\ominus}$. Such ion pairs often play an important role in ionic reactions in solvents of low dielectric constant (Section 8-7F).

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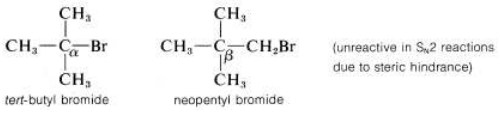
8.8: Structural and Solvent Effects in S_N Reactions

We shall consider first the relationship between the structures of alkyl derivatives and their reaction rates toward a given nucleophile. This will be followed by a discussion of the relative reactivities of various nucleophiles toward a given alkyl derivative. Finally, we shall comment in more detail on the role of the solvent in S_N reactions.

8.8.1: Structure of the Alkyl Group, R, in S_N2 Reactions

The rates of S_N2-displacement reactions of simple alkyl derivatives, RX, follow the order *primary* $R >$ *secondary* $R \gg$ *tertiary* R. In practical syntheses involving S_N2 reactions, the primary compounds generally work very well, secondary isomers are fair, and the tertiary isomers are almost completely impractical. Steric hindrance appears to be particularly important in determining S_N2 reaction rates, and the slowness of tertiary halides seems best accounted for by steric hindrance to the back-side approach of an attacking nucleophile by the alkyl groups on the reacting carbon. Pertinent data, which show how alkyl groups affect S_N2 reactivity toward iodide ion, are given in Table 8-1. Not only do alkyl groups suppress reactivity when on the same carbon as the leaving group X, as in *tert*-butyl bromide, but they also have retarding effects when located one carbon away from the leaving group. This is evident in the data of Table 8-1 for 1-bromo-2,2-dimethylpropane (neopentyl bromide), which is very unreactive in S_N2 reactions. Scale models indicate the retardation to be the result of steric hindrance by the methyl groups located on the adjacent β carbon to the approaching nucleophile:



tert-butyl bromide neopentyl bromide

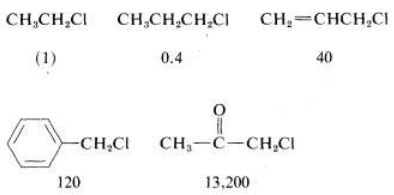
Table 8-1
Rates of S_N2 Displacement of Alkyl Bromides with Iodide Ion in 2-Propanone (Acetone) Relative to Ethyl Bromide at 25°

$RBr + I^{\ominus} \longrightarrow RI + Br^{\ominus}$

R: (α substitution)	CH_3-	CH_3CH_2-	$CH_3-CH(CH_3)-$	$CH_3-C(CH_3)_2-$
relative rate:	145	(1)	0.0078	<0.00051

R: (β substitution)	CH_3CH_2-	$CH_3-CH_2-CH_2-$	$CH_3-CH(CH_3)-CH_2-$	$CH_3-C(CH_3)_2-CH_2-$
relative rate:	(1)	0.82	0.036	0.000012

In addition to steric effects, other structural effects of R influence the S_N2 reactivity of RX. A double bond β to the halogen,[6] as in 2-propenyl, phenylmethyl (benzyl), and 2-oxopropyl chlorides enhances the reactivity of the compounds toward nucleophiles. Thus the relative reactivities toward $I^{\ominus}$ in 2-propanone are



Possible reasons for these high reactivities will be discussed later (Section 14-3B).

8.8.2: Structure of the Alkyl Group, R, in S_N1 Reactions

The rates of S_N1 reactions of simple alkyl derivatives follow the order *tertiary* $R \gg$ *secondary* $R >$ *primary* R, which is exactly opposite that of S_N2 reactions. This is evident from the data in Table 8-2, which lists the relative rates of hydrolysis of some alkyl bromides; only the secondary and tertiary bromides react at measurable rates, and the tertiary bromide reacts some 10^5 times faster than the secondary bromide.

Why do tertiary alkyl compounds ionize so much more rapidly than either secondary or primary compounds? The reason is that tertiary alkyl cations are more *stable* than either secondary or primary cations and therefore are formed more easily. You will appreciate this better by looking at the energy diagram of Figure 8-4, which shows the profile of energy changes for hydrolysis of an alkyl compound, RX, by the S_N1 mechanism. The *rate* of

Table 8-2
Rates of Hydrolysis of Alkyl Bromides in Water at 50° Relative to Ethyl Bromide

$RBr \longrightarrow R^{\oplus} + Br^{\ominus} \xrightarrow{H_2O} ROH + HBr$

R:	CH_3-	CH_3CH_2-	$CH_3CH(CH_3)-$	$(CH_3)_3C-$
relative rate:	1.05[a]	(1.00)[a]	11.6	1.2×10^6

[a]The reaction mechanism is almost surely S_N2 with solvent acting as the nucleophile because addition of hydroxide ion causes the reaction rate to increase markedly (see Section 8-4B). The relative rate given can be regarded only as an upper limit to the actual S_N1 value, which may be as much as 10^5 times slower.

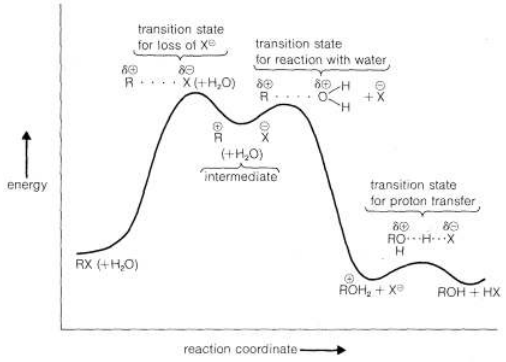
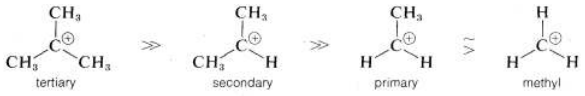


Figure 8-4: Profile of energy changes for hydrolysis of RX by the S_N1 mechanism in accord with the steps $RX \overset{\text{slow}}{\rightarrow} R^{\oplus}X^{\ominus} \underset{\text{fast}}{\overset{H_2O}{\rightarrow}} R\overset{\oplus}{O}H_2 + X^{\ominus} \rightarrow ROH + HX$. The last step is not part of the S_N1 process itself but is included for completeness. The water molecule shown in parentheses $(+H_2O)$ is necessary to balance the equations, but it should not be considered to be different from the other water molecules in the solvent until it is specifically involved in the second transition state.

reaction is determined by the ionization step, or by the energy of the transition state relative to that of the reactants. Actually, the energy of the transition state is only slightly higher than the energy of the ionic intermediates $R^{\oplus}X^{\ominus}$. Thus to a first approximation, we can say that the rate of ionization of RX will depend on the energies of the ions formed. Now if we compare the rates for a series of compounds, RX, all having the same leaving group, X, but differing only in the structure of R, their relative rates of ionization will correspond to the relative stabilities of $R^{\oplus}$. The lower energy of $R^{\oplus}$, the faster will be the rate of ionization. Therefore the experimental results suggest that the sequence of carbocation stabilities is *tertiary* $R^{\oplus} \gg$ *secondary* $R^{\oplus} \gg$ *primary* $R^{\oplus}$.

Just why this sequence is observed is a more difficult question to answer. Notice in the following stability sequence that alkyl cations are more stable the more alkyl groups there are on the positive carbon:



The simplest explanation for why this is so is that alkyl groups are more **polarizable** than hydrogens. In this case, more polarizable means the electrons of the alkyl groups tend to move more readily toward the positive carbon than do those of the hydrogens. Such movements of electrons transfer part of the charge on the cationic carbon to the alkyl groups, thereby spreading the charge over a greater volume. This constitutes *electron delocalization*, which results in enhanced stability (see Section 6-5A).

An alternative way of explaining how the cationic charge is spread over the alkyl groups of a tertiary cation, such as the *tert*-butyl cation, is to write the cation as a hybrid of the following structures:

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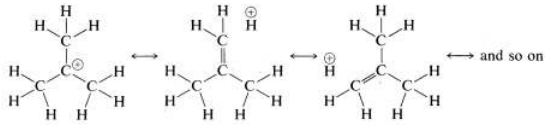
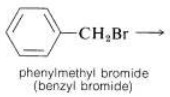
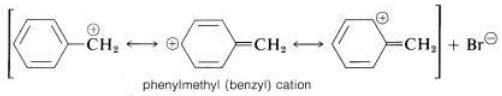
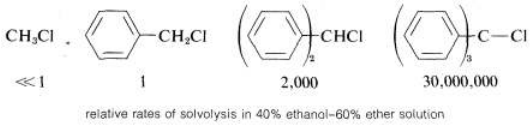


Other organohalogen compounds besides secondary and tertiary alkyl compounds can react by S_N1 mechanisms provided they have the ability to form reasonably stabilized carbon cations. Examples include 2-propenyl (allylic) and phenylmethyl (benzylic) compounds, which on ionization give cations that have delocalized electrons (see Section 6-6):

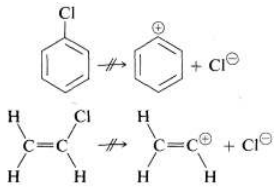




In general, the more stabilized the carbon cation from an alkyl halide, the more reactive the compound will be in S_N1-type reactions. This is especially apparent in the reactivities of compounds with phenyl groups on the reacting carbon. As the number of phenyl groups increases from zero to three, the S_N1 reactivity of the chlorides increases by more than 10^7 because of increasing stabilization of the carbon cation by the phenyl groups:

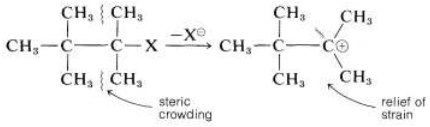


In contrast, compounds such as chlorobenzene and chloroethene, in which the halogen is attached directly to a multiply bonded carbon atom, do *not* exhibit S_N1-type reactions. Evidently then, unsaturated carbon cations such as phenyl or ethenyl are appreciably less stable (more difficult to form) than *tert*-alkyl cations:



Reasons for this will be considered in Section 14-4B.

Steric hindrance is relatively unimportant in S_N1 reactions because the rate is independent of the nucleophile. In fact, steric acceleration is possible in the solvolysis of highly branched alkyl halides through relief of steric compression between the alkyl groups in the halide by formation of a planar cation:



Along with the effect R has on the *rate* at which an alkyl compound RX reacts by an S_N1 mechanism, the group R also affects the nature of the products obtained. The intermediate alkyl cations $R^{\oplus}$ may react in various ways to give products of substitution, elimination, and rearrangement. Elimination pathways are discussed more fully starting in Section 8-8, and rearrangement of carbon cations in Section 8-9B.

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8.8.3: The Leaving Group

The reactivity of a given alkyl derivative, RX, in either S_N1 or S_N2 reactions, is influenced strongly by the leaving group, X. The choice of leaving group is therefore an important consideration in any synthesis involving S_N reactions.

From the foregoing discussion of structural effects in the R group on S_N reactivity, particularly in S_N1 reactions, we might expect the *stability* of $:X$ as an ion or neutral molecule to play a major role in determining how good or poor X is as a leaving group. The stability of $:X$ is indeed important - the problem is that there are several factors that contribute to the stavility and hence the lability of the leaving group.

For the purpose of initially identifying good and poor leaving groups, consider development of a practical synthesis of diethyl ether. One route is by way of S_N2 displacement using an ethyl compound, CH_3CH_2X, and ethoxide ion:

$$CH_3CH_2X + CH_3CH_2O^{\ominus} \longrightarrow CH_3CH_2OCH_2CH_3 + X^{\ominus}$$

Many CH_3CH_2X compounds have X groups that are quite unsatisfactory in this reaction. They include compounds such as ethane, propane, ethanol, ethyl methyl ether, ethylamine, and ethyl ethanoate; the respective groups, $H^{\ominus}$, $CH_3^{\ominus}$, $HO^{\ominus}$, $CH_3O^{\ominus}$, $NH_2^{\ominus}$, and $CH_3CO_2^{\ominus}$ all can be classified as *very poor* leaving groups. The more reactive ethyl derivatives (see Table 8-3) include the halides, particularly ethyl iodide, and sulfonic acid derivatives; the corresponding anions $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$, and $RS(O_2)O^{\ominus}$ therefore are *moderate to good* leaving groups. Table 8-3 includes pertinent data for the rates of ether formation from various alkyl compounds and illustrates that the relative abilities of groups to leave are about the same in S_N1 reactions as they are in S_N2 reactions.

Table 8-3
Dependence of Rate of S_N Reactions on the Leaving Group, X

S_N2 reaction: $CH_3CH_2X + C_2H_5O^{\ominus} \xrightarrow[25°]{C_2H_5OH} CH_3CH_2OCH_2CH_3 + X^{\ominus}$

X:	$-O-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-C_6H_5$	—I	—Br	—Cl	—F
relative rate[a]:	5.8	1.9	(1.0)	0.024[b]	–
C—X bond energy (kcal):	–	53	69	82	109

S_N1 reaction: $(CH_3)_2CHX + C_2H_5OH \xrightarrow[50°]{80\%\ C_2H_5OH} (CH_3)_2CHOCH_2CH_3 + HX$

X	$-O-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-C_6H_5$	—I	—Br	—Cl
relative rate[a]	76.3	–	(1.0)	0.0131

[a]The rates are relative to the bromo compound as 1.0. [b]At 40°.

Why are groups such as $I^{\ominus}$ and $RSO_3^{\ominus}$ good leaving groups, whereas others such as $H^{\ominus}$, $HO^{\ominus}$ and $NH_2^{\ominus}$ are poor? The simplest correlation is with the strength of HX as an *acid*. This is very reasonable because the ease of loss of $X^{\ominus}$, as from $(CH_3)C-X$ in an S_N1 reaction, would be expected to be related, to some degree at least, to the ease of ionization of $H-X$ to $H^{\oplus}$ and $X^{\ominus}$. Therefore the stronger HX is as an acid, the better X will be as a leaving group. Thus HF is a relatively weak acid and $F^{\ominus}$ is not a very good leaving group; $H-I$ is a very strong acid and $I^{\ominus}$ is a good leaving group. The usual order of reactivity of alkyl halides, $R-I > R-Br > R-Cl > R-F$ (when R is the same group throughout), is in accord with the acid strengths of the halogen acids. SImilarly, CF_3CO_2- is a much better leaving group than CH_3CO_2-, and we find that trifluoroethanoic acid, CF_3CO_2H is a several thousand times stronger acid than ethanoic acid, CH_3CO_2H. For the same reason, $CF_3SO_3^{\ominus}$ is a better leaving group than $CH_3XO_3^{\ominus}$.

This correlation can be extended easily to groups that leave as neutral X :. For example, $ROH_2^{\oplus} \rightarrow R^{\oplus} + H_2O$ occurs far more readily than $ROH \rightarrow R^{\oplus} + OH^{\ominus}$ and we know that $H_3O^{\oplus}$ is a stronger acid (or better proton donor) than H_2O.

The relationship between $X^{\ominus}$ as a leaving group and HX as an acid is very useful because much information is available on acid strengths. However, it is not a very fundamental explanation unless we can explain why some acids are strong acids and others are weak acids. One factor is the strength of the $H-X$ bond, but here we need to remember that the usual bond strengths are for dissociation to radicals or atoms, not ions, and for the gas, not for solutions. If we write the steps relating the bond-dissociation energy to the energy of ionic dissociation in solution, we see that for variations in X, in addition to the bond energy, the electron affinity of $X\cdot$, the solvation energy of $X^{\ominus}$, and the solvation energy of HX, also will be contributing factors.

$H—X(g) \longrightarrow H\cdot(g) + X\cdot(g)$	bond-dissociation energy
$X\cdot(g) + e^{\ominus} \longrightarrow X{:}^{\ominus}(g)$	electron affinity of X·
$H\cdot(g) \longrightarrow H^{\oplus}(g) + e^{\ominus}$	ionization energy of H·
$H—X(g) \longrightarrow H^{\oplus}(g) + X{:}^{\ominus}(g)$	energy of ionic dissociation in the gas
$H—X(aq) \longrightarrow H—X(g)$	− energy of solution of HX
$H^{\oplus}(g) \longrightarrow H^{\oplus}(aq)$	solvation energy of $H^{\oplus}$
$X{:}^{\ominus}(g) \longrightarrow X{:}^{\ominus}(aq)$	solvation energy of $X^{\ominus}$
$H—X(aq) \longrightarrow H^{\oplus}(aq) + X{:}^{\ominus}(aq)$	energy of ionic dissociation in water

Figure 8-5 and Table 8-3).

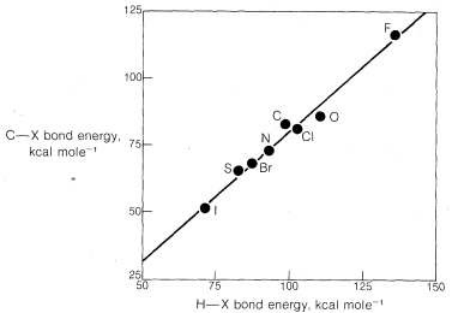


Figure 8-5: Plot of $C-X$ bond energies against $H-X$ bond energies, using the data of Table 4-3

8.8.4: Enhancement of Leaving Group Abilities by Electrophilic Catalysis

In general, a leaving group that leaves as a neutral molecule is a much better leaving group than one that leaves as an anion. Alcohols, ROH, are particularly *unreactive* in S_N reactions because $OH^{\ominus}$ is a very poor leaving group. However, if a strong acid is present, the reactivity of the alcohol is enhanced greatly. The acid functions by donating a proton to the oxygen of the alcohol, thereby transforming the hydroxyl function into $ROH_2^{\oplus}$, which has a much better leaving group, H_2O, in place of $OH^{\ominus}$. The S_N reactions of ethers and esters are acid-catalyzed for the same reason.

Heavy-metal salts, particularly those of silver, mercury, and copper, catalyze S_N1 reactions of alkyl halides in much the same way that acids catalyze the S_N reactions of alcohols. A heavy-metal ion functions by complexing with the unshared electrons of the halide, thereby making the leaving group a metal halide rather than a halide ion. This acceleration of the rates of halide reactions is the basis for a qualitative test for alkyl halides with silver nitrate in ethanol solution:

$$R{:}\ddot{\underset{\cdot\cdot}{X}}{:} \overset{Ag^{\oplus}}{\rightleftharpoons} R{:}\ddot{\underset{\cdot\cdot}{X}}{:}\cdots Ag^{\oplus} \xrightarrow[(-AgX)]{\text{slow}} R^{\oplus} \xrightarrow{HY} RY + H^{\oplus}$$

Silver halide precipitates at a rate that depends upon the structure of the alkyl group, *tertiary* > *secondary* > *primary*. Tertiary halides usually react immediately at room temperature, whereas primary halides require heating. That complexes actually are formed between organic halides and silver ion is indicated by an increase in water solubility in the presence of silver ion for those halides that are slow in forming carboncations.

8.8.5: The Nucleophilic Reagent

The nucleophilicty of a particular reagent ($:Y$, $:Y^{\ominus}$, or $H\ddot{Y}$) can be defined as its ability to donate an electron pair to another atom (see Section 8-1). In fact, the S_N2 reactivity of a reagent toward a methyl derivative can be taken to measure its nucleophilicty toward carbon. The relative reaction rates of some nucleophiles toward methyl bromide are listed in order of increasing nucleophilicity in Table 8-4, together with their basicities as measured by K_b. Important generalizations can be made from these data provided that one recognizes that they may apply only to hydroxylic solvents.

1. For the atoms representing any one group (column) of the periodic table, nucleophilicty *increases* with increasing atomic number: $I^{\ominus} > Br^{\ominus} >$

Table 8-4
Reactivities of Various Nucleophiles toward Methyl Bromide in Water at 50°

Nucleophile	Approximate reaction half-time, hr[a]	Rate relative to water	K_b^c
H_2O	1,100[b]	(1)	10^{-16}
$CH_3CO_2^\ominus$	2.1	5.2×10^2	10^{-11}
$Cl^\ominus$	1	1.1×10^3	$\sim 10^{-20}$
$Br^\ominus$	0.17	7.8×10^3	$< 10^{-20}$
$N_3^\ominus$	0.11	1.0×10^4	10^{-11}
$HO^\ominus$	0.07	1.6×10^4	55
$C_6H_5NH_2$	0.04	3.1×10^4	10^{-10}
$SCN^\ominus$	0.02	5.9×10^4	10^{-14}
$I^\ominus$	0.01	1.1×10^5	$< 10^{-22}$

[a]Time in hours required for half of methyl bromide to react at constant (1*M*) concentration of nucleophile.
[b]Calculated from data for pure water, assuming water to be 55*M*.
[c]Defined as the equilibrium constant for $X^\ominus + H_2O \rightleftharpoons HX + OH^\ominus$ or $X + H_2O \rightleftharpoons HX^\oplus + OH^\ominus$.

$Cl^\ominus > F^\ominus$; $HS^\ominus > HO^\ominus$; $PH_3 > NH_3$. Thus, other things being equal, larger atoms are better nucleophiles.

2. For nucleophiles having the same atomic number of the entering atom (e.g., oxygen nucleophiles), there is usually a good correlation between the basicity of the reagent and its nucleophilicity. Thus a weak base such as $CH_3CO_2^\ominus$ is a poorer nucleophile than a strong base such as $^\ominus OH$. The poorer $X^\ominus$ is as a leaving group, the better it is as an entering group.

3. For nucleophiles of different atomic numbers, nucleophilicity usually does *not* parallel basicity. For example, for the halogens the reactivity sequence $I^\ominus > Br^\ominus > Cl^\ominus$ is opposite to the sequence for basicity $Cl^\ominus > Br^\ominus > I^\ominus$. Similarly, sulfur anions such as $HS^\ominus$ are better nucleophiles but *weaker* bases than corresponding oxyanions such as $HO^\ominus$.

4. A number of nucleophilic agents, which are very reactive in S_N2 reactions, are of the type $X - Y$, where both atoms have unshared electron pairs. Examples include $HOO^\ominus$, $H_2NO^\ominus$, $ClO^\ominus$, and H_2NNH_2, all of which are more reactive than the closely related nucleophiles $HO^\ominus$ and NH_3.

Why is the correlation between basicity and nucleophilcity so poor for atoms of different atomic number? it is now clear from much research that the dominant effect is associated with differences in the solvation energies of the ions, as defined for halide ions by the following equations:

$$F^\ominus(g) \longrightarrow F^\ominus(aq) \qquad \Delta H^\circ = -117 \text{ kcal}$$
$$Cl^\ominus(g) \longrightarrow Cl^\ominus(aq) \qquad \Delta H^\circ = -85 \text{ kcal}$$
$$Br^\ominus(g) \longrightarrow Br^\ominus(aq) \qquad \Delta H^\circ = -78 \text{ kcal}$$
$$I^\ominus(g) \longrightarrow I^\ominus(aq) \qquad \Delta H^\circ = -68 \text{ kcal}$$

The solvation energies of small ions with concentrated charge always are greater than those of large ions with diffuse charge.

When an ion participates in a nucleophilic attack on carbon, it must slough off some of the solvent molecules that stabilize it in solution. Otherwise, the ion cannot get close enough to the carbon, to which it will become attached, to begin forming a bond. Sloughing off solvent molecules will be less favorable for a small ion than a large ion. Consequently, we expect $Cl^\ominus$ to be less reactive than $I^\ominus$.

Strong evidence for solvation effects on reactivity is provided by the fact that chloride ion is *more* reactive than iodide in solvents that have low solvation energies for anions (see Section 8-7F). Furthermore, in the gas phase where solvation effects are absent, $F^\ominus$ is more reactive than any of the other halide ions toward chloromethane:

$$X^\ominus(g) + CH_3Cl(g) \longrightarrow CH_3X(g) + Cl^\ominus(g)$$
(gas-phase reactivity sequence $F^\ominus > Br^\ominus > I^\ominus$)

It should be recognized that S_N reactions may be reversible when both the leaving group X and the entering group Y are good entering and leaving groups, respectively. In such circumstances, the position of the equilibrium often can be changed by suitably adjusting the reaction conditions. Thus 48% aqueous hydrogen bromide can convert alcohols to alkyl bromides (Equation 8-6, forward direction), whereas the reverse reaction (hydrolysis) is achieved by high water concentration:

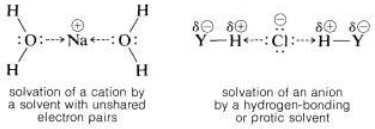
$$CH_3-\underset{\displaystyle OH}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-CH_2CH_3 + HBr \rightleftharpoons CH_3-\underset{\displaystyle Br}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-CH_2CH_3 + H_2O \qquad (8\text{-}6)$$

https://chem.libretexts.org/@go/page/22217

8.8.6: The Nature of the Solvent

The rates of S_N reactions are sensitive to the nature and composition of the solvent. This is easy to understand for S_N1 reactions because the ionizing power of a solvent is crucial to the ease of formation of ions $\overset{\oplus}{R}$ and $\overset{\ominus}{X}$ from RX.

Actually, two factors are relevant in regard to the ionizing ability of solvents. First, a high dielectric constant increases ionizing power by making it easier to separate ions. This is because the force between charged particles varies inversely with the dielectric constant of the medium.[7] Thus water, with a dielectric constant of 80, is 40 times more effective than a hydrocarbon with a dielectric constant of 2. Second, and usually more important, is the ability of the solvent to solvate the separated ions. Cations are solvated most effectively by compounds of elements in the first row of the periodic table that have unshared electron pairs. Examples are ammonia, water, alcohols, carboxylic acids, sulfur dioxide, and methylsulfinylmethane [dimethyl sulfoxide, $(CH_3)_2\,SO$]. Anoins are solvated most efficiently by solvents having hydrogen attached to a strongly elecronegative element Y so the $H-Y$ bond is strongly polarized as $\overset{\delta\oplus}{H}\cdots\overset{\delta\ominus}{Y}$. Such solvents usually are called **protic solvents**. Protic solvents form hydrogen bonds to the leaving group, which assist ionization in much the same way that silver ion catalyzes ionization of alkyl halides (Section 8-7D). We can represent solvation by the following structural formulas, but it must be recognized that the number of solvent molecules involved in close interacitons can be as large as four or six, or as small as one:



The most effective ionizing solvents are those that effectively solvate both anions and cations. Water strikes an excellent compromise with regard to the structural features that make up ionizing power, that is, dielectric constant *and* solvating ability. From this, we expect *tert*-butyl chloride to ionize much more readily in water than in ether, because ethers can solvate only cations effectively, whereas water can solvate both anions and cations. The fact is that S_N1 ionizations usually are so difficult that S_N1 reactions seldom occur in solvents that cannot effectively solvate *both* anions and cations, even if the dielectric constant of the solvent is high. Solvation by hydrogen bonding is especially helpful in assisting ionization. Solvents that cannot provide such hydrogen bonding [e.g., CH_3OCH_3, $(CH_3)_3\,N$, CH_3NO_2, CH_3CN, $(CH_3)_2\,SO$] generally are poor for S_N1 reactions. These solvents are called **aprotic** solvents. An important exception is liquid sulfur dioxide, SO_2, which promotes S_N1 ionization by having a high dielectric constant and being able to solvate both anions and cations.

A list of protic and aprotic solvents, their dielectric constants, boiling points, and melting points is given in Table 8-5. This table will be useful in selecting solvents for nucleophilic substitution reactions.

With regard to S_N2 reactions, the solvent can affect profoundly the reactivity of a given nucleophile. Thus anions such as $Cl^{\ominus}$ and $CN^{\ominus}$, which are weakly nucleophilic in hydroxylic solvents and in poor ionizing solvents such as 2-propanone (acetone), become very significantly nucleophilic in polar aprotic sovlents such as $(CH_3)_2\,SO$. The reason is that for salts such as $NaCl$ and $NaCN$ the aprotic solvent preferentially solvates the cation, leaving the anion relatively bare. This dissociation of the anion from the cation together with its poor solvation makes the anion abnormally reactive as a nucleophile.

Table 8-5
Solvent Properties

Compound	Formula	Dielectric constant, ϵ^{20}	bp, °C	mp, °C	Solubility in water
hydrogen cyanide	HCN	115	26	−14	+
methanamide (formamide)	$HCONH_2$	84	210.5	2.5	+
hydrogen fluoride	HF	84[a]	19.7	−83.7	+
water	H_2O	80	100	0	+
methanoic (formic) acid	HCO_2H	58	100	8.5	+
methylsulfinylmethane (dimethyl sulfoxide)	$(CH_3)_2SO$	45	189	18	+
1,2,3-propanetriol (glycerol)	$HOCH_2CHOHCH_2OH$	42.5	290 (dec)	17.8	+
ethanenitrile (acetonitrile)	CH_3CN	38.8	81.6	−45	+
N,N-dimethylmethanamide (dimethylformamide)	$HCON(CH_3)_2$	–	153	−61	+
nitromethane	CH_3NO_2	38	101.2	−29	+[b]
methanol	CH_3OH	32.6	64.7	−97.8	+
ethanol	CH_3CH_2OH	24	78.5	−118	+
2-propanone (acetone)	CH_3COCH_3	21	56.5	−94	+
ammonia	NH_3	17	−33	−78	+
sulfur dioxide	SO_2	17.6[c]	−10	−72	[d]
azabenzene (pyridine)	C_5H_5N	12.3	115	−42	+
dichloromethane	CH_2Cl_2	9.1	40	−95	−
ethanoic (acetic) acid	CH_3CO_2H	6.2	118	16.7	+
trichloromethane (chloroform)	$CHCl_3$	4.8	61	−64	−
diethyl ether	$(C_2H_5)_2O$	4.3	35	−116	−
carbon disulfide	CS_2	2.6	46.5	−111.6	−
1,4-dioxacyclohexane (dioxane)	$O[(CH_2)_2]_2O$	2.2	101	11.8	+
tetrachloromethane (carbon tetrachloride)	CCl_4	2.2	76.7	−23	−
benzene	C_6H_6	2.3	80.1	5.5	−
cyclohexane	C_6H_{12}	2.0	80.7	6.5	−

[a]At 0°. [b]Slightly soluble. [c]At −20°. [d]Reacts with water.

[6]The Greek letters α, β, γ are used here not as nomenclature, but to designated the positions along a carbon chain from a functional group, X: $C_\omega \cdots C_\delta - C_\gamma - C_\beta - C_\alpha - X$ (also see Section 7-10).

[7]Specifically, electrostatic force $= q_1 q_2 / r_{12}^2 \epsilon$ in which q_1 and q_2 are the charges, r_{12} is the distance between the charges, and ϵ is the dielectric constant of the medium; $\epsilon = 1$ for a vacuum.

8.8.7: Contributors and Attributions

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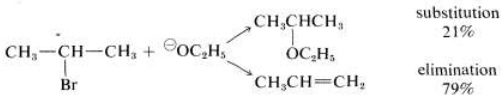
8.9: The E2 Reaction

8.9.1: Kinetics and Mechanism

The conditions used for substitution reactions by the S_N2 mechanism very often lead to elimination. The reaction of 2-bromopropane with sodium ethoxide in ethanol provides a good example:

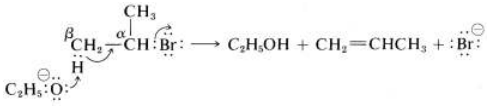


Elimination to give propene competes with substitution to give ethyl isopropyl ether. Furthermore, the rate of elimination, like the rate of substitution, is proportional to the concentrations of 2-bromopropane and ethoxide ion. Thus elimination here is a second-order reaction (it may be helpful to review Section 8-4 at this point):

rate of substitution $= k_S\,[RBr]\left[\overset{\ominus}{O}C_2H_5\right]$

rate of elimination $= k_E\,[RBr]\left[\overset{\ominus}{O}C_2H_5\right]$

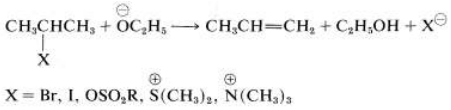
As to the *mechanism* of this kind of elimination, the attacking base, $^{\ominus}OC_2H_5$, removes a proton from the β carbon more or less simultaneously with the formation of the double bond and the loss of bromide ion from the neighboring carbon:



The abbreviation for this mechanism is E2, E for elimination and 2 for bimolecular, there being two reactants involved in the transition state.

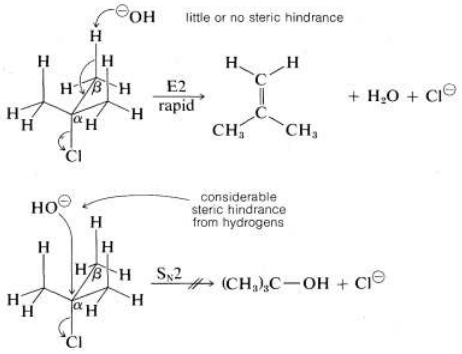
8.9.2: Structural Effects

Structural influences on E2 reactions have been studied in some detail. Like the competing S_N2 process, a good leaving group is necessary and of these, the most commonly used are the halides, Cl, Br, and I; sulfonate esters, $RS(O_2)O-$; and -onium ions such as ammonium, $\overset{\oplus}{N}R_4$, and sulfonium, $\overset{\oplus}{S}R_3$:

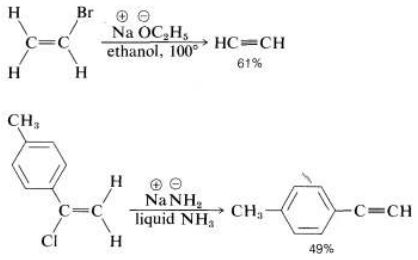


Rather strong bases generally are required to bring about the E2 reaction. The effectiveness of a series of bases generally parallels their base strengths, and the order $\overset{\ominus}{N}H_2 > \overset{\ominus}{O}C_2H_5 > \overset{\ominus}{O}H > \overset{\ominus}{O}CCH_3$ is observed for E2 reactions. This fact is important in planning practical syntheses, because the E2 reaction tends to predominate with strongly basic, slightly polarizable reagents such as amide ion, $\overset{\ominus}{N}H_2$, or ethoxide ion, $\overset{\ominus}{O}C_2H_5$. In contrast, S_N2 reactions tend to be favored with weakly basic nucleophiles such as iodide ion or ethanoate ion (unless dipolar aprotic solvents are used, which may markedly change the reactivity of anionic nucleophiles).

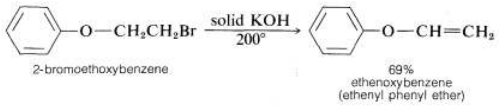
As for the alkyl group, there are two important structural effects to notice. First, at least one $C-H$ bond adjacent (β) to the leaving group is required. Second, the ease of E2 elimination follows the order *tertiary* $R >$ *secondary* $R >$ *primary* R. Unlike S_N2 reactions, which are *not* observed for tertiary alkyl compounds because of steric hindrance to the approach of the nucleophile to carbon, the related E2 reaction usually occurs readily with tertiary RX compounds. The reason is that little or no steric hindrance is likely for the approach of a base to a hydrogen unless the base is exceptionally bulky:



The reactivity order also appears to correlate with the $C - X$ bond energy, inasmuch as the tertiary alkyl halides both are more reactive and have weaker carbon-halogen bonds than either primary or secondary halides (see Table 4-6). In fact, elimination of HX from haloalkenes or haloarenes with relatively strong $C - X$ bonds, such as chloroethene or chlorobenzene, is much less facile than for haloalkanes. Nonetheless, elimination does occur under the right conditions and constitutes one of the most useful general methods for the synthesis of alkynes. For example,

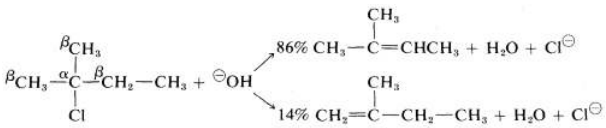


The conditions and reagents used for E2 and S_N2 reactions are similar enough that it is difficult to have one occur without the other. However, E2 elimination is favored over S_N2 substitution by (a) strongly basic nucleophiles, (b) bulky nucleophiles, and (c) increasing alkyl substitution at the α carbon. It also is observed that increasing the reaction temperature generally leads to an increase in elimination at the expense of substitution. In fact, surprisingly good yields of alkene or alkyne can be obtained by adding a halogen compound directly to molten or very hot KOH with no solvent present, whereupon the product is formed rapidly and distills immediately from the hot reaction mixture:

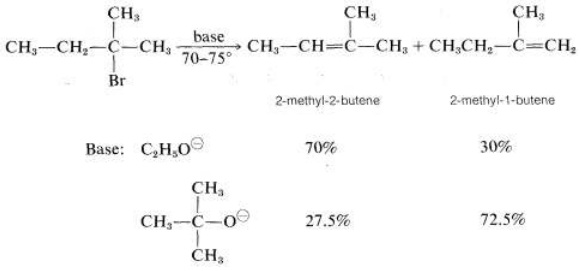


8.9.3: Orientation Effects in Elimination Reactions

With halides having unsymmetrical R groups, such as 2-chloro-2-methylbutane, it is possible to form two or more different alkenes, the proportion depending on the relative rates at which the different β hydrogens are removed. Most E2 eliminations of alkyl halides with common bases, such as $HO^{\ominus}$, $C_2H_5O^{\ominus}$, and $NH_2^{\ominus}$, tend to give mixtures of alkenes with a preference for the most stable alkene, which usually is the one with the *fewest* hydrogens or *most* alkyl groups attached to the carbons of the double bond. Thus



However, the precise distribution of alkenes formed is found to vary enough with the nature of the leaving group, or the base used, so either product will predominated with some combination of reagents or conditions. For example, a change in the base alone can be decisive:



8.9.4: Stereochemistry of E2 Reactions

The E2 reaction occurs most easily if the molecule undergoing reaction can assume a conformation, 2, in which the leaving groups, H and X, are trans to each other and the atoms $H-C_\beta-C_\alpha-X$ lie in one plane. Elimination then proceeds from opposite sides of the incipient double bond to give an alkene of structure 3. We shall call this mode of elimination **antarafacial** to distinguish

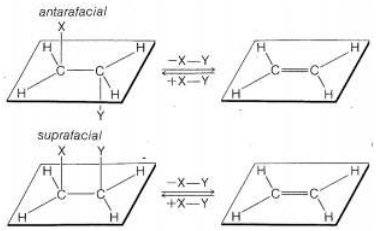
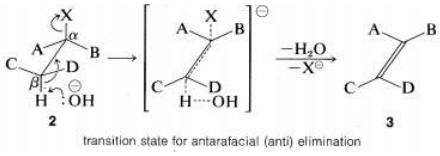
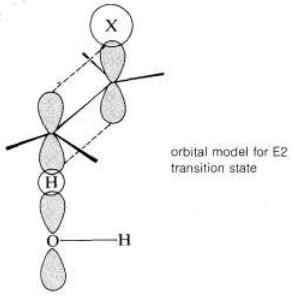


Figure 8-6: Schematic representation of antarafacial (literally "opposite-face") and suprafacial (literally "above-face") elimination or addition of a reagent $X-Y$ to ethene

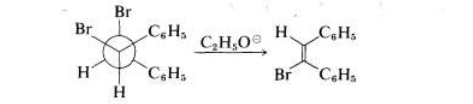
it from another possible mode of elimination that is called **suprafacial**. (See Figure 8-6).[8]



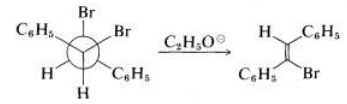
The transition state for conversion of 2 to 3 is particularly reasonable because it combines some of the geometry of both the reactants and the products and therefore gives the best overlap of the reacting orbitals necessary for the formation of the π bond. This is shown more explicitly below.[9]



As an illustration of the stereospecificity of eliminations, the meso compound 4 gives the *cis*-alkene 5, whereas the D, L isomers 6 give the *trans*-alkene 7 with ethoxide. Both reactions clearly proceed by antarafacial elimination:



meso-1,2-dibromo-1,2-diphenylethane **4** *cis*-1-bromo-1,2-diphenylethene **5**



D,L **6** *trans* **7**

When antarafacial elimination is rendered difficult by the inability of the reacting groups to acquire the desired trans arrangement, then suprafacial elimination can occur, although less readily. An example is chlorocyclopentane, in which *H* and *X* cannot assume a trans configuration without very considerable strain but which does undergo suprafacial elimination at a reasonable rate:

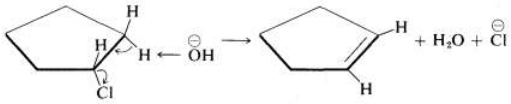
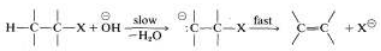


Figure 8-6. At the risk of annoying those who often rightly dislike complicated names for simple processes, we have chosen to adopt the proposal of R. B. Woodward and R. Hoffman, that elimination (or addition) which involves a same-side cleavage (or formation) of bonds be called suprafacial and the opposite-side cleavage (or formation) of bonds be called antarafacial. The alternative of using syn for suprafacial and *anti* for antarafacial would be simpler and easier to remember, but the terms syn and anti already are used for configurations, which is exactly what we want to avoid. The problem with the terms cis elimination (or addition) and trans elimination (or addition) is that they do not necessarily lead to products that, by other conventions, are understood to be cis and trans products, respectively, For example, to say that "trans elimination leads to cis product" is a needless confusion. It is much clearer to say that "antarafacial elimination gives the cis product" - and now there is no confusion of the mode of elimination with whatever stereochemical convention identifies the product.

[9]Persuasive arguments have been made that many E2 reactions proceed by the sequence



If this is so, antarafacial elimination still is predicted to be favored.

8.9.5: Contributors and Attributions

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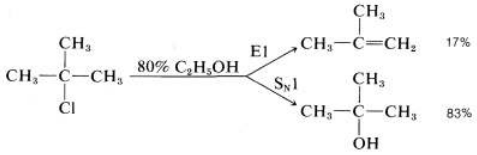
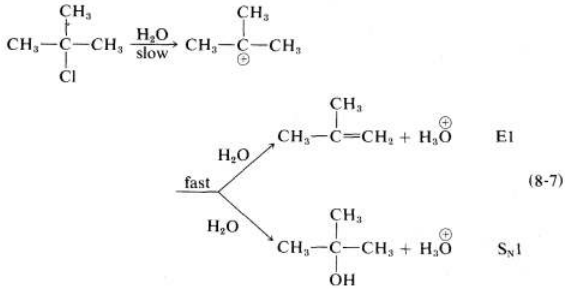
8.10: The E1 Reaction

8.10.1: Scope and Mechanism

Many secondary and tertiary halides undergo E1 elimination in competition with the S_N1 reaction in neutral or acidic solutions. For example, when *tert*-butyl chloride solvolyzes in 80% aqueous ethanol at 25°, it gives 83% *tert*-butyl alcohol by substitution and 17% 2-methylpropene by elimination:

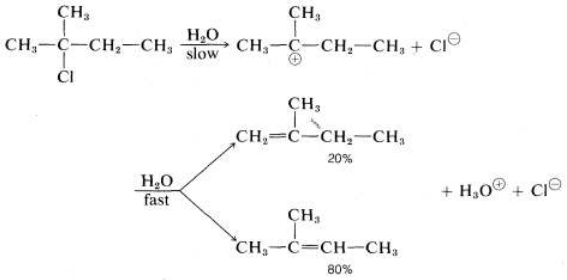


The ratio of substitution and elimination remains constant throughout the reaction, which means that each process has the kinetic order with respect to the concentration of *tert*-butyl halide. The S_N1 and E1 reactions have a common rate-determining step, namely, slow ionization of the halide. The solvent then has the choice of attacking the intermediate carbocation at the positive carbon to effect substitution, or at a β hydrogen to effect elimination:



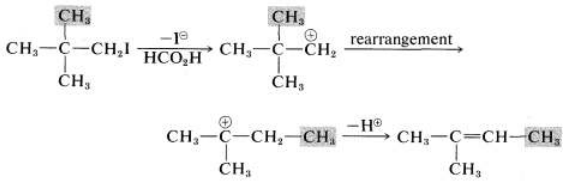
Factors influencing the E1 reactions are expected to be similar to those for the S_N1 reactions. An ionizing solvent is necessary, and for easy reaction the RX compound must have a good leaving group and form a relatively stable $R^{\oplus}$ cation. Therefore the E1 orders of reaction rates are $X = I > Br > Cl > F$ and *tertiary* $R >$ *secondary* $R >$ *primary* R.

With halides such as 2-chloro-2-methylbutane, which can give different alkenes depending on the direction of elimination, the E1 reaction is like the E2 reaction in tending to favor the most stable or highly substituted alkene:



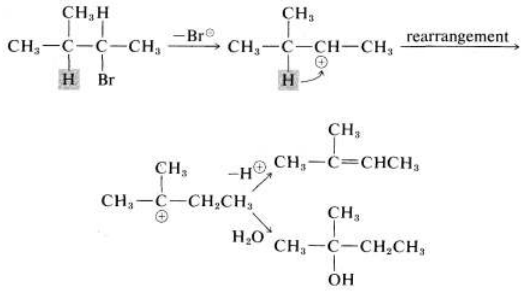
8.10.2: Rearrangement of Carbon Cations

Another feature of E1 reactions (and also of S_N1 reactions) is the tendency of the initially formed carbocation to rearrange, especially if a more stable carbocation is formed thereby. For example, the very slow S_N1 solvolysis of neopentyl iodide in methanoic acid leads predominantly to 2-methyl-2-butene:



In this reaction, ionization results in migration of a methyl group with its bonding pair of electrons from the β to the α carbon, thereby transforming an unstable primary carbocation to a relatively stable tertiary carbocation. Elimination of a proton completes the reaction.

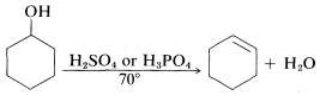
Rearrangements involving shifts of hydrogen (as $H:^{\ominus}$) occur with comparable ease if a more stable carbocation can be formed thereby:



Rearrangements of carbocations are among the fastest organic reactions known and must be reckoned with as a possibility whenever carbocation intermediates are involved.

8.10.3: Acid-Catalyzed Elimination Reactions

Alcohols and ethers rarely undergo substitution or elimination unless strong acid is present. As we noted in Section 8-7D the acid is necessary to convert a relatively poor leaving group ($HO^{\ominus}$, $CH_3O^{\ominus}$) into a relatively good one (H_2O, CH_3OH). Thus the dehydration of alcohols to alkenes is an acid-catalyzed reaction requiring strong acids such as sulfuric or phosphoric acid:



These are synthetically useful reactions for the preparation of alkenes when the alkene is less available than the alcohol. They can occur by either the E1 or E2 mechanism depending on the alcohol, the acid catalyst, the solvent, and the temperature.

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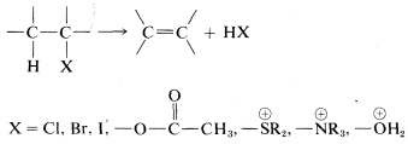
8.11: Elimination Reactions

Generally, an alkyl derivative, under appropriate conditions, will eliminate HX, where X is commonly a halide, ester, or -onium function, provided that there is a hydrogen located on the carbon adjacent to that bearing the X function:



An important feature of many elimination reactions is that they occur with the same combination of reagents that cause nucleophilic substitution. In fact, elimination and substitution often are competitive reactions. Therefore it should be no surprise that substitution and elimination have closely related mechanisms.

8.11.1: Contributors and Attributions

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8.E: Nucleophilic Substitution and Elimination Reactions (Exercises)

Exercise 8-1 Write Lewis structures for each of the following reagents and classify them as either electrophilic, nucleophilic, both, or neither by evaluating whether they will react appreciably with hydroxide ion, $HO^{\ominus}$, or hydronium ion, $H_3O^{\oplus}$. Write equations for each of the reactions involved.

a. NH_3
b. $NH_2{}^-$
c. $Na^{\oplus}$
d. $Cl^{\ominus}$
e. Cl_2
f. CH_4
g. $CN^{\ominus}$
h. CH_3OH
i. $CH_3\overset{\oplus}{O}H_2$
j. $BF_4{}^-$
k. HBr
l. $HC\equiv C{:}^{\ominus}$
m. $:CH_2$
n. FSO_3H
o. SO_3

Exercise 8-2 Identify the electrophile and the nucleophile in each of the following reactions:

a. $CH_3I + \overset{\ominus}{O}CH_3 \rightarrow CH_3{-}O{-}CH_3 + I^{\ominus}$

b. $CH_2{=}CH_2 + Br_2 \rightarrow \overset{\oplus}{C}H_2{-}CH_2{-}Br + Br^{\ominus}$

c. $CH_3NH_2 + CH_3I \rightarrow (CH_3)_2NH + HI$

Exercise 8-3 Calculate ΔH^0 for the polar reaction of one mole of bromomethane with water in accord with the equation $CH_3Br + H_2O \rightarrow CH_3OH + HBr$ (a) in the gas phase and (b) with all of the participants in dilute aqueous solution. For Part (a) you will need the bond energies of Table 4-3 and for Part (b) you will require the bond energies and the following ΔH^0 values:

Exercise 8-4 Ethyl chloride $(0.1\ M)$ reacts with potassium iodide $(0.1\ M)$ in 2-propanone (acetone) solution at 60° to form ethyl iodide and potassium chloride at a rate (v) of $5.44 \times 10^{-7}\ mol\ L^{-1}\ s^{-1}$.

a. If the reaction proceeded by an S_N2 mechanism, what is the value of k (in proper units) and what would be the *rate* of the reaction in moles per liter per sec at $0.01\ M$ concentrations of both reactants? Show your method of calculation.

b. Suppose the rate were proportional to the square of the potassium iodide concentration and the first power of the ethyl chloride concentration. What would be the rate with $0.01\ M$ reactants?

c. It one starts with solutions initially $0.1\ M$ in both reactants, the rate of formation of ethyl iodide initially is 5.44×10^{-7} $mol\ L^{-1}\ s^{-1}$, but falls as the reaction proceeds and the reactants are used up. Plot the rate of formation of ethyl iodide against the concentration of ethyl chloride as the reaction proceeds (remembering that one molecule of ethyl chloride consumes one molecule of potassium iodide). Assume that the rate of reaction is proportional to the first power of the ethyl chloride concentration; and to (1) the zeroth power, (2) the first power, and (3) the second power of the potassium iodide concentration.

d. What kind of experimental data would one need to determine whether the rate of the reaction of ethyl chloride with potassium iodide is first order in each reactant or second order in ethyl chloride and zero order in potassium iodide?

Exercise 8-5 The rate of solvolysis of *tert*-butyl chloride in aqueous solution is unaffected by having sodium azide, $\overset{\oplus}{Na}\overset{\ominus}{N}{=}\overset{\oplus}{N}{=}\overset{\oplus}{N}$, in the solution, yet the products include both 2-azido-2-methylpropane, 1, and *tert*-butyl alcohol:

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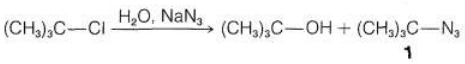
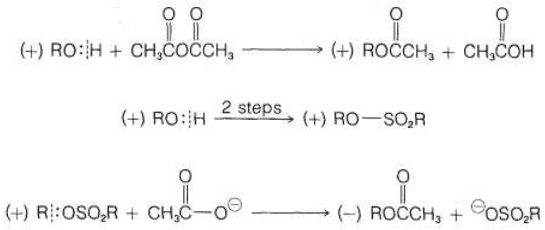


1

Show how this information can be used to determine whether an S_N1 or an S_N2 mechanism occurs in the solvolysis of *tert*-butyl chloride in aqueous solution.

Exercise 8-6 What inference as to reaction mechanism might you make from the observation that the rate of hydrolysis of a certain alkyl chloride in aqueous 2-propanone is *retarded* by having a moderate concentration of lithium chloride in the solution?

Exercise 8-7 Equations 8-3 through 8-5 show how Kenyon and Phillips established that inversion of configuration accompanies what we now recognize to be S_N2 substitutions. For each reaction, we indicate whether $R{-}O$ or $O{-}H$ is broken by an appropriately placed vertical line. Explain how the sequence of steps shows that inversion occurs in the S_N2 reaction of Equation 8-5. The symbols $(+)$ or $(-)$ designate for each compounds the sign of the rotation α of the plane of polarized light that it produces.



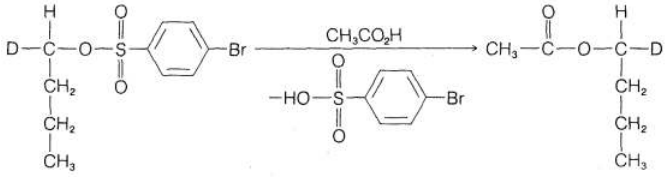
Exercise 8-8 Explain how, in the presence of bromide ion, either enantiomer of 2-bromobutane racemizes (Section 5-1B) in 2-propanone solution at a rate that is first order in $Br^{\ominus}$ and first order in 2-bromobutane.

Exercise 8-9* When either of the enantiomers of 1-deuterio-1-bromobutane is heated with bromide ion in 2-propanone, it undergoes an S_N2 reaction that results in a slow loss of its optical activity. If radioactive bromide ion $(Br^{*\ominus})$ is present in the solution, radioactive 1-deuterio-1-bromobutane is formed by the same S_N2 mechanism in accord with the following equation:

$$CH_3CH_2CH_2CHDBr + Br^{*\ominus} \xrightarrow{\text{2-propanone}} CH_3CH_2CH_2CHDBr^* + Br^{\ominus} \qquad (8.E.1)$$

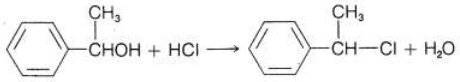
Within experimental error, the time required to lose 10% of the optical activity is just equal to the time required to have 5% of the $CH_3CH_2CH_2CHDBr$ molecules converted to $CH_3CH_2CH_2CHDBr^*$ with radioactive bromide ion. Explain what we can conclude from these results as to the degree to which the S_N2 reaction produces inversion of configuration of the primary carbon of 1-deuterio-1-bromobutane.

Exercise 8-10 What can be concluded about the mechanism of the solvolysis of 1-butyl derivatives in ethanoic acid from the projection formulas of the starting material and product of the following reaction?



Would you call this an S_N1 or S_N2 reaction?

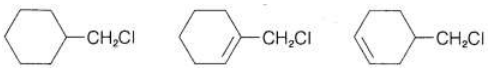
Exercise 8-11 In the reaction of 1-phenylethanol with concentrated HCl, 1-phenylethyl chloride is formed:

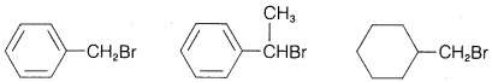


If the alcohol originally has the *D* configuration, what configuration would the resulting chloride have if formed (a) by the S_N2 mechanism and (b) by the S_N1 mechanism?

Exercise 8-12 Predict which compound in each of the following groups reacts most rapidly with potassium iodide in 2-propanone as solvent by the S_N2 mechanism. Give your reasoning and name the substitution product by the IUPAC system.

a. $(CH_3)_3CCH_2Cl$ $(CH_3)_3CCl$ $CH_3CH_2CH_2CH_2Cl$

b. 

c. 

Exercise 8-13 Which of the monobromine-substituted methylcyclohexanes would you judge to be the most reactive in (a) S_N2-type displacement and (b) S_N1-type displacement?

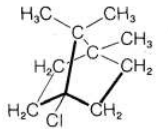
Exercise 8-14 Answer the question in the preceding exercise, but with the monobromine-substituted 1-methylcyclohexenes.

Exercise 8-15 Select the compounds from the following list that would be expected to hydrolyze *more rapidly* than phenylmethyl (benzyl) chloride by the S_N1 mechanism:

a. 2-phenylmethyl chloride
b. diphenylmethyl chloride
c. 1-phenylmethyl chloride
d. (chloromethyl)cyclohexane
e. 1-chloro-4-methylbenzene

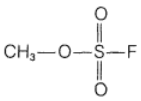
Exercise 8-16 Explain the following observations:

a. The tertiary chloride, apocamphyl chloride, is unreactive in either S_N1 or S_N2 reactions. For example, no reaction occurs when its solution in aqueous ethanol containing 30% potassium hydroxide is refluxed for 20 hours.



b. Chloromethyl alkyl (or aryl) ethers, $ROCH_2Cl$, are very reactive in S_N1 solvolysis reactions. Compared to chloromethane, the rate of hydrolysis of chloromethyl phenyl ether is about 10^{14}. Also, the rate of hydrolysis is retarded significantly by lithium chloride.

Exercise 8-17 Methyl sulfides are prepared conveniently by the S_N2 reaction of a CH_3X derivative with a sulfur nucleophile: $RS^{\ominus} + CH_3X \rightarrow RSCH_3 + X^{\ominus}$. The rate of the reaction with a given $RS^{\ominus}$. If you are uncertain of the pK_a of the acids HX, look them up in an appropriate reference, such as the *CRC Handbook of Physics and Chemistry*.

a. dimethyl sulfate, $(CH_3O)_2SO_2$
b. methyl nitrate, CH_3ONO_2
c. methyl cyanide (ethanenitrile), CH_3CN
d. methyl fluoride, CH_3F
e. methyl iodide, CH_3I
f. methyl fluorosulfonate, 
g. methyl acetate (ethanoate),
h. methanol, CH_3OH

Exercise 8-18 Account for the following observations:

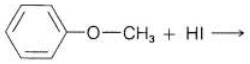
a. *tert*-Alkyl fluorides are unreactive in S_N1 solvolysis reactions *unless* a strong acid is present.

b. *D*-1-Phenylethyl chloride dissolved in *aqueous* 2-propanone containing mercuric chloride loses much of its optical activity before undergoing hydrolysis to give racemic 1-phenylethanol.

c. 1-Bromobutane can be prepared by heating 1-butanol with a mixture of sodium bromide and sulfuric acid. The reaction fails, however, if the sulfuric acid is omitted.

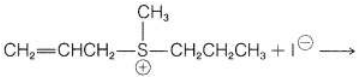
d. Benzenoxide (phenoxide) ion, $C_6H_5O^{\ominus}$, is a better leaving group than ethoxide, $C_2H_5O^{\ominus}$.

Exercise 8-19 Using the discussion in Section 8-7 of how the structure of R and X influence the S_N reactivity of RX, predict the favored course of each of the following reactions. Give your reasoning.

a. 

b. $(CH_3)_3C{-}O{-}CH_3 + HI \rightarrow$

c. $CF_3{-}O{-}CH_3 + HBr \rightarrow$

d. 

Exercise 8-20 Methyl ethers of the type $R{-}O{-}CH_3$ cannot be prepared by the reaction of the alcohol ROH with CH_3I, but if Ag_2O is present the following reaction occurs under mild conditions:

$$2R{-}OH + Ag_2O + 2CH_3I \rightarrow 2ROCH_3 + 2AgI + H_2O \tag{8.E.2}$$

Explain how Ag_2O promotes this reaction.

Exercise 8-21 Explain each of the following observations:

a. Methyl sulfide $(CH_3)_2S$ reacts with $C_6H_5COCH_2Cl$ in benzene to give the sulfonium salt, $C_6H_5COCH_2\overset{\oplus}{S}(CH_3)_2Cl^{\ominus}$, which precipitates as it is formed. Attempts to recrystallize the product from ethanol result in formation of methyl sulfide and $C_6H_5COCH_2Cl$.

b. S_N2 displacements of alkyl chlorides by $\overset{\ominus}{O}H$ often are catalyzed by iodide ion, $RCl + :\overset{\ominus}{O}H \xrightarrow{I^{\ominus}} ROH + Cl^{\ominus}$ and may result in a product with *less* than 100% of inverted configuration at the carbon carrying the chlorine.

c.* Tris(trifluoromethyl)amine, $(CF_3)_3N$, is completely nonnucleophilic, whereas trimethylamine is a good nucleophile.

Exercise 8-22 Classify the following solvents according to effectiveness for solvation of (i) cations and (ii) anions:

a. 2-propanone, CH_3COCH_3
b. tetrachloromethane, CCl_4
c. anhydrous hydrogen fluoride, HF
d. trichloromethane, $CHCl_3$
e. trimethylamine, $(CH_3)_3N$
f. trimethylamine oxide, $(CH_3)_3\overset{\oplus}{N}-\overset{\ominus}{O}$

Exercise 8-23* Would you expect the S_N2 reaction of sodium cyanide with methyl bromide to be faster, slower, or about the same with $(CH_3)_2S{=}O$ or ethanol as solvent? Explain.

Exercise 8-24 An alternative mechanism for $E2$ elimination is the following:

$$CH_3CH_2Cl + OH^{\ominus} \overset{\text{fast}}{\rightleftharpoons} {}^{\ominus}:CH_2CH_2Cl + H_2O \xrightarrow{\text{slow}} CH_2{=}CH_2 + Cl^{\ominus} \tag{8.E.3}$$

a. Would this mechanism lead to overall second-order kinetics with respect to the concentrations of $OH^{\ominus}$ and ethyl chloride? Explain.

b. This mechanism as written has been excluded for several halides by carrying out the reaction in deuterated solvents such as D_2O and C_2H_5OD. Explain how such experiments could be relevant to the reaction mechanism.

c. Does the test in Part b also rule out $CH_3CH_2Cl + \overset{\ominus}{O}H \xrightarrow{\text{slow}} :\overset{\ominus}{C}H_2CH_2Cl + H_2O \xrightarrow{\text{fast}} CH_2{=}CH_2 + Cl^{\ominus}$? Explain.

Exercise 8-25 Write equations and mechanisms for all the products that might reasonably be expected from the reaction of 2-chlorobutane with a solution of potassium hydroxide in ethanol.

Exercise 8-26

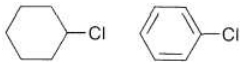
a. Why is potassium *tert*-butoxide, $\overset{\oplus}{\mathrm{K}}\overset{\ominus}{\mathrm{O}}\mathrm{C}(\mathrm{CH_3})_3$, an excellent base for promoting elimination reactions of alkyl halides, whereas ethylamine, $\mathrm{CH_3CH_2NH_2}$, is relatively poor for the same purpose?

b. Potassium *tert*-butoxide is many powers of ten more effective a reagent for achieving $E2$ eliminations in methylsulfinylmethane (dimethyl sulfoxide) than in *tert*-butyl alcohol. Explain.

Exercise 8-27 Which one of the following groups of compounds would eliminate HCl most readily on reaction with potassium hydroxide? Draw the structure of the product and name it.

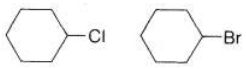
a. $(\mathrm{CH_3})_3\mathrm{CCl}$ $\mathrm{CH_3CH_2CH_2CH_2Cl}$ $\mathrm{CH_3CH(Cl)CH_2CH_3}$

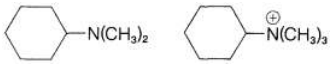
b. $(\mathrm{CH_3})_3\mathrm{CCH_2Cl}$ $(\mathrm{CH_3})_2\mathrm{CHCH_2Cl}$

c. 

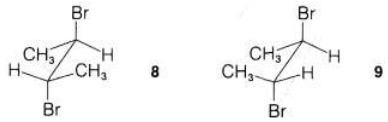
Exercise 8-28 Which one of each of the following pairs of compounds would react most rapidly with potassium hydroxide in an $E2$ -type elimination? Draw the structure of the product and name it.

a. $(\mathrm{CH_3})_3\mathrm{COH}$ $(\mathrm{CH_3})_3\mathrm{CCl}$

b. 

c. 

Exercise 8-29 Write all the possible staggered conformations for each of the isomers of 2,3-dibromobutane, 8 and 9:



Show the structures of the alkenes that could be formed from each by antarafacial $E2$ elimination of one mole of hydrogen bromide with hydroxide ion. Which alkene should more readily eliminate further to form 2-butyne? Explain.

Exercise 8-30 For the reaction of Equation 8-7, would you expect the ratio of *tert*-butyl alcohol to 2-methylpropene to change significantly with changes in the nature of the leaving group [i.e., Cl, Br, I, or $\overset{\oplus}{\mathrm{S}}(\mathrm{CH_3})_2$]? Give your reasoning.

Would you expect the same or different behavior as X is changed, if elimination were occurring by an $E2$ *mechanism* with the solvent acting as the base? Explain.

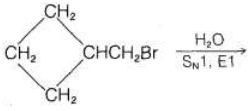
Exercise 8-31 The reaction of *tert*-butyl chloride with water is accelerated strongly by sodium hydroxide. How would the ratio of elimination to substitution products be affected thereby? Explain.

Exercise 8-32 Explain how $(\mathrm{CH_3})_2\mathrm{CDCHBrCH_3}$ (where D is the hydrogen isotope of mass 2) might be used to determine whether 2-methyl-2-butene is formed directly from the bromide in an $E1$ reaction, or by rearrangement and elimination as shown in the preceding equations.

Exercise 8-33 Predict the products of the following reactions:

a. $\mathrm{CH_3CH_2CBr(CH_3)CH_2CH_3} \xrightarrow[S_N1,\ E1]{\mathrm{H_2O}}$

b. $(\mathrm{CH_3})_3\mathrm{CCH(CH_3)Cl} \xrightarrow[S_N1,\ E1]{\mathrm{H_2O}}$

c. 

Exercise 8-34 Write reaction sequences, using specific and appropriate compounds, that illustrate the following conversions:

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a. alcohol → ether

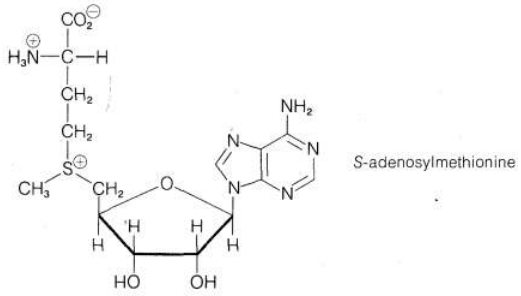
b. alcohol → alkene

c. alcohol → alkyl chloride

d. alcohol → nitrile ($\mathrm{ROH} \rightarrow \mathrm{RCN}$)

e. alkyl chloride → sulfonium salt → alkene

Exercise 8-35 S-Adenosylmethionine is a biologically important compound that reacts in the S_N2 manner with the *amino group* of phosphorylated 2-aminoethanol, $\mathrm{NH_2CH_2CH_2OPO_3H_2}$. Which carbon of S-adenosylmethionine would be most likely to undergo an S_N2 reaction with an $\mathrm{RNH_2}$ compound? Give your reasoning and write the structures of the expected products.



Exercise 8-36 Nitriles, RCN, can be prepared by S_N2 displacement of alkyl derivatives, RX, by using sodium or potassium cyanide:

$$\mathrm{RX + NaCN \rightarrow RCN + NaX} \tag{8.E.4}$$

a. Which of the following solvents would be most suitable for this reaction: water, 2-propanone, ethanol, benzene, $\mathrm{(CH_3)_2S{=}O}$, or pentane? Give reasons for your choice.

b. Which of the six isomeric monobromoderivatives of 1-methylcyclohexane would you expect to react most rapidly with sodium cyanide? Why?

c. If you wished to make 2-phenylethanenitrile, $\mathrm{C_6H_5CH_2CN}$, which of the following phenylmethyl compounds, $\mathrm{RCH_2X}$, would you select to convert to the nitrile? $\mathrm{X = -F, -OH, -OCOCH_3, -H, -NH_2, -O_3SCH_3, -SO_3{-}CH_3}$. Why?

Exercise 8-37 Give a plausible explanation for each of the following observations:

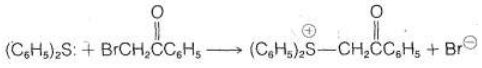
a. Aqueous sodium chloride will *not* convert *tert*-butyl alcohol to *tert*-butyl chloride but concentrated hydrochloric acid will.

b. Better yields are obtained in the synthesis of isopropyl methyl ether starting with methyl iodide rather than sodium methoxide:

$$\mathrm{CH_3I + (CH_3)_2CHO^{\ominus}Na^{\oplus} \rightarrow (CH_3)_2CHOCH_3 + Na^{\oplus}I^{\ominus}} \tag{8.E.5}$$

$$\mathrm{(CH_3)_2CHI + CH_3O^{\ominus}Na^{\oplus} \rightarrow (CH_3)_2CHOCH_3 + Na^{\oplus}I^{\ominus}} \tag{8.E.6}$$

c. The following reaction proceeds only if an equivalent amount of silver fluoroborate, $\mathrm{Ag^{\oplus}BF_4{}^{\ominus}}$, is added to the reaction mixture:



d. 1-Bromo-2-butene reacts with water to give a mixture of 2-buten-1-ol, 3-buten-2-ol, and some 1,3-butadiene.

Exercise 8-38 Which compound in the following pairs would react faster under the reaction conditions? Draw the structures of the major products expected.

a. $\mathrm{C_6H_5CH_2CH_2Br}$ or $\mathrm{C_6H_5C(CH_3)(Br)CH_3}$ in ethanol-water solution.

b. Same as in Part a, but with potassium iodide in acetone.

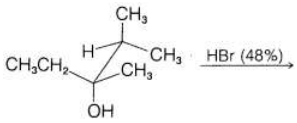
c. Same as in Part a, but with potassium hydroxide in ethanol.

d. $\mathrm{CH_3CH_2\overset{\oplus}{N}(CH_3)_3\ \overset{\ominus}{B}F_4}$ or $\mathrm{CH_3CH_2\overset{\oplus}{N}(CH_3)_3\ \overset{\ominus}{O}CH_3}$ on heating in methanol solution.

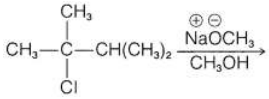
Exercise 8-39 Show the products of the following reactions and indicate the stereochemistry where important.

a. *trans*-1-bromo-3-methylcyclopentane $\xrightarrow[\text{acetone}]{\text{KI}}$

b. *trans*-1-chloro-2-methylcyclopentane $\xrightarrow[\textit{tert}\text{-butyl alcohol}]{{}^{\oplus}\text{K}^{\ominus}\text{OC(CH}_3)_3}$

c. 

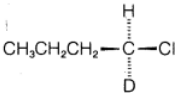
d. *D*-2-butanol $\xrightarrow{\text{potassium metal}}$ potassium salt $\xrightarrow{L\text{-2-chlorobutane}}$

e. 

f. *meso*-1,2-dibromo-1,2-diphenylethane $\xrightarrow{{}^{\oplus}\text{K}^{\ominus}\text{OC(CH}_3)_3}$

Exercise 8-40 The S_N1 reactions of many RX derivatives that form moderately stable carbocations are substantially retarded by adding $X^{\ominus}$ ions. However, such retardation is diminished, at given $X^{\ominus}$ concentrations, by adding another nucleophile such as ${N_3}^{\ominus}$. Explain.

Exercise 8-41 The reaction of 1-chlorobutane with sodium hydroxide to give 1-butanol is catalyzed by sodium iodide.



a. Work out the stereochemistry to be expected for both the catalyzed and the uncatalyzed reactions if (optically active) were used as the starting material. Show your reasoning.

b. Does retention of configuration, as the overall result of an S_N2, automatically preclude operation of the usual mechanism? Explain.

Exercise 8-42* Suppose a water solution was made up initially to be 0.01 M in methyl bromide and 1.0 M in sodium ethanoate at 50°. In water, the S_N2 rate constant for reaction of hydroxide ion with methyl bromide at 50° is 30×10^{-4} L mol^{-1} sec^{-1}, whereas that of ethanoate ion at 50° is 1.0×10^{-4} L mol^{-1} sec^{-1}. The ionization constant of ethanoic acid at 50° is 1.8×10^{-5}. In the following, neglect the rates of the reactions of methyl bromide with water or ethanoic acid and any further reactions of ethanoate:

a. Calculate the hydroxide-ion concentration in the initial solution.

b. Calculate the initial rates of formation of methyl ethanoate and methanol.

c. Compute the concentrations of the organic products when the reaction is complete. Show your reasoning and justify any assumptions.

d. What kind of information would be needed to predict what products would be expected from a solution of methyl bromide and sodium hydroxide in methanol? Explain.

Exercise 8-43 Indicate how you would synthesize each of the following substances from the given organic starting materials and any other necessary organic or inorganic reagents. Specify reagents and conditions. (You may have to use reactions discussed in Chapter 4.)

a. $CH_2{=}CH{-}CH_2OCOCH_3$ from propene
b. $CH_3{-}O{-}CH_2CH_3$ from ethanol
c. $CH_3{-}O{-}C(CH_3)_3$ from *tert*-butyl alcohol
d. cyclohexene from cyclohexane

Exercise 8-44 Which compound in each of the following pairs would you expect to react more readily with (A) potassium iodide in 2-propanone, (B) concentrated sodium hydroxide in ethanol, and (C) silver nitrate in aqueous ethanol? Write equations for all the reactions involved and give your reasoning with respect to the predicted orders of reactivity.

a. methyl chloride and isobutyl chloride with A, B, and C

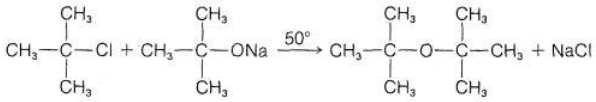
b. methyl chloride and *tert*-butyl chloride with A, B, and C

c. *tert*-butyl chloride and 1-fluoro-2-chloro-2-methylpropane with B and C

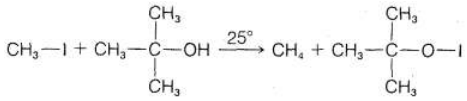
d. 1-chloro-2-butene and 4-chloro-1-butene with A, B, and C

Exercise 8-45 Classify each of the following reactions from the standpoint of yield, side reactions, and reaction rate as good, fair, or bad synthetic procedures for preparation of the indicated products under the given conditions. Show your reasoning and designate any important side reactions.

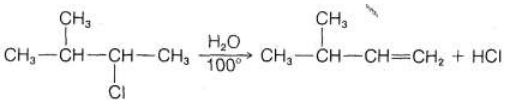
a.



b.

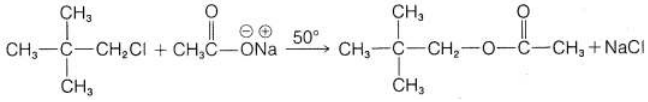


c.

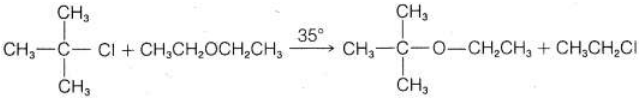


d.

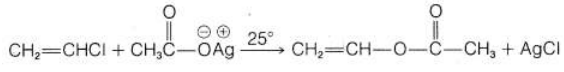
e.



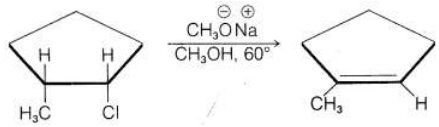
f.



g.



h.



Exercise 8-46 Consider each of the following compounds to be in unlabeled bottles in pairs as indicated. For each pair give a chemical test (preferably a test-tube reaction) that will distinguish between the two substances. Write equations for the reactions involved.

	Bottle A	*Bottle B*
a.	$(CH_3)_3CCH_2Cl$	$CH_3CH_2CH_2CH_2Cl$
b.	$BrCH{=}CHCH_2Cl$	$ClCH{=}CHCH_2Br$
c.	$(CH_3)_3CCl$	$(CH_3)_2CHCH_2Cl$
d.	$CH_3CH{=}CHCl$	$CH_2{=}CHCH_2Cl$
e.	$(CH_3)_2C{=}CHCl$	$CH_3CH_2CH{=}CHCl$
f.	$CH_3CH_2CH{=}CHCl$	$CH_2{=}CHCH_2CH_2Cl$

(8.E.7)

Exercise 8-47 Why does the following $E1$ reaction give more of the least substituted alkene? (Use models.)

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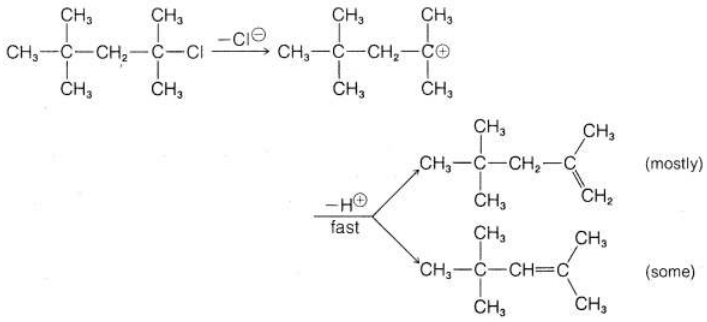

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CHAPTER OVERVIEW

9: Separation, Purification, and Identification of Organic Compounds

Separations can be achieved by differences in physical properties, such as differences in boiling point, or by chemical means, wherein differences in physical properties are enhanced by chemical reactions. In this chapter we will consider some separations of compounds based on differences in physical properties. Chemical procedures will be discussed elsewhere in connection with the appropriate classes of compounds.

9.1: Prelude to Separation, Purification, and Identification
9.2: How do we know when an Organic Compounds is Pure?
9.3: Chromatographic Separation Procedures
9.4: Why Can't We See Molecules?
9.5: Atomic Energy States and Line Spectra
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9.7: Microwave (Rotational) Spectra
9.8: Infrared (Rovibrational) Spectroscopy
9.9: Raman Spectroscopy
9.10: Electronic Spectra of Organic Molecules
9.11: Nuclear Magnetic Resonance Spectroscopy
9.12: Mass Spectroscopy
9.E: Separation, Purification, and Identification of Organic Compounds (Exercises)

9.1: Contributors and Attributions

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9.1: Prelude to Separation, Purification, and Identification

The separation of mixtures of compounds to give the pure components is of great practical importance in chemistry. Many synthetic reactions give mixtures of products and it is necessary for you to have a reasonably clear idea of how mixtures of compounds can be separated. Almost all compounds of biochemical interest occur naturally as components of very complex mixtures from which they can be separated only with considerable difficulty.

Separations can be achieved by differences in physical properties, such as differences in boiling point, or by chemical means, wherein differences in physical properties are enhanced by chemical reactions. In this chapter we will consider some separations of compounds based on differences in physical properties. Chemical procedures will be discussed elsewhere in connection with the appropriate classes of compounds.

Identification and structure determination are often closely allied to the problem of separation. Once a compound is separated, how do we determine whether it is identical to some previously known compound (identification) or, if that can't be done, how do we determine its chemical structure? The spectroscopic properties of molecules have proven to be extremely informative for both identification and structure determination and this chapter is mainly concerned with the application of spectroscopy for such purposes. We will give you now an overview of the spectroscopic properties of the major classes of organic compounds. In subsequent chapter, spectroscopic properties will be discussed in the context of the class of compounds under consideration.

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9.2: How do we know when an Organic Compounds is Pure?

The classical criteria for determining the purity of organic compounds are correct elemental compositions (Section 1-1A) and sharpness of melting point or constancy of boiling point. Important though these analytical and physical criteria are, they can be misleading or even useless. For instance, the analytical criterion is of no help with possible mixtures of isomers because these mixtures have the same elemental composition. The simple physical criteria are not applicable to substances that decompose when one attempts to determine the melting point or boiling point. Furthermore, boiling points are not very helpful for liquids that are mixtures of substances with nearly the same boiling point or are **azeotropes**.[1] Similar difficulties may be encountered with mixtures of solid substances that form mixed crystals or are **eutectics**.[2] Much sharper criteria for the purity of organic compounds now are provided through use of "super-separation" methods to see if any contaminants can be separated, or by spectroscopic techniques, as will be discussed later in this chapter. We begin here with a brief description of chromatographic methods of separation.

[1]An azeotrope is a mixture of two or more substances that boils at a constant temperature, either higher or lower than any of its constituents. Thus an 8.5:1 mole mixture of ethanol and water boils like a pure substance, distilling at 78.2^{o}, which is lower than the boiling point of ethanol (78.5^{o}) or of water (100°). In contrast, a 1.35:1 mole mixture of methanoic (formic) acid and water boils at 107.1^{o}, which is higher than the boiling points of either methanoic acid (100.7^{o}) or water (100°).

[2]When solid substances are mixed, the melting point of each normally is depressed. The eutectic mixture is the mixture of the solids with the lowest melting point.

9.2.1: References

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9.3: Chromatographic Separation Procedures

9.3.1: Gas-Liquid Chromatography

Many separation methods are based on **chromatography**, that is, separation of the components of a mixture by differences in the way they become distributed (or **partitioned**) between two different phases. To illustrate with an extreme example, suppose we have a mixture of gaseous methane and ammonia and contact this mixture with water. Ammonia, being very soluble in water (~$90\ \mathrm{g}$ per $100\ \mathrm{g}$ water at $1\ \mathrm{atm}$ pressure), will mostly go into the *water phase*, whereas the methane, being almost insoluble (~$0.003\ \mathrm{g}$ per $100\ \mathrm{g}$ of water) will essentially remain entirely in the *gas phase*. Such a separation of methane and ammonia would be a one-stage partitioning between gas and liquid phases and, clearly, could be made much more efficient by contacting the gas layer repeatedly with fresh water. Carried through many separate operations, this partitioning procedure is, at best, a tedious process, especially if the compounds to be separated are similar in their distributions between the phases. However, partitioning can be achieved nearly automatically by using **chromatographic columns**, which permit a **stationary phase** to be contacted by a **moving phase**. To illustrate, suppose a sample of a gaseous mixture of ammonia and methane is injected into a long tube (column) filled with glass beads moistened with water (the stationary phase), and a slow stream of an inert **carrier gas**, such as nitrogen or helium, is passed in to push the other gases through. A multistage partitioning would occur as the ammonia dissolves in the water and the resulting gas stream encounters fresh water as it moves along the column. Carrier gas enriched with methane would emerge first and effluent gas containing ammonia would come out later. This is a crude description of the method of **gas-liquid chromatography** (abbreviated often as glc, GC, or called vapor-phase chromatography, vpc). This technique has become so efficient as to revolutionize the analysis and separation of almost any organic substance that has even a slight degree of volatility at some reasonably attainable temperature. The most modern glc equipment runs wholly under computer control, with preprogrammed temperatures and digital integration of the detector output. A wide variety of schemes is available for measuring the concentration of materials in the effluent carrier gas, and some of these are of such extraordinary sensitivity that only very small samples are necessary (10^{-9} g, or less).

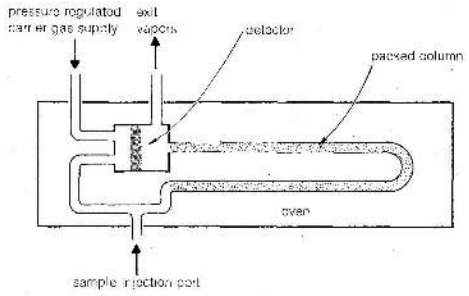

Figure 9-1: Schematic diagram of a gas-liquid chromatography apparatus. The detector is arranged to measure the difference in some property of the carrier gas alone versus the carrier gas plus effluent sample at the exit. Differences In thermal conductivity are particularly easy to measure and give reasonably high detection sensitivities.

In the usual glc procedure, a few microliters of an organic liquid to be analyzed are injected into a vaporizer and carried with a stream of gas (usually helium) into a long heated column that is packed with a porous solid (such as crushed firebrick) impregnated with a nonvolatile liquid. Gas-liquid partitioning occurs, and small differences between partitioning of the components can be magnified by the large number of repetitive partitions possible in a long column. Detection often is achieved simply by measuring changes in thermal conductivity of the effluent gases. A schematic diagram of the apparatus and a typical separation pattern are shown in Figures 9-1 and 9-2. The method is extraordinarily useful for detection of minute amounts of impurities provided these are separated from the main peak. Glc also can be used effectively to purify materials as well as to detect impurities. To do this, the sample size and the size of the apparatus may be increased, or an automatic system may be used wherein the products from many small-scale runs are combined.

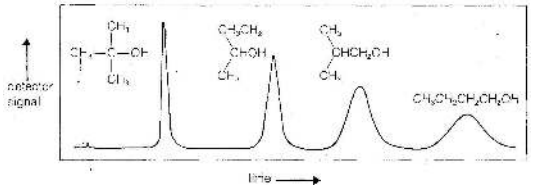

Figure 9-2: A gas-liquid chromatogram of a mixture of the isomeric butanols at constant column temperature. A tiny peak on the far left is a trace of air injected with the sample. The retention times of the various isomers are in the same order as the boiling points, which are, from left to right, 82°, 99.5°, 108°, and 117°. The areas under each peak correspond to the relative amounts of material present. Raising the column temperature at a preprogrammed rate while developing the chromatogram speeds up the removal of the slower-moving components and sharpens their peaks. Also, by diversion of the gas stream to appropriate cold traps it is possible to collect pure fractions of each component.I

9.3.2: Liquid-Solid Chromatography

Liquid-solid chromatography originally was developed for the separation of colored substances, hence the name chromatography, which stems from the Greek word *chroma* meaning color. In a typical examination, a colored substance suspected of containing colored impurities is dissolved in a suitable solvent and the solution allowed to percolate down through a column packed with a solid adsorbent, such as alumina or silica, as shown in Figure 9-3. The "chromatogram" then is "developed" by passing through a suitable solvent that washes the **adsorbate** down through the column. What one hopes for, but may not always find, is that the components of the mixture will be adsorbed *unequally* by the solid phase so distinct bands or zones of color appear. The bands at the top of the column contain the most strongly adsorbed components and the bands at the bottom the least strongly held components. The zones may be separated mechanically, or sufficient solvent can be added to wash, or **elute**, the zones of adsorbed materials sequentially from the column for further analysis.

Liquid-solid chromatography in the form just described was developed first by the Russian biochemist M. S. Tswett, about 1906. In recent years, many variations have been developed that provide greater convenience, better separating power, and wider applicability. In **thin-layer chromatography**, which is especially useful for rapid analyses, a solid adsorbent containing a suitable binder is spread evenly on a glass plate, a drop of solution to be analyzed is placed near one edge and the plate is placed in a container with the edge of the plate below the spot, dipping into an eluting solvent. The solvent ascends the plate and the materials in the spot move upward at different rates, as on a Tswett column. Various detecting means are used - simple visual observation for colored compounds, differential fluorescence under ultraviolet light, and spraying of the plate with substances that will give colored materials with the compounds present. In favorable cases, this form of liquid-solid chromatography can be carried out with submicrogram quantities of materials.

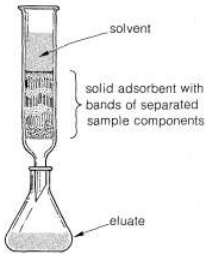

Figure 9-3: A simple chromatographic column for liquid-solid chromatography

An extremely important improvement on the Tswett procedure is **high-pressure solid-liquid chromatography (HPLC)**. Increasing the input pressure on the system to 20-70 atm improves the speed of separations by permitting the use of much smaller solid particles (with more surface area) than would be practical for gravity-flow Tswett columns. Automatic monitoring of the column effluent by ultraviolet spectroscopy (Section 9-9) or by changes in the refractive index usually provides an effective means of determining how the separation is proceeding. With such techniques chromatograms similar to Figure 9-2 are obtained. High-pressure liquid chromatography (hplc) has great advantages for analysis and separation of high-molecular-weight heat-sensitive compounds that are unsuitable for glc.

An ingenious variation of solid-liquid chromatography is to use a solid support to which material is attached that has a specific affinity for a particular substance to be separated. The technique is especially useful for separating enzymes, and the immobile

phase can be constructed from compounds known to react with, or be complexed by, the enzyme. Some other forms of chromatography are discussed in Sections 25-4B and 25-7E.

Observation of a single peak in a given chromatographic procedure is evidence, albeit not definitive evidence, for purity. Contaminants with nearly the same properties may be very difficult to separate and, if knowing the degree of purity is highly important, one can run chromatograms with a variety of different adsorbents to see if each gives the same result. If they do, the presumption of purity improves, although it is desirable to determine whether the spectroscopic techniques to be described in the following section permit the same conclusion.

9.3.3: References

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9.4: Why Can't We See Molecules?

The most straightforward way to determine the structures of molecules would be to "see" how the nuclei are arranged and how the electrons are distributed. This is not possible with visible light, because the wavelengths of visible light are very much longer than the usual molecular dimensions. A beam of electrons can have the requisite short wavelengths, but small organic molecules are destroyed rapidly by irradiation with electrons of the proper wavelengths. Nonetheless, **electron microscopy** is a valuable technique for the study of large molecules, such as DNA, which can be stained with heavy-metal atoms before viewing, or are themselves reasonably stable to an electron beam (Figures 9-4 and 9-5).

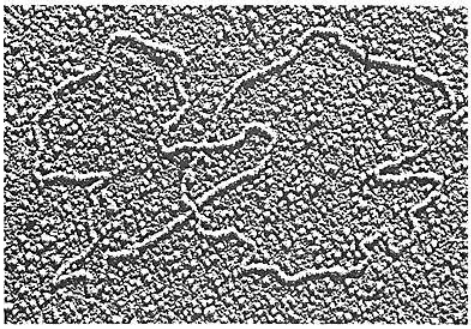


Figure 9-4: Electron micrograph (x40,000) of two linked (catenated) cyclic mitochondrial DNA molecules from a culture of human cells. The DNA was stained with uranyl acetate, then shadowed with platinum and palladium atoms in high vacuum to make the molecules easily visible in the electron microscope. (Photograph supplied by Dr. B. S. Hudson and the late Dr. J. Vinograd.)

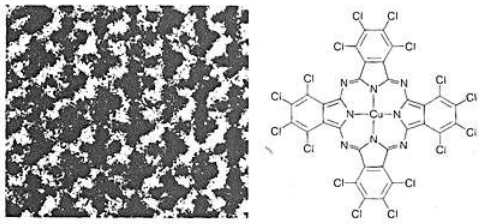
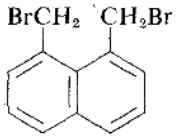


Figure 9-5: Electron micrograph (x150,000) of a thin layer of copper hexadecachlorophthalocyanine molecules. The molecules are tilted about 26° from the horizontal plane. (Courtesy JEOL, Ltd.)

Virtually all parts of the spectrum of electromagnetic radiation, from x rays lo radio waves, have some practical application for the study of organic molecules. The use of **x-ray diffraction** for determination of the structures of molecules in crystals is of particular value, and in the past ten years this technique has become almost routine. Figure 9-6 shows the detailed arrangement of the carbons, hydrogens, and bromines in 1,8-bis(bromomethyl)naphthalene, 1, as determined by x-ray diffraction. The apparatus and techniques used are highly complex and are not available yet to very many organic laboratories.[3]



1

Other diffraction methods include **electron diffraction**, which may be used to’determine the structures of gases or of volatile liquid substances that cannot be obtained as crystals suitable for x-ray diffraction, and **neutron diffraction**, which has special application for crystals in which the exact location of hydrogens is desired. Hydrogen does not have sufficient scattering power for x rays to be located precisely by x-ray diffraction.

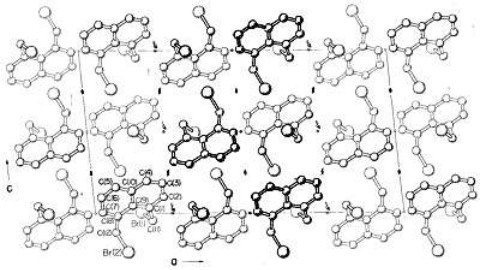


Figure 9-6: Bond lengths, angles, and arrangement of carbons and bromines in a crystal of 1,8-bis(bromomethyl)naphthalene, 1, as determined by x-ray diffraction. Notice that the preferred conformation in the crystal has the bromines on opposite sides of the naphthalene ring.

The diffraction methods can be used to determine complete structures of organic molecules, but they are not sufficiently routine to be utilized generally in practical organic laboratory work. For this reason, in the remainder of this chapter we will emphasize those forms of spectroscopy that are generally available for routine laboratory use. As will be seen, these methods are used by organic chemists in more or less empirical ways. In general, spectroscopic methods depend on some form of excitation of molecules by absorption of electromagnetic radiation and, as we have said, virtually all parts of the electromagnetic spectrum have utility in this regard. The commonly used span of the electromagnetic spectrum is shown in Figure 9-7 along with a comparison of the various units that are employed to express energy or wavelength.

The major kinds of spectroscopy used for structural analysis of organic compounds are listed in Table 9-1. The range of frequencies of the absorbed radiation are shown, as well as the effect produced by the radiation and specific kind of information that is utilized in structural analysis. After a brief account of the principles of spectroscopy, we will describe the methods that are of greatest utility to practical laboratory work. Nonetheless, it is very important to be aware of the other, less routine, methods that can be used to solve special problems, and some of these are discussed in this chapter and in Chapters 19 and 27.

You may have problems with the relationships among the variety of wavelength and frequency units commonly used in spectroscopy. The relationship between wavelength, frequency, and velocity should become clear to you by considering yourself standing on a pier watching ocean waves going by. Assuming the waves are uniformly spaced, there will be a uniform distance between the crests, which is λ, the wavelength. The wave crests will pass by at a certain number per minute, which is ν, the frequency. The velocity, c, at which the crests move by you is related to λ and ν by the relationship $c = \lambda\nu$.

This is not really very complicated and it applies equally well to water waves or electromagnetic radiation. What is almost needlessly complicated is the variety of units commonly used to express λ and ν for electromagnetic radiation. One problem is tradition, the other is the desire to avoid very large or very small numbers. Thus, as Figure 9-7 shows, we may be interested in electromagnetic wavelengths that differ by as much as a factor of 10^{16}. Because the velocity of electromagnetic radiation in a vacuum is constant at $3 \times 10^8\ \mathrm{m\ sec^{-1}}$, the frequencies will differ by the same factor.

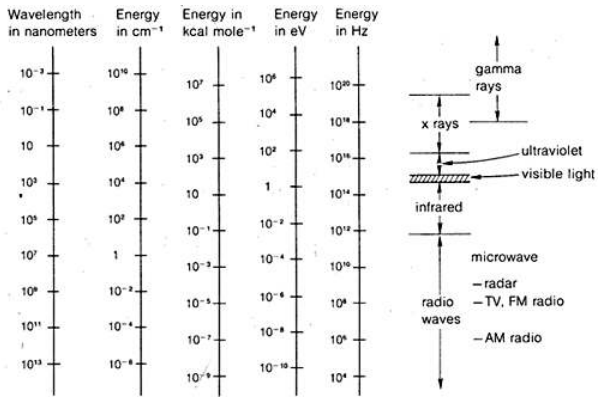


Figure 9-7: The span of the spectrum of electromagnetic radiation used in spectroscopic investigations of organic compounds along with comparison of some of the various units commonly employed for wavelength and energy of the radiation on log scales.

Units commonly used for *wavelength* are meters (m), centimeters (cm), nanometers (nm), and microns (μ). In the past, angstroms ($\mathring{A}$) and millimicrons ($\mathrm{m}\mu m$) also were used rather widely.

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$$1\ \text{m} = 10^2\ \text{cm} = 10^9\ \text{nm} = 10^6\ \mu m \tag{9.4.1}$$

$$10^{-2}\ \text{m} = 1\ \text{cm} = 10^7\ \text{nm} = 10^4\ \mu m \tag{9.4.2}$$

$$10^{-6}\ \text{m} = 10^{-4}\ \text{cm} = 10^3\ \text{nm} = 1\ \mu m \tag{9.4.3}$$

$$10^{-9}\ \text{m} = 10^{-7}\ \text{cm} = 1\ \text{nm} = 10^{-3}\ \mu m = 1\ \text{m}\mu m = 10\ \text{Å} \tag{9.4.4}$$

Frequency units are in cycles per second (cps) or hertz (Hz), which are equivalent (radians per second are used widely by physicists).

Table 9-1: *Principal Spectroscopic Techniques Currently in Use for Analysis of Molecular Structure*

Spectroscopic technique	Energy range of absorbed radiation (in wave numbers, cm $^{-1}$)*	Type of excitation produced by absorbed radiation	Information obtained
Ion cyclotron resonance	10^{-6} to 10^{-5}	Excitation of ions moving in circular orbits in a magnetic field	Rates and equilibria for reactions of ions with neutral molecules in the gas phase (Section 27-8)
Nuclear magnetic resonance (nmr)	10^{-5} to 10^{-3}	Changes in nuclear spin orientations in a magnetic field	Chemical shifts and coupling constants; rapid reaction rates (Sections 9-10, 27-1, and 27-2)
Electron spin resonance (esr)	10^{-4} to 1	Excitation of unpaired electron-spin orientations in a magnetic field	Electron distribution in radicals, electron-transfer reactions (Section 27-9)
Microwave	1 to 100	Rotational excitation	Spacings of rotational energy levels; bond distances and bond angles (Section 9-6)
Infrared (ir)	100 to 10,000	Rotational-vibrational excitation	Rotational and vibrational energy levels of molecules (Section 9-7)
Raman	100 to 4,000	Rotational-vibrational excitation	Rotational and vibrational energy levels of molecules (Section 9-8)
Visible	5,000 to 25,000	Electronic excitation accompanied by vibration-rotation changes	Electronic energy levels of molecules (Section 9-9)
Ultraviolet	25,000 to 50,000	Electronic excitation accompanied by vibration-rotation changes	Electronic energy levels of molecules (Sections 9-9 and 28-1)
Photoelectron	10^5 to 10^6	Ejection of an electron from the valence or inner shell	Ionization energies of valence or inner-shell electrons of molecules (Section 27-5)
Mossbauer	10^5 to 10^6	Excitation of atomic nuclei	Electric field gradients at the nucleus produced by differences in bond types (Section 27-6)
Mass spectrometry	Excitation produced by electrons with energies of about 10^5 cm^{-1}	Molecular ionization and fragmentation	Molecular weights; modes of fragmentation (Sections 9-11 and 27-7)

*These ranges are not meant to be precise, but to give you a general idea of the energy changes involved. One wave number (cm^{-1}) is equivalent to 2.86 cal mole^{-1}. Also see Figure 9-7 for comparison with other commonly used units of energy and wavelength.

Figure 9-7 generally to be large. As a result, it is common to use wave numbers instead of Hz or MHz (megahertz). The frequency in wave number is simply the frequency ν in Hz divided by c, the velocity of light in cm. Wave-number units are cm^{-1} and we can think of the wave number $\tilde{\nu}$ as being the number of wave crests per centimeter.

$$1\ \text{Hz} = 10^{-6}\ \text{MHz} \cong 3.3 \times 10^{-11}\ \text{cm}^{-1} \tag{9.4.5}$$

$$10^6\ \text{Hz} = 1\ \text{MHz} \cong 3.3 \times 10^{-5}\ \text{cm}^{-1} \tag{9.4.6}$$

$$3 \times 10^{10}\ \text{Hz} = 3 \times 10^4\ \text{MHz} \cong 1\ \text{cm}^{-1} \tag{9.4.7}$$

[3]A useful description of how molecular structures can be determined by "x-ray vision" is given in Chapter XI of *Organic Molecules in Action* by M. Goodman and F. Morehouse, Gordon and Breach, New York, 1973.

9.4.1: References

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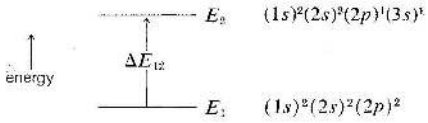
9.5: Atomic Energy States and Line Spectra

The energies of the hydrogenlike orbitals of various atoms were mentioned in Chapter 6 and, in particular, we showed a diagram of the most stable state $(1s)^2\,(2s)^2\,(2p)^2$ of a carbon atom (Figure 6-4). Transfer of one of the $2p$ electrons to the $3s$ orbital requires excitation of the atom to a higher energy state and this can be achieved by absorption of electromagnetic radiation of the proper wavelength. The usual way that such excitation occurs is by absorption of a single **quantum** of radiant energy, and we can say that the absorption of this amount of energy ΔE_{12}, corresponds to excitation of the atom from the **ground state** with energy E_1 to an **excited state** of configuration $(1s)^2\,(2s)^2\,(2p)^1\,(3s)^1$ and energy E_2:



The difference in energy, ΔE_{12}, is related directly to the frequency (ν, sec^{-1}) or wavelength (λ, nm)[4] of the absorbed quantum of radiation by the equation

$$\Delta E_{12} = h\nu = \frac{hc}{\lambda} \tag{9.1}$$

in which h is Planck's constant and c is the velocity of light. The relationship $\Delta E = h\nu$ often is called the *Bohr frequency condition*.

For chemical reactions, we usually express energy changes in $\mathrm{kcal\ mol}^{-1}$. For absorption of one quantum of radiation by each atom (or each molecule) in one mole, the energy change is related to λ by

$$\Delta E_{12} = \frac{28,600}{\lambda(nm)}\ kcal/mol \tag{9.2}$$

As defined, ΔE_{12} corresponds to one **einstein** of radiation.

What we have developed here is the idea of a spectroscopic change being related to a change in energy associated with the absorption of a quantum of energy. **Spectra** are the result of searches for such absorptions over a range of wavelengths (or frequencies). If one determines and plots the degree of absorption by a monoatomic gas such as sodium vapor as a function of wavelength, a series of very sharp absorption bands or lines are observed, hence the name **line spectra**. The lines are sharp because they correspond to specific changes in electronic configuration without complication from other possible energy changes.

[4]See Section 9-3 for discussion of the units of frequency and wavelength.

9.5.1: References

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9.6: Energy States of Molecules

The energy states and spectra of molecules are much more complex than those of isolated atoms. In addition to the energies associated with molecular electronic states, there is kinetic energy associated with vibrational and rotational motions. The total energy, E, of a molecule (apart from its translational[5] and nuclear energy) can be expressed as the sum of three terms:

$$E = E_{electronic} + E_{vibrational} + E_{rotational} \tag{9.6.1}$$

Absorption of electromagnetic radiation by molecules occurs not only by electronic excitation of the type described for atoms, but also by changes in the vibrational and rotational energies.

Both rotations and vibrations of molecules are quantized. This means that only particular values of rotational angular momentum or vibrational energy are possible. We speak of these permitted values of the energies as the vibrational and rotational energy levels.

[5]Translational energy is not very important in connection with spectroscopy and will not be considered here.

9.6.1: References

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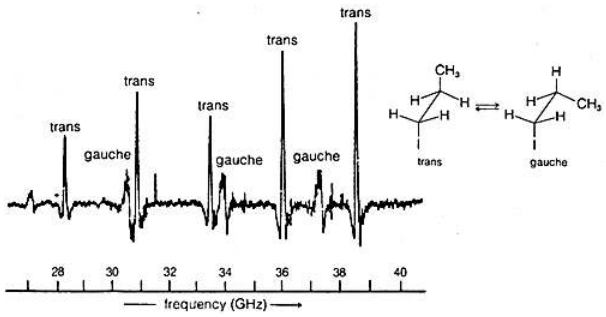
9.7: Microwave (Rotational) Spectra

Rotational energy levels normally are very closely spaced so low-energy radiation, such as is produced by radio transmitters operating in the microwave region, suffices to change molecular rotational energies. Because electronic and vibrational energy levels are spaced much more widely, and because changes between them, are induced only by higher-energy radiation, microwave absorptions by gaseous substances can be characterized as essentially pure “rotational spectra.” It is possible to obtain rotational moments of inertia from microwave spectra, and from these moments to obtain bond angles and bond distances for simple molecules.

An example of the use of microwave spectra is provided by Figure 9-8, which shows separate rotational absorptions observed for trans and gauche conformations of propyl iodide (cf. Section 5-2).

Although microwave spectroscopy, being confined to gases, is not a routine method in the organic laboratory, it is important to us here in setting the stage for the consideration of more complex absorptions that occur with infrared radiation.



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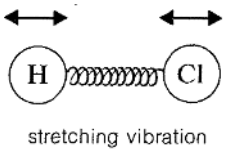
9.8: Infrared (Rovibrational) Spectroscopy

At the turn of the nineteenth century Sir William Herschel discovered invisible radiation beyond the red end of the visible region of the electromagnetic spectrum. This radiation appropriately is called *infrared*, meaning "beneath the red," and it encompasses the wavelength region from 10^3 nm to 10^6 nm. You probably are familiar with the common applications of infrared to radiant heating and photography. In addition to these uses, infrared spectroscopy has become the most widely used spectroscopic technique for investigating organic structures.

Infrared spectroscopy was the province of physicists and physical chemists until about 1940. At that time, the potential of infrared spectroscopy as an analytical tool began to be recognized by organic chemists. The change was due largely to the production of small, quite rugged infrared spectrophotometers and instruments of this kind now are virtually indispensable for chemical analysis. A brief description of the principles and practice of this spectroscopic method is the topic of this section.

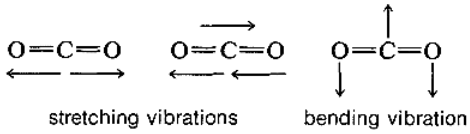
9.8.1: General Considerations of Infrared Spectroscopy

Absorption of infrared radiation causes transitions between *vibrational* energy states of a molecule. A simple diatomic molecule, such as H–Cl, has only one vibrational mode available to it, a stretching vibration somewhat like balls on the ends of a spring:



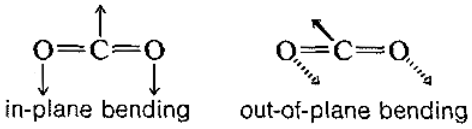
stretching vibration

Molecules with three or more atoms can vibrate by stretching and also by bending of the chemical bonds, as indicated below for carbon dioxide:



stretching vibrations bending vibration

The absorption frequencies in the infrared spectra of molecules correspond to changes in the stretching or bending vibrations or both. In general, a polyatomic molecule with n atoms will have $3n - 6$ modes of vibration of which $n - 1$ are stretching vibrations and $2n - 5$ are bending vibrations. There are circumstances, however, where fewer vibrational modes are possible. If the molecule is linear, like CO_2, then there are $3n - 5$ possible vibrations, and some of these vibrations may be equivalent (degenerate vibrations in the language of spectroscopists). For example, CO_2 should have $3n - 5$ or 4 vibrational modes, two of which are stretching and two of which are bending modes. However, the two bending modes are equivalent because the *direction* in which the molecule bends is immaterial; in-plane or out-of-plane bending are the same:



in-plane bending out-of-plane bending

Diatomic molecules such as HCl have one vibrational mode, but it is important to note that *symmetrical diatomic molecules*, such as O_2, N_2, Cl_2, F_2, and H_2, *do not absorb in the infrared region of the spectrum*. This is because absorption cannot occur if the vibration is electrically symmetrical. Fortunately, then, the infrared spectra can be recorded in air because the main components of air, N_2 and O_2, do not interfere.

In practice, infrared spectra can be obtained with gaseous, liquid, or solid samples. The sample containers (cells) and the optical parts of the instrument are made of rock salt ($NaCl$) or similar material that transmits infrared radiation (glass is opaque).

Typical infrared spectra are shown in Figure 9-9 for 2-propanone (acetone), $CH_3–CO–CH_3$, and 2-butanone (methyl ethyl ketone), $CH_3–CO–CH_2–CH_3$. In accord with current practice, the position of absorption (horizontal scale) is recorded in units of wave numbers ($\bar{\nu}$, cm^{-1}; see Section 9-3). The vertical scale measures the intensity of radiation transmitted through the sample. Zero

transmission means complete absorption of radiation by the sample as at $1740\ \mathrm{cm^{-1}}$ in Figure 9-9. The other absorption bands in Figure 9-9 that correspond to excitation of stretching or bending vibrations are not as intense as the absorption at $1740\ \mathrm{cm^{-1}}$.

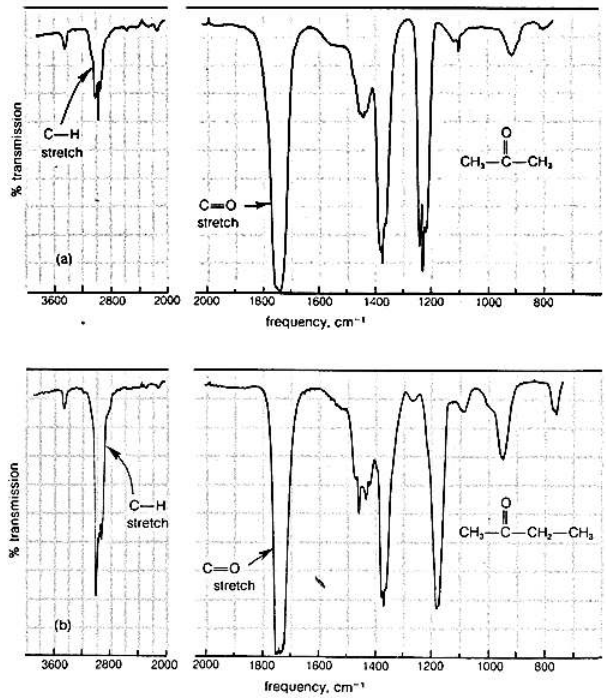


Figure 9-9: Infrared absorption spectra of (a) 2-propanone and (b) 2-butanone in the vapor phase.

9.8.2: Characteristic Stretching Vibrations of Infrared Spectroscopy

What information can we derive about molecular structure from the vibrational bands of infrared spectra? Absorption of radiation in the range of $5000\text{-}1250\ \mathrm{cm^{-1}}$ is characteristic of the types of bonds present in the molecule, and corresponds for the most part to stretching vibrations. For example, we know that the C–H bonds of alkanes and alkyl groups have characteristic absorption bands around $2900\ \mathrm{cm^{-1}}$; an unidentified compound that shows absorption in this region will very likely have alkane-type C–H bonds.

More explicitly, the band observed for 2-propanone (Figure 9-9a) at $3050\ \mathrm{cm^{-1}}$ arises from absorption of infrared radiation, which causes transitions between the ground vibrational state (or lowest vibrational energy level) of a C–H bond and the first excited vibrational energy level for stretching of that C–H bond. The band at $1740\ \mathrm{cm^{-1}}$ corresponds to the infrared absorption that causes transitions between vibrational energy levels of the C=O bond. The reason that these are transitions from the vibrational ground state is because, at room temperature, by far the largest portion of the molecules are in this state (cf. Exercise 9-9).

Stretching frequencies characteristic of the most important types of bonds found in organic molecules are given in Table 9-2. You will notice that the absorption band for each bond type is described by its position within a more or less broad frequency range and by its shape (broad, sharp) and intensity (strong, medium, weak).

A qualitative discussion of the factors that determine infrared band position and band intensities follows. To a first approximation, a chemical bond resembles a mechanical spring that vibrates with a stretching frequency $\bar{\nu}$ ($\mathrm{cm^{-1}}$),

$$\bar{\nu} = \frac{1}{2\pi c}\sqrt{\frac{k}{\frac{m_1 m_2}{m_1 + m_2}}} \tag{9.3}$$

in which k is the force constant, and m_1 and m_2 are the masses of the individual atoms at each end of the bond. The force constant k is a measure of the stiffness of the bond and usually is related to the bond strength. From Equation 9-3, we can see that the heavier the bonded atoms, the smaller will be the vibrational frequency of the bond provided k remains essentially constant.[6] Thus if we increase m_2 while holding k and m_1 constant we expect the frequency to decrease. This is just what occurs when we change the $C-H$ bond to a $C-D$ bond. We also see that the frequency decreases in the order C–H > C–C > C–N > C–O, which also is in the order of increasing m_2, but here matters are more complicated because k also changes.

Other things being equal, it requires more energy to stretch a bond than to bend it. Therefore the infrared bands arising from changes in the stretching vibrations are found at higher frequencies than are those arising from changes in the bending vibrations.

Another consequence of Equation 9-3 is that if m_1 and m_2 remain the same, the larger the value of k, the higher will be the vibrational frequency. Because k is expected to run more or less parallel to the bond strength, and because multiple bonds are stronger than single bonds, the absorption frequencies of multiple bonds are higher than for single bonds. Examples are the absorption of $C=C$ at $2100\ \mathrm{cm}^{-1}$, $C=C$ at $1650\ \mathrm{cm}^{-1}$, and $C-C$ at $1000\ \mathrm{cm}^{-1}$.

Other effects besides mass and bond strength also affect infrared absorption frequencies. The structural environment of a bond is particularly important. Thus the absorption frequency of a $\mathrm{C{-}H}$ bond depends on whether it is an alkyl, alkenyl, alkynyl, or aryl $\mathrm{C{-}H}$ bond (see Table 9-2).

The intensity of an infrared absorption band arising from changes in the vibrational energy is related to the electrical symmetry of the bond. More symmetrical, less polarized bonds give weaker absorptions. In fact, if the bond is completely symmetrical, there is no infrared absorption. In contrast, unsymmetrical molecules in which the bonds are quite polarized, such as $C=O$ bonds, show strong infrared absorptions.

Notice in Figure 9-9 that infrared spectra of organic molecules do not show very sharp absorption lines. This is because changes in rotational energies can occur together with the vibrational changes. The reason can be seen more clearly in Figure 9-10, in which each vibrational level, such as E_1 and E_2, of a molecule has associated with it closely spaced rotational levels. Transitions between E_1 and E_2 also may involve changes in rotational levels. This gives a "band" of closely spaced lines for any given vibrational change. For complex molecules, particularly in the liquid state, the "rotational fine structure" of a given vibrational band usually cannot be resolved.

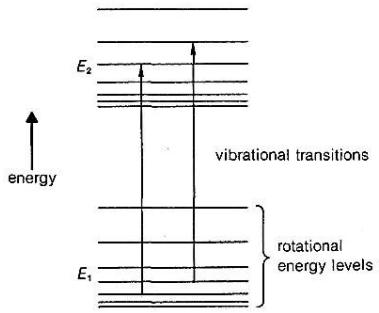
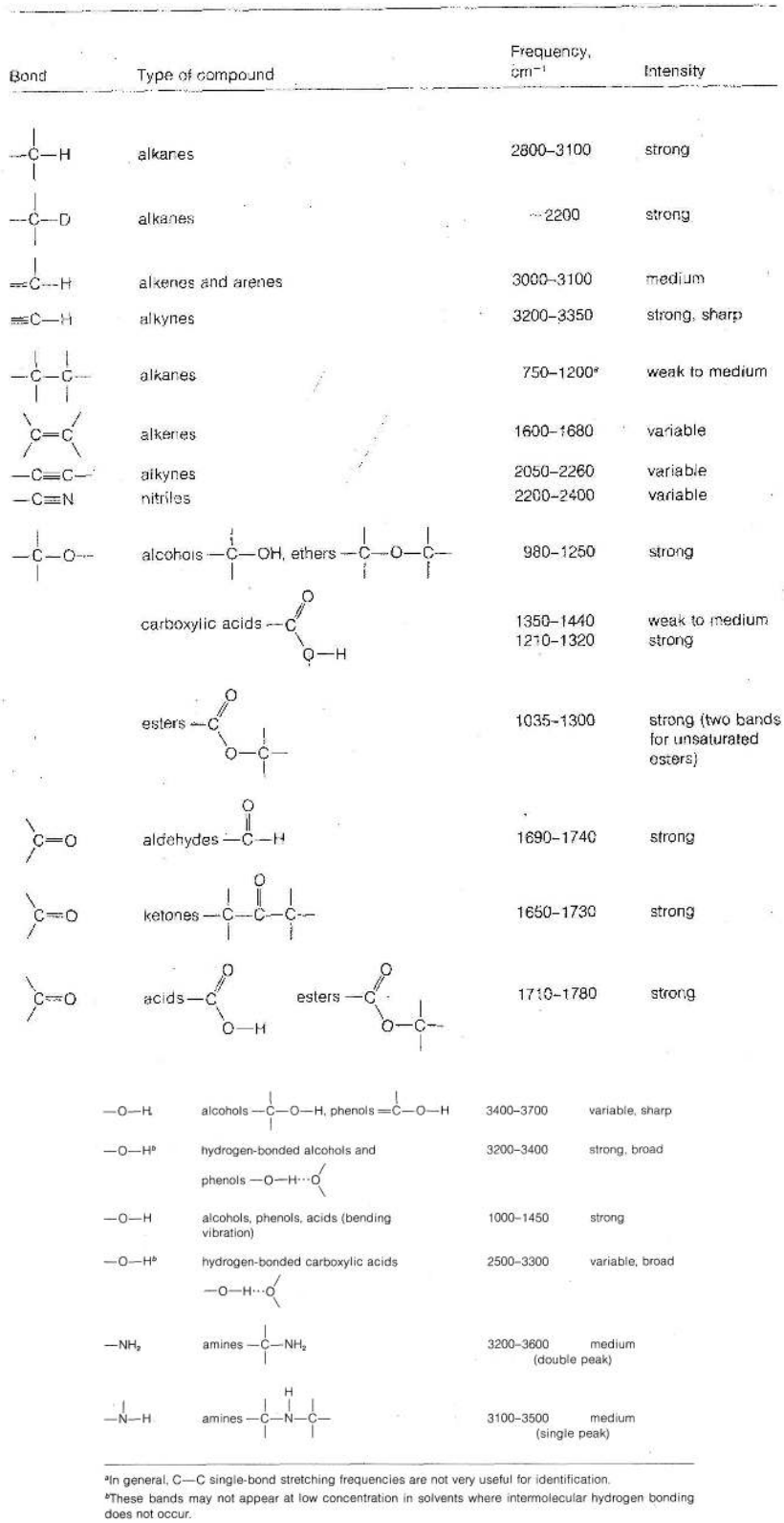


Figure 9-10: Schematic vibrational and rotational energy levels. The arrows correspond to infrared vibrational-rotational transitions of different energies.

Table 9-2: Some Characteristic Infrared Absorption Frequencies



Bond	Type of compound	Frequency, cm^{-1}	Intensity
—C—H	alkanes	2800–3100	strong
—C—D	alkanes	~2200	strong
=C—H	alkenes and arenes	3000–3100	medium
≡C—H	alkynes	3200–3350	strong, sharp
—C—C—	alkanes	750–1200[a]	weak to medium
C=C	alkenes	1600–1680	variable
—C≡C—	alkynes	2050–2260	variable
—C≡N	nitriles	2200–2400	variable
—C—O—	alcohols —C—OH, ethers —C—O—C—	980–1250	strong
	carboxylic acids —C(=O)—O—H	1350–1440 1210–1320	weak to medium strong
	esters —C(=O)—O—C—	1035–1300	strong (two bands for unsaturated esters)
C=O	aldehydes —C(=O)—H	1690–1740	strong
C=O	ketones —C(=O)—C—C—	1650–1730	strong
C=O	acids —C(=O)—O—H; esters —C(=O)—O—C—	1710–1780	strong
—O—H	alcohols —C—O—H, phenols =C—O—H	3400–3700	variable, sharp
—O—H[b]	hydrogen-bonded alcohols and phenols —O—H···O	3200–3400	strong, broad
—O—H	alcohols, phenols, acids (bending vibration)	1000–1450	strong
—O—H[b]	hydrogen-bonded carboxylic acids —O—H···O	2500–3300	variable, broad
$—NH_2$	amines —C—NH_2	3200–3600 (double peak)	medium
—N—H	amines —C—N(H)—C—	3100–3500 (single peak)	medium

[a] In general, C—C single-bond stretching frequencies are not very useful for identification.
[b] These bands may not appear at low concentration in solvents where intermolecular hydrogen bonding does not occur.

Figure 9-10, of $1.7\ \text{kcal mol}^{-1}$ to $10.3\ \text{kcal mol}^{-1}$.

9.8.3: The Fingerprint Region

Infrared absorption bands between $1250\ \text{cm}^{-1}$ and $675\ \text{cm}^{-1}$ generally are associated with complex vibrational and rotational energy changes of the molecule as a whole and are quite characteristic of particular molecules. This part of the spectrum is often called the

"fingerprint" region and is extremely useful for determining whether the samples are chemically identical. The spectra of 2-propanone and 2-butanone are seen to be very similar in the region $4000\ \text{cm}^{-1}$ to $1250\ \text{cm}^{-1}$ but quite different from $1250\ \text{cm}^{-1}$ to $675\ \text{cm}^{-1}$. The fingerprint region of the spectrum is individual enough so that if the infrared spectra of two samples are indistinguishable in the range of frequencies from $3600\ \text{cm}^{-1}$ to $675\ \text{cm}^{-1}$, it is highly probable that the two samples are of the same compound (or the same mixture of compounds).

Characteristic stretching and bending frequencies occur in the fingerprint region, but they are less useful for identifying functional groups, because they frequently overlap with other bands. This region is sufficiently complex that a complete analysis of the spectrum is seldom possible.

9.8.4: Alkanes and Cycloalkanes

The infrared spectra of the alkanes show clearly absorptions corresponding to the $C-H$ stretching frequencies at $2850\ \text{cm}^{-1}$ to $3000\ \text{cm}^{-1}$. The $C-C$ stretching absorptions have variable frequencies and are usually weak. Methyl (CH_3-) and methylene ($-CH_2-$) groups normally have characteristic $C-H$ bending vibrations at $1400\ \text{cm}^{-1}$ to $1470\ \text{cm}^{-1}$. Methyl groups also show a weaker band near $1380\ \text{cm}^{-1}$. Two sample infrared spectra that illustrate these features are given in Figure 9-11.

The infrared spectra of the cycloalkanes are similar to those of the alkanes, except that when there are no alkyl substituents the characteristic

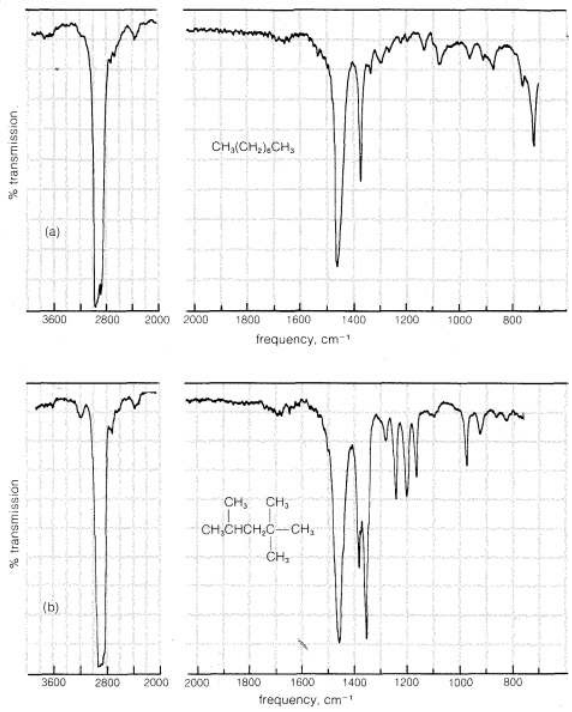


Figure 9-11: Infrared spectra of (a) octane and (b) 2,2,4-trimethylpentane as pure liquids. Notice the $C-H$ stretching around $2900\ \text{cm}^{-1}$ and $C-H$ bending frequency around $1460\ \text{cm}^{-1}$. The bands near $1370\ \text{cm}^{-1}$ for 2,2,4-trimethylpentane are characteristic of methyl $C-H$ bending frequencies.

bending frequencies of methyl groups at $1380\ \text{cm}^{-1}$ are absent. A moderately strong CH_2 "scissoring" frequency is observed between $1440\ \text{cm}^{-1}$ and $1470\ \text{cm}^{-1}$, the position depending somewhat on the size of the ring. These features of the infrared spectra of cycloalkanes are illustrated in Figure 9-12 using cyclooctane and methylcyclohexane as examples.

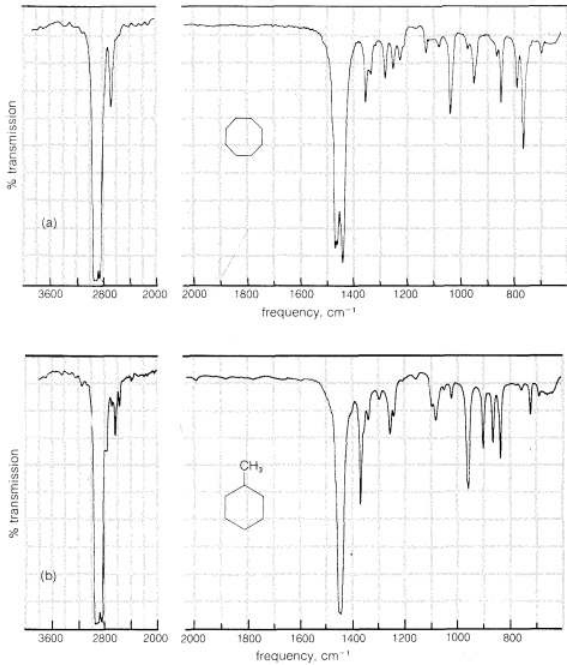


Figure 9-11.

9.8.5: Applications of Infrared Spectroscopy to Structure Determination

Infrared spectra are very useful both for identification of specific organic compounds, and for determining types of compounds. For example, Figure 9-13 shows the infrared spectrum of a substance, $C_4H_6O_2$, for which we wish to determine the compound type and, if possible, the specific structure. The most informative infrared absorptions for determining the compound type are between $1500\ \text{cm}^{-1}$ and $3600\ \text{cm}^{-1}$. Two groups of bands in this region can be seen at about $1700\ \text{cm}^{-1}\ (s)$ and $3000\ \text{cm}^{-1}\ (s)$, where (s) means strong; if we used (m) it would mean medium, and (w) would mean weak. From Table 9-2 we can see that these bands are indicative of $C=O$ ($1700\ \text{cm}^{-1}$) and hydrogen-bonded OH of carboxylic acids ($3000\ \text{cm}^{-1}$). The presumption is that there is a $-CO_2H$ group in the molecule, and we can derive some reassurance from the fact that the molecular formula $C_4H_6O_2$ has enough oxygens to allow for this possibility.

Table 9-2 also shows that a $-CO_2H$ group should have a $C-O$ absorption band between $1350\ \text{cm}^{-1}$ and $1400\ \text{cm}^{-1}$ and $O-H$ absorption (bending frequency) between $1000\ \text{cm}^{-1}$ and $1410\ \text{cm}^{-1}$, and there is indeed a band of medium intensity at $1350\ \text{cm}^{-1}$ and a strong band at $1240\ \text{cm}^{-1}$. These absorptions, being in the fingerprint region, do not *prove* that the compound is a carboxylic acid; but if there were no absorptions in the $1000\ \text{cm}^{-1}$ to $1400\ \text{cm}^{-1}$ range, the presence of a $-CO_2H$ group would be highly questionable.

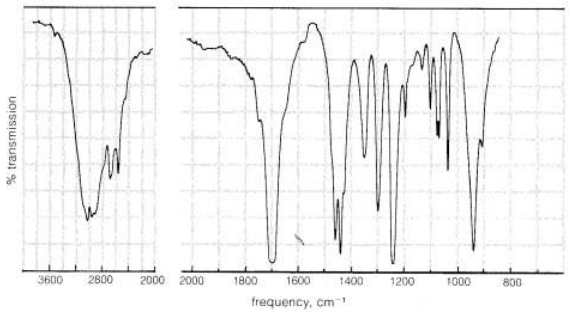


Figure 9-13: Infrared spectrum of a compound, $C_4H_6O_2$

Tentatively, then, we may write a partial structure for $C_4H_6O_2$ as

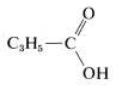


Figure 9-13. The alternative to a double bond would be a ring, which for C_3H_5 has to be a cyclopropyl ring. The structure that is most compatible with the spectrum is

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cyclopropanecarboxylic acid

Final identification may be possible by comparison with an authentic spectrum of cyclopropanecarboxylic acid, if it is available in one of the several standard compendia of infrared spectra. A total of about 150,000 infrared spectra are available for comparison purposes. You should check with the reference section of your library to see what atlases of spectral data are available to you.

The foregoing example illustrates the way structures can be determined from infrared spectral data. For many purposes, the infrared frequencies given in Table 9-2 are both approximate and incomplete. However, you could be easily frustrated in interpreting spectral data by being burdened with a very detailed table in which the unimportant is mixed with the important. The ability to use extensive tables effectively comes with experience. You should remember that tabulated infrared frequencies indicate only the *range* in which a given vibrational transition will fall. The exact value for a particular compound usually is meaningless because it will change depending on whether the spectrum is taken of the solid, liquid, or gaseous states, the solvent used, the concentration, and the temperature.

[6]Remember that lower frequency means longer wavelengths and lower energy.

9.8.6: References

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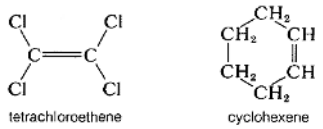
9.9: Raman Spectroscopy

Raman spectroscopy often is a highly useful adjunct to infrared spectroscopy. The experimental arrangement for Raman spectra is quite simple in principle. Monochromatic light, such as from an argon-gas laser, is passed through a sample, and the light scattered at right angles to the incident beam is analyzed by an optical spectrometer.

Raman spectra arise as a result of light photons being "captured" momentarily by molecules in the sample and giving up (or gaining) small increments of energy through changes in the molecular vibrational and rotational energies before being emitted as scattered light. The changes in the vibrational and rotational energies result in changes in wavelength of the incident light. These changes are detected as lines falling both above and below the wavelength of the incident light. The line positions in Raman spectra always are reported in wave numbers. Highly efficient laser Raman spectrometers are commercially available.

Although changes in wavelength in Raman scattering correspond to absorption or emission of infrared radiation, infrared and Raman spectra are not always identical. Indeed, valuable information about molecular symmetry may be obtained by comparison of infrared and Raman spectra. When a bond is *electrically symmetrical* it does not absorb infrared radiation and, for this reason, symmetrical diatomic molecules such as H_2 and O_2, which are always electrically symmetrical, do not give infrared absorption spectra. However, excitation of symmetrical vibrations does occur in Raman scattering.[7] In a molecule such as ethene, $CH_2 = CH_2$, the double-bond stretching vibration is symmetrical, because both ends of the molecule are the same. As a result, the double-bond stretching absorption is not observable in the infrared spectrum of ethene and is weak in all nearly symmetrically substituted ethenes. Nonetheless, this vibration appears strongly in the Raman spectrum of ethene and provides evidence for a symmetrical structure for ethene.



Figures 9-15 and 9-16.

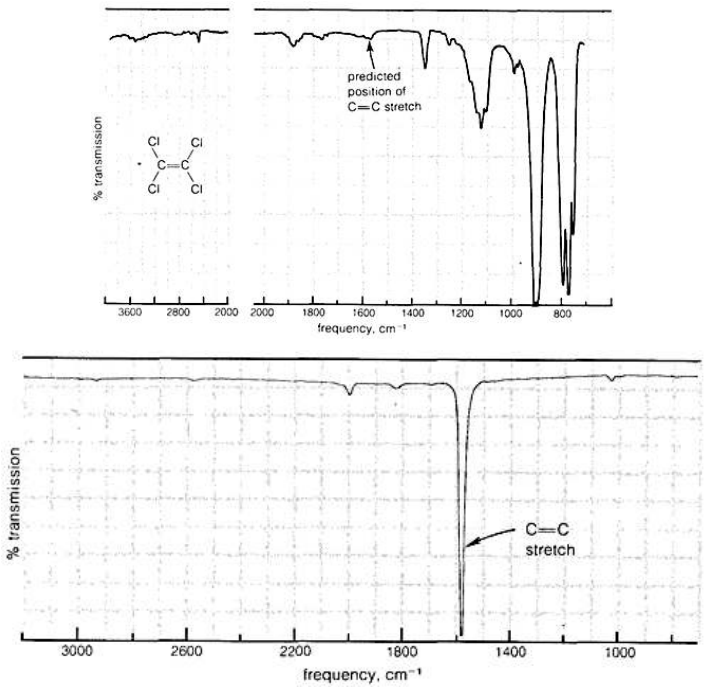


Figure 9-15: Infrared (top) and Raman spectra (bottom) of tetrachloroethene (notice that the spacings and alignment of the horizontal scales are not the same). The Raman spectrum was supplied courtesy of the Applied Physics Corporation.

Absorption due to the stretching vibration of the double bond in tetrachloroethene ($1570\ \mathrm{cm}^{-1}$ is strong in the Raman and absent in the infrared, whereas that arising from the less symmetrical double bond of cyclohexene ($1658\ \mathrm{cm}^{-1}$) is weak in the infrared and slightly stronger in the Raman.

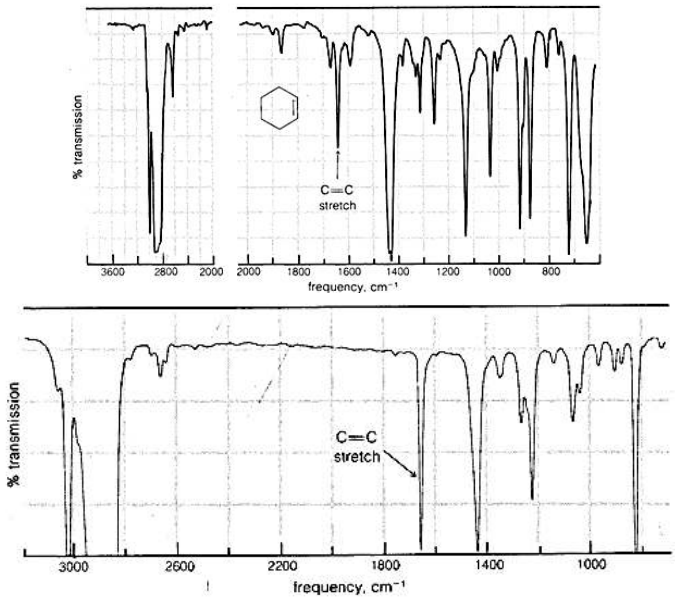


Figure 9-16: Infrared (top) and Raman spectra (bottom) of cyclohexene (notice that the spacings and alignment of the horizontal scales are not the same). The Raman spectrum was supplied courtesy of the Applied Physics Corporation.

[7]This is in accord with the spectroscopic "selection rules," derived from theoretical arguments, that predict which transitions between rotational and vibrational energy levels are "allowed" and which are "forbidden."

9.9.1: References

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9.10: Electronic Spectra of Organic Molecules

9.10.1: General Characteristics

A year after Herschel discovered infrared radiation, Johann Ritter discovered radiation beyond the violet end of the visible spectrum. This radiation came to be known as *ultraviolet* and soon was recognized as being especially effective in causing chemical reactions. Absorption of light in the ultraviolet and visible regions produces changes in the electronic energies of molecules associated with excitation of an electron from a stable to an unstable orbital. Because the energy required to excite the valence-shell electrons of molecules is comparable to the strengths of chemical bonds, absorption may lead to chemical reactions. We discussed this briefly in Chapter 4 in connection with photochemical halogenation of alkanes; a more detailed account of photochemistry is given in Chapter 28.

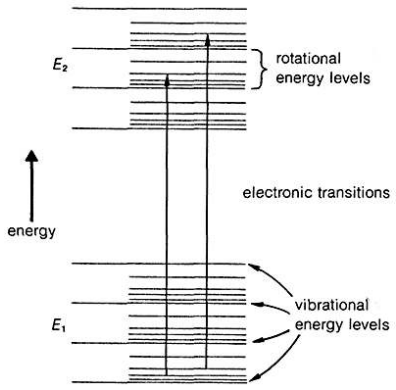


Figure 9-17: Schematic representation of electronic, vibrational, and rotational energy levels. The vertical scale is greatly distorted; rotational energy levels are normally 10^{-4}-10^{-2} $\mathrm{kcal\ mol^{-1}}$ apart, vibrational energy levels are 1-10 $\mathrm{kcal\ mol^{-1}}$ apart, while electronic transitions involve 10-1000 $\mathrm{kcal\ mol^{-1}}$.

The transition of an electron from the ground state, E_1, to an excited electronic state, E_2, is accompanied by vibrational and rotational changes in the molecule, as shown in Figure 9-17. In condense phase samples, it usually is not possible to resolve the resulting absorption *bands* well enough to see the fine structure due to vibration-rotation transitions. Consequently, absorptions due to electronic excitation are relatively broad.

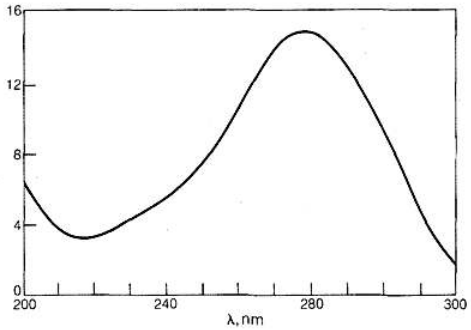


Figure 9-18: The ultraviolet spectrum of 2-propanone (acetone) in cyclohexane

The ultraviolet spectrum of 2-propanone (acetone) is shown in Figure 9-18. The weak absorption, which peaks (i.e., has λ_{max} at 280 nm, is the result of excitation of one of the unshared electrons on oxygen to a higher energy level. This is called an $n \rightarrow \pi^*$ (often $N \rightarrow A$) transition, in which n denotes that the excited electron is one of the unshared n electrons on oxygen and π^* (pi star) denotes that the excited electron goes to a high-energy *antibonding* orbital of the carbon-oxygen double bond (cf. Sections 6-2 and 6-4C). The same kind of $n \rightarrow \pi^*$ transition occurs at about the same wavelength and intensity for many simple compounds of the type $\mathrm{R_2C{=}O}$ and $\mathrm{RCH{=}O}$, in which R is an alkyl group. In a very schematic way, we can write

$$R_2C::\underset{\cdot\cdot}{O}: \xrightarrow{n \longrightarrow \pi^*} R_2C^{\cdot}\!:\underset{\cdot\cdot}{O}\cdot$$

Figure 9-18), which is a different kind of excitation. This is ascribed to raising an electron in the π-bonding orbital (Section 6-4C) of the carbon-oxygen double bond to the π^* orbital. Such transitions are called $\pi \rightarrow \pi^*$, and occur generally for substances with double bonds:

$$R_2C::\underset{\cdot\cdot}{O}: \xrightarrow{\pi \longrightarrow \pi^*} R_2C\!:\!\underset{\cdot\cdot}{O}:$$

Figure 9-19).

Table 9-3
Some Electronic Transitions of Simple Organic Molecules

Compound	Type	λ_{max}, nm	ϵ_{max}[a]	Solvent[b]
$(CH_3)_2C{=}O$	$n \longrightarrow \pi^*$	280.0	15	cyclohexane
	$\pi \longrightarrow \pi^*$[c]	190.0	1,100	
	$n \longrightarrow \sigma^*$[c]	156.0	strong	
$CH_2{=}CH_2$	$\pi \longrightarrow \pi^*$	175.0	10,000	vapor
$CH_2{=}CH{-}CH{=}CH_2$	$\pi \longrightarrow \pi^*$	217.0	20,900	hexane
$CH_3{-}CH{=}CH{-}CH{=}CH{-}CH_3$	$\pi \longrightarrow \pi^*$	227.0	22,500	hexane
$CH_2{=}CH{-}CH_2{-}CH_2{-}CH{=}CH_2$	$\pi \longrightarrow \pi^*$	185.0	20,000	alcohol
$CH_3{-}C{\equiv}CH$	$\pi \longrightarrow \pi^*$	186.5	450	cyclohexane
$CH_2{=}CH{-}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}{=}O$	$n \longrightarrow \pi^*$	324.0	24	alcohol
	$\pi \longrightarrow \pi^*$	219.0	3,600	
CH_4	$\sigma \longrightarrow \sigma^*$[d]	121.9	strong	vapor
$CH_3{-}CH_3$	$\sigma \longrightarrow \sigma^*$[d]	135.0	strong	vapor
$CH_3{-}Cl$	$n \longrightarrow \sigma^*$[e]	172.5	weak	vapor
$CH_3{-}Br$	$n \longrightarrow \sigma^*$[e]	204.0	200	vapor
$CH_3{-}I$	$n \longrightarrow \sigma^*$[e]	257.5	365	pentane
$CH_3{-}O{-}H$	$n \longrightarrow \sigma^*$[e]	183.5	150	vapor
$CH_3{-}O{-}CH_3$	$n \longrightarrow \sigma^*$[e]	183.8	2,520	vapor
$(CH_3)_3N$	$n \longrightarrow \sigma^*$[e]	227.3	900	vapor

[a]The molar extinction coefficient ϵ is a measure of the absorption efficiency at the wavelength λ_{max}. Because the amount of absorption is proportional to the concentration (c moles liter^{-1}) and thickness of the sample (l cm), ϵ is obtained from the equation

$$\epsilon = \frac{1}{cl} \log_{10} \frac{I_0}{I} \quad \text{or} \quad \epsilon cl = A$$

in which I_0/I is the ratio of intensity of incident light I_0 to transmitted light I. The percent transmission of a solution is $(I/I_0) \times 100$ and the absorbance $A = \log I_0/I$. Substances for which ϵ is independent of concentration are said to obey Beer's law (or the Beer–Lambert law).

[b]It is necessary to specify the solvent because λ_{max} and ϵ_{max} vary somewhat with solvent.

[c]These assignments are not certain.

[d]Transitions $\sigma \longrightarrow \sigma^*$ correspond to excitation of a σ electron of a single bond to a higher-energy antibonding orbital of the single bond, σ^* (sigma star).

[e]Transitions $n \longrightarrow \sigma^*$ correspond to excitation of an electron of an unshared pair to an antibonding orbital (σ^*) of a σ bond.

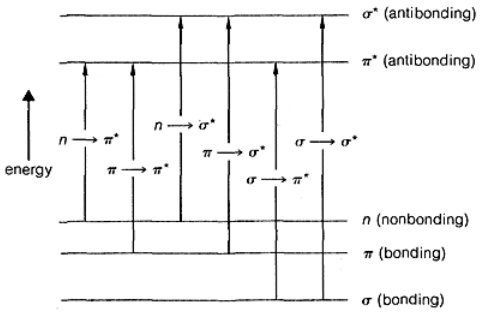
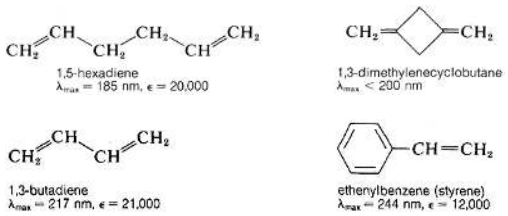


Figure 9-19: Sequence of electronic orbital energies, showing different kinds of transitions in approximate order of increasing energy, left to right. The $\sigma \rightarrow \pi^*$ and $\pi \rightarrow \sigma^*$ transitions usually have low transition probabilities, meaning the bands have low or zero intensities.

9.10.2: Effects of Conjugation on Electronic Spectra

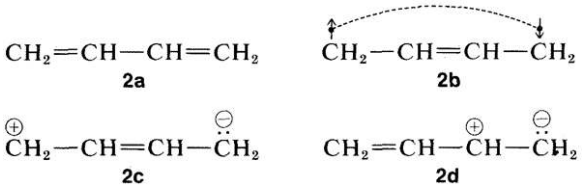
The $\pi \rightarrow \pi^*$ transition for ethene has $\lambda_{\max} = 175$ nm and $\epsilon_{\max} = 10,000$. It would be expected that an alkadiene would give an absorption spectrum similar to that of ethene but with a larger ϵ, because there are more double bonds per mole to absorb radiation. This expectation is more or less realized for compounds such as 1,5-hexadiene and 1,3-dimethylenecyclobutane, which have isolated double bonds, but not for 1,3-butadiene or ethenylbenzene, which have conjugated double bonds (Section 3-3):



In general, *conjugated systems of double bonds absorb radiation of longer wavelengths and with greater intensity than corresponding systems of isolated double bonds.* This means that the difference in energy between the normal and excited states of conjugated systems is *less* than for isolated systems of double bonds. For 1,3-butadiene and 1,5-hexadiene we can calculate from Equation 9-2

that the transition energy is about $23\ \text{kcal}$ less for the conjugated system. The ground state of 1,3-butadiene is stabilized by perhaps $3\ \text{kcal}$ relative to a nonconjugated system of double bonds, which means that the excited state must be much more stabilized than this if the transition energy is to be $23\ \text{kcal}$ less than for 1,5-hexadiene.

Why is the excited state of a conjugated system of double bonds stabilized more, relative to the ground state, than for a nonconjugated system? Resonance theory provides an explanation (see Section 6-5). Of the several conventional valence-bond structures that can be written for 1,3-butadiene, four of which are shown here, $2a$-$2d$, only structure $2a$ has a low enough energy to be dominant for the ground state of 1,3-butadiene:



Now, when the molecule is excited to the extent of $132\ \text{kcal mol}^{-1}$ by $217\ \text{nm}$ ultraviolet light, its energy is so large that pairing schemes such as $2b$, $2c$, and $2d$, which are too unfavorable to contribute very much to the ground state, can be very important for the excited state. Thus the stabilization energy of the excited state, which has a multiplicity of nearly equal-energy pairing schemes, is expected to be greater than that of the ground state with one dominant pairing scheme.

The more double bonds in the conjugated system, the smaller the energy difference between the normal and excited states. The diphenylpolyenes of formula $C_6H_5-(CH=CH)_n-C_6H_5$ absorb radiation at progressively *longer* wavelengths as n is increased. This is apparent from the colors of the compounds, which range from colorless with $n=1$, to orange with $n=2-7$, to red with $n=8$, as $\lambda_{\max}$ goes from the ultraviolet into the visible region of the electromagnetic spectrum.

Similar effects are found with conjugated C=O and C=N double bonds. For example, the electronic spectra of 2-butanone and 3-buten-2-one are shown in Figure 9-20.

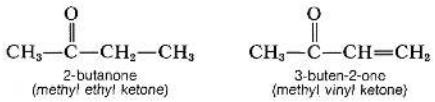


Figure 9-20.

Conjugation also can influence infrared spectra. Transitions arising from $C=C$ and $C=O$ stretching vibrations generally are more intense and are shifted to slightly lower frequencies (longer wavelengths) for conjugated compounds relative to nonconjugated compounds. Thus the $C=C$ stretching of 1-butene occurs at $1650\ \text{cm}^{-1}$, whereas that of 1,3-butadiene is observed at $1597\ \text{cm}^{-1}$.

Alkanes and cycloalkanes have no low-energy electronic transitions comparable to conjugated systems or molecules with nonbonding electrons. Therefore alkanes and cycloalkanes show no absorption above $200\ \text{nm}$ and are good solvents to use for electronic spectroscopy.

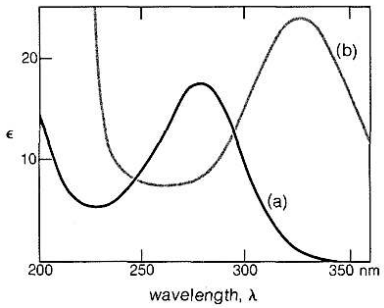


Figure 9-20: Electronic spectra of (a) 2-butanone and (b) 3-buten-2-one in cyciohexane solution

9.10.3: Applications of Electronic Spectroscopy

How do we use electronic spectroscopy in chemical analysis? The two principal applications are structure determinations and quantitative analysis. The position and intensity of an electronic absorption band provides information as to chemical structure. Such absorptions normally are not as useful as infrared absorptions because they do not give as detailed information. For our purposes here, the main points to remember are:

1. A weak absorption ($\epsilon = 10 - 100$) suggests an $n \rightarrow \pi^*$ transition of an isolated carbonyl group. If this absorption is found in the region 270-$350\ \mathrm{nm}$ an aldehyde or ketone is probable.
2. Somewhat stronger absorptions ($\epsilon = 100 - 4,000$) between $200\ \mathrm{nm}$ and $260\ \mathrm{nm}$ may correspond to $\pi \rightarrow \sigma^*$ transitions.
3. Strong absorptions ($\epsilon = 10,000 - 20,000$) usually are characteristic of $\pi \rightarrow \pi^*$ transitions. If absorption occurs above $200\ \mathrm{nm}$, a conjugated system of multiple bonds is indicated. Each additional carbon-carbon double bond shifts $\lambda_{\max}$ about $30\ \mathrm{nm}$ to longer wavelengths and enhances the intensity of absorption. Conjugation also shifts $\lambda_{\max}$ of $n \rightarrow \pi^*$ transitions to longer wavelengths.

If we are dealing with compounds for which the wavelengths and the molar intensities of the absorption bands are known, then we can use the degree of absorption for quantitative analysis with the aid of the Beer-Lambert law (see Table 9-3 for definitions):

$$A = \epsilon c l \tag{9.10.1}$$

By measuring the absorbance A of a sample of known ϵ in a cell of known path length I, the concentration c may be determined. Because changes in absorbance reflect changes in concentration, it is possible to use absorbance measurements to follow rates of chemical reactions, to determine equilibrium constants (such as the dissociation constants of acids and bases), and to follow conformational changes in bio-organic molecules such as proteins and nucleic acids.

The capacity of electronic spectroscopy for performing qualitative and quantitative of the elements in chemical compounds has been done and applications have been made to elements of low atomic number, such as carbon and oxygen. Electronic spectra has been developed in the study of this elements and it’s compounds.

9.10.4: References

- John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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9.11: Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy is extremely useful for identification and analysis of organic compounds. The principle on which this form of spectroscopy is based is simple. The nuclei of many kinds of atoms act like tiny magnets and tend to become aligned in a magnetic field. In NMR spectroscopy, we measure the energy required to change the alignment of magnetic nuclei in a magnetic field. To illustrate the procedure with a simple example, consider the behavior of a proton (^1H) in a magnetic field. There are two possible alignments of this magnetic nucleus with respect to the direction of the applied field, as shown in Figure 9-21. The nuclear magnets can be aligned either with the field direction, or opposed to it. The two orientations are not equivalent, and energy is required to change the more stable alignment to the less stable alignment.

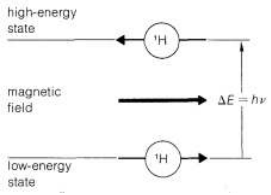

Figure 9-21: Schematic representation of the possible alignments of a magnetic nucleus (here hydrogen) in an applied magnetic field. Transitions between the two states constitute the phenomenon of nuclear magnetic resonance. The arrows through the nuclei represent the average component of their nuclear magnetic moment in the field direction.

A schematic diagram of an NMR instrument is shown in Figure 9-22. When a substance such as ethanol, $CH_3 - CH_2 - OH$, the hydrogens of which have nuclei (protons) that are magnetic, is placed in the transmitter coil and the magnetic field is increased gradually, at certain field strengths radio-frequency energy is absorbed by the sample and the ammeter indicates an increase in the flow of current in the coil. The overall result is a spectrum such as the one shown in Figure 9-23. This spectrum is detailed enough to serve as a useful "fingerprint" for ethanol, and also is simple enough that we will be able to account for the origin of each line. It is the purpose of this section to explain how the complexities of spectra such as that of Figure 9-23 can be interpreted in terms of chemical structure.

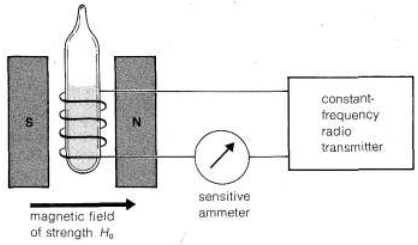

Figure 9-22: Essential features of a simple NMR spectrometer

For what kinds of substances can we expect nuclear magnetic resonance absorption to occur? Magnetic properties always are found with nuclei of odd-numbered masses, ^1H, ^{13}C, ^{15}N, ^{17}O, ^{19}F, ^{31}P, and so on, as well as for nuclei of even mass but odd atomic number, ^2H, ^{10}B, ^{14}N, and so on.[8] Nuclei such as ^{12}C, ^{16}O, and ^{32}S, which have even mass and atomic numbers, have *no* magnetic properties and do *not* give nuclear magnetic resonance signals. For various reasons, routine use of NMR spectra in organic chemistry is confined to ^1H, ^{19}F, ^{13}C, and ^{31}P. We shall be concerned in this chapter only with NMR spectra of hydrogen (^1H) and of carbon (^{13}C).

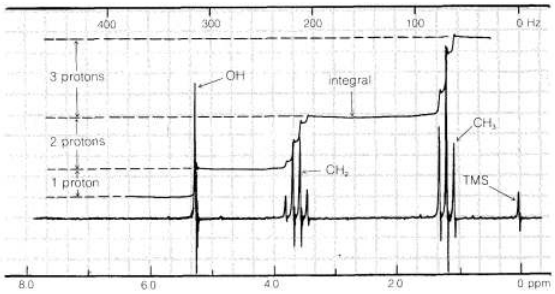

Figure 9-23: Proton NMR spectrum of ethanol (containing a trace of hydrochloric acid). Chemical shifts are relative to tetramethylsilane $(CH_4)_4\,Si$, that is, TMS $= 0.00$ ppm. The stepped line is an integral of the areas under each of the resonance lines.

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The kind of NMR spectroscopy we shall discuss here is limited in its applications because it can be carried out only with *liquids* or *solutions*. Fortunately, the allowable range of solvents is large, from hydrocarbons to concentrated sulfuric acid, and for most compounds it is possible to find a suitable solvent.

Nuclear magnetic resonance spectra may be so simple as to have only a single absorption peak, but they also can be much more complex than the spectrum of Figure 9-23. However, it is important to recognize that no matter how complex an NMR spectrum appears to be, in involves just *three* parameters: **chemical shifts**, **spin-spin splittings**, and **kinetic** (reaction-rate) **processes**. We shall have more to say about each of these later. First, let us try to establish the relationship of NMR spectroscopy to some of the other forms of spectroscopy we have already discussed in this chapter.

9.11.1: The Relation of NMR to Other Kinds of Spectroscopy

Nuclear magnetic resonance[9] spectroscopy involves transitions between possible energy levels of magnetic nuclei in an applied magnetic field (see Figure 9-21). The transition energies are related to the frequency of the absorbed radiation by the familiar equation $\Delta E - h\nu$. An important difference between nmr and other forms of spectroscopy is that ΔE is influenced by the strength of the applied field. This should not be surprising, because if we are to measure the energy of changing the direction of alignment of a magnetic nucleus in a magnetic field, then the stronger the field the more energy will be invloved.

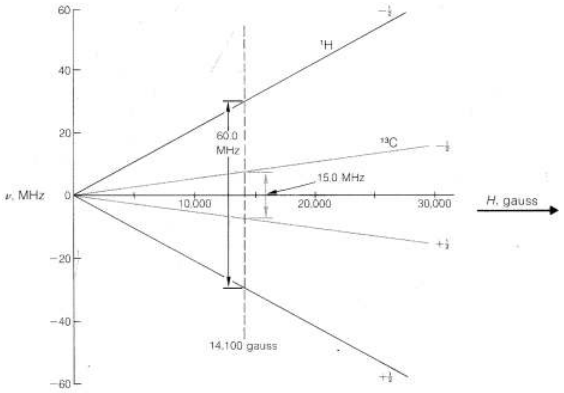
Nuclear spin (symbolized as I) is a quantized property that correlates with nuclear magnetism such that when I is zero the nucleus has no spin and no magnetic properties. Examples are ^{12}C and ^{16}O. Several nuclei of particular interest to organic chemists - ^{1}H, ^{13}C, ^{15}, ^{19}, and ^{31}P - have spin of $\frac{1}{2}$. With $I = \frac{1}{2}$ there are only *two* magnetic energy states of the nucleus in a magnetic field. These states are designated with the **spin quantum numbers** $+\frac{1}{2}$ and $-\frac{1}{2}$. The difference in energy between these states, ΔE, is given by

$$\Delta E = \gamma h H = h\nu \tag{9.11.1}$$

or

$$\nu = \gamma H \tag{9.11.2}$$

in which h is Planck's constant, ν is in hertz, γ is a nuclear magnetic constant called the **gyromagnetic ratio**,[10], and H is the magnetic field strength at the nucleus. In general, H will not be exactly equal to H_o, the applied magnetic field and, as we will see, this difference leads to important chemical information. Each *kind* of nucleus (^{1}H, ^{13}C, ^{15}N, etc.) has its own γ value and, consequently, will undergo transitions at different frequencies at any particular value of H. This should become clearer by study of Figure 9-24.



There are several modes of operation of an nmr spectrometer. First and most common, we hold ν constant and vary (or "sweep") H_o. Close to $\nu = \gamma H$, energy is absorbed by the nuclei and the current flow from the transmitter increases until ν is exactly equal to γH. Further increase of H_o makes $\nu < \gamma H_o$ and the current flow decreases. The form of the energy-absorption curve as a function of H_o when H_o is changed very slowly is shown in Figure 9-25a. The peak is centered on the point where $\nu = \gamma H$. When H_o is changed more rapidly, transient effects are observed on the peak, which are a consequence of the fact that the nuclei do not revert instantly from the $-\frac{1}{2}$ to $+\frac{1}{2}$ state. The resulting

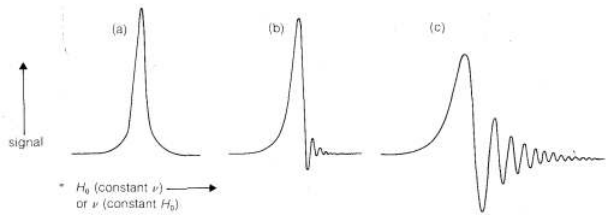


Figure 9-25: Comparison of sweep rates on nmr absorption curves; (a) 500-sec sweep, (b) 50-sec sweep, (c) 10-sec sweep, The "ringing" in the faster sweep curves is a transient effect that has a small effect on the position of the peak and none on the integral.

phenomenon is called "ringing" and is shown in Figures 9-25b and 9-25c. Evidence of ringing also will be seen on peaks of Figure 9-23.

An alternative method of running an nmr spectrometer is to hold the magnetic field constant and to sweep the transmitter frequency through the resonances. This mode of operation is more like other forms of spectroscopy and gives the same line shapes as sweeping the field (Figure 9-25).

What energy is associated with a ^1H nmr transition? The magnitude of this energy may be calculated from the relationship between energy and wavelength (frequency) of the absorbed radiation (Section 9-4). That is,

$$\Delta E = \frac{28,600}{\lambda} \text{kcal mol}^{-1} \tag{9.11.3}$$

and

$$\lambda = \frac{c}{\nu} \tag{9.11.4}$$

The frequency ν is the operating frequency of the spectrometer, which we will take as 60 MHz or 6×10^7 Hz (cycles sec^{-1}), and the velocity of light is 3×10^8 m sec^{-1}. Hence

$$\lambda = \frac{3 \times 10^8 \times 10^9 \,(\text{nm sec}^{-1})}{6 \times 10^7 \,(\text{Hz})} = 5 \times 10^9 \text{ nm} \tag{9.11.5}$$

and

$$\Delta E = \frac{28,600}{5 \times 10^9} = 5.7 \times 10^{-6} \text{ kcal mol}^{-1} \tag{9.11.6}$$

This is a very small energy difference, which means that only very few more of the nuclei are in the more stable $+\frac{1}{2}$ state than in the less stable $-\frac{1}{2}$ state. The equilibrium constant K for $-\frac{1}{2} \rightleftharpoons +\frac{1}{2}$ calculated from Equation 4-2 for 25° (298 \: \text{K}\)) and neglecting possible entropy effects is 1.000010!

9.11.2: The Chemical Shift

The plot of signal against magnetic field strength for ethanol in Figure 9-23 shows three principal groups of lines corresponding to the three varieties of hydrogen present: methyl (CH_3), methylene (CH_3), and hydroxyl (OH). Differences in the field strengths at which signals are obtained for nuclei of the same kind, such as protons, but located in different molecular environments, are called **chemical shifts**.

Another very important point to notice about Figure 9-23 is that the intensities of the three principal absorptions are in the ratio of 1:2:3, corresponding to the ratio of the number of each kind of proton (OH, CH_2, CH_3) producing the signal. In general, *areas under the peaks of a spectrum* such as in Figure 9-23 *are proportional to the number of nuclei in the sample that give those peaks*. The areas can be measured by electronic integration and the integral often is displayed on the chart, as it is in Figure 9-23, as a stepped line increasing from left to right. The height of each step corresponds to the relative number of nuclei of a particular kind. Unless special precautions are taken, integrals usually should not be considered accurate to better than about 5%.

Why do protons in different molecular environments absorb at different field strengths? The field strength H at a particular nucleus is *less* than the strength of the external magnetic field H_o. This is because the valence electrons around a particular nucleus and around neighboring nuclei respond to the applied magnetic field so as to **shield** the nucleus from the applied field. The way this shielding occurs is as follows.

First, when an atom is placed in a magnetic field, its electrons are forced to undergo a rotation about the field axis, as shown in Figure 9-26. Second,

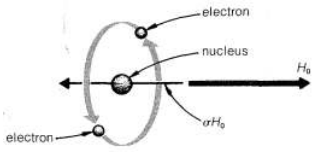


Figure 9-26: Induced magnetic field σH_o at the nucleus as the result of rotation of electrons about the nucleus in an applied magnetic field H_o.

rotation of the electrons around the nucleus is a circulation of charge, and this creates a *small* magnetic field at the nucleus *opposite* in the direction to H_o. Third, the magnitude of this *diamagnetic*[11] effect is directly proportional to H_o and can be quantified as σH_o, in which σ is the proportionality constant. It is important to recognize that σ is not a nuclear property but depends on the *chemical* environment of the atom. Each chemically different proton will have a different value of σ and hence a different chemical shift.

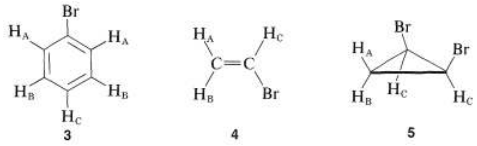
The actual field H at the nucleus will be $H_o - \sigma H_o$. Because σ acts to reduce the strength of the applied field at the nucleus, it is called the **magnetic shielding parameter**. The more shielding there is, the stronger the applied field must be to satisfy the resonance condition,

Common usage is: upfield, *more* shielding; downfield, *less* shielding; and you should remember that field-sweep spectra always are recorded with the field *increasing* from *left* to *right*.

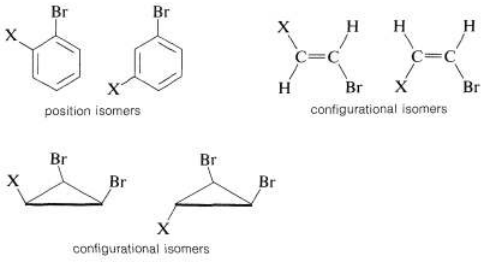
$$\underset{\text{less shielding}}{\overset{\text{low field}}{\longleftarrow}} H_o \underset{\text{more shielding}}{\overset{\text{high field}}{\longrightarrow}}$$

9.11.3: Chemical Shift and Stereochemistry

The value of nmr spectroscopy in structure determination lies in the fact that chemically different nuclei absorb at different field strengths. In later sections we will be concerned with correlating the chemical shifts with structural features. However, before proceeding furher it is extremely important that you be able to identify the number and kind of nonequivalent protons in a given structure, and therefore the number of chemical shifts to expect. This number is not always self-evident, especially when subtle factors of stereochemistry intervene. For this reason, we suggest that you inspect structures 3-5 to convince yourself that the protons labeled with different letter subscripts in any one molecule are indeed chemically different.



One way of checking whether two protons are in equivalent environments is to imagine that each is separately replaced with a different atom or group. If the product of replacing H_A is identical with that obtained by replacing H_B, then H_A and H_B are chemically equivalent. If the two products are nonidentical, then H_A and H_B are nonequivalent. For example, replacement of H_A or H_B in 3, 4, and 5 by an atom X would give different products. Therefore, H_A and H_B are nonequivalent in 3, 4, and 5.



Matters become more complicated with substances such as 6 and 7:

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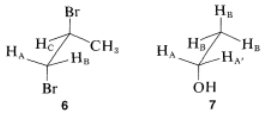
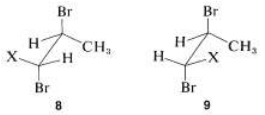
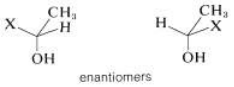


Notice that 6 represents a chiral molecule and if H_A and H_B each are replaced with X we get 8 and 9, which are diastereomers (see Section 5-5). You can verify this with molecular models if necessary. Diastereomers have different chemical and physical properties; therefore H_A and H_B in 6 are nonequivalent. They often are called **diastereotopic** hydrogens.

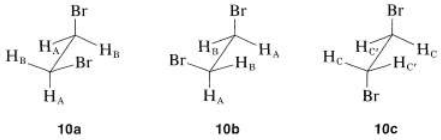


What of the two methylene protons in ethanol, 7, which we have labeled as H_A $H_{A'}$? Are they identical? In a sense they are not identical because, if each were replaced by X, we would have a pair of enantiomers. Therefore, H_A and $H_{A'}$ sometimes are called **enantiotopic** hydrogens.



But, you will recall that enantiomers are chemically indistinguishable unless they are in a chiral environment. Therefore we expect shifts of enantiotopic hydrogens to be identical, unless they are in a chiral environment. To summarize, enantiotopic protons normally will have the same chemical shifts, whereas diastereotopic protons normally will have different chemical shifts.

We so far have ignored the relationship of chemical shifts to conformational equilibria. Consider a specific example, 1,2-dibromoethane, for which there are three staggered conformations 10a, 10b, and 10c:



Each of these conformations is expected to have its own nmr spectrum. The two gauche forms, 10a and 10b, are enantiomers and their spectra should be identical. The hydrogens H_A in 10a each are trans to the bromine on the adjacent carbon, while the H_B hydrogens are cis to the same bromines (see Section 5-5A). Consequently the H_A and H_B hydrogens are nonequivalent and would be expected to have different chemical shifts. In contrast, all of the hydrogens of the anti conformer, 10c, are equivalent and would have the same chemical shift. Therefore we would expect to observe three chemical shifts arising from H_A, H_B, and H_C for a mixture of 10a, 10b, and 10c. However, the actual spectrum of 1,2-dibromoethane shows only *one sharp proton signal* under ordinary conditions. The reason is that the magnetic nuclei can absorb the exciting radiation. The result is that we observe an *average* chemical shift, which reflects the relative shifts and populations of the three conformers present. If we can go to a sufficiently low temperature to make interconversion of the conformations slow (on the order of 10 times per second), then we will expect to see the three different chemical shifts H_A, H_B, and H_C with intensities corresponding to the actual populations of the conformations at the sample temperature. This is one example of the effect of rate processes on nmr spectra. Other examples and a more detailed account of how to relate the appearance of the signal to the rates of the exchange processes are given in Section 27-2.

9.11.4: Chemical-Shift Standards and Units

Chemical shifts *always* are measured with reference to a standard. For protons or ^{13}C in organic molecules, *the customary standard is a tetramethylsilane*, $(CH_3)_4 Si$, which gives strong, sharp nmr signals in regions where only a very few other kinds of protons or carbon nuclei absorb. Chemical shifts often are expressed in Hz (cycles per second) relative to tetramethylsilane (TMS). These may seem odd units for magnetic field strength but because resonance occurs at $\nu = \gamma H$, either frequency units (Hz, radians sec^{-1}) or magnetic field units (gauss) are appropriate.

Ten years ago, most nmr spectrometers operated for protons with radio-frequency (rf) transmitters set at 60 MHz (6×10^7 cycles per second) but there has been a proliferation of different proton-operating frequencies and now 30, 60, 90, 100, 220, 270, 300 and 360

MHz machines are commercially available. The cost of these machines is roughly proportional to the square of the frequency, and one well may wonder why there is such an exotic variety available and what this has to do with the chemical shift. High operating frequencies are desirable because chemical shifts increase with spectrometer frequency, and this makes the spectra simpler to interpret. A 12-fold increase in operating frequency (as from 30 MHz to 360 MHz) means a 12-fold increase in H_o at the point of resonance (remember $\nu = \gamma H$) and this means also a 12-fold increase in σH_o. Thus resonances that differ because they correspond to different σ values will be *twelve times farther apart* at 360 MHz than at 30 MHz. This can produce a dramatic simplification of spectra, as can be seen from Figure 9-27, which shows the effect of almost a factor of four in ν on the proton nmr spectrum of 2-methyl-2-butanol.[12]

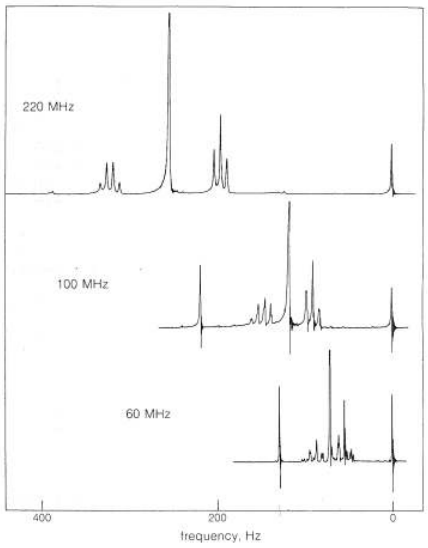


Figure 9-27: Comparison of the proton nmr spectra of 2-methyl-2-butanol at rf transmitter frequencies of 60, 100, and 220 MHz. The line at 165 Hz in the 60-MHz spectrum is due to the OH protons, and this is off-scale to the left in the 220-MHz spectrum. The large single line in the center of the spectra arises from the resonances of the six methyl hydrogens. The line at 0 Hz is TMS in each case.

To reiterate, chemical shifts are strictly proportional to spectrometer frequency, thus lines 100 Hz apart at 60 MHz will be 167 Hz apart at 100 MHz. This might seem to make comparisons of nmr spectra on different spectrometers hopelessly complex but, because of the proportionality of shifts to frequency (or field), *if we divide the measured shifts in* Hz (relative to the same standard) for any spectrometer *by the transmitter frequency in* MHz, *we get a set of frequency-independent shifts in parts per million (*ppm, which are useful for all nmr spectrometers. Nmr shifts reported in ppm relative to TMS as zero, as shown in Figure 9-23, are called δ (delta) values:

$$\delta = \frac{(\text{chemical shift downfield in Hz relative to TMS}) \times 10^6}{\text{spectrometer frequency in Hz}} \tag{9.11.7}$$

Thus, if at 60 MHz a proton signal comes 100 Hz downfield relative to tetramethylsilane, it can be designated as being $\left(+100 \text{ Hz} \times 10^6\right) / 60 \times 10^6 \text{ Hz} = +1.67 : \text{ppm}$ relative to tetramethylsilane. At 100 MHz, the line then will be $\left(1.67 \times 10^{-6}\right)\left(100 \times 10^6\right)$ = 167 Hz downfield from tetramethylsilane. Typical proton chemical shifts relative to TMS are given in Table 9-4.[13] The values quoted for each type of proton may, in practice, show variations of 0.1-0.3 ppm. This is not unreasonable, because the chemical shift of a given proton is expected to depend somewhat on the nature of the particular molecule involved, and also on the solvent, temperature, and concentration.

A positive δ value means a shift to lower field (or lower frequency) with respect to TMS, whereas a negative δ signifies a shift to higher field (or higher frequency). The δ convention is accepted widely, but you often find in the literature proton shifts with reference to TMS reported as "τ values." The τ scale has the TMS reference at +10 ppm, so most proton signals fall in the range of $\tau = 0$ to $\tau = +10$. A τ value can be converted to the appropriate δ value by subtracting it from 10. Life with nmr spectra would be simpler if the τ scale would just go away.

9.11.5: Correlations Between Structure and Chemical Shifts

Protonc chemical shifts are very valuable for the determination of structures, but to use the shifts in this way we must know something about the correlations that exist between chemical shift and structural environment of protons in organic compounds. The most important effects arise from differences in electronegativity, types of carbon bonding, hydrogen bonding, and chemical exchange.

9.11.5.1: Electronegativity

Consider first the chemical shifts of protons attached to an sp^3 carbon, .

The degree of shielding of the proton by the carbon valence electrons depends on the character of the substituent atoms and groups present, and particularly on their electron-attracting power, or electronegativity. For a grouping of the type , the shielding will be *less* as X is more electron withdrawing relative to hydrogen:

If X is electron-withdrawing, the proton is deshielded.

For example, the proton chemical shifts of the methyl halides (Table 9-4) show decreasing shielding, hence progressively low-field chemical shifts with increasing halogen electronegativity $(\mathrm{F} > \mathrm{Cl} > \mathrm{Br} > \mathrm{I})$:

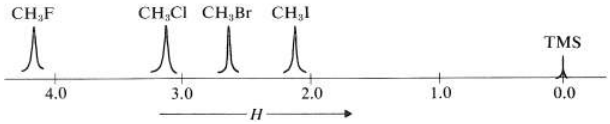


Figure 9-28 shows how the shift differences between the $\mathrm{CH_3}-$ and the $-\mathrm{CH_2}-$ protons in some $\mathrm{CH_3CH_2X}$ derivatives depend on the electronegativity of X, using the electronegativity defined by L. Pauling (see Section 10-4B). The trend is not wholly linear, but the proton chemical-shift differences become larger the more electronegative X becomes. We can predict with some confidence, therefore, that a molecule such as $\mathrm{XCH_2CH_2Y}$ will have lower-field chemical shifts (larger δ) for $\mathrm{XCH_2}-$ than for $-\mathrm{CH_2Y}$ if X is more electronegative than Y:

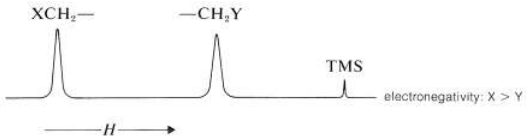


Table 9-4: *Typical Proton Chemical-Shift Values* (δ) *in Dilute* $\mathrm{CHCl_3}$ *Solutions*

Substituted Alkanes

X	δ CH_3X	δ RCH_2X	δ R_2CHX	σ[a]
—H	0.23	0.9	1.25	0.00
—R	0.9	1.25	1.5	0.47
—F	4.26	4.4	–	–
—Cl	3.05	3.4	4.0	2.53
—Br	2.68	3.33	4.1	2.33
—I	2.16	3.2	4.2	1.82
—OH	3.47	3.6	3.6	2.56
—OR	3.3	3.4	–	2.36
—OAr	3.7	3.9	–	3.23
—O—C(=O)—R	3.6	4.1	5.0	3.13
—O—C(=O)—Ar	3.8	4.2	5.1	–
—SH	2.44	2.7	–	–
—SR	2.1	2.5	–	1.64
$-NR_2$	2.2	2.6	2.9	1.57
—NHC(=O)R	2.8	–	3.2	–
$-NO_2$	4.28	4.4	4.7	–
—CHO	2.20	2.3	2.4	1.70
—C(=O)—R	2.1	2.4	2.5	1.70
—C(=O)—Ar	2.6	3.0	3.4	1.70
—C(=O)—OH	2.07	2.3	2.6	1.55

Substituted Alkanes

X	δ CH_3X	δ RCH_2X	δ R_2CHX	σ[a]
—C(=O)—OR	2.1	2.3	2.6	1.55
—C(=O)—NH_2	2.02	2.2	–	1.59
$-CR=CR_2$	1.8	2.3	2.6	1.32
$-C_6H_5$	2.3	2.7	2.9	1.85
—C≡CR	2.0	–	–	1.44
—C≡N	2.0	2.3	2.7	1.70

Multiple-Bonded C—H

$R_2C=CH_2$	$R_2C=CHR$		R—C(=O)—H	RC≡C—H
~5.0	~5.3	7.3	~9.7	~2.5

OH, NH, and SH Compounds

ROH	ArOH	RC(=O)—OH	RNH_2	$R_3\overset{\oplus}{N}H$	RC(=O)NH_2	RSH	ArSH
0.5–5	5–8	9–12	~1.0	~7.5	~7.8	~1.5	~3.0

[a]Effective shielding constants relative to H as zero. The use of these σ values is described in Section 9-10E.

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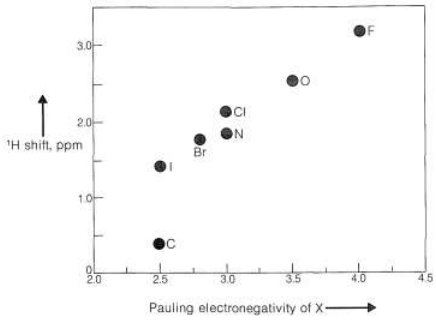


Figure 9-28: Chemical-shift differences between the CH_3 and CH_2 protons of CH_3CH_2X derivatives as a function of the Pauling electronegativity of X (see Section 10-5A).

When two electronegative groups, X and Y, are bonded to the *same* carbon, as in XCH_2Y, the protons are expected to be less shielded and come into resonance downfield of the methylenes of XCH_2CH_2Y. There is an approximate relationship (see below) between the shifts of the XCH_2Y protons and the effective shielding constants (σ) of X and Y known as *Shoolery's rule*.

$$\delta = 0.23 + \sigma_x + \sigma_y \tag{9-4}$$

Appropriate values of σ for use with this equation are given in Table 9-4.

9.11.5.2: Effects of Carbon Bond Type

The shifts of the protons of alkanes and cycloalkanes fall in the range of 0.9-1.5 ppm with C—H protons coming at the low-field end of this range and $-CH_3$ protons coming at the high-field end (see Table 9-4).

Alkenic hydrogens (vinyl hydrogens, $>C{=}CH-$) normally are observed between 4.6-6.3 ppm toward *lower* fields than the shifts of protons in alkanes and cycloalkanes. This means that alkenic hydrogens in an organic compound can be easily distinguished from alkane hydrogens.

Aromatic protons, such as those in benzene, have shifts at still lower fields and commonly are observed at 7-8 ppm. In contrast, alkynic protons of the type $-C \equiv CH$ give resonances that are *upfield* of alkenic or aromatic protons and come at 2-3 ppm. Another effect associated with multiple bonds is the large difference in shift between a $-CH(OCH_3)_2$ proton, which normally comes at about 5.5 ppm, and aldehyde protons, $-CH{=}O$, which are much farter *downfield* at 9-11 ppm.

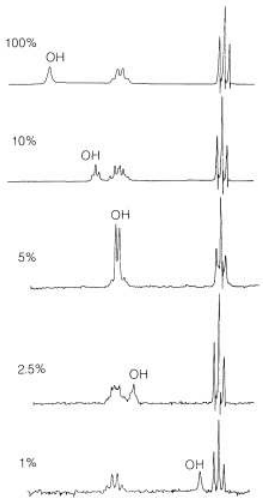
Clearly, the shifts of a proton depend on whether the carbon forms single, double, or triple bonds. In a magnetic field, the circulation of electrons in the π orbitals of multiple bonds induced by the field (Figure 9-26) generates diamagnetic shielding effects in some regions of the multiple bond and paramagnetic deshielding effects in other regions. Apparently, protons attached to double-bonded carbons are in the deshielding zones and thus are downfield while protons attached to triple-bonded carbons are in the shielding zones and are observed at rather high field.

9.11.5.3: Hydrogen Bonding

When a proton is directly bonded to a strongly electronegative atom such as oxygen or nitrogen its chemical shift is critically dependent on the nature of the solvent, temperature, concentration, and whether acidic or basic impurities are present. The usual variations in chemical shift for such protons are so large (up to 5 ppm for alcohols) that no very useful correlations exist.

Hydrogen bonding is the major reason for the variable chemical shifts of OH and NH protons. In general, hydrogen bonding results in *deshielding*, which causes the resonances to move downfield. The extent of hydrogen bonding varies with concentration, temperature, and solvent, and changes in the degree of hydrogen bonding can cause substantial shift changes. This is very evident in the nmr spectrum of ethanol taken at different concentrations in CCl_4 (Figure 9-29). The hydroxyl resonance will be seen to move upfield by hydrogen bonding through equilibria such as

$$2ROH \rightleftharpoons R{-}\underset{\displaystyle H}{\underset{|}{O}}\cdots H{-}O{-}R$$



Section 9-10I. There is no significant change in the relative shifts of the CH_2 and CH_3 lines as the concentration is changed.

9.11.5.4: Chemical Exchange

Many OH and NH compounds are weak acids and weak bases and can undergo autoprotolysis, which means that a proton can be transferred from one molecule to another. Suppose we have a compound such as 2-aminoethanol, $H_2NCH_2CH_2OH$. This substance normally would be expected to have an NH_2 proton resonance at about 1 ppm and an OH proton resonance at about 3 ppm. Autoprotolysis equilibria can *exchange* the protons between the molecules and also from one end to the other as shown below, even if the equilibria are not very favorable.

$$NH_2CH_2CH_2OH \overset{\rightarrow}{\leftarrow}{}^{\oplus} NH_3CH_2CH_2O^{\ominus} \tag{9-5}$$

$$2NH_2CH_2CH_2OH \overset{\rightarrow}{\leftarrow}{}^{\oplus} NH_3CH_2CH_2OH + N_2CH_2CH_2O^{\ominus} \tag{9-6}$$

Such equilibria can be established very rapidly, especially if traces of a strong acid or a strong base are present. In such circumstances, a *single* average $(-NH_2,\ -OH)$ proton signal is observed, because the excitation of a given proton from its lower-energy magnetic state to its higher-energy magnetic state occurs while it is partly on oxygen and partly on nitrogen. This is the same kind of chemical shift averaging that occurs for rapidly equilibrating conformations (see Section 9-10C).

9.11.6: Application of Chemical Shifts to Structure Determination

To see how nmr and infrared spectra can be used together for structure determination we shall work through a representative example.

The objective is to assign a structure to the compound $C_4H_8O_3$ whose nmr spectrum is shown in Figure 9-30 and whose infrared spectrum shows prominent bands at $2900\ cm^{-1}$, $1750\ cm^{-1}$, $1000\ cm^{-1}$, and $1100\ cm^{-1}$.

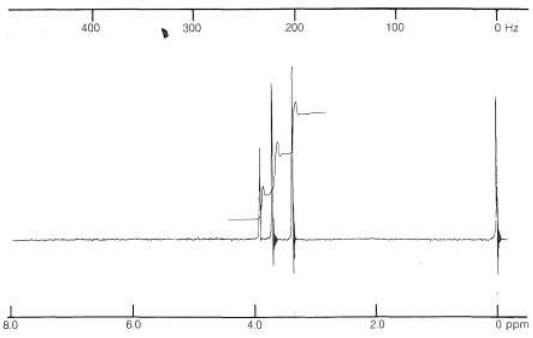


Figure 9-30: Proton nmr spectrum of a compound, $C_4H_8O_3$, at 60 MHz relative to TMS $= 0.00$ ppm.

The infrared spectrum indicates $\ce{C=O}$ ($1750\ \mathrm{cm^{-1}}$), C–H ($2900\ \mathrm{cm^{-1}}$), and C–O ($1000\ \mathrm{cm^{-1}}$, $1100\ \mathrm{cm^{-1}}$). The position of the carbonyl band suggests that it is probably an ester, $\ce{R-C(=O)-O-R}$. A carboxylic acid is ruled out because there is no sign of an O–H stretch.

The nmr spectrum shows three kinds of signals corresponding to three kinds of protons. The integral shows these are in the ratio of 2:3:3. From this, we can conclude that they are two different kinds of $\ce{CH3-}$ groups and a $\ce{-CH2-}$ group.

The chemical shifts of the presumed $\ce{CH3}$ groups are at $3.70\ \mathrm{ppm}$ and $3.35\ \mathrm{ppm}$. Because the compound contains only C, H, and O, the data of Table 9-4 suggest that these resonances arise from $\ce{OCH3}$ groups. The low-field resonance is likely to be $\ce{-C(=O)-OCH3}$ (we know from the infrared that there probably is an ester function), while the higher-field resonance is possibly an ether function, $\ce{-OCH3}$. If you put all of this information together, you find that $\ce{CH3OCH2CO2CH3}$ is the only possible structure. To check whether the $\ce{CH2}$ resonance at $3.9\ \mathrm{ppm}$ is consistent with the assigned structure we can calculate a shift value from Equation 9-4:

$$\delta = 0.23 + \sigma_{OCH_3} + \sigma_{O=COCH_3} \tag{9.11.8}$$

$$\delta = 0.23 + 2.36 + 1.55 = 4.14\ \mathrm{ppm} \tag{9.11.9}$$

The agreement between the calculated and observed shifts is not perfect, but is within the usual range of variation for Equation 9-4. We can be satisfied that the assigned structure is correct.

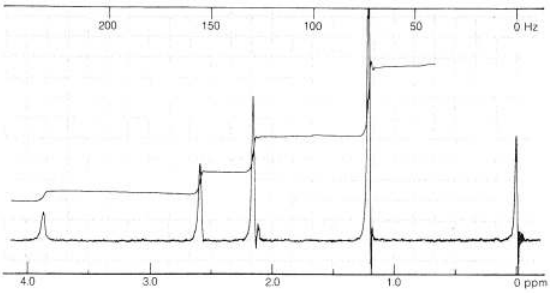


Figure 9-31: Proton nmr spectrum of a compound, $\ce{C4H8O3}$, at $60\ \mathrm{MHz}$ relative to TMS at $0.00\ \mathrm{ppm}$ The stepped line is the integral running from left to right.

9.11.7: Spin-Spin Splitting - What We Observe

If you look at the nmr spectrum of ethanol, $\ce{CH3CH2OH}$, in Figure 9-23, you will see that the $\ce{CH2}$ resonance is actually a group of *four* lines and the $\ce{CH3}$ resonance is a group of *three* lines. This three-four line pattern for the grouping $\ce{CH3CH2X}$ $(\mathrm{X} \neq \mathrm{H})$ also is evident in the $220\ \mathrm{MHz}$ spectrum of 2-methyl-2-butanol (Figure 9-27) and in the $60\ \mathrm{MHz}$ spectrum of ethyl iodide (Figure 9-32).

Why do certain proton resonances appear as groups of equally spaced lines rather than single resonances? The facts are that *nonequivalent* protons on contiguous carbons $\ce{H_B-C-C-H_A}$, such as ethyl derivatives $\ce{CH3CH2X}$, interact magnetically to "split" each other's resonances. This multiplicity of lines produced by the mutual interaction of magnetic nuclei is called "**spin-spin splitting**", and while it complicates nmr spectra, it also provides valuable structural information, as we shall see.

An example of a complex proton spectrum is that of ethyl iodide (Figure 9-32). To a first approximation, the two main groups of lines appear as *equally spaced* sets of three and four lines, arising from what are called "first-order spin-spin interactions". Matters are further complicated by additional splitting of the "three-four" pattern of ethyl iodide, as also can be seen in Figure 9-32. This additional splitting is called "second-order" splitting.

When there are so many lines present, how do we know what we are dealing with? From where to we measure the chemical shift in a complex group of lines?

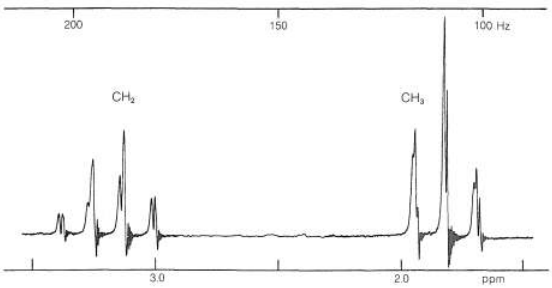
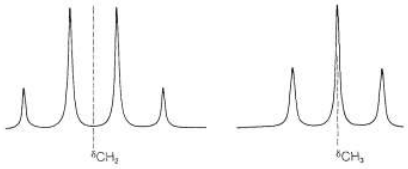


Figure 9-32: High-resolution nmr spectrum of ethyl iodide, CH_3CH_2I, at 60 MHz relative to TMS, 0.00 ppm. The first-order splitting pattern is seen in the well-separated "three-four" line pattern for the $CH_3{-}CH_2$ resonances. The second-order splitting is the additional fine structure superimposed on the three-four pattern.

First, the chemical shift normally is at the *center* of the group of lines corresponding to first-order splitting. In ethyl iodide, the chemical shift of the methyl protons is in the center of the quartet:



Second, the chemical shift can be recognized by the fact that it is directly proportional to the transmitter frequency, ν. If we double ν, the chemical shifts double. In contrast, the first-order spin-spin splittings remain the same. By this we mean that the magnitude (in Hz) of the spacing between the lines of a split resonance is independent of the transmitter frequency, ν. This spacing corresponds to what is called the **spin-spin coupling constant**, or simply the **coupling constant**, and is symbolized by J.

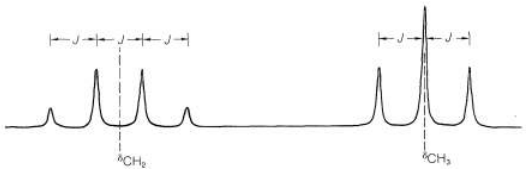


Figure 9-27).

Third, the second-order splitting tends to disappear with increasing transmitter frequency. For ethyl iodide (Figure 9-32), the second-order splitting at 60 MHz is barely discernible at 100 MHz and disappears at 200 MHz. This also can be seen to occur for the three-four splitting pattern of 2-methyl-2-butanol as a function of ν (Figure 9-27).

The next question is how can we understand and predict what spin-spin splitting patterns will be observed? And how do they give us structural information? The important point is that the *multiplicity of lines for protons of a given chemical shift often is seen to be* $(n+1)$*, in which* n *is the number of protons on the contiguous carbons*. For example, the CH_2 resonance of the ethyl group of ethyl iodide is a *quartet* of lines because of the spin-spin interaction with the neighboring three protons $(n = 3)$ of the methyl group. Likewise, the CH_3 group is a *triplet* of lines because of spin-spin interactions with the two protons $(n = 2)$ of the methylene group.

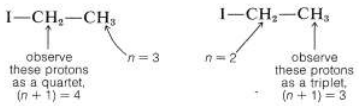


Figure 9-33, where X and Y are groups that give no spin interactions with the protons. The value of these patterns, when observed, lies in the way that they indicate the number of equivalent protons on contiguous carbons. For instance, a two-three line pattern, where the two-part has an integrated intensity twice that of the three-part, suggests the grouping $XCH_2{-}CHY_2$.

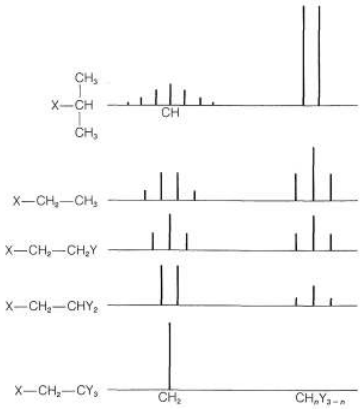


Figure 9-33: Schematic proton nmr spectra, X and Y are nonmagnetic nuclei. For 2-propane derivatives, as at the top, the (\ce{CH_3}\) resonances are double because of the splitting produced by the single proton on C2. For the ethane derivatives, the right set of lines is always a triplet when observable because of the two protons of the $\mathrm{X{-}CH_2{-}}$ group. We assume here that the chemical shifts of the $\mathrm{CH}_n\mathrm{Y}_{3-n}$ protons are independent of the number of Y substituents.

The ratios of the line intensities in the spin-spin splitting patterns of Figure 9-33 usually follow simple rules. A doublet appears as two lines of equal intensity; a triplet as three lines in the ratio 1:2:1; a quartet as four lines in the ratio 1:3:3:1; a quintet as 1:4:6:4:1, and so on. The intensities follow the binomial coefficients for $(x+y)^n$, where n is the number of protons in the splitting group. Thus when $n=4$, we have $x^4+4x^3y+6x^2y^2+4xy^3+y^4$, or 1:4:6:4:1.

The spectrum of $(\mathrm{CH_3O})_2\mathrm{CHCH_3}$ (Figure 9-34) provides an excellent example of how nmr shows the presence of contiguous protons. The symmetrical doublet and 1:3:3:1 quartet are typical of the interaction between a single proton and an adjacent group of three, that is, $\mathrm{CH{-}CH_3}$. The methyl protons of the $(\mathrm{CH_3O})$ groups are too far from the others to give demonstrable spin-spin splitting; thus they appear as a single six-proton resonance.

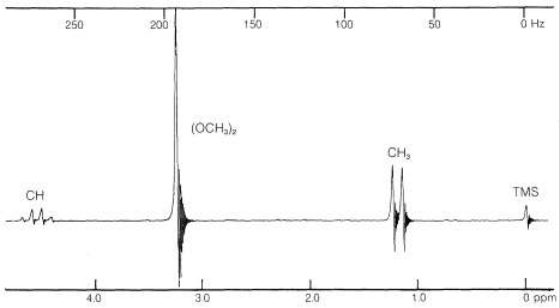
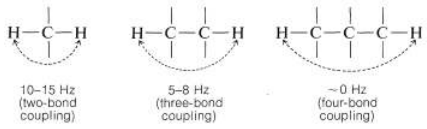
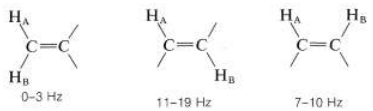


Figure 9-34: *Proton nmr spectrum of 1,1-dimethoxyethane (dimethyl acetal),* $(\mathrm{CH_3O})_2\mathrm{CHCH_3}$, *at* 60 MHz *relative to TMS,* 0.00 ppm.

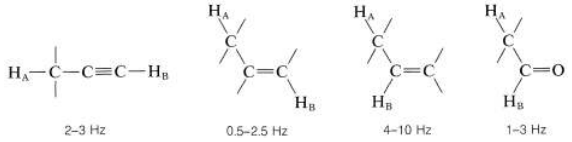
In general, the magnitude of the spin-spin splitting effect of one proton on another proton (or group of equivalent protons) depends on the *number and kind* of intervening chemical bonds and on the spatial relationships between the groups. For simple systems without double bonds and with normal bond angles, we usually find for *nonequivalent* protons (i.e., having different chemical shifts):



Where restricted rotation or double- and triple-bonded groups are involved, widely divergent splittings are observed. For double bonds, the **two-bond couplings** between two nonequivalent hydrogens located on one end are characteristically small, while the **three-bond couplings** in $-\mathrm{HC{=}CH}-$ are larger, especially for the trans configuration:



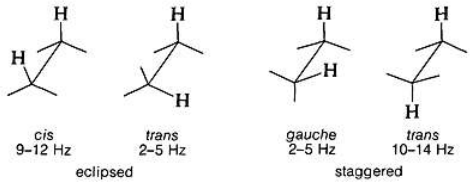
Coupling through four or more bonds is significant for compounds with double or triple bonds. Examples of these so-called **long-range couplings** and some other useful splitting values follow:



Finally, chemically equivalent protons do not split each other's resonances.

9.11.8: Proton-Proton Splittings and Conformational Analysis

A very important characteristic of three-bond proton-proton couplings, $\mathrm{H{-}C{-}C{-}H}$, is the way that they depend on the conformation at the $\mathrm{C{-}C}$ bond. Typical values for several particular conformations are



For protons in groups such as ethyl groups, in which rotation is rapid and the favored conformations are staggered (but none of the staggered conformations is preferred over the others), average proton-proton splittings are observed. The average for $\mathrm{CH_3CH_2-}$ splittings is about $7\ \mathrm{Hz}$, which corresponds to $[2 \times 4.5\ (\mathrm{gauche}) \div 12\ (\mathrm{trans})]/3$.

9.11.9: Proton-Proton Splittings and Chemical Exchange

You may have wondered why the hydroxyl proton of ethanol produces a single resonance in the spectrum of Figure 9-23. It is quite reasonable to expect that the hydroxyl proton would be split by the neighboring methylene protons because they are only three bonds apart, however, this coupling will not be observed if the hydroxyl protons are exchanging rapidly between the ethanol molecules (Section 9-10E). When proton exchange is rapid, the spin interactions between the $-\mathrm{CH_2}-$ and $-\mathrm{OH}$ protons average to zero. At intermediate exchange rates, the coupling manifests itself through line broadening or by actually giving multiple lines. If you look at the several spectra of ethanol in Figure 9-29, you will notice how the shape of the OH resonance varies from a broad singlet to a distinct triplet.

Rapid chemical exchange of magnetic nuclei is not the only way that spin-coupling interactions can be averaged to zero. The same effect can be achieved by a technique known as double resonance. To understand how this is done, consider two coupled protons $\mathrm{H_A}$ and $\mathrm{H_B}$ having different chemical shifts. Suppose that $\mathrm{H_A}$ is selectively irradiated at its resonance frequency ν_A while at the same time we observe the resonance signal of $\mathrm{H_B}$. The coupling between $\mathrm{H_A}$ and $\mathrm{H_B}$ disappears, and $\mathrm{H_B}$ shows a *single* resonance. Why is this so? By irradiation of $\mathrm{H_A}$, the $\mathrm{H_A}$ nuclei are changed from the +1/2 state to -1/2 and back again sufficiently rapidly that the neighboring nucleus $\mathrm{H_B}$ effectively “sees” neither one state nor the other. The magnetic interaction between the states therefore averages to zero. This decoupling of magnetic nuclei by double resonance techniques is especially important in $^{13}\mathrm{C}$ NMR spectroscopy (Section 9-10L) but also is used to simplify proton spectra by selectively removing particular couplings.

9.11.10: Use of Nuclear Magnetic Resonance Spectroscopy in Organic Structural Analysis

The solution of a typical structural analysis problem by nmr methods utilizes at least four kinds of information obtained directly from the spectrum. They are: chemical shifts (δ), line intensities (signal areas), spin-spin splitting patterns (line mulitplicities), and coupling constants (J). We already have shown how chemical shifts are used in the absence of spin-spin splitting. We now will illustrate how more complex spectra may be analyzed.

Figure 9-35 shows the proton nmr spectrum for a compound of formula $\mathrm{C_3H_6O}$. There are three principal groups of lines at 9.8, 2.4, and $1.0\ \mathrm{ppm}$. Look at the multiplicity of these groups before reading further.

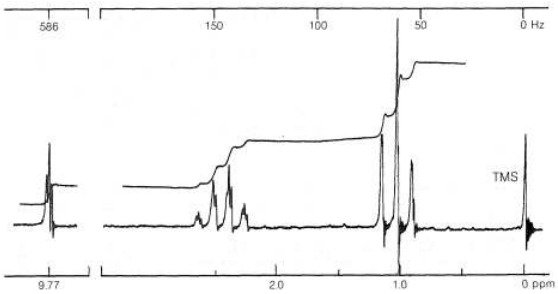


Figure 9-35: Nmr spectrum and integral for a compound of formula C_3H_6O at 60 Hz relative to TMS.

There are several ways to approach a problem such as this, but probably the easiest is to start with the integral. The relative heights of the stepped integral for the principal groups of lines can be obtained by a pair of dividers, with a ruler, or with horizontal lines as in Figure 9-35. The integral suggests that one hydrogen is responsible for the resonance at 9.8 ppm, two hydrogens at 2.4 ppm, and three at 1.0 ppm. Three hydrogens in a single group suggest a CH_3- group, and because there is a three-four splitting pattern, it is reasonable to postulate CH_3-CH_2-. Subtracting C_2H_5 from the given formula C_3H_6O leaves CHO, which, with normal valences, has to be $-CH=O$. The spectrum thus appears to be consistent with the structure $CH_3CH_2CH=O$ (propanal) as judged from the molecular formula and the spin-spin splitting pattern, which indicates the CH_3CH_2- grouping. To be sure of the structure, we should check it against *all* of the available information. First, from the shifts (Table 9-4) we see that the single proton at 9.8 ppm fits almost perfectly for RCHO, the two-proton $-CH_2C=O$ resonance at 2.4 ppm is consistent with that reported for $-CH_2COR$, while the three-proton line at 1.0 ppm checks with 0.9 ppm for CH_3R.

What about the couplings? The three-four pattern has a spacing of slightly over 7 Hz, which is just right for an ethyl group (compare Figures 9-23 and 9-32). The doubling up (almost obscured by second-order splitting) of the $-CH_2-$ resonance and the splitting of the $-CH=O$ resonance into a 1:2:1 triplet indicate about a 2-Hz coupling for the $-CH_2-CH=O$ group. Three-bond couplings between $-CHO$ and adjacent $-CH_2-$ protons appear to be generally smaller than $-CH_2-CH_3$ couplings.

We usually would not rely on nmr alone in a structure-analysis problem of this kind, but would seek clues or corroboration from the infrared, electronic, or other spectra, as well as chemical tests. In later chapters we will have many problems that will be facilitated by the use of both nmr and infrared spectra. A further worked example will illustrate the approach.

A compound has the composition C_3H_3Br and gives the infrared and nuclear magnetic resonance spectra shown in Figure 9-36. The problem is how to use this information to deduce the structure of the compound. The molecular formula tells us the number and kind of atoms *and* the number of multiple bonds or rings. The formulas of the corresponding C_3 hydrocarbon without the bromine would be C_3H_4, or *four* hydrogens less than the saturated alkane C_3H_8. This means there must be two double bonds or the equivalent - one triple bond or one ring and one double bond.[14] Because from the formula we suspect unsaturation, we should check this out with the infrared spectrum. There is a band at 2120 cm^{-1}, which is indicative of an unsymmetrically substituted $-C\equiv C-$ group (Table 9-2). The strong, sharp band at 3300 cm^{-1} further tells us that the substance is a 1-alkyne $-C\equiv C-H$.

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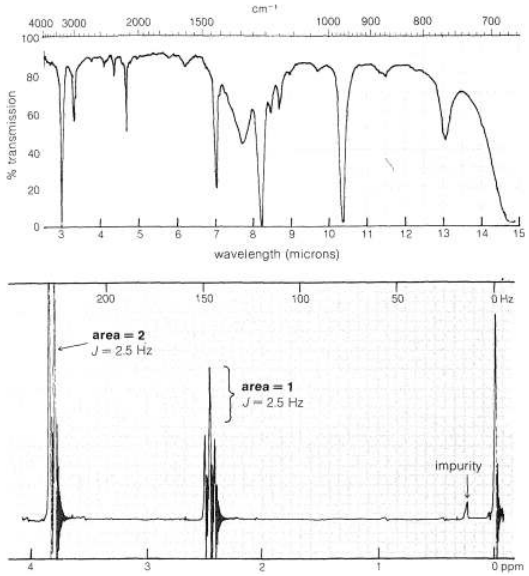


Figure 9-36: Infrared and nmr spectra for a compound of formula C_3H_3Br. The infrared spectrum here is different from others shown in this book in being linear in wavelength, λ, instead of in wave numbers, $\tilde{\nu}$. The units of wavelength here are microns $(10^{-6}\ \text{cm})$.

The proton nmr spectrum shows that there are only two principal groups of lines - a two-proton doublet at $3.85\ \text{ppm}$ and a one-proton triplet at $2.45\ \text{ppm}$. The two-three splitting pattern combined with the 2:1 proton ratio suggests a CH_2 group coupled with a CH group. The structure must be a 3-bromo-propyne, $BrCH_2C \equiv CH$. To confirm the assignment, the chemical shifts should be checked (Table 9-4). The $\equiv C-H$ at $2.45\ \text{ppm}$ agrees well with the tabulated value of $2.5\ \text{ppm}$. There is no tabulated data for $-C \equiv C-CH_2Br$ but the observed shift at $3.85\ \text{ppm}$ is at slightly lower fields than the tabulated $3.33\ \text{ppm}$ for $-CH_2Br$. This is expected because of the triple bond. The correlation of Equation 9-4 predicts a value of $4.0\ \text{ppm}$.

Very often, a proton will be spin-coupled to two or more *different* protons, and the couplings are not necessarily the same. When this happens, the resulting spectrum can be quite complex, as our next example shows.

A compound C_9H_{10} gives the nmr spectrum of Figure 9-37. There are clearly four kinds of protons in the molecule at $\delta = 7.28\ \text{ppm}$, $5.35\ \text{ppm}$, $5.11\ \text{ppm}$, and $1.81\ \text{ppm}$. Although the integral is not shown, the main groups of lines have intensities from the low-field to high-field in the ratio of 5:1:1:3.

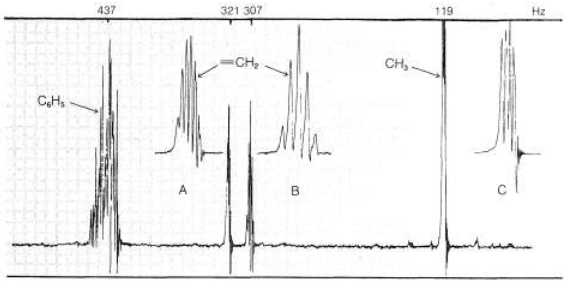


Figure 9-37: Nuclear magnetic resonance spectrum of C_9H_{10} at 60 MHz. The calibrations are relative to the protons of TMS. The insets show the peaks centered on 321, 307, and 119 Hz with an expanded scale. The spacing between the peaks is $1.5\ \text{Hz}$ for Group B at $307\ \text{Hz}$, and $0.75\ \text{Hz}$ for Groups A and C at 321 and $119\ \text{Hz}$. The C_9H_{10} protons are coupled to each other, not to A, B, or C.

The five-proton signal at $7.28\ \text{ppm}$ is typical of a phenyl group, C_6H_5, and the one-proton signals at 5.35 and $5.11\ \text{ppm}$ are in the region for alkenic protons, $-CH=C\diagdown$. The three-proton signal at $1.81\ \text{ppm}$ is typical of a methyl group on a carbon-carbon double bond, $CH_3-C=C\diagdown$.

There are only three ways to put together a phenyl ring, $CH_3-C=C\diagdown$, and two $HC=$ protons such that they add up to C_9H_{10}. They are

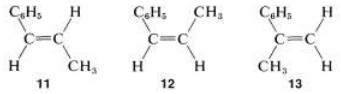


Figure 9-37, and the three mutually coupled groups are labeled as A, B, and C.

Coupling between A and B (designated by the constant J_{AB}) should give four lines, two for A and two for B, as shown in Figure 9-38. Because A and B also are coupled to the three hydrogens of the methyl group (C), each of the four lines corresponding to J_{AB} will be further split (into 1:3:3:1 quartets). If $J_{AC} \neq J_{BC}$, then the spacing of the lines in the two sets of quartets will not be the same.

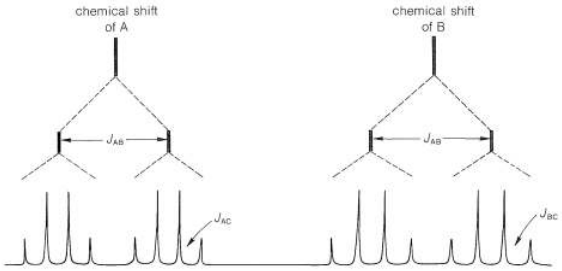
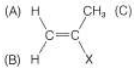


Figure 9-38: Spin-spin splitting patterns predicted for the nmr signals of the two alkenic protons (A and B) of a methyl-substituted alkene of the type  where $J_{AB} \gg J_B > J_{AC}$.

According to the foregoing analysis, the maximum number of lines observable for the A and B resonances is sixteen (8 for A and 8 for B). In fact, only eleven are visible (6 for A and 5 for B), which means that some of the sixteen possible lines must overlap. Without examining all possibilities, we can see that the actual situation can be reproduced if $J_{AB} \cong J_{BC} = 2J_{AC}$. The only structure that is consistent with $J_{AB} = 1.5$ Hz is 13, or 2-phenylpropene; the other possibilities are excluded because J_{AB} should be about 10 Hz for 12 and 16 Hz for 11.

9.11.11: Chemical-Shift Effects on Spin-Spin Splitting

The simple $n + 1$ rule for predicting the multiplicity of spin-coupled proton signals often breaks down whenever the chemical-shift difference between the protons in different groups becomes comparable to coupling constants for magnetic interaction between the groups. Under these circumstances, you may expect to see more lines, or lines in different positions with different intensities, than predicted from the simple first-order treatment. One example is the effect of changing chemical shift on a two-proton spectrum with $J = 10$ Hz (Figure 9-44).

We see in Figure 9-44 that even when the shift is 7.5 times larger than the coupling, the outside lines are weaker than the inside lines. This general kind of asymmetry of line intensities also is apparent in the spectrum of ethyl iodide (Figure 9-32), in which the lines of each group are more like 0.7:2.5:3.5:1.3 and 1.2:2.0:0.8, rather than the 1:3:3:1 and 1:2:1 ratios predicted from the first-order treatment. The asymmetry is such that two groups of lines that are connected by spin-spin splitting in effect "point" to one another - the lines on the "inside" of the pattern are stronger than predicted from the first-order treatment, whereas those on the "outside" are weaker. The effect can be put to practical use, as illustrated in the following exercise.

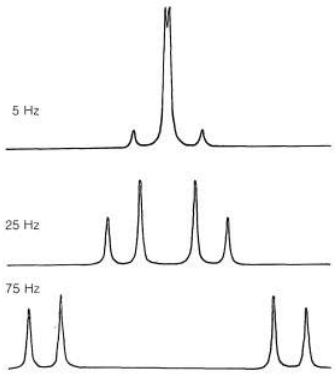
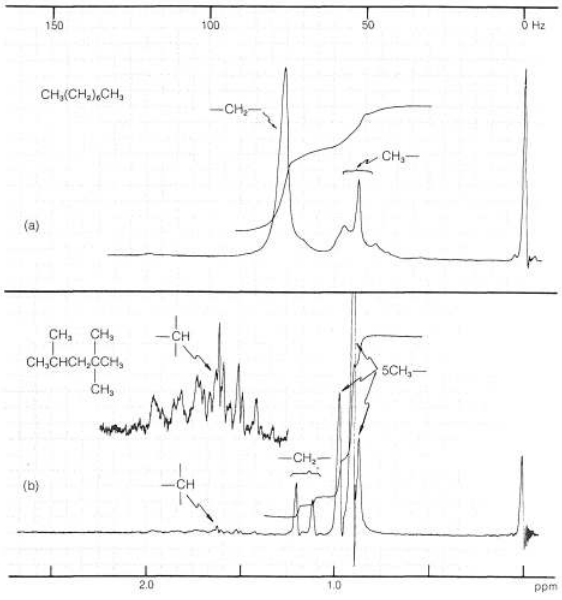


Figure 9-44: Representation of the changes in line positions and intensities for a two-proton system with a coupling constant, J, of $10\ \text{Hz}$ and the indicated chemical-shift differences. Only a single sharp line is observed if the shift difference is zero.

To explain the effect of chemical shifts on second-order splitting is beyond the scope of this book. In fact, we haven't really explained first-order splitting, although more on this topic will be found in Section 27-3. But regardless of how many lines appear in a complex nmr spectrum, they can be rationalized in terms of the chemical shifts, coupling constants, and exchange effects. Furthermore, the overall signal intensities remain proportional to the number of protons giving rise to the signals.

When there are many hydrogens and small chemical-shift differences, as in alkanes, the proton nmr spectra may have so many closely spaced resonance lines that they merge together to give a series of smooth, more-or-less featureless peaks. The proton spectrum of octane (Figure 9-46a) is an excellent example of this type of spectrum. Useful information often can be obtained from such spectra as to the ratio of CH_3 : CH_2 : CH by investigation of the integrals over the range of alkane proton absorptions. Figure 9-46 illustrates how this can be done for octane and 2,2,4-trimethylpentane.



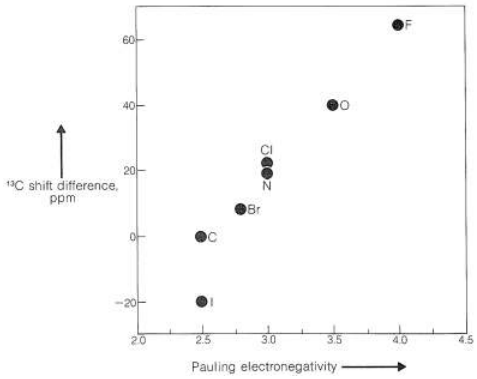
9.11.12: Carbon-13 Nuclear Magnetic Resonance Spectroscopy

In recent years ^{13}C nmr spectroscopy using ^{13}C of natural abundance (1.1%) has become an important tool for organic structural analysis. That this did not happen sooner is because ^{13}C has a much smaller magnetic moment than ^{1}H and the small moment combined with the small natural abundance means that ^{13}C is harder to detect in the nmr than ^{1}H by a factor of 5700. This is a large difference and can be put in the proper context in the following way. Suppose two people are talking in a noisy room and one is trying to hear the other. The common request is "talk louder". If this is not possible then the request is "say it again" or "talk more slowly". Either of the latter requests amounts to an integration of signal versus noise and takes time. Improvement in signal-to-noise for a given communication is achieved as the *square root* of the *time* of communication. On the crucial *time basis*, ^{13}C nmr

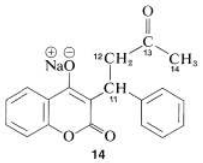
signals require $(5700)^2 \cong 30,000,000$ times more time to get the same signal-to-noise ratio as in ^1H nmr for the same number of nuclei per unit volume. This is a problem.

Electronic improvements and use of communication theory, with emphasis on the "say-it-again" technique, have provided the means for obtaining routine ^{13}C spectra for even fairly dilute solutions of quite complex molecules.

Some of the same kinds of structural effects are important for ^{13}C chemical shifts as for proton chemical shifts (Section 9-10E). For example, there is a similar parallel between ^{13}C shift differences in compounds of the type $CH_3{-}CH_2{-}X$ and electronegativity (Figure 9-47) as between the corresponding proton shifts and electronegativity (Figure 9-28). It is important to notice that ^{13}C shifts in ppm units are much larger than those of protons. This is because carbon uses p orbitals in forming bonds, whereas hydrogen uses s orbitals. We therefore will expect to find the the nuclei of other elements that use p orbitals in bonding, such as ^{15}N, ^{19}F, and ^{31}P, also will have larger shifts than for protons, as indeed they do.



A structural application of ^{13}C nmr, which shows its power in an area where ^1H nmr is indecisive, is shown in Figure 9-48. Here, we see the high-field ^{13}C resonances of a substance known variously as Coumadin, or the sodium salt of warfarin, 14, which is used widely as a blood anticoagulant in the treatment of diseases such as phlebitis. It also has substantial utility as a rat poison because of its anticoagulant action.



14

Figure 9-48 show no splittings of the ^{13}C resonances by the hydrogens directly attached to the carbons, even though such splittings normally are quite large $(125 - 320\ Hz)$. The reason is that, while the ^{13}C spectra were taken, protons were simultaneously subjected to strong irradiation at their resonance frequency, which, as far as spin-spin splitting goes, causes them to act as nonmagnetic nuclei, such as Cl, Br, and I. This double-resonance technique for removing the $^{13}C{-}H$ splittings is called proton decoupling (see Section 9-10I).

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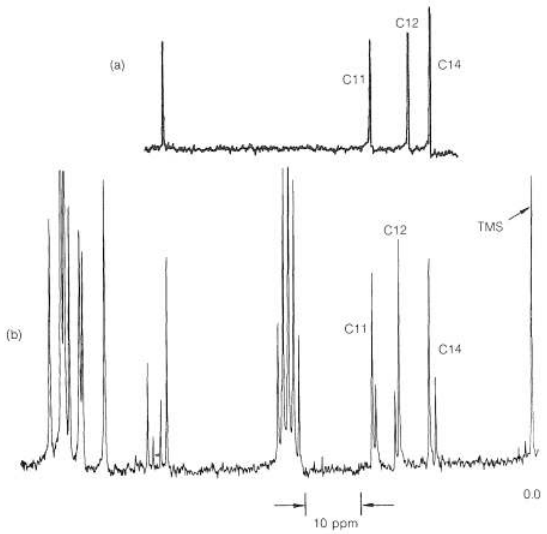


Figure 9-48: Proton-decoupled ^{13}C nmr spectrum at 15.1 MHz of the upfield region of (a) the sodium salt of warfarin (14) showing on the right side the resonances of C11, C12, and C14. This part of the spectrum can be compared with the more complete ^{13}C spectrum (b) of warfarin itself (16 and 17). The gaggle of evenly spaced sharp peaks toward the center of the spectrum arises from the solvent, $O(CD_2CD_2)_2O$.

There is no indication of any abnormality in the chemical shifts of carbons 11, 12, and 14 shown in Figure 9-48a. Furthermore, there is a downfield resonance 216.5 ppm from the carbons of TMS (not shown in Figure 9-48a) which is typical of a $C{=}O$ carbon corresponding to C13. When 14 is treated with acid, we expect the product (warfarin) of structure 15 to be formed, which should have a ^{13}C spectrum much like that shown in Figure 9-48a.

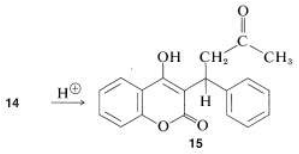
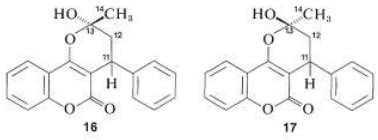


Figure 9-48a now come in unequal pairs. Futhermore, the $C{=}O$ carbon resonance of 14 has disappeared and two new lines are observed at 99.6 ppm and 103.4 ppm farther upfield.

The ^{13}C data indicate clearly that warfarin is not 15 in solution but is a mixture of two diastereomers (16 and 17, called cyclic hemiketals) resulting from addition of the $-OH$ group of 15 to the $C{=}O$ bond:



This is one example of the power of ^{13}C nmr to solve subtle structural problems.

[8]Although the principal isotopes of Cl, Br, and I have magnetic properties, because of the special character of all of these isotopes, they act in organic compounds as though they were *nonmagnetic*.

[9]*Resonance* in the sense used here means that the radio-frequency absorption takes place at specified "resonance" frequencies. However, you will see that almost all of the forms of spectroscopy we discuss in this book involve "resonance" absorption in the same sense.

[10]Here, γ is in Hz per gauss; physicists usually define γ in radians per second per gauss.

[11]From the Greek prefix *dia* meaning through, across. The opposite of diamagnetic is **paramagnetic**; *para* meaning alongside. We shall use this term later.

[12]In addition to giving better separation of the lines and clearer spectra, going to higher fields also has the beneficial effect of increasing the proportions of the nuclei in the $+\frac{1}{2}$ state, thereby giving more intense, easier-to-detect resonances.

[13]Many other proton-shift values are available in *NMR Spectra Catalog*, Volume 1 and 2, Varian Associates, Palo Alto, Calif., 1962, 1963.

[14]If two rings were present, this also would give four hydrogens less than the alkane. However, two rings are not possible with only three carbons.

9.11.13: References

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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9.12: Mass Spectroscopy

The usual application of mass spectroscopy to organic molecules involves bombardment with a beam of medium-energy electrons ($50\text{-}100\ \text{eV}$ or $1150\text{-}2300\ \text{kcal mol}^{-1}$) in high vacuum, and analysis of the charged particles and fragments so produced. Most mass spectrometers are set up to analyze positively charged fragments, although negative-ion mass spectrometry also is possible. The elements of a mass spectrometer are shown in Figure 9-51. The positive ions produced by electron impact are accelerated by the negatively charged accelerating plates and sweep down to the curve of the analyzer tube where they are sorted as to their mass-to-charge ((m/e) ratio by the analyzing magnet. With good resolution, only the ions of a single mass number will pass through the slit and impinge on the collector, even when the mass numbers are in the neighborhood of several thousand. The populations of the whole range of mass numbers of interest can be determined by plotting the rate of ion collection as a function of the magnetic field of the analyzing magnet.

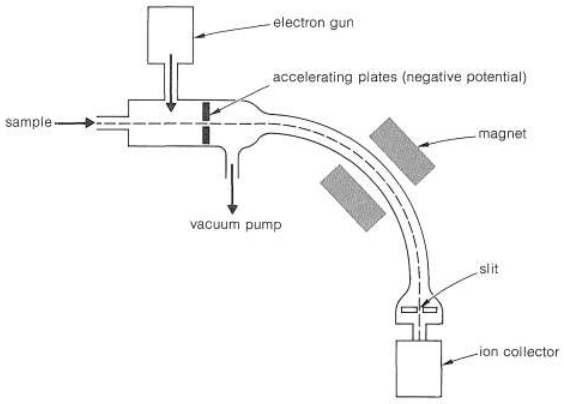


Figure 9-51: Schematic diagram of a mass spectrometer.

Mass spectra of 2-propanone, 2-butanone, and propanal are shown in Figure 9-52. Each peak represents ions of particular masses formed as the result of fragmentation of the molecule produced by electron impact into CH_3^+, CH_3CH_2^+, $\text{CH}_3\text{CO}^{\oplus}$, and so on. The "cracking patterns" are, of course, functions of the energy of the bombarding electrons and serve as an extraordinarily individual fingerprint of the particular molecules. For instance, 2-propanone and propanal are isomers, yet their cracking patterns are strikingly different.

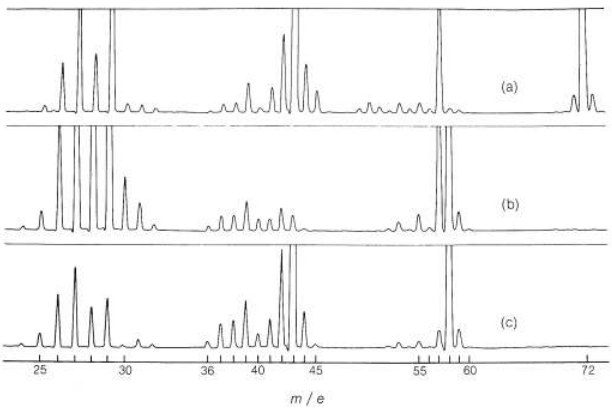


Figure 9-52: The mass spectra of (a) 2-butanone, (b) propanal, and (c) 2-propanone. These spectra were supplied through the courtesy of Dr. D. P. Stevenson of the Shell Development Company.

The peak that is highest in mass number is of considerable importance because it corresponds to the parent molecule M minus one electron (designated as M^+) and provides a highly accurate method for measuring molecular weights. Incorrect molecular weights will be obtained if the positive ion, M^+, becomes fragmented before it reaches the collector, or if two fragments combine to give a fragment heavier than M^+. The peak of M^+ is especially weak with alcohols and branched-chain hydrocarbons, which readily undergo fragmentation by loss of water or side-chain groups. With such compounds the peak corresponding to M^+ may be 0.1% or less of the highest peak in the spectrum, which is called the **base peak** and usually is assigned an arbitrary intensity of 100.

The pressure of the sample in the ion source of a mass spectrometer is usually about 10^{-5} mm, and, under these conditions, buildup of fragments to give significant peaks with m/e greater than M^+ is rare. One exception to this is the formation of $(M+1)^+$ peaks resulting from transfer of a hydrogen atom from M to M^+. The relative intensities of such $(M+1)^+$ peaks are usually sensitive to the sample pressure and may be identified in this way.

With the molecular weight available from the M^+ peak with reasonable certainty, the next step is to determine the *molecular formula*. If the resolution of the instrument is sufficiently high, quite exact masses can be measured, which means that ions with m/e values differing by one part in 50,000 can be distinguished. At this resolution it is possible to determine the elemental composition of each ion from its exact m/e value.

Many mass spectrometers in routine use are incapable of resolving ions with m/e values that differ by less than one mass unit. In this event, the determination of elemental composition can be determined by the method of *isotope abundance*. We will illustrate this with the following simple example.

The highest peaks corresponding to M^+ in the mass spectrum of an unknown sample have m/e equal to 64 and 66 with relative intensities of 3:1. What is the elemental composition? The 3:1 abundance ratio is uniquely characteristic of the chlorine isotopes, $^{35}\mathrm{Cl}$:$^{37}\mathrm{Cl}$ = 3:1. The mass peaks at 64 and 66 are therefore both molecular ions; the 64 peak is of an ion containing $^{35}\mathrm{Cl}$ and the 66 peak is of an ion containing $^{37}\mathrm{Cl}$. The remaining atoms in the molecule must add up to $(64-35)=29$, or $(66-37)=29$ mass units. There are several possible combinations of C, H, N, and O that give mass 29; they are $\mathrm{N_2H}$, CHO, $\mathrm{CH_3N}$, and $\mathrm{C_2H_5}$.[15] Of these, the combination with Cl that makes the most chemical sense is $\mathrm{C_2H_5}$, and the formula of the molecule therefore is $\mathrm{C_2H_5Cl}$, chloroethane.

This example illustrates how m/e values of *ions that differ only in isotopic composition can be used to determine elemental compositions*. The important isotopes for this purpose in addition to those of chlorine are the stable isotopes of natural abundance, $^{13}\mathrm{C}$ (1.1%), $^{15}\mathrm{N}$ (0.37%), $^{17}\mathrm{O}$ (0.04%), and $^{18}\mathrm{O}$ (0.20%). As a further example, suppose that we have isolated a hydrocarbon and have determine from its mass spectrum that $M^+ = 86$ mass units. In the absence of any combination reactions there will be an $(M+1)^+$ ion corresponding to the same molecular ion but with *one* $^{13}\mathrm{C}$ ion in place of $^{12}\mathrm{C}$. The intensity ratio $(M+1)^+/M^+$ will depend on the number of carbon atoms present, because the more carbons there are the greater the probability will be that one of them is $^{13}\mathrm{C}$. The greater the probability, the larger the $(M+1)^+/M^+$ ratio. For n carbons, we expect

$$\frac{\text{abundance of } (M+1)^+}{\text{abundance of } M^+} = n \times \%^{13}\mathrm{C}\,\text{abundance}/100 \tag{9.12.1}$$

If the measured $(M+1)^+/M^+$ ratio is 6.6:100, then

$$\frac{6.6}{100} = n \times 1.1/100 \tag{9.12.2}$$

$$n = 6 \tag{9.12.3}$$

The only hydrocarbon formula with $M^+ = 86$ and $n = 6$ is $\mathrm{C_6H_{14}}$.

Nitrogen $as\backslash(^{15}\mathrm{N})$ and oxygen (as $^{17}\mathrm{O}$) also contribute to $(M+1)^+$, if present, while $^{18}\mathrm{O}$ and *two* $^{13}\mathrm{C}$'s contribute to $(M+2)^+$. The calculated intensities of $(M+1)^+$ and $(M+2)^+$ relative to M^+ (as 100) are tabulated in Table 9-5 for elemental composition of ions up to $\mathrm{C_{20}}$. The table applies to fragment ions as well as molecular ions, but the intensity data from fragment ions very often is complicated by overlapping peaks.

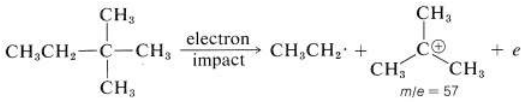
Table 9-5: *Isotopic Contributions for Carbon and other Elements to Intensities of* $(M+1)^+$ *and* $(M+2)^+$ *relative to* M^+ *(100)*

C_n	$(M+1)^+$	$(M+2)^+$	C_n	$(M+1)^+$	$(M+2)^+$
C_1	1.1	0.000	C_{11}	12.1	0.67
C_2	2.2	0.012	C_{12}	13.2	0.80
C_3	3.3	0.036	C_{13}	14.2	0.94
C_4	4.4	0.073	C_{14}	15.4	1.10
C_5	5.5	0.12	C_{15}	16.5	1.27
C_6	6.6	0.18	C_{16}	17.6	1.46
C_7	7.7	0.25	C_{17}	18.7	1.65
C_8	8.8	0.34	C_{18}	19.8	1.86
C_9	9.9	0.44	C_{19}	20.9	2.07
C_{10}	11.0	0.54	C_{20}	22.0	2.30

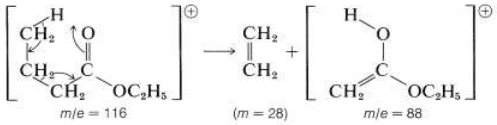
For each additional element present, add per atom
$(M+1)^+$ ^{15}N, 0.37; ^{17}O, 0.04; ^{33}S, 0.80
$(M+2)^+$ ^{18}O, 0.20; ^{34}S, 4.44; ^{37}Cl, 32.5; ^{81}Br, 98

The next step in the analysis of a mass spectrum is to see what clues as to structure can be obtained from the fragment ions. It would be a serious error to imagine that in mass spectra nothing is observed but simple nonspecific fragmentation of organic molecules on electron impact. Actually, even though electron impact produces highly unstable molecular ions, there is a strong tendency for breakdown to occur by reasonable chemical processes, and this may involve straightforward fragmentation or rearrangement of atoms from one part of the molecule to another.

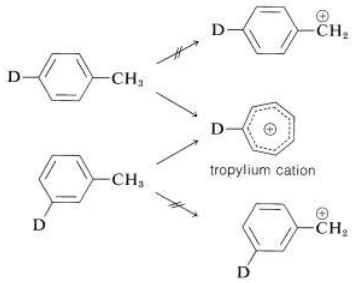
In general, fragmentation occurs at the weakest bonds, and the most abundant fragments also are the most stable ones. For instance, hydrocarbons fragment preferentially at branch points, partly because the C–C bonds are weaker here than elsewhere along the chain, and partly because the ionic fragments are more stable. As an example, consider 2,2-dimethylbutane. There is no molecular ion evident in its mass spectrum because it cleaves so readily at the quaternary carbon to give the m/e 57 peak corresponding to the most abundant fragment ion. This ion is presumably the *tert*-butyl cation and the alternate cleavage to the less stable ethyl cation with $m/e = 29$ is much less significant.



An excellent example of a rearrangement with fragmentation is provided by the M^+ ion of ethyl butanoate, which breaks down to give ethene and the M^+ ion of an isomer of ethyl ethanoate called its "enol form".



An interesting and complex rearrangement occurs on electron impact with methylbenzene (toluene). An intense peak is observed having m/e for $C_7H_7^+$, but the ion involved appears to be a symmetrical $C_7H_7^+$ ion, rather than a phenylmethyl cation. The evidence for this is that the fragmentation patterns found in the mass spectrometry of the ion itself are the same, no matter which of the monodeuteriomethylbenzenes is used as starting material. This rearrangement occurs because of the high delocalization energy of the symmetrical $ceC_7H_7^{\oplus}$ ion (usually called "tropylium cation") and because its charge is spread out more evenly over the carbons than would be the charge for the phenylmethyl cation (see Section 8-7B).



[15]Tabulations of elemental compositions of C, H, N and O for mass values up to 250 are listed in many texts on mass spectrometry. Consult these tables to see all possible alternatives. See also J. H. Beynon, *Mass Spectrometry and its Applications to Organic Chemistry*, Elsevier Publishing Co., Amsterdam, 1960.

9.12.1: References

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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9.E: Separation, Purification, and Identification of Organic Compounds (Exercises)

Exercise 9-1 Suppose you are standing on the end of a pier watching the waves and, between your position and a buoy $200\ \text{m}$ straight out, you count 15 wave crests. Further, suppose a wave crest comes by every 15 seconds. Calculate ν in Hz, λ in m, c in m sec^{-1}, and $\bar{\nu}$ in km^{-1}.

Exercise 9-2 Blue light has $\bar{\nu} = 20,800\ \text{cm}^{-1}$. Calculate ν in Hz and λ in nm.

Exercise 9-3 Calculate the energy in kcal mol^{-1} that corresponds to the absorption of 1 einstein of light of $589.3\ \text{nm}$ (sodium *D* line) by sodium vapor. Explain how this absorption of light by sodium vapor may have chemical utility.

Exercise 9-4

a. Use Equations 9-1 and 9-2 to calculate the wavelength in nm and energy in kcal of an einstein of radiation of radio-frequency energy in the broadcast band having $\nu = 1\ \text{MHz}$ (1 megahertz) $= 10^6\ \text{sec}^{-1}$ and knowing that the velocity of light is approximately $3 \times 10^8\ \text{m sec}^{-1}$.

b. In photoelectron spectroscopy, x-rays with energies of approximately $1250\ \text{eV}$ are used ($1\ \text{eV}$ (electron volt) $\text{mol}^{-1} = 23.05$ kcal). What would λ (in nm) be for such x-rays?

Exercise 9-5 The microwave spectrum of pure *trans*-2-butenoic acid $(CH_3CH{=}CHCO_2H)$ shows patterns exactly like those of Figure 9-8, which indicate the presence of two different *conformations*. What are these conformations, and why are there only two of them? (You may be helped by reviewing Section 6-5.)

Exercise 9-6 Use Equation 9-3 and any other pertinent data to predict which compound in each group would absorb in the infrared at the highest frequency for the changes in the stretching vibration of the specified bond. Give your reasoning.

a. R−Cl, R−Br, R−F (carbon-halogen)
b. $CH_3{-}NH_2$, $CH_2{=}NH$, $HC \equiv N$ (carbon-nitrogen)

Exercise 9-7 Which compound in each group would have the most intense infrared absorption band corresponding to stretching vibrations of the bonds indicated? Give your reasoning.

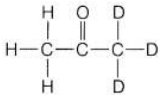
a. $(CH_3)_2C{=}O$, $(CH_3)_2C{=}CH_2$ (multiple bond)
b. $CH_3{-}CH_3$, $CH_3{-}O{-}CH_3$ (C−C vs. C−O)
c. $CH_3C \equiv CH$, $CH_3C \equiv CCH_3$ (multiple bond)
d. H−Cl, Cl−Cl

Exercise 9-8* How many vibrational modes are possible for (a) CS_2 (linear), (b) $BeCl_2$ (linear), and (c) SO_2 (angular)? Show your reasoning.

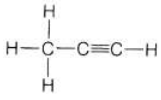
Exercise 9-9* Suppose an infrared absorption occurs at $3000\ \text{cm}^{-1}$. Calculate the corresponding frequency ν in sec^{-1}; λ in nm, angstroms, and microns, and energy change in kcal mol^{-1}. Using Equation 4-2 and neglecting ΔS, calculate the fraction of the molecules that would be in the ground state and in the first vibrational excited state (above ground state by $3000\ \text{cm}^{-1}$) at 298°K.

Exercise 9-10 Use Table 9-2 to map the approximate positions and intensities expected for the characteristic infrared bands corresponding to the stretching vibrations of the various kinds of bonds in the following molecules:

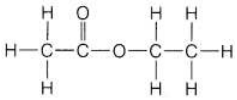
a. 1,1,1-trideuteriopropanone (trideuterioacetone)

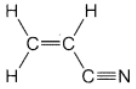


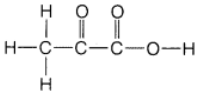
b. propyne

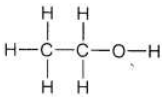


c. ethyl ethanoate (ethyl acetate)



d. propanenitrile (acrylonitrile) 

e. 2-oxopropanoic acid (pyruvic acid) 

f. ethanol (ethyl alcohol) (both as pure liquid and as a dilute solution in CCl_4) 

Exercise 9-11 The infrared spectra shown in Figure 9-14 are for compounds of formula C_3H_O and $C_3H_6O_2$. Use the data in Table 9-2 and the molecular formulas to deduce a structure for each of these substances from its infrared spectrum. Indicate clearly which lines in the spectra you identify with the groups in your structures.

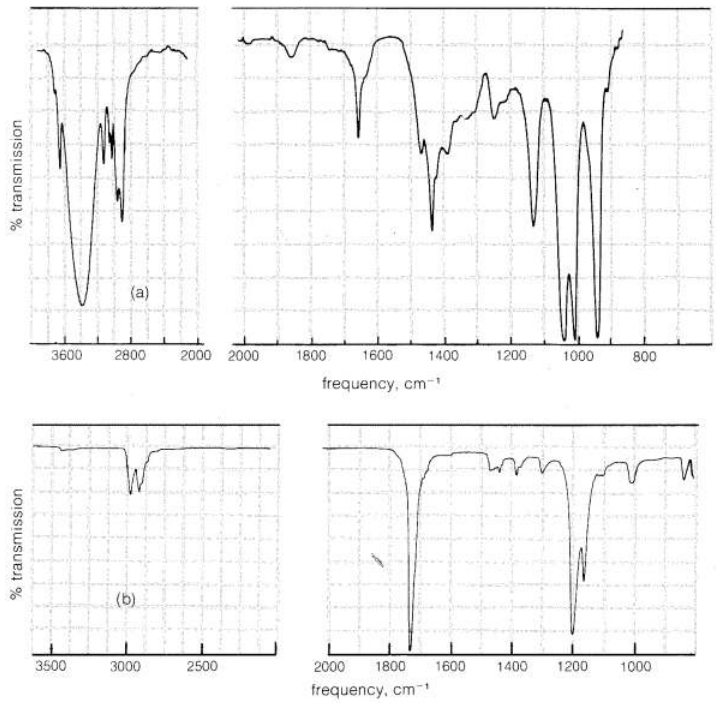


Figure 9-14: *Infrared spectra for Exercise 9-11. Spectrum (a) corresponds to* C_3H_6O *and Spectrum (b) to* $C_3H_6O_2$.

Exercise 9-12* Classify the following molecules according to the general characteristics expected for their infrared and Raman spectra:

a. $HC \equiv CH$
b. ICl
c. CO
d. $CF_2{=}CH_2$ (double-bond stretch only)
e. $(CH_3)_2C{=}CH_2$
f. $CH_3CH{=}CHCH_3$

Exercise 9-13* Carbon dioxide gives two infrared absorption bands but only one Raman line. This Raman line corresponds to a *different* vibration than the infrared absorptions. Decide which vibrational modes are infrared active (i.e., make the molecule electrically unsymmetrical during at least part of the vibration) and which is Raman active (i.e., occurs so the molecule is electrically symmetrical at all times during the vibration, see Section 9-7A).

Exercise 9-14 List the kinds of electronic transitions that would be expected for azaethene (methyleneimine), $CH_2{=}NH$, in order of increasing energy. Use the data in Table 9-3 to predict approximately the wavelengths at which the three lowest-energy transitions

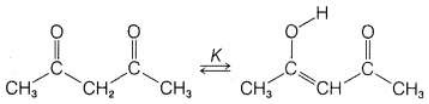
should occur.

Exercise 9-15 Calculate the percentage of the incident light that would be absorbed by an $0.010\ \mathrm{M}$ solution of 2-propanone (acetone) in cyclohexane contained in a quartz cell $0.1\ \mathrm{cm}$ long at $280\ \mathrm{nm}$ and at $190\ \mathrm{nm}$ (see footnote *a* of Table 9-3).

Exercise 9-16 Explain why the absorption band at $227.3\ \mathrm{nm}$ for trimethylamine, $(CH_3)_3N$, disappears in *acid* solution.

Exercise 9-17 A compound of formula C_4H_6O has two absorption bands in the ultraviolet: $\lambda = 320\ \mathrm{nm}$, $\epsilon = 30$ and $\lambda = 218\ \mathrm{nm}$, $\epsilon = 18,000$ in ethanol solution. Draw three possible structures that are consistent with this information.

Exercise 9-18 2,4-Pentadione exists in equilibrium with 4-hydroxy-3-penten-2-one:

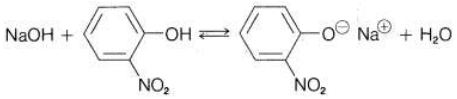


The infrared spectrum of the liquid mixture shows a broad absorption band at 3000-2700 cm^{-1} and an intense absorption band at $1613\ \mathrm{cm}^{-1}$. In cyclohexane solution, the substances has λ_{max} at 272 nm with $\epsilon_{max} = 12,000$.

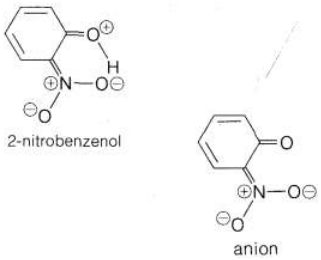
a. What can you conclude from this data as to the magnitude of K, the equilibrium constant for the interconversion of the two forms?

b. What can you deduce from the fact that the absorption at $272\ \mathrm{nm}$ is much weaker in aqueous solution (pH 7) than it is in cyclohexane?

Exercise 9-19* The electronic absorption spectrum of 2-nitrobenzenol has λ_{max} in $0.1\ \mathrm{M}$ HCl at $350\ \mathrm{nm}$. In $0.1\ \mathrm{M}$ NaOH, the benzenol is largely converted to its anion, and λ_{max} shifts to $415\ \mathrm{nm}$.



The ground-state resonance forms of 2-nitrobenzenol and its anion include



Explain how the relative importance of these resonance forms to the ground and excited states of 2-nitrobenzenol and its anion can account for the fact that the anion absorbs at longer wavelengths than does 2-nitrobenzenol. (Review Section 6-5B)

Exercise 9-20* A solution containing the two forms of the important coenzyme nicotinamide adenine dinucleotide (abbreviated $NAD^{\oplus}$ and NADH; see Section 15-6C for structures) has an absorbance in a 1-cm cell of 0.311 at $340\ \mathrm{nm}$ and 1.2 at $260\ \mathrm{nm}$. Both $NAD^{\oplus}$ and NADH absorb at $260\ \mathrm{nm}$, but only NADH absorbs at $340\ \mathrm{nm}$. The molar extinction coefficients are

Compound	260 nm	340 nm
$NAD^{\oplus}$	18,000	~ 0
NADH	15,000	6220

(9.E.1)

Calculate the proportions of $NAD^{\oplus}$ and NADH in the mixture.

Exercise 9-21 Use Figure 9-24 to map the nmr spectrum you would expect for $^{13}CCl_3\ ^1H$ in a field-sweep spectrometer in which the transmitter frequency is kept constant at $30\ \mathrm{MHz}$ and the magnetic field is swept from 0 to 30,000 gauss. Do the same for a frequency-sweep spectrometer when the magnetic field is kept constant at 10,000 gauss and the frequency is swept from 0 to 100 MHz. (For various reasons, practical spectrometers do not sweep over such wide ranges of field or frequency.)

Exercise 9-22* In nmr experiments, structural inferences sometimes are drawn from differences in resonance frequencies as small as 1 Hz. What difference in energy in kcal mol^{-1} does 1 Hz represent?

Exercise 9-23* The *intensity* of nmr signals normally increases markedly with decreasing temperature because more magnetic nuclei are in the $+\frac{1}{2}$ state. Calculate the equilibrium constant at -90° for the $+\frac{1}{2}$ and $-\frac{1}{2}$ states of ^1H in a magnetic field of 42,300 gauss when the resonance frequency is 180 MHz.

Exercise 9-24

a. Identify the protons with different chemical shifts in each of the structures shown. Use letter subscripts H_A, H_B, and so on, to designate nonequivalent protons. Use models if necessary.

(i) *cis*- and *trans*-2-butene
(ii) 1,3-butadiene
(iii) 1-chloro-2,2-dimethylbutane
(iv) 2-butanol
(v) *trans*-1,2-dibromocyclopropane

b.* Why does 3-methyl-2-butanol have three methyl resonances with different chemical shifts in its proton nmr spectrum?

c.* For the compounds in Part a designated those protons (if any) that are enantiotopic or diastereotopic.

Exercise 9-25 Use Equation 9-4 to calculate the chemical shift of the $-\text{CH}_2-$ protons on

a. CH_2Cl_2
b. $\text{ClCH}_2\text{OCH}_3$
c. $\text{C}_6\text{H}_5\text{CH}_2\text{CO}_2\text{H}$

Exercise 9-26 If the $-\text{NH}_2$ protons of 2-aminoethanol, $\text{NH}_2\text{CH}_2\text{CH}_2\text{OH}$, have a shift of 1.1 ppm and the $-\text{OH}$ proton has a shift of 3.2 ppm, what will be the observed average ($-\text{NH}_2$, $-\text{OH}$) proton shift if exchange is very fast?

Exercise 9-27 In reasonably concentrated solution in water, ethanoic acid (acetic acid) acts as a weak acid (less than 1% dissociated). Ethanoic acid gives two proton nmr resonance lines at 2 and 11 ppm, relative to TMS, whereas water gives a line at 5 ppm. Nonetheless, mixtures of ethanoic acid and water are found to give only two lines. The position of one of these lines depends on the ethanoic acid concentration, whereas the other one does not. Explain how you would expect the position of the concentration-dependent line to change over the range of ethanoic acid concentrations from 0-100%.

Exercise 9-28 The proton nmr spectrum of a compound of formula $\text{C}_6\text{H}_{12}\text{O}_2$, is shown in Figure 9-31. The signals are shown relative to TMS as the standard, and the stepped line is the integral of the area under the peaks from left to right. The infrared spectrum of the same compound shows a broad band at 3300 cm^{-1} and a strong band at 1700 cm^{-1}. Deduce the structure of the compound and name it by the IUPAC system.

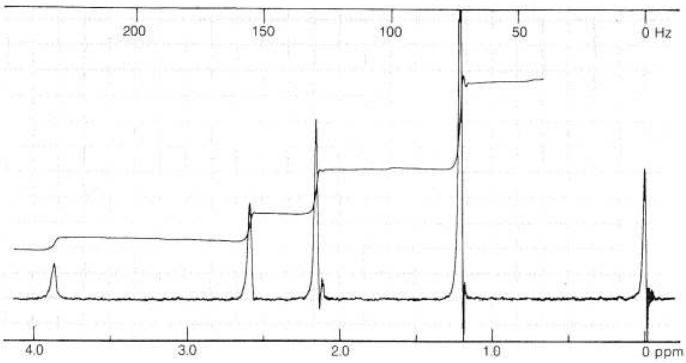


***Figure 9-31:** Proton nmr spectrum of a compound, $\text{C}_6\text{H}_{12}\text{O}_2$, at 60 MHz relative to TMS at 0.00 ppm. The stepped line is the integral running from left to right. See Exercise 9-28.*

Exercise 9-29 Sketch the proton chemical shifts in ppm and Hz as well as the integral you would expect for each of the following substances at 60 MHz. (The spin-spin splitting of the resonance lines evident in Figures 9-23 and 9-27, but not seen in Figure 9-31,

can be safely neglected with all of the compounds listed.)

a. $(CH_3)_3CCH_2OCH_3$
b. $CH_2COC(CH_3)_3$
c. $HCOC(CH_3)_2CHO$
d.
e. $(CH_3)_2C{=}CCl_2$
f. $(CH_3)_3COC \equiv CH$
g. $(CH_2Cl)_3CCO_2H$
h.* *cis*-1-methyl-4-*tert*-butyl-1,2,2,3,3,4,5,5,6,6-decachlorocyclohexane

Exercise 9-30 Write structures for compounds with the following descriptions (There may be more than one correct answer, but only one answer is required.)

a. C_2H_6O with *one* proton nmr shift
b. C_6H_{12} with *one* proton nmr shift
c. C_5H_{12} with *one* proton nmr shift
d. C_4H_8O with *two* different proton nmr shifts
e. $C_4H_8O_2$ with *three* different proton nmr shifts
f. C_4Cl_8 with *two* different ^{13}C nmr shifts

Exercise 9-31 Sketch the proton nmr spectrum and integral expected at 60 MHz, with TMS as standard, for the following substances. Show the line positions in Hz; neglect spin-spin couplings smaller than 1 to 2 Hz and all second-order effects. Remember that chlorine, bromine, and iodine (but not fluorine) act as nonmagnetic nuclei.

a. CH_3Cl
b. CH_3CH_2Cl
c. $(CH_3)_2CHCl$
d. $CH_3CCl_2CH_2Cl$
e. $(CH_3)_3CCl$
f. $CHCl_2CHBr_2$
g. $CH_3CHClCOCH_3$
h. $CH_3CH_2CO_2CH_2CH_3$
i. $ClCH_2CH_2CH_2I$
j. $(ClCH_2)_3CH$

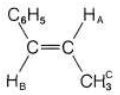
Exercise 9-32* The proton-proton coupling in 1,1,2,2-tetrachloroethane cannot be observed directly because the chemical shift is zero. However, measurements of the splittings in $CClH-{}^{13}{}_2{}^{12}CCl_2H$ show that the proton-proton coupling in $CHCl_2CHCl_2$ is 3.1 Hz. Explain how you can use this information to deduce the favored conformation of $CHCl_2CHCl_2$. Draw a sawhorse representation of the preferred conformation.

Exercise 9-33 The proton-proton coupling in *meso*-2,3-dibromobutanedioic acid (determined by the same procedure as for 1,1,2,2-tetrachloroethane, see Exercise 9-32) is 11.9 Hz. Write a sawhorse structure for the preferred conformation of this molecule.

Exercise 9-34*

a. Show how the assignment of $J_{AB} = J_{BC} = 2J_{AC}$ leads to the prediction of four equally spaced and equally intense lines for the methyl resonance of 2-phenylpropene.

b. What would the splittings of the alkenic and methyl protons look like for *trans*-1-phenylpropene if $J_{AB} = 16$ Hz, $J_{AC} = 4$ Hz, and $J_{BC} = 0$ Hz?



Exercise 9-35 Interpret fully each of the proton nmr spectra shown in Figure 9-40 in terms of the given structures. For spin-spin splittings, explain how the patterns arise and predict the intensities expected from simple theory.

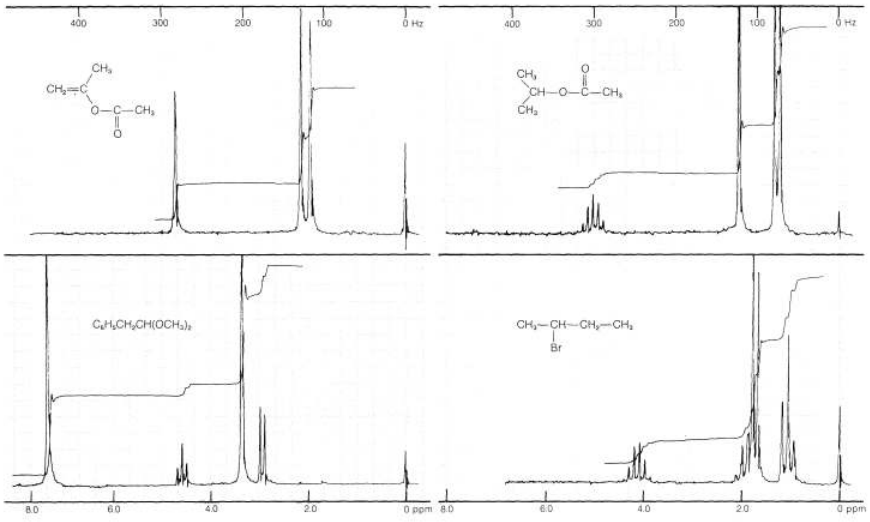


Figure 9-40: *Proton nmr spectra at* 60 MHz *relative to TMS* $= 0.00$ ppm. *See Exercise 9-35.*

Exercise 9-36 Figure 9-41 shows proton nmr spectra and integrals at 60 MHz for three simple organic compounds. Write a structure for each substance that is in accord with both its molecular formula and nmr spectrum. Explain how you assign each of the lines in the nmr spectrum.

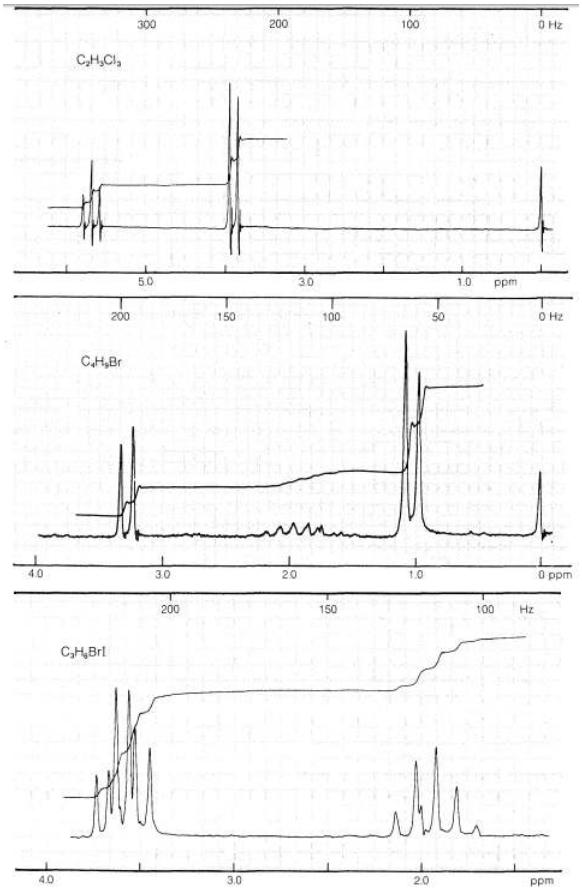


Figure 9-41: *Proton nmr spectra and integrals for some simple organic compounds at* 60 MHz *relative to TMS,* 0.00 ppm. *See Exercise 9-36.*

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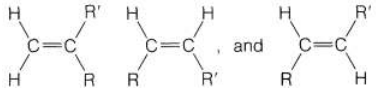
Exercise 9-37 Figure 9-42 shows the proton nmr spectrum of a compound, $C_5H_8O_2$. Which of the following structures fits the spectrum best? Explain. Remember that the protons of



are expected to be nonequivalent; that is, they have different chemical shifts if R and R′ are different groups.

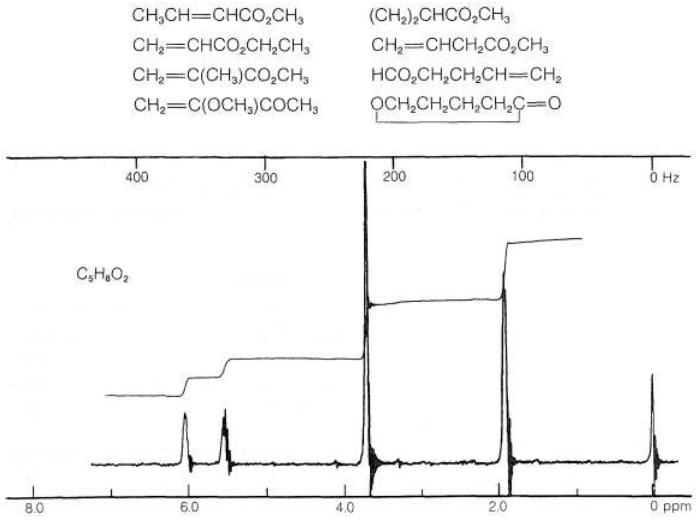
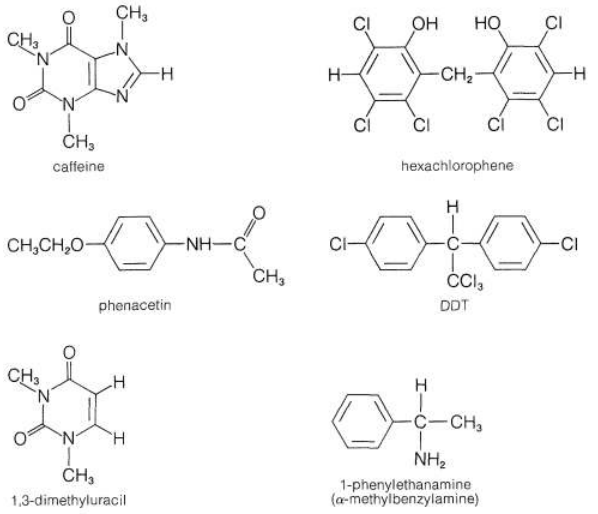


Figure 9-42: *Proton spectrum of a compound,* $C_5H_8O_2$*, at* 60 MHz *relative to TMS as standard. See Exercise 9-37.*

Exercise 9-38 Suppose that you had six unlabeled bottles containing caffeine, hexachlorophene, phenacetin, DDT, 1,3-dimethyluracil, and 1-phenylethanamine. The nmr spectrum of each of these compounds is shown in Figure 9-43. Match the lettered spectra with the appropriate individual structures so the bottles can be labeled properly. Give your reasoning.



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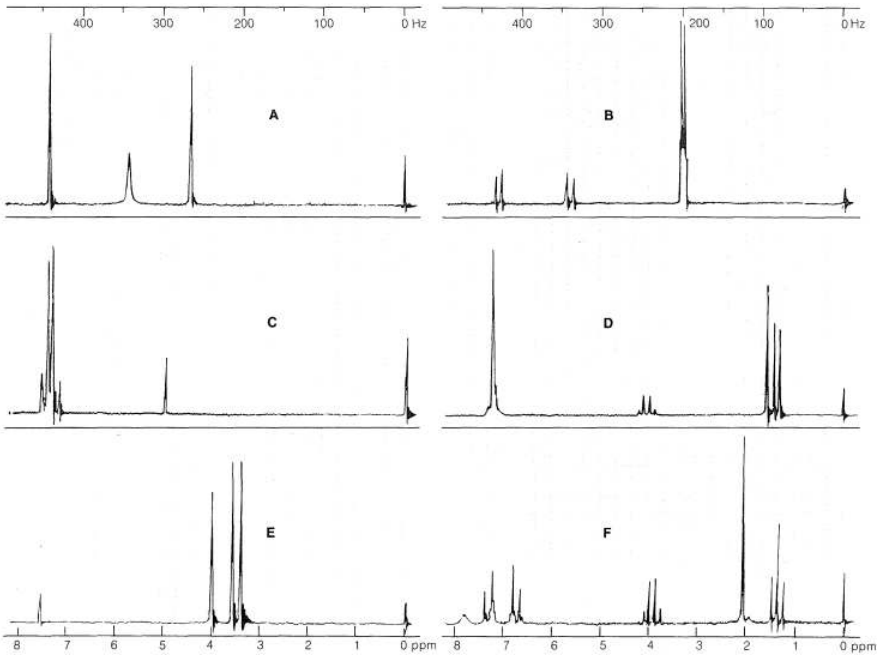

Figure 9-43: *Proton nmr spectra of compounds at* 60 MHz. *See Exercise 9-38.*

Exercise 9-39 Show how one can use the asymmetry of the line intensities of the 60-MHz proton spectrum in Figure 9-45 to show which groups of lines are interconnected by spin-spin coupling. Write structural formulas for the compounds involved that fit the observed splitting patterns and chemical shifts.

Exercise 9-40 Explain why it is correct to characterize 16 and 17 as diastereomers and not enantiomers.

Exercise 9-41* When one takes the proton nmr spectrum of ordinary trichloromethane (chloroform, $CHCl_3$) under high gain, the spectrum shown in Figure 9-49 is obtained. The weak outside peaks are separated by 210 Hz and together have an integrated intensity of slightly over 1% of the main peak. Explain how these weak proton signals arise.

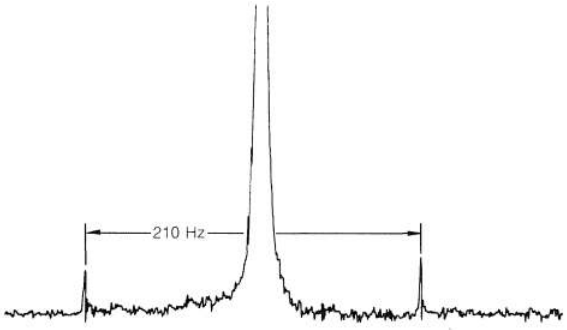

Figure 9-49: *Proton nmr spectrum at* 60 MHz *of trichloromethane taken with high-detection sensitivity. See Exercise 9-41.*

Exercise 9-42* With reference to the data summarized in Figure 9-47 and the discussion in Section 9-10L, sketch qualitatively the proton-decoupled ^{13}C spectra you would expect for

a. $(CH_3)_3CCH_2OH$
b. $CCl_3CH_2OCOCH_3$

Exercise 9-43* Figure 9-50 shows the ^{1}H and ^{13}C nmr spectra of a compound $C_6H_{10}O$. With the aid of these spectra, deduce the structure of $C_6H_{10}O$. It will be seen that the ^{13}C spectrum is quite simple, even though the proton spectrum is complex and difficult to interpret.

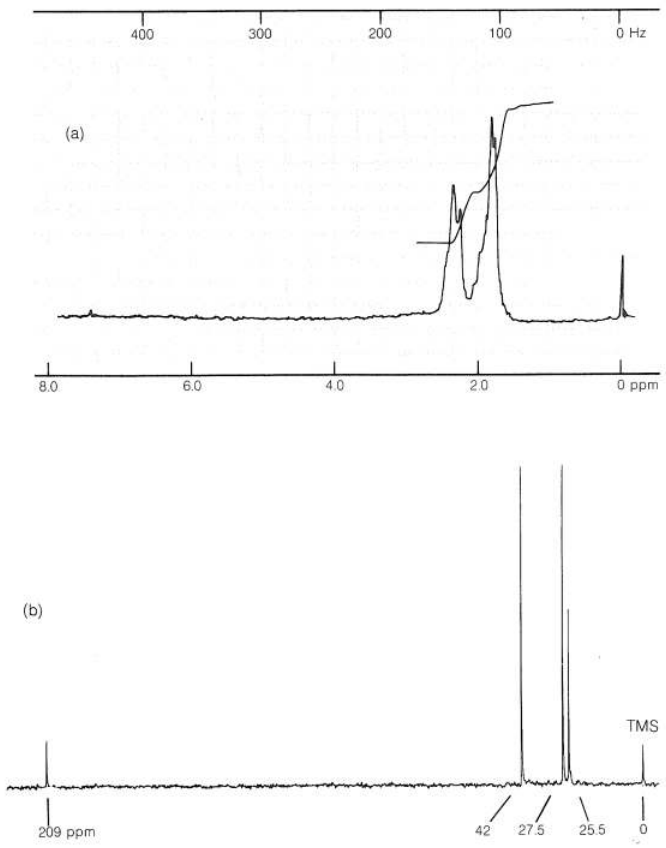

Figure 9-50: *(a) Proton and (b)* ^{13}C *spectra of a compound* $C_6H_{10}O$ *taken at* $60\ MHz$ *and* $15.1\ MHz$*, respectively. Because of the special way the* ^{13}C *spectrum was determined, the peak at* $209\ ppm$ *is smaller than it should be. The intensity of this peak is, correctly, the same as the peak at* $25.5\ ppm$*. See Exercise 9-43.*

Exercise 9-44 Explain how a mass spectrometer, capable of distinguishing between ions with m/e values differing by one part in 50,000, could be used to tell whether an ion of mass 29 is $C_2H_5^+$ or CHO^+.

Exercise 9-45

a. Calculate the relative intensities of the $(M+1)^+$ and $(M+2)^+$ ions for a molecule of elemental composition $C_3H_7NO_2$.

b. The M^+, $(M+1)^+$, and $(M+2)^+$ ion intensities were measured as 100, 8.84, and 0.54 respectively, and the molecular weight as 120. What is the molecular formula of the compound?

c. In our example of how natural ^{13}C can be used to determine the number of carbon atoms in a compound with $M^+ = 86$ and a $(M+1)^+/M^+$ ratio of 6.6/100, we neglected the possible contribution to the $(M+1)^+$ peak of the hydrogen isotope of mass 2 (deuterium). The natural abundance of deuterium is 0.015%. For a compound of composition C_6H_{14}, how much do you expect the deuterium to contribute to the intensity of the $(M+1)^+$ peak relative to the M^+ peak?

Exercise 9-46 Show how the molecular weights of 2-propanone, propanal, and 2-butanone can be estimated from the mass spectra in Figure 9-52. Suggest a possible origin for the strong peaks of mass 57 in the spectra of propanal and 2-butanone, which is essentially absent in 2-propanone, although 2-propanone (and 2-butanone) show strong peaks at mass 43.

Exercise 9-47 The mass spectrum of propylbenzene has a prominent peak at mass number 92. With (3,3,3-trideuteriopropyl)benzene, this peak shifts to 93. Write a likely mechanism for breakdown of propylbenzene to give a fragment of mass number 92.

Exercise 9-48 The mass spectra of alcohols usually show peaks of $(M-18)$, which correspond to loss of water. What kind of mechanisms can explain the formation of $(M-18)$ peaks, and no $(M-19)$ peaks, from 1,1-dideuterioethanol and 1,1,1,3,3-pentadeuterio-2-butanol?

Exercise 9-49 Explain how the postulated rearrangement of the M^+ ion of ethyl butanoate (Section 9-11) is supported by the fact that the 2,2-dideuterio compound gives a peak with $m/e = 90$, the 3,3-dideuterio isomer gives a m/e 88 peak, while the 4,4,4-trideuterio isomer gives a m/e 89 peak.

Exercise 9-50 What is the likely structure for the major fragment ion with $m/e = 45$ derived from methoxyethane (methyl ethyl ether) on electron impact?

Exercise 9-51 A certain halogen compound gave a mass spectrum with molecular ion peaks at m/e 136 and 138 in about equal intensities. The nmr spectrum of this compound gave only a single resonance around 1.2 ppm. What is the structure of the compound? Give your reasoning.

Exercise 9-52* The mass spectra of three compounds, A, B, and C, are given below in tabular form. Only the peaks of significant intensity are reported.

A		B		C	
m/e	*I*	*m/e*	*I*	*m/e*	*I*
27	12.8	37	3.28	27	19.69
41	13.0	38	8.57	28	5.74
42	5.91	50	13.70	29	19.19
*43	100.00	51	16.30	*31	100.00
44	2.47	*77	48.28	32	1.42
45	0.98	*112	100.00	33	0.19
*71	3.94	113	6.84	43	8.13
*86	10.0	*114	32.14	*45	43.89
87	0.56	115	2.10	*46	18.89
88	0.04	116	0.06	47	0.43

a. Compound A is $CH_3CH_2CH_2COCH_3$. Show how this material can fragment to give the peaks marked with an asterisk and, where possible, how the isotope peaks help establish your assignments.

b. Determine the molecular weight and the molecular formula of Compounds B and C from the spectral data. Suggest a likely structure for each peak marked with an asterisk.

9.E.1: Contributors

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CHAPTER OVERVIEW

10: Alkenes and Alkynes I - Ionic and Radical Addition Reactions

With few exceptions, the multitude of reactions discussed in introductory texts are classified as **ionic reactions**. By this we mean that nucleophilic and electrophilic sites in reacting molecules bond to each other. Furthermore, charged species such as carbocations, carbanions, conjugate acids and conjugate bases are often intermediates on the reaction path, the overall transformation taking place in two or more discrete steps. Ionic reactions normally occur in solution, and changes in solvents may have dramatic consequences. Free-radical addition is an addition reaction in organic chemistry involving free radicals. The addition may occur between a radical and a non-radical, or between two radicals.

10.1: Prelude to Alkenes and Alkynes
10.2: Physical and Spectroscopic Properties of Alkenes and Alkynes
10.3: The Reactivity of Multiple Carbon-Carbon Bonds
10.4: Electrophilic Additions to Alkenes
10.5: Orientation in Addition to Alkenes
10.6: Electrophilic Addition Reactions of Alkynes
10.7: Nucleophilic Addition Reactions
10.8: Radical-Chain Addition Reactions to Alkenes
10.9: Polymerization of Alkenes
10.10: Alkylation of Alkenes
10.E: Alkenes and Alkynes I (Exercises)

10.1: Contributors and Attributions

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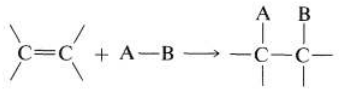
10.1: Prelude to Alkenes and Alkynes

Carbon-carbon double and triple bonds undergo a wide variety of addition reactions in which *one* of the multiple bonds is broken and two new bonds to carbon are formed:



The importance of such reactions to synthetic organic chemistry is paramount. It is our intention in this and the following chapter to show the great diversity, utility, and specificity of addition reactions of alkenes and alkynes.

We will begin with a brief discussion of the physical and spectroscopic properties of alkenes and alkynes. But the major emphasis in the chapter is on two main types of reactions, ionic addition and radical-chain addition. For ionic additions we will make extensive use of the classification of reagents as electrophiles and nucleophiles, as described in Chapter 8.

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10.2: Physical and Spectroscopic Properties of Alkenes and Alkynes

10.2.1: Physical Properties

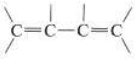
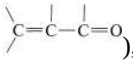
In general, the physical properties of alkenes are similar to those of alkanes. The data of Table 10-1 allow comparison of the boiling points, melting points, and densities of several alkenes with the corresponding alkanes that have the same carbon skeleton. Like the continuous-chain alkanes, the 1-alkenes form a homologous series of compounds that show regular changes in physical properties with increasing chain length. The boiling points, melting points, and densities of the simple alkynes (also included in Table 10-1) are somewhat higher than those of the corresponding alkanes or alkenes, and these properties also show regular changes as the chain length is increased.

Table 10-1: *Comparison of Physical Properties of Alkanes, Alkenes, and Alkynes*

Hydrocarbon	Formula	Bp, °C	Mp, °C	Density, d_4^{20}
ethane	$CH_3—CH_3$	−88.6	−183[a]	
ethene	$CH_2=CH_2$	−105	−169	
ethyne	$CH\equiv CH$	−83	−81	
propane	$CH_3—CH_2—CH_3$	−42.1	−187[a]	0.501[b]
propene	$CH_3—CH=CH_2$	−47.8	−185[a]	0.514[b]
propyne	$CH_3—C\equiv CH$	−23.2	−102.7	0.706[b]
butane	$CH_3—CH_2—CH_2—CH_3$	−0.5	−138	0.579[b]
1-butene	$CH_3—CH_2—CH=CH_2$	−6.3	−185[a]	0.595[b]
cis-2-butene	$CH_3—CH=CH—CH_3$	3.7	−139	0.621[b]
trans-2-butene	$CH_3—CH=CH—CH_3$	0.9	−106	0.604[b]
1-butyne	$CH_3—CH_2—C\equiv CH$	8.1	−126	0.65[b]
2-butyne	$CH_3—C\equiv C—CH_3$	27.0	−32	0.691
pentane	$CH_3—CH_2—CH_2—CH_2—CH_3$	36.1	−129	0.626
1-pentene	$CH_3—CH_2—CH_2—CH=CH_2$	30.0	−165	0.641
cis-2-pentene	$CH_3—CH_2—CH=CH—CH_3$	37.9	−151	0.656
trans-2-pentene	$CH_3—CH_2—CH=CH—CH_3$	36.4	−140	0.648
1-pentyne	$CH_3—CH_2—CH_2—C\equiv CH$	40.2	−106	0.690
2-pentyne	$CH_3—CH_2—C\equiv C—CH_3$	56.1	−109	0.711
hexane	$CH_3—CH_2—CH_2—CH_2—CH_2—CH_3$	68.7	−95	0.659
1-hexene	$CH_3—CH_2—CH_2—CH_2—CH=CH_2$	63.5	−140	0.674
cis-2-hexene	$CH_3—CH_2—CH_2—CH=CH—CH_3$	68.8	−141	0.687
trans-2-hexene	$CH_3—CH_2—CH_2—CH=CH—CH_3$	67.9	−133	0.678
cis-3-hexene	$CH_3—CH_2—CH=CH—CH_2—CH_3$	66.4	−138	0.680
trans-3-hexene	$CH_3—CH_2—CH=CH—CH_2—CH_3$	67.1	−113	0.677
1-hexyne	$CH_3—CH_2—CH_2—CH_2—C\equiv CH$	71	−132	0.716
2-hexyne	$CH_3—CH_2—CH_2—C\equiv C—CH_3$	84.0	−88	0.732
3-hexyne	$CH_3—CH_2—C\equiv C—CH_2—CH_3$	81.8	−105	0.724

[a]At the triple point (i.e., the temperature at which the solid, liquid, and vapor all are in equilibrium).
[b]Under pressure.

10.2.2: Spectroscopic Properties of Alkenes

The *infrared spectra of alkenes* are sufficiently different from those of alkanes in most instances to make it possible to recognize when a double bond is present. For example, in the infrared spectrum of 1-butene (Figure 10-1) the absorption band near $1650\ \text{cm}^{-1}$ is characteristic of the stretching vibration of the double bond. In general, the intensity and position of this band depends on the structure of the alkene; it varies with the degree of branching at the double bond, with the presence of a second unsaturated group in conjugation with the first (i.e.,  or ), and with the symmetry of the substitution of the double bond (see Section 9-7B). However, in many cases the absorption bands caused by the various modes of vibration of the alkenic C–H bonds frequently are more useful for detecting a double bond and identifying its type than is the absorption band caused by C=C stretch. With 1-butene, absorptions arising from the C–H vibrations of the terminal $=CH_2$ group occur near $3100\ \text{cm}^{-1}$, $1420\ \text{cm}^{-1}$, and $915\ \text{cm}^{-1}$, and those of the $-CH=$ grouping near $3020\ \text{cm}^{-1}$, $1420\ \text{cm}^{-1}$, and $1000\ \text{cm}^{-1}$. In general, absorption bands at these frequencies are from the grouping $-CH=CH_2$. The bands near $1420\ \text{cm}^{-1}$ are due to in-plane bending, whereas those at $915\ \text{cm}^{-1}$ to $1000\ \text{cm}^{-1}$ arise from out-of-plane bending. The other intense absorptions, near $1460\ \text{cm}^{-1}$ and $3000\ \text{cm}^{-1}$, are due to C–H vibrations of the CH_3CH_2- group (see Section 9-7D). These illustrate a further point - namely, the positions of the infrared absorptions of alkyl C–H bonds are significantly different from those of alkenic C–H bonds.

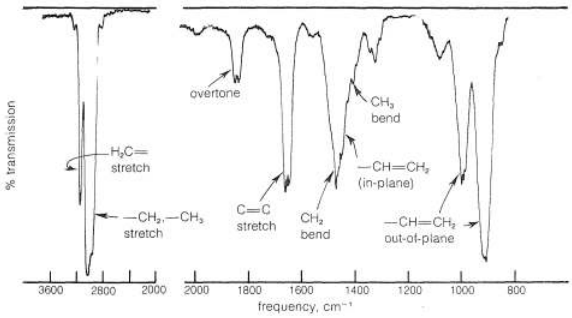
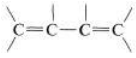
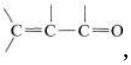


Figure 10-1: Infrared spectrum of 1-butene showing the vibrational assignments made to the various absorptions.

The double bonds of an alkene with no alkenic hydrogens are difficult to detect by infrared spectroscopy and in such cases Raman spectroscopy is helpful (see Section 9-8).

The infrared absorption of 1-butene that occurs at $1830\ \text{cm}^{-1}$ (Figure 10-1) falls in the region where stretching vibrations of alkene bonds usually are not observed. However, this band actually arises from an **overtone** (harmonic) of the $=CH_2$ out-of-plane bending at $915\ \text{cm}^{-1}$. Such overtone absorptions come at exactly *twice* the frequency of the fundamental frequency, and whenever an absorption like this is observed that does not seem to fit with the normal fundamental vibrations, the possibility of its being an overtone should be checked.

With regard to *electronic spectra*, a π electron of a simple alkene can be excited to a higher energy (π^*) state by light of wavelength $180\ \text{nm}$ to $100\ \text{nm}$. However, many other substances absorb in this region of the spectrum, including air, the quartz sample cell, and most solvents that might be used to dissolve the sample, and as a result the spectra of simple alkenes are not obtained easily with the usual ultraviolet spectrometers. When the double bond is conjugated as in  or  , then the wavelengths of maximum absorption shift to longer wavelengths and such absorptions are determined more easily and accurately (also see Section 9-9B).

In proton *nmr spectra*, the chemical shifts of alkenic hydrogens are toward lower fields than those of alkane hydrogens and normally fall in the range of $4.6\text{-}5.3\ \text{ppm}$ relative to TMS (see section 9-10E and Table 9-4). Spin-spin couplings of alkenic hydrogens are discussed in Section 9-10G and 9-10J.

10.2.3: Spectroscopic Properties of Alkynes

The *infrared spectrum* of a monosubstituted alkyne such as ethynylbenzene, $C_6H_5C \equiv CH$ (Figure 10-4), has a strong band near $3300\ \text{cm}^{-1}$, which is characteristic of the carbon-hydrogen stretching vibration in the grouping $\equiv C-H$. At a lower frequency (longer wavelength) around $2100\ \text{cm}^{-1}$, there is a band associated with the stretching vibration of the triple bond (also see Figure 9-36). Therefore the presence of the grouping $-C \equiv CH$ in a molecule may be detected readily by infrared spectroscopy. However, the triple bond of a disubstituted alkyne, $R-C \equiv C-R$, is detected less easily because there is no $\equiv C-H$ absorption near $3300\ \text{cm}^{-1}$, and furthermore the $C \equiv C$ absorption sometimes is of such low intensity that it may be indiscernible. Raman spectroscopy (Section 9-8) or chemical methods must then be used to confirm the presence of a triple bond.

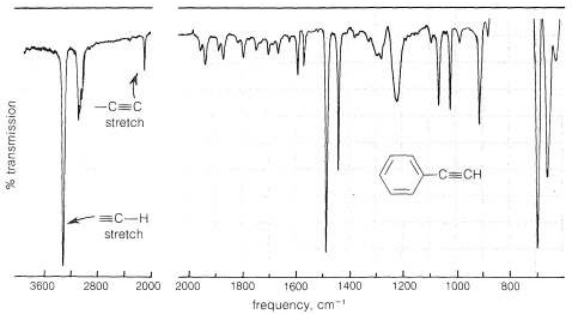


Figure 10-4: Infrared spectrum of ethynylbenzene in carbon tetrachloride solution.

Alkynes, like alkenes, undergo *electronic absorption* strongly only at wavelengths in the relatively inaccessible region below $200\ \text{nm}$. However, when a triple bond is conjugated with one or more unsaturated groups, radiation of longer wavelength is absorbed.

To illustrate, ethyne absorbs at $150\ \text{nm}$ and $173\ \text{nm}$, whereas 1-buten-3-yne $(CH_2{=}CH{-}C\ {\equiv}\ CH)$ absorbs at $219\ \text{nm}$ and $227.5\ \text{nm}$. The effects of such conjugation on spectra is discussed in more detail in Section 9-9B.

The proton *nuclear magnetic resonance* spectrum of ethynylbenzene is shown in Figure 10-5. The peaks near $435\ \text{Hz}$ and $185\ \text{Hz}$ correspond to resonances of the phenyl and $\equiv C{-}H$ protons, respectively. The difference in chemical shift between the two types of protons is considerably larger than between alkenic and aromatic protons come into resonance at higher magnetic fields (i.e., they are subject to more diamagnetic shielding, Section 9-10E) than alkenic or aromatic protons. In fact, the $\equiv C{-}H$ protons of alkynes have chemical shifts approaching those of alkyl protons. (Also see Figure 9-36.)

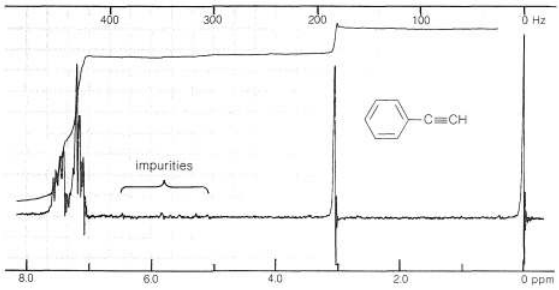


Figure 10-5: The proton nmr spectrum and integral of ethynylbenzene at $60\ \text{MHz}$ relative to TMS as 0.00. This spectrum also illustrates the use of nmr for detection of small amounts of impurities. The almost imperceptible peaks around $6\ \text{ppm}$ are in the correct locations for alkene hydrogens. The integral indicates that the ratio of alkene to ethyne hydrogens is on the order of 1:15. The substance most likely to give rise to the peaks is ethenylbenzene (styrene, $C_6H_5CH{=}CH_2$) and, if so, it is present to the extent of about 2%.

The *mass spectra* of alkenes and alkynes usually give distinct molecular ions; however, the fragmentation is often complex and not easily interpreted.

10.2.4: References

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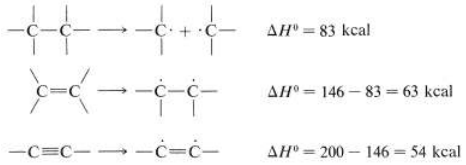
10.3: The Reactivity of Multiple Carbon-Carbon Bonds

In the early days of organic chemistry, alkenes were described as "unsaturated" because, in contrast to the "saturated" alkanes, they were found to react readily with substances such as halogens, hydrogen halides, oxidizing agents, and so on. Therefore, the "chemical affinity" of alkenes was regarded as unsatisfied or "unsaturated". (Also see Section 1-1I.)

One reason alkenes and alkynes react more readily than alkanes is because the carbon-carbon bonds of a multiple bond are individually weaker than normal carbon-carbon single bonds. Consider the bond energies involved. According to Table 4-3, the strengths of carbon-carbon single, double, and triple bonds are 83, 146, and 200 kcal, respectively. From these values we can calculate that cleavage of one-half of a carbon-carbon double bond should require 63 kcal and cleavage of one-third of a carbon-carbon triple bond should require 54 kcal:



As a result, addition reactions to multiple bonds are expected to be about 20-30 kcal more exothermic than the corresponding cleavage reactions of carbon-carbon single bonds, as estimated here for reaction with bromine:

The substantial difference in the heats of reaction of ethane, ethene, and ethyne with bromine is reflected in a very important practical consideration in handling ethyne (acetylene), namely its thermodynamic stability relative to solid carbon and hydrogen gas. Unlike ethane, both ethene and ethyne can be shown from bond energies to be unstable with respect to formation of solid carbon and gaseous hydrogen:

Although this does not seem to offer particular problems with ethene, an explosive decomposition of ethyne to carbon and hydrogen may occur if the gas is compressed to 10-20 $\mathrm{kg\ cm^{-2}}$. Even liquid ethyne (bp \sim 83^\text{o}\)) must be handled with care. Ethyne is not used commercially under pressure unless it is mixed with an inert gas and handled in rugged equipment. Ethyne burns with pure oxygen to give a very hot flame that is widely used for welding. For this purpose, the gas is dissolved under about $15\ \mathrm{kg\ cm^{-2}}$ in 2-propanone (acetone, $\mathrm{CH_3{-}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}{-}CH_3}$, bp 56.5°) and contained in cylinders packed with diatomaceous earth.

Why is ethyne so much less stable than ethene or ethane? First, C–C bonds are not as strong as C–H bonds. Therefore a gain in stability usually is to be expected when C–H bonds are made at the expense of C–C bonds; ethene and ethane each have more C–H bonds than ethyne has. Second, ethyne has six electrons held between the two carbons and these electrons experience considerable mutual interelectronic repulsion. This accounts for the fact that the *average* C–C bond strength for the triple bond of an alkyne is $200/3 = 67$ kcal, compared to $146/2 = 73$ kcal for the double bond of an alkene and 83 kcal for a normal single bond of an alkane.

10.3.1: References

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10.4: Electrophilic Additions to Alkenes

The reactions of alkanes discussed in Chapter 4 are *homolytic* processes, which means that the bonds are made and broken through radical or atomic intermediates. In contrast, the S_N and E reactions of alkyl halides, considered in Chapter 8, involve heterolytic bond cleavage and ionic reagents or products. An especially important factor contributing to the differences between the reactions of the alkanes and alkyl halides is the slight ionic character of C–H compared to C-halide bonds (see Section 1-3). The alkenes are like the alkanes in being nonpolar compounds (Section 4-1) and it may come as a surprise that many important reactions of alkenes are heterolytic reactions. Why should this be so? No doubt because the electrons in the alkene double bonds are more exposed and accessible than the electrons in an alkane C–C bond.

This is evident from the atomic-orbital models of ethene described in Section 6-4C. The electrons of the double bond are pushed outward by their mutual repulsions, and their average positions are considerably farther from the bond axis than the electron positions of a single bond (Figure 10-6). In such circumstances, electrophilic reagents, which act to acquire electrons in chemical reactions (Section 8-1), are expected to be particularly reactive. This is actually the case. Furthermore, reagents that are primarily nucleophilic (electron-donating) are notoriously poor for initiating reactions at carbon-carbon double bonds. Exceptions occur when the double bonds carry substituents with a sufficiently high degree of electron-attracting power to reduce the electron density in the double bond enough to permit attack by a nucleophilic agent.

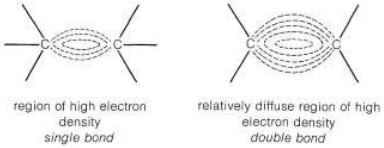
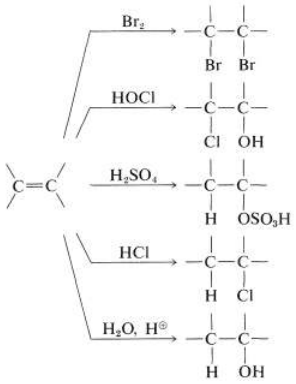
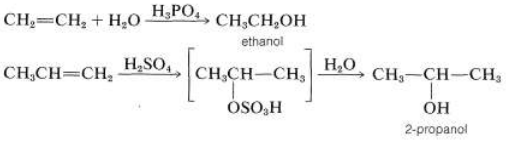


Figure 10-6: Schematic representations of average densities of electrons in carbon-carbon single and double bonds.

Example of electrophilic reagents that normally add to carbon-carbon double bonds of alkenes to give saturated compounds include halogens (Cl_2, Br_2, and I_2), hydrogen halides (HCl and HBr), hypohalous acids (HOCl and HOBr), water, and sulfuric acid:



The mechanisms of these reactions have much in common and have been studied extensively from this point of view. They also have very considerable synthetic utility. The addition of water to alkenes (hydration) is particularly important for the preparation of a number of commercially important alcohols. Thus ethanol and 2-propanol (isopropyl alcohol) are made on a very large scale by the hydration of the corresponding alkenes (ethene and propene) using sulfuric or phosphoric acids as catalysts. The nature of this type of reaction will be described later.



10.4.1: The Stepwise Ionic Mechanism, Halogen Addition

We shall give particular attention here to the addition of bromine to alkenes because this reaction is carried out very conveniently in the laboratory and illustrates a number of important points about electrophilic addition reactions. Much of what follows applies to

addition of the other halogens, except fluorine.

A significant observation concerning bromine addition is that it and many of the other reactions listed above proceed in the dark and are *not* influenced by radical inhibitors. This is evidence against a radical-chain mechanism of the type involved in the halogenation of alkanes (Section 4-4D). However, it does not preclude the operation of radical-addition reactions under other conditions, and, as we shall see later in this chapter, bromine, chlorine, and many other reagents that commonly add to alkenes by ionic mechanisms also can add by radical mechanisms.

One alternative to a radical-chain reaction for bromine addition to an alkene would be the simple four-center, one-step process shown in Figure 10-7.

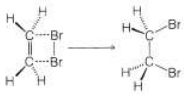


Figure 10-7: Representation of a one-step suprafacial mechanism for addition of bromine to ethene. Gas-phase additions appear to proceed in this manner.

The mechanism of Figure 10-7 cannot be correct for bromine addition to alkenes in solution for two important reasons. First, notice that this mechanism requires that the two C–Br bonds be formed on the *same* side of the double bond, and hence produce *suprafacial addition*. However, there is much evidence to show that bromine and many other reagents add to alkenes to form *antarafacial addition* products (Figure 10-8).

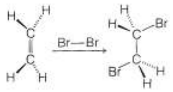
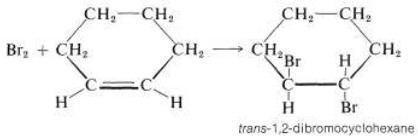


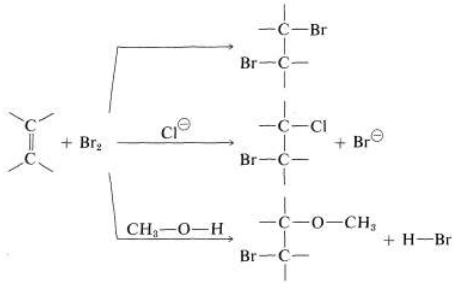
Figure 10-8: Antarafacial addition of bromine to ethene, usually observed in solution.

Cyclohexene adds bromine to give *trans*-1,2-dibromocyclohexane:



The cis isomer is not formed at all. To give the trans isomer, the two new C–Br bonds have to be formed on *opposite sides* of the double bond by antarafacial addition. But this is impossible by a one-step mechanism because the Br–Br bond would have to stretch too far to permit the formation of both C–Br bonds at the same time.

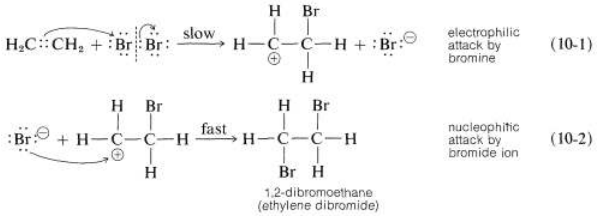
The second piece of evidence against the mechanism of Figure 10-7 is that bromine addition reactions carried out in the presence of more than one nucleophilic reagent usually give mixtures of products. Thus the addition of bromine to an alkene in methanol solution containing lithium chloride leads not only to the expected dibromoalkane, but also to products resulting from attack by chloride ions and by the solvent:



The intervention of extraneous nucleophiles suggests a *stepwise* mechanism in which the nucleophiles compete for a reactive intermediate formed in one of the steps.

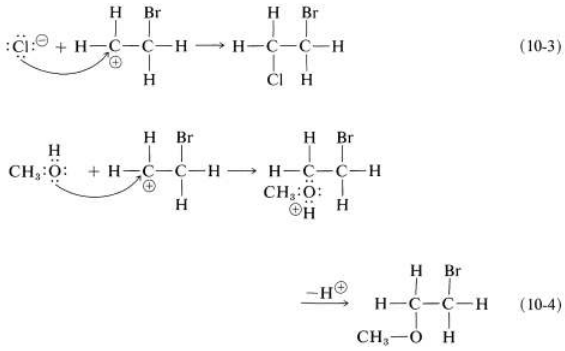
A somewhat oversimplified two-step mechanism that accounts for most of the foregoing facts is illustrated for the addition of bromine to ethene. [In the formation shown below, the curved arrows are not considered to have real mechanistic significance, but

are used primarily to show which atoms can be regarded as nucleophilic (donate electrons) and which as electrophilic (accept electrons). The arrowheads always should be drawn to point to the atoms that are formulated as accepting a pair of electrons.]



The first step (which involves electrophilic attack by bromine on the double bond) produces a bromide ion and a carbocation, as shown in Equation 10-1.[1]

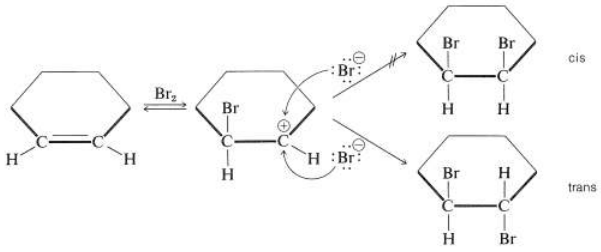
As we know from our study of S_N1 reactions (Section 8-4), carbocations react readily with nucleophilic reagents. Therefore in the second step of the bromine-addition mechanism, shown in Equation 10-2, the bromoethyl cation is expected to combine rapidly with bromide ion to give the dibromo compound. However, if other nucleophiles, such as $Cl^{\ominus}$ or CH_3OH, are present in solution, they should be able to compete with bromide ion for the cation, as in Equations 10-3 and 10-4, and mixtures of products will result:



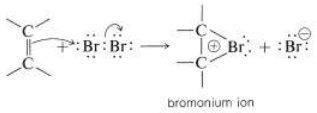
To account for the observation that all of these reactions result in antarafacial addition, we must conclude that the first and second steps take place from *opposite sides of the double bond*.

10.4.2: Why Antarafacial Addition?

The simple carbocation intermediate of Equation 10-1 does not account for formation of the antarafacial-addition product. The results with S_N1 reactions (Section 8-6) and the atomic-orbital representation (see Section 6-4E) predict that the bonds to the positively charged carbon atom of a carbocation should lie in a plane. Therefore, in the second step of addition of bromine to cycloalkenes, bromide ion could attack either side of the planar positive carbon to give a mixture of *cis*- and *trans*-1,2-dibromocyclohexanes. Nonetheless, antarafacial addition occurs exclusively:

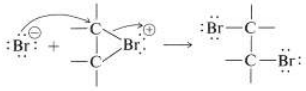


To account for the stereospecificity of bromine addition to alkenes, it has been suggested that in the initial electrophilic attack of bromine a cyclic intermediate is formed that has bromine bonded to *both* carbons of the double bond. Such a "bridged" ion is called a **bromonium ion** because the bromine formally carries the positive charge:

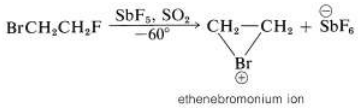


(10-5)

An S_N2-type of attack of bromide ion, or other nucleophile, at carbon on the side *opposite* to the bridging group then results in formation of the antarafacial-addition product:



We may seem to have contradicted ourselves because Equation 10-1 shows a carbocation to be formed in bromine addition, but Equation 10-5 suggests a bromonium ion. Actually, the formulation of intermediates in alkene addition reactions as "open" ions or as cyclic ions is a controversial matter, even after many years of study. Unfortunately, it is not possible to determine the structure of the intermediate ions by any direct physical method because, under the conditions of the reaction, the ions are so reactive that they form products more rapidly than they can be observed. However, it is possible to generate stable bromonium ions, as well as the corresponding chloronium and iodonium ions. The technique is to use low temperatures in the absence of any strong nucleophiles and to start with a 1,2-dihaloalkane and antimony pentafluoride in liquid sulfur dioxide:

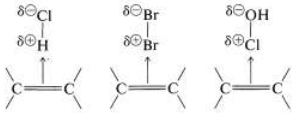


The $C_2H_4Br^{\oplus}$ ions produced in this way are relatively stable and have been shown by nmr to have the cyclic halonium ion structure.

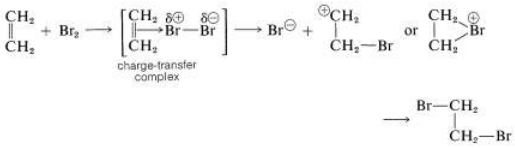
10.4.3: Complexes of Electrophilic Agents with Double Bonds

There is a further aspect of polar additions to alkenes that we should consider, namely, that electrophilic reagents form loose complexes with the π electrons of the double bonds of alkenes *prior* to reaction by addition. Complexes of this type are called **charge-transfer complexes** (or π **complexes**). Formation of a complex between iodine and cyclohexene is demonstrated by the fact that iodine dissolves in cyclohexene to give a *brown* solution, whereas its solutions in cyclohexane are *violet*. The brown solution of iodine in cyclohexene slowly fades as addition occurs to give colorless *trans*-1,2-diiodocyclohexane.

Precise Lewis structures cannot be written for charge-transfer complexes, but they commonly are represented as



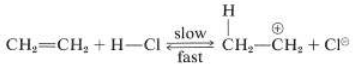
with the arrow denoting that electrons of the double bond are associated with the electrophile. These complexes probably represent the first stage in the formation of addition products by a sequence such as the following for bromine addition:



10.4.4: Addition of Proton Acids

We have seen that electrophiles can react with alkenes to form carbon-halogen bonds by donating positive halogen, $Br^{\oplus}$, $Cl^{\oplus}$, or $I^{\oplus}$. Likewise, carbon-hydrogen bonds can be formed by appropriately strong proton donors, which, of course, are typically strong proton acids. These acids are more effective in the absence of large amounts of water because water can compete with the alkene as a proton acceptor (also see Section 10-3E). Hydrogen chloride addition to ethene occurs by way of a proton-transfer step to give the

ethyl cation and a chloride ion (Equation 10-6) followed by a step in which the nucleophilic chloride ion combines with the ethyl cation (Equation 10-7):



(10-6)

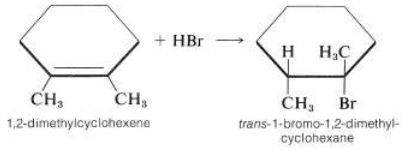
(10-7)

All of the hydrogen halides HF, HCl, HBr, and HI) will add to alkenes. Addition of hydrogen fluoride, while facile, is easily reversible. However, a solution of 70% anhydrous hydrogen fluoride and 30% of the weak organic base, pyridine, which is about 1/10,000 times as strong as ammonia, works better, and with cyclohexene gives fluorocyclohexane. With hydrogen iodide, care must be taken to prevent I_2 addition products resulting from iodine formed by oxidation reactions such as

$$4HI + O_2 \rightarrow 2I_2 + 2H_2O \tag{10.4.1}$$

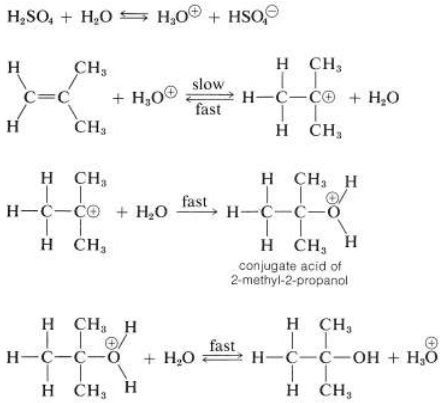
With hydrogen bromide, radical-chain addition may intervene unless the reaction conditions are controlled carefully (this will be discussed in Section 10-7).

The stereochemistry of addition depends largely on the structure of the alkene, but for simple alkenes and cycloalkenes, addition occurs predominantly in an antarafacial manner. For example, hydrogen bromide reacts with 1,2-dimethylcyclohexene to give the antarafacial addition product:



10.4.5: Hydration

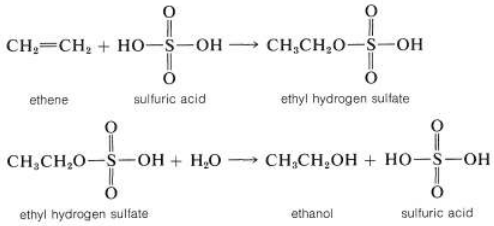
We mentioned previously that the hydration of alkenes required a strong acid as a catalyst, because water itself is too weak an acid to initiate the proton-transfer step. However, if a small amount of a strong acid such as sulfuric acid is present, hydronium ions, $H_3O^{\oplus}$, are formed in sufficient amount to protonate reasonably reactive alkenes, although by no means as effectively as does concentrated sulfuric acid. The carbocation formed then is attacked rapidly by a nucleophilic water molecule to give the alcohol as its conjugate acid,[2] which regenerates hydronium ion by transferring a proton to water. The reaction sequence follows for 2-methylpropene:



In this sequence, the acid acts as a *catalyst* because the hydronium ion used in the proton addition step is regenerated in the final step.

Sulfuric acid (or phosphoric acid) is preferred as an acid catalyst for addition of water to alkenes because the conjugate base, HSO_4^- (or $H_2PO_4^-$), is a poor nucleophile and does not interfere in the reaction. However, if the water concentration is kept low by using concentrated acid, addition occurs to give sulfate (or phosphate) esters. The esters formed with sulfuric acid are either alkyl acid sulfates $R{-}OSO_3H$ or dialkyl sulfates $(RO)_2SO_2$. In fact, this is one of the major routes used in the commercial production of

ethanol and 2-propanol. Ethen and sulfuric acid give ethyl hydrogen sulfate, which reacts readily with water in a second step to give ethanol:



10.4.6: Aqueous versus Nonaqueous Acids. Acid Strengths

One of the more confusing features of organic chemistry is the multitude of conditions that are used to carry out a given kind of reaction, such as the electrophilic addition of proton acids to different alkenes. Strong acids, weak acids, water, no water - Why can't there be a standard procedure? The problem is that alkenes have very different tendencies to accept protons. In the vapor phase, ΔH^0 for addition of a proton to ethene is about $35\ \text{kcal}$ more positive than for 2-methylpropene, and although the difference should be smaller in solution, it still would be large. Therefore we can anticipate (and we find) that a much more powerful proton donor is needed to initiate addition of an acid to ethene than to 2-methylpropene. But why not use in all cases a strong enough acid to protonate *any* alkene one might want to have a proton acid add to? Two reasons: First, strong acids can induce undesirable side reactions, so that one usually will try not to use a stronger acid than necessary; second, very strong acid may even prevent the desired reaction from occurring!

In elementary chemistry, we usually deal with acids in more or less dilute aqueous solution and we think of sulfuric, hydrochloric, and nitric acids as being similarly strong because each is essentially completely disassociated in dilute water solution:

$$\text{HCl} + \text{H}_2\text{O} \overrightarrow{\leftarrow} \text{H}_3\text{O}^{\oplus} + \text{Cl}^{\ominus} \tag{10.4.2}$$

This does not mean they actually are equally strong acids. It means only that each of the acids is sufficiently strong to donate all of its protons to water. We can say that water has a "leveling effect" on acid strengths because as long as an acid can donate its protons to water, the solution has but one acid "strength" that is determined by the $\text{H}_3\text{O}^{\oplus}$ concentration, because $\text{H}_3\text{O}^{\oplus}$ is where the protons are.

Now, if we use poorer proton acceptors as solvent we find the proton-donating powers of various "strong" acids begin to spread out immensely. Furthermore, new things begin to happen. For example, ethene is not hydrated appreciably by dilute aqueous acid; it just is too hard to transfer a proton from hydronium ion to ethene. So we use concentrated sulfuric acid, which is strong enough to add a proton to ethene. But now we don't get hydration, because any water that is present in concentrated sulfuric acid is virtually all converted to $\text{H}_3\text{O}^{\oplus}$, which is non-nucleophilic!

$$\text{H}_2\text{SO}_4 + \text{H}_2\text{O} \rightarrow \text{H}_3\text{O}^{\oplus} + \text{HSO}_4{}^{-} \tag{10.4.3}$$

However, formation of $\text{H}_3\text{O}^{\oplus}$ leads to formation of $\text{HSO}_4{}^{-}$, which has enough nucleophilic character to react with the $\text{CH}_3\text{CH}_2{}^{+}$ to give ethyl hydrogen sulfate and this is formed instead of the conjugate acid of ethanol (Section 10-3E). The epitome of the use of stronger acid and weaker nucleophile is with liquid SO_2 (bp $\sim 10^{\circ}$) as the solvent and HBF_6 as the acid. This solvent is a very poor proton acceptor (which means that its conjugate acid is a very good proton donor) and $\text{SbF}_6{}^{-}$ is an extremely poor nucleophile. If we add ethene to such a solution, a stable solution of $\text{CH}_3\text{CH}_2{}^{+}\text{SbF}_6{}^{-}$ is formed. The reason is that there is no better proton acceptor present than $\text{CH}_2{=}\text{CH}_2$ and no nucleophile good enough to combine with the cation.

10.4.7: A Biological Hydration Reaction

The conversion of fumaric acid to malic acid is an important biological hydration reaction. It is one of a cycle of reactions (Krebs citric acid cycle) involved in the metabolic combustion of fuels (amino acids and carbohydrates) to CO_2 and H_2O in a living cell.

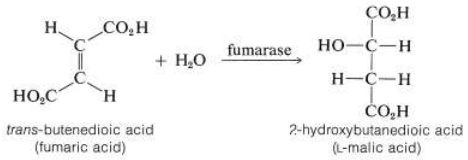


Figure 10-9.

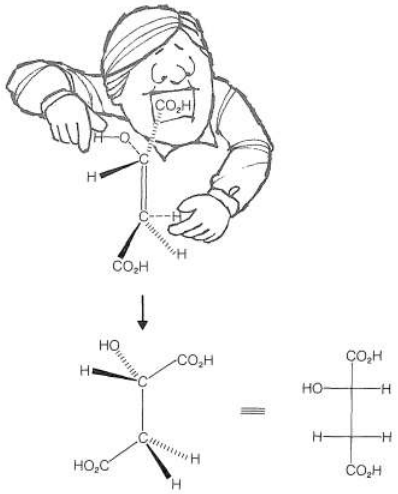


Figure 10-9: Representation of the course of enzyme-induced hydration of fumaric acid (trans-butenedioic acid) to give L-malic acid (L-2-hydroxy-butanedioic acid). If the enzyme complexes with either $-CO_2H$ *(carboxyl) group of fumaric acid, and then adds* OH *from* its right *hand and* H *from* its left, *the proper stereoisomer (L) is produced by antarafacial addition to the double bond. At least three* particular *points of contact must occur between enzyme and substrate to provide the observed stereospecificity of the addition. Thus, if the enzyme functions equally well with the alkenic hydrogen or the carboxyl toward its mouth (as shown in the drawing) the reaction still will give antarafacial addition, but D,L-malic acid will be the product.*

[1]An alternative to Equation 10-1 would be to have Br_2 ionize to $Br^{\oplus}$ and $Br^{\ominus}$, with a subsequent attack of $Br^{\oplus}$ on the double bond to produce the carbocation. The fact is that energy required for such an ionization of Br_2 is prohibitively large even in water solution $(\Delta H^0 \geq 80\ \text{kcal})$. One might well wonder why Equation 10-1 could possibly be more favorable. The calculated ΔH^0 for $CH_2{=}CH_2 + Br_2 \rightarrow {\cdot}CH_2{-}CH_2Br + Br{\cdot}$ is $+41$ kcal, which is only slightly more favorable than the ΔH^0 for $Br_2 \rightarrow 2Br{\cdot}$ of 46.4 kcal. However, available thermochemical data suggest that the ease of transferring an electron from ${\cdot}CH_2CH_2Br$ to $Br{\cdot}$ to give $^{\oplus}CH_2CH_2Br + Br^{\ominus}$ is about 80 kcal more favorable than $2Br{\cdot} \rightarrow Br^{\oplus} + Br^{\ominus}$. Thus the overall ΔH^0 of Equation 10-1 is likely to be about 85 kcal more favorable than $Br_2 \rightarrow Br^{\oplus} + Br^{\ominus}$.

[2]The terms **conjugate acid** and **conjugate base** are very convenient to designate substances that are difficult to name simply as acids, bases, or salts. The conjugate acid of a compound X is $XH^{\oplus}$ and the conjugate base of HY is $Y^{\ominus}$. Thus $H_3O^{\oplus}$ is the conjugate acid of water, while $OH^{\ominus}$ is its conjugate base. Water itself is then both the conjugate base of $H_3O^{\oplus}$ and the conjugate acid of $OH^{\ominus}$

10.4.8: References

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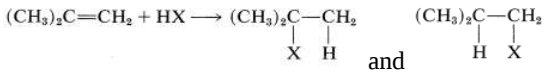
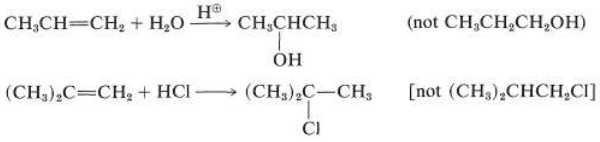
10.5: Orientation in Addition to Alkenes

10.5.1: Addition of HX

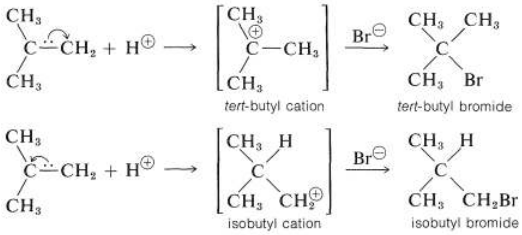
Addition of an unsymmetrical substance such as HX to an unsymmetrical alkene theoretically can give two products:



Both products are seldom formed in equal amounts; in fact, one isomer usually is formed to the exclusion of the other. For example, the hydration of propene gives 2-propanol (not 1-propanol), and hydrogen chloride adds to 2-methylpropene to give *tert*-butyl chloride (not isobutyl chloride):



To understand the reason for the pronounced selectivity in the orientation of addition of electrophiles, it will help to consider one example, hydrogen bromide addition to 2-methylpropene. Two different carbocation intermediates could be formed by attachment of a proton to one or the other of the double bond carbons:



Subsequent reactions of the cations with bromide ion give *tert*-butyl bromide and isobutyl bromide. In the usual way of running these additions, the product is very pure *tert*-butyl bromide.

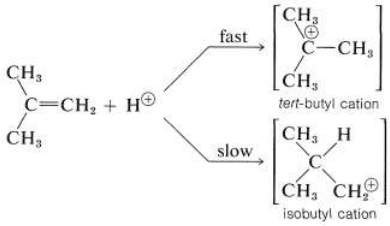
How could be have predicted which product would be favored? The first step is to decide whether the prediction is to be based on (1) which of the two products is the *more stable*, or (2) which of the two products if formed *more rapidly*. If we make a decision on the basis of product stabilities, we take into account ΔH^0 values, entropy effects, and so on, to estimate the equilibrium constants K_{eq} for the reactants and each product. When the ratio of the products is determined by the ratio of their equilibrium constants, we say the overall reaction is subject to **equilibrium** (or **thermodynamic**) **control**. Equilibrium control requires that the reaction be *reversible*.

When a reaction is carried out under conditions in which it is *not reversible*, the ratio of the products is determined by the relative rates of formation of the various products. Such reactions are said to be under **kinetic control**.

The products obtained in a reaction subject to kinetic control are not necessarily the same as those obtained under equilibrium control. Indeed, the equilibrium constant for interconversion of *tert*-butyl bromide and isobutyl bromide at 25° is 4.5, and if the addition of hydrogen bromide to 2-methylpropene were under equilibrium control, the products would be formed in this ratio:

$$K_{eq} = \frac{[\text{tert-butyl bromide}]}{[\text{isobutyl bromide}]} = 4.5 \tag{10.5.1}$$

But the addition product is $99 + \%$ *tert*-butyl bromide so the reaction clearly is kinetically controlled, *tert*-butyl being formed considerably faster than isobutyl bromide. *The slow, or rate-determining, step in this reaction is the formation of the intermediate cation rather than the reaction of the cation with bromide ion.* So to account for the formation of *tert*-butyl bromide we have to consider why the *tert*-butyl cation is formed more rapidly than the isobutyl cation:



As we have seen in Section 8-7B, alkyl groups are more electron donating than hydrogen. This means that the more alkyl groups there are on the positive carbon of the cation, the more stable and the more easily formed the cation will be. The reason is that electron-donating groups can partially compensate for the electron deficiency of the positive carbon. As a result, we can predict that the *tert*-butyl cation with three alkyl groups attached to the positive center will be formed more readily than the primary isobutyl cation with one alkyl group attached to the positive center.

Thus the problem of predicting which of the two possible products will be favored in the addition of unsymmetrical reagents to alkenes under kinetic control reduces to predicting which of two possible carbocation intermediates will be formed most readily. With simple alkenes, we shall expect the preference of formation of the carbocations to be in the order:

tertiary > *secondary* > *primary*.

The reaction scheme can be represented conveniently in the form of an energy diagram (Figure 10-10). The activation energy, $\Delta H^{\ddagger}_{\text{tert}}$ for the formation of the *tert*-butyl cation is less than $\Delta H^{\ddagger}_{\text{prim}}$ for the formation of the isobutyl cation because the tertiary ion is much more stable (relative to the reactants) than the primary ion, and therefore is formed at the faster rate. The second step, to form the product from the intermediate cation, is very rapid and requires little activation energy. Provided that the reaction is *irreversible*, it will take the lowest-energy path and form exclusively *tert*-butyl bromide. However, if the reaction mixture is allowed to stand for a long time, isobutyl bromide begins to form. Over a long period, the products equilibrate and, at equilibrium, the product distribution reflects the relative stabilities of the *products* rather than the stability of the transition states for formation of the intermediates.

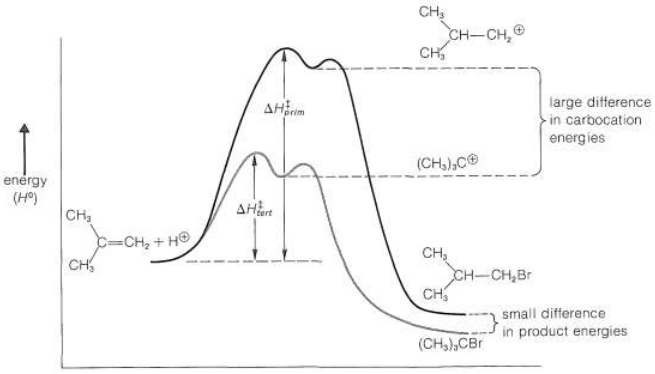


Figure 10-10: Energy diagram showing the progress of addition of hydrogen bromide to 2-methylpropene.

A rather simple rule, formulated in 1870 and known as **Markownikoff's rule**, correlates the direction of *kinetically controlled* additions of HX to unsymmetrical alkenes. This rule, an important early generalization of organic reactions, may be stated as follows: *In addition of* HX *to an unsymmetrical carbon-carbon double bond, the hydrogen of* HX *goes to that carbon of the double bond that carries the greater number of hydrogens*. It should be clear that Markownikoff's rule predicts that addition of hydrogen bromide to 2-methylpropene will give *tert*-butyl bromide.

10.5.2: Addition of Other Reagents to Unsymmetrical Alkenes. The Electronegativity Chart

We can extend Markownikoff's rule to cover additions of substances of the general type X–Y to unsymmetrically substituted alkenes when a clear-cut decision is possible as to whether X or Y is the more electrophilic atom of X–Y. If the polarization of the X–Y bond is such that X is positive, $^{\delta\oplus}$X–Y$^{\delta\ominus}$, then X will be expected to add as X$^{\oplus}$ to the alkene to form the more stable carbocation. This step will determine the direction of addition. For example, if we know that the O–Br bond of HOBr is polarized as $\overset{\delta\ominus}{\text{HO}} - \overset{\delta\oplus}{\text{Br}}$, then we can predict that addition of HOBr to 2-methylpropene will give 1-bromo-2-methyl-2-propanol:

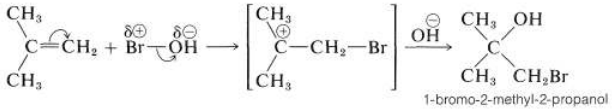


Figure 10-11), the elements of each horizontal row in the periodic table are arranged in order of increasing electronegativity from left to right. In a given horizontal row of the periodic table, electronegativity increases with increasing atomic number. However, electronegativity decreases with increasing atomic number in a given vertical column of the periodic table.

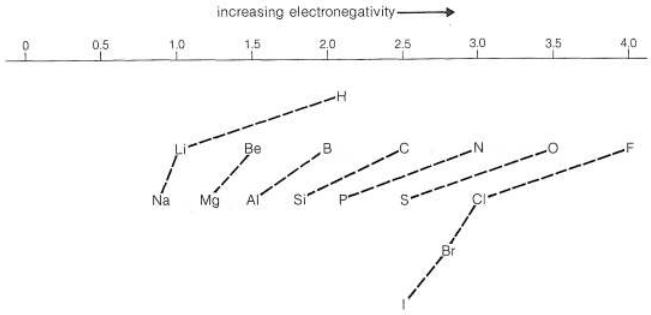


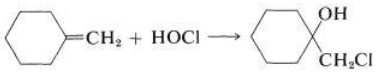
Figure 10-11: Pauling electronegativities of elements. The dashed lines connect elements in particular vertical columns of the periodic table.

Pauling's value for the electronegativity of carbon makes it slightly more electron-attracting than hydrogen. However, we expect that the electron-attracting power of a carbon atom (or of other elements) will depend also on the electronegativities of the groups to which it is attached. In fact, many experimental observations indicate that carbon in methyl or other alkyl groups is significantly *less* electron-attracting than hydrogen. Conversely, the CF_3- group is, as expected, far *more* electron-attracting than hydrogen.

The direction of polarization of bonds between various elements may be predicted from Figure 10-11. For example, an $O-Cl$ bond should be polarized so the oxygen is negative; a $C-N$ bond should be polarized so the nitrogen is negative:

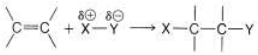
$$\overset{\delta\ominus}{O} - - - \overset{\delta\oplus}{Cl} \quad \overset{\delta\oplus}{C} - - - \overset{\delta\ominus}{N} \tag{10.5.2}$$

We then can predict that, in the addition of $HOCl$ to an alkene, the chlorine will add preferentially to form the more stable of two possible carbon cations. Generally, this means that chlorine will bond to the carbon carrying the greater number of hydrogens:



A number of reagents that are useful sources of electrophilic halogen are included in Table 10-2. Some of these reagents, notably those with $O-$halogen or $N-$halogen bonds, actually are sources of hypohalous acids, HOX, and function to introduce halogen and hydroxyl groups at carbon. There are very few good fluorinating agents whereby the fluorine is added as $F^{\oplus}$.

Table 10-2: *Reagents that add to Alkenes by Electrophilic Attack:*



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Reagent (X—Y)		Adduct	
Name	Structure	Name	Structure
sulfuric acid	H—OSO_3H	sulfate ester	H—C—C—OSO_3H
hydrogen fluoride[a]	H—F	fluoroalkane	H—C—C—F
hydrogen chloride	H—Cl	chloroalkane	H—C—C—Cl
hydrogen bromide	H—Br	bromoalkane	H—C—C—Br
water[b]	H—OH	alcohol	H—C—C—OH
alcohol[b]	H—OR	ether	H—C—C—OR
carboxylic acid[b]	H—OCR	carboxylic ester	H—C—C—OCR
trifluoromethyl hypofluorite	F—O—CF_3	2-fluoroalkyl trifluoromethyl ether	F—C—C—OCF_3
chlorine	Cl—Cl	dichloroalkane	Cl—C—C—Cl
hypochlorous acid	Cl—OH	chloroalcohol	Cl—C—C—OH
tert-butyl hypochlorite[c]	Cl—$OC(CH_3)_3$	chloroalcohol	Cl—C—C—OH
N-chlorosuccinimide[c]		chloroalcohol	Cl—C—C—OH
N-chlorosuccinimide and hydrogen fluoride[a]		chlorofluoroalkane	Cl—C—C—F
bromine	Br—Br	dibromoalkane	Br—C—C—Br
bromine chloride	Br—Cl	bromochloroalkane	Br—C—C—Cl
cyanogen bromide	Br—CN	bromonitrile	Br—C—C—CN
bromine azide	Br—N_3	bromoalkyl azide	Br—C—C—N_3
hypobromous acid	Br—OH	bromoalcohol	Br—C—C—OH
N-bromosuccinimide[c]		bromoalcohol	Br—C—C—OH
N-bromosuccinimide and hydrogen fluoride[a]		bromofluoroalkane	Br—C—C—F
iodine	I—I	diiodoalkane	I—C—C—I
iodine chloride	I—Cl	chloroiodoalkane	I—C—C—Cl
hypoiodous acid	I—OH	iodoalcohol	I—C—C—OH
N-iodosuccinimide and hydrogen fluoride[a]		iodofluoroalkane	I—C—C—F
sulfenyl chlorides	RS—Cl	chlorothioether	RS—C—C—Cl
nitrosyl chloride	O=N—Cl	chloronitrosoalkane	O=N—C—C—Cl
nitryl iodide	O_2N—I	nitroiodoalkane	O_2N—C—C—I
mercuric salts[d]	XHg—X	alkylmercuric compound	XHg—C—C—X
thallium salts	XTl—X	alkylthallium compound	XTl—C—C—X
alkanes[e]	R—H	alkane	R—C—C—H
boranes[f]	R_2B—H	trialkylborane	R_2B—C—C—H
peroxyacids[g]	HO—O—C—R	oxirane	

[a]A 70% solution of anhydrous hydrogen fluoride in pyridine (a rather weak nitrogen base).
[b]Weak acids require a strong acid catalyst to initiate electrophilic attack.
[c]In aqueous solution; serves as source of HOX, X = Br or Cl.
[d]See Section 10-5A. [e]See Section 10-9. [f]See Section 11-6. [g]See Section 11-7D.

10.5.3: Additions to Substituted Alkenes

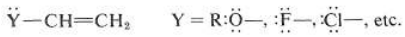
For alkenes that have halogen or similar substituents at the doubly bonded carbons, the same principles apply as with the simple alkenes. That is, under kinetic control the preferred product will be the one derived from the more stable of the two possible intermediate carbon cations. Consider a compound of the type $Y{-}CH{=}CH_2$. If Y is *more* electron-attracting than hydrogen, then hydrogen halide should add in such a way as to put the proton of HX on the YCH= end and X on the $=CH_2$ end. The reason is that the positive carbon is expected to be more favorably located if it is not attached directly to an electron-attracting substituent:

$$Y{-}CH{=}CH_2 + H^{\oplus} \rightleftharpoons Y{-}\underset{\text{Y is more electron-attracting than hydrogen}}{\overset{H}{\overset{|}{C}}H{-}\overset{\oplus}{C}H_2} \xrightarrow{X^{\ominus}} Y{-}CH_2{-}CH_2{-}X$$

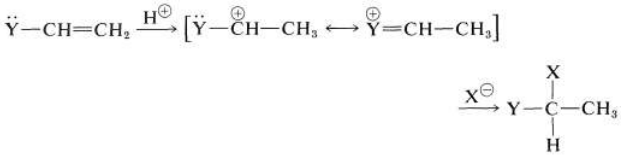
The addition goes as predicted, *provided that the atom directly attached to the carbon of the double bond carries no unshared (nonbonding) electron pairs*. For example,

$$CF_3{-}CH{=}CH_2 + HCl \rightarrow CF_3{-}CH_2{-}H_2{-}Cl \qquad (10.5.3)$$

Such substituents are relatively uncommon, and most of the reported H–X additions have been carried out with Y groups having unshared electron pairs on an atom connected directly to a carbon of the double bond:



These substituents usually are strongly electronegative relative to hydrogen, and this often causes diminished reactivity of the double bond toward electrophiles. Nonetheless, *the preferred orientation of* HX *additions situates the positive charge of the intermediate carbocation next to the substituent*:



The electron-attracting power of the substituent is more than counterbalanced by stabilization of the intermediate cation by the ability of the substituents to delocalize their *unshared* electrons to the adjacent positive carbon (see Section 6-6).

10.5.4: References

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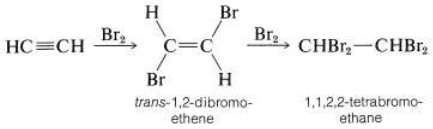
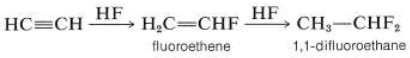
10.6: Electrophilic Addition Reactions of Alkynes

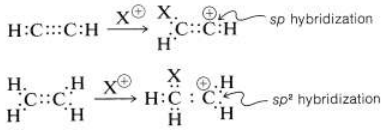
The alkynes behave in many ways as if they were doubly unsaturated alkenes. For example, bromine adds to ethyne in two stages - first to give *trans*-1,2-dibromoethene by antarafacial addition, and finally to give 1,1,2,2-tetrabromoethane:



Likewise, anhydrous hydrogen fluoride adds first to give fluoroethene and ultimately to give 1,1-difluoroethane:

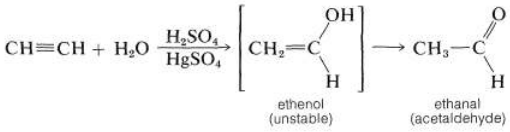


However, there is an interesting contrast in reactivity. Alkynes are substantially *less* reactive than corresponding alkenes toward many electrophiles. This is perhaps surprising because the electrons of a triple bond, like those of a double bond, are highly exposed, which suggests that the reactivity (nucleophilicity) of a triple bond should be high. Evidently this is not the case. A simple but reasonable explanation is that the carbocation formed from the alkyne is less stable than that from the alkene because it cannot achieve the sp^2 hybrid-orbital configuration expected to be the most stable arrangement for a carbocation (see Section 6-4E):

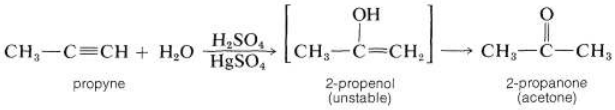


10.6.1: Hydration of Alkynes

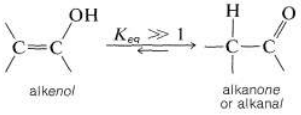
Alkynes, unlike alkenes, are not hydrated readily in aqueous acid unless a mercuric salt is present as a catalyst. Also, the products that are isolated are either aldehydes or ketones instead of alcohols. Even though the addition of one molecule of water to ethyne probably gives ethenol (vinyl alcohol) initially, this compound is unstable relative to its structural isomer (ethanal) and rapidly rearranges:



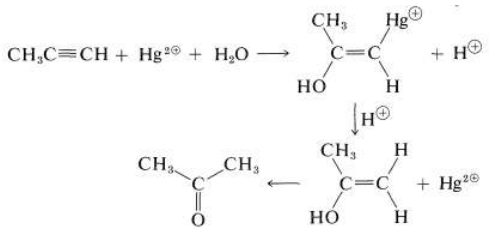
Similarly, addition of water to propyne leads to 2-propanone by way of its unstable isomer, 2-propenol:



In general, the position of equilibrium for interconversion of a carbonyl compound with the corresponding alkenol (or *enol*), having the hydroxyl group attached to the double bond, lies far on the side of the carbonyl compound:



Because mercuric salts catalyze the hydration of alkynes, they probably are acting as electrophiles. Mercuric salts are known to add to both alkenes and alkynes, and if the reaction mixture is acidic, the carbon-mercury bond is cleaved to form a carbon-hydrogen bond. The overall sequence in propyne hydration may be written as follows:



10.6.2: References

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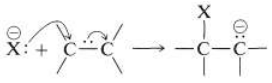
10.7: Nucleophilic Addition Reactions

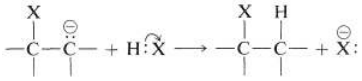
When a stepwise ionic addition reaction involves *nucleophilic* attack at carbon as a first step, it is described as a **nucleophilic addition**. Reactions of this type often are catalyzed by bases, which generate the required nucleophile. For example, consider the addition of some weakly acidic reagent HX to an alkene. In the presence of a strong base ($^{\ominus}$OH), HX could give up its proton to form the conjugate base $X^{\ominus}$, which is expected to be a much better nucleophile than HX:

$$H : X + {}^{\ominus} OH \rightleftharpoons H_2O + : X^{\ominus} \tag{10.7.1}$$

What can follow with an alkene is an *ionic chain reaction* with the following two propagating steps. First, the nucleophile attacks at carbon to form a carbon anion (carbanion) intermediate (Equation 10-8). Second, electrophilic transfer of a proton from HX to the carbanion forms the adduct and regenerates the nucleophile (Equation 10-9). The overall reaction is the addition of HX to the double bond:

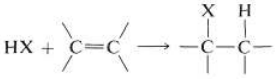


(10-8)

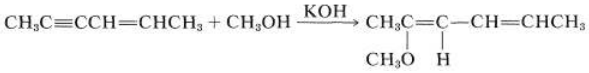


(10-9)

Net reaction:



The HX reagent can be water, an alcohol (ROH), a thiol (RSH), an amine (RNH_2), or hydrogen cyanide (HCN) or other carbon acids (i.e., compounds with acidic C–H bonds). However, nucleophilic addition of these reagents to simple alkenes *rarely* is encountered. To have nucleophilic addition the double bond must be substituted with strongly electron-withdrawing groups such as carbonyl-containing groups, NO_2, C ≡ N, or positively charged ammonium or sulfonium groups. However, alkynes generally are more reactive towards nucleophiles than they are toward electrophiles. For example, with a base catalyst, 2-hexen-4-yne adds methanol across the triple bond, leaving the double bond untouched:



(Nonetheless, the double bond seems to be necessary because a corresponding addition is not observed for 2-butyne, $CH_3C \equiv CCH_3$.)

Many nucleophilic addition reactions have considerable synthetic value, particularly those involving addition of carbon acids, such as HCN, because they provide ways of forming carbon-carbon bonds. More of their utility will be discussed in Chapters 14, 17, and 18.

10.7.1: References

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10.8: Radical-Chain Addition Reactions to Alkenes

The early literature concerning the addition of hydrogen bromide to unsymmetrical alkenes at best is confused. Sometimes the same alkene was reported to give addition both according to, and in opposition to, the principles discussed for electrophilic ionic addition (Section 10-4). Much of the uncertainty on the addition of hydrogen bromide was removed by the classical researches of M. S. Kharasch and F. R. Mayo (1933) who showed that there must be two reaction mechanisms, each giving a different product. Kharasch and Mayo found, in the presence of radical inhibitors, hydrogen bromide adds to propene in a rather slow reaction to give pure 2-bromopropane:

$$CH_3CH{=}CH_2 + HBr \xrightarrow[\text{radical inhibitors}]{\text{slow}} CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_3$$

With light, peroxides, radical initiators, and in the absence of radical inhibitors a rapid radical-chain addition of hydrogen bromide occurs to yield 80% or more of 1-bromopropane:

$$CH_3CH{=}CH_2 + HBr \xrightarrow[\text{peroxides}]{\text{fast}} CH_3CH_2CH_2Br$$

Similar effects have been noted occasionally with hydrogen chloride, but never with hydrogen iodide or hydrogen fluoride. A few substances apparently add to alkenes only by radical mechanisms, and always add in the opposite way to that expected for electrophilic ionic addition.

The ionic addition of hydrogen bromide was discussed in Section 10-4 and will not be considered further at this point. Two questions with regard to the so-called *abnormal addition* will be given special attention. Why does the radical mechanism give a product of different structure than the ionic addition? Why does the radical addition occur readily with hydrogen bromide but rarely with the other hydrogen halides?

The abnormal addition of hydrogen bromide is catalyzed strongly by peroxides, which have the structure R—O—O—R and decompose thermally to give RO· radicals (see Section 4-5B):

$$R{-}\ddot{\underset{\cdot\cdot}{O}}{:}\ddot{\underset{\cdot\cdot}{O}}{-}R \longrightarrow 2R{-}\ddot{\underset{\cdot\cdot}{O}}\cdot \qquad \Delta H^0 = +35 \text{ kcal}$$

The RO· radicals can react with hydrogen bromide in two ways, to abstract either hydrogen atoms or bromine atoms:

$$RO\cdot + HBr \begin{cases} \longrightarrow ROH + Br\cdot & \Delta H^0 = -23 \text{ kcal} \\ \longrightarrow ROBr + H\cdot & \Delta H^0 = +39 \text{ kcal} \end{cases}$$

Clearly, the formation of ROH and a bromine atom is energetically more favorable. The overall process of decomposition of peroxide and attack on hydrogen bromide, which results in the formation of a bromine atom, can initiate a radical-chain addition of hydrogen bromide to an alkene.

$$\text{chain propagation} \begin{cases} CH_3CH{=}CH_2 + Br\cdot \longrightarrow CH_3\dot{C}H{-}CH_2Br & \\ & \Delta H^0 = -5 \text{ kcal} \\ CH_3\dot{C}H{-}CH_2Br + HBr \longrightarrow CH_3CH_2CH_2Br + Br\cdot & \\ & \Delta H^0 = -11 \text{ kcal} \end{cases}$$

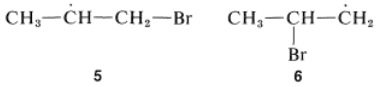
$$\text{chain termination: } R'\cdot + R'\cdot \longrightarrow R'{-}R' \qquad R'\cdot = \text{atom or radical}$$

The two chain-propagating steps, taken together, are exothermic by 16 kcal and have a fairly reasonable energy balance between the separate steps. The reaction chains apparently are rather long, because the addition is strongly inhibited by radical traps and only traces of peroxide catalyst are needed.

10.8.1: Orientation of Addition

The direction of addition of hydrogen bromide to propene clearly depends on which end of the double bond the bromine atom attacks. The important question is which of the two possible carbon radicals that may be formed is the more stable, the 1-bromo-2-

propyl radical, 5, or the 2-bromo-1-propyl radical, 6:



5 6

From C–H bond-dissociation energies of alkanes (see Table 5-6), the ease of formation and stabilities of the carbon radicals is seen to follow the sequence *tertiary* > *secondary* > *primary*. By analogy, the *secondary* 1-bromo-2-propyl radical, 5, is expected to be more stable and more easily formed than the *primary* 2-bromo-1-propyl radical, 6. The product of radical addition should be, and indeed is, 1-bromopropane:

Other reagents, such as the halogens, also can add to alkenes and alkynes by both radical-chain and ionic mechanisms. Radical addition usually is initiated by light, whereas ionic addition is favored by low temperatures and no light. Nevertheless, it often is difficult to keep both mechanisms from operating at the same time. This is important even when the alkene is symmetrical because, although the adduct will then have the same structural formula regardless of mechanism, the stereochemical configurations may differ. Electrophilic addition of halogens generally is a stereospecific antarafacial addition, but radical-chain additions are less stereospecific.

There are many reagents that add to alkenes only by radical-chain mechanisms. A number of these are listed in Table 10-3. They have in common a relatively weak bond, X–Y, that can be cleaved homolytically either by light or by chemical initiators such as peroxides. In the propagation steps, the radical that attacks the double bond does so to produce the more stable carbon radical. For addition to simple alkenes and alkynes, the more stable carbon radical is the one with the fewest hydrogens or the most alkyl groups at the radical center.

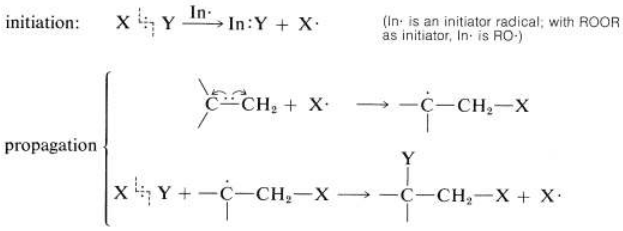
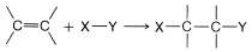
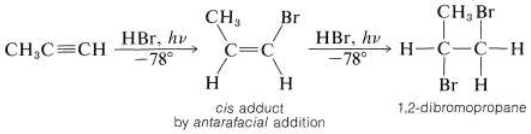


Table 10-3: *Reagents that add to Alkenes by Radical-Chain Mechanisms*



Reagent (X—Y)		Adduct	
Name	Structure	Name	Structure
hydrogen bromide	H—Br	bromoalkane	H—C—C—Br
bromine	Br—Br	dibromoalkane	Br—C—C—Br
polyhalomethanes	Cl—CCl_3	polyhaloalkanes	Cl—C—C—CCl_3
	Br—CCl_3		Br—C—C—CCl_3
	I—CF_3		I—C—C—CF_3
sulfonyl halides	Cl—SO_2R	halosulfones	Cl—C—C—SO_2R
alcohols			
methanol	H—CH_2OH	primary alcohol	H—C—C—CH_2OH
primary	H—CHROH	secondary alcohol	H—C—C—CHROH
secondary	H—CR_2OH	tertiary alcohol	H—C—C—CR_2OH
carboxylic acids	H—CR_2CO_2H	carboxylic acids	H—C—C—CR_2CO_2H
aldehydes	H—C(=O)R	ketones	H—C—C—C(=O)R
thiols	H—SR	thioethers	H—C—C—SR
amines	H—NR_2	alkylamines	H—C—C—NR_2
silanes	H—SiR_3	alkylsilanes	H—C—C—SiR_3
phosphines	H—PR_2	alkylphosphines	H—C—C—PR_2

The principles of radical addition reactions of alkenes appear to apply equally to alkynes, although there are fewer documented examples of radical additions to triple bonds. Two molecules of hydrogen bromide can add to propyne first to give *cis*-1-bromopropene (by antarafacial addition) and then 1,2-dibromopropane:



10.8.2: References

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10.9: Polymerization of Alkenes

One of the most important technical reactions of alkenes is their conversion to higher-molecular-weight compounds or **polymers** (Table 10-4). A polymer is defined as a *long-chain molecule with recurring structural units*. Thus polymerization of propene gives a long-chain hydrocarbon with recurring $-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-$ units:

$$n \times \underset{\text{propene (propylene)}}{CH_3CH{=}CH_2} \longrightarrow \underset{\text{polypropene (polypropylene)}}{\left[\begin{array}{c} CH_3 \\ | \\ CH-CH_2 \end{array}\right]_n} \qquad \Delta H^\circ = -n \times 20 \text{ kcal}$$

Table 10-4: *Alkene Monomers and Their Polymers*

Monomer	Formula	Type of addition polymerization	Polymer or Trade Name	Uses
ethene	$CH_2{=}CH_2$	radical (high pressure), coordination	polyethene	film, containers, piping
chloroethene (vinyl chloride)	$CH_2{=}CHCl$	radical	polyvinyl chloride (PVC)	film, insulation, piping, leatherette
fluoroethene	$CH_2{=}CHF$	radical	Tedlar	coatings
chlorotrifluoroethene	$CF_2{=}CFCl$	radical	Kel-F	gaskets, insulation
tetrafluoroethene	$CF_2{=}CF_2$	radical	Teflon	gaskets, valves, insulation, coatings
propene	$CH_3CH{=}CH_2$	coordination	polypropene, Herculon	fibers, molded articles
2-methylpropene	$(CH_3)_2C{=}CH_2$	cationic	Vistanex, Oppanol, butyl rubber	pressure-sensitive adhesives
styrene	$C_6H_5CH{=}CH_2$	radical	polystyrene	molded articles
propenenitrile (acrylonitrile)	$CH_2{=}CHCN$	radical	Orlon, Acrilan	acrylic fibers
methyl 2-methyl-propenoate (methyl methacrylate)	$CH_2{=}C(CH_3)CO_2CH_3$	radical anionic	Lucite, Plexiglas	coatings, molded articles

Most technically important polymerizations of alkenes occur by chain mechanisms and may be classed as anion, cation, or radical reactions, depending upon the character of the chain-carrying species. In each case, the key steps involve successive additions to molecules of the alkene, the differences being in the number of electrons that are supplied by the attacking agent for formation of the new carbon-carbon bond. For simplicity, these steps will be illustrated by using ethene, even though it does not polymerize very easily by any of them:

$$R{-}CH_2{-}\overset{\ominus}{C}H_2{:} + CH_2{=}CH_2 \longrightarrow R{-}CH_2{-}CH_2{-}CH_2{-}\overset{\ominus}{C}H_2{:}, \text{ etc.}$$

$$R{-}CH_2{-}\overset{\oplus}{C}H_2 + CH_2{=}CH_2 \longrightarrow R{-}CH_2{-}CH_2{-}CH_2{-}\overset{\oplus}{C}H_2, \text{ etc.}$$

$$R{-}CH_2{-}CH_2{\cdot} + CH_2{=}CH_2 \longrightarrow R{-}CH_2{-}CH_2{-}CH_2{-}CH_2{\cdot}, \text{ etc.}$$

10.9.1: Anionic Polymerization

Initiation of alkene polymerization by the anion-chain mechanism may be formulated as involving an attack by a nucleophilic reagent $Y^\ominus$ on one end of the double bond and formation of a carbanion:

$$\overset{\ominus}{Y}{:} + CH_2{=}CH_2 \longrightarrow \underset{\text{carbanion}}{Y{:}CH_2{-}\overset{\ominus}{C}H_2{:}}$$

Attack by the carbanion on another alkene molecule would give a four-carbon carbanion, and subsequent additions to further alkene molecules would lead to a high-molecular-weight anion:

$$Y{:}CH{-}\overset{\ominus}{C}H_2{:} + CH_2{=}CH_2 \longrightarrow Y{:}CH_2{-}CH_2{-}CH_2{-}\overset{\ominus}{C}H_2{:}$$

$$\xrightarrow{n \times CH_2{=}CH_2} Y{:}CH_2{-}CH_2{+}CH_2{-}CH_2{\rightarrow}_n CH_2{-}\overset{\ominus}{C}H_2{:}$$

The growing chain can be terminated by any reaction (such as the addition of a proton) that would destroy the carbanion on the end of the chain:

$$\mathrm{Y{:}CH_2{-}CH_2{-}(CH_2{-}CH_2)_n CH_2{-}\overset{\ominus}{C}H_2{:}} \xrightarrow{H^{\oplus}} \mathrm{Y{:}CH_2{-}CH_2{-}(CH_2{-}CH_2)_n CH_2{-}CH_2{-}H}$$

Anionic polymerization of alkenes is quite difficult to achieve because few anions (or nucleophiles) are able to add readily to alkene double bonds (see Section 10-6). Anionic polymerization occurs readily only with alkenes substituted with sufficiently powerful electron-attracting groups to expedite nucleophilic attack. By this reasoning, alkynes should polymerize more readily than alkenes under anionic conditions, but there appear to be no technically important alkyne polymerizations in operation by this or any other mechanism. Perhaps this is because the resultant polymer would be highly conjugated, and therefore highly reactive, and may not survive the experimental conditions:

$$n \times \underset{\text{ethyne}}{\mathrm{HC{\equiv}CH}} \longrightarrow \underset{\text{polyethyne (expected to be unstable)}}{\mathrm{YHC{=}CH{-}(CH{=}CH)_n CH{=}CH_2}}$$

10.9.2: Cationic Polymerization

Polymerization of an alkene by acidic reagents can be formulated by a mechanism similar to the addition of hydrogen halides to alkene linkages. First, a proton from a suitable acid adds to an alkene to yield a carbocation. Then, in the absence of any other reasonably strong nucleophilic reagent, another alkene molecule donates an electron pair and forms a longer-chain cation. Continuation of this process can lead to a high-molecular-weight cation. Termination can occur by loss of a proton. The following equations represent the overall reaction sequence:

$$\mathrm{H^{\oplus} + CH_2{=}CH_2 \rightleftharpoons CH_3{-}\overset{\oplus}{C}H_2 \xrightarrow{CH_2=CH_2} CH_3{-}CH_2{-}CH_2{-}\overset{\oplus}{C}H_2}$$

$$\xrightarrow{n \times CH_2=CH_2} \mathrm{CH_3{-}CH_2{-}(CH_2{-}CH_2)_n CH_2{-}\overset{\oplus}{C}H_2}$$

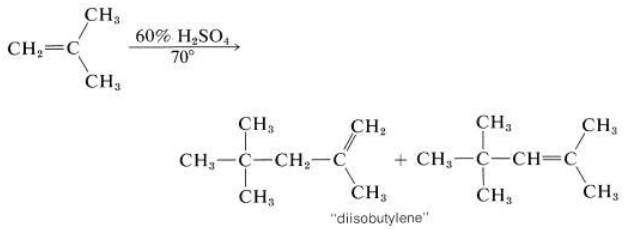
$$\xrightarrow{-H^{\oplus}} \mathrm{CH_3{-}CH_2{-}(CH_2{-}CH_2)_n CH{=}CH_2}$$

Ethene does not polymerize by the cationic mechanism because it does not have sufficiently electron-donating groups to permit easy formation of the intermediate growing-chain cation. 2-Methylpropene has electron-donating alkyl groups and polymerizes much more easily than ethene by this type of mechanism. The usual catalysts for cationic polymerization of 2-methylpropene are sulfuric acid, hydrogen fluoride, or a complex of boron trifluoride and water. Under nearly anhydrous conditions a very long chain polymer called polyisobutylene is formed.

$$n \times \underset{\substack{\text{2-methylpropene}\\ \text{(isobutylene)}}}{\mathrm{CH_2{=}C(CH_3)_2}} \xrightarrow{BF_3 \cdot H_2O} \underset{\substack{\text{poly-2-methylpropene}\\ \text{(polyisobutylene)}}}{\mathrm{CH_3{-}C(CH_3)_2{-}(CH_2{-}C(CH_3)_2)_{n-2}{-}CH_2{-}C(CH_3){=}CH_2}}$$

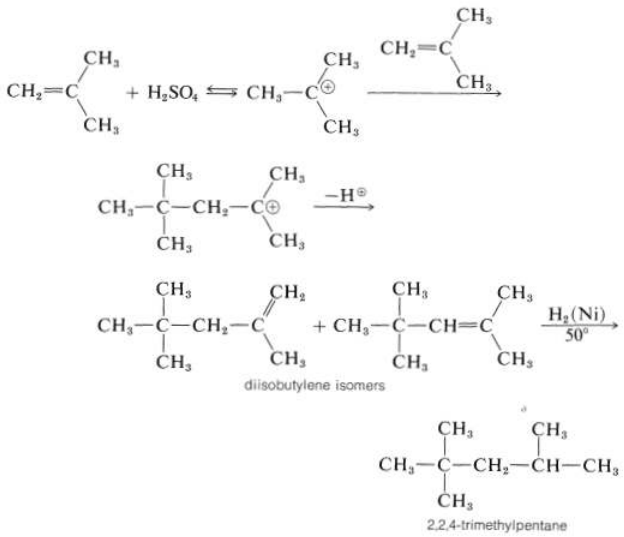
Polyisobutylene fractions of particular molecular weights are very tacky and are used as adhesives for pressure-sealing tapes.

In the presence of 60% sulfuric acid, 2-methylpropene is *not* converted to a long-chain polymer, but to a mixture of eight-carbon alkenes. The mechanism is like that of the polymerization of 2-methylpropene under nearly anhydrous conditions, except that chain termination occurs after only one 2-methylpropene molecule has been added:



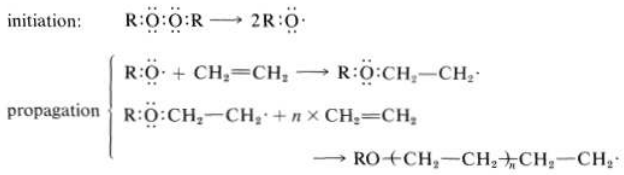
The short chain length is due to the *high water concentration*; the intermediate carbocation loses a proton to water *before* it can react with another alkene molecule.

The proton can be lost in two different ways, and a mixture of alkene isomers is obtained. The alkene mixture is known as "diisobutylene" and has a number of commercial uses. Hydrogenation yields 2,2,4-trimethylpentane (often erroneously called "isooctane"), which is used as the standard "100 antiknock rating" fuel for internal-combustion gasoline engines:

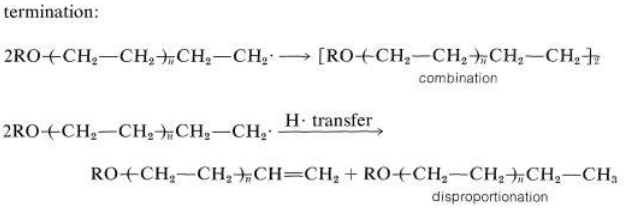


10.9.3: Radical Polymerization

Ethene can be polymerized with peroxide catalysts under high pressure ($1000\ \text{atm}$ or more, literally in a cannon barrel) at temperatures in excess of $100°$. The initiation step involves formation of radicals, and chain propagation entails stepwise addition of radicals to ethene molecules.



Chain termination can occur by any reaction resulting in combination or disproportionation of free radicals.



The polyethene produced in this way has from 100 to 1000 ethene units in the hydrocarbon chain. The polymer possesses a number of desirable properties as a plastic and is used widely for electrical insulation, packaging films, piping, and a variety of molded

articles. Propene and 2-methylpropene do not polymerize satisfactorily by radical mechanisms.

10.9.4: Coordination Polymerization

A relatively low-pressure, low-temperature ethene polymerization has been achieved with an aluminum-molybdenum oxide catalyst, which requires occasional activation with hydrogen (Phillips Petroleum process). Ethene also polymerizes quite rapidly at atmospheric pressure and room temperature in an alkane solvent containing a suspension of the insoluble reaction product from triethylaluminum and titanium tetrachloride (Ziegler process). Both the Phillips and Ziegler processes produce very high-molecular-weight polyethene with exceptional physical properties. The unusual characteristics of these reactions indicate that no simple anion, cation, or radical mechanism can be involved. It is believed that the catalysts act by coordinating with the alkene molecules in somewhat the same way that hydrogenation catalysts combine with alkenes (Section 11-2A).

Polymerization of propene by the Ziegler process gives a very useful plastic material. It can be made into durable fibers or molded into a variety of shapes. Copolymers (polymers with more than one kind of monomer unit in the polymer chains) of ethene and propene made by the Ziegler process have highly desirable rubberlike properties and are potentially the cheapest useful elastomers (elastic polymers). A Nobel Prize was shared in 1963 by K. Ziegler and G. Natta for their work on alkene polymerization.

The properties and uses of polymers are discussed in greater detail in Chapters 13 and 29. The most important alkene monomers used in addition polymerizations are listed in Table 10-4 along with some names and uses of the corresponding polymers.

10.9.5: References

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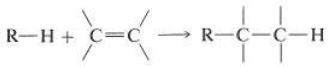
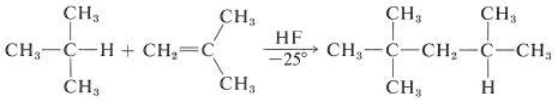
10.10: Alkylation of Alkenes

Addition of a saturated hydrocarbon (R–H) to an alkene to yield a saturated hydrocarbon of higher molecular weight is known as **alkylation**:

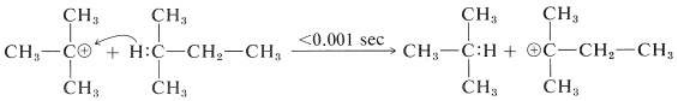


Such reactions are used by the petroleum industry to produce medium-molecular-weight hydrocarbons from smaller molecules. A particularly important example is afforded by the addition of 2-methylpropane to 2-methylpropene in the presence of sulfuric acid or anhydrous hydrogen fluoride to yield 2,2,4-trimethylpentane:

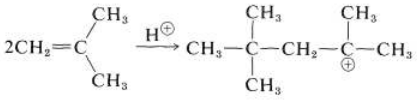


The overall reaction appears to be different from any so far discussed, because it involves addition of a nonpolar reagent (RH) to an alkene bond.

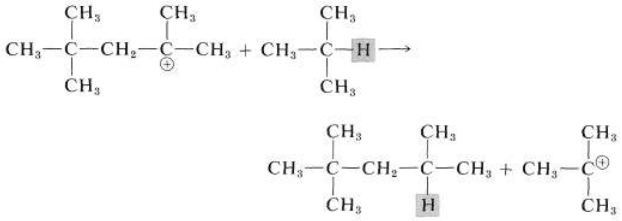
The key to the mechanism of hydrocarbon alkylation was provided by the discovery by P. D. Bartlett, in 1940, that a carbocation can react rapidly with a hydrocarbon having a tertiary hydrogen to yield a new carbocation and a new hydrocarbon. Some of these "hydrogen-transfer" reactions are extraordinarily fast and may be complete in seconds or less. The hydrogen is transferred with *both* bonding electrons ($H^{\ominus}$). For example,



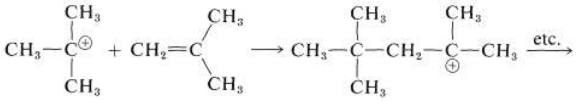
With the knowledge that the hydrogen transfer is fast, the alkylation of 2-methylpropene with 2-methylpropane can be formulated as involving first polymerization of two 2-methylpropene molecules under the influence of the sulfuric acid catalyst to give the same octyl cation as was postulated for the dimerization of 2-methylpropene:



The octyl cation then can undergo a hydrogen-transfer reaction with 2-methylpropane to furnish 2,2,4-trimethylpentane and a *tert*-butyl cation:



Attack by the *tert*-butyl cation on another molecule of 2-methylpropene produces an eight-carbon tertiary cation, which them proceeds to another molecule of "alkylate":



This is an important example of a *cationic chain* reaction.

10.10.1: References

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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10.E: Alkenes and Alkynes I (Exercises)

Exercise 10-1 Deduce possible structures of the substances whose infrared spectra are shown in Figure 10-2. Assign as many of the bands as you can to *specific* stretching and bending vibrations by comparison with Figure 10-1. Be sure your structural assignments fit with the spectrum - that is, think twice about assigning a structure than has $-CH_2-$ groups if there are no $-CH_2-$ bands in the spectrum, or that has no $-CH_3$ groups when there appear to be strong $-CH_3$ absorptions.

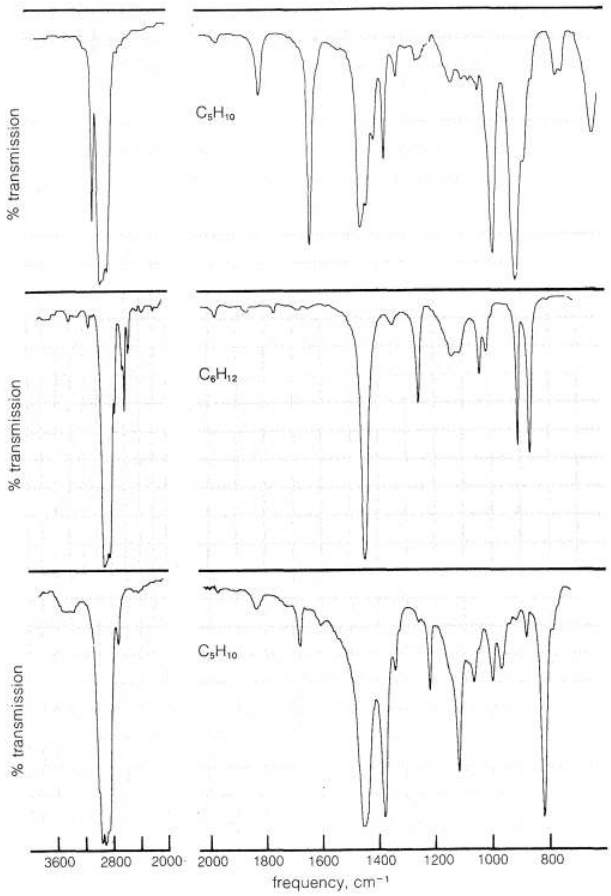


Figure 10-2: *Infrared spectra for Exercise 10-1.*

Exercise 10-2 Deduce the structures of the substances whose proton nmr spectra are shown in Figure 10-3. Analyze the spectra in as much detail as you can in terms of chemical shifts and spin-spin splitting.

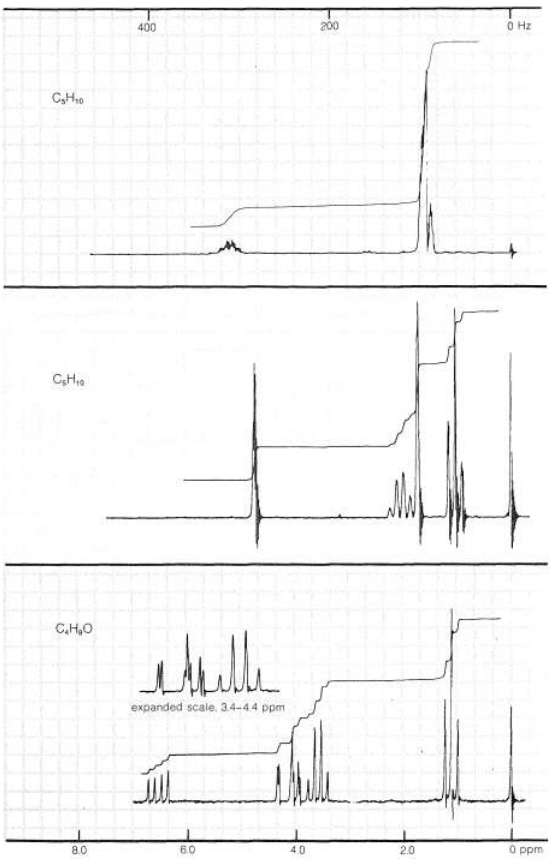


Figure 10-3: *Proton nmr spectra at* 60 MHz *with TMS as the standard at* 0 ppm. *See Exercise 10-2.*

Exercise 10-3 Sketch the principal features you would expect for the infrared and proton nmr spectra of each of the following substances. (It will be helpful to review Sections 9-7 and 9-10.)

a. $CH_3C \equiv CCH_3$
b. $CH_3C \equiv CH$ (expect a four-bond coupling of about 3 Hz)
c. $CH_3CH_2C \equiv CCH_2CH_3$
d. $HC \equiv C{-}CH{=}C{-}C \equiv CH$ (cis and trans)

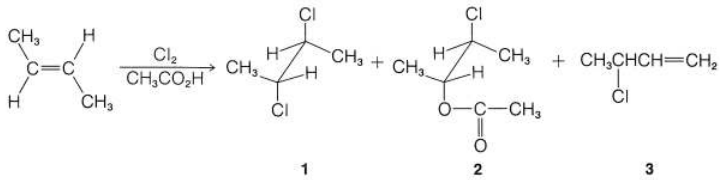
Exercise 10-4 Deduce the structure of a compound with the following spectral properties:

Mass spectrum	Infrared	Nmr
m/e 82 (highest mass number)	3320 cm^{-1} (s)	δ 0.93, area 3, triplet
m/e 39 (base peak)	2950 cm^{-1} (s)	1.18–1.65, 4, complex
	2120 cm^{-1} (m)	1.73, 1, closely spaced triplet
	1460 cm^{-1} (s)	
	1375 cm^{-1} (w)	2.16, 2, complex
	640 cm^{-1} (s)	

No electronic absorption was evident at wavelengths longer than 200 nm.

Exercise 10-5 Use the bond energies (Table 4-3) to calculate ΔH^0 for the addition of Br_2, Cl_2, I_2, HOCl, HCl, HBr, HI, and H_2O to ethene in the gas phase. The addition of HCl, HBr, and HI is energetically unfavorable in dilute water solution. Why should this be so?

Exercise 10-6 Addition of chlorine to *trans*-2-butene in ethanoic acid (acetic acid, CH_3CO_2H as solvent gives 74% *meso*-2,3-dichlorobutane, 1, 24% 2-chloro-1-methylpropyl ethanoate, 2, and 2% 3-chloro-1-butene, 3. (*Note:* 2 is formed as a *D*,*L* pair, although only one enantiomer is shown here.)



Write a mechanism to show how all three products could be obtained from a common chloronium ion intermediate. Draw structures for the products expected from addition of chlorine to *cis*-2-butene in ethanoic acid. Show the configurations. If necessary, review Section 5-5 before working this problem.

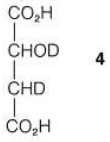
Exercise 10-7 In the formation of ethenebromonium ion from 1-bromo-2-fluoroethane and SbF_5 is SO_2, is the SbF_5 playing the role of an acid, a base, an electrophile, or a nucleophile? How strong a nucleophile do you judge SbF_6^- to be? Explain.

Exercise 10-8 Show the steps involved in the formation of ethyl hydrogen sulfate from ethene and sulfuric acid. Show how diethyl sulfate, $(CH_3CH_2O)_2SO_2$, could be formed from the same reagents.

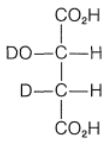
Exercise 10-9* Suppose we were gradually to add water to a solution of $C_3H_2^+-SbF_6^-$ and excess $HSbF_6$ in SO_2. What changes would you expect to take place? Write equations for the reactions you expect to occur.

Exercise 10-10* Assess the possibility of adding ammonia, NH_3, to 2-methylpropene with the aid of sulfuric acid as a catalyst.

Exercise 10-11* Show by projection formulas the stereochemical course you would expect for the *acid-catalyzed* addition of D_2O to fumaric acid to give the deuterated malic acid 4. Be sure you consider the stereochemistry of the $C-D$ bond relative to the $C-O$ bond. Indicate your reasoning.



Exercise 10-12* The hydration of fumaric acid catalyzed by *fumarase* in D_2O leads to malic acid with only *one* $C-D$ bonds, which is selectively removed when malic acid is enzymatically reconverted to fumaric acid. The configuration of deuteriomalic acid prepared in this way has been shown to correspond to the following projection formula:



Deduce the stereochemistry of both the forward and backward reactions (hydration and dehydration) from this information.

Exercise 10-13 Explain how Markownikoff's rule for orientation in electrophilic additions can be accounted for in terms of the modern view of how these reactions occur, using the reaction of HCl with 1-methylcyclohexene as an example.

Exercise 10-14 Predict the major product(s) of each of the following electrophilic addition reactions (under conditions of kinetic control):

a. 1-butene with concentrated H_2SO_4
b. 2-methylpropene in 10% aqueous H_2SO_4
c. 2-methyl-2-butene with Br_2 in methanol as solvent.

Exercise 10-15 Arrange ethene, propene, and 2-methylpropene in order of expected ease of hydration with aqueous acid. Show your reasoning.

Exercise 10-16 Use the electronegativity chart of Figure 10-11 and Table 10-2 to predict the products of the following additions under conditions of kinetic control. Indicate the configuration of the products where possible.

a. 2-methyl-2-butene with ICl, and with INO_2
b. a carbon-nitrogen double bond with water

c. N-bromosuccinimide and cyclohexene in aqueous medium

d. 2-methylpropene with HOF

e. 2-methylpropene with N-bromosuccinimide and 70% hydrogen fluoride in pyridine (Notice that the pyridine serves only to moderate the activity of the hydrogen fluoride.)

Exercise 10-17 Make atomic-orbital models of the 1- and 2-fluoroethyl carbocations (CH_3CHF^+ and $FCH_2CH_2^+$). Predict which should be formed more rapidly by the addition of H^+ to fluoroethene. Give your reasoning.

Exercise 10-18 Predict the predominant product from addition of hydrogen chloride to each of the following alkenes. Give your reasoning.

a. $CH_2{=}CCl_2$

b. $(CH_3)_2C{=}CCl_2$

c. $CF_3{-}CH{=}CH{-}CH_3$

d. $CH_3OCH{=}CHF$

Exercise 10-19 The ethenyl carbocation, $CH_2{-}CH^{\oplus}$, apparently is formed much more easily by addition of a proton from HCl to ethyne than it is by S_N1 reactions of ethenyl chloride. Deduce from bond energies why this should be so.

Exercise 10-20 Show how the rearrangement of ethenol to ethanal could take place in aqueous solution with water behaving as both a proton acceptor (base) and a proton donor (acid).

Exercise 10-21 Predict the predominant products in each of the following reactions. Show the expected configurations of the intermediates and products.

a. 2-butyne with mercuric ethanoate, $Hg(OCOCH_3)_2$, in ethanoic acid

b. ethenylbenzene with aqueous sulfuric acid containing mercuric sulfate, $HgSO_4$

c. ethyne with mercuric chloride in methanol

(*Note:* A mercuric salt of structure HgX_2 is a potential source of an electrophile, $HgX^{\oplus}$. Mercuric sulfate probably is a source of the electrophilic cation, $HgOSO_3H^{\oplus}$, in aqueous sulfuric acid.)

Exercise 10-22 Show the steps involved in the base-initiated addition of methanol to 2-hexen-4-yne (review Section 6-6).

Exercise 10-23 Sodium chloride in the presence of $OH^{\ominus}$ with 2-hexen-4-yne does not yield $CH_3CCl{=}CH{-}CH{=}CHCH_3$. Explain.

Exercise 10-24 Write two different radical mechanisms for peroxide-initiated addition of hydrogen chloride to alkenes and consider the energetic feasibility for each.

Exercise 10-25 Calculate the ΔH^0 values for initiation and chain-propagation steps of radical addition of hydrogen fluoride, hydrogen chloride, and hydrogen iodide to an alkene. Would you expect these reagents to add easily to double bonds by such a mechanism?

Exercise 10-26

a. Bromine adds to diethyl fumarate (diethyl *trans*-butenedioate) to give the meso adduct 7, and to diethyl maleate (diethyl *cis*-butenedioate) to give the *D*,*L* adduct 8, provided that the reaction mixtures are kept at 25° or less and are carefully protected from light. Deduce whether the stereochemistry of the reaction is suprafacial or antarafacial under these conditions.

$$C_2H_5O_2C{-}CH{=}CH{-}CO_2C_2H_5 \xrightarrow{Br_2} C_2H_5O_2CCHBr{-}CHBrCO_2C_2H_5$$

diethyl fumarate (trans) ⟶ meso adduct **7**

diethyl maleate (cis) ⟶ D,L adduct **8**

b.* Diethyl maleate rearranges rapidly to diethyl fumarate on irradiation with ultraviolet light, provided that a trace of bromine is present. Irradiation of *equimolar* amounts of bromine and diethyl maleate leads to a mixture of *D*,*L* and meso adducts. Under these conditions the fumarate ester gives only the meso adduct. Show the steps involved in these transformations and explain clearly why the light-induced addition to the cis ester is not stereospecific.

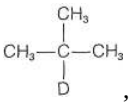
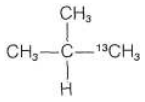
Exercise 10-27 A radical of structure $CH_3\dot{C}{=}CHBr$ is involved in the light-induced addition of HBr to propyne. What geometry would you expect it to have? Draw an atomic-orbital picture of the radical with particular attention to the hybridization of orbitals

at the radical center.

Exercise 10-28 Bromotrichloromethane, $BrCCl_3$, adds to 1-octene by a radical-chain mechanism on heating in the presence of a peroxide catalyst. Use the bond-energy tables to devise a feasible mechanism for this reaction and work out the most likely structure for the product. Show your reasoning. Show the most likely product of addition of $BrCCl_3$ to 1-octyne. [*Note:* Radical-chain reactions involve abstraction of atoms, not abstraction of groups.]

Exercise 10-29 Propenenitrile (acrylonitrile, $CH_2{=}CHCN$) will polymerize readily at -50° in a polar solvent [e.g., dimethylmethanamide, $HCON(CH_3)_2$] under the influence of sodium cyanide, $NaCN$. Show the initiation and propagation steps of this reaction, and predict the structure of the polymer. Why is a polar solvent necessary? Why does this polymerization proceed but not that of propene under the same conditions?

Exercise 10-30 Write a reasonable mechanism for termination of ethene polymerization by disproportionation. Calculate ΔH^0 values for termination of the chain reaction by combination and disproportionation. Which is the more favorable process?

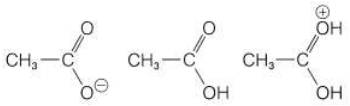
Exercise 10-31 It has been reported that a mixture of 2-methylpropane-2-D,  , and 2-methylpropane-1-^{13}C,  , (^{13}C is the stable carbon isotope of mass 13) is converted only very slowly by sulfuric acid to a mixture containing the two starting materials, ordinary 2-methylpropane and 2-methylpropane-1-^{13}C-2-D.

The reaction is speeded up greatly by addition of small amounts of 2-methylpropene. Explain. Would you expect any significant formation of D_2SO_4 when the reaction is carried out in the presence of 2-methylpropene? Why?

Exercise 10-32 For each of the following groups of substances designate which is the strongest electrophile and which is the strongest nucleophile. Give your reasoning.

a. H_2O $H_3O^{\oplus}$ $HO^{\ominus}$

b. I_2 $I^{\ominus}$ $H_2\overset{\oplus}{O}I$

c. 

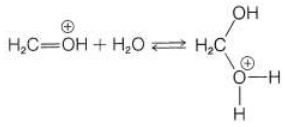
d. $CH_3\ddot{N}H_2$ $CH_3\ddot{N}H^{\ominus}$ $CH_3\overset{\oplus}{N}H_3$

e. $HO{-}NO_2$ $H_2\overset{\oplus}{O}{-}NO_2$ $^{\oplus}NO_2$ $^{\ominus}O{-}NO_2$

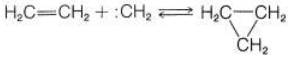
f. HF $HF + SbF_5$ $SbF_6{}^-$ F^-

g. FSO_3H $ClSO_3H$ $HOSO_3{}^-$

Exercise 10-33 Identify the nucleophile and the electrophile in each of the following reactions:

a. 

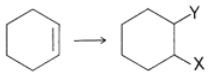
b. $H_2C{=}CH_2 + Br_2 \rightleftharpoons H_2C(Br)\overset{\oplus}{C}H_2 + Br^{\ominus}$

c. 

d. $CH_2{=}CHCN + NH_2{}^- \rightleftharpoons NH_2{-}CH_2 - \overset{\ominus}{C}HCN$

Exercise 10-34 Indicate what reagents and conditions would convert cyclohexane to the following derivatives:

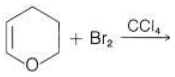
	X	Y
a.	Cl	H
b.	OH	H
c.	Cl	OH
d.	$-OCCH_3$ (O)	H
e.	F	Br



Exercise 10-35 Use the electronegativity chart (Figure 10-11) to predict how the indicated bond would be expected to be polarized for each of the following compounds:

a. H_3C-H
b. H_3Si-H
c. CH_3-Li
d. CH_3-MgCH_3
e. CH_3S-Cl
f. H_2N-SCH_3
g. H_2N-OH
h. H_2N-Br
i. H_2P-Cl
j. $(CH_3)_3Si-Cl$

Exercise 10-36 Draw structures for the major products of each of the following reactions. Indicate the stereochemistry of the product, where possible (D is deuterium, the hydrogen isotope of mass 2.)

a. 

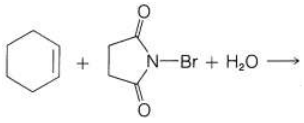
b. $CH_3CH{=}CH_2 + HF \rightarrow$

c. *cis*-1-phenylpropene $+DBr \xrightarrow{CH_2Cl_2}$

d. $C_6H_5C \equiv CCH_3 + HCl + CH_3COOH$ (solvent) $\rightarrow$

e. $CH_3C \equiv CH \xrightarrow{1.\ HgCl_2} \xrightarrow{2.\ DCl}$

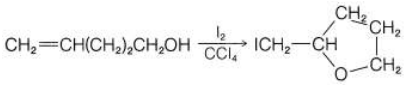
f. $C_6H_5CH{=}CH_2 + CH_3SCl \rightarrow$

g. 

Exercise 10-37 Why is molecular fluorine generally unsatisfactory as a reagent to convert alkenes to 1,2-difluoroalkanes?

Exercise 10-38 Why does the addition of chlorine to 2-pentene in methanol give a mixture of the following products?
2,3-dichloropentane (16%)
2-chloro-3-methoxypentane (35%)
3-chloro-2-methoxypetane (49%)

Exercise 10-39 Suggest a mechanism to account for the following reaction:



Exercise 10-40 In Section 1-1I, the addition of bromine to tetrachloroethene was reported to be catalyzed by aluminum bromide. What is the function of aluminum bromide in this addition?

Exercise 10-41 Evaluate (show your reasoning) the possibility that the following reaction will give the indicated product.

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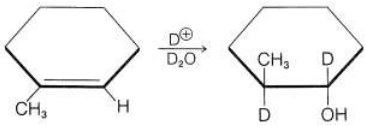


If you do not think the indicated product would be important, write the structure(s) of the product(s) you think would be more likely to be found.

Exercise 10-42 2-Methylpropene reacts with ethene and hydrogen chloride under polar conditions to yield 1-chloro-3,3-dimethylbutane. Show a mechanism for this reaction that is consistent with the reactants, conditions, and product. Give your reasoning.

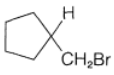
Exercise 10-43 2-Methylpropane (containing traces of 2-methylpropene) is converted by a *large* excess of deuteriosulfuric acid (D_2SO_4) rather rapidly to 2-methylpropane with only nine deuteriums.

a. Write a polar mechanism for this hydrogen-exchange reaction that is in harmony with the known chemical properties of sulfuric acid and that predicts exchange of no more than nine of the ten hydrogens of 2-methylpropane.

b. Explain how 2-methylpropane-D_9 can be formed more rapidly than 2-methylpropane-D_n with $n < 9$ in the early stages of the reaction.

Exercise 10-44 Suggest how each of the following compounds may be prepared. Assume any necessary starting hydrocarbons are available. Specify the reaction conditions as closely as possible and indicate when isomer separations may be necessary.

a.

b. 

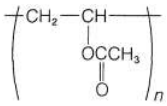
c. 1,1,1-trichloro-3-bromohexane

d. $C_6H_5COCH_2CH_3$

e. $C_6H_5CH(OH)CH_3$

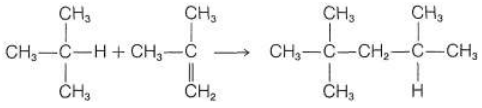
f. $Cl_2CHCHCl_2$

g. $CH_2{=}CHOCOCH_3$ (ethenyl ethanoate)

h. 

Exercise 10-45 Calculate ΔH^0 values for the following reactions in the gas phase per mole of the principal reactants, using the bond-energy table (Table 4-3).

a. $n \times CH_2{=}CH_2 \rightarrow -(CH_2{-}CH_2)_n-$

b. 

Exercise 10-46 Use bond energies (Table 4-3) to investigate the possibility of adding water to propene, using peroxide (ROOR) catalysts. It has been reported that γ rays, such as from a cobalt-60 source, decompose water into H· and HO·. Could such radiation initiate a *chain*-addition reaction of water to propene? How about a nonchain mechanism (i.e., one γ-ray photon per molecule of reacting propene)? In a nonchain mechanism, would you expect to get 1-propanol or 2-propanol? What other products may be obtained in a nonchain reaction? Give your reasoning in detail.

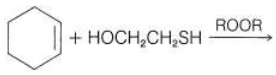
Exercise 10-47 Use bond energies (Table 4-3) to investigate the energetic feasibility of adding ammonia (NH_3) to an alkene by a radical-chain mechanism with the aid of a peroxide (ROOR) catalyst. What product would you expect to obtain from propene and

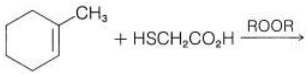
ammonia by a radical mechanism of addition?

Exercise 10-48 Draw an energy diagram similar to Figure 10-10 for the progress of a two-step reaction $\mathrm{A + BC \rightleftharpoons A{-}B{-}C \overset{D}{\longrightarrow} A{-}B + C{-}D}$ in which the first step is a rapidly established equilibrium and the second step is the slow or rate-determining step. Label the diagram to show what part represents the transition state, reaction intermediate, overall energy of activation $(\Delta H')$, and overall standard enthalpy change (ΔH^0) for the process $\mathrm{A + BC + D \rightarrow AB + CD}$. Assume that the overall equilibrium constant, $K_{eq} > 1$.

Exercise 10-49 Complete the following equations showing the structures of the expected products under the reaction conditions:

a. $\mathrm{CH_2{=}CHCN + (C_2H_5)_3SiH \overset{ROOR}{\longrightarrow}}$

b. 

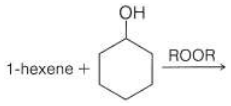
c. 

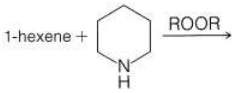
d. 1-octene $\mathrm{+ Cl_3SiH \overset{ROOR}{\longrightarrow}}$

e. $\mathrm{(CH_3)_2C{=}CH_2 + CCl_4 \overset{ROOR}{\longrightarrow}}$

f. $\mathrm{HC \equiv CCH_2OCOCH_3 + BrCCl_3 \overset{ROOR}{\longrightarrow}}$

g. $\mathrm{CH_3C \equiv CH + CF_3I \overset{h\nu}{\longrightarrow}}$

h. 

i. 

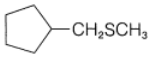
j. 1-hexene + $\mathrm{CH_3CO_2H \overset{ROOR}{\longrightarrow}}$

Exercise 10-50 This problem illustrates one of the complications that can arise in radical-addition reactions.

Cyclohexene reacts with bromotrichloromethane at 40° in the presence of small quantities of peroxides to give a mixture of products: 2-bromo-1-trichloromethylcyclohexane (67%) and 3-bromocyclohexene (33%). Account for the formation of both of these products under the reaction conditions.

Exercise 10-51 Describe how you would prepare each of the following compounds from the indicated starting materials. Specify the reagents and reaction conditions as closely as possible.

a. $\mathrm{HO_2CCH_2CH_2CH_2CH_2CO_2H}$ (hexanedioic acid) from $\mathrm{CH_3CO_2H}$ (ethanoic acid) and $\mathrm{HC \equiv CH}$ (ethyne) by a radical-chain addition

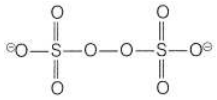
b. 

from methylenecyclopentane

c. $\mathrm{CH_3(CH_2)_7COCH_3}$ (2-decanone) from 1-octene

d. 2-decanone from 1-decyne

Exercise 10-52* The molecular weight of a polymer obtained by radical-addition polymerization can be reduced by addition of a thiol, RSH. For example, when propenoic acid (acrylic acid) is polymerized in the presence of potassium peroxodisulfate, $\mathrm{K_2S_2O_8}$, adding mercaptoethanoic acid, $\mathrm{HSCH_2CO_2H}$, causes the average molecular weight of the polymer molecule to become much smaller. Draw the structure of the polymer and explain how the thiol compound functions to reduce the molecular weight. Would an alcohol do as well? Show how the potassium peroxodisulfate could function as an initiator. Would you expect it to decompose more rapidly in alkaline or strongly acidic solution? Explain.



Exercise 10-53

a. 1-Bromocyclopentene adds hydrogen bromide on irradiation with ultraviolet light to give 94% *cis*-1,2-dibromocyclopentane and 6% of the trans isomer. Explain why 1,1-dibromocyclopentane is not obtained and why the cis isomer predominates.

b. From your answer to the questions in Part a, predict the structure and stereochemistry of the major products in the following reactions:

(i) $\mathrm{CH_3{-}C\ \equiv C{-}CH_3 + 2HBr \xrightarrow{ROOR}}$

(ii) $\mathrm{CH_3C\ \equiv CBr + HBr \xrightarrow{h\nu}}$

(iii) *cis*$\mathrm{{-}CH_3CH{=}CHCH_3 + DBr \xrightarrow{ROOR}}$

(iv) $\mathrm{HC\ \equiv CH + DCl \xrightarrow{HgCl_2}}$ (monoaddition product of DCl)

10.E.1: Contributors

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CHAPTER OVERVIEW

11: Alkenes and Alkynes II - Oxidation and Reduction Reactions. Acidity of Alkynes

Further chemistry of alkenes and alkynes is described in this chapter, with emphasis on addition reactions that lead to reduction and oxidation of carbon- carbon multiple bonds. First we explain what is meant by the terms reduction and oxidation as applied to carbon compounds. Then we emphasize hydrogenation, which is reduction through addition of hydrogen, and oxidative addition reactions with reagents such as ozone, peroxides, permanganate, and osmium tetroxide. We conclude with a section on the special nature of 1-alkynes, their acidic behavior, and how the conjugate bases of alkynes can be used in synthesis to form carbon-carbon bonds.

11.1: Oxidation-Reduction of Organic Compounds
11.2: Hydrogenation with Heterogeneous Catalysts
11.3: Heats of Hydrogenation
11.4: Hydrogenation with Homogeneous Catalysts
11.5: Hydrogenation with Diimide
11.6: Addition of Boron Hydrides to Alkenes. Organoboranes
11.7: Oxidation Reactions
11.8: Terminal Alkynes as Acids
11.E: Alkenes and Alkynes II (Exercises)

11.1: Contributors and Attributions

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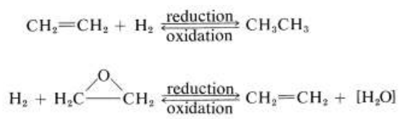
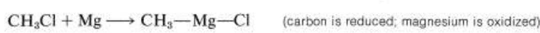
11.1: Oxidation-Reduction of Organic Compounds

An organic compound commonly is said to be "reduced" if reaction leads to an increase in its hydrogen content or a decrease in its oxygen content. The compound would be "oxidized" if the reverse change took place:



This is a very unsatisfactory definition because many oxidation-reduction or **redox** reactions do not involve changes in hydrogen or oxygen content, as the following example illustrates:



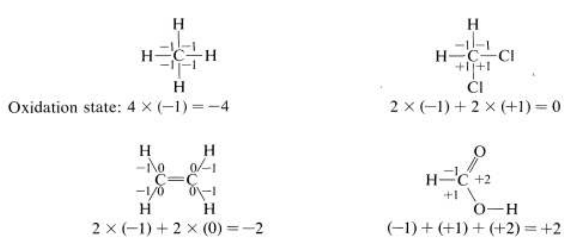
Redox reactions are better defined in terms of the concept of electron transfer. Thus *an atom is said to be oxidized if, as the result of a reaction, it experiences a net loss of electrons; and is reduced if it experiences a net gain of electrons*. This simple definition can be used to identify oxidation or reduction processes at carbon in terms of a scale of oxidation states for carbon based on the electronegativities of the atoms attached to carbon. The idea is to find out whether in a given reaction carbon becomes more, or less, electron-rich. We will use the following somewhat arbitrary rules:

1. Elementary carbon is assigned the zero oxidation state.
2. The oxidation state of any chemically bonded carbon may be assigned by adding -1 for each more electropositive atom and $+1$ for each more electronegative atom, and 0 for each carbon atom bonded directly to the carbon of interest (see Figure 10-11) for the Pauling electronegativity scale). That is,
   -1 for electropositive atoms, H, B, Na, Li, Mg,
   $+1$ for electronegative atoms, halogens O, N, S, and
   0 for carbon.
   The rationale for this mode of operation can be seen if we look more closely at the example of $\mathrm{CH_3Cl} + \mathrm{Mg} \rightarrow \mathrm{CH_3{-}Mg{-}Cl}$. Chlorine is more electronegative than either carbon or magnesium. Carbon is more electronegative than magnesium. Thus $\mathrm{CH_3Cl}$ is written properly with a polar bond as $\overset{\delta\oplus}{\mathrm{C}}\mathrm{H_3} - - - \overset{\delta\ominus}{\mathrm{Cl}}$, whereas the $\mathrm{C{-}Mg}$ bond is oppositely polarized, $\overset{\delta\ominus}{\mathrm{C}}\mathrm{H_3} - - - \overset{\delta\oplus}{\mathrm{Mg}}$. If all of the bonds were ionized completely, we could write

$$\mathrm{CH_3}^+ + \mathrm{Cl}^{\ominus} + \mathrm{Mg}^0 \rightarrow \mathrm{CH_3} :^{\ominus} + \mathrm{Mg}^{2\oplus} + \mathrm{Cl}^{\ominus} \tag{11.1.1}$$

   and it would be completely clear that carbon gains two electrons (is reduced), while magnesium loses two electrons (is oxidized). But because covalent, or at most polar, bonds actually are involved, it is much more difficult to determine whether oxidation or reduction occurs.
3. In compounds with multiple bonds ($\rangle C{=}O$, $-C{\equiv}N$), the attached heteroatom is counted twice or three times, depending on whether the bond is double or triple.
4. A formal positive charge on carbon changes the oxidation state by $+1$, and a formal negative charge by -1; an odd electron on carbon leaves the oxidation state unchanged.

To illustrate, the oxidation state of carbon in four representative examples is determined as follows:



Using this approach, we can construct a carbon oxidation scale, as in Table 11-1. Any reaction that increases the degree of oxidation of carbon corresponds to a loss of electrons (oxidation), and a reaction that decreases the oxidation level corresponds to a gain of electrons (reduction). Two examples follow:

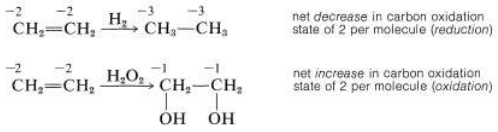


Table 11-1: *Carbon Oxidation States of Representative Organic Compounds (*$\mathrm{R} = alkyl$*)*

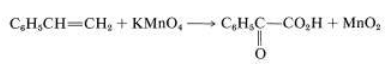
Compound	Structure	Oxidation state
carbon dioxide	O=C=O	+4
tetrachloromethane	CCl_4	+4
isocyanates	RN=C=O	+4
carboxylic acids	R—C(=O)—OH	+3
nitriles	RC≡N	+3
ketones	$R_2C{=}O$	+2
trichloromethane	$CHCl_3$	+2
ketenes	$R_2C{=}C^{*}{=}O$	+2(*)
tert-alcohols	R_3COH	+1
aldehydes	RCH=O	+1
methanal	$H_2C{=}O$	0
dichloromethane	CH_2Cl_2	0
alkanes	R_4C	0
benzene	C_6H_6	−1 (per carbon)
alkanes	R_3CH	−1
ethyne	HC≡CH	−1 (per carbon)
alkanes	R_2CH_2	−2
ethene	$CH_2{=}CH_2$	−2 (per carbon)
chloromethane	CH_3Cl	−2
methanol	CH_3OH	−2
methyl cation	$CH_3^{\oplus}$	−2
methyl radical	$CH_3\cdot$	−3
alkanes	RCH_3	−3
methyl anion	$CH_3:^{\ominus}$	−4
methane	CH_4	−4

OXIDATION ↑ REDUCTION ↓

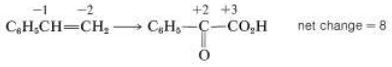
We recommend this scheme of oxidation states only as an aid to identify and balance redox reactions. Also, the terminology "redox" should not be confused with the mechanism of a reaction, as there is no connection between them. A moment's reflection also will show that virtually all reactions theoretically can be regarded as redox reactions, because in almost every reaction the reacting atoms experience some change in their electronic environments. Traditionally, however, reactions are described as redox reactions of carbon only when there is a *net* change in the oxidation state of the carbon atoms involved. An indication of just how arbitrary this is can be seen by the example of addition of water to ethene. This reaction usually is not regarded as an oxidation-reduction reaction because there is no *net* change in the oxidation state of the ethene carbons, despite the fact that, by our rules, one carbon is oxidized and the other reduced:

$$\overset{-2}{\mathrm{CH_2}} = \overset{-2}{\mathrm{CH_2}} + \mathrm{H_2O} \rightarrow \overset{-3}{\mathrm{CH_3}}\overset{-1}{\mathrm{CH_2}}\mathrm{OH} \tag{11.1.2}$$

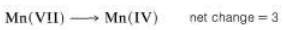
Apart from indicating when oxidation or reduction occurs, the oxidation scales is useful in balancing redox equations. For example, consider the following oxidation of ethenylbenzene (styrene) with potassium permanganate:



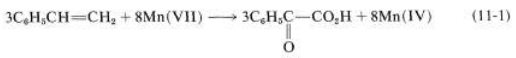
To determine how many moles of permanganate ion are required to oxidize one mole of styrene in this reaction, first determine the net change in oxidation state of the reacting carbons:



Second, determine the net change in oxidation state of manganese for $\mathrm{MnO_4^-} \rightarrow \mathrm{MnO_2}$:

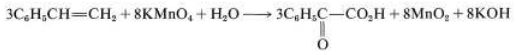


Therefore we need three moles of styrene for every eight moles of permanganate:

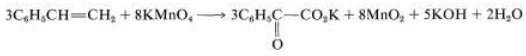


(11-1)

To get the overall atom and electrical balance for Equation 11-1, the requisite amounts of H_2O must be added, but the 3:8 ratio will remain unchanged:



Because KOH reacts in a nonoxidative way with carboxylic acids to form carboxylate salts $\left(\ce{RCO_2H} + \ce{KOH} \rightarrow \ce{RCO_2K} + \ce{H_2O} \right)$, the final equation is



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11.2: Hydrogenation with Heterogeneous Catalysts

Addition of hydrogen to a multiple bond is **hydrogenation**. It is applicable to almost all types of multiple bonds and is of great importance in synthetic chemistry, particularly in the chemical industry. Probably the most important technical example is production of ammonia by the hydrogenation of nitrogen:

$$3H_2 + N{\equiv}N \rightleftharpoons 2NH_3 \qquad \begin{matrix}\Delta H^0 = -22.0 \text{ kcal } (25^\circ) \\ \Delta G^0 = -\ 8.0 \text{ kcal } (25^\circ)\end{matrix}$$

This may appear to be a simple process, but in fact it is difficult to carry out because the equilibrium is not very favorable. High pressures ($150\text{-}200\ \text{atm}$) are required to get a reasonable conversion, and high temperatures ($430\text{-}510^\circ$) are necessary to get reasonable reaction rates. A catalyst, usually iron oxide, also is required. The reaction is very important because ammonia is used in ever-increasing amounts as a fertilizer either directly or through conversion to urea or ammonium salts.

Production of ammonia requires large quantities of hydrogen, most of which comes from the partial oxidation of hydrocarbons with water or oxygen. A simple and important example is the so-called "methane-steam gas" reaction, which is favorable only at very high temperatures because of the entropy effect in the formation of H_2 (see Section 4-4B):

$$CH_4 + H_2O \longrightarrow CO + 3H_2 \qquad \begin{matrix}\Delta H^0 = +51.0 \text{ kcal } (25^\circ) \\ \Delta G^0 = +33.9 \text{ kcal } (25^\circ)\end{matrix}$$

Therefore the fertilizer industry is allied closely with the natural gas and petroleum industries, and for obvious reasons ammonia and hydrogen often are produced at the same locations.,

Alkenes and alkynes add hydrogen much more readily than does nitrogen. For example, ethene reacts rapidly and completely with hydrogen at ordinary pressures and temperatures in the presence of metal catalysts such as nickel, platinum, palladium, copper, and chromium:

$$CH_2{=}CH_2 + H_2 \xrightarrow{\text{metal catalyst}} CH_3CH_3 \qquad \begin{matrix}\Delta H^0 = -32.7 \text{ kcal } (25^\circ) \\ \Delta G^0 = -24.1 \text{ kcal } (25^\circ)\end{matrix}$$

These reactions are unlike any we have encountered so far. They are **heterogeneous** reactions, which means that the reacting system consists of two or more phases. Usually, the metal catalyst is present as a finely divided solid suspension in the liquid or solution to be reduced. Alternatively, the metal is deposited on an inert solid support such as carbon, barium sulfate, alumina (Al_2O_3), or calcium carbonate. Then the mixture of the liquid substrate and solid catalyst is shaken or stirred in a hydrogen atmosphere. However, then actual reaction takes place at the surface of the metal catalyst and is an example of **heterogeneous** or **surface catalysis**.

11.2.1: Mechanism of Hydrogenation

The exact mechanisms of heterogeneous reactions are difficult to determine, but much interesting and helpful information has been obtained for catalytic hydrogenation. The metal catalyst is believed to act by binding the reactants at the surface of a crystal lattice. As an example, consider the surface of a nickel crystal (Figure 11-1). The nickel atoms at the surface have fewer neighbors (lower covalency) than the atoms in the interior of the crystal. The surface atoms therefore have residual bonding capacity and might be expected to combine with a variety of substances.

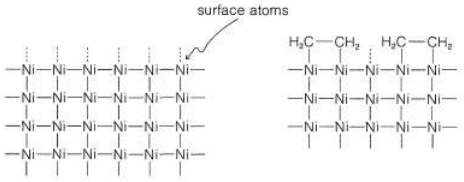


Figure 11-1: Left: Schematic representation of a nickel crystal in cross section showing residual valences at the surface atoms. Right: Adsorption of ethene on the surface of the nickel crystal with formation of $C{-}Ni$ bonds.

It has been shown experimentally that ethene combines exothermically $(\Delta H^0 = -60\ \text{kcal/mol})$ and reversibly with a metal surface. Although the precise structure of the ethene-nickel complex is unknown, the bonding to nickel must involve the electrons of the

double bond because saturated hydrocarbons, such as ethane, combine only weakly with the nickel surface. A possible structure with carbon-nickel σ bonds is shown in Figure 11-1.

Hydrogen gas combines with nickel quite readily with dissociation of the $\mathrm{H{-}H}$ bonds and formation of $\mathrm{Ni{-}H}$ bonds (nickel hydride bonds). The overall hydrogenation process is viewed as a series of reversible and sequential steps, as summarized in Figure 11-2. First the reactants, hydrogen and ethene, are adsorbed on the surface of the metal catalyst. The energies of the metal-hydrogen and metal-carbon bonds are such that, in a second step, a hydrogen is transferred to carbon to give an ethyl attached to nickel. This is the halfway point. In the next step, the nickel-carbon bond is broken and the second carbon-hydrogen bond is formed. Hydrogenation is now complete and the product is desorbed from the catalyst surface.

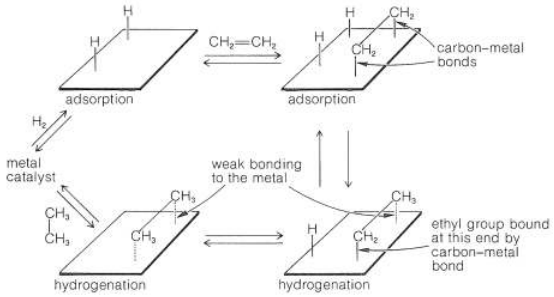
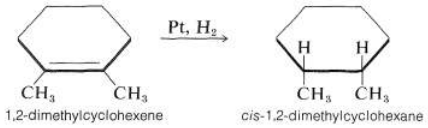


Figure 11-2: A possible cycle of reactions for catalytic hydrogenation of ethene. Ethane is held much less tightly than ethene on the catalyst surface, so as long as ethene is present no significant amount of ethane is bound.

Ethane has a low affinity for the metal surface and, when desorbed, creates a vacant space for the adsorption of new ethene and hydrogen molecules. The cycle continues until one of the reagents is consumed or some material is adsorbed that "poisons" the surface and makes it incapable of further catalytic activity. Because the reaction occurs only on the surface, small amounts of a catalyst poison can completely stop the reaction.

As might be expected for the postulated mechanism, the spacings of the metal atoms in the crystal lattice are quite important in determining the hydrogenation rates. The mechanism also accounts for the observation that *hydrogen usually adds to an alkene in the suprafacial manner*. To illustrate, 1,2-dimethylcyclohexene is reduced to *cis*-1,2-dimethylcyclohexane:



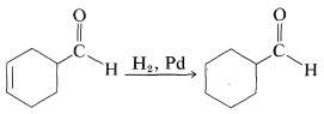
11.2.2: Catalyst Activity and Selectivity

For maximum catalytic activity, the metal usually is prepared in a finely divided state. This is achieved for platinum and palladium by reducing the metal oxides with hydrogen prior to hydrogenation of the alkene. A specially active form of nickel ("Raney nickel") is prepared from a nickel-aluminum alloy. Sodium hydroxide is added to the alloy to dissolve the aluminum. The nickel remains as a black powder which is pyrophoric (burns in air) if not kept moist:

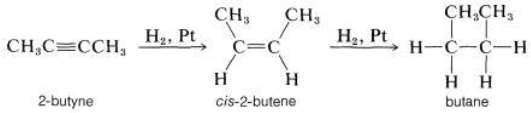
$$\mathrm{2Ni{-}Al + 2OH^{\ominus} + 2H_2O \rightarrow 2Ni + 2_2AlO^{-} + 3H_2} \tag{11.2.1}$$

Highly active platinum, palladium, and nickel catalysts also can be obtained by reduction of metal salts with sodium borohydride $(\mathrm{NaBH_4})$.

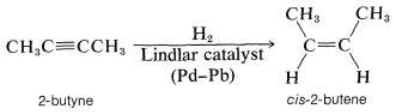
As mentioned previously, multiple bonds are not hydrogenated with equal facility. This fact can be used to advantage in carrying out selective reactions. For instance, hydrogenation of a carbon-carbon double bond can be achieved without simultaneously reducing a carbonyl bond in the same molecule. For example the carbon-carbon double bond of the following aldehyde can be reduced selectively:



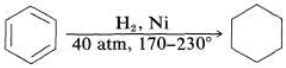
Alkynes are hydrogenated more easily than alkenes mainly because alkynes are adsorbed more readily on the catalyst surface. Hydrogenation proceeds in stages, first to the *cis*-alkene and then to the alkane. For example,



Normally, it is not possible to stop the hydrogenation of an alkyne at the alkene stage, but if the catalyst is suitably deactivated, addition to the triple bond can be achieved without further addition occurring to the resulting double bond. The preferred catalyst for selective hydrogenation of alkynes is palladium partially "poisoned" with a lead salt (**Lindlar catalyst**). This catalyst shows little affinity for adsorbing alkenes and hence is ineffective in bringing about hydrogenation to the alkane stage:



Aromatic hydrocarbons are hydrogenated with considerable difficulty, requiring higher temperatures, higher pressures, and longer reaction times than for alkenes or alkynes:



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11.3: Heats of Hydrogenation

In addition to having synthetic applications, catalytic hydrogenation is useful for analytical and thermochemical purposes. The analysis of a substance for the number of carbon-carbon double bonds it contains is carried out by measuring the uptake of hydrogen for a known amount of sample. Measurement of the heat evolved in the hydrogenation of alkenes gives information as to the relative stabilities of alkenes, provided that the differences in ΔS^0 values are small.

The experimental values of ΔH^0 for hydrogenation of a number of alkenes and alkynes are listed in Table 11-2. The ΔH^0 calculated from average bond energies is $-30\ \mathrm{kcal/mol}$ for a double bond and $-69\ \mathrm{kcal/mol}$ for a triple bond. The divergences from these values reflect the influence of structure on the strengths of multiple bonds. Some important generalizations can be made:

1. The more alkyl groups or other substituents there are on the multiple bond, the less heat is evolved on hydrogenation. Because less heat evolved signifies a stronger, more stable bond, it appears that alkyl substitution increases the stability (strength) of the multiple bond.
2. Trans isomers of 1,2-dialkyl-substituted ethenes evolve less heat (are more stable) than the corresponding cis isomers. This is the result of molecular overcrowding in the cis isomers from nonbonded interactions between two alkyl groups on the same side of the double bond. The effect amounts to almost $10\ \mathrm{kcal/mol}$ with two *cis-tert*-butyl groups. This effect is another manifestation of steric hindrance and can be seen most clearly with space-filling models (Figure 11-3).

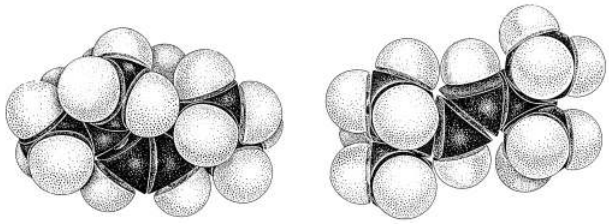

Figure 11-3: Space-filling models of cis- and trans-2,2,5,5-tetramethyl-3-hexene, which show the difference in steric interactions between the tert-*butyl groups.*

3. Conjugated dienes are more stable than isolated dienes (compare 1,3- and 1,4-pentadiene).
4. Cumulated dienes appear to be less stable than conjugated or isolated dienes (see 1,2-propadiene).

Table 11-2: *Heats of Hydrogenation of Gaseous Alkenes and Alkynes* $(\mathrm{kcal/mol,\ 1\ atm,\ 25^\circ})$

Compound	Formula	$-\Delta H^0$
ethene	$CH_2{=}CH_2$	32.8
propene	$CH_3CH{=}CH_2$	30.1
1-butene	$CH_3CH_2CH{=}CH_2$	30.3
cis-2-butene	$CH_3CH{=}CHCH_3$	28.6
trans-2-butene	$CH_3CH{=}CHCH_3$	27.6
2-methyl-2-butene	$(CH_3)_2C{=}CHCH_3$	26.9
2,3-dimethyl-2-butene	$(CH_3)_2C{=}C(CH_3)_2$	26.6
cis-2-pentene	$CH_3CH{=}CHC_2H_5$	28.6
trans-2-pentene	$CH_3CH{=}CHC_2H_5$	27.6
cis-2,2,5,5-tetramethyl-3-hexene	$(CH_3)_3C{-}CH{=}CH{-}C(CH_3)_3$	36.2
trans-2,2,5,5-tetramethyl-3-hexene	$(CH_3)_3C{-}CH{=}CH{-}C(CH_3)_3$	26.9
ethyne	$CH{\equiv}CH$	74.4
propyne	$CH_3C{\equiv}CH$	69.1
1,2-propadiene	$CH_2{=}C{=}CH_2$	71.3
1,3-butadiene	$CH_2{=}CH{-}CH{=}CH_2$	57.1
1,3-pentadiene	$CH_3CH{=}CH{-}CH{=}CH_2$	54.1
1,4-pentadiene	$CH_2{=}CHCH_2CH{=}CH_2$	60.8

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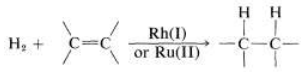
11.4: Hydrogenation with Homogeneous Catalysts

Hydrogen addition to multiple bonds is catalyzed by certain complex metal salts *in solution*. This may be described as **homogeneous** catalysis and, compared to heterogeneous catalysis, is a relatively new development in the area of hydrogenation reactions. Rhodium and ruthenium salts appear to be generally useful catalysts:



At present, homogeneous catalysis for routine hydrogenation reactions offers little advantage over the convenience and simplicity of heterogeneous catalysis. Suprafacial addition of hydrogen is observed with both types of catalytic systems. However, greater selectivity can be achieved with homogeneous catalysts because they appear to be more sensitive to steric hindrance and are less likely to cause rearrangement, dissociation, and hydrogenation of other bonds (e.g., $-NO_2$ and $\diagup\!\!\diagdown C{=}O$).

The most thoroughly investigated homogeneous hydrogenation catalyst is the four-coordinated rhodium complex $Rh\,[(C_6H_5)_3P]_3\,Cl$. This catalyst is called *Wilkinson's catalyst* after its discoverer, G. Wilkinson. In 1973, the Nobel Prize in chemistry was awarded jointly to Wilkinson and E. O. H. Fischer for their respective contributions to the field of *organometallic chemistry*. As you will see in this and later chapters, compounds with carbon-metal bonds (organometallic compounds) are extremely useful reagents, reactive intermediates, or catalysts in organic reactions. To a very large extent, the work of Fischer and Wilkinson created the current interest and developments in the field of transition-metal organic chemistry, which will be discussed in Chapter 31.

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11.5: Hydrogenation with Diimide

There are alternative ways to add hydrogen to a multiple bond besides the catalytic methods described in the previous sections. The most useful of these are homogeneous reactions utilizing diimide, HN=NH, and diborane, B_2H_6.

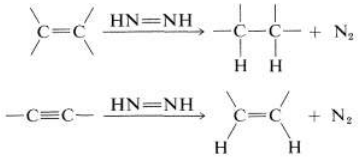
The behavior and reactivity of diimide can be understood best by considering the thermochemistry of hydrogenation of nitrogen:

$$N{\equiv}N + H_2 \longrightarrow \underset{\text{diimide}}{HN{=}NH} \qquad \Delta H^0 = +43.2 \text{ kcal}$$

$$HN{=}NH + H_2 \longrightarrow \underset{\text{hydrazine}}{H_2NNH_2} \qquad \Delta H^0 = -21.6 \text{ kcal}$$

$$H_2NNH_2 + H_2 \longrightarrow 2\ NH_3 \qquad \Delta H^0 = -43.6 \text{ kcal}$$

The first step is strongly endothermic and is the main hurdle to overcome in the hydrogenation of nitrogen to ammonia. Conversely, the reverse reaction, which is the dehydrogenation of diimide, is strongly exothermic. Therefore we may expect that diimide will have a pronounced tendency to revert to molecular nitrogen. This is in fact so and, at normal temperatures, diimide exists only as a transient intermediate that cannot be isolated. It is extremely reactive and readily transfers hydrogen to carbon-carbon multiple bonds:

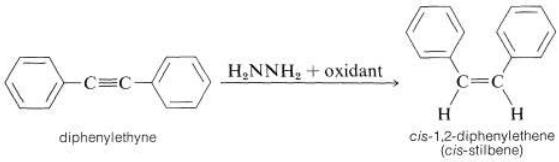


In practice, diimide is generated as it is needed in the presence of the compound to be hydrogenated. There are various ways to do this, but one of the simplest methods is dehydrogenation of hydrazine with oxidizing agents such as atmospheric oxygen or hydrogen peroxide:

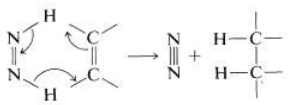
$$H_2N{-}N_2 \xrightarrow[\text{or } O_2]{H_2O_2} HN{=}NH + 2H^{\oplus} + 2e^{\ominus} \qquad (11.5.1)$$

Hydrazine actually has been used as a hydrogenating agent for over sixty years, but it was not until the 1960's that the diimide intermediate in such reactions was recognized.

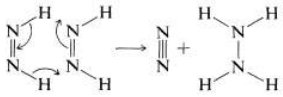
The hydrogenation step is stereospecific and transfers hydrogen in the suprafacial manner. For example, alkynes are converted to *cis*-alkenes:



There are no detectable intermediate stages or rearrangements in diimide hydrogenation. The reaction is visualized as a six-center (**pericyclic**) process in which the bonds are broken and made in a concerted fashion:



An important difference between diimide hydrogenation and catalytic hydrogenation is that diimide will react only with symmetrical or nonpolar bonds (C=C, C ≡ C, N=N), whereas hydrogen can add, albeit reluctantly, to polar bonds (C=O, C=N). Diimide does not attack the stronger polar bonds probably because it does not survive long enough to do so. It selfdestructs in the absence of a reactive substrate to give nitrogen and hydrazine:



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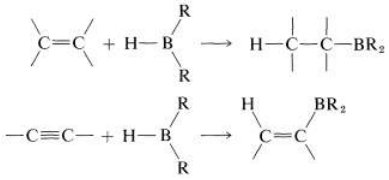
11.6: Addition of Boron Hydrides to Alkenes. Organoboranes

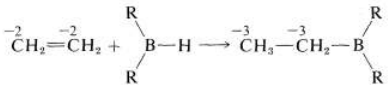
An especially valuable group of intermediates can be prepared by addition of an compound to carbon-carbon double or triple bonds:



The reaction is called **hydroboration** and is a versatile synthesis of organoboron compounds. One example is the addition of diborane, B_2H_6, to ethene. Diborane behaves as though it is in equilibrium with BH_3 ($B_2H_6 \rightleftharpoons 2BH_3$), and addition proceeds in three stages:

$$CH_2{=}CH_2 + BH_3 \text{ (from } B_2H_6) \longrightarrow CH_3CH_2BH_2 \quad \text{ethylborane}$$
$$CH_2{=}CH_2 + CH_3CH_2BH_2 \longrightarrow (CH_3CH_2)_2BH \quad \text{diethylborane}$$
$$CH_2{=}CH_2 + (CH_3CH_2)_2BH \longrightarrow (CH_3CH_2)_3B \quad \text{triethylborane}$$

The monoalkylborane, RBH_2, and the dialkylborane, R_2BH, seldom are isolated because they rapidly add to the alkene. These additions amount to reduction of both carbons of the double bond:

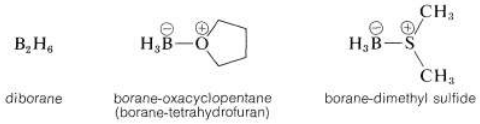


Organoboranes can be considered to be organometallic compounds. Elemental boron does not have the properties of a metal, and boron-carbon bonds are more covalent than ionic. However, boron is more electropositive than either carbon or hydrogen and when bonded to carbon behaves like most metals in the sense that bonds are polarized with R negative and boron positive:

Hydroboration and the many uses of organoboranes in synthesis were developed largely by H. C. Brown and co-workers. In our discussion, we shall give more detail on hydroboration itself, and then describe several useful transformations of organoboranes.

11.6.1: Hydroboration

The simplest borane, BH_3, exists as the dimer, B_2H_6, or in complexed form with certain ethers or sulfides:



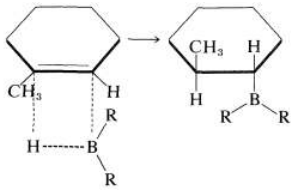
Any of these BH_3 compounds adds readily to most alkenes at room temperature or lower temperatures. The reactions usually are carried out in ether solvents, although hydrocarbon solvents can be used with the borane-dimethyl sulfide complex. When diborane is the reagent, it can be generated either *in situ* or externally through the reaction of boron trifluoride with sodium borohydride:

$$3\overset{\oplus}{Na}\overset{\ominus}{B}H_4 + 4BF_3 \rightarrow 2_2BH_6 + 3\overset{\oplus}{Na}\overset{\ominus}{B}F_4 \qquad (11.6.1)$$

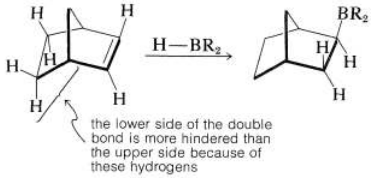
Hydroborations have to be carried out with some care, because diborane and many alkylboranes are highly reactive and toxic substances; many are spontaneously flammable in air.

With unsymmetrical alkenes, hydroboration occurs so that *boron becomes attached to the less-substituted end of the double bond*:

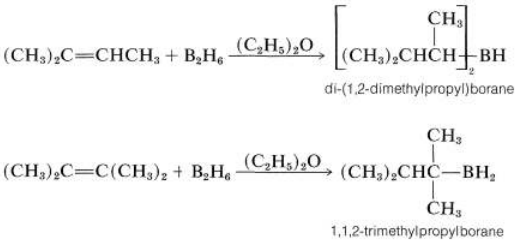
These additions are *suprafacial additions*:



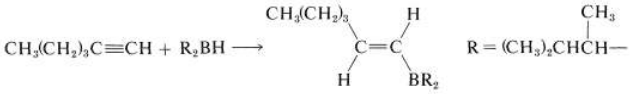
Furthermore, when there is a choice, addition occurs preferentially from the less crowded side of the double bond:



If the alkene is a bulky molecule, borane may add only one or two alkene molecules to give either mono- or dialkylborane, RBH_2 or R_2BH, respectively, as the following reactions show:

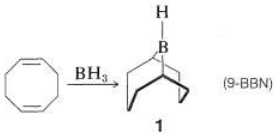


These bulky boranes still possess $B-H$ bonds and can add further to a multiple bond, but they are highly selective reagents and add only if the alkene or alkyne is unhindered. This selectivity can be useful, particularly to 1-alkynes, which are difficult to stop at the alkenylborane stage when using diborane:

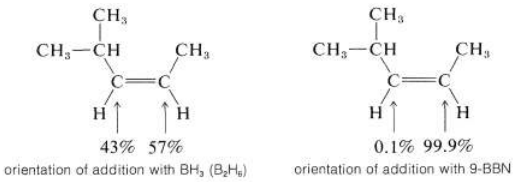


With a bulky dialkylborane, such as di-(1,2-dimethylpropyl)borane, further addition to the alkenylborane does not occur.

An especially selective hydroborating reagent is prepared from 1,5-cyclooctadiene and borane. The product is a bicyclic compound of structure 1 (often abbreviated as 9-BBN), in which the residual $B-H$ bond adds to unhindered alkenes with much greater selectivity than is observed with other hydroborating reagents. It is also one of the few boranes that reacts sufficiently slowly with oxygen that it can be manipulated in air.



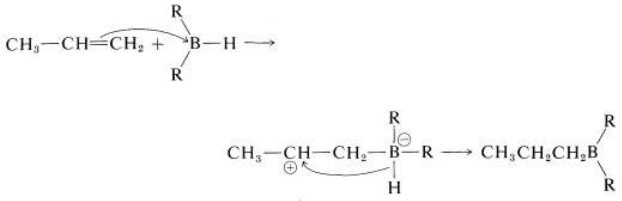
An example of the difference in selectivity in the hydroboration of *cis*-4-methyl-2-pentene with B_2H_6 and 1 follows:



11.6.2: Mechanism of Hydroboration

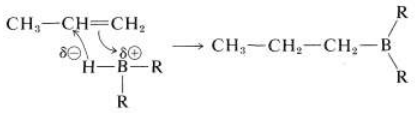
According to the electronegativity chart (Figure 10-11), the boron-hydrogen bond is polarized in the sense $\overset{\delta\oplus}{\mathrm{B}}---\overset{\delta\ominus}{\mathrm{H}}$. Therefore the direction of addition of $\mathrm{B_2H_6}$ to propene is that expected of a *polar* mechanism whereby the electrophilic boron atom becomes bonded to the less-substituted carbon of the double bond.

Stepwise mechanism



However, there is no firm evidence to suggest that a carbocation intermediate is formed through a stepwise electrophilic addition reaction. For this reason, the reaction often is considered to be a *four-center concerted addition*.

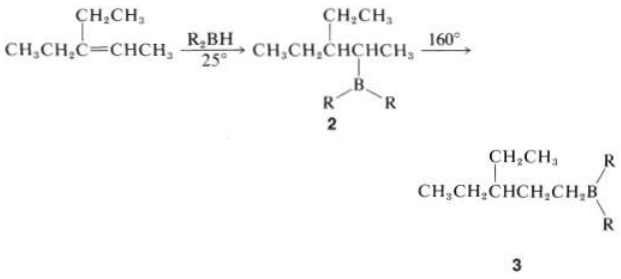
Concerted mechanism



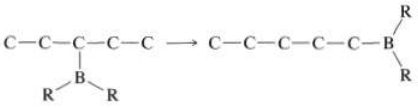
The stepwise formulation explains why boron becomes attached to the less-substituted carbon, but does not account for the fact that the reactions show no other characteristics of carbocation reactions. This could be because of an expected, extraordinarily fast rate of hydride-ion transfer to the carbocation. A more serious objection to the stepwise mechanism is that alkynes react more rapidly than alkenes, something which normally is not observed for stepwise electrophilic additions (cf. Section 10-5).

11.6.3: Isomerization of Alkylboranes

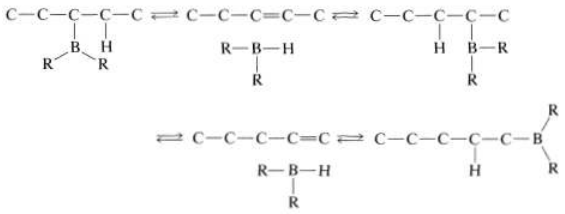
Some alkylboranes rearrange at elevated temperatures $(160°)$ to form more stable isomers. For example, the alkylborane 2, produced by hydroboration of 3-ethyl-2-pentene, rearranges to 3 on heating:



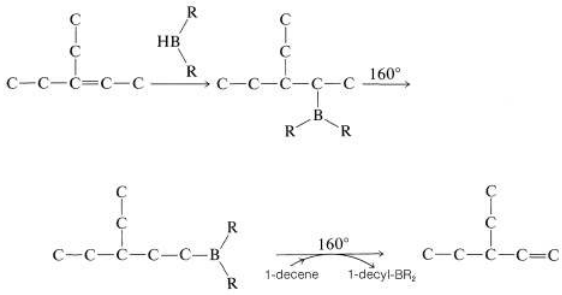
In general, the boron in alkylboranes prefers to be at the *end* of a hydrocarbon chain so it is bonded to a *primary* carbon where steric crowding around boron is least severe. Thus rearrangement tends to proceed in the direction



Rearrangement is associated with the fact that hydroboration is reversible at elevated temperatures. This makes possible a sequence of elimination-addition reactions in which boron becomes attached to different carbons and ultimately leads to the most stable product that has boron bonded to the carbon at the end of the chain:

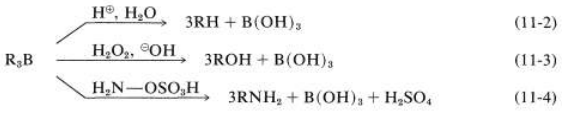


Rearrangement of alkylboranes can be used to transform alkenes with double bonds in the middle of the chain into *less stable* 1-alkenes; for example, $RCH{=}CHCH_3 \rightarrow RCH_2{-}CH{=}CH_2$. The procedure involves hydroboration of the starting alkene in the usual manner; the borane then is isomerized by heating. An excess of 1-decene (bp 170°) then is added to the rearranged borane and the mixture is reheated. Heating causes the alkylborane to dissociate into 1-alkene and HBR_2; the 1-decene "scavenges" the HBR_2 as it forms, thereby allowing a more volatile 1-alkene (bp $< 170^{\circ}$) to be removed by simple distillation. Thus, for the rearrangement of 3-ethyl-2-pentene to 3-ethyl-1-pentene,



11.6.4: Synthetic Reactions of Organoboranes

Alkylboranes formed in the hydroboration of alkenes and alkynes seldom are isolated; for the most part they are used as reactive intermediates for the synthesis of other substances. In the reactions of alkylboranes, the $B{-}C$ bond is cleaved in the sense $B^{\oplus} - C^{\ominus}$ so that carbon is transferred to other atoms, such as H, O, N, and C, *with* its bonding electron pair:



In the first of these reactions (Equation 11-2), a hydrocarbon is produced by the cleavage of a borane, R_3B, with aqueous acid, or better, with anhydrous propanoic acid, $CH_3CH_2CO_2H$. The overall sequence of hydroboration-acid hydrolysis achieves the reduction of a carbon-carbon multiple bond without using hydrogen and a metal catalyst or diimide (Table 11-3):

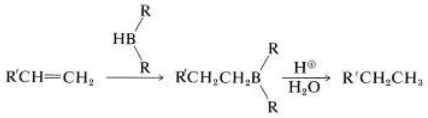


Table 11-3: *Some Methods of Hydrogenation of Carbon-Carbon Multiple Bonds*

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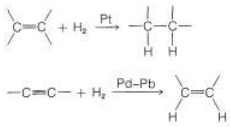
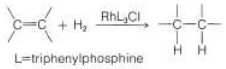
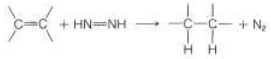
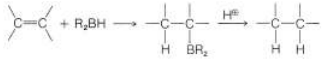
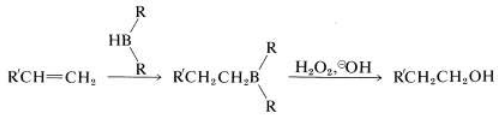
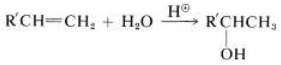
Reaction	Comment
1. *Heterogeneous catalytic hydrogenation* 	Requires a transition metal catalyst, Pt, Pd, Ni, etc. Addition is suprafacial from least hindered side. Rearrangements can occur. Alkynes are reduced to *cis*-alkenes over Lindlar catalyst, Pd–Pb (Section 11-2).
2. *Homogeneous catalytic hydrogenation*  L=triphenylphosphine	Catalyst is a soluble complex salt of rhodium or ruthenium; suprafacial addition occurs to the least hindered double bond (Section 11-4)
3. *Diimide reduction* 	Diimide is generated *in situ* by oxidation of H_2NNH_2; suprafacial addition occurs (Section 11-5).
4. *Hydroboration–Protolysis* 	Hydroboration is suprafacial; protolysis occurs with retention (Section 11-6).

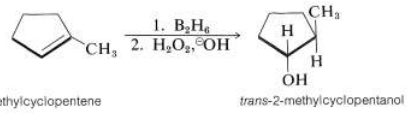
The second reaction (Equation 11-3) achieves the synthesis of a *primary* alcohol by the oxidation of the alkylborane with hydrogen peroxide in basic solution. Starting with a 1-alkene, one can prepare a primary alcohol in two steps:



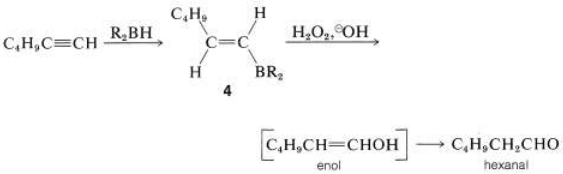
This sequence complements the direct hydration of 1-alkenes, which gives *secondary* alcohols:



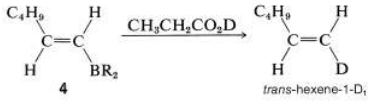
Hydroboration of an alkene and subsequent reactions of the product trialkylborane, either with hydrogen peroxide or with acid, appear to be highly stereospecific. For example, 1-methylcyclopentene gives exclusively *trans*-2-methylcyclopentanol on hydroboration followed by reaction with alkaline hydrogen peroxide. This indicates that, overall, *the reactions result in suprafacial addition of water to the double bond*:



Hydroboration of an alkyne followed by treatment of the alkenylborane with basic peroxide provides a method of synthesis of aldehydes and ketones. Thus hydroboration of 1-hexyne and oxidation of the 1-hexenylborane, 4, with hydrogen peroxide gives hexanal by way of the enol:

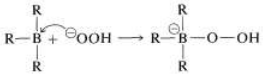


If 4 is treated with deuteriopropanoic acid, replacement of $-BR_2$ by deuterium occurs with *retention* of configuration, forming *trans*-hexene-1-D_1:

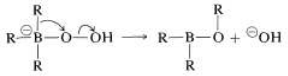


11.6.5: Mechanism of Oxidation of Alkylboranes

The stereospecific oxidation of alkylboranes occurs with hydrogen peroxide by an interesting and important general type of rearrangement which, for these reactions, involves migration of an organic group from boron to oxygen. The first step in the oxidation depends on the fact that tricoordinate boron has only six electrons in its valence shell and therefore behaves as if it were electron-deficient. The first step is bond formation at boron by the strongly nucleophilic peroxide anion (from $H_2O_2 + OH^{\ominus} \rightleftharpoons^{\ominus} OOH + H_2O$) to give a tetracovalent boron intermediate:

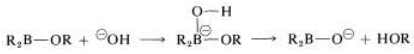


In the second step, an alkyl group moves *with its bonding electron pair* from boron to the neighboring oxygen and, in so doing, displaces hydroxide ion. *The stereochemical configuration of the migrating* R *group is retained:*



(11-5)

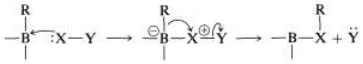
Reaction is completed by hydrolysis of the B—O bond:



All three groups on boron are replaced in this manner.

The rearrangement step (Equation 11-5) is an example of many related rearrangements in which a group, R, migrates with its bonding electrons from one atom to an adjacent atom. We already have encountered an example in the rearrangement of carbocations (Section 8-9B):

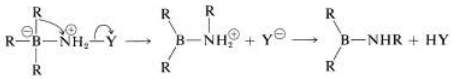
The difference between the carbocation rearrangement and the rearrangement of Equation 11-5 is that R migrates from boron to oxygen as $HO^{\ominus}$ departs in what might be considered an internal S_N2 reaction. We can generalize this kind of reaction of boron with a substance, X—Y, as in Equation 11-6:



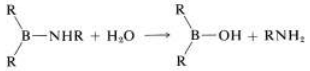
(11-6)

An example of the use of an X—Y reagent is conversion of alkylboranes to primary amines with hydroxylaminesulfonic acid, H_2NOSO_3H (Equation 11-4). The key steps are attack of the nucleophilic nitrogen at boron,

followed by rearrangement,



and hydrolysis,



11.6.6: Contributors and Attributions

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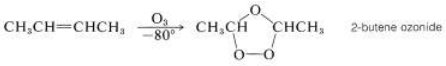
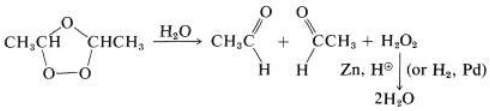
11.7: Oxidation Reactions

11.7.1: Ozonization

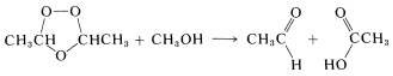
Most alkenes react readily with ozone (O_3), even at low temperatures, to yield cyclic peroxidic derivatives known as **ozonides**. For example,



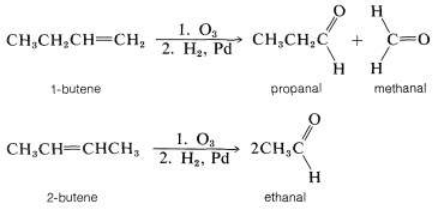
These substances, like most compounds with peroxide $(O-O)$ bonds, may explode violently and unpredictably. Therefore ozonizations must be carried out with appropriate caution. The general importance of these reactions derives not from the ozonides, which usually are not isolated, but from their subsequent products. The ozonides can be converted by hydrolysis with water and reduction, with hydrogen (palladium catalyst) or with zinc and acid, to carbonyl compounds that can be isolated and identified. For example, 2-butene gives ethanal on ozonization, provided the ozonide is destroyed with water and a reducing agent which is effective for hydrogen peroxide:



An alternative procedure for decomposing ozonides from di- or trisubstituted alkenes is to treat them with methanol (CH_3OH). The use of this reagent results in the formation of an aldehyde or ketone and a carboxylic acid:



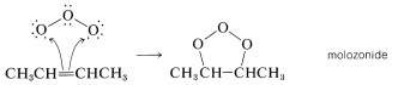
The overall ozonization reaction sequence provides an excellent means for locating the positions of double bonds in alkenes. The potentialities of the method may be illustrated by the difference in reaction products from the 1- and 2-butenes:



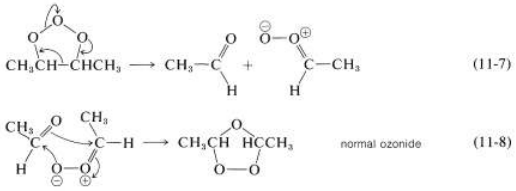
11.7.2: Mechanism of Ozonization

Ozonization of alkenes has been studied extensively for many years, but there is still disagreement about the mechanism (or mechanisms) involved because some alkenes react with ozone to give oxidation products other than ozonides. It is clear that the ozonide is not formed directly, but by way of an unstable intermediate called a **molozonide**. the molozonide then either isomerizes to the "normal" ozonide or participates in other oxidation reactions. Although the structure of normal ozonides has been established beyond question, that of the molozonide, which is very unstable even at -100°, is much less certain.

The simplest and most widely accepted mechanism involves formation of a molozonide by a direct **cycloaddition** of ozone to the double bond.[1]

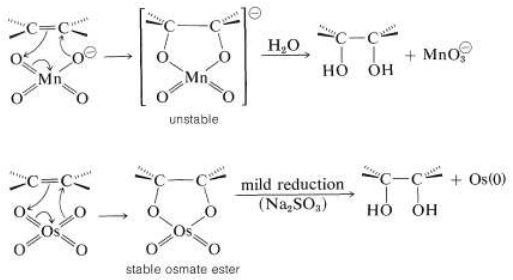


Isomerization of the molozonide appears to occur by a fragmentation-recombination reaction, as shown in Equations 11-7 and 11-8:

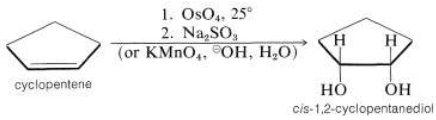


11.7.3: Hydroxylation of Alkenes

Several oxidizing reagents react with alkenes under mild conditions to give, as the overall result, addition of hydrogen peroxide as HO−OH. Of particular importance are alkaline permanganate (MnO_4^-) and osmium tetroxide (OsO_4), both of which react in an initial step by a suprafacial cycloaddition mechanism like that postulated for ozone.



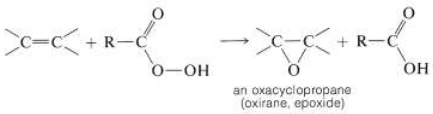
Each of these reagents produces *cis*-1,2-dihydroxy compounds (diols) with cycloalkenes:



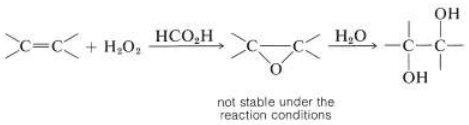
Osmium tetroxide is superior to permanganate in giving good yields of diol, but its use is restricted because it is a very costly and very toxic reagent.

11.7.4: Oxidation with Peroxidic Compounds. Oxacyclopropane (Oxirane) Formation

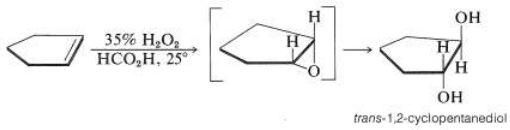
Alkenes can be oxidized with peroxycarboxylic acids, RCO_3H, to give oxacyclopropanes (oxiranes, epoxides), which are three-membered cyclic ethers:



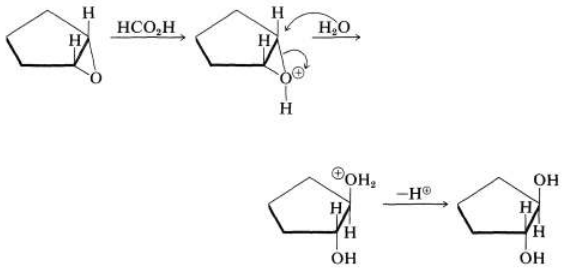
The reaction, known as **epoxidation**, is valuable because the oxacyclopropane ring is cleaved easily, thereby providing a route to the introduction of many kinds of functional groups. In fact, oxidation of alkenes with peroxymethanoic acid (peroxyformic acid), prepared by mixing methanoic acid and hydrogen peroxide, usually does not stop at the oxacyclopropane stage, but leads to ring-opening and the subsequent formation of a diol:



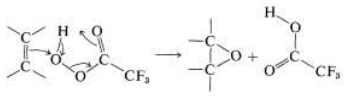
This is an alternative scheme for the hydroxylation of alkenes (see Section 11-7C). However, the overall stereochemistry is opposite to that in permanganate hydroxylation. For instance, cyclopentene gives *trans*-1,2-cylcopentanediol. First the oxirane forms by suprafacial addition and then undergoes ring opening to give the trans product:



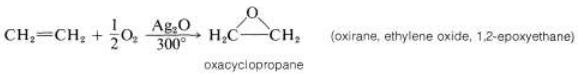
The ring opening is a type of S_N2 reaction. Methanoic acid is sufficiently acidic to protonate the ring oxygen, which makes it a better leaving group, thus facilitating nucleophilic attack by water. The nucleophile always attacks from the side remote from the leaving group:



The peroxyacids that are used in the formation of oxacyclopropanes include peroxyethanoic (CH_3CO_3H), peroxybenzoic $(C_6H_5CO_3H)$, and trifluoroperoxyethanoic (CF_3CO_3H) acids. A particularly useful peroxyacid is 3-chloroperoxybenzoic acid, because it is relatively stable and is handled easily as the crystalline solid. The most reactive reagent is trifluoroperoxyethanoic acid, which suggests that the peroxyacid behaves as an electrophile (the electronegativity of fluorine makes the CF_3 group strongly electron-attracting). The overall reaction can be viewed as a **cycloaddition**, in which the proton on oxygen is transferred to the neighboring carbonyl oxygen more or less simultaneously with formation of the three-membered ring:



A reaction of immense industrial importance is the formation of oxacyclopropane itself (most often called ethylene oxide) by oxidation fo ethene with oxygen over a silver oxide catalyst at 300°:



Oxacyclopropane is used for many purposes, but probably the most important reaction is ring opening with water to give 1,2-ethanediol (ethylene glycol, bp 197°). This diol, mixed with water, is employed widely in automotive cooling systems to provide both a higher boiling and lower freezing coolant than water alone:

Propene and higher alkenes are not efficiently epoxidized by oxygen and Ag_2O in the same way as ethene because of competing attack at other than the double-bond carbons.

[1]The ozone structure shown here with single electrons having paired spins on the terminal oxygens accords both with the best available quantum mechanical calculations and the low dipole moment of ozone, which is not consonant with the conventional $O{=}\overset{\oplus}{O}-\overset{\ominus}{O}$ structure. See W. A. Goddard III, T. H. Dunning, Jr., W. J. Hunt, and P. J. Hay, *Accounts of Chemical Research* **6**, 368 (1973).

11.7.5: Contributors and Attributions

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11.8: Terminal Alkynes as Acids

A characteristic and synthetically important reaction of ethyne and 1-alkynes is salt ("acetylide") formation with very strong bases. In such reactions the alkynes behaves as an acids in the sense that they give up protons to suitably strong bases:

$$\mathrm{R{-}C{\equiv}C{:}H + base \rightleftarrows RC{\equiv}C{:}^{\ominus} + \overset{\oplus}{H}{-}base}$$

Water is too weak a base to accept protons from alkynes; consequently no measurable concentration of $H_3O^{\oplus}$ is expected from the ionization of alkynes in dilute aqueous solutions. Therefore we have no quantitative measure of 1-alkyne acidity in aqueous solution other than that it probably is about 10^{10} times less acidic than water, as judged from measurements in other solvents to be discussed shortly. In the gas phase, however, the situation is reversed, and *ethyne is a stronger acid than water*:

$$\begin{aligned} &HC{\equiv}CH(aq) + K^{\oplus}{}^{\ominus}OH(aq) \xleftarrow{H_2O} HC{\equiv}C{:}^{\ominus}K^{\oplus}(aq) + H_2O \qquad K \ll 1 \\ &HC{\equiv}CH(g) + {}^{\ominus}OH(g) \rightleftarrows HC{\equiv}C{:}^{\ominus}(g) + H_2O(g) \qquad K \gg 1 \end{aligned}$$

This reversal is of little practical value because organic reactions *involving* ions normally are not carried out in the gas phase. However, it should alert us to the tremendous role that solvents play in determining acidities by their abilities (some much more than others) to stabilize ions by the property known as **solvation**. (Section 11-8A.)

Liquid ammonia is a more useful solvent than water for the preparation of 1-alkyne salts. A substantial amount of the alkyne can be converted to the conjugate base by amide anions (potassium or sodium amide) because a 1-alkyne is a stronger acid than ammonia.

$$\underset{\text{potassium amide}}{\mathrm{R{-}C{\equiv}C{:}H + K^{\oplus}{:}\ddot{N}H_2^{\ominus}}} \xrightarrow[-33^{\circ}]{NH_3(l)} \underset{\text{potassium alkynide}}{\mathrm{R{-}C{\equiv}C{:}^{\ominus}K^{\oplus}}} + \ddot{N}H_3$$

The acidity of the terminal hydrogen in 1-alkynes provides a simple and useful test for 1-alkynes. With silver-ammonia solution ($AgNO_3$ in aqueous ammonia), 1-alkynes give insoluble silver salts, whereas disubstituted alkynes do not:

$$\underset{\substack{\text{(R = H, alkyl,}\\ \text{or aryl)}}}{\mathrm{R{-}C{\equiv}C{-}H}} + \overset{\oplus}{Ag}(NH_3)_2 \longrightarrow \underset{\substack{\text{silver alkynide}\\ \text{(silver acetylide)}}}{\mathrm{R{-}C{\equiv}C{-}Ag}} + NH_3 + \overset{\oplus}{N}H_4$$

The silver "acetylides" appear to have substantially covalent carbon-metal bonds and are less ionic than sodium and potassium alkynides. Silver-ammonia solution may be used to precipitate 1-alkynes from mixtures with other hydrocarbons. The 1-alkynes are regenerated easily from the silver precipitates by treatment with strong inorganic acids. It should be noted, however, that silver alkynides may be shock sensitive and can decompose explosively, especially when dry.

11.8.1: Thermodynamics of Solvation of Ions and Its Importance

Some idea of the importance of solvation can be gained from the calculated ΔH for the following process:

$$\mathrm{Na^+\,(g) + Cl^-\,(g) \;\rightarrow Na^+\,(aq) + Cl^-\,(aq)} \tag{11.8.1}$$

with $DeltaH^o = -187\,kcal$.

The solvation energies of ions are so large that relatively small differences for different ions can have a very large effect on equilibrium constants. Thus, the ratio between the relative acidities of ethyne and water in the gas phase and in water of 10^{12} corresponds at 25° to an overall ΔG^0 difference in solvation energies of approximately 16 kcal, which is less than 10% of the total solvation energies of the ions. Further difficulties arise because of differences between solvation energies and interactions between the ions in different solvents. Thus the acidities of 1-alkynes relative to other acids have been found to change by a factor of 10^{11} in different solvents. For this reason, we must be particularly careful in comparing the rates and equilibrium constants of ionic reactions to take proper account of solvation and ion interaction effects.

An excellent rule of thumb is that, other things being equal, large ions are more stable than small ions in the gas phase, with the opposite being true in polar solvents, where small ions are more strongly solvated (thus more stable) than large ions. For comparison,

$$
\begin{array}{lll}
(1) & \mathrm{Li}^{\oplus}(g) + \mathrm{F}^{\ominus}(g) \longrightarrow \mathrm{Li}^{\oplus}(aq) + \mathrm{F}^{\ominus}(aq) & \Delta H^{\circ} = -246 \text{ kcal} \\
(2) & \mathrm{Li}^{\oplus}(g) + \mathrm{I}^{\ominus}(g) \longrightarrow \mathrm{Li}^{\oplus}(aq) + \mathrm{I}^{\ominus}(aq) & \Delta H^{\circ} = -211 \text{ kcal} \\
(3) & \mathrm{K}^{\oplus}(g) + \mathrm{F}^{\ominus}(g) \longrightarrow \mathrm{K}^{\oplus}(aq) + \mathrm{F}^{\ominus}(aq) & \Delta H^{\circ} = -199 \text{ kcal} \\
(4) & \mathrm{K}^{\oplus}(g) + \mathrm{I}^{\ominus}(g) \longrightarrow \mathrm{K}^{\oplus}(aq) + \mathrm{I}^{\ominus}(aq) & \Delta H^{\circ} = -165 \text{ kcal}
\end{array}
$$

From (1) minus (3), the solvation energy of gaseous $\mathrm{Li}^{\oplus}$ is 47 kcal mol^{-1} greater than $\mathrm{K}^{\oplus}$; and from (1) minus (2), that of $\mathrm{F}^{\ominus}$ is 35 kcal mol^{-1} greater than that of $\mathrm{I}^{\ominus}$. Such differences in solvation energies can have considerable effects on reactivity, and you may remember from Section 8-7E that $\mathrm{F}^{\ominus}$ is a weaker nucleophile than $\mathrm{I}^{\ominus}$, largely because of its greater solvation energy.

11.8.2: Why is Ethyne a Stronger Acid than Ethane or Ethene?

If we compare acid strengths of the simple hydrocarbons, we find that ethyne is substantially more acidic than ethene or ethane in the gas phase or in solution. Why is this? The simplest explanation is that there is a direct connection between C–H acidity and the amount of s character associated with the σ-bonding carbon orbital. Other things being equal, acidity increases with increasing s character in the carbon orbital.

order of acid strength:	$\mathrm{HC{\equiv}CH} \gg$	$\mathrm{H_2C{=}CH_2} \gg$	$\mathrm{H_3C{-}CH_3}$
hybrid carbon σ orbital:	sp	sp^2	sp^3

Figure 11-4).

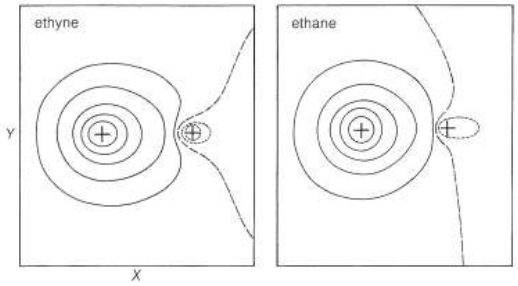


Figure 11-4: Generalized valence bond (GVB) orbitals for one hydrogen of ethyne (left) and of ethane (right); see Section 6-7. The hydrogen and carbon nuclei are located in the xy plane of the coordinate system at the positions indicated by crosses, the hydrogen nucleus being on the left. The long dashes indicate locations of change in orbital phase. The dotted lines are contour lines of electron amplitude of opposite phase to the solid lines. Notice how the contours of the ethyne hydrogen orbital are distorted toward carbon compared to those of the ethane hydrogen orbital. (Drawing courtesy W. A. Goddard III.)

11.8.3: Alkynide Anions as Nucleophiles

1-Alkynes are very weak acids, hence their conjugate bases, $\mathrm{RC} \equiv \mathrm{C}^{\ominus}$, are quite strong bases. These anions also are reactive carbon nucleophiles, and it is this property that makes them useful for organic synthesis. Recall from Chapter 8 that one of the most generally useful organic reactions is a displacement reaction in which an anionic nucleophile, $\mathrm{Nu}^{\ominus}$, attacks an alkyl derivative, RX, to displace $\mathrm{X}^{\ominus}$ and form a new bond between carbon and the nucleophile:

$$\mathrm{Nu{:}^{\ominus} + R{-}X \longrightarrow Nu{:}R + {:}X^{\ominus}}$$

The displaced group X often is a halide ion (chloride, bromide, or iodide), and if the entering nucleophile $\mathrm{Nu}^{\ominus}$ is an alkynide anion, the reaction leads to formation of a carbon-carbon bond:

$$\mathrm{CH_3C{\equiv}C{:}^{\ominus} + CH_3I \longrightarrow CH_3C{\equiv}CCH_3 + I^{\ominus}}$$

With those RX derivatives that undergo nucleophilic displacement readily, this is a general method of forming a C–C bond, thereby leading to substituted alkynes. The alkynide salts generally used are those of lithium, sodium, potassium, or magnesium.

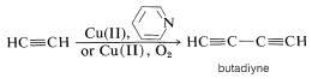
11.8.4: Coupling Reactions of Alkynes

Another reaction of 1-alkynes that extends the carbon chain is a coupling reaction in which the alkyne dimerizes under the influence of a cuprous salt, usually cuprous ammonium chloride:

$$\mathrm{HC{\equiv}CH \xrightarrow{Cu(NH_3)_2^{\oplus}Cl^{\ominus}} HC{\equiv}C{-}CH{=}CH_2}$$ butenyne (vinylacetylene)

This addition of one molecule of alkyne to another is formally analogous to the dimerization of alkenes under the influence of sulfuric acid (see Section 10-9), but the mechanisms are quite different.

If the reaction is carried out in the presence of an oxidizing agent, such as O_2 or a cupric salt dissolved in pyridine (a weak base), a different product is obtained. Under these conditions, oxidative coupling occurs to give a conjugated diyne:



butadiyne

Although the details of the mechanisms of these alkyne reactions are not known, it is likely that the ability of 1-alkynes to form carbon-metal bonds with metals such as copper is a key factor. Other oxidative coupling reactions occur with transition metals, and this will be discussed in detail in Chapter 31.

11.8.5: Contributors and Attributions

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11.E: Alkenes and Alkynes II (Exercises)

Exercise 11-1 For each of the following reactions determine the oxidation state of the carbons in the reactants and products and decide whether the overall changes involve oxidation, reduction, or neither.

a. $CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$

b. $CH_3CH{=}CH_2 + HCl \rightarrow CH_3CH(Cl)CH_3$

c. $CH_3CH{=}CH_2 + HOCl \rightarrow CH_3CH(OH)CH_2Cl$

d. $(CH_3)_2C{=}CH_2 + (CH_3)_3CH \rightarrow (CH_3)_2CHCH_2C(CH_3)_3$

e. $n(CH_2{=}CHCN) \rightarrow -(CH_2CH(CN))_n-$

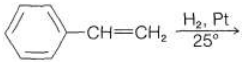
f. $CH_3OH \rightarrow CH_2{=}O + H_2$

Exercise 11-2 Balance each of the following equations. You may need to add H_2O to one side or the other of the equations.

a. $\overset{\oplus}{K}\overset{\ominus}{MnO_4} + RCH{=}CH_2 \rightarrow RC\overset{\ominus}{O_2}\overset{\oplus}{K} + CH_2{=}O + MnO_2$

b. $CrO_3 + C_6H_5CH_2CH_3 \rightarrow C_6H_5CH_2CO_2H + Cr^{3\oplus}$

Exercise 11-3 Draw structures for the products expected from the following reactions. Show configurations where significant.

a. 

b. *cis*-2-butene $\xrightarrow[25^\circ]{D_2,\ Pt}$

c. $CH_2{=}CHCOCH_3 \xrightarrow[25^\circ]{H_2,\ Pt}$

d. 1-penten-3-yne $\xrightarrow{H_2,\ Pd-Pb}$

e. $C_6H_5C \equiv CC_6H_5 \xrightarrow{H_2,\ Pd-Pb}$

f. 1,3-dimethylcyclopentene $\xrightarrow[25^\circ]{H_2,\ Pt}$

Exercise 11-4* The conditions of catalytic hydrogenation sometimes lead to rearrangement of a double bond from one location to another. Using 1-butene as an example, show how operation of the *equilibria* shown in the mechanism of Figure 11-2 could lead to rearrangement of 1-butene to 2-butene over a hydrogenation catalyst in the presence of H_2. If D_2 were used for reduction of 1-butene under these circumstances, suggest where and how much deuterium might be introduced into the butane formed.

Exercise 11-5 Use bond energies to explain the following facts:

a. Ethyne is more easily hydrogenated catalytically than nitrogen.

b. Ethyne is more easily hydrogenated catalytically than ethene.

c. Ethene is more easily hydrogenated catalytically than methanal (CH_2O).

d. In the hydrogenation of nitrogen, ammonia is formed; in contrast, the hydrogenation of ethyne leads to ethane, not methane.

Exercise 11-6

a. Would you expect a carbon-nitrogen triple bond to be hydrogenated more, or less, easily than a carbon-carbon triple bond?

b. Why is it difficult to hydrogenate a tetrasubstituted alkene such as 2,3-dimethyl-2-butene?

Exercise 11-7* Accurate ΔH^0 and ΔG^0 values in kcal mol^{-1} for hydrogen addition to 1-butene, *cis*- and *trans*-2-butene in the gas phase at 25° follow:

	ΔH^0	ΔG^0 (25°)
$CH_2{=}CHCH_2CH_3$	−30.12	−12.94
$CH_3CH{=}CHCH_3$ (*cis*)	−28.48	−11.64
$CH_3CH{=}CHCH_3$ (*trans*)	−27.48	−10.95

a. From the data (and after reviewing Section 4-4B), calculate ΔS^0 for each of these reactions at 25° $(298\ \mathrm{K})$. Why is ΔS^0 so large for these reactions?

b. Calculate ΔH^0, ΔG^0, and ΔS^0 for $CH_2{=}CHCH_2CH_3 \rightarrow CH_3CH{=}CHCH_3$ (*trans*) and for $CH_3CH{=}CHCH_3$ (*cis*) $\rightarrow CH_3CH{=}CHCH_3$ (*trans*). Are the ΔS^0 values in accord with your expectations? What can you conclude as to how good a qualitative measure heats of hydrogenation are of relative alkene stabilities?

Exercise 11-8 Consider that it is necessary to synthesize pure samples of *D*,*L*-hexane-3,4-D_2 and *meso*-hexane-3,4-D_2. Show how this might be done both with diimide and catalytic-type reductions, assuming that any necessary deuterium-labeled reagents and six-carbon organic compounds are available.

Exercise 11-9

a. Show how 1 is formed by hydroboration of 1,5-cyclooctadiene.

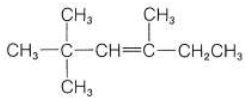
b. What product would you expect from the hydroboration of 2,4-dimethyl-1,4-pentadiene with BH_3?

c. Explain why diborane adds to methylcyclohexene to give tris-(*trans*-2-methylcyclohexyl)borane in preference to the cis isomer.

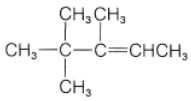
Exercise 11-10 What products would you expect from hydroboration of the following alkenes with a dialkylborane, R_2BH, followed by isomerization at 160°?

a. $CH_3CH{=}CHCH_3$

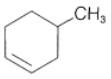
b.



c.

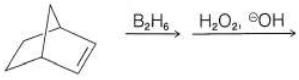


d.



Exercise 11-11 Predict the products in each step of the following reaction sequences:

a.



b. $(CH_3)_2C{=}CHCH_3 \xrightarrow{B_2H_6} \xrightarrow{C_2H_5C{\equiv}CC_2H_5} \xrightarrow{H_2O_2,\ {}^{\ominus}OH}$

c. $(CH_3)_2C{=}CHCH_3 \xrightarrow{B_2H_6} \xrightarrow{C_2H_5C{\equiv}CC_2H_5} \xrightarrow{CH_3CH_2CO_2D}$

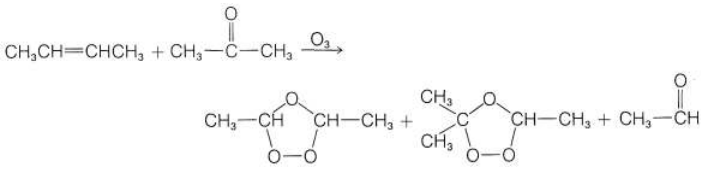
Exercise 11-12

a. Draw the structure and configuration of the product expected of the reaction between 1-bromo-1-hexyne and diethylborane, $(C_2H_5)_2BH$.

b. When the product is treated with sodium methoxide, $NaOCH_3$, then with propanoic acid, *trans*-3-octene is formed. Show the steps involved in forming this *trans*-alkene.

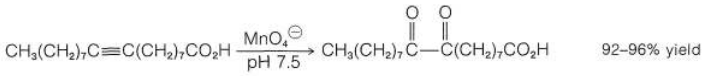
Exercise 11-13 A hydrocarbon of formula $C_{11}H_{18}$ on reaction with ozone in dichloromethane gave, after the addition of water and finely divided zinc, three products in equimolar amounts that were identified as 2-butanone $(CH_3COCH_2CH_3)$, methanal (CH_2O), and cyclohexane-1,4-dione . Draw the structure of the hydrocarbon $C_{11}H_{18}$.

Exercise 11-14* When 2-butene reacts with ozone in the presence of 2-propanone, two structurally different ozonides are obtained, as well as ethanal:



Suggest how these products can be formed from the molozonide(s) of 2-butene.

Exercise 11-15 Alkynes react more slowly than alkenes with permanganate and usually give dicarbonyl compounds. An example follows:



a. What is the change in oxidation state of carbon in this reaction?

b. If Mn(VII) is reduced to Mn(IV), how many moles of permanganate are required per mole of alkyne?

Exercise 11-16 Starting with cyclohexene, show how you could prepare each of the following compounds:

a. the epoxide of cyclohexene
b. *cis*-cyclohexane-1,2-diol
c. *trans*-cyclohexane-1,2-diol

Exercise 11-17 Suppose you were given four unlabeled bottles, each of which is known to contain one of the following compounds: pentane, 1-pentene, 2-pentyne, or 1-pentyne. Explain how you could use simple chemical tests (preferably test-tube reactions) to identify the contents of each bottle. (Notice that all four compounds are low-boiling liquids.)

Exercise 11-18* Show how the (\Delta H\) values of the following processes can be combined to calculate the heat of solution of $\mathrm{Na}^{\oplus}(g) + \mathrm{Cl}^{\ominus}(g)$ at 298°K.

$$\begin{aligned}
&\mathrm{Na}(s) + \tfrac{1}{2}\mathrm{Cl}_2(g) \rightarrow \mathrm{Na}^{\oplus}(aq) + \mathrm{Cl}^{\ominus}(aq) && \Delta H^0 = -97\ \text{kcal}\\
&\mathrm{Na}(g) \rightarrow \mathrm{Na}^{\oplus}(g) + \mathrm{e}^- && \Delta H^0 = +118\ \text{kcal}\\
&\mathrm{Cl}^{\ominus}(g) \rightarrow \mathrm{Cl}\cdot(g) + \mathrm{e}^- && \Delta H^0 = +83\ \text{kcal}\\
&\tfrac{1}{2}\mathrm{Cl}_2(g) \rightarrow \mathrm{Cl}\cdot(g) && \Delta H^0 = +29\ 29\\
&\mathrm{Na}(s) \rightarrow \mathrm{Na}(g) && \Delta H^0 = +26\ \text{kcal}
\end{aligned} \qquad (11.E.1)$$

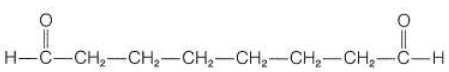
Exercise 11-19 A serious contamination in butenyne made by dimerization of ethyne with cuprous ion is 1,5-hexadien-3-yne. Show how this substance can be formed.

Exercise 11-20 The following physical properties and analytical data pertain to two isomeric hydrocarbons, A and B, isolated from a gasoline:

	bp, °C	mp, °C	%C	%H
A	68.6	−141	85.63	14.34
B	67.9	−133	85.63	14.34

Both *A* and *B* readily decolorize bromine and permanganate solutions and give the same products on ozonization. Suggest possible structures for *A* and *B*. What experiments would you consider necessary to further establish the structures and configurations of *A* and *B*?

Exercise 11-21 It is possible to synthesize two isomeric cycloalkenes of formula $\mathrm{C_8H_{14}}$. Both of these compounds react with hydrogen in the presence of platinum to give cyclooctane, and each, on ozonization followed by reduction, gives:



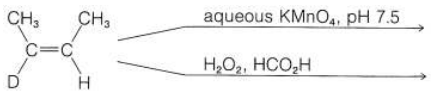
a. What are the structures of the two compounds?

b. Would the two substances give the same compound on hydroxylation with potassium permanganate?

Exercise 11-22 When 5-decyne is heated with diborane at 160° and the product is oxidized with hydrogen peroxide in basic solution, 1,10-decanediol is obtained. Write equations to show the several reactions involved in these transformations. You need not show detailed mechanisms.

Exercise 11-23

a. Draw the structures and configurations of the products that will be formed by the following reactions of *cis*-2-butene-2-D:

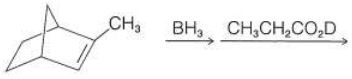


b. What is the stereochemical relationship between the products of the two reactions in Part a?

Exercise 11-24* Show the structures of the products expected in each step of the following sequences. Be sure to indicate the stereochemistry of reactions where this is important. Remember that D is the hydrogen isotope of mass 2.

a. *cis*-2-butene $\xrightarrow{C_2NND_2}$

b. 1-methylcyclohexene $\xrightarrow{BH_3}\xrightarrow{160^{\circ}}\xrightarrow{H_2O_2,\ ^{\ominus}OH}$

c. 

d. propyne $\xrightarrow{R_BD}\xrightarrow{CH_3CH_2CO_2H}\xrightarrow{O_3}\xrightarrow{H_2O,\ Zn}$

e. 2-butyne $\xrightarrow{R_2BH}\xrightarrow{H_2O_2,\ ^{\ominus}OH}$

f. $CH_3C\equiv CH \xrightarrow{R_2BD}\xrightarrow{CH_3CH_2CO_2D}$

g. 3-methylcyclopentene $\xrightarrow{BH_3}\xrightarrow{160^{\circ}}\xrightarrow[\text{(as trapping agent)}]{CH_3(CH_2)_7CH=CH_2}$

h. 1-pentene $\xrightarrow{HBr,\ ROOR}\xrightarrow{CH_3C\equiv CNa}\xrightarrow{H_2,\ Pd-Pb}\xrightarrow{O_3}\xrightarrow{Na_2SO_3}$

i. 1-pentene $\xrightarrow{BH_3}\xrightarrow{H_2N-OSO_3H}$

Exercise 11-25 Two stable compounds of formula C_6H_6 react with bromine and with $KMnO_4$. On hydrogenation with a platinum catalyst at 25°, both absorb two moles of hydrogen and form cyclohexane. Write possible structures for these substances and explain how electronic spectra may be used to tell which compound is which.

Exercise 11-26 Suppose one added hydrogen as H_2 to the cyclopropene double bond of 1-methoxy-2-phenyl-3,3-dimethylcyclopropene. Explain how the proton nmr of the product can be used to infer whether the hydrogen added to the double bond in the suprafacial or antarafacial manner. (Review Section 9-10G and 9-10H.)

Exercise 11-27 In the hydrogenation of 1,2-dimethylcyclohexene over a platinum catalyst, the suprafacial addition product is formed. Assuming that the mechanism of this hydrogenation is as shown in Figure 11-2, what conditions must be put on the stereochemistry of each of the postulated steps in order that the overall reaction be suprafacial?

Exercise 11-28* When *optically active* 3-methylhexane is shaken with a nickel catalyst in the presence of deuterium gas $(D_2 = {}^2H_2)$ it, like other alkanes, undergoes slow exchange of hydrogen for deuterium at the various carbons. The key observation is that substitution of D for H at C_3 causes racemization (i.e., formation of equal amounts of deuterated 3-methylhexane with the two possible configurations at C_3). Assuming that racemization and deuterium exchange occur *only* by way of the steps shown in Figure 11-2, determine how many steps backward the reaction has to go to produce the racemized, exchanged 3-methylhexane. To work this problem you will need to determine whether, when one starts with optically active 3-methylhexane, the various possible intermediate structures in Figure 11-2 would be chiral or not and how many steps back one would have to go to get to an achiral system. If you are uncertain about chirality we suggest that you review Section 5-1B.

Figure 11-29 Calculate ΔH^0 for the reaction $CH_3{-}C \equiv C{-}H \rightarrow CH_2{=}C{=}CH_2$ from bond energies and also from ΔH^0 values for the following reactions:

$$\begin{aligned} CH_3C \equiv CH + 2H_2 &\rightarrow CH_3CH_2CH_2 \quad \Delta H^0 = -69.1 \text{ kcal} \\ CH_2{=}C{=}CH_2 + 2H_2 &\rightarrow CH_3CH_2CH_3 \quad \Delta H^0 = -71.3 \text{ kcal} \end{aligned} \tag{11.E.2}$$

Explain why the value of ΔH^0 calculated form bond energies might be unreliable for the last reaction.

Exercise 11-30

a. Write a mechanism for the sulfuric acid-induced dimerization of 2-methyl-2-butene, indicating the products you expect to be formed. (It will be helpful to review Section 10-8B.)

b. Ozonization of the actual alkene mixture that is formed gives (along with a mixture of aldehydes and ketones) substantial amounts of 2-butanone $(CH_3COCH_2CH_3)$. Write a structure and reaction mechanism for formation of a C_{10}-olefin that reasonably might be formed in the dimerization reaction and that, on ozonization, would yield 2-butanone and a C_6-carbonyl compound. (Consider how sulfuric acid might cause the double bond in 2-methyl-2-butene to shift its position.)

Exercise 11-31 How would you distinguish between the components in each of the following pairs using chemical methods (preferably test-tube reactions)?

a. $CH_3CH_2C \equiv CH$ and $CH_3C \equiv CCH_3$
b. $CH_3CH_2C \equiv CH$ and $CH_2{=}CH{-}CH{=}CH_2$
c. $C_6H_5C \equiv CC_6H_5$ and $C_6H_5CH_2CH_2C_6H_5$

Exercise 11-32 How could you distinguish between the compounds in the previous exercise, using spectroscopic methods?

11.E.1: Contributors

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CHAPTER OVERVIEW

12: Cycloalkanes, Cycloalkenes and Cycloalkynes

Many important hydrocarbons, known as cycloalkanes, contain rings of carbon atoms linked together by single bonds. The simple cycloalkanes of formula $(CH_2)_n$, make up a particularly important homologous series in which the chemical properties change in a much more dramatic way with increasing n than do those of the acyclic hydrocarbons $\mathrm{CH_3(CH_2)_{n-1}H}$. The cycloalkanes with small rings (n = 3-6) are of special interest in exhibiting chemical properties intermediate between those of alkanes and alkenes. In this chapter we will show how this behavior can be explained in terms of angle strain and steric hindrance, concepts that have been introduced previously and will be used with increasing frequency as we proceed further. We also discuss the conformations of cycloalkanes, especially cyclohexane, in detail because of their importance to the chemistry of many kinds of naturally occurring organic compounds. Some attention also will be paid to polycyclic compounds, substances with more than one ring, and to cycloalkenes and cycloalkynes.

12.1: Nomenclature and Physical Properties of Cycloalkanes
12.2: Spectroscopic Properties of Cyclohexanes
12.3: Conformations of Cycloalkanes
12.4: Strain in Cycloalkane Rings
12.5: Chemical Properties
12.6: The Larger Cycloalkanes and their Conformations
12.7: Cycloalkenes and Cycloalkanes
12.8: Nomenclature of Polycycloalkanes
12.9: Conformations of Decalin
12.10: Strain in Polycyclic Molecules
12.E: Cycloalkanes, Cycloalkenes, and Cycloalkynes (Exercises)

12.1: Contributors and Attributions

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12.1: Nomenclature and Physical Properties of Cycloalkanes

The nomenclature and physical properties of cycloalkanes covers the the IUPAC systems of naming cycloalkanes. The physical properties of cycloalkanes can explain each cycloalkane molecular structure and the relative size from simple propane to multiple carbon containing cycloakane like cyclononane.

For a review, **cycloalkanes** contain rings of of carbon atoms linked together by a single bonds. The simple cycloalkanes of formula $(CH_2)_n$ make up a particularly homologous series in which the chemical properties change in a much more dramatic way with increasing n than do those of the acyclic hydrocarbons $CH_3(CH_2)_{n-1}H$. The cycloalkanes with small rings (n = 3-6) are of special interest in exhibiting chemical properties intermediate between those of alkanes and alkenes. In this chapter we will show how this behavior can be explained in terms of angle strain and steric hindrance, concepts that have been introduced previously and will be used with increasing frequency as we proceed further.

The IUPAC system for naming cycloalkanes and cycloalkenes was presented in some detail in Sections 3-2 and 3-3, and you may wish to review that material before proceeding further. Additional procedures are required for naming polycyclic compounds, which have rings with common carbons, and these will be discussed later in this chapter. Furthermore, given below are the table of physical properties of cycloalkanes from propane to cyclononane.

Table 12-1: Physical Properties of Alkanes and Cycloalkanes

Compounds	Boiling Point ^oC	Melting Point ^oC	Density (g/ml)
propane	-42	-187	0.580
cyclopropane	-33	-127	0.689
butane	-0.5	-135	0.579
cyclobutane	13	-90	0.689
pentane	36	-130	0.626
cyclopentane	49	-94	0.746
hexane	69	-95	0.659
cyclohexane	81	7	0.778
heptane	98	-91	0.684
cycloheptane	119	-8	0.810
octane	126	-57	0.703
cyclooctane	151	15	0.830
nonane	151	-54	0.718
cyclononane	178	11	0.845

The melting and boiling points of cycloalkanes (Table 12-1) are somewhat higher than those of the corresponding alkanes. In contrast to the more rigid cyclic compounds, the general “floppiness” of open-chain hydrocarbons makes them harder to fit into a crystal lattice (hence their lower melting points) and less hospitable toward neighboring molecules of the same type (hence their lower boiling points). The nomenclature and physical properties of cycloalkanes also includes conformation of cycloalkanes, especially cyclohexane in later discussion because of their importance to the chemistry of many kinds of naturally occurring organic compounds. The nomenclature and physical properties of cycloalkanes will also cover polycyclic compounds, substances with more than one ring, and to the cycloalkenes and cycloalkynes.

12.1.1: Contributors and Attributions

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12.2: Spectroscopic Properties of Cyclohexanes

The spectroscopic properties of cycloalkanes are considerably similar to those of alkanes. We mentioned previously the main features of their infrared spectra (Section 9-7D), and that their lack of ultraviolet absorption at wavelengths down to 200 nm makes them useful solvents for the determination of ultraviolet spectra of other substances (Section 9-9B).

Some spectoscopic properties of cycloalkanes has been notable in the proton NMR spectra. The proton NMR spectra of alkanes and cycloalkanes are characteristic but difficult to interpret because the chemical shifts between the various kinds of protons are usually small. Although proton spectra of simple cycloalkanes, $(CH_2)_n$, show one sharp line at room temperature, when alkyl substituents are present, *small* differences in chemical shifts between the ring hydrogens occur and, with spin-spin splitting, provide more closely spaced lines than normally can be resolved. The complexity so introduced can be seen by comparing the proton spectra of cyclooctane and methylcyclohexane shown in Figure 12-1. For methyl-substituted cycloalkanes the methyl resonances generally stand out as high-field signals centered on 0.9 ppm, and the area of these signals relative to the other $C-H$ signals may be useful in indicating how many methyl groups there are (see Section 9-10K, especially Figure 9-46). However, in cyclopropanes the ring protons have abnormally small chemical shifts ($\delta = 0.22$ for cyclopropane), which often overlap with the shifts of methyl groups ($\delta \cong 0.9$ ppm).

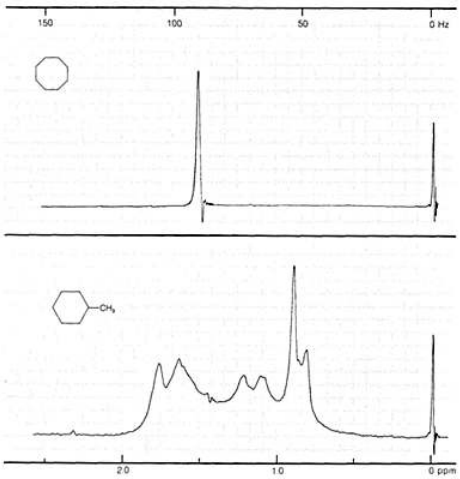

Figure 12-1: Proton NMR spectra of cyclooctane and methylcyclohexane at 60 MHz with TMS as standard (0 ppm).

Although spectroscopic properties of cycloalkanes in proton spectra are not very useful for identification purposes, ^{13}C NMR spectra are very useful. Chain-branching and ring-substitution normally cause quite large chemical-shift changes, and it is not uncommon to observe ^{13}C shifts in cycloalkanes spanning 35 ppm. Some special features of application of ^{13}C NMR spectra to conformational analysis of cycloalkanes are described in Section 12-3D.

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12.3: Conformations of Cycloalkanes

The equilibria (relative stabilities) and equilibration (rate of interconversion) of the rotational conformations of ethane and butane were discussed in Section 5-2. If you review this material, it will be clear that forming a ring from a hydrocarbon chain will greatly reduce the number of possible staggered and eclipsed conformations. We will begin our discussion with cyclohexane because of its special importance, proceed to smaller rings, then give a brief exposition of the conformations of the larger rings.

12.3.1: Cyclohexane Conformations

If the carbons of a cyclohexane ring were placed at the corners of a regular *planar* hexagon, all the $\mathrm{C{-}C{-}C}$ bond angles would have to be 120°. Because the expected normal $\mathrm{C{-}C{-}C}$ bond angle should be near the tetrahedral value of 109.5°, the suggested planar configuration of cyclohexane would have *angle strain* at each of the carbons, and would correspond to less stable cyclohexane molecules than those with more normal bond angles. The actual normal value for the $\mathrm{C{-}C{-}C}$ bond angle of an open-chain $-\mathrm{CH_2{-}CH_2{-}CH_2}-$ unit appears to be about 112.5°, which is 3° greater than the tetrahedral value. From this we can conclude that the angle strain at each carbon of a planar cyclohexane would be $(120^{\circ} - 112.5^{\circ}) = 7.5^{\circ}$. Angle strain is not the whole story with regard to the instability of the planar form, because in addition to having $\mathrm{C{-}C{-}C}$ bond angles different from their normal values, the planar structure also has its carbons and hydrogens in the unfavorable *eclipsed* arrangement, as shown in Figure 12-2.

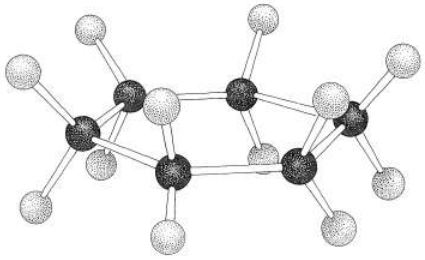

Figure 12-2: Cyclohexane in the strained planar configuration showing how the hydrogens become eclipsed.

If the carbon valence angles are kept near the tetrahedral value, you will find that you can construct ball-and-stick models of the cyclohexane six-carbon ring with two quite different conformations. These are known as the "chair" and "boat" conformations (Figure 12-3). It has not been possible to separate cyclohexane at room temperature into pure isomeric forms that correspond to these conformations, and actually the two forms appear to be rapidly interconverted. The chair conformation is considerably more stable and comprises more than 99.9% of the equilibrium mixture at room temperature.[1]

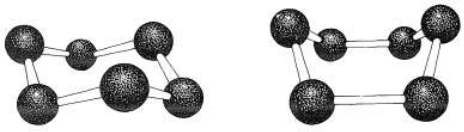

Figure 12-3: Chair (left) and boat (right) conformations of the six carbons of a cyclohexane ring with normal $\mathrm{C{-}C{-}C}$ bond angles.

Why is the boar form less stable than the chair form, if both have normal $\mathrm{C{-}C{-}C}$ bond angles? The answer is that the boat form has unfavorable nonbonded interactions between the hydrogen atoms around the ring. If we make all of the bond angles normal and orient the carbons to give the "extreme boat" conformation of Figure 12-4, a pair of 1,4 hydrogens (the so-called "flagpole" hydrogens) have to be very close together $(1.83\ \text{Å})$. Hydrogens this close together would be on the rising part of a repulsion potential energy curve, such as Figure 4-6, for hydrogen-hydrogen nonbonded interactions. This *steric hindrance* at an $\mathrm{H{-}H}$ distance of 1.83 Å corresponds to a repulsion energy of about $3\ \text{kcal mol}^{-1}$. There is still another factor that makes the extreme boat unfavorable; namely, that the eight hydrogens along the "sides" of the boat are eclipsed, which brings them substantially closer together than they would be in a staggered arrangement (about 2.27 Å compared with 2.50 Å). This is in striking contrast with the chair form (Figure 12-5), for which adjacent hydrogens are in staggered positions with respect to one another all around the ring. Therefore the chair form is expected to be more stable than the boat form because it has less repulsion between the hydrogens.

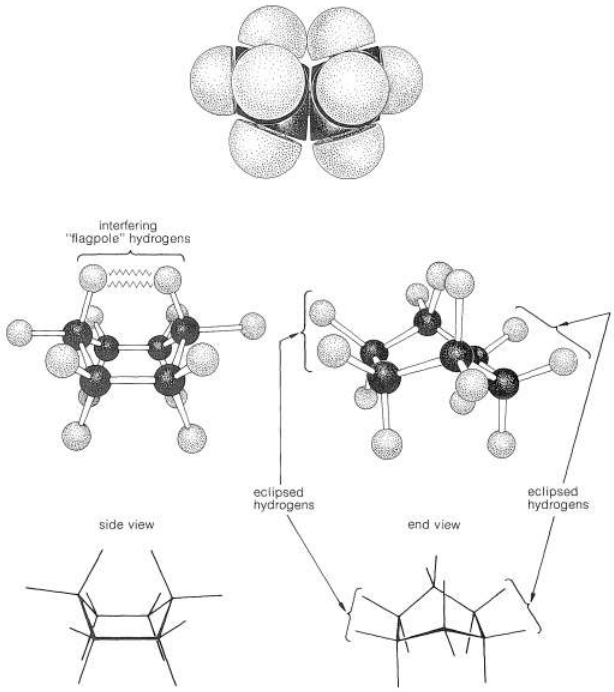

Figure 12-4: Extreme boat form of cyclohexane showing interfering and eclipsed hydrogens. Top, space-filling model; center, ball-and-stick model; bottom, sawhorse representations.

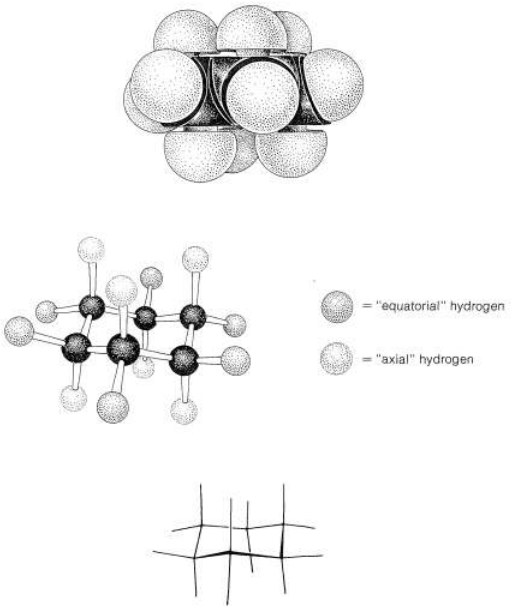

Figure 12-5: Chair form of cyclohexane showing equatorial and axial hydrogens. Top, space-filling model; center, ball-and-stick model; bottom, sawhorse representation. Notice that all the axial positions are equivalent and all the equatorial positions are equivalent. By this we mean that a substituent on any one of the six axial positions gives the same axial conformation, whereas a substituent on any one of the six equatorial positions gives the same equatorial conformation.

You should make and inspect models such as those in Figure 12-3 to see the rather striking difference between the chair and boat conformations that is not obvious from the diagrams. You will find that the chair structure is quite rigid, and rotation does *not* occur around the C–C bonds with interconversion to the boat structure. In contrast, the boat form is quite flexible. Rotation about the C–C bonds permits the ring to twist one way or the other from the extreme boat conformation to considerably more stable, equal-energy conformations, in which the flagpole hydrogens move farther apart and the eight hydrogens along the sides become largely but not completely staggered. These arrangements are called the **twist-boat** (sometimes **skew-boat**) conformations (see Figure 12-6) and are believed to be about $5\ \text{kcal mol}^{-1}$ less stable than the chair form.

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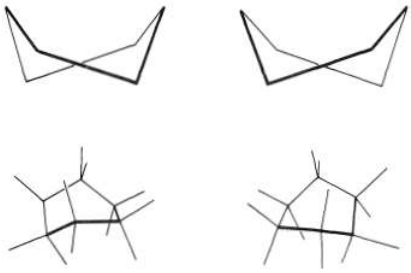


Figure 12-6: The twist-boat conformations of cyclohexane.

It is possible to measure the spectral properties of the twist-boat form by a very elegant technique employed by F. A. L. Anet. Because the equilibrium constant for conversion of chair to boat increases with temperature, a considerable proportion of the molecules exist as the twist-boat form in the vapor at 800°. If such vapor is allowed to impinge on a surface cooled to $20\ \mathrm{K}$, the film condensate contains about 25% of the twist-boat form. At this low temperature, the twist-boat form is converted to the more stable chair form at a very slow rate. Infrared spectra can be taken of the boat-chair mixture at $10\ \mathrm{K}$. If the mixture is allowed to warm to $75\ \mathrm{K}$, the normal equilibrium favoring the chair form is established in a short time.

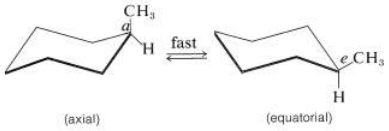
12.3.2: Dreiding Models

The spatial arrangement (stereochemistry) of cyclohexane and other organic compounds are studied conveniently with the aid of *Dreiding models*, which are made with standard bond angles and scaled bond distances. The bonds have stainless-steel rods that make a snap-fit into stainless-steel sleeves. Rotation is smooth about the bonds and there is sufficient flexibility to accommodate some angle strain. Dreding models of the conformations of cyclohexane are shown in Figure 12-7. Notice that these models correspond closely to the sawhorse representations in Figures 12-4, 12-5, and 12-6.

Figure 12-7: Dreiding models of the cyclohexane conformations.

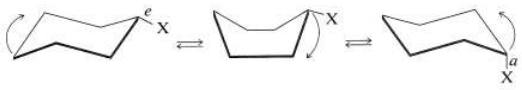
12.3.3: Conformational Equilibria and Equilibration for Cyclohexane Derivatives

Figure 12-5 shows that there are two distinct kinds of hydrogen in the chair form of cyclohexane - six that are close to the "average" plane of the ring (called **equatorial** hydrogens) and three above and three below this average plane (called **axial** hydrogens). This raises interesting questions in connection with substituted cyclohexanes: For example, is the methyl group in methylcyclohexane equatorial or axial? Since only *one* methylcyclohexane is known, the methyl group must be exclusively equatorial (e), exclusively axial (a), or the two forms must be interconverted so rapidly that they cannot be separated into isomeric forms. It appears that the latter circumstance prevails, with the ring changing rapidly from one chair form to another by flipping one end of the chair up and the other end down:



Such a change would cause a substituent in an axial position to go to an equatorial position and *vice versa*. This process is called **ring inversion** and its rate often is called the **inversion frequency**. With cyclohexane, inversion is so fast at room temperature that, on average, the molecules, flip about 100,000 times per second, over an energy barrier of about $11\ \mathrm{kcal\ mol^{-1}}$.

You will understand this flipping process if you make a model of a cyclohexane ring carrying a single substituent. By manipulating the model you can discover some of the different ways the process can occur. The simplest route is simply to flip up one corner of the ring to convert the chair into a boat and then flip down the opposite carbon:



Because of the flexibility of the boat conformation, it is possible to transform it to other boat conformations whereby carbons other than the one indicated flip down and complete the interconversion.

At room temperature the conformation of methylcyclohexane with the methyl equatorial is more stable than the one with the methyl axial by $1.7\ \text{kcal mol}^{-1}$. The same is true of all monosubstituted cyclohexanes to a greater or lesser degree. Reasons for this can be seen from space-filling models (Figure 12-8), which show that a substituent group has more room when the substituent is equatorial than when it is axial. In the axial position the substituent is considerably closer to the two axial hydrogens on the same side of the ring than to other hydrognes, even hydrogens on adjacent carbons when the substituent is in the equatorial position (Figure 12-8). For example, when the substituent is bromine, which has a $\text{C}-\text{Br}$ bond length of 1.94 Å, the distance from axial bromine to the axial hydrogen at C_3 or C_5 on the same side of the ring is about 2.7 Å. In contrast, the distance from equatorial bromine to any of the hydrogens on the adjacent carbons is about 3.1 Å.

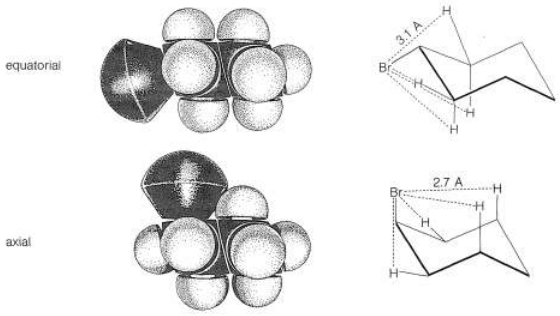


Figure 12-8: Space-filling models of equatorial and axial chair conformations of cyclohexyl bromide. Significant nonbonded interactions are indicated for the sawhorse formulas by dashed lines; these interactions are more severe in the axial than the equatorial conformation.

There is a very important general aspect of the difference between these two nonbonded $\text{H}\cdots\text{Br}$ interactions at 2.7 Å and 3.1 Å. Whenever two nonbonded atoms are brought close together, and before the massive repulsion sets in (which is so evident in Figure 4-6), there is a slight *dip* in the energy curve corresponding to *attraction*.[2] For nonbonded $\text{H}\cdots\text{Br}$ interactions the bottom of the dip comes at about 3.1 Å (Figure 12-9), and the resulting attraction between the atoms will provide some stabilization of the equatorial conformation relative to the axial conformation.

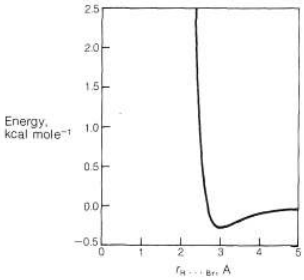


Figure 4-6). Other nonbonded pairs of atoms have similar curves, but with different positions and depths of the minima. The minima usually are considerably deeper with atoms of higher atomic number. The ratios of the attractive forces at the lowest point for $\text{He}\cdots\text{He}$, $\text{Ne}\cdots\text{Ne}$, $\text{Ar}\cdots\text{Ar}$, $\text{Kr}\cdots\text{Kr}$, and $\text{Xe}\cdots\text{Xe}$ are 1:4:14:21:28.

Weak attractive forces between nonbonded atoms are called *van der Waals attractive forces, London*[3] *forces,* or *dispersion forces,* and are of great importance in determining the properties of liquids. They also can be expected to play a role in determining conformation equilibria whenever the distances between the atoms in the conformations correspond to the so-called *van der Walls minima*.

Table 12-2 shows the contribution made by various substituents to the free-energy change from the axial to the equatorial orientations of the substituent. Thus, for bromine, the free-energy change, ΔG^0, is $-0.5\ \text{kcal mol}^{-1}$, which means that at 25°, the equilibrium constant, K, for the axial $\rightleftharpoons$ equatorial equilibrium is about 2.3 (from $-2.303RT\log K = \Delta G^0$; see Section 4-4A).

From many studies it is known that the interconversion of conformations with the substituent in the equatorial and the axial positions occurs about 100,000 times per second, which corresponds to a transition-state energy (activation energy) of about 11 kcal mol^{-1} above the ground-state energy. The rate decreases as the temperature is lowered. If one cools chlorocyclohexane to its melting point (-44°), the substance crystallizes to give the pure equatorial isomer. The crystals then can be cooled to -150° and dissolved at this temperature in a suitable solvent. At -150° it would take about 130 days for half of the equatorial form to be converted to the axial form. However, when the solution is warmed to -60° the equatorial conformation is converted to the equilibrium mixture in a few tenths of a second.

Table 12-2: *A Selection of ΔG^0 for the Change from Axial to Equatorial Orientation of Substituents for Monosubstituted Cyclohexanes*

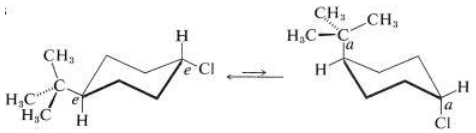
Substituent	$-\Delta G^{\circ}$, kcal mole^{-1}	Substituent	$-\Delta G^{\circ}$, kcal mole^{-1}
CH_3-	1.7	O_2N-	1.1
C_2H_5-	1.8	$N\equiv C-$	0.2
$(CH_3)_2CH-$	2.2	CH_3O-	0.5
$(CH_3)_3C-$	≥5.0		0.7
F	0.3		
Cl	0.5		1.3
Br	0.5		
I	0.5	C_6H_5-	3.0

[a]Values from F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Amer. Chem. Soc.* **91,** 344 (1969) and J. A. Hirsch in "Topics in Stereochemistry," Vol I, N. L. Allinger and E. L. Eliel, Ed., Interscience Publishers, New York, 1967.

12.3.4: Cis-Trans Isomerism and Conformational Equilibria for Cyclohexane Derivatives

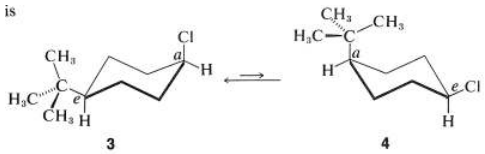
The cis-trans isomerism of cyclohexane derivatives (Section 5-1A) is complicated by conformational isomerism. For example, 4-*tert*-butylcyclohexyl chloride theoretically could exist in four stereoisomeric chair forms, 1, 2, 3, and 4.

trans



1 2

cis



3 4

Figure 12-11).

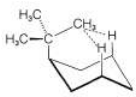


Figure 12-10: 1,3-interactions in a cyclohexane ring with an axial tert-butyl group.

Figure 12-11: Twist-boat conformation of cis-1,*4-di*-tert-*butylcyclohexane.*

Use of ^{13}C nmr spectroscopy to determine whether a substituent is in an axial or equatorial position is well illustrated with *cis*- and *trans*-4-*tert*-butylcyclohexanols, 5 and 6:

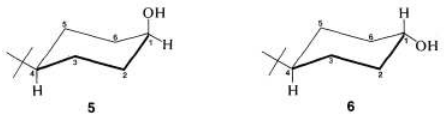


Figure 12-12. At -110°, the equatorial form is 99% of the mixture and is interconverted only very slowly with the 1% of axial form. Despite the strong ^{13}C nmr signals from the equatorial form, the chemical shifts of C_3, C_5, and CH_3 carbons of the axial form are sufficiently different that they can be seen upfield of the methyl resonance of the equatorial form.

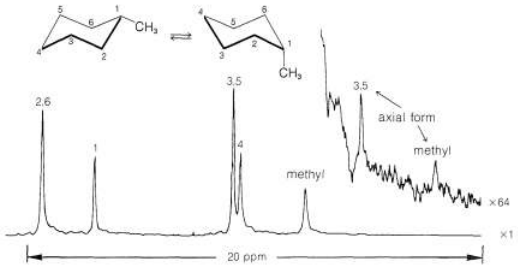


Figure 12-12: Proton-decoupled, 63.1 MHz, ^{13}C spectrum of methylcyclohexane at -110°. The upper right curve was taken with the signal sensitivity control turned up by a factor of 64. (Courtesy of Dr. F. A. L. Anet.)

12.3.5: Cyclopentane

The five $-CH_2-$ groups of cyclopentane theoretically could form a regular planar pentagon (internal angles of 108°) with only a little bending of the normal $C-C-C$ bond angles. Actually, cyclopentane molecules are *not* flat. The planar structure has completely eclipsed hydrogens, which makes it less stable by about 10 kcal mol^{-1} than if there were no eclipsed hydrogens. The result is that each molecule assumes a puckered conformation that is the best compromise between distortion of bond angles and eclipsing of hydrogens. The best compromise conformations have the ring twisted with one or two of the $-CH_2-$ groups bent substantially out of a plane passed through the other carbons (Figure 12-14). The flexibility of the ring is such that these deformations move rapidly around the ring.

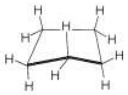


Figure 12-14: Nonplanar conformation of cyclopentane. Notice that the forward carbon is out of the plane of the other four.

12.3.6: Cyclobutane

Formation of a four-membered ring of carbon atoms can be achieved only with substantial distortion of the normal valence angles of carbon, regardless of whether the ring is planar or nonplanar. In cyclobutane, for example, if the valence bonds are assumed to lie along straight lines drawn between the carbon nuclei, each $C-C-C$ bond angle will be 19.5° smaller than the 109.5° tetrahedral value:

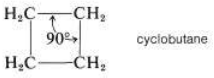


Figure 12-15).

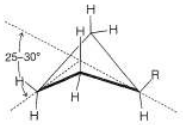
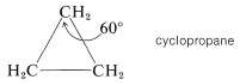


Figure 12-15: Nonplanar cyclobutane conformation with a substituent R in the less hindered, quasi-equatorial position. The dihedral angle between the two halves of the bent ring usually is 25° to 30°, that is, a 25° to 30° deviation from planarity.

12.3.7: Cyclopropane

The three carbon atoms of the cyclopropane ring lie in a plane. Therefore the angle strain is expected to be considerable because each $C-C-C$ valence angle must be deformed 49.5° from the tetrahedral value. It is likely that some relief from the strain associated with the eclipsing of the hydrogens of cyclopropane is achieved by distortion of the $H-C-H$ and $H-C-C$ bond angles:



cyclopropane

12.3.7.1: "Cycloethane" (Ethene)

If one is willing to consider a carbon-carbon double bond as a two-membered ring, then ethene, C_2H_4, is the simplest possible cycloalkane ("cycloethane"). As such, C_2H_4 has $C-C-C$ valence angles of 0° and therefore an angle strain of 109.5^o at each CH_2 group compared to the tetrahedral value:

12.3.8: Contributors and Attributions

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[1]Pioneering work on the conformations of cyclohexane and its derivatives was carried out by O. Hassel (Norway) and D. H. R. Barton (United Kingdom) for which they shared a Nobel Prize in 1969.

[2]The vertical scale of Figure 4-6 does not permit seeing the dip in the curve resulting from attractive forces between neon atoms. It is deepest when r is about $3.12\ \AA$ and amounts to $0.070\ \text{kcal mol}^{-1}$.

[3]After F. London, who developed a quantum-mechanical theory of the origin of these forces and also pioneered many quantum calculations of great consequence to chemistry, including bonding in H_2, which will be discussed in Section 21-1.

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12.4: Strain in Cycloalkane Rings

12.4.1: The Baeyer Theory

Many of the properties of cyclopropane and its derivatives are similar to the properties of alkenes. In 1890, the famous German organic chemist, A. Baeyer, suggested that cyclopropane and cyclobutane derivatives are different from cyclopentane and cyclohexane, because their $C-C-C$ angles cannot have the tetrahedral value of $109.5°$. At the same time, Baeyer hypothesized that the difficulties encountered in synthesizing cycloalkane rings from C_7 upward was the result of the angle strain that would be expected if the large rings were regular planar polygons (see Table 12-3). Baeyer also believed that cyclohexane had a planar structure like that shown in Figure 12-2, which would mean that the bond angles would have to deviate $10.5°$ from the tetrahedral value. However, in 1895, the then unknown chemist H. Sachse suggested that cyclohexane exists in the strain-free chair and boat forms discussed in Section 12-3. This suggestion was not accepted at the time because it led to the prediction of several possible isomers for compounds such as chlorocyclohexane. The idea that such isomers might act as a single substance, as the result of rapid equilibration, seemed like a needless complication, and it was not until 1918 that E. Mohr proposed a definitive way to distinguish between the Baeyer and Sachse cyclohexanes. As will be discussed in Section 12-9, the result, now known as the Sachse-Mohr theory, was complete confirmation of the idea of nonplanar large rings.

Table 12-3: *Strain and Heats of Combustion of Cycloalkanes*

Cycloalkane, $(CH_2)_n$	n	Angle strain at each CH_2, deg[a]	Heat of combustion,[b] ΔH°, kcal mole^{-1}	Heat of combustion per CH_2, $\Delta H^\circ/n$, kcal	Total strain,[c] kcal mole^{-1}
ethene	2	109.5	337.2	168.6	22.4
cyclopropane	3	49.5	499.9	166.6	27.7
cyclobutane	4	19.5	655.9	164.0	26.3
cyclopentane	5	1.5	793.4	158.7	6.4
cyclohexane	6	(10.5)[d]	944.8	157.5	0.4
cycloheptane	7	(19.1)[d]	1108.1	158.4	6.3
cyclooctane	8	(25.5)[d]	1268.9	158.6	9.7
cyclononane	9	(30.5)[d]	1429.5	158.8	12.9
cyclodecane	10	(34.5)[d]	1586.1	158.6	12.1
cyclopentadecane	15	(46.5)[d]	2362.5	157.5	1.5
open-chain alkane				157.4	

[a] Angle strain calculated as the difference between the internal angle of a regular polygon and the tetrahedral angle of 109.5°. The actual strain values are somewhat different because the observed $CH_2—CH_2—CH_2$ angles are about 112.5° in linear hydrocarbons (Section 12-3A).

[b] For gaseous hydrocarbons to give liquid water at 25°. Data from S. Kaarsemaker and J. Coops, *Rec. Trav. Chim.* **71,** 261 (1952); J. Coops, H. Van Kamp, W. A. Lambgreats, B. J. Visser, and H. Dekker, *Rec. Trav. Chim.* **79,** 1226 (1960); and D. R. Shull, E. F. Westrum, Jr., and G. C. Sinke, *The Chemical Thermodynamics of Organic Compounds,* John Wiley and Sons, Inc., New York, 1969.

[c] Calculated by subtracting ($n \times 157.4$) from the observed heat of combustion. [d] Assuming planar rings.

Because cyclopentane and cyclobutane (Sections 12-3E and 12-3F) also have nonplanar carbon rings, it is clear that the Baeyer postulate of planar rings is not correct. Nonetheless, the idea of angle strain in small rings is important. There is much evidence to show that such strain produces thermodynamic instability and usually, but not always, enhanced chemical reactivity.

12.4.2: Heats of Combustion of Cycloalkanes and Strain Energies

The strain in ring compounds can be evaluated quantitatively by comparing the heats of combustion per CH_2 group, as in Table 12-3. The data indicate that cyclohexane is virtually strain-free, because the heat of combustion per CH_2 is the same as for alkanes $(157.4 \text{ kcal mol}^{-1})$. The increase for the smaller rings clearly reflects increasing angle strain and, to some extent, unfavorable interactions between nonbonded atoms. For rings from C_7 to C_{12} there appears to be a residual strain for each additional CH_2 of 1 to $1.5 \text{ kcal mol}^{-1}$. These rings can be puckered into flexible conformations with normal $C-C-C$ angles, but as will be shown in Section 12-6, from C_7 to C_{13} such arrangements all have pairs of partially eclipsed or interfering hydrogens. The larger cycloalkanes such as cyclopentadecane appear to be essentially strain-free.

We expect that the total strain in cycloalkanes of the type $(CH_2)_n$ should decrease rapidly in the order $n = 2 > n = 3 > n = 4$. However, the data of Table 12-3 show that the order actually is $3 \cong 4 > 2$. This difference in order often is disguised by dividing the heats of combustion by the numbers of CH_2 groups and showing that the heats of combustion per CH_2 are at least in the order expected from bond-angle strain. This stratagem does not really solve the problem.

It is important to recognize that when we evaluate strain from the heats of combustion per CH_2 group, we are assuming that the $C-H$ bonds have the *same* strength, independent of n. However, the bond-dissociation energies of each of the $C-H$ bonds of ethene and cyclopropane are greater than of the C_2-H bonds of propane (Table 4-6). Any amount that these bonds are *stronger* than normal will make the strain energies judged from heats of combustion appear to be *less*. If we take the $C-H$ bonds to be on average $2\ \text{kcal mol}^{-1}$ stronger in cyclobutane, $6\ \text{kcal mol}^{-1}$ stronger in cyclopropane, and $13\ \text{kcal mol}^{-1}$ in ethene, we can correct the carbon-carbon strain energies accordingly. For cyclobutane the corrected strain then is 8×2 (for the eight $C-H$ bonds) $+ 26.3$ (total strain from Table 12-3) $= 42.3\ \text{kcal mol}^{-1}$. The corresponding figures for cyclopropane are $6 \times 6 + 27.6 = 63.6\ \text{kcal mol}^{-1}$, and for ethene, $4 \times 13 + 22.4 = 74.4\ \text{kcal mol}^{-1}$. The results support the intuitive expectations by giving larger differences in the right direction for the strain energies of cyclobutane, cyclopropane, and ethene. Whether this analysis is quantitatively correct or not, it does give some indication of why *strain energy* is not a very precise concept - unless we can reliably estimate the *net* effects of a strain.

12.4.3: Contributors and Attributions

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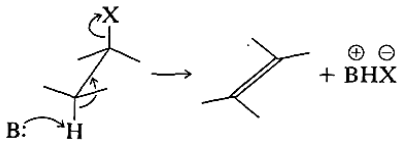
12.5: Chemical Properties

Strain in small-ring cycloalkanes has a profound influence on their heats of combustion (Table 12-3). We reasonably expect that other chemical properties also will be affected. Indeed, like alkenes, cyclopropane and cyclobutane undergo C—C bond cleavage reactions that are not observed for cyclopentane and cyclohexane, or for saturated, open-chain hydrocarbons. A summary of these reactions is presented in Table 12-4. It will be seen that the reactions result in cleavage of a C—C bond to give an open-chain compound with normal bond angles. Relief of angle strain is an important contributing factor to the driving force for these reactions. Therefore, ethene is highly reactive, whereas cyclopropane and cyclobutane are somewhat less reactive. The C—C bonds of the larger, relatively strain-free cycloalkanes are inert, so these substances resemble the alkanes in their chemical behavior. Substitution reactions, such as chlorination of cyclopentane and higher cycloalkanes, generally are less complex than those of the corresponding alkanes because there are fewer possible isomeric substitution products. Thus cyclohexane gives only one monochloro product, whereas hexane gives three isomeric monochloro hexanes.

Conformation has a major influence on the chemical reactivity of cycloalkanes. To understand its effect in any one reaction, we first need to know what the conformation is of the transition state, and this requires a knowledge of the reaction mechanism. Next, we have to decide what amount of energy is required for the reactants to achieve transition-state conformations. For example, consider the E_2 elimination discussed in Section 8-8D. The preferred transition state requires the leaving groups to be antarafacial and coplanar:



For cyclohexane derivatives to react in this way, the transition-state conformation must have both leaving groups *axial*:

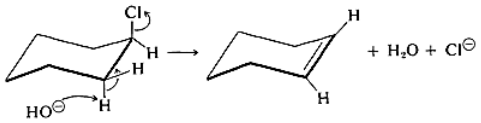


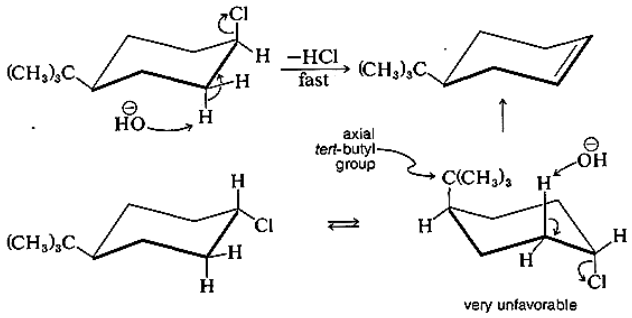
Table 12-4: *Ring-Cleavage Reactions of Cycloalkanes*

Reaction	"Cycloethane" $n=2$	Cyclopropane $n=3$	Cyclobutane $n=4$	Cyclopentane $n=5$	Cyclohexane $n=6$
$(CH_2)_n + Br_2 \longrightarrow (CH_2)_{n-2}(CH_2Br)_2$	very readily[a]	slowly[b]	inert	inert	inert
$(CH_2)_n + H_2SO_4 \longrightarrow (CH_2)_{n-2}(CH_3)(CH_2OSO_3H)$	readily	readily	?	inert	inert
$(CH_2)_n + KMnO_4 \longrightarrow (CH_2)_{n-2}(CH_2OH)_2$	readily	inert	inert	inert	inert
$(CH_2)_n + H_2 \longrightarrow (CH_2)_{n-2}(CH_3)_2$	readily	readily at 120°	readily at 200°	inert	inert

[a]By either polar or radical mechanisms.

[b]Reactions by polar mechanisms are very slow with bromine alone, but apparently are accelerated by electrophilic agents, which activate bromine by facilitating formation of $Br^{\oplus}$ by complexing with $Br^{\ominus}$ (e.g., HBr, $FeBr_3$, etc.). Cyclopropane reacts rather rapidly with bromine by a radical-chain mechanism, even at −78°, if bromine atoms are formed by light irradiation.

For this reason, compounds such as *cis*-4-*tert*-butylchlorocyclohexane eliminate HCl much more readily by the E_2 mechanism than do the corresponding trans isomers.



To have the antarafacial coplanar mechanism of cycloalkanes operate with the trans isomer, the transition state would have to have the *tert*-butyl group in the highly unfavorable axial position.

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12.6: The Larger Cycloalkanes and their Conformations

The Baeyer strain theory suggested that the larger cycloalkanes ring are difficult to synthesize because of angle strain associated with planar rings, as calculated in Table 12-3. We now know that, except for cyclopropane, none of the cycloalkanes have planar carbon rings and that the higher cycloalkanes have normal or nearly normal bond angles. The reason that the higher cycloalkanes are generally difficult to synthesize from open-chain compounds is not so much angle strain, as Baeyer hypothesized, but the low probability of having reactive groups on the two fairly remote ends of a long hydrocarbon chain come together to effect cyclization. Usually, coupling of reactive groups on the ends of *different* molecules occurs in preference to cyclization, unless the reactions are carried out in very dilute solutions. This is called the **high-dilution** technique for achieving ring formation when the ring-forming reaction has to compete with rapid inter-molecular reactions.

With regard to conformations of the larger cycloalkanes, we first note that the chair form of cyclohexane is a "perfect" conformation for a cycloalkane. The $C-C-C$ bond angles are close to their normal values, all the adjacent hydrogens are staggered with respect to one another, and the 1,3-axial hydrogens are not close enough together to experience nonbonded repulsions. About the only qualification one could put on the ideality of the chair form is that the trans conformation of butane is somewhat more stable than the gauche conformation (Section 5-2), and that all of the $C-C-C-C$ segments of cyclohexane have the gauche arrangement. Arguing from this, J. Dale[6] has suggested that large cycloalkane rings would tend to have trans $C-C-C-C$ segments to the degree possible and, indeed, cyclotetradecane seems to be most stable in a rectangular conformation with trans $C-C-C-C$ bond segments (Figure 12-16). This conformation has a number of possible substituent positions, but because only single isomers of monosubstituted cyclotetradecanes have been isolated, rapid equilibration of the various conformational isomers must occur. Other evidence indicates that the barrier to interconversion of these conformations is about $7\ \mathrm{kcal\ mol^{-1}}$.

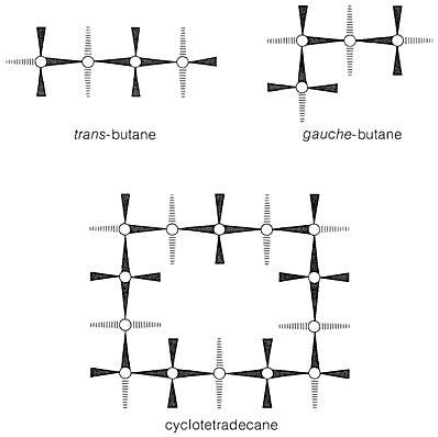
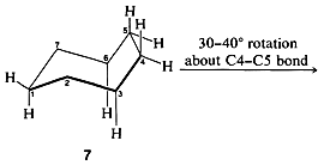


Figure 12-16 Favored conformation of cyclotetradecane as proposed by Dale. For comparison, the trans and gauche forms of butane are shown by the same convention. (The convention implies that the wedged lines are $C-C$ or $C-H$ bonds projecting out of the plane of the paper, with the wide end closest to you, and the broken lines are $C-H$ bonds projecting behind the plane of the paper. The result is an "aerial" view of the molecule in the most stable staggered conformation.)

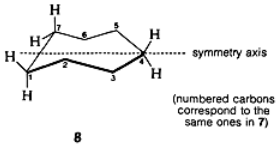
With the cycloalkanes having 7 to 10 carbons, there are problems in trying to make either trans or gauche $C-C-C-C$ segments, because the sizes of these rings do not allow the proper bond angles or torsional angles, or else there are more or less serious nonbonded repulsions. Consequently each of these rings assumes a compromise conformation with some eclipsing, some nonbonded repulsions, and some angle distortions. Brief comments on some of these conformations follow. It will be useful to use molecular models to see the interactions involved.

12.6.1: Cycloheptane

Possible conformations for cycloheptane include the "comfortable" appearing chair form, 7. However, this form has eclipsed hydrogens at C_4 and C_5 as well as nonbonded interactions between the axial-like hydrogens on C_3 and C_6. The best compromise conformation is achieved by a 30°-40° rotation around the C_4-C_5 bond to relieve the eclipsing of the hydrogens. This spreads the interfering hydrogens at C_3 and C_6 and results in a somewhat less strained conformation called the *twist chair*. The twist chair, 8, is very flexible and probably only about $3\ \mathrm{kcal\ mol^{-1}}$ of activation is required to interconvert the various possible monosubstituted cycloheptane conformations.



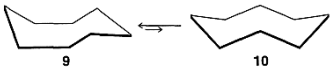
7



8

12.6.2: Cyclooctane

There are several more or less reasonable looking cyclooctane conformations. After much research it now is clear that the favored conformation is the *boat-chair*, 9, which is in equilibrium with a few tenths percent of the *crown* conformation, 10 :



9 10

The activation energy for interconversion of these two forms is about $10\ \text{kcal mol}^{-1}$. The boat-chair conformation 9 is quite flexible and movement of its CH_2 groups between the various possible positions occurs with an activation energy of only about $5\ \text{kcal mol}^{-1}$.

12.6.3: Cyclononane

Several more or less reasonable conformations of cyclononane also can be developed, but the most favorable one is called the *twist-boat-chair*, which has three-fold symmetry (Figure 12-17). The activation energy for inversion of the ring is about $6\ \text{kcal mol}^{-1}$.

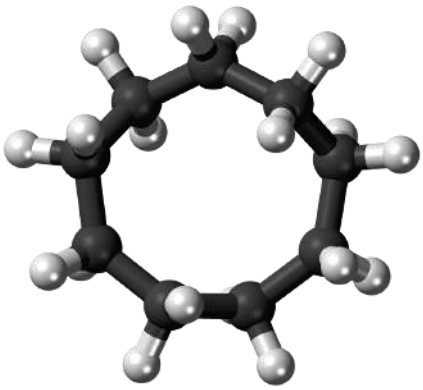
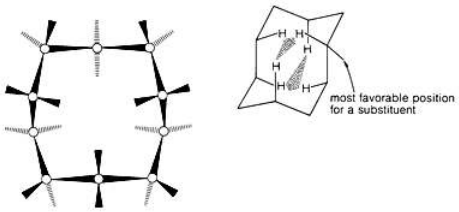


Figure 12-17: Twist boat-chair conformation of cyclononane (Public Domain; Jynto). I**Color code:** Carbon, C: black Hydrogen, H: white

12.6.4: Cyclodecane

The stable conformation of cyclodecane (Figure 12-18) is similar to that of cyclotetradecane (Figure 12-16). However, there are relatively short $H\cdots H$ distances and the $C{-}C{-}C$ bond angles are somewhat distorted because of cross-ring hydrogen-hydrogen repulsions. The most stable position for a substituent on the cyclodecane ring is the one indicated in Figure 12-18. The least stable positions are those in which a substituent replaces any of the six hydrogens shown, because nonbonded interactions are particularly strong at these positions. The activation energy for interconversion of substituent positions is about $6\ \text{kcal mol}^{-1}$.



Most stable conformation of cyclodecane; Dale and sawhorse representations. The shaded area in the sawhorse convention indicates substantial nonbonded H · · · H interactions.

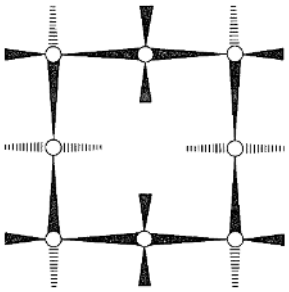


Figure 12-16).

[6]Pronounced Dalluh.

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12.7: Cycloalkenes and Cycloalkanes

The C−C=C angle in alkenes normally is about 122°, which is 10° larger than the normal C−C−C angle in cycloalkanes. This means that we would expect about 20° more angle strain in small-ring cycloalkenes than in the cycloalkanes with the same numbers of carbons in the ring. Comparison of the data for cycloalkenes in Table 12-5 and for cycloalkanes in Table 12-3 reveals that this expectation is realized for cyclopropene, but is less conspicuous for cyclobutene and cyclopentene. The reason for this is not clear, but may be connected in part with the C−H bond strengths (see Section 12-4B).

Cyclopropene has rather exceptional properties compared to the other cycloalkenes. It is quite unstable and the liquid polymerizes spontaneously although slowly, even at −80°. This substance, unlike other alkenes, reacts rapidly with iodine and behaves like an alkyne in that one of its double-bond hydrogens is replaced in silver-ammonia solution to yield an alkynide-like silver complex.

Table 12-5: *Properties of Some Cycloalkenes and Cycloalkynes*

Compound	Mp, °C	Bp, °C	$-\Delta H^\circ$ of hydrogenation,[a] kcal mole^{-1}	Net strain energy,[b] kcal mole^{-1}
"cycloethene" (ethyne)	−81	−84	42[c]	35
cyclopropene	–	−36	54	53
cyclobutene	–	2	31	28
cyclopentene	−135	44	27	4
cyclohexene	−104	83	30	1
cycloheptene	−56	115	27	4
cis-cyclooctene	−12	138	24	5
trans-cyclooctene	−59	143	33	14
cis-cyclononene	–	168	25	9
trans-cyclononene	–	$95^{30\ mm}$	28	12
cyclooctyne	–	$57^{22\ mm}$	69[d]	16[e]
cyclononyne	–	$62^{13\ mm}$	62[d]	12[e]
cyclodecyne	–	$80^{12\ mm}$	56[d]	5[e]

[a]For the vapor state, calculated from data summarized by P. von R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Amer. Chem. Soc.* **92,** 2377 (1970).

[b]Calculated assuming that the normal heat of hydrogenation of a cis-disubstituted double bond is 29 kcal mole^{-1} (cf. Table 11-2). With cyclopropene as an example, the net strain energy is obtained as 54 − 29 + 28 = 53 kcal mole^{-1}, where 54 kcal is the experimental $-\Delta H^\circ$ of hydrogenation, −29 kcal is ΔH° for hydrogenation of a normal cis-disubstituted alkene, and 28 kcal is the strain energy of cyclopropane, the hydrogenation product.

[c]For hydrogenation to $CH_2{=}CH_2$.

[d]Estimated from the data of R. B. Turner, A. D. Jarrett, P. Goebel, and B. J. Mallon, *J. Amer. Chem. Soc.* **95,** 790 (1973).

[e]Calculated assuming the heat of hydrogenation of a disubstituted alkyne normally is 63 kcal mole^{-1}.

Figure 12-20b) are stable and thus resolvable.

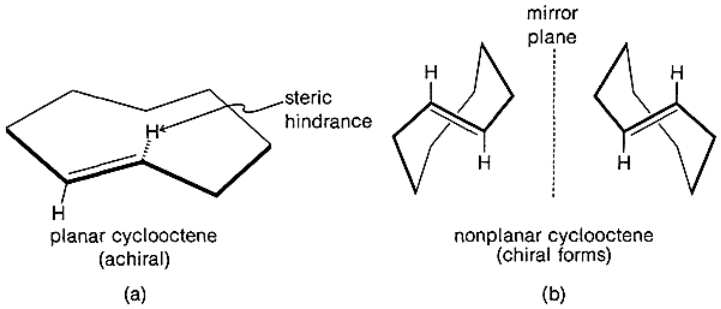

Figure 12-20 Representation of (a) achiral and (b) chiral conformations of trans-cycloalkenes, using trans-cyclooctene *as a specific example. For* trans-*cyclooctene, the achiral state is highly strained because of interference between the "inside" alkenic hydrogen and the* CH_2 *groups on the other side of the ring. Consequently the mirror-image forms are quite stable. With* trans-*cyclononene, the planar state is much less strained and, as a result, the optical isomers are much less stable. With* trans-*cyclodecene, it has not been possible to isolate mirror-image forms because the two forms corresponding to (b) are interconverted through achiral planar conformations corresponding to (a) about* 10^{16} *times faster than with* trans-*cyclooctene.*

The C−C=C bond angles in alkynes normally are 180° and the angle strain involved in making a small-ring cycloalkyne, such as cyclopropyne, apparently is prohibitive. The smallest reasonably stable member of the series is cyclooctyne, and its properties, along with those of some higher homologs, are shown in Table 12-5. Strong evidence has been adduced for the existence of cyclopentyne, cyclohexyne, and cycloheptyne as unstable reaction intermediates.

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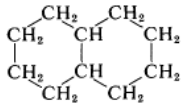
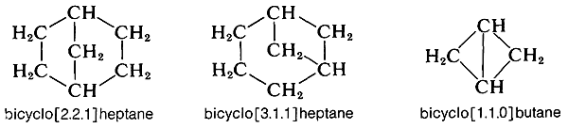
12.8: Nomenclature of Polycycloalkanes

There are many hydrocarbons and hydrocarbon derivatives with two or more rings having common carbon atoms. Such a substance is decalin, which has ten carbons arranged in two six-membered rings:



decalin
(bicyclo[4.4.0]decane)
(decahydronaphthalene)

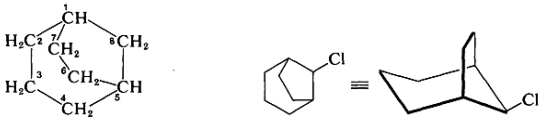
Compounds of this type usually are named by attaching the prefix *bicyclo* to the name of the open-chain hydrocarbon with the *same total number of carbon atoms as in the rings*. Thus decalin, which has ten carbons in the ring system, is a *bicyclodecane*. Next, we have to have a way to specify the sizes of the rings, which is done by counting the number of carbon atoms in each of the chains connecting the two atoms that constitute the **ring junctions** or **bridgeheads**. Decalin has *four* carbons in each of two chains and *none* in the third. Therefore, decalin is *bicyclo[4.4.0]decane*. Notice that the numbers are enclosed in square brackets after the prefix "bicyclo" and before the name of the hydrocarbon. The numbers are listed in order of decreasing magnitude and are properly separated by periods, not commas. Some other examples follow:



bicyclo[2.2.1]heptane | bicyclo[3.1.1]heptane | bicyclo[1.1.0]butane

To name substituted polycycloalkanes, a numbering system is required. In the IUPAC system the *main* ring is the one containing the largest number of carbon atoms. Two of the carbons in the main ring serve as junctions for the main bridge, which is chosen to be as large as possible, consistent with the choice of the main ring. Additional rules are required for more complex cases, but these are not of interest to us here.

In numbering bicyclic ring systems that have two ring junctions, one of them is chosen as C_1. The numbering proceeds along the *longest* chain of carbons to the next junction, then continues along the next longest chain, and finally is completed along the shortest chain. For example,

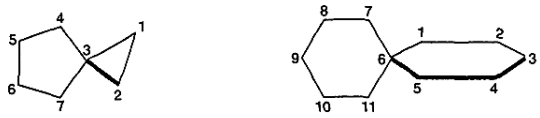


bicyclo[3.2.1]octane

8-chlorobicyclo[3.2.1]octane
11

Here, the main ring has seven carbons (C_1 to C_7) and there is a one-carbon bridge (C_8).

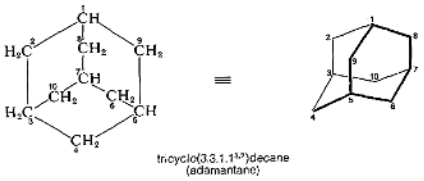
When the hydrocarbon rings have only one carbon in common, they are called *spiranes* and are given systematic names in accord with the following examples:



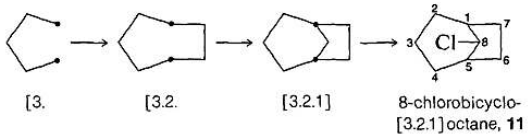
spiro[2.4]heptane | spiro[5.5]undecane

Notice that for spiranes the numbering starts next to the junction point in the *smaller* ring.

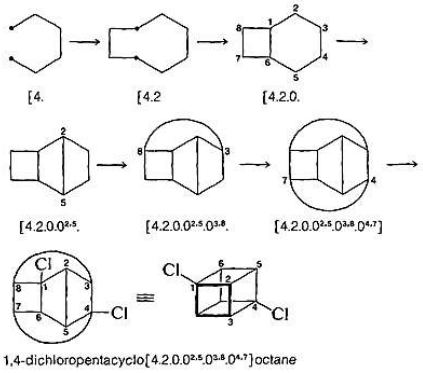
The naming of tricycloalkanes follows the same general system.[7] The largest ring and its main linkage form a bicyclic system, and the location of the fourth or *secondary* linkage is shown by superscripts. The systematic name of the interesting hydrocarbon adamantane is given below as an example; its conformation also is shown. The largest ring in adamantane is eight-membered and the carbons that constitute it could be selected in several different ways. The carbon chosen as C_9 lies between C_1 and C_5, not between the higher-numbered C_3 and C_7:



To generate a structure from a name such as 8-chlorobicyclo[3.2.1]octane, 11, start with a pair of junction atoms, connect them as prescribed, then number the initial skeleton, make the final connections, and locate the substituents. The steps follow:



A further and more complicated example is 1,4-dichloropentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane:



The most difficult part of the whole procedure may be generating the final structure in appropriate perspective. The task of doing this can be simplified greatly by the use of molecular models.

[7]To determine whether a given bridged polycylic ring system should be *bicyclo-*, *tricyclo-*, and so on, use the rule that the number of rings is equal to the minimum number of bond cleavages to convert the ring system into an *acyclic* hydrocarbon having the same number of carbons.

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12.9: Conformations of Decalin

The six-membered rings of decalin, like those of cyclohexane, are expected to be most stable in the chair form. However, there are two possible ways in which two chairs can be joined (Figure 12-21). The ring-junction hydrogens may be either on the same side of the molecule (*cis*-decalin) or on opposite sides (*trans*-decalin). When the two rings are joined through two equatorial-type bonds, *trans*-decalin results, whereas an axial-equatorial union gives *cis*-decalin. Both isomers are known, and the trans isomer is about 2 kcal mol^{-1} more stable than the cis isomer, largely because of relatively unfavorable nonbonded interactions within the concave area of *cis*-decalin (see Figure 12-22).

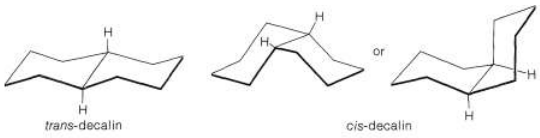

Figure 12-21: Chair conformations of the decalins. The two drawings of the cis conformation represent the same arrangement of atoms but different perspectives.

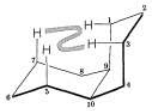

Figure 12-22: Representation of cis-decalin showing nonbonded interactions (shaded areas). The numbering of the decalin ring is the currently accepted convention, which is not the same as the numbering system used generally for bicyclic systems, as described in Section 12-8.

It is of historical interest to note that the Baeyer strain theory with its planar rings predicts only one form of decalin with the ring-junction hydrogens on the same side of the molecule (Figure 12-23). The Sachse-Mohr concept of puckered strain-free rings allows for two isomers. In fact, Mohr predicted that the two isomers of decalin should exist before W. Hückel (1925) succeeded in preparing them. Both isomers occur in petroleum.

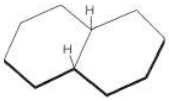

Figure 12-23: Baeyer formulation of decalin which, with planar rings, allows for only the cis configuration at the ring conjunction.

At this point, it probably will be helpful to construct models of *cis*- and *trans*-decalins to appreciate the following: (a) The two compounds cannot interconvert unless $\text{C}-\text{C}$ or $\text{C}-\text{H}$ bonds first are broken. (b) *trans*-Decalin is a relatively rigid system and, unlike cyclohexane, the two rings cannot flip from one chair form to another. Accordingly, the orientation of the substituent is fixed in the chair-chair conformation of *trans*-decalin. (c) The chair-chair forms of *cis*-decalin are relatively flexible, and inversion of both rings at once occurs fairly easily (the barrier to inversion is about 14 kcal mol^{-1}). A substituent therefore can interconvert between axial and equatorial conformations (Figure 12-24).

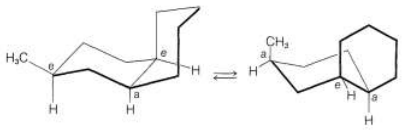

Figure 12-24: Ring inversion in cis-decalin, *which takes a substituent from the equatorial to the axial position. In both conformations, each ring is a chair form. You should check this process with ball-and-stick models.*

The ramifications of conformational analysis of flexible and rigid ring systems are of considerable importance to the understanding of stability and reactivity in polycyclic systems. This will become increasingly evident in later discussions.

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12.10: Strain in Polycyclic Molecules

Knowing the importance of angle and eclipsing strain in the small-ring cycloalkanes, we should expect that these strains would become still more important in going from cyclobutane to bicyclo[1.1.0]butane or from cyclooctane to pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane (cubane). This expectation is borne out by the data in Table 12-6, which gives the properties of several illustrative small-ring polycyclic molecules that have been synthesized only in recent years.

The extraordinary strain energy of cubane $(\sim 142\ \text{kcal mol}^{-1})$ is worthy of special note. It is roughly equal to six times the strain energy of a single cyclobutane ring $(\sim 26\ \text{kcal mol}^{-1})$ as befits a molecule made up of six cyclobutane rings as faces. Despite this, cubane is surprisingly stable to spontaneous decomposition processes, although it will rearrange under the influence of metal or acid catalysts.

Another extraordinarily strained polycyclic hydrocarbon that has been prepared is prismane (the Ladenburg structure for benzene).

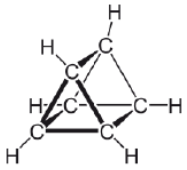

Figure: Chemical structure of prismane. (Public Domain; NEUROtiker).

This substance is a liquid that decomposes explosively when heated. In *dilute* solution at 100°, it is converted slowly to benzene.

One of the most interesting types of polycyclic carbon compounds prepared in recent years is the group of tricyclic substances known as "propellanes." A typical example is tricyclo [3.2.2.0^{1,5}]nonane, which sometimes is called [3.2.2]propellane, 12. The physical properties of several of these are included in Table 12-6. A quick look at formula 12 probably does not suggest any great structural difference from the bicyclic compounds we have discussed previously. However, if one tries to construct a ball-and-stick model of 12, one soon concludes that the propellanes are truly extraordinary substances in that all four carbon bonds at the bridgehead carbons extend, not to the comers of a tetrahedron, or even a distorted tetrahedron as for a cyclopropane ring, but away from the carbon on the *same side* of a plane through the carbon as in 13:

Table 12-6: *Properties of Some Small-Ring Polycyclic Hydrocarbons*

Name	Structure	Mp, °C	Bp, °C	Heat of formation[a] ΔH^0, kcal mole^{-1}	Strain energy,[b] kcal mole^{-1}
bicyclo[1.1.0]butane		–	8	51.9	59
spiro[2.2]pentane		−107	39	44.2	56
bicyclo[2.1.0]pentane		–	45.5	37.6	50
cubane		130–131	–	148.7	143
tricyclo[4.2.2.0^{1,6}]		32	109[11 mm]	–	–
tricyclo[3.2.2.0^{1,5}]nonane		11	–	–	–
tricyclo[3.2.1.0^{1,5}]octane		–	45[25 mm]	–	~60[c]
bicyclo[3.3.1]-1-nonene		–	~60[5 mm]	–	~12[d]

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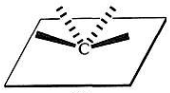
[a]These values are for formation of the respective compound from C(s) and $H_2(g)$ at 25°C.

[b]The strain energies are calculated as the difference in heats of formation in the preceding column and the heats of formation of an imaginary strainless compound with the same number of C–H and C–C bonds, having bond energies as given in Table 4-3, and C(s) ⟶ C(g) with $\Delta H^\circ = +171.3$ kcal mole^{-1}.

[c]Estimated from heats of combustion of similarly constituted compounds.

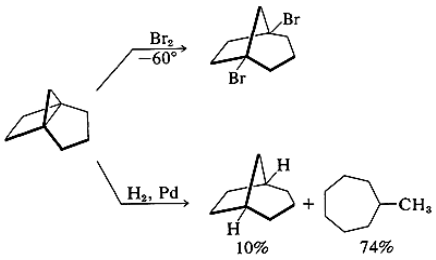
[d]Estimated from the heat of hydrogenation.

12

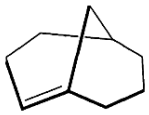


13

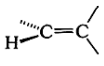
Angle strain is severe. Accordingly, [3.2.1]propellane reacts rapidly with bromine at -60° and with hydrogen over palladium at room temperature:



Still another way to torture the valence angles of carbon is to twist a double bond by connecting it to the bridgehead carbon of a bicyclic system with reasonably small rings, as in bicyclo[3.3.1]-1-nonene, 14:

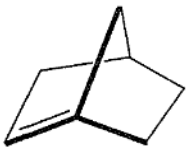


14



15

As with 12, it might appear that there is nothing unusual about 14. But a ball-and-stick model of 14 reveals that the carbon-carbon double bond is in a strained configuration like 15. Some of the properties of 14 are given in Table 12-6. That compounds with a double bond to a bridgehead carbon, such as 14, should be highly strained is known as “Bredt’s Rule.” The most spectacular example of this form of molecular distortion reported so far is bicyclo[2.2.1]-1-heptene, 16, for which evidence has been adduced that it is an unstable reaction intermediate:



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12.E: Cycloalkanes, Cycloalkenes, and Cycloalkynes (Exercises)

Exercise 12-1 Write expanded structures showing the C–C bonds for each of the following condensed formulas. Name each substance by the IUPAC system.

a. $(CH_2)_{10}$
b. $(CH_2)_5CHCH_3$
c. $(CH_3)_2C(CH_2)_6CHCH_2H_5$
d. the position and configurational isomers of trimethylcyclobutane
e. $(CH_2)_6CHCH_2C(CH_3)_2CH_2Cl$
f. $[(CH_2)_2CH]_2C(CH_3)C_2H_5$

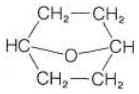
Exercise 12-2 The energy required to distort C–C–C bond angles from their normal values is approximately 17.5 cal (not kcal!) per degree squared per mole. Assuming the normal angle to be $112.5°$, calculate the angle-strain energy of a mole of planar cyclohexane (Figure 12-2). The actual C–C–C bond angles of cyclohexane are $111.5°$; what strain energy corresponds to this angle?

Exercise 12-3* Figure 5-8 indicates that the difference in energy between the conformation of butane with eclipsed methyls and the gauche form is about 5 kcal mol^{-1}. Use this number to estimate the contribution of eclipsing tot he instability of planar cyclohexane. Then calculate the instability of planar cyclohexane by including the angle strain from Exercise 12-2 in your estimate.

Exercise 12-4 Using the sawhorse convention, draw the possible conformations of chlorocyclohexane with the ring carbons in the planar, in the chair, and in the extreme boat forms. Arrange these in order of expected stability. Show your reasoning.

Exercise 12-5 Draw the preferred conformation of each of the following:

a. isopropylcyclohexane
b. cyclohexylcyclohexane
c.



Exercise 12-6*

a. It commonly is stated that the bulkier the substituent, the more favorable will be the conformation in which it occupies an equatorial position. However, it will be seen from Table 12-2 that the $-\Delta G^0$ values for the halogens (F, Cl, Br, and I) are not very large and all are about the same, although there is no question that iodine is a much bulkier substituent than fluorine. Use the following data to account qualitatively for the smallness and the commonality of the $-\Delta G^0$ factors for halogens. In the following table, r_{C-X} is the normal carbon-halogen bond distance, r_e is the distance calculated from the halogen to the nearest hydrogens when equatorial, r_a is the same distance when the halogen is axial, and r_0 is the distance corresponding to the minimum on a nonbonded halogen-hydrogen interaction curve, such as shown in Figure 12-9.

Halogen	r_{C-X}, A	r_e, A	r_a, A	r_0, A
F	1.38	2.7	2.5	2.6
Cl	1.77	3.0	2.6	3.0
Br	1.94	3.1	2.7	3.1
I	2.13	3.2	2.8	3.4

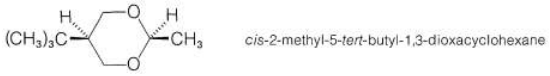
b. How stable would you expect the diaxial conformation of *cis*-1,3-diiodocyclohexane to be relative to the diequatorial conformation? Give your reasoning.

Exercise 12-7 Assuming the effects of substituents in the 1- and 4-positions of cyclohexane on the free energies of equatorial-axial equilibria can be assessed by simple addition of the ΔG^0 values of Table 12-2, calculate the relative free energies of 1, 2, 3, and 4. Use these values to calculate equilibrium constants for $1 \rightleftharpoons 2$, $3 \rightleftharpoons 4$, and $1 \rightleftharpoons 3$ at $25°$.[4]

Exercise 12-8 Explain why simple additivity of ΔG^0 values as proposed in Exercise 12-7 to predict axial-equatorial equilibria for cis and trans 1,4-disubstituted cyclohexanes would be expected to give poor results with 1,2- and 1,3-disubstituted cyclohexanes.

Exercise 12-9 Draw the possible chair conformations of *trans*- and *cis*-1,3-dimethylcyclohexane. Is the cis or the trans isomer more likely to be the more stable? Explain.

Exercise 12-10 With *cis*-2-methyl-5-*tert*-butyl-1,3-dioxacyclohexane,[5] the conformation with *tert*-butyl axial is more favorable than the conformation with *tert*-butyl equatorial.



cis-2-methyl-5-*tert*-butyl-1,3-dioxacyclohexane

Explain why this should be so and predict what should be the favored conformation for *trans*-2-methyl-4-*tert*-butyl-1,3-dioxacyclohexane.

Exercise 12-11 With reference to Figure 12-12, sketch the proton-decoupled ^{13}C spectrum you would expect for methylcyclohexane at 25°. Give your reasoning. (Review Section 9-10C.)

Exercise 12-12* The ^{19}F NMR spectrum of 1,1-difluorocyclohexane at several temperatures and $56.4\ MHz$ is shown in Figure 12-13.

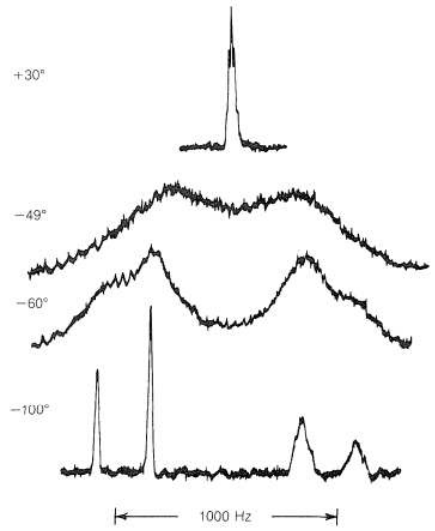
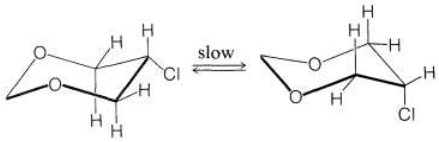


Figure 12-13: *Changes in the ^{19}F NMR spectrum of 1,1-difluorocyclohexane with temperature at $56.4\ MHz$ (see Exercise 12-12). Generally, $H-C-C-F$ spin-spin splittings are on the order of $5\text{-}15\ Hz$ and change with rotational angles in much the same way as for $H-C-C-H$ couplings.*

a. Explain why this spectrum changes so drastically with temperature and account for the appearance of four groups of lines observed at -100°. (Review Sections 9-10C and 9-10I.)

b. Sketch the ^{19}F spectrum you would expect for 1,1-difluoro-4-*tert*-butylcyclohexane at 25°. Give you reasoning.

Exercise 12-13* Proton NMR spectra often are used to determine whether a substituent is axial or equatorial. Explain what differences one might expect to see in the *splitting* of the NMR signal from the $-CHCl-$ proton of each of the following two conformations at a temperature low enough so interconversion is very slow. (Review Sections 9-10H and 9-10J.)



Exercise 12-14 Given the favored nonplanar conformation of cyclobutane (Figure 12-15), predict whether *cis*-1,2-dibromocyclobutane will be more, or less, stable than the corresponding trans isomer. Do the same for the *cis*- and *trans*-1,3-dibromocyclobutanes. Give your reasoning.

Exercise 12-15 Write structural formulas for all of the possible cis-trans isomers of the following compounds and designate the configuration of each by name (see Section 5-1):

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a. 1,3-dichlorocyclopentane
b. 1,1,3-trimethylcyclohexane
c. 1,2,3-trimethylcyclopropane
d. (3-methylcyclobutyl)-3-methylcyclobutane

Exercise 12-16 Use the data of Table 12-3 and any needed bond energies to calculate ΔH^0 for the following reaction in the vapor state at 25° with $n = 3$, 4, and 5:

$$(CH_2)_n \rightarrow CH_3(CH_2)_{n-3}CH{=}CH_2 \tag{12.E.1}$$

What can you conclude about the stability of the cycloalkanes with $n = 3$, 4, and 5 with respect to corresponding open-chain compounds with double bonds? Include consideration of the possible entropy effects, Section 4-4B.

Exercise 12-17 Use the heats of combustion to liquid water given in Table 12-3 and appropriate bond energies to calculate ΔH^0 (vapor) for ring-opening of the cycloalkanes with bromine in the range $n = 2$ to $n = 6$:

$$(CH_2)_n + Br_2 \rightarrow (CH_2)_{n-2}(CH_2Br)_2 \tag{12.E.2}$$

Exercise 12-18 Investigate the thermodynamic feasibility of the following propagation steps for opening the rings of cycloalkanes with $n = 2$ to $n = 6$ by a radical-chain mechanism:

$$(CH_2)_n + Br\cdot \rightarrow BrCH_2{-}(CH_2)_{n-2}{-}CH_2\cdot \tag{12.E.3}$$

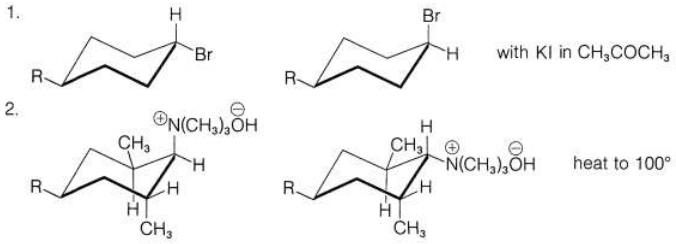
$$BrCH_2{-}(CH_2)_{n-2}{-}CH_2\cdot + Br_2 \rightarrow (CH_2)_{n-2}(CH_2Br)_2 + Br\cdot \tag{12.E.4}$$

Use $83\ \text{kcal mol}^{-1}$ for the bond-dissociation energy of a normal C–C bond and $68\ \text{kcal mol}^{-1}$ for the bond-dissociation energy of a C–Br bond. (An easy way to solve a problem of this type is first to calculate ΔH of each step for cyclohexane, for which there is no strain, then to make suitable corrections for the strain that is present for smaller values of n.)

Exercise 12-19 Show how the reactions described in Table 12-4 could be used to determine whether a hydrocarbon of formula C_4H_8 is methylcyclopropane, cyclobutane, or 1-butene $(CH_3CH_2CH{=}CH_2)$. Write equations for the reactions used.

Exercise 12-20

a. Consider that all of the following cyclohexane derivatives have R as a very large group so the conformations shown are the most stable ones. Which member of each pair would you expect to react more rapidly under the given conditions and why? Draw the structure and configuration of the major product. (Review Section 8-8.)



b. Make sawhorse-type drawings of the possible products of antarafacial addition of bromine to 4-*tert*-butylmethylcyclohexene. Which isomer would you expect to be formed most rapidly? Give your reasoning.

Exercise 12-21* Formation of a cycloalkane $(CH_2)_n$ by reactions such as

$$Br{-}(CH_2)_n{-}ZnBr \rightarrow (CH_2)_n + ZnBr_2 \tag{12.E.5}$$

occurs in competition with other reactions such as

$$2Br{-}(CH_2)_n{-}ZnBr \rightarrow Br{-}(CH_2)_{2n}{-}ZnBr + ZnBr_2 \tag{12.E.6}$$

a. Explain why cyclization reactions of this kind carried out in *dilute* solutions are likely to give better yields of $(CH_2)_n$ than in *concentrated* solutions.

b. Make graphs that show, as a function of n in the range 3 to 15, how the yield of cycloalkane might be expected to depend on (1) the total strain in the ring formed (see Table 12-3), and (2) the probability that at any given instant the reactive ends will be oriented properly with respect to one another so as to permit cyclization.

c. Explain how the factors considered in Part b must be balanced relative to one another to account for the reported yields of cyclization products for the following ring sizes: $(CH_2)_3 > 80\%$; $(CH_2)_4 > 7\%$; $(CH_2)_6$ 45%; larger rings $< 10\%$.

Exercise 12-22* If the twist-chain conformation 8 were rigid rather than flexible, how many different monochlorocycloheptanes would you expect (a) excluding mirror-image isomers and (b) including mirror-image isomers?

Exercise 12-23* A conformation of cyclooctane called *boat-boat* can be formed by having two gauche C–C–C–C segments, as shown in Figure 12-19. As drawn, this conformation has all hydrogens staggered and normal C–C–C bond angles. Explain why it is not a favorable conformation. Use of models will be very helpful.

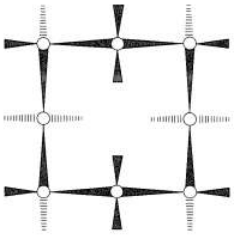
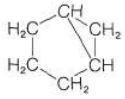


Figure 12-19: *Boat-boat conformation of cyclooctane, based on two gauche forms of butane (see Exercise 12-23).*

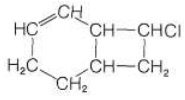
Exercise 12-24 Space-filling models (Section 2-2B) indicate that the chiral forms of *trans*-cyclopentadecene are likely to be readily interconverted at room temperature. How and where might *trans*-cyclopentadecene be substituted to give stable chiral forms that possess a chiral center but *no* chiral carbon atoms?

Exercise 12-25 Name each of the following compounds by an accepted system:

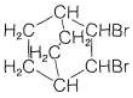
a.



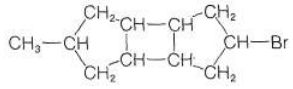
b.



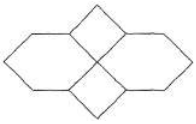
c.



d.



e.



f.

Exercise 12-26 Use ball-and-stick models to assess the degree of stability to be expected for a decalin with chair-form rings and an axial-axial ring fusion.

Exercise 12-27 The equatorial form of methylcyclohexane is $1.5\ \text{kcal mol}^{-1}$ more stable than the axial form because the axial form has steric hindrance between the methyl and two hydrogens, one in the 3- and the other in the 5-position. Knowing that *cis*-decalin

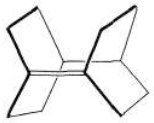
is about $2\ \text{kcal mol}^{-1}$ less stable than *trans*-decalin, what would you estimate for the relative stabilities of *cis*- and *trans*-9-methyldecalin (numbering as in Figure 12-22)?

Exercise 12-28 Name prismane according to the system described in Section 12-8.

Exercise 12-29 Draw a sawhorse-style formula for bicyclo[1.1.0]butane and formulas for all of the eight possible dichlorobicyclo[1.1.0]butanes (including chiral forms).

Exercise 12-30* How could you phrase Bredt's rule so it could distinguish between the lack of stability of 16 and the stability of bicyclo[5.5.0]-1,2-decene, both compounds having a double-bonded carbon at a ring junction?

Exercise 12-31* Using the system described in Section 12-8, name the following compound:



To what degree do you think this compound violates Bredt's rule? (Use of ball-and-stick models will be helpful here.) By what kind of mechanism would you expect bromine to add to the double bond? (Review Sections 12-3A, 12-5, 10-6, and 10-7.)

Exercise 12-32 Write structural formulas for substances (one for each part) that fit the following descriptions. Make sawhorse drawings of the substances for which conformational problems are involved.

a. a compound of formula C_4H_8 that reacts slowly with sulfuric acid and also with bromine (light induced)
b. the most highly strained isomer of C_5H_{10}
c. the possible products from treatment of 1-ethyl-2-methylcyclopropane with bromine (light-induced)
d. the least-stable chair and the least-stable boat conformations of *cis*-1,4-dichlorocyclohexane
e. the most stable geometrical isomer of 1,3-di-*tert*-butylcyclobutane
f. a compound with a six-membered ring that is most stable with the ring in a boat form
g. *trans*-bicyclo[7.1.0]decane
h. the most stable conformation of *trans*-1,3-di-*tert*-butylcyclohexane
i. the most stable conformation of *cis*-2-*tert*-butyl-*cis*-decalin
j. a boat-boat conformation of *cis*-decalin
k. *trans*,*trans*,*trans*-tricyclo[8.4.0.$0^{2,7}$]tetradecane

Exercise 12-33 The ΔH^0 value for hydrogenation of cyclopropane to propane at 25° in the vapor state is $-37.5\ \text{kcal mol}^{-1}$. Use this value and any other bond energies to calculate the bond energies of the C–C bonds in cyclopropane on the assumption that all of its C–C bonds are equally strong and the C–H bonds are $6\ \text{kcal mol}^{-1}$ stronger than normal. Notice than, by definition, the bond energies must give the proper value of ΔH^0 for the following reaction:

$$(\text{CH}_2)_3\,(g) \rightarrow 3\text{C}\,(g) + 6\text{H}\,(g) \tag{12.E.7}$$

Use your cyclopropane bond energies to calculate ΔH^0 values for the following reactions:

a. $(\text{H}_2)_3 \rightarrow \cdot\text{CH}_2\text{–CH}_2\text{–CH}_2\cdot$ (normal C–C bonds)
b. $2(\text{CH}_2)_3 \rightarrow (\text{CH}_2)_6$

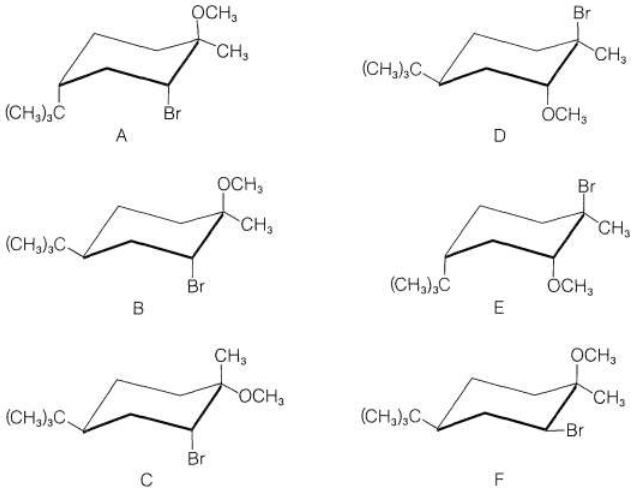
Exercise 12-34 Draw structural formulas in reasonable perspective for each of the following substances:

a. the cis and trans isomers of bicyclo[3.3.0]octane
b. *trans*-tricyclo[3.1.0.$0^{2,6}$]hexane
c. tricyclo[3.1.$0^{2,6}$]hexane
d. *trans*-2,6-dichlorobicyclo[2.2.2]octane
e. quinquecyclo[4.4.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]decane

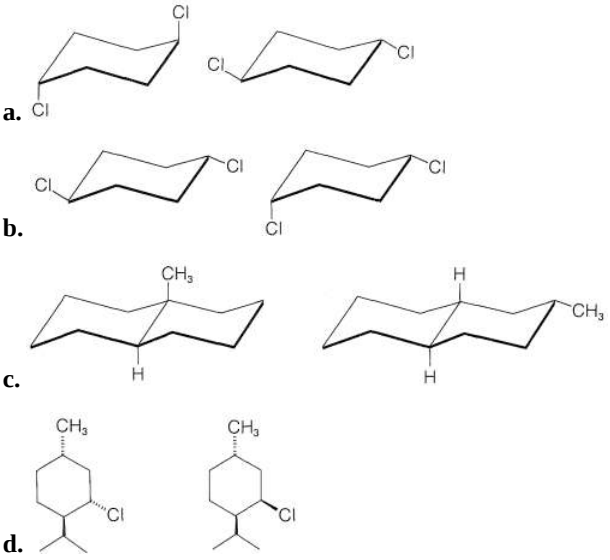
Exercise 12-35 Draw each of the following compounds in perspective to show the preferred conformation. Construct models if in doubt.

a. 2-*tert*-butyl-*trans*-decalin
b. bicyclo[2.2.2]octane
c. spiro[5.4]decane
d. *trans*-3-phenyl-1-methylcyclohexane

Exercise 12-36 When bromine adds to 4-*tert*-butyl-1-methylcyclohexane in CH_3OH solution, which of the following structures, A-F, would be the major product? Give your reasoning in detail.



Exercise 12-37 Which conformational or position isomer in each of the following pairs would you expect to be the most stable (of lowest energy)? (Models will be helpful.)



[4]It is important to notice that, in some cases, simple additivity of ΔG^0 values can give quite erroneous results when the groups involved are polar. Thus *trans*-1,4-dichlorocyclohexane appears to be more stable in the diaxial conformation than in the diequatorial conformation.

[5]The *oxa* prefix to the name of a hydrocarbon means that a carbon in the chain has been replaced by oxygen (see Section 15-11A).

12.E.1: Contributors

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CHAPTER OVERVIEW

13: Polyfunctional Compounds, Alkadienes, and Approaches to Organic Synthesis

Organic compounds of natural origin rarely have simple structures. Most have more than one functional group in each molecule. Usually the chemical behavior of a functional group is influenced significantly by the presence of another functional group, especially when the groups are in close proximity. Indeed, the complexities that are associated with polyfunctionality are of central importance in biochemical reactions and in the design of organic syntheses. For this reason, you will need to gain experience in judging how and when functional groups in the same molecule interact with one another. We will start by considering the chemistry of alkadienes, which are hydrocarbons with two carbon-carbon double bonds.

13.1: General Comments on Alkadienes
13.2: 1,3- or Conjugated Dienes. Electrophilic and Radical Addition
13.3: Cycloaddition Reactions
13.4: Polymerization Reactions of Conjugated Dienes
13.5: Cumulated Alkadienes
13.6: Approaches to Planning Practical Organic Syntheses
13.7: Building the Carbon Skeleton
13.8: Introducing Functionality
13.9: Construction of Ring Systems by Cycloaddition
13.10: Protecting Groups in Organic Synthesis
13.11: Building the Carbon Skeleton
13.E: Polyfunctional Compounds, Alkadienes, and Approaches to Organic Synthesis (Exercises)

13.1: Contributors and Attributions

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13.1: General Comments on Alkadienes

The molecular properties of alkadienes depend on the relationship between the double bonds, that is, whether they are **cumulated**, **conjugated**, or **isolated**:

- 2,3-pentadiene (cumulated)

$$\mathrm{CH_3CH{=}C{=}CHCH_3} \tag{13.1.1}$$

- 1,3-pentadiene (conjugated)

$$\mathrm{CH_2{=}CH{-}CH{=}CHCH_3} \tag{13.1.2}$$

- 1,4-pentadiene (isolated)

$$\mathrm{CH_2{=}CH{-}CH_2{-}CH{=}CH_2} \tag{13.1.3}$$

The properties of a compound with isolated double bonds, such as 1,4-pentadiene, generally are similar to those of simple alkenes because the double bonds are essentially isolated from one another by the intervening $\mathrm{CH_2}$ group. However, with a conjugated alkadiene, such as 1,3-pentadiene, or a cumulated alkadiene, such as 2,3-pentadiene, the properties are sufficiently different from those of simple alkenes (and from each other) to warrant separate discussion. Some aspects of the effects of conjugation already have been mentioneed, such as the influence on spectroscopic properties (Section 9-9B). The emphasis here will be on the effects of conjugation on chemical properties. The reactions of greatest interest are addition reactions, and this chapter will include various types of addition reactions: electrophilic, radical, cycloaddition, and polymerization.

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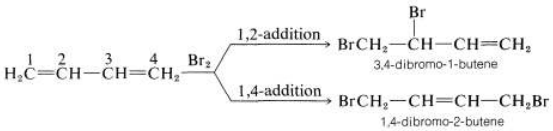
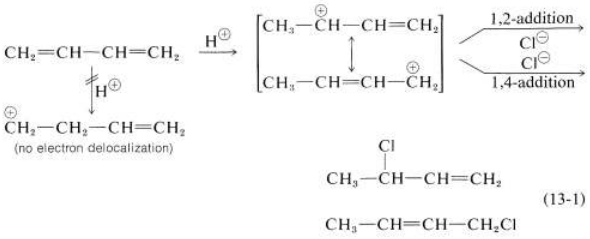
13.2: 1,3- or Conjugated Dienes. Electrophilic and Radical Addition

The reactions of 1,3-butadiene are reasonably typical of conjugated dienes. The compound undergoes the usual reactions of alkenes, such as catalytic hydrogenation or radical and polar additions, but it does so *more readily* than most alkenes or dienes that have isolated double bonds. Furthermore, the products frequently are those of 1,2 *and* **1,4 addition:**

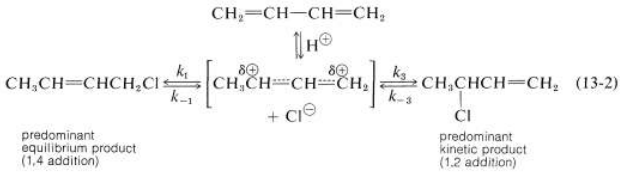


Formation of both 1,2- and 1,4-addition products occurs not only with halogens, but also with other electrophiles such as the hydrogen halides. The mechanistic course of the reaction of 1,3-butadiene with hydrogen chloride is shown in Equation 13-1. The first step, as with alkenes, is formation of a carbocation. However, with 1,3-butadiene, if the proton is added to C_1 (but not C_2), the resulting cation has a substantial delocalization energy, with the charge distributed over two carbons (review Sections 6-5 and 6-5C if this is not clear to you). Attack of $Cl^{\ominus}$ as a nucleophile at one or the other of the positive carbons yields the 1,2- or the 1,4-addition product:



(13-1)

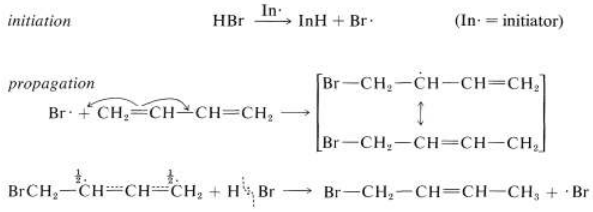
An important feature of reactions in which 1,2 and 1,4 additions occur in competition with one another is that the ratio of the products can depend on the temperature, the solvent, and also on the *total time of reaction*. The reason for the dependence on the reaction time is that the formation of the carbocation is *reversible*, and the ratio of products at equilibrium need not be the same as the ratio of the rates of attack of $Cl^{\ominus}$ at C_1 and C_3 of the carbocation. This is another example of a difference in product ratios resulting from kinetic control *versus* equilibrium control.



(13-2)

The fact is that at low temperatures the 1,2 product predominates because it is formed more rapidly, and the back reactions, corresponding to k_{-1} or k_{-3}, are slow (Equation 13-2). However, at equilibrium[1] the 1,4 product is favored because it is more stable, not because it is formed more rapidly.

Conjugated dienes also undergo addition reactions by radical-chain mechanisms. Here, the addition product almost always is the 1,4 adduct. Thus radical addition of hydrogen bromide to 1,3-butadiene gives l-bromo-2-butene, presumably by the following mechanism:



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[1]The equilibrium ratio is obtained as follows. At equilibrium $k_1/k_{-1} = [CH_3CH{=}CHCH_2Cl] / [R^{\oplus}] [Cl^{\ominus}]$ and $k_{-3}/k_3 = [R^{\oplus}] [Cl^{\ominus}] / [CH_3CHClCH{=}CH_2]$, in which $R^{\oplus}$ is the concentration of delocalized carbocation. Multiplication of these equations gives $k_1k_{-3}/k_{-1}k_3 = [CH_3CH{=}CHCH_2Cl] / [CH_3CHClCH{=}CH_2] = K_{eq}$.

13.2.1: Contributors and Attributions

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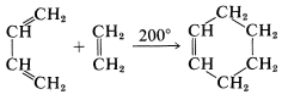
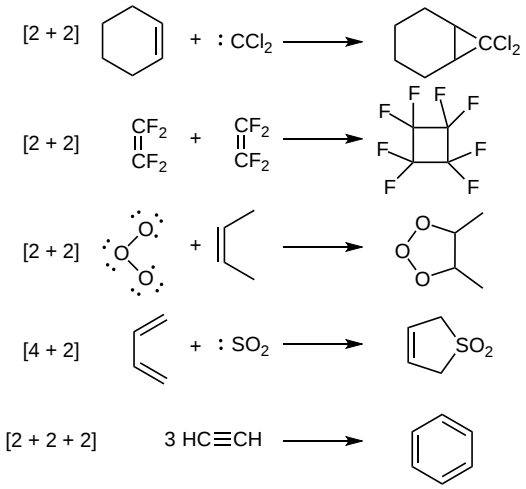
13.3: Cycloaddition Reactions

There are a variety of reactions whereby rings are formed through addition to double or triple bonds. An especially simple example is the addition of ethene to 1,3-butadiene to give cyclohexene:



This is the prototype **Diels-Alder** reaction, which has proved so valuable in synthesis that it won its discoverers, O. Diels and K. Alder, the Nobel Prize in chemistry in 1950.

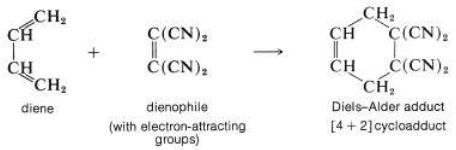
The Diels-Alder reaction is both a 1,4 addition or ethene to 1,3-butadiene and a 1,2 addition of butadiene to ethene. It can be called a **[4 + 2] cycloaddition** and as such results in the formation of a six-membered ring. Many other cycloadditions are known, such as [2 + 2], other types of [4 + 2], and [2 + 2 + 2], which give different size of rings. Some specific examples follow:



The synthetic importance of these reactions is very great and, because many of them often involve dienes, we will discuss their general characteristics in this chapter. The most valuable cycloaddition reaction almost certainly is the [4 + 2], or Diels-Alder, reaction and will be discussed in detail.

13.3.1: [4 + 2] Cycloadditions

There is one very important point you should remember about the Diels-Alder reaction: The reaction usually occurs well only when the [2] component is substituted with electron-attracting groups and the [4] component is substituted with electron-donating groups, or the reverse. The most common arrangement is to have the alkene (usually referred to as the **dienophile**) substituted with electron-attracting groups such as $-CO_2H$, $-COR$, or $-C \equiv N$. For example,



A list of the more reactive dienophiles carrying electron-attracting groups is given in Table 13-1. Ethene and other simple alkenes generally are poor dienophiles and react with 1,3-butadiene only under rather extreme conditions and in low yield.

However, when the diene is substituted with several electron-attracting groups such as chlorine or bromine, electron-donating groups on the *dienophile* facilitate the reaction. Many substances, such as 2-methylpropene, that act as dienophiles with hexachlorocyclopentadiene simply will not undergo [4 + 2] addition with cyclopentadiene itself:

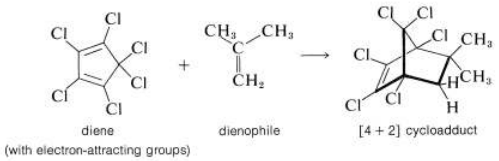
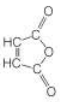
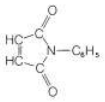
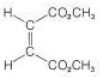
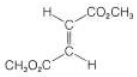
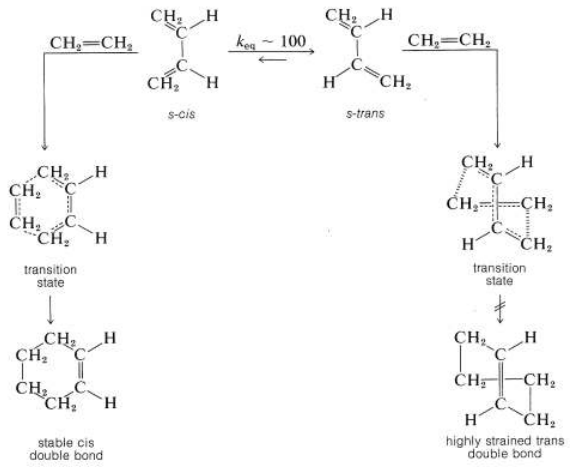


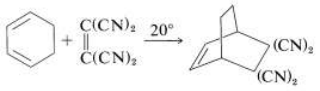
Table 13-1: *Reactive Dienophiles with 1,3-Butadiene and Similar Dienes*

Name	Formula	Name	Formula
tetracyanoethene	$(NC)_2C{=}C(CN)_2$	propenenitrile (acrylonitrile)	$CH_2{=}CH{-}CN$
2-butenal (crotonaldehyde)	$CH_3CH{=}CH{-}CHO$	propenal (acrolein)	$CH_2{=}CH{-}CHO$
3-phenylpropenoic acid (cinnamic acid, cis and trans)	$C_6H_5CH{=}CH{-}CO_2H$	ethyl propenoate (ethyl acrylate)	$CH_2{=}CH{-}CO_2C_2H_5$
cis-butenedioic anhydride (maleic anhydride)		*N*-phenyl-*cis*-butenimide (*N*-phenylmaleimide)	
dimethyl *cis*-butenedioate (dimethyl maleate)		dimethyl *trans*-butenedioate (dimethyl fumarate)	
1-nitropropene	$CH_3CH{=}CH{-}NO_2$	2-nitro-1-phenylethene	$C_6H_5CH{=}CH{-}NO_2$

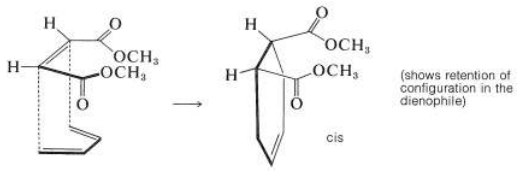
The Diels-Alder reaction is *highly stereospecific*. The diene reacts in an unfavorable conformation in which its double bonds lie in a plane on the same side (cis) of the single bond connecting them. This *s-cis* (or **cisoid**) conformation is required to give a stable product with a cis double bond. Addition of ethene to the alternate and more stable (**transoid**) conformation would give an impossibly strained *trans*-cyclohexene ring. Possible transition states for reaction in each conformation follow, and it will be seen that enormous molecular distortion would have to take place to allow addition of ethene to the transoid conformation:



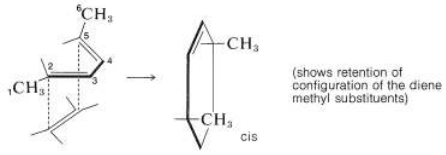
Cyclic dienes usually react more readily than open-chain dienes, probably because they have their double bonds fixed in the proper conformation for [4 + 2] cycloaddition, consequently the price in energy of achieving the *s-cis* configuration already has been paid:



Further evidence of stereospecificity in [4 + 2] additions is that the configurations of the diene and the dienophile are *retained* in the adduct. This means that the reactants (or addends) come together to give *suprafacial* addition. Two examples follow, which are drawn to emphasize how suprafacial addition occurs. In the first example, dimethyl *cis*-butadioate adds to 1,3-butadiene to give a cis-substituted cyclohexene:

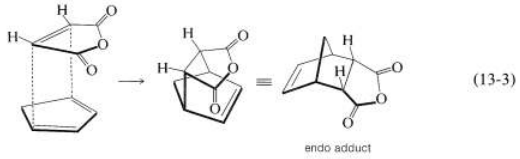


In the second example, suprafacial approach of a dienophile to the 2,5 carbons of *trans*,*trans*-2,4-hexadiene is seen to lead to a product with two methyl groups on the same side of the cyclohexene ring:

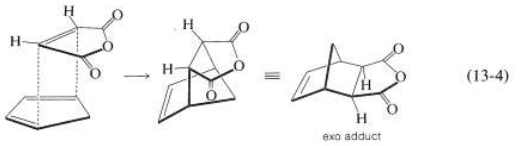


(The use of models will help you visualize these reactions and their stereochemistry.)

There is a further feature of the Diels-Alder reaction that concerns the stereochemical orientation of the addends. In the addition of *cis*-butanedioic anhydride (maleic anhydride) to cyclopentadiene there are two possible ways that the diene and the dienophile could come together to produce different products. These are shown in Equations 13-3 and 13-4:



(13-3)

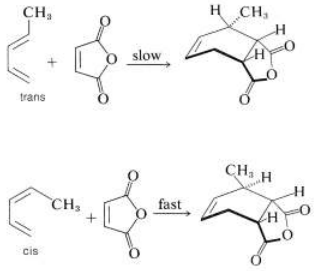


(13-4)

In practice, the adduct with the endo[2] configuration usually is the major product. As a general rule, Diels-Alder additions tend to proceed to favor that orientation that corresponds to having the diene double bonds and the unsaturated substituents of the dienophile closest to one another. This means that addition by Equation 13-3 is more favorable than by Equation 13-4, but the degree of endo-exo stereospecificity is not as high as the degree of stereospecificity of suprafacial addition to the diene and dienophile.

There are exceptions to favored endo stereochemistry of Diels-Alder additions. Some of these exceptions arise because the *addition reaction is reversible*, dissociation being particularly important at high temperature. The exo configuration is generally more stable than the endo and, given time to reach equilibrium (cf. Section 10-4A), the exo isomer may be the major adduct. Thus endo stereospecificity can be expected only when the additions are subject to *kinetic control*.

The reactivities of dienes in the Diels-Alder reaction depend on the number and kind of substituents they possess. The larger the substituents are, or the more of them, at the ends of the conjugated system, the slower the reaction is likely to be. There also is a marked difference in reactivity with diene configuration. Thus *trans*-1,3-pentadiene is substantially less reactive toward a given dienophile (such as maleic anhydride) than is *cis*-1,3-pentadiene. In fact, a mixture of the cis and trans isomers can be separated by taking advantage of the difference in their reactivities on cycloaddition:



13.3.2: Mechanism of the Diels-Alder Reaction

There is little evidence to support simple radical or polar mechanisms (such as we have discussed previously) for the Diels-Alder reaction. As the result of many studies the reaction seems best formulated as a process in which the bonds between the diene and the dienophile are formed essentially simultaneously:

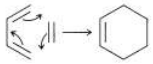


Figure 13-1, we may say that the reaction follows curve A and not curve B on the plots of energy versus reaction coordinate. Although it is difficult to prove experimentally that the reaction is concerted, we shall see in Chapter 21 that there are theoretical reasons to expect it to be so, despite the high degree of ordering (unfavorable entropy, Section 4-4B) that the transition state must have in order that all of the participating bonds can be made and broken at once.

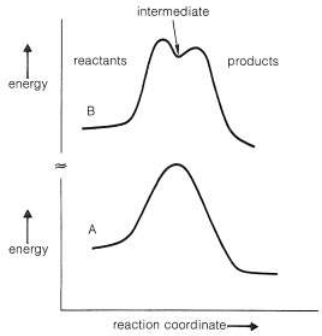
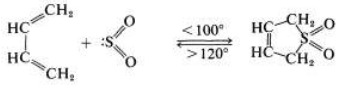


Figure 13-1: Schematic representation of energy versus reaction coordinate for (A) a concerted reaction and (B) a stepwise reaction involving formation of an unstable intermediate. Curve B has been drawn to have the highest energy point (the transition state) come before the intermediate is formed. For many processes the highest energy point comes after the intermediate is formed. If the highest energy point comes after the intermediate is formed, then the intermediate will be more or less in equilibrium with the reactants.

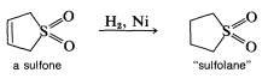
We already have discussed a few addition reactions that appear to occur in a concerted manner. These include the addition of diimide, ozone, and boron hydrides to alkenes (Sections 11-5, 11-7A, and 11-6B). Concerted reactions that have cyclic transition states often are called **pericyclic reactions**. Other examples will be considered in later chapters.

13.3.3: A [4 + 2] Cycloaddition

We indicated previously that sulfur dioxide (SO_2) and 1,3-butadiene form a [4 + 1] cycloaddition product:

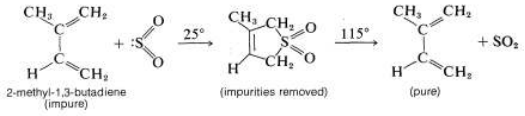


This reaction is more readily reversible than most Diels-Alder reactions, and the product largely dissociates to the starting materials on heating to 120°. The cycloadduct is an unsaturated cyclic **sulfone**, which can be hydrogenated to give the saturated cyclic sulfone known as "sulfolane":



This compound is used extensively in the petrochemical industry as a selective solvent.

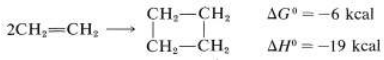
The reversibility of the diene-SO_2 cycloaddition makes it useful in the purification of reactive dienes. 2-Methyl-1,3-butadiene (isoprene) is purified commercially in this manner prior to being polymerized to rubber (Section 13-4):



Neither 1,3-cyclopentadiene nor 1,3-cyclohexadiene react with sulfur dioxide, probably because the adducts would be too highly strained:

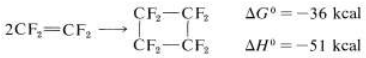
13.3.4: Some [2 + 2] Cycloadditions

Many naturally occurring organic compounds contain six-membered carbon rings, but there are relatively few with four-membered carbon rings. After encountering the considerable ease with which six-membered rings are formed by [4 + 2] cycloaddition, we might expect that the simpler [2 + 2] cycloadditions to give four-membered rings also should go well, provided that strain is not too severe in the products. In fact, the dimerization of ethene is thermodynamically favorable:

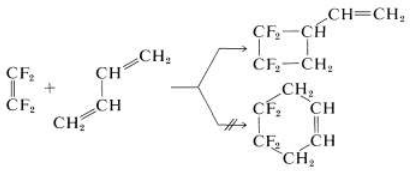


Nonetheless, this and many other [2 + 2] cycloaddition reactions do not occur on simple heating.

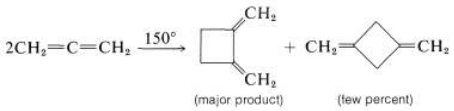
However, there are a few exceptions. One is the dimerization of tetrafluoroethene, which perhaps is not surprising, considering the favorable thermodynamic parameters:

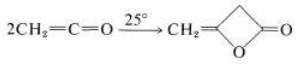


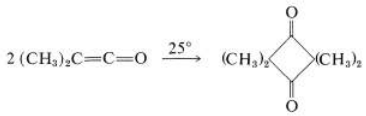
What is surprising is that addition of $CF_2{=}CF_2$ to 1,3-butadiene gives a cyclobutane and *not* a cyclohexane, although the [2 + 2] product probably is about $25\ \text{kcal mol}^{-1}$ less stable than the [4 + 2] product:

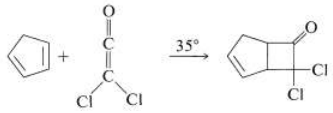


Such [2 + 2] *thermal* additions generally are limited to polyhaloethenes and a few substances with cumulated double bonds, such as 1,2-propadiene $(CH_2{=}C{=}CH_2)$ and ketenes $(R_2C{=}C{=}O)$. Some examples follow:

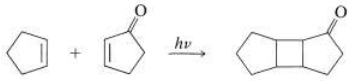








Many [2 + 2] cycloadditions that do not occur by simply heating the possible reactants can be achieved by *irradiation* with ultraviolet light. The following example, [2 + 2] addition of 2-cyclopentenone to cyclopentene, occurs photochemically but not thermally:

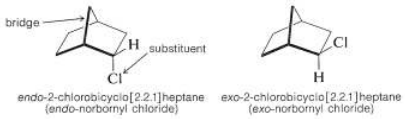


In all such photochemical cycloadditions the energy required to achieve a *cycloaddition* transition state, which can amount to $100\ \text{kcal mol}^{-1}$ or more, is acquired by absorption of light.

Thermodynamically unfavorable cycloaddition products can be formed photochemically. A striking example is the photochemical conversion of norbornadiene to quadricyclene. The reverse of this reaction can occur with almost explosive violence in the presence of appropriate metal catalysts or on simple heating:

Why do some [2 + 2] cycloadditions occur thermally and others photochemically? What is special about fluoroalkenes and cumulated dienes? The answers are complex, but it appears that most *thermal* [2 + 2] cycloadditions, unlike the Diels-Alder [4 + 2] cycloadditions, go by *stepwise* routes (see Section 21-11). Why the two types of thermal cycloaddition have different mechanisms will be discussed in Sections 21-10A and B.

[2]In general, the designation *endo* or *exo* refers to configuration in bridged or polycyclic ring systems such as those shown in Equations 13-3 and 13-4. With reference to the bridge atoms, a substituent is exo if it is on the same side as the bridge, or endo if it is on the opposite side. Further examples are



In drawing endo and exo isomers, it is best to represent the actual spatial relationships of the atoms as closely as possible. The cyclohexane ring is shown here in the boat form (Section 12-3A) because it is held in this configuration by the methylene group that bridges the 1,4 positions. If you do not see this, we strongly advise that you construct models.

13.3.5: Contributors and Attributions

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- Layne A. Morsch (University of Illinois Springfield)

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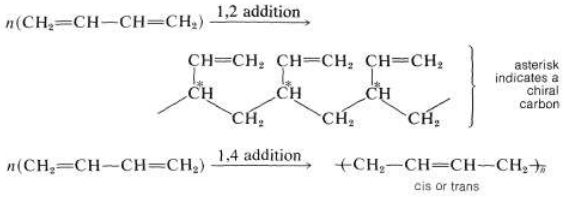
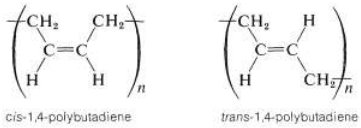
13.4: Polymerization Reactions of Conjugated Dienes

The general character of alkene polymerization by radical and ionic mechanisms was discussed briefly in Section 10-8. The same principles apply to the polymerization of alkadienes, with the added feature that there are additional ways of linking the monomer units. The polymer chain may grow by either 1,2 or 1,4 addition to the monomer. With 1,3-butadiene, for example,



In 1,2 addition, a chiral carbon (marked with *) is created as each molecule of the monomer adds to the growing chain radical. The physical properties of the polymer greatly depend on whether these carbons have the same or different configurations, as we will show in greater detail in Chapter 29. However, in polymer nomenclature, an **isotactic** polymer is one with essentially all chiral carbons having the same configuration, whereas an **atactic** polymer has a *random* ordering of the chiral carbons with different configurations.

For polymerization of 1,3-butadiene by 1,4 addition, there are no chiral carbons, but there is the possibility of cis-trans isomerism:

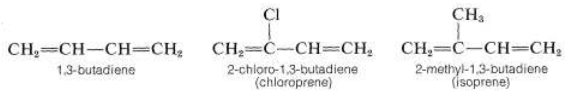


A polymer made of identical repeating units is called a **homopolymer**. If the units are nonidentical, as when different monomers are polymerized, the product is called a **copolymer**.

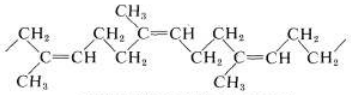
Many of the polymers formed from conjugated dienes are elastic and are used to manufacture synthetic rubbers. The raw polymers usually are tacky and of little direct use, except as adhesives and cements. They are transformed into materials with greater elasticity and strength by **vulcanization**, in which the polymer is heated with sulfur and various other substances called **accelerators**, with the result that the polymer chains become cross-linked to one another by carbon-sulfur and carbon-carbon bonds. Some of the cross-linking appears to occur by addition to the double bonds, but the amount of sulfur added generally is insufficient to saturate the polymer. With large proportions of sulfur, hard rubber is formed such as is used in storage-battery cases.

Because of the many double bonds present, diene rubbers are sensitive to air oxidation unless **antioxidants** are added to inhibit oxidation.

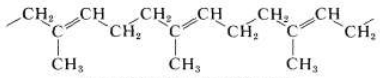
The more important dienes for the manufacture of synthetic rubbers are 1,3-butadiene, 2-chloro-1,3-butadiene (chloroprene), and 2-methyl-1,3-butadiene (isoprene):



Several rubbers that have desirable properties of elasticity, flexibility, abrasive resistance, and resistance to chemicals are listed in Table 13-2. The homogeneity of these polymers depends greatly on the way in which they are prepared, particularly on the polymerization catalyst employed. A synthetic rubber that is virtually identical to natural Hevea rubber is made from 2-methyl-1,3-butadiene (isoprene) using finely divided lithium metal or transition-metal catalysts; the product is formed almost exclusively by cis 1,4 addition[3]:



natural rubber (cis-1,4-polyisoprene)



gutta-percha (*trans*-1,4-polyisoprene)

Table 13-2: *Synthetic Rubbers*

Monomer	Formula	Catalyst	Polymer	Type of addition
1,3-butadiene	$CH_2{=}CH{-}CH{=}CH_2$	Li	polybutadiene	~100% cis 1,4
1,3-butadiene	$CH_2{=}CH{-}CH{=}CH_2$	Na	polybutadiene	24–30% cis and trans 1,4
1,3-butadiene and ethenylbenzene (styrene)	$CH_2{=}CH{-}CH{=}CH_2$ $C_6H_5CH{=}CH_2$	*a*	GRS[b]	
1,3-butadiene and propenenitrile (acrylonitrile)	$CH_2{=}CH{-}CH{=}CH_2$ $CH_2{=}CH{-}CN$	*a*	Buna N[c]	
2-chloro-1,3-butadiene (chloroprene)	$CH_2{=}CH{-}C(Cl){=}CH_2$	*a*	neoprene	mostly trans 1,4
2-methyl-1,3-butadiene (isoprene)	$CH_2{=}CH{-}C(CH_3){=}CH_2$	Li or Ziegler	essentially identical with natural rubber	~100% cis 1,4
2-methylpropene and 2-methyl-1,3-butadiene (isoprene)	$(CH_3)_2C{=}CH_2$ $CH_2{=}CH{-}C(CH_3){=}CH_2$	$AlCl_3$	butyl rubber	

[a]No simple formula can be given, but peroxide-type catalysts, particularly peroxosulfate salts, are used most commonly.

[b]GRS means Government Rubber-Styrene type and is an obsolete notation introduced during World War II.

[c]Originally developed in Germany during World War II.

Figure 13-2. This ordered arrangement cannot be deformed easily, hence the material is hard and brittle. However, when the double bonds are cis, steric hindrance prevents the chains from assuming a similar ordered structure and the bulk of the material exists in a noncrystalline (amorphous) state with randomly oriented chains. When the cis polymer is stretched, the chains straighten out and tend to become oriented; but because this is an unstable state, the material snaps back to the amorphous state when released. The overall process accounts for the elastic properties of rubber and other similar materials.

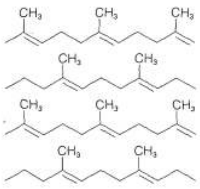


Figure 13-2: Schematic representation of the configuration of chains in gutta-percha (trans-1,4-polyisoprene).

Polymerization of 2-methylpropene in the presence of small amounts of 2-methyl-1,3-butadiene (isoprene) gives a copolymer with enough double bonds to permit cross-linking of the polymer chains through vulcanization. The product is a hard-wearing, chemically resistant rubber called “butyl rubber.” It is highly impermeable to air and is used widely for inner tubes for tires.

[3]Synthetic rubber has provided severe competition for natural rubber and, for many years, it seemed as though rubber plantations eventually would become extinct. However, rising petroleum prices and higher 2-methyl-1,3-butadiene costs coupled with methods developed for greatly increasing the output of rubber latex per tree, and the fact that natural rubber has superior properties in radial automobile tires, have reversed the trend and rubber plantations currently are being expanded.

13.4.1: Contributors and Attributions

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13.5: Cumulated Alkadienes

13.5.1: Structure and Stereoisomerism

The 1,2-dienes, which have cumulated double bonds, commonly are called allenes. The simplest example is 1,2-propadiene,

$CH_2{=}C{=}CH_2$ 1,2-propadiene

Figure 13-4). In this formulation each of two electrons of the central atom form collinear $sp\,\sigma$ bonds to the terminal sp^2-hybridized carbons. The two remaining electrons of the central carbon occupy p orbitals and form π bonds through overlap of these p orbitals and the p orbitals of the terminal carbons.

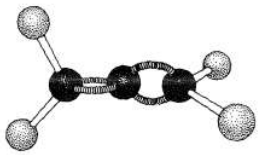


Figure 13-3: Ball-and-stick model of 1,2-propadiene.

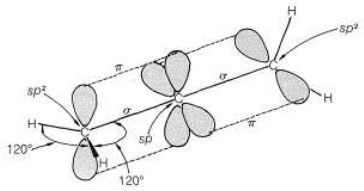


Figure 13-4: Atomic-orbital model of 1,2-propadiene.

Allenes of the type $RR'C{=}C{=}CRR'$ are *chiral* molecules and can exist in two stereoisomeric forms, one being the mirror image of the other and neither being superimposable on the other (i.e., enantiomers, Figure 13-5).

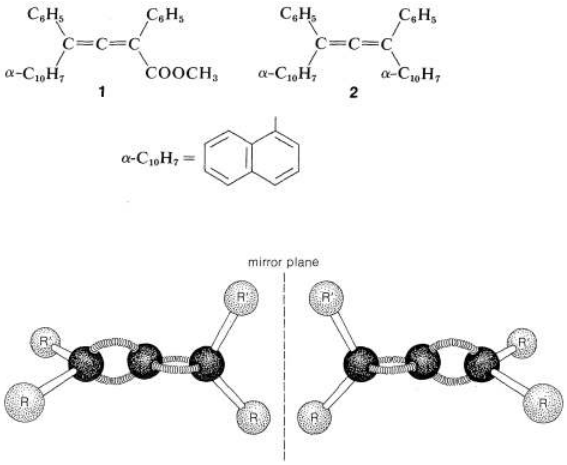
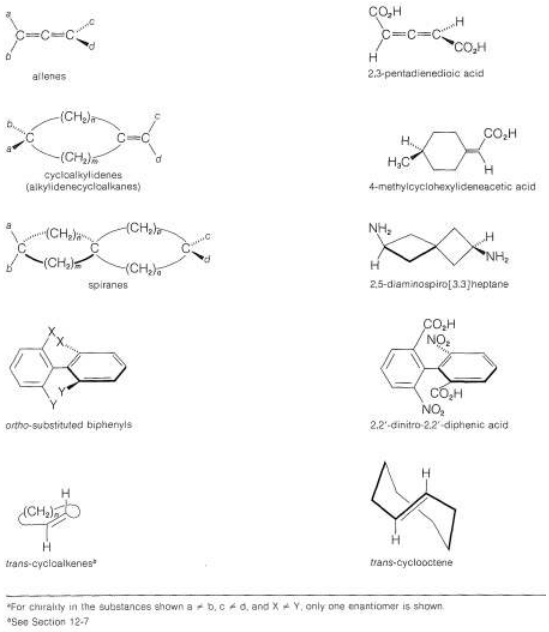


Figure 13-5: Enantiomers of a substituted allene of the type $RR'C{=}C{=}CRR'$.

Verification of the chirality of such allenes (originally proposed by van't Hoff in 1875) was slow in coming and was preceded by many unsuccessful attempts to resolve suitably substituted allenes into their enantiomers. The first successful resolutions were achieved in 1935 for the enantiomers of two compounds 1 and 2. This was a classic achievement because it dispelled the suspicion prevalent at the time that rotation about the bonds of the cumulated diene system was free enough to preclude the isolation of configurationally stable enantiomers.

The chirality observed in this kind of substituted allene is a consequence of dissymmetry resulting from restricted rotation about the double bonds, not because of a tetrahedral atom carrying four different groups. Restricted rotation occurs in many other kinds of compounds and a few examples are shown in Table 13-3, which includes *trans*-cycloalkenes (Section 12-7), cycloalkylidenes, spiranes, and *ortho*-substituted biphenyl compounds. To have enantiomers, the structure must not have a plane or center of symmetry (Section 5-5).

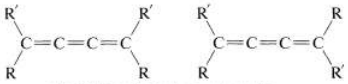
Table 13-3: *Examples of Chiral Substances Resulting from Restricted Rotation About Double or Single Bonds*[a]



The chirality of biphenyls results from restricted rotation about a *single* bond imposed by the bulky nature of ortho substituents. Models will help you visualize the degree of difficulty of having the substituents pass by one another. If $\mathrm{X = H}$ and $\mathrm{Y = F}$ (Table 13-3), the enantiomers are not stable at room temperature; if $\mathrm{X = H}$ and $\mathrm{Y = Br}$, they are marginally stable; if $\mathrm{X = H}$ and $\mathrm{Y = I}$, the rate of loss of optical activity is about 700 times slower than with $\mathrm{Y = Br}$. This is in keeping with the fact that the atomic size of the halogens increases in the order $\mathrm{F < Br < I}$.

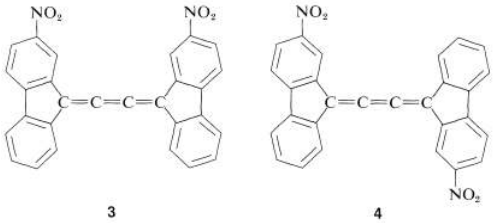
13.5.1.1: Cis-Trans Isomerism

In a cumulated triene, or any cumulated polyene with an *odd* number of double bonds, the atoms connected to the terminal carbons lie in the same plane, just as they do in an ordinary alkene. Van't Hoff pointed out that suitably substituted cumulated polyenes of this type should then have cis and trans forms:



cis and trans forms of a cumulated triene

Like the resolution of allenes, the separate existence of cis and trans isomers of cumulated trienes was not verified until many years after van't Hoff's original predictions, but a separation finally was achieved, in 1954, by R. Kuhn and K. Scholler for compounds 3 and 4:



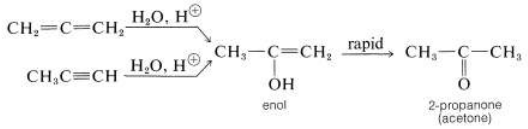
3 4

There are relatively few cis-trans forms of 1,2,3-alkatrienes known. They appear to interconvert readily on mild heating, which suggests that one of the double bonds has a lower rotational barrier than is normal for an alkene double bond.

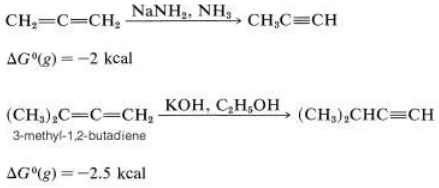
13.5.2: Chemistry of Allenes

The properties of allenes are similar to those of alkenes, although the pure compounds often are difficult to prepare and are not indefinitely stable. Allenes undergo many of the usual double-bond reactions, being readily hydrogenated, adding bromine, and

being oxidized with potassium permanganate solution. The hydration of allenes resembles the hydration of alkynes in giving initially an unstable enol that rapidly rearranges to a ketone:

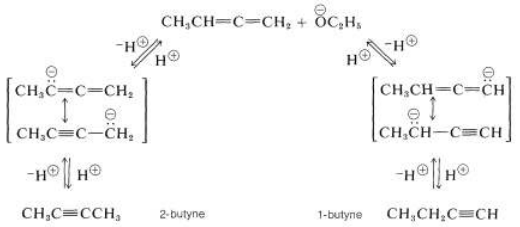


Allenes are not as stable as dienes with conjugated or isolated double bonds. The heats of hydrogenation (Table 11-2) indicate that the order of stability is conjugated dienes > isolated dienes > cumulated dienes. The relative instability of allenes probably reflects extra strain as the result of one carbon atom forming two double bonds. 1,2-Propadiene is slightly more strained than that of propyne. It is not surprising then that 1,2-propadiene isomerizes to propyne. This isomerization occurs under the influence of strongly basic substances such as sodium amide in liquid ammonia or potassium hydroxide in ethyl alcohol:



Indeed, one of the difficulties associated with syntheses of allenes and alkynes (which often are carried out in the presence of strong bases) is the concurrent formation of isomerization products.

The basic catalyst in the isomerization of 1,2-butadiene to butynes acts by removing an alkenic proton from the hydrocarbon. Two different anions can be formed, each of which is stabilized by electron delocalization involving the adjacent multiple bond. Either anion can react with the solvent by proton transfer to form the starting material or an alkyne. At equilibrium the most stable product, which is 2-butyne, predominates [1-butyne $(g) \rightleftharpoons$ 2-butyne (g), $\Delta G^0 = -4.0\ \text{kcal mol}^{-1}$]:



13.5.3: Contributors and Attributions

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13.6: Approaches to Planning Practical Organic Syntheses

Chemistry is unique among the physical and life sciences in one very important respect. It can be manipulated extensively to man's design. That is, molecular structures can be designed and then constructed by choosing appropriate chemical reactions. This is **chemical synthesis**, which has been developed to such a degree that the economies and indeed the living standards of the industrialized nations have come to depend on it. Not everyone agrees that the present state of civilization in the industrialized nations is a way station to the millenium. But whether one agrees or not, there is no question that chemical synthesis has played an enormous role in making possible the accessories of modem life.

Chemical synthesis is not a science that can be taught or learned by any well-defined set of rules. Some classify synthesis as more art than science because, as with all really creative endeavors, to be very successful requires great imagination conditioned by a wealth of background knowledge and experience. The problems of synthesis basically are problems in design and planning. Given the objective of synthesizing a specific organic compound, there always is a variety of ways that the objective can be achieved, either from the same or from different starting materials. What we hope to do here is to show how one can go about developing efficient syntheses from available starting materials. However, *practice* in planning syntheses is imperative to obtaining a good grasp of the principles and problems involved. This will be up to you; no one else can do it for you. Practice also will help greatly to convert short-term memories of organic reactions to longer-term memories through repeated review and demonstrated relevance.

13.6.1: Methodology

In almost all syntheses the **target compound** is defined precisely, both as to structure and stereochemistry. Regardless of whether the synthesis is destined to be carried out on an industrial scale or on a laboratory scale, careful planning is required. The usual methodology for the planning stage involves two, not wholly independent, steps. First, one considers the various possible ways the desired *carbon skeleton* can be constructed, either from smaller molecules or by changes in some existing skeleton. Second, means are considered for generation of desired *functional groups* on the desired carbon skeleton. In many cases, the desired functional groups can be generated as a consequence of the reactions whereby the desired skeleton itself is generated. Alternative syntheses almost always are possible and one should proceed on the notion that the first sequence one thinks of is unlikely to be the best.

The choice of the best route usually is made by considering:

1. The availability of the starting materials
2. The cost of the starting materials and the equipment needed
3. The simplicity of the various steps and the scale of synthesis
4. The number of separate steps involved
5. The yield in each step
6. The ease of separation and purification of the desired product from by-products and stereoisomers

These considerations are dealt with in the following sections and in subsequent chapters.

13.6.2: Starting Materials

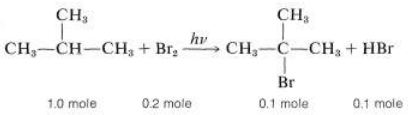
Availability of the starting materials obviously is a limiting factor in any synthetic operation. As far as laboratory-type synthesis is concerned, "availability" means that the starting materials either may be bought "off the shelf" or may be prepared easily by standard methods from other inexpensive and available compounds. For large-scale industrial syntheses, the limiting factor usually is the cost of the starting materials, including the energy required.

But in some cases the limiting factor may be problems in disposal of the byproducts. Costs will vary according to geographical location and will fluctuate widely, as with crude oil costs, so as to cause obsolescence and constant change in the chemical industry. However, it is worth remembering that the cheapest organic starting materials available are methane, ethene, ethyne, propene, butenes, benzene, and methylbenzene (toluene). Any chemical that can be prepared easily in high yield from one of these hydrocarbons is likely to be relatively inexpensive, readily available, and useful as a starting material in more involved syntheses.

13.6.3: The Yield Problem

Among the factors considered in choosing among several possible synthetic routes is: Which gives the best yield? The definition of **yield** and its distinction from another useful term, **conversion**, should be clearly understood. To help you understand, consider a

specific example, the bromination of 2-methyl-propane to give *tert*-butyl bromide as the desired product. This type of reaction is carried on best with an excess of hydrocarbon to avoid polysubstitution (Section 4-5), and if we use such an excess of hydrocarbon, bromine will be the **limiting reagent**. This means simply that the amount of the desired product that could be formed is determined, or limited, by the amount of bromine used:



Suppose we start with one mole of hydrocarbon and 0.2 mole of bromine and, after a specified reaction time, 0.1 mole of bromine has reacted. If only the desired product were formed, and there were no other losses of hydrocarbon or bromine,

$$\%\ \text{conversion} = \frac{\text{moles of limiting reagent reacted}}{\text{moles of limiting reagent initially present}} = \frac{0.1}{0.2} \times 100 = 50\% \tag{13.6.1}$$

If there are no losses in isolating the product or in recovering unused starting material, then

$$\%\ \text{yield} = \frac{\text{moles of product}}{\text{moles of limiting reagent initially present}} = \frac{0.1}{0.1} \times 100 = 100\% \tag{13.6.2}$$

Now suppose all of the 0.2 mole of bromine reacts, 0.08 mole of the desired product can be isolated, and 0.7 mole of hydrocarbon is recovered. Under these circumstances, the percent conversion is 100%, because all of the bromine has reacted. The yield can be figured in different ways depending on which starting material one wishes to **base the yield**. Based on bromine (which would be logical because bromine is the more expensive reagent) the yield of *tert*-butyl bromide is $(0.08/0.2) \times 100 = 40\%$. However, one also could base the yield of *tert*-butyl bromide on the unrecovered hydrocarbon, and this would be $[0.08/(1.0 - 0.7)] \times 100 = 27\%$.

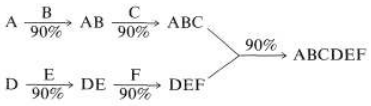
In a multistep synthesis, the overall percent yield is the product of the fractional yields in each step times 100 and decreases rapidly with the number of steps. For this reason, a low-yield step along the way can mean practical failure for the overall sequence. Usually, the best sequence will be the one with the fewest steps. Exceptions arise when the desired product is obtained as a component of a mixture that is difficult to separate. For example, one could prepare 2-chloro-2-methylbutane in one step by direct chlorination of 2-methyl-butane (Section 4-5A). But because the desired product is very difficult to separate from the other, isomeric monochlorinated products, it is desirable to use a longer sequence that may give a lower yield but avoids the separation problem. Similar separation problems would be encountered in a synthesis that gives a mixture of stereoisomers when only one isomer is desired. Again, the optimal synthesis may involve a longer sequence that would be stereospecific for the desired isomer.

One way of maximizing the yield is to minimize the number of sequential steps and, whenever possible, to use *parallel* rather than *sequential* reactions. For example, suppose that we wish to synthesize a compound ABCDEF by linking together A, B, C, D, E, and F. The sequential approach would involve at least five steps as follows:

$$\text{A} \xrightarrow{\text{B}} \text{AB} \xrightarrow{\text{C}} \text{ABC} \xrightarrow{\text{D}} \text{ABCD} \xrightarrow{\text{E}} \text{ABCDE} \xrightarrow{\text{F}} \text{ABCDEF} \tag{13.6.3}$$

If each of these steps proceeds in 90% yield, the overall yield would be $(0.90)^5 \times 100 = 59\%$.

One possible parallel approach would involve synthesis of the fragments ABC and DEF followed by the combination of these to ABCDEF:



There are still at least five reaction steps, but only three sequential steps; and if each of these proceeds in 90% yield, the overall yield would be $(0.90)^3 \times 100 = 73\%$. The parallel approach is especially important in the synthesis of polymeric substances such as peptides, proteins, and nucleic acids in which many subunits have to be linked.

Finally, product yields are very dependent on manipulative losses incurred in each step by isolating and purifying the synthetic intermediates. The need to minimize losses of this kind is critically important in very lengthy syntheses.

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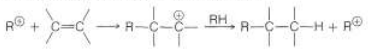
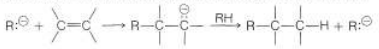
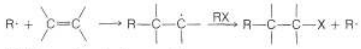
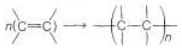
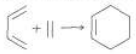
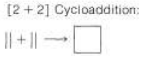
13.7: Building the Carbon Skeleton

According to the suggested approach to planning a synthesis, the primary consideration is how to construct the target carbon skeleton starting with smaller molecules (or, alternatively, to reconstruct an existing skeleton). Construction of a skeleton from smaller molecules almost always will involve formation of carbon-carbon bonds. Up to this point we have discussed only a few reactions in which carbon-carbon bonds are formed and these are summarized in Table 13-4. Other important reactions that can be used to enlarge a carbon framework will be discussed in later chapters.

Table 13-4: *Some Carbon-Carbon Bond-Forming Reactions with Section Reference*

Reaction	Section reference
1. Addition of carbon electrophiles to alkenes: 	10-9
2. Addition of carbon nucleophiles to suitably activated alkenes: 	10-6
3. Addition of carbon radicals to alkenes: 	10-7
4. Addition polymerization reactions: 	10-8
5. Displacement reactions with alkynide anions: $RC{\equiv}C{:}^{\ominus} + R'X \longrightarrow RC{\equiv}CR' + X^{\ominus}$	11-8C
6. Displacement reactions with cyanide ion: ${}^{\ominus}C{\equiv}N + RX \longrightarrow RC{\equiv}N + X^{\ominus}$	8-7F
7. Coupling reactions of 1-alkynes: $2RC{\equiv}CH \xrightarrow{Cu(I)} RC{\equiv}C{-}C{\equiv}CR$	11-8D
8. [4 + 2] Cycloaddition: 	13-3A
9. [2 + 2] Cycloaddition: 	13-3D

The most logical approach to planning the synthesis of a particular carbon framework requires that one work *backward* by mentally fragmenting the molecule into smaller pieces that can be "rejoined" by known C–C bond-forming reactions. The first set of pieces in turn is broken into smaller pieces, and the mental fragmentation procedure is repeated until the pieces correspond to the carbon skeletons of readily available compounds. There almost always will be several different backward routes, and each is examined for its potential to put the desired functional groups at their proper locations. In almost all cases it is important to use reactions that will lead to pure compounds without having to separate substances with similar physical properties.

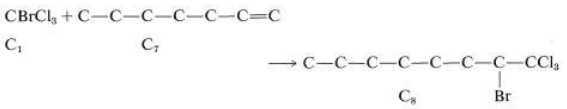
13.7.1: Example

A typical synthesis problem would be to devise a preparation of *cis*-2-octene, given the restrictions that the starting materials have fewer than eight carbons, and that we use the C–C bond-forming reactions we have discussed up to now. The reasoning involved in devising an appropriate synthesis with the given restrictions will be outlined for this example in detail.

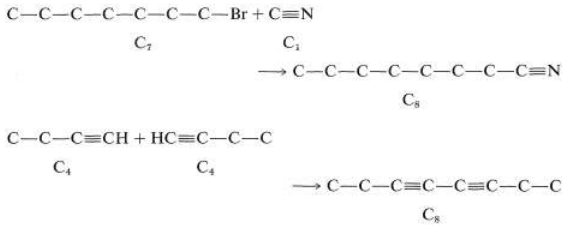
First, we can see that the carbon skeleton of the desired product can be divided to give the following combinations of fragments:

$$C{-}C{-}C{-}C{-}C{-}C{-}C{-}C \longrightarrow \begin{cases} C{-}C{-}C{-}C + C{-}C{-}C{-}C \\ C{-}C{-}C + C{-}C{-}C{-}C{-}C \\ C{-}C + C{-}C{-}C{-}C{-}C{-}C \\ C + C{-}C{-}C{-}C{-}C{-}C{-}C \end{cases}$$

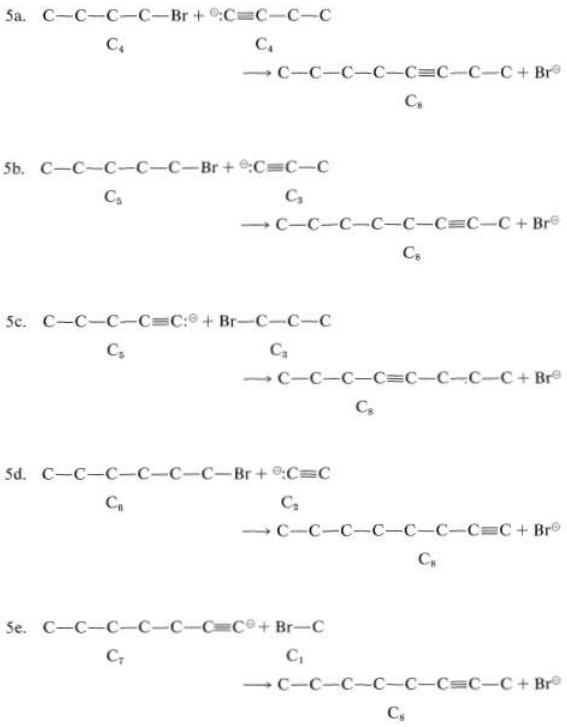
Next, we have to decide what reaction or reactions would be useful to put these fragments together to reform the C_8 chain. If we look at the list of available reactions in Table 13-4[4] for C–C bond formation, we can rule out 1, 2, 4, 8, and 9: 1 and 4 because the reactions are unsuitable for making unbranched chains; 8 and 9 because they make rings, not chains; and 2 because it does not work well in the absence of activating groups. Reaction 3 could be used to combine C_1 and C_7 units to give C_8, as by the radical addition of $CBrCl_3$ to 1-heptene:



Reactions 6 and 7 could also be used to make C_8, 6 by linking C_7 to C_1 and 7 by putting together two C_4 units.[5]

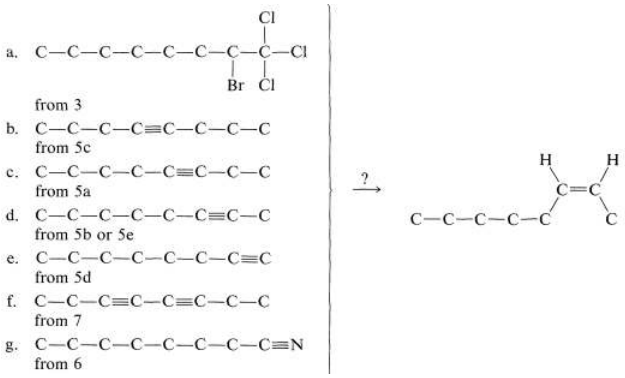


Reaction 5 could be useful for all of the possible ways of dividing C_8. Some of the possible combinations are:

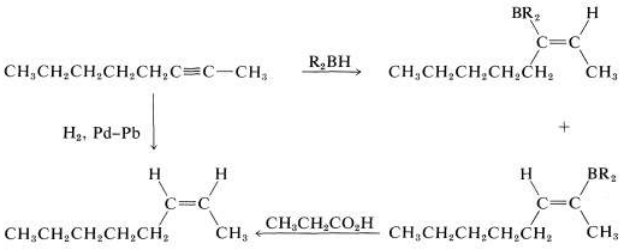


This does not exhaust the possibilities because, as 5b and 5e show, Reaction 5 can be used to make the same C_8 compound from different sets of starting materials.

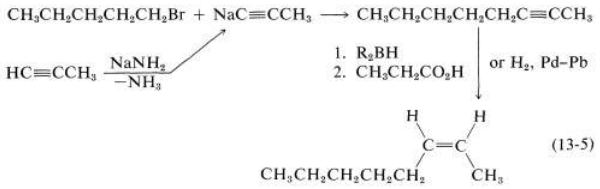
We now have to consider how to convert the C_8 materials that we might make into *cis*-2-octene. The possibilities are:



Of these, d is the obvious choice for first consideration because it has its functionality, a single triple bond, between the same two carbons we wish to have joined by a cis double bond in the product. Now, we have to ask if there are reactions that will convert $-C \equiv C-$ to *cis*- . Two possibilities were mentioned previously - hydrogenation of a triple bond with the Lindlar catalyst (Section 11-2B) and hydroboration followed by treatment with propanoic acid (Section 11-6D):



Either of these two reactions provides a simple and straightforward way of converting 2-octyne to *cis*-2-octene, so a satisfactory answer to the original problem is



(13-5)

You can see that even with having available only seven C–C bond-forming reactions and two ways of converting $-C \equiv C- \rightarrow$, considerable amount of logical screening is required to eliminate unsuitable possibilities. The skilled practitioner makes this kind of diagnosis quickly in his head; at the outset you will find it useful to write the steps in your screening in the same way as we have done for this example.

[4]You may wish to review the sections cited for each reaction to be sure you understand the judgments we make here as to the suitability of particular reactions for the purpose at hand.

[5]Reaction 7 could also be used to make C_8 by other combinations, such as of C_5 and C_3, but these would give undesirable mixtures of products. Thus, $C–C–C–C \equiv CH + HC \equiv C–C \rightarrow C–C–C–C \equiv C–C \equiv C–C + C–C \equiv \cdot C–C \equiv C–C + C–C–C–C \equiv C–C \equiv C–C–C–C$

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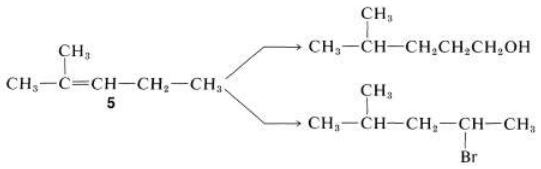
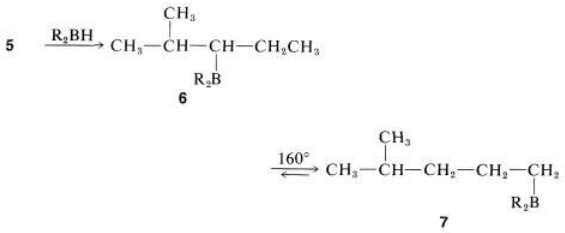
13.8: Introducing Functionality

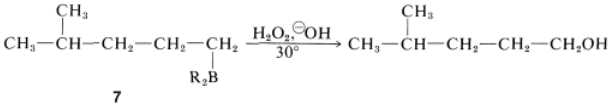
As we have seen in the previous section, it may be easy to construct the carbon skeleton of the target compound of a synthesis, but with a reactive functional group at the wrong carbon. Therefore it is important also to have practice at shifting reactive entry points around to achieve the final desired product. We shall illustrate this form of molecular chess with reactions from previous post. A typical problem may be to devise syntheses for achieving the following conversions:



If you proceed as in the previous section, you will see that the starting material and products have the same number of carbons and the same general bonding arrangement of those carbons. Getting the functionality to the right carbons is now the problem. If you review the reactions discussed up to now, you will find that the only good way of getting a reactive group at the end of a chain starting with a reactive group in the middle of the chain is borane isomerization (Section 11-6C). The borane, 6, can be obtained from the starting material, 5, by hydroboration (Section 11-6) and, on heating, 6 will be converted to 7:

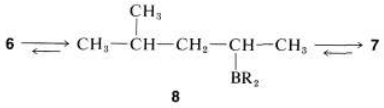


Production of 4-methyl-1-pentanol from the substituted alkylborane, 7, can be achieved by oxidation (Section 11-6D):



The three steps - hydroboration, isomerization, and oxidation - thus constitute a reasonable synthesis of the first desired compound.

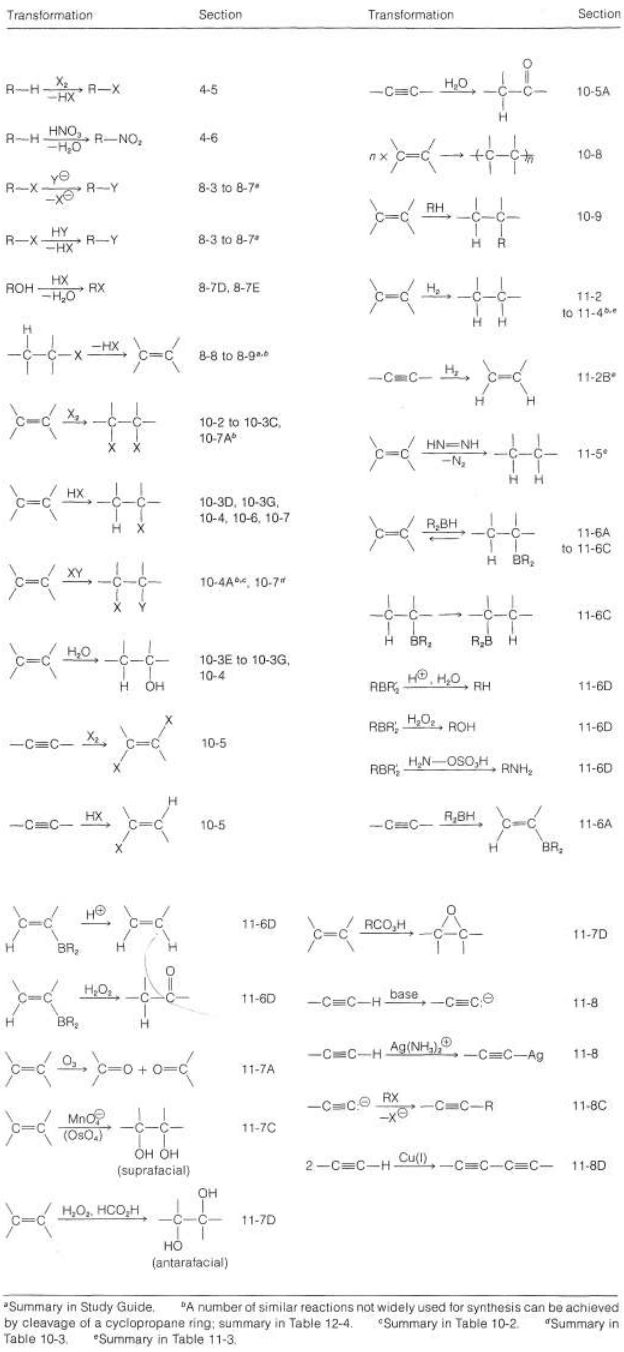
The second desired product is a little more tricky because the isomerization of 6 to 7 cannot be stopped at the alkylborane, 8:



The best procedure to get the desired product is to generate the 1-alkene from the borane with 1-decene (Section 11-6C) and then add hydrogen bromide by a *polar* mechanism (Section 10-4). Incursion of radical-chain addition must be avoided because it would give 1-bromo-4-methylpentane (Section 10-7):

A very brief summary of the transformations that we have studied so far, which do not change the carbon skeleton, is given in Table 13-5 along with appropriate section references. In using this table, it is necessary to check the specific sections to be sure the reaction is applicable to the conversion that you wish to achieve and to determine the proper conditions for the reaction.

Table 13-5: *Summary of Useful Synthetic Transformations*



[a]Summary in Study Guide. [b]A number of similar reactions not widely used for synthesis can be achieved by cleavage of a cyclopropane ring; summary in Table 12-4. [c]Summary in Table 10-2. [d]Summary in Table 10-3. [e]Summary in Table 11-3.

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13.9: Construction of Ring Systems by Cycloaddition

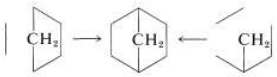
Another example of a synthesis problem makes use of the cycloaddition reactions discussed here. Consider the synthesis of bicyclo[2.2.1]heptane, 9, from compounds with fewer carbons.

bicyclo[2.2.1]heptane, **9**

Whenever a ring has to be constructed, you should consider the possibility of cycloaddition reactions, especially [4 + 2] cycloaddition by the Diels-Alder reaction. A first glance at 9, written in the usual sawhorse-perspective formula, might lead to overlooking the possibility of constructing the skeleton by [4 + 2] addition, because the compound seems only to be made up of five-membered rings. If the structure is rewritten as 10, the six-membered ring stands out much more clearly:

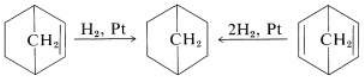
bicyclo[2.2.1]heptane, **10**

If we now try to divide the six-membered ring into [2] and [4] fragments, we find that there are only two *different* ways this can be done:

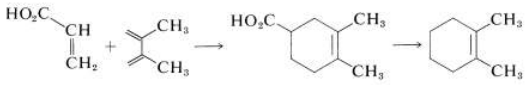


The left division corresponds to a simple [4 + 2] cycloaddition, whereas the right division corresponds to a complex reaction involving formation of three ring bonds at once. Actual Diels-Alder reactions require diene and dienophile starting materials, and two possibilities, using 1,3-cyclopentadiene as the diene and ethene or ethyne as dienophile, follow:

Either of the products can be converted to bicyclo[2.2.1]heptane by hydrogenation (Table 13-5):



Neither ethene nor ethyne is a very good dienophile but [4 + 2] cycloadditions of either with 1,3-cyclopentadiene go well at temperatures of 160-180° because 1,3-cyclopentadiene is a very reactive diene. Achieving the overall result of addition of ethene or ethyne to a less reactive diene could necessitate a synthetic sequence wherein one of the reactive dienophiles listed in Table 13-1 is used to introduce the desired two carbons, and the activating groups are subsequently removed. An example follows:



Reactions that can be used to remove a $-CO_2H$ group will be discussed in Chapter 18.

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13.10: Protecting Groups in Organic Synthesis

One of the major problems in organic synthesis is the suppression of unwanted side reactions. Frequently the desired reaction is accompanied by reaction at other parts of the molecule, especially when more than one functional group is present. Functional groups usually are the most reactive sites in the molecule, and it may be difficult or even impossible to insulate one functional group from a reaction occurring at another. Therefore any proposed synthesis must be evaluated at each step for possible side reactions that may degrade or otherwise modify the structure in an undesired way. To do this will require an understanding of how variations in structure affect chemical reactivity. Such understanding is acquired through experience and knowledge of reaction mechanism and reaction stereochemistry.

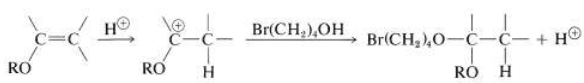
To illustrate the purpose and practice of protecting groups in organic synthesis, let us suppose that the synthesis of *cis*-2-octene, which we outlined in Section 13-7, has to be adapted for the synthesis of 5-octyn-1-ol. We could write the following:

$$CH_3CH_2C{\equiv}CH \xrightarrow{NaNH_2} CH_3CH_2C{\equiv}\overset{\ominus}{C}{:}\overset{\oplus}{Na} \xrightarrow{BrCH_2CH_2CH_2CH_2OH} CH_3CH_2C{\equiv}C(CH_2)_4OH$$

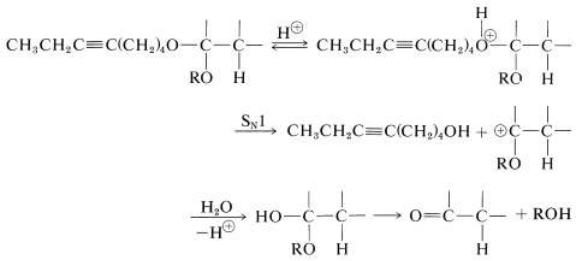
However, the synthesis as written would fail because the alkyne is a weaker acid than the alcohol (Section 11-8), and the alkynide anion would react much more rapidly with the acidic proton of the alcohol than it would displace bromide ion from carbon:

$$CH_3CH_2C{\equiv}\overset{\ominus}{C}{:}\overset{\oplus}{Na} + HOCH_2CH_2CH_2CH_2Br \longrightarrow CH_3CH_2C{\equiv}CH + \overset{\oplus}{Na}\overset{\ominus}{O}(CH_2)_4Br$$

The hydroxyl group of 4-bromo-1-butanol therefore must be protected *before* it is allowed to react with the alkynide salt. There are a number of ways to protect hydroxyl groups, but one method, which is simple and effective, relies on the fact that unsaturated ethers of the type are very reactive in electrophilic addition reactions (Section 10-4). An alcohol readily adds to the double bond of such an ether in the presence of an acid catalyst:



The protected compound is a much weaker acid than the alkyne, and the displacement reaction can be carried out with the alkynide salt without difficulty. To obtain the final product, the protecting group must be removed, and this can be done in dilute aqueous acid solution by an S_N1 type of substitution (Sections 8-7D and 8-7E):



13.10.1: Some Common Protecting Groups in Organic Synthesis

Hydroxyl (OH) protecting groups in Organic Synthesis

Protection of alcohols:

Acetyl (Ac) – Removed by acid or base.

Benzoyl (Bz) – Removed by acid or base, more stable than Ac group.

Benzyl (Bn, Bnl) – Removed by hydrogenolysis. Bn group is widely used in sugar and nucleoside chemistry.

β-Methoxyethoxymethyl ether (MEM) – Removed by acid.

Dimethoxytrityl, [bis-(4-methoxyphenyl)phenylmethyl] (DMT) – Removed by weak acid. DMT group is widely used for protection of 5′-hydroxy group in nucleosides, particularly in oligonucleotide synthesis.

Methoxymethyl ether (MOM) – Removed by acid.

Methoxytrityl [(4-methoxyphenyl)diphenylmethyl, MMT) – Removed by acid and hydrogenolysis.

p-Methoxybenzyl ether (PMB) – Removed by acid, hydrogenolysis, or oxidation.

Methylthiomethyl ether – Removed by acid.

Pivaloyl (Piv) – Removed by acid, base or reductant agents. It is substantially more stable than other acyl protecting groups.

Tetrahydropyranyl (THP) – Removed by acid.

Trityl (triphenylmethyl, Tr) – Removed by acid and hydrogenolysis.

Silyl ether (most popular ones include trimethylsilyl (TMS), tert-butyldimethylsilyl (TBDMS), tri-iso-propylsilyloxymethyl (TOM), and triisopropylsilyl (TIPS) ethers) – Removed by acid or fluoride ion. (such as NaF, TBAF (Tetra-n-butylammonium fluoride, HF-Py, or HF-NEt3)). TBDMS and TOM groups are used for protection of 2′-hydroxy function in nucleosides, particularly in oligonucleotide synthesis.

Methyl Ethers – Cleavage is by TMSI in DCM or MeCN or Chloroform. An alternative method to cleave methyl ethers is BBr3 in DCM

Ethoxyethyl ethers (EE) – Cleavage more trivial than simple ethers e.g. 1N Hydrochloric acid

Amine protecting groups in Organic Synthesis

Protection of amines:

Carbobenzyloxy (Cbz) group – Removed by hydrogenolysis

p-Methoxybenzyl carbonyl (Moz or MeOZ) group – Removed by hydrogenolysis, more labile than Cbz

tert-Butyloxycarbonyl (BOC) group (Common in solid phase peptide synthesis) – Removed by concentrated, strong acid. (such as HCl or CF3COOH)

9-Fluorenylmethyloxycarbonyl (FMOC) group (Common in solid phase peptide synthesis) – Removed by base, such as piperidine

Acetyl (Ac) group is common in oligonucleotide synthesis for protection of N4 in cytosine and N6 in adenine nucleic bases and is removed by treatment with a base, most often, with aqueous or gaseous ammonia or methylamine. Ac is too stable to be readily removed from aliphatic amides.

Benzoyl (Bz) group is common in oligonucleotide synthesis for protection of N4 in cytosine and N6 in adenine nucleic bases and is removed by treatment with a base, most often with aqueous or gaseous ammonia or methylamine. Bz is too stable to be readily removed from aliphatic amides.

Benzyl (Bn) group – Removed by hydrogenolysis

Carbamate group – Removed by acid and mild heating.

p-Methoxybenzyl (PMB) – Removed by hydrogenolysis, more labile than Benzyl

3,4-Dimethoxybenzyl (DMPM) – Removed by hydrogenolysis, more labile than p-methoxybenzyl

p-methoxyphenyl (PMP) group – Removed by Ammonium cerium(IV) nitrate (CAN)

Tosyl (Ts) group – Removed by concentrated acid (HBr, H2SO4) & strong reducing agents (sodium in liquid ammonia or sodium naphthalenide)

Other Sulfonamides (Nosyl & Nps) groups – Removed by samarium iodide, tributyltin hydride

Carbonyl protecting groups in Organic Synthesis

Protection of carbonyl groups:

Acetals and Ketals – Removed by acid. Normally, the cleavage of acyclic acetals is easier than of cyclic acetals.

Acylals – Removed by Lewis acids.

Dithianes – Removed by metal salts or oxidizing agents.

Carboxylic acid protecting groups in Organic Synthesis

Protection of carboxylic acids:

Methyl esters – Removed by acid or base.

Benzyl esters – Removed by hydrogenolysis.

tert-Butyl esters – Removed by acid, base and some reductants.

Silyl esters – Removed by acid, base and organometallic reagents.

Orthoesters – Removed by mild aqueous acid to form ester, which is removed according to ester properties.

Oxazoline – Removed by strong hot acid (pH < 1, T > 100 °C) or alkali (pH > 12, T > 100 °C), but not e.g. LiAlH4, organolithium reagents or Grignard (organomagnesium) reagents

Phosphate protecting groups in Organic Synthesis

2-cyanoethyl – removed by mild base. The group is widely used in oligonucleotide synthesis.

Methyl (Me) – removed by strong nucleophiles e.c. thiophenole/TEA.

Terminal alkyne protecting groups in Organic Synthesis

propargyl alcohols in the Favorskii reaction,

silyl groups, especially in protection of the acetylene itself

Orthogonal protection in Organic Synthesis

Orthogonal protection is a strategy allowing the deprotection of multiple protective groups one at a time each with a dedicated set of reaction conditions without affecting the other. It was introduced in the field of peptide synthesis by Robert Bruce Merrifield in 1977. As a proof of concept orthogonal deprotection is demonstrated in a photochemical transesterification by trimethylsilyldiazomethane utilizing the kinetic isotope effect:

Orthogonal protection Application In Photochemistry

Due to this effect the quantum yield for deprotection of the right-side ester group is reduced and it stays intact. Significantly by placing the deuterium atoms next to the left-side ester group or by changing the wavelength to 254 nm the other monoarene is obtained.

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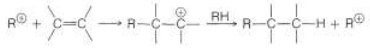
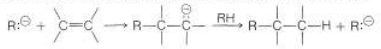
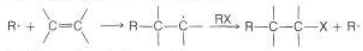
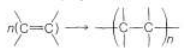
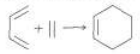
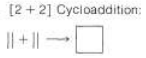
13.11: Building the Carbon Skeleton

According to the suggested approach to planning a synthesis, the primary consideration is how to construct the target carbon skeleton starting with smaller molecules (or, alternatively, to reconstruct an existing skeleton). Construction of a skeleton from smaller molecules almost always will involve formation of carbon-carbon bonds. Up to this point we have discussed only a few reactions in which carbon-carbon bonds are formed and these are summarized in Table 13-4. Other important reactions that can be used to enlarge a carbon framework will be discussed in later chapters.

Table 13-4: *Some Carbon-Carbon Bond-Forming Reactions with Section Reference*

Reaction	Section reference
1. Addition of carbon electrophiles to alkenes: 	10-9
2. Addition of carbon nucleophiles to suitably activated alkenes: 	10-6
3. Addition of carbon radicals to alkenes: 	10-7
4. Addition polymerization reactions: 	10-8
5. Displacement reactions with alkynide anions: $RC{\equiv}C:^{\ominus} + R'X \longrightarrow RC{\equiv}CR' + X^{\ominus}$	11-8C
6. Displacement reactions with cyanide ion: $^{\ominus}C{\equiv}N + RX \longrightarrow RC{\equiv}N + X^{\ominus}$	8-7F
7. Coupling reactions of 1-alkynes: $2RC{\equiv}CH \xrightarrow{Cu(I)} RC{\equiv}C{-}C{\equiv}CR$	11-8D
8. [4 + 2] Cycloaddition: 	13-3A
9. [2 + 2] Cycloaddition: 	13-3D

The most logical approach to planning the synthesis of a particular carbon framework requires that one work *backward* by mentally fragmenting the molecule into smaller pieces that can be "rejoined" by known C–C bond-forming reactions. The first set of pieces in turn is broken into smaller pieces, and the mental fragmentation procedure is repeated until the pieces correspond to the carbon skeletons of readily available compounds. There almost always will be several different backward routes, and each is examined for its potential to put the desired functional groups at their proper locations. In almost all cases it is important to use reactions that will lead to pure compounds without having to separate substances with similar physical properties.

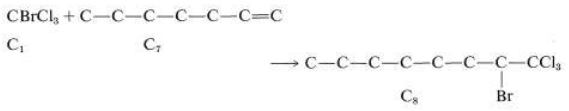
13.11.1: Example

A typical synthesis problem would be to devise a preparation of *cis*-2-octene, given the restrictions that the starting materials have fewer than eight carbons, and that we use the C–C bond-forming reactions we have discussed up to now. The reasoning involved in devising an appropriate synthesis with the given restrictions will be outlined for this example in detail.

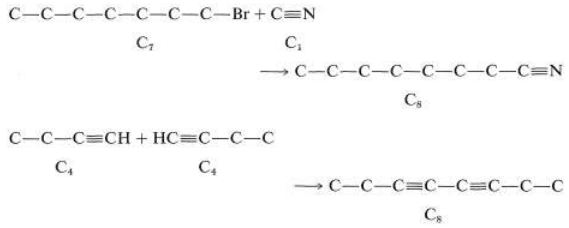
First, we can see that the carbon skeleton of the desired product can be divided to give the following combinations of fragments:

$$C{-}C{-}C{-}C{-}C{-}C{-}C{-}C \longrightarrow \begin{cases} C{-}C{-}C{-}C + C{-}C{-}C{-}C \\ C{-}C{-}C + C{-}C{-}C{-}C{-}C \\ C{-}C + C{-}C{-}C{-}C{-}C{-}C \\ C + C{-}C{-}C{-}C{-}C{-}C{-}C \end{cases}$$

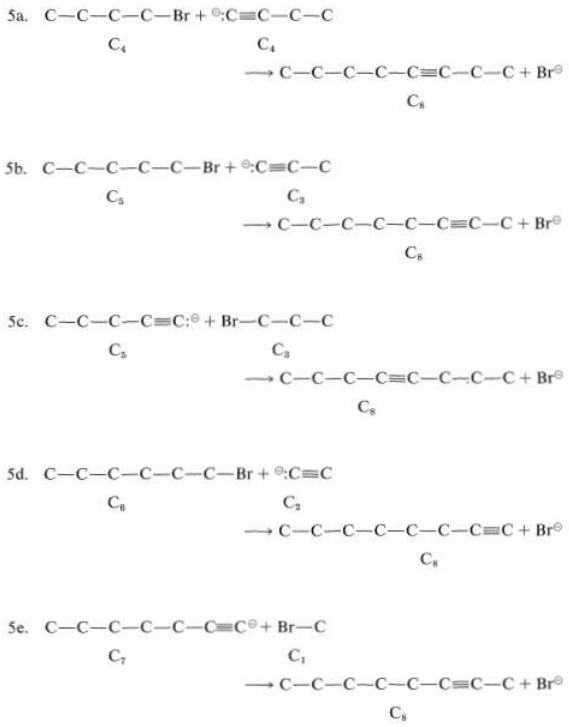
Next, we have to decide what reaction or reactions would be useful to put these fragments together to reform the C_8 chain. If we look at the list of available reactions in Table 13-4[4] for C–C bond formation, we can rule out 1, 2, 4, 8, and 9: 1 and 4 because the reactions are unsuitable for making unbranched chains; 8 and 9 because they make rings, not chains; and 2 because it does not work well in the absence of activating groups. Reaction 3 could be used to combine C_1 and C_7 units to give C_8, as by the radical addition of $CBrCl_3$ to 1-heptene:



Reactions 6 and 7 could also be used to make C_8, 6 by linking C_7 to C_1 and 7 by putting together two C_4 units.[5]

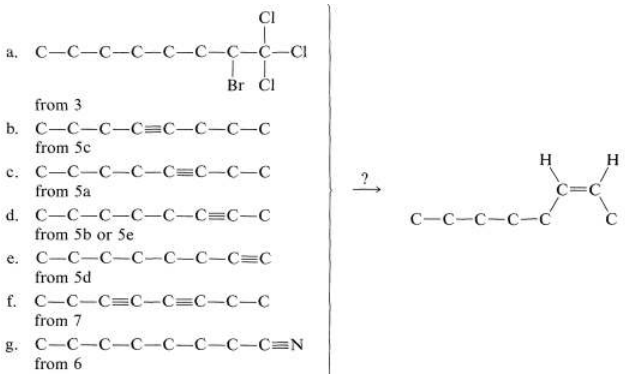


Reaction 5 could be useful for all of the possible ways of dividing C_8. Some of the possible combinations are:

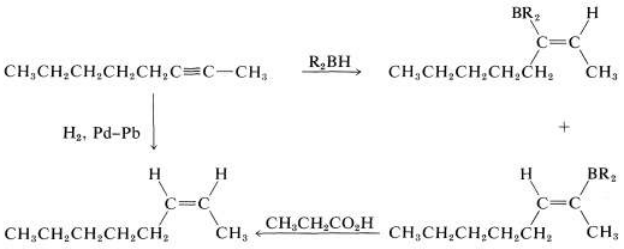


This does not exhaust the possibilities because, as 5b and 5e show, Reaction 5 can be used to make the same C_8 compound from different sets of starting materials.

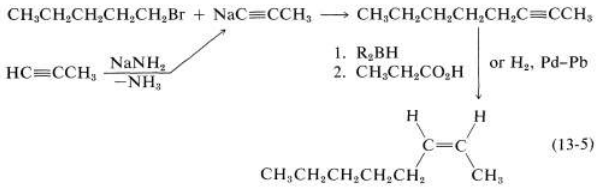
We now have to consider how to convert the C_8 materials that we might make into *cis*-2-octene. The possibilities are:



Of these, d is the obvious choice for first consideration because it has its functionality, a single triple bond, between the same two carbons we wish to have joined by a cis double bond in the product. Now, we have to ask if there are reactions that will convert $-C \equiv C-$ to *cis*- . Two possibilities were mentioned previously - hydrogenation of a triple bond with the Lindlar catalyst (Section 11-2B) and hydroboration followed by treatment with propanoic acid (Section 11-6D):



Either of these two reactions provides a simple and straightforward way of converting 2-octyne to *cis*-2-octene, so a satisfactory answer to the original problem is



You can see that even with having available only seven C–C bond-forming reactions and two ways of converting $-C \equiv C- \rightarrow$, considerable amount of logical screening is required to eliminate unsuitable possibilities. The skilled practitioner makes this kind of diagnosis quickly in his head; at the outset you will find it useful to write the steps in your screening in the same way as we have done for this example.

[4]You may wish to review the sections cited for each reaction to be sure you understand the judgments we make here as to the suitability of particular reactions for the purpose at hand.

[5]Reaction 7 could also be used to make C_8 by other combinations, such as of C_5 and C_3, but these would give undesirable mixtures of products. Thus, $C–C–C–C \equiv CH + HC \equiv C–C \rightarrow C–C–C–C \equiv C–C \equiv C–C + C–C \equiv \cdot C–C \equiv C–C + C–C–C–C \equiv C–C \equiv C–C–C–C$

13.11.2: Contributors and Attributions

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13.E: Polyfunctional Compounds, Alkadienes, and Approaches to Organic Synthesis (Exercises)

Exercise 13-1 1,4-Pentadiene is different from propene in some of its chemical properties; for example, removal of the hydrogens at the 3-position by attack of radicals is much easier than the removal of those on the methyl group of propene. Explain why this should be so. (The rules of Section 6-5B will be helpful in this connection.)

Exercise 13-2 Draw an energy diagram, analogous to Figure 10-10 representing the reaction of Equation 13-1 for the addition of HCl to 1,3-butadiene, that reflects the fact that the 1,4 adduct is more stable, but is formed less rapidly than the 1,2 adduct. (Notice that of the two ways a proton from HCl can add to 1,3-butadiene, only *one* gives a carbocation that is delocalized.)

Exercise 13-3 Write the structures of the intermediates and the addition products expected in each of the following reactions (you may wish to review Chapters 10 and 11):

a. $CH_2{=}C(CH_3){-}CH{=}CH_2 \xrightarrow[20^\circ]{Cl_2,\ CHCl_3}$

b. 2,3-dimethyl-1,3-butadiene $\xrightarrow{B_2H_6}\ \xrightarrow{H_2O_2,\ NaOH}$ (product has formula $C_6H_{14}O_2$)

c. butadiene $\xrightarrow[\text{peroxide}]{C_6H_5SH}$

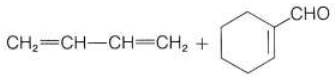
d. 4-methyl-1,3-pentadiene $\xrightarrow{Ni,\ H_2\ (1\ mole)}$

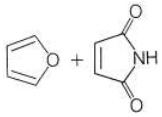
Exercise 13-4 What products would you expect from the Diels-Alder addition of tetracyanoethane to *cis*,*trans*-2,4-hexadiene and *cis*,*cis*-2,4-hexadiene? Explain.

Exercise 13-5 Draw the two possible orientations of diene to dienophile for the addition of *cis*-butanedioic anhydride to *trans*,*trans*-2,4-hexadiene. Which adduct would you expect to form preferentially? Explain.

Exercise 13-6 Predict the [4 + 2] addition products of the following reactions; show your reasoning:

a. 1,3-cyclopentadiene + *trans*-$C_6H_5CH{=}CHCO_2H$

b. 

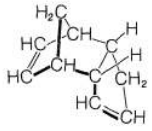
c. 

d. *cis*,*trans*-2,4-hexadiene plus *cis*-butenedioic anhydride

e. 1,3-cyclopentadiene + $CH_2{=}CHCN$

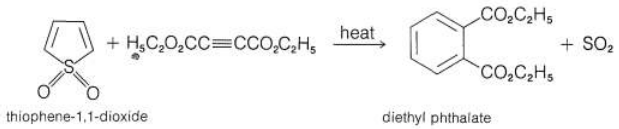
f. *trans*-1,3-pentadiene plus propenal (two possible structural isomers)

Exercise 13-7 The following hydrocarbon degrades on heating by a reverse Diels-Alder reaction. What product(s) does it give?



Exercise 13-8* Formation of the addition product of SO_2 and 1,3-butadiene has $\Delta H^0 = -16.5\ \text{kcal mol}^{-1}$ for the vapor phase. Assuming the equilibrium constant K is unity at $00^\circ C$, calculate ΔS^0 for the reaction. Compare this value with the ΔS^0 that you can calculate for addition of ethene to 1,3-butadiene, which has $\Delta G^0 = -27$: kcal and $\Delta H^0 = -47\ \text{kcal}$. Estimate the temperature in $^\circ C$ that would be required for the equilibrium between ethene and 1,3-butadiene to have $K = 1$. (You may be interested to know that an early route for preparation of 1,3-butadiene involved passing cyclohexane through a tube containing a red-hot wire spiral, $\sim 900^\circ C$.)

Exercise 13-9* Diethyl phthalate is formed by heating thiopene-1,1-dioxide and diethyl butynedioate:



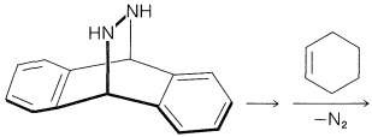
Show the steps involved in this reaction, with the knowledge that the dioxide by *itself* does not decompose at the reaction temperature.

Exercise 13-10* Draw structures for the possible [4 + 2] addition or decomposition products in the following reactions:

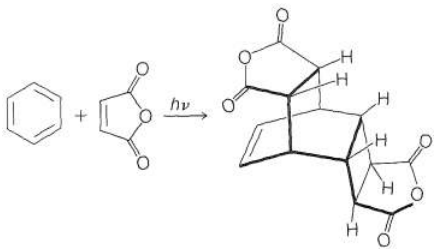
a. dimerization of 2-methylpropenal (methacrolein), $CH_2{=}C(CH_3)CHO$ (two possible structural isomers)

b. 1-ethenylcyclohexene + $SO_2 \xrightarrow{100^\circ}$

c.



Exercise 13-11* Suggest a mechanism to show how the following compound may be formed by irradiation of a solution of *cis*-butenedioic anhydride (maleic anhydride) in benzene:



Exercise 13-12 Formulate chain initiation, propagation, and termination steps for the polymerization of 1,3-butadiene by a mixture of 1,2 and 1,4 addition using a peroxide catalyst. Consider carefully possible structures for the growing-chain radical. Show the expected structure of the polymer and calculate ΔH^0 for the polymerization reaction.

Exercise 13-13* The rearrangement of 1,2-butadiene to 2-butyne shown in Section 13-5B uses ethoxide ion as a basic *catalyst*. When one mole of 1,2-butadiene is treated with one mole of sodium amide in liquid ammonia, and water is added, the product is 1-butyne. Show the steps involved and explain why the product is different when an equivalent amount of a very strong base is used. (You may wish to review Section 11-8.)

Exercise 13-14 Suppose one treated $100\ g$ of propene with $125\ g$ of chlorine in the presence of water and isolated $25\ g$ of excess propene, $130\ g$ of 1,2-dichloropropane, $40\ g$ of 1-chloro-2-propanol, and no chlorine from the reaction mixture. Calculate a percent yield and a percent conversion for the products based (a) on propene and (b) on chlorine.

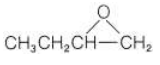
Exercise 13-15 Syntheses have been carried out with one hundred or more sequential reactions. If the yield in each step is 99%, what would be the overall yield after one hundred steps? Repeat the calculation for a yield of 99.9% in each step. What do you conclude from these calculations about the importance of yield in multistep syntheses? (It is interesting to contemplate how even simple organisms can synthesize molecules by what appear to be sequences of 10,000 or more separate steps with very few, if any, errors, and what means the organisms have to check the accuracy of the sequence after each incorporation of a new subunit.)

Exercise 13-16 Devise a synthesis of 2-chloro-2,4,4-trimethylpentane from organic compounds with four carbons or less and any necessary inorganic reagents. Your synthesis should involve the C–C bond-forming reactions listed in Table 13-4 and other reactions shown in Table 13-5. The product should be 2-chloro-2,4,4-trimethylpentane and not a mixture of its isomers.

Exercise 13-17 Show how each of the following compounds could be synthesized from the indicated starting material and other appropriate organic or inorganic reagents. Specify the reaction conditions, mention important side reactions, and justify the practicality of any isomer separations.

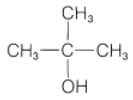
a. 1,3-butadiene from ethyne

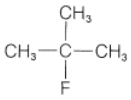
b. 2-hexyne from propyne

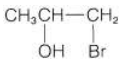
c.  from 2-butyne

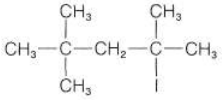
d. cyanocyclohexane from 1,3-butadiene

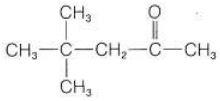
Exercise 13-18 Indicate how you would synthesize each of the following compounds from ethene, propene, 2-methylpropene, or 2-methylpropane, and appropriate inorganic reagents. Specify reagents and the reaction conditions, and justify the practicality of any isomer separations. If separations are not readily possible, estimate the proportion of the desired compound in the final product.

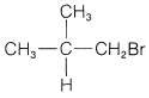
a. 

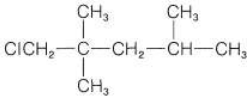
b. 

c. 

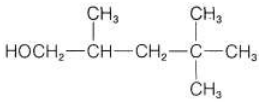
d. 

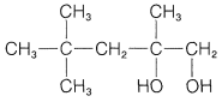
e. 

f. 

g. 

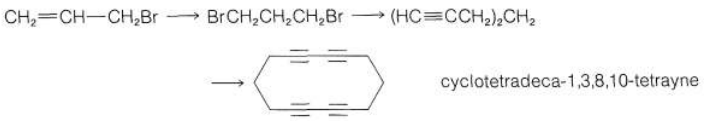
h. $CH_3-CH_2-CH_2OH$

i. 

j. 

Exercise 13-19 Assume that it is necessary to synthesize *meso*-1,4-diphenyl-2,3-butanediol. How could you do this if the only organic reagents at your disposal are methylbenzene and ethyne? In devising a suitable scheme, use any inorganic reagents you consider necessary and specify the reaction conditions (catalysts, solvent, use of acids or bases, and temperature) as closely as possible.

Exercise 13-20 The following key intermediates can be used in a synthesis of cyclotetradeca-1,3,8,10-tetrayne. Write the reagents and conditions for achieving transformations between the key intermediates. Be as specific as possible. Notice that more than one step many be involved in any given transformation.



Exercise 13-21 Devise a synthesis of 3-hexyn-1,6-diol from two-carbon compounds using the unsaturated cyclic ether, , as a protecting reagent for hydroxyl groups.

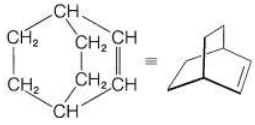
Exercise 13-22 Using the proposed mechanism for the Diels-Alder reaction, explain why you would *not* expect a reactive dienophile to form [4 + 2] cycloaddition products with the following compounds:

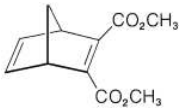
a. 1,3-butadiyne
b. 3,4-dimethylidenecyclobutene (Refer to Section 6-6.)
c. 3-methylidenecyclohexane

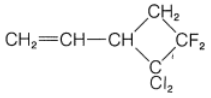
Exercise 13-23 Write the *last* step in a synthesis of each of the following substances (give approximate reaction conditions):

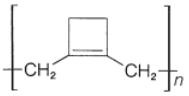
a. $CH_2{=}CHCHBrCH_3$

b.

c. 

d. 

e. 

f. 

g. $-[CH_2{-}CF{=}CH{-}CH_2]_n-$

Exercise 13-24* 1,2-Propadiene adds hydrogen chloride to yield 2-chloropropene. However, the possibility exists that initial attack of a proton might lead to the 2-propenyl cation (Section 6-6), which then would react with chloride ion to form 3-chloropropene. Using the rules for application of the resonance method (Section 6-5B) and the atomic-orbital model for 1,2-propadiene (Figure 13-4), rationalize why a 2-propenyl cation might not be formed easily by addition of a proton to 1,2-propadiene and why 2-chloropropene is the observed product.

Exercise 13-25 How many stereoisomers would you expect for each of the following compounds? Indicate your reasoning and draw appropriate structural formulas for each one.

a. 1,3-pentadiene
b. cyclodecene
c. 1,2,3-trimethylcyclopropane
d. 2,4,6-octatriene
e. 1,3-dichloro-1,2-propadiene

f. 1,4-dichloro-1,2,3-butatriene

g. ethylidene-3-methylcyclohexane

Exercise 13-26 Write structural formulas for the products you would expect from each of the following reactions:

a. 1,2-propadiene and hypochlorous acid (1 mole)

b. 1,3-pentadiene with hydrogen chloride (1 mole)

c. ozonization of 1,3-butadiene followed by reduction with zinc

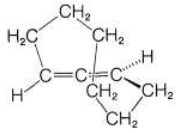
d. 1,3-butadiene with hypochlorous acid (2 moles)

e. 1,3-butadiene with propenoic acid followed by bromine

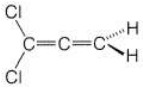
f. 2,3-pentadiene and iodine monochloride

Exercise 13-27 Which of the following structures are chiral and which are achiral? (Models will be very helpful.)

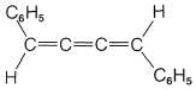
a.



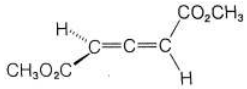
b.



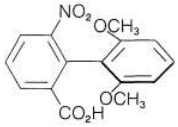
c.



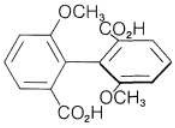
d.



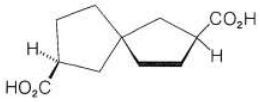
e.



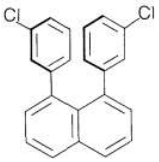
f.



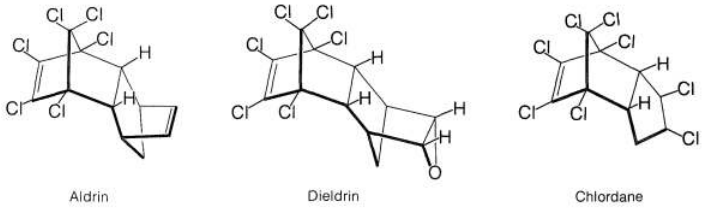
g.



h.

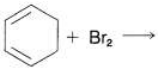


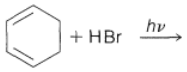
Exercise 13-28* Several widely used pesticides are highly chlorinated polycyclic compounds derived from hexachloropentadiene. They include Aldrin, Dieldrin, and Chlordane. Use of these substances is to be curtailed greatly because of undesirable environmental effects.



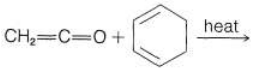
Suggest a plausible synthesis for each of these compounds from readily available C_2-C_5 compounds, including hexachlorocyclopentadiene. Proceed as in Section 13-7 to see how the carbon framework can be broken down to more familiar smaller fragments and then reconstructed by known reactions.

Exercise 13-29 Suggest reasonable structures for the products of the following reactions:

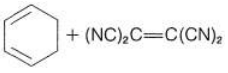
a. 

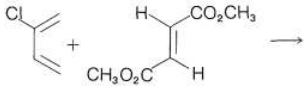
b. 

c. $C_6H_5C\equiv CH + F_2C{=}CF_2 \xrightarrow{\text{heat}}$

d. 

Exercise 13-30 Draw structures for the products of each of the following reactions, each of which takes place at room temperature or higher. Indicate the stereochemistry expected.

a. 

b. 

c. $CH_2{=}CH{-}CH{=}CH_2 + CH_2{=}CH{-}C\equiv N \rightarrow$

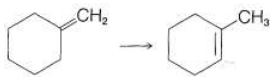
d. *trans*-$C_6H_5CH{=}CH{-}CH{=}CH_2 + CH_2{=}CHCO_2CH_3 \rightarrow$

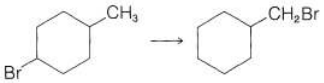
Exercise 13-31* In Section 10-5 we showed that ethyne is much less reactive toward chlorine than is ethene. The same is true for hydrogen chloride. However, when hydrogen chloride adds to 3-butenyne, it adds to the triple bond instead of the double bond, thereby forming 2-chloro-1,3-butadiene instead of 3-chloro-1-butyne. With reference to the discussion in Section 13-2, explain why the order of reactivity of the double and triple bonds of 3-butenyne toward electrophilic reagents may be different from that of ethene and ethyne?

Exercise 13-32 Draw structures for the different ways in which a monomer unit could be added to a growing chain in a radical-chain polymerization of 2-chloro-1,3-butadiene.

Exercise 13-33 Show how you would carry out the following transformations. Notice that each is an example of changing the position or nature of the functional group without affecting the carbon skeleton.

a. $CH_3CH_2C\equiv CCH_2CH_3 \rightarrow CH_3CH_2CH_2CH_2C\equiv CH$

b. 

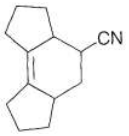
c. 

d. $C_6H_5C\equiv CCH_3 \rightarrow C_6H_5CH_2COCH_3$

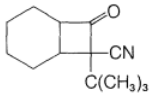
e. $CH_3C \equiv CCH_3 \rightarrow CH_3CH{=}CDCH_3$ (cis)

Exercise 13-34 Cycloaddition reactions are valuable for the synthesis of carbocyclic compounds. Each of the following compounds can be formed by either a [4 + 2] or [2 + 2] cycloaddition as a last step in the synthesis. Draw the structures of the reagents you think would undergo cycloaddition to give the compounds shown.

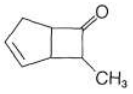
a.



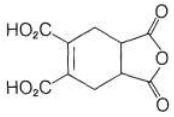
b.



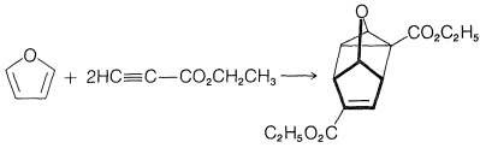
c.



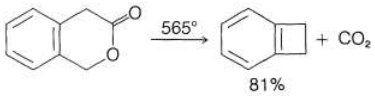
d.



Exercise 13-35 The following reaction occurs in good yield. Show the steps involved in forming the product.



Exercise 13-36* Indicate the steps involved in the following synthesis of bicyclo[4.2.0]-2,4,6-octatriene (benzocyclobutene):



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CHAPTER OVERVIEW

14: Organohalogen and Organometallic Compounds

The general term of "organohalogen" refers to compounds with covalent carbon-halogen bonds. Substances such a bromomethane (CH_3Br) and chloroethene ($CH_2=CHCl$), are examples of organohalogen compounds, whereas others such as the methylammonium chloride salt, which have no carbon-halogen bonds, are not. This chapter is only concerned with compounds that have covalent carbon-halogen bonds.

14.1: Prelude to Organohalogen and Organometallic Compounds
14.2: Physical Properties of Organohalogen and Organometallic Compounds
14.3: Spectroscopic Properties
14.4: Alkyl Halides
14.5: Alkenyl and Alkynyl Halides
14.6: Cycloalkyl Halides
14.7: Aryl Halides
14.8: Polyhalogenated Alkanes and Alkenes
14.9: Organometallic Compounds from Organohalogen Compounds
14.10: Properties of Organometallic Compounds
14.11: Preparation of Organometallic Compounds
14.12: Organomagnesium Compounds
14.13: Organomagnesium and Organolithium Compounds in Synthesis
14.E: Organohalogen and Organometallic Compounds (Exercises)

Thumbnail: Structure of 1-Chlorobenzene.

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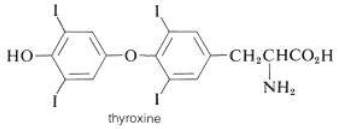
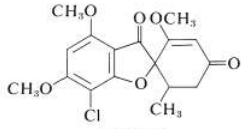
14.1: Prelude to Organohalogen and Organometallic Compounds

There is wide diversity in the nature of organohalogen compounds but, of necessity, we have restricted this chapter to alkyl, cycloalkyl, alkenyl, alkynyl, and aryl halides. Some of the chemistry of the carbon-halogen bonds already will be familiar to you because it involves the addition, substitution, and elimination reactions discussed in previous chapters. To some extent, we will amplify these reactions and consider nucleophilic substitution by what are called the *addition-elimination* and *elimination-addition* mechanisms. Subsequently, we will discuss the formation of carbon-metal bonds from carbon-halogen bonds. The latter type of reaction is of special value because compounds that have carbon-metal bonds are potent reagents for the formation of carbon-carbon bonds, as we will show later in this chapter.

Although large numbers of organohalogens are known, very few of them occur naturally. Thyroid hormones (e.g., thyroxine) that contain iodine are exceptions; other organohalogens are found as mold metabolites (such as griseofulvin) and in marine organisms:

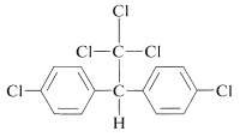


thyroxine

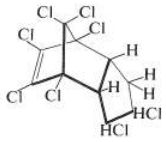


griseofulvin

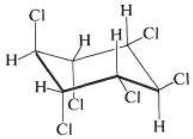
Almost all of the organohalogen compounds in use today are synthetic in origin. You may wonder why, if nature doesn't choose to make them, man elects to do so. The main interest to us here is that they are very useful intermediates for the synthesis of a wide range of other compounds. However, vast quantities of synthetic halogen compounds, particularly polyhalogen compounds, are used as pesticides, cleaning solvents, anaesthetics, aerosol propellants, refrigerants, polymers, and so on. The wisdom of this massive use of materials that are foreign to our natural environment gradually is being reevaluated as the long-term detrimental effects of many of these chemicals become known. For example, many of the chlorinated hydrocarbons such as DDT, Chlordane, and Lindane, which have been used very widely as insecticides, now are at least partially banned because of concern for their long-term effects on nontarget species, including man.



1,1,1-trichloro-2-bis(4-chlorophenyl)ethane (DDT)



(Chlordane)



1,2,3,4,5,6-hexachlorocyclohexane (Lindane)

Sometimes the long-term effects are quite unexpected and difficult to predict. For example, millions of kilograms of CF_2Cl_2, which is used as a propellant, have been released into the atmosphere from aerosol cans. This compound appears to be wholly free of direct adverse physiological effects. However, as the substance diffuses into the upper atmosphere, it is slowly decomposed by sunlight to produce chlorine atoms. Serious danger then is possible because chlorine atoms are known to catalyze the decomposition of ozone, and it is the ozone layer in the upper atmosphere that absorbs most of the sun's ultraviolet radiation that is strongly harmful to life.

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14.2: Physical Properties of Organohalogen and Organometallic Compounds

The physical properties of haloalkanes are much as one might expect. Volatility decreases: (a) with increasing molecular weight along a homologous series, (b) with increasing atomic number of the halogen, and (c) with the structure of the alkyl group in the order such that *tertiary* < *secondary* < *primary* for isomeric halides. These trends are apparent from the physical properties listed in Table 14-1, which includes data for simple halogen derivatives of alkanes, alkenes, alkynes, and arenes.

Table 14-1: *Physical Properties of Organic Halides*

Name	Formula	MW	Mp, °C	Bp, °C	Density, d_4^{20}, g ml^{-1}
Alkyl halides					
fluoromethane	CH_3F	34	−142	−78	–
chloromethane	CH_3Cl	50.5	−97	−24	–
bromomethane	CH_3Br	95	−94	4.5	$1.730^{0/4}$
iodomethane	CH_3I	142	−67	42.8	2.28
tetrafluoromethane	CF_4	88	−184	−129	–
tetrachloromethane	CCl_4	154	−23	76.7	1.594
chloroethane	CH_3CH_2Cl	64.5	−138	12.3	$0.9214^{0/4}$
1-chloropropane	$CH_3CH_2CH_2Cl$	78.5	−122	47	$0.890^{20/20}$
1-chlorobutane	$CH_3CH_2CH_2CH_2Cl$	92.5	−123	78.5	0.886
2-chlorobutane	$CH_3CH_2CH(Cl)CH_3$	92.5	−131	68	0.871
2-chloro-2-methylpropane	$(CH_3)_3C—Cl$	92.5	−27	51	$0.847^{15/4}$
Alkenyl halides					
fluoroethene	$CH_2=CHF$	46	−161	−72	–
chloroethene	$CH_2=CHCl$	62.5	−160	−14	0.911
1,1-dichloroethene	$CH_2=CCl_2$	97	−123	31.7	1.213
tetrafluoroethene	$CF_2=CF_2$	100	−131	−76	1.519
tetrachloroethene	$CCl_2=CCl_2$	165.8	−22	121	1.623
Alkynyl halides					
fluoroethyne	$HC\equiv CF$	44	>−196	−104	–
chloroethyne	$HC\equiv CCl$	60.5	−126	−32	–
bromoethyne	$HC\equiv CBr$	105	–	4.7	–
iodoethyne	$HC\equiv CI$	152	–	32	–
Aryl halides					
fluorobenzene	C_6H_5F	96.0	−42	85	1.024
chlorobenzene	C_6H_5Cl	112.5	−45	132	1.107
bromobenzene	C_6H_5Br	157	−31	156	1.495
iodobenzene	C_6H_5I	204	−31	189	1.832
2-chloromethylbenzene		126.5	−36	159	1.0817
3-chloromethylbenzene		126.5	−49	162	1.0732
4-chloromethylbenzene		126.5	7.5	162	1.0697

The boiling points of many halogen compounds are similar to hydrocarbons of the same molecular weight, but there are some conspicuous exceptions. Iodomethane, for example, has about the same molecular weight as decane (MW 142), but the boiling point of iodomethane is 132° *lower* than that of decane. Likewise, fluorocarbons (e.g., tetrafluoromethane, CF_4, MW 88, bp -129°) are far more volatile than hydrocarbons of similar weights (e.g., hexane, C_6H_{14}, MW 86, bp 69°).

In general, halogen compounds are insoluble in water but are readily soluble in organic solvents and, with the exception of some fluoro and monochloro compounds, they are more dense than water. Aryl halides are fairly pleasant smelling liquids, but arylmethyl (benzylic) halides of structure $ArCH_2X$ are irritating to the eyes, skin, and nasal passages. Toxicity varies, but the chlorinated hydrocarbons such as CCl_4 ("carbon tet") and $CHCl_2—CHCl_2$ are quite toxic and should be used with care.

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14.3: Spectroscopic Properties

Organohalogen compounds give rise to strong absorptions in the *infrared* arising from stretching vibrations of the carbon-halogen bond. The frequency of absorption decreases as the mass of the halogen increases. For monohaloalkanes the absorptions useful for identification are those of C–F at 1100-1000 cm^{-1} and C–Cl at 850-550 cm^{-1}. The C–Br and C–I absorptions are below 690 cm^{-1} and therefore are out of range of most commercial spectrophotometers. Because these bands are in the fingerprint region or far infrared, it is difficult to infer the presence of halogen in a molecule solely from its infrared spectrum.

Apart from fluorine, the magnetic properties of halogen nuclei do not complicate proton or ^{13}C *nuclear magnetic resonance spectra* of organohalogen compounds. But fluorine (^{19}F) has a spin of 1/2 and causes spin-spin splitting of the resonances of neighboring magnetic nuclei (^{13}C, ^{1}H, and other ^{19}F nuclei). Proton chemical shifts are influenced strongly by the presence of halogen, which serves to deshield neighboring protons by electronegativity effects (see Section 9-10E).

The *mass spectra* of chlorine- and bromine-containing compounds clearly show the abundance ratios of the stable isotopes ^{35}Cl: $^{37}Cl = 3{:}1$ and ^{79}Br:$^{81}Br = 1{:}1$ in the molecular ions and those ionic fragments which contain halogens (Section 9-11).

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14.4: Alkyl Halides

The important chemistry of alkyl halides, RX, includes the nucleophilic (S_N) displacement and elimination (E) reactions discussed in Chapter 8. Recall that *tertiary* alkyl halides normally are reactive in ionization (S_N1) reactions, whereas *primary* halides, and to a lesser extent *secondary* halides, are reactive in S_N2 reactions, which occur by a concerted mechanism with inversion of configuration (Sections 8-4 to 8-7).

Elimination competes with substitution in many S_N reactions and can become the major pathway at high temperatures or in the presence of strong base. Elimination (E_2), unlike displacement (S_N2), is insensitive to steric hindrance in the alkyl halide. In fact, the E_2 reactivity of alkyl halides is *tert* RX > *sec* RX > *prim* RX, which is opposite to their S_N2 reactivity.

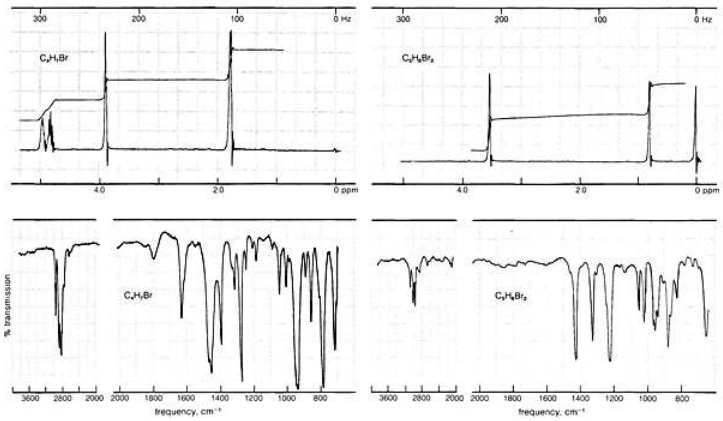


Figure 14-1: Infrared and proton nmr spectra of substance C_4H_7Br and substance $C_5H_8Br_2$. NMR spectra are at 60 MHz with reference to TMS at 0.0.

Several useful reactions for the synthesis of alkyl halides that we already have encountered are summarized below with references to the sections that supply more detail:

$$RH + Cl_2 \xrightarrow{h\nu} RCl + HCl \qquad \text{(Section 4-5)}$$

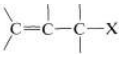
$$RCH{=}CH_2 + HCl \longrightarrow RCHCH_3 \quad (Cl) \qquad \text{(Section 10-4)}$$

$$RCH{=}CH_2 + HBr \xrightarrow[\text{or peroxides}]{h\nu} RCH_2CH_2Br \qquad \text{(Section 10-7)}$$

$$ROH + HBr \longrightarrow RBr + H_2O \qquad \text{(Section 8-7D)}$$

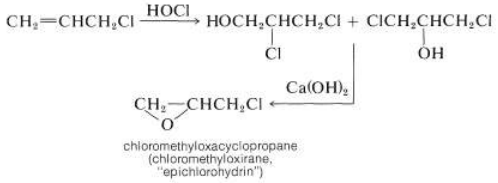
A summary of these and some other reactions for the synthesis of alkyl halides or organohalogen compounds is given in Table 14-5.

14.4.1: Allylic (2-Propenyl) Halides

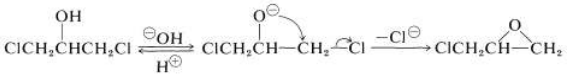
Halogen compounds in which the carbon-halogen bond is adjacent to a double bon, as in  are known as **allylic halides**. The simplest example is 3-chloropropene, $CH_2{=}CHCH_2Cl$, which is made on a large scale by the radical chlorination of propene at 400°:

$$CH_2{=}CH{-}CH_3 + Cl_2 \xrightarrow{400^\circ} CH_2{=}CH{-}CH_2{-}Cl + HCl$$

Most of the 3-chloropropene prepared in this manner is converted to other important compounds. For example, addition of hypochlorous acid gives a mixture of dichloropropanols, which on treatment with base gives a substance known commercially as "epichlorohydrin":

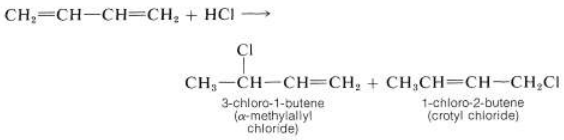


The ring closure reaction with $Ca(OH)_2$ is an internal S_N2 reaction. Hydroxide ion converts the alcohol to an alkoxide ion that acts as a nucleophile in displacing the neighboring chlorine:

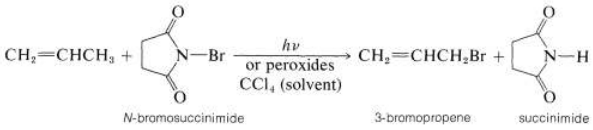


The epichlorohydrice so produced is used primarily to make epoxy resins (see Section 29-5E), although some of it is hydrolyzed to glycerol:

A general method for preparing allylic halides is by addition of hydrogen halides to conjugated dienes. This reaction usually produces a mixture of 1,2- and 1,4-addition products (see Section 13-2):

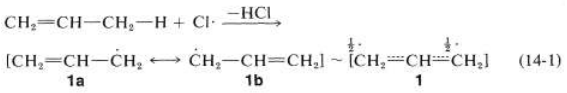


A second general method involves the bromination of alkene with *N*-bromosuccinimide (the **Wohl-Ziegler** reaction). A radical-chain reaction takes place between *N*-bromosuccinimide (NBS) and alkenes, which commonly is initiated by light, peroxides, or other catalysts, and yields allylic bromides:

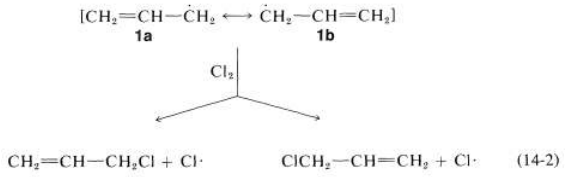


This reaction, like the chlorination of propene, is highly selective in that the so-called allylic C–H is attacked preferentially.

From bond energies (Table 4-6) we know that the weakest C–H bonds of propene are to the allylic hydrogens, $H_2C{=}CHCH_2{-}H$. Therefore, in the first step of radical-chain chlorination of propene, an allylic hydrogen is removed by a chlorine atom (Equation 14-1). The allylic C–H bonds are weaker than the alkenic C–H bonds because of the extra stabilization of the radical obtained on hydrogen abstraction (Equation 14-1). Two equivalent valence-bond structures (1*a* and 1*b*) can be written for the 2-propenyl radical; the electron delocalization enhances the stability of the radical (see Section 6-5C):



In the second step of the chain reaction (Equation 14-2) the propenyl radical can form a carbon-halogen bond at either end by abstracting a halogen atom from the halogenating agent:



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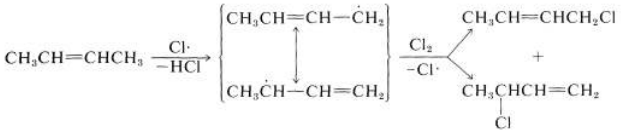
The $Cl\cdot$ atom produced now can participate in Reaction 14-1, thereby continuing the chain. With propene the intermediate radical gives the same product, 2-propenyl chloride, irrespective of whether a chlorine atom is transferred to the 1- or 3-carbon. However, the radical formed by removal of an allylic hydrogen from 2-butene gives a mixture of products:



14.4.2: S_N Reactions of Allylic Halides

The carbon-halogen bonds of allylic halides are especially reactive in both S_N1 and S_N2 reactions (Table 14-6). The reasons for the enhanced S_N1 reactivity have been discussed previously (Section 8-7B). For example, the ease with which 1-chloro-2-butene ionizes compared to 1-chlorobutane is attributed to the stability of the 2-butenyl cation, which is distributed between C_1 and C_3, and the nucleophile (water) attacks at both positions to give mixtures of products. The same results are obtained if one starts with 3-chloro-1-butene because the same cation is formed:

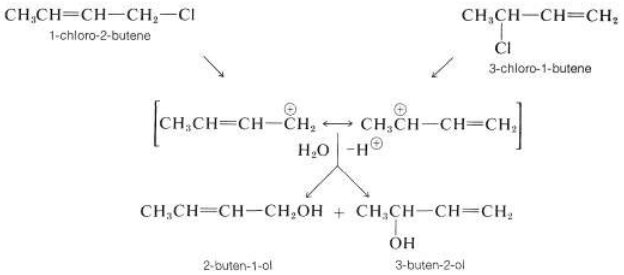


Figure 14-2.

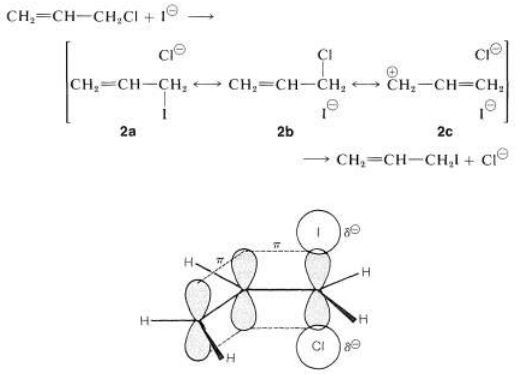
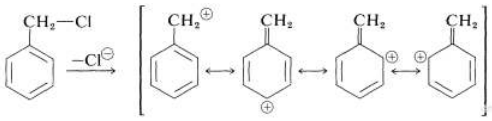


Figure 14-2: Atomic-orbital representation of the transition state for S_N2 displacement of 3-chloropropene (allyl chloride) with iodide ion. The halide orbitals are represented as spherical for simplicity. The purpose of this figure is to show the π bonding, which can stabilize the transition state.

14.4.3: Benzylic (Phenylmethyl) Halides

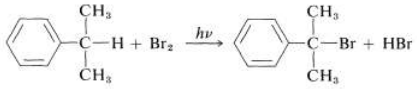
Reactivities comparable to allylic halides are found in the nucleophile displacement reactions of benzylic halides by S_N1 and S_N2 mechanisms (Table 14-6). The ability of the benzylic halides to undergo S_N1 reactions clearly is related to the stability of the resulting benzylic cations, the electrons of which are extensively delocalized. Thus, for phenylmethyl chloride,



When the halogen substituent is located two or more carbons from the aryl group as in 2-phenylethyl bromide, $C_6H_5CH_2CH_2Br$, the pronounced activating effect evident in benzylic halides disappears, and the reactivity of the halides is essentially that of a primary

alkyl halide (e.g., $CH_3CH_2CH_2Br$).

Benzylic halides can be prepared by the same radical-halogenating agents that give allylic halides from alkenes. These include Cl_2, Br_2, *N*-bromosuccinimide (Section 14-3A), SO_2Cl_2, and *tert*-butyl hypochlorite:



The benzylic C–H bond is weaker and more restrictive then primary alkane C–H bonds because of the stabilization of benzylic radicals (see Table 4-6).

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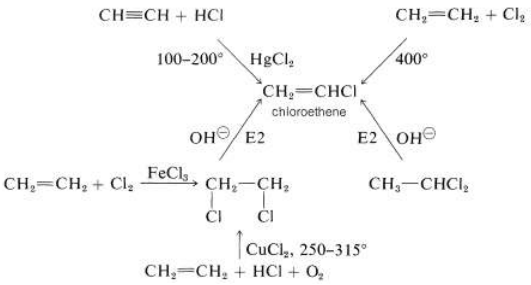
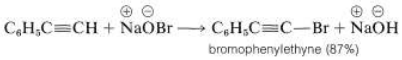
14.5: Alkenyl and Alkynyl Halides

The most readily available alkenyl halide is chloroethene (vinyl chloride), which can be prepared by a number of routes:



The most economical commercial preparation is high-temperature chlorination of ethene. A useful modification of this process uses hydrogen chloride in place of chlorine. An oxidizing agent is required to raise the oxidation state of chlorine in HCl to that of Cl_2; molecular oxygen is used for this purpose along with cupric salts as catalysts.

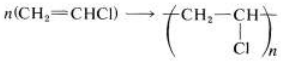
General methods of preparation for alkenyl and alkynyl halides are listed in Table 14-5. By the alkynyl halides we mean 1-halo-alkynes. One interesting method by which they may be prepared employs 1-alkynes with hypohalites:



This kind of reaction does not proceed with either alkanes or alkenes.

14.5.1: Uses of Alkenyl Halide

Chloroethene is produced in vast quantities for the production of polymers (polyvinyl chloride) and copolymers:



These polymers commonly are described as PVC plastics or less specifically as “vinyl.” They are materials that may be either flexible or rigid according to what they are mixed with, and they are used in the manufacture of many familiar articles such as plastic curtains, rainwear, floor tile, synthetic leather goods, upholstery, table mats, phonograph records, insulation, plastic pipes, tubing, and packaging materials.

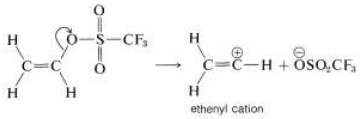
Recently, it has been found that persons working in plants that manufacture and use chloroethene have an unusually high incidence of an unusual type of liver cancer. As a result, strict safety regulations and pollution standards have been set for plants where chloroethene is made or used. The once widespread use of chloroethene as a propellant for aerosol cans has been curtailed. Polyvinyl chloride itself seems to be quite safe, but there are possible problems with its incorporation into interior building materials, clothing, and upholstery because heat, such as fire, causes polyvinyl chloride to decompose, thereby producing hydrogen chloride as one decomposition product. In closed areas the toxicity of hydrogen chloride gas may be as serious a hazard as the fire itself. Other polymers may give off similarly toxic products on strong heating.

14.5.2: Chemical Properties

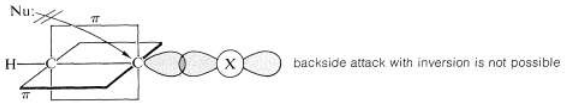
The outstanding chemical characteristic of alkenyl halides is their general inertness in S_N1 and S_N2 reactions. Thus chloroethene fails to react with silver nitrate in ethanol (i.e., low S_N1 reactivity), fails to react with potassium iodide in acetone (i.e., low S_N2 reactivity), and only reacts slowly with sodium hydroxide to give ethyne (low $E2$ reactivity). The haloalkynes, such as $RC \equiv C{-}Cl$, are similarly unreactive.

It is not surprising that $=C{-}X$ and $\equiv C{-}X$ bonds are hard to break heterolytically. In general, $C{-}X$ bonds are strong in alkenyl halides (cf. Table 4-6) and this property tends to make them less reactive than alkyl halides. Furthermore, double- and triple-bonded carbons are more strongly electron-attracting than saturated sp^3 carbons, which is the reason why 1-alkynes and alkenes are stronger acids (Section 11-8) than alkanes. Consequently it is easier to break a $\equiv C{-}H$ bond in the sense $C^{\ominus}H^{\oplus}$ than as $\equiv C^{\oplus}H^{\ominus}$. It

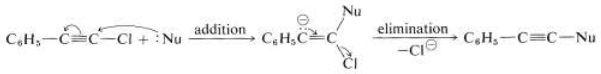
also will be more difficult to ionize a carbon-halogen bond to $C^{\oplus}X^{\ominus}$ if the carbon is unsaturated. Therefore ethenyl and ethynyl cations, such as $CH_2{=}CH^{\oplus}$ and $HC \equiv C^{\oplus}$, are difficult to generate from the corresponding halides. Superior leaving groups are required, such as trifluoromethanesulfonate, $-OSO_3CF_3$ (Section 8-7C):



The reason for the lack of S_N2 reactivity in ethenyl or ethynyl halides may be that the attacking nucleophile is unable to react by the concerted inversion mechanism that invariably is observed with alkyl halides:



Nevertheless, substitution of the halogen does occur under some circumstances. In such cases, the nucleophile first *adds* to the multiple bond, and in a subsequent step the halogen leaves as halide ion. This is an "addition-elimination" mechanism, of which we will have more examples later:



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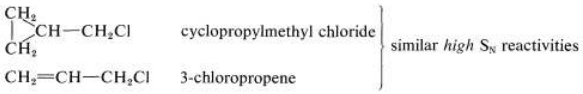
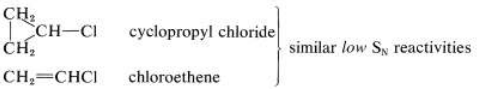
14.6: Cycloalkyl Halides

The cycloalkyl halides, except for cyclopropyl halides, have physical and chemical properties that are similar to those of the open-chain secondary halides and can be prepared by the same types of reactions (Table 14-5). All the cycloalkyl halides undergo S_N2 reactions rather slowly and, with nucleophiles that are reasonably basic ($^{\ominus}OH$, $^{\ominus}OC_2H_5$, $^{\ominus}C \equiv N$, etc.), $E2$ reactions can be expected to predominate (Table 14-6). The rate of carbocation formation leading to S_N1 and $E1$ reactions is sensitive to ring size but, except for the small-ring halides, the carbocation reactions are normal in most other respects.

The cyclopropyl halides are exceptional in that their behavior is much more like alkenyl halides than like secondary alkyl halides. Thus cyclopropyl chloride undergoes S_N1 and S_N2 reactions much less rapidly than isopropyl or cyclohexyl chlorides. A relationship between the reactivity of cyclopropyl chloride and chloroethene is not surprising in view of the general similarity between cyclopropane rings and double bonds (Section 12-5). This similarity extends to cyclopropylmethyl derivatives as well. Cyclopropylmethyl chloride is reactive in both S_N1 and S_N2 reactions in much the same way as 3-chloropropene:





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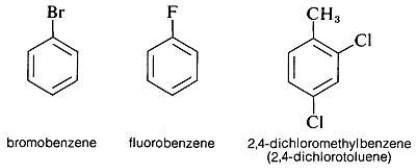
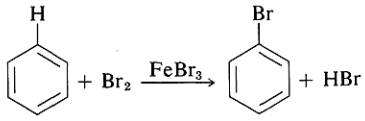
14.7: Aryl Halides

Aryl halides have a halogen directly bonded to a carbon of an aromatic ring. Examples are bromobenzene, fluorobenzene, and 2,4-dichloromethylbenzene:



Some of the methods by which alkyl halides are prepared do not work for aryl halides because it is difficult to form C-halogen bonds at aromatic ring carbons by nucleophilic displacement reactions. The most common ways of forming C_{aryl}-halogen bonds are by substitution of $C_{aryl}-H$ by electrophilic halogenating agents (e.g., Br_2 or Cl_2),



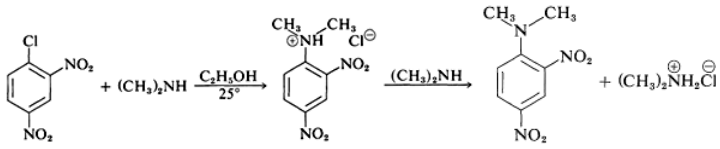
and by replacement of $C-NH_2$ by $C-$halogen. These reactions are listed in Table 14-5 and will be discussed in more detail in Chapters 22 and 23.

14.7.1: Nucleophilic Aromatic Displacement Reactions

The carbon-halogen bonds of aryl halides are like those of alkenyl halides in being much stronger than those of alkyl halides (see Table 4-6). *The simple aryl halides generally are resistant to attack by nucleophiles in either S_N1 or S_N2 reactions* (Table 14-6). However, this low reactivity can be changed dramatically by changes in the reaction conditions and the structure of the aryl halide. In fact, nucleophilic displacement becomes quite rapid (a) when the aryl halide is activated by substitution with strongly electron-attracting groups such as NO_2, and (b) when very strongly basic nucleophilic reagents are used.

14.7.2: Addition-Elimination Mechanism of Nucleophilic Substitution

Although the simple aryl halides are inert to the usual nucleophilic reagents, *considerable activation is produced by strongly electron-attracting substituents provided these are located in either the* ortho *or* para *positions, or both*. For example, the displacement of chloride ion from 1-chloro-2,4-dinitrobenzene by dimethylamine occurs readily in ethanol solution at room temperature. Under the same conditions chlorobenzene completely fails to react; thus the activating influence of the two nitro groups amounts to a factor of at least 10^8:



A related reaction is that of 2,4-dinitrofluorobenzene with the amino groups of peptides and proteins, and this reaction provides a means for analysis of the *N*-terminal amino acids in polypeptide chains. (See Section 25-7B.)

In general, the reactions of activated aryl halides closely resemble the S_N2-displacement reactions of aliphatic halides. The same nucleophilic reagents are effective (e.g., $CH_3O^{\ominus}$, $HO^{\ominus}$, and RNH_2); the reactions are second order overall (first order in halide and first order in nucleophile); and for a given halide the more nucleophilic the attacking reagent, the faster the reaction. However, there must be more than a subtle difference in mechanism because an aryl halide is unable to pass through the same type of transition state as an alkyl halide in S_N2 displacements.

The generally accepted mechanism of nucleophilic aromatic substitution of aryl halides carrying activating groups involves two steps that are closely analogous to those briefly described in Section 14-4 for alkenyl and alkynyl halides. The first step involves attack of the nucleophile $Y^{\ominus}$ at the carbon bearing the halogen substituent to form an intermediate carbanion 4 (Equation 14-3). The

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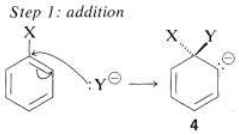
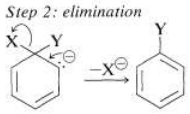
aromatic system is destroyed on forming the anion, and the carbon at the reaction site changes from planar (sp^2 bonds) to tetrahedral (sp^3 bonds).



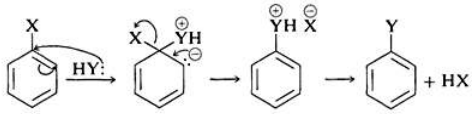
(14-3)

In the second step, loss of an anion, $X^{\ominus}$ *minus* or $Y^{\ominus}$, regenerates an aromatic system, and, if $X^{\ominus}$ is lost, the overall reaction is nucleophilic displacement of X by Y (Equation 14-4).

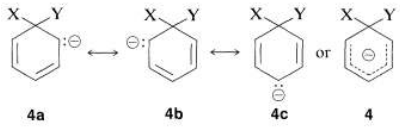


(14-4)

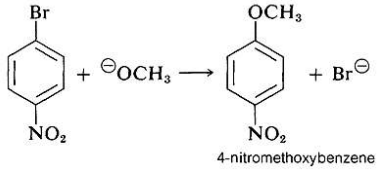
In the case of a neutral nucleophilic reagent, Y or HY, the reaction sequence would be the same except for the necessary adjustments in the charge of the intermediate:



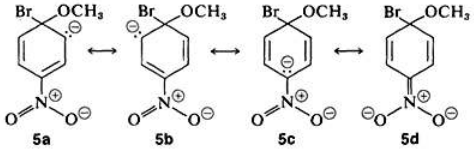
Why is this reaction pathway generally unfavorable for the simple aryl halides? The answer is that the intermediate 4, which we can express as a hybrid of the valence-bond structures 4*a*-4*c*, is too high in energy to be formed at any practical rate. Not only has 4 lost the aromatic stabilization of the benzene ring, but its formation results in transfer of negative charge to the ring carbons, which themselves are not very electronegative:



However, when s*trongly electron-attracting groups are located on the ring at the* ortho-para *positions, the intermediate anion is stabilized by delocalization of electrons from the ring carbons to more favorable locations on the substituent groups*. As an example, consider the displacement of bromine by OCH_3 in the reaction of 4-bromonitrobenzene and methoxide ion:

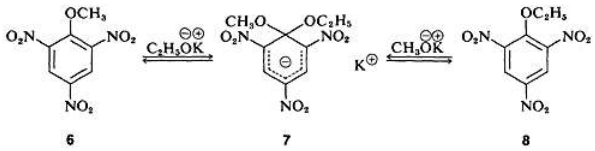


The anionic intermediate formed by *addition* of methoxide ion to the aryl halide can be described by the valence-bond structures 5*a* -5*d*. Of these structures 5*d* is especially important because in it the charge is transferred from the ring carbons to the oxygen of the nitro substituent:



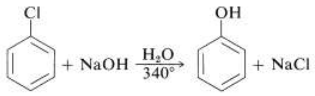
Substituents in the meta positions have much less effect on the reactivity of an aryl halide because delocalization of electrons to the substituent is not possible. No formulas can be written analogous to 5*c* and 5*d* in which the negative charges are both on atoms next to positive nitrogen, $\overset{\ominus}{C}-\overset{\oplus}{N}-\overset{\ominus}{O}$ and $\overset{\ominus}{O}-\overset{\oplus}{N}-\overset{\ominus}{O}$,

In a few instances, stable compounds resembling the postulated reaction intermediate have been isolated. One classic example is the complex 7 (isolated by J. Meisenheimer), which is the product of the reaction of either the methyl aryl ether 66 with potassium ethoxide, or the ethyl aryl ether 8 and potassium methoxide:

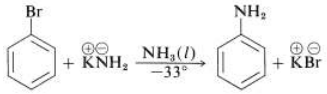


14.7.3: Elimination-Addition Mechanism of Nucleophilic Aromatic Substitution. Arynes

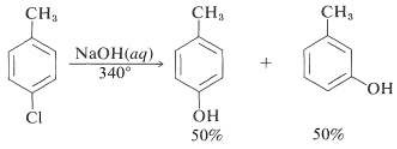
The reactivities of aryl halides, such as the halobenzenes, are exceedingly low toward nucleophilic reagents that normally effect displacements with alkyl halides and activated aryl halides. Substitutions do occur under forcing conditions of either high temperatures or very strong bases. For example, chlorobenzene reacts with sodium hydroxide solution at temperatures around 340° and this reaction was once an important commercial process for the production of benzenol (phenol):



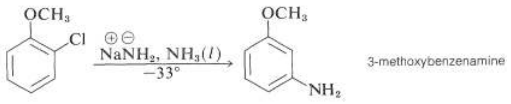
In addition, aryl chlorides, bromides, and iodides can be converted to areneamines $ArNH_2$ by the conjugate bases of amines. In fact, the reaction of potassium amide with bromobenzene is extremely rapid, even at temperatures as low as -33° with liquid ammonia as solvent:



However, displacement reactions of this type differ from the previously discussed displacements of activated aryl halides in that rearrangement often occurs. That is, *the entering group does not always occupy the same position on the ring as that vacated by the halogen substituent*. For example, the hydrolysis of 4-chloromethylbenzene at 340° gives an equimolar mixture of 3- and 4-methylbenzenols:

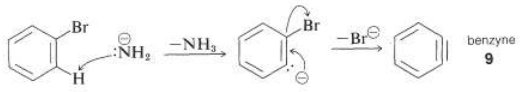


Even more striking is the exclusive formation of 3-methoxybenzenamine in the amination of 2-chloromethoxybenzene. Notice that this result is a violation of the principle of least structural change (Section 1-1H):



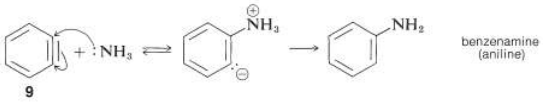
The mechanism of this type of reaction has been studied extensively, and much evidence has accumulated in support of a stepwise process, which proceeds first by base-catalyzed *elimination* of hydrogen halide (HX) from the aryl halide - as illustrated below for the amination of bromobenzene:

Elimination

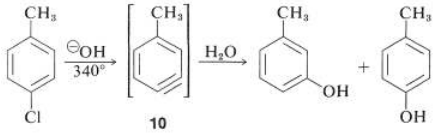


The product of the elimination reaction is a highly reactive intermediate 9 called **benzyne**, or **dehydrobenzene**, which differs from benzene in having two less hydrogen and an extra bond between two ortho carbons. Benzyne reacts rapidly with any available nucleophile, in this case the solvent, ammonia, to give an addition product:

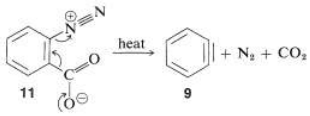
Addition



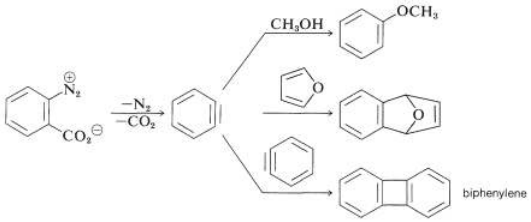
The rearrangements in these reactions result from the attack of the nucleophile at one or the other of the carbons of the extra bond in the intermediate. With benzyne the symmetry is such that no rearrangement would be detected. With substituted benzynes isomeric products may result. Thus 4-methylbenzyne, 10, from the reaction of hydroxide ion with 4-chloro-1-methylbenzene gives both 3- and 4-methylbenzenols:



In the foregoing benzyne reactions the base that produces the benzyne in the elimination step is derived from the nucleophile that adds in the addition step. This need not always be so, depending on the reaction conditions. In fact, the synthetic utility of aryne reactions depends in large part of the success with which the aryne can be generated by one reagent but captured by another. One such method will be discussed in Section 14-10C and involves organometallic compounds derived from aryl halides. Another method is to generate the aryne by thermal decomposition of a 1,2-disubstituted arene compound such as 11, in which both substituents are leaving groups - one leaving with an electron pair, the other leaving without:



When 11 decomposes in the presence of an added nucleophile, the benzyne intermediate is trapped by the nucleophile as it is formed. Or, if a conjugated diene is present, benzyne will react with it by a [4 + 2] cycloaddition. In the absence of other compounds with which it can react, benzyne will undergo [2 + 2] cycloaddition to itself:

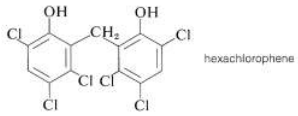


14.7.4: Uses for Aryl Halogen Compounds

As with most organic halides, aryl halides most often are synthetic intermediates for the production of other useful substances. For example, chlorobenzene is the starting aryl halide for the synthesis of DDT; it also is a source of benzenol (phenol, Section 14-6C) which, in turn, has many uses (Section 26-1).

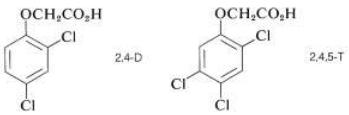
Several aromatic chloro compounds are used extensively as insecticides, herbicides, fungicides, and bactericides. They also have acquired much notoriety because in some instances their indiscriminate usage has led to serious problems. For example, hexachlorophene is an external bactericide that until recently was used in cosmetic preparations such as soaps, deodorants, and so

on. Its use has been discontinued because of compelling evidence that it can be absorbed through the skin in amounts that are dangerous, if not lethal, for infants and small children.



hexachlorophene

Other pesticides, notably DDT and the herbicides 2,4-D and 2,4,5-T have been partially banned for different reasons.



2,4-D 2,4,5-T

14.7.5: Contributors and Attributions

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14.8: Polyhalogenated Alkanes and Alkenes

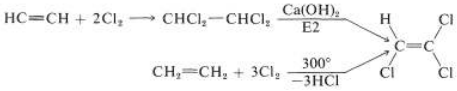
14.8.1: Useful Compounds

Polychlorination of methane yields the di-, tri-, and tetrachloromethanes cheaply and efficiently:

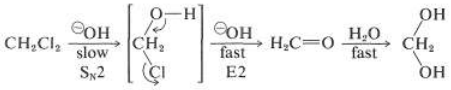
These substances have excellent solvent properties for nonpolar and slightly polar substances. Chloroform once was used widely as an inhalation anesthetic. However, it has a deleterious effect on the heart and is oxidized slowly by atmospheric oxygen to highly toxic carbonyl dichloride (phosgene, $COCl_2$). Commercial chloroform contains about 1% ethanol, which destroys any $COCl_2$ formed by oxidation.

Carbon tetrachloride commonly was employed as a cleaning solvent, although its considerable toxicity entails considerable hazard when used indiscriminately. It has been used as a fire-extinguishing fluid for petroleum fires, but its toxicity and tendency to form still more toxic carbonyl dichloride makes it undesirable for confined areas. The common laboratory practice of removing traces of water from solvents with metallic sodium should *not* be applied to halogenated compounds; carbon tetrachloride-sodium mixtures are shock sensitive and can detonate.

Trichloroethene ("Tri-Clene", bp 87°) is a widely used dry-cleaning solvent. It can be prepared from either ethene or ethyne:



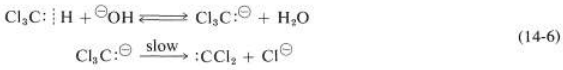
Compared with monohaloalkanes, polyhalogen compounds have quite different reactivities and behavior toward nucleophiles and bases. Thus dichloromethane reacts with hydroxide ion by an S_N2 mechanism much less readily than methyl chloride. The chloromethanol formed then undergoes a rapid $E2$ elimination to give methanal (formaldehyde), a substance that exists in water largely as dihydroxymethane:



Trichloromethane (chloroform) reacts quite differently with base than does chloromethane or dichloromethane - as will be described in the following section.

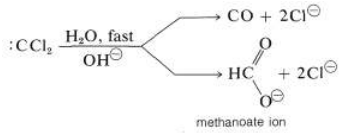
14.8.2: α Elimination. Carbenes

Trihalomethanes, such as trichloromethane (chloroform), are quite reactive toward strong base. The base, such as hydroxide, removes the hydrogen of $HCCl_3$ as a proton much more rapidly than it attacks the carbon in the S_N2 manner. The carbanion so formed, $Cl_3C^{\ominus}$, is unstable and loses chloride ion to form a highly reactive neutral intermediate, $:CCl_2$, called **dichlorocarbene**:



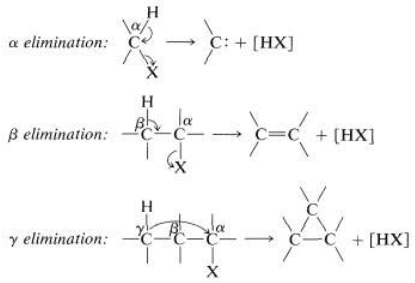
(14-6)

This intermediate has only six valence electrons around carbon and therefore is strongly electrophilic. In aqueous solution it reacts rapidly to form carbon monoxide and methanoate (formate) ion:



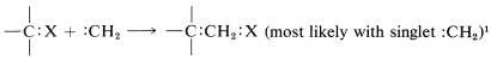
The formation of $:CCl_2$ from $HCCl_3$ by the reactions of Equation 14-6 results in the elimination of HCl - the leaving groups, H and Cl, both originating from the *same* carbon atom. Such reactions are not uncommon and are called α eliminations or 1,1 eliminations

to distinguish them from $E1$ and $E2$ reactions, which are β eliminations or 1,2 eliminations. Still other possibilities are reactions such as γ or 1,3 eliminations, but these take on the character of internal S_N2 reactions and will not be considered in detail here.

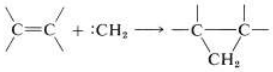


The product of α elimination is a neutral species that resembles a carbocation in having only six carbon valence electrons. The simplest carbene is $:CH_2$, methylene. *Carbenes are highly reactive*, so much so that they cannot be isolated. Their involvement in reactions usually has to be inferred from the nature of the products or the reaction kinetics. The characteristic carbene reactions involve forming an electron-pair bond to the carbene carbon by reacting with σ bonds, π bonds, or unshared pairs (n). Some of these reactions are illustrated here for methylene $:CH_2$.[1]

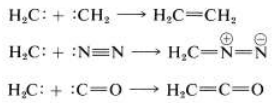
with σ bonds (insertion):



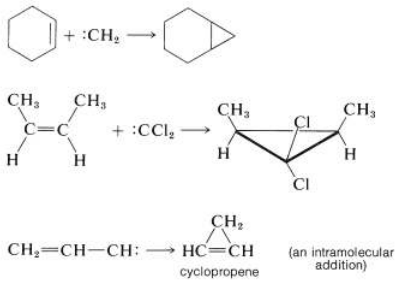
with π bonds ([2 + 1] cycloaddition):



with unshared pairs (dimerization, addition):



Carbenes are much more reactive toward carbon-carbon double bonds than toward single bonds. Without doubt the most useful feature of α elimination is that it provides a practical route to cyclopropanes and cyclopropenes by [2 + 1] cycloaddition of carbenes to double or triple bonds. These additions are stereospecific *suprafacial* additions if they involve singlet carbenes, but can give mixtures with triplet carbenes:



Carbene precursors are compounds that have or acquire good leaving groups (e.g., halide ions). Thus, halogen compounds frequently are carbene sources. Trihalomethanes are the oldest known sources of dihalocarbenes; but there are other methods for generating carbenes, and some of these are listed for reference in Table 14-2 (see also Section 14-10C). There is a question as to whether a "free" carbene actually is formed in some of these reactions, particularly those involving metals, but for our purposes we will classify them as routes to carbenes or carbenelike species.

Table 14-2: *α-Elimination Reactions Producing Carbene Intermediates*[a]

Reaction	Comments
1. *Trihalomethanes and strong base* $Br_3CH + {}^{\ominus}OC(CH_3)_3 \longrightarrow Br_3C: + Br^{\ominus} + HOC(CH_3)_3$	Gives dihalocarbenes; to trap the carbene with an alkene, an aprotic solvent is preferred.
2. *Haloalkanes and alkyllithiums* $Br_4C + CH_3Li \longrightarrow [Br_3C{-}Li] + CH_3Br$ $\downarrow$ $Br_2C: + LiBr$	Tetrahalomethanes give dihalocarbenes. (See Section 14-10C.)
$RCH_2Cl + C_4H_9Li \longrightarrow \left[RCH\begin{matrix}Li\\Cl\end{matrix}\right] + C_4H_{10}$ $\downarrow$ $RCH: + LiCl$	Suitable for generation of alkyl or aryl carbenes.
3. *Diiodomethane and zinc* (Simmons–Smith Reaction) $CH_2I_2 + Zn \xrightarrow{Cu} [IZnCH_2I]$ $\downarrow$ $\triangle$ ":CH_2" + ZnI_2	Appears to generate a singlet :CH_2 metal complex; zinc must be activated with copper.
4. *Dissociation of trihaloacetates* $Cl_3C{-}\overset{O}{\overset{\|}{C}}{-}O^{\ominus} \xrightarrow{heat} [Cl_3C^{\ominus}:] + CO_2$ $\downarrow$ $Cl_2C: + Cl^{\ominus}$	Salt is heated in aprotic solvent (e.g., 1,2-dimethoxyethane).
5. *Dissociation of trihalomethylmercury compounds* $C_6H_5HgCCl_2Br \longrightarrow Cl_2C: + C_6H_5HgBr$	
6. *Dissociation of diazoalkanes* $H_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N}: \xrightarrow[\text{or heat}]{h\nu} H_2C: + N_2$	Widely applicable to formation of alkyl, aryl, keto, and carboalkoxy carbenes.
7. *Dissociation of ketenes* $H_2C{=}C{=}O \xrightarrow{h\nu} H_2C: + CO$	

[a]These reactions normally produce singlet carbenes. However, the singlet CH_2: formed in Reactions 6 and 7 may undergo some interconversion to the more stable triplet form,[1] especially if an otherwise inert material is present that can facilitate the singlet–triplet transformation.

Many carbenes, like carbocations, rearrange to more stable structures by the migration of a neighboring group to the electron-deficient carbon. Thus phenylmethylcarbene rearranges to ethenylbenzene (styrene):

$$\underset{\text{phenylmethylcarbene}}{C_6H_5{-}\overset{H}{C}{-}CH_2} \longrightarrow \underset{\text{ethenylbenzene}}{C_6H_5CH{=}CH_2}$$

14.8.3: Fluorochloromethanes

Replacement of either one or two of the chlorines of carbon tetrachloride by fluorine can be achieved readily with antimony trifluoride containing some antimony pentachloride. The reaction stops after two chlorines have been replaced. The antimony trifluoride can be regenerated continuously from the antimony chloride by addition of anhydrous hydrogen fluoride:

$$3CCl_4 + SbF_3 \xrightarrow[\text{bp } 25^\circ]{SbCl_5} 3CFCl_3 + SbCl_3$$

$$3CCl_4 + 2SbF_3 \xrightarrow[\text{bp } -30^\circ]{SbCl_5} 3CF_2Cl_2 + 2SbCl_3$$

Both products are useful as refrigerants, particularly for household refrigerators and air-conditioning units, under the trade name Freon. Difluorodichloromethane (Freon 12) also is employed as a propellant in aerosol bombs, shaving-cream dispensers, and other such containers. It is nontoxic, odorless, nonflammable, and will not react with hot concentrated mineral acids or metallic sodium. This lack of reactivity is generally characteristic of the difluoromethylene group, provided the fluorines are not located on an unsaturated carbon. Attachment of a fluorine atom to a carbon atom bonded to one or more chlorine atoms tends greatly to reduce the reactivity of the chlorines toward almost all types of reagents. Possible environmental problems associated with these substances were discussed in the introduction to this chapter.

14.8.4: Fluorocarbons

During World War II, plastics and lubricating compounds of unusual chemical and thermal stability were required for many applications, in particular for pumping apparatus used to separate ^{235}U from ^{238}U by diffusion of corrosive uranium hexafluoride

through porous barriers. It was natural to consider the use of substances made only of carbon and fluorine (fluorocarbons) for such purposes, and considerable effort was spent on methods of preparing compounds such as $-(CF_2)-_n$. Today, many such substances are in common use. These often are called "perfluoro-" compounds, which indicates that all available hydrogens of the parent compound are replaced by fluorine. Thus perfluorocyclohexane is $(CF_2)_6$. A widely used perfluorocarbon is the plastic material $-(CF_2)-_n$, which is produced in quantity by radical polymerization of tetrafluoroethene:

$$n(CF_2{=}CF_2) \xrightarrow{R\cdot} {+}CF_2{-}CF_2{+}_n$$

The product ("Teflon") is a solid, chemically inert substance that is stable to around 300°. It makes excellent electrical insulation and gasket materials. It also has self-lubricating properties, which are exploited in the preparation of low-adhesion surfaces (such as "nonstick" fry pans) and light-duty bearings.

Tetrafluoroethene can be made on a commercial scale by the following method:

$$3CHCl_3 + 2SbF_3 \xrightarrow{SbCl_5} 3CHClF_2 + 2SbCl_3$$
$$2CHClF_2 \xrightarrow[90\%\text{ yield}]{700\text{–}900^\circ} CF_2{=}CF_2 + 2HCl$$

The latter reaction involves difluorocarbene $(:CF_2)$:

$$CHClF_2 \longrightarrow :CF_2 + HCl$$
$$2\,:CF_2 \longrightarrow CF_2{=}CF_2$$

In the presence of peroxides, tetrafluoroethene polymerizes to the long-chain polymer. If peroxides are excluded, [2 + 2] cycloaddition occurs in high yield to give octafluorocyclobutane (see Section 13-3D):

$$2CF_2{=}CF_2 \longrightarrow \begin{matrix} CF_2{-}CF_2 \\ | \quad\quad | \\ CF_2{-}CF_2 \end{matrix}$$

Similar cycloaddition reactions occur with chlorotrifluoroethene and 1,1-dichloro-2,2-difluoroethene.

Radical polymerization of chlorotrifluoroethene gives a useful polymer (Kel-F) that is similar to Teflon.

An excellent elastomer of high chemical resistance (Viton) can be made by copolymerizing hexafluoropropene with 1,1-difluoroethene. The product is stable to 300° and is not attacked by hot concentrated nitric acid. Although expensive, it is unrivaled among elastomers for chemical durability under extreme conditions.

14.8.5: Properties of Fluorocarbons

The fluorocarbons have extraordinarily low boiling points relative to the hydrocarbons of comparable molecular weight. As seen in Figure 14-3, their boiling points are nearly the same or even lower than those of the alkanes or cycloalkanes with the same number of carbons. Thus octafluorocyclobutane or boils 17° lower than cyclobutane, despite an almost fourfold greater molecular weight!

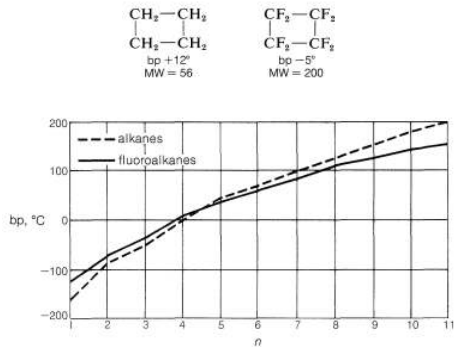


Figure 14-3: Boiling points of straight-chain fluorocarbons $(C_nF_{2n_2})$ and hydrocarbons $(C_nH_{2n_2})$.

Fluorocarbons are very insoluble in most polar solvents and are only slightly soluble in alkanes in the kerosene range. The higher-molecular-weight fluorocarbons are not even miscible in all proportions with their lower-molecular-weight homologs.

The physiological properties of organofluorine compounds vary widely. Dichlorodifluoromethane and the saturated fluorocarbons appear to be completely nontoxic. In contrast, perfluoro-2-methylpropene is exceedingly toxic, more so than the war gas, carbonyl dichloride ($COCl_2$). Sodium fluoroethanoate (CH_2FCO_2Na) and 2-fluoroethanol are toxic fluorine derivatives of oxygen-containing organic substances. The fluoroethanoate salt is sold commercially as a rodenticide. Interestingly, sodium trifluoroethanoate is nontoxic.

Fluorocarbon derivatives have another interesting and potentially useful property. They dissolve large quantities of oxygen. This fact, combined with their nontoxicity, has led to their use as blood replacements in heart surgery on experimental animals. Mice can live totally immersed in oxygen-saturated liquid fluorocarbons.

[1]Life with carbenes is substantially complicated by the fact that there are two different forms (singlet and triplet) of $:CH_2$ and presumably of all other carbenes. The two forms of $:CH_2$ differ considerably in their reactivity. One is the **singlet**, which has its unshared electrons paired, while the other is the **triplet** with the same electrons unpaired. For $:CH_2$, the singlet form is the less stable and more reactive, whereas with $:CCl_2$, the triplet is the less stable and more reactive.

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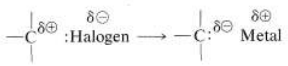
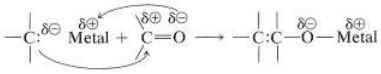
14.9: Organometallic Compounds from Organohalogen Compounds

One of the more important reactions of organohalogen compounds is the formation of **organometallic** compounds by replacement of the halogen by a metal atom. Carbon is positive in carbon-halogen bonds and becomes negative in carbon-metal bonds, and therefore carbon is considered to be *reduced* in formation of an organometallic compound (Section 11-1):



This transformation is of value because it makes an electrophilic carbon into a nucleophilic carbon. Organometallic compounds are a convenient source of nucleophilic carbon. A typical example of their utility is the way the achieve addition of nucleophilic carbon to carbonyl groups with formation of carbon-carbon bonds:



In this chapter we will restrict our discussion of organometallic compounds to the alkyl and aryl compounds of magnesium and lithium, and the sodium and potassium salts of 1-alkynes. These substances normally are derived directly or indirectly from organohalogen compounds and are used very widely in organic synthesis. Organometallic compounds of transition metals and of boron are discussed in Chapters 11 and 31.

14.9.1: Contributors and Attributions

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14.10: Properties of Organometallic Compounds

How carbon-metal bonds are formed depends on the metal that is used. Conditions that are suitable for one metal may be wholly unsuited for another. Some organometallic compounds react very sluggishly even toward acids, whereas others react avidly with water, oxygen, carbon dioxide, and almost all solvents but the alkanes themselves. Reactivity increases with increasing polarity of the carbon-metal bond, which is determined by the electropositivity of the metal. Strongly electropositive metals, such as sodium and potassium, form largely ionic bonds to carbon, as we have mentioned in the case of alkynide salts, $RC \equiv C^{\ominus}Na^{\oplus}$ (Section 11-8). Estimates of the ionic character of various carbon-metal bonds are given in Table 14-3, and it will be seen that *organosodium and organopotassium compounds have the most ionic bonds and they are, in fact, among the most reactive organometallic compounds known*. Many organosodium and organopotassium compounds burn spontaneously when exposed to air and react violently with water and carbon dioxide. As might be expected from their saltlike character, they are nonvolatile and do not dissolve readily in nonpolar solvents. In contrast, the more covalent, less ionic, organometallic compounds, such as $(CH_3)_2Hg$, are far less reactive; they are stable in air, quite volatile, and dissolve in nonpolar solvents.

Table 14-3: Percent Ionic Character of Carbon-Metal Bonds[a]

Bond	Percent Ionic Chateracter	Bond	Percent Ionic Chateracter	Bond	Percent Ionic Chateracter
C-K	51%	**C-Mg**	35%	**C-Sn**	12%
C-Na	47%	**C-Al**	22%	**C-Pb**	12%
C-Li	43%	**C-Zn**	18%	**C-Hg**	9%
C-Ca	43%	**C-Cd**	15%		

Source: L. Pauling, The Nature of the Chemical Bond, Cornell University Press, Ithaca, N.Y. 3rd, 1960, Chap. 3

All of these compounds must be handled with great care because some are dangerously reactive and others are very toxic. They seldom are isolated from the solutions in which they are prepared, but are used immediately in other reactions.

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14.11: Preparation of Organometallic Compounds

14.11.1: Metals with Organic Halides

The reaction of a metal with an organic halide is a convenient method for preparation of organometallic compounds of reasonably active metals such as lithium, magnesium, and zinc. Ethers, particularly diethyl ether and oxacyclopentane (tetrahydrofuran), provide inert, slightly polar media in which organometallic compounds usually are soluble. Care is necessary to exclude moisture, oxygen, and carbon dioxide, which would react with the organometallic compound. This can be accomplished by using an inert atmosphere of nitrogen or helium.

$$CH_3Br + 2Li \xrightarrow{(CH_3CH_2)_2O} CH_3Li + LiBr \quad \text{methyllithium}$$

$$CH_3CH_2Br + Mg \xrightarrow{(CH_3CH_2)_2O} CH_3CH_2MgBr \quad \text{ethylmagnesium bromide}$$

The reactivity order of the halides is $I > Br > Cl \gg F$. Whereas magnesium and lithium react well with chlorides, bromides, and iodides, zinc is satisfactory only with bromides and iodides. Mercury only reacts when amalgamated with sodium. Sodium and potassium present special problems because of the high reactivity of alkylsodium and alkylpotassium compounds toward ether and organic halides. Alkane solvents usually are necessary.

Alkenyl, alkynyl, and aryl halides, like alkyl halides, can be converted to the corresponding magnesium and lithium compounds. However, the reaction conditions, such as choice of solvent, can be critical. Bromoethene, for instance, can be converted to ethenylmagnesium bromide in good yield if the solvent is oxacyclopentane [tetrahydrofuran, $(CH_2)_4O$]:

$$CH_2{=}CH{-}Br + Mg \xrightarrow{\text{oxacyclopentane}} CH_2{=}CH{-}MgBr$$

The more reactive allylic and benzylic halides present a problem - not so much in forming the organometallic derivative as in keeping it from reacting further with the starting halide. An often unwanted side reaction in the preparation of organometallic compounds is a displacement reaction, probably of the S_N2 type:

$$CH_2{=}CH{-}CH_2{-}Cl: + R^{\delta\ominus}\cdots{}^{\delta\oplus}MgX \longrightarrow CH_2{=}CH{-}CH_2{-}R + MgXCl$$

This problem can be lessened greatly by using a large excess of magnesium and dilute solutions of the allylic halide to minimize the coupling reaction.

The same difficulty also occurs in the preparation of alkylsodium compounds. The starting halide RX couples with RNa (to give R–R and NaX) or is converted to an alkene. These reactions appear to involve radical intermediates undergoing combination and disproportionation (Section 10-8C):

$$CH_3CH_2{-}Br + Na\cdot \longrightarrow CH_3CH_2\cdot + Br^{\ominus} + Na^{\oplus}$$

$$CH_3CH_2\cdot + Na\cdot \longrightarrow CH_3CH_2Na$$

$$2CH_3CH_2\cdot \longrightarrow CH_3CH_2CH_2CH_3 \quad \text{coupling (combination)}$$

$$2CH_3CH_2\cdot \longrightarrow CH_2{=}CH_2 + CH_3CH_3 \quad \text{disproportionation}$$

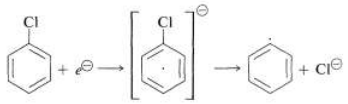
In the absence of metallic sodium, ethylsodium probably still reacts with ethyl bromide by a radical reaction rather than S_N2 or $E2$. This happens because $CH_3CH_2^-$ tends to lose an electron easily and can act like metallic sodium to donate an electron to CH_3CH_2Br to form an ethyl radical and itself become an ethyl radical:

$$CH_3CH_2{:}^{\ominus} + CH_3CH_2{-}Br \longrightarrow 2CH_3CH_2\cdot + Br^{\ominus}$$

Reactions between the resulting radicals then produce butane, ethane, and ethene.

The point at which one can expect S_N2 and $E2$ reactions to go faster than radical formation as the structures of the halides and the nature of the metal are changed is not yet clearly defined. However, it is becoming increasingly evident that there are substitution

reactions of "unactivated" aryl halides that proceed without rearrangement by way of radical intermediates. The key step in these reactions is donation of an electron to one of the unfilled π orbitals of the ring and subsequent ejection of a halide ion:



Such a mechanism probably is involved in the formation of organometallic compounds from aryl halides and metals.

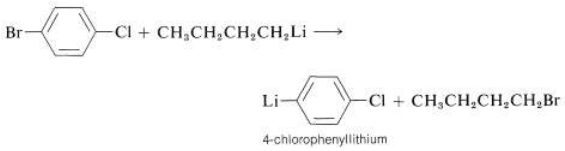
14.11.2: Some Other Preparations of Organometallic Compounds

Brief descriptions follow of less general but very useful methods of forming organometallic compounds (also see Table 14-7). In each of these preparations the solvent must be inert to all of the organometallic compounds involved.

14.11.2.1: Halogen-Metal Exchange

$$\mathrm{RBr} + \mathrm{R'Li} \rightleftharpoons \mathrm{RLi} + \mathrm{R'Br} \tag{14.11.1}$$

The equilibrium in these reactions favors formation of the organometallic compound with the metal attached to the more electronegative R group. The method is mainly used in the preparation of organolithium compounds derived from unreactive halides such as aryl, ethenyl, or ethynyl halides. These halides do not always react readily with lithium metal, but may react well with butyllithium:



14.11.2.2: Displacement of One Metal by Another

$$\mathrm{R_2Hg} + 2\mathrm{Na} \rightleftharpoons 2\mathrm{RNa} + \mathrm{Hg} \tag{14.11.2}$$

Here the equilibrium is such that the R group favors attachment to the more electropositive metal.

14.11.2.3: Organometallic Compounds with Metal Halides

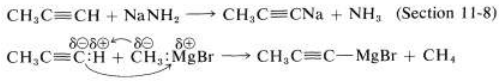
$$\mathrm{RMgCl} + \mathrm{HgCl_2} \rightleftharpoons \mathrm{RHgCl} + \mathrm{MgCl_2} \tag{14.11.3}$$

$$\mathrm{RLi} + \mathrm{CuI} \rightleftharpoons \mathrm{RCu} + \mathrm{LiI} \tag{14.11.4}$$

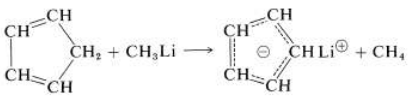
The equilibrium favors the products with R connected to the less electropositive metal so the reaction tends to form a less reactive organometallic compound from a more reactive one.

14.11.2.4: Organometallic Compounds from Acidic Hydrocarbons

Some organometallic compounds are prepared best by the reaction of a strong base or an alkyl metal derivative with an acidic hydrocarbon, such as an alkyne:

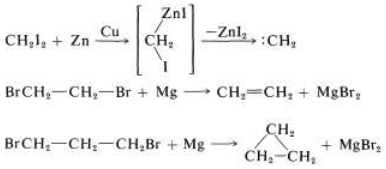


An especially important example is that of 1,3-cyclopentadiene, which is acidic because its conjugate base (cyclopentadienide anion) is greatly stabilized by electron delocalization. The anion is formed easily from the hydrocarbon and methyllithium:



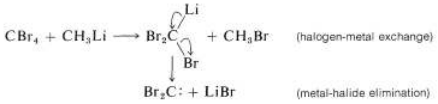
14.11.3: Organometallic Compounds from Polyhalogen Compounds

Diorganometallic compounds cannot be prepared from dihalides if the halogens are separated by three $C-C$ bonds or less because elimination or other reactions usually predominate. With active metals and 1,1-, 1,2-, or 1,3-dihalides, the following reactions normally occur:

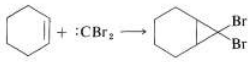


When the halogens are at least four carbons apart a diorganometallic compound can be formed:

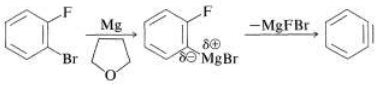
Carbenes, $R_2C:$ (Section 14-7B) are produced by α eliminations from polyhalogen compounds with organometallic reagents. The first step is halogen-metal exchange and this is followed by elimination of metal halide:



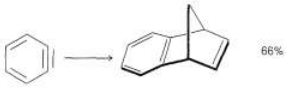
Elimination reactions of this type can be useful in synthesis for the formation of carbon-carbon bonds. For example, if dibromocarbene is generated in the presence of an alkene, it will react by cycloaddition to give a cyclopropane derivative:



A related example is the generation of benzyne from 1-bromo-2-fluorobenzene with magnesium in oxacyclopentane (tetrahydrofuran). If the temperature is kept around 0°, 2-fluorophenylmagnesium bromide is formed. At higher temperatures, magnesium halide is eliminated and benzyne results:



If a diene is present, the benzyne will react with it by a [4 + 2] cycloaddition as in the following example:



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14.12: Organomagnesium Compounds

For many years the most important organometallic compounds for synthetic purposes have been the organomagnesium halides, or **Grignard reagents**. They are named after Victor Grignard, who discovered them and developed their use as synthetic reagents, for which he received a Nobel Prize in 1912. As already mentioned, these substances customarily are prepared in dry ether solution from magnesium turnings and an organic halide:

$$CH_3I + Mg \xrightarrow{\text{ether}} CH_3MgI \qquad 95\%\ \text{yield}$$

Chlorides often react sluggishly and, in addition, may give an unwelcome precipitate of magnesium chloride, which, unlike magnesium bromide and iodide, is only very slightly soluble in ether. Organomagnesium fluorides eluded preparation until quite recently.

Although we usually write the structure of a Grignard reagent as RMgX, in which X is a halogen, the structure of the reagent in ether solution is more complex. There is a rapidly established equilibrium between the organomagnesium halide (RMgX) and the corresponding dialkylmagnesium (RMgR):

$$2\mathrm{RMgX} \rightleftharpoons \mathrm{R_2Mg} + \mathrm{MgX_2} \tag{14.12.1}$$

Both of these species, RMgX and $\mathrm{R_2Mg}$, are reactive, and in ether solvents are solvated by coordination of the ether oxygen to magnesium. They further associate as dimers or higher polymers in solution. Although it is an oversimplification to regard a Grignard reagent as RMgX, most of the reactions can be rationalized easily by this simple structure.

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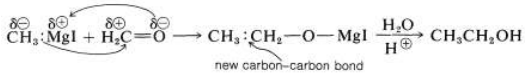
14.13: Organomagnesium and Organolithium Compounds in Synthesis

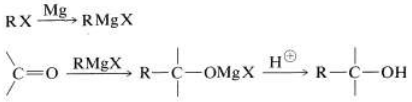
14.13.1: Additions to Carbonyl Groups. Synthesis of Alcohols

The most important synthetic use of Grignard reagents and organolithium reagents is to form new carbon-carbon bonds by addition to *polar* multiple bonds, particularly carbonyl bonds. An example is the addition of methyl-magnesium iodide to methanal:

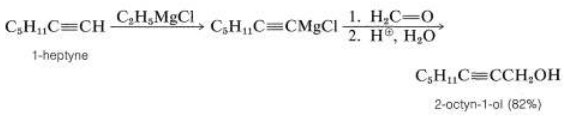


The yields of addition products in reactions of this kind are generally high. The adducts have metal-oxygen bonds that can be broken readily by acid hydrolysis to give the organic product. Grignard reagents seldom add to carbon-carbon multiple bonds (however, see Section 14-12D).

With suitable variations of the carbonyl compound, a wide range of compounds can be built up from substances containing fewer carbon atoms per molecule. The products formed when several types of carbonyl compounds react with Grignard reagents are listed in Table 14-4. The sequence of reactions starting with an organic halide, RX, amounts to the addition of R–H across a carbonyl bond.[2]



Primary alcohols can be prepared by the addition of RMgX or RLi to methanal, $CH_2{=}O$,



Alcohols of formula RCH_2CH_2OH can be prepared by addition of RMgX to oxacyclopropane (oxirane):

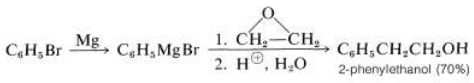
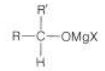
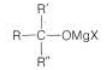
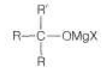
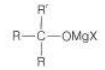
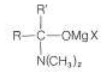


Table 14-4: *Products from the Reaction of Grignard Reagents* (RMgX) *with Carbonyl Compounds*

Reactant		Product	Hydrolysis product	Customary yield
methanal (formaldehyde)		RCH_2OMgX	*prim*-alcohol, RCH_2OH	good
other aldehydes			*sec*-alcohol,	good
ketone			*tert*-alcohol,	good to poor
carbon dioxide	CO_2	RCO_2MgX	carboxylic acid, RCO_2H	good
carboxylic ester			*tert*-alcohol,	good to poor
acid chloride			*tert*-alcohol,	good to poor
N,N-dimethylcarboxamide			ketone,	good to poor

Secondary alcohols are obtained from aldehydes, whereas ketones give *tertiary alcohols*:

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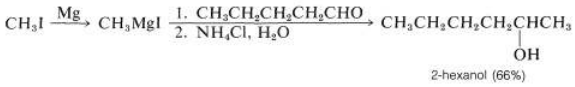
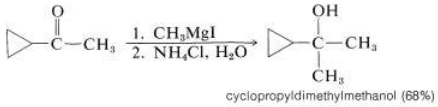
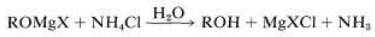
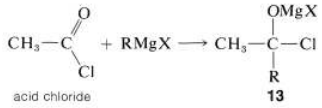


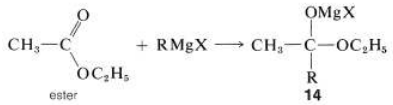


Hydrolysis of the intermediate $\mathrm{R{-}OMgX}$ compound is achieved best with aqueous ammonium chloride solution. Addition of water gives an unpleasant mess of $\mathrm{Mg(OH)_2}$ whereas addition of strong acids such as HCl or $\mathrm{H_2SO_4}$ can lead to side reactions of dehydration and so on, especially with tertiary alcohols (Section 8-9C):

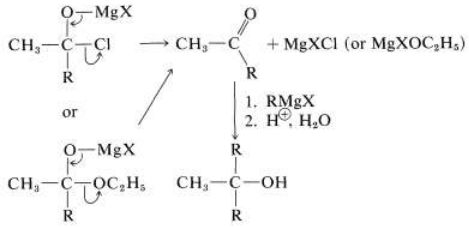


Tertiary alcohols also are obtained from both acyl halides, RCOCl, and esters, $\mathrm{RCO_2R}$, by the addition of *two* moles of Grignard reagent. The first mole of RMgX adds to the carbonyl bond to give the adducts 13 or 14:

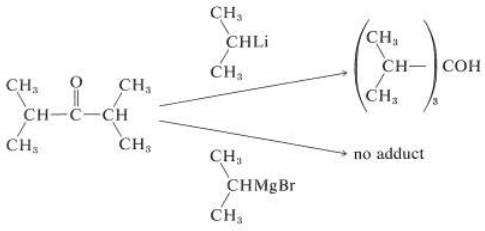




However, these first-formed adducts are unstable and decompose to a ketone, $\mathrm{CH_3COR}$, and magnesium salts, MgXCl or $\mathrm{MgXOC_2H_5}$. The ketone usually cannot be isolated, but reacts rapidly with more RMgX ultimately to give a tertiary alcohol:



Organolithium compounds behave very much like Grignard reagents, but with increased reactivity. They offer advantages over the magnesium compounds when the R group or the carbonyl compound is highly branched. For instance, isopropyllithium adds in good yield to 2,4-dimethyl-3-pentanone, whereas isopropylmagnesium bromide fails completely to give the normal addition product:



Failure of Grignard reagents to add in the normal way generally is because reactions by alternative paths occur more rapidly. If the Grignard reagent has a hydrogen on the carbon adjacent to the point of attachment of $\mathrm{-MgX}$ (i.e., a β hydrogen), then reduction can occur, with the effect of adding $\mathrm{H_2}$ to the carbonyl group.

Side reactions - reduction

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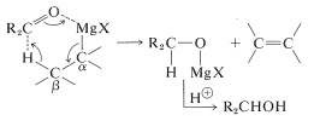
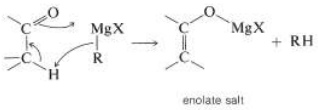


Furthermore, if the carbonyl compound has a hydrogen located on the carbon next to the carbonyl group, the Grignard reagent can behave as a base and remove this hydrogen as a proton. The result is that the compound becomes an enolate salt and RMgX becomes RH.

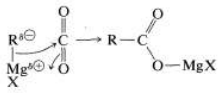
Side reactions - enolization



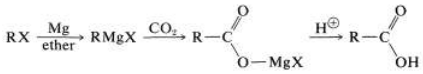
Apparently, the complicating side reactions observed with RMgX are not nearly as important with RLi. The reasons for this difference are not well understood.

14.13.2: Synthesis of Carboxylic Acids

The reaction of carbon dioxide with Grignard reagents initially gives a magnesium salt of a carboxylic acid, $\mathrm{RCO_2MgX}$:

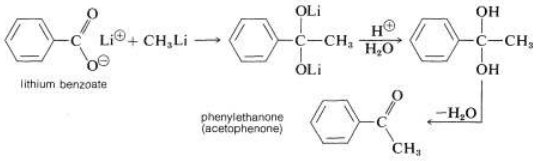


This salt, which has a carbonyl group, in principle could add a second RMgX. However, further addition is usually slow, and for most practical purposes the reaction stops at this stage. If the reaction can go further, the *worst* way to run it is by bubbling $\mathrm{CO_2}$ into the Grignard solution. This exposes the first-formed $\mathrm{RCO_2MgX}$ to excess RMgX and may lead to further addition reactions. The easy way to avoid this problem is to pour the RMgX solution onto powdered dry ice (solid $\mathrm{CO_2}$). Hydrolysis of the product (here a stronger acid than $\mathrm{NH_4Cl}$ is required) generates the carboxylic acid, $\mathrm{RCO_2H}$:

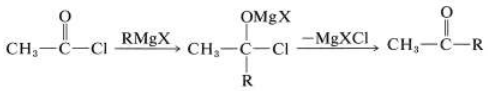


14.13.3: Synthesis of Ketones

Although organomagnesium compounds are not sufficiently reactive to add to carboxylate anions, alkyllithium compounds add quite well. A useful synthesis of methyl ketones involves the addition of methyllithium to the lithium salt of a carboxylic acid:



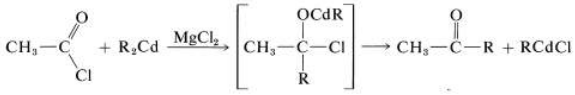
Other methods begin with acid chlorides or esters and attempt to add only *one* mole of RMgX:



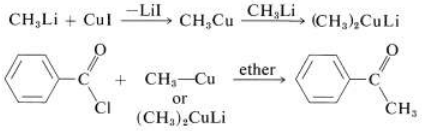
The disadvantage of using Grignard reagents for this purpose is that they add very rapidly to the ketone as it is formed. There are two ways in which this disadvantage can be minimized. First, one can add the Grignard solution to an excess of acid chloride solution (the so-called “inverse addition” procedure) to keep the concentration of RMgX in the reaction mixture low, and hope that the reaction will stop at the ketone stage. However, this device seldom works very well with acid chlorides. Better results can be obtained with RMgX and $\mathrm{R'CON(CH_3)_2}$. The second method is to use a less reactive organometallic compound - one that will react with RCOCl but not with $\mathrm{R_2C{=}O}$. One easy way to do this is to add cadmium chloride to the Grignard solution, whereby an

organocadmium compound, R_2Cd, is formed (cf. Section 14-10B, Method 3). In the presence of magnesium halides, R_2Cd reacts moderately rapidly with acid chlorides, but only slowly with ketones. The addition therefore can be arrested at the ketone stage:

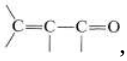
$$2RMgCl + CdCl_2 \rightarrow R_2Cd + 2MgCl_2 \qquad (14.13.1)$$



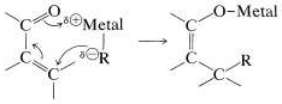
Alkylcopper compounds, R–Cu, also are selective reagents that react with acid chlorides to give ketones, but do not add to esters, acids, aldehydes, or ketones. The R–Cu compounds can be prepared fromCuI and the alkyllithium. With an excess of the alkyllithium, the alkylcopper is converted to R_2CuLi:



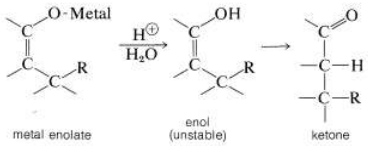
14.13.4: 1,4 Additions to Unsaturated Carbonyl Compounds

A conjugated alkenone,  , can react with an organometallic reagent by a normal 1,2 addition across the carbonyl group, or by 1,4 addition to the conjugated system.

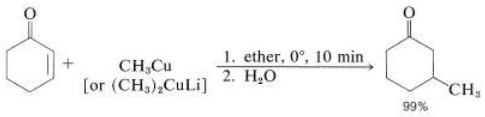
1,4 addition



On hydrolysis, the 1,4 adduct first yields the corresponding enol, but this is normally unstable and rearranges rapidly to the ketone. The final product therefore corresponds to addition of R–H across the carbon-carbon double bond:

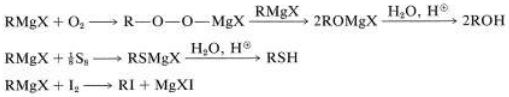


Organomagnesium and organolithium compounds can add both 1,2 and 1,4 to alkenones, and the relative importance of each mode of addition depends on the structure of the reactants. This sort of dual behavior can be a nuisance in synthetic work because it leads to separation problems and low yields. Organocopper compounds are a great help in this situation because they show a very high selectivity for 1,4 addition and add to unsaturated ketones in excellent yield:



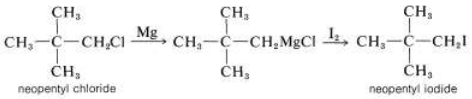
14.13.5: Oxygen, Sulfur, and Halogens

Grignard reagents react with oxygen, sulfur, and halogens to form substances containing C–O, C–S, and C–X bonds, respectively:



These reactions are not often important for synthesis because the products, ROH, RSH, and RX, can be obtained more conveniently and directly from alkyl halides by S_N1 and S_N2 displacement reactions, as described in Chapter 8. However, when both S_N1 and

S_N2 reactions are slow or otherwise impractical, as for neopentyl derivatives, the Grignard reactions can be very useful:



Also, oxygenation of a Grignard reagent at *low* temperatures provides an excellent method for the synthesis of hydroperoxides:

$$RMgX + O_2 \xrightarrow{-70^\circ} ROOMgX \xrightarrow{H^\oplus} ROOH$$

To prevent formation of excessive amounts of the alcohol, **inverse addition** is desirable (i.e., a solution of Grignard reagent is added to ether through which oxygen is bubbled rather than bubbling oxygen through a solution of the Grignard reagent).

Table 14-5: *Methods of Preparation of Organic Halides*

Reaction	Comments
Alkyl halides	
1. *Alcohols and hydrogen halides* $ROH + HBr \longrightarrow RBr + H_2O$ $ROH + HCl \xrightarrow{ZnCl_2} RCl + H_2O$	Reactivity: *tertiary* > *secondary* > *primary*; chlorides require $ZnCl_2$ as catalyst (Section 15-5A); rearrangement is common when the displacement is S_N1 type.
2. *Alcohols and phosphorus halides* $3ROH + PBr_3 \xrightarrow{\text{pyridine}} 3RBr + H_3PO_3$	Best with *primary* ROH; pyridine (azabenzene, a weak nitrogen base) acts to keep the acidity low, which may reduce side reactions such as rearrangement.
3. *Alcohols and thionyl chloride* $ROH + SOCl_2 \xrightarrow{\text{pyridine}} RCl + SO_2 + HCl$	As in Method 2. (See Section 15-5A.)
4. *Halogenation of hydrocarbons* $RH + X_2 \xrightarrow{h\nu} RX + HX$	Radical-chain reaction (Sections 4-4 and 4-5); Br_2 is more selective than Cl_2; used for preparation of 2-propenyl and arylmethyl halides; other reagents include SO_2Cl_2 (Section 4-5B), *tert*-butyl hypochlorite and *N*-bromosuccinimide (Section 14-3A).
5. *Addition of hydrogen halides to alkenes* $RCH{=}CH_2 \xrightarrow{HX} RCH(X){-}CH_3$ $RCH{=}CH_2 \xrightarrow{HBr,\ peroxides} RCH_2CH_2Br$	See Sections 10-4 and 10-7.
6. *Addition of halogens to alkenes* $RCH{=}CH_2 + X_2 \longrightarrow RCHXCH_2X$	Gives 1,2-dihalides (Section 10-3A).
7. *Inorganic halides and carbonyl compounds* $R_2C{=}O \xrightarrow{PCl_5} R_2CCl_2$ $R_2C{=}O \xrightarrow{MoF_6} R_2CF_2$	Gives 1,1-dihalides (Section 16-4D).
8. *Organometallic compounds and halogens* $RMgX + X_2 \longrightarrow RX + MgX_2$ $RHgX + X_2 \longrightarrow RX + HgX_2$	Of limited use because the RX compound is usually the source of the organometallic reagent (however, see Section 14-12E).
9. *Chloromethylation of arenes* $ArH + CH_2O + HCl \xrightarrow[(-H_2O)]{} ArCH_2Cl$	Electrophilic substitution of ArH; gives benzylic (arylmethyl) chlorides (see Section 26-4A, Exercise 22-21).
Alkenyl halides	
10. *Addition of halogens and hydrogen halides to alkynes* $RC{\equiv}CH + HX \longrightarrow RCX{=}CH_2 + RCH{=}CHX$ $RC{\equiv}CH + X_2 \longrightarrow RCX{=}CHX$	May require mercury catalyst (Section 10-5).
11. *Elimination of hydrogen halides from dihalides* $RCHXCH_2X \xrightarrow{\text{base}} RCH{=}CHX + RCX{=}CH_2$ $RCH_2CHX_2 \xrightarrow{\text{base}} RCH{=}CHX$	E2 (see Section 8-8).
1-Alkynyl halides	
12. *Halogenation of alkynide salts* $RC{\equiv}CNa + X_2 \longrightarrow RC{\equiv}CX$	As in Method 8.
13 *Halogenation of 1-alkynes with hypohalites* $RC{\equiv}CH + HOX \longrightarrow RC{\equiv}CX$	Very useful (Section 14-4).

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14. *Elimination of hydrogen halides* $RCH{=}CX_2 \xrightarrow{base} RC{\equiv}CX$	As in Method 11.
15. *Chloroethynylation of electrophilic carbon* $ClC{\equiv}CH \xrightarrow{NaNH_2} ClC{\equiv}CNa \xrightarrow{RX} ClC{\equiv}CR$	See Sections 14-10B and 11-8C.
Aryl halides	
16. *Halogenation of arenes* $ArH + X_2 \longrightarrow ArX + HX$	Electrophilic substitution of ArH; may require a catalyst [Fe(II) or I_2]; used for Cl_2 and Br_2 (see Section 22-4D).
17. *From aromatic amines* $ArNH_2 \xrightarrow{HONO} Ar\overset{\oplus}{N_2} \xrightarrow[Cu(I)/Cu(II)]{X^\ominus} ArX$	Amine is converted to diazonium salt ($ArN_2^{\oplus}$), which is replaced by halide ion; a copper catalyst is required (see Section 23-10B).

Table 14-6: *Reactivities of Organohalogen Compounds in Displacement and Elimination Reactions*

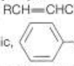
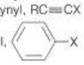
Organic halide	S_N2	Reactivity E2	S_N1, E1
prim-alkyl, RCH_2X	good	fair	very poor
sec-alkyl, R_2CHX	fair	fair	fair
tert-alkyl, R_3CX	poor	good	good
allylic, $RCH{=}CHCH_2X$	good	–	good
benzylic,  $-CH_2X$	good	–	good
alkenyl, $RCH{=}CHX$	poor	fair	poor
alkynyl, $RC{\equiv}CX$	poor	–	poor
aryl,  $-X$	very poor	–	poor

Table 14-7: *Methods of Preparation of Organometallic Compounds*

Method	Reaction
1. *Organohalogen compounds with metals:* solvent is diethyl ether or oxacyclopentane (tetrahydrofuran); inert atmosphere desirable to keep out moisture and air; mostly used for magnesium and lithium	$RX + Mg \xrightarrow{ether} RMgX$
2. *Halogen–metal exchange:* used when Method 1 fails because the halide is unreactive	$RX + R'Li \longrightarrow RLi + R'X$
3. *Metal–metal exchange:* replacement of one metal by a less electropositive metal	$RLi + CuI \longrightarrow RCu + LiI$
4. *Metal–metal exchange:* replacement of one metal by a more electropositive metal	$R_2Mg + 2Li \longrightarrow 2RLi + Mg$
5. *Replacement of acidic hydrogen*	$RC{\equiv}CH \xrightarrow[NH_3]{NaNH_2} RC{\equiv}CNa$ $RC{\equiv}CH + RMgX \longrightarrow RC{\equiv}CMgX + RH$

[2]It is not possible to add RH to $\gt C{=}O$ directly because ΔG^0 generally is somewhat unfavorable [$+5$ kcal for $CH_4 + (CH_3)_2C{=}O \rightarrow (CH_3)_3COH$]. How we get around this unfavorable equilibrium in practice provides an interesting example of how energy can be (and is) squandered to achieve some particular desired result; for example, the reaction $CH_3CH_3 + CH_3CHO \rightarrow CH_3CH_3CH(CH_3)OH$ has $\Delta H^0 = -12$ kcal but $\Delta G^0 = +0.5$ kcal. A possible sequence is

$$\begin{aligned} &CH_3CH_3 + Br_2 \longrightarrow CH_3CH_2Br + HBr && \Delta H^0 = -10\ \text{kcal} \\ &CH_3CH_2Br + 2Li \longrightarrow CH_3CH_2Li + LiBr && \Delta H^0 = -76\ \text{kcal} \\ &CH_3CH_2Li + CH_3CH{=}O \longrightarrow CH_3CH_2CH(CH_3)OLi && \\ &CH_3CH_2CH(CH_3)OLi + H_2O \longrightarrow CH_3CH_2CH(CH_3)OH + LiOH\ (aq) && \Big\}\ \Delta H^0 = -71\ \text{kcal} \end{aligned}$$

The overall result is the expenditure of $10 + 76 + 71 = 157$ kcal to achieve a reaction that itself has $\Delta H^0 = -12$ kcal, but an unfavorable ΔG^0. (Li is used in this example rather than Mg because the heat of formation of C_2H_5MgBr is not available.)

14.13.6: Contributors

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14.E: Organohalogen and Organometallic Compounds (Exercises)

Exercise 14-1 Deduce the structures of the two compounds whose NMR and infrared spectra are shown in Figure 14-1. Assign as many of the infrared bands as you can and analyze the NMR spectra in terms of chemical shifts and spin-spin splittings.

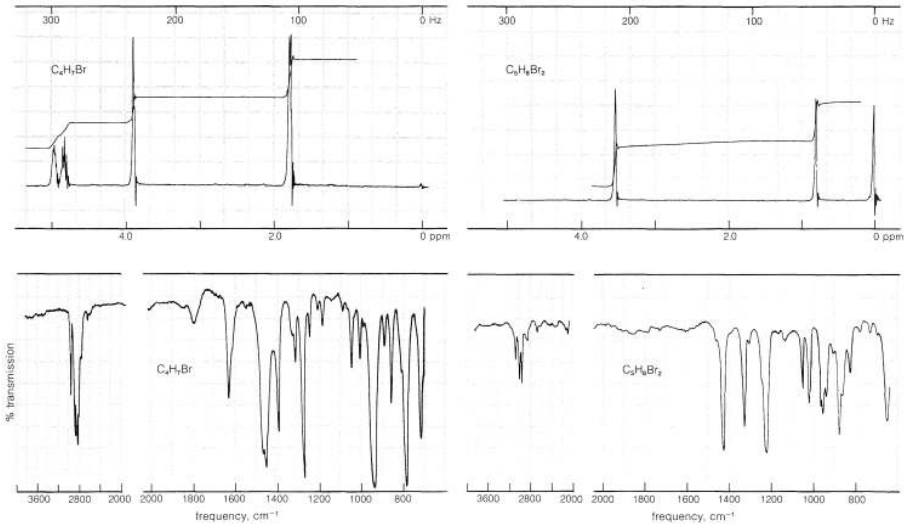


Figure 14-1: *Infrared and proton NMR spectra of substance* C_4H_7Br *and substance* $C_5H_8Br_2$ *(see Exercise 14-1). NMR spectra are at* $60\ MHz$ *with reference to TMS at* 0.0.

Exercise 14-2

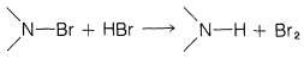
a. Methyl iodide can be prepared from potassium iodide and dimethyl sulfate. Why is dimethyl sulfate preferable to methanol in reaction with potassium iodide?

b. 1-Bromobutane can be prepared from 1-butanol and sodium bromide in concentrated sulfuric acid. What is the function of the sulfuric acid?

c. Some people like to put salt in their beer. Assess the possibility of CH_3CH_2Cl poisoning from the reaction of $NaCl$ with the ethanol in beer. Give your reasoning.

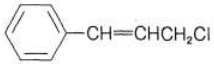
d. Both isopropyl bromide and *tert*-butyl bromide react with sodium ethoxide in ethanol. Which bromide would give the most alkene? Which bromide would give the most alkene on solvolysis in 60% aqueous ethanol? Of the two reagents, sodium ethoxide in ethanol or 60% aqueous ethanol, which would give the most alkene with each bromide? Give your reasoning.

Exercise 14-3 The reaction of N-bromosuccinimide (NBS) with alkenes to produce allylic bromides is though to involve molecular bromine produced by the reaction



Show the propagation steps that probably are involved in the radical-chain bromination of cyclohexane with NBS, assuming that bromine atoms are produced from NBS in the initiation steps. What by-products would you anticipate?

Exercise 14-4 Give a reasonable method for the synthesis of the following compounds from organic compounds not containing a halogen. Indicate the structures of any major by-products expected.

a. 

b. $HC \equiv CCH_2Br$

c.

d. $CH_3-CH(Cl)-CH=CH-CH_2CH_3$

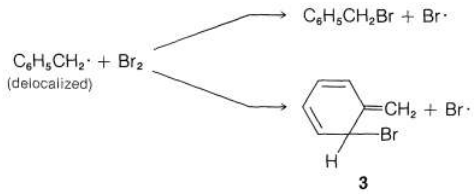
e. $(CH_2=CH)_2CHCl$

Exercise 14-5 In the presence of only traces of ionizing agents, either pure 1-chloro-2-butene or 3-chloro-1-butene is converted slowly to a 50-50 equilibrium mixture of the two chlorides. Explain.

Exercise 14-6

a. Write the initiation and propagation steps involved in the radical bromination of methylbenzene (toluene) with bromine. Write the low-energy valence-bond structures of the intermediate phenylmethyl radical.

b. Calculate ΔH^0 for the following reactions of the radical, using the $C-Br$ bond strength of $C_6H_5CH_2Br$ $(55\ kcal)$, and any other necessary bond energies. Assume that stabilization arising from electron delocalization is $38\ kcal$ for a phenyl group (Section 6-5A) and $5\ kcal$ for the triene structure 3.



3

What can you conclude from these calculations about the stability of 3 and the likelihood of its formation in this kind of bromination?

Exercise 14-7 Explain the following observations.

a. 1,2-Propadiene gives 3-chloropropyne on radical chlorination with either Cl_2 or *tert*-butyl hypochlorite.

b. 1-Chloro-2-propanone could be regarded as a kind of allylic chloride, but it is very unreactive under S_N1 conditions although it is highly reactive in S_N2 reactions.

c. The enantiomers of 3-chloro-1-butene racemize somewhat more rapidly than they give solvolysis products, under conditions that favor S_N1 reactions when a good ionizing but *weakly nucleophilic* solvent is used.

Exercise 14-8 Would you expect the behavior of 3-chloropropyne to more nearly resemble 1-chloropropane or 3-chloropropane in nucleophilic displacement reactions? Give your reasoning.

Exercise 14-9 Arrange the following halides in order of expected *increasing reactivity* towards (a) sodium iodide in acetone and (b) silver nitrate in ethanol. Indicate your reasoning.

$$C_6H_5CH_2CH_2Cl,\ C_5H_5C\equiv CCl,\ C_6H_5C\equiv CCH_2Cl,\ C_6H_5CH=CHCl \tag{14.E.1}$$

Exercise 14-10 Write a reasonable mechanism for the formation of phenylethanoic acid on heating phenylbromoethyne with potassium hydroxide in aqueous alcohol:

$$C_6H_5C\equiv CBr \xrightarrow[KOH]{H_2O-C_2H_5OH} \xrightarrow{H^{\oplus}} C_6H_5CH_2CO_2H \tag{14.E.2}$$

Exercise 14-11

a. Write resonance structures analogous to structures 5*a* through 5*d* to show the activating effect of $-C\equiv N$ and $-SO_2R$ groups in nucleophilic substitution of the corresponding 4-substituted chlorobenzenes.

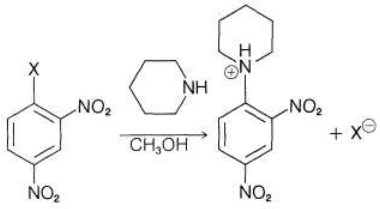
b. How would you expect the introduction of methyl groups *ortho* to the activating group to affect the reactivity of 4-bromonitrobenzene and 4-bromocyanobenzene toward ethoxide ion? (Investigate the geometry of the anion intermediate.)

Exercise 14-12 Would you expect 4-bromonitrobenzene or (4-bromophenyl)-trimethylammonium chloride to be more reactive in bimolecular replacement of bromine by ethoxide ion?

Exercise 14-13* Would you expect 4-chloromethoxybenzene and 4-chlorotrifluoromethylbenzene to be more, or less, reactive than chlorobenzene toward methoxide ion? Explain.

Exercise 14-14* Whereas the order of reactivity of alkyl halides toward a given nucleophile is $\mathrm{I} > \mathrm{Br} > \mathrm{Cl} \gg \mathrm{F}$, the reverse order of reactivity frequently is observed with aryl halides $(\mathrm{F} \gg \mathrm{Cl} \cong \mathrm{Br} \cong \mathrm{I})$. What does this signify regarding the relative rates of the addition and elimination steps (Equations 14-3 and 14-4) in this kind of aromatic substitution?

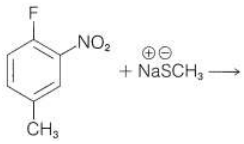
Exercise 14-15 The reactions of several 1-substituted 2,4-dinitrobenzenes with piperidine (azacyclohexane), Equation 14-5, proceed at nearly the same rate, *independent of the nature of* X. Rationalize this observation in terms of a mechanism of nucleophilic aromatic substitution.

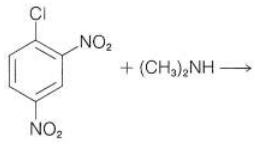


X = C_6H_5S, Br, Cl, $C_6H_5SO_2$, *p*-$NO_2C_6H_4O$, I

Exercise 14-16* The reaction of 1-fluoro-2,4-dinitrobenzene with dimethylamine is catalyzed by weak bases. How may this observation be explained? (Consider possible intermediates, rate-determining steps, etc.)

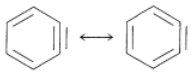
Exercise 14-17 Write the products of the following reactions:

a.


b.


c.

Exercise 14-18 Two valence-bond structures are possible for benzyne:



How do these differ from the Kekulé structures usually written for benzene? Devise an atomic-orbital model for benzyne.

Exercise 14-19 The intervention of benzyne in the amination of chlorobenzene, bromobenzene, and iodobenzene with sodium amide in liquid ammonia originally was demonstrated by J. D. Roberts using $^{14}\mathrm{C}$-labeled halobenzenes. Show explicitly how the use of a chlorobenzene-$^{14}\mathrm{C}$ label could differentiated between amination by *addition-elimination* (Section 14-6B) versus amination by *elimination-addition (benzyne mechanism)*.

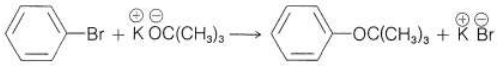
Exercise 14-20 In the hydrolysis of chlorobenzene-1-$^{14}\mathrm{C}$ with $4\ \mathrm{M}$ aqueous sodium hydroxide at 340°, the products are 58% benzenol-1-$^{14}\mathrm{C}$ and 42% benzenol-2-$^{14}\mathrm{C}$. Calculate the percentage of reaction proceeding (a) by an elimination-addition mechanism, and (b) by direct nucleophilic displacement. Would you expect the amount of direct displacement to increase, or decrease, if the reaction were carried out (a) at 240° and (b) with lower concentrations of sodium hydroxide? Give you reasoning.

Exercise 14-21 Explain the following observations:

a. 2,6-Dimethylchlorobenzene does not react with potassium amide in liquid ammonia at -33°.

b. Fluorobenzene, labeled with deuterium in the 2- and 6-positions, undergoes rapid exchange of deuterium for hydrogen in the presence of potassium amide in liquid ammonia, but does not form benzenamine (aniline).

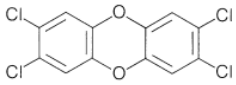
Exercise 14-22* Bromobenzene reacts rapidly with potassium *tert*-butoxide in $(CH_3)_2SO$ (methylsulfinylmethane, dimethyl sulfoxide, DMSO) to give *tert*-butyl phenyl ether:



A comparable reaction does not take place in *tert*-butyl alcohol as solvent (see Section 8-7F). Suggest a mechanism for the reaction and explain why DMSO is a better solvent for the reaction than *tert*-butyl alcohol. What products would you expect to be formed using 4-bromo-1-methylbenzene in place of bromobenzene?

Exercise 14-23* Both 2,4-D and 2,4,5-T are herbicides that have been used for weed control and as defoliating agents in jungle warfare. Apart from the arguments for or against the use of chemicals for such purposes, there have been reports of serious dermatitis among the industrial workers who produce these substances.

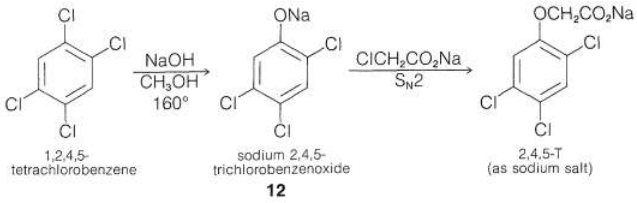
The cause finally was traced to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which is produced as an impurity in the manufacture of 2,4,5-T.



TCDD

This substance (TCDD) is very toxic. In addition to the dermatitis in produces, it is a potent teratogen (induces birth abnormalities). The lethal does is less than 10^{-6} g for guinea pigs. Its presence in 2,4,5-T can be eliminated, but the conditions by which it is formed are pertinent to our present discussion.

The production of 2,4,5-T involves the substitution of one chlorine of 1,2,4,5-tetrachlorobenzene with hydroxide ion to give 12. This is followed by a second displacement reaction, this time on chloroethanoate by the sodium salt of 12:



12

If the temperature of the first step exceeds 160°, then two molecules of 12 react in a double nucleophilic displacement to give TCDD.

a. Write reasonable mechanisms for the steps by which two molecules of 12 are converted to TCDD.

b. Would you expect TCDD to be formed in the preparation of 2,4-D from 1,2,4-trichlorobenzene? Explain.

Exercise 14-24 What products would you expect from the reaction of bromoform, $CHBr_3$, with potassium *tert*-butyl alcohol in the presence of (a) *trans*-2-butene and (b) *cis*-2-butene?

Exercise 14-25* Devise atomic-orbital models of the singlet and triplet forms of $:CH_2$. Of these one has a much greater $H-C-H$ angle than the other. Deduce whether the triplet or the singlet form should have the wider $H-C-H$ angle. (Remember the Pauli principle, Section 6-1.)

Exercise 14-26 Write the structures of the products of the following equations:

a. $C_6H_5CH_2CH_2MgBr + (CH_3)_2SO_4 \rightarrow$

b. $C_2H_5MgBr + CH_3C \equiv C-CH_2Br \rightarrow$

c. $CH_2=CH-CH_2Li + CH_2=CH-CH_2Cl \rightarrow$

d. $CH_3CH_2CH_2MgBr + ClCH_2OCH_3 \rightarrow$

e. $C_4H_9Na + C_4H_9Br \rightarrow$

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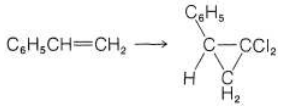
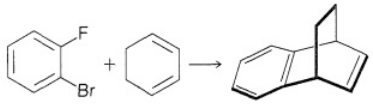
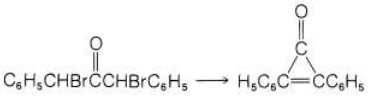
Exercise 14-27* Show the steps involved in the formation of 2,3-pentadiene from *cis*-2-butene (1 mole), carbon tetrabromide (1 mole), and methyllithium (2 moles). (See Section 14-7B for pertinent reactions.)

Exercise 14-28* Show how the following transformations might be achieved. Define the reaction conditions as closely as possible. More than one step may be required.

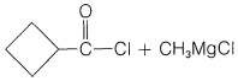
a. 

b. 

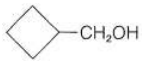
c. 

Exercise 14-29 Addition of Grignard reagents, $RMgX$, to diethyl carbonate, $O{=}C(OC_2H_5)_2$, gives tertiary alcohols, R_3COH, on hydrolysis. Write the steps involved in this reaction.

Exercise 14-30 Write structures for the products of the following reactions involving Grignard reagents. Show the structures of both the intermediate substances and the substances obtained after hydrolysis with NH_4Cl solution. Unless otherwise specified, assume that sufficient Grignard reagent is used to effect those addition reactions that occur readily at room temperature.

a. $C_6H_5MgBr + C_6H_5CHO$
b. $CH_3MgI + CH_3CH_2CO_2C_2H_5$
c. $CH_3CH_2MgBr + ClCO_2C_2H_5$
d. $C_6H_5MgBr + (CH_3O)_2C{=}O$
e. 

Exercise 14-31 Show how each of the following substances could be prepared from the indicated organic halide and any other appropriate organic compounds:

a.  from

b. $CH_2{=}CHC(CH_3)_2OH$ from CH_3I

c. $C_6H_5C \equiv CCH_2OH$ from C_2H_5Cl

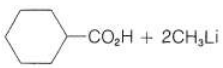
d. $CH_3CH_2CH(OH)CH_3$ from C_2H_5Cl

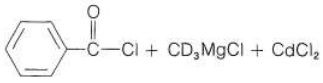
Exercise 14-32 Write structures for the addition, enolization, and reduction products possible for the following reactions:

a. $CH_3COCH_3 + (CH_3)_3CMgX$
b. $C_6H_5COC_6H_5 + CH_3CH_2MgX$
c. $C_6H_5CH{=}CHCO_2C_2H_5 + C_6H_5MgX$

Exercise 14-33 Grignard reagents, such as CH_3MgI, often add to the triple bond of nitriles, $RC \equiv N$, to give adducts that, on hydrolysis, yield ketones, RCO_CH_3. Show the possible steps involved.

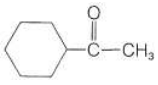
Exercise 14-34 Show the products expected from the following combinations of reagents. Write the structures of the initial adducts and also the products they give on acid hydrolysis:

a. $(CH_3)_3CMgCl + CO_2$
b. 

c. 

d. $CH_3{-}COCl + CD_3Li + CuI$

Exercise 14-35 Show how the following compounds could be synthesized by reasonable reactions from the indicated compound and any other needed reagents:

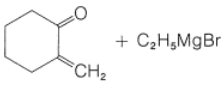
a.  from chlorocyclohexane

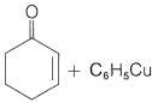
b. $C_6H_5C \equiv CCO_2H$ from phenylethyne

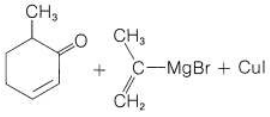
c. $ClC \equiv CCO_2H$ from ethyne

Exercise 14-36 Predict the products expected from the reactions of the following compounds:

a. $CH_2{=}CH{-}CO{-}CH_3 + C_2H_5MgBr$

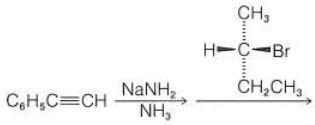
b. 

c. 

d. 

Exercise 14-37 Would you expect the overall energy change (*after hydrolysis*) to be more favorable for 1,2 or 1,4 addition of a Grignard reagent to $CH_2{=}CH{-}COCH_3$? Give your reasoning.

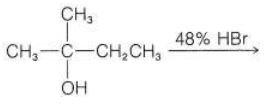
Exercise 14-38 What products do you expect from the following reactions? Give your reasoning. Show the structures of the intermediate compounds in sequences of the type $\rightarrow\rightarrow$.

a. 

b. $CH_2{=}CH_2 \xrightarrow{ICl} \xrightarrow[heat]{KOH}$

c.

d. $CH_3CH_2OH + KI + H_3PO_4 \xrightarrow{reflux}$

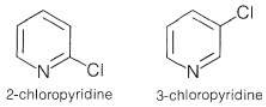
e. 

Exercise 14-39 In the reaction of 14-38e, when the aqueous acid is mixed with 2-methyl-2-butanol, the mixture is initially homogenous, but it soon separates into two phases. Explain why two phases appear. On separation of the phases using a separatory funnel, which layer (upper or lower) would contain the organic product? If you were unsure, how could you quickly find out?

Exercise 14-40 Suppose one could hydrolyze pure *cis*-1-chloro-2-butene exclusively by (a) the S_N1 mechanism or (b) the S_N2 mechanism. Would you expect the 2-butenol formed in each case to be the cis isomer, the trans isomer, or a mixture? Explain.

Exercise 14-41 The intermediate carbocation formed by S_N1 reactions of either 3-chloro-3-methyl-1-butene or 4-chloro-2-methyl-2-butene reacts with water to give a mixture of 2-methyl-3-buten-2-ol and 3-methyl-2-buten-1-ol. Which alcohol would you expect to predominate under conditions of *equilibrium* control? On the bases of steric hindrance, charge distribution in the cation, and so on, which alcohol should be favored under conditions of *kinetic* control? (Review Sections 6-5C, 10-4A, and 11-3.) Give your reasoning.

Exercise 14-42 Explain why 2-chloropyridine is more reactive than 3-chloropyridine in nucleophilic substitution reactions.

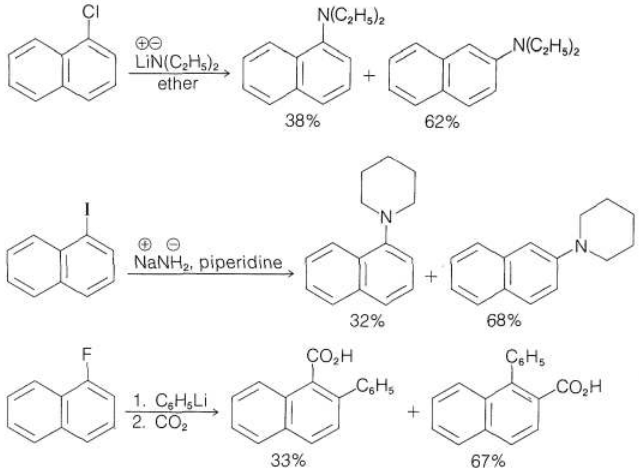


Exercise 14-43 Explain why 2-chloropyridine reacts with potassium amide (KNH_2) in liquid ammonia solution at -33° to give 2-aminopyridine, whereas 3-chloropyridine under the same conditions gives a mixture of 65% 4-amino- and 35% 3-aminopyridine.

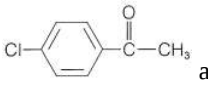
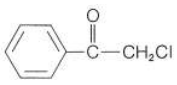
Exercise 14-44 Write a structural formula for a compound that fits each of the following descriptions:

a. an aryl halogen compound that reacts with sodium iodide in acetone but not with aqueous silver nitrate solution
b. an organic fluoro compound that is more reactive in displacement reactions than the corresponding iodo compound
c. an aryl bromide that cannot undergo substitution by the elimination-addition (benzyne) mechanism
d. the monobromonitronaphthalene expected to be *least* reactive toward ethoxide ion in ethanol

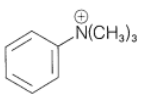
Exercise 14-45 Explain why the substitution reactions of the following halonaphthalenes give about the same ratio of 1- and 2-naphthyl products independently of the halogen substituent and the nucleophilic reagent. Show the steps involved.



Exercise 14-46 For each of the following pairs of compounds describe a chemical test, preferably a test-tube reaction, that will distinguish between the two compounds. Write a structural formula for each compound and equations for the reactions involved.

a. chlorobenzene and phenylmethyl chloride
b. 4-nitrochlorobenzene and 3-nitrochlorobenzene
c.  and 
d. $CH_3C \equiv C{-}Br$ and $BrCH_2C \equiv CH$

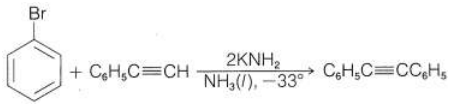
Exercise 14-47 Show how benzyne can be formed from the following reagents:

a. fluorobenzene and phenyllithium
b.  $+KNH_2$

c. 1,2-dibromobenzene + butyllithium

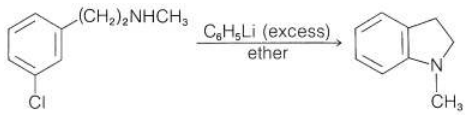
Exercise 14-48 Indicate the steps involved in each of the following transformations:

a.

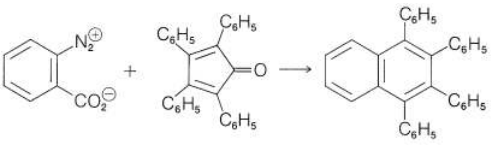


The reaction does not occur unless more than one mole of KNH_2 per mole of C_6H_5Br is used.

b.

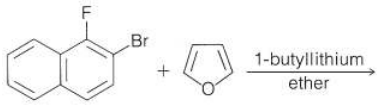


c.

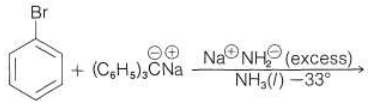


Exercise 14-49 Predict the products of the following reactions:

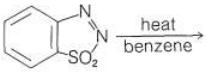
a.



b.



c.



Exercise 14-50 Nucleophilic displacement of the halogen of 3,5-dimethyl-4-nitrobromobenzene is much slower than with the corresponding compound lacking the methyl groups. Give a reasonable explanation of this observation. (Construction of molecular models will help.)

Exercise 14-51 Methylmagnesium halides have been employed as analytical reagents for the determination of the number of acidic hydrogens in a molecule (the *Zerewitinoff determination*). The method involves measuring the amount of methane produced from a given weight of compound (such as RH, with an acidic hydrogen) by the following reaction:

$$CH_3MgI + RH \rightarrow CH_4 + RMgI \tag{14.E.3}$$

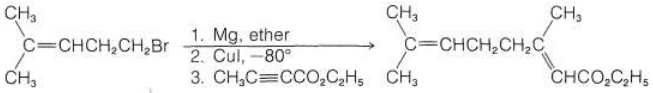
Excess methylmagnesium iodide and $0.1776\ g$ of Compound **A** (formula $C_4H_{10}O_3$) react to give $84.1\ mL$ of methane collected over mercury at $740\ mm$ and $25°$. How many acidic hydrogens does Compound **A** possess per molecule? Suggest a possible structure on the basis that spectral data indicate (a) there is no $C{=}O$ group in the molecule and (b) **A** is achiral.

Exercise 14-52 From the nature of the carbon-metal bonds in organometallic compounds, predict the products of the following reactions. Give your reasoning.

a. $CH_3MgCl + ICl$
b. $C_6H_5Li + CH_3OH$
c. $CH_3Li + HC \equiv CH$
d. $C_6H_5Li + CuI$

Exercise 14-53

a. Show the steps and reaction intermediates by which the product is formed in the following reaction sequence:



b. Draw structures for the products in each step of the following sequence:

$$C_2H_5Cl \xrightarrow{\text{Mg, ether}} \xrightarrow{C_6H_5C\equiv CH} \xrightarrow{CO_2} \xrightarrow{CH_3Li} \xrightarrow{H^{\oplus},\ H_2O} \tag{14.E.4}$$

Exercise 14-54 The following experimental observations have been reported:

1. *tert*-Butyl chloride was added to lithium metal in dry ether at 35°. A vigorous reaction ensued with evolution of hydrocarbon gases. After all the lithium metal was consumed, the mixture was poured onto dry ice. The only acidic product that could be isolated (small yield) was 4,4-dimethylpentanoic acid.

2. *tert*-Butyl chloride was added to lithium metal in dry ether at -40°. After all the lithium had reacted, the mixture was carbonated and gave a good yield of 2,2-dimethylpropanoic acid.

3. *tert*-Butyl chloride was added to lithium metal in dry ether at -40°. After all the lithium was consumed, ethene was bubbled through the mixture at -40° until no further reaction occurred. Carbonation of this mixture gave a good yield of 4,4-dimethylpentanoic acid.

a. Give a reasonably detailed analysis of the results obtained and show as best you can the mechanisms involved in each reaction.

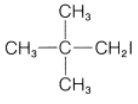
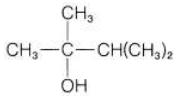
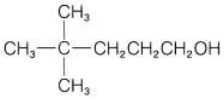
b. Would similar behavior be expected with methyl chloride? Explain.

c. Would you expect that a substantial amount of 6,6-dimethylheptanoic acid would be found in Observation 3? Explain.

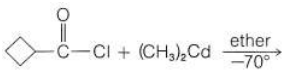
Exercise 14-55 Predict the products of each of the following Grignard reactions before and after hydrolysis. Give reasoning or analogies for each.

a. $CH_3MgI + HCO_2C_2H_5 \rightarrow$
b. $CH_3CH_2CH(MgBr)CH_3 +$ 2,4-dimethyl-3-pentanone $\rightarrow$
c. $CH_3CH_2MgBr + CS_2 \rightarrow$
d. $CH_3CH_2MgBr + NH_3 \rightarrow$

Exercise 14-56 Show how each of the following substances can be synthesized from the indicated starting materials by a route that involves organometallic substances in at least one step.

a. $(CH_3)_3C{-}D$ from $(CH_3)_3CCl$
b. $CH_3C \equiv C{-}CO_2H$ from $CH \equiv CH$
c.  from $(CH_3)_4C$
d.  (three ways)
e. from
f.  from $(CH_3)_3CCH_2Cl$
g. 1,5-hexadiene from propene

Exercise 14-57 Predict the products of each of the following reactions both before and after hydrolysis:

a. 

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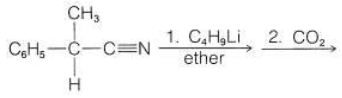
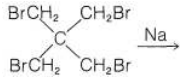
b.



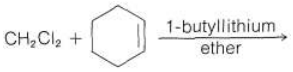
c. $HC \equiv CCH_2Br \xrightarrow{Mg^{-}\text{ether}} \xrightarrow{HC\equiv CCH_2Br}$

d. $(CH_3)_3CBr \xrightarrow{Mg^{-}\text{ether}} \xrightarrow{O_2,\ -70^{\circ}}$

e.



f.



Exercise 14-58 Each of the following equations represents a "possible" but not actually feasible Grignard synthesis. Consider each equation and determine why it will not proceed satisfactorily as written. *Give your reasoning* and show what the actual product will be.

a. $(CH_3)_3CMgBr + [(CH_3)_2CH]_2C{=}O \rightarrow\rightarrow (CH_3)_3C[(CH_3)_2CH]_2COH$

b. $(CH_3)_3CCH_2MgBr + [(CH_3)_3C]_2C{=}O \rightarrow\rightarrow (CH_3)_3CCH_2[(CH_3)_3C]_2COH$

c. $CH_3MgI + CH_3(CH_3)_2COCl \rightarrow\rightarrow CH_3(CH_3)_2COCH_3$

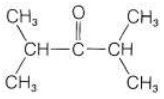
d. $CH_3MgI{+}CH_3CCH{=}N{-}CH_3 \rightarrow\rightarrow CH_3CH_2N(CH_3)_2$

e. $BrCH_2CH_2O_2CCH_3 \xrightarrow[(CH_2H_5)_2O]{Mg}$ Grignard reagent $\xrightarrow{CH_2O} \rightarrow HOCH_2CH_2CH_2O_2CCH_3$

f. $CH_2{=}CHCH_2MgCl + C_2H_5Br \rightarrow CH_2{=}CH(CH_2)_2CH_3$

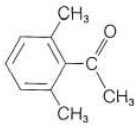
Exercise 14-59 What products would you expect to predominate in the following reactions:

a. C_6H_5MgBr+



b. $CH_3MgBr + (CH_3)_3CCOC(CH_3)_3$

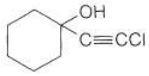
c. CH_3MgBr+



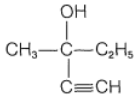
Exercise 14-60 Suggest possible reactions by which the following compounds could be prepared from ethyne and any other necessary compounds:

a. $ClC \equiv C(CH_2)_4C \equiv CCl$

b.



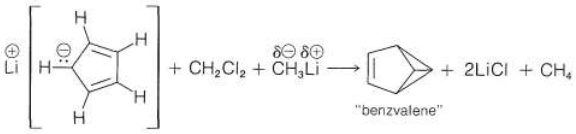
c.



d. $CH_2{=}CHCH_2C \equiv CCH_3$

Exercise 14-61* The rate of addition of dimethylmagnesium to excess diphenylmethanone (benzophenone) in diethyl ether initially is cleanly second order, that is, first order in ketone and first order in $(CH_3)_2Mg$. As the reaction proceeds, the rate no longer follows a strictly second-order rate overall. Suggest how the apparent specific rate could change as the reaction proceeds.

Exercise 14-62* An interesting isomer of benzene is "benzvalene" (tricyclo[2.1.1.$0^{5,6}$]-2-hexene). This substance, which like prismane (Section 12-10) can decompose with explosive violence, has been synthesized by T. Katz from lithium cyclopentadienide, dichloromethane, and methyllithium:



Write a mechanism for this reaction that you can support by analogy with other reactions discussed in this chapter or by reasonable mechanistic arguments.

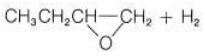
Exercise 14-63 Table 14-4 shows that the addition of RMgX to $\mathrm{R'CON(CH_3)_2}$ gives $\mathrm{RCOR'}$, although addition of RMgX to $\mathrm{R'CO_2CH_3}$ and $\mathrm{R'COCl}$ lead to $\mathrm{R'R_2COH}$. Assuming that similar mechanistic steps are involved throughout, why might $\mathrm{R'CON(CH_3)_2}$ give a different product than $\mathrm{R'CO_2CH_3}$ or $\mathrm{R'COCl}$? Show your reasoning.

Exercise 14-64 The formation of alcohols with organometallic compounds by the Grignard synthesis can be used to achieve the reaction $\mathrm{RH + {-}C{=}O}$ to give $\mathrm{R{-}C{-}OH}$, which generally has an *unfavorable* equilibrium constant. If you were looking for an industrial synthesis of 2-butanol by a reaction that would have a *favorable* equilibrium constant, which of the following might be *better* candidates than $\mathrm{CH_3CH_3 + CH_3CH{=}O \rightarrow CH_3CH_2CH(CH_3)OH}$. Give your reasoning.

a. $\mathrm{CH_2{=}CH_2 + CH_3CH_2OH}$

b. $\mathrm{CH_3CH_3 + CH_3CH_2OH}$

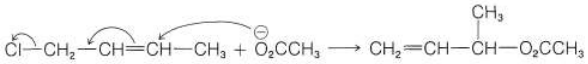
c. $\mathrm{CH_3CH_2CH_2CH_3 + \frac{1}{2}O_2}$

d. 

e. $\mathrm{CH_3CH_2CH{=}CH_2 + H_2O}$

Exercise 14-65 Compound X, of formula $\mathrm{C_3H_5Br_3}$, with methyllithium formed bromocyclopropane and 3-bromopropene. The NMR spectrum of X showed a one-proton triplet at $5.9\ \mathrm{ppm}$, a two-proton triplet at $3.55\ \mathrm{ppm}$, and a complex resonance centered at $2.5\ \mathrm{ppm}$ downfield from TMS. What is the structure of X? Account for the products observed in its reaction with methyllithium.

Exercise 14-66* There have been many proposals for the occurrence of a so-called S_N2' mechanism that would produce a concerted substitution with rearrangement for allylic halides. One possible example is



Consider whether this mechanism is operating for the particular example from the following experimental results. Give your reasoning.

1. Silver ethanoate in ethanoic acid with 1-chloro-2-butene gives 65% 2-butenyl ethanoate and 35% 1-methyl-2-propenyl ethanoate.

2. Ethanoate ion $(1\ \mathrm{M})$ in ethanoic acid with 1-chloro-2-butene gives a mixture of about 85% 2-butenyl ethanoate and 15% 1-methyl-2-propenyl ethanoate. About 36% of the overall reaction product results from a process that is *zero order* in ethanoate ion, whereas 64% comes from a process that is *first order* in ethanoate ion.

3. Ethanoate ion in 2-propanone reacts with 1-chloro-2-butene to give only 2-butenyl ethanoate, and with 3-chloro-1-butene to give only 1-methyl-2-propenyl ethanoate

(This exercise involves many of the ideas developed in Chapter 8 and you may wish to review Sections 8-4A, 8-4B, and 8-7, especially 8-7F.)

14.E.0.1: Contributors

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CHAPTER OVERVIEW

15: Alcohols and Ethers

The physical, chemical and spectroscopic properties of alcohols are relative to it’s chemical structures. Alcohols are compounds of the general formula ROH, where R is any alkyl or substituted alkyl group. The simple ethers, ROR, do not have O-H bonds, and most of their reactions are limited to the substituent groups. Before turning to the specific chemistry of alcohols and ethers, we remind you that the naming alcohols and ethers is summarized in naming alcohols, phenols and Naming Ethers.

15.1: Prelude to Alcohols and Ethers
15.2: Physical Properties of Alcohols; Hydrogen Bonding
15.3: Spectroscopic Properties of Alcohols
15.4: Preparation of Alcohols
15.5: Chemical Reactions of Alcohols. Reactions Involving the O-H Bond
15.6: Reactions Involving the C-O Bond of Alcohols
15.7: Oxidation of Alcohols
15.8: Polyhydric Alcohols
15.9: Unsaturated Alcohols - Alkenols
15.10: Protection of Hydroxyl Groups
15.11: Types and Reactions of Simple Ethers
15.12: Cyclic Ethers
15.E: Alcohols and Ethers (Exercises)

15.1: Contributors and Attributions

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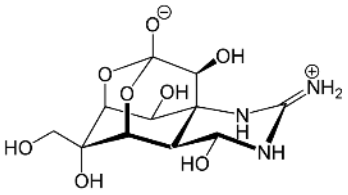
15.1: Prelude to Alcohols and Ethers

The physical, chemical and spectroscopic properties of alcohols are relative to it's chemical structures. Alcohols are compounds of the general formula ROH, where R is any alkyl or substituted alkyl group. The hydroxyl group (OH groups) is the characteristic functional group of alcohols and is one of the most important functional groups of naturally occurring organic molecules. All carbohydrates and their derivatives, including nucleic acids, have hydroxyl groups. Some amino acids, most steroids, many terpenes, and plant pigments have hydroxyl groups. These substances serve many diverse purposes for the support and maintenance of life. One extreme example is the potent toxin tetrodotoxin, which is isolated from puffer fish and has obvious use for defense against predators. This compound has special biochemical interest, having six different hydroxylic functions arranged on a cagelike structure:



Stick figure of the tetrodotoxin molecule, $C_{11}H_{17}N_3O_8$. *(Public Domain; Ayacop).*

On the more practical side, vast quantities of simple alcohols —methanol, ethanol, 2-propanol, 1-butanol —and many ethers are made from petroleum-derived hydrocarbons. These alcohols are widely used as solvents and as intermediates for the synthesis of more complex substances.

The reactions involving the hydrogens of alcoholic OH groups are expected to be similar to those of water, HOH, the simplest hydroxylic compound. Alcohols, ROH, can be regarded in this respect as substitution products of water. However, with alcohols we shall be interested not only in reactions that proceed at the O-H bond but also with processes that result in cleavage of the C-O bond, or changes in the organic group R.

The simple ethers, ROR, do not have O-H bonds, and most of their reactions are limited to the substituent groups. The chemistry of ethers, therefore, is less varied than that of alcohols. This fact is turned to advantage in the widespread use of ethers as solvents for a variety of organic reactions, as we already have seen for Grignard reagents. Nonetheless, cyclic ethers with small rings show enhanced reactivity because of ring strain and, for this reason, are valuable intermediates in organic synthesis.

Before turning to the specific chemistry of alcohols and ethers, we remind you that the naming alcohols and ethers is summarized in naming alcohols, phenols and Naming Ethers.

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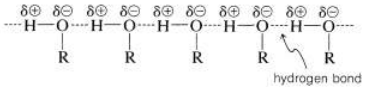
15.2: Physical Properties of Alcohols; Hydrogen Bonding

Comparison of the physical properties of alcohols with those of hydrocarbons of comparable molecular weight shows several striking differences, especially for those with just a few carbons. Alcohols are substantially less volatile, have higher melting points, and greater water solubility than the corresponding hydrocarbons (see Table 15-1), although the differences become progressively smaller as molecular weight increases.

Table 15-1: *Comparison of Physical Properties of Alcohols and Hydrocarbons*

Alcohol	Hydrocarbon	Molecular weight	Bp, °C	Mp, °C
CH_3OH		32	65	−98
	CH_3CH_3	30	−89	−172
CH_3CH_2OH		46	78.5	−117.3
	$CH_3CH_2CH_3$	44	−42.2	−189.9
$CH_3CH_2CH_2OH$		60	97.2	−127
	$CH_3CH_2CH_2CH_3$	58	−0.6	−135
$CH_3(CH_2)_3CH_2OH$		88	138	−79
	$CH_3(CH_2)_4CH_3$	86	69	−95
$CH_3(CH_2)_8CH_2OH$		158	228	6
	$CH_3(CH_2)_9CH_3$	156	196	−26

The reason for these differences in physical properties is related to the high polarity of the hydroxyl group which, when substituted on a hydrocarbon chain, confers a measure of polar character to the molecule. As a result, there is a significant attraction of one molecule for another that is particularly pronounced in the solid and liquid states. This polar character leads to association of alcohol molecules through the rather positive hydrogen of one hydroxyl group with a correspondingly negative oxygen of another hydroxyl group:



This type of association is called “hydrogen bonding,” and, although the strengths of such bonds are much less than those of most conventional chemical bonds, they are still significant (about 5 to 10 kcal per bond). Clearly then, the reason alcohols have higher boiling points than corresponding alkyl halides, ethers, or hydrocarbons is because, for the molecules to vaporize, additional energy is required to break the hydrogen bonds. Alternatively, association through hydrogen bonds may be regarded as effectively raising the molecular weight, thereby reducing volatility (also see Section 1-3).

The water solubility of the lower-molecular-weight alcohols is pronounced and is understood readily as the result of hydrogen bonding with water molecules:

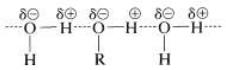


Figure 15-1). Indeed, the physical properties of higher-molecular-weight alcohols are very similar to those of the corresponding hydrocarbons (Table 15-1). The importance of hydrogen bonding in the solvation of ions was discussed in Section 8-7F.

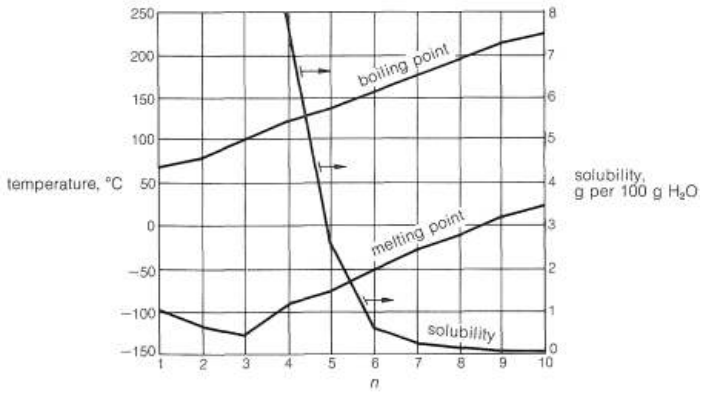


Figure 15-1: Dependence of melting points, boiling points, and water solubilities of straight-chain primary alcohols $H-(CH_2)_n-OH$ on n. The arrows on the solubility graph indicate that the scale is on the right ordinate.

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15.3: Spectroscopic Properties of Alcohols

The hydrogen-oxygen bond of a hydroxyl group gives a characteristic absorption band in the *infrared* but, as we may expect, this absorption is considerably influenced by hydrogen bonding. For example, in the vapor state (in which there is essentially no hydrogen bonding), ethanol gives an infrared spectrum with a fairly sharp absorption band at $3700\ \mathrm{cm}^{-1}$, owing to a free or unassociated hydroxyl group (Figure 15-2a). In contrast, this band is barely visible at $3640\ \mathrm{cm}^{-1}$ in the spectrum of a 10% solution of ethanol in carbon tetrachloride (Figure 15-2b). However, there is a relatively broad band around $3350\ \mathrm{cm}^{-1}$, which is characteristic of hydrogen-bonded hydroxyl groups. The shift in frequency of about $300\ \mathrm{cm}^{-1}$ arises because hydrogen bonding weakens the $\mathrm{O{-}H}$ bond; its absorption frequency then will be lower. The association band is broad because the hydroxyl groups are associated in aggregates of various sizes and shapes. This produces a variety of different kinds of hydrogen bonds and therefore a spectrum of closely spaced $\mathrm{O{-}H}$ absorption frequencies.

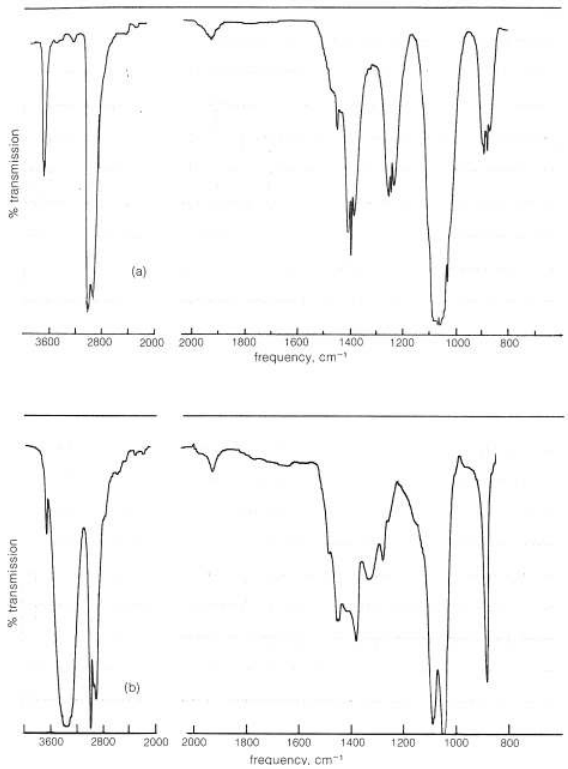
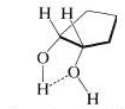


Figure 15-2: Infrared spectrum of ethanol (a) in the vapor phase and (b) as a 10% solution in carbon tetrachloride.

In very dilute solutions of alcohols in nonpolar solvents, hydrogen bonding is minimized. However, as the concentration is increased, more and more of the molecules become associated and the intensity of the infrared absorption band due to associated hydroxyl groups increases at the expense of the free-hydroxyl band. Furthermore, the frequency of the association band is a measure of the strength of the hydrogen bond. The lower the frequency relative to the position of the free hydroxyl group, the stronger is the hydrogen bond. As we shall see in Chapter 18 the hydroxyl group in carboxylic acids $(\mathrm{RCO_2H})$ forms stronger hydrogen bonds than alcohols and accordingly absorbs at lower frequencies (lower by about $400\ \mathrm{cm}^{-1}$, see Table 9-2).

The infrared spectra of certain 1,2-diols (glycols) are interesting in that they show absorption due to *intramolecular* hydrogen bonding. These usually are fairly sharp bands in the region $3450\ \mathrm{cm}^{-1}$ to $3570\ \mathrm{cm}^{-1}$, and, in contrast to bands due to intermolecular hydrogen bonding, they do not change in intensity with concentration. A typical example is afforded by *cis*-1,2-cyclopentanediol:



cis-cyclopentane-1,2-diol

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Besides the O–H stretching vibrations of alcohols, there is a bending O–H vibration normally observed in the region 1410-1260 cm^{-1}. There also is a strong C–O stretching vibration between 1210 cm^{-1} and 1050 cm^{-1}. Both these bands are sensitive to structure as indicated below:

	—O—H bend, cm^{-1}	C—O stretch, cm^{-1}
primary alcohol:	1260–1350	1053–1085 (s)
secondary alcohol:	1260–1350	1087–1125 (s)
tertiary alcohol:	1310–1410	1124–1205 (s)

The influence of hydrogen bonding on the *proton nmr spectra* of alcohols has been discussed previously (Section 9-10E). You may recall that the chemical shift of the OH proton is variable and depends on the extent of association through hydrogen bonding; generally, the stronger the association, the lower the field strength required to induce resonance. Alcohols also undergo intermolecular OH proton exchange, and the rate of this exchange can influence the line-shape of the OH resonance, the chemical shift, and the incidence of spin-spin splitting, as discussed in more detail in Sections 9-10E and 9-10I. Concerning the protons on carbon bearing the hydroxyl group, that is, $-\overset{|}{C}H-OH$, they are deshielded by the electron-attracting oxygen atom and accordingly have chemical shifts some 2.5-3.0 ppm to *lower* fields than alkyl protons.

Perhaps you are curious as to why absorptions are observed in the infrared spectrum of alcohols that correspond *both* to free and hydrogen-bonded hydroxyl groups, whereas only *one* OH resonance is observed in their proton nmr spectra. The explanation is that the lifetime of any molecule in either the free or the associated state is long enough to be detected by infrared absorption but much too short to be detected by nmr. Consequently, in the nmr one sees only the average OH resonance of the nonhydrogen-bonded and hydrogen-bonded species present. The situation here is very much like that observed for conformational equilibration (Section 9-10C).

The longest-wavelength *ultraviolet absorption* maxima of methanol and methoxymethane (dimethyl ether) are noted in Table 9-3. In each case the absorption maximum, which probably involves an $n \rightarrow \sigma^*$ transition, occurs about 184 nm, well below the cut-off of the commonly available spectrometers.

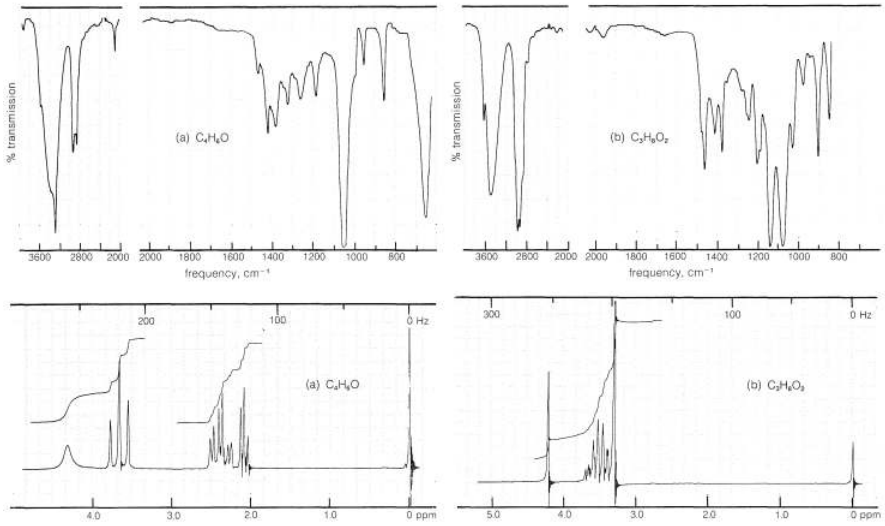
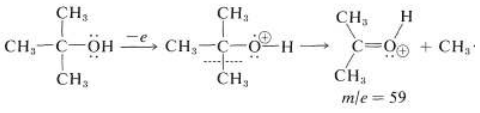
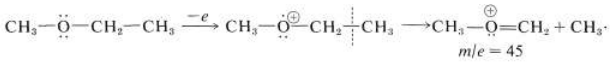


Figure 15-3: Proton nmr and infrared spectra (a) of C_4H_6O and (b) of C_3H_8O.

The *mass spectra* of alcohols may not always show strong molecular ions. The reason is that the M^+ ions readily fragment by α cleavage. The fragment ions are relatively stable and are the gaseous counterparts of protonated aldehydes and ketones:



Ethers also fragment by α cleavage:



15.3.1: Contributors and Attributions

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15.4: Preparation of Alcohols

Many of the common laboratory methods for the preparation of alcohols have been discussed in previous post or will be considered later; thus to avoid undue repetition we shall not consider them in detail at this time. Included among these methods are hydration (Section 10-3E) and hydroboration (Section 11-6D), addition of hypohalous acids to alkenes (Section 10-4B), S_N1 and S_N2 hydrolysis of alkyl halides (Sections 8-4 to 8-7) and of allylic and benzylic halides (Sections 14-3B and 14-3C), addition of Grignard reagents to carbonyl compounds (Section 14-12), and the reduction of carbonyl compounds (Sections 16-4E and 16-5). These methods are summarized in Table 15-2.

Some of the reactions we have mentioned are used for large-scale industrial production. For example, ethanol is made in quantity by the hydration of ethene, using an excess of steam under pressure at temperatures around 300° in the presence of phosphoric acid:

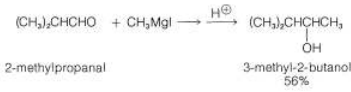
$$CH_2{=}CH_2 + H_2O \xrightleftharpoons{300^\circ,\ H_3PO_4} CH_3CH_2OH$$

A dilute solution of ethanol is obtained, which can be concentrated by distillation to a constant-boiling point mixture that contains 95.6% ethanol by weight. Dehydration of the remaining few percent of water to give "absolute alcohol" is achieved either by chemical means or by distillation with benzene, which results in preferential separation of the water. Ethanol also is made in large quantities by fermentation, but this route is not competitive for industrial uses with the hydration of ethene. Isopropyl alcohol and *tert*-butyl alcohol also are manufactured by hydration of the corresponding alkenes.

Table 15-2: *General Methods of Preparation of Alcohols*

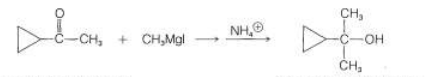
Reaction	Comment
1. *Hydration of alkenes* $RCH{=}CH_2 \xrightarrow{H^\oplus,\ H_2O} RCHCH_3$ (OH) $CH_3CH{=}C(CH_3)_2 \xrightarrow{H_2SO_4,\ H_2O} CH_3CH_2C(CH_3)_2$ (OH) 2-methyl-2-butene → 2-methyl-2-butanol, 74%	Ease of preparation is *tert.* > *sec.* > *prim.* alcohol; ease of dehydration follows same sequence. Rearrangement is a frequent complication. See Sections 8-9B and 10-3E.
2. *Hydroboration of alkenes* $RCH{=}CH_2 \xrightarrow[2.\ H_2O_2,\ HO^\ominus]{1.\ B_2H_6} RCH_2CH_2OH$ 1-methylcyclohexene $\xrightarrow[BF_3,\ \text{ether}]{NaBH_4}$ (B) $\xrightarrow{H_2O_2,\ HO^\ominus}$ *trans*-2-methylcyclohexanol, 90%	Diborane is best made *in situ* from $NaBH_4$ and BF_3 (Section 11-6E). The trialkylborane can be oxidized (without isolation) by H_2O_2. Reaction is stereospecific – suprafacial addition occurs to the less-hindered side of the double bond, and oxidation with hydrogen peroxide occurs with retention of configuration.
3. *Reaction of organometallic compounds with carbonyl compounds* a. *primary alcohols from methanal (formaldehyde)* cyclohexylmagnesium chloride + $CH_2{=}O$ (methanal) $\xrightarrow{H^\oplus}$ cyclohexylcarbinol, 69%	See Section 14-12A. Methanal and RMgX give primary alcohols.

b. *secondary alcohols from aldehydes*



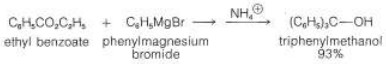
2-methylpropanal — 3-methyl-2-butanol, 56%

c. *tertiary alcohols from ketones*



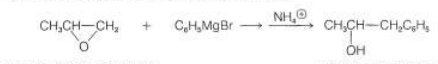
cyclopropylethanone — 2-cyclopropyl-2-propanol, 68%

d. *tertiary alcohols from esters, acid halides, and anhydrides*



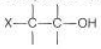
ethyl benzoate — phenylmagnesium bromide — triphenylmethanol, 93%

4. *Reaction of Grignard reagents with cyclic ethers*

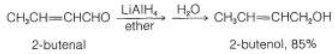


2-methyloxacyclopropane (2-methyloxirane) — 1-phenyl-2-propanol, 60%

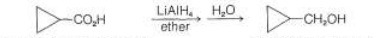
Limited to three- and four-membered rings. Reaction is an S_N2-type displacement (Section 14-12A). Oxacyclopropanes often are used as a means of increasing chain length by two carbons in one step. A major side product is a haloalcohol,



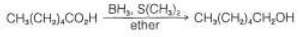
5. *Reduction of carbonyl compounds with metal hydrides or boranes*
a. *primary alcohols from aldehydes, acids, acid halides, and esters*



2-butenal — 2-butenol, 85%

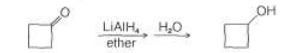


cyclopropanecarboxylic acid — cyclopropylmethanol, 77%



hexanoic acid — 1-hexanol, 100%

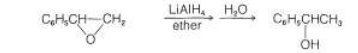
b. *secondary alcohols from ketones*



cyclobutanone — cyclobutanol, 90%

Excellent results are obtained with $LiAlH_4$ (see Section 16-4E), which is fairly selective and normally does not reduce C=C. Sodium borohydride, $NaBH_4$, is more selective and does not reduce carbonyl groups of acids and derivatives; it also may be used in aqueous and alcoholic solution, whereas $LiAlH_4$ may not. Borane (BH_3) in oxacyclopentane readily reduces aldehydes and acids to primary alcohols (Section 16-4E).

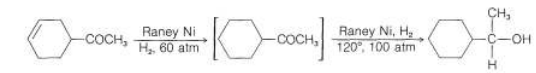
6. *Reduction of cyclic ethers with metal hydrides*



2-phenyloxacyclopropane (2-phenyloxirane) — 1-phenylethanol

Most used in the case of oxacyclopropanes. Orientation is such that $H:^{\ominus}$ from $LiAlH_4$ attacks *least*-hindered position. In the presence of $AlCl_3$, 2-phenylethanol is formed.

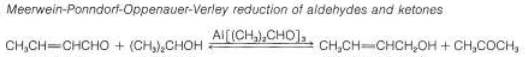
7. *Catalytic hydrogenation of carbonyl compounds*



3-cyclohexenylethanone — 1-cyclohexylethanol, 96%

Catalytic reduction is nonselective and reduces (see Section 11-2B and compare with method 5).

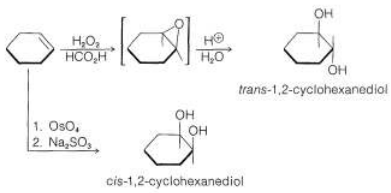
8. *Meerwein-Ponndorf-Oppenauer-Verley reduction of aldehydes and ketones*



2-butenal — 2-propanol — 2-buten-1-ol, 60%

See Section 16-4E. Reducing agent is usually aluminum isopropoxide; 2-propanone is formed and is removed by distillation, which shifts equilibrium to right. Carbon–carbon double bonds are unaffected.

9. *1,2-Glycols from alkenes*



An epoxide is formed from alkene and peroxymethanoic acid ($H_2O_2 + HCO_2H$) but is cleaved by the HCO_2H present to a *trans*-diol. Alternatively, osmium tetroxide may be used in *tert*-butyl alcohol and leads to the *cis*-diol. Potassium permanganate in neutral can be useful for preparation of *cis*-glycols. (See Section 11-7D.)

10. *Hydrolysis of alkyl and allylic halides*

See Sections 8-4 to 8-7.

11. *Hydrolysis of esters*

Of limited use because the ester often is prepared from the alcohol.

12. *Aldol condensation*

Gives β-hydroxy carbonyl compounds (see Section 17-3A).

13. *Cleavage of ethers*

See Section 15-10 and Exercise 15-40.

In Methods 3a to 3d, enolization of carbonyl compound and reduction of RMgX are side reactions that become important for hindered ketones and bulky Grignard reagents (Section 14-12A). Ammonium chloride is used to hydrolyze the reaction mixtures in preparation of tertiary alcohols to avoid dehydration. Organolithium compounds are superior to RMgX for preparation of bulky tertiary alcohols.

The industrial synthesis of methyl alcohol involves hydrogenation of carbon monoxide. Although this reaction has the favorable ΔH^0 value of $-28.4\ \text{kcal mol}^{-1}$, it requires high pressures and high temperatures and a suitable catalyst; excellent conversions are achieved using zinc oxide-chromic oxide as a catalyst:

$$CO + 2H_2 \xrightarrow[ZnO\text{–}CrO_3]{400^\circ,\ 200\ atm} CH_3OH$$

Various methods of synthesis of other alcohols by reduction of carbonyl compounds will be discussed in Section 16-4E.

15.4.1: Contributors and Attributions

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15.5: Chemical Reactions of Alcohols. Reactions Involving the O-H Bond

15.5.1: Acidic Properties

Several important chemical reactions of alcohols involve only the oxygen-hydrogen bond and leave the carbon-oxygen bond intact. An important example is salt formation with acids and bases. Alcohols, like water, are both weak bases and weak acids. The acid ionization constant (K_a) of ethanol is about 10^{-18}, slightly less than that of water. Ethanol can be converted to its conjugate base by the conjugate base of a weaker acid such as ammonia $\left(K_a \sim 10^{-35}\right)$, or hydrogen $\left(K_a \sim 10^{-38}\right)$. It is convenient to employ sodium metal or sodium hydride, which react vigorously but controllably with alcohols:

$$C_2H_5OH + Na^{\oplus}NH_2^{\ominus} \rightleftharpoons C_2H_5O^{\ominus}Na^{\oplus} + NH_3$$

sodium amide (sodamide) — sodium ethoxide

$$2C_2H_5OH + 2Na \longrightarrow 2C_2H_5O^{\ominus}Na^{\oplus} + H_2$$

$$C_2H_5OH + Na^{\oplus}H^{\ominus} \longrightarrow C_2H_5O^{\ominus}Na^{\oplus} + H_2$$

The order of acidity of various liquid alcohols generally is water > *primary* > *secondary* |(>\) *tertiary* ROH. By this we mean that the equilibrium position for the proton-transfer reaction (Equation 15-1) lies more on the side of ROH and $OH^{\ominus}$ as R is changed from *primary* to *secondary* to *tertiary*; therefore, *tert*-butyl alcohol is considered less acidic than ethanol:

$$ROH + OH^{\ominus} \rightleftharpoons RO^{\ominus} + HOH \tag{15-1}$$

However, in the gas phase the order of acidity is reversed, and the equilibrium position for Equation 15-1 lies increasingly on the side of $RO^{\ominus}$ as R is changed from *primary* to *secondary* to *tertiary*. *tert*-Butyl alcohol is therefore *more* acidic than ethanol in the gas phase. This seeming contradiction appears more reasonable when one considers what effect solvation (or the lack of it) has on equilibria expressed by Equation 15-1. In solution, the larger anions of alcohols, known as **alkoxide ions**, probably are less well solvated than the smaller ions, because fewer solvent molecules can be accommodated around the negatively charged oxygen in the larger ions:

$CH_3O^{\ominus}$ methoxide — $C_2H_5O^{\ominus}$ ethoxide — $(CH_3)_2CHO^{\ominus}$ isopropoxide — $(CH_3)_3CO^{\ominus}$ *tert*-butoxide

Acidity of alcohols therefore decreases as the size of the conjugate base increases. However, “naked” gaseous ions are more stable the larger the associated R groups, probably because the larger R groups can stabilize the charge on the oxygen atom better than the smaller R groups. They do this by polarization of their bonding electrons, and the bigger the group, the more polarizable it is. (Also see Section 11-8A, which deals with the somewhat similar situation encountered with respect to the relative acidities of ethyne and water.)

15.5.2: Basic Properties

Alcohols are bases similar in strength to water and accept protons from strong acids. An example is the reaction of methanol with hydrogen bromide to give methyloxonium bromide, which is analogous to the formation of hydroxonium bromide with hydrogen bromide and water:

$$CH_3\ddot{O}H + HBr \rightleftharpoons CH_3\overset{H}{\underset{\cdot\cdot}{\ddot{O}}}H^{\oplus} + Br^{\ominus}$$

methyloxonium bromide

$$H\ddot{O}H + HBr \rightleftharpoons H\overset{H}{\underset{\cdot\cdot}{\ddot{O}}}H^{\oplus} + Br^{\ominus}$$

hydroxonium bromide

Figure 15-4). The melting point reaches a maximum at 50-50 mole percent of each component.

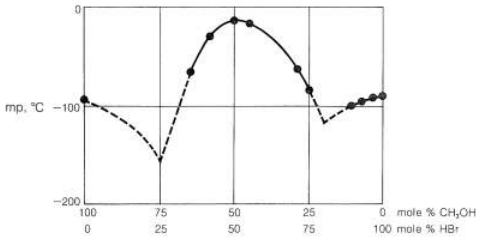


Figure 15-4: Melting points of mixtures of methanol and hydrogen bromide

15.5.3: Nucleophilic Properties - Ether Formation

Alkoxide ion formation is important as a means of generating a strong nucleophile that will readily form C–O bonds in S_N2 reactions. Thus ethanol reacts very slowly with methyl iodide to give methyl ethyl ether, but sodium ethoxide in ethanol solution reacts quite rapidly:

$$CH_3I + C_2H_5OH \xrightleftharpoons{\text{slow}} CH_3OC_2H_5 + HI$$

$$CH_3I + C_2H_5O^{\ominus}Na^{\oplus} \xrightarrow{\text{fast}} CH_3OC_2H_5 + \overset{\oplus}{N}a\overset{\ominus}{I}$$

In fact, the reaction of alkoxides with alkyl halides or alkyl sulfates is an important general method for the preparation of ethers, and is known as the **Williamson synthesis**. Complications can occur because the increase of nucleophilicity associated with the conversion of an alcohol to an alkoxide ion always is accompanied by an even greater increase in eliminating power by the $E2$ mechanism. The reaction of an alkyl halide with alkoxide then may be one of elimination rather than substitution, depending on the temperature, the structure of the halide, and the alkoxide (Section 8-8). For example, if we wish to prepare isopropyl methyl ether, better yields would be obtained if we were to use methyl iodide and isopropoxide ion rather than isopropyl iodide and methoxide ion because of the prevalence of $E2$ elimination with the latter combination:

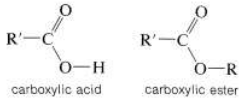
$$CH_3I + (CH_3)_2CHO^{\ominus} \xrightarrow{S_N2} (CH_3)_2CHOCH_3 + I^{\ominus}$$

$$(CH_3)_2CHI + CH_3O^{\ominus} \xrightarrow{E2} CH_3CH{=}CH_2 + CH_3OH + I^{\ominus}$$

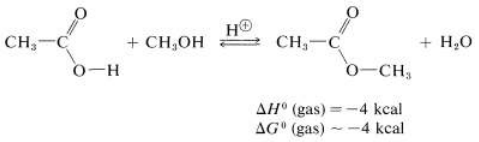
Potassium *tert*-butoxide is an excellent reagent to achieve $E2$ elimination because it is strongly basic and so bulky as to not undergo S_N2 reactions readily.

15.5.4: Nucleophilic Properties. Ester Formation

An ester may be thought of as a carboxylic acid in which the acidic proton has been replaced by some organic group, R,

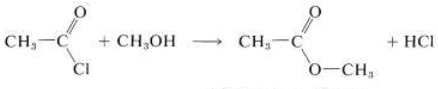


Esters can be prepared from carboxylic acids and alcohols provided an acidic catalyst is present,

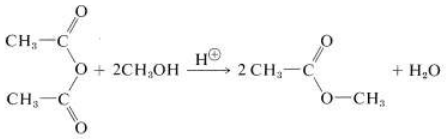


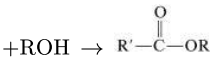
ΔH^0 (gas) = −4 kcal
ΔG^0 (gas) ~ −4 kcal

or they can be prepared from acyl halides and alcohols or carboxylic anhydrides and alcohols:



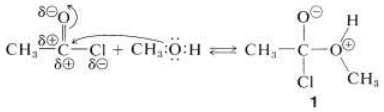
ΔH^0 (gas) = −14 kcal
ΔG^0 (gas) = −14 kcal

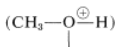


These reactions generally can be expressed by the equation  which overall is a nucleophilic displacement of the X group by the nucleophile ROH. However, the mechanism of displacement is quite different from the S_N2 displacements of alkyl derivatives, $R'X + ROH \rightarrow R'OR + HX$, and closely resembles the nucleophilic displacements of activated aryl halides (Section 14-6B) in being an *addition-elimination* process.

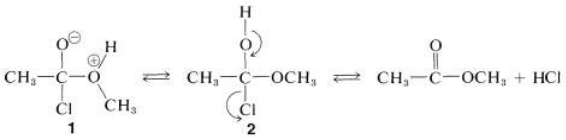
Acyl halides have a rather positive carbonyl carbon because of the polarization of the carbon-oxygen and carbon-halogen bonds. Addition of a nucleophilic group such as the oxygen of an alcohol occurs rather easily.

addition



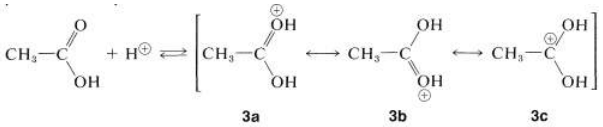
The complex 1 contains both an acidic group  and a basic group , so that a proton shifts from one oxygen to the other to give 2, which then rapidly loses hydrogen chloride by either an $E1$- or $E2$-type elimination to form the ester.

elimination

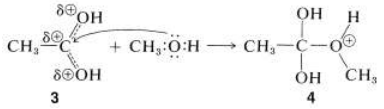


A similar but easily reversible reaction occurs between alcohols and carboxylic acids, which is slow in either direction in the absence of a strong mineral acid. The catalytic effect of acids, such as H_2SO_4, HCl, and H_3PO_4 is produced by protonation of the carbonyl oxygen of the carboxylic acid, thereby giving 3. This protonation greatly enhances the affinity of the carbonyl carbon for an electron pair on the oxygen of the alcohol (i.e., 3 → 4).

protonation step



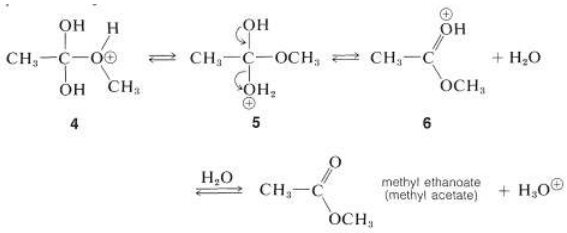
addition step



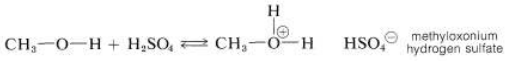
Subsequently, a proton is transferred from the OCH_3 to an OH group of 4 to give 5. This process converts the OH into a good leaving group (H_2O). When H_2O leaves, the product, 6, is the conjugate acid of the ester. Transfer of a proton from 6 to a base such

as H_2O or HSO_4^- completes the reaction, giving the neutral ester and regenerating the acid catalyst.

proton transfer and elimination



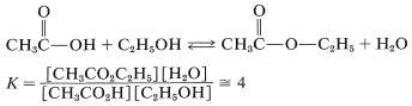
Although a small amount of strong acid catalyst is essential in the preparation of esters from acids and alcohols, the amount of acid catalyst added must not be too large. The reason for the "too much of a good thing" behavior of the catalyst can be understood from the basic properties of alcohols (Section 15-4B). If too much acid is present, then too much of the alcohol is converted to the oxonium salt:



Clearly, formation of the methyloxonium ion can operate only to *reduce* the nucleophilic reactivity of methanol toward the carbonyl carbon of the carboxylic acid.

Another practical limitation of esterification reactions is *steric hindrance*. If either the acid or the alcohol participants possesses highly branched groups, the positions of equilibrium are less favorable and the rates of esterification are slow. In general, the ease of esterification for alcohols, ROH, by the mechanism described is *primary* R > *secondary* R > *tertiary* R with a given carboxylic acid.

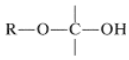
As mentioned, esterification is reversible, and with ethanol and ethanoic acid the equilibrium constant for the liquid phase is about 4 ($\Delta G^0 = -0.8$ kcal) at room temperature, which corresponds to 66% conversion to ester:



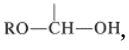
The reaction may be driven to completion by removing the ester or water or both as they are formed.

15.5.5: Nucleophilic Properties - Hemiacetal, Hemiketal, and Acetal Formation

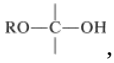
The structural unit,



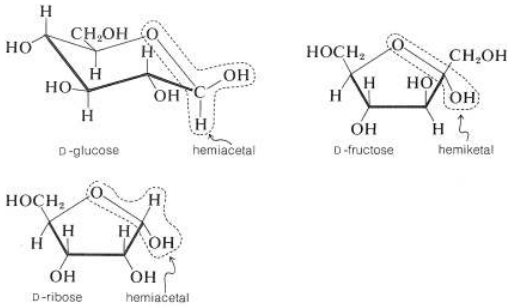
possesses both an alkoxyl (OR) and a hydroxyl (OH) group on the *same* carbon. This arrangement, although often unstable, is an important feature of carbohydrates such as glucose, fructose, and ribose. When the grouping is of the type



it is called a **hemiacetal**, and if it is



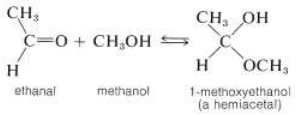
with no hydrogen attached to the carbon, it is called a **hemiketal**:



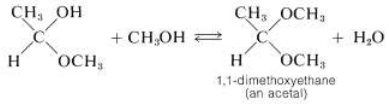
Each of these compounds has several other hydroxyl groups, but only one of them is a hemiacetal or hemiketal hydroxyl. Be sure you can identify which one.

The **acetal function** has two alkoxy (OR) groups and a hydrogen on the same carbon, $\mathrm{RO{-}\overset{\displaystyle H}{\overset{|}{C}}{-}OR}$, whereas the ketal function has the same structure but with no hydrogen on the carbon. These groupings also are found in carbohydrates and in carbohydrate derivatives, and are called **glycosido functions** (see Chapter 20).

For our present purposes, we are interested in the ways in which hemiacetals, acetals, hemiketals, and ketals are formed. Hemiacetals and hemiketals can be regarded as products of the addition of alcohols to the carbonyl groups of aldehydes and ketones. Thus methanol adds to ethanal to give a hemiacetal, 1 -methoxyethanol:

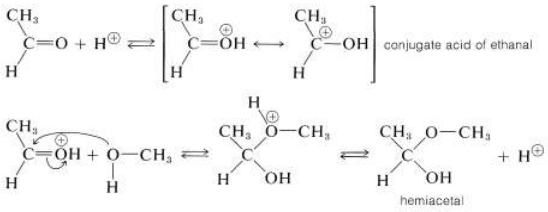


Acetals and ketals result from substitution of an alkoxy group for the OH group of a hemiacetal or hemiketal. Thus methanol can react with 1-methoxyethanol to form the acetal, 1,1-dimethoxyethane, and water:



The reactions of alcohols with aldehydes and ketones are related to the reactions of alcohols with acids (esterification) discussed in the preceding section. Both types involve addition of alcohols to carbonyl groups, and both are acid-catalyzed.

Acid catalysis of $\mathrm{RO{-}\overset{\displaystyle H}{\overset{|}{C}}{-}OH}$ formation, like ester formation, depends on formation of the conjugate acid of the carbonyl compound. This is expected to enhance the positive (electrophilic) character of the carbonyl carbon so that the nucleophilic alcohol can add readily to it:



The hemiacetal can react further, also with the aid of an acidic catalyst. Addition of a proton can occur in two ways, to give 7 or 8:

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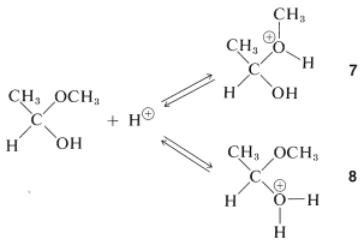
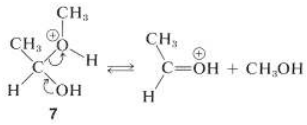
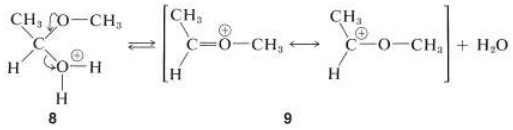


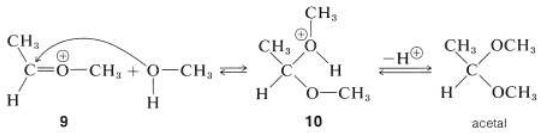
The first of these, 7, has CH_3OH as a leaving group and reverts back to the conjugate acid of ethanal. This is the reverse of acid-catalyzed hemiacetal formation:



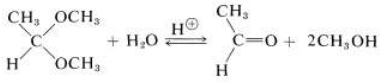
The second of these,8, has H_2O as a leaving group and can form a new entity, the methoxyethyl cation, 9:



The ion 9 resembles $CH_3CH{=}\overset{\oplus}{O}H$ and can be expected to behave similarly by adding a second molecule of alcohol to the electrophilic carbon. The product, 10, is then the conjugate acid of the acetal and loses a proton to give the acetal:



Formation of hemiacetals and acetals, as well as of hemiketals and ketals, is reversible under acidic conditions, as we already have noted for acid-catalyzed esterification. The reverse reaction is *hydrolysis* and the equilibrium for this reaction can be made favorable by having an excess of water present:



The position of equilibrium in acetal and hemiacetal formation is rather sensitive to steric hindrance. Large groups in either the aldehyde or the alcohol tend to make the reaction less favorable. Table 15-3 shows some typical conversions in acetal formation when 1 mole of aldehyde is allowed to come to equilibrium with 5 moles of alcohol. For ketones, the equilibria are still less favorable than for aldehydes, and to obtain reasonable conversion the water must be removed as it is formed.

Table 15-3: Conversion of Aldehydes to Acetals with Various Alcohols (1 Mole of Aldehyde to 5 Moles of Alcohol)

	Percent Conversion to Acetal			
Aldehyde	Ethanol	Cycloehexane	2-Propoanol	tert-Butyl Alcohol
CH_3CHO	78%	56%	43%	23%
$(CH_3)_2CHCHO$	71%	-	23%	-
$(CH_3)_3CCHO$	56%	16%	11%	-
C_6H_5CHO	39%	235	13%	-

15.5.6: Contributors and Attributions

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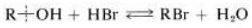
15.6: Reactions Involving the C-O Bond of Alcohols

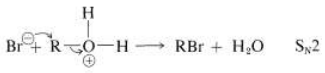
15.6.1: Electrophilic Properties of Alcohols

Alkyl halide formation from an alcohol and a hydrogen halide affords an important example of a reaction wherein the C–O bond of the alcohol is broken:

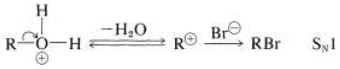


The reaction is reversible and the favored direction depends on the water concentration. Primary bromides often are prepared best by passing dry hydrogen bromide into the alcohol heated to just slightly below its boiling point.

Halide formation proceeds at a useful rate only in the presence of strong acid, which can be furnished by excess hydrogen bromide or, usually and more economically, by sulfuric acid. The alcohol accepts a proton from the acid to give an alkyloxonium ion, which is more reactive in subsequent displacement with bromide ion than the alcohol (by either S_N2 or S_N1 mechanisms) because H_2O is a better leaving group than $OH^{\ominus}$:

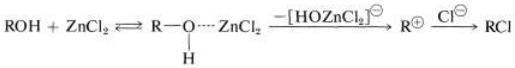


or

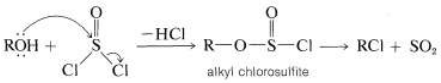


Whether the displacement reaction is an S_N1 or S_N2 process depends on the structure of the alcohol. In general, the primary alcohols are considered to react by S_N2 and the secondary and tertiary alcohols by S_N1 mechanisms.

Hydrogen chloride is less reactive than hydrogen bromide toward primary alcohols, and a catalyst (zinc chloride) may be required. A solution of zinc chloride in concentrated hydrochloric acid (Lucas reagent) is a convenient reagent to differentiate between primary, secondary, and tertiary alcohols with less than eight or so carbons. Tertiary alcohols react very rapidly to give an insoluble layer of alkyl chloride at room temperature. Secondary alcohols react in several minutes, whereas primary alcohols form chlorides only on heating. The order of reactivity is typical of S_N1 reactions. Zinc chloride probably assists in the breaking of the C–O bond of the alcohol much as silver ion aids ionization of RCl (Section 8-7D):

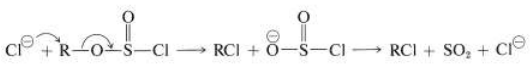


Thionyl chloride, $O{=}SCl_2$, is useful for the preparation of alkyl chlorides, especially when the use of strongly acidic reagents, such as zinc chloride and hydrochloric acid, is undesirable. Thionyl chloride can be regarded as the acid chloride of sulfurous acid, $O{=}S(OH)_2$, and like most acid chlorides the halogen is displaced readily by alcohols. Addition of 1 mole of an alcohol to 1 mole of thionyl chloride gives an unstable alkyl chlorosulfite, which generally decomposes on mild heating to yield the alkyl chloride and sulfur dioxide:

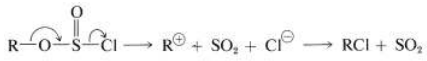


Chlorides can be prepared in this way from primary and secondary, but not tertiary, alcohols. In practice, an equivalent of a weak base, such as pyridine (azabenzene), is added to neutralize the hydrogen chloride that is formed. If the acid is not removed, undesirable degradation, elimination, and rearrangement reactions may occur.

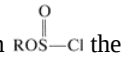
The thionyl chloride reaction apparently can proceed from the alkyl chlorosulfite stage by more than one mechanism: an ionic S_N2 chain reaction with chloride ion,



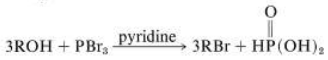
or an S_N1-like ionization and collapse of the resulting $R^{\oplus}Cl^{\ominus}$ ion pair to give RCl:



or

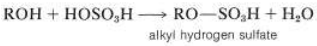
Obviously, the greater the S_N2 reactivity associated with  the better the S_N2 reaction will go and, conversely, if $R^{\oplus}$ is formed easily from the S_N1 reaction is likely to be favored.

Other halides that are useful in converting alcohols to alkyl halides are PCl_5, PCl_3, PBr_3, and PI_3, which are acid halides of phosphorus oxyacids. As with thionyl chloride, a weak base often is used to facilitate the reaction. The base acts to neutralize the acid formed, and also to generate bromide ion for S_N reactions:

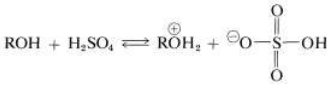


15.6.2: Sulfate and Sulfonate Esters

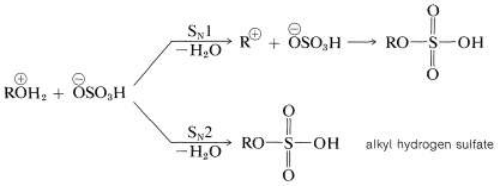
It is possible to prefer esters of sulfuric acid by the reaction of an alcohol with the acid:



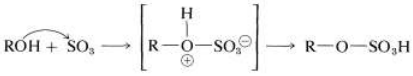
The reaction is closely related to alkyl halide formation under strongly acidic conditions, whereby conversion of the alcohol to an oxonium salt is a first step:



Conversion of the oxonium hydrogen sulfate to the ester probably proceeds by an S_N2 mechanism with primary alcohols and an S_N1 mechanism with tertiary alcohols:



An alternative mechanism, which operates either in 100%, or in fuming sulfuric acid (which contains dissolved SO_3), is addition of sulfur trioxide to the OH group:



The sodium salts of alkyl hydrogen sulfate esters have useful properties as detergents if the alkyl group is large, C_{12} or so:

The mechanism of detergent action will be considered in more detail in Chapter 18.

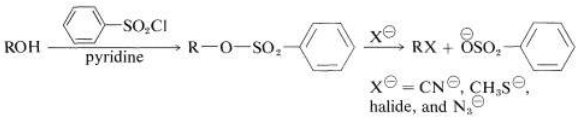
In principle, dialkyl sulfates could be formed by an S_N2 reaction between an alkyloxonium salt and an alkyl sulfate ion:

Indeed, if methanol is heated with fuming sulfuric acid, dimethyl sulfate, $CH_3O(SO_2)OCH_3$, is obtained; but other alcohols are better converted to dialkyl sulfates by oxidation of the corresponding dialkyl *sulfites* formed by the reaction of 1 mole of thionyl chloride $(SOCl_2)$ with 2 moles of the alcohol:

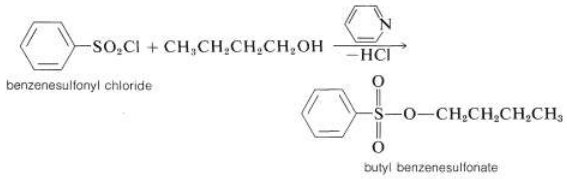
The reason that dialkyl sulfates seldom are prepared by direct reaction of the alcohol with H_2SO_4 is that the mono esters react rapidly on heating to eliminate sulfuric acid and form alkenes, as explained in Section 15-5C.

Sulfonic acids, $R{-}SO_2{-}OH$ or $Ar{-}SO_2{-}OH$, are oxyacids of sulfur that resemble sulfuric acid, $HO{-}SO_2{-}OH$, but in which sulfur is in a lower oxidation state.

Sulfonate esters are useful intermediates in displacement reactions (Section 8-7C) and provide a route for the conversion of an alcohol, ROH, to RX by the sequence:

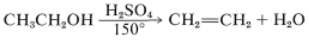


Sulfonate esters usually are prepared through treatment of the alcohol with the acid chloride (sulfonyl chloride) in the presence of pyridine (azabenzene):

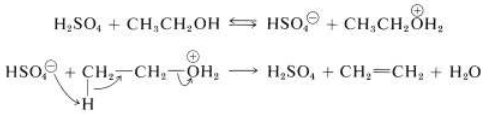


15.6.3: Dehydration of Alcohols with Strong Acids

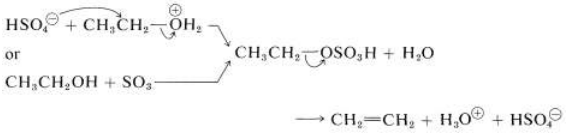
In the reaction of an alcohol with hot concentrated sulfuric acid, the alcohol is dehydrated to an alkene:



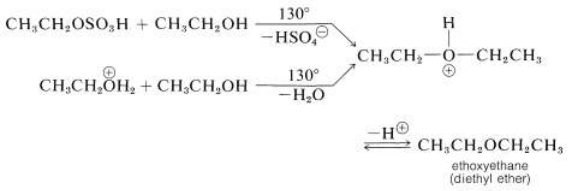
This is the reverse of acid-catalyzed hydration of alkenes discussed previously (Section 10-3E) and goes to completion if the alkene is allowed to distill out of the reaction mixture as it is formed. One mechanism of dehydration involves proton transfer from sulfuric acid to the alcohol, followed by an *E*2 reaction of hydrogen sulfate ion or water with the oxonium salt of the alcohol:



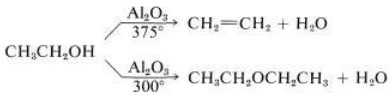
Alternatively, the alkyl hydrogen sulfate could be formed and eliminate sulfuric acid by an *E*2 reaction:



At lower temperatures the oxonium salt or the alkyl hydrogen sulfate may react by an S_N displacement mechanism with excess alcohol in the reaction mixture, thereby forming a dialkyl ether. Although each step in the reaction is reversible, ether formation can be enhanced by distilling away the ether as fast as it forms. Diethyl ether is made commercially by this process:

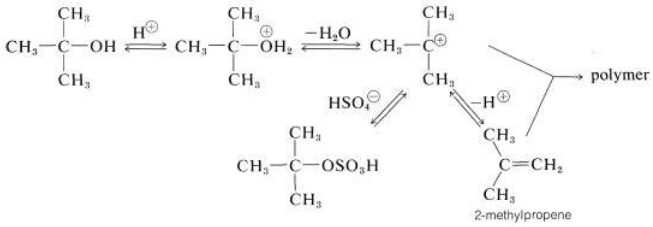


Most alcohols also will dehydrate at fairly high temperatures in the presence of solid catalysts such as silica gel or aluminum oxide to give alkenes or ethers. The behavior of ethanol is reasonably typical of primary alcohols and is summarized in the following equations:



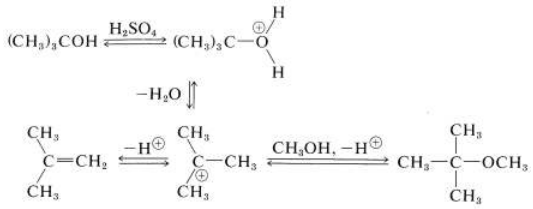
15.6.4: C—O Bond Cleavage of Tertiary Alcohols

Tertiary alcohols react with sulfuric acid at much lower temperatures than do most primary or secondary alcohols. The reactions typically are S_N1 and $E1$ by way of a tertiary carbocation, as shown here for *tert*-butyl alcohol and sulfuric acid:



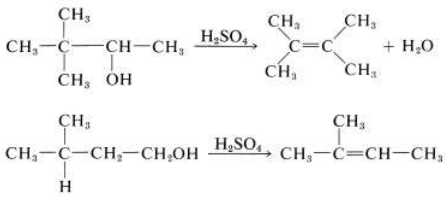
2-Methylpropene can be removed from the reaction mixture by distillation and easily is made the principal product by appropriate adjustment of the reaction conditions. If the 2-methylpropene is not removed as it is formed, polymer and oxidation products become important. Sulfuric acid often is an unduly strenuous reagent for dehydration of tertiary alcohols. Potassium hydrogen sulfate, copper sulfate, iodine, phosphoric acid, or phosphorus pentoxide may give better results by causing less polymerization and less oxidative degradation which, with sulfuric acid, results in the formation of sulfur dioxide.

The S_N1-$E1$ behavior of tertiary alcohols in strong acids can be used to advantage in the preparation of *tert*-butyl ethers. If, for example, a mixture of *tert*-butyl alcohol and methanol is heated in the presence of sulfuric acid, the tertiary alcohol reacts rapidly *but reversibly* to produce 2-methylpropene by way of the *tert*-butyl cation. This cation can be trapped by the methanol to form *tert*-butyl methyl ether. High yields of ethers can be obtained in this way:

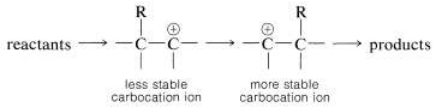


15.6.5: Carbocation Rearrangements

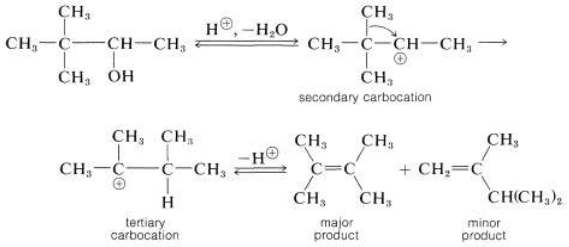
Rearrangement of the alkyl groups of alcohols is very common in dehydration, particularly in the presence of strong acids, which are conducive to carbocation formation. Typical examples showing both methyl and hydrogen migration follow:



The key step in each such rearrangement is isomerization of a carbocation, as discussed in Section 8-9B. Under kinetic control, the final products always correspond to rearrangement of a less stable carbocation to a more stable carbocation. (Thermodynamic control may lead to quite different results, Section 10-4A.)

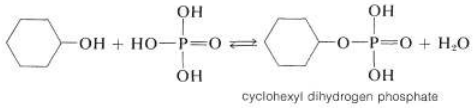


In the dehydration of 3,3-dimethyl-2-butanol, a secondary carbocation is formed initially, which rearranges to a tertiary carbocation when a neighboring methyl group *with* its bonding electron pair migrates to the positive carbon. The charge is thereby transferred to the tertiary carbon:

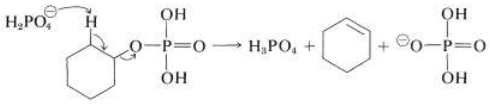


15.6.6: Phosphate Esters

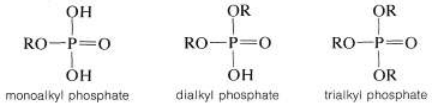
Phosphoric acid (H_3PO_4) often is used in place of sulfuric acid to dehydrate alcohols. This is because phosphoric acid is less destructive; it is both a weaker acid and a less powerful oxidizing agent than sulfuric acid. Dehydration probably proceeds by mechanisms similar to those described for sulfuric acid (Section 15-5C) and very likely through intermediate formation of a *phosphate ester*:



The ester can eliminate H_3PO_4, as sulfate esters eliminate H_2SO_4, to give alkenes:



The chemistry of phosphate esters is more complicated than that of sulfate esters because it is possible to have one, two, or three alkyl groups substituted for the acidic hydrogens of phosphoric acid:



Also, phosphoric acid forms an extensive series of anhydrides (with P–O–P bonds), which further diversify the number and kind of phosphate esters. The most important phosphate esters are derivatives of mono-, di-, and triphosphoric acid (sometimes classified as ortho-, pyro-, and meta-phosphoric acids, respectively):

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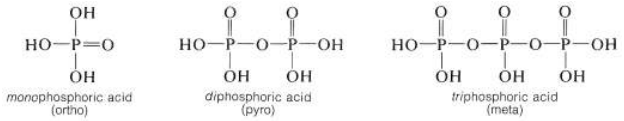
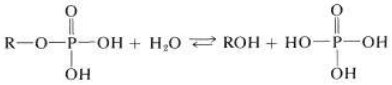
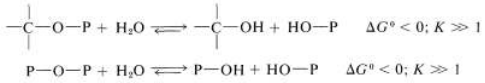


The equilibrium between the esters of any of these phosphoric acids and water favors hydrolysis:

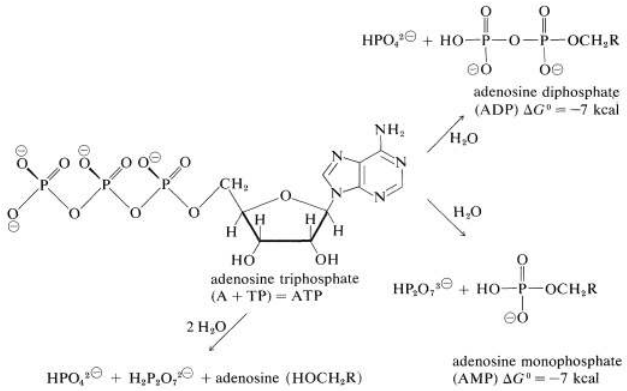


However, phosphate esters are *slow* to hydrolyze in water (unless a catalyst is present). The difference in kinetic and thermodynamic stability of phosphate esters toward hydrolysis is used to great effect in biological systems.

Of particular importance is the conversion of much of the energy that results from photosynthesis, or from the oxidation of fats, carbohydrates, and proteins in cells into formation of phosphate ester bonds $(C{-}O{-}P)$ or phosphate anhydride bonds $(P{-}O{-}P)$. The energy so stored is used in other reactions, the net result of which is hydrolysis:

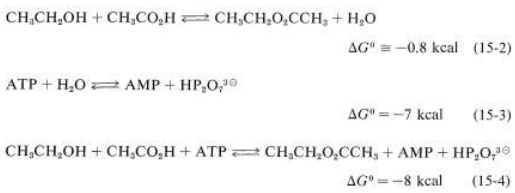


The substance that is the immediate source of energy for many biological reactions is adenosine triphosphate (ATP). Although this is a rather large and complex molecule, the business end for the purpose of this discussion is the *triphosphate* group. Hydrolysis of this group can occur to give adenosine diphosphate (ADP), adenosine monophosphate (AMP), or adenosine itself:

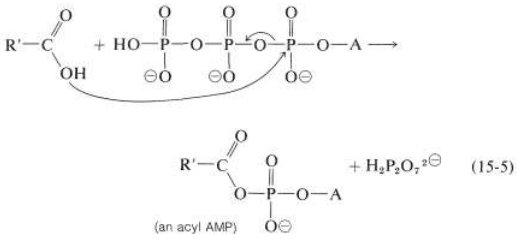


(The phosphate groups are repesented here as the major ionized form present at pH $\cong 7$ in solutions of ATP.)

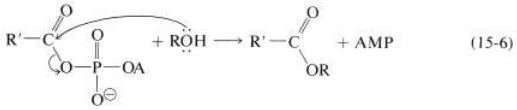
All of these hydrolysis reactions are energetically favorable $(\Delta G^0 < 0)$, but they do not occur directly because ATP reacts slowly with water. However, hydrolysis of ATP is the indirect result of other reactions in which it participates. For example, as we showed in Section 15-4D, equilibrium for the direct formation of an ester from a carboxylic acid and an alcohol in the liquid phase is not very favorable (Equation 15-2). However, if esterification can be coupled with ATP hydrolysis (Equation 15-3), the overall reaction (Equation 15-4) becomes much more favorable thermodynamically than is direct esterification.



The ATP hydrolysis could be coupled to esterification (or other reactions) in a number of ways. The simplest would be to have the ATP convert one of the participants to a more reactive intermediate. For esterification, the reactive intermediate is an acyl derivative of AMP formed by the displacement of diphosphate from ATP:



The acyl AMP is like an acyl chloride, $RCOCl$, in having a leaving group (AMP) that can be displaced with an alcohol:



The net result of the sequence in Equations 15-5 and 15-6 is esterification in accord with Equation 15-4. It is not a catalyzed esterification because in the process one molecule of ATP is converted to AMP and diphosphate for each molecule of ester formed. The AMP has to be reconverted to ATP to participate again. These reactions are carried on by cells under the catalytic influence of enzymes. The adenosine part of the molecule is critical for the specificity of action by these enzymes. Just how these enzymes function obviously is of great interest and importance.

If the role of phosphate esters, such as ATP, in carrying out reactions such as esterification in aqueous media under the influence of enzymes in cells is not clear to you, think about how you would try to carry out an esterification of ethanol in dilute water solution. Remember that, with water in great excess, the equilibrium will be quite unfavorable for the esterification reaction of Equation 15-2. You might consider adding CH_3COCl, for which the equilibrium for ester formation is much more favorable (Section 15-4D). However, CH_3COCl reacts violently with water to form CH_3CO_2H, and this reaction destroys the CH_3COCl before it has much chance to react with ethanol to give the ester. Clearly, what you would need is a reagent that will convert CH_3CO_2H into something that will react with ethanol in water to give the ester with a favorable equilibrium constant and yet not react very fast with water. The phosphate esters provide this function in biochemical systems by being quite unreactive to water but able to react with carboxylic acids under the influence of enzymes to give acyl phosphates. These acyl phosphates then can react with alcohols under the influence of other enzymes to form esters in the presence of water.

15.6.7: Contributors and Attributions

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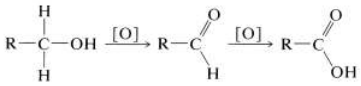
15.7: Oxidation of Alcohols

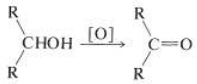
According to the scale of oxidation levels established for carbon (see Table 11-1), primary alcohols (RCH_2OH) are at a lower oxidation level than either aldehydes $(RCHO)$ or carboxylic acids (RCO_2H). With suitable oxidizing agents, primary alcohols in fact can be oxidized first to aldehydes and then to carboxylic acids.

primary alcohols

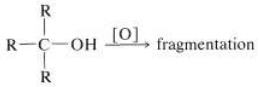


Unlike the reactions discussed previously in this chapter, oxidation of alcohols involves the alkyl portion of the molecule, or more specifically, the $C-H$ bonds of the hydroxyl-bearing carbon (the α carbon). Secondary alcohols, which have only one such $C-H$ bond, are oxidized to ketones, whereas tertiary alcohols, which have no $C-H$ bonds to the hydroxylic carbon, are oxidized only with accompanying degradation into smaller fragments by cleavage of carbon-carbon bonds.

secondary alcohols



tertiary alcohols



15.7.1: Industrial Oxidation of Alcohols

Conversion of ethanol to ethanal is carried out on a commercial scale by passing gaseous ethanol over a copper catalyst at 300°:

$$CH_3CH_2OH \xrightarrow[300^{\circ}]{Cu} CH_3CH{=}O + H_2 \qquad \Delta H^{\circ}(25^{\circ}) = +15 \text{ kcal}$$

At room temperature this reaction is endothermic with an equilibrium constant of about 10^{22}. At 300° conversions of 20%-50% per pass can be realized and, by recycling the unreacted alcohol, the yield can be greater than 90%.

Another commercial process uses a silver catalyst and oxygen to combine with the hydrogen, which makes the net reaction substantially exothermic:

$$CH_3CH_2OH + \tfrac{1}{2}O_2 \xrightarrow{Ag} CH_3CH{=}O + H_2O \qquad \Delta H^{\circ} = -43 \text{ kcal}$$

In effect, this is a partial combustion reaction and requires very careful control to prevent overoxidation. In fact, by modifying the reaction conditions (alcohol-to-oxygen ratio, temperature, pressure, and reaction time), the oxidation proceeds smoothly to ethanoic acid:

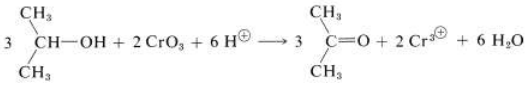
$$CH_3CH_2OH + O_2 \xrightarrow[550^{\circ}]{Ag} CH_3CO_2H + H_2O$$

Reactions of this type are particularly suitable as industrial processes because they generally can be run in continuous-flow reactors, and can utilize a cheap oxidizing agent, usually supplied directly as air.

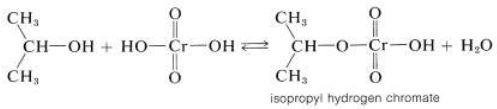
15.7.2: Oxidation of Alcohols

15.7.2.1: Chromic Acid Oxidation

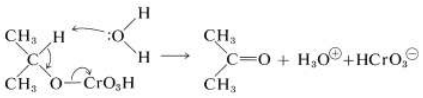
Laboratory oxidation of alcohols most often is carried out with chromic acid (H_2CrO_4), which usually is prepared as required from chromic oxide (CrO_3) or from sodium dichromate $(Na_2Cr_2O_7)$ in combination with sulfuric acid. Ethanoic (acetic) acid is a useful solvent for such reactions:



The mechanism of the chromic acid oxidation of 2-propanol to 2-propanone (acetone) has been investigated very thoroughly. It is a highly interesting reaction in that it reveals how changes of oxidation state can occur in a reaction involving a typical inorganic and a typical organic compound. The initial step is reversible formation of an isopropyl ester of chromic acid. This ester is unstable and is not isolated:

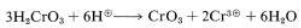


The subsequent step is the slowest in the sequence and appears to involve attack of a base (water) at the alpha hydrogen of the chromate ester concurrent with elimination of the $HCrO_3^-$ group. There is an obvious analogy between this step and an $E2$ reaction (Section 8-8A):

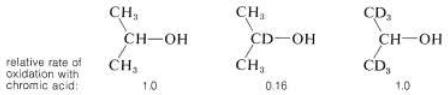


The transformation of chromic acid (H_2CrO_4) to H_2CrO_3 amounts to the reduction of chromium from an oxidation state of $+6$ to $+4$. Disproportionation of Cr(IV) occurs rapidly to give compounds of Cr(III) and Cr(VI):

or



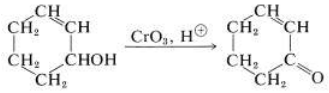
The $E2$ character of the ketone-forming step has been demonstrated in two ways. First, the rate of decomposition of isopropyl hydrogen chromate to 2-propanone and H_2CrO_3 is strongly accelerated by efficient proton-removing substances. Second, the hydrogen on the α carbon clearly is removed in a slow reaction because *the overall oxidation rate is diminished sevenfold by having a deuterium in place of the α hydrogen*. No significant slowing of oxidation is noted for 2-propanol having deuterium in the methyl groups:



Carbon-deuterium bonds normally are broken more slowly than carbon-hydrogen bonds. This so-called **kinetic isotope effect** provides a general method for determining whether particular carbon-hydrogen bonds are broken in slow reaction steps.

Primary alcohols are oxidized by chromic acid in sulfuric acid solution to aldehydes, but to stop the reaction at the aldehyde stage, it usually is necessary to remove the aldehyde from the reaction mixture as it forms. This can be done by distillation if the aldehyde is reasonably volatile:

Unsaturated alcohols can be oxidized to unsaturated ketones by chromic acid, because chromic acid usually attacks double bonds relatively slowly:



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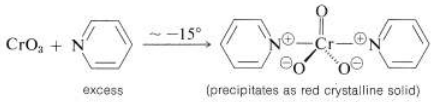
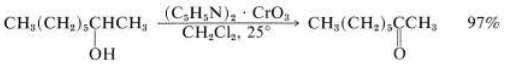
However, complications are to be expected when the double bond of an unsaturated alcohol is particularly reactive or when the alcohol rearranges readily under strongly acidic conditions. It is possible to avoid the use of strong acid through the combination of chromic oxide with the weak base azabenzene (pyridine). A crystalline solid of composition $(C_5H_5N)_2 \cdot CrO_3$ is formed when CrO_3 is added to excess pyridine at low temperatures. (Addition of pyridine to CrO_3 is likely to give an uncontrollable reaction resulting in a fire.)



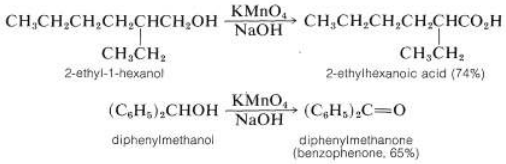
The pyridine-CrO_3 reagent is soluble in chlorinated solvents such as dichloromethane, and the resulting solutions rapidly oxidize $>CHOH$ to $>C{=}O$ at ordinary temperatures:



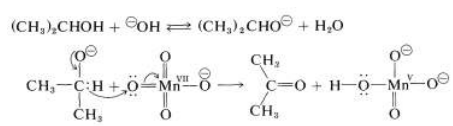
The yields usually are good, partly because the absence of strong acid minimizes degradation and rearrangement, and partly because the product can be isolated easily. The inorganic products are insoluble and can be separated by filtration, thereby leaving the oxidized product in dichloromethane from which it can be easily recovered.

15.7.2.2: Permanganate Oxidation

Permanganate ion, MnO_4^-, oxidizes both primary and secondary alcohols in either basic or acidic solution. With primary alcohols the product normally is the carboxylic acid because the intermediate aldehyde is oxidized rapidly by permanganate:

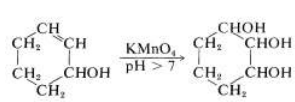


Oxidation under *basic* conditions evidently involves the alkoxide ion rather than the neutral alcohol. The oxidizing agent, MnO_4^-, abstracts the alpha hydrogen from the alkoxide ion either as an atom (one-electron transfer) or as hydride, $H^\ominus$ (two-electron transfer). The steps for the two-electron sequence are:



In the second step, permanganate ion is reduced from Mn(VII) to Mn(V). However, the stable oxidation states of manganese are $+2$, $+4$, and $+7$; thus the Mn(V) ion formed disproportionates to Mn(VII) and Mn(IV). The normal manganese end product from oxidations in basic solution is manganese dioxide, MnO_2, in which Mn has an oxidation state of $+4$ corresponding to Mn(IV).

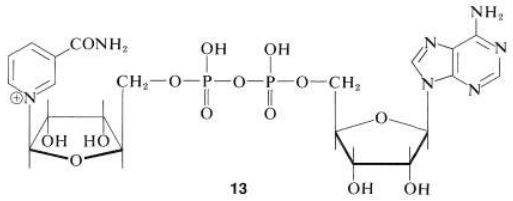
In Section 11-7C we described the use of permanganate for the oxidation of alkenes to 1,2-diols. How is it possible to control this reaction so that it will stop at the diol stage when permanganate also can oxidize $>CHOH$ to $>C{=}O$? Overoxidation with permanganate is always a problem, but the relative reaction rates are very much a function of the pH of the reaction mixture and, in basic solution, potassium permanganate oxidizes unsaturated groups more rapidly than it oxidizes alcohols:



15.7.3: Biological Oxidations

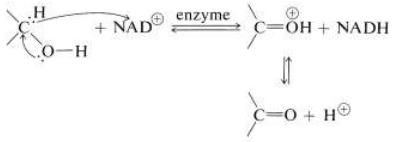
There are many biological oxidations that convert a primary or secondary alcohol to a carbonyl compound. These reactions cannot possibly involve the extreme pH conditions and vigorous inorganic oxidants used in typical laboratory oxidations. Rather, they occur at nearly neutral pH values and they all require enzymes as catalysts, which for these reactions usually are called *dehydrogenases*.

An important group of biological oxidizing agents includes the pyridine nucleotides, of which nicotinamide adenine dinucleotide ($NAD^{\oplus}$, 13) is an example:

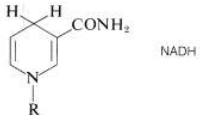


13

This very complex molecule functions to accept hydride $(H^{\ominus})$ or the equivalent $(H^{\oplus} + 2e^{-})$ from the α carbon of an alcohol:

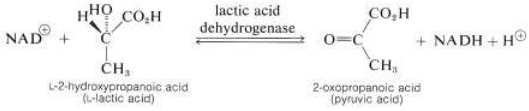


The reduced form of $NAD^{\oplus}$ is abbreviated as $NADH$ and the $H^{\ominus}$ is added at the 4-position of the pyridine ring:

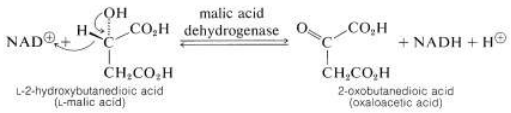


NADH

Some examples follow that illustrate the remarkable specificity of this kind of redox system. One of the last steps in the metabolic breakdown of glucose (glycolysis; Section 20-10A) is the reduction of 2-oxopropanoic (pyruvic) acid to *L*-2-hydroxypropanoic (lactic) acid. The reverse process is oxidation of *L*-lactic acid. The enzyme *lactic acid dehydrogenase* catalyses this reaction, and it functions only with the *L*-enantiomer of lactic acid:

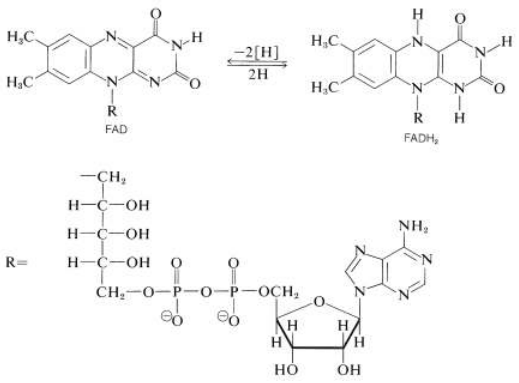


A second example, provided by one of the steps in metabolism by way of the Krebs citric acid cycle (see Section 20-10B), is the oxidation of *L*-2-hydroxy-butanedioic (*L*-malic) acid to 2-oxobutanedioic (oxaloacetic) acid. This enzyme functions only with *L*-malic acid:



All of these reactions release energy. In biological oxidations much of the energy is utilized to form ATP from ADP and inorganic phosphate (Section 15-5F). That is to say, electron-transfer reactions are coupled with ATP formation. The overall process is called **oxidative phosphorylation**.

Another important oxidizing agent in biological systems is flavin adenine dinucleotide, FAD. Like $NAD^{\oplus}$, it is a two-electron acceptor, but unlike $NAD^{\oplus}$, it accepts two electrons as $2H\cdot$ rather than as $H^{\ominus}$. The reduced form, $FADH_2$, has the hydrogens at ring nitrogens:



15.7.4: Contributors

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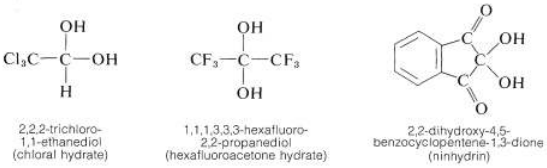
15.8: Polyhydric Alcohols

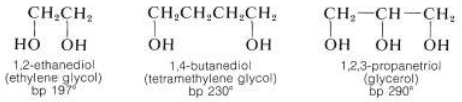
The simplest example of an alcohol with more than one hydroxyl group is methanediol or methylene glycol, $HOCH_2OH$. The term "glycol" indicates a *diol*, which is a substance with two alcoholic hydroxyl groups. Methylene glycol is reasonably stable in water solution, but attempts to isolate it lead only to its dehydration product, methanal (formaldehyde):

$$HO{-}CH_2{-}OH \rightleftharpoons H_2C{=}O + H_2O$$

This behavior is rather typical of *gem*-diols (*gem* = geminal, that is, with both hydroxyl groups on the *same* carbon atom). The few *gem*-diols of this kind that can be isolated are those that carry strongly electron-attracting substituents such as the following:



Polyhydric alcohols in which the hydroxyl groups are situated on different carbons are relatively stable, and, as we might expect for substances with multiple polar groups, they have high boiling points and considerable water solubility, but low solubility in nonpolar solvents:



1,2-Diols are prepared from alkenes by oxidation with reagents such as osmium tetroxide, potassium permanganate, or hydrogen peroxide (Section 11-7C). However, ethylene glycol is made on a commercial scale from oxacyclopropane, which in turn is made by air oxidation of ethene at high temperatures over a silver oxide catalyst (Section 11-7D).

Ethylene glycol has important commercial uses. It is an excellent permanent antifreeze for automotive cooling systems because it is miscible with water in all proportions and a 50% solution freezes at -34° $(-29^\circ F)$. It also is used as a solvent and as an intermediate in the production of polymers (polyesters) and other products (Chapter 29).

The trihydric alcohol, 1,2,3-propanetriol (glycerol), is a nontoxic, water-soluble, viscous, hygroscopic liquid that is used widely as a humectant (moistening agent). It is an important component of many food, cosmetic, and pharmaceutical preparations. At one time, glycerol was obtained on a commercial scale only as a by-product of soap manufacture through hydrolysis of fats, which are glyceryl esters of long-chain alkanoic acids. The major present source is by synthesis from propene (Section 14-3A). The trinitrate ester of glycerol (nitroglycerin) is an important but shock-sensitive explosive:

Dynamite is a much safer and more controllable explosive, and is made by absorbing nitroglycerin in porous material such as sawdust or diatomaceous earth. Dynamite has largely been replaced by cheaper explosives containing ammonium nitrate as the principal ingredient.

Glycerol, as a constituent of fats and lipids, plays an important role in animal metabolism.

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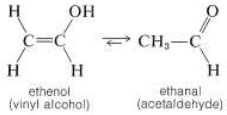
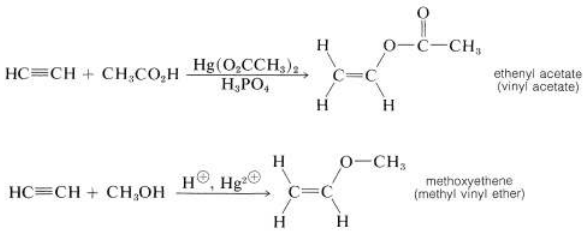
15.9: Unsaturated Alcohols - Alkenols

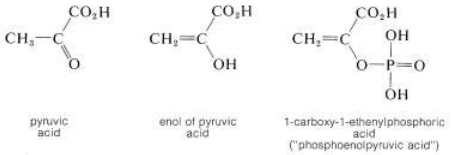
The simplest unsaturated alcohols, ethenol (vinyl alcohol), is unstable with respect to ethanal and has never been isolated (see Sections 10-5A and 13-5B):



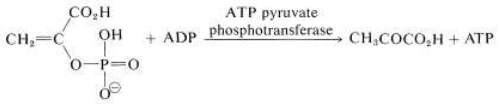
Other simple unsaturated alkenols (enols) also rearrange to carbonyl compounds. However, ether and ester derivatives of enols are known and can be prepared by the addition of alcohols and carboxylic acids to alkynes. The esters are used to make many commercially important polymers (Chapter 29):



The enol of 2-oxopropanoic acid (pyruvic acid) is of special biological interest because the phosphate ester of this compound is, like ATP (Section 15-5F), a reservoir of chemical energy that can be utilized by coupling its hydrolysis $(\Delta G^0 = -13\ \text{kcal})$ to thermodynamically less favorable reactions:

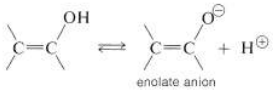


In fact, the ester can be utilized to synthesize ATP from ADP; that is, it is a phosphorylating agent, and a more powerful one than ATP:

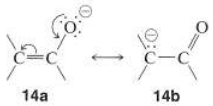


15.9.1: Acidity of Enols

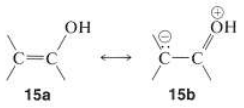
Enols usually are unstable and are considerably more acidic than saturated alcohols. This means that the conjugate bases of the enols (the *enolate anions*) are more stable relative to the enols themselves than are alkoxide ions relative to alcohols. (Enolate anions are important reagents in the chemistry of carbonyl compounds and will be discussed in detail in Chapter 17.)



The important factor here is delocalization of the negative charge on oxygen of enolate anions, as represented by the valence-bond structures 14*a* and 14*b*:

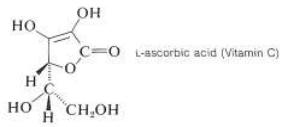


Because acidity depends on the *difference* in energy of the acid and its conjugate base, we must be sure that the stabilization of the enolate anion by electron delocalization represented by $14a$ and $14b$ is greater than the analogous stabilization of the neutral enol represented by $15a$ and $15b$:

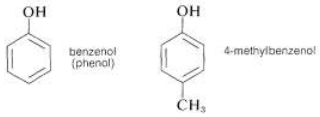


The rules for evaluating valence-bond structures (Section 6-5B) tell us that the stabilization will be greatest when there are two or more nearly equivalent low-energy electron-pairing schemes. Inspection of $14a$ and $14b$ suggests that they will be more nearly equivalent than $15a$ and $15b$ because, although $14b$ and $15b$ have a negative charge on the carbon, in $15b$ the oxygen has a positive charge. Another way of putting it is that $15b$ represents an electron-pairing scheme with a **charge separation**, which intuitively is of higher energy than $15a$ with no charge separation. Structures corresponding to $14b$ and $15b$ are not possible for saturated alkanols or their anions, hence we can see that enols should be more acidic than alcohols.

Ascorbic acid (Vitamin C) is an example of a stable and quite acidic enol, or rather an enediol. It is a di-acid with pK_a values of 4.17 and 11.57:



Other important examples of stable enol-type compounds are the aromatic alcohols, or *phenols*. The K_a's of these compounds are about 10^{-10}, some 10^8 times larger than the K_a's for alcohols.



The chemistry of these compounds, including their stability as enols, is discussed in Chapter 26.

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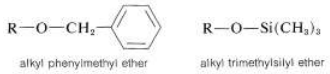
15.10: Protection of Hydroxyl Groups

By now it should be apparent that hydroxyl groups are very reactive to many reagents. This is both an advantage and a disadvantage in synthesis. To avoid interference by hydroxyl groups, it often is necessary to protect (or mask) them by conversion to less reactive functions. The general principles of how functional groups are protected were outlined and illustrated in Section 13-9. In the case of alcohols the hydroxyl group may be protected by formation of an ether, an ester, or an acetal.

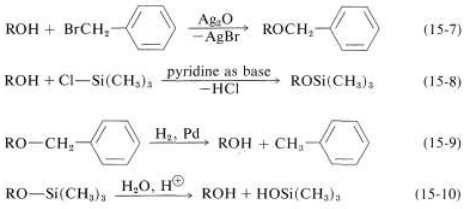
15.10.1: Ether Formation

A good protecting group is one that does everything you want it to do *when* you want it to. It must be easily put into place, stable to the reagents from which protection is required, *and* easily removed when desired. For this reason simple ethers such as methyl or ethyl ethers usually are not suitable protecting groups because they cannot be removed except under rather drastic conditions (Section 15-10).

More suitable ethers are phenylmethyl and trimethylsilyl ethers:

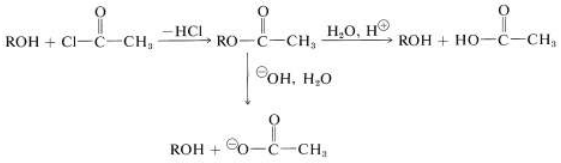


Both of these ethers are prepared easily by nucleophilic displacements (Equations 15-7 and 15-8) and can be converted back to the parent alcohol under mild conditions, by catalytic hydrogenation for phenylmethyl ethers (Equation 15-9), or by mild acid hydrolysis for trimethylsilyl ethers (Equation 15-10):



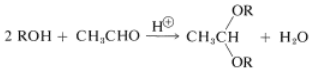
15.10.2: Ester Formation

Esters are formed from the alcohol and acyl halide, anhydride, or acid (Section 15-4D). The alcohol can be regenerated easily by either acid or base hydrolysis of the ester:

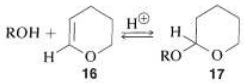


15.10.3: Acetal Formation

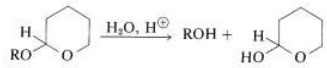
We have seen that alcohols can be converted *reversibly* to acetals under acidic conditions (Section 15-4E). The acetal function is a very suitable protecting group for alcohols under basic conditions, but is not useful under acidic conditions because acetals are not stable to acids:



An excellent reagent to form acetals is the unsaturated cyclic ether, 16. This ether adds alcohols in the presence of an acid catalyst to give the acetal 17:



The 3-oxacyclohexene (dihydropyran) protecting group can be removed readily by treating the acetal, 17, with aqueous acid:



An example of the use of 16 to protect an OH function is given in Section 13-10.

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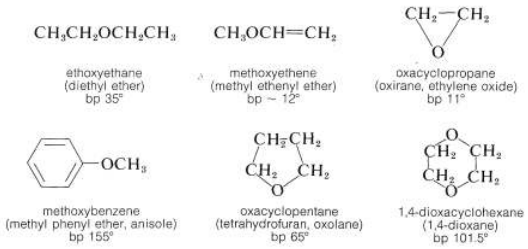
15.11: Types and Reactions of Simple Ethers

Substitution of the hydroxyl hydrogens of alcohols by hydrocarbon groups gives compounds known as ethers. These compounds may be classified further as open-chain, cyclic, saturated, unsaturated, aromatic, and so on. For the naming of ethers, see Sections 7-3 and 15-11A.

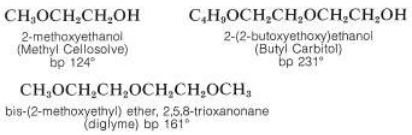


The most generally useful methods of preparing ethers already have been discussed (Sections 8-7C, 8-7E, 15-4C, and 15-5C). These and some additional special procedures are summarized in Table 15-4.

Table 15-4: *General Methods of Preparation of Ethers*

Reaction	Comment
1. *Reaction of alkoxides and alkyl compounds (Williamson synthesis)* $R'O^{\ominus} + RX \longrightarrow ROR' + X^{\ominus}$ $CH_3CH_2CH_2CH_2O^{\ominus} + CH_3I \longrightarrow CH_3CH_2CH_2CH_2OCH_3 + I^{\ominus}$ 1-methoxybutane, methyl butyl ether (70%)	S_N2 reaction and suitable only for primary RX (Sections 8-7A and 8-7C); *tert*-alkoxides are too bulky. Alkyl halides, alkyloxonium salts, sulfates, and sulfonates can be employed as RX component.
2. *Dehydration of alcohols* $ROH + H^{\oplus} \rightleftharpoons \overset{\oplus}{R}OH_2 \xrightarrow{ROH} ROR + H_3O^{\oplus}$ $(CH_3)_3COH + CH_3CH_2OH \xrightarrow{15\%\ H_2SO_4} (CH_3)_3COCH_2CH_3$ 2-ethoxy-2-methylpropane, ethyl *tert*-butyl ether (95%)	S_N1 or S_N2 reaction, depending on structure (Section 15-5C); excellent procedure for preparation of mixed ethers, ROR', where one R group is tertiary and the other primary (Section 15-5D).
$CH_2{=}CH{-}CH_2OH + C_2H_5OH \xrightarrow{H_2PtCl_4} CH_2{=}CH{-}CH_2{-}OC_2H_5 + H_2O$ 3-ethoxy-1-propene, 2-propenyl ethyl ether	Chloroplatinic acid is a specific catalyst for ether formation from allylic alcohols. Rearrangements may be observed (Section 14-3B).
3. *Methylation of alcohols with diazomethane* $ROH + CH_2N_2 \xrightarrow{H^{\oplus}} ROCH_3 + N_2$ $CH_3(CH_2)_6CH_2OH + CH_2N_2 \xrightarrow{HBF_4} CH_3(CH_2)_6CH_2OCH_3 + N_2$ 1-methoxyoctane, methyl octyl ether (87%)	Best with unhindered *prim.* and *sec.* alcohols. An acid catalyst is necessary (HBF_4 or BF_3), but acids with nucleophilic anions are unsatisfactory. Reaction probably involves intermediate formation of methyldiazonium ion, $CH_3N_2^{\oplus}$.
4. *Addition of alcohols to alkenes* $ROH + C{=}C \xrightarrow{H^{\oplus}} RO{-}C{-}C{-}H$	See Method 1, Table 15-2.

In general, ethers are low on the scale of chemical reactivity because the carbon-oxygen bond is not cleaved readily. For this reason ethers frequently are employed as inert solvents in organic synthesis. Particularly important in this connection are diethyl ether, diisopropyl ether, tetrahydrofuran, and 1,4-dioxane. The mono- and dialkyl ethers of 1,2-ethanediol, 3-oxa-1,5-pentanediol, and related substances are useful high-boiling solvents. Unfortunately, their trade names are not very rational. Abbreviated names are in common use, such as “polyglymes,” “Cellosolves,” and “Carbitols.” For reference, **Cellosolves** are monoalkyl ethers of 1,2-ethanediol; **Carbitols** are monoalkyl ethers of 3-oxa-1,5-pentanediol; **polyglymes** are dimethyl ethers of 3-oxa-1,5-pentanediol or 3,6-dioxa-1,8-octanediol and are called **diglyme** and **triglyme**, respectively.



The spectroscopic properties of ethers are unexceptional. Like alcohols, they have no electronic absorption beyond $185\ \text{nm}$; the important infrared bands are the C–O stretching vibrations in the region $1000\text{-}1230\ \text{cm}^{-1}$; their proton nmr spectra show deshielding of the *alpha* hydrogens by the ether oxygen ($\delta_{HC_\alpha OC} \sim 3.4\ \text{ppm}$). The mass spectra of ethers and alcohols are very similar and give abundant ions of the type $R{-}\overset{\oplus}{O}{=}C$ (R = H or alkyl) by α-cleavage (see Section 15-2).

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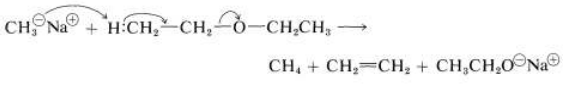
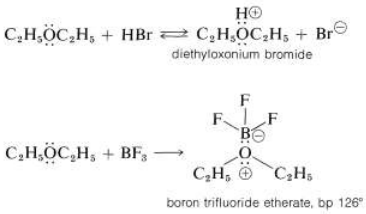
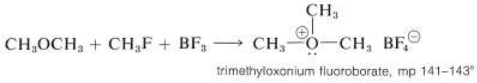
Unlike alcohols, ethers are not acidic and usually do not react with bases. However, exceptionally strong basic reagents, particularly certain alkali-metal alkyls, will react destructively with many ethers:



Ethers, like alcohols, are weakly basic and are converted to highly reactive salts by strong acids (e.g., H_2SO_4, $HClO_4$, and HBr) and to relatively stable coordination complexes with Lewis acids (e.g., BF_3 and RMgX):

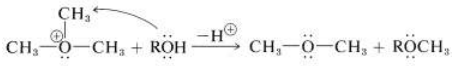


Dimethyl ether is converted to trimethyloxonium fluoroborate by the combination of boron trifluoride and methyl fluoride:

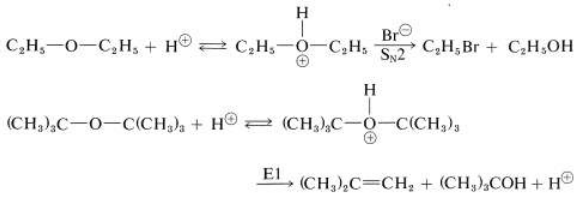


Both trimethyl- and triethyloxonium salts are fairly stable and can be isolated as crystalline solids. They are prepared more conveniently from the appropriate boron trifluoride etherate and chloromethyloxacyclopropane (epichlorohydrin).

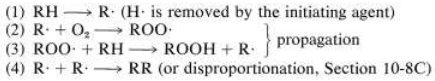
Trialkyloxonium ions are much more susceptible to nucleophilic displacement reactions than are neutral ether molecules. The reason is that ROR is a better leaving group than $RO^{\ominus}$. In fact, trimethyloxonium salts are among the most effective methylating reagents known:



Ethers can be cleaved under strongly acidic conditions by intermediate formation of dialkyloxonium salts. Hydrobromic and hydroiodic acids are especially useful for ether cleavage because both are strong acids and their anions are good nucleophiles. Tertiary alkyl ethers are very easily cleaved by acid reagents:



Ethers are susceptible to attack by halogen atoms and radicals, and for this reason they are not good solvents for radical reactions. In fact, ethers are potentially hazardous chemicals, because in the presence of atmospheric oxygen radical-chain formation of peroxides occurs, and peroxides are unstable, explosion-prone compounds. This process is called **autoxidation** and occurs not only with ethers but with many aldehydes and hydrocarbons. The reaction may be generalized in terms of the following steps involving initiation (1), propagation (2 and 3), and termination (4).



The initiation and termination steps can occur in a variety of ways but it is the chain-carrying steps, 2 and 3, that effect the overall destruction of the compound. Commonly used ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, and 1,4-dioxane often become seriously contaminated with peroxides formed by autoxidation on prolonged storage and exposure to air and light.

Purification of ethers frequently is necessary before use, and caution always should be exercised in the last stages of distilling them, because the distillation residues may contain dangerously high concentrations of explosive peroxides.

15.11.1: Contributors and Attributions

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15.12: Cyclic Ethers

15.12.1: Nomenclature of Cyclic Ethers

Ring compounds containing nitrogen, oxygen, sulfur, or other elements as ring atoms generally are known as *heterocyclic* compounds, and the ring atoms other than carbon are the *hetero* atoms. Over the years, the more common heterocyclic compounds have acquired a hodge-podge of trivial names, such as ethylene oxide, tetrahydrofuran, and dioxane. Systematic naming of ring compounds is necessary but, unfortunately, several competing systems have been developed. We prefer the simplest procedure, which is to name the simple heterocycles as *oxa*, *aza*, and *thia*-derivatives of cycloalkanes. However, this procedure has not been accepted (or adopted) universally and we are obliged to deal with the usages in existing literature. Having lived through at least two cycles of drastic changes in these matters, the authors hope that the simple procedure will prevail in the long run, but the long run is still ahead.

We summarize here the rules of the so-called Hantzsch-Widman nomenclature system for heterocycles, which currently is the fashionable procedure, although relegated to second-class status by a recent, very practical approach to organic nomenclature.[1]

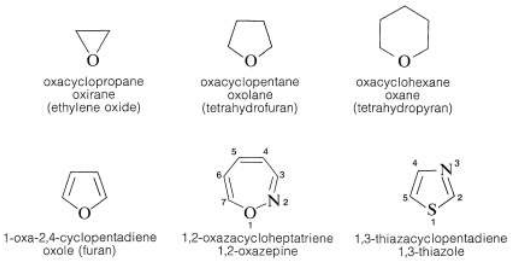
1. Ring size is denoted by the stem, *ir*, *et*, *ol*, *in*, *ep*, *oc*, *on*, or *ec* for 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered rings, respectively.
2. The kind of hetero atom present is indicated by the prefix, *oxa*, *thia*, or *aza* for oxygen, sulfur, or nitrogen, respectively; the prefixes *dioxa*, *dithia*, or *diaza* denote two oxygen, sulfur, or nitrogen atoms. When two or more different hetero atoms are present, they are cited in order of preference: oxygen before sulfur before nitrogen, as in the prefixes *oxaza* for one oxygen and one nitrogen, and *thiaza* for one sulfur and one nitrogen.
3. The degree of unsaturation is specified in the suffix. A list of appropriate suffixes and their stems according to ring sizes is given in Table 15-5. Notice that the suffix changes slightly according to whether the ring contains nitrogen.

Table 15-5: *Stems, Suffix, and Ring Size of Heterocyclic Compounds*

		Stem + suffix			
		Ring contains nitrogen		Ring contains no nitrogen	
Ring size	Stem	Unsaturated[a]	Saturated	Unsaturated[a]	Saturated
3	-ir-	-irine	-iridine	-irene	-irane
4	-et-	-ete	-etidine	-ete	-etane
5	-ol-	-ole	-olidine	-ole	-olane
6	-in-	-ine	*b*	-in	-ane
7	-ep-	-epine	*b*	-epin	-epane
8	-oc-	-ocine	*b*	-ocin	-ocane
9	-on-	-onine	*b*	-onin	-onane
10	-ec-	-ecine	*b*	-ecin	-ecane

[a]Corresponding to maximum number of double bonds, excluding cumulative double bonds.
[b]The prefix "perhydro" is attached to the stem and suffix of the parent unsaturated compound.

4. *Numbering of the ring starts with the hetero atom* and proceeds around the ring so as to give substituents (or other hetero atoms) the lowest numbered positions. When two or more *different* hetero atoms are present, oxygen takes precedence over sulfur and sulfur over nitrogen for the number one position. Examples follow to illustrate both the heterocycloalkane and the Hantzsch-Widman systems. Trivial names also are included.



Although Hantzsch-Widman system works satisfactorily (if you can remember the rules) for monocyclic compounds, it is cumbersome for polycyclic compounds. In the case of oxiranes it is simplest for *conversational* purposes to name them as oxides of the cycloalkenes or *epoxy* derivatives of the corresponding cycloalkanes. The oxabicycloalkane names seem preferable for indexing purposes, particularly because the word “oxide” is used in many other connections.

15.12.2: Reactivity of Cyclic Ethers - Oxacyclopropanes (Oxiranes)

Oxacyclopropane (oxirane), the simplest cyclic ether, is an outstanding exception to the generalization that most ethers are resistant to cleavage. Like cyclopropane, the three-membered ring is highly strained and readily opens under mild conditions. Indeed, the importance of oxacyclopropane as an industrial chemical lies in its readiness to form other important compounds. The major products derived from it are shown in Figure 15-5.

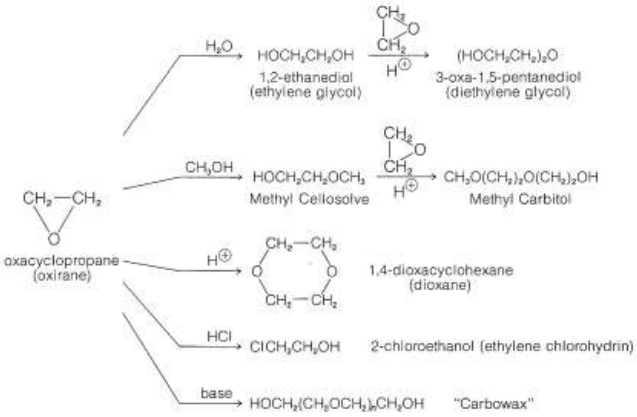
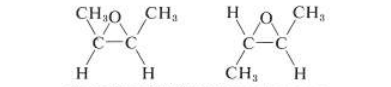


Figure 15-5: Important commercial reactions of oxacyclopropane (oxirane, ethylene oxide).

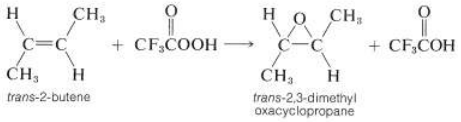
The lesser known four-membered cyclic ether, oxacyclobutane (oxetane), $(CH_2)_3O$, also is cleaved readily, but less so than oxacyclopropane. Oxacyclopentane (oxolane, tetrahydrofuran) is a relatively unreactive water-miscible compound with desirable properties as an organic solvent. It often is used in place of diethyl ether in Grignard reactions and reductions with lithium aluminum hydride.

15.12.3: Preparation of Oxacyclopropane

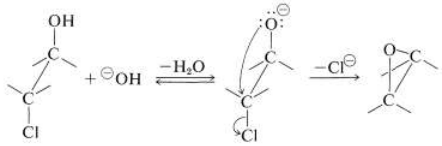
Three-membered cyclic ethers are important as reactive intermediates in organic synthesis. Like the cyclopropanes, the vicinal[2] disubstituted compounds have cis and trans isomers:



The most important method of preparation involves oxidation, or "epoxidation", of an alkene with a peroxycarboxylic acid, RCO_3H. This reaction achieves suprafacial addition of oxygen across the double bond, and is a type of electrophilic addition to alkenes:

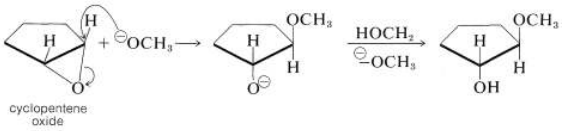


Oxacyclopropanes also can be prepared from vicinal chloro- or bromoalcohols and a base. This is an *internal* S_N2 reaction and, if the stereochemistry is correct, proceeds quite rapidly, even if a strained ring is formed:

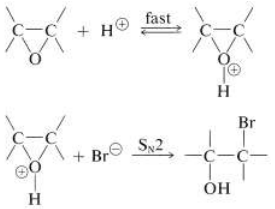


15.12.4: Ring-Opening Reactions of Oxacyclopropanes

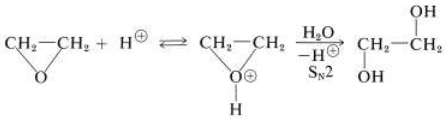
Unlike most ethers, oxacyclopropanes react readily with nucleophilic reagents. These reactions are no different from the nucleophilic displacements previously encountered in Chapter 8, except that the leaving group, which is the oxygen of the oxide ring, remains a part of the original molecule. The stereochemistry is consistent with an S_N2 mechanism because inversion of configuration at the site of attack occurs. Thus cyclopentene oxide yields products with the trans configuration:



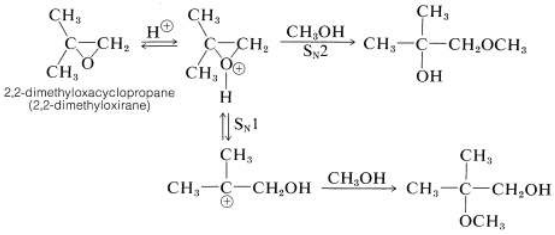
Acidic conditions also can be used for the cleavage of oxacyclopropane rings. An oxonium ion is formed first, which subsequently is attacked by the nucleophile in an S_N2 displacement or forms a carbocation in an S_N1 reaction. Evidence for the S_N2 mechanism, which produces inversion, comes not only from the stereochemistry but also from the fact that the rate is dependent on the concentration of the nucleophile. An example is ring opening with hydrogen bromide:



The same kind of mechanism can operate in the formation of 1,2-diols by acid-catalyzed ring-opening with water as the nucleophile:



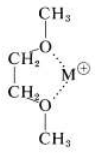
Some acid-catalyzed solvolysis reactions of oxacyclopropanes appear to proceed by S_N1 mechanisms involving carbocation intermediates. Evidence for the S_N1 mechanism is available from the reactions of unsymmetrically substituted oxacyclopropanes. For example, we would expect the conjugate acid of 2,2-dimethyloxacyclopropane to be attacked by methanol at the primary carbon by an S_N2 reaction and at the tertiary carbon by an S_N1 reaction:



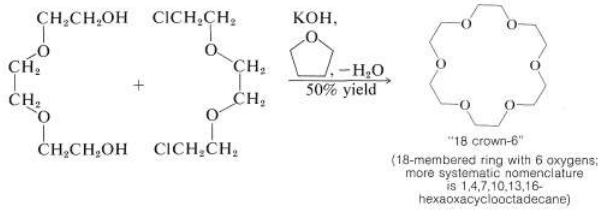
Because both products actually are obtained, we can conclude that both the S_N1 and S_N2 mechanisms occur. The S_N1 product, the tertiary ether, is the major product.

15.12.5: Metal Complexes of Cyclic Polyethers

We have emphasized the contrasts in properties between the ionic compounds such as sodium chloride, and the nonpolar organic compounds, such as the alkanes and arenes. There are great difficulties in dissolving the extreme types of these substances in a mutually compatible medium for carrying on chemical reactions, as, for example, in S_N reactions of organic halides with alkali-metal salts (Sections 8-3 and 8-7F). The essence of the problem is that electrostatic forces in ionic crystals of inorganic salts are strong, and nonpolar solvents simply do not have the solvating power for ions to make dissolution of the crystals a favorable process. However, it has long been known that polyethers, such as the "glymes" (Section 15-10), are able to assist in the dissolution of ionic compounds through their ability to solvate metal cations by providing multiple complexing sites:

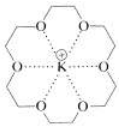


In 1967, C. J. Pedersen reported the synthesis of a series of cyclic polyethers, which he called "crown ethers", that have shown great promise for brining together what traditionally have been regarded as wholly incompatible substances - even achieving measurable solubilities of salts such as $NaCl$, KOH, and $KMnO_4$ in benzene. The crown ethers can be regarded as cyclic "glymes" and are available by S_N2-type cyclization reactions:



The crown ethers and many modifications of them (especially with nitrogen replacing one or more of the oxygens) function by coordinating with metal cations and converting them into less polar entities that are more stable in solution, even in a nonpolar solvent, than they are in the crystal.

Many of the crown ethers have considerable specificity with regard to the metal with which they complex. Ring size as well as the number and kind of hetero atoms are very important in this connection. 18-Crown-6 is especially effective for potassium:



An important application for the crown ethers in synthetic work is for solubilization of salts such as KCN in nonpolar solvents for use in S_N2 displacements. If the solvent has a low anion-solvating capability, then the reactivity of the anion is enhanced greatly. Consequently many displacement reactions that proceed slowly at elevated temperatures will proceed at useful rates at room temperatures, because the energy of "desolvating" the anion before it undergoes S_N2 displacement is low (Section 8-7F). For example, potassium fluoride becomes a potent nucleophilic reagent in nonpolar solvents when complexed with 18-crown-6:

$$CH_3(CH_2)_6CH_2Br + KF \xrightarrow[CH_3CN]{\text{18-crown-6}} \underset{92\%}{CH_3(CH_2)_6CH_2F} + KBr$$

15.12.6: Acetals and Ketals as Ethers

The grouping $C{-}O{-}C{-}O{-}C$ is characteristic of an acetal or a ketal (see Section 15-4E), but it also can be regarded as an ether with two ether links to one carbon. Compared to other ethers (except for the oxacyclopropanes), substances with the $C{-}O{-}C{-}O{-}C$ group are very active toward acidic reagents, as pointed out in connection with their formation from alcohols (Section 15-4E) and their sue as protecting groups for the OH function (Section 15-9C).

[1]J. H. Fletcher, O. C. Dermer, and R. B. Fox (Editors), "Nomenclature of Organic Compounds, Principles and Practice." *Advances in Chemistry Series, No. 126*, American Chemical Society, Washington, D.C., 1974.

[2]*Vicinal* means substituted on adjacent carbons.

15.12.7: Contributors and Attributions

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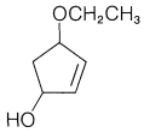
15.E: Alcohols and Ethers (Exercises)

Exercise 15-1

a. Draw the structure of 4-methoxy-1-penten-3-ol.

b. Name the following structure by the IUPAC system:



Exercise 15-2 Explain how hydrogen bonding makes *cis*-cyclopentane-1,2-diol substantially more volatile (bp 119° at $22\ \text{mm}$ of Hg) than *trans*-cyclopentane-1,2-diol (bp 136° at $22\ \text{mm}$ of Hg).

Exercise 15-3 What type of infrared absorption bands due to hydroxyl groups would you expect for *trans*-cyclobutane-1,2-diol and butane-1,2-diol (a) in very dilute solution, (b) in moderately concentrated solution, and (c) as pure liquids? Give your reasoning.

Exercise 15-4 Suggest a likely structure for the compound of molecular formula $\text{C}_4\text{H}_6\text{O}$ whose proton NMR and infrared spectra are shown in Figure 15-3a. Show your reasoning. Do the same for the compound of formula $\text{C}_3\text{H}_8\text{O}_2$, whose spectra are shown in Figure 15-3b.

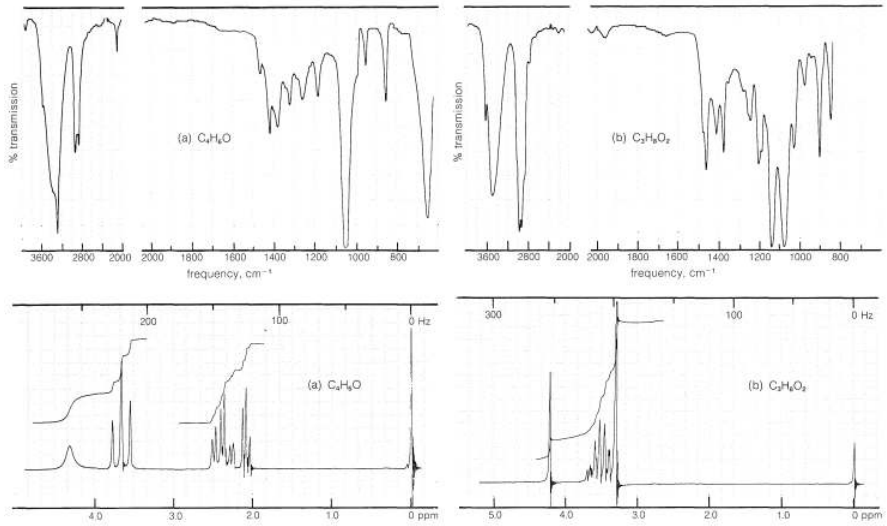
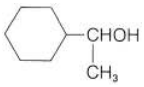
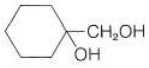


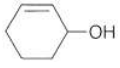
Figure 15-3: *Proton NMR and infrared spectra of (a) of* $\text{C}_4\text{H}_6\text{O}$ *and (b) of* $\text{C}_3\text{H}_8\text{O}_2$*; see Exercise 15-4.*

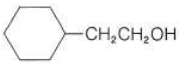
Exercise 15-5 Pure, dry ethanol has a triplet NMR resonance for its OH proton and a quintet resonance for its CH_2 protons. If 5% by weight of water is added to the ethanol, a new single peak is observed about $0.8\ \text{ppm}$ upfield of the ethanol OH triplet. If 30% by weight of water is added, there is only a single large OH resonance, and the CH_2 resonance becomes a quartet. Explain the changes produced in the NMR spectrum by adding water.

Exercise 15-6 Show how the following alcohols may be prepared from cyclohexene and any other needed reagents. Several steps may be necessary.

a. 

b. 

c. 

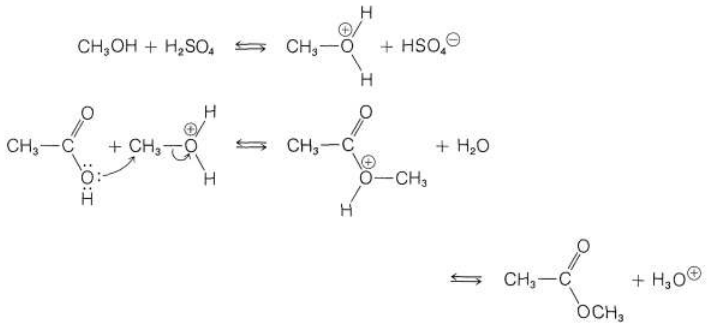
d. 

Exercise 15-7 What order of *basicity* would you predict for water, methanol, isopropyl alcohol, and *tert*-butyl alcohol *in the gas phase?* Give your reasoning.

Exercise 15-8 Suggest a practical method for preparation of the following ethers. Show the reaction conditions as closely as possible.

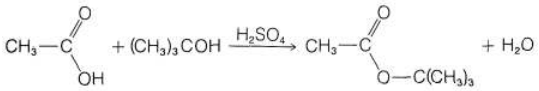
a. methoxyethane
b. 3-ethoxy-1-butene
c. methoxycyclohexane

Exercise 15-9 An alternative and plausible mechanism for esterification of carboxylic acids is shown by the following steps:



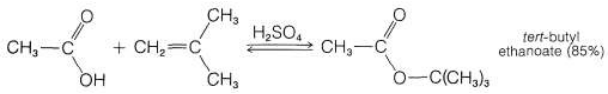
This mechanism corresponds to an S_N2 displacement of water from the methyloxonium ion by the acid. How could you distinguish between this mechanism and the addition-elimination mechanism using heavy oxygen (^{18}O) as a tracer?

Exercise 15-10 Formation of *tert*-butyl ethanoate by direct esterification goes very poorly:



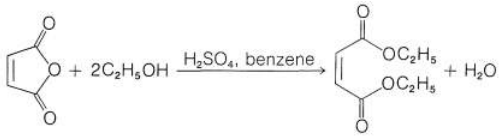
Explain why the reaction fails, and indicate the products you actually expect to form on heating a mixture of ethanoic acid and *tert*-butyl alcohol with sulfuric acid as a catalyst.

Exercise 15-11 A suitable method of preparing *tert*-butyl esters is to add the carboxylic acid to 2-methylpropene. Good yields can be obtained if a strong acid catalyst is used, if water is excluded, and if the temperature is kept low:



Write a mechanism for the reaction that accounts for the need for a strong acid catalyst, and why anhydrous conditions and low temperatures are necessary.

Exercise 15-12 The diethyl ester of *cis*-butenedioic acid can be prepared by heating the corresponding anhydride with ethanol and concentrated H_2SO_4 in benzene in a *mole* ratio of perhaps 1:2.5:0.25.



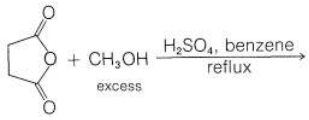
Write the steps that occur in this reaction and explain how the use of benzene and *more* than a catalytic amount of H_2SO_4 makes the formation of the diethyl ester thermodynamically more favorable than with just a catalytic amount of H_2SO_4.

Exercise 15-13 Complete the following reactions by drawing structures for the major organic products expected.

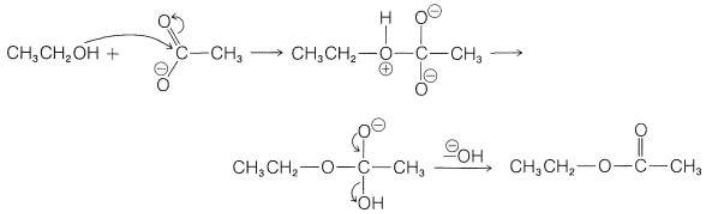
a. D-$CH_3CH_2CH(OH)CH_3 + CH_3CO_2H \xrightarrow{H^\oplus}$

b. $CH_3COCl + CH_2{=}CH{-}CH_2OH \rightarrow$

c.



Exercise 15-14 One can conceive of an esterification procedure involving the reaction of ethanol with ethanoate ion in accord with the following mechanism:



Assess the likelihood of the occurrence of this reaction at a reasonable rate *and* the favorableness of its overall equilibrium constant.

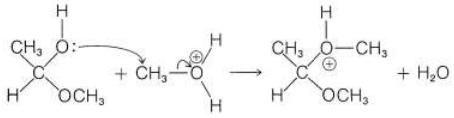
Exercise 15-15 How can D-glucose, D-fructose, and D-ribose be considered products of the addition of an alcohol to the carbonyl group of an aldehyde or ketone? Name each of the carbonyl compounds by the IUPAC system. For the ribose carbonyl structure, determine the configuration at each chiral center, using the D,L system.

Exercise 15-16 Hemiacetal formation is catalyzed by both acids *and* bases, but acetal formation is catalyzed only by acids. Write the steps involved in the formation of 1-methoxyethanol from ethanal in methanol containing sodium methoxide:

$$CH_3CHO + CH_3OH \xrightarrow{NaOCH_3} CH_3CH(OH)OCH_3 \qquad (15.E.1)$$

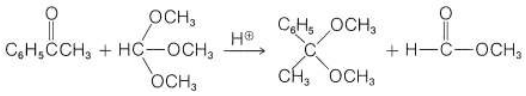
Explain why 1,1-dimethoxymethane cannot be prepared from ethanal and methanol with a basic catalyst.

Exercise 15-17 The slow step in an alternative mechanism for acetal formation may be as follows:



How could this mechanism be distinguished experimentally from the one give in Section 15-4E?

Exercise 15-18 Ketals are not always capable of being made in practical yields by the direct reaction of alcohols with ketones because of unfavorable equilibria. Satisfactory preparations of $RO{-}C{-}OR$ with R = methyl or ethyl are possible through the reactions of ketones with trimethoxy- or triethoxymethane. This process requires an acid catalyst:



Write the mechanistic steps involved in this acid-induced methoxy exchange reaction.

Exercise 15-19 Look at the structure of tetrodotoxin in Section 15-0. What would you expect to happen to the hydroxyl at the bridgehead position in dilute base?

Exercise 15-20 If you wished to convert D-1-phenylethanol to L-1-chloro-1-phenylethane, which of the following reagents and conditions would you use? Give reasons for your choice.

a. HCl and $ZnCl_2$

b. $SOCl_2$ alone

c. $SOCl_2$ with pyridine

Exercise 15-21 Write the steps that could plausibly take place in the reaction of a primary alcohol with phosphorus tribromide in the presence of the weak base pyridine to give an alkyl bromide.

Exercise 15-22 Methylmagnesium iodide with 2-butenal gives an addition product that, when hydrolyzed with dilute sulfuric acid and extracted with ether, yields an ether solution of impure 3-penten-2-ol. Attempted purification by distillation of the ether extract gives only 1,3-pentadiene and di(1-methyl-2-butenyl) ether. Write equations for each of the reactions involved. How could you avoid ether and diene formation in the preparation of 3-penten-2-ol by this method?

Exercise 15-23 What are the expected products on heating the following alcohols with strong sulfuric acid? Give your reasoning.

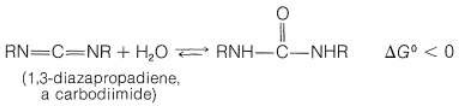
a. cyclohexanol
b. a mixture of methanol and 1-methylcyclohexanol
c. $(CH_2)_2C{=}CHCH_2OH$

Exercise 15-24* It is possible to prepare amides from tertiary alcohols and alkanenitriles, RCN, in concentrated sulfuric acid as the catalyst (Ritter reaction), as illustrated in the equation for the synthesis of N-*tert*-butylethanamide:

$$(CH_3)_2COH + CH_3CN \xrightarrow{H_2SO_4} CH_3CONHC(CH_3)_3 \qquad (15.E.2)$$

Show the steps in the mechanism of this reaction, given the fact that nitrilium ions of structure $R{-}C{\equiv}\overset{\oplus}{N}{-}R$ are likely to be intermediates.

Exercise 15-25* The equilibrium for the formation of urea compounds from the hydrolysis of substances called "carbodiimides" is a thermodynamically favorable reaction:

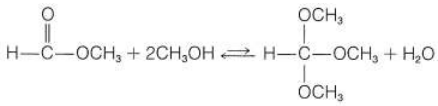


When coupled with an esterification involving an acid and an alcohol this reaction gives excellent conversions, although *not* in aqueous solution because the nucleophilic reactivities of water and alcohols are rather similar. Show the possible steps by which carbodiimides can achieve this conversion:

$$CH_3CO_2H + CH_3OH + RN{=}C{=}NR \rightleftharpoons CH_3CO_2CH_3 + RNHCONHR \qquad (15.E.3)$$

(In Chapter 25 we shall encounter reactions of amines and amino acids in which carbodiimides can be used in the presence of water. The difference is that amine nitrogen generally is more nucleophilic than water.)

Exercise 15-26* Trialkoxyalkanes, $R'C(OR)_3$, sometimes are called "orthoesters". They may be regarded as derived from alcohols and esters, although they seldom are prepared by this direct route because the following equilibrium is quite unfavorable:

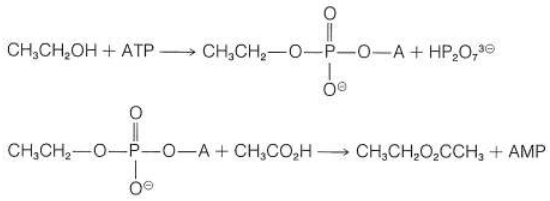


a. On the basis of the resonance theory, why should we expect the equilibrium for orthoester formation to be unfavorable?

b. Explain why trimethoxymethane and methanol together give a higher conversion of a ketone to the corresponding ketal than methanol alone does in the presence of an acid catalyst.

c. How many one synthesize $HC(OC_2H_5)_3$ from $CHCl_3$? (Review Section 14-7B.)

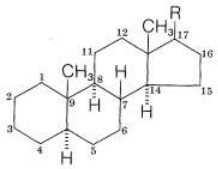
Exercise 15-27 A *possible* mechanism for producing esterification of an alcohol coupled with ATP hydrolysis would be the following:



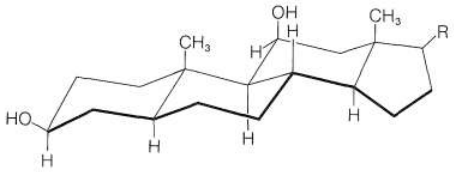
Work out possible mechanisms for each of these steps and decide whether this sequence is likely to be as feasible as the one described by Equations 15-5 and 15-6. Give your reasoning. How could you determine experimentally which mechanistic path was being followed?

Exercise 15-28 In the conversion of 2-propanol to 2-propanone with chromic acid, which is the redox step, esterification or elimination? What is the change in oxidation level of carbon in this reaction?

Exercise 15-29* The ring system, 11, is found in many naturally occurring compounds known as **steroids**. Several important representatives of this class of compound have secondary hydroxyl groups at C_3 and C_{11}, with configurations represented by the sawhorse drawing, 12:



11



12

Explain in detail how steric hindrance would lead you to expect that the relative reactivity of these two hydroxyl groups in esterification is $C_3 > C_{11}$. and in chromic acid oxidation is $C_{11} > \ce{C_3}$).

Exercise 15-30 How many moles of permanganate would be required to oxidize (a) one mole of cyclohexanol to cyclohexanone and (b) one mole of phenylmethanol (benzyl alcohol) to benzenecarboxylic acid in basic solution? (Review Section 11-1 if you have difficulty.)

Exercise 15-31 Show the mechanistic steps you expect to be involved in the oxidation of benzenecarbaldehyde (benzaldehyde) to benzenecarboxylic (benzoic) acid in an alkaline solution of potassium permanganate.

Exercise 15-32 Explain why oxidation of secondary alcohols with ^{18}O-labeled potassium permanganate produces an ^{18}O-containing ketone in *acidic* solution, but not in *basic* solution.

Exercise 15-33 The oxidation of $(CH_3)_2CDOH$ is one seventh as fast as the oxidation of $(CH_3)_2CHOH$ using potassium permanganate in acidic solution. What does this tell us about the mechanism of the reaction in acidic solution?

Exercise 15-34* For the transformations $NAD^{\oplus} + H^{\oplus} + 2e^{\ominus} \rightleftharpoons NADH$ and $FAD + 2H^{\oplus} + 2e^{\ominus} \rightarrow FADH_2$, determine which atoms undergo a change in oxidation level, and by how much, according to the rules set up in Section 11-1.

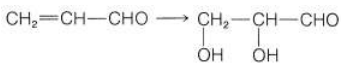
Exercise 15-35 How would you synthesize (a) *meso*-2,3-butanediol and (b) *D*,*L*-2,3-butanediol from *cis*-2-butene?

Exercise 15-36* Write equations for the dissociation of ascorbic acid to give progressively a monoanion and a dianion. Assigna p K_a to each dissociation and make your structures clear as to which are the acidic protons. Why is ascorbic acid a stronger diacid than cyclopentane-1,2-diol?

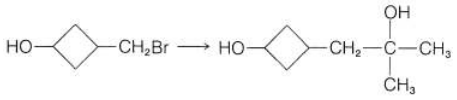
Exercise 15-37 The $O{-}C$ bond of phenylmethyl ethers is reduced more readily by hydrogen over a metal catalyst than the $O{-}C$ bond of methyl or ethyl esters. How do you account for this?

Exercise 15-38 Devise suitable reactions for the following conversions. (Indicate the specific protecting groups for the OH function appropriate for the reactions that you use.)

a. $HOCH_2CH_2CHO \rightarrow HO_2CCH_2CH(CH_3)OH$

b. 

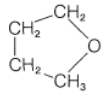
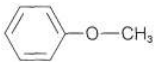
https://chem.libretexts.org/@go/page/81262

c. 

Exercise 15-39 Write the mechanistic steps involved in the acid-catalyzed addition of alcohols to the cyclic ether 16. Why does cyclohexene react far less readily than 16 with alcohols under acidic conditions? Write equations for the steps involved in the hydrolysis of 17 with aqueous acid.

Would you anticipate ethoxyethene to be a comparably useful reagent for the protection of hydroxyl groups? Explain.

Exercise 15-40 Predict the products likely to be formed on cleavage of the following ethers with hydroiodic acid:

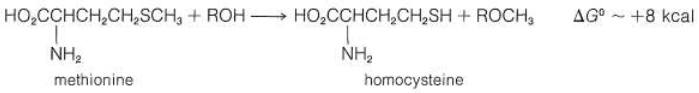
a. $CH_2{=}CH{-}CH_2{-}O{-}CH_3$
b. $CH_3CH_2{-}O{-}CH{=}CH_2$
c. $(CH_3)_3CCH_2{-}O{-}CH_3$
d. $(CH_3)_3COCH_3$
e. 
f. 

Exercise 15-41

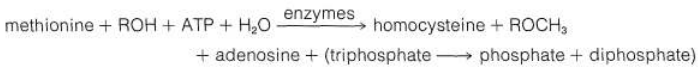
a. Explain why trimethyloxonium salts will convert alcohols to methyl ethers at neutral or acidic pH, whereas either methyl iodide or dimethyl sulfate requires strongly basic reaction conditions.

b. What products would you expect from the reactions of trimethyloxonium fluoroborate with (1) ethanethiol, C_2H_5SH, (2) diethylamine, $(C_2H_5)_2NH$, and (3) hydrogen bromide.

Exercise 15-42 The amino acid methionine is a methyl donor in biological methylation of hydroxyl groups. However, direct methylation has an unfavorable free energy change:



When coupled with hydrolysis of ATP (Section 15-5F) methylation becomes favorable as the result of the overall process:

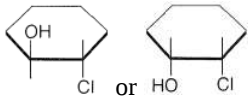


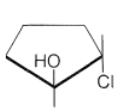
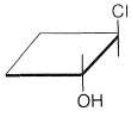
Suggest a sequence of reasonable steps for this process on the basis that sulfides, RSR, are both excellent nucleophiles and good leaving groups. It is implicit that all steps will be enzyme-catalyzed, although the way the enzymes function is unknown. Each step must be energetically reasonable because enzymes, like other catalysts, cannot induce thermodynamically unfavorable reactions.

Exercise 15-43 Draw structures for the following compounds and name each as an oxa-, aza-, or thiacycloalkane (cycloalkene, cycloalkadiene, and so on, as appropriate).

a. aziridine
b. thiirane
c. oxetan-2-one
d. 1,3-diazole
e. 1,3,5-trioxan
f. 3-phenyloxolane
g. perhydroazepine

Exercise 15-44 Which member of the following pairs of compounds would you expect to react faster with hydroxide ion?

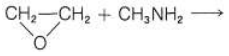
a.  or

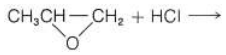
b.  or 

c. HOC_2CH_2Cl or $HOCH(Cl)CH{=}CH_2$

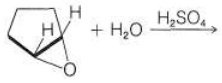
Exercise 15-45 Oxacyclopropanes tend to polymerize under basic conditions. Draw the structure of the polymer obtained on polymerization of *D*-2-methyloxacyclopropane catalyzed by $Na^{\oplus}\,{}^{\ominus}OCH_3$. Would you expect it to be formed with all *D*, all *L*, alternating *D* and *L*, or with random configurations of the chiral atoms in the chain?

Exercise 15-46 Draw the structures, showing the stereochemistry where necessary, for the products you would expect from the following reactions:

a. 

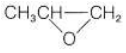
b. 

c. *meso*-dimethyloxacyclopropane + $(CH_3)_3O^{\oplus} + BF_4{}^- + CH_3OH \rightarrow$

d. 

Exercise 15-47 Show how you would synthesize each of the following alcohols, ethers, or acetals from the given organic starting materials and other necessary organic or inorganic reagents. Specify reagents and conditions as closely as possible.

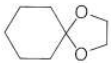
a. $CH_3OCH_2CH_2OCH_3$ from ethene

b.  from 1-propanol

c. $(CH_2{=}CHCH_2)_2O$ from $CH_2{=}CHCH_2Cl$

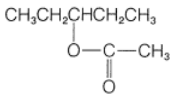
d. *trans*-1,2-cyclohexanediol from cyclohexene

e. from cyclohexanol

f.  from cyclohexanol and 1,2-ethanediol

Exercise 15-48 Show how you would convert each of the following alcohols to the indicated products. Specify necessary reagents and conditions.

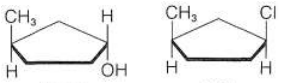
a. 1-propanol to $CH_3CH_2CH_2CH(CH_3)Cl$

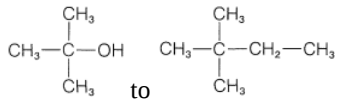
b. ethanol to 

c. $(CH_3)_3COH$ to $(CH_3)_2CHCH_2Br$

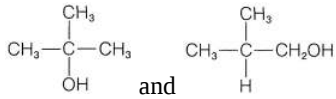
d. 1-butanol to $CH_3CH_2CH(OSO_3H)CH_3$

e. $(CH_3)_2C(OH)CH_2CH_3$ to $CH_3CH_2C(CH_3)_2CHO$

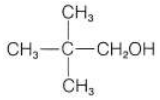
f.  (trans) to (cis)

g. 

Exercise 15-49 Give for each of the following pairs of compounds a chemical test, preferably a test-tube reaction, that will distinguish between the two substances. Describe the observation by which the distinction is made and write an equation for each reaction.

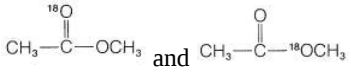
a. 

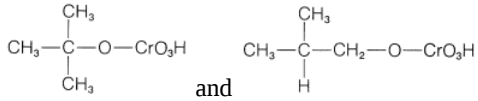
b. $CH_2{=}CH{-}CH_2CH_2OH$ and $CH_3CH{=}CH{-}CH_2OH$

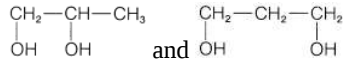
c.  and $CH_3{-}CH(CH_3){-}CH_2CH_2OH$

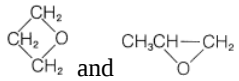
d. $CH_3CH_2{-}O{-}SO_2{-}O{-}CH_2CH_3$ and $CH_3CH_2CH_2CH_2{-}O{-}SO_3H$

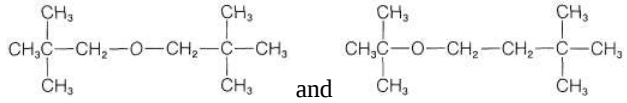
e. CH_3COCl and $ClCH_2COOH$

f. 

g. 

h. 

i. 

j. 

Exercise 15-50 Suppose you were given unlabeled bottles, each of which is known to contain one of the following compounds: 1-pentanol, 2-pentanol, 2-methyl-2-butanol, 3-penten-1-ol, 4-pentyn-1-ol, 1-butoxybutane, and 1-pentyl acetate. Explain how you could use simple chemical tests (test-tube reactions only) to identify the contents of each bottle.

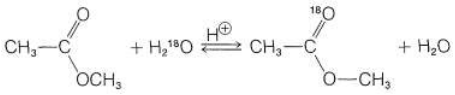
Exercise 15-51 Either *tert*-butyl alcohol or 2-methylpropene treated with strong sulfuric acid and hydrogen peroxide (H_2O_2) gives a mixture of two reasonably stable liquid compounds (A and B), the ratio of which depends on whether the hydrogen peroxide or organic starting material is in excess. The molecular formula of A is $C_4H_{10}O_2$, whereas B is $C_8H_{18}O_2$.

Treatment of A and B with hydrogen over a nickel catalyst results in quantitative conversion of each compound to *tert*-butyl alcohol. A reacts with acyl halides and anhydrides, whereas B is unaffected by these reagents. Treatment of 1 mole of A with excess methylmagnesium iodide in diethyl ether solution produces 1 mole of methane and 1 mole each of *tert*-butyl alcohol and methanol. One mole of B with excess methylmangesium iodide produces 1 mole of 2-methoxy-2-methylpropene and 1 mole of *tert*-butyl alcohol.

When B is heated with chloroethane, it causes chloroethane to polymerize. When B is heated *alone*, it yields 2-propanone and ethane, and if heated in the presence of *oxygen*, it forms methanol, 2-propanone, methanal, and water.

Determine the structure of A an dB and write equations for all reactions involved, showing the mechanisms and intermediates that are important for each. Write at least one structure for A and for B that is isomeric with your preferred structures and show how these substances would behave in each of the given reactions.

Exercise 15-52 The reaction of methyl ethanoate with water to give methanol and ethanoic acid is catalyzed by strong mineral acids such as sulfuric acid. Furthermore, when hydrolysis is carried out in water enriched in the rare oxygen isotope, ^{18}O, the following exchange takes place *faster* than formation of methanol:



No methanol-^{18}O $(CH_3{}^{18}OH)$ is formed in hydrolysis under these conditions.

a. Write a stepwise mechanism that is in harmony with the acid catalysis and with the results obtained in ^{18}O water. Mark the steps of the reaction that are indicated to be fast or slow.

b. The reaction depends on methyl ethanoate having a proton-accepting ability comparable to that of water. Why? Consider different ways of adding a proton to methyl ethanoate and decide which is most favorable on the basis of structural theory. Give your reasoning.

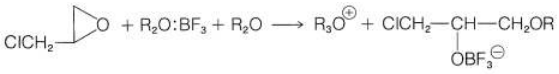
c. Explain why the reaction is slowed down in the presence of very high concentrations of sulfuric acid.

Exercise 15-53 Write a mechanism for the reaction of *trans*-2-butene with trifluoroperoxoethanoic acid to give *trans*-2,3-dimethyloxacyclopropane that is consistent with the fact that the reaction is first order in each participant and gives suprafacial addition.

Exercise 15-54 2,2,4,4-Tetramethyl-3-oxapentane (di-*tert*-butyl ether) is very unstable to acidic reagents. Devise a synthesis of the compound that you think might have a reasonable chance for success. Give your reasoning.

Exercise 15-55 How would you expect the fraction of elimination toward the methyl groups, as opposed to elimination toward the methylene group, to compare in $E1$ and $E2$ reactions of 2-chloro-2-methylbutane and the corresponding deuterium-labeled chloride, 2-chloro-2-methylbutane-3-D_2? Give your reasoning. (Review Sections 8-8 and 15-6B.)

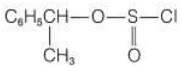
Exercise 15-56 Triethyloxonium fluoroborate can be prepared from 1-chloromethyloxacyclopropane and a BF_3-etherate according to the equation



The boron in the complex boron anion ends up as $BF_4{}^-$, but the details of this reaction need not concern you. Write the steps that you expect to be involved in the reaction to form $R_3O^{\oplus}$ and that you can support by analogy with other reactions discussed in this chapter.

Exercise 15-57 Support your explanation of each of the following facts by reasoning based on mechanistic considerations:

a. *D*-1-Phenylethanol reacts with thionyl chloride, $SOCl_2$, in pyridine to give *L*-1-phenylethyl chloride by way of an intermediate chlorosulfite ester,



b. 2-Buten-1-ol and $SOCl_2$ in ether and a one-molar equivalent of tributylamine gives 1-chloro-2-butene. In the absence of the base, the rearrangement product, 3-chloro-1-butene, is obtained.

Exercise 15-58 1,2-Ethanediol (ethylene glycol) is a familiar "antifreeze". However, it also is used in automotive cooling systems in climates that rarely, if ever, reach temperatures at which water would freeze. What other function, as important as lowering the freezing point, does the diol serve when added to automotive cooling systems?

15.E.1: Contributors

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CHAPTER OVERVIEW

16: Carbonyl Compounds I- Aldehydes and Ketones. Addition Reactions of the Carbonyl Group

The carbonyl group is a structural feature of many different types of compounds. It is present in carbon dioxide and in methanal, which represent respectively the high and low extremes in the level of oxidation of a carbonyl carbon. In between, there are carbonyl compounds ranging from aldehydes and ketones to carboxylic acids and their derivatives (esters, amides, anhydrides, and acyl halides). In this and succeeding chapters we describe the chemistry of these compounds with the intent of emphasizing the similarities that exist between them. The differences turn out to be more in degree than in kind. Even so, it is convenient to discuss aldehydes and ketones separately from carboxylic acids and, following some general observations about the carbonyl group, this chapter mainly is concerned with aldehydes and ketones.

16.1: Prelude to Aldehydes and Ketones
16.2: The Carbonyl Bond
16.3: Physical Properties
16.4: Spectroscopic Properties
16.5: Typical Carbonyl-Addition Reactions
16.6: Catalytic Hydrogenation
16.7: Reduction of Carbonyl Compounds to Hydrocarbons
16.8: Oxidation of Carbonyl Compounds
16.9: Protection of Carbonyl Groups
16.10: Preparative Methods for Aldehydes and Ketones
16.11: General Methods for the Preparation of Aldehydes and Ketones
16.E: Carbonyl Compounds I (Exercises)

16.1: Contributors and Attributions

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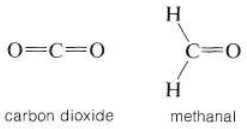
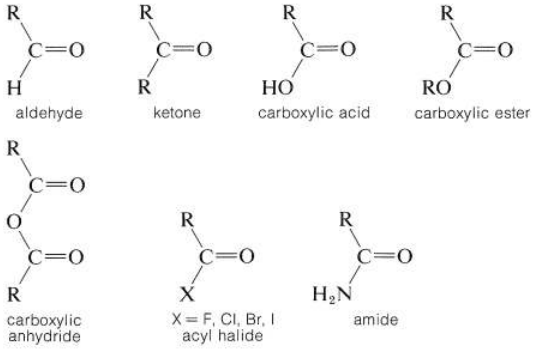
16.1: Prelude to Aldehydes and Ketones

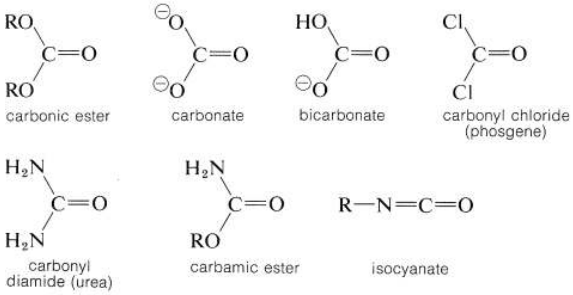
The carbonyl group, $-C=O$, is a structural feature of many different types of compounds. It is present in carbon dioxide and in methanal, which represent respectively the high and low extremes in the level of oxidation of a carbonyl carbon:



In between, there are carbonyl compounds ranging from aldehydes and ketones to carboxylic acids and their derivatives (esters, amides, anhydrides, and acyl halides). The naming of these compounds is described in Sections 7-4 to 7-7.

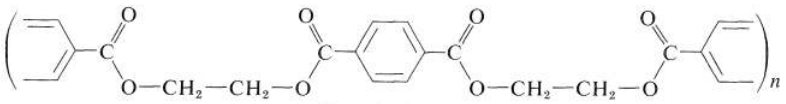


At the upper end of the oxidation scale, along with CO_2, are the carbonic acid derivatives such as carbonic esters, amides, halides, and carbonate salts, and isocyanates:

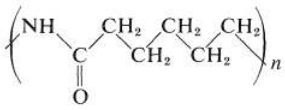


In this and succeeding chapters we describe the chemistry of these compounds with the intent of emphasizing the similarities that exist between them. The differences turn out to be more in degree than in kind. Even so, it is convenient to discuss aldehydes and ketones separately from carboxylic acids and, following some general observations about the carbonyl group, this chapter mainly is concerned with aldehydes and ketones.

Apart from CO_2 and metal carbonates, the most abundant carbonyl compounds of natural origin are carboxylic esters and amides. These occur as fats and lipids, which are esters of long-chain alkanoic acids, and as proteins, which are polyamides of natural amino acids. The same structural features are found in certain synthetic polymers, in particular the polyesters (e.g., Dacron) and the polyamides (e.g., nylon 6):



Dacron (polyester)



nylon 6 (polyamide)

Compared to carboxylic and carbonic acid derivatives, the less highly oxidized carbonyl compounds such as aldehydes and ketones are not so widely-spread in nature. That is not to say that they are unimportant. To the contrary, aldehydes and ketones are of great importance both in biological chemistry and in synthetic organic chemistry. However, the high reactivity of the carbonyl group in these compounds enables them to function more as intermediates in metabolism or in synthesis than as end products. This fact will become evident as we discuss the chemistry of aldehydes and ketones. Especially important are the *addition* reactions of carbonyl groups, and this chapter is mostly concerned with this kind of reaction of aldehydes and ketones.

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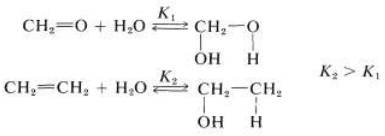
16.2: The Carbonyl Bond

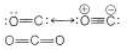
16.2.1: Comparison with Carbon-Carbon Double Bonds

The carbonyl bond is both a strong bond and a reactive bond. The bond energy varies widely with structure, as we can see from the carbonyl bond energies in Table 16-1. Methanal has the weakest bond $(166\ \text{kcal})$ and carbon monoxide the strongest $(237.3\ \text{kcal})$. Irrespective of these variations, the carbonyl bond not only is significantly *stronger* but also is *more reactive* than a carbon-carbon double bond. A typical difference in stability and reactivity is seen in hydration:



The equilibrium constant for ethene hydration is considerably greater than for methanal hydration, largely because the carbon-carbon double bond is *weaker*. Even so, methanal adds water rapidly and reversibly at room temperature without need for a catalyst. The corresponding addition of water to ethene occurs only in the presence of strongly acidic catalysis (Section 10-3E, Table 15-2).

Table 16-1: *Carbonyl Bond Energies*

Compounds	Bond energy (kcal mole^{-1})
	257.3
O=C=O	192.0[a]
$H_2C{=}O$	166.0
$H_2C{=}C{=}O$	184.8
RCH=O (aldehydes)	176
$R_2C{=}O$ (ketones)	179
(alkenes)	146

[a]Average of $\Delta H°$ for breaking both of the C=O bonds.

16.2.2: Structure and Reactivity

The reactivity of the carbonyl bond is primarily due to the difference in electronegativity between carbon and oxygen, which leads to a considerable contribution of the dipolar resonance form with oxygen negative and carbon positive:

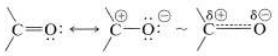


Figure 16-1. The carbon is sp^2-hybridized so that its σ bonds (one of which is to oxygen) lie in one plane. The remaining p orbital on carbon is utilized to form a π bond to oxygen. The polarity of the carbon-oxygen double bond implies that the electrons of the π bond (and also the σ bond) are associated more with oxygen than with carbon. This is supported by the dipole moments[1] of aldehydes and ketones, which indicate the degree of the polarization of the $C{=}O$ bonds; the dipole moments are in the neighborhood of 2.7 D, which corresponds to 40-50% ionic character for the carbonyl bond.

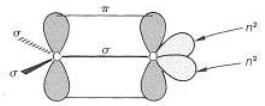
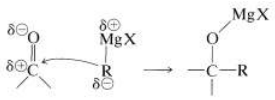


Figure 16-1: Atomic-orbital description of the carbonyl group. The σ bonds to carbon are coplanar, at angles near to $120°$; the two pairs of unshared electrons on oxygen are shown as occupying orbitals n.

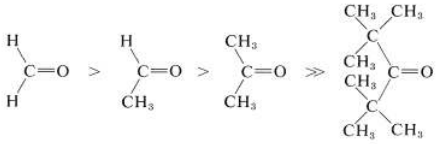
The polarity of the carbonyl bond facilitates addition of water and other polar reagents relative to addition of the same reagent to alkene double bonds. This we have seen previously in the addition of organometallic compounds $\overset{\delta\ominus}{\text{R}}{-}\overset{\delta\oplus}{\text{MgX}}$ and $\overset{\delta\ominus}{\text{R}}{-}\overset{\delta\oplus}{\text{Li}}$ to carbonyl compounds (Section 14-12A). Alkene double bonds are normally untouched by these reagents:



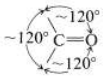
Likewise, alcohols add readily to carbonyl compounds, as described in Section 15-4E. However, we must keep in mind the possibility that, whereas additions to carbonyl groups may be rapid, the equilibrium constants may be small because of the strength of the carbonyl bond.

16.2.3: Further Considerations of Reactivity

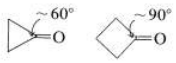
The important reactions of carbonyl groups characteristically involve addition at one step or another. For the reactions of organometallic reagents and alcohols with carbonyl compounds (Chapters 14 and 15), you may recall that steric hindrance plays an important role in determining the ratio between addition and other, competing reactions. Similar effects are observed in a wide variety of other reactions. We expect the reactivity of carbonyl groups in addition processes to be influenced by the size of the substituents thereon, because when addition occurs the substituent groups are pushed back closer to one another. In fact, reactivity and equilibrium constant decrease with increasing bulkiness of substituents, as in the following series (also see Table 15-3):



Strain effects also contribute to reactivity of cyclic carbonyl compounds. The normal bond angles around a carbonyl group are about 120°:



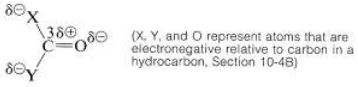
Consequently if the carbonyl group is on a small carbocyclic ring, there will be substantial angle strain and this will amount to about $120^{\circ} - 60^{\circ} = 60^{\circ}$ of strain for cyclopropanone,



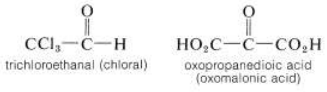
and $120^{\circ} - 90^{\circ} = 30^{\circ}$ of strain for cyclobutanone (both values being for the $\angle C{-}C{-}C$ at the carbonyl group). Addition of a nucleophile such as CH_3OH (cf. Section 15-4E) to these carbonyl bonds creates a tetrahedral center with less strain in the ring bonds to C_1:

Thus the hemiketal from cyclopropanone will have $109.5^{\circ} = 60^{\circ} = 49.5^{\circ}$, and that from cyclobutanone $109.5^{\circ} - 90^{\circ} = 19.5^{\circ}$ of strain at C_1. This change in the angle strain means that a sizable enhancement of *both* the reactivity and equilibrium constant for addition is expected. In practice, the strain effect is so large that cyclopropanone reacts rapidly with methanol to give a stable hemiketal from which the ketone cannot be recovered. Cyclobutanone is less reactive than cyclopropanone, but more reactive than cyclohexanone or cyclopentanone.

Electrical effects also are important in influencing the ease of addition to carbonyl groups. Electron-attracting groups facilitate the addition of nucleophilic reagents to carbon by increasing its positive character:



Thus compounds such as the following add nucleophilic reagents readily:



[1]An electrical dipole results when unlike charges are separated. The magnitude of the dipole, its **dipole moment**, is given by $e \times r$, where e is the magnitude of the charges and r is the distance the charges are separated. Molecular dipole moments are measured in debye units (D). A pair of ions, $\overset{\oplus}{\mathrm{C}}$ and $\overset{\ominus}{\mathrm{O}}$, as *point charges* at the $\mathrm{C{=}O}$ distance of $1.22\ \mathring{A}$, would have a dipole moment of $5.9\ \mathrm{D}$. Thus, if the dipole moment of a carbonyl compound is $2.7\ \mathrm{D}$, we can estimate the "% ionic character" of the bond to be $(2.7/5.9) \times 100 = 46\%$. The analysis is oversimplified in that the charges on the atom are not point charges and we have assumed that all of the ionic character of the molecule is associated with the $\mathrm{C{=}O}$ bond. One should be cautious in interpreting dipole moments in terms of the ionic character of bonds. Carbon dioxide has *no* dipole moment, but certainly has polar $\mathrm{C{=}O}$ bonds. The problem is that the dipoles associated with the $\mathrm{C{=}O}$ bonds of CO_2 are equal and *opposite in direction* to each other and, as a result, cancel. Thus, $\overset{\delta\ominus}{\mathrm{O}}-\overset{\delta\oplus}{\mathrm{C}}-\overset{\delta\ominus}{\mathrm{O}}$ has no *net* dipole moment, even though it has highly polar bonds.

16.2.4: Contributors and Attributions

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16.3: Physical Properties

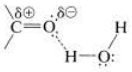
The polarity of the carbonyl group is manifest in the physical properties of carbonyl compounds. Boiling points for the lower members of a series of aldehydes and ketones are 50-80° *higher* than for hydrocarbons of the same molecular weight; this may be seen by comparing the data of Table 16-2 (physical properties of aldehydes and ketones) with those in Table 4-1 (physical properties of alkanes).

Table 16-2: *Physical Properties of Aldehydes and Ketones*

Compound	Formula	Mp, °C	Bp, °C	d_4^t, g ml^{-1}	Solubility in water[a]
methanal	CH_2O	−92	−21	0.815^{-20}	+
ethanal	CH_3CHO	−121	21	0.7951^{18}	+
propanal	CH_3CH_2CHO	−81	49	0.7966^{25}	+
2-propenal	$CH_2{=}CHCHO$	−87	52	0.8410^{20}	+
2-butenal	$CH_3CH{=}CHCHO$	−69	105	0.8575^{15}	+
butanal	$CH_3CH_2CH_2CHO$	−99	76	0.8170^{20}	sl.
2-methylpropanal	$(CH_3)_2CHCHO$	−66	64	0.7938^{20}	+
benzenecarbaldehyde (benzaldehyde)	C_6H_5CHO	−26	179	1.0504^{15}	v. sl.
2-propanone	CH_3COCH_3	−94	56	0.7899^{20}	+
2-butanone	$CH_3COCH_2CH_3$	−86	80	0.8054^{20}	+
3-buten-2-one	$CH_3COCH{=}CH_2$		80	0.8636^{20}	+
cyclobutanone			99	0.9548[9]	+
cyclopentanone		−58.2	130	0.9480^{20}	+
cyclohexanone		−45	155	0.9478^{20}	+
4-methyl-3-penten-2-one	$(CH_3)_2C{=}CHCOCH_3$	−59	130	0.8653^{20}	+
phenylethanone (acetophenone)	$C_6H_5COCH_3$	20.5	202	1.0236^{25}	v. sl.
2,3-butanedione	$CH_3COCOCH_3$		88	0.9904^{15}	+
2,4-pentanedione	$CH_3COCH_2COCH_3$	−23	139[746]	0.9721	+

[a]A plus sign means the compound is soluble; however, it may not be soluble in all proportions—sl means slightly soluble.

The water solubility of the lower-molecular-weight aldehydes and ketones is pronounced (see Table 16-2). This is to be expected for most carbonyl compounds of low molecular weight and is the consequence of hydrogen-bonding between the water and the electronegative oxygen of the carbonyl group:



solvation of carbonyl compounds through hydrogen bonding

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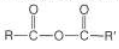
16.4: Spectroscopic Properties

16.4.1: Infrared Spectra

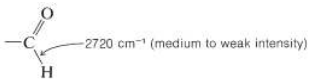
A carbonyl group in a compound can be positively identified by the strong infrared absorption band in the region $1650\text{-}1850\ \mathrm{cm^{-1}}$, which corresponds to the stretching vibration of the carbon-oxygen double bond. The position of the band within this frequency range depends on the molecular environment of the carbonyl group. As a result, we frequently can tell from the band position whether the structure is an aldehyde, ketone, carboxylic acid, ester, amide, or anhydride. The date of Table 16-3 show typical infrared absorption frequencies for specific types of carbonyl compounds. Thus aldehydes and ketones absorb at slightly lower frequencies (longer wavelengths) than carboxylic esters and anhydrides. We usually find that absorption shifts to lower frequencies $(\sim 20\ \mathrm{cm^{-1}})$ when the carbonyl group is conjugated with other multiple bonds, as in aromatic ketones, $\mathrm{C_6H_5COCH_3}$.

Table 16-3: *Characteristic Infrared Absorption Frequencies of Carbonyl Compounds*[a]

Functional group	Frequency (C=O stretch), $\mathrm{cm^{-1}}$	Functional group	Frequency (C=O stretch), $\mathrm{cm^{-1}}$
amides	1680	carboxylic acids	1710
ketones	1715	acyl halides	1800
aldehydes	1725	carboxylic anhydrides 	1820 1760
carboxylic esters	1735		

[a]The quoted frequencies are for typical open-chain saturated hydrocarbon chains (R). Conjugation and cyclic structures will influence the absorption frequency.

Aldehydes can be distinguished from ketones by a band at $2720\ \mathrm{cm^{-1}}$ which is characteristic of the $\mathrm{C{-}H}$ stretching vibration of an aldehyde function:



This band is unusually low in frequency for a $\mathrm{C{-}H}$ stretching vibration; although the band is rather weak, it occurs in a region of the spectrum where other absorptions generally are absent so it can be identified with no special difficulty.

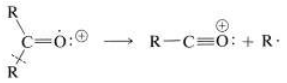
16.4.2: Electronic Absorption Spectra

Aldehydes and ketones absorb ultraviolet light in the region $275\text{-}295\ \mathrm{nm}$, and the result is excitation of an unshared electron on oxygen to a higher energy level. This is the $n \rightarrow \pi^*$ transition discussed in Section 9-9. A more intense $\pi \rightarrow \pi^*$ transition occurs about \180\)-$190\ \mathrm{nm}$, which corresponds to excitation of an electron from a π-bonding orbital to a π-antibonding orbital. Neither of these absorptions is especially useful for specific identification unless the carbonyl group is conjugated, in which case the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi$ bands occur at longer wavelengths (by $30\text{-}40\ \mathrm{nm}$). For example, if you suspect that a compound is an *alkenone* from its infrared spectrum, you easily could tell from the λ_{max} of the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ absorptions of the compound whether it is a conjugated alkenone. The absorption frequency would be expected around $320\ \mathrm{nm}$ and $220\ \mathrm{nm}$ (see Figure 9-20).

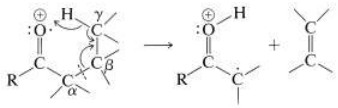
16.4.3: Mass Spectra

Aldehydes and ketones generally give moderately intense signals due to their molecular ions, $\mathrm{M^+}$. Thus the determination of the molecular weight of a ketone by mass spectroscopy usually is not difficult. Furthermore, there are some characteristic fragmentation patterns that aid in structural identification. These are:

- α *cleavage*



- *transfer of γ hydrogen with β cleavage* (**McLafferty rearrangement**)



16.4.4: NMR Spectra

The character of the carbonyl bond gives rise to very low-field nmr absorptions for the proton of an aldehyde group $(-\mathrm{CH{=}O})$. As Table 9-4 shows, these absorptions are some $4\ \mathrm{ppm}$ to lower fields than alkenyl hydrogens ($-\mathrm{CH{=}C}\langle$). Some of this difference in shift can be ascribed to the polarity of the carbonyl group $\overset{\delta\oplus}{\mathrm{C}} = \overset{\delta\ominus}{\mathrm{O}}$, which reduces electron density around the aldehyde hydrogen (see Section 9-10E). The effect appears to carry over in much smaller degree in the α positions, and protons of the type $\mathrm{CH_3{-}\overset{|}{C}{=}O}$ are about $0.3\ \mathrm{ppm}$ to lower fields than those of $\mathrm{CH_3{-}\overset{|}{C}{=}C}\langle$.

16.4.5: Contributors and Attributions

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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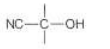
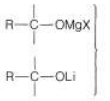
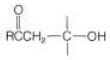
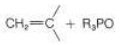
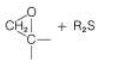
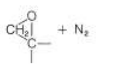
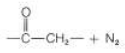
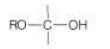
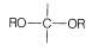
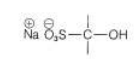
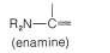
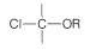
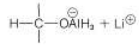
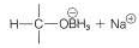
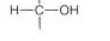
16.5: Typical Carbonyl-Addition Reactions

We turn now to discuss a few specific addition reactions of the carbonyl groups of aldehydes and ketones. We shall not attempt to provide an extensive catalog of reactions, but will try to emphasize the principles involved with especially important reactions that are useful in synthesis.

Grignard reagents, organolithium compounds, and the like generally add to aldehydes and ketones rapidly and irreversibly, but the same is not true of many other reagents; their addition reactions may require acidic or basic catalysts; the adducts may be formed reversibly and with relatively unfavorable equilibrium constants. Also, the initial adducts may be unstable and react further by elimination. (We recommend that you review Section 15-4E to see examples of these points.) To organize this very large number of addition reactions, we have arranged the reactions according to the nucleophile that adds to the carbonyl carbon. The types of nucleophiles considered here form C–C, C–O, C–N, C-halogen, C–S, and C–H bonds. A summary is given in Table 16-4.

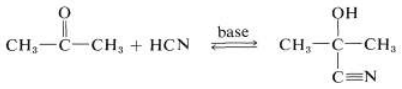
Table 16-4: *Addition Reactions of Aldehydes and Ketones*

Reagent (Nu—E)	Adduct (to C=O)	Conditions	Comments
NC—H		basic catalysts	synthesis of cyanoalkenes, carboxylic acids, Section 16-4A
R—MgX R—Li		ether solvent, no catalyst needed	synthesis of alcohols, Section 14-12A
		acidic or basic catalysts	synthesis of hydroxy-ketones, hydroxyaldehydes, and their dehydration products (see Section 17-3)
		strongly basic medium	synthesis of alkenes, Section 16-4A
		strongly basic medium	oxacyclopropane synthesis, Section 16-4A
			oxacyclopropanes, Section 16-4A
			ketones, Section 16-4A
RO—H		acidic or basic catalysts	Section 15-4E
RO—H		acidic catalysts	useful to protect carbonyl and alcohol functions (see Sections 16-8 and 15-9)
		aqueous $NaHSO_3$ solution	purification, Section 16-4B
RNH_2		acidic catalysts	Section 16-4C, Table 16-5
R_2NH		acidic catalysts	Section 16-4C
Cl—H, ROH		acidic catalysts	Section 16-4D, synthesis of α-halo ethers
		ether solution	Section 16-4E, synthesis of alcohols
		alcohols or aqueous solutions	Section 16-4E, synthesis of alcohols
		strongly basic catalysts or	Section 16-4E, synthesis of alcohols

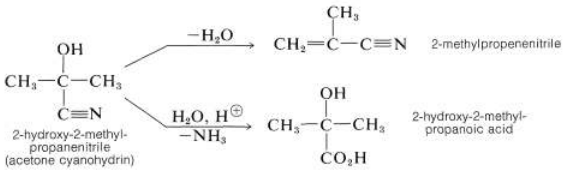
16.5.1: Addition of Carbon Nucleophiles

16.5.1.1: Cyanohydrin Formation

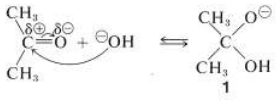
Hydrogen cyanide adds to many aldehydes and ketones to give hydroxylnitriles, usually called "cyanohydrins":



The products are useful in synthesis - for example, in the preparation of cyanoalkenes and hydroxy acids:

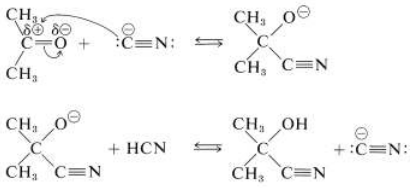


An important feature of cyanohydrin formation is that it requires a basic catalyst. In the absence of base, the reaction does not proceed, or is at best very slow. In principle, the basic catalyst may activate either the carbonyl group or hydrogen cyanide. With hydroxide ion as the base, one reaction to be expected is a reversible addition of hydroxide to the carbonyl group:



However, such addition is not likely to facilitate formation of cyanohydrin because it represents a *competitive* saturation of the carbonyl double bond. Indeed, if the equilibrium constant for this addition were large, an excess of hydroxide ion could inhibit cyanohydrin formation by tying up the ketone as the adduct 1.

Hydrogen cyanide itself has no unshared electron pair on carbon and does not form a *carbon-carbon* bond to a carbonyl carbon. However, a small amount of a strong base can activate hydrogen cyanide by converting it to cyanide ion, which can function as a carbon nucleophile. A complete sequence for cyanohydrin formation follows:



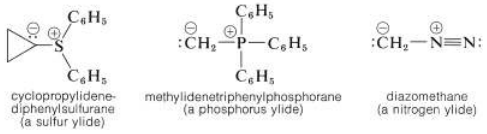
The second step regenerates the cyanide ion. Each step of the reaction is reversible but, with aldehydes and most nonhindered ketones, formation of the cyanohydrin is reasonably favorable. In practical syntheses of cyanohydrins, it is convenient to add a strong acid to a mixture of sodium cyanide and the carbonyl compound, so that hydrogen cyanide is generated *in situ*. The amount of acid added should be insufficient to consume all the cyanide ion, therefore sufficiently alkaline conditions are maintained for rapid addition.

16.5.1.2: Addition of Organometallic Reagents (See Section 14-12A)

16.5.1.3: Addition of Enolate Anions (See Section 17-3)

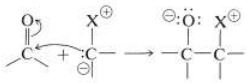
16.5.1.4: Addition of Ylide Reagents

There are a number of rather interesting substances for which we can write important dipolar valence-bond structures of the type . The important factor with these structures is that the negative end of the dipole is *carbon with an unshared electron pair*. The positive end of the dipole can be several kinds of atoms or groups, the most usual being sulfur, phosphorus, or nitrogen. Some examples (each written here as a single dipolar valence-bond structure) are:

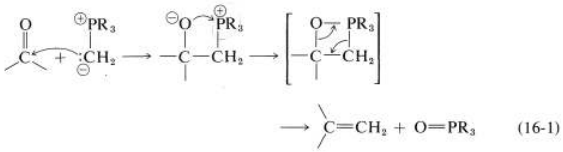


The systematic naming of these substances is cumbersome, but they have come to be known as **ylides**. The genesis of this name may seem obscure, but it is an attempt to reconcile the presence of a C–X σ bond, which is covalent and nonpolar as in alk*yl* derivatives, as well as an ionic bond as in metal hal*ides*. Hence, the combination *yl-lide*.[2]

As we might expect from the dipolar structure, ylides can behave as carbon nucleophiles to form carbon-carbon bonds by addition to the carbonyl groups of aldehydes and ketones:

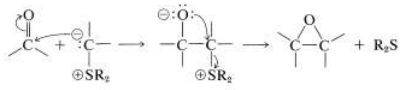


However, the further course of reaction depends on the type of ylide used. In the case of phosphorus ylides, the overall reaction amounts to a very useful *synthesis of alkenes* by the transfer of oxygen to phosphorus and carbon to carbon, as summarized in Equation 16-1. This is called the **Witting reaction**:

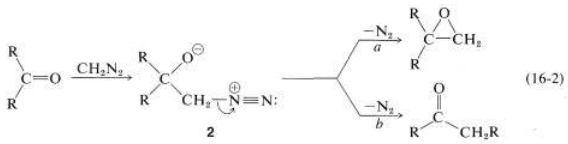


(16-1)

Reactions with sulfur ylides proceed differently. The prodcuts are oxacylcopropanes (oxiranes) - not alkenes. The addition step proceeds as with the phosphorus ylides, but the negatively charged oxygen of the dipolar adduct then displaces the sulfonium group as a neutral sulfide. This is an intramolecular S_N2 reaction similar to the formation of oxacyclopropanes from vicinal chloroalcohols (Section 15-11C):

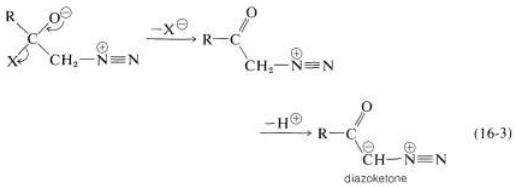


As for the nitrogen ylides, a useful reagent of this type is diazomethane, CH_2N_2. Diaxomethane can react with carbonyl compounds in different ways, depending on what happens to the initial adduct 2. Oxacyclopropanes are formed if the nitrogen is simply displaced (as N_2) by oxygen (Path a, Equation 16-2). Ketones of rearranged carbon framework result if nitrogen is displaced $as\backslash(N_2)$ by $R^{\ominus}$ which moves over to the CH_2 group (Path b, Equation 16-2):



(16-2)

Diazoketones, $RCOCHN_2$, are formed if there is a good leaving group, such as halogen, on the carbonyl (Equation 16-3). Under these circumstances the reactant is an acid halide, not an aldehyde or ketone:



(16-3)

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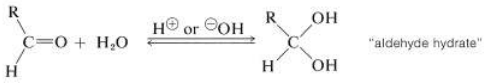
16.5.2: Addition of Oxygen and Sulfur Nucleophiles

16.5.2.1: Alcohols, Thiols, Water

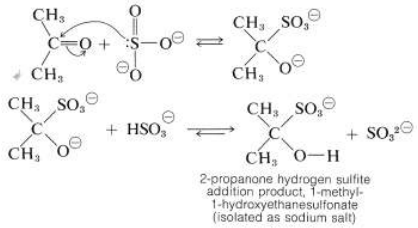
We already have discussed additions of alcohols and, by analogy, thiols (RSH) to carbonyl compounds (see Section 15-4E). We will not repeat this discussion here except to point out that addition of *water* to the carbonyl group of an aldehyde is analogous to hemiacetal formation (Section 15-4E) and is catalyzed both by acids and bases:



The equilibrium for hydrate formation depends both on steric and electrical factors. Methanal is 99.99% hydrated in aqueous solution, ethanal is 58% hydrated, and 2-propanone is not hydrated significantly. The hydrates seldom can be isolated because they readily revert to the parent aldehyde. The only stable crystalline hydrates known are those having strongly electronegative groups associated with the carbonyl (see Section 15-7).

16.5.2.2: Hydrogen Sulfite (Bisulfite) Addition to Carbonyl Compound

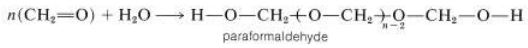
Several carbonyl additions have characteristics similar to those of cyanohydrin formation. A typical example is the addition of sodium hydrogen sulfite, which proceeds readily with good conversion in aqueous solution with most aldehydes, methyl ketones, and unhindered cyclic ketones to form a carbon-sulfur bond. No catalyst is required because sulfite is an efficient nucleophilic agent. The addition step evidently involves the sulfite ion - not hydrogen sulfite ion:



The addition products often are nicely crystalline solids that are insoluble in excess concentrated sodium hydrogen sulfite solution. Whether soluble or insoluble, the addition products are useful for separating carbonyl compounds from substances that do not react with sodium hydrogen sulfite.

16.5.2.3: Polymerization of Aldehydes

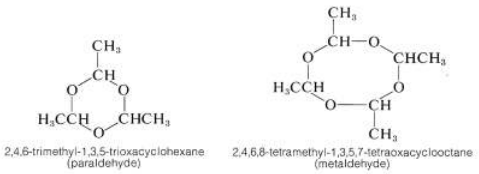
A reaction closely related to acetal formation is the polymerization of aldehydes. Both linear and cyclic polymers are obtained. For example, methanal in water solution polymerizes to a solid ling-chain polymer called paraformaldehyde or "polyoxymethylene":



This material, when strongly heated, reverts to methanal; it therefore is a convenient source of gaseous methanal. When heated with dilute acid, paraformaldehyde yields the solid trimer, 1,3,5-trioxycyclohexane (mp $61°$). The cyclic tetramer is also known.

Long-chain methanal polymers have become very important as plastics in recent years. The low cost of paraformaldehyde is highly favorable in this connection, but the instability of the material to elevated temperatures and dilute acids precludes its use in plastics. However, the "end-capping" of polyoxymethylene chains through formation of esters or acetals produces a remarkable increase in stability, and such modified polymers have excellent properties as plastics. Delrin (DuPont) is a stabilized methanal polymer with exceptional strengths and ease of molding.

Ethanal (acetaldehyde) polymerizes under the influence of acids to the cyclic trimer, "paraldehyde", and a cyclic tetramer, "metaldehyde". Paraldehyde has been used as a relatively nontoxic sleep-producing drug (hypnotic). Metaldehyde is used as a poison for snails and slugs, "Snarol". Ketones do not appear to form stable polymers like those of aldehydes.



16.5.3: Nitrogen Nucleophiles

16.5.3.1: Reactions of RNH_2 Derivatives with Carbonyl Compounds

A wide variety of substances with $-NH_2$ groups react with aldehydes and ketones by an addition-elimination sequence to give $\diagup C{=}N-\diagdown$ compounds and water. These reactions usually require acid catalysts:

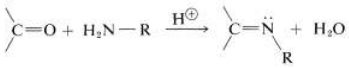
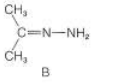
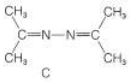
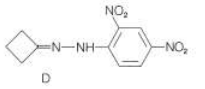
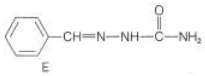


Table 16-5 summarizes several important reactions of this type and the nomenclature of the reactants and products.

Table 16-5: *Products from Reactions of Carbonyl Compounds with* RNH_2 *Derivatives*

Reactant	Typical product[a]	Class of product
H_2N-R (R = alkyl, aryl, or hydrogen) amine	$CH_3CH{=}N-CH_3$ A	imine[b] (Schiff's base)
H_2N-NH_2 hydrazine	 B	hydrazone
	 C	azine
H_2N-NHR (R = alkyl, aryl) substituted hydrazine	 D	hydrazone[c]
$H_2NNHCNH_2$ semicarbazide	 E	semicarbazone[c]
$HO-NH_2$ hydroxylamine	$CH_2{=}N-OH$ F	oxime[c]

[a]The nomenclature of these substances is at best difficult. The first-choice names used here are those recommended by J. H. Fletcher, O. C. Dermer, and R. B. Fox, Eds. "Nomenclature of Organic Compounds," *Advances in Chemistry Series, No. 126*, American Chemical Society, Washington, D.C., 1974. These are far from common usage names as yet and, for conversational purposes, you will find it best to say the name of the compound along with the class of product formed, as in the italicized names below.

A. ethylidenemethanamine, 2-aza-2-butene, *methylimine of ethanal;*
B. 1-methylethylidenediazane, 1-methylethylidenehydrazine, 1,2-diaza-3-methyl-2-butene, *hydrazone of 2-propanone;*
C. bis(1-methylethylidene)diazine, bis(1-methylethylidene)hydrazine, 2,5-dimethyl-3,4-diaza-2,4-hexadiene, *azine of 2-propanone;*
D. 1-cyclobutylidene-2-(2,4-dinitrophenyl)diazane, cyclobutylidene-2,4-dinitrophenylhydrazine, *2,4-dinitrophenylhydrazone of cyclobutanone;*
E. 2-phenylmethylidenediazanecarboxamide, *semicarbazone of benzenecarbaldehyde;*
F. methylideneazanol, *oxime of methanal.*

[b]These are either ketimines or aldimines, according to whether the carbonyl compound is a ketone or an aldehyde. For R = H, the imine product generally is unstable and polymerizes.

[c]Usually these derivatives are solids and are excellent for the isolation and characterization of aldehydes and ketones.

Figure 16-4 shows schematically the type of behavior observed. We can understand the maximum in rate by considering the rates and equilibria involving RNH_2 and the carbonyl compound as well as the rate of dehydration, Equations 16-4 through 16-6.

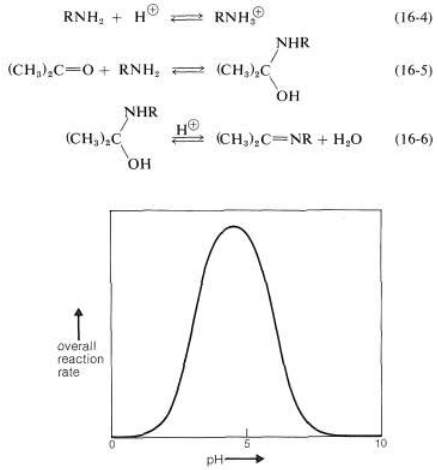
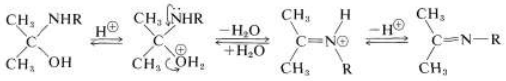


Figure 16-4: Schematic variation of the rate of condensation of RNH_2 with a carbonyl compound as a function of pH.

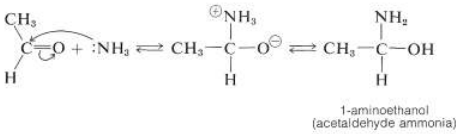
Clearly, if the unshared electron pair on the nitrogen of RNH_2 is combined with a proton, Equation 16-4, it cannot attack the carbonyl carbon to give the aminoalkanol as in Equation 16-5. So at high acid concentration (low pH) we expect the rate and the equilibrium for the overall reaction to be unfavorable. In more dilute acid, the rate picks up because there is more free RNH_2 in solution. Dehydration of the aminoalkanol (Equation 16-6) is acid catalyzed; this reaction normally is fast at pH values smaller than 3-4. Therefore, the slow step at pH < 4 is addition of RNH_2 to the carbonyl group as per Equation 16-5. As the pH is increased above 4, the addition becomes progressively faster because less RNH_2 is tied up as RNH_3^+. However, then the dehydration step, Equation 16-6, decreases in rate because it requires an acid catalyst. At pH 6 (remember that going from pH 4 to pH 6 is a 100-fold decrease in $H^\oplus$ concentration), dehydration is the slow step, and at higher pH values it finally becomes too slow to give a useful overall rate of reaction. This sequence of changes in rate and equilibria has been shown to account precisely for rate *vs*. pH curves such as in Figure 16-4.

Dehydration of $(CH_3)_2CHNR(OH)$ to $(CH_3)_2C{=}NR$ involves acid catalysis in very much the same way as in acetal formation (Section 15-4E):

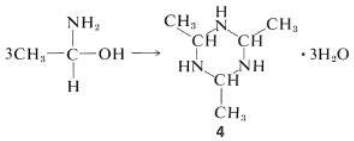


16.5.3.2: Addition of Ammonia to Aldehydes

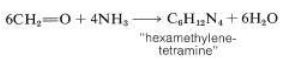
Ammonia adds readily to many aldehydes. For example,



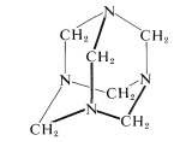
The aldehyde-ammonia adducts usually are not very stable. They readily undergo dehydration and polymerization. 1-Aminoethanol, for example, gives a cyclic trimer composition $C_6H_{15}N_3 \cdot 3H_2O$, mp 97°, with structure 4:



Methanal and ammonia react by a different course with the formation of a substance known as "hexamethylenetetramine":

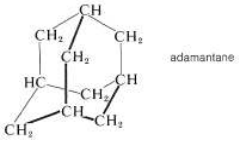


The product is a high-melting solid (mp $> 230^{\circ}$ d.) and its structure has been established by x-ray diffraction (Section 9-3). In fact, it was the first organic substance whose structure was determined in this way. The high melting point is clearly associated with the considerable symmetry and rigidity of the cage structure:



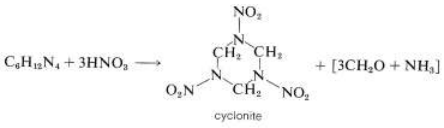
1,3,5,8-tetrazatricyclo[3.3.1.1^{3,7}]decane
(hexamethylenetetramine)

The corresponding all-carbon compound, adamantane (Section 12-8), also has a high melting point (268°):



adamantane

Treatment of hexamethylenetetramine with nitric acid gives the high explosive "cyclonite", which often is designated as RDX and was widely used in World War II:



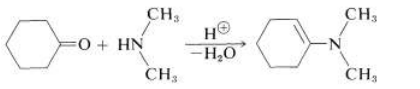
cyclonite

Then methanal and ammonia that split off the cage structure during the reaction with nitric acid need not be wasted. In the large-scale manufacture of cyclonite, a combination of nitric acid, ammonium nitrate, and ethanoic anhydride is used, which results in full utilization of the methanal and ammonia:

$$C_6H_{12}N_4 + 4HNO_3 + 2NH_4NO_3 + 6(CH_3CO)_2O \rightarrow 2_3CH_6O_6N_6 + 12CH_3CO_2H \qquad (16.5.1)$$

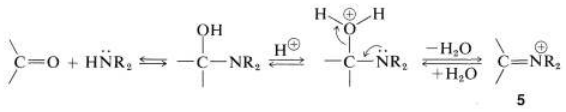
16.5.3.3: Enamines

Secondary amino compounds of the type $R_2N{-}H$ add to aldehyde and ketone carbonyl groups in an acid-catalyzed reaction in much the same way as do RNH_2 compounds - with one important difference. The product contains the structural unit $C{=}C{-}N$ rather than $C{-}C{=}N$; and because there is a carbon-carbon double bond, such a substance is called an enamine (alk*ene* + *amine*). An example is:



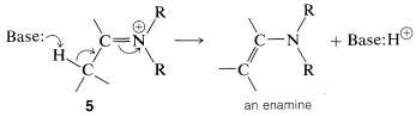
N,N-dimethyl-1-cyclohexenamine

The course of this reaction can be understood if we notice that loss of OH from the initial product leads to an immonium ion, 5, that cannot lose a proton and form a $C{=}N$ bond:



5

However, if there is a hydrogen on a carbon attached to the immonium carbon, it is possible for such a hydrogen to be lost as a proton with concurrent formation of the neutral enamine:

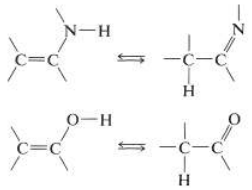


5 an enamine

Enamine formation, like many other carbonyl addition reactions, is readily reversible, and the carbonyl compound can be recovered by hydrolysis with aqueous acids. For this reason, to obtain a good conversion of carbonyl compound to enamine, it usually is necessary to remove the water that is formed by distilling it away from the reaction mixture.

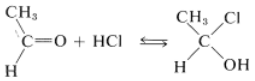
Enamines are useful synthetic intermediates for the formation of carbon-carbon bonds, as we will discuss in greater detail in Section 17-4B.

Enamines generally are unstable if there is a hydrogen on nitrogen. They rearrange to the corresponding imine. This behavior is analogous to the rearrangement of alkenols to carbonyl compounds (Section 10-5A):

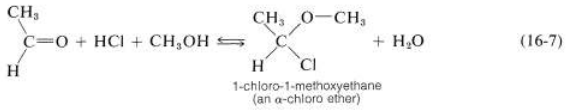


16.5.4: Hydrogen-Halide Addition to Carbonyl Groups and Replacement of Carbonyl by Halogen

Addition of hydrogen halides to carbonyl groups usually is so easily reversible as to preclude isolation of the addition products:



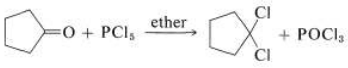
However, many aldehydes react with alcohols in the presence of an excess of hydrogen chloride to give α-chloro ethers:



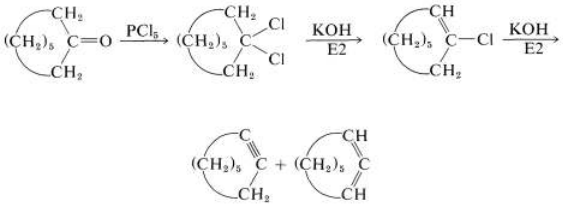
(16-7)

In carrying out laboratory syntheses of α-chloro ethers, gaseous hydrogen chloride is passed into a mixture of the alcohol and aldehyde. Aqueous HCl is not useful because the excess water gives an unfavorable equilibrium. α-Chloro ethers are highly reactive compounds that very readily undergo S_N2 as well as S_N1 and $E1$ reactions. Two simple examples, methoxychloromethane (chloromethyl methyl ether) and chloromethoxychloromethane (bis-chloromethyl ether), have been put under severe restrictions as the result of tests that show they have strong chemical carcinogenic properties.

Replacement of the carbonyl function by two chlorines occurs with phosphorus pentachloride in ether:



This reaction is useful in conjunction with $E2$ elimination to prepare alkenyl halides, allenes, and alkynes. Cycloalkenyl halides are easily prepared, but because of angle strain the cycloalkynes and cycloallenes with fewer than eight atoms in the ring cannot be isolated (see Section 12-7):



Replacement of a carbonyl group by *gem*-fluorines[3] can be achieved with molybdenum hexafluoride or sulfur tetrafluoride. Sulfur tetrafluoride converts carboxyl functions to trifluoromethyl groups:

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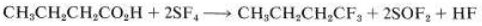
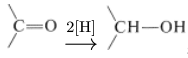
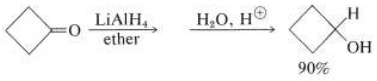


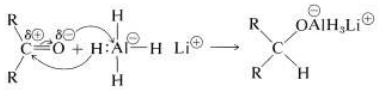
16.5.5: Hydride as a Nucleophile. Reduction of Carbonyl Compounds

16.5.5.1: Metal and Boron Hydrides

In recent years, inorganic hydrides such as lithium aluminum hydride, $LiAlH_4$, and sodium borohydride, $NaBH_4$, have become extremely important as reducing agents of carbonyl compounds. These reagents have considerable utility, especially with sensitive and expensive carbonyl compounds. The reduction of cyclobutanone to cyclobutanol is a good example, and you will notice that the net reaction is the addition of hydrogen across the carbonyl double bond,  ,

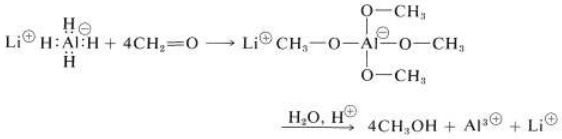


With the metal hydrides, the key step is transfer of a hydride ion to the carbonyl carbon of the substance being reduced.



The hydride transfer is analogous to the transfer of $R^{\ominus}$ from organometallic compounds to carbonyl groups (Section 14-12A).

Lithium aluminum hydride is best handled like a Grignard reagent, because it is soluble in ether and is sensitive to both oxygen and moisture. (Lithium hydride is insoluble in organic solvents and is not an effective reducing agent for organic compounds.) All four hydrogens on aluminum can be utilized:



The reaction products must be decomposed with water and acid as with the Grignard complexes. Any excess lithium aluminum hydride is decomposed by water and an acid with evolution of hydrogen:

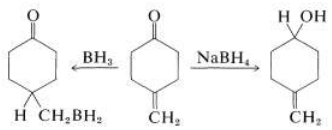
$$LiAlH_4 + 2H_2SO_4 \rightarrow \frac{1}{2}Li_2SO_4 + \frac{1}{2}{}_2Al(SO_4)_3 + 4H_2 \qquad (16.5.2)$$

Lithium aluminum hydride usually reduces carbonyl groups without affecting carbon-carbon double bonds. It is, in addition, a good reducing agent for carbonyl groups of carboxylic acids, esters, and other acid derivatives, as will be described in Chapter 18.

Sodium borohydride is a milder reducing agent than lithium aluminum hydride and will reduce aldehydes and ketones, but not acids or esters. It reacts sufficiently slowly with water in neutral or alkaline solution that reductions which are reasonably rapid can be carried out in water solution without appreciable hydrolysis of the reagent:

$$NaBH_4 + 4CH_2{=}O + 3H_2O \rightarrow 4CH_3OH + NaOB(OH)_2 \qquad (16.5.3)$$

Borane (as BH_3 in tetrahydrofuran or dimethyl sulfide) is an even milder reducing agent than BH_4^+ for the carbonyl group of aldehydes and ketones. This difference in reactivity can be used to advantage when selective reduction is necessary. For example, borohydride reduces a ketone carbonyl more rapidly than a carbon-carbon double bond, whereas borane reduces the carbon-carbon double bond more rapidly than carbonyl:



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A useful comparison of the reactivities of boranes and metal hydrides toward various types of multiple bonds is given in Table 16-6.

Table 16-6: *Comparison of Products and Reactivities of Functional Groups for Reduction with Borane and Metal Hydrides*[a,b]

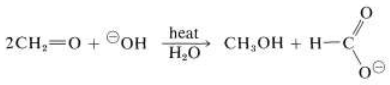
Functional group	Reduction product[c] LiAlH$_4$	NaBH$_4$	BH$_3$
—CO$_2$H	—CH$_2$OH (6)		—CH$_2$OH (1)
>C=C<			>CH—CH< (2)
—CHO	—CH$_2$OH (1)	—CH$_2$OH (1)	—CH$_2$OH (3)
>C=O	>CHOH (2)	>CHOH (2)	>CHOH (4)
—COCl	—CH$_2$OH (3)	—CH$_2$OH (3)	
—C—C—O	>CH—C—OH (4)	>CH—C—OH (4)	
—CO$_2$R	—CH$_2$OH (5)		
—CONR$_2$	—CH$_2$NR$_2$ (6) or —CHO		
—C≡N	—CH$_2$NH$_2$ (7) or —CHO		
>C=NOH	>CHNH$_2$ (8)		
—C—NO$_2$	—C—NH$_2$ (9)		
—CH$_2$X[d]	—CH$_3$ (10)		

[a]Numbers in parenthesis indicate order of reactivity in the vertical column with (1) as the most reactive. [b]No product is listed where reaction normally is too slow to be of practical value. [c]After hydrolysis. [d]X is halogen or sulfonate, —O—SO$_2$—Ar.

16.5.5.2: The Cannizzaro Reaction

A characteristic reaction of aldehydes without α hydrogens is the self oxidation-reduction they undergo in the presence of strong base. With methanal as an example,

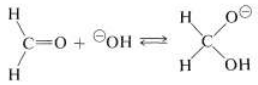
$$2CH_2{=}O + {}^{\ominus}OH \xrightarrow[H_2O]{heat} CH_3OH + H{-}C(=O)O^{\ominus}$$



If the aldehyde has α hydrogens, other reactions usually occur more rapidly.

The mechanism of this reaction, usually called the **Cannizzaro reaction**,[4] combines many features of other processes studied in this chapter. The first step is reversible addition of hydroxide ion to the carbonyl group:

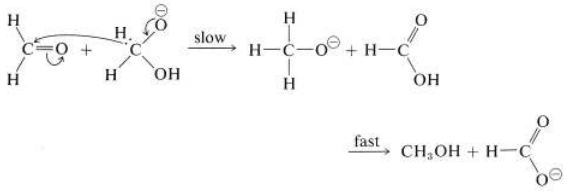
$$H_2C{=}O + {}^{\ominus}OH \rightleftharpoons H_2C(O^{\ominus})OH$$



A hydrogen can be transferred as hydride ion to methanal from the hydroxyalkoxide ion, thereby reducing the methanal to methanol:

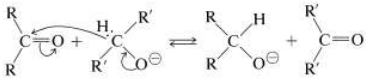
$$H_2C{=}O + H_2C(O^{\ominus})OH \xrightarrow{slow} H{-}C(H)_2{-}O^{\ominus} + H{-}C(=O)OH$$

$$\xrightarrow{fast} CH_3OH + H{-}C(=O)O^{\ominus}$$

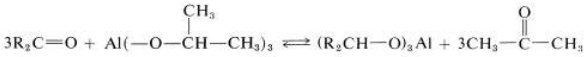


16.5.5.3: Reduction with Aluminum Alkoxides

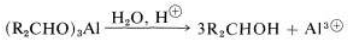
Hydride transfer similar to that of the Cannizzaro reaction also may be achieved from a C–H grouping in an alkoxide ion corresponding to a primary or secondary, but not a tertiary, alcohol. This is expected to be a reversible reaction, because the products are another alkoxide and another carbonyl compound:



To utilize this equilibrium process as a practical reduction method requires rather special conditions. It is preferable to use an aluminum alkoxide, $Al(OR)_3$, rather than a sodium alkoxide, $\overset{\oplus}{Na}\overset{\ominus}{O}R$, to ensure that the reaction mixture is not too strongly basic. (Carbonyl compounds, particularly aldehydes, are sensitive to strong bases.) The overall reaction may be written



for which the alkoxide is derived from 2-propanol. The advantage of this method is that the reaction can be driven essentially to completion by distilling out the 2-propanone as it is formed. The reduction product subsequently can be obtained by acid hydrolysis of the aluminum alkoxide:



16.5.5.4: Biological Reactions

These have been discussed already in the context of the reverse reactions - oxidation of alcohols (Section 15-6C).

[2]Pronounced variously as *ill/id*, *yill/id*, *ill/ide*, *yill/ide*. The dipolar structures usually written for ylides are an oversimplified representation of the bonding in these substances.

[3]*Gem* is an abbreviation for *geminal* (twinned) and is a common *conversational* designation for arrangements having two identical substituents on one carbon.

[4]Named after its discoverer, the same Cannizzaro who, in 1860, made an enormous contribution to the problem of obtaining self-consistent atomic weights (Section 1-1).

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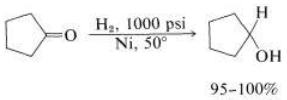
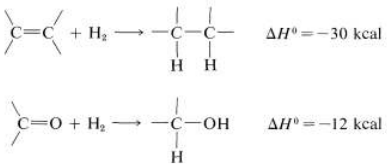
16.6: Catalytic Hydrogenation

The simplest large-scale procedure for reduction of aldehydes and ketones to alcohols is by catalytic hydrogenation:



95–100%

The advantage over most other kinds of reduction is that usually the product can be obtained simply by filtration from the catalyst, then distillation. The common catalysts are nickel, palladium, copper chromite, or platinum activated with ferrous ion. Hydrogenation of aldehyde and ketone carbonyl groups is much slower than of carbon-carbon double bonds so more strenuous conditions are required. This is not surprising, because hydrogenation of carbonyl groups is calculated to be less exothermic than that of carbon-carbon double bonds:



It follows that it is generally difficult to reduce a carbonyl group in the presence of a carbon-carbon double bond by hydrogenation without also saturating the double bond. Other reducing agents are more selective (Section 16-4E).

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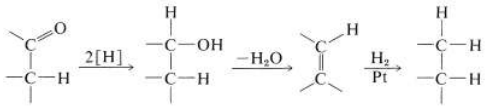
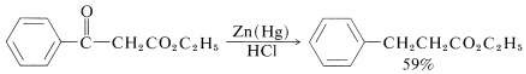
16.7: Reduction of Carbonyl Compounds to Hydrocarbons

There are several methods of transforming $\rangle C{=}O$ to $\rangle CH_2$. In some cases, the following three-step sequence of conventional reactions may be useful:



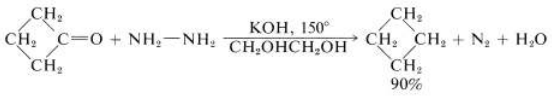
This route requires a hydrogen α to the carbonyl function and may give rearrangement in the dehydration step (Sections 8-9B and 15-5E). Alternatively, the hydroxyl can be converted to a better leaving group (halogen or sulfonate ester), which then may be displaced by $H^{\ominus}$ (as $LiAlH_4$; see Table 16-6):

More direct methods may be used, depending on the character of the R groups of the carbonyl compound. If the R groups are stable to a variety of reagents there is no problem, but with sensitive R groups not all methods are equally applicable. When the R groups are stable to acid but unstable to base, the **Clemmensen** reduction with amalgamated zinc and hydrochloric acid is often very useful.

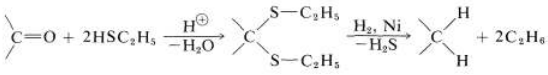


The mechanism of the Clemmensen reduction is not well understood. It is clear that in most cases the alcohol is *not* an intermediate, because the Clemmensen conditions do not suffice to reduce most alcohols to hydrocarbons.

When the R groups of the carbonyl compound are stable to base but not to acid, the **Huang-Minlon modification of the Wolff-Kishner reduction** usually gives good results. This procedure involves heating the carbonyl compound in a high-boiling polar solvent, such as 1,2-ethanediol, with hydrazine and potassium hydroxide and driving the reaction to completion by distilling out the water formed:



When the carbonyl compound is sensitive to both acids and bases, or for other reasons gives poor yields in both the Clemmensen and Wolff-Kishner reductions, a recourse may be reduction of the corresponding thioacetal or thioketal with hydrogen-saturated Raney nickel (Section 11-2B):



Thioketals, unlike ordinary ketals, are formed readily from ketones and thiols (RSH) in the presence of acid catalysts. The desulfurization procedure usually goes well, but the product is rather difficult to separate by extraction from the large excess of Raney nickel required for optimum yields.

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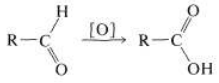
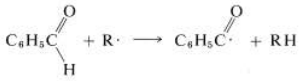
16.8: Oxidation of Carbonyl Compounds

Aldehdyes are oxidized easily by moist silver oxide or by potassium permanganate solution to the corresponding acids. The mechanism of the permanganate oxidation has some resemblance to the chromic acid oxidation of alcohols (Section 15-6B):



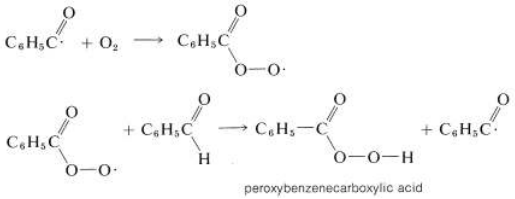
Many aldehydes are oxidized easily by atmospheric oxygen in a radical-chain mechanism. Oxidation of benzenecarbaldehyde to benzenecarboxylic acid has been studied particularly well and involves formation of a peroxy acid as an intermediate. Reaction is initiated by a radical $\mathrm{R}\cdot$ which breaks the relatively weak aldehyde $\mathrm{C{-}H}$ bond $(86\ \mathrm{kcal})$.

- *initiation*

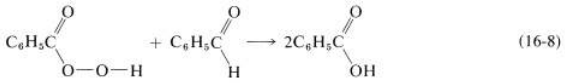


The benzenecarbonyl radical, $\mathrm{C_6H_5\dot{C}O}$, then propagates a chain reaction.

- *propagation*

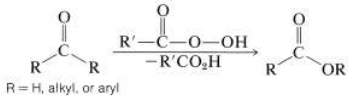


The peroxy acid formed then reacts with benzenecarbaldehyde to give two molecules of carboxylic acid:

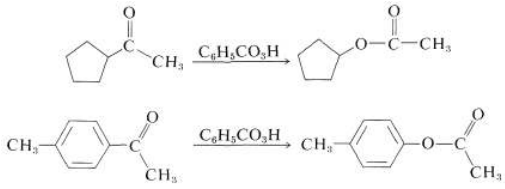


(16-8)

The oxidation of benzenecarbaldehyde with peroxybenzenecarboxylic acid (Equation 16-8) is an example of a reaction of wide applicability in which aldehydes are oxidized to carboxylic acids, and ketones are oxidized to esters.



The reaction, which is known as the **Baeyer-Villiger oxidation**, has synthetic utility, particularly for the oxidation of ketones to esters because ketones normally are difficult to oxidize without degrading the structure to smaller fragments. Two examples of the Baeyer-Villiger reaction follow:



The mechanism of the Baeyer-Villiger oxidation has been studied extensively and is of interest because it involves a rearrangement step in which a substituent group (R) moves from carbon to oxygen. The reaction sequence is shown in Equations 16-9 through 16-11:

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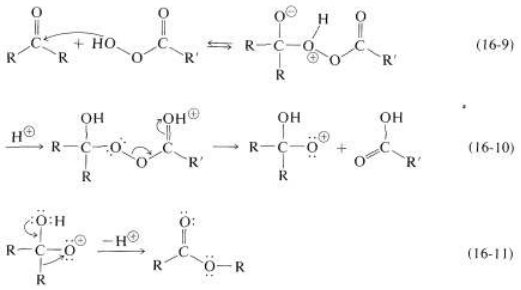

In the first step, Equation 16-9, the peroxy acid adds to the carbonyl group. The adduct has several oxygen atoms on which protons can reside, and there will be rapid shifts of protons between these oxygens. However, at some stage the structure will be appropriate to allow elimination of a molecule of carboxylic acid, $\mathrm{R'CO_2H}$, Equation 16-10. The resulting intermediate has an electron-deficient oxygen atom with only six valence electrons. As with carbocations and borane complexes (Sections 8-9B, 15-5E, 11-6E, and 16-9D,G), a neighboring R group can move over with its bonding electron-pair to the electron-deficient (oxygen) atom, Equation 16-11. You will notice that for aldehydes, the aldehyde hydrogen migrates in preference to the alkyl or aryl group. In the other examples given, a cycloalkyl migrates in preference to a methyl group, and aryl in preference to methyl.

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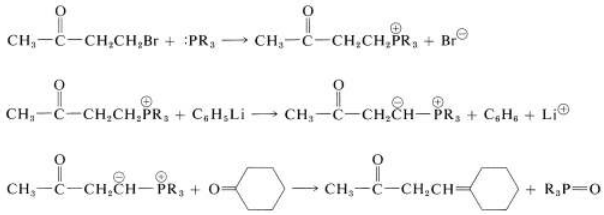
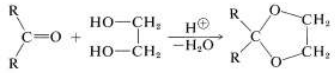
16.9: Protection of Carbonyl Groups

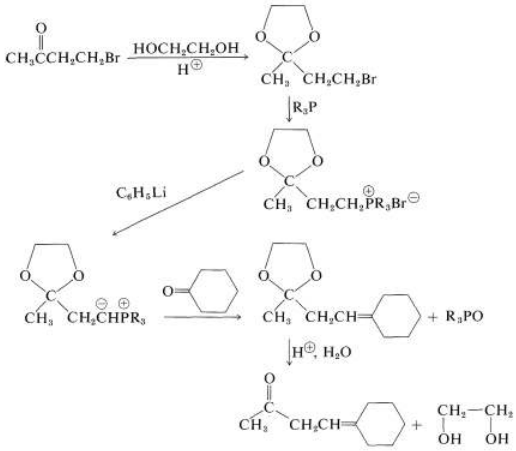
There are few reactions of aldehydes and ketones that do not in some way affect the carbonyl function. For this reason, it may be necessary to protect the carbonyl function when it is desirable to avoid reaction at this function. For example, you may plan to synthesize 4-cyclohexylidene-2-butanone by way of a Wittig reaction (Section 16-4A), which would involve the following sequence:



This synthesis would *fail* in the second step because the phenyllithium would add irreversibly to the carbonyl group. To avoid this, the carbonyl group would have to be protected or blocked, and the most generally useful method of blocking is to convert the carbonyl group to a ketal, usually a cyclic ketal:



With the carbonyl group suitably protected, the proposed synthesis would have a much better chance of success:



Notice that the carbonyl group is regenerated by acid hydrolysis in the last step.

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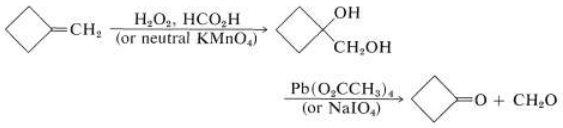
16.10: Preparative Methods for Aldehydes and Ketones

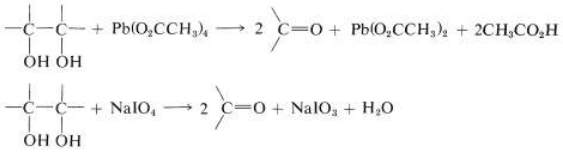
A number of useful reactions for the preparation of aldehydes and ketones, such as ozonization of alkenes and hydration of alkynes, have been considered in previous chapters. These and other methods of preparation are summarized in Tables 16-7 and 16-8 at the end of the chapter. Only a few rather general methods that we have not discussed will be taken up here.

16.10.1: Oxidation of 1,2-Diols and Alkenes

Aldehydes and ketones often can be prepared by oxidation of alkenes to 1,2-diols (Sections 11-7C and 11-7D), followed by oxidative cleavage of the 1,2-diols with lead tetraethanoate or sodium periodate. For example,

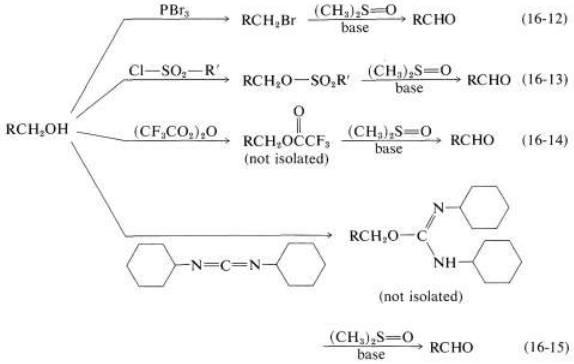


Cleavage of glycols with these reagents proceeds according to the following stoichiometry:



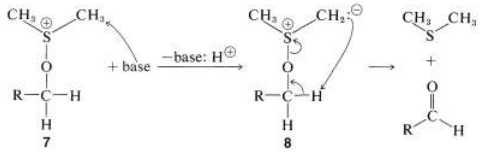
16.10.2: Oxidation of Primary Alcohols and Related Compounds

In Chapter 15 primary alcohols, RCH_2OH, were shown to be readily oxidized to aldehydes, $RCHO$, and secondary alcohols, R_2CHOH, to ketones, R_2CO, by inorganic reagents such as CrO_3 and $KMnO_4$. However, it is a problem to avoid overoxidation with primary alcohols because of the ease with which aldehydes are oxidized to acids, $RCHO \rightarrow RCO_2H$. A milder oxidant is methylsulfinylmethane [dimethyl sulfoxide, $(CH_3)_2S{=}O$], and this reagent can be used to prepare aldehydes from alcohols by way of an intermediate such as the ester or halide in which the OH group is converted to a better leaving group:



Whichever method is employed, the key step is the formation of an alkoxysulfonium salt, 7, by a displacement reaction involving dimethyl sulfoxide as an oxygen nucleophile. (Notice that the $S{=}O$ bond, like the $C{=}O$ bonds, is strongly polarized as $\overset{\oplus}{S}-\overset{\ominus}{O}$.)

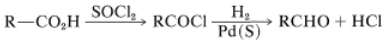
In the examples listed in Equations 16-12 through 16-15, the X group is Br, $-OSO_2R'$, $-O_2CCF_3$, and $C_6H_{11}\overset{-O}{\underset{|}{N}}HC{=}NC_6H_{11}$, respectively. In the nest step a sulfur ylide, 8, is formed from the reaction of a base with 7, but the ylide evidently is unstable and fragments by an internal $E2$ reaction to form an aldehyde:



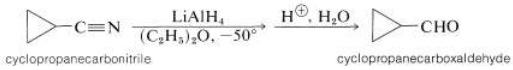
16.10.3: Reduction of Carboxylic Acids to Aldehydes

Conversion of a carboxylic acid to an aldehyde by direct reduction is not easy to achieve, because acids generally are difficult to reduce, whereas aldehydes are easily reduced. Thus the problem is to keep the reaction from going too far.

The most useful procedures involve conversion of the acid to a derivative that either is more easily reduced than an aldehyde, or else is reduced to a substance from which the aldehyde can be generated. The so-called **Rosenmund reduction** involves the first of these schemes; in this procedure, the acid is converted to an acyl chloride, which is reduced with hydrogen over a palladium catalyst to the aldehyde in yields up to 90%. The rate of reduction of the aldehyde to the corresponding alcohol is kept at a low level by poisoning the catalyst with suflur:

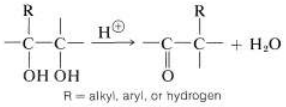


Metal hydrides, such as lithium aluminum hydride, also can be used to reduce derivatives of carboxylic acids (such as amids and nitriles see Table 16-6) to aldehydes. An example follows:



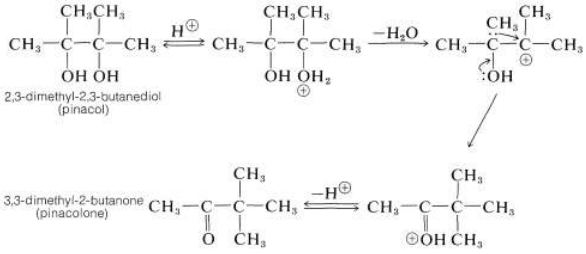
16.10.4: Rearrangements of 1,2-Diols

Many carbonyl compounds can be synthesized by acid-catalyzed rearrangements of 1,2-diols (a type of reaction often called the "pinacol-pinacolone" rearrangement).



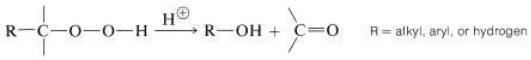
The general characteristics of the reaction are similar to those of carbocation rearrangements (Section 8-9B). The acid assists the reaction by protonating one of the –OH groups to make it a better leaving group. The carbocation that results then can undergo rearrangement by shift of the neighboring R group with its pair of bonding electrions to give a new, thermodynamically more stable species with a carbon-oxygen double bond (see Section 16-7).

The prototype of this rearrangement is the conversion of pinacol to pinacolone as follows:

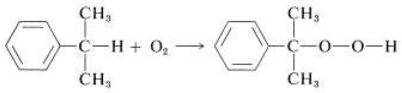


16.10.5: Rearrangements of Hydroperoxides

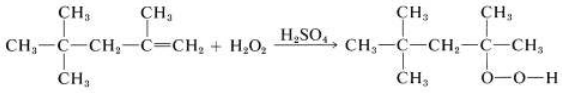
An important method of preparing carbonyl (and hydroxy) compounds, especially on an industrial scale, is through rearrangements of alkyl hydroperoxides:



The peroxides can be made in some cases by direct air oxidation of hydrocarbons,

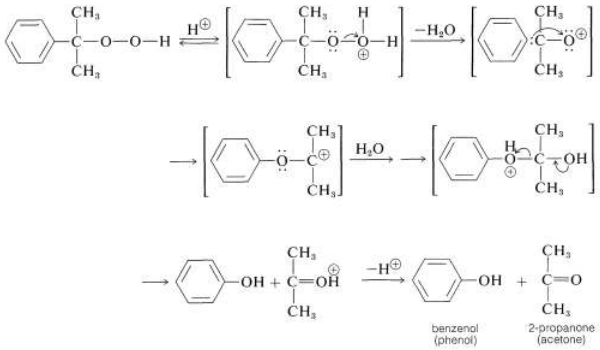


and in others by sulfuric acid-induced addition of hydrogen peroxide (as $H{-}O_2H$) to double bonds:



(Notice that hydrogen peroxide in methanoic acid behaves differently toward alkenes in producing addition of $HO{-}OH$, Section 11-7D.) The direct air oxidation of hydrocarbons is mechanistically similar to that of benzenecarbaldehyde (Section 16-7).

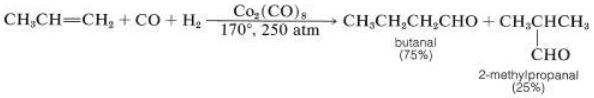
The rearrangements of hydroperoxides are acid-catalyzed and are analogous to carbocation rearrangements except that positive oxygen (with only *six* valence electrons) instead of positive carbon is involved in the intermediate stage:



In principle, either phenyl or methyl could migrate to the positive oxygen, but only phenyl migration occurs in this case. The rearrangement reaction is closely related to the Baeyer-Villiger reaction (Section 16-7).

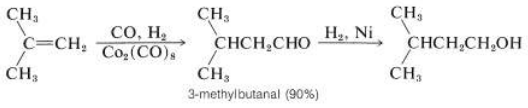
16.10.6: Aldehydes by Hydroformylation of Alkenes

This reaction is important for a number of reasons. It is an industrial synthesis of aldehydes from alkenes by the addition of carbon monoxide and hydrogen in the presence of a cobalt catalyst. A prime example is the synthesis of butanal from propene, in which 2-methylpropanal also is formed:



As you can see, the reaction formally amounts to the addition of methanal as $H{-}CHO$ to the alkene double bond. Because one additional carbon atom is introduced as a "formyl" CHO group, the reaction often is called *hydroformylation*, although the older name, *oxo reaction*, is widely used.

Hydroformylation to produce aldehydes is the first step in an important industrial route to alcohols. The intermediate aldehydes are reduced to alcohols by catalytic hydrogenation. Large quantities of C_4-C_8 alcohols are prepared by this sequence:



The history of the oxo reaction is also noteworthy. It was developed originally in Germany in the years following World War I. At that time, the German chemical industry was faced with inadequate supplies of petroleum. Many German chemists therefore turned

to research on ways by which hydrocarbons could be synthesized from smaller building blocks, particularly carbon monoxide and hydrogen derived from coal. The success achieved was remarkable and led to alkane and alkene syntheses known as the **Fischer-Tropsch process**:

$$n\mathrm{CO} + (2n+1)\mathrm{H_2} \xrightarrow[\text{catalyst}]{\text{cobalt}} \mathrm{C}_n\mathrm{H}_{2n+2} + n\mathrm{H_2O}$$
$$n\mathrm{CO} + 2n\mathrm{H_2} \longrightarrow \mathrm{C}_n\mathrm{H}_{2n} + n\mathrm{H_2O}$$

This reaction in turn led to the discovery that aldehydes were formed by the further addition of carbon monoxide and hydrogen to alkenes, and was further developed as the oxo process for production of alcohols. The combination $\mathrm{CO} + \mathrm{H_2}$ often is called "synthetic gas". It is prepared by the reduction of water under pressure and at elevated temperatures by carbon (usually coke), methane, or higher-molecular-weight hydrocarbons:

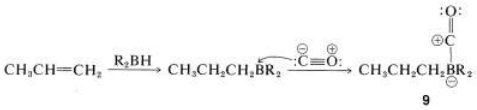
$$\mathrm{C} + \mathrm{H_2O} \longrightarrow \mathrm{CO} + \mathrm{H_2}$$
$$\mathrm{CH_4} + \mathrm{H_2O} \longrightarrow \mathrm{CO} + 3\mathrm{H_2}$$

16.10.7: Carbonylation of Alkylboranes

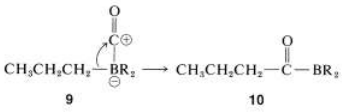
The aldehyde synthesis by hydroformylation of alkenes described in the preceding section can be achieved indirectly using boron hydrides. An oversimplified expression of this reaction is

$$\mathrm{CH_3CH{=}CH_2} \xrightarrow{\mathrm{R_2BH,\ CO}} \mathrm{CH_3CH_2CH_2CHO}$$

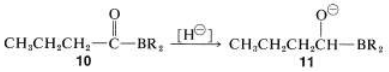
The overall reaction is quite complex but involves a rearrangement similar to that described for the hydroboration-oxidation of alkenes (Section 11-6E). The first step is hydroboration of the alkene to a trialkylborane. When the trialkylborane is exposed to carbon monoxide, it reacts (carbonylates) to form a tetracovalent boron, 9:



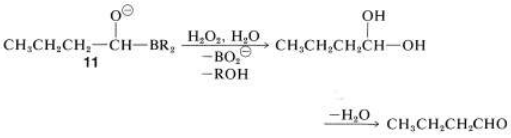
The complex 9 is unstable and rearranges by transfer of an alkyl group from boron to the electron-deficient carbonyl carbon to give 10:



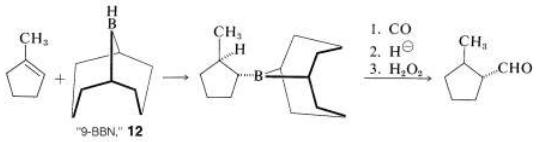
Now, if a metal-hydride reducing agent, such as $\mathrm{LiAlH_4}$, is present, the carbonyl group of 10 is reduced and 11 is formed:



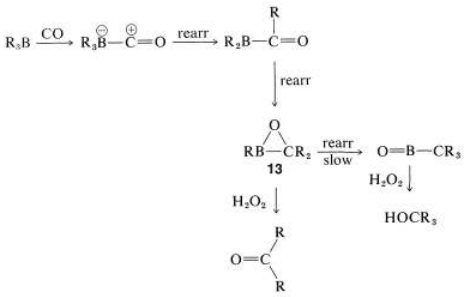
The reduction product, 11, can be converted to an aldehyde by oxidation with aqueous hydrogen peroxide, provided the pH is carefully controlled. (Remember, aldehydes are unstable in strong base.)



You may have noticed that only *one* of the three alkyl groups of a trialkylborane is converted to an aldehyde by the carbonylation-reduction-oxidation sequence. To ensure that carbonylation takes the desired course without wasting the starting alkene, hydroboration is achieved conveniently with a hindered borane, such as "9-BBN", 12. With 12, only the least-hindered alkyl group rearranges in the carbonylation step:



Carbonylation of alkylboranes also can produce ketones. The conditions are similar to those in the aldehyde synthesis except that the hydride reducing agent is omitted. By omitting the reducing agent, a second boron-to-carbon rearrangement can occur. Oxidation then produces a ketone:



Rearrangement will continue a third time (ultimately to produce a tertiary alcohol) unless movement of the alkyl group remaining on boron in 13 is prevented by steric hindrance.

16.10.8: Contributors and Attributions

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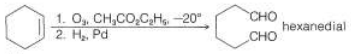
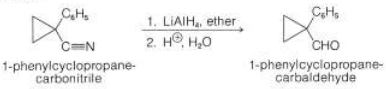
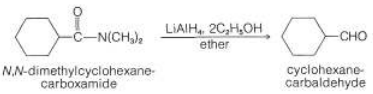
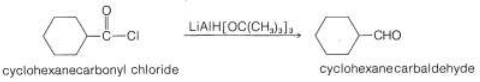
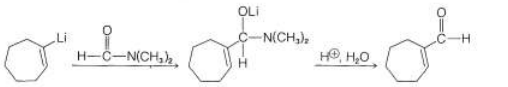
16.11: General Methods for the Preparation of Aldehydes and Ketones

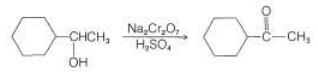
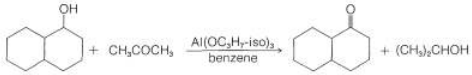
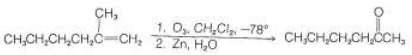
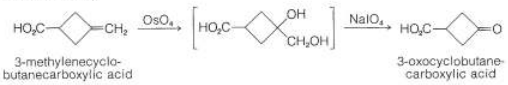
Table 16-7: *General Methods for the Preparation of Aldehydes and Ketones*[a]

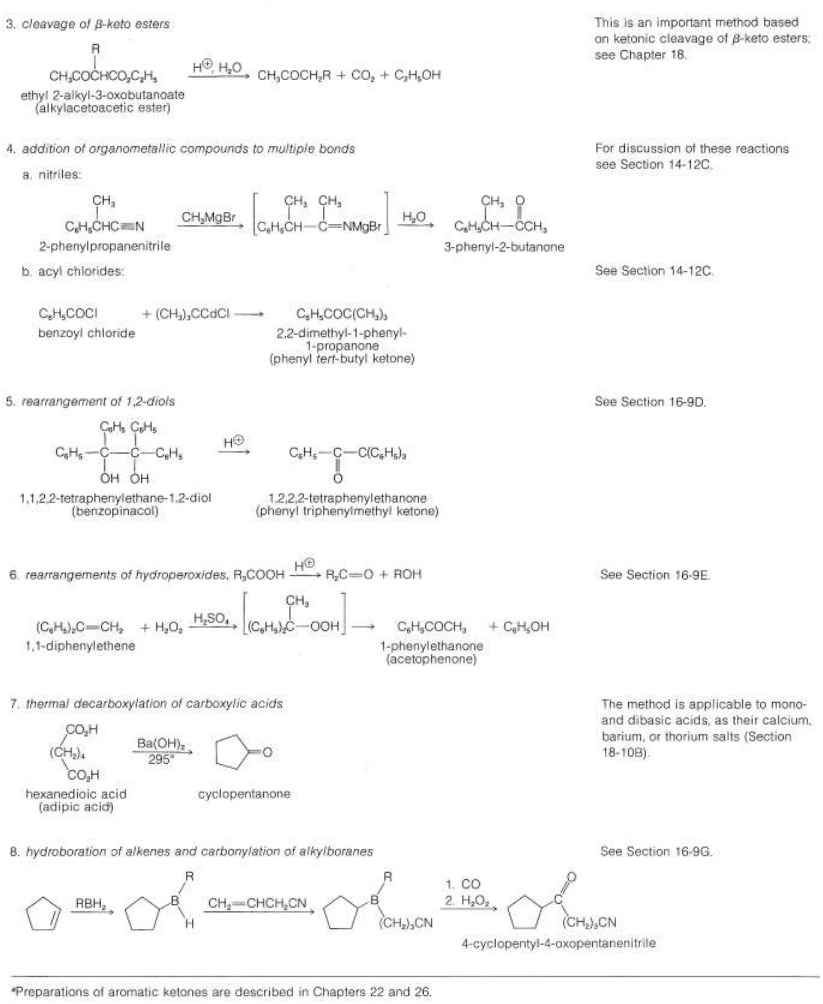
Reaction	Comment
1. *oxidation of alkenes with ozone*, $RCH{=}CH_2 \xrightarrow[2.\ H_2,\ Pd]{1.\ O_3} RCHO + H_2C{=}O$	See Section 11-7A; of limited preparative use; mainly used to locate position of double bonds in structure determinations.
 cyclohexene → hexanedial	
2. *oxidative cleavage of 1,2-diols*, $RCHCH_2$ (HO, OH) $\xrightarrow[\text{or } Pb(OCOCH_3)_4]{NaIO_4} RCHO + H_2C{=}O$	The 1,2-diols may be generated from alkenes *in situ* (see discussion in Section 16-9A and Method 2b, Table 16-8).
$C_6H_5CH_2CHCH_2$ (HO, OH) $\xrightarrow{Pb(OCOCH_3)_4} C_6H_5CH_2CHO + H_2C{=}O$	
3-phenylpropane-1,2-diol → phenylethanal	
3. *oxidation of primary alcohols*, $RCH_2OH \xrightarrow{[O]} RCHO$	See Section 15-6B; useful for the preparation of volatile aldehydes because with these, further oxidation usually can be prevented by distilling the product out of the reaction mixture.
a. chromic acid:	
$CH_3CH_2CH_2OH \xrightarrow[H_2SO_4]{Na_2Cr_2O_7} CH_3CH_2CHO$	
1-propanol → propanal	
b. aluminum alkoxides (Oppenauer oxidation):	See Section 16-4E; often useful for low-boiling aldehydes that can be distilled out of mixture as formed, thereby preventing condensation reactions; aluminum isopropoxide or *tert*-butoxide commonly are used as catalysts; carbon–carbon double bonds are not attacked.
$(CH_3)_2C{=}CHCH_2CH_2CH_2OH + C_6H_5CH{=}CHCHO \xrightarrow{Al(OC_3H_7\text{-iso})_3}$	
5-methyl-4-hexen-1-ol + 3-phenylpropenal → $(CH_3)_2C{=}CHCH_2CH_2CHO$ + $C_6H_5CH{=}CHCH_2OH$	
5-methyl-4-hexenal + 3-phenyl-2-propen-1-ol	
c. dimethyl sulfoxide:	See Sections 16-9B and 18-7C
$HC{\equiv}C(CH_2)_5CH_2OH \xrightarrow{HI} HC{\equiv}C(CH_2)_5CH_2I \xrightarrow[NaHCO_3]{(CH_3)_2SO} HC{\equiv}C(CH_2)_5CHO$	
7-octyn-1-ol → 7-octynal	
4. *Rosenmund reduction of acyl chlorides*, $ROCl \xrightarrow{H_2} RCHO$	See Section 16-9C; palladium on $BaSO_4$ is used as the catalyst in presence of sulfur.
$C_6H_5CH_2\overset{O}{\overset{\|}{C}}{-}Cl \xrightarrow[S,\ \text{toluene},\ 125°]{H_2,\ Pd\text{–}BaSO_4} C_6H_5CH_2CHO$	
phenylethanoyl chloride → phenylethanal	
5. *reductions with lithium aluminum hydride*	
a. nitriles:	See Section 16-9C.
 1-phenylcyclopropanecarbonitrile → 1-phenylcyclopropanecarbaldehyde	
b. amides:	Ethanol and $LiAlH_4$ produce $Li[AlH_3(OC_2H_5)_2]$, which is milder than $LiAlH_4$; the amide must be tertiary ($—CONR_2$, where $R \neq H$).
 *N,N*-dimethylcyclohexanecarboxamide → cyclohexanecarbaldehyde	
c. acyl chlorides:	The reducing agent is prepared from $LiAlH_4$ and *tert*-butyl alcohol—it is milder than $LiAlH_4$ (see Method 5b); the preferred solvent is diglyme, $(CH_3OCH_2CH_2)_2O$.
 cyclohexanecarbonyl chloride → cyclohexanecarbaldehyde	

6. *addition of Grignard reagents to 1,1,1-triethoxymethane (ethyl orthoformate)* $CH_3(CH_2)_4MgBr + HC(OC_2H_5)_3 \longrightarrow CH_3(CH_2)_4CH(OC_2H_5)_2 + C_2H_5OMgBr$ pentylmagnesium bromide → 1,1-diethoxyhexane $CH_3(CH_2)_4CH(OC_2H_5)_2 \xrightarrow{HCl,\ H_2O} CH_3(CH_2)_4CHO$ hexanal	The addition product is an acetal, which can be hydrolyzed in dilute acid to the aldehyde.
7. *addition of organometallic compounds to N,N-dimethylmethanamide*  1-cycloheptenecarbaldehyde	The tertiary amine, $R_2CHN(CH_3)_2$, often is a major product with RMgX and $HCON(CH_3)_2$. See Section 14-12C.
8. *hydration of alkynes* $HC{\equiv}CH + H_2O \xrightarrow{Hg^{2\oplus},\ H^{\oplus}} [H_2C{=}CHOH] \longrightarrow CH_3CHO$ ethyne → ethanal	A commercial synthesis of ethanal; see Section 10-5A.
9. *hydrolysis of aldehyde derivatives* – includes hydrogen sulfite addition compounds, acetals, oximes, Schiff's bases, hydrazones, and semicarbazones	More useful for the purification than for preparation of aldehydes.
10. *addition of carbon monoxide and hydrogen to alkenes* cyclopentene → cyclopentanecarbaldehyde (65%)	See Section 16-9F.
11. *hydroboration of alkenes and carbonylation of alkylboranes* $CH_2{=}CHCH_2CN \xrightarrow{R_2BH} R_2BCH_2CH_2CH_2CN \xrightarrow{CO} \xrightarrow{H^{\ominus}} \xrightarrow{[O]} HCCH_2CH_2CH_2CN$ 3-butenenitrile → 5-oxopentanenitrile	See Section 16-9G; R_2BH = "9-BBN"

[a]Preparations of aromatic aldehydes are described in Chapters 22 and 26.

Table 16-8: *General Methods for the Preparation of Ketones*[a]

Reaction	Comment
1. *oxidation of secondary alcohols*, $R_2CHOH \xrightarrow{[O]} R_2C{=}O$	See Section 15-6.
a. with chromic acid:  1-cyclohexylethanol → 1-cyclohexylethanone	
b. Oppenauer oxidation:  α-decalol + 2-propanone → α-decalone + $(CH_3)_2CHOH$	See Section 16-4E.
2. *oxidation of alkenes*, $R_2C{=}CR_2 \xrightarrow{[O]} 2R_2C{=}O$	See Section 11-7A and Method 1, Table 16-7.
a. with ozone: 	
b. via 1,2-diols:  3-methylenecyclobutanecarboxylic acid → 3-oxocyclobutanecarboxylic acid	See Section 16-9A and Method 2, Table 16-7.



*Preparations of aromatic ketones are described in Chapters 22 and 26.

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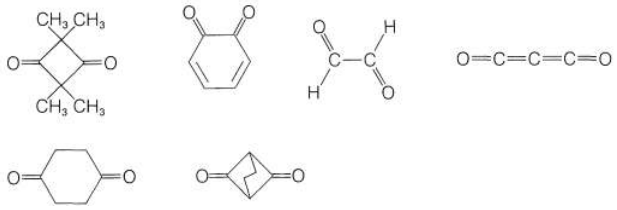
16.E: Carbonyl Compounds I (Exercises)

Exercise 16-1 Draw valence-bond structures and an atomic-orbital model for carbon monoxide. Why can the bond energy of this molecule be expected to be higher than for other carbonyl compounds (see Table 16-1)? Explain why the dipole moment of CO is very small (0.13 debye).

Exercise 16-2 Which of the following compounds would you expect to have zero or nearly zero dipole moments? Give your reasoning and don't forget possible conformational equilibria. (Models will be helpful.)



Exercise 16-3 The discussion in Section 16-1B explicitly refers to addition of *polar* reagents to carbonyl groups. Therefore an ionic mechanism is implied. Consider whether the same reactivity differences would be expected for ethene and methanal in the *radical-chain* addition of hydrogen bromide to methanal and ethene initiated by peroxides. What about the relative equilibrium constants? Show your reasoning. (Review Section 10-7.)

Exercise 16-4 Which compound in each of the following pairs would you expect to be more reactive toward addition of a common nucleophilic agent such as hydroxide ion to the carbonyl bond? Indicate your reasoning.

a. 2-propanone and 1,1,1-trichloro-2-propanone
b. 2,2-dimethylpropanal and 2-propanone
c. methyl 2-oxopropanoate and methyl 3-oxobutanoate
d. 2-propanone and 2,3-butanedione
e. 2-oxopropanenitrile and 2-propanone
f. ketene $(CH_2{=}C{=}O)$ and cyclobutanone
g. bicyclo[2.1.1]-5-hexanone and cyclobutanone

Exercise 16-5 Use the infrared spectra given in Figure 16-2 and the data of Tables 9-2 and 16-3 to deduce the type of carbonyl compound giving rise to each spectrum.

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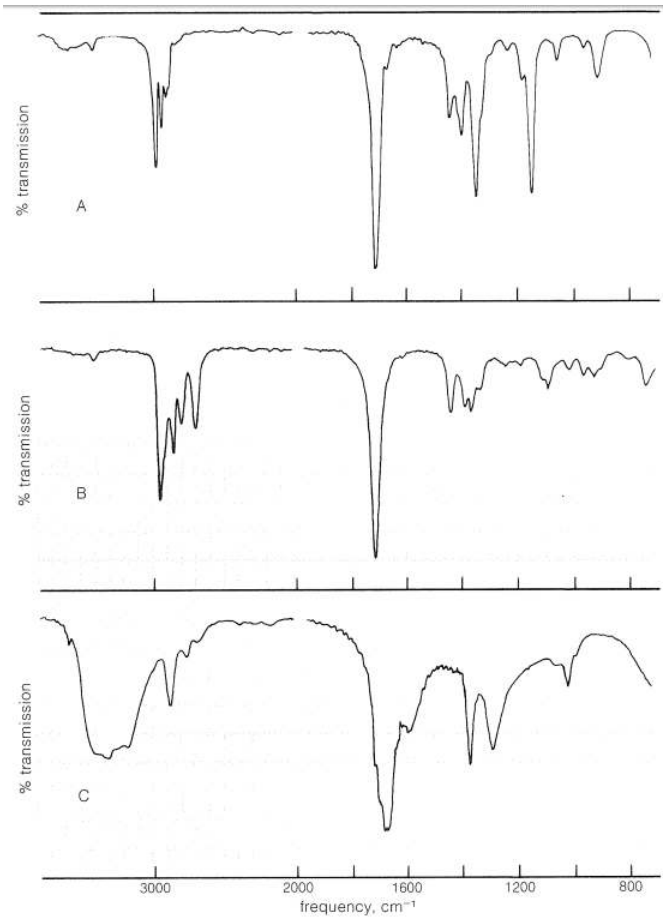

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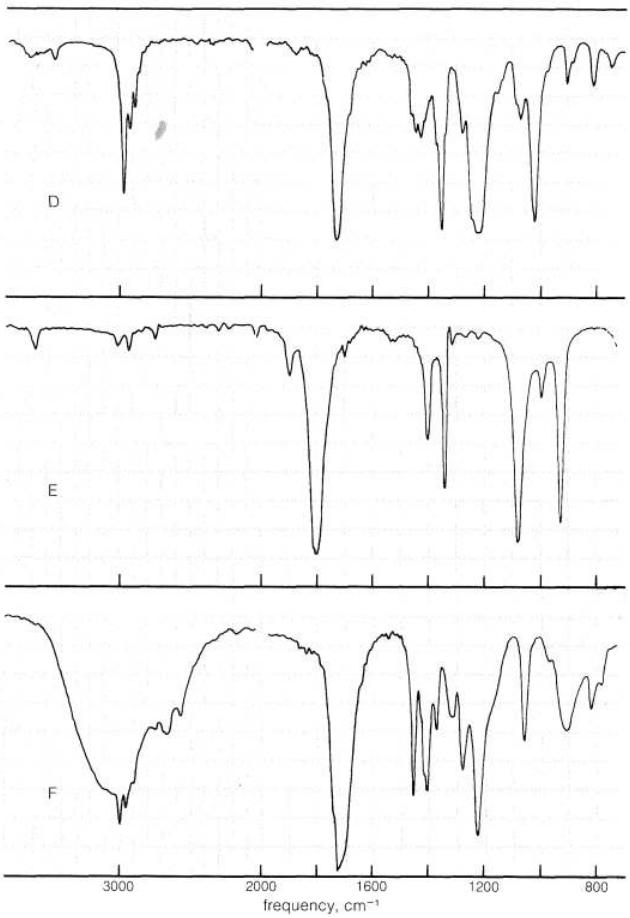
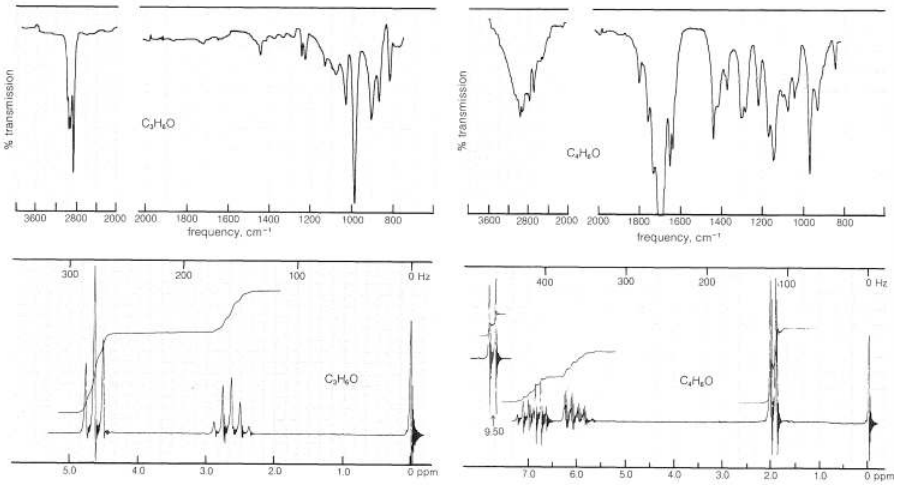


Figure 16-2: *Infrared spectra for Exercise 16-5.*

Exercise 16-6 A hydrocarbon isolated from a plant extract was treated with ozone, and the ozonide decomposed with zinc to give two ketones, A and B, which were readily separated by gas chromatography. Ketone A gave a mass spectrum identical with that of Figure 9-52c while ketone B gave mass spectral peaks at $m/e = 100\,(\mathrm{M}^+)$, 85, 58, and 43. With this information, suggest possible structures for these ions and the parent hydrocarbon. Give your reasoning.

Exercise 16-7 Show how structures can be deduced for the four substances with the infrared and NMR spectra shown in Figure 16-3.



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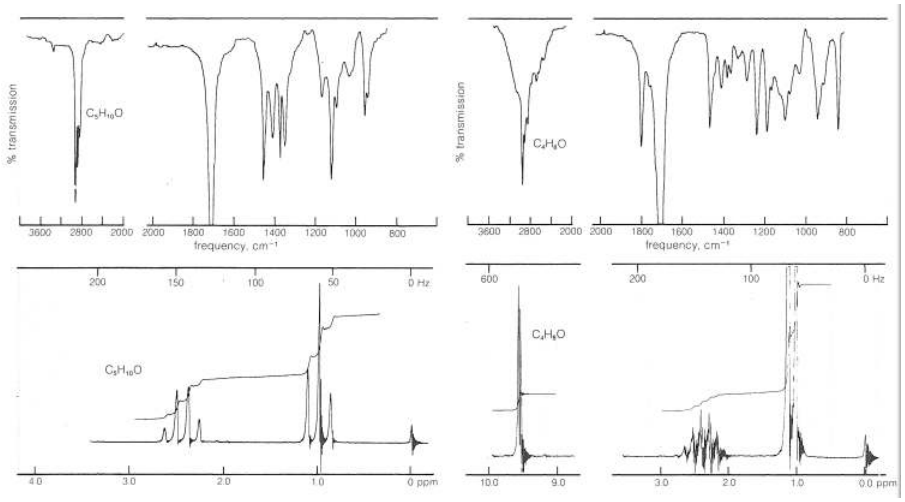


Figure 16-3: *Infrared and proton NMR spectra of four organic compounds. See Exercise 16-7.*

Exercise 16-8 Assuming that you had ready access to ultraviolet, infrared, NMR, and mass spectrometers, which spectral technique would you select to differentiate as unambiguously as possible between the following pairs of compounds? Give your reasoning in enough detail to show that you understand how well each technique is capable of distinguishing between the members of each pair (D = hydrogen of mass 2)

a. 2-butanone and 2-butanone-D_3
b. 3-cyclohexenone and 2-cyclohexenone
c. 4-penten-2-one and 4,4-dichloro-1-pentene
d. propanal and 2-butanone
e. 3-hexanone-6-D_3 and 3-hexanone-1-D_3

Exercise 16-9 Write equations to show the steps involved in the following carbonyl-addition reactions: (a) base-catalyzed addition of ethanol to ethanal to form the corresponding hemiacetal, 1-ethoxyethanol; (b) formation of 1-ethoxyethanol from ethanol and ethanal, but under conditions of acid catalysis; (c) formation of 1,1-diethoxyethane from 1-ethoxyethane and ethanol with an acid catalyst; and (d) formation of diethyl carbonate $(CH_3CH_2O)_2C{=}O$ from ethanol and carbonyl dichloride.

Exercise 16-10 One possible way of carrying out the cyanohydrin reaction would be to dispense with hydrogen cyanide and just use the carbonyl compound and sodium cyanide. Would the *equilibrium constant* for cyanohydrin formation be more favorable, or less favorable, with 2-propanone and sodium cyanide in water compared to 2-propanone and hydrogen cyanide in water? Give your reasoning.

Exercise 16-11 What should be the equation for the rate of formation of 2-propanone cyanohydrin by the mechanism given in Section 16-4A, (a) if the first step is slow and the second fast?. (b) If the second step is slow and the first fast? (Review Sections 4-4C and 8-4A.)

Exercise 16-12 Explain what factors would operate to make the equilibrium constant for cyanohydrin formation 1000 times greater for cyclohexanone than for cyclopentanone. Why? What would you expect for cyclobutanone relative to cyclopentanone? Why?

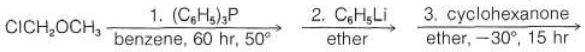
Exercise 16-13

a. Phosphorus ylides can be prepared by heating triphenylphosphine, $(C_6H_5)_3P$, with a primary alkyl halide, RCH_2X, in a solvent such as benzene. The initial product then is mixed with an equivalent quantity of a very strong base, such as phenyllithium in ether. Write equations for the reactions and probable mechanisms involved, using ethyl bromide as the alkyl halide.

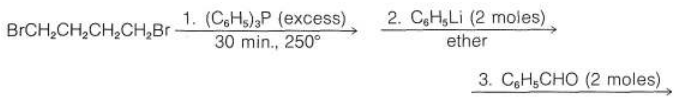
b. Using the phosphorus ylide prepared according to Part a, draw structures for the products you would expect it to form with 2-pentanone.

Exercise 16-14 Show the structures of the reaction products to be expected in each of the steps listed.

a.



b.



Exercise 16-15*

a. Write valence-bond structures for diazomethane, CH_2N_2, that accord with the fact that the actual molecule is a gas at room temperature and has a much smaller dipole moment (see Section 16-1B) than is suggested by the dipolar structure, $\overset{\ominus}{C}H_2-\overset{\oplus}{N}\equiv N$.

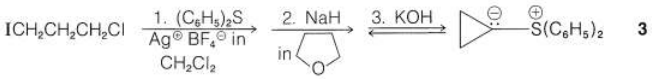
b. 1,2-Diazacyclopropene, CH_2N_2, is a stable isomer of diazomethane. Would you expect this substance to act as an ylide? Give your reasoning.

c. Phosphorus and sulfur ylides of the type $-\overset{\ominus}{C}-\overset{\oplus}{X}$, but not the corresponding nitrogen ylides, $\overset{\ominus}{C}H_2-\overset{\oplus}{N}(CH_3)_3$, are not to be regarded as being strictly dipolar, but rather to possess C−X bonds with considerable double-bond character, as expressed by the valence-bond structures

Use Figure 6-4 to explain why phosphorus and sulfur ylides are more stable than corresponding nitrogen ylides.

Exercise 16-16*

a. Show the intermediate substances and indicate the probable mechanisms involved in the synthesis of the sulfur ylide 3 by the following sequence:



3

b. Draw structures for the products expected from the reaction of 3 with cyclopentanone.

Exercise 16-17 The equilibrium constants for hydration are especially large for methanal, trichloroethanal, cyclopropanone, and compounds with the grouping $-COCOCO-$. Explain.

Exercise 16-18 Sodium hydrogen sulfite addition products are decomposed to the parent carbonyl compounds when treated with mild acid or mild alkali. Write equations for the reactions involved and explain why the substances are unstable both in acid and base.

Exercise 16-19 Explain how sodium hydrogen sulfite might be used to separate cyclohexanone (bp $156°$) from cyclohexanol (bp $161°$).

Exercise 16-20 Write a reasonable mechanism for the polymerization of methanal in water solution under the influence of a basic catalyst. Would you expect base catalysis to produce any 1,3,5-trioxacyclohexane? Why?

Exercise 16-21 How many different configurational isomers are there for paraldehyde? Draw the conformation expected to be most stable for each. Review Section 12-3D.

Exercise 16-22* What kind of reagents might be used to convert paraformaldehyde into a more thermally stable material? Give your reasoning.

Exercise 16-23* Why should the equilibrium for formation of $(CH_3)_2C{=}NR$ from $(CH_3)_2C{=}O$ and RNH_2 be less favorable in strong acid than in neutral water solution? Be sure you consider the equilibria for the interaction of the acid with *all* of the participants. Give your reasoning.

Exercise 16-24

https://chem.libretexts.org/@go/page/81263

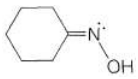
a. How many different positional and stereoisomers are possible of a monomethyl-substituted hexamethylenetetramine?

b. How many stereoisomers are possible for structure 4?

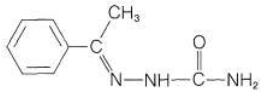
c. Name compound 4 as an azacycloalkane in accord with the systematic rules for cyclic compounds (Sections 12-8 and 15-11A).

Exercise 16-25 Suggest a method of synthesis of each of the following compounds, starting with an appropriate aldehyde or ketone. Indicate which of the products you expect to be mixtures of configurational isomers.

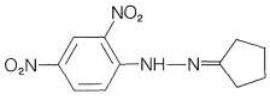
a.



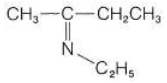
b.



c.

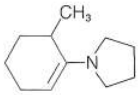


d.



Exercise 16-26 Write an equation to show the rearrangement of ethylidenemethanamine to N-methylethenamine ($CH_2{=}CH{-}NHCH_3$). Use bond energies to calculate the ΔH^0 of the rearrangement. Assuming $\Delta S^0 = 0$, which would be the more stable isomer? Would you expect that corrections for electron delocalization may be necessary for either of these compounds? Give your reasoning.

Exercise 16-27 How could you prepare the enamine 6 from suitable ketone and amine starting materials?



6

Specify the catalyst required and draw the structure of an by-products that you may expect to form in the reaction.

Exercise 16-28 Write equations to show how you would convert 2-butanone to 2-methoxy-2-methylthiobutane by way of the corresponding α-chloro ether.

Exercise 16-29 Write a reasonable mechanism for the reaction of hydrogen chloride and methanol with methanal to give methoxychloromethane (methyl chloromethyl ether), Equation 16-7, that is consistent with the fact that the reaction occurs under conditions where neither dichloromethane nor chloromethane is formed.

Exercise 16-30 Cyclopentanone-1-^{14}C treated successively with phosphorus pentachloride and alkali gives 1-chlorocyclopentane-1-^{14}C. This substance on treatment with phenyllithium at 120° affords ^{14}C-labeled 1-phenylcyclopentene, which on vigorous oxidation gives benzoic acid ($C_6H_5CO_2$) containing in its carboxyl carbon just half of the total ^{14}C of the 1-phenylcyclopentene. Write equations for all the reactions involved and write a mechanism for the phenyllithium substitution that accounts for the ^{14}C distribution.

Exercise 16-31* Work out reasonable mechanisms for the reactions of phosphorus pentachloride and sulfur tetrafluoride with carbonyl groups. Both phosphorus and sulfur can accommodate five (or more) bonded atoms, and the structure of phosphorus pentachloride in the solid state is $[PCl_4^+]\,[PCl_6^-]$.

Exercise 16-32 Show how you could prepare the following substances from the indicated starting materials:

a. 4-methylcyclohexanone from 4-methylenecyclohexanone

b. 4-(hydroxymethyl)cyclohexanone from 4-oxocyclohexanecarboxylic acid

c. 4-hydroxybutanoic acid from 4-oxobutanoic acid

d. 2,2,2-trichloroethanol from 2,2,2-trichloroethanal

Exercise 16-33 Assume that an equimolar mixture of methanal and 2,2-dimethylpropanal (each undergoes the Cannizzaro reaction by itself) is heated with sodium hydroxide solution. Write equations for the various possible combinations of Cannizzaro reactions which may occur. Would you expect methanal used in excess to reduce, or oxidize, 2,2-dimethylpropanal? Give your reasoning.

Exercise 16-34 Benzenecarbaldehyde (benzaldehyde, C_6H_5CHO) is oxidized to benzenecarboxylic acid (benzoic acid, $C_6H_5CO_2H$) by acid permanganate. The rate of the oxidation is proportional to the concentrations of $H^{\oplus}$, aldehyde, and MnO_4^-. The reaction is much slower with C_6H_5CDO than with C_6H_5CHO. When the reaction is carried wout in $H_2\ ^{18}O$ with C_6H_5CHO and MnO_4^-, the product is $C_6H_5CO_2H$. With C_6H_5CHO, H_2O, and $Mn\ ^{18}{}_4O^-$, the $C_6H_5CO_2H$ contains ^{18}O. Write a mechanism for the reaction that is consistent with all the above facts. (Notice that the C_6H_5 group is not involved.) Give your reasoning.

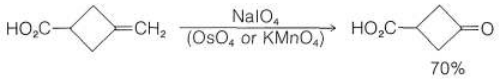
Exercise 16-35 A radical-chain reaction similar to that described for the air oxidation of benzaldehyde occurs in the peroxide-initiated addition of aldehydes to alkenes (see Table 10-3). Write a mechanism for the peroxide-induced addition of ethanal to propene to give 2-pentanone.

Exercise 16-36* Certain aldehydes decompose to hydrocarbons and carbon monoxide when *heated* in the presence of peroxides:

$$(CH_3)_2CHCH_2CHO \xrightarrow{ROOR} (CH_3)_2CHCH_3 + CO \qquad (16.E.1)$$

Write a reasonable chain mechanism for such reactions that is supported by calculations of the ΔH^0 values for the propagation steps. Use needed data from Table 4-3 and Table 4-6. Your answer should reflect the fact that this reaction does not proceeds well with most aldehydes unless the reactants are heated (above about 120°).

Exercise 16-37 An elegant modification of the two-step procedure to prepare ketones from alkenes by hydroxylation and oxidative cleavage of the diol formed uses a small amount of potassium permanganate (or osmium tetroxide, OsO_4) as the catalyst and sodium periodate as the oxidizing agent:



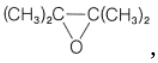
Explain how the reaction sequence could operate to enable $KMnO_4$ (or OsO_4) to function overall as a *catalyst* rather than as a *reagent*.

Exercise 16-38 Write mechanism for the oxidative cleavage of 1,2-diols by lead tetraethanoate and sodium periodate based on consideration of the mechanism of chromic acid oxidation (Section 15-6B).

Exercise 16-39 Explain how resonance can be used to account for the fact that the ΔH^0 for reduction of CH_3CO_2H to CH_3CHO is about $18\ kcal\ mol^{-1}$ more positive than calculated from bond energies, whereas ΔH^0 for the corresponding reduction of CH_3COCl to CH_3CHO is about as expected from bond energies. Would you expect ΔH^0 for reduction of CH_3CONH_2 to be as expected from the pertinent bond energies? Why?

Exercise 16-40 Write a sequence of reactions whereby 2-methylpropene may be converted to 2-methylpropanal by way of a pinacol-type rearrangement. Would you expect any concomitant formation of 2-butanone? Explain.

Exercise 16-41 Predict the products to be expected from acid-catalyzed rearrangement of 1,2-propanediol and 2-methyl-2,3-butanediol.

Exercise 16-42 Treatment of tetramethyloxacyclopropane, 

, with acid products pinacolone. Explain.

Exercise 16-43 How could one dehydrate 2,3-dimethyl-2,3-butanediol to 2,3-dimethyl-1,3-butadiene without forming excessive amounts of 3,3-dimethyl-2-butanone in the process?

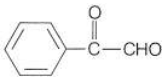
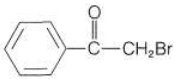
Exercise 16-44 Strong acid converts 1,1-diphenyl-1,2-ethanediol first to diphenylethanal and then more slowly to 1,2-diphenylethanone (benzyl phenyl ketone). Explain how and why kinetic and equilibrium control may be expected in this case to give different products.

Exercise 16-45 Write equations for the acid-catalyzed rearrangement of 1,3,3-trimethylbutyl hydroperoxide and predict the favored product therefrom.

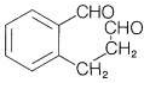
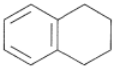
Exercise 16-46 Propose a possible synthesis of each of the following compounds from the indicated reagents and conditions where specified. Assume that any additional needed reagents are available. Reactions from other parts of Section 16-9 may be used.

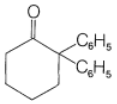
a. cyclohexanecarbaldehyde from cyclohexane by way of a hydroformylation reaction

b. cyclopentylmethanol from cyclopentene

c.  from 

d. heptanal from 1-heptene and $(CH_3)_2S{=}O$

e.  from  (two ways)

f.  from $(C_6H_5)_2C{=}O$ and cyclopentane by way of a Wittig reaction (Section 16-4A)

Exercise 16-47*

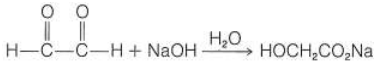
a. Show the steps and reaction conditions by which 2-methyl-1,3-butadiene can be converted to 3-methylcyclopentanone by an alkylborane, RBH_2, when R is a large alkyl group.

b. Suggest a route to each of the following compounds from the indicated starting materials: (1) 2-methyl-4-heptanone from propene and 2-methylpropene, and (2) octanedial from 1,5-hexadiene.

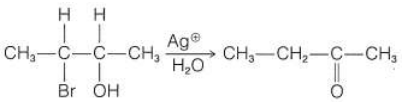
Exercise 16-48 Write equations for the synthesis of the following substances based on the indicated starting materials. Give the reaction conditions as accurately as possible.

a. 2-methylpropanal from 3-methylbutanol
b. 1-cyclobutylethanone from cyclobutanecarboxylic acid
c. pentanedial from cyclopentanone
d. cyclubutane from methylenecyclobutane
e. 2,2,2-trichloroethyl trichloroethanoate from 2,2,2-trichloroethanal
f. cyclopentene-1-carboxylic acid from cyclopentanone

Exercise 16-49 Write reasonable mechanisms for each of the following reactions. Support your formulations with detailed analogies insofar as possible.

a. 

b. $CH_3COC_3 + NH_2OH \xrightarrow[H_2O]{Na_2CO_3} CH_3C(NOH)CH_3 + H_2O$ (Notice that this is a *base*-catalyzed reaction.)

c. 

d. Hexamethylenetetramine from methanal and ammonia. (Consider the possibility of $CH_2{=}NH$ as an intermediate for the stepwise formation of N,N′,N″-tris(hydroxymethyl)-1,3,5-triazacyclohexane as an intermediate followed by acid-induced condensation of the latter with ammonia.)

Exercise 16-50 It is important to be able to decide whether a plausible-looking reaction actually will proceed as written. The following equations represent "possible" synthetic reactions. Consider each carefully and decide whether it will proceed as written. Show your reasoning. If you think another reaction would occur, write an equation for it.

a. $CH_3CH(OC_2H_5)_2 + 2NaOCH_3 \xrightarrow[50^o]{\text{excess } CH_3OH} CH_3CH(OCH_3)_2 + 2_2NaOCH_5$

b. $(CH_3)_3CCOCH_2CH_3 + KMnO_4 \xrightarrow[KOH]{H_2O} (CH_3)_3COH + CH_3CH_2CO_2K$

c. $CH_3CCL(CH_3)CH_2Cl + 2NaOCH_3 \xrightarrow[50^o]{CH_3OH} CH_3C(CH_3)(OCH_3)CH_2OCH_3 + 2NaCl$

d. $CH_3CH_2CH{=}O + C_6H_5CO_3H \rightarrow CH_3CH_2O{-}COH + C_6H_5CO_2H$

e. $O{=}CH{-}CO_2H + NaBH_4 \xrightarrow{CH_3OH} O{=}CH{-}CH_2OH$

f. $CH_2{=}O + (CH_3)_2C{=}O + NaOH \rightarrow HCO_2Na + (CH_3)_2CHOH$

Exercise 16-51 Write a mechanism for the oxidation of sodium methanoate (formate) to carbon dioxide by potassium permanganate which is consistent with the following facts:

(a) $v = k\,[HCO_2{}^-]\,[MnO_4{}^-]$

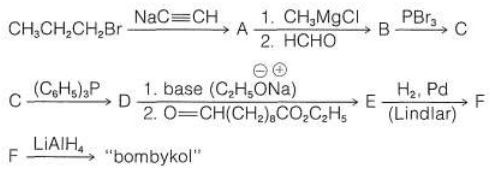
(b) the CO_2 has no ^{18}O in it if oxidized with $Mn\,^{18}O_4{}^-$

(c) $DCO_2{}^-$ is oxidized at one seventh the rate of $HCO_2{}^-$

Compare your mechanism with that generally accepted for the Cannizzaro reaction.

Exercise 16-52 2-Propanone reacts with trichloromethane in the presence of potassium hydroxide to give 1,1,1-trichloro-2-methyl-2-propanol. What is likely to be the mechanism of this reaction? What further evidence could be gained to establish the mechanism? (If you do not see a possible answer, refer to Section 14-7B for helpful information.)

Exercise 16-53 The structure of the sex attractant of the silkworm, "bombykol", is given in Section 5-6 as structure 30. The compound has been synthesized by the route given below. Write the structures of each of the synthetic intermediates A-F.



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CHAPTER OVERVIEW

17: Carbonyl Compounds II- Enols and Enolate Anions. Unsaturated and Polycarbonyl Compounds

Some of the most useful reactions of carbonyl compounds involve carbon-hydrogen bonds adjacent to the carbonyl group. Such reactions, which can be regarded as the backbone of much synthetic organic chemistry, usually result in the replacement of the hydrogen by some other atom or group. The important examples we will consider in this chapter are halogenation, alkylation, and aldol reactions of aldehydes and ketones.

17.1: Prelude to Enols and Enolate Anions, Unsaturated, and Polycarbonyl Compounds
17.2: Enolization of Aldehydes and Ketones
17.3: Halogenation of Aldehydes and Ketones
17.4: Nucleophilic Addition Reactions of Enolate Anions
17.5: Nucleophilic Substitution with Enolate Anions
17.6: α,β-Unsaturated Aldehydes and Ketones
17.7: Ketenes
17.8: 1,2-Dicarbonyl Compounds
17.9: 1,3-Dicarbonyl Compounds
17.10: 1,4-Dicarbonyl Compounds
17.11: Tricarbonyl Compounds
17.12: Cyclopropanones and Cyclopropenones
17.E: Carbonyl Compounds II (Exercises)

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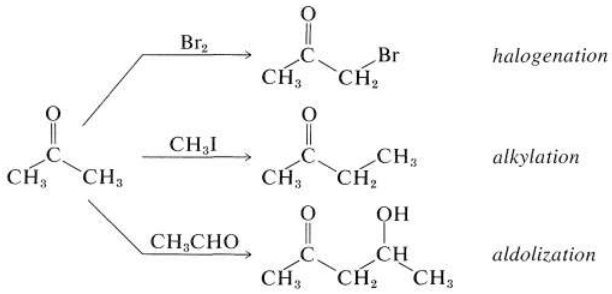
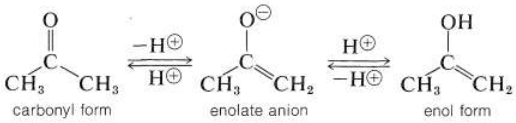
17.1: Prelude to Enols and Enolate Anions, Unsaturated, and Polycarbonyl Compounds

Some of the most useful reactions of carbonyl compounds involve carbon-hydrogen bonds adjacent to the carbonyl group. Such reactions, which can be regarded as the backbone of much synthetic organic chemistry, usually result in the replacement of the hydrogen by some other atom or group, as in the sequence $\mathrm{H{-}C{-}C{=}O} \rightarrow \mathrm{X{-}C{-}C{=}O}$. The important examples we will consider in this chapter are halogenation, alkylation, and aldol reactions of aldehydes and ketones, illustrated here for 2-propanone:



Although these reactions lead to many diverse products depending on the reagents and conditions, they have one feature in common - they proceed by way of the enol or the enolate anion of the parent carbonyl compound:



Therefore, to understand the nature of these reactions we first must understand the conditions that convert aldehydes and ketones to their enol forms or the anions of those enol forms.

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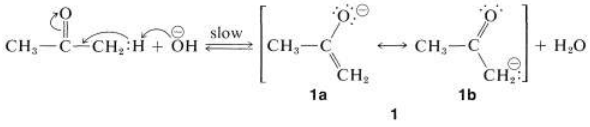
17.2: Enolization of Aldehydes and Ketones

Transformation of a carbonyl compound to an enol at a useful rate normally requires either a basic catalyst or an acidic catalyst and, of course, at least one hydrogen on the α carbon. The features of each type of catalysis follow.

17.2.1: Enolization in Basic Solution. C—H Acidity of Carbonyl Compounds

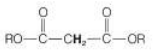
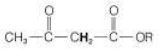
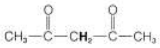
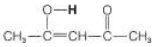
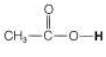
With a basic catalyst such as hydroxide ion, the first step in enolization is removal of a proton from the α position to give the enolate anion 1:



1

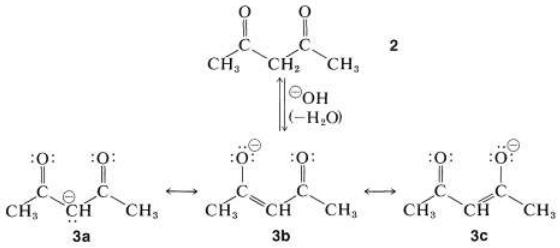
Normally, C—H bonds are highly resistant to attack by basic reagents, but removal of a proton *alpha* to a carbonyl group results in the formation of a considerably stabilized anion with a substantial proportion of the negative charge on oxygen, as represented by the valence-bond structure 1*a*. Carbonyl compounds such as 2-propanone therefore are weak acids, only slightly weaker than alcohols (compare the pK_a values for some representative compounds in Table 17-1).[1]

Table 17-1: C—H *and* O—H *Acidities of Some Representative Compounds*[a]

C—H Acidity		O—H Acidity	
Compound	pK_a	Compound	pK_a
	25		18
	20		14
	17		11
	13		16
	11		10
	9		9
	10		5
	25		4

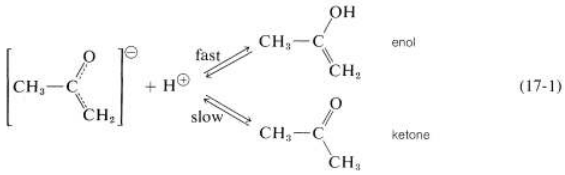
[a]These are approximate values; the acidic hydrogen is shown in boldface type; pK_a is defined in Section 8-1.

Two carbonyl groups greatly increase the acidity. For example, 2,4-pentanedione (acetylacetone, 2) has a p$K_a \cong 9$, which is comparable to the O—H acidity of phenols (see Table 17-1). The reason is that the enolate anion 3 has the charge largely shared by the two oxygen atoms (cf. 3*b* and 3*c*). As a result, the enolate anion 3 is stabilized more with respect to the ketone than the enolate anion from 2-propanone is stabilized relative to 2-propanone:



17.2.2: Enol Formation from Enolate Anions

You will notice from Structures $1a$ and $1b$ that because the negative charge of the enolate anion is distributed on both oxygen and carbon, the ion can, in principle, combine with a proton at either site. If the enolate ion adds a proton to oxygen, the enol is formed; if it adds a proton to carbon, the ketone is formed:

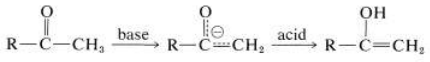


(17-1)

Ions of this type, which can react at either of two different sites, often are called **ambident ions**.

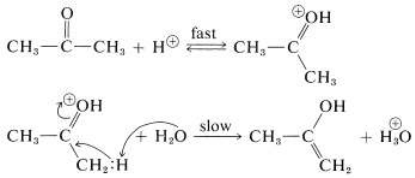
In fact, enolate anions add a proton at oxygen at least 10^{10} times faster than at carbon; the proton also is removed from oxygen much faster than from carbon. Thus the enolate anion of 2-propanone is in rapid equilibrium with the enol, but is converted back and forth to the ketone only slowly (Equation 17-1).

Another important point is that, although enolization by way of enolate anions requires a basic catalyst, both an acid and a base are necessary: a base to form the enolate anion; an acid to donate a proton to the anion to form the enol. If there is no acid available that is strong enough to donate a proton to the anion, then only the enolate anion is formed:



17.2.3: Enolization in Acid Solution

Catalysis of the enolization of 2-propanone by acids involves first, oxonium-salt formation and second, removal of an α proton with water or other proton acceptor (base):



This sequence differs from enolization induced by basic catalysis (as discussed in Section 17-1B) in that the enol is formed directly and not subsequent to the formation of the enolate anion. The proton addition to the carbonyl oxygen greatly facilitates proton removal from the α carbon because of the electron-attracting power of the positively charged oxygen. Nevertheless, this last step is the *rate-determining* for enolization in acid solution.

17.2.4: Stabilities of Enols

The equilibrium position between a simple ketone and its enol usually lies far on the side of the ketone (see Table 17-2). However, there are some interesting and important exceptions to this generalization. For instance, the influence of *two* carbonyl groups on the enol content is very striking, as we can see from the fact that 85% of 2,4-pentanedione is the enol form at equilibrium:

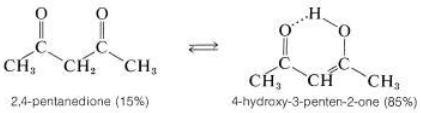
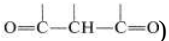
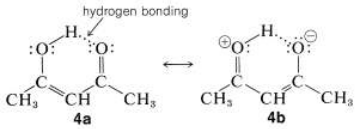


Table 17-2: *The Enol Content of Some Carbonyl Compounds*

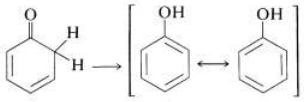
Compound	Percent enol (solvent)
2-propanone, CH_3COCH_3	1.5×10^{-4} (H_2O)
cyclopentanone,	0.013 (H_2O)
cyclohexanone,	0.0004 (H_2O)
2,4-pentanedione, $CH_3COCH_2COCH_3$	16 (H_2O) 85 (none)
5,5-dimethylcyclohexane-1,3-dione,	95 (H_2O)
2,4-cyclohexadienone, (keto form of phenol)	~100

The enol form of 2,4-pentanedione (and of related dicarbonyl compounds of the type ) not only is stabilized by electron-delocalization, as shown in Structures 4*a* and 4*b*, but by hydrogen-bonding of the acidic hydrogen between the two oxygens:



Of course, such stabilization is not possible for the keto form.

An extreme example of the stabilization of an enol by electron delocalization is benzenol (phenol), which exists 100% in the enol form. In this case the extra stability of the benzene ring is the important factor:



In the succeeding sections of this chapter we will discuss several important reactions that take place by way of enols or enolate anions.

[1]The important difference between 2-propanone and ethanol as acids is that the *rate* of establishment of equilibrium with 2-propanone or similar compounds where ionization involves breaking a C–H bond is very much *slower* than the corresponding reaction with O–H bonds.

17.2.5: Contributors and Attributions

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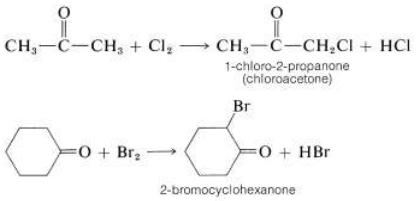
17.3: Halogenation of Aldehydes and Ketones

17.3.1: Synthesis of α-Halo Ketones

Halogenation of saturated aldehydes and ketones usually occurs exclusively by replacement of hydrogens *alpha* to the carbonyl group:



The reagents that commonly are used to halogenate carbonyl compounds are those that are used to halogenate alkanes (e.g. Cl_2, Br_2, SO_2Cl_2, and *N*-bromoamides; see Sections 4-4 and 14-3). However, the characteristics of the two types of halogenation normally are very different. 2-Propanone has been particularly well studied, and the important features of the halogenation of this compound are summarized as follows:

1. 2-Propanone reacts easily with chlorine, bromine, *and* iodine.
2. 2-Propanone reacts at the *same* rate with *each* halogen. Indeed, the rate of formation of the 1-halo-2-propanone is *independent* of the concentration of the halogen, even at very low halogen concentrations.
3. The halogenation of 2-propanone is catalyzed by both acids and bases. The rate expressions for formation of 1-halo-2-propanone in water solution are:
    - at moderate $OH^{\ominus}$ concentrations

$$v = k\,[CH_3COCH_3]\,[OH^{\ominus}] \tag{17.3.1}$$

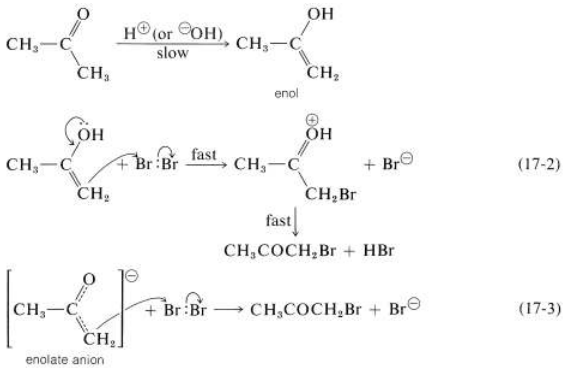
    - at moderate $H^{\oplus}$ concentrations

$$v = k'\,[CH_3COCH_3]\,[H^{\oplus}] \tag{17.3.2}$$

The ratio of k to k' is 12,000, which means that hydroxide ion is a much more effective catalyst than is hydrogen ion.

> *The hydroxide ion is a much more effective catalyst than is hydrogen ion*

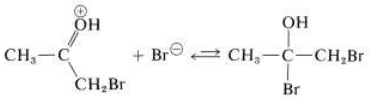
To account for the role of the catalysts and the independence of the rate from the halogen concentration, the ketone necessarily must be slowly converted by the catalysts to something that can react *rapidly* with halogen to give the products. This something is either the enol or the enolate anion of 2-propanone:



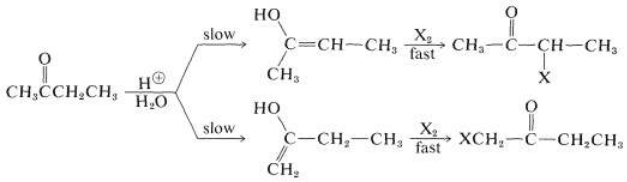
As long as the first step is slow compared with the steps of Equations 17-2 and 17-3, the overall rate of reaction will be independent of both the concentration of halogen and whether it is chlorine, bromine, or iodine (cf. Section 4-4C).

The reaction of either the enol or the enolate anion (Equations 17-2 or 17-3) with Br_2 resembles the first step in the electrophilic addition of halogens to carbon-carbon multiple bonds (Section 10-3A). However, the second step, addition of the nucleophilic

halide, if it occurs at all, does not produce any stable product:



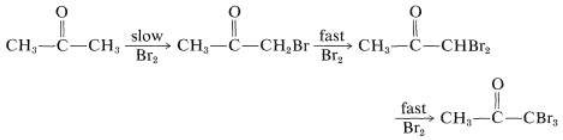
Unsymmetrical ketones, such as 2-butanone, can form two different enols that will react with halogens to give isomeric halo ketones:



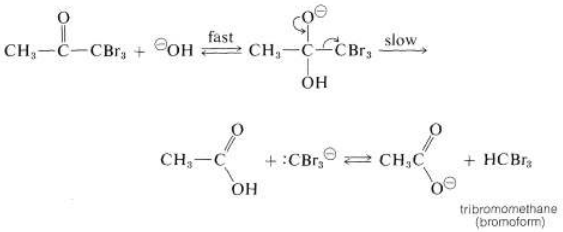
The composition of the product mixture will depend on the relative rates of formation of the isomeric enols, provided that the halogenation step is not a reversible reaction. Barring any serious steric effects that influence the rate of reaction, the more rapidly formed enol generally is the more thermodynamically stable enol.

17.3.2: The Haloform Reaction

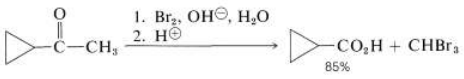
The previous discussion of the halogenation of ketones is incomplete in one important respect concerning *base-induced* halogenation. That is, once an α-halo ketone is formed, the other hydrogens on the same carbon are rendered more acidic by the electron-attracting effect of the halogen and are replaced much more rapidly than the first hydrogen:



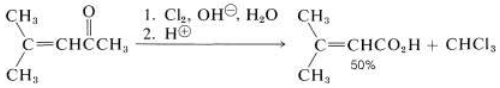
The result is that, if the monobromoketone is desired, the reaction is carried out best with an *acidic* catalyst rather than a basic catalyst. A further complication in the base-catalyzed halogenation of a methyl ketone is that the trihaloketone formed is attacked readily by base, thereby resulting in cleavage of a carbon-carbon bond:



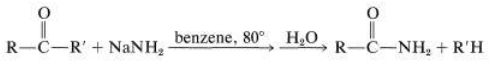
This sequence is called the **haloform reaction** because it results in the production of chloroform, bromoform, or iodoform, depending upon the halogen used. The haloform reaction is a useful method for identification of methyl ketones, particularly when iodine is used, because iodoform is a highly insoluble, bright-yellow solid. The reaction also is very effective for the synthesis of carboxylic acids when the methyl ketone is more available than the corresponding acid:



Because the haloform reaction is fast, in some cases it can be used to prepare unsaturated acids from unsaturated ketones without serious complications caused by addition of halogen to the double bond:



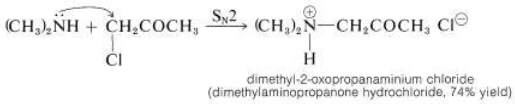
A reaction somewhat similar to the cleavage of haloforms with hydroxide occurs with ketones that do not have α-hydrogens through the action of sodium amide:



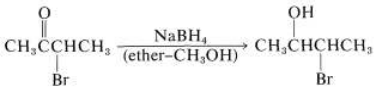
This reaction, called the **Haller-Bauer reaction**, has utility for the preparation of amides of the types $\mathrm{ArCONH_2}$ and *tert*-$\mathrm{RCONH_2}$, and, through hydrolysis, the corresponding carboxylic acids.

17.3.3: Reactions of α-Halo Ketones

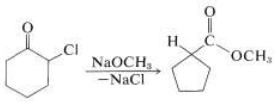
The halogen of an α-halo aldehyde or an α-halo ketone is exceptionally *unreactive* in S_N1-displacement reactions, but is exceptionally *reactive* in S_N2 displacements, compared with the halogen of alkyl halides having comparable potential steric effects. Similar behavior is observed with α-halo carboxylic acids and is discussed in Chapter 18.



In some circumstances, the production of a 2-halo alcohol by reduction of the carbonyl group of an α-halo ketone with metal hydrides is a useful synthetic reaction:



When one attempts $E2$ reactions with α-halo ketones using strong bases such as alkoxides, an interesting rearrangement pathway may occur called the **Favorskii rearrangement**. In this reaction, the α-halo ketone is converted to an ester. For example, 2-chlorocyclohexanone is converted to the methyl ester of cyclopentanecarboxylic acid by treatment with sodium methoxide in ether:



The mechanism of this reaction has been the subject of many investigations.

17.3.4: Contributors and Attributions

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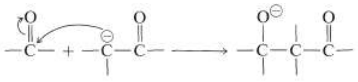
17.4: Nucleophilic Addition Reactions of Enolate Anions

17.4.1: The Aldol Addition

A most important property of enolate anions, at least as far as synthesis is concerned, is their excellent nucleophilicity, which enables them to *add* to double bonds and to participate in nucleophilic substitution. When the addition is to a carbonyl double bond, it is called an **aldol addition** (Equation 17-4). Additions of enolate anions to carbon-carbon double bonds usually are classified as **Michael additions** (Equation 17-5), and these are discussed in Sections 17-5B and 18-9D. The principles of S_N nucleophilic reactions of enolate anions (Equation 17-6) will be considered in Section 17-4, and their synthetic applications in detail in Chapter 18.



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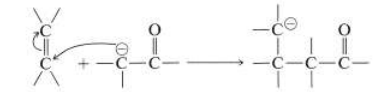

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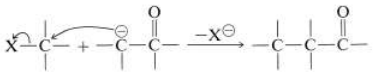
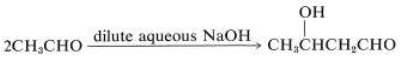


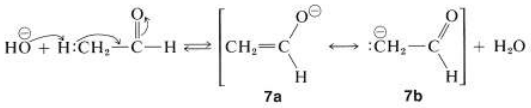
(17-6)

The products of aldol addition are β-hydroxy aldehydes (*ald-ols*) or β-hydroxyl ketones (*ket-ols*). A typical example is the reaction of ethanal with base and, if the conditions are reasonably mild, the product is 3-hydroxybutanal:

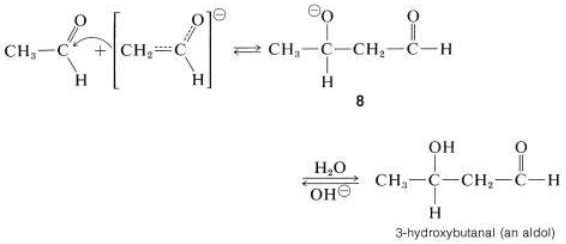


The overall reaction corresponds to a dimerization of ethanal, that is, an addition of one ethanal molecule to another with formation of a new carbon-carbon bond. The synthetic value of the reaction lies in the fact that it can be used to build large molecules from smaller molecules (see Section 13-7).

Formation of the enolate anion, 7, by removal of an α hydrogen by base is the first step in the aldol addition:



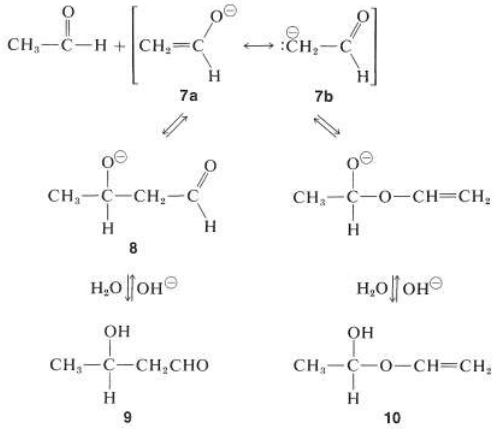
The anion then adds to the carbonyl group of a second molecule of ethanal in a manner analogous to the addition of other nucleophiles to carbonyl groups (e.g., cyanide ion, Section 16-4A). The adduct so formed, 8, rapidly adds a proton to the alkoxide oxygen to form the aldol, 3-hydroxybutanal. This last step regenerates the basic catalyst, $OH^{\ominus}$:



17.4.2: Ambident Nature of Enolate Ions in Aldol Addition

The two possible valence-bond structures of the enolate anion, 7*a* and 7*b*, show that the anion should act as an **ambident nucleophile** - a nucleophile with nucleophilic properties associated with *both* carbon and oxygen. The addition step in the aldol reaction therefore may be expected to take place in either of two ways: The anion could attack as a *carbon* nucleophile to form a carbon-carbon bond, 8, leading ultimately to the aldol, 9, or it might attack as an *oxygen* nucleophile to form a carbon-oxygen bond,

thereby leading to the hemiacetal, 10. By this reasoning, we should obtain a mixture of products 9 and 10. However, the aldol 9 is the only one of these two possible products that can be isolated:



Why is only one of these products formed? To understand this, you must recognize that aldol reactions are reversible and therefore are subject to *equilibrium* rather than *kinetic* control (Section 10-4A). Although the formation of 10 is mechanistically reasonable, it is not reasonable on thermodynamic grounds. Indeed, while the overall ΔH^0 (for the vapor) calculated from bond energies is -4 kcal mol^{-1} for the formation of the aldol, it is $+20.4$ kcal mol^{-1} for the formation of 10.[2] Therefore, the reaction is overwhelmingly in favor of the aldol as the more stable of the two possible products.

17.4.3: Position of the Equilibrium in Aldol Additions

The equilibrium constant is favorable for the aldol addition of ethanal, as in fact it is for most aldehydes. For ketones, however, the reaction is much less favorable. With 2-propanone (acetone) only a few percent of the addition product "diacetone alcohol", 11 is present at equilibrium:

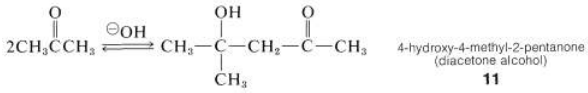


Figure 17-2.

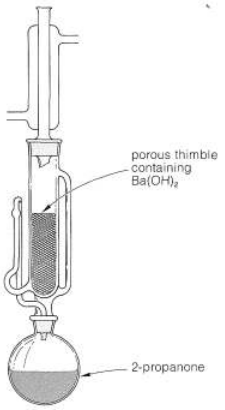
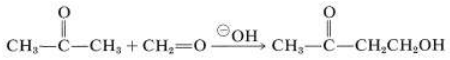


Figure 17-2 Apparatus for the aldol addition of 2-propanone

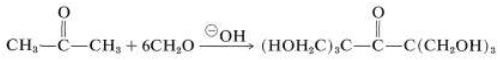
The 2-propanone is boiled and the hot condensate from the reflux condenser flows back over solid barium hydroxide contained in the porous thimble and comes to equilibrium with the addition product 11. The barium hydroxide is retained by the porous thimble and the liquid phase returns to the boiler where the 2-propanone, which boils 110° below the temperature at which 11 boils, is selectively vaporized and returns to the reaction zone to furnish more adduct.

The key step in aldol addition requires an electron-pair donor (nucleophile) and an electron-pair acceptor (electrophile). In the formation of 3-hydroxybutanal or 11, both roles are played by one kind of molecule, but there is no reason why this should be a necessary condition for reaction. Many kinds of mixed aldol additions are possible.

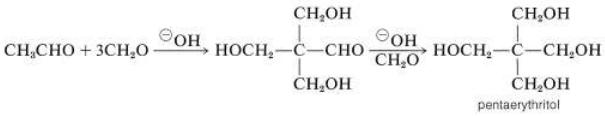
Consider the combination of methanal and 2-propanone. Methanal cannot form an enolate anion because it has no α hydrogens. However, it is expected to be a particularly good electron-pair acceptor because of freedom from steric hindrance and the fact that it has an unusually weak carbonyl bond ($166\ \text{kcal}$ compared to $179\ \text{kcal}$ for 2-propanone). In contrast, 2-propanone forms an enolate anion easily but is relatively poor as the electrophile. Consequently the addition of 2-propanone to methanal should and does occur readily:



The problem is not to get addition, but rather to keep it from going too far. Indeed, all six α hydrogens of 2-propanone can be replaced easily by $-CH_2OH$ groups:



A commercially important mixed addition involves ethanal and an excess of methanal in the presence of calcium hydroxide. Addition occurs three times and the resulting trihydroxymethylethanal (which has no α hydrogens) undergoes a "crossed Cannizzaro" reaction with more methanal to give a tetrahydroxy alcohol known as "pentaerythritol::

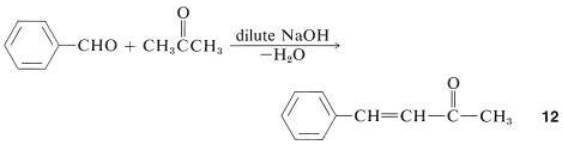


Pentaerythritol is used widely in the preparation of surface coatings and in the formation of its tetranitrate ester, pentaerythrityl tetranitrate [PETN, $C(CH_2ONO_2)_4$], which is an important high explosive.

17.4.4: Dehydration of Aldol Addition Products

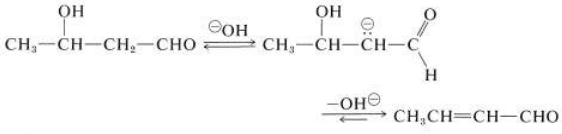
An important property of aldol addition products is the ease with which they eliminate water in the presence of either acids or bases. For example, when 3-hydroxybutanal is heated in the basic solution in which it is formed (by aldol addition of ethanal), 2-butenol results:

The ease of dehydration compared with simple alcohols is related to the fact that the product is a *conjugated* alkenone. The stabilization energy of the conjugated system makes the equilibrium constant for dehydration especially favorable. In many cases the aldol adduct is only an intermediate in aldol reactions because it dehydrates more rapidly than it can be isolated. Such is most often the case when the dehydration product is a polyunsaturated conjugated aldehyde or ketone. 2-Propanone and bezenecarbaldehyde (benzaldehyde), for instance, give the unsaturated ketone 12 in cold aqueous sodium hydroxide solution:



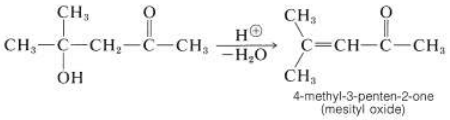
Although the equilibrium for aldol addition may be unfavorable, when dehydration of the aldol product is rapid, $C-C$ bond formation may be pushed to completion by conversion of the aldol to the α,β-unsaturated ketone.

The mechanism of base-catalyzed dehydration of aldols involves formation of an enolate anion by removal of a proton from the C_2 or *alpha* carbon and subsequent elimination of the hydroxyl group as hydroxide ion:

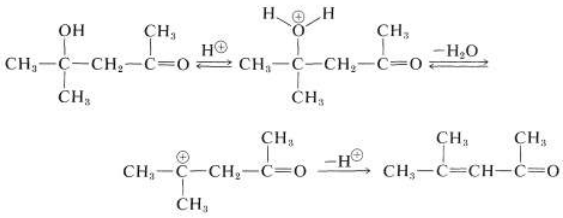


This last step is one of the rare examples in which the leaving group is $OH^{\ominus}$. Generally, hydroxide is a poor leaving group in substitution (S_N1 or S_N2) or elimination ($E1$ or $E2$) reactions (see Section 8-7C).

Dehydration of aldols to α,β-unsaturated carbonyl compounds usually is achieved best with acidic catalysts. An example is the dehydration of the aldol from 2-propanone to give 4-methyl-3-penten-2-one:

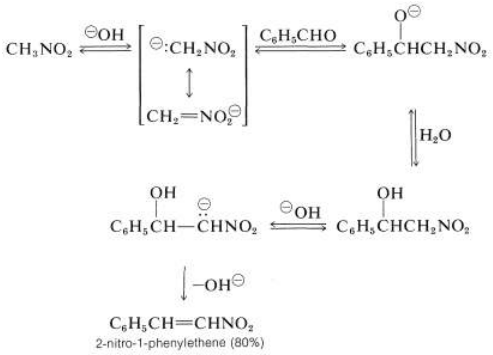


If this reaction were attempted under basic conditions, extensive reversion of the aldol to 2-propanone would occur (see Section 17-3C). Under acidic conditions, however, the process is a straightforward proton transfer to oxygen followed by elimination of water and proton transfer from carbon:

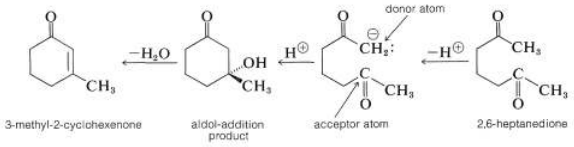


17.4.5: The Use of Aldol Addition Reactions in Synthesis

Aldol reactions provide a valuable synthetic method for forming carbon-carbon bonds. They can be adapted to extend the length of a carbon chain, to form cyclic compounds, and to provide intermediates that can be transformed into more useful materials. An important feature of these intermediates is that functional groups useful for later reactions are located close to or on the carbons of the newly formed C–C bond. There is an almost bewildering number of variations on the aldol reaction and we shall not mention all of them. The main thing to recognize in all of these reactions is that the acceptor molecule always is a carbonyl compound, best an aldehyde, sometimes a ketone, even an ester (see Section 18-8E). The donor molecule is some type of carbanion; usually, but not always, an enolate anion. However, any substance that has a C–H acidity in the pK_a range of 25 or less can be converted easily to a carbanion, which in principle may serve as the donor in aldol additions. Examples are listed in Table 17-1 and include not only aldehydes and ketones but esters, nitriles, and nitro compounds. The use of a nitroalkane in aldol addition is shown in the following sequence. The use of esters as the donor is discussed further in Section 18-8E.

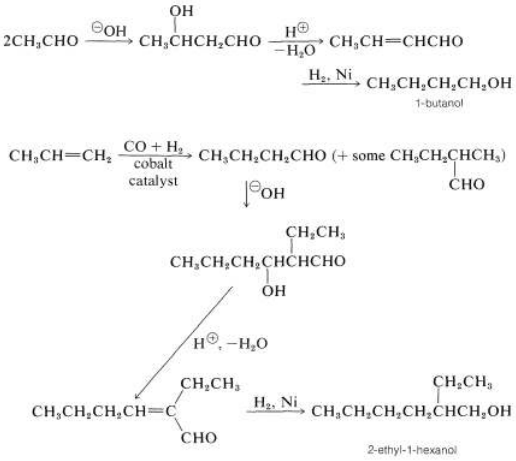


Cyclic products can be formed by aldol additions provided the donor carbanion and acceptor carbonyl are part of the *same* molecule. For example, consider how the synthesis of 3-methyl-2-cyclohexanone could be achieved from acyclic substances. The carbon-carbon bond formed in this process of aldol addition closes the ring and ultimately becomes the double bond in the conjugated system when the aldol product undergoes dehydration. Working backwards, we have the sequence



and the starting material for the synthesis therefore is 2,6-heptanedione. Because ΔG^0 for the formation of aldol products is not very favorable, cyclizations involving aldol reactions usually will not proceed to give strained carbocyclic rings.

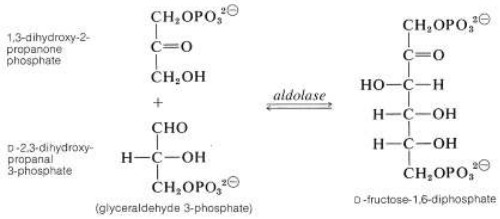
The *industrial* importance of aldol reactions is in the synthesis of alcohols, especially 1-butanol and 2-ethyl-1-hexanol:



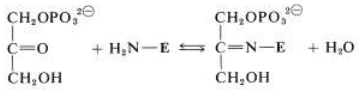
Notice that the combination of hydroformylation (Section 16-9F), aldol addition, dehydration, and hydrogenation takes a simple alkene (propene) to an alcohol with more than twice as many carbons.

17.4.6: A Biological Aldol Addition

One of the reactions in the metabolism of carbohydrates by the glycolic pathway is a type of aldol addition. In this reaction *D*-fructose (as the 1,6-diphosphate ester) is formed from *D*-glyceraldehyde and 1,3-dihydroxypropanone (both as monophosphate esters). The process is readily reversible and is catalyzed by an enzyme known as *aldolase*:

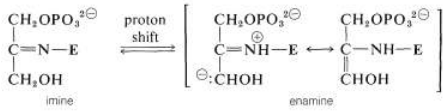


It seems likely that this reaction could occur in quite the same way as in the laboratory aldol reactions discussed so far, because the enolate anion of the donor molecule (dihydroxypropanone) is not expected to be formed in significant amount at the pH of living cells. In fact, there is strong evidence that the enzyme behaves as an amino (ENH_2) compound and reacts with the carbonyl group of dihydroxypropanone to form an imine, analogous to the reactions described in Section 16-4C:

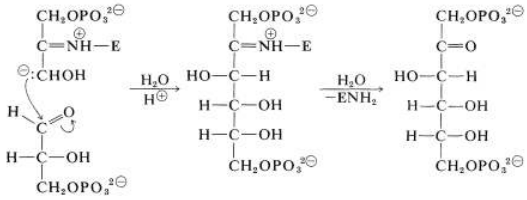


This implies that the imine form of dihydroxypropanone is a key intermediate in the overall aldol-type addition.

How can the imine behave as the carbon *donor* in addition to the aldehyde carbonyl of glyceraldehyde 3-phosphate? It is unlikely to do so directly, but it can rearrange to an enamine which, as we will explain in Section 17-4B, can act as a carbon nucleophile:



Attack of the nucleophilic carbon of the enamine at the aldehyde carbonyl of glyceraldehyde 3-phosphate forms the aldol of the imine which, on hydrolysis, gives the aldol and regenerates the enzyme:



By using the neutral enamine as the carbon nucleophile rather than an enolate anion, the biological system avoids the need for strongly basic reaction conditions in aldol addition.

[2]This value probably is too large by 3 to 4 kcal, because resonance stabilization of alkoxyalkanes has been ignored in this calculation.

17.4.7: Contributors and Attributions

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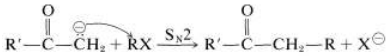
17.5: Nucleophilic Substitution with Enolate Anions

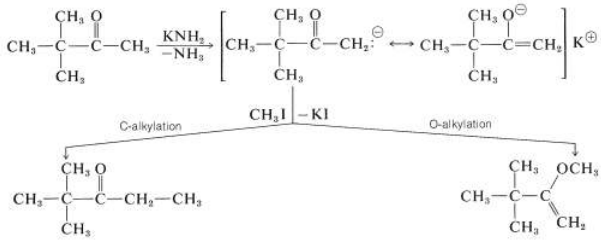
17.5.1: Alkylation of Ketones

The synthetic chemistry of enolate anions is centered on their nucleophilic and basic properties. Accordingly these ions participate in S_N2 reactions with suitable alkyl compounds:



However, there are a number of complicating factors to consider. First, the basic conditions needed to form the enolate ions often lead to side reactions such as aldol addition and $E2$ elimination of RX compounds. Aldol addition is minimized if the carbonyl compound is a ketone with a structure unfavorable for aldol addition or if *all* of the carbonyl compound is converted to its enolate. To convert all of a simple carbonyl to its enolate usually requires a very strong base, such as NH_2^+ in an aprotic solvent or liquid ammonia. Because the enolate anion itself is a strong base, best results are obtained when the halide, RX, does not undergo $E2$ reactions readily.

The second complication arises if the alkyl compound reacts with both carbon and oxygen of the nucleophilic enolate anion. The carbon product is the result of "C-alkylation", whereas the oxygen product is the result of "O-alkylation":

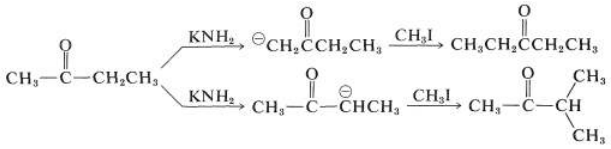


The possibility of the enolate anion acting as if its charge were effectively concentrated on carbon or on oxygen was discussed previously in connection with aldol addition (Section 17-3B). However, the situation there was quite different from the one here, because aldol addition is easily reversible, whereas alkylation is not. Furthermore, while the aldol reaction involving C–O bond formation is unfavorable $(\Delta H^0 = +20\ \text{kcal mol}^{-1})$ compared to C–C bond formation $(\Delta H^0 = -4\ \text{kcal mol}^{-1})$, both O- and C-alkylation of the anion have $\Delta H^0 < 0$.

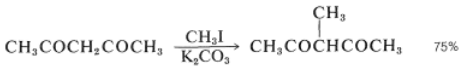
Whether C- or O-alkylation predominates depends on kinetic control (Section 10-4A). It is not a simple matter to predict which of the two positions of the enolate will be more nucleophilic, and in fact, mixtures of products often are obtained in distributions that depend on the solvent used, the temperature, the nature of X, and the nature of the base employed to form the anion. O-Alkylation tends to occur with ketones of high enol content (which usually means that the enolate anion will have especially high charge density on oxygen) and with alkylating agents possessing a high degree of S_N2 reactivity.

There is another correlation that seems to have validity in many situations, at least where kinetic control is dominant; namely, the *freer* (less associated) the ambident anions is from its cation, the *more likely* is the electrophile to attack the atom of the anion with the *highest* negative charge. Thus O-alkylation of the sodium enolate of 2-propanone is favored in aprotic solvents that are good at solvating cations [such as $(CH_3)_2SO$, Section 8-7F].

In the alkylation of unsymmetrical ketones, formation of more than one enolate anion is possible, and when this occurs, mixtures of products are obtained. Thus,

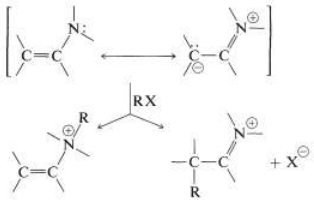


However, when one of the possible enolate anions is especially stabilized, either by conjugation or by strong electron-withdrawing groups, that enolate usually is the dominant form and only one product is formed. Thus 2,4-pentanedione is methylated at C_3, not at C_1:

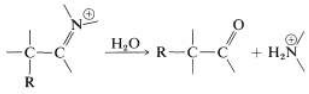


17.5.2: Alkylation of Enamines

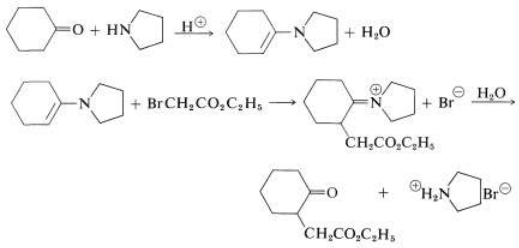
Enamines (Section 16-4C), like enolate anions, have two reactive positions and, in principle, can give either N- or C-alkylation.



Both products may be formed, but they can be separated readily because, on treatment with dilute acid, only the C-alkylation product hydrolyzes to a ketone. Generally, the alkylated ketone is the desired product:



Alkylation of enamines therefore is a feasible, and sometimes much more useful, alternative to the direct alkylation of ketones because it proceeds under less strongly basic conditions. The sequence starts with conversion of a ketone to an enamine, $-\overset{|}{\underset{|}{CH}}-\overset{|}{\underset{|}{C}}=O \xrightarrow{RNH_2} -\overset{|}{\underset{|}{C}}=\overset{|}{\underset{|}{C}}-NR_2 + H_2O$, followed by C-alkylation of the enamine, $-\overset{|}{\underset{|}{C}}=\overset{|}{\underset{|}{C}}-NR_2 \xrightarrow{RX} RC-\overset{|}{\underset{|}{C}}=\overset{\oplus}{N}R_2 + X^{\ominus}$, and ends with hydrolysis to the alkylated ketone, $RC-\overset{|}{\underset{|}{C}}=\overset{\oplus}{N}R_2 + H_2O \rightarrow RC-\overset{|}{\underset{|}{C}}=O + R_2NH_2^-$. A typical example of the use of enamines for alkylation of a ketone follows:



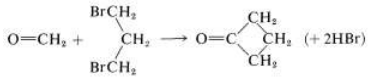
Several important biological reactions utilize enamine intermediates as carbon nucleophiles in C–C bond-forming reactions. One example is discussed in Section 17-3F.

17.5.3: Alkylation of Sulfur-Stabilized Carbanions

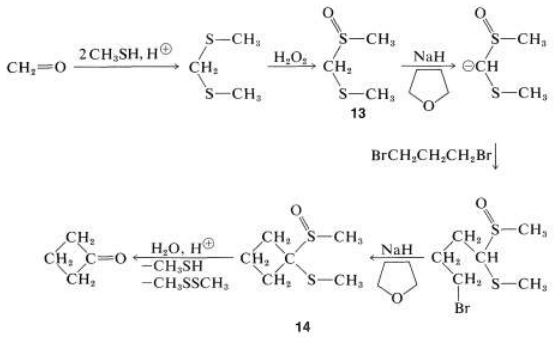
The chemistry of carbanions stabilized by groups other than carbonyl functions is closely analogous to the chemistry of enolate anions. We have seen that C–H acidity of compounds with the structural feature $X-\overset{|}{\underset{|}{C}}-H$ can be significant (pK_a of 25 or less) when X is an atom or group that can effectively delocalize the negative charge on carbon in $X-\overset{|}{\underset{|}{C}}:^{\ominus}$. Typical X groups are C=O, C ≡ N, PR_3^+, SR_2^+, SO_2R, and SR. Consequently, we can expect that carbanions of the type $X-\overset{|}{\underset{|}{C}}:^{\ominus}$, when formed, will resemble enolate anions and will undergo addition reactions to C=O and C=C, and will be alkylated with halides of good S_N2 reactivity. In fact, the reactions of ylides discussed in Section 16-4A are examples of the addition of phosphorus-, sulfur-, and nitrogen-stabilized carbanions to carbonyl groups.

Sulfur in its higher oxidation states (e.g., sulfone, $-SO_2-$) is especially effective in stabilizing adjacent carbanion centers. However, from a synthetic standpoint there are disadvantages to the sulfone grouping in that the better stabilized carbanions also are the least reactive, and subsequent removal of the sulfone grouping can be difficult. A good balance between carbanion stability,

carbanion reactivity, and ease of C–S bond cleavage is present in the structures $RS-CH_2-SR$ and $RS-CH_2-\overset{O}{\overset{\|}{S}}R$. This is illustrated below for a strikingly simple concept for preparing cyclobutanone, in which the ring carbons are derived from methanal and 1,3-dibromopropane:



To achieve this synthesis, the methanal first is converted to a thioketal, which then is partially oxidized to give 13. Treatment of 13 with a strong base converts it to the carbanion, which can be readily alkylated. By using 1,3-dibromopropane and two equivalents of base, a double displacement forms the cyclic product, 14. The sulfur groups of 14 can be removed easily by acid hydrolysis to give cyclobutanone:



17.5.4: Contributors and Attributions

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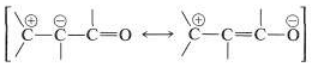
17.6: α,β-Unsaturated Aldehydes and Ketones

17.6.1: Structure and Spectral Properties

The most generally useful preparation of α,β-unsaturated carbonyl compounds is by dehydration of aldol addition products, as described in Section 17-3D. Conjugation of the carbonyl group and double bond has a marked influence on spectroscopic properties, particularly on ultraviolet spectra, as the result of stabilization of the excited electron states, which for $\pi \rightarrow \pi^*$ transitions can be described in terms of important contributions of polar resonance structures (see Sections 9-9B and 16-3B):

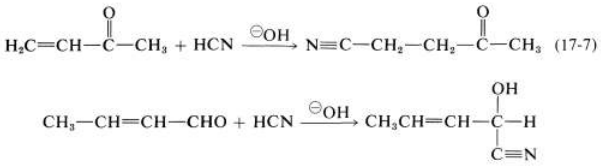


Such resonance is much less important in the ground state but is still sufficiently important to account for the moderate differences in dipole moments between saturated and α,β-unsaturated aldehydes and ketones; for example,

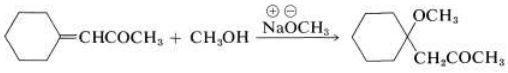
The effect of conjugation also is reflected in infrared carbonyl frequencies (Section 16-3) and NMR spectra. With respect to the latter, it is found that the protons on the β carbon of α,β-unsaturated carbonyl compounds usually come at 0.7 to 1.7 ppm *lower* fields than ordinary alkenic protons. The effect is smaller for the α protons.

17.6.2: Addition Reactions

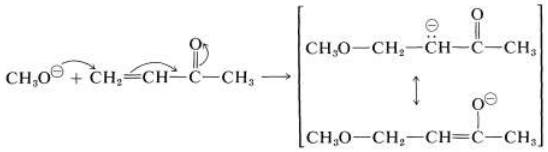
There are many addition reactions of α,β-unsaturated aldehydes, ketones, and related compounds that are the same as the carbonyl addition reactions described previously. Others are quite different and result in addition to the *alkene* double bond. Organometallic compounds are examples of nucleophilic reagents that can add to either the alkene or the carbonyl bonds of conjugated ketones (Section 14-12D). Hydrogen cyanide behaves likewise and adds to the carbon-carbon double bond of 3-butene-2-one, but to the carbonyl group of 2-butenal:



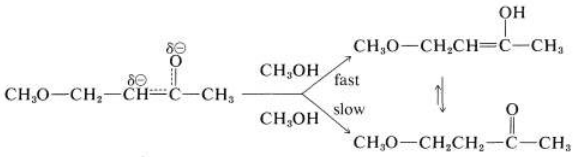
All of these reactions may be classified as nucleophilic additions, but when addition occurs at the alkene bond, the orientation always is such that the nucleophile adds at the β carbon. An example is the addition of methanol catalyzed by sodium methoxide:



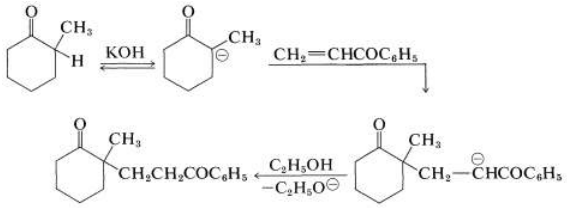
Nucleophilic reagents normally do not attack carbon-carbon double bonds (Section 10-6). The adjacent carbonyl function therefore must greatly enhance the reactivity of the double bond toward such reagents. This enhancement is not surprising when it is realized that the attack of a nucleophile produces a stabilized enolate anion:



The products are formed from the enolate intermediate by proton transfer to either carbon or oxygen. If the proton adds to oxygen the enol is formed, which is unstable with respect to the ketone and ultimately will rearrange:

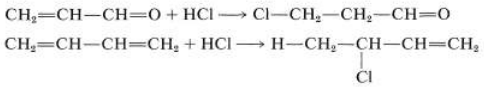


Reactions of this type are referred to in a variety of terms, many of which are rather confusing and nondescriptive. They sometimes are classified as **1,4-additions**, implying that addition occurs across the terminal protons of the conjugated system. A synonymous term is **conjugate addition**. When the nucleophile is a carbanion, the reaction is called a **Michael addition**. Thus, by this definition, Equation 17-7 represents a Michael addition. Another, perhaps more typical, example is the addition of an enolate to a conjugated ketone:



Michael-type additions, like aldol additions, are useful for the formation of carbon-carbon bonds.

Electrophilic addition of hydrogen halides to α,β-unsaturated aldehydes and ketones places the halogen on the β carbon. This orientation is opposite to that observed for related additions to conjugated dienes:



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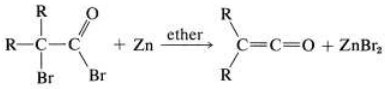
17.7: Ketenes

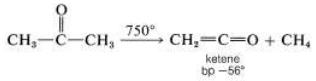
17.7.1: Preparation of Ketenes

Substances with cumulated carbonyl and carbon-carbon double bonds, , are called ketenes and, as may be expected, have interesting and unusual properties. Ketene itself, $CH_2{=}C{=}O$, and its monosubstitution products, $RCH{=}C{=}O$ (R = alkyl or aryl), are called **aldoketenes**, whereas disubstituted ketenes, $R_2C{=}C{=}O$, are called **ketoketenes**.

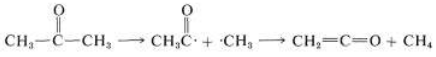
There are relatively few general methods for preparing ketenes. The simplest procedure is to treat an α-bromoacyl bromide with zinc, but the yields usually are not very good:



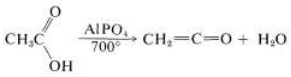
Several special methods are available for the preparation of ketene itself. The most convenient laboratory preparation is to pass 2-propanone vapor over a coil of resistance wire heated electrically to a dull red heat; air is excluded to avoid simple combustion:



The weakest bonds are the $C{-}C$ bonds and, at $750°$, fragmentation yields a methyl radical and an ethanoyl radical:

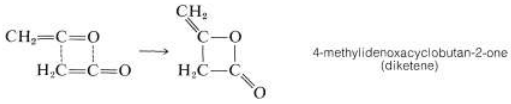


Transfer of a hydrogen atom (i.e., disproportionation) gives methane and ketene. Industrially, ketene is best prepared by dehydration of ethanoic acid:



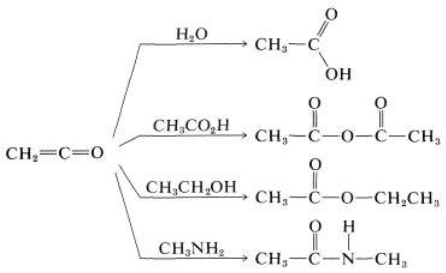
17.7.2: Reactions of Ketenes

Ketene has a boiling point of $-56°$ and normally would be stored under pressure in steel cylinders. However, this is not possible because ketene is unstable with respect to formation of a dimer known as "diketene":

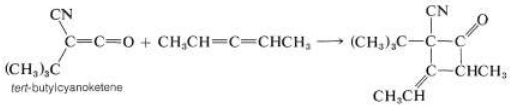


The dimer also is a highly reactive substance with such unusual characteristics that its structure was not firmly established until 1956, almost 48 years after it first was prepared.

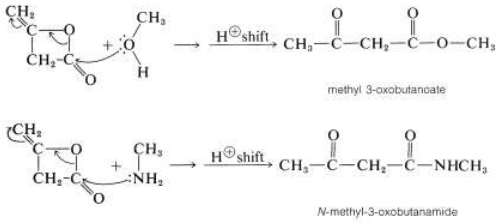
Ketenes in general are useful reagents for acylating alcohols, ROH, and amines, RNH_2, because the reactions involve additions; there are no by-products to be separated:



Ketenes also can be used for the synthesis of cyclobutane derivatives through [2 + 2] cycloadditions with suitably active alkenes (Section 13-3D):



Diketene is very useful in synthesis, particularly through its reactions with alcohols and amines to give derivatives of 3-oxobutanoic acid:



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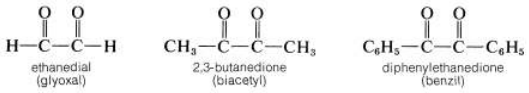
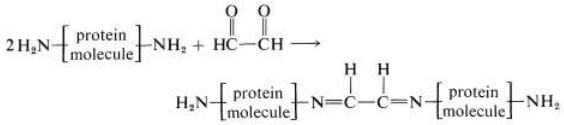
17.8: 1,2-Dicarbonyl Compounds

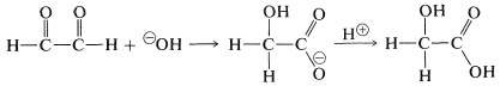
Some typical and important members of this class have structures as follows:



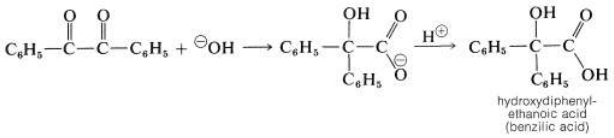
Most of the 1,2-dicarbonyl compounds are yellow. Ethanedial is unusual in being yellow in the liquid state, but green in the vapor state. It has very reactive aldehyde groups and is employed in the manufacture of plastics and as a component of embalming fluids to harden proteins by linking together their amino groups through imine formation:



Ethanedial undergoes an internal Cannizzaro reaction with alkali to give hydroxyethanoic (glycolic) acid:



An analogous reaction occurs with diphenylethanedione, which results in carbon-skeleton rearrangement. This is one of the few carbon-skeleton rearrangements brought about by basic reagents, and is known as the "**benzilic acid rearrangement**".



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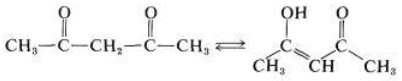
17.9: 1,3-Dicarbonyl Compounds

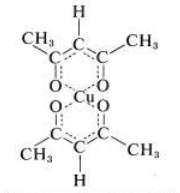
Much of the chemistry of 1,3-dialdehydes, aldehyde ketones, and diketones already has been mentioned in this chapter and is well illustrated in the properties of 2,4-pentanedione,



The liquid ketone exists 85% in the enol form and is moderately acidic. The K_a in water is $\cong 10^{-9}$. The enol form is stabilized significantly by both electron delocalization and hydrogen bonding. The amount of enol present at equilibrium depends on the solvent, and is smallest in hydrogen-bonding solvents and largest in nonpolar solvents such as carbon tetrachloride.

The reactions discussed in this chapter that depend on the formation of enolate anions (i.e., halogenation, aldol addition, and alkylation) often proceed smoothly and under milder conditions with 1,3-diketones than with monoketones. This is because the 1,3-diketones are stronger acids and therefore can form the enolate anion with weaker bases. The principal synthetic methods for preparing 1,3-dicarbonyl compounds will be discussed in Chapter 18.

With 2,4-pentanedione, polyvalent metal cations often form very stable and only slightly polar enolate salts, better known as **metal chelates**. Cupric ion forms a particularly stable dark-blue chelate:



2,4-pentanedionatocopper(II)
(cupric acetylacetonate)

The beryllium chelate of 2,4-pentanedione is another example of a stable chelate; it melts at 108°, boils at 270°, and is soluble in many organic solvents. By replacing the methyl groups of 2,4-pentanedione with *tert*-butyl groups, a diketone is obtained which, with many metals including transition and rare-earth metals, forms complexes that often are highly soluble in nonpolar organic solvents. The interior of these chelates is saltlike but the exterior is hydrocarbonlike and nonpolar, which accounts for the substantial solubility in nonpolar solvents.

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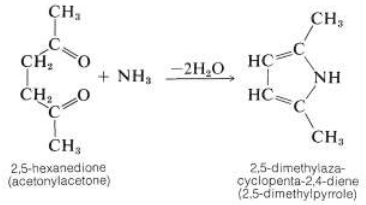
17.10: 1,4-Dicarbonyl Compounds

Most of the reactions of the 1,4-dicarbonyl compounds are the conventional reactions expected for isolated carbonyl groups. An important exception is formation of azacylclopentadiene (pyrrole) derivatives from 1,4-dicarbonyl compounds and ammonia or primary amines:



These reactions are reasonably general and also can be used to prepare compounds with oxygen and sulfur in five-membered rings.

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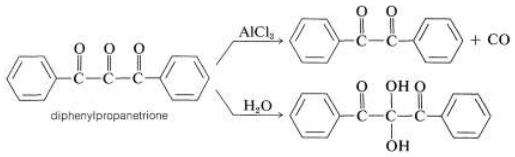
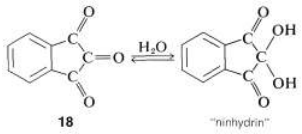
17.11: Tricarbonyl Compounds

The properties of tricarbonyl compounds are for the most part as expected, except when the three groups are contiguous to one another, as in diphenylpropanetrione. With such compounds, the central carbonyl group is highly reactive; it is lost, as carbon monoxide, in the presence of acidic catalysts such as aluminum chloride, and adds water readily to give a monohydrate:



We shall consider the hydrate of the cyclic triketone, 18, known as "ninhydrin", later in connection with amino acids:



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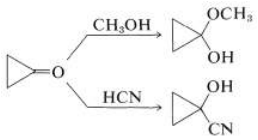
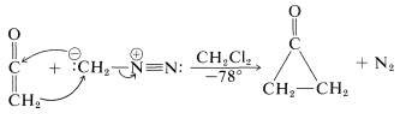
17.12: Cyclopropanones and Cyclopropenones

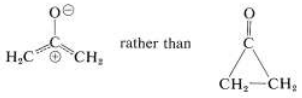
Cyclopropanones deserve special comment, not because of their practical importance (they have no commercial value at this time), but because of their novel behavior and reactivity. No unambiguous synthesis of cyclopropanones was known prior to 1965, and the older textbooks usually contained statements such as "cyclopropanones apparently cannot exist". However, they had been postulated as intermediates in various reactions (see, for example, the Favorskii rearrangement, Section 17-2C), but until recently had defied isolation and identification. The problem is that the three-ring ketone is remarkably reactive, especially towards nucleophiles. Because of the associated relief of angle strain, nucleophiles readily add to the carbonyl group without the aid of a catalyst and give good yields of adducts from which the cyclopropanone is not easily recovered:



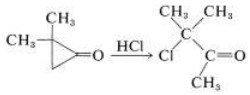
To avoid destructive side reactions, cyclopropanones have to be prepared at low temperatures in the absence of nucleophiles. A good example is the synthesis of cyclopropanone itself from ketene and diazomethane (see Section 16-4A):



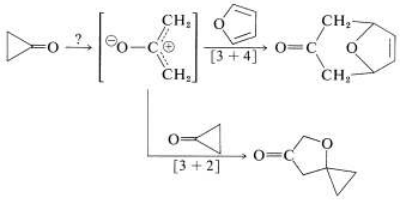
When seemingly simple organic structures defy isolation, this usually stimulates many theoretical and experimental studies in an effort to rationalize anomalous behavior. In the case of cyclopropanone, the possibility was considered that the molecule might preferably exist as an open-chain dipolar structure rather than as the cyclic ketone:



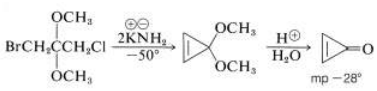
Although the spectral properties of cyclopropanones and the easy formation of hydrates and hemiketals are inconsistent with the dipolar form, some reactions of cyclopropanones do indicate that the ring carbons are much more electrophilic than in other cyclic or acyclic ketones. For example, nucleophilic ring opening often occurs easily:



Also, both [3 + 4] cycloadditions of cyclopropanone to dienes and [3 + 2] additions to carbonyl groups have been observed. These reactions seem easiest to understand if cyclopropanone can behave as if it had, or could be converted to, a dipolar open-chain structure:



Cyclopropenone has been prepared by a route that illustrates the value of the acetal grouping in protecting ketone groups (Section 16-8):



https://chem.libretexts.org/@go/page/22286

Cyclopropenone undergoes many interesting reactions - one example is Diels-Alder addition, the product of which in methanol solution is a hemiketal. That the hemiketal is favored for the adduct, but not for cyclopropenone, indicates that the double bond of cyclopropenone has a considerable effect on the reactivity of the carbonyl group.

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17.E: Carbonyl Compounds II (Exercises)

Exercise 17-1 Other groups in addition to carbonyl groups enhance the acidities of adjacent C–H bonds. For instance, nitromethane, CH_3NO_2, has p$K_a = 10$; ethanenitrile, CH_3CN, has a p$K_a \cong 25$. Explain why these compounds behave as weak acids. Why is CH_3COCH_3 a stronger acid than $CH_3CO_2CH_3$?

Exercise 17-2 Draw valence-bond structures to represent the anions derived from the following compounds in the presence of a strong base. Assume that the base functions to remove the most acidic proton.

a. $CH_3COCH_2CO_2CH_3$

b. CH_3COCH_2CN

c.

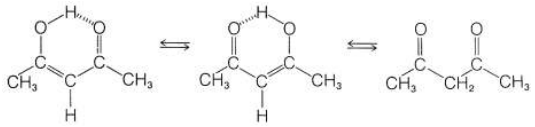
d.* $CH_3COCH_2\overset{\oplus}{S}(CH_3)_2$

Exercise 17-3 Explain why the *D* or *L* enantiomer of a chiral ketone such as 4-phenyl-3-methyl-2-butanone racemizes in the presence of dilute acid or dilute base.

Exercise 17-4

a. The proton NMR spectrum of 2,4-pentanedione is shown in Figure 17-1. Interpret this spectrum by assigning each resonance to a structurally different proton, and explain why the broad resonance at 15 ppm is at unusually low field strengths.

b. What does this spectrum indicate about the *rates* of the establishment of each of the following equilibria?

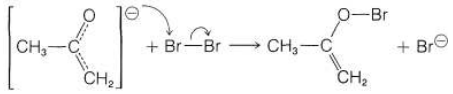


Give your reasoning (review Sections 9-10E and 9-10C).

Exercise 17-5

a. Would you expect the enol or the enolate anion of 2-propanone to be more reactive toward bromine if each were present at the same concentration? Why?

b. Would you expect the enolate anion to react with bromine at the oxygen? Explain. (Consider the bond energies involved!)



Exercise 17-6 Would you anticipate any significant difference in the rate of halogenation between CH_3COCH_3 and CD_3COCD_3 under (a) basic conditions and (b) acidic conditions? Explain. (Review Section 15-6B.)

Exercise 17-7 A detailed study of the rate of bromination of 2-propanone in water, in the presence of ethanoic acid and ethanoate ions, has shown that $v = \left\{6 \times 10^{-9} + 5.6 \times 10^{-4}\,[H_3O^+] + 1.3 \times 10^{-7}\,[CH_3CO_2H] + 7\,[OH^-] + 3.3 \times 10^{-6}\,[CH_3CO_2^-] + 3.5 \times 10^{-6}\,[CH_3CO_2H]\,[CH_3CO_2^-]\right\}[CH_3COCH_3]$ in which the rate v is expressed in mol L^{-1} sec^{-1} when the concentrations are in mol L^{-1}.

a. Calculate the rate of the reaction for a 1 M solution of 2-propanone in water at pH 7 in the absence of CH_3CO_2H and $CH_3CO_2^-$.

b. Calculate the rate of the reaction for 1 M 2-propanone in a solution made by neutralizing 1 M ethanoic acid with sufficient sodium hydroxide to give pH 5.0 (K_a of ethanoic acid $= 1.75 \times 10^{-5}$).

c. Explain how the numerical values of the coefficients for the rate equation may be obtained from observations of the reaction at various pH values and ethanoate ion concentrations.

d. The equilibrium concentration of enol in 2-propanone is estimated to be $\sim 1.5 \times 10^{-4}\%$. If the rate of conversion of 1 M 2-propanone to enol at pH 7 (no CH_3CO_2H or $CH_3CO_2^-$ present) is as calculated in Part a, calculate the rate of the reverse reaction from *enol* to *ketone* at pH 7 if the enol were present in 1 M concentration.

e. Suggest a mechanistic explanation for the term $3.5 \times 10^{-6}\,[CH_3CO_2H]\,[CH_3CO_2^-]$ in the rate expression.

Exercise 17-8 In which of the ketones studied in Section 17-1 would you expect the rate-limiting step in halogenation to be the reaction of the enol with halogen rather than formation of the enol?

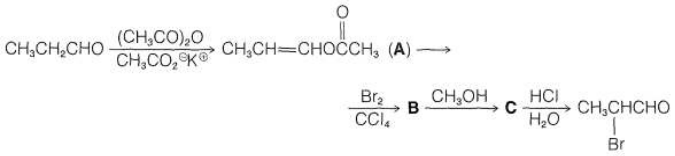
Exercise 17-9

a. Explain why 2-butanone is halogenated preferentially on the ethyl side with an acidic catalyst. (Review of Section 11-3 should be helpful.)

b. What product would predominate in the acid-catalyzed bromination of 1-phenyl-2-propanone? Give your reasoning.

Exercise 17-10 When a small amount of bromine is added to a solution of cyclohexanone in carbon tetrachloride, the brown-red bromine color persists for quite some time. Subsequent additions of bromine result in more rapid reaction and finally the bromine is decolorized almost as rapidly as it can be poured in (until all of the ketone has reacted). Explain this sequence of events.

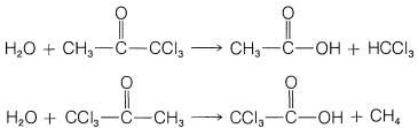
Exercise 17-11 The direct halogenation of aldehydes under either acidic or basic conditions is complicated by side reactions involving either oxidation of the aldehyde $-\mathrm{CHO}$ group or additions to the $-\mathrm{CH{=}O}$ double bond. Therefore the synthesis of α-halo aldehydes by the procedure described for ketones is not of much practical value. The enol ethanoate is made by treating the aldehyde with ethanoic anhydride and potassium ethanoate. The overall sequence follows:



Write the structures of the intermediate products, **B** and **C**, and the steps involved in each of the reactions to produce **A**, **B**, **C**, and 2-bromopropanal. What is the function of potassium ethanoate in the formation of **A**? (You may wish to review Sections 15-4D and 15-4E.)

Exercise 17-12 Trichloromethane (chloroform) at one time was synthesized commercially by the action of sodium hypochlorite on ethanol. Formulate the reactions that may reasonably be involved. What other types of alcohols may be expected to give haloforms with halogens and base?

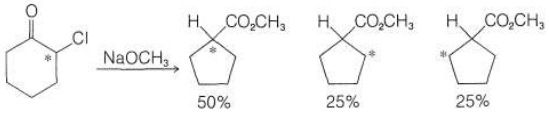
Exercise 17-13 The ΔH^0 values calculated from bond energies for the following reactions in the vapor phase are equal $(\sim 9\ \mathrm{kcal\ mol^{-1}})$:



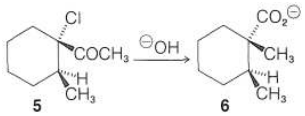
Explain why the first, but not the second, reaction proceeds rapidly with the aid of sodium hydroxide. Would you expect ethanoic acid to undergo the haloform reaction? Explain.

Exercise 17-14* The Haller-Bauer cleavage of 2,2-dimethyl-1-phenyl-1-propanone with sodium amide forms benzenecarboxamide and 2-methylpropane. Write a mechanism for the Haller-Bauer reaction analogous to the haloform cleavage reaction.

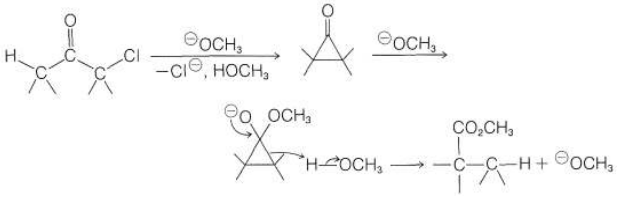
Exercise 17-15* When 2-chlorocyclohexanone-2-^{14}C was treated with sodium methoxide, the ^{14}C label in the methyl cyclopentanecarboxylate formed was found at the 1-position (50%) and 2,5-positions (50%) of the ring:



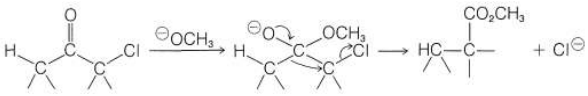
In the related reaction of the chiral chloroketone 5, which has the configuration shown, the product is the cyclohexanecarboxylic acid, 6, with the configuration as shown:



These facts have been interpreted as indicating a mechanism involving the following intermediates (where $^{\ominus}\mathrm{OCH_3}$ is used as the base):



Show in detail how the given results are in accord with this mechanism and how they rule out the following alternative scheme:



Exercise 17-16 When the aldol reaction of ethanal is carried on in D_2O containing $OD^{\ominus}$, using moderate concentrations of undeuterated ethanal, the product formed in the *early* stages of the reaction contains *no* deuterium bound to carbon. Assuming the mechanism discussed in this section to be correct, what can you conclude as to which step in the reaction is the *slow* step? What then would be the kinetic equation for the reaction? What would you expect to happen to the kinetics and the nature of the product formed in D_2O at *very low* concentrations of ethanal?

Exercise 17-17 What would be the products expected from aldol additions involving propanal, 2,2-dimethylpropanal, and a mixture of the two aldehydes?

Exercise 17-18 At what point would the system shown in Figure 17-2 cease to produce more 11? What would happen if some barium hydroxide were to get through a hole in the thimble and pass into the boiler? Why is barium hydroxide more suitable for this preparation than sodium hydroxide?

Exercise 17-19 To obtain high yields of the *mono* adduct 4-hydroxy-2-butanone, from aldol addition of 2-propanone to methanal, it usually is necessary to use an apparatus such as that shown in Figure 17-3. The 2-propanone is placed in the round-bottom flask with a weak *nonvolatile* acid, such as butanedioic (succinic) acid, $(CH_2CO_2H)_2$. The 2-propanone is heated in the flask and the vapors are condensed and returned to the flask through the column that is packed with glass beads. When a good flow of 2-propanone is attained through the column, a basic solution of methanal is slowly dripped in. Explain how this arrangement ensures a high conversion to the monohydroxymethyl derivative, $HOCH_2CH_2COCH_3$, with a minimum of reversion to 2-propanone and methanal. Why is $(CH_3)_2C(OH)CH_2COCH_3$ (11) not formed in significant amounts?

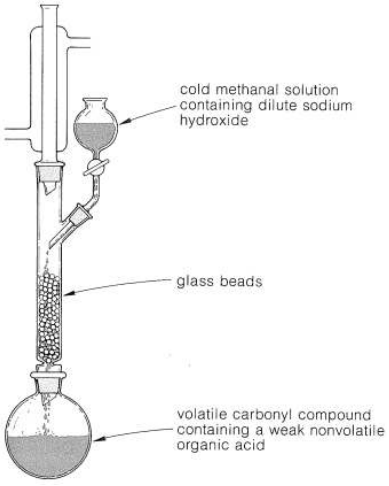


Figure 17-3: *Apparatus for the preparation of monohydroxymethane aldol-addition products from methanal and carbonyl compounds with more than one α hydrogen.*

Exercise 17-20 Predict the principal products to be expected in each of the following reactions; give your reasoning:

a. $CH_3CHO + (CH_3)_2CO \xrightarrow{NaOH}$

b. $(CH_3)_2C(OH)CH_CCOCH_3 \xrightarrow{NaOH}$

c. $CH_2O + (CH_3)_3CCHO \xrightarrow{NaOH}$

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d. $CH_2O + (CH_3)_2CHCHO \xrightarrow{Ca(OH)_2}$

Exercise 17-21

a. A useful modification of aldol addition to methanal, known as the **Mannich reaction**, uses a secondary amine (usually as its hydrochloride salt) to selectively introduce *one* carbon atom at the alpha position of an aldehyde or ketone. The actual product is the salt of an amino ketone. For example,

$$C_6H_5COCH_3 + CH_2O + (CH_3)_2\overset{\oplus}{N}H_2\overset{\ominus}{Cl} \xrightarrow[(solvent)]{C_2H_5OH} C_6H_5COCH_2CH_2\overset{\oplus}{N}H(CH_3)_2\overset{\ominus}{Cl} \quad (17.E.1)$$

Write the steps involved in this reaction, assuming that an intermediate imminium ion, $(CH_3)_2\overset{\oplus}{N}{=}CH_2$, is formed from the amine and methanal.

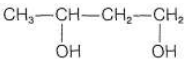
b. Show how the reaction product - the so-called Mannich base - could be converted to $C_6H_5COCH{=}CH_2$.

Exercise 17-22 Explain why many β-halo ketones undergo $E2$ elimination with considerable ease. What kinds of β-halo ketones do not undergo such elimination readily?

Exercise 17-23 Aldol additions also occur in the presence of acidic catalysts. For example, 2-propanone with dry hydrogen chloride slowly yields $(CH_3)_2C{=}CHCOCH_3$ (mesityl oxide) and $(CH_3)_2C{=}CHCOCH{=}C(CH_3)_2$ (phorone). Write mechanisms for the formation of these products, giving particular attention to the way in which the new carbon-carbon bonds are formed.

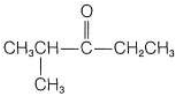
Exercise 17-24 What features of the base-catalyzed dehydration of 3-hydroxybutanal make it a more favorable and faster reaction than would be expected for a base-catalyzed dehydration of 2-butanol? Give your reasoning.

Exercise 17-25 Show how the following compounds can be synthesized from the indicated starting materials by a route having as at least one step an aldol addition:

a.  from ethanal

b. $CH_3CH{=}CH{-}CH_2OH$ from ethanal

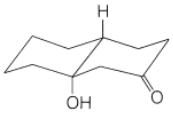
c. $(CH_3)_2CHCH_2CH_2CH_3$ from 2-propanone

d.  from propanal

e. $C_6H_5CH_2CH_2CH_2CH_2CHO$ from benzenecarbaldehyde and ethanal

Exercise 17-26 Devise a reasonable synthesis of each of the following compounds from the indicated starting materials. Assume that other needed reagents are available. (Not all of the syntheses involve aldol-addition reactions, but all involve at some stage or the other carbonyl-addition reactions.)

a. propenenitrile from ethanal
b. 1-(trichloromethyl)cyclohexanol from cyclohexanone
c. 2,2-dimethyl-1,3-propanediol from 2-methylpropanal
d. 2-(phenylmethylidene)cyclohexanone form cyclohexanone
e. 2,3-diphenylpropenenitrile from phenylethanenitrile

f.  from a compound with only one cyclohexane ring

g. 3-methyl-2-cyclopentenone from an open-chain compound

Exercise 17-27 If methyl iodide gives mainly C-alkylation with the enolate anion of 2-propanone, which of the following halides would you expect to be candidates to give O-alkylation: *tert*-butyl chloride, phenylmethyl chloride, 3-chloropropene, neopentyl chloride?

Exercise 17-28

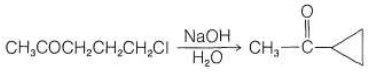
a. Alkylation of ketones is much less successful with ethyl and higher primary halides than for methyl halides. Explain why competing reactions may be particularly important for such cases.

b. What would you expect to happen if you were to try to alkylate ethanal with KNH_2 and CH_3I?

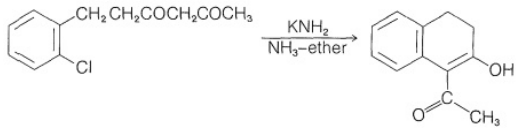
Exercise 17-29 If you wished to prepare the methyl ether of 4-hydroxy-3-penten-2-one by O-alkylation, what base and which fo the methylating agents listed would you choose? CH_3Cl, CH_3I, $CH_3OCO_2OCH_3$, $(CH_3)_3\overset{\oplus}{O}\overset{\ominus}{B}F_4$, or $(CH_3)_2O$. Give your reasoning.

Exercise 17-30 Show the steps that are likely to take place in the following transformations:

a.



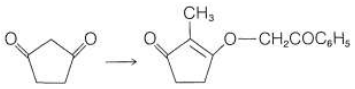
b.



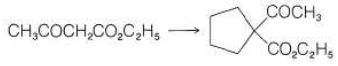
(Review Section 14-6.)

Exercise 17-31 Show how the following transformations can be carried out. Indicate the conditions, particularly the bases used, necessary reagents, and any expected byproducts.

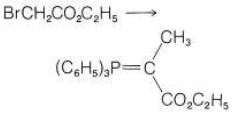
a.



b.

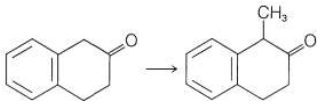


c.



Exercise 17-32* The immonium ion formed on C-alkylation of an enamine is easily hydrolyzed to a ketone. Write the steps involved and show how this reaction differs from the acid-catalyzed formation of enamines discussed in Section 16-4C.

Exercise 17-33* Show how the following transformation could be achieved by way of an enamine:



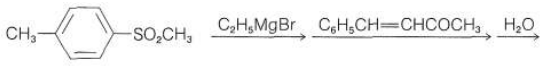
Indicate what other alkylation products may be formed and explain why the one shown is the actual product.

Exercise 17-34* Show the products formed in each step of the following reactions:

a. $CH_3SOCH_2SCH_3 \xrightarrow{NaH} \xrightarrow{CH_3(CH_2)_5Br} \xrightarrow[HCl]{H_2O}$

b. $(CH_3)_2CHCHO + HS(CH_2)_3SH \xrightarrow{HCl} \xrightarrow{CH_3(CH_2)_3Li} \xrightarrow{CH_3(CH_2)_4I} \xrightarrow[Ni,\ (Raney)]{H_2}$

c.



Exercise 17-35 Interpret the proton NMR spectra given in Figure 17-4 in terms of structures of compounds with the molecular formulas $C_6H_{10}O$ and C_9H_8O. The latter substance has a phenyl (C_6H_5) group. Show how each compound may be synthesized from substances with fewer carbons.

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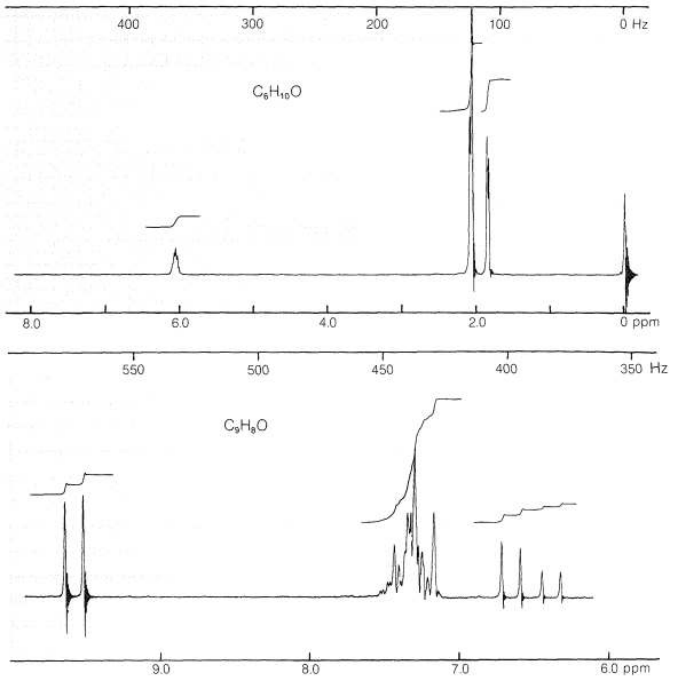


Figure 17-4: *Proton NMR spectra at* 60 MHz *with tetramethylsilane as standard. See Exercise 17-35.*

Exercise 17-36

a. Explain why the addition of HCl to propenal gives a different orientation than in the addition of HCl to 1,3-butadiene. (Review Section 13-2.)

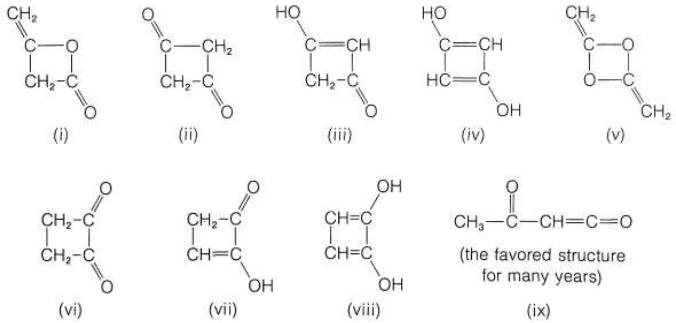
b. What products would you expect from the addition of bromine to 3-buten-2-one? Would you expect this addition to be more, or less, rapid than the addition of bromine to 1-butene? Why?

Exercise 17-37 On what basis can you account for the fact that HCN adds to the carbonyl group of 3-butenal and to the double bond of 3-buten-2-one? Would you expect the carbonyl or the double-bond addition product of HCN to 3-buten-2-one to be more thermodynamically favorable? Give your reasoning.

Exercise 17-38 Write reasonable mechanisms for the reaction of ketene with alcohols and amines. Would you expect these reactions to be facilitated by acids, or by bases?

Exercise 17-39 Write a mechanism for the acid-catalyzed reaction of methanol with diketene that accords with the nature of the reagents involved.

Exercise 17-40 The following structures have been proposed, or could be proposed, for diketene. Show how infrared, Raman, ultraviolet, and NMR spectroscopy may be used to distinguish between the possibilities (if necessary review Chapter 9).



Exercise 17-41 1-Propen-1-one (methylketene) forms a dimer, $C_6H_8O_2$, by [2 + 2] cycloaddition with itself. The NMR spectrum of the dimer is shown in Figure 17-5. Assign a structure to the dimer consistent with the spectrum.

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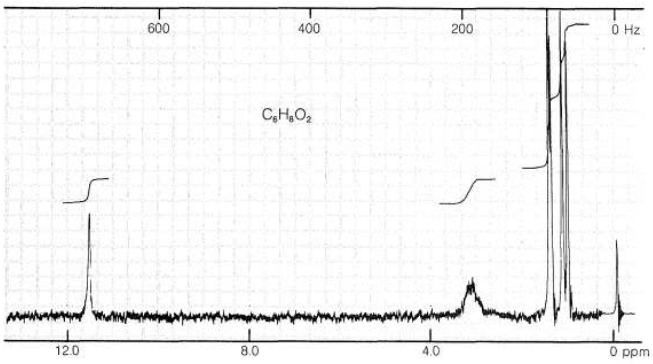
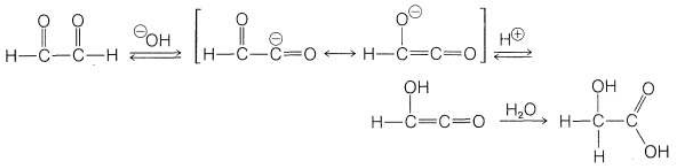


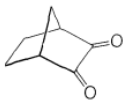
Figure 17-5: *Proton NMR spectrum at* 60 MHz *with tetramethylsilane as standard.*

Exercise 17-42 What experiments may be done to prove or disprove the following mechanism for rearrangement of ethanedial to hydroxyethanoic acid?



Exercise 17-43 Write a mechanism analogous to that for the Cannizzaro reaction for the benzilic acid transformation. What product would you expect to be formed from diphenylethanedione with potassium *tert*-butoxide in *tert*-butyl alcohol? Would you expect a benzilic acid-type rearrangement to occur with 2,3-butanedione? Give your reasoning.

Exercise 17-44 1,2-Cyclopentanedione exists substantially is the monoenol, whereas 2,3-butanedione exists as the diketo form. Suggest explanations for this behavior that take into account possible conformational differences between the two substances. How easily would you expect dione 15 to enolize? Why?



15

Exercise 17-45 2,6-Bicyclo[2.2.2]octanedione, 16, exhibits no enolic properties. Explain.

16

Exercise 17-46* If the keto form of 2,4-pentanedione is more stable than the enol form in water solution, why does it also have to be a weaker acid than the enol form in water solution?

Exercise 17-47 Interpret the proton NMR spectrum shown in Figure 17-6 in terms of possible structures of compounds with molecular formula $C_{10}H_{10}O_2$ with one phenyl group, C_6H_5-.

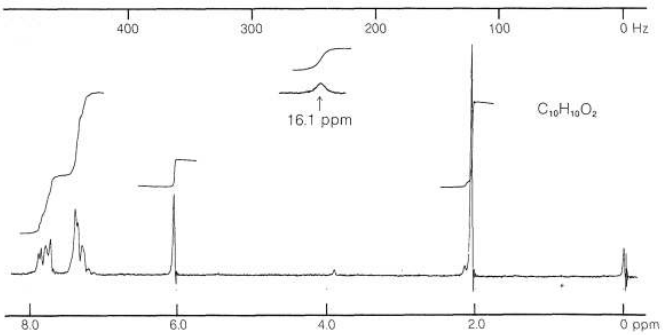


Figure 17-6: *Proton NMR spectrum of* $C_{10}H_{10}O_2$ *at* 60 MHz *with tetramethylsilane as the standard. The integral of the offset peak at* 16.1 ppm *has the same vertical scale as the other integral lines. See Exercise 17-47.*

Exercise 17-48 Write a reasonable mechanism, supported by analogy, for the acid-catalyzed dehydration of 2,5-hexanedione to 2,5-dimethyloxacyclopenta-2,4-diene, 17.

17

Exercise 17-49* Devise a synthesis of diphenylpropanetrione from 1,3-diphenyl-1,3-propanedione, $(C_6H_5CO)_2CH_2$. How could you determine whether the center or one of the flanking carbonyl groups is lost, as carbon monoxide, with aluminum chloride?

Exercise 17-50* What properties would you expect for 1,3,5-cyclohexanetrione?

Exercise 17-51 It is just as important to be able to recognize reactions which do not work as it is to recognize reactions that do work. The following equations represent "possible" synthetic reactions. Consider each carefully and decide whether it will proceed as written. *Show your reasoning*. If you think a different reaction will take place, write an equation for it.

a. $CH_3COCH_3 + 6Br_2 + 8NaOH \rightarrow 2CHBr_3 + Na_2CO_3 + 6NaBr + 6H_2O$

b. $CH_3CHO + NaNH_2 + (CH_3)_3CCl \rightarrow (CH_3)_3CCH_2CHO + NH_3 + NaCl$

c. $(CH_3)_2CHCOCH_3 + CH_2{=}O \xrightarrow{Ca(OH)_2} (CH_3)_2C(CH_2OH)COCH_3$

d. $CH_3CHO + CH_3CO_2C_2H_5 \xrightarrow{OH^{\ominus}} CH_3CH(OH)CH_2CO_2C_2H_5$

e. $CH_3COCH_2COCH_3 + CH_2{=}C{=}O \rightarrow CH_3COOC(CH_3){=}CHCOCH_3$

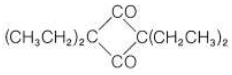
Exercise 17-52 Write equations for a practical laboratory synthesis of each of the following substances from the indicated starting materials (several steps may be required). Give reagents and conditions.

a. from

b. $CH_2{=}CHCOCH_3$ grom CH_3COCH_3

c. $(CH_3)_3CCO_2H$ from $(CH_3)_2C(OH)C(CH_3)_2OH$

d. $(CH_3)_3CCOC(CH_3)_3$ from $CH_3CH_2COCH_2CH_3$

e.  from $(CH_3CH_2)_2CHCOBr$

f. $(CH_3)_2CHCH_2COCH_2Br$ from CH_3COCH_3

g. $CH_3CH_2CH(OH)CN$ from CH_3CHO

h. $(CH_3)_2CHCH_2CH(CH_3)_2$

i. $CH_3CH_2CH(CH_3)CHO$ from $CH_3CH_2CH_2CHO$

j. $CH_3C(CH_2OCOCH_3)_3$ from CH_3CH_2CHO

k. $(CH_3)_3CCH_2CH_2CH_3$ from $(CH_3)_3CCOCH_3$

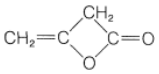
Exercise 17-53 For each of the following pairs of compounds show explicitly how a chemical test, preferably a test-tube reaction, can be used to distinguish between the two compounds. Describe the observation by which the distinction is made.

a. $CH_3COCH_2CH_2COCH_3$ and $CH_3COCH_2COCH_3$

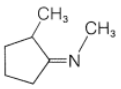
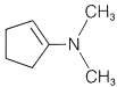
b. $(CH_3CH_2CH_2CH_2)_2CO$ and $[(CH_3)_3C]_2CO$

c. $(CH_3)_2C(OH)CH_2COCH_3$ and $(CH_3)_2CHCH(OH)COCH_3$

d. $C_6H_5COCOC_6H_5$ and $C_6H_5COCH_2COC_6H_5$

e.  and $CH_3COCH{=}C{=}O$

f. $CH_3CH{=}C{=}O$ and $CH_2{=}CH{-}CH{=}O$

g.  and 

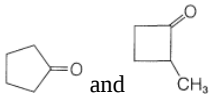
h. $ClCH_2CH_2COCH_3$ and $CH_3CH(Cl)COCH_3$

Exercise 17-54 How may spectroscopic means be used to distinguish between the pairs of compounds in Exercise 17-53?

Exercise 17-55 How may spectroscopic methods be used to distinguish between the isomeric compounds in the following pairs:

a. $CH_3CH{=}CHCOCH_3$ and $CH_2{=}CHCH_2COCH_3$

b. $CH_3CH_2CO_2H$ and CH_3COCH_2OH

c.  and

d. $C_6H_5COCH_2COC_6H_5$ and 4-$CH_3C_6H_4COCOC_6H_5$

e. $CH_3CH{=}C{=}O$ and $(CH_3)_2C{=}O$

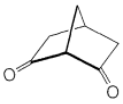
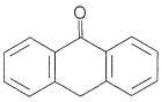
f.

g. $CH_3COCH(CH_3)COCH_3$ and $CH_3COCH{=}C(OCH_3)CH_3$

Exercise 17-56

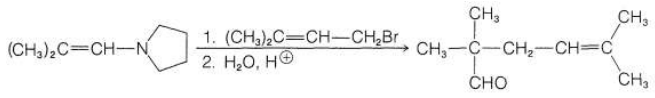
a. Calculate the percentage of enol present in 1-phenyl-1,3-butanedione from its proton NMR spectrum (Figure 17-6).

b. Estimate the amount of enol expected to be present at equilibrium as either small, medium, or large for each of the following compounds. Give your reasoning.

1. $C_6H_5COCH_2C_6H_5$
2. $CH_3COC(CH_3)_2COCH_3$
3. 
4. 

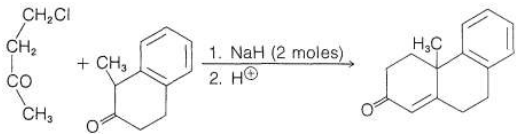
Exercise 17-57 Write the steps involved, showing probable mechanisms, for each of the following reactions:

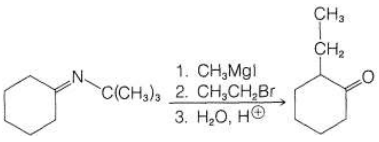
a. $(C_6H_5)_2CHCHO + CH_2{=}O \xrightarrow{K_2CO_3} (C_6H_5)_2C(CH_2OH)_2$

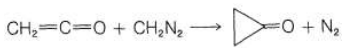
b. 

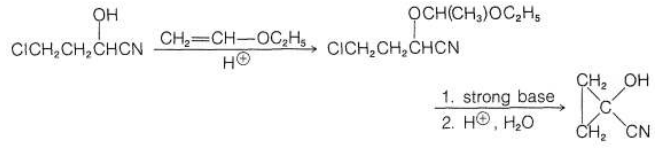
c. $C_6H_5COCH(CN)_2 + CH_2N_2 \xrightarrow{ether} C_6H_5C(OCH_3){=}C(CN)_2$

d. $(C_6H_5)_2C{=}C{=}O \xrightarrow[2.\ H_2O]{1.\ LiAlH_4} (C_6H_5)_2CHCHO$

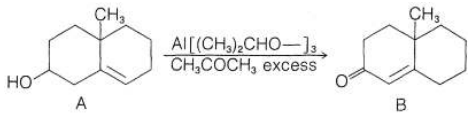
e. 

f. 

g. 

h. 

Exercise 17-58 Explain why oxidation of compound A leads to the α,β-unsaturated ketone B.



Exercise 17-59 The proton NMR spectra of two compounds of formulas C_4H_7OCl and C_4H_7OBr are shown in Figure 17-7. Assign to each compound a structure that is consistent with its spectrum. Show your reasoning. Give a concise description of the chemical properties to be expected for each compound.

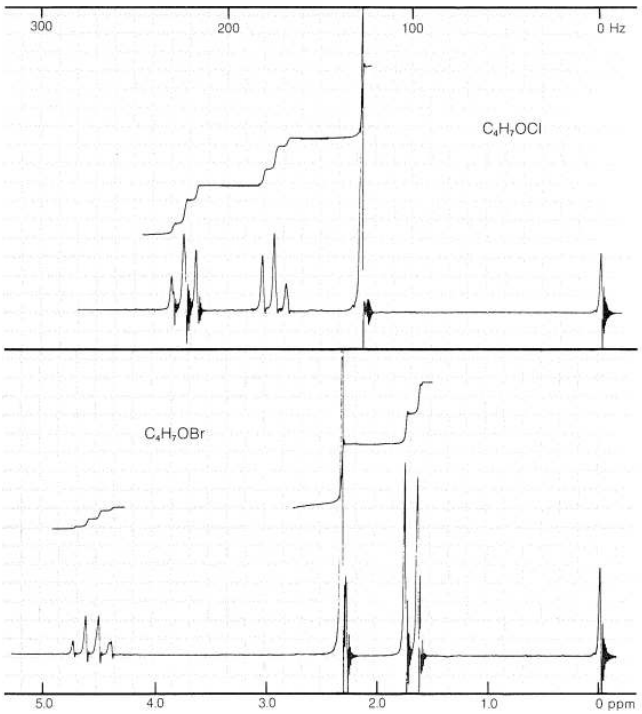


***Figure 17-7:** Proton NMR spectra at 60 MHz with TMS as standard. See Exercise 17-59.*

Exercise 17-60 Explain why β,γ-unsaturated aldehydes and ketones usually are relatively difficult to synthesize and are found to rearrange readily to the α,β-unsaturated isomers, particularly in the presence of basic reagents:

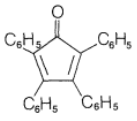
$$CH_2{=}CH{-}CH_2{-}CHO \xrightarrow{\text{base}} CH_3{-}CH{=}CH{-}CHO \qquad (17.E.2)$$

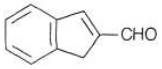
Exercise 17-61 Devise a synthesis of each of the following compounds using as a key step an aldol-type addition reaction:

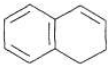
a. $C_6H_5CH{=}CHCOC_6H_5$

b. $C_6H_5CH{=}CHCOCH{=}CHC_6H_5$

c. $C_6H_5CH{=}C(COCH_3)_2$

d. 

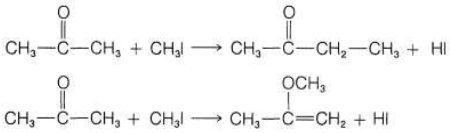
e.* 

from 

Exercise 17-62 Alkenyl ethers (enol ethers) of the type $ROCH{=}CH_2$ are more stable to rearrangement to $O{=}CH{-}CH_2R$ than is an enol such as $HOCH{=}CH_2$ to $O{=}CH{-}CH_3$. Why? What conditions would you expect to be favorable for rearrangement of an alkenyl ether?

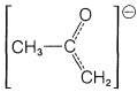
Exercise 17-63 How would you expect the proton NMR spectrum of cyclopropanone in the cyclic ketone and dipolar ion structures (Section 17-11) to differ? Show your reasoning.

Exercise 17-64* Calculate ΔH^0 from bond energies (Table 4-3) for C- and O-alkylation of 2-propanone with CH_3I in accord with the following equations:



Compare your answers with the ΔH^0 values calculated for O- and C-addition in the aldol reaction (Section 17-3B).

How can it be that *both* C- and O-alkylation of the anion



with CH_3I have $\Delta H < 0$? (Notice that the pK_a of 2-propanone is about 20 and that of HI is about -9.)

17.E.1: Contributors

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CHAPTER OVERVIEW

18: Carboxylic Acids and Their Derivatives

Almost all of the basic *types* of reactions now have been covered: addition, elimination, substitution, and rearrangement by polar, radical, and concerted mechanisms. Indeed, if you have been looking for similarities, you will have seen that most of the reactions discussed in the preceding three chapters are variations on basic types we have discussed earlier. Furthermore, most of the basic structural effects that determine chemical reactivity also have been covered in previous chapters: bond energies, steric hindrance, electronegativity, electron delocalization, hydrogen bonding, solvation, and conformational influences.

You might well ask what is left. The answer is, a great deal - but now we will be concerned mostly with putting concepts together, moving from the simple to the complex. For example, in this chapter we will be trying to understand the ways that carboxylic acids, which possess the $-\mathrm{COOH}$ functional group, are similar to and different from alcohols, which have the $-\mathrm{OH}$ group, and aldehydes and ketones, which have $\mathrm{C{=}O}$ bonds.

18.1: Prelude to Carboxylic Acids and Their Derivatives
18.2: Physical Properties of Carboxylic Acids
18.3: Some Chemical Properties of Carboxylic Acids
18.4: Reactions at the Carbonyl Carbon of Carboxylic Acids
18.5: Decarboxylation of Carboxylic Acids
18.6: Reactions at the \(\alpha\) Carbons of Carboxylic Acids
18.7: Functional Derivatives of Carboxylic Acids
18.8: Reactions at the Carbonyl Carbon of Acid Derivatives
18.9: Reactions at the \(\alpha\) Carbons of Carboxylic Acid Derivatives
18.10: Reactions of Unsaturated Carboxylic Acids and Their Derivatives
18.11: Dicarboxylic Acids
18.12: Methods of Preparation of Carboxylic Acids and Their Derivatives
18.E: Carboxylic Acids and Their Derivatives (Exercises)

18.1: Contributors and Attributions

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18.1: Prelude to Carboxylic Acids and Their Derivatives

Almost all of the basic *types* of reactions now have been covered: addition, elimination, substitution, and rearrangement by polar, radical, and concerted mechanisms. Indeed, if you have been looking for similarities, you will have seen that most of the reactions discussed in the preceding three chapters are variations on basic types we have discussed earlier. Furthermore, most of the basic structural effects that determine chemical reactivity also have been covered in previous chapters: bond energies, steric hindrance, electronegativity, electron delocalization, hydrogen bonding, solvation, and conformational influences.

You might well ask what is left. The answer is, a great deal - but now we will be concerned mostly with putting concepts together, moving from the simple to the complex. For example, in this chapter we will be trying to understand the ways that carboxylic acids, which possess the $-\mathrm{COOH}$ functional group, are similar to and different from alcohols, which have the $-\mathrm{OH}$ group, and aldehydes and ketones, which have $\mathrm{C{=}O}$ bonds.

Subsequently we will look at acids that also possess OH or $\mathrm{NH_2}$ substituent groups (or both) and develop a rationale for the behavior of these combinations in terms of effects we already have discussed. Insofar as possible, you should try to do this yourself whenever you encounter a substance with a new set of combinations or functional groups on its molecules. You often will be in error (as many experts will be), because even in you take account of all of the structural effects, as well as the possible reactions or interactions, the overall result of these frequently is very difficult to judge in advance. In one case, steric hindrance may dominate, in another, electron delocalization, and so on. Still, trying to assess the effects and possible reactions leads to understanding and recognition of what the alternatives are, even if the resultant of them is difficult to assess.[1] Continuing study can be expected to develop an instinct for what is "good" chemistry and what is not.

We have described previously the acidic properties of several types of compounds: alkynes, alkenes, and alkanes (Sections 11-8 and 13-5B); halides (Section 14-7B); alcohols (Section 15-4A); and carbonyl compounds (Section 17-1A). Now we come to compounds that we actually call *acids* - the **carboxylic acids**, $\mathrm{RCO_2H}$. Are these acids different in kind, or only in degree, from other acidic compounds discussed before? This is not a simple question and deserves some thought. In the most widely used sense, acids are proton donors but, as we have seen, their abilities to donate a proton to water vary over an enormous range: $\mathrm{CH_4}$ has a K_a of $< 10^{-40}$, whereas HI has a K_a of $\sim 10^{9}$. This represents a difference in ionization energies of more than $70\ \mathrm{kcal\ mol^{-1}}$. The differences in K_a are only differences in degree, because examples are available of acids with K_a values in all parts of the range of K_a values. An important difference in kind was mentioned in Section 17-1B, namely, that acids with the same K_a values can differ greatly in the *rates* at which they give up a proton to a given base, such as water. Carbon acids, in which the proton comes from a $\mathrm{C{-}H}$ bond, may react *more than* 10^{10} *times slower* than an oxygen acid with the same K_a in which the proton is give up from an $\mathrm{O{-}H}$ bond.

Tradition reserves the use of the name "acid" for substances that transfer protons measurably to water. Thus the carboxylic acids stand out from alkynes, halides, alcohols, and simple aldehydes and ketones in giving water solutions that are "acidic" to indicator papers or pH meters as the result of proton transfers from the carboxylic groups:

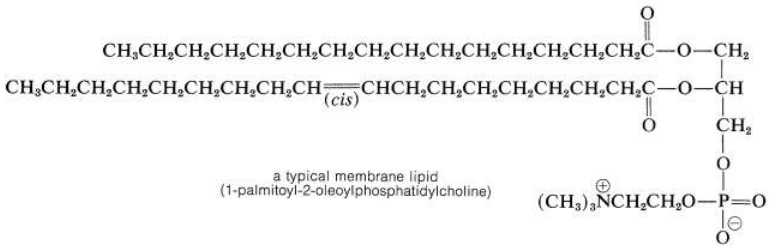
$$\mathrm{RCO_2H + H_2O \rightleftharpoons RCO_2^- + H_3O^+} \tag{18.1.1}$$

Even so, carboxylic acids are not very strong acids and, in a $1\ \mathrm{M}$ water solution, a typical carboxylic acid is converted to ions to the extent of only about 0.5%.

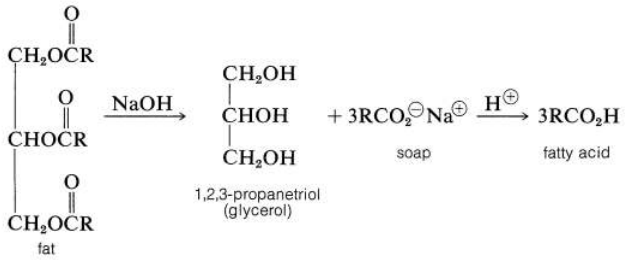
The nomenclature of carboxylic acids and their derivatives was discussed in Section 7-6. Many carboxylic acids have trivial names and often are referred to as "fatty acids". This term applies best to the naturally occurring straight-chain saturated and unsaturated aliphatic acids, which, as esters, are constituents of the fats, waxes, and oils of plants and animals. The most abundant of these fatty acids are palmitic, stearic, oleic, and linoleic acids. They occur as **glycerides**, which are esters of the trihydric alcohol, 1,2,3-propanetriol (glycerol):

$\mathrm{CH_3(CH_2)_{14}CO_2H}$	hexadecanoic (palmitic) acid
$\mathrm{CH_3(CH_2)_{16}CO_2H}$	octadecanoic (stearic) acid
$\mathrm{CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H}$	*cis*-9-octadecenoic (oleic) acid
$\mathrm{CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H}$	*cis*-9-*cis*-12-octadecadienoic (linoleic) acid

Fats or glycerides belong to a class of biomolecules known as **lipids**. The traditional definition of *a lipid is a water-insoluble organic compound that can be extracted from cells and tissues by nonpolar solvents* (chloroform, ether, benzene). Compounds that meet this definition are substantially hydrocarbonlike, although they may differ widely in structure. They include not only esters of long-chain fatty acids but steroids (Section 30-4), terpenes (Section 30-3), and prostaglandins (Section 30-7). These nonpolar substances serve a variety of different biological functions, but lipids derived from fatty acids are most important for energy storage (Sections 18-8F and 20-10) and as components of membranes. **Phosphoglycerides** represent an important class of membrane lipids derived from glycerol. The hydroxyl groups of glycerol are esterified with two fatty-acid chains and one phosphate-ester residue. One of the phosphate-ester groups carries a highly *polar* $-\mathrm{N}(\mathrm{CH_3})_2^+$ group, the importance of which is indicated in Section 18-2F:



Hydrolysis of fats with alkali (e.g., sodium hydroxide) yields salts of the fatty acids, and those of the alkali metals, such as sodium or potassium, are useful as soaps:



The properties of salts of long-chain carboxylic acids that make them useful as soaps will be discussed in Section 18-2F.

General methods for the preparation of carboxylic acids are summarized in Table 18-5, at the end of the chapter.

[1]The major problem with assessing the resultant to be expected from opposing factors in chemical reactions is that relatively small energy differences can cause great differences in which product is favored. For an equilibrium such as $\mathrm{A} \rightleftharpoons \mathrm{B}$ at $25^{\circ}\mathrm{C}$, a $5.5\ \mathrm{kcal\ mol^{-1}}$ change in ΔG^0 (Section 4-4A) can cause the equilibrium to shift from 99% in favor of A to 99% in favor of B.

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18.2: Physical Properties of Carboxylic Acids

18.2.1: Hydrogen Bonding

Carboxylic acids show a high degree of association through hydrogen bonding. We have encountered such bonding previously with alcohols; however, acids form stronger hydrogen bonds than alcohols because their O–H bonds are more strongly polarized as $-\overset{\delta\ominus}{O}-\overset{\delta\oplus}{H}$. Furthermore, carboxylic acids are able to form hydrogen bonds to the negative oxygen of the carbonyl dipole rather than just to the oxygen of another hydroxyl group. Carboxylic acids in the solid and liquid states mostly exist as cyclic dimers, and these dimeric structures persist to some extent even in the vapor state and in dilute solution in hydrocarbon solvents:

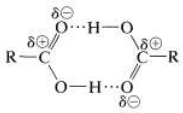


Figure 18-1, which is a plot of boiling points versus n (the total number of carbon atoms) for the homologous series $CH_3(CH_2)_{n-2}X$, in which X is $-CO_2H$, $-CH_2OH$, or $-CH_2Cl$.

Table 18-1: *Physical Properties of Representative Carboxylic Acids*

Acid	Structure	Solubility, g/100 g H_2O	mp, °C	bp, °C	K_a (H_3O) at 25°C
methanoic (formic)	HCO_2H	∞	8.4	100.7	1.77×10^{-4}
ethanoic (acetic)	CH_3CO_2H	∞	16.6	118.1	1.75×10^{-5}
propanoic (propionic)	$CH_3CH_2CO_2H$	∞	−22	141.1	1.3×10^{-5}
butanoic (butyric)	$CH_3CH_2CH_2CO_2H$	∞	−8	163.5	1.5×10^{-5}
2-methylpropanoic (isobutyric)	$(CH_3)_2CHCO_2H$	20^{20}	−47	154.5	1.4×10^{-5}
pentanoic (valeric)	$CH_3(CH_2)_3CO_2H$	3.3^{16}	−34.5	187	1.6×10^{-5}
hexadecanoic (palmitic)	$CH_3(CH_2)_{14}CO_2H$	insol.	64	390	
octadecanoic (stearic)	$CH_3(CH_2)_{16}CO_2H$	0.034^{25}	69.4	360 d	
chloroethanoic (chloroacetic)	$ClCH_2CO_2H$	sol.	63	189	1.4×10^{-3}
dichloroethanoic (dichloroacetic)	Cl_2CHCO_2H	8.63	5–6	194	5×10^{-2}
trichloroethanoic (trichloroacetic)	Cl_3CCO_2H	120^{25}	58	195.5	1×10^{-1}
trifluoroethanoic (trifluoroacetic)	F_3CCO_2H	∞	−15	72.4	strong[a]
2-chlorobutanoic (α-chlorobutyric)(D,L)	$CH_3CH_2CHClCO_2H$	sol. hot		$101^{15\,mm}$	1.4×10^{-3}
3-chlorobutanoic (β-chlorobutyric)(D,L)	$CH_3CHClCH_2CO_2H$		44	$116^{23\,mm}$	8.9×10^{-5}
4-chlorobutanoic (γ-chlorobutyric)	$ClCH_2CH_2CH_2CO_2H$		16	$196^{22\,mm}$	3.0×10^{-5}
5-chloropentanoic (δ-chlorovaleric)	$ClCH_2(CH_2)_2CO_2H$		18	$130^{11\,mm}$	2×10^{-5}
methoxyethanoic (methoxyacetic)	$CH_3OCH_2CO_2H$	sol.		203	3.3×10^{-4}
cyanoethanoic (cyanoacetic)	$N{\equiv}CCH_2CO_2H$	sol.	66	$108^{0.15\,mm}$	4×10^{-3}
3-butenoic (vinylacetic)	$CH_2{=}CHCH_2CO_2H$	sol.	−39	163	3.8×10^{-5}
benzenecarboxylic (benzoic)	$C_6H_5CO_2H$	0.27^{18}	122	249	6.5×10^{-5}
phenylethanoic (phenylacetic)	$C_6H_5CH_2CO_2H$	1.66^{20}	76.7	265	5.6×10^{-5}

[a]The term "strong" acid implies essentially complete dissociation to $RCO_2^{\ominus}$ and $H_3O^{\oplus}$ in aqueous solution.

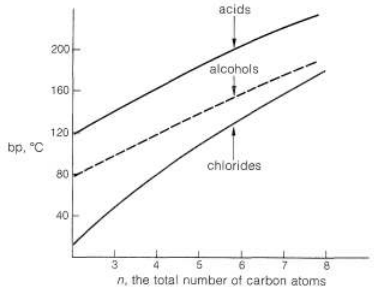
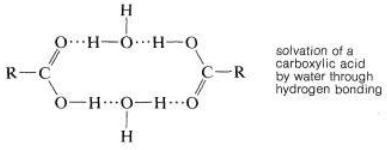


Figure 18-1: Boiling points of acids, $CH_3(CH_2)_{n-2}CO_2H$; alcohols, $CH_3(CH_2)_{n-2}CH_2OH$; and alkyl chlorides, $CH_3(CH_2)_{n-2}CH_2Cl$

Hydrogen bonding also is responsible for the high water solubility of the simple carboxylic acids with less than five carbons; water molecules can solvate the carbonyl group through hydrogen bonds. Nonetheless, as the chain length of the hydrocarbon residue R increases, the solubility decreases markedly, because the proportion of polar to nonpolar groups becomes smaller.



solvation of a carboxylic acid by water through hydrogen bonding

18.2.2: Spectra of Carboxylic Acids

The *infrared spectra* of carboxylic acids provide clear evidence for the hydrogen bonding discussed in the preceding section. This is illustrated in Figure 18-2, which shows the spectrum of ethanoic acid in carbon tetrachloride solution, together with those of ethanol and ethanal for comparison.

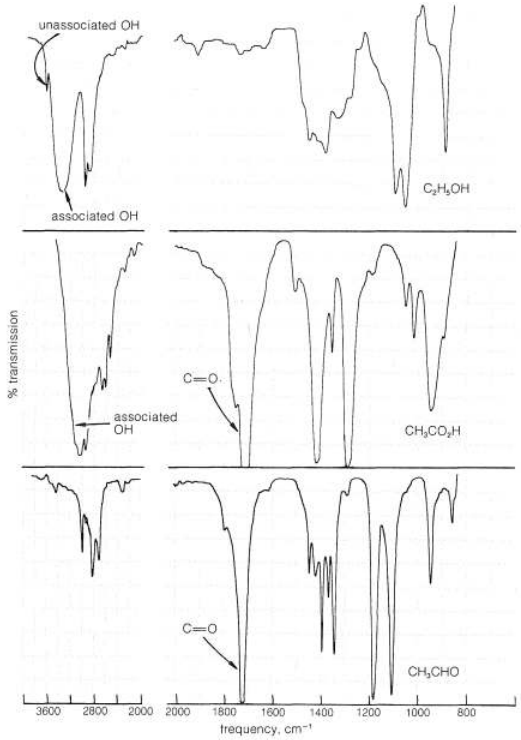


Figure 18-2: Infrared spectra of ethanol, ethanoic acid, and ethanal as 10% solutions in carbon tetrachloride.

The spectrum of ethanol has two absorption bands that are characteristic of the OH bond; one is a sharp band at $3640\ \mathrm{cm}^{-1}$, which corresponds to free or unassociated hydroxyl groups, and the other is a broad band centered on $3350\ \mathrm{cm}^{-1}$ due to hydrogen-bonded groups. The spectrum of ethanoic acid shows no absorption from free hydroxyl groups but, like that of ethanol, has a very broad intense absorption ascribed to associated OH groups. However, the frequency of absorption, $3000\ \mathrm{cm}^{-1}$, is shifted appreciably from that of ethanol and reflects stronger hydrogen bonding than in ethanol. The absorption due to the carbonyl group of ethanoic acid $(1740\ \mathrm{cm}^{-1})$ is broad, but is at about the same position as the carbonyl absorption in ethanal.

The carboxyl function does absorb *ultraviolet* radiation, but the wavelengths at which this occurs are appreciably shorter than for carbonyl compounds such as aldehydes and ketones, and, in fact, are out of the range of most commercial ultraviolet spectrometers. Some idea of how the hydroxyl substituent modifies the absorption properties of the carbonyl group in carboxylic acids can be seen from Table 18-2, in which are listed the wavelengths of maximum light absorption $(\lambda_{\max})$ and the extinction coefficients at maximum absorption $(\epsilon_{\max})$ of several carboxylic acids, aldehydes, and ketones.

Table 18-2: *Wavelengths for Maximum Ultraviolet Absorption of Some Carboxylic Acids, Aldehydes, and Ketones* $(n \rightarrow \pi^*)$

Compound	λ_{max}, nm	ϵ_{max}	Solvent	Compound	λ_{max}, nm	ϵ_{max}	Solvent
ethanoic acid	204	40	water	2-propanone	270	16	alcohol
ethanoic acid	197	60	hexane	butanoic acid	207	74	water
ethanal	293	12	hexane	butanal	290	18	hexane

Figure 18-3 by the spectra of phenylethanoic acid $(C_6H_5CH_2CO_2H)$ and phenylmethanol $(C_6H_5CH_2OH)$. The chemical shift of the carboxylic acid proton is here about $9\ \mathrm{ppm}$ toward lower magnetic fields than that of the hydroxyl proton of the alcohol. This behavior parallels that of the enol hydrogens of 1,3-dicarbonyl compounds and is similarly related to hydrogen-bond formation (Section 17-1D).

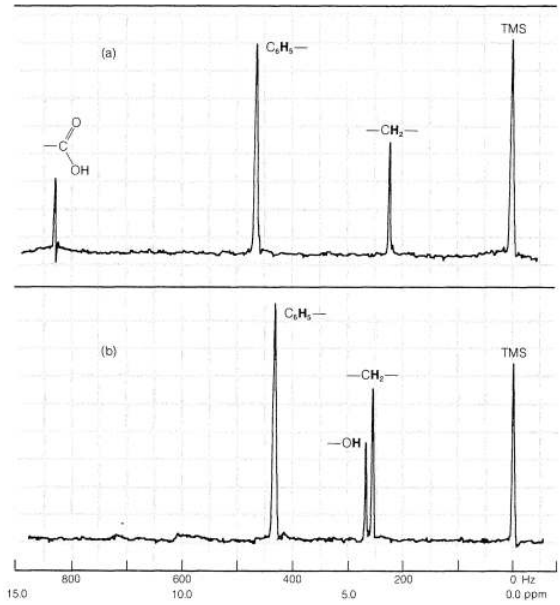


Figure 18-3: Proton nmr spectra of (a) phenylethanoic acid and (b) phenylmethanol in carbon tetrachloride solution at 60 MHz relative to TMS.

18.2.3: Contributors and Attributions

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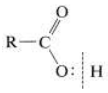
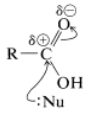
18.3: Some Chemical Properties of Carboxylic Acids

Most of the reactions of carboxylic acids belong to one of four principal classes, depending on the point in the molecule where the reaction occurs.

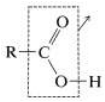
a. **Reactions involving the** $\mathrm{O{-}H}$ **bond** - these include acid dissociation and solvolytic reactions.



b. **Reactions at the carbonyl bond** - most of which involve attack by a nucleophile $:\mathrm{Nu}$ on the carbonyl carbon with subsequent cleavage of a $\mathrm{C{-}O}$ bond. Examples are esterification, acyl chloride formation, and reduction with hydrides.



c. **Decarboxylation** - these are reactions in which the $\mathrm{R{-}C}$ bond is broken in such a way that $\mathrm{CO_2}$ is lost and $\mathrm{R{-}H}$ is formed.



d. **Substitution on the** R **group** - substitutions for hydrogen or halogen at the 2-carbon are especially important.

We will emphasize the way in which the chemistry of carboxylic acids in each of these categories can be correlated with the principles outlined in previous chapters.

18.3.1: Dissociation of Carboxylic Acids. The Resonance Effect

Compared with mineral acids such as hydrochloric, perchloric, nitric, and sulfuric acids, the carboxylic acids, $\mathrm{CH_3(CH_2)_nCO_2H}$, are weak. The extent of dissociation in aqueous solution is relatively small, the acidity constants, K_a, being approximately 10^{-5} (see Table 18-1).

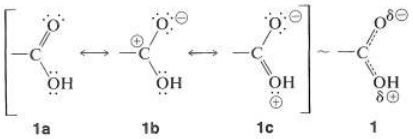
$$\mathrm{RCO_2H + H_2O \rightleftharpoons RCO_2^{\ominus} + H_3O^{\oplus}}$$

$$K_\mathrm{a} = \frac{[\mathrm{RCO_2^{\ominus}}][\mathrm{H_3O^{\oplus}}]}{[\mathrm{RCO_2H}]} \sim 10^{-5} \quad \text{for R} = \mathrm{CH_3(CH_2)_n{-}}$$

Even though the carboxylic acids are weak acids, they are many orders of magnitude stronger than the corresponding alcohols, $\mathrm{CH_3(CH_2)_nCH_2OH}$. Thus the K_a of ethanoic acid, $\mathrm{CH_2CO_2H}$, is 10^{11} *times larger* than that of ethanol, $\mathrm{CH_3CH_2OH}$.

The acidity of the carboxyl group arises, at least in part, from the polar nature of the carbonyl group, the polarity of which can be ascribed to contributions of the structure

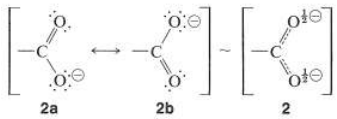
For a carboxyl group, these structures and an additional possibility are shown by $1a$, $1b$, and $1c$:



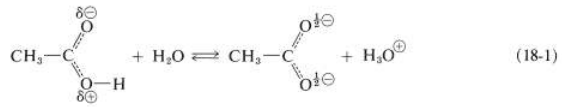
1a **1b** **1c** **1**

Although the uncharged structure, $1a$, is of major importance, structures $1b$ and $1c$ make significant contributions. The stabilization is substantial and carboxylic acids are more stable than would be expected, from summing up their bond energies, by fully $18\ \text{kcal mol}^{-1}$.

The stabilization energy of the carboxylate anion is substantially greater than that of the acid, because the anion is a resonance hybrid of two energetically *equivalent* structures, $2a$ and $2b$, whereas the acid is represented by a hybrid of *nonequivalent* structures, $1a$ through $1c$:



The rules for resonance stress that the greatest stabilization is expected when the contributing structures are equivalent (Section 6-5B). Therefore we can conclude that the resonance energy of a carboxylate anion should be greater than that of the corresponding acid. Consequently we can say that there is a "driving force" (a gain in stability) that promotes the dissociation of carboxylic acids. The fact that alcohols are far weaker acids than carboxylic acids may be attributed to the lack of stabilization of alkoxide ions compared to that of carboxylate anions. The difference in energy corresponding to the dissociation of a carboxylic acid (Equation 18-1) relative to that of an alcohol (Equation 18-2) actually amounts to about $15\ \text{kcal mol}^{-1}$:

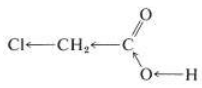


18.3.2: The Inductive Effect and Acid Strengths

You may have noticed that there are considerable differences between the strengths of some of the acids listed in Table 18-1. Methanoic acid and almost all the substituted ethanoic acids are stronger than ethanoic acid. In fact, trifluoroethanoic acid is similar in strength to hydrochloric acid. The substituent groups clearly can have a profound effect on acid strength by what commonly is called the **inductive effect**, an effect related to the electronegativity of the substituent. The inductive effect is different from resonance effects discussed in Section 18-2A in that it is associated with substitution on the *saturated* carbon atoms of the chain. The inductive effect of the substituent makes the acid stronger or weaker (relative to the unsubstituted acid), depending on whether the substituent is electron-attracting or electron-donating relative to hydrogen.

The electronegativity scale (Section 10-4B) shows chlorine to be more electron-attracting than hydrogen, and chloroethanoic acid is an 80-times stronger acid than ethanoic acid itself. Substitution by more chlorines enhances the acidity. Dichloroethanoic acid is 3000 times and trichloroethanoic acid is 5000 times more acidic than ethanoic acid. Moving the position of substitution along the chain away from the carboxyl group makes the effect smaller, and 4-chlorobutanoic acid is only a two-times stronger acid than butanoic acid (Table 18-1).

The inductive effect of the substituent can be considered to be transmitted to the carboxyl group in two rather different ways. Most frequently, the substituent is regarded as causing shifts in the average distributions of the bonding electrons along the chain of atoms between it and the carboxyl proton. This produces a succession of electron shifts along the chain, which, for an electron-attracting substituent, increases the acid strength by making it more energetically feasible for the $-\text{OH}$ hydrogen of the carboxyl group to leave as a proton:

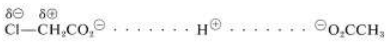


Many other groups besides halogens exhibit electron-withdrawing acid-enhancing inductive effects. Among these are nitro $(-\text{NO}_2)$, methoxy (CH_3O), carbonyl $(\text{RCOR}'$, as in aldehydes, ketones, acids, esters, and amides), cyano or nitrile $(-\text{C} \equiv \text{N})$, and trialkylammonium $\left(\text{R}_3\overset{\oplus}{\text{N}} -\right)$. Alkyl groups - methyl, ethyl, isopropyl, and so on - are the only substitutents listed in Table 18-1 that

are acid-weakening relative to hydrogen (as can be seen by comparing the K_a values of the longer-chain acids with those of methanoic and ethanoic acids). We may take this to mean that alkyl groups *release* electrons to the carboxyl group.

18.3.3: The Electrostatic Interpretation of Acid Strengths

The other possible mode of transmission of the polar effect of a substituent group is a purely electrostatic one, sometimes called the "field effect", in which the dipole of the substituent produces an electrostatic field at the carboxyl proton, which helps or hinders ionization depending on the way in which the dipole is oriented with respect to the carboxyl group. It is easiest to visualize how the electrostatic theory operates by considering a proton midway between two well-separated carboxylate anions and deciding with which one the proton can combine more favorably. The more favorable one will correspond to the more basic carboxylate anion and the weaker carboxylic acid. With $CH_3CO_2^-$ and $ClCH_2CO_2^-$ as examples, and remembering that the Cl–C bond is polarized as $\overset{\delta\ominus}{Cl}-\overset{\delta\oplus}{C}$, we can write:



The proton will be attracted by both $-CO_2^-$ groups and the differences in electrostatic energy of its combination with one or the other of the carboxylate groups will depend on the influence of the $\overset{\delta\ominus}{Cl}-\overset{\delta\oplus}{C}H_2$ dipole. The $\overset{\delta\ominus}{Cl}$ end of the dipole will attract the proton, but the $\overset{\delta\oplus}{C}H_2$ end will repel it. The repulsion effect will be more important because the $\overset{\delta\oplus}{C}H_2$ is *closer* than $\overset{\delta\ominus}{Cl}$ to the final point of attachment of the proton to the carboxylate oxygen.[2] Thus, the proton will go more favorably to $CH_3CO_2^-$ than to $ClCH_2CO_2^-$, which means that $ClCH_2CO_2H$ is a stronger acid than CH_3CO_2H.

Quantitative application of electrostatic theory to the effect of substituents on the ionization of carboxylic acids, such as chloroethanoic acid, is rendered difficult by the fact that the polarized $\overset{\delta\ominus}{Cl}-\overset{\delta\oplus}{C}H_2$ bond and the proton cannot be treated as if they were point charges in a vacuum. The intervening and surrounding matter must be taken into account. This is especially true for water solutions because a molecule of an organic acid in water is a cavity of low dielectric constant immersed in a medium of high dielectric constant. Therefore, when ionization occurs the proton goes from inside the cavity through the boundary into the water. At the same time, the nature of the cavity must change because it then contains an anion, not a neutral molecule.

18.3.4: What Part Does Entropy Play in the Dissociation of Carboxylic Acids?

We have discussed the influence of substituents on acid strengths of simple carboxylic acids as though the full electrostatic effect of the substituent were exerted solely on the ΔH of ionization. However, careful thermodynamic analysis of acidities in aqueous solution show that entropy effects (Section 4-4B) are very important. This may seem surprising because entropy effects ought to be small for *relative* acid strengths, which can be assessed by the constants for simple equilibria such as Equation 18-3, in which (1) there are the same number of molecules on each side of the equation, and (2) the constraints on the species involved hardly seem different from one side of the equation to the other:

(18-3)

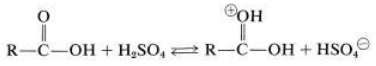
The entropy effects associated with these equilibria have to do with the "invisible" participant, water, which is involved in an intimate way, although by convention we omit it from equations such as 18-3. Solvation of ions puts constraints on water molecules, and the same electrostatic effects that change the ease of removing the proton act to change the degree and nature of solvation, thereby requiring consideration of entropy effects on the equilibria.

If solvation entropy effects are important, how can we justify using simple electrostatic theory to account for changes in acid strengths produced by substituents? The answer lies in ΔG; whatever the electrostatic effects are doing to balance between ΔH and ΔS, it is ΔG that determines the equilibrium constant and ΔG quite consistently follows the predictions of simple electrostatic considerations. Furthermore, the relative acid strengths of a number of substituted ethanoic acids have been determined in the gas phase by ion-cyclotron resonance (Section 27-8), under conditions where association and solvent effects are absent (Section 11-8A). In the gas phase, entropy effects are small and the relative acidities are in the order expected from the electronegativity scale, provided on corrects for the ion-size effect that we encountered previously with respect to the gas-phase acidities of alkynes and alcohols (Section 11-8B and 15-4A). Thus fluoroethanoic acid is weaker than chloroethanoic acid in the gas phase, whereas the

reverse is true in water solution. The difference may be due simply to the fact that larger ions are in general more stable than smaller ions in the gas phase.

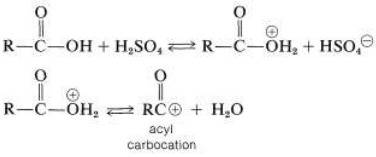
18.3.5: Carboxylic Acids as Bases

In addition to their acidic properties, carboxylic acids also can act as weak bases when the carbonyl oxygen accepts a proton from a strong acid, such as H_2SO_4, $HClO_4$, or $HSbF_6$ in SO_2 (Equation 18-4). Such protonation is an important step in acid-catalyzed esterification, as discussed in Section 15-4D:



(18-4)

A proton also can add to the hydroxyl oxygen (Equation 18-5). The resulting conjugate acid normally is less favorable than its isomer with the proton on the carbonyl group. Nonetheless, this conjugate acid plays a role in esterification when the R group is particularly bulky and, in addition, has electron-donating properties, thereby favoring ionization to an acyl carbocation (as in Equation 18-6; see also Section 18-3A):



(18-5)

(18-6)

18.3.6: Salts of Carboxylic Acids as Soaps. Micelle Formation

Carboxylic acids have an important practical use in the form of their metal salts as *soaps*. We have mentioned how fats, which are 1,2,3-propanetriol (glyceryl) esters of long-chain acids, can be hydrolyzed with alkali to give the corresponding carboxylate salts. It has been known as far back as Roman times (Pliny) that such substances have value for cleaning purposes.[3] These salts have a complicated interaction with water because they are very polar at the salt end of the molecule and very nonpolar at the long-chain hydrocarbon end of the molecule. These hydrocarbon ends are not compatible with a polar solvent such as water.[4]

When minute amounts of soaps are put into water, instead of forming simple solutions, the molecules become concentrated at the surface of the water, with the saltlike ends sticking down into the water and the hydrocarbon chains forming a layer on the surface. This arrangement greatly reduces the surface tension of the water and contributes to the startling properties of soap films and bubbles. At higher concentrations, the solutions become turbid as the result of **micelle** formation. Micelles are sizable aggregates of soap molecules, wherein the hydrocarbon chains form a region of low polarity that is stabilized by having the polar salt ends of the molecules in contact with the water (Figure 18-4).

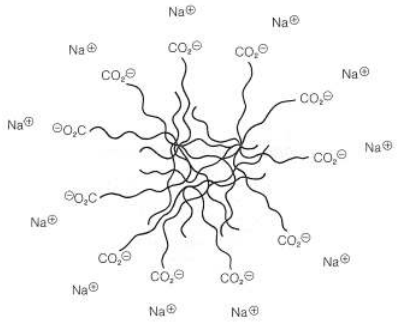


Figure 18-4: Schematic diagram of a soap micelle in water solution.

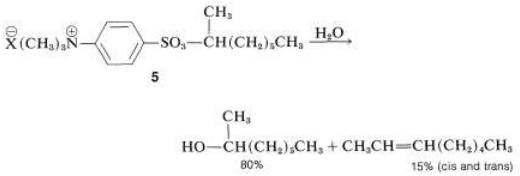
The cleansing action of soap is partly due to the way soap lowers the surface tension of the water thereby helping it to penetrate into fabrics, and also to the ability of the micelles to solubilize oils and greases by taking them into their hydrocarbon regions.

A major disadvantage of the simple carboxylate soaps is that they combine with the calcium and magnesium ions normally present in most tap water to form insoluble scums, which interfere with the cleansing process. Many so-called **detergents** have been developed that do not have this disadvantage - an example is sodium 4-dodecanylbenzenesulfonate, whose calcium and magnesium salts are water soluble.

Roberts and Caserio Screenshot 18-2-16.png

When carboxylate salts are put into *nonpolar* solvents, **reversed micelles** often are formed, where the polar parts of the molecules are on the inside and the nonpolar parts are on the outside.

Pronounced differences have been observed for the rates of chemical reactions in micelles as compared to pure water. For example, the solvolysis of the 1-methylheptyl sulfonate, 5, in dilute water solution proceeds 70 times *slower* when sufficient sodium dodecanyl sulfate $\left(\overset{\oplus}{\mathrm{Na}}\overset{\ominus}{\mathrm{O}}_3{}_{12}\mathrm{SOCH}_{25}\right)$ is added to provide about twice as many dodecanyl sulfate ions in the micelle state as there are molecules of 5 present:



This slowing of the solvolysis reaction by the alkyl sulfate requires that 5 be almost completely imprisoned by the micelles, because that part of 5 free in water would hydrolyze rapidly. An important result is in the stereochemistry of the reaction, which changes from 100% inversion with optically active 5 in pure water to only 56% inversion in the micelles. Micelles of the opposite polarity, made from hexadecyltrimethylammonium bromide, $\mathrm{C}_{16}\mathrm{H}_{33}\overset{\oplus}{\mathrm{N}}(\mathrm{CH}_3)_3\overset{\ominus}{\mathrm{Br}}$, have no effect on the rate of solvolysis of 5.

Studies of this type have been made on a number of systems and are of great interest because of the light they may shed on the structure and function of biological membranes.

There is a close resemblance between fatty-acid salts and phospholipids in that both possess long hydrocarbon tails and a polar head. Phospholipids also aggregate in a polar medium to form micelles *and* continuous bilayer structures such as shown in Figure 18-5. The bilayer lipid structure is very important to the self-sealing function of membranes and their impermeability to very polar molecules.

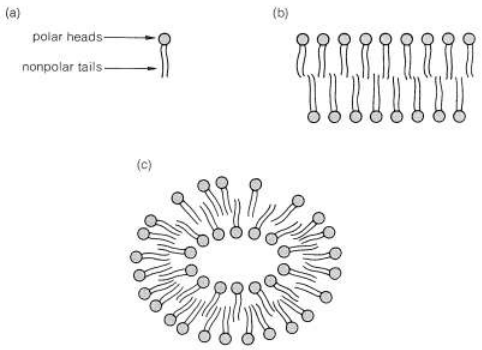


Figure 18-5: Schematic representation of (a) a membrane lipid, (b) a bilayer structure formed by lipid molecules in polar media; the interior of the bilayer is nonpolar, and (c) a continuous bilayer structure (liposome) with polar interior and exterior.

[2]The electrostatic energy involved in brining two charges from a distance r_1 to a distance r_2 apart is given by $(e_1e_2/D)\,(1/r_1 - 1/r_2)$, where e_1 and e_2 are the magnitude of the charges and D is the dielectric constant of the medium (Section 8-7F). If e_1 and e_2 have the same sign, the energy is positive, and with opposite signs the energy is negative. For calibration, the electrostatic energy resulting from bringing a positive charge from a large distance $(1/r_1 \sim 0)$, up to a negative charge at a distance of 1 Å in a vacuum $(D = 1)$ is -335 kcal mol^{-1}.

[3]Until the 19th century soaps were made by boiling animal or vegetable fats with wood ashes, which contain, besides silica, considerable amounts of potassium carbonated. The resulting mixture of potassium carboxylate salts gives a "soft" soap, and this can be converted to a "hard" soap by treatment with excess NaCl, which forms the less soluble sodium carboxylate salts. The KCl formed goes into the aqueous phase.

[4]One might well wonder why soap molecules do not simply crystallize out of water solution if the hydrocarbon chains are incompatible with water. However, the crystal packing of the polar salt parts of the molecule is not likely to be very compatible

with the hydrocarbon parts and, furthermore, most soaps are salts of mixtures of aliphatic acids and this hardly helps crystallization to occur.

18.3.7: Contributors and Attributions

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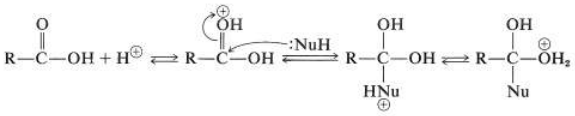
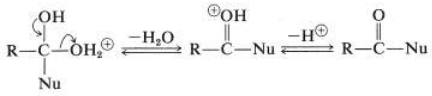
18.4: Reactions at the Carbonyl Carbon of Carboxylic Acids

Many important reactions of carboxylic acids involve attack on the carbon of the carbonyl group by nucleophilic species. These reactions frequently are catalyzed by acids, because addition of a proton or formation of a hydrogen bond to the carbonyl oxygen makes the carbonyl carbon more vulnerable to nucleophilic attack. The following equations illustrate how an acid-catalyzed reaction operates with a neutral nucleophile $(H{-}Nu)$:



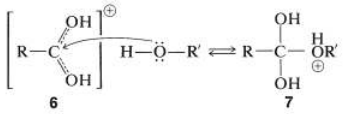
Subsequent cleavage of a $C{-}O$ bond and loss of a proton yields a displacement product:



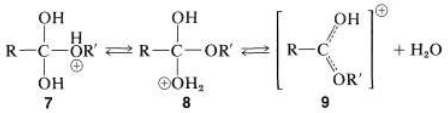
An important example of this type of reaction is the formation of esters, which was discussed previously in connection with the reactions of alcohols in Section 15-4D. Similar addition-elimination mechanisms occur in many reactions at the carbonyl groups of acid derivatives. A less obvious example of addition to carboxyl groups involves hydride ion $(H^{\ominus})$ and takes place in lithium aluminum hydride reduction of carboxylic acids (Sections 16-4E and 18-3C).

18.4.1: Esterification

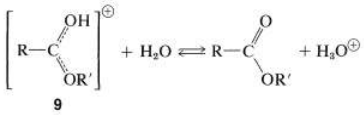
Esters, RCO_2R', are formed from carboxylic acids and alcohols in the presence of acid catalysts. The key step in esterification is the nucleophilic attack of a neutral alcohol molecule, $R'OH$, at the carbonyl carbon of the conjugate acid of the carboxylic acid, $RC(OH)_2{}^+$, 6:



The intermediate, 7, either can revert to the starting materials or form a second intermediate, 8, by proton transfer. Loss of water from 8 leads to the conjugate acid of the ester, 9:



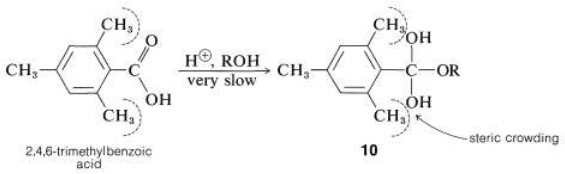
The final step in formation of the ester is proton transfer from 9 to the solvent:



All the steps in ester formation are reversible, but the equilibrium in the $C{-}O$ bond-making and -breaking processes are not very favorable, and an excess of one reactant (usually the alcohol) or removal of one product (most often water) is required to give a good yield of ester.

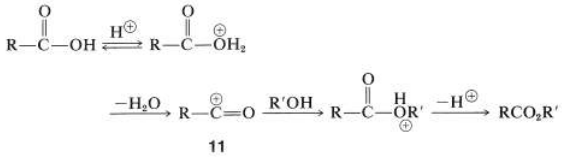
The usefulness of direct ester formation from alcohols and acids is limited to those alcohols or acids that do not undergo extensive side reactions in the presence of strong acids. Furthermore, if the alcohol is particularly bulky the reaction usually will not proceed satisfactorily because the intermediates 7 and 8 (as well as the product) are rendered unstable by crowding of the substituent groups.

Bulky groups in the esterifying acid also hinder the reaction. A classic example is 2,4,6-trimethylbenzoic (mesitoic) acid, which cannot be esterified readily under normal conditions because the methyl groups *ortho* to the carboxyl group make the transition state for formation of the intermediate 10 less favorable relative to the starting acid than would be the case for less hindered acids, such as ethanoic acid:

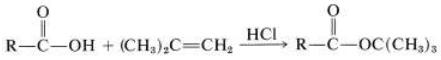


The important point is the *difference* in steric hindrance between the acid and the intermediate. If you make a scale model you will see that in the acid, the carboxyl group, being planar, can have reduced hindrance by turning about its bond to the ring so as to be between the methyl groups. However, no such relief is possible with 10, in which the $-C(OH)_2OR$ carbon is tetrahedral.

Esterification of acids with bulky substituents, such as 2,4,6-trimethylbenzoic acid, can be achieved through formation of acyl cations. This is done by simply dissolving the carboxylic acid in strong sulfuric acid, whereby the acyl cation 11 is formed, and then pouring the solution into an excess of cold alcohol (see also Equations 18-5 and 18-6). This procedure works because it avoids the formation of a hindered tetrahedral intermediate similar to 10 and instead forms the conjugate acid directly:



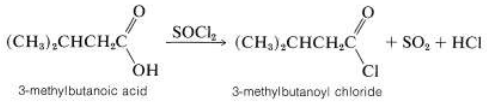
Esterification of carboxylic acids with bulky alcohols is unsatisfactory. However, tertiary alkyl esters often can be prepared by addition of the acid to the appropriate *alkene* using an acid catalyst:



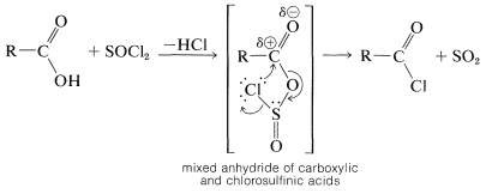
The success of such addition reactions depends on formation of a stable carbocation from the alkene under conditions where the most reactive nucleophile present is the carboxylic acid.

18.4.2: Acyl Chloride Formation

Carboxylic acids react with phosphorus trichloride, phosphorus pentachloride, or thionyl chloride with replacement of OH by Cl to form acyl chlorides, RCOCl:



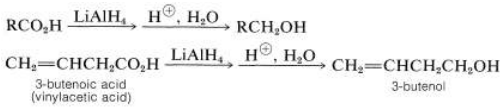
Although detailed mechanisms have not been established, the first step is thought to be formation of an unstable mixed anhydride, which then extrudes SO_2 and "collapses" with attach of chloride at the carbonyl carbon. A similar mechanism occurs in the formation of alkyl chlorides from alcohols and thionyl chloride (Section 15-5A):



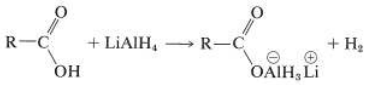
Most acyl halides are stable, distillable liquids. However, methanoyl chloride, HCOCl, decomposes to carbon monoxide and hydrogen chloride at room temperature.

18.4.3: Reduction of Carboxylic Acids

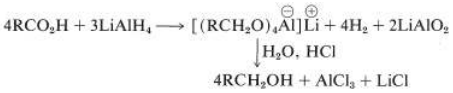
Generally, carboxylic acids are difficult to reduce either by catalytic hydrogenation or by sodium and alcohol. Nonetheless, reduction to primary alcohols proceeds smoothly with lithium aluminum hydride, $LiAlH_4$:



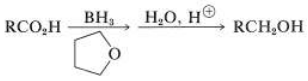
The first step in lithium aluminum hydride reduction of carboxylic acids is formation of a complex aluminum salt of the acid and hydrogen:



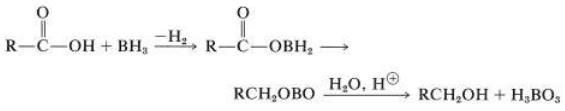
Reduction then proceeds by successive transfers of hydride ion, (\ce{H}^\ominus\), from aluminum to carbon. The first such transfer reduces the acid salt to the oxidation level of the aldehyde; reduction does not stop at this point, however, but continues rapidly to the alcohol. Insufficient information is available to permit very specific structures to be written for the intermediates in the lithium aluminum hydride reduction of carboxylic acids. However, the product is a complex aluminum alkoxide, from which the alcohol is freed by hydrolysis:



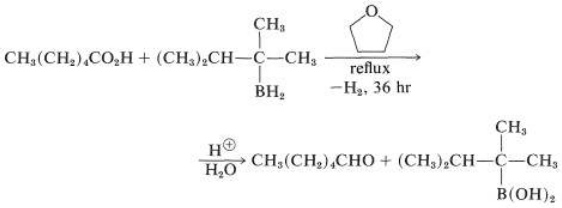
Sodium borohydride, $NaBH_4$, is too mild a reducing agent to transfer hydride to carboxylic acids, and one may suspect that borane, BH_3, also would be ineffective. However, this is not the case and borane in oxacyclopentane (tetrahydrofuran) reduces carboxylic acids more rapidly than it adds to alkene double bonds (see Tale 16-5):



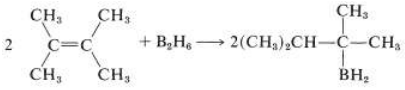
The reason for the high reactivity lies in the fact that the acid first converts the borane to an acyloxyborane, which then undergoes an intramolecular rearrangement in which the carbonyl group is reduced. Hydrolysis gives the alcohol:



Special methods are required for the direct reduction of RCO_2H to $RCHO$. Aldehydes can be obtained directly by the slow reduction of carboxylic acids with 2,3-dimethyl-2-butylborane in oxacyclopentane solution. One hydrogen of the borane is wasted through reaction with the acidic hydrogen of the carboxyl group to give hydrogen. An example is



The borane is prepared through the addition of B_2H_6 to 2,3-dimethyl-2-butene and, because of steric hindrance, only the monoalkylborane is formed (Section 11-6A):



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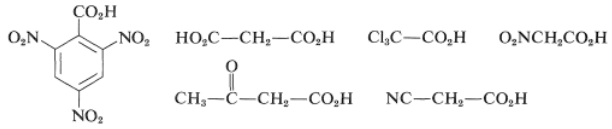
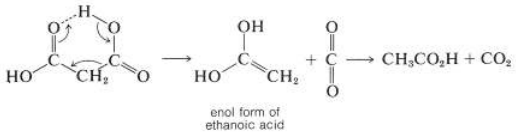
18.5: Decarboxylation of Carboxylic Acids

The decarboxylation of RCO_2H to give RH and CO_2 can be calculated from bond energies and the stabilization energy of the carboxyl group to have $\Delta H^0 = -7$ kcal mol^{-1}. This does not mean that the reaction goes easily. Special structural features are required. The simple aliphatic carboxylic acids do not lose carbon dioxide on heating, but when there are strongly electron-attracting groups attached to the α carbon, decarboxylation often proceeds readily at 100-150°. Examples include

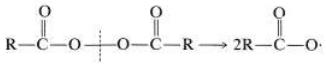


3-Butenoic acid also undergoes decarboxylation but has to be heated to above 200°:

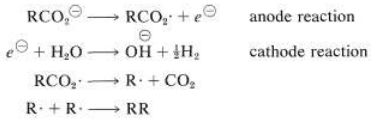
The mechanisms of thermal decarboxylation probably are not the same for all cases, but when the acid has a *double-bonded* function such as O=C, N=C, O=N, or C=C attached to the α carbon then a cyclic elimination process appears to occur. For propanedioic acid the process is



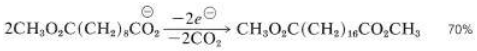
Carboxylate radicals can be generated in several ways. One is the thermal decomposition of diacyl peroxides, which are compounds with rather weak O–O bonds:



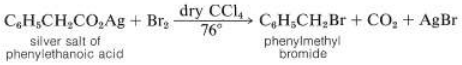
Another method involves electrolysis of sodium or potassium carboxylate solutions, known as **Kolbe electrolysis**, in which carboxylate radicals are formed by transfer of an electron from the carboxylate ion to the anode. Decarboxylation may occur simultaneously with, or subsequent to, the formation of carboxylate radicals, leading to hydrocarbon radicals, which subsequently dimerize:



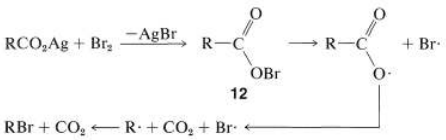
An example is



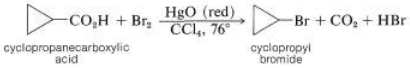
Decarboxylation of the silver salts of carboxylic acids in the presence of bromine or chlorine, the **Hunsdiecker reaction**, often is useful for the synthesis of alkyl halides:



The mechanism of this reaction seems to involve formation of carboxylate radicals through decomposition of an acyl hypobromic intermediate, 12:

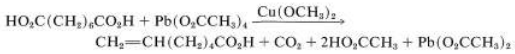


The Hunsdiecker reaction has certain disadvantages, mainly because it requires use of the pure *dry* silver salt, which is often difficult to prepare. With some acids, however, excellent results can be obtained using the acid itself and an excess of red mercuric oxide in place of the silver salt.



or by heating the acid with lead tetraethanoate, $Pb(O_2CCH_3)_4$, and iodine,

A somewhat similar decarboxylation reaction with formation of an alkene can be achieved by heating a carboxylic acid with lead tetraethanoate, $Pb(O_2CCH_3)_4$, in the presence of a catalytic amount of $Cu(OCH_3)_2$. A useful example is



There is some competing decarboxylation of the ethanoic acid, but the conversions in this kind of reaction are usually good. The key steps in the reaction probably are exchange of carboxylic acid groups on tetravalent lead, cleavage of the $Pb{-}O$ bond to give the carboxylate radical, decarboxylation, oxidation of the alkyl radical by Cu (II) to give the cation $[R\cdot + Cu(II) \rightarrow R^{\oplus} + Cu(I)]$, and finally loss of a proton to form the alkene.

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18.6: Reactions at the α Carbons of Carboxylic Acids

18.6.1: Halogenation

Bromine reacts smoothly with carboxylic acids in the presence of small quantities of phosphorus to form alpha-bromocarboxylic acids (**Hell-Volhard-Zelinsky reaction**):

$$CH_3CH_2COOH + Br_2 \xrightarrow{P} \underset{\text{2-bromopropanoic acid}}{CH_3CHBrCOOH} + HBr$$

The reaction is slow in the absence of phosphorus, whose function appears to be to form phosphorus tribromide, which then reacts with the acid to give the acyl bromide:

$$2P + 3Br_2 \longrightarrow 2PBr_3$$
$$CH_3CH_2CO_2H + PBr_3 \longrightarrow CH_3CH_2COBr + POBr + HBr$$

Formation of the acyl bromide speeds up the reaction because acid-catalyzed enolization of the acyl bromide occurs much more readily than enolization of the parent acid. Bromine probably reacts with the enol of the acyl bromide in the same way as it reacts with the enols of ketones (Section 17-2A).

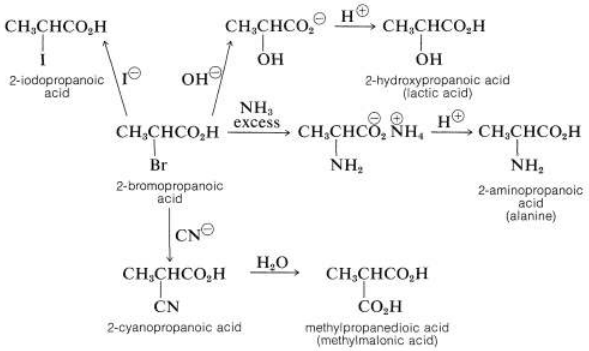
The final step is the formation of the α-bromo acid by bromine exchange between the α-bromoacyl bromide and the parent acid; the acyl bromide, which is necessary for continued reaction, is thus regenerated:

$$CH_3CHBr\overset{O}{\overset{\|}{C}}Br + CH_3CH_2CO_2H \longrightarrow CH_3CH_2\overset{O}{\overset{\|}{C}}Br + CH_3CHBrCO_2H$$

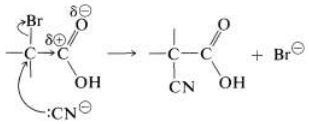
This bromination reaction results exclusively in alpha substitution and therefore is limited to carboxylic acids with α hydrogens. Chlorine with a trace of phosphorus reacts similarly but with less overall specificity, because concurrent free-radical chlorination can occur at all positions along the chain (as in hydrocarbon halogenation; see Section 4-6A).

18.6.2: Substitution Reactions of α-Haloalkanoic Acids

The halogen of an α-haloalkanoic acid is replaced readily by nucleophilic reagents such as $CN^{\ominus}$, $OH^{\ominus}$, $I^{\ominus}$, and NH_3. Thus a variety of α-substituted carboxylic aids may be prepared by reactions that are analogous to S_N2 substitution of alkyl halides:

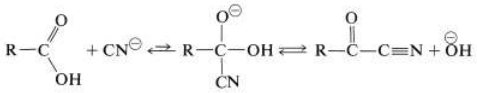


Facile S_N2 substitution reactions of halogens are expected from the electron-attracting characteristics of the neighboring carbonyl function, which should make the transition state for attack by a nucleophilic reagent more favorable:

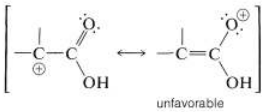


Perhaps it may seem surprising that the carboxyl carbon is not attacked by the nucleophilic agents, because we have stressed earlier the susceptibility of carbonyl groups to nucleophilic reagents. No stable product results, however, from addition to the carbonyl

group by the type of reagents considered here. Thus with cyanide ion the equilibrium constant for addition is unfavorable because of the associated loss of stabilization energy of the carboxyl group.



The S_N1 reactivity of α-haloalkanoic acids is particularly low. This is reasonable because formation of a cationic center at the α carbon should be difficult, because of the positive character of the carbonyl carbon. Furthermore, little, if any, help could be expected through electron delocalization because the corresponding valence-bond structure has a *positive*, single-bonded oxygen:



Similar considerations apply to the S_N1 and S_N2 reactions of α-halo aldehydes and α-halo ketones (Section 17-2C).

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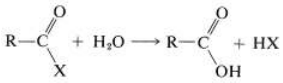
18.7: Functional Derivatives of Carboxylic Acids

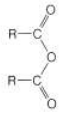
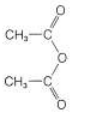
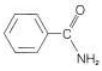
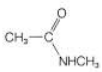
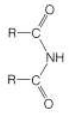
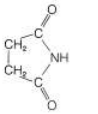
A **functional derivative** of a carboxylic acid is a substance formed by replacement of the hydroxyl group of the acid by some other group, X, such that it can be hydrolyzed back to the acid in accord with Equation 18-7:



(18-7)

By this definition, an amide, $RCONH_2$, but not a ketone, $RCOCH_3$, is a functional derivative of a carboxylic acid. Several derivatives of carboxylic acids are give in Table 18-3, and methods for preparation of these derivatives are summarized in Tables 18-6 and 18-7 at the end of the chapter.

Table 18-3: *Functional Derivatives of Carboxylic Acids*

		Example	
Derivative	Structure	Structure	Name
esters			ethyl ethanoate (ethyl acetate)
acyl halides	X = F, Cl, Br, I		benzenecarbonyl bromide (benzoyl bromide)
anhydrides			ethanoic anhydride (acetic anhydride)
amides (primary)			benzenecarboxamide (benzamide)
amides (secondary and tertiary)			*N*-methylethanamide (*N*-methylacetamide)
			N,N-dimethylmethanamide (*N,N*-dimethylformamide)
imides			butanimide (azacyclopenta-2,5-dione, succinimide)
acyl azides			ethanoyl azide (acetyl azide)

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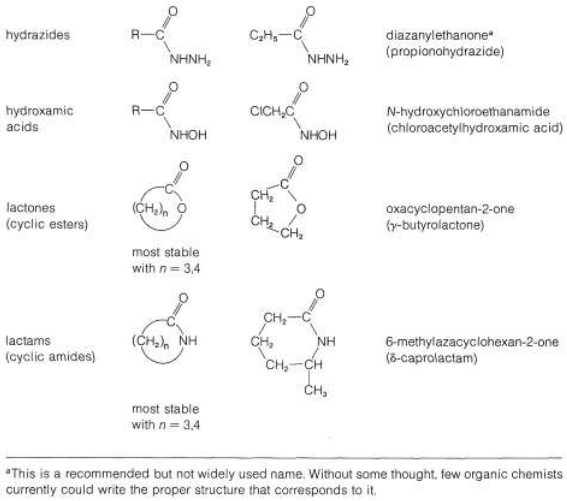


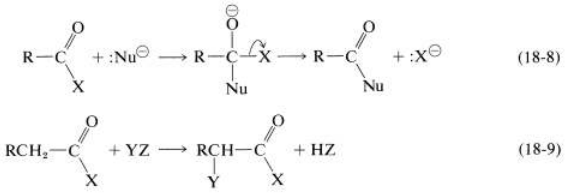
*This is a recommended but not widely used name. Without some thought, few organic chemists currently could write the proper structure that corresponds to it.

The common structural feature of the compounds listed in Table 18-3 is the acyl group $\mathrm{RCO}-$. However, nitriles, $\mathrm{RC}\equiv\mathrm{N}$, often are considered to be acid derivatives, even though the acyl group is not present as such, because hydrolysis of nitriles leads to carboxylic acids:

$$\underset{\substack{\text{ethanenitrile}\\\text{(acetonitrile)}}}{\mathrm{CH_3C{\equiv}N}} + 2\mathrm{H_2O} \xrightarrow{\mathrm{H^{\oplus}}} \underset{\substack{\text{ethanoic acid}\\\text{(acetic acid)}}}{\mathrm{CH_3COOH}} + \mathrm{NH_3}$$

The chemistry of nitriles will be discussed in Section 24-5.

The two main types of reactions of carboxylic acid derivatives with which we now shall be concerned are the replacement of X by attack of a nucleophile $\mathrm{Nu}^{\ominus}$ at the carbonyl carbon with subsequent cleavage of the C–X bond (Equation 18-8), and substitution at the α carbon facilitated by the carbonyl group (Equation 18-9):



18.7.1: Contributors and Attributions

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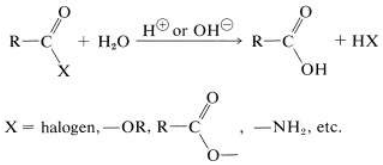
18.8: Reactions at the Carbonyl Carbon of Acid Derivatives

18.8.1: Displacement Reactions

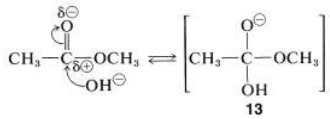
Hydrolysis of most acid derivatives to the parent acids is acid- or base-catalyzed:



X = halogen, —OR, , —NH_2, etc.

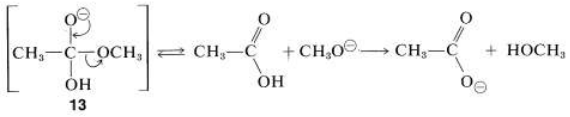
However, acyl halides and anhydrides usually hydrolyze rapidly without the aid of an acidic or basic catalyst, when *in solution*. It is important to recognize that an insoluble acyl halide or anhydride often reacts slowly with water. Esters and amides hydrolyze much more slowly, and for useful rates require a catalyst. The hydrolysis of amides is of exceptional importance in biochemistry and will be discussed in more detail in Chapters 24 and 25.

Acid-catalyzed hydrolysis of esters is the reverse of acid-catalyzed ester formation discussed previously. *Base-induced ester hydrolysis* (**saponification**) *is an irreversible reaction*. The initial step is the attack of hydroxide ion at the carbonyl carbon:



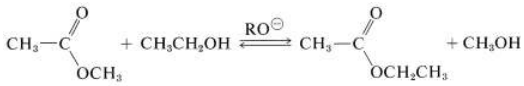
13

The intermediate anion, 13, so formed then either loses $OH^{\ominus}$ and reverts to the original ester, or it loses $CH_3O^{\ominus}$ to form the acid. The overall reaction is irreversible because once the acid is formed, it immediately is converted to the carboxylate anion, which is stabilized to such a degree that it is not attacked by the alcohol and will not reform the starting ester. Consequently, the reaction goes to completion in the direction of hydrolysis:



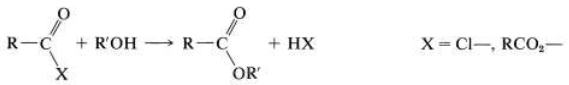
13

Ester interchange is closely related to ester hydrolysis. This is a base-catalyzed reaction that is useful to replace the alcohol group of an ester with a different alcohol group. The catalyst is alkoxide ion and the equilibrium constant is close to unity, unless the alcohols differ greatly in size. An example is

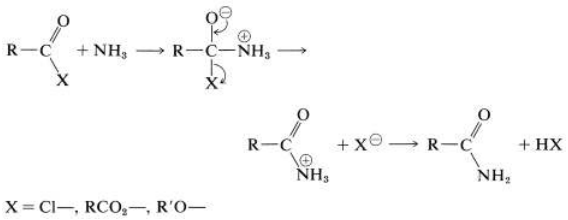


in which $RO^{\ominus}$ is either $CH_3O^{\ominus}$ or $CH_3CH_2O^{\ominus}$.

The formation of esters from acid chlorides and anhydrides according to the following equation has been discussed:



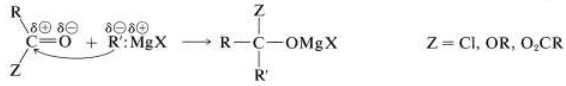
Amides can be obtained from acyl halides, carboxylic anhydrides, or esters with amines or ammonia. The mechanisms of these reactions are very similar to the corresponding reactions of alcohols:



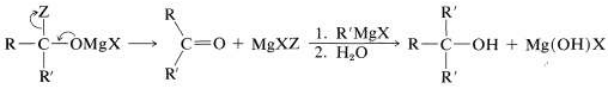
We will discuss this kind of reaction further in Chapters 24 and 25.

18.8.2: Reactions with Organometallic Compounds

The reactions of several carboxylic acid derivatives with organomagnesium and organolithium compounds were described in Section 14-12. The key step in these reactions is addition of the organometallic compound, as $R^{\delta\ominus}M^{\delta\oplus}$, to the carbonyl group. For a Grignard reagent,

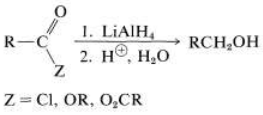


The reaction normally does not stop at this stage; MgXZ is eliminated and the resulting ketone rapidly reacts with another molecule of organometallic compound. On hydrolysis, a tertiary alcohol is formed with at least two identical alkyl groups on the tertiary carbon:

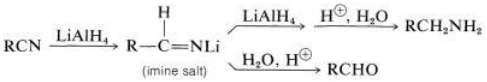


18.8.3: Reduction of Acid Derivatives

Esters, chlorides, and anhydrides are reduced by lithium aluminum hydride in the same general way as the parent acids (Section 18-3C), the difference being that no hydrogen is evolved. The products after hydrolysis are primary alcohols:



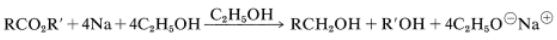
Nitriles can be reduced to amines by lithium aluminum hydride. An imine salt is an intermediate product; if the reaction is carried out under the proper conditions, this salt is the major product and provides an aldehyde on hydrolysis (see Section 16-4C):



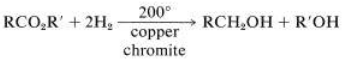
Amides are reduced to primary amines, and N-substituted amides to secondary and tertiary amines:

Borane also will reduce esters, amides, and nitriles to the same products as does $LiAlH_4$, but with reduced reactivity (Table 16-6).

Although lithium aluminum hydride and boranes are very useful reagents, they are expensive and impractical to employ on a large scale. Other methods of reduction then may be necessary. Of these, the most important are reduction of esters with sodium and ethanol (acids do not react readily),



and high-pressure hydrogenation over a copper chromite catalyst,



18.8.4: Contributors and Attributions

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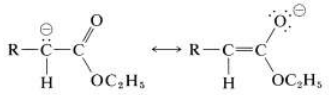
18.9: Reactions at the α Carbons of Carboxylic Acid Derivatives

18.9.1: The Acidic Properties of Esters with α Hydrogens

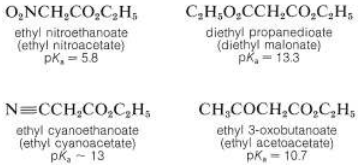
Many important synthetic reactions in which C–C bonds are formed involve esters and are brought about by basic reagents. This is possible because the α hydrogens of an ester, such as $RCH_2CO_2C_2H_5$, are weakly acidic, and a strong base, such as sodium ethoxide, can produce a significant concentration of the ester anion at equilibrium:

$$RCH_2CO_2C_2H_5 + C_2H_5O^{\ominus} \rightleftharpoons \overset{\ominus}{R}CHCO_2C_2H_5 + C_2H_5OH$$

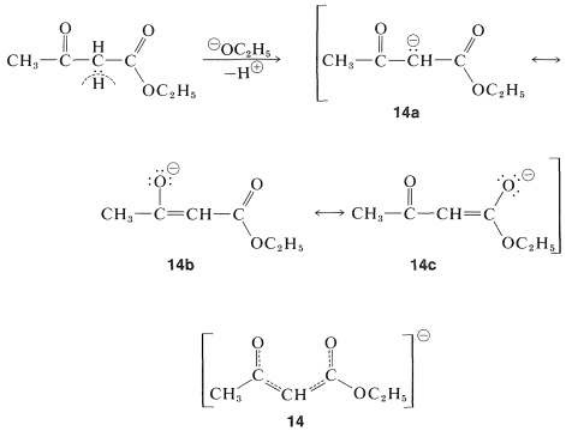
The acidity of α hydrogens is attributed partly to the electron-attracting inductive effects of the ester oxygens, and partly to resonance stabilization of the resulting anion (Section 17-1A):



When the α carbon of the ester carries a second strongly electron-attracting group, the acidity of α hydrogen is greatly enhanced. Examples of such compounds follow:

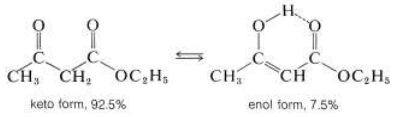


The stabilization of the anions of these specially activated esters is greater than for simple esters because of the electron-withdrawing inductive effects of the substituents but more importantly because the negative charge can be distributed over more than two centers. Thus for the anion of ethyl 3-oxobutanoate we can regard all three of the valence-bond structures, 14*a* through 14*c*, as important in contributing to the hybrid, 14:



The anion, 14, is sufficiently stable relative to the ester that the K_a is about 10^{-11} in water solution (Table 17-1).

Ethyl 3-oxobutanoate exists at room temperature as an equilibrium mixture of keto and enol tautomers in the ratio of 92.5 to 7.5. The presence of enol can be shown by rapid titration with bromine, but is more evident from the proton nmr spectrum (Figure 18-6), which shows absorption of the hydroxyl, alkenyl, and methyl protons of the enol form, in addition to absorptions expected for the keto form:



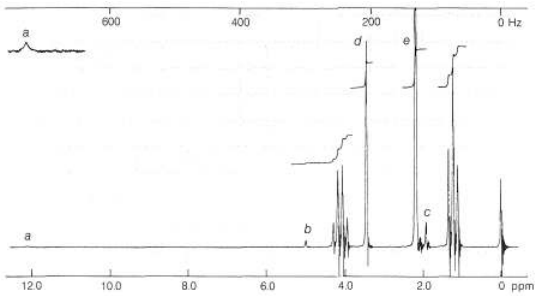
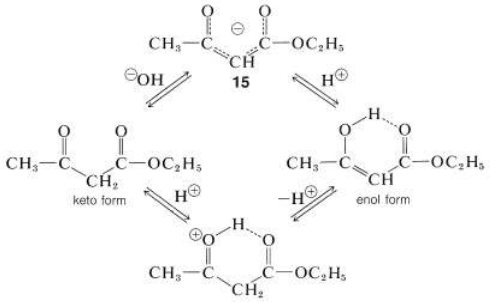


Figure 18-6: Proton nmr spectrum of ethyl 3-oxobutanoate (ethyl acetoacetate) at 60 MHz, calibrations are relative to tetramethylsilane at 0.00 ppm. Peaks marked a, b, and c *are assigned, respectively, to the* OH, *alkenyl, and methyl protons of the enol form, whereas peaks* d *and* e *are assigned to the* α-CH_2 *and methyl protons, respectively, of the keto form. The quartet of lines at* 4.2 ppm *and the triplet at* 1.3 ppm *result from the ethyl groups of both keto and enol forms.*

Interconversion of the enol and keto forms of ethyl 3-oxobutanoate is powerfully catalyzed by bases through the anion, 15, and less so by acids through the conjugate acid of the keto form:



Nonetheless, if contact with acidic and basic substances is rigidly excluded to the extent of using quartz equipment in place of glass (glass normally has a slightly alkaline surface), then interconversion is slow enough that it is possible to separate the lower-boiling enol from the keto form by fractional distillation under reduced pressure. The separated isomers are indefinitely stable when stored at -80° in quartz vessels.

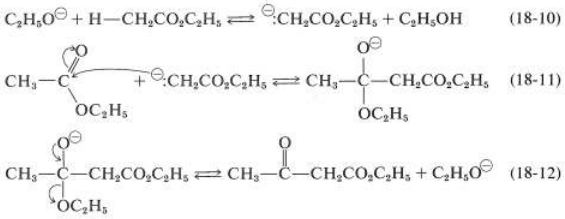
18.9.2: The Claisen Condensation

One of the most useful of the base-induced reactions of esters is illustrated by the self-condensation of ethyl ethanoate under the influence of sodium ethoxide to give ethyl 3-oxobutanoate:

$$CH_3CO_2C_2H_5 + H{-}CH_2CO_2C_2H_5 \xrightarrow{{}^{\ominus}OC_2H_5} CH_3COCH_2CO_2C_2H_5 + C_2H_5OH \qquad (18.9.1)$$

This reaction, called the **Claisen condensation**, is interesting because, from consideration of bond and stabilization energies, it is expected to be unfavorable thermodynamically with ΔH^0 (vapor) equal to $6\ \text{kcal mol}^{-1}$. This expectation is realized in practice, and much effort has been expended to determine conditions by which practical yields of the condensation product can be obtained.

The Claisen condensation resembles *both* the aldol addition (Section 17-3) and carbonyl additions of acid derivatives discussed previously (Sections 16-4 and 18-7). The first step, as shown in Equation 18-10, is the formation of the anion of ethyl ethanoate which, being a powerful nucleophile, attacks the carbonyl carbon of a second ester molecule (Equation 18-11). Elimination of ethoxide ion then leads to the β-keto ester, ethyl 3-oxobutanoate (Equation 18-12):



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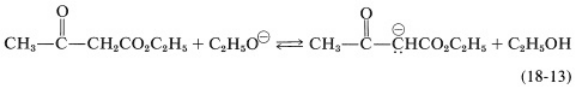
The sum of these steps represents an unfavorable equilibrium, and satisfactory yields of the β-keto ester are obtained only if the equilibrium can be shifted by removal of one of the products.

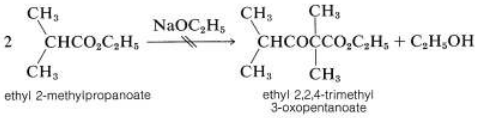
One simple way of doing this is to remove the ethanol by distillation as it is formed; however, this may be difficult to carry to completion and, in any case, is self-defeating if the starting ester is low-boiling. Alternatively, one can use a large excess of sodium ethoxide. This is helpful because ethanol is a weaker acid than the ester enol, and *excess ethoxide shifts the equilibrium to the right through conversion of the β-keto ester to the enolate salt* (Equation 18-13).



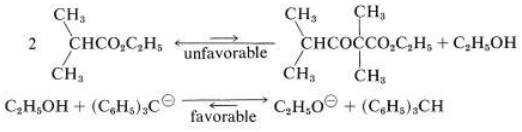
(18-13)

Obviously, the condensation product must be recovered from the enol salt and isolated under conditions that avoid reversion to starting materials. The best procedure is to quench the reaction mixture by pouring it into an excess of cold dilute acid.

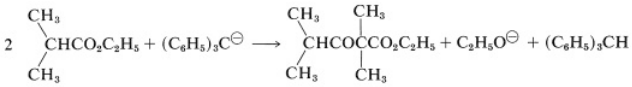
A limitation on the Claisen condensation is that although the starting ester need have only *one* α hydrogen for Reactions 18-10 through 18-12 to occur, *two* α hydrogens are necessary for a favorable equilibrium utilizing the ionization reaction of Equation 18-13. As a result, it is not surprising to find that ethyl 2-methylpropanoate fails to condense with itself in the presence of sodium ethoxide, because the condensation product has no α hydrogen next to the ester group:



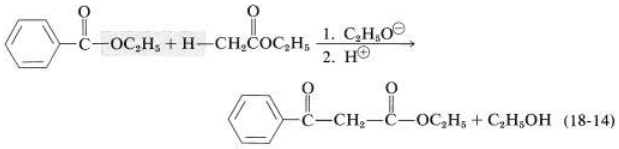
However, it an excess of a very much stronger base than sodium ethoxide is used [such as triphenylmethylsodium, $(C_6H_5)_3C^{\ominus}Na^{\oplus}$], this same condensation does take place in reasonable yields. The reason is that the base is now strong enough to convert the alcohol formed in the reaction to sodium ethoxide, thus shifting the equilibrium to the right:



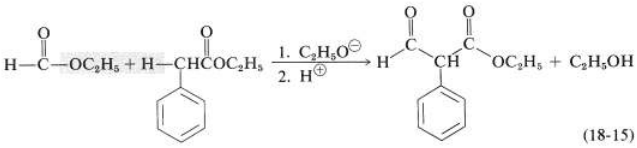
The overall reaction then is



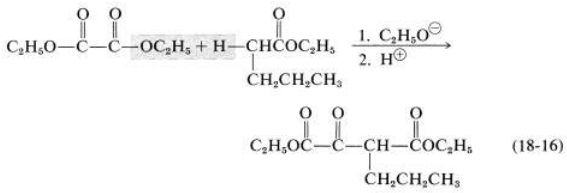
Claisen condensations can be carried out between two *different* esters but, because there are four possible products, mixtures often result. Less difficulty is encountered if one of the esters has no α hydrogen and reacts readily with a carbanion according to Equations 18-11 and 18-12. The reaction then has considerable resemblance to the mixed aldol additions discussed in Section 17-3C. Among the useful esters without α hydrogens, and with the requisite electrophile reactivity, are those of benzenecarboxylic, methanoic, ethanedioic, and carbonic acids. Several practical examples of mixed Claisen condensations are shown in Equations 18-14 through 18-16 (all of the products exist to the extent of 10% or so as the enol forms):



(18-14)

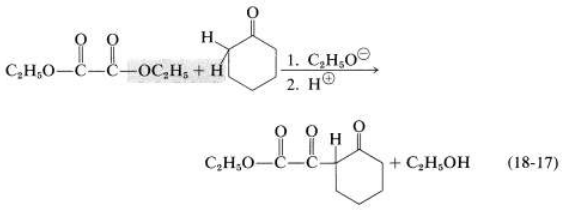


(18-15)



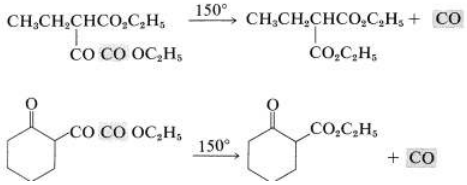
(18-16)

An important variation on the Claisen condensation is to use a ketone as the anionic reagent. This often works well because ketones usually are more acidic than simple esters and the base-induced self-condensation of ketones (aldol addition) is thermodynamically unfavorable (Section 17-3C). A typical example is the condensation of cyclohexanone with diethyl ethanedioate (diethyl oxalate):



(18-17)

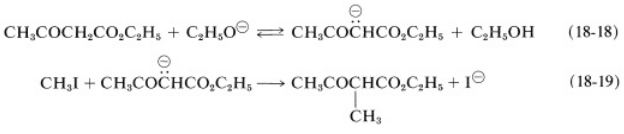
α-Keto esters of the type formed according to Equations 18-16 and 18-17 have synthetic utility in that they lose carbon monoxide when strongly heated:



A somewhat similar decarbonylation reaction was mentioned previously for diphenylpropanetrione (Section 17-10).

18.9.3: Alkylation of Ester Anions

The anions of esters such as ethyl 3-oxobutanoate and diethyl propanedioate can be alkylated with alkyl halides. These reactions are important for the synthesis of carboxylic acids and ketones and are similar in character to the alkylation of ketones discussed previously (Section 17-4A). The ester is converted by a strong base to the enolate anion, Equation 18-18, which then is alkylated in an S_N2 reaction with the alkyl halide, Equation 18-19. Usually, C-alkylation predominates:



(18-18)

(18-19)

Esters of propanedioic (malonic) acid can be alkylated in a similar fashion (Equation 18-20):

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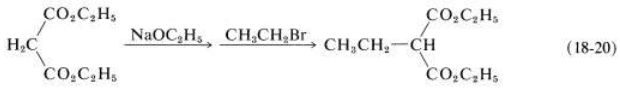
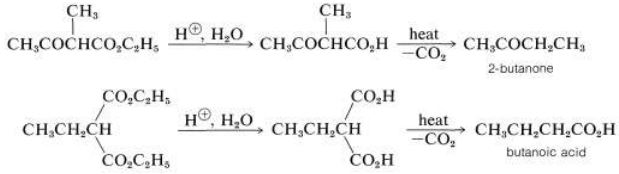


(18-20)

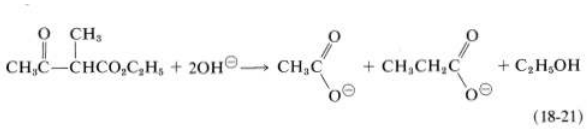
Unfortunately, monoalkylation seldom occurs cleanly by the above sequence whenever the monoalkylation product has an α hydrogen located so as to permit dialkylation to occur. In practice, alkylation reactions, using one mole of ester, one mole of sodium ethoxide, and one mole of an alkyl halide (e.g., CH_3I), give a mixture of the starting ester, its mono- and dialkylation products. The situation is more favorable when large alkyl groups are introduced, because then the physical properties and reactivities of the starting materials and of mono- and dialkylation products differ considerably. Usually dialkylation is inhibited by having a bulky alkyl group in the monoalkylation product.

Alkyl-substituted 3-oxobutanoic and propanedioic esters can be hydrolyzed under acidic conditions to the corresponding acids, and when these are heated they readily decarboxylate (Section 18-4). *Alkyl 3-oxobutanoic esters thus yield methyl alkyl ketones, whereas alkylpropanedioic esters produce carboxylic acids:*



These reactions commonly are known as the **acetoacetic-ester ketone** and the **malonic-ester acid** syntheses, respectively.

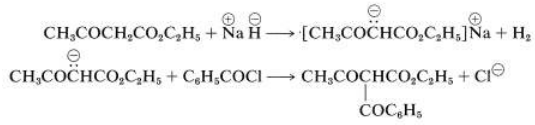
Alkyl 3-oxobutanoic esters react with concentrated alkali by a *different* path to reverse the Claisen condensation:



(18-21)

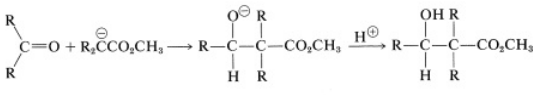
18.9.4: Acylation of Ester Anions

Enolate anions of esters, such as ethyl 3-oxobutanoate or diethyl propanedioate, react with acyl halides or anhydrides to give *acylation* products. These reactions are carried out best using sodium hydride instead of sodium ethoxide for production of the enol salt, because then no alcohol is liberated to react with the acyl halide or anhydride:

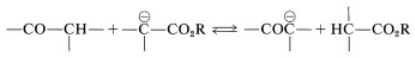


18.9.5: Aldol-Type Additions of Ester Anions and the Reformatsky Reaction

Addition of an ester anion to the carbonyl group of an aldehyde or ketone is a type of *aldol* addition (Section 17-3):



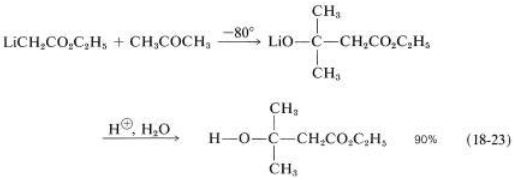
There are certain difficulties in achieving this type of aldol reaction. First, alkali-induced ester hydrolysis would compete with addition. Second, a Claisen condensation of the ester might intervene, and third, the ester anion is a *stronger base* than the enolate anions of either aldehydes or ketones, which means reaction could be defeated by proton transfer of the type



However, a useful synthetic reaction can be achieved in the following way. First, the ester anion is formed in the absence of water without causing a Claisen condensation or other carbonyl addition. This can be done with ethyl ethanoate by treating it with lithium bis(trimethylsilyl)amide in oxacyclopentane solution at -80°:

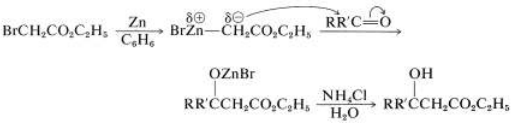
The advantage of $LiN[Si(CH_3)_3]_2$ as the base in this reaction is that $\overset{\ominus}{N}[Si(CH_3)_3]_2$ is a reasonably strong base; it is bulky, which inhibits addition to the carbonyl; and it also forms a weakly basic amine, $HN[Si(CH_3)_3]_2$, which does not interfere in the subsequent reactions.

The solution of ethyl lithioethanoate must be kept cold and treated promptly with an aldehyde or ketone. Thus, with 2-propanone,

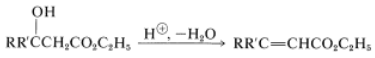


For the reaction to be successful, the carbonyl addition has to be faster than the proton transfer reaction, $LiCH_2CO_2C_2H_5 + CH_3COCH_3 \rightarrow CH_3CO_2C_2H_5 + LiCH_2COCH_3$ and, at -80°, this is the case. This synthesis of β-hydroxy esters is a beautiful example of how rates of competing reactions can be manipulated to obtain a high yield of a desired addition product that may not be the most thermodynamically favorable one.

A closely related synthesis of β-hydroxy esters is provided by the Reformatsky reaction. This synthesis starts with an aldehyde or ketone, $RCOR'$, and an α-bromo ester, such as ethyl bromoethanoate. Zinc in a nonhydroxylic solvent (usually benzene) transforms the bromo ester into an organozinc compound, which then adds to the aldehyde or ketone carbonyl. Hydrolysis produces the β-hydroxy ester:

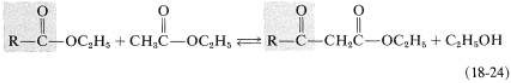


As do aldols, β-hydroxy esters dehydrate (usually readily) to α,β-unsaturated carbonyl compounds.



18.9.6: Biological Claisen Condensations and Aldol Additions. Fatty Acid Metabolism

The overall results of a Claisen condensation is the transfer of an acyl group $(RCO-)$ from one ester molecule to another:



(18-24)

Figure 18-7. Although it is large and complex, the reactive part for our discussion here is the thiol (SH) group. The thioester equivalent of the Claisen condensation of Equation 18-24 is

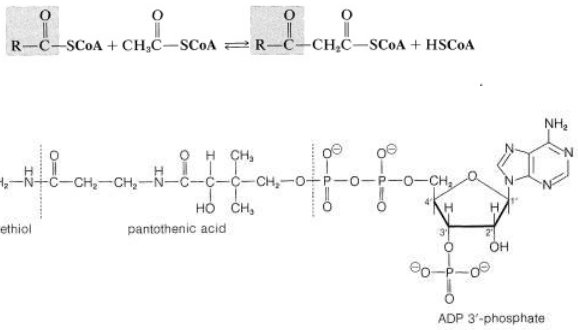


Figure 18-7: The structure of coenzyme A (HSCoA) showing the segments of which it can be considered to be constructed. The thiol group at the left end of the molecule reacts to form thioesters of the type $\mathrm{RCOS-CoA}$. The other parts of the coenzyme A molecule provide the structural elements that permit a high degree of specificity for interactions with enzymes.

The reverse of the above reaction is a key step in the *oxidative degradation* of fatty acids. This reverse Claisen condensation (catalyzed by *thiolase*) involves the cleavage of a carbon-carbon bond of a β-keto ester of coenzyme A by another molecule of coenzyme A to give a new acyl derivative ($\mathrm{RCO-S}$**CoA**) and ethanoyl (acetyl) derivative ($\mathrm{CH_3O-S}$**CoA**):

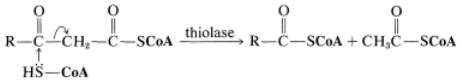


Figure 18-8 and involve a sequence of enzymatic transformations of the type

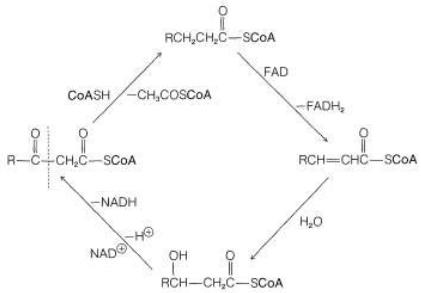


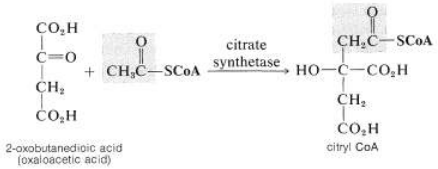
Figure 18-8: Steps in the metabolic oxidation of a fatty acid. In each cycle of reactions, one mole of $\mathrm{CH_3COSCoA}$ is formed and the alkyl group R is shortened by two carbons.

After formation of the β-keto thioester, it is cleaved by **CoA**SH, and the resulting thioester goes back into the sequence *two carbons shorter* than before. In this way, a fatty acid is degraded from the carboxyl end, two carbons at a time.

There are two principle pathways for utilization of the ethanoyl coenzyme A ($\mathrm{CH_3CO-S}$**CoA**) formed in each turn of the oxidation cycle of Figure 18-8. Either it is used to synthesize larger molecules such as fatty acids, steroids, and so on, as will be described in Section 30-5A, or the acyl group is oxidized to $\mathrm{CO_2}$ and $\mathrm{H_2O}$:

$$\mathrm{CH_3CO-S}\textbf{CoA} \xrightarrow{[\mathrm{O}]} 2\mathrm{CO_2} + \mathrm{H_2O} + \mathrm{HS}\textbf{CoA}$$

The oxidation of the acyl group of coenzyme A is the net outcome of the **citric acid** or **Krebs cycle** (Section 20-10B). We will be interested here in the entry point of the cycle whereby ethanoyl coenzyme A is employed in a reaction that builds the $\mathrm{C_6}$ chain of citric acid (3-carboxy-3-hydroxypentanedioic acid) from $\mathrm{C_2}$ and $\mathrm{C_4}$ pieces:



This reaction is quite special in that it is an *aldol-type addition* in which a thioester is the donor (nucleophile) and a keto acid is the acceptor (electrophile). From the discussion in Section 18-8E, you will see that reactions of this kind involving an ester as the

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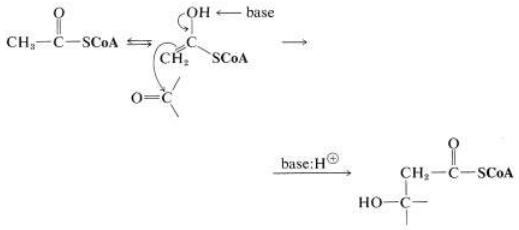
donor and an aldehyde or ketone as the acceptor can be achieved in the laboratory only under rather special conditions. For the thioester to function as a nucleophile at the α carbon under the restraints imposed by having the reaction occur at the physiological pH, the catalyzing enzyme almost certainly must promote formation of the enol form of the thioester. The enol then could add to the ketone carbonyl with the assistance of a basic group on the enzyme. This kind of catalysis by enzymes is discussed in Section 25-9C.



[5]Considerable confusion is possible because of the way in which biochemists use abbreviated names and formulas for the acyl derivatives of coenzyme A. To emphasize the vital –SH group, coenzyme A is usually written as **CoA**SH. However, the acyl derivatives most often are called acetyl **CoA** and the like, not acetyl S**CoA**, and you could well get the erroneous impression that the sulfur has somehow disappeared in forming the acyl derivative. We will include the sulfur in formulas such as CH_3COS**CoA**, but use the customary names such as acetyl **CoA** without including the sulfur. To make clear that **CoA** does not contain cobalt, **CoA** is printed in this text in boldface type.

18.9.7: Contributors and Attributions

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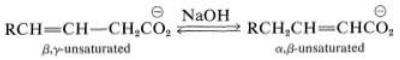
18.10: Reactions of Unsaturated Carboxylic Acids and Their Derivatives

Unsaturated carboxylic acids of the type $\mathrm{RCH{=}CH(CH_2)_nCOOH}$ usually exhibit the properties characteristic of isolated double bonds and isolated carboxyl groups when n is large and the functional groups are far apart. As expected, exceptional behavior is found most commonly when the groups are sufficiently close together to interact strongly, as in α,β-unsaturated acids, $\mathrm{R\overset{\beta}{C}H{=}\overset{\alpha}{C}CO_2H}$. We shall emphasize those properties that are exceptional in the following discussion.

18.10.1: Migration of the Double Bond

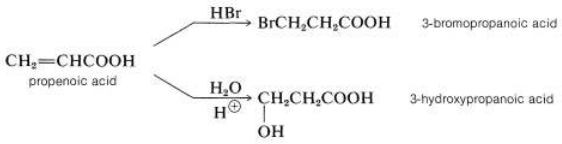
In the presence of strong base, α,β- and β,γ-unsaturated carboxylic acids tend to interconvert by migration of the double bond:



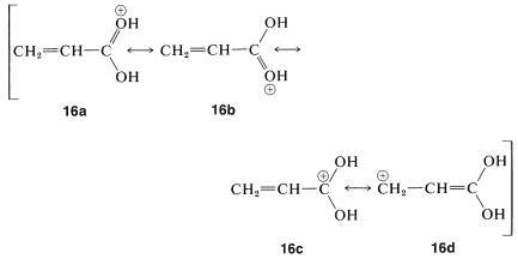
Ester derivatives, $\mathrm{RCH{=}CH{-}CH_2COOR'}$, and the corresponding unsaturated aldehydes and ketones, $\mathrm{RCH{=}CH{-}CH_2COR'}$, are much more prone to this type of rearrangement than are the acids.

18.10.2: Hydration and Hydrogen Bromide Addition

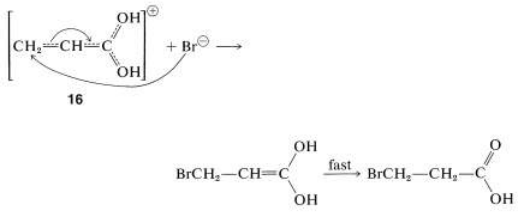
Like alkenes, the double bonds of α,β-unsaturated acids can be brominated, hydroxylated, hydrated, and hydrobrominated, although the reactions often are relatively slow. In the addition of unsymmetrical reagents the direction of addition is *opposite* to that observed for alkenes (anti-Markovnikov). Thus propenoic (acrylic) acid adds hydrogen bromide and water to form 3-bromo- and 3-hydroxypropanoic acids:



These additions are analogous to the addition of halogens and halogen acids to 1,3-butadiene (Section 13-2). In the first step, a proton is transferred to the carbonyl oxygen. The resulting conjugate acid can be regarded as a resonance hybrid of structures $16a$-$16d$:



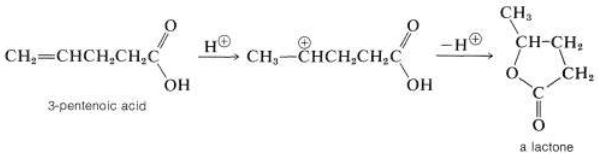
In the second step, a nucleophile (such as $\mathrm{Br^{\ominus}}$ or a water molecule) attacks an electron-deficient carbon of the hybrid 16. Attack at the carboxyl carbon may occur but does not lead to a stable product. Attack of the nucleophile at the β carbon, however, produces the enol form of the β-substituted acid, which then is converted rapidly to the normal carboxylic acid:



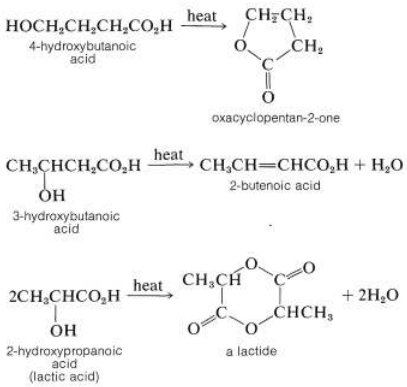
18.10.3: Lactone Formation

When the double bond of an unsaturated acid is farther down the carbon chain than between the alpha and beta positions, the so-called "conjugate addition" is not possible. Nonetheless, the double bond and carboxyl group frequently interact in the presence of acidic catalysts because the carbocation that results from addition of a proton to the double bond has a built-in nucleophile (the carboxyl group), which may attack the cationic center to form a cyclic ester called a *lactone*.

Lactone formation only occurs readily by this mechanism when a five- or six-membered ring can be formed:



Five- or six-membered lactones also are formed by internal esterification when either γ- or δ-hydroxy acids are heated. Under similar conditions, β-hydroxy acids are dehydrated to α,β-unsaturated acids, whereas α-hydroxy acids undergo bimolecular esterification to substances with six-membered dilactone rings called **lactides**:

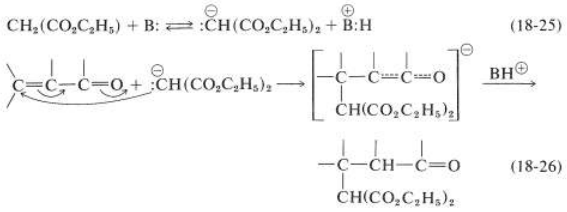


18.10.4: More on the Michael Addition

The foregoing examples of addition to the double bonds of unsaturated carboxylic acids all involve activation by an electrophilic species such as $H^{\oplus}$. Conjugate addition also may occur by nucleophilic attack on acid derivatives, the most important being the base-catalyzed Michael addition (Section 17-5B) and 1,4-addition of organometallic compounds (Section 14-12D). In all of these reactions a nucleophilic agent, usually a carbanion, attacks the double bond of an α,β-unsaturated compound in which the double bond is conjugated with, and activated by, a strongly electronegative unsaturated group (such as $-CN$, $-NO_2$, etc.). In the Michael addition, the carbanion usually is an enolate salt.

The overall reaction is illustrated here by the specific example of the addition of diethyl propanedioate (diethyl malonate) to ethyl 3-phenylpropenoate (ethyl cinnamate):

The mechanism of this kind of transformation, with diethyl propanedioate as the addend, is outlined in Equations 18-25 and 18-26. The basic catalyst required for the Michael addition (here symbolized as B :) serves by forming the corresponding anion:

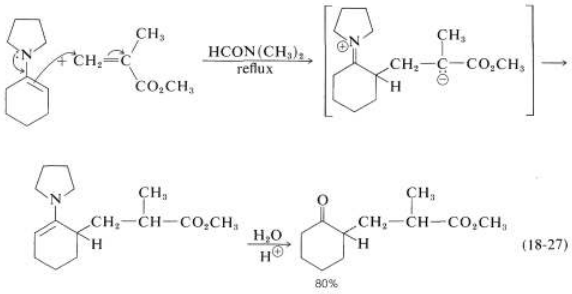


(18-25)

(18-26)

A variety of nucleophilic agents can be used; propanedinitrile, 3-oxobutanoate esters, and cyanoethanoate esters all form relatively stable carbanions and function well in Michael addition reactions. Obviously, if the carbanion is *too* stable, it will have little or no tendency to attack the double bond of the α,β-unsaturated acid derivative.

Enamines (Sections 16-4C and 17-4B) are excellent addends in many Michael-type reactions. An example is provided by the addition of N-(1-cyclohexenyl)-azacyclopentane to methyl 2-methylpropanoate:



(18-27)

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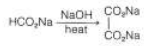
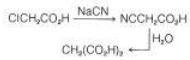
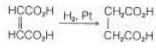
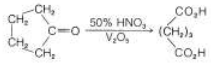
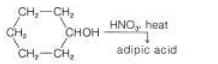
18.11: Dicarboxylic Acids

Acids in which there are two carboxyl groups separated by a chain of more than five carbon atoms $(n > 5)$ for the most part have unexceptional properties, and the carboxyl groups behave more or less independently of one another.

However, when the carboxyl groups are closer together the possibilities for interaction increase; we shall be interested primarily in such acids. A number of important dicarboxylic acids are listed in Table 18-4 together with their physical properties, methods of manufacture, and commercial uses.

Table 18-4: *Dicarboxylic Acids*

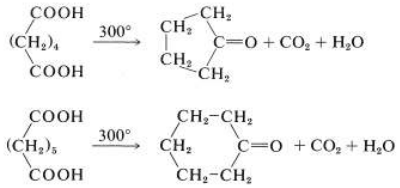
Acid	Formula	Mp, °C	$K_1 \times 10^5$ at 25°	$K_2 \times 10^5$ at 25°	Commercial preparation	Principal commercial uses
ethanedioic (oxalic)		189	3500	5.3		analytical, reducing, and bleaching agent; rust, paint, varnish, and ink remover
propanedioic (malonic)		136 dec.	171	0.22		employed as ethyl ester in synthesis of carboxylic acids and manufacture of barbiturates
butanedioic (succinic)		185	6.6	0.25		manufacture of lacquers and dyes
pentanedioic (glutaric)		98	4.7	0.29		
hexanedioic (adipic)		152	3.7	0.24		important in condensation polymerization, particularly for manufacture of nylon and urethane foams
heptanedioic (pimelic)		105	3.4	0.26	reverse Claisen condensation of 2-carbethoxycyclohexanone	
cis-butenedioic (maleic)		130	1170	0.026	catalytic oxidation of benzene to the anhydride	mainly used in the form of the anhydride in Diels–Alder diene synthesis; polymers, particularly fiberglass compositions
trans-butenedioic (fumaric)		sub. 200	93	2.9	from glucose by bacterial action	
1,2-benzenedicarboxylic (phthalic)		231	130	0.39[16]	air oxidation of naphthalene and 1,2-dimethylbenzene	used as anhydride in organic synthesis and in manufacture of coating materials such as polyester
1,4-benzenedicarboxylic (terephthalic)		>300	31	1.5	air oxidation of 1,4-dimethylbenzene	polyester fibers such as Dacron

18.11.1: Acidic Properties of Dicarboxylic Acids

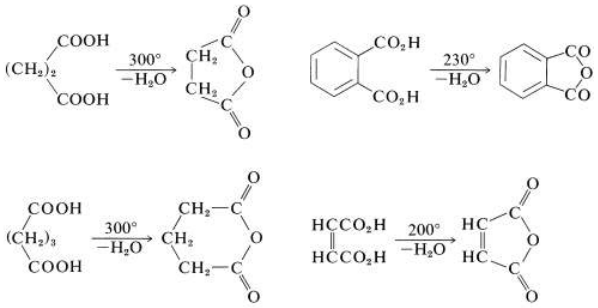
The inductive effect of one carboxyl group is expected to enhance the acidity of the other. In Table 18-4 we see that the acid strength of the dicarboxylic acids, as measured by the first acid-dissociation constant, K_1, is higher than that of ethanoic acid $(K_a = 1.5 \times 10^{-5})$ and decreases with increasing number of bonds between the two carboxyl groups. The second acid-dissociation constant, K_2, is smaller than K_a for ethanoic acid (with the exception of oxalic acid) because it is more difficult to remove a proton under the electrostatic attraction of the nearby carboxylate anion (see Section 18-2C).

18.11.2: Thermal Behavior of Dicarboxylic Acids

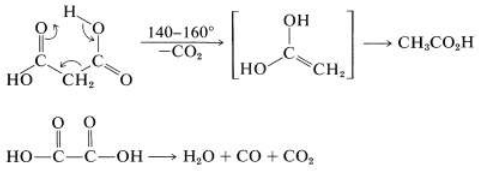
The reactions that occur when dicarboxylic acids are heated depend critically upon the chain length separating the carboxyl groups. Cyclization usually is favored if a strainless five- or six-membered ring can be formed. Thus hexanedioic and heptanedioic acids decarboxylate and cyclize to cyclopentanone and cyclohexanone, respectively:



Butanedioic and pentanedioic acids take a different course. Rather than form the strained cyclic ketones, cyclopropanone and cyclobutanone, both acids form cyclic anhydrides that have five- and six-membered rings, respectively. 1,2-Benzenedicarboxylic (phthalic) and *cis*-1,4-butenedicarboxylic (maleic) acids behave similarly:

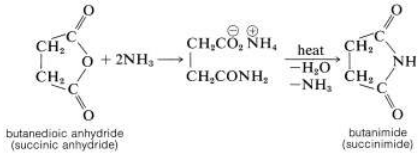


Because of their short chains, propanedioic and ethanedioic acids simply decarboxylate when heated (Section 18-4):

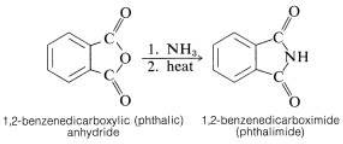


18.11.3: Imides from Dicarboxylic Acids

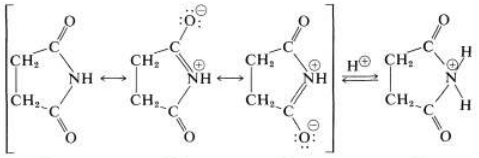
The cyclic anhydride of butanedioic acid reacts with ammonia, as may be expected for a typical anhydride; but the product, when strongly heated, forms a cyclic imide (butanimide):



1,2-Benzenedicarboxylic (phthalic) anhydride behaves similarly, giving 1,2-benzenedicarboximide (phthalimide):

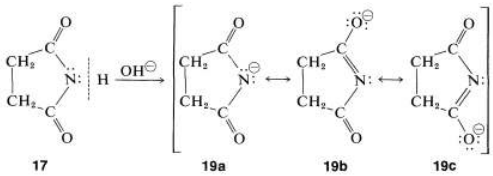


Unlike amines, imides do not have basic properties in water solution; the electron pair of nitrogen is partly delocalized over the carbonyl groups, as indicated by 17*a* to 17*c*. This stabilization is lost if a proton is added to nitrogen to give the conjugate acid, 18:



17a 17b 17c 18

Imides are, in fact, quite acidic and readily dissolve in alkali-metal hydroxide solutions to give salts. Like carboxylic acids and 1,3-dicarbonyl compounds, imides are acidic primarily because the stabilization of the anion is greater than that of the acid. This can be seen by comparison of the resonance structures that may be written for the imide, 17, with those of the anion, 18. Separation of positive and negative charge, as in Structures 17*b* and 17*c*, increases the energy of such structures. There is no charge separation in the anion; thus 19*b* and 19*c* are more important with respect to their hybrid than are 17*b* and 17*c* to their hybrid. (You may wish to review the corresponding argument for the acidity of carboxylic acids, Section 18-2A.)

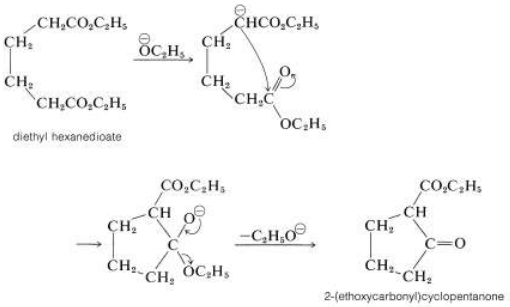


17 19a 19b 19c

The salts of imides are useful in synthesis, as is described in Section 23-9D.

18.11.4: The Dieckmann Condensation

Esters of most dicarboxylic acids, except propanedioic esters, undergo Claisen condensation in much the same way as do esters of monocarboxylic acids (see Section 18-8B). However, when a strainless five- or six-membered ring can be formed, an intramolecular Claisen condensation, called the **Dieckmann condensation**, may take place which would result in the formation of a cyclic β-keto ester:

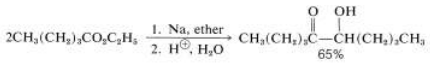


diethyl hexanedioate

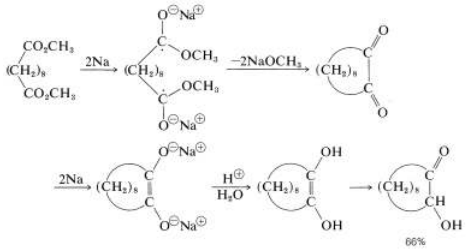
2-(ethoxycarbonyl)cyclopentanone

18.11.5: The Acyloin Reaction

A useful method of forming carbon-carbon bonds involves reduction of esters with sodium metal in aprotic solvents such as ether or benzene and is called the **acyloin reaction**:



This interesting reaction is especially useful for the synthesis of medium- and large-ring compounds from dicarboxylic esters, and is effective for ring sizes that cannot be made by the Dieckmann condensation or decarboxylation (Section 18-10B). Radical anions formed by addition of sodium to the ester groups appear to be the key intermediates for carbon-carbon bond formation. Thus, for dimethyl decanedioate:



18.11.6: Contributors and Attributions

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18.12: Methods of Preparation of Carboxylic Acids and Their Derivatives

Table 18-5: *Methods of Preparation of Carboxylic Acids*[a]

Reaction	Comment
1. *Hydrolysis of nitriles* $RCN \xrightarrow[H^{\oplus} \text{ or } OH^{\ominus}]{H_2O} RCONH_2 \xrightarrow[H^{\oplus} \text{ or } OH^{\ominus}]{H_2O} RCO_2H$	Acid or base catalyzed; amide is formed first, then hydrolyzed to the acid; a useful laboratory synthesis if the nitrile is accessible as by S_N2 reactions of RX (Section 8-7F).
2. *Hydrolysis of esters and amides* $RCO_2R' \xrightarrow[H^{\oplus} \text{ or } OH^{\ominus}]{H_2O} RCO_2H + R'OH$ $RCONH_2 \xrightarrow{H^{\oplus} \text{ or } OH^{\ominus}} RCO_2H + NH_3$	Useful where the starting material can be prepared by alkylation of 3-oxobutanoate or propanedioate esters and similar reactions.
3. *Carbonation of organometallic compounds* $RMgX \xrightarrow{CO_2} RCO_2MgX \xrightarrow{H_2O,\ H^{\oplus}} RCO_2H$ $RLi \xrightarrow{CO_2} RCO_2Li \xrightarrow{H_2O,\ H^{\oplus}} RCO_2H$	Usually carried out by pouring solution of organometallic compound over powdered Dry Ice and stirring efficiently; an important and versatile reaction (see Section 14-12B).
4. *Malonic ester synthesis* $RX + CH_2(CO_2C_2H_5)_2 \xrightarrow{NaOC_2H_5} RCH(CO_2C_2H_5)_2$ $\xrightarrow[2.\ \text{heat } (-CO_2)]{1.\ H_2O,\ H^{\oplus}} RCH_2CO_2H$ $R'X + RCH(CO_2C_2H_5)_2 \xrightarrow{NaOC_2H_5} RR'C(CO_2C_2H_5)_2$ $\xrightarrow[2.\ \text{heat } (-CO_2)]{1.\ H_2O,\ H^{\oplus}} RR'CHCO_2H$	An important reaction for synthesis of alkyl and dialkylethanoic acids (RX and R'X are primary or secondary alkyl halides); *dicarboxylic* acids (RX = haloester); unsaturated acids (RX = an unsaturated halide, best for allylic halides); β-keto acids (R = acyl chloride); (see Sections 18-8C and 18-8D).
5. *Acetoacetic ester syntheses* $RX + CH_3COCH_2CO_2C_2H_5 \xrightarrow{NaOC_2H_5} CH_3COCHCO_2C_2H_5$ (R) $\xrightarrow[2.\ H^{\oplus}]{1.\ OH^{\ominus}} RCH_2CO_2H$ $R'X + CH_3COCHCO_2C_2H_5 \xrightarrow{NaOC_2H_5} CH_3COCCO_2C_2H_5$ (R, R') $\xrightarrow[2.\ H^{\oplus}]{1.\ OH^{\ominus}} RR'CHCO_2H$	No particular advantage over 4; in fact, ketones may be formed in competition with acids in acetoacetic-ester synthesis (see Section 18-8B).
6. *Arndt–Eistert reaction* $RCOCl + CH_2N_2 \longrightarrow RCOCHN_2 \xrightarrow[Ag_2O]{H_2O} RCH_2CO_2H$ diazomethane; diazoketone	Useful method of preparing next-higher homologue of an acid (see Sections 16-4A and 24-7C).
7. *Oxidation of primary alcohols and aldehydes* $RCH_2OH \xrightarrow{[O]} RCHO \xrightarrow{[O]} RCO_2H$	Oxidizing agents are $KMnO_4$ ($H^{\oplus}$ or $OH^{\ominus}$), CrO_3, HNO_3, and Ag_2O. (Ag_2O only works for aldehydes.)
8. *Oxidation of alkenes* $RCH{=}CH_2 \xrightarrow{[O]} RCO_2H$	Oxidizing agents are $KMnO_4$ ($H^{\oplus}$ or $OH^{\ominus}$), CrO_3, and HNO_3; used mainly for structure determination; further degradation may occur.
9. *Oxidation of methyl ketones (haloform reaction)* $RCOCH_3 \xrightarrow{Br_2,\ NaOH} [RCOCBr_3] \xrightarrow[2.\ H^{\oplus}]{1.\ NaOH} RCO_2H + CHBr_3$	Hypochlorites may be used in place of Br_2 and NaOH; limited by possible substitution of halogen in R radical (see Section 17-2B).
10. *Cannizzaro reaction* $2RCHO \xrightarrow{NaOH} RCH_2OH + RCO_2H$	Useful only when aldehyde has no α hydrogen and cannot then undergo an aldol condensation (see Section 16-4E).
11. *Baeyer–Villiger oxidation of ketones with peracids* $RCOR + R'C(=O)-O-O-H \longrightarrow RCO_2R + R'CO_2H$ $\xrightarrow{H^{\oplus},\ H_2O}$ $RCO_2H + ROH$	Generally useful method for aliphatic and aryl ketones without double bonds; oxidizing agents commonly used are peroxybenzoic acid ($C_6H_5CO_3H$), peroxyethanoic acid (CH_3CO_3H), and trifluoroperoxyethanoic acid (CF_3CO_3H); the last is prepared from trifluoroethanoic anhydride and H_2O_2 and used in the presence of NaH_2PO_4 as a buffering agent (Section 16-7).

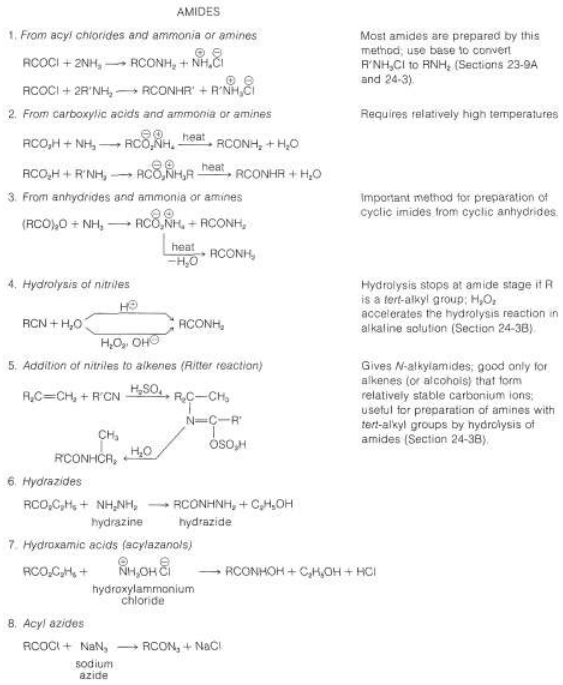
[a]Methods specific for the preparation of aromatic acids are discussed in Chapter 26.

Table 18-6: *Methods of Preparation of Carboxylic Esters*

Reaction	Comment
1. *From carboxylic acids and primary alcohols* $RCO_2H + R'OH \overset{H^\oplus}{\rightleftharpoons} RCO_2R' + H_2O$	Generally limited to primary alcohols; acidic catalysts include H_2SO_4, HCl, BF_3; for details and mechanism see Sections 15-4D and 18-3A.
2. *From acid chlorides and alcohols* $RCOCl + R'OH \longrightarrow RCO_2R' + HCl$	Versatile reaction; works well with *prim.*, *sec.*, and *tert.* alcohols; a base may be necessary to remove HCl, because *tert*-aliphatic alcohols may give alkenes and *tert*-butyl chlorides.
3. *From anhydrides and alcohols* $(RCO)_2O + R'OH \xrightarrow{H^\oplus} RCO_2R' + RCO_2H$ $\xrightarrow[H^\oplus]{R'OH} RCO_2R' + H_2O$	Widely applicable; acid-catalyzed.
4. *Ester interchange* $RCO_2R' + R''OH \overset{H^\oplus \text{ or } OH^\ominus}{\rightleftharpoons} RCO_2R'' + R'OH$	Acid- and base-catalyzed; generally limited to primary alcohols (for discussion, see Section 18-7A).
5. *From carboxylate salts, thionyl chloride, and alcohols* $R'OH + SOCl_2 \longrightarrow \underset{\text{alkyl chlorosulfite}}{R'OSOCl} + HCl$ $RCO_2Na + R'OSOCl \longrightarrow RCO_2R' + SO_2 + NaCl$	Limited to primary alcohols; it amounts to an S_N2 displacement of chlorosulfite group by carboxylate ion; steric hindrance in the carboxylate salt seems unimportant.
6. *From carboxylate salts and alkyl halides* $RCO_2Na + R'X \longrightarrow RCO_2R' + NaX$	Restricted to primary halides with high S_N2 reactivity.
7. *Alcoholysis of nitriles* $RCN + R'OH \xrightarrow{H^\oplus, H_2O} RCO_2R' + NH_4^\oplus$	Analogous to hydrolysis of nitriles, Method 1, Table 18-5.
8. *Diazomethane and carboxylic acids* $RCO_2H + CH_2N_2 \longrightarrow RCO_2CH_3 + N_2$	High yield, clean reaction, but diazomethane is a reactive, explosive, and toxic compound; useful for methyl esters of rare or acid-sensitive carboxylic acids.

Table 18-7: *Methods of Preparationof Acyl Halides, Anhydrides, Amides, and Related Compounds*

Reaction	Comment
ACYL HALIDES	
1. *From thionyl chloride and carboxylic acids* $RCO_2H + SOCl_2 \longrightarrow RCOCl + HCl + SO_2$	Most acyl chlorides are prepared by this method; anhydride formation is sometimes an objectionable side reaction.
2. *From phosphorus halides and carboxylic acids* $3RCO_2H + PBr_3 \longrightarrow 3RCOBr + H_3PO_3$ $RCO_2H + PCl_5 \longrightarrow RCOCl + POCl_3 + HCl$	Separation difficulties from H_3PO_3 and $POCl_3$ sometimes occur.
3. *From thionyl chloride and anhydrides*	Useful only when anhydride is more accessible than the parent acid.
 1,2-benzenedicarboxylic anhydride → 1,2-benzenedicarbonyl dichloride	
4. *Acyl fluorides, bromides, and iodides from chlorides* $RCOCl + HX \longrightarrow RCOX + HCl$ in which HX = HF, HBr, or HI	Sometimes the only route available t halides other than the chloride.
5. *From ethanedioyl dichloride* $RCO_2H + \underset{\text{COCl}}{\text{COCl}} \longrightarrow RCOCl + CO + CO_2 + HCl$	Usually an excellent method.
ANHYDRIDES	
1. *From acid halides and carboxylic acids* $RCO_2H + R'COCl \xrightarrow{\text{pyridine}} RCO{-}O{-}COR' + HCl$	The most frequently used method; simple or mixed anhydrides can be prepared.
2. *From acid halides and carboxylic salts* $RCO_2Na + R'COCl \longrightarrow RCO{-}O{-}COR' + NaCl$	
3. *From ketene and carboxylic acids* $CH_2{=}C{=}O + RCO_2H \longrightarrow RCO{-}O{-}COCH_3$	Commercial preparation of ethanoic anhydride (Section 17-6B).



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18.E: Carboxylic Acids and Their Derivatives (Exercises)

Exercise 18-1 Explain why the proton line position of the acidic hydrogen of a carboxylic acid, dissolved in a nonpolar solvent such as carbon tetrachloride, changes much less with concentration than does that of the OH proton of an alcohol under the same conditions (Section 9-10E).

Exercise 18-2 Make atomic-orbital models of ethanoic acid and ethanol and of the ethanoate anion and ethoxide anion. Show how these models can be used to explain the greater acidity of ethanoic acid relative to ethanol.

Exercise 18-3 The K_a for the first ionization of carbonic acid, $O{=}C(OH)_2 + H_2O \rightleftharpoons O{=}C(OH)O^{\ominus} + H_3O^{\oplus}$, is about 1000 times *smaller* than K_a for ethanoic acid. Show how this fact can be rationalized by considering the expected relative stabilization energies of carbonic acid and the hydrogen carbonate ion compared to those of ethanoic acid and ethanoate anion.

Exercise 18-4 Which acid in each of the following pairs would you expect to be the stronger? Give your reasoning.

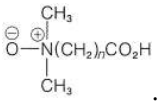
a. $(CH_3)_3\overset{\oplus}{N}CH_2CO_2H$ or $(CH_3)_2NCH_2CO_2H$

b. $(CH_3)_3\overset{\oplus}{N}CH_2CO_2H$ or $(CH_3)_2\overset{\oplus}{N}(\overset{\ominus}{O})CH_2CO_2H$

c. $(CH_3)_3CCO_2H$ or CH_3CO_2H

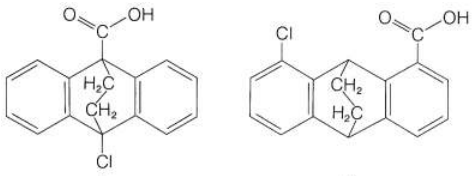
d. $CH_3OCH_2CO_2H$ or $CH_3SCH_2CO_2H$

e. $CH_2{=}CH{-}CH_2CO_2H$ or $HC \equiv C{-}CH_2CO_2H$

Exercise 18-5* Simple electrostatic considerations suggest that the acidities of carboxylic acids of the type $(CH_3)_3\overset{\oplus}{N}(CH_2)_nCO_2H$ should decrease much more *slowly* with increasing n than the acidities of the type 

. Explain why this should be so.

Exercise 18-6* The chloro acid 3 is a stronger acid than the acid without the chlorine, whereas the chloro acid 4 is a weaker acid than the corresponding acid with no chlorine. Explain why this can be expected from simple electrostatic theory. (Models may be helpful.)



Exercise 18-7* Fluoroethanoic acid is only about twice as acidic as chloroethanoic acid, even though fluorine is much more electronegative than chlorine (Section 10-4B). The lengths of aliphatic C–F bonds are about 1.38 Å, whereas those of C–Cl bonds are 1.78 Å. How could this difference in bond lengths tend to compensate for the differences in electronegativity between chlorine and fluorine and make the acids similar in strength?

Exercise 18-8 Explain why the equilibrium of Equation 18-5 is *less* favorable than that of Equation 18-4.

Exercise 18-9 Use bond energies and the stabilization energy of ethanoic acid ($18\ \text{kcal mol}^{-1}$, Section 18-2A) to calculate ΔH^0 for the addition of water to ethanoic acid to give 1,1,1-trihydroxyethane. Compare the value you obtain with a calculated ΔH^0 for the hydration of ethanal in the vapor phase. Would you expect the rate, the equilibrium constant, or both, for the hydration of ethanoic acid in water solution to be increased in the presence of a strong acid such as sulfuric acid? Explain.

Exercise 18-10 Predict the outcome of an attempted esterification of ethanoic acid with *tert*-butyl alcohol in the presence of dry HCl.

Exercise 18-11 What would you expect to happen to the ^{18}O label in a mixture of ethanoic acid, hydrochloric acid, and $H_2{}^{18}O$? Explain.

Exercise 18-12 Benzoic acid is not esterified by the procedure that is useful for 2,4,6-trimethylbenzoic acid because, when benzoic acid is dissolved in sulfuric acid, it gives the conjugate acid and no acyl cation. Explain why the acyl cation, 11 of 2,4,6-trimethylbenzoic acid might be more stable, relative to the conjugate acid of benzoic acid. (Among other factors, consider the geometries of the various species involved.)

Exercise 18-13 Predict the product of decarboxylation of 2-methyl-3-butenoic acid.

Exercise 18-14 Explain why decarboxylation of 2,2-dimethyl-3-oxobutanoic acid, $CH_3COC(CH_3)_2CO_2H$, in the presence of bromine gives 3-methyl-3-bromo-2-butanone, $CH_3COC(CH_3)_2Br$.

Exercise 18-15 What information would you need to calculate ΔH^0 for the reaction $CH_3CO_2\cdot \rightarrow CO_2 + \cdot CH_3$?

Exercise 18-16 Why does Kolbe electrolysis not give RH by the reaction $RCO_2\cdot \xrightarrow{-CO_2} R\cdot \xrightarrow{H_2O} RH$?

Exercise 18-17* At higher voltages than normally used in the Kolbe electrolysis, salts of carboxylic acid in hydroxylic solvents produce (at the anode) *alcohols* and *esters* of the type ROH and RCO_2R. Explain how this can occur.

Exercise 18-18* Write a sequence of mechanistic steps that embody the suggestions given for conversion of $HO_2C(CH_2)_6CO_2H$ to $CH_2{=}CH(CH_2)_4CO_2H$ with $Pb(O_2CCH_3)_4$ and $Cu(OCH_3)_2$ as a catalyst. Complete the steps necessary to give all of the products and regenerate the catalyst. The role of Cu(II) in the oxidation of radicals is discussed briefly in Section 23-10B.

Exercise 18-19 Write the steps in the phosphorus-catalyzed bromination of propanoic acid and explain why propanoyl bromide is expected to undergo acid-catalyzed bromination more readily than propanoic acid. (Review Section 17-1.)

Exercise 18-20* Optically active sodium 2-bromopropanoate is converted to sodium 2-hydroxypropanoate in water solution. The product has the *same* stereochemical configuration at C_2 as the starting material and the reaction rate is *independent* of added $OH^{\ominus}$ at moderate concentrations. At higher concentrations of $OH^{\ominus}$, the rate becomes *proportional* to the $OH^{\ominus}$ concentration and the 2-hydroxypropanoate formed has the *opposite* configuration to the starting material. Write appropriate mechanisms to explain these facts. Give your reasoning. (It may be helpful to review Sections 8-5 and 15-11.)

Exercise 18-21 The following substances have boiling points as indicated:

ethyl ethanoate (77°)

ethanoic anhydride (140°)

ethanoic acid (118°)

ethanamide (221°)

Account for these differences on the basis of molecular weight and hydrogen bonding.

Exercise 18-22 Why is a carboxylate anion more resistant to attack by nucleophilic agents, such as CH_3OH or $CH_3O^{\ominus}$, than is the corresponding ester?

Exercise 18-23

a. Develop a mechanism for ester interchange between ethanol and methyl ethanoate catalyzed by alkoxide that is consistent with the mechanism of base-induced ester hydrolysis.

b. Why doesn't it matter whether one uses methoxide or ethoxide as the catalyst?

c. If one used *D*-2-butyl ethanoate as the starting ester and methanol as the exchanging alcohol, what would be the configuration fo the 2-butanol formed with methoxide as a catalyst?

Exercise 18-24 Ester interchange also can produce (but more slowly) with an acidic instead of a basic catalyst. Write a mechanism for this reaction consistent with acid-catalyzed ester formation (Section 18-3A).

Exercise 18-25 By analogy with the reaction mechanisms already discussed, propose a mechanism for each of the following reactions:

a. $C_6H_5CO_2CH_3 + C_2H_5OH \xrightarrow{H^{\oplus}} C_6H\text{-}5\,CO_2C_2H_5 + CH_3OH$

b. $CH_3COCl + CH_3CH_2OH \rightarrow CH_3CO_2CH_2CH_3 + HCl$

c. $CH_3CO_2O + CH_3OH \xrightarrow{H^\oplus} CH_3CO_2CH_3 + CH_3CO_2H$

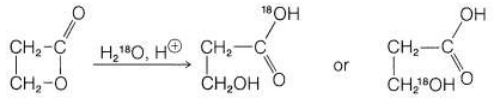
d. $CH_3CONH_2 + H_3O^+ \xrightarrow{H_2O} CH_3CO_2H + NH_4^+$

e. $CH_3CONH_2 + OH^- \rightarrow CH_3CO_2^- + NH_3$

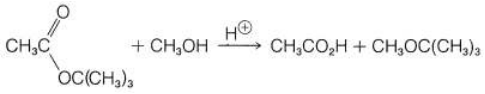
f. $CH_3COCl + 2NH_3 \rightarrow CH_3CONH_2 + NH_4Cl$

g. $CH_3CO_2CH_3 + CH_3NH_2 \rightarrow CH_3CONHCH_3 + CH_3OH$

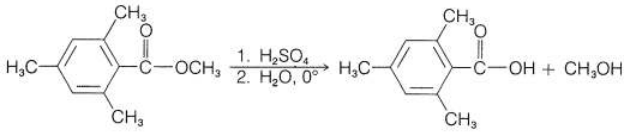
Exercise 18-26 What can you conclude about the mechanism of acid-catalyzed hydrolysis of oxacyclobutan-2-one (β-propiolactone) from the following equation:



Exercise 18-27 Write a plausible mechanism supported by analogy for the following reaction:



Exercise 18-28 Explain why the base-induced hydrolysis of methyl 2,4,6-trimethylbenzoate is unusually slow. Write a mechanism for the hydrolysis of methyl 2,4,6-trimethylbenzoate that occurs when the ester is dissolved in concentrated sulfuric acid and the solution poured into a mixture of ice and water (see Section 18-3A):



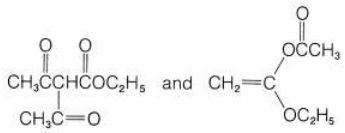
Exercise 18-29 Grignard reagents add to N,N-dialkylalkanamides, $RCONR'_2$, to give ketones after hydrolysis. With esters or acyl chlorides, a tertiary alcohol is the usual product. Explain why, on the basis of the stability of the $RR'CZ(OMgX)$ intermediate, the amides may be expected to be less likely than esters or acyl chlorides to give tertiary alcohols. How could you use an N,N-dialkylalkanamide to prepare an aldehyde with the aid of a Grignard reagent?

Exercise 18-30 Explain why 2,4-pentanedione can be expected to contain much more enol at equilibrium than does ethyl 3-oxobutanoate. How much enol would you expect to find in diethyl propanedioate? In 3-oxobutanal? Explain.

Exercise 18-31 Arguing from the factors that appear to regulate the ratio of C- to O-alkylation of enolate anions (Section 17-4), show how you could decide whether the reaction of the sodium enolate salt of ethyl 3-oxobutanoate with a strong acid would give, as the *initial* product, mostly the enol form, mostly the keto form, or the equilibrium mixture.

Exercise 18-32 When a small amount of sodium ethoxide is added to ethyl 3-oxobutanoate, the proton NMR peaks marked *a*, *b*, and *c* in Figure 18-6 disappear. Explain why this should be so. (You may wish to review Section 9-10E.)

Exercise 18-33 Possible byproducts of the Claisen condensation of ethyl ethanoate are



Explain how these products may be formed and why they are not formed in significant amounts.

Exercise 18-34 Ethanol has a K_a of 10^{-18} and ethyl 3-oxobutanoate has $K_a = 10^{-11}$. Calculate ΔG^0 for the reaction of sodium ethoxide with the ester as per Equation 18-13. (See Section 4-4A.)

Exercise 18-35 Write structures for all of the Claisen condensation products that reasonably may be expected to be formed from the following ester mixtures and sodium ethoxide:

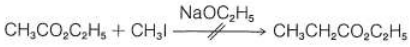
a. ethyl ethanoate and ethyl propanoate
b. diethyl carbonate and 2-propanone
c. diethyl ethanedioate and ethyl 2,2-dimethylpropanoate

Exercise 18-36 Show how the following substances may be synthesized by Claisen-type condensations from the indicated starting materials. Specify the reagents and reaction conditions as completely as possible.

a. ethyl 2-methyl-3-oxopentanoate from ethyl propanoate
b. ethyl 2,4-dioxopentanoate from 2-propanone
c. diethyl 2-phenylpropanedioate from ethyl phenylethanoate
d. 2,4-pentanedione from 2-propanone
e. 2,2,6,6-tetramethyl-3,5-heptanedione from 3,3-dimethyl-2-butanone
f. ethyl 2,2-dimethyl-3-phenyl-3-oxopropanoate from 2-methylpropanoate

Exercise 18-37 What advantages and disadvantages may sodium hydride (NaH) have as the base used in the Claisen condensation?

Exercise 18-38 Why does the following reaction fail to give ethyl propanoate?



Exercise 18-39 Show a synthesis of 3-ethyl-2-pentanone from ethyl 3-oxobutanoate. What advantage would this route have over alkylation of 2-pentanone with sodium amide and ethyl iodide? (Section 17-4A.)

Exercise 18-40 How could you prepare diethyl methylpropanedioate that is *free* of diethyl propanedioate and diethyl dimethylpropanedioate? (Review Section 18-8B to find an alternative synthesis not involving alkylation.)

Exercise 18-41 Show how one could prepare cyclobutanecarboxylic acid from diethyl propanedioate and a suitable dihalide.

Exercise 18-42 Write a mechanism based on analogy with other reactions in this chapter that will account for the strong alkali-induced cleavage of ethyl 2-methyl-3-oxobutanoate in accord with Equation 18-21.

Exercise 18-43*

a. In the formation of $\mathrm{LiCH_2CO_2C_2H_5}$ (Equation 18-22), would it be better to add the ester to the solution of the base in oxacyclopentane, or the reverse? Give your reasoning.

b. Suppose a solution formed in accord with Equation 18-23 were allowed to stand (before adding acid and water) until equilibrium is established between the various possible Claisen, mixed-Claisen, and aldol-addition products described in Sections 18-8B and 17-3C. What products would you then expect to be formed on hydrolysis with dilute acid and water? Which would be expected to predominate? Give your reasoning.

c. Show how you could synthesize methyl 2-(1-cyclohexenyl)ethanoate from cyclohexanone by the reactions described in Section 18-8E.

Exercise 18-44* The formation of an acyl coenzyme A, $\mathrm{RCO{-}S\mathbf{CoA}}$, from coenzyme A and a carboxylic acid is coupled to a cleavage reaction of ATP to give AMP:

$$\mathrm{RCO_2H + ATP + \mathbf{CoA}{-}SH \rightleftharpoons RCO{-}S\mathbf{CoA} + AMP + PP} \qquad (18.E.1)$$

Write the possible steps involved in this esterification reaction. (Review Section 15-5F.)

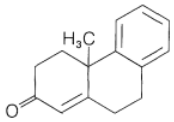
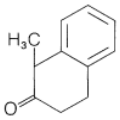
Exercise 18-45 Write a mechanism for the base-catalyzed equilibration of α,β- and β,γ-unsaturated esters. Which isomer would you expect to predominate? Why does this type of isomerization proceed less readily for the carboxylate anions than for the esters? Would γ,δ-unsaturated esters rearrange readily to the α,β-unsaturated esters? Why, or why not?

Exercise 18-46 Would you expect 3-butenoic acid to form a lactone with a five- or a four-membered ring when heated with a catalytic amount of sulfuric acid?

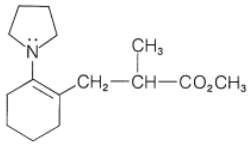
Exercise 18-47 Explain why the Michael addition of diethyl propanedioate to 3-phenylpropenoic acid is unlikely to be successful.

Exercise 18-48* The Michael-addition product that results from ethyl 3-phenylpropenoate and diethyl propanedioate, in principle, also can be formed by sodium ethoxide-catalyzed addition of ethyl ethanoate to ethyl (2-carbethoxy)-3-phenylpropenoate. Work out the course of this reaction along the lines of Equations 18-25 and 18-26 and explain why it is less likely to be successful than the addition of diethyl propanedioate to ethyl 3-phenylpropenoate. It will be helpful to compare the various possible acid-base equilibria involved in the two possible routes to the same Michael-addition product.

Exercise 18-49 Show how the following substances can be prepared by syntheses based on Michael additions. In some cases, additional transformations may be required.

a. 3-phenylpentanedioic acid from ethyl 3-phenylpropenoate
b. 3,5-diphenyl-5-oxopentanenitrile from 1,3-diphenylpropenone (benzalacetophenone)
c. 4,4-(dicarbethoxy)heptanedinitrile from propenenitrile (acrylonitrile)
d.  from  and 3-butene-2-one

Exercise 18-50 Explain how steric hindrance would lead one to expect that the proton-transfer product in the addition of N-(1-cyclohexenyl)azacyclopentane to methyl 2-methylpropenoate would have the structure shown in Equation 18-27, rather than the following:



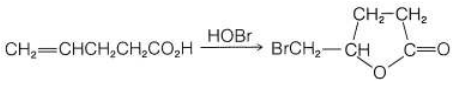
Exercise 18-51 The *cis*- and *trans*-butenedioic acids give the same anhydride on heating, but the *trans* acid must be heated to much higher temperatures than the *cis* acid to achieve anhydride formation. Explain. Write a reasonable mechanism for both reactions.

Exercise 18-52 Write equations for a practical laboratory synthesis of the following substances from the indicated starting materials (several steps may be required). Give reagents and conditions:

a. butanoic acid from 1-propanol
b. 2,2-dimethylpropanoic acid from *tert*-butyl chloride
c. 2-methylpropanoic acid from 2-methylpropene
d. 2-bromo-3,3-dimethylbutanoic acid from *tert*-butyl chloride
e. cyclobutylmethanol-1-^{14}C, $(CH_2)_3CH\,^{14}CH_2OH$, from cyclobutanecarboxylic acid and $Ba\,^{14}CO_3$
f. 4-pentenamide from 3-chloropropene
g. 2,2-dimethylpropyl 2,2-dimethylpropanoate from *tert*-butyl chloride

Exercise 18-53 Write reasonable mechanisms for each of the following reactions:

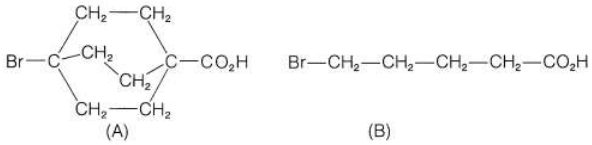
a. *cis*-$CH_3CH{=}CHCO_2H \xrightarrow[2.\ H^{\oplus}]{1.\ {}^{\ominus}OH,\ 100^{\circ}}$ *trans*-$CH_3CH{=}CHCO_2H$

b. 

c. $CH_3CO_2CH_3 + CH_3CH_2CO_2H \overset{H^{\oplus}}{\rightleftharpoons} CH_3CH_2CO_2CH_3 + CH_3CO_2H$

The order of reactivity for CH_3CO_2R is $R = CH_3- > CH_3CH_2- \gg (CH_3)_2CH-$.

Exercise 18-54 4-Bromobicyclo[2.2.2]octane-1-carboxylic acid (A) is a considerably stronger acid than 5-bromopentanoic acid (B). Explain. (*Hint:* Consider the possible conformations and modes of transmission of the electrical effect of the C–Br dipole.)



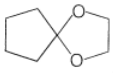
Exercise 18-55 *tert*-Butyl ethanoate is converted to methyl ethanoate by sodium methoxide in methanol about *one tenth as fast* as ethyl ethanoate is converted to methyl ethanoate under the same conditions. With dilute HCl in methanol, *tert*-butyl ethanoate is *rapidly* converted to 2-methoxy-2-methylpropane and ethanoic acid, whereas ethyl ethanoate goes *more slowly* to ethanol and methyl ethanoate.

a. Write reasonable mechanisms for each of the reactions and show how the relative-rate data agree with your mechanisms.

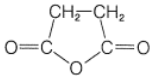
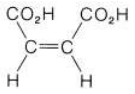
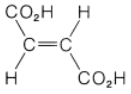
b. How could one use ^{18}O as a tracer to substantiate your proposed mechanisms?

Exercise 18-56 It has been reported that esters (RCO_2R') in ^{18}O water containing sodium hydroxide are converted to in competition with alkaline hydrolysis. The rates of both exchange and hydrolysis reactions are proportional to $OH^{\ominus}$ concentration. Explain what these facts mean with regard to the mechanism of ester hydrolysis.

Exercise 18-57 Write equations for a practical laboratory synthesis of each of the following substances from the indicated starting materials (several steps may be required). Give reagents and conditions.

a. 2-chloroethyl bromoethanoate from ethanol and/or ethanoic acid
b. 2-methoxy-2-methylpropanamide from 2-methylpropanoic acid
c. 3,5,5-trimethyl-3-hexanol from 2,4,4-trimethyl-1-pentene (commercially available)
d. 3,3-dimethylbutanal from 2,2-dimethylpropanoic acid
e. 2,3,3-trimethyl-2-butanol from 2,3-dimethyl-2-butene
f. the 1,2-ethanediol ketal of cyclopentanone,  , from hexanedioic acid

Exercise 18-58 For each of the following pairs of compounds give a chemical test, preferably a test-tube reaction, that will distinguish between the two substances. Write an equation for each reaction.

a. HCO_2H and H_3CCO_2H
b. $CH_3CO_2C_2H_5$ and $CH_3OCH_2CO_2H$
c. $CH_2{=}CHCO_2H$ and $CH_3CH_2CO_2H$
d. CH_3COBr and $BrCH_2CO_2H$
e. $BrCH_2CH_2CH_2CO_2CH_3$ and $CH_3CH_2CHBrCO_2CH_3$
f. $(CH_3CH_2CO)_2O$ and 
g.  and 
h. $HC\equiv CCO_2CH_3$ and $CH_2{=}CHCO_2CH_3$
i. $CH_3CO_2NH_4$ and CH_3CONH_2
j. $CH_2{=}CH{-}CH_2CH_2CO_2H$ and $CH_3CH_2CH{=}CHCO_2H$
k. $(CH_3CO)_2O$ and $CH_3CO_2CH_2CH_3$

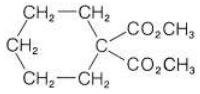
Exercise 18-59 Explain how you could distinguish between the pairs of compounds listed in Exercise 18-58 by spectroscopic means. Be *specific* about what would be observed.

Exercise 18-60 Suppose you were given four bottles, each containing a different isomer (2-, 3-, 4-, or 5-) of hydroxypentanoic acid. Explain in detail how you could distinguish the various isomers by chemical reactions.

Exercise 18-61 Compound A $(C_4H_8O_3)$ was optically active, quite soluble in water (giving a solution acidic to litmus), and, on strong heating, yielded B $(C_4H_6O_2)$, which was optically *inactive*, rather water-soluble (acidic to litmus), and reacted much more readily with $KMnO_4$ than did A. When A was oxidized with dilute chromic acid solution, it was converted to a volatile liquid C (C_3H_6O), which did not react with $KMnO_4$, and gave a yellow precipitate with I_2 and $NaOH$ solution.

Write appropriate structures for the lettered compounds and equations for all of the reactions mentioned. Is Compound A defined by the above description? Explain.

Exercise 18-62 Name each of the following substances by the IUPAC system:

a. 

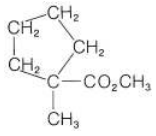
b. Extra close brace or missing open brace

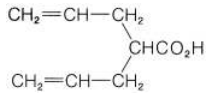
c. $CH_3CH_3COC(CH_3)_2CON(CH_3)_2$

d. $HOCH{=}CHCO_2C_2H_5$

e. $C_2H_5OCOCOCH_2CO_2C_2H_5$

f. $C_2H_5O_2CCH_2CH(CO_2C_2H_5)COCO_2C_2H_5$

g. 

h. 

i. $CH_3CH_2COCH(CH_3)CH_2CH_2CH(CH_3)_2$

j. $CH_3CH_2CH_2CH(CH_2CH{=}CH_2)CO_2H$

k. $CH_3COCH(CO_2C_2H_5)_2$

l. $C_6H_5CH{=}CH{-}CH(OH)CH_2CO_2C_2H_5$

Exercise 18-63 Write equations for the synthesis of each of the substances in Exercise 18-62 a-l from compounds with fewer carbon atoms, using the type of reactions discussed in Sections 18-9 and 18-10. You may wish to review Sections 13-6 to 13-9 before beginning.

Exercise 18-64 Direct reduction of aldehydes with 2,3-dimethyl-2-butylborane proceeds rapidly and gives the corresponding alcohol. Nonetheless, reduction of carboxylic acids with the same borane (Section 18-3C) proceeds slowly and gives high yields of aldehydes. Explain why the reaction of RCO_2H with the 2,3-dimethyl-2-butylborane produces $RCHO$ instead of RCH_2OH.

18.E.1: Contributors

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CHAPTER OVERVIEW

19: More on Stereochemistry

The fundamentals of structure and stereochemistry have been considered in previous chapters in some detail. There are, however, practical aspects of stereochemistry that have not yet been mentioned, particularly with regard to chiral compounds. How, for instance, can a racemic mixture be separated into its component enantiomers (resolution); what methods can be used to establish the configuration of enantiomers; how can we tell if they are pure; and how do we synthesize one of a pair of enantiomers preferentially (asymmetric synthesis)? In this chapter, some answers to these questions will be described briefly.

Optical activity is an associated phenomenon of chirality and has long been used to monitor the behavior of chiral compounds. Brief mention of this was made earlier (Section 5-1C), but now the origin and measurement of optical rotation will be examined in more detail.

19.1: Plane-Polarized Light and the Origin of Optical Rotation
19.2: Specific Rotation
19.3: Separation or Resolution of Enantiomers
19.4: Enantiomeric Purity
19.5: Absolute And Relative Configuration
19.6: The R,S Convention for Designating Stereochemical Configurations
19.7: E,Z Notation
19.8: Prochirality
19.9: Optical Rotatory Dispersion and Circular Dichroism
19.10: Asymmetric Synthesis
19.11: Racemization
19.E: More on Stereochemistry (Exercises)

19.1: Contributors and Attributions

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19.1: Plane-Polarized Light and the Origin of Optical Rotation

Electromagnetic radiation, as the name implies, involves the propagation of both electric and magnetic forces. At each point in an ordinary light beam, there is a component electric field and a component magnetic field, which are perpendicular to each other and oscillate in all directions perpendicular to the direction in which the beam propagates. In plane-polarized light the component electric field oscillates as in ordinary light, except that the direction of oscillation is contained within a single plane. Likewise, the component magnetic field oscillates within a plane, the planes in question being perpendicular to each other. A schematic representation of the electric part of plane-polarized light and its interaction with an optical isomer is shown in Figure 19-1. The beam of polarized light, XY, has a component electric field that oscillates in the plane AOD. At the point O the direction of oscillation is along OE. If now at O the beam encounters a substance which has the power to cause the direction of oscillation of the electrical field to rotate through an angle α to the new direction OE' in the plane COB, the substance is said to be *optically active*.

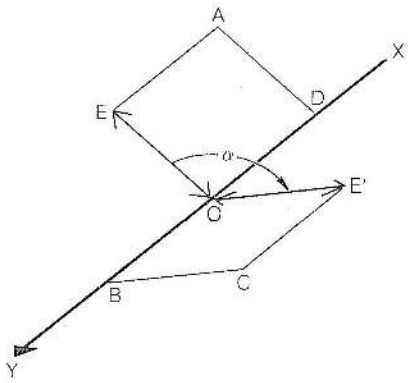

Figure 19-1: Schematic representation of the electrical component of plane-polarized light and optical rotation. The beam is assumed to travel from X toward Y.

A clockwise rotation, as the observer looks towards the beam, defines the substance as dextrorotatory (i.e., rotates to the right) and the angle α is taken as a positive $(+)$ rotation. If the rotation is counterclockwise the substance is described as levorotatory (i.e., rotates to the left) and the angle α is taken as a negative $(-)$ rotation.

The question naturally arises as to why some substances interact with polarized light in this manner whereas others do not. We shall oversimplify the explanation because a rigorous treatment involves rather complex mathematics. However, it is not difficult to understand that the electric forces in a light beam impinging on a molecule will interact to some extent with the electrons within the molecule. Although radiant energy actually may not be absorbed by the molecule to promote it to higher, excited electronic-energy states (see Section 9-9A), a perturbation of the electronic configuration of the molecule can occur. One can visualize this process as a polarization of the electrons brought about by the oscillating electric field associated with the radiation.

This interaction is important to us here because it causes the electric field of the radiation to change its direction of oscillation. The effect produced by any one molecule is extremely small, but in the aggregate may be measurable as a net rotation of the plane-polarized light. Molecules such as methane, ethene and 2-propanone, which have enough symmetry so that each is identical with its reflection, do not rotate plane-polarized light. This is because the symmetry of each is such that every optical rotation in one direction is canceled by an equal rotation in the opposite direction. However, a molecule with its atoms so disposed in space that it is not symmetrical to the degree of being superimposable on its mirror image will have a net effect on the incident polarized light, because then the electromagnetic interactions do not average to zero. We characterize such substances as having chiral configurations and as being optically active.

A useful model for explanation of optical rotation considers that a beam of plane-polarized light is the vector resultant of two oppositely rotating beams of circularly polarized light. This will be clearer if we understand that circularly polarized light has a component electric field that varies in direction but not in magnitude so that the field traverses a helical path in either a clockwise or counterclockwise direction, as shown in Figure 19-2.

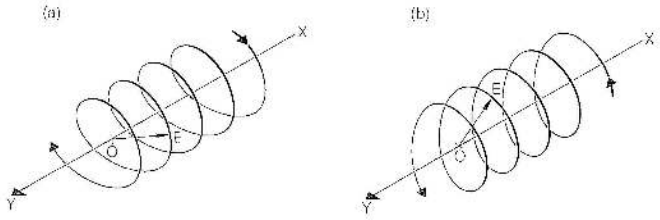

Figure 19-2: Circularly polarized light. The helix represents the path followed by the component electric field of a light beam, XY, and may rotate clockwise (a) or counterclockwise (b).

The resultant of the two oppositely rotating electric vectors lies in a plane, and the magnitude of the resultant varies as a sine wave, shown in Figure 19-3. This amounts to plane-polarized light.

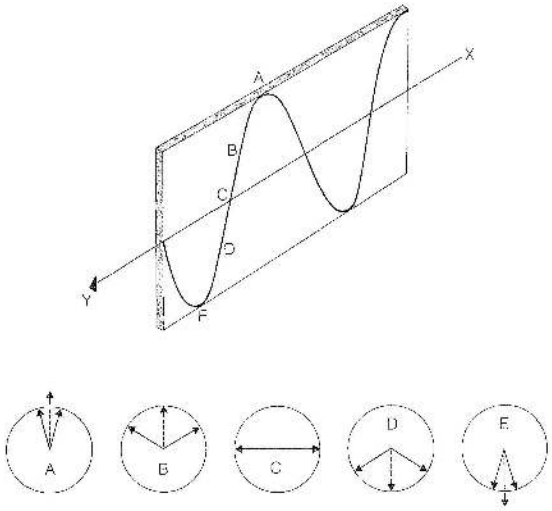

Figure 19-3 Plane-polarized light as the vector sum of two oppositely rotating beams of circularly polarized light. The phases of the two electric vectors and their resultant are shown separately for the points A, B, C, D, and E to clarify that the resultant vector oscillates in the form of a sine wave.

When circularly polarized light travels through an assemblage of one kind of chiral molecules, the velocity of light observed for one direction of circular polarization is different from that for the other direction of polarization. This is eminently reasonable because, no matter how a chiral molecule is oriented, the molecule presents a different aspect to circularly polarized light rotating in one direction than to that rotating in the other direction. Consequently if the electric vectors of two circularly polarized light beams initially produce a resultant that lies in a plane, and the beams then encounter a medium in which they have different velocities, one beam will move steadily ahead of the other. This will cause a continual rotation of the plane of their resultant until they again reach a medium in which they have equal velocities.

19.1.1: Contributors and Attributions

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19.2: Specific Rotation

Optical rotation is the usual and most useful means of monitoring enantiomeric purity of chiral molecules. Therefore we need to know what variables influence the magnitude of optical rotation.

The measured rotation, α, of a chiral substance varies with the concentration of the solution (or the density of a pure liquid) and on the distance through which the light travels. This is to be expected because the magnitude of α will depend on the *number* as well as the kind of molecules the light encounters. Another important variable is the wavelength of the incident light, which always must be specified even though the sodium D line $(589.3\ \text{nm})$ commonly is used. To a lesser extent, α varies with the temperature and with the solvent (if used), which also should be specified. The optical rotation of a chiral substance usually is reported as a specific rotation $[\alpha]$, which is expressed by the Equations 19-1 or 19-2

For solutions:

$$[\alpha]_{\lambda}^{t} = \frac{100\alpha}{l \times c} \tag{19-1}$$

For neat liquids:

$$[\alpha]_{\lambda}^{t} = \frac{\alpha}{l \times d} \tag{19-2}$$

with

- α is the measured rotation in degrees
- t is the temperature
- λ is the wavelength of light
- l is the length in decimeters of the light path through the solution
- c is the concentration in grams of sample per 100 ml of solution
- d is the density of liquid in grams ml^{-I}

For example, quinine (Section 19-3A) is reported as having $[\alpha]_D = -117^{o}\,(c = 1.5,\ \text{CHCl}_3)\,(t = 17^{o})$, which means that it has a levorotation of 117 degrees for sodium D light $(589.3\ \text{nm})$ at a concentration of $1.5\ \text{g}$ per $100\ \text{mL}$ of chloroform solution at 17°C when contained in a tube 1 decimeter long.

Frequently, molecular rotation, $[M]$, is used in preference to specific rotation and is related to specific rotation by Equation 19-3:

$$[M]_{\lambda}^{t} = \frac{[\alpha]_{\lambda}^{t} \times M}{100} \tag{19-3}$$

in which M is the molecular weight of the compound. Expressed in this form, optical rotations of different compounds are directly comparable on a molecular rather than a weight basis. The effects of wavelength of the light in the polarized beam on the magnitude and sign of the observed optical rotation are considered in Section 19-9.

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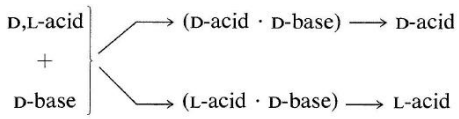
19.3: Separation or Resolution of Enantiomers

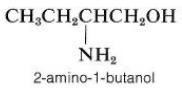
Because the physical properties of enantiomers are identical, they seldom can be separated by simple physical methods, such as fractional crystallization or distillation. It is only under the influence of another chiral substance that enantiomers behave differently, and almost all methods of resolution of enantiomers are based upon this fact. We include here a discussion of the primary methods of resolution.

19.3.1: Chiral Amines as Resolving Agents. Resolution of Racemic Acids

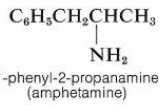
The most commonly used procedure for separating enantiomers is to convert them to a mixture of diastereomers that will have different physical properties: melting point, boiling point, solubility, and so on (Section 5-5). For example, if you have a racemic or *D*,*L* mixture of enantiomers of an acid and convert this to a salt with a *chiral* base having the *D* configuration, the salt will be a mixture of two diastereomers, (*D* acid · *D* base) and (*L* acid · *D* base). These diastereomeric salts are *not* identical and they are *not* mirror images. Therefore they will differ to some degree in their physical properties, and a separation by physical methods, such as crystallization, may be possible. If the diastereomeric salts can be completely separated, the acid regenerated from each salt will be either exclusively the *D* or the *L* enantiomer:



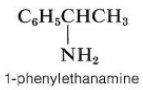
Resolution of chiral acids through the formation of diastereomeric salts requires adequate supplies of suitable chiral bases. Brucine, strychnine, and quinine frequently are used for this purpose because they are readily available, naturally occurring chiral bases. Simpler amines of synthetic origin, such as 2-amino-1-butanol, amphetamine, and 1-phenylethanamine, also can be used, but first they must be resolved themselves.



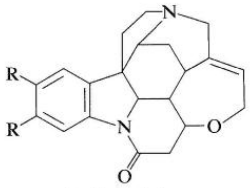
2-amino-1-butanol



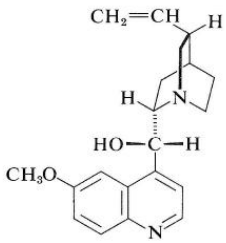
1-phenyl-2-propanamine
(amphetamine)



1-phenylethanamine



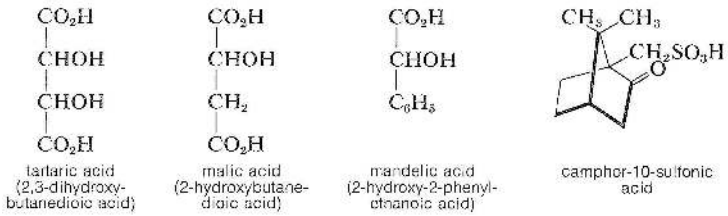
R = H, strychnine
R = OCH_3, brucine



quinine
(antimicrobial)
(antimalarial)

19.3.2: Resolution of Racemic Bases

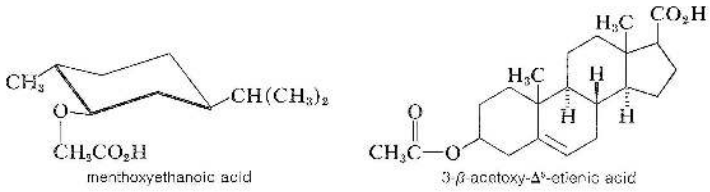
Chiral acids, such as (+)-tartaric acid, (−)-malic acid, (−)-mandelic acid, and (+)-camphor-10-sulfonic acid, are used for the resolution of a racemic base.



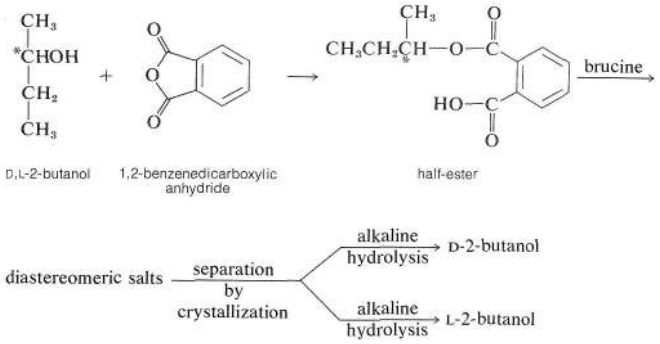
The principle is the same as for the resolution of a racemic acid with a chiral base, and the choice of acid will depend both on the ease of separation of the diastereomeric salts and, of course, on the availability of the acid for the scale of the resolution involved. Resolution methods of this kind can be tedious, because numerous recrystallizations in different solvents may be necessary to progressively enrich the crystals in the less-soluble diastereomer. To determine when the resolution is complete, the mixture of diastereomers is recrystallized until there is no further change in the measured optical rotation of the crystals. At this stage it is hoped that the crystalline salt is a pure diastereomer from which one pure enantiomer can be recovered. The optical rotation of this enantiomer will be a maximum value if it is "optically" pure because any amount of the other enantiomer could only reduce the magnitude of the measured rotation α.

19.3.3: Resolution of Racemic Alcohols

To resolve a racemic alcohol, a chiral acid can be used to convert the alcohol to a mixture of diastereomeric esters. This is not as generally useful as might be thought because esters tend to be liquids unless they are very high-molecular-weight compounds. If the diastereomeric esters are not crystalline, they must be separated by some other method than fractional crystallization (for instance, by chromatography methods, Section 9-2). Two chiral acids that are useful resolving agents for alcohols are:



The most common method of resolving an alcohol is to convert it to a *half*-ester of a dicarboxylic acid, such as butanedioic (succinic) or 1,2-benzenedicarboxylic (phthalic) acid, with the corresponding anhydride. The resulting half-ester has a free carboxyl function and may then be resolvable with a chiral base, usually brucine:



19.3.4: Other Methods of Resolution

One of the major goals in the field of organic chemistry is the development of reagents with the property of "**chiral recognition**" such that they can effect a clean separation of enantiomers in one operation without destroying either of the enantiomers. We have not achieved that ideal yet, but it may not be far in the future. Chromatographic methods (Section 9-2), whereby the stationary phase is a chiral reagent that adsorbs one enantiomer more strongly than the other, have been used to resolve racemic compounds, but such resolutions seldom have led to both pure enantiomers on a *preparative* scale.

Other methods, called **kinetic resolutions**, are excellent when applicable. The procedure takes advantage of differences in reaction rates of enantiomers with chiral reagents. One enantiomer may react more rapidly, thereby leaving an excess of the other enantiomer behind. For example, racemic tartaric acid can be resolved with the aid of certain penicillin molds that consume the dextrorotatory enantiomer faster than the levorotatory enantiomer. As a result, almost pure $(-)$-tartaric acid can be recovered from the mixture:

A disadvantage of resolutions of this type is that the more reactive enantiomer usually is not recoverable from the reaction mixture.

The crystallization procedure employed by Pasteur for his classical resolution of $(\pm)$-tartaric acid (Section 5-1C) has been successful only in a very few cases. This procedure depends on the formation of individual crystals of each enantiomer. Thus if the crystallization of sodium ammonium tartrate is carried out below 27°, the usual racemate salt does not form; a mixture of crystals of the $(+)$ and $(-)$ salts forms instead. The two different kinds of crystals, which are related as an object to its mirror image, can be separated manually with the aid of a microscope and subsequently may be converted to the tartaric acid enantiomers by strong acid. A variation on this method of resolution is the seeding of a saturated solution of a racemic mixture with crystals of one pure enantiomer in the hope of causing crystallization of just that one enantiomer, thereby leaving the other in solution. Unfortunately, very few practical resolutions have been achieved in this way.

Even when a successful resolution is achieved, some significant problems remain. For instance, the resolution itself does not provide information on the actual configuration of the $(+)$ or $(-)$ enantiomer. This must be determined by other means (see Section 19-5). Also, it is not possible to tell the enantiomeric purity (optical purity) of the resolved enantiomers without additional information. This point is discussed further in the next section.

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19.4: Enantiomeric Purity

The term **enantiomeric purity** (or **optical purity**) is defined as the fractional excess of one enantiomer over the other. This is expressed in Equation 19-4 in terms of the moles (or weights) of the two enantiomers, n_1, and n_2, and is equal to the ratio of the observed optical rotation, α_{obs}, and to the optical rotation of either pure enantiomer, α_0:

$$\text{enantiomeric purity of } n_1 = \frac{n_1 - n_2}{n_1 + n_2} = \frac{\alpha_{\text{obs}}}{\alpha_0} \tag{19-4}$$

Thus a racemic mixture ($n_1 = n_2$) has an enantiomeric purity of zero. Any other enantiomeric composition in principle can be determined provided the mixture has a measurable rotation and the rotation of the pure enantiomer, α_0, is known. Unfortunately, there is no simple method of calculating α_0, in advance. In fact, specific rotations of optically pure compounds are determined most reliably from Equation 19-4 after measurement of enantiomeric purity by independent methods.

Virtually all of the methods for determining enantiomeric purity rely on the differences in chemical, physical, or spectroscopic properties of diastereomers derived from enantiomeric mixtures. We will mention here two of the most straightforward methods, based on gas-liquid chromatography and nuclear magnetic resonance.

19.4.1: Determination of Enantiomeric Purity by Gas Chromatography

This method amounts to a complete resolution of the type described in Section 19-3D, but on an analytical scale. For example, assume that you have a partially resolved compound, A, consisting of unequal amounts of the enantiomers A_+ and A_-. By reaction with a second chiral *enantiomerically pure* substance, B_+, A is converted to a mixture of diastereomers A_+B_+ and A_-B_+. Because these diastereomers are chemically and physically different, the mixture usually can be analyzed by gas-liquid chromatography (Section 9-2A). If the reaction of B_+ with A_+ and A_- was quantitative, the relative areas of the two peaks eluting from the column correspond to the ratio of the diastereomers A_+B_+/A_-B_+, and thus to the ratio of enantiomers A_+/A_-, from which the enantiomeric purity of the partially resolved mixture can be calculated.

An alternative and very direct approach is to separate the enantiomers on a column in which the stationary liquid phase is a chiral compound. The diastereomeric interaction is between A_+ or A_- and the chiral liquid phase, and may be sufficiently different to permit separation of A_+ from A_-. The ratio of the amounts of A_+ and A_- corresponds to the enantiomeric purity.

19.4.2: Determination of Enantiomeric Purity by NMR Spectroscopy

The nmr chemical shifts of nuclei of enantiomeric compounds A_+ and A_- are identical in achiral solvents. However, in a chiral solvent (enantiomerically pure) A_+ and A_- will be effectively converted to diastereomers as the result of **chiral solvation** and, accordingly, their nuclei will have nonidentical chemical shifts. Provided that the shift differences are large enough to permit the resonances of one chirally solvated enantiomer to be resolved from those of the other, the ratio of enantiomers A_+/A_- can be determined from the ratio of their corresponding nmr signal intensities.

Alternatively, with a pure chiral reagent the enantiomeric mixture may be converted (*quantitatively*) to diastereomers. The nuclei of the diastereomeric compounds are expected to have small differences in chemical shifts, even in achiral solvents, and integration of their respective signal intensities should correspond to the ratio of diastereomers, and hence to the ratio of enantiomers in the original mixture.

Application of the above-described nmr methods for the determination of enantiomeric composition is difficult, if not impossible, if the chemical-shift differences are too small $(0.02\,\text{ppm})$ or if the resonances overlap extensively. This problem often can be solved by utilizing the ability of certain chelates of rare earth metals (the **lanthanide** metals) to complex with organic compounds, particularly with alcohols, ketones, amines, and other Lewis bases. Chemical shifts in the presence of even small amounts of lanthanide chelates usually are spread over a much wider range of field strengths than for the pure compounds. As discussed previously in Sections 9-10D and 9-10K, increasing chemical shifts can greatly simplify otherwise complex nmr spectra. The shifts are produced by these lanthanide compounds because the electrons on the metal atoms are not all paired, so that the metal atoms are *paramagnetic* (possess a net electron spin). In an applied magnetic field the unpaired electrons circulate around the metal atoms and produce an induced field (Figure 9-26) which, depending on the nature of the metal, can act either to increase or reduce the applied magnetic field, H_0.

In the complex formed between the lanthanide reagent and the organic substrate, the chemical shifts most strongly affected are those of nuclei close to the paramagnetic metal atom. The resonances of these nuclei also are broadened by the paramagnetic metal (Section 27-1), and this is undesirable. The lanthanide complexes that produce these large shift changes are called **shift reagents**. Most of them are chelate salts of substituted 2,4-pentanediones, especially of 2,2,6,6-tetramethyl-3,5-heptanedione (Section 17-8).

There are several useful shift reagents, usually of europium, in which the organic ligands are chiral. An example is 1:

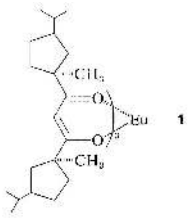
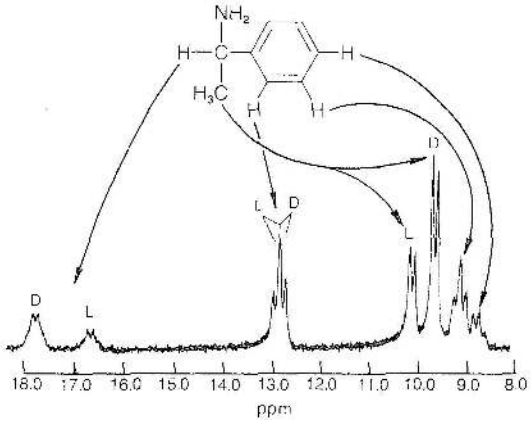


Figure 19-4) of the enantiomers of 1-phenylethanamine in the presence of 1. Although not all of the resonances are separated equally, the resolution is good for the resonances of nuclei closest to the metal atom and permits an estimate of the ratio of enantiomers as about 2:1 and the enantiomeric purity as 33%.



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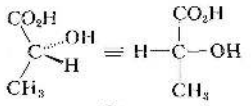
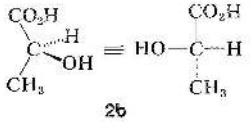
19.5: Absolute And Relative Configuration

The sign of rotation of plane-polarized light by an enantiomer is not easily related to its configuration. This is true even for substances with very similar structures. Thus, given lactic acid, $CH_3CHOHCO_2H$, with a specific rotation $+3.82^o$, and methyl lactate, $CH_3CHOHCO_2CH_3$, with a specific rotation -8.25^o, we cannot tell from the rotation alone whether the acid and ester have the same or a different arrangement of groups about the chiral center. Their relative configurations have to be obtained by other means.

If we convert $(+)$-lactic acid into its methyl ester, we can be reasonably certain that the ester will be related in configuration to the acid, because esterification should not affect the configuration about the chiral carbon atom. It happens that the methyl ester so obtained is levorotatory, so we know that $(+)$-lactic acid and $(-)$-methyl lactate have the same relative configuration at the asymmetric carbon, even if they possess opposite signs of optical rotation. However, we still do not know the absolute configuration; that is, we are unable to tell which of the two possible configurations of lactic acid, $2a$ or $2b$, corresponds to the dextro or $(+)$-acid and which to the levo or $(-)$-acid:



2a



2b

Until 1956, the absolute configuration of no optically active compound was known. Instead, configurations were assigned relative to a standard, *glyceraldehyde*, which originally was chosen by E. Fischer (around 1885) for the purpose of correlating the configuration of carbohydrates. Fischer arbitrarily assigned the configuration $3a$ to dextrorotatory glyceraldehyde, which was known as D-$(+)$-glyceraldehyde. The levorotatory enantiomer, $3b$, is designated as L-$(-)$-glyceraldehyde. (If you are unsure of the terminology D and L, or of the rules for writing Fischer projection formulas, review Sections 5-3C and 5-4.)

3a

D-(+)-glyceraldehyde

3b

L-(−)-glyceraldehyde

The configurations of many compounds besides sugars now have been related to glyceraldehyde, including α-amino acids, terpenes, steroids, and other biochemically important substances. Compounds whose configurations are related to D-$(+)$-glyceraldehyde are said to belong to the D series, and those related to L-$(-)$-glyceraldehyde belong to the L series.

At the time the choice of absolute configuration for glyceraldehyde was made, there was no way of knowing whether the configuration of $(+)$-glyceraldehyde was in reality $3a$ or $3b$. However, the choice had a 50% chance of being correct, and we now know that $3a$, the D configuration, is in fact the correct configuration of $(+)$-glyceraldehyde. This was established through use of a special x-ray crystallographic technique, which permitted determination of the absolute disposition of the atoms in space of sodium rubidium $(+)$-tartrate. The configuration of $(+)$-tartaric acid (Section 5-5) previously had been shown by chemical means to be opposite to that of $(+)$-glyceraldehyde. Consequently the absolute configuration of any compound now is known once it has been correlated directly or indirectly with glyceraldehyde. For example,

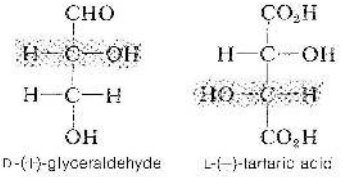
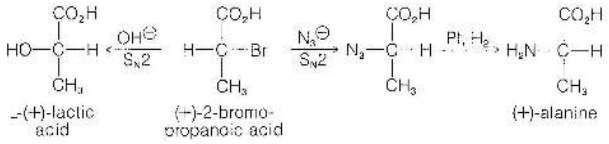
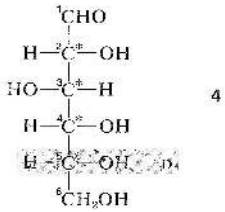


Figure 19-5 whereby the configuration of $(+)$-lactic acid is related to the amino acid $(+)$-alanine. Because $(+)$-lactic acid has been related to L-$(-)$-glyceraldehyde, it follows that the absolute configurations are L-$(+)$-lactic acid and L-$(+)$-alanine.



When there are several chiral carbons in a molecule, the configuration at one center usually is related directly or indirectly to glyceraldehyde, and the configurations at the other centers are determined relative to the first. Thus in the aldehyde form of the important sugar, $(+)$-glucose, there are *four* chiral centers, and so there are $2^4 = 16$ possible stereoisorners. The projection formula of the isomer that corresponds to the aldehyde form of natural glucose is 4. By convention for sugars, the configuration of the *highest-numbered chiral carbon* is referred to glyceraldehyde to determine the overall configuration of the molecule. For glucose, this atom is C_5, next to the CH_2OH group, and has the hydroxyl group on the right. Therefore, naturally occurring glucose, which has a $(+)$ rotation, belongs to the D series and is properly called D-$(+)$-glucose:



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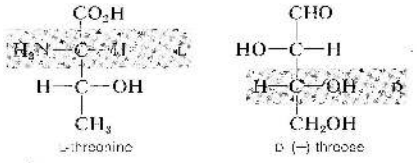
However, the configurations of α-amino acids possessing more than one chiral carbon are determined by the *lowest*-numbered chiral carbon, which is the carbon *alpha* to the carboxyl group. Thus, even though the natural α-amino acid, threonine, has exactly the same kind of arrangement of substituents as the natural sugar, threose, threonine by the amino-acid convention belongs to the L -series, whereas threose by the sugar convention belongs to the D-series:



A serious ambiguity arises for compounds such as the active tartaric acids. If the amino-acid convention is used, $(+)$-tartaric acid falls in the D series; by the sugar convention, it has the L configuration. One way out of this dilemma is to use the subscripts s and g to denote the amino-acid or carbohydrate conventions, respectively. Then the absolute configuration of $(+)$-tartaric acid can be designated as either D_s-$(+)$-tartaric acid of L_g-$(+)$-tartaric acid.

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19.6: The R,S Convention for Designating Stereochemical Configurations

There are certain disadvantages to the *D*,*L* system using Fischer projection formulas to denote configuration about a chiral center, and we already have seen how ambiguity arises in the case of the tartaric acids (Section 19-5). A more systematic way of denoting configuration that may eventually replace the *D*,*L* system, at least for simple compounds, is known as the *R*,*S* or Cahn-Ingold-Prelog convention, after its originators.

To denote the configuration of a chiral center by the *R*,*S* convention, the groups at the center are assigned an order of precedence according to a specific set of rules based on atomic numbers. Suppose a carbon atom is bonded to four different substituents, which we will designate *A*,*B*, *C*, and *D* and to which we assign the following priority sequences: *A* before *B* before *C* before *D*. If we now view the arrangement of *A*, *B*, and *C* from the site remote from the substituent of *lowest* priority, *D*, as shown in Figure 19-6, and the sequence turns out to be $A \rightarrow B \rightarrow C$ in the *clockwise* direction, then the configuration is said to be *R*. If the sequence $A \rightarrow B \rightarrow C$ occurs in the counterclockwise direction, the configuration is *S*. The symbols *R* and *S* are taken from the Latin words *rectus* and *sinister*, meaning right and left, respectively.

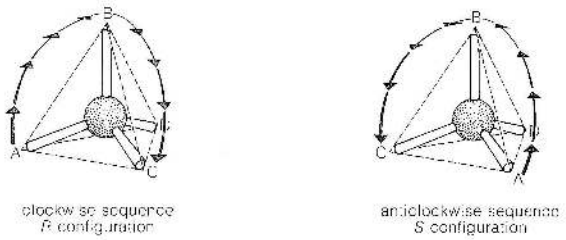
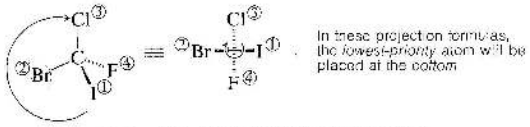


Figure 19-6: Designation of configuration about an asymmetric center by the *R*,*S* system. Substituent priority decreases in the order *A*, *B*, *C*, *D*.

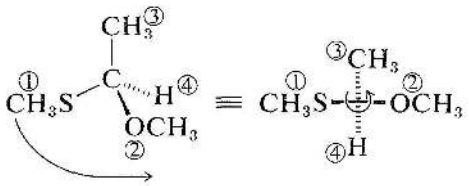
The understanding of *R* and *S* is simple; the problems are in assigning the priority sequences for actual substituents. The rules follow:

1. *Priority is given to the substituent atoms that have the highest atomic number*. This means that four different atoms arranged tetrahedrally about the chiral center have a priority sequence that decreases with decreasing atomic number. For example, the sequence among the halogens is I > Br > Cl > F, and Structure 5 (shown here in perspective and in projection) therefore has the *R* configuration:



5 1 ⟶ 2 ⟶ 3 clockwise = *R* configuration

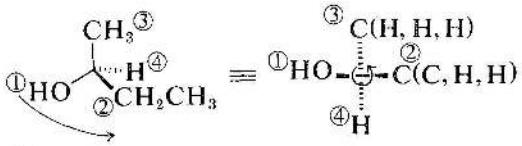
For more complex substituents, *priority is determined by the atomic number of the first bonded atom*. The sequence CH_3S > CH_3O > NH_2 > CH_3 > H thus reflects the fact that atomic number decreases in the order S > O > N > C > H. Structure 6 accordingly has the *S* configuration:



6 1 ⟶ 2 ⟶ 3 counterclockwise = *S* configuration

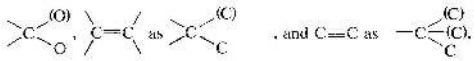
2. The first atoms in two or more substituents often are identical, in which case it is necessary to explore further and compare the atomic numbers of the second attached atoms. *Precedence is given to the substituent with a second atom of higher atomic number*. For example, in 2-butanol, $CH_3CH(OH)CH_2CH_3$, two of the groups at the chiral atom have carbon as the first atom. We therefore must compare the other atoms bonded to these two carbons. It is convenient to represent the arrangement at the

chiral atom as shown in 7, where the first atoms are shown attached to the chiral center and the second atoms are listed in their priority order; thus, (C, H, H) for ethyl and (H, H, H) for methyl:

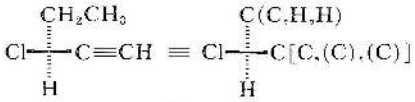


7 1 ⟶ 2 ⟶ 3 anticlockwise = *S* configuration

When we compare (H, H, H) with (C, H, H) in 7, we give ethyl precedence over methyl because carbon has a higher atomic number than hydrogen. The configuration 7 therefore must be *S*.

3. Double and triple bonds are treated as if they had duplicate or triplicate single bonds. Thus a carbonyl group, , is treated as if it were  where the symbols in parentheses represent the duplicate atoms.

Let us see how this works for 3-chloro-1-pentyne, 8:

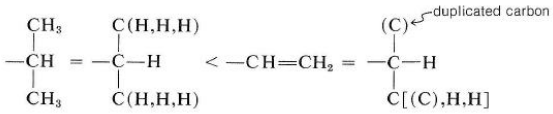


8

The first-atom priority sequence is Cl > C and C > H. We now need to order $-CH_2CH_3$ and $-C\equiv CH$ and, in doing this, we compare the three atoms attached to the first carbon of the ethyl group (C, H, H) with the three attached to the first carbon of the ethynyl group [C, (C), (C)]. On this basis, ethynyl comes ahead of ethyl, and the overall sequence is $Cl > C\equiv CH > CH_2CH_3 > H$, so 8 will have the *S* configuration.

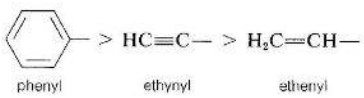
The sequence rules described thus far can be used without ambiguity in most of the examples we are likely to meet. The important thing to remember is to look at the kind of atoms attached as far out as necessary. Suppose we have to compare the aldehyde group, $-CH{=}O$, with the dimethoxymethyl group, $CH(OCH_3)_2$. The first atoms are the same (C), the second atoms are the same [O, (O), H], and the difference arrives at the third-atom level where we are comparing lone pairs (priority zero) with carbons. Thus $-CH(OCH_3)_2$, outranks $-CH{=}O$.

Comparison of groups such as isopropyl and ethenyl is more difficult and requires knowing what the convention is when we have to go to the far end of a double bond. A useful way of writing these groups is as follows:



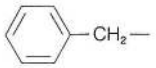
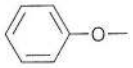
We put ethenyl ahead of isopropyl because [(C), H, H] takes priority over (H, H, H). It is important to understand that the nonduplicated carbon is considered to be connected to the duplicated carbon as well as the two hydrogens in arriving at the connection pattern ((C), H, H).

The same kind of logic leads to the following sequence:

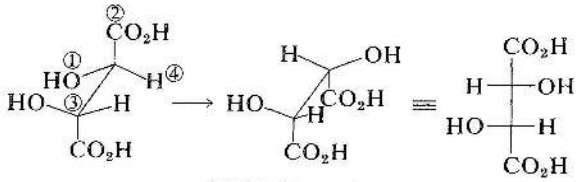


A more comprehensive list of priorities among groups is given in Table 19-1. It will be a good exercise to go through this list and work out how the priorities are established.

***Table 19-1**: Some Common Groups in Order of Increasing Sequence-Rule Preference*

No.	Substituent name	Structure	No.	Substituent name	Structure
0	lone pair				
1	hydrogen	H	19	methoxycarbonyl	$CH_3O-\overset{\overset{O}{\|}}{C}-$
2	deuterium	^2H, *d*, or D	20	amino	H_2N-
3	methyl	CH_3-	21	methylamino	CH_3NH-
4	ethyl	CH_3CH_2-	22	dimethylamino	$(CH_3)_2NH-$
5	2-propenyl	$CH_2{=}CHCH_2-$	23	nitro	O_2N-
6	2-propynyl	$HC{\equiv}CCH_2-$	24	hydroxy	$HO-$
7	phenylmethyl		25	methoxy	CH_3O-
8	isopropyl	$(CH_3)_2CH-$	26	phenoxy	
9	ethenyl	$CH_2{=}CH-$			
10	cyclohexyl		27	ethanoyloxy	$CH_3-\overset{\overset{O}{\|}}{C}-O-$
			28	fluoro	$F-$
11	1-propenyl	$CH_3CH{=}CH-$	29	mercapto	$HS-$
12	*tert*-butyl	$(CH_3)_3C-$	30	methylthio	CH_3S-
13	ethynyl	$HC{\equiv}C-$			
14	phenyl		31	methylsulfinyl	$CH_3-\overset{\overset{O}{\|}}{S}-$
15	1-propynyl	$CH_3C{\equiv}C-$	32	methylsulfonyl	$CH_3-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-$
16	methanoyl	$H-\overset{\overset{O}{\|}}{C}-$	33	sulfo	$HO-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-$
17	ethanoyl	$CH_3-\overset{\overset{O}{\|}}{C}-$	34	chloro	$Cl-$
			35	bromo	$Br-$
18	carboxyl	$HO-\overset{\overset{O}{\|}}{C}-$	36	iodo	$I-$

If more than one chiral center is present, the configuration at each is specified by the symbol R or S together with the number of the chiral atom. Thus the configuration of $(+)$-tartaric acid is known to be that designated in the name $(2R,3R)$-$(+)$-tartaric acid:



The R,S system is quite general and has many advantages (and a few disadvantages) compared with the D,L notation for simple molecules. For diastereomers, it provides much clearer notations than *meso*, *erythro*,[1] and *threo*[1] that have been used for many years to designate the configurations of achiral and chiral diastereomers having two chiral carbon atoms:

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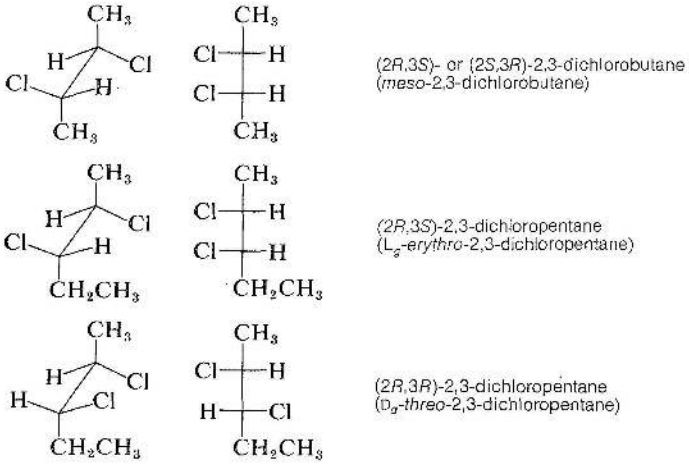
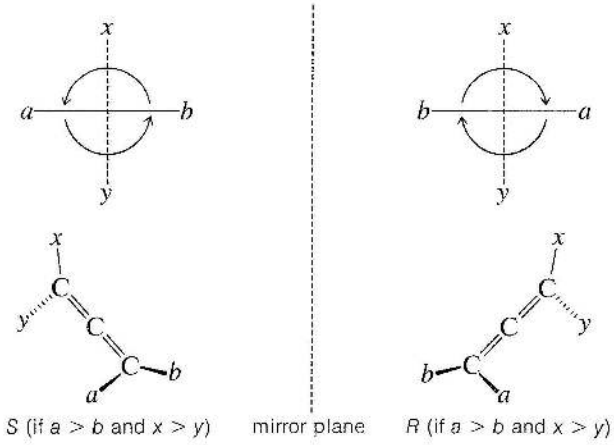


The R,S system can be used to designate the configuration of a molecule with no chiral carbons but with a chiral center as, for example, a chiral 1,2-diene (Section 13-5A). To do this for a 1,2-diene, the molecule is best drawn in projection, looking along the C=C=C bond with the *highest-ranking* group in *front*. The bonds in the rear will then project at 90° to the bonds of the groups in front. For a 1,2-diene, *ab*C=C=C*xy*, where is the highest ranking group, the possible enantomeric projections are:



We now determine the priority of the groups and then assign the configurations R and S as shown, provided that the highest-ranking group is in front and $a > b$ and $x > y$. In proceeding this way, it is important to recognize that no matter what the priority is of the group b based on atomic number, *b always outranks a rear group* so that the priority sequence is $a \rightarrow b \rightarrow x$ with R clockwise and S counterclockwise.

[1]The prefixes *erythro* and *threo* are used for configurations of compounds with two differently substituted chiral carbons having similar groups on each carbon. If in the Fischer projection formula the similar groups are on the same side, the configuration is *erythro*. If the similar groups are on opposite sides, the configuration is *threo*.

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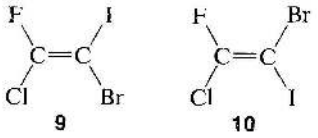
19.7: E,Z Notation

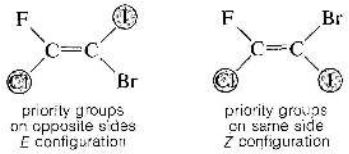
The configuration about double bonds is undoubtedly best specified by the cis-trans notation when there is no ambiguity involved. Unfortunately, many compounds cannot be described adequately by the cis-trans system. Consider, for example, configurational isomers of 1-fluoro-1-chloro-2-bromo-2-iodo-ethene, 9 and 10. There is no obvious way in which the cis-trans system can be used:



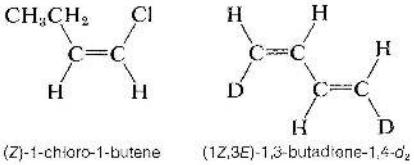
9 10

A system that is easy to use and which is based on the sequence rules already described for the *R*,*S* system works as follows:

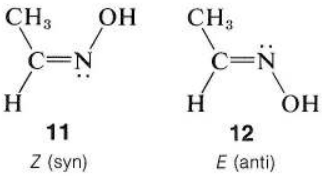
1. An order of precedence is established for the two atoms or groups attached to *each* end of the double bond according to the sequence rules of Section 19-6. When these rules are applied to 1-fluoro-1-chloro-2-bromo-2-iodoethene, the priority sequence is:
    - at carbon atom 1, $\mathrm{Cl} > \mathrm{F}$
    - at carbon atom 2, $\mathrm{I} > \mathrm{Br}$
2. Examination of the two configurations shows that the two priority groups - one on *each* end - are either on the same side of the double bond or on opposite sides:



The *Z* isomer is designated as the isomer in which the top priority groups are on the *same* side (*Z* is taken from the German word *zusammen* - together). The *E* isomer has these groups on *opposite* sides (*E*, German for *entgegen* - across).[2] Two further examples show how the nomenclature is used:



This system is especially useful for oximes, which have the structural feature $-\mathrm{C{=}N{-}OH}$. The two possible configurations at the double bond in the oxime of ethanal are 11 and 12:



The cis-trans notation does not work well here, and structure 11 has the *Z* configuration and 12 the *E* configuration. In the older chemical literature, these stereoisomers were designated as *syn* and *anti* forms, but these names are really no better than *cis* and *trans*.

[2]It would have been simpler to remember if *E* stood for *same side* and *Z* for *opposite side*, but it is too late now.

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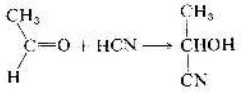
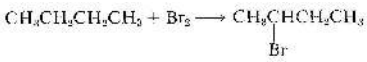
19.8: Prochirality

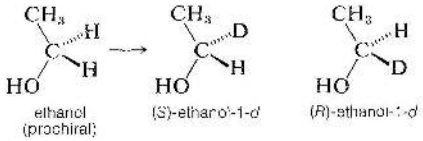
In the transformations shown in Equations 19-5 and 19-6, the organic reactants are symmetrical molecules (with no chiral centers), but the products are asymmetric molecules (each has a chiral carbon):



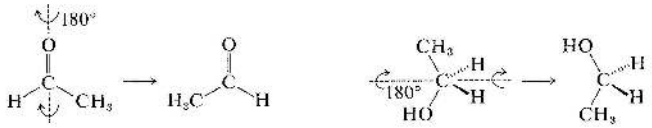


There is a special term for molecules that are achiral but which can be converted to molecules with chiral centers by a single chemical substitution or addition reaction. They are said to be **prochiral**.

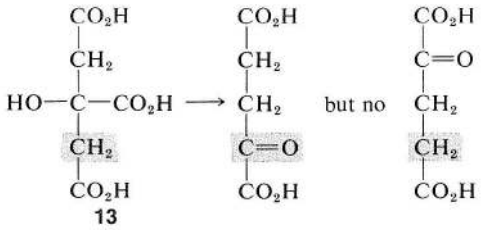
By this definition, ethanol is a prochiral molecule. The two methylene hydrogens are *enantiotopic* (Section 9-10C) and substituting each separately (with, say, one deuterium) leads to a pair of enantiomers:



Prochiral molecules can be distinguished readily from more symmetrical molecules because they lack a two-fold symmetry axis passing through the prochiral center, as the following rotations show:



Organic chemists have not had much use for *prochirality*, but it is an important concept for biochemists following the stereochemistry of bio-organic reactions. Almost all biochemical reactions are under the control of enzymes, which function asymmetrically even on symmetrical (but prochiral) molecules. Thus it has been found that only one of the two methylene groups of citric acid, 13, is converted by enzymes (from rat liver) to the carbonyl of 2-oxobutanedioic acid:



The notation *prochiral center* is useful in molecules that already have one or more chiral centers. Development of chirality from prochirality in such cases would lead to diastereomers, as shown in the conversions of 14 and 15:

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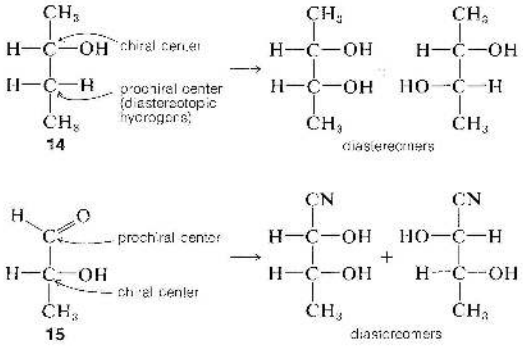

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19.9: Optical Rotatory Dispersion and Circular Dichroism

Optical rotations usually are measured at just one wavelength, namely $589.3\ \text{nm}$, simply because sodium-vapor lamps provide an especially convenient source of monochromatic light. Measurements at other wavelengths are less easily made without specialized instruments, with which relatively few laboratories are currently equipped. Nevertheless, much information has been obtained about structure, conformation, and configuration of organic compounds from measurements of optical rotation as a function of wavelength (i.e., **optical rotatory dispersion**).

Like other phenomena involving interactions between electromagnetic radiation and organic molecules, as in infrared, ultraviolet, and nmr spectroscopy, optical rotatory dispersion curves often are quite sensitive to small changes in structure. As an example, the rotatory dispersion curves for enantiomers of *cis*- and *trans*-10-methyl-2-decalones, 16 and 17, are reproduced in Figure 19-7:

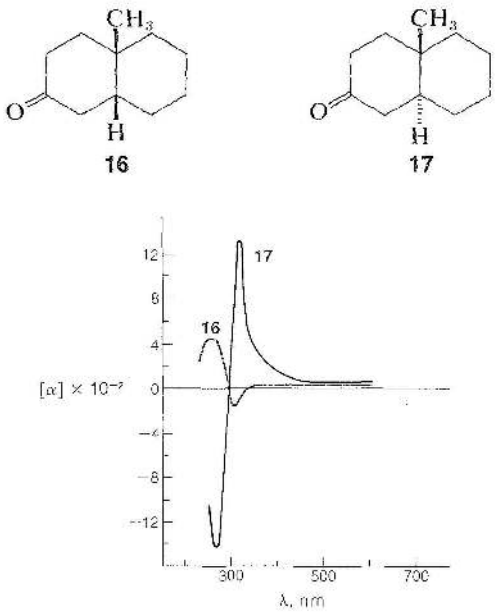


Figure 19-7: Rotatory dispersion curves for cis-10-methyl-2-decalone, 16, and trans-10-methyl-2-decalone 17. *(By permission from C. Djerassi, O*ptical Rotatory Dispersion, *McGraw-Hill Book Co., New York, 1960.)*

Only a small positive rotation is observed for the particular enantiomers at the wavelength of the sodium line $(589.3\ \text{nm})$ compared to the large, both positive and negative, rotations found at wavelengths between $270\ \text{nm}$ and $400\ \text{nm}$. If we measure the rotations as a function of wavelength and if, as we approach shorter wavelengths, the rotation rises to a *maximum* before changing sign, as it does with the trans isomer, 17, then the compound is said to exhibit a **positive Cotton effect**. The opposite behavior, as with the cis isomer, 16, is called a **negative Cotton effect**. The wavelength at the center point for the very rapid change in rotation for 17 is $300\ \text{nm}$ and corresponds to the $n \rightarrow \pi^*$ absorption maximum of the carbonyl group in the ultraviolet absorption curve of the same compound. Thus excitation of the carbonyl group by absorption of ultraviolet light and strong rotatory dispersion of polarized light are associated phenomena. In fact, when a substance exhibits a Cotton effect, not only does it transmit clockwise and counterclockwise circularly polarized light with unequal velocities (Section 19-1), it also absorbs the two forms of light unequally.

This means that the molar extinction coefficients of the two enantiomers (ϵ_l and ϵ_r) are unequal in circularly polarized light. These differences in absorption (ϵ_l and ϵ_r) can be measured as a function of wavelength, and the curves obtained are called **circular dichroism** curves. They have positive or negative signs (Cotton effect) just as for optical rotatory dispersion curves.

Most of the research on optical rotatory dispersion to date has been with optically active ketones because the carbonyl chromophore conveniently has a weak absorption band in the $300\ \text{nm}$ region. Compounds with chromophores that absorb light *strongly* in the ultraviolet usually are unsatisfactory for rotatory dispersion measurements because insufficient incident light is transmitted to permit measurement of optical rotation. Weak absorption bands below about $210\ \text{nm}$ have not been exploited because of experimental difficulties in making the necessary measurements.

Many rotatory dispersion curves have been obtained for optically active ketones derived from steroids and triterpenes, which are monocyclic, bicyclic, and open-chain compounds. Enough data have been accumulated so that the various shapes and magnitudes of the curves are recognized as characteristic of particular structural features. A good illustration is provided by the rotatory dispersion curves for the *cis*- and *trans*-8-methylhydrindan-5-ones, 18 and 19, which are shown in Figure 19-8:

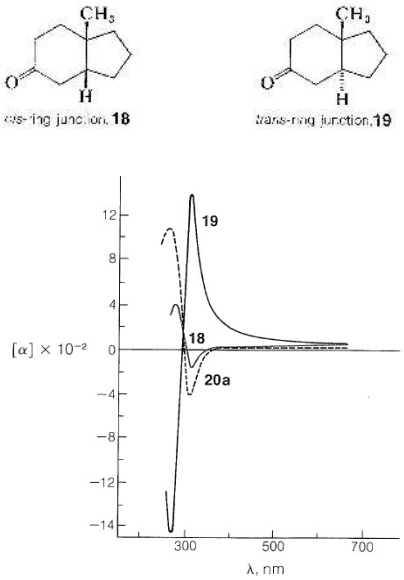
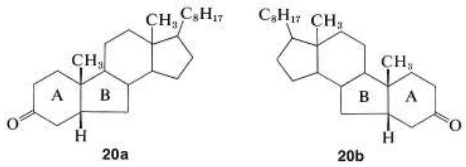


Figure 19-8: Rotatory dispersion curves for trans-8-methylhydrindan-5-one, 19, cis-8-methylhydrindan-5-one, 18, *and* B-*norcoprostan-3-one*, 20*a*. *(By permission from C. Djerassi*, Optical Rotatory Dispersion, *McGraw-Hill Book Co., New York, 1960.)*

The remarkable differences in these curves are due to changes in the environment of the carbonyl groups arising from the different configurations of the hydrogens at the ring junctions. Because the rotatory dispersion curve of the closely related structure 20*a* is very similar to that of the *cis*-hydrindanone, 18, the rings labeled *A* and *B* in 20*a* can be inferred also to be cis oriented (see Figure 19-8):



Rotatory dispersion curves often are helpful in establishing configurations; thus the relative configurations of compounds 18 and 20*a* must be the same because, if they were not, the two curves would resemble mirror images of one another. Therefore, if the absolute configuration of 18 corresponds to the formula shown, then compound 20*a* has the configuration shown and not 20*b*.

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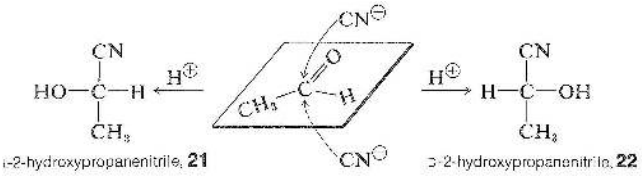
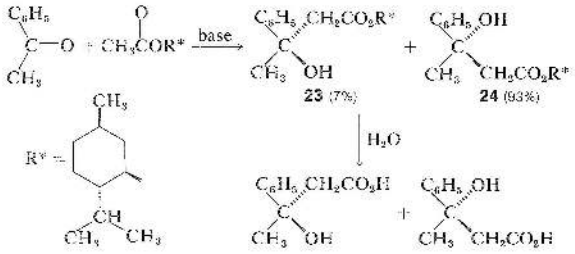
19.10: Asymmetric Synthesis

If one could prepare 2-hydroxypropanenitrile from ethanal and hydrogen cyanide in the absence of any chiral reagent and produce an excess of one enantiomer over the other, this would constitute an **absolute asymmetric synthesis** - that is, creation of preferential chirality (optical activity) in a symmetrical environment from symmetrical reagents:



This obviously is unlikely for the given example because there is no reason for cyanide ion to have anything other than an exactly equal chance of attacking above or below the plane of the ethanal molecule, producing equal numbers of molecules of the enantiomers, 21 and 22. However, when a chiral center is created through reaction with a dissymmetric (chiral) reagent, we should not expect an exactly 1:1 mixture of the two possible isomers. For example, in an aldol-type addition (Section 18-8E) of a chiral ester to a prochiral ketone the two configurations at the new chiral center in the products 23 and 24 are not equally favored. That is to say, asymmetric synthesis is achieved by the influence of one chiral center (R^*) on the development of the second:



You will notice that the reaction products 23 and 24 are diastereomers, not enantiomers. Asymmetric synthesis can be achieved only when the possible transition states for reaction are diastereomeric because they then will have different energies and will lead to products at different rates. The larger the energy difference between diastereomeric transition states, the more stereochemical preference there will be for one chirality over the other.

The degree of stereochemical control displayed by the first chiral center usually depends on how close it is to the second - the more widely separated they are, the less steric control there is. Another factor is the degree of electronic control. If all the groups are very much the same electrically and sterically, not much stereochemical control is to be expected. Even when the chiral centers are close neighbors, asymmetric induction is seldom 100% efficient in simple molecules. In biochemical systems, however, asymmetric synthesis is highly efficient.

The stereospecificity of living organisms is imperative to their efficiency. The reason is that it is just not possible for an organism to be so constructed as to be able to deal with all of the theoretically possible isomers of molecules with many asymmetric centers. Thus a protein molecule not uncommonly has 100 or more different asymmetric centers; such a molecule would have 2^{100} or 10^{30} possible optical isomers. A vessel with a capacity on the order of 10^7 liters would be required to hold all of the possible stereoisomeric molecules of this structure if no two were identical. An organism so constituted as to be able to deal specifically with each one of these isomers would be very large indeed.

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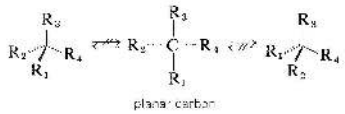
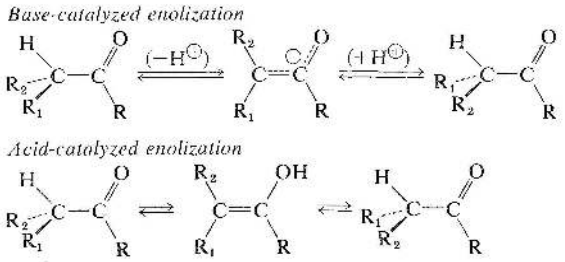
19.11: Racemization

Optically active biphenyl derivatives (Section 13-5A) are racemized if the two aromatic rings at any time pass through a coplanar configuration by rotation about the central bond. This can be brought about more or less easily by heat, unless the 2,2'-*ortho* substituents are very large.

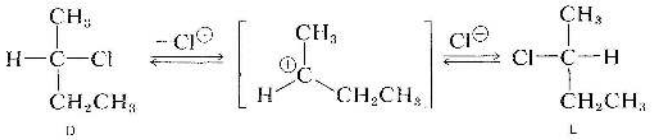
The way in which compounds with asymmetric carbon atoms are racemized is more complicated. One possibility would be for a tetrahedral chiral carbon attached to *four* groups to become planar and achiral without breaking any bonds. Theoretical calculations indicate that this is not a likely process for chiral tetravalent carbon but, as we will see, it does occur with chiral carbon and other chiral atoms that are attached to *three* groups:



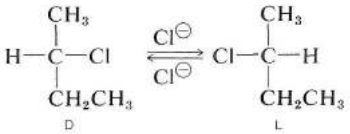
Optically active carbonyl compounds of the type $-CHC{=}O$, in which the *alpha* carbon is asymmetric, are racemized by both acids and bases, and from Section 17-1 we can be sure that this is related to enolization. Formation of either the enol or the enolate anion will destroy the asymmetry of the α carbon so that, even if only trace amounts of enol are present at any given time, eventually all of the compound will be racemized. However, the mechanism requires both that there be an α hydrogen and that the center of symmetry be located at this α carbon. Otherwise, acids and bases are ineffective in catalyzing racemization.



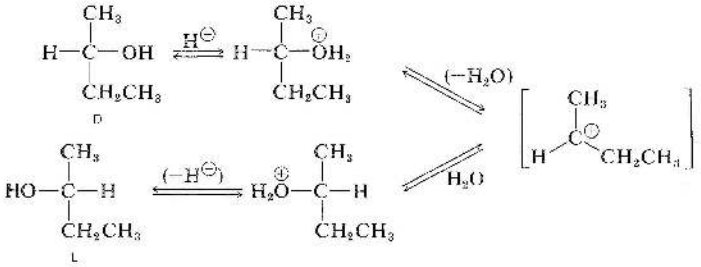
The racemization of an optically active secondary halide with the chiral carbon carrying the halogen (e.g., 2-chlorobutane) may occur ih solution and, usually, the more polar and better ionizing the solvent is, the more readily the substance is racemized. Ionization of the halide by an S_N1 process probably is responsible, and this certainly would be promoted by polar solvents (Section 8-6). All indications are that an alkyl carbocation once dissociated from its accompanying anion is planar; and, when such an ion recombines with the anion, it has equal probability of forming the D and L enantiomers:



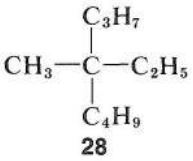
Optically active halides also can be racemized by an S_N2 mechanism. A solution of active 2-chlorobutane in 2-propanone containing dissolved lithium chloride becomes racemic. Displacement of the chloride of the halide by chloride ion inverts configuration at the atom undergoing substitution (see Section 8-5). A second substitution regenerates the original enantiomer. Eventually, this back-and-forth process produces equal numbers of the D and L forms; the substance then is racemic:



Asymmetric alcohols often are racemized by strong acids. Undoubtedly, ionization takes place, and recombination of the carbocation with water leads to either enantiomer:

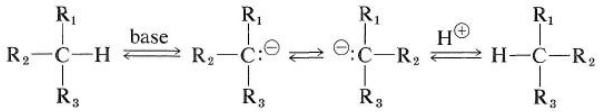


In contrast to halides, alcohols, and carbonyl compounds, hydrocarbons may be extremely difficult to racemize. This is particularly true for a compound with a quaternary asymmetric center, such as methylethylpropylbutylmethane, 28, which has no "handle" to allow one to convert the asymmetric carbon to a symmetric condition by simple chemical means:



28

However, hydrocarbons that have a hydrogen atom at the asymmetric carbon may be racemized if they can be converted either to carbocations or to carbanions. The ease of carbanion-type racemization will depend on the acidity of the attached hydrogen and on the stereochemical stability of the intermediate carbanion that is formed. If the configuration of the carbanion intermediate inverts, racemization will result (also see Section 6-4E):



The carbocation type of racemization of an optically active hydrocarbon can occur by the exchange reaction described in Section 10-9.

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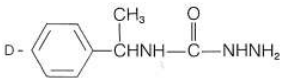
19.E: More on Stereochemistry (Exercises)

Exercise 19-1 Indicate the reagents you would use to resolve the following compounds. Show the reactions involved and specify the physical method you believe would be the best to separate the diastereomers.

a. 1-phenyl-2-propanamine
b. 2,3-pentadienedioic acid
c. 1-phenylethanol

Exercise 19-2 Using equations, show the reactions whereby the following chiral reagents could be used to resolve aldehydes and ketones. (Review Sections 15-4E and 16-4C.)

a. (2*D*, 3*L*)-2,3-butanediol

b. 

Exercise 19-3 The specific rotation of optically pure 2-methylbutanoic acid is $[\alpha]_D \pm 19.34^\circ$ (neat) $(t = 21^\circ)$. Assume that you resolved the racemic acid with $(+)$-1-phenylethanamine and obtained a rotation for the product of $+10.1^\circ$ (neat) $(t = 21^\circ)$; calculate the enantiomeric purity (in percent) of the resolved acid. What results would you anticipate if you used the $(-)$-amine in place of the $(+)$-amine? What effect on your resolution would there be if the resolving agent contained 90% of the $(+)$-amine and 10% of the \(\left(- \right)-amine?

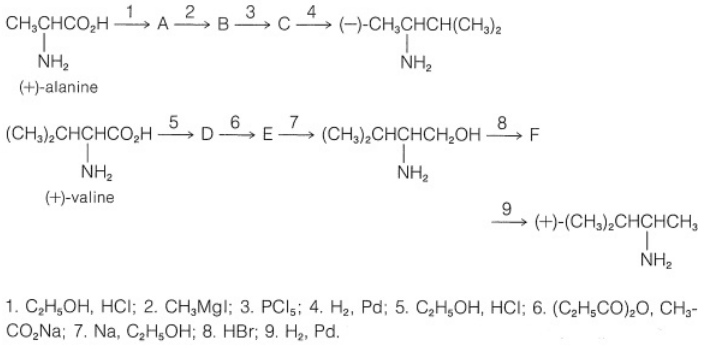
Exercise 19-4 Suppose one were to try to resolve a mixture of *D*-2-butyl *D*-2-methoxypropanoate and *L*-2-butyl *D*-2-methoxypropanoate by careful fractional distillation. How could one follow the degree of separation of these two diastereomers by proton NMR? Be sure to explain exactly what you would be looking for in the NMR spectra and which peaks could be most helpful.

Exercise 19-5 When optically active 1-phenylethanamine is dissolved in *racemic* 1-phenyl-2,2,2-trifluoroethanol, the $^{19}\mathrm{F}$ NMR resonance shows two sets of doublets separated by $2\ \mathrm{Hz}$ at $56\ \mathrm{MHz}$. With the racemic amine, only a doublet $^{19}\mathrm{F}$ resonance is observed.

a. Explain the difference between the $^{19}\mathrm{F}$ NMR spectra in the optically active and racemic solvents. (Don't forget the $-\mathrm{CH}-\mathrm{CF_3}$ spin-spin splitting.)

b. How could such spectra be used to follow the progress of an attempt to resolve 1-phenyl-2,2,2-trifluoroethanol into its enantiomers?

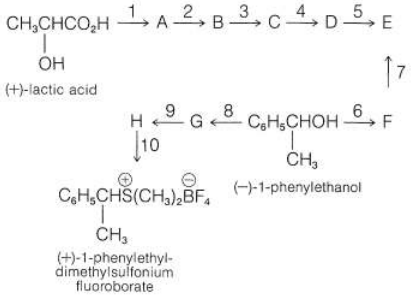
Exercise 19-6 $(+)$-Alanine and $(+)$-valine have been related in configuration by the following reaction sequence:



1. C_2H_5OH, HCl; 2. CH_3MgI; 3. PCl_5; 4. H_2, Pd; 5. C_2H_5OH, HCl; 6. $(C_2H_5CO)_2O$, CH_3CO_2Na; 7. Na, C_2H_5OH; 8. HBr; 9. H_2, Pd.

Show the structure and configuration of the products in each step, given that $(+)$-alanine has the *L* configuration. Is the configuration of $(+)$-valine *D* or *L*?

Exercise 19-7 $(+)$-Lactic acid has the *L* configuration. On the basis of the following transformations, deduce the absolute configurations of $(-)$-1-phenylethanol and $(+)$-1-phenylethyldimethylsulfonium fluoroborate. Write equations to show the structure and configuration of the products in each step. Reactions 5 and 7 both give E with the same sign of rotation.

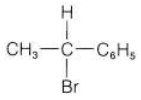


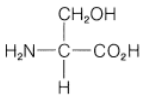
1. C_2H_5OH, HCl; 2. CH_3I, Ag_2O; 3. $BrMg(CH_2)_5MgBr$; 4. H_3PO_4, heat; 5. H_2, Pt; 6. H_2, Ni, high pressure, heat; 7. K, CH_3I; 8. PCl_5; 9. $NaSCH_3$; 10. $(CH_3)_3\overset{\oplus}{O}\,BF_4^{\ominus}$.

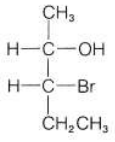
Exercise 19-8 Determine by the sequence rules the priority sequence in the pairs of groups listed.

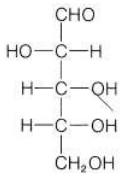
a. cyano, $C \equiv N$, vs. carboxamide, $-CONH_2$.
b. 2-methylcyclohexyl vs. 4,4-dimethylcyclohexyl
c. 1-propenyl vs. 2-butyl
d. phenyl vs. 1-cyclohexyl
e. chloromethyl vs. hydroxymethyl

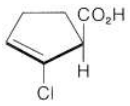
Exercise 19-9 Designate the configuration at each asymmetric carbon in each of the following projection or stereo formulas by both the *D*,*L* and *R*,*S* systems:

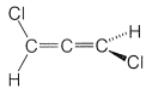
a.


b.


c.


d.


e.


f.


Exercise 19-10 Draw "saw-horse" and projection formulas for each of the following compounds, and designate whether the particular enantiomer is *erythro*, *threo*, *cis*, or *trans*:

a. (*S*)-hydroxyphenylethanoic acid
b. (1*R*,2*S*)-1,2-dimethylcyclopropane
c. (2*S*,3*S*)-3-bromo-2-butanol
d. (2*S*,3*R*)-3-amino-2-butanol

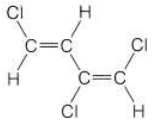
https://chem.libretexts.org/@go/page/22793

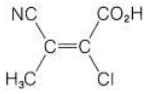
e. (1*S*,3*S*)-1,3-cyclohexanediol
f. (2*R*,3*R*)-2-chloro-2,3-dimethylpentanoic acid
g.* (*R*)-2,3-pentadiene

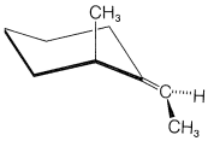
Exercise 19-11 Draw structures for the following compounds in order to unambiguously specify configuration:

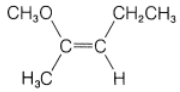
a. the *Z* isomer formed from the reaction of phenylmethanamine with 2-butanone
b. (2*E*,4*Z*)-3-chloro-2,4-hexadiene

Exercise 19-12 How would you name the compounds shown below in order to unambiguously specify both structure and configuration? Use the cis-trans system when possible. Notice that it is wrong to assume that *Z* will invariably be cis or *E* will be trans in the two systems.

a. 

b. 

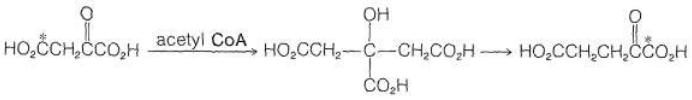
c. 

d. 

Exercise 19-13* Designate which of the following structures are chiral, prochiral, and/or achiral. Specify which carbon atoms are prochiral centers.

a. ethenylbenzene (styrene)
b. *cis*-2-butene
c. 2-propanone (acetone)
d. 2-butanone
e. glycine, $H_2NCH_2CO_2H$
f. butanedioic acid, $(CH_2CO_2H)_2$
g. 2-methylbutanedioic acid, $CH_3CH(CH_2CO_2H)CO_2H$
h. 1-chloro-2-phenylethane

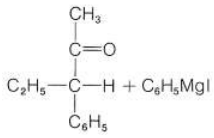
Exercise 19-14* One part of the citric acid cycle (Sections 18-8F and 20-10B) in metabolism converts 2-oxobutanedioic acid by way of citric acid to 2-oxopentanedioic acid:



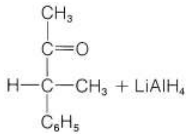
If the 4-carboxyl carbon of the 2-oxobutanedioic acid is enriched in ^{13}C, only the 1-carboxyl carbon of the 2-oxopentanedioic acid contains excess ^{13}C. Explain in general terms how the intermediate citric acid must be labeled to have the ^{13}C turn up in the 1-carboxyl of the 2-oxopentanedioic acid.

Exercise 19-15 Write structures showing the configuration of each of the possible products to be expected from the following reactions.

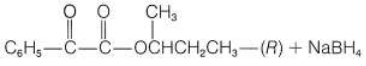
a.



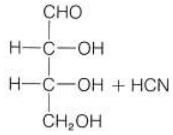
b.



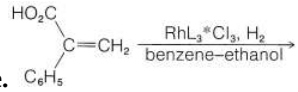
c.



d.



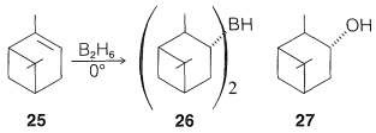
e.



(L^* is a chiral phosphorus ligand attached to Rh)

Exercise 19-16

a. When (+)-α-pinene, 25, reacts with diborane, a dialkylborane, 26, is formed:

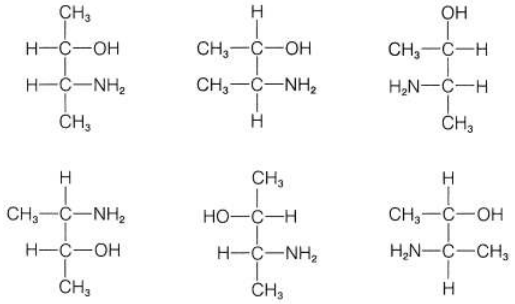


25 26 27

When 26 reacts with *cis*-2-butene in $CH_3OCH_2CH_2OCH_2CH_2OCH_3$ as solvent, a trialkylborane is produced. Oxidation of this product with H_2O_2 yields isopinocampheol, 27, and (−)-2-butanol in 76% enantiomeric purity. Write equations for these reactions and account for the observed asymmetric synthesis.

b. 3-Methylcyclopentene can be partially resolved by reaction with less than an equimolar amount of 25. The residual alkene has an optical activity corresponding to about 65% enantiomeric purity. Explain how this partial resolution arises. Why is it necessary to use less than an equivalent of 25?

Exercise 19-17. Which of the following projection formulas represent the same isomer? Write each in its proper form as a Fischer projection formula of 3-amino-2-butanol.



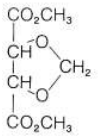
Exercise 19-18. Draw Fischer projection formulas for all the possible different configuration isomers of the following substances:

a. 1,2,3,4-tetrachlorobutane
b. methylethylpropylboron
c. 2,3-dibromopropanoic acid

d. 3-bromo-2,5-hexanediol

e. methyl hydrogen tartrate (a half-ester)

f. *sec*-butyl lactate

g. 

Exercise 19-19 Predict the stereochemical configuration of the products from each of the following reactions. Write projection formulas for the starting materials and products.

a. *D*-2-butanol with ethanoic anhydride

b. *D*-2,3-dimethyl-3-hexanol with hydrochloric acid

c. a chiral monoethanoate ester of 1,2,3-propanetriol (with the *D* configuration) and aqueous sodium hydroxide

d. *D*-2-bromobutane with sodium cyanide

e. *D*-2,2,4-trimethyl-3-hexanone with bromine and dilute base

f.* *D*-4-methyl-3-hexanone with methylmagnesium bromide

Exercise 19-20 Write projection formulas for the following compounds and rename them by the *R*,*S* system:

a. *threo*-1,2-diphenyl-1-bromo-2-chloroethane

b. *erythro*-3-deuterio-2-butanol (or *erythro*-2-butanol-3-^{2}H)

c. *meso*-2,3-dimethylbutanedioic acid

d. the diastereomers of the salt from *D*,*L*-1-phenylethanamine and *D*-2-hydroxybutanedioic acid (hydroxysuccinic acid)

Exercise 19-21 Explain how one could use techniques for resolution of enantiomers to determine experimentally whether hydrogen peroxide in methanoic acid adds cis or trans to cyclopentene, assuming the possible addition products to be unknown.

Exercise 19-22 Devise a reaction scheme for relating the configuration of (+)-2-butanol to glyceraldehyde. Think carefully about the reaction mechanisms involved in devising your scheme.

Exercise 19-23 Discuss possible procedures for resolution of ethyl *D*,*L*-lactate (ethyl 2-hydroxypropanoate bp 155°) into ethyl *D*-lactate and ethyl *L*-lactate.

Exercise 19-24 When *trans*-2-butene is treated with bromine, it yields a 2,3-dibromobutane which, with zinc in ethanol, regenerates *trans*-2-butene. Similarly, *cis*-2-butene gives a 2,3-dibromobutane, which yields *cis*-2-butene with zinc in ethanol.

a. Write projection formulas for all the different stereoisomeric 2,3-dibromobutanes.

b. From your knowledge of the mechanism of bromine addition to alkenes, predict which isomer of 2-butene would be formed from an optically active 2,3-dibromobutane with zinc. Show your reasoning in detail.

c. Write a mechanism for the reaction of zinc with 2,3-dibromobutane that is in agreement with the stereochemical result of the reaction.

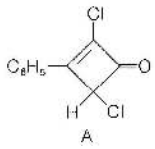
Exercise 19-25* *meso*-2,3-Dibromobutane is converted to quite pure *trans*-2-butene with potassium iodide in acetone, whereas *D*,*L*-2,3-dibromobutane gives *cis*-2-butene with the same reagent. In contrast, *meso*-1,2-dibromo-1,2-dideuterioethane yields only *cis*-1,2-dideuterioethene with potassium iodide in acetone. Explain how the different results can be reconciled without the necessity of postulating fundamentally different mechanisms for the elimination steps.

Exercise 19-26 It has been found that *meso*- and *D*,*L*-2,3-butanediols give different mixtures of 2-butanone and 2-methylpropanal on treatment with sulfuric acid. From consideration of the influence of steric hindrance on the detailed mechanism of the reaction, predict which butanediol diastereomer will give more 2-methylbutanal. (The vital stage of the reaction is likely to be where the migrating group is halfway between the old and new positions.)

Exercise 19-27* It has been stated that (+)-tartaric acid is "fully described" by the *D*-configuration because, if either asymmetric carbon is reduced to a CH_2 group, *D*-2-hydroxybutanedioic acid is formed. Which configuration would be assigned to (+)-tartaric

acid, if either one of the carboxyls were reduced to a methyl group, the hydroxyl next to the remaining carboxyl reduced to CH_2, and the product compared to *D*- and *L*-3-hydroxybutanoic acids?

Exercise 19-28* Compound A racemizes readily on heating to 100°, but the rate is *not* affected by chloride ion and is the *same* in chloroform and ethanoic acid. Racemization in deuterioethanoic acid (CH_3CO_2D) gives only undeuterated racemic A. Devise a mechanism for the reaction in accord with all the experimental facts.



A

Exercise 19-29 How could you tell whether a chloroform solution of an optically active compound showing a rotation of -100° was actually levorotatory by -100° or dextrotatory by $+260^{\circ}$?

Exercise 19-30 Solutions of optically active 2,2'-diiodobiphenyl-5,5'-dicarboxylic acid racemize at a measurable rate on heating. Racemization of active 2,3,2',3'-tetraiodobiphenyl- 5,5'-dicarboxylic acid goes many thousand times more slowly.

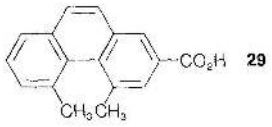
Make a scale drawing of the transition state (planar) for racemization; deduce from it the reason for the very slow racemization of the tetraiodo diacid. Use the following bond distances (note that the benzene ring is a regular hexagon):

$$\begin{aligned} \text{C—C (benzene ring)} &= 1.40\ \text{Å} \\ \text{C—C (between rings)} &= 1.47\ \text{Å} \\ \text{C—H} &= 1.07\ \text{Å} \\ \text{C—I} &= 2.05\ \text{Å} \end{aligned} \tag{19.E.1}$$

The van der Waals' radii of iodine and hydrogen are 2.15 Å and 1.20 Å, respectively.

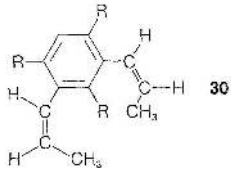
Exercise 19-31

a. Compounds of type 29 have been found to be resolvable into optically active forms. Explain.



29

b. How many stereoisomers would you predict could exist of structure 30, provided that the R groups were sufficiently large to prevent free rotation about the single bonds connecting the 1-propenyl groups to the ring?



30

Exercise 19-32 Consider the following transformations:

cyclohexanone-1-^{14}C $\xrightarrow{Cl_2,\ H^{\circ}plus}$ 2-chlorocyclohexanone-x-^{14}C $\xrightarrow{NaBH_4}$ *trans*-2-chlorocyclohexanol-x-^{14}C $\xrightarrow{\text{resolve}}$ (*R*)-*trans*-2-chlorocyclohexanol-x-^{14}C $\xrightarrow{NaOH}$ cyclohexene-x-^{14}C oxide $\xrightarrow{HCl}$ *trans*-2-chlorohexanol-x-^{14}C $\xrightarrow{\text{resolve}}$ (*R*)-*trans*-2-chlorocyclohexanol-x-^{14}C.

Write appropriate structural formulas for each substance, showing clearly at what position (x) the ^{14}C is located in each. If necessary, review Sections 15-11C and 15-11D.

19.E.1: Contributors

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CHAPTER OVERVIEW

20: Carbohydrates

Carbohydrates are a major class of naturally occurring organic compounds, which come by their name because they usually have, or approximate, the general formula $C_n(H_2O)_m$, with n equal to or greater than three. Among the well-known carbohydrates are various sugars, starches, and cellulose, all of which are important for the maintenance of life in both plants and animals. Although the structures of many carbohydrates appear to be quite complex, the chemistry of these substances usually involves only two functional groups - *ketone* or *aldehyde carbonyls* and *alcohol hydroxyl* groups. The carbonyl groups normally do not occur as such, but are combined with hydroxyl groups to form hemiacetal or acetal linkages of the kind discussed in Section 15-4E. An understanding of stereochemistry is particularly important to understanding the properties of carbohydrates. Configurational and conformational isomerism play an important role. For this reason, you may wish to review Chapter 5 and Sections 12-3 and 19-5.

20.1: Prelude to Carbohydrates
20.2: Classification and Occurrence of Carbohydrates
20.3: The Structure and Properties of D-Glucose
20.4: Conventions for Indicating Ring Size and Anomer Configurations of Monosaccharides
20.5: Derivatives of Glucose
20.6: Glycosides
20.7: Disaccharides
20.8: Polysaccharides
20.9: Vitamin C
20.10: Formation of Carbohydrates by Photosynthesis
20.11: The Generation of Energy from Carbohydrate Metabolism
20.E: Carbohydrates (Exercises)

20.1: Contributors and Attributions

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20.1: Prelude to Carbohydrates

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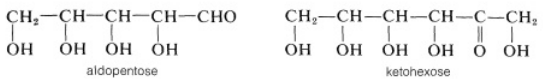
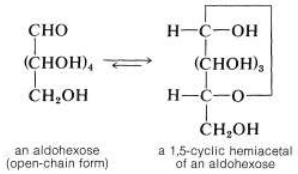
20.2: Classification and Occurrence of Carbohydrates

The simple sugars, or **monosaccharides**, are the building blocks of carbohydrate chemistry. They are polyhydroxy aldehydes or ketones with five, six, seven, or eight carbon atoms that are classified appropriately as **pentoses**, **hexoses**, **heptoses**, or **octoses**, respectively. They can be designated by more specific names, such as **aldohexose** or **ketohexose**, to denote the kind of carbonyl compound they represent. For example, and aldopentose is a five-carbon sugar with an aldehyde carbonyl; a ketohexose is a six-carbon sugar with a ketone carbonyl:

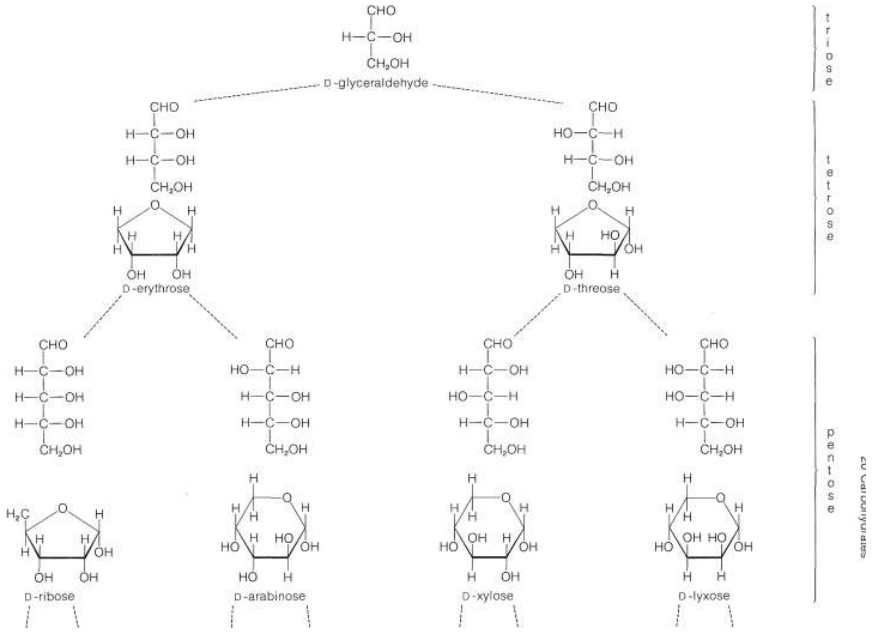


However, it is important to keep in mind that the carbonyl groups of sugars usually are combined with one of the hydroxyl groups in the same molecule to form a cyclic hemiacetal or hemiketal. These structures once were written as follows, and considerable stretch of the imagination is needed to recognize that they represent oxacycloalkane ring systems:



The saccharides have long and awkward names by the IUPAC system, consequently a highly specialized nomenclature system has been developed for carbohydrates. Because this system (and those like it for other natural products) is unlikely to be replaced by more systematic names, you will find it necessary to memorize some names and structures. It will help you to remember the meaning of names such as aldopentose and ketohexose, and to learn the names and details of the structures of glucose, fructose, and ribose. For the rest of the carbohydrates, the nonspecialist needs only to remember the kind of compounds that they are.

The most abundant five-carbon sugars are *L*-arabinose, *D*-ribose, 2-deoxy-*D*-ribose,[1] and *D*-xylose, which all are **aldopentoses**. Both the open-chain and cyclic structures of the *D*-aldoses up to C_6 are shown in Figure 20-1.



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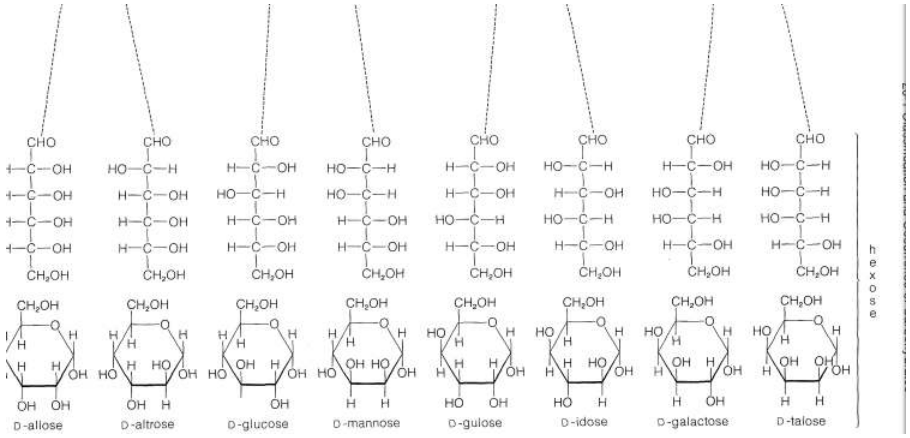

Figure 20-1: Structure and configuration of the *D*-aldoses from C_3 to C_6, showing the configurational relationship to *D*-glyceraldehyde. Open-chain and cyclic forms are shown. The oxacyclohexane (pyranose) form is more stable than the oxacyclopentane (furanose) form for the free sugar. The oxacyclopentane structure is shown for ribose because this is the form in which is occurs in many important substance, such as the nucleic acids. Only the α anomers are shown (see Section 20-2B).

The common six-carbon sugars (hexoses) are *D*-glucose, *D*-fructose, *D*-galactose, and *D*-mannose. They all are **aldohexoses**, except *D*-fructose, which is a **ketohexose**. The structures of the ketoses up to C_6 are shown for reference in Figure 20-2. The occurrence and uses of the more important ketoses and aldoses are summarized in Table 20-1.

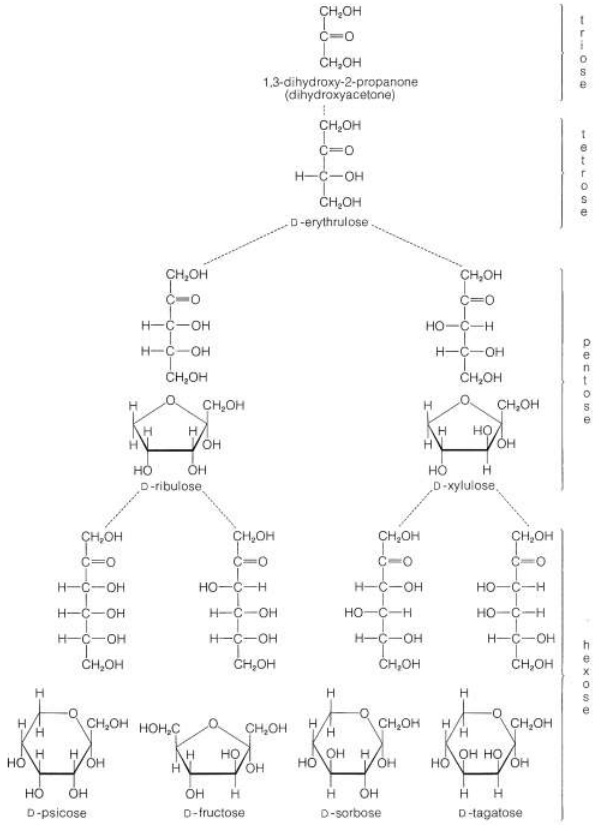

Figure 20-1), the cyclic form is predominantly an oxacyclohexane (pyranose) ring in the free sugar, but the oxacyclopentane (furanose) form is shown because it occurs widely in this form as the disaccharide, sucrose. Only the α anomers are shown (see Section 20-2B).

Table 20-1: *Occurrence, Physical Properties, and Uses of Some Natural Sugars*

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Sugar	Mp, °C	$[\alpha]_D^{20-25}$ in H_2O[a]	Occurrence and use
Monosaccharides			
Trioses, $C_3H_6O_3$			
D-glyceraldehyde	syrup	+8.7	Intermediate in carbohydrate biosynthesis and metabolism.
1,3-dihydroxy-2-propanone	81	–	As above.
Tetroses, $C_4H_8O_4$			
D-erythrose	syrup	−14.5	As above.
Pentoses, $C_5H_{10}O_5$			
L-arabinose	160	+105	Free in heartwood of coniferous trees; widely distributed in combined form as glycosides and polysaccharides.
D-ribose	87	−23.7	Carbohydrate component of nucleic acids and coenzymes.
D-xylose	145	+18.8	Called *wood sugar* because it is widely distributed in combined form in polysaccharides, such as in agricultural wastes as corn cobs, straw, cottonseed hulls.
Hexoses, $C_6H_{12}O_6$			
D-glucose	146	+52.7	Free in blood, other body fluids, and in plants; abundant combined as polysaccharides.
D-fructose	102	−92.4	Free in fruit juices and honey; combined as in sucrose and plant polysaccharides.
D mannose	132	+14.6	Component of polysaccharides.
D-galactose	167	+80.2	Called *brain sugar* because it is a component of glycoproteins in brain and nerve tissue; also found in oligo- and polysaccharides of plants.
Heptoses, $C_7H_{14}O_7$			
sedoheptulose	syrup	+8.2	Detected in succulent plants; an intermediate in carbohydrate biosynthesis and metabolism.
Oligosaccharides			
Disaccharides			
sucrose	160–186	+66.5	Beet sugar and cane sugar. (D-glucose + D-fructose)
lactose	202	+52.6	Milk sugar of mammals. (D-galactose + D-glucose)
maltose	103	+130	Hydrolytic product of starch. (D-glucose + D-glucose)
Trisaccharides			
raffinose	78	+105	(D-glucose + D-fructose + D-galactose)
Polysaccharides			
cellulose (poly-D-glucose)			Occurs in all plants as a constituent of cell walls; as structural component of woody and fibrous plants.
starch (poly-D-glucose)			As food reserves in animals (glycogen), and in plants.
chitin (polyethanamido sugar)			Found in marine animals, insects, fungi, and green algae.
hemicelluloses			
plant gums			

[a]Rotation at equilibrium concentration of anomers and of pyranose and furanose forms (Sections 20-2B and 20-2C).

[1]*Deoxy* means lacking a hydroxyl group, and 2-deoxyribose is simply ribose without an OH group at the 2-carbon.

20.2.1: Contributors and Attributions

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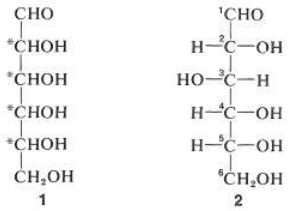
20.3: The Structure and Properties of D-Glucose

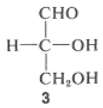
20.3.1: Configuration

Glucose is by far the most abundant monosaccharide; it occurs free in fruits, plants, honey, in the blood of animals, and combined in many glycosides, disaccharides, and polysaccharides. The structure and properties of glucose will be considered in greater detail than those of the other monosaccharides, not only because of its importance, but because much of what can be said about glucose also can be said about the other monosaccharides.

Glucose is an aldohexose, which means that it is a six-carbon sugar with a terminal aldehyde group, shown by 1:

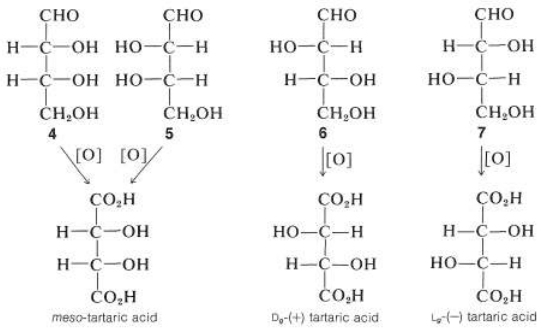


The carbons labeled with an asterisk in 1 are chiral; thus there are 2^4, or sixteen, possible configurational isomers. All are known - some occur naturally and the others have been synthesized (see Table 20-1). The problem of identifying glucose as a particular one of the sixteen possibilities was solved by Emil Fischer during the latter part of the nineteenth century, for which he was awarded the Nobel Prize in chemistry in 1902. The configurations he deduced for each of the chiral carbons, C_2-C_5, are shown in the projection formula 2.[2] Although Fischer was aware that natural glucose could be the enantiomer of Structure 2, his original guess at the *absolute* configuration proved to be correct and the configuration at C_5 is the same as the configuration of the simplest "sugar" *D*-(+)-glyceraldehyde, 3, (see Section 19-5). Therefore natural glucose is specifically *D*-glucose:

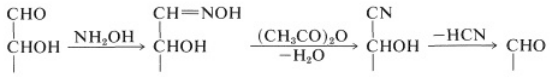


The complete logic of Fischer's procedures for determination of the configuration of glucose is too involved to be explained here in detail. What you will be unable to fully appreciate is the great difficulties of working with carbohydrates - that is, their considerable solubility in water, instability to strong oxidizing agents and acidic or basic reagents, reluctance to crystallize, and their tendency to decompose rather than give sharp melting points. Fortunately for Fischer, many different pentoses and hexoses already were available from the efforts of earlier investigators, and the principles of optical isomerism were well understood as the result of the work of van't Hoff.

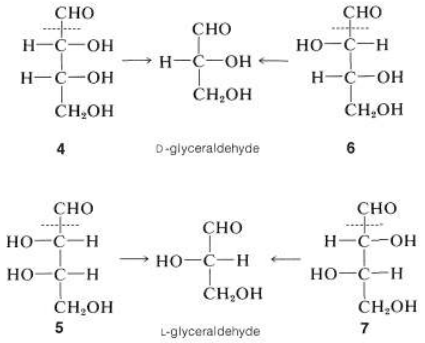
Two of the key ideas used by Fischer can be illustrated best with aldotetroses because they have only two chiral carbons and far fewer possible structures to consider. Writing the four possibilities as the aldehyde rather than hemiacetal structures, we have 4-7. Of these, 4 and 5 constitute a pair of enantiomers, as do 6 and 7. These pairs can be identified by careful oxidation of the terminal groups to give the corresponding tartaric (2,3-dihydroxybutanedioic) acids. Oxidation of both 4 and 5 gives *meso*-tartaric acid, whereas oxidation of 6 and 7 gives, respectively, (+) and (−) tartaric acids:



It should be clear from this that the configurations of 6 and 7 are established by being related to the respective *chiral* tartaric acids. However, we have no way of telling which of the tetroses represented by 4 and 5 is *D* and which is *L*, because, on oxidation, they give the same achiral tartaric acid. What we need to do is relate one or the other of the chiral carbons of these tetroses to the corresponding carbon of either 6 or 7. One way that this can be done is by the **Wohl degradation**, whereby the chain length is reduced by one carbon by removing the aldehyde carbon:

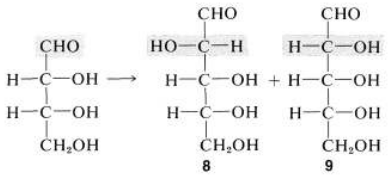


As applied to 4, 5, 6, and 7, the Wohl degradation forms enantiomers of glyceraldehyde:

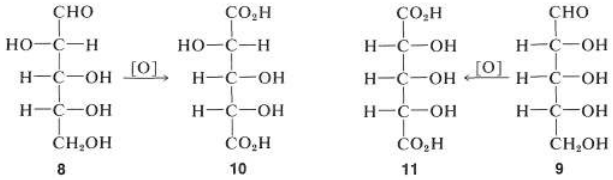


Here we see that 4 and 6 give the same enantiomer, *D*-glyceraldehyde, and therefore have the same configuration of their highest-numbered asymmetric carbon. In contrast, 5 and 7 give *L*-glyceraldehyde and thus must be similarly related. By this kind of procedure, the configurations of 4 to 7 can be established unequivocally, although, as you might imagine, it is far easier to do on paper than in the laboratory.

Knowing the configurations of the tetroses aids in establishing the configurations of the pentoses. Thus, 4, by **Kiliani-Fischer cyanohydrin synthesis**,[3] can be converted to a mixture of two aldopentoses, 8 and 9, by *adding* a carbon at the aldehyde end of the molecule. The configurations of the two carbons at the lower end of the starting materials remain unchanged, but two diastereomeric aldopentoses are formed in the syntheses because a new chiral center is created:

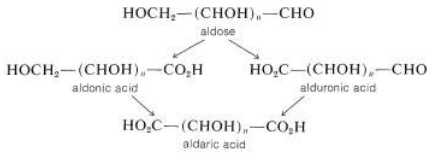


Products 8 and 9 present a new configurational problem, but a less difficult one than before, because the configurations of two of the three chiral centers already are known. Controlled oxidation of 8 and 9 will give *different* diastereomeric 2,3,4-trihydroxypentanedioic acids, 10 and 11, respectively:



Of these, 11 is *achiral* (*meso*), whereas 10 is *chiral*. Therefore, by simply determining which oxidation product is optically active, and hence chiral, we can assign the configurations of 8 and 9. Direct comparison of these synthetic aldopentoses with the naturally occurring compounds then could be used as proof of the structure of natural aldopentoses. By this reasoning 8 turns out to be *D*-arabinose and 9 is *D*-ribose.

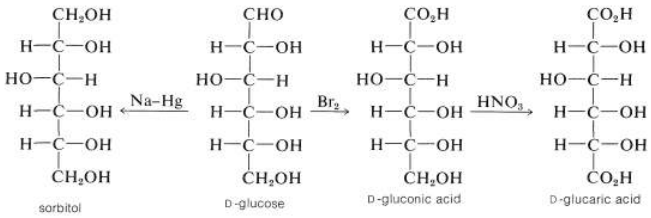
Some of the key reactions in carbohydrate chemistry involve oxidation of aldoses to carboxylic acids. There is a simple nomenclature system for these acids. In abbreviated notation, the products of oxidation at C_1, C_6, or both are called:



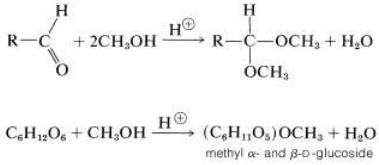
The carboxylic acids derived from glucose are therefore gluconic acid, glucuronic acid, and glucaric acid.

20.3.2: Hemiacetal Formation. Anomers of Glucose

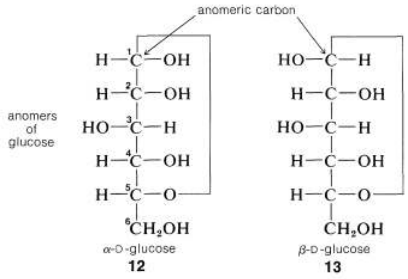
Although glucose has some of the properties expected of an aldehyde, it lacks others. For example, it forms certain carbonyl derivatives (e.g., oxime and cyanohydrin), and can be reduced to the hexahydroxyhexane (sorbitol), and oxidized with bromine to gluconic acid (a monocarboxylic acid). (With nitric acid, oxidation proceeds further to give the dicarboxylic acid, *D*-glucaric acid.)



Glucose also will reduce Fehling's solution $[Cu(II) \rightarrow Cu(I)]$ and Tollen's reagent $[Ag(I) \rightarrow Ag(0)]$ and, for this reason, is classified as a **reducing sugar**.[4] However, it fails to give a hydrogen sulfite addition compound and, although it will react with amines (RNH_2), the products are not the expected Schiff's bases of the type $-C{=}NR$. Furthermore, glucose forms two *different* monomethyl derivatives (called methyl α-*D*-glucoside and methyl β-*D*-glucoside) under conditions that normally convert an aldehyde to a dimethyl acetal:

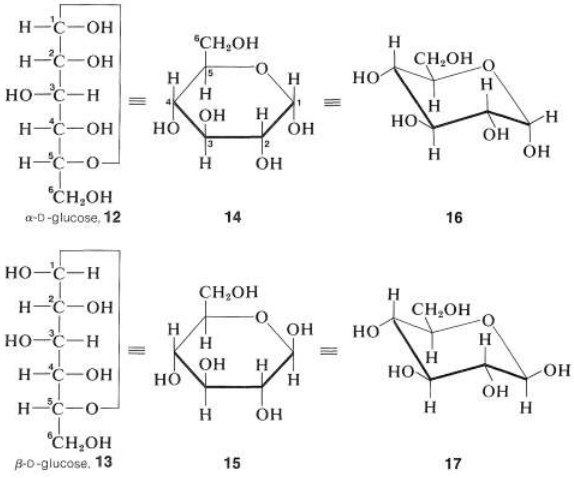


All of these reactions can be explained on the bases that the carbonyl group is not free in glucose but is combined with one of the hydroxyl groups, which turns out to be the one at C_5, to form a hemiacetal, 12 or 13. Why are two hemiacetals possible? Because a new asymmetric center is created at C_1 by hemiacetal formation, and this leads to diastereomeric forms of *D*-glucose called α-*D*-glucose and β-*D*-glucose. In general, carbohydrate stereoisomers that differ only in configuration at the hemiacetal carbon are called **anomers**:

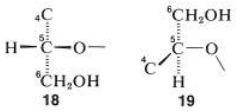


Although formulas 12 and 13 show the *configurations* at each of the chiral centers, they do not provide the crucial information for understanding the properties of glucose with respect to the *arrangement of the atoms in space*. Conversion of a projection formula such as 12 or 13 to a three-dimensional representation is not at all a trivial task. We have indicated the procedure for doing in before

(Sections 5-3C and 5-5). The result of these procedures applied to 12 and 13 are the so-called Haworth projection formulas, 14 and 15, and the sawhorse conformations, 16 and 17:



You should be able to satisfy yourself that the configuration at C_5 is the same in both Fischer and Haworth representations. This amounts to asking if 18 and 19 represent the same configurations:

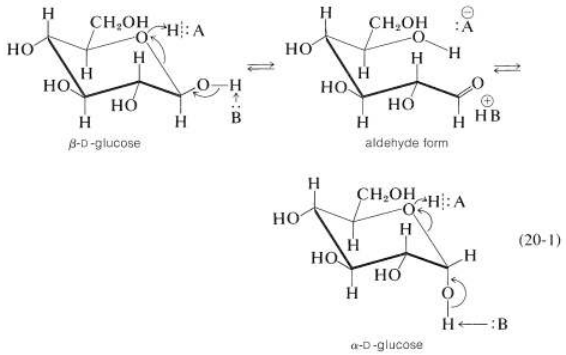


They do, but if you have trouble visualizing this, it will be very helpful to use a ball-and-stick model to see that 18 and 19 are different representations of the same configuration. If you do not have models, remember that if transposition of any three groups converts one projection into the other, the formulas are identical. Thus 18 and 19 have the same configuration because 18 becomes 19 by transposition of C_4 with CH_2OH, then C_4 with H.

X-ray studies of crystalline α- and β-*D*-glucose show that these molecules have their atoms arranged in space as correspond to 16 and 17. This is what we would expect from our studies of cyclohexane conformations (Sections 12-3A to 12-3D), because for the β form, *all* of the substituents on the oxacyclohexane ring are in equatorial positions, and for the α form, all except the hydroxyl at the **anomeric** carbon (C_1) are equatorial.

20.3.3: Mutarotation of the Anomeric Forms of Glucose

Although the crystalline forms of α- and β-*D*-glucose are quite stable, in solution each form slowly changes into an equilibrium mixture of both. The process can be observed as a decrease in the optical rotation of the α anomer $(+112^\circ)$ or an increase for the β anomer $(+18.7^\circ)$ to the equilibrium value of 52.5°. The phenomenon is known as **mutarotation** and commonly is observed for reducing sugars. Both acids and bases catalyze mutarotation; the mechanism, Equation 20-1, is virtually the same as described for acid- and base-catalyzed hemiacetal and hemiketal equilibria of aldehydes and ketones (see Section 15-4E):



(20-1)

At equilibrium, about 64% of the β anomer and 36% of the α anomer are present. The amount of the free aldehyde form at equilibrium is very small (about 0.024 mole percent in neutral solution). Preponderance of the β anomer is attributed to the fact that glucose exists in solution in the chair conformation with the large $-CH_2OH$ group equatorial. In this conformation, the hydroxyl substituent at C_1 is equatorial in the β anomer and axial in the α anomer; hence the β anomer is slightly more stable. When glucose is in the aldehyde form, the hydroxyl at C_4 also could add to the aldehyde carbonyl to produce a hemiacetal with a five-membered ring. This does not occur to a significant degree with glucose because the hemiacetal with the six-membered ring and many equatorial groups is more stable. With other sugars, mixtures of five- and six-membered hemiacetal or ketal rings and their respective anomers are produced in water solution.

Carbon-13 nmr spectra (Section 9-10L) provide an especially powerful tool for studying the anomeric forms of sugars. For example, with glucose the resonances of C_1, C_3, and C_5 of the α anomer are seen in Figure 20-3 to be shifted substantially upfield relative to those of the β anomer because of the axial substituent effect (Section 12-3D).

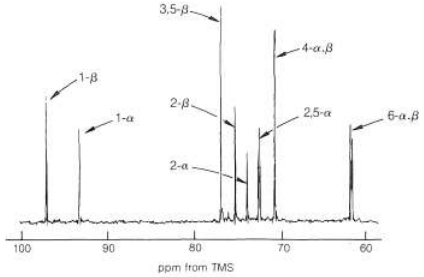
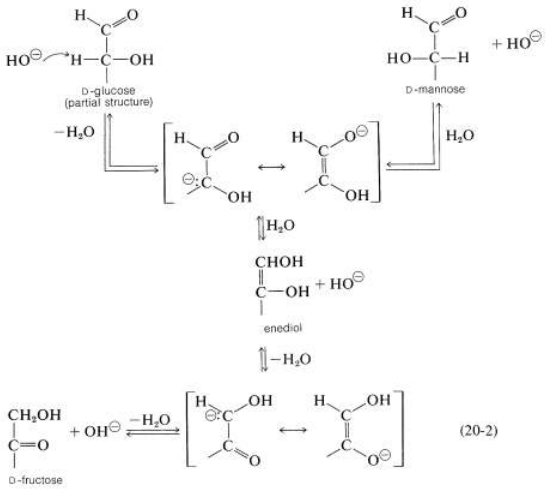


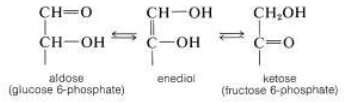
Figure 9-50 the relative peak heights do not correspond to relative amounts of α and β forms present.)

20.3.4: Aldose ⇋ Ketose Rearrangements

In the presence of dilute base, *D*-glucose rearranges to a mixture containing the anomers of *D*-glucose ($\sim 64\%$), *D*-fructose ($\sim 31\%$), and *D*-mannose (3%). This interconversion undoubtedly involves enolization of the hexoses by way of a common enediol intermediate according to Equation 20-2:

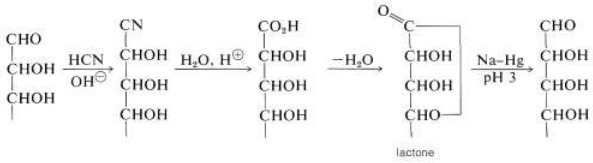


The rearrangement is of interest because the corresponding enzymatic interconversion of aldoses and ketoses is an important part of the biosynthetic, photosynthetic, and metabolic pathways, as we shall see in Section 20-9. Although the biochemical rearrangement also may proceed by way of enediol intermediates, it is highly stereospecific and yields only *one* of two possible stereoisomeric aldoses. For example, glucose, but not mannose, can be enzymatically interconverted with fructose as the 6-phosphate ester derivative:



Figures 5-12 and 5-13.

[3]The steps of the Kiliani-Fischer synthesis are:



[4]In general, reducing sugars are hemiacetals or hemiketals and the nonreducing sugars are acetals or ketals. The difference is between the presence of the structural elements C–O–C–O–H and C–O–C–O–C.

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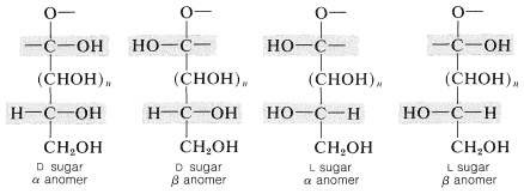
20.4: Conventions for Indicating Ring Size and Anomer Configurations of Monosaccharides

The oxide ring is six-membered in some sugars and five-membered in others, and it is helpful to use names that indicate the ring size. The five- and six-membered oxide rings bear a formal relationship to oxa-2,5-cyclohexadiene and oxa-2,4-cyclopentadiene that commonly are known as pyran and furan, respectively:

Figures 20-1 and 20-2).

There is an important question as to which one of the two anomeric forms of a sugar should be designated as α and which one as β. The convention is simple; the α anomer is the one that has the *same* configuration of the OH at the anomeric carbon as the carbon which determines the configuration of the sugar itself:



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20.5: Derivatives of Glucose

20.5.1: Determination of the Oxide Ring Size

Although we now have powerful spectroscopic methods available to determine the sizes of the oxide rings formed by the simple monosaccharides, the way in which this was done chemically for glucose highlights the difference in reactivity between ether and alcohol functions. The acid-catalyzed methylation of glucose with methanol to give two distinct glucosides, methyl α-*D*-glucoside and methyl β-*D*-glucoside, corresponds to displacement of the hemiacetal hydroxyl by methoxyl to form an acetal (see left side of Figure 20-4).

The remaining four hydroxyl groups can be methylated in basic solution by dimethyl sulfate or by methyl iodide and silver oxide in N,N-dimethylmethanamide, $HCON(CH_3)_2$, solution. Hydrolysis of either of these pentamethyl glucose derivatives with aqueous acid affects only the acetal linkage and leads to a tetramethylated glucose, 20, as shown in Figure 20-4.

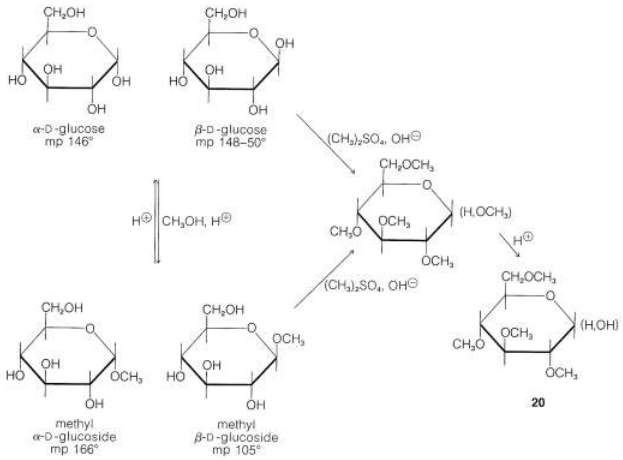
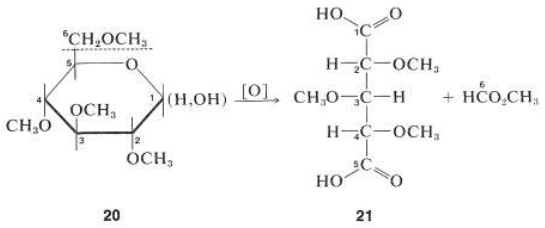
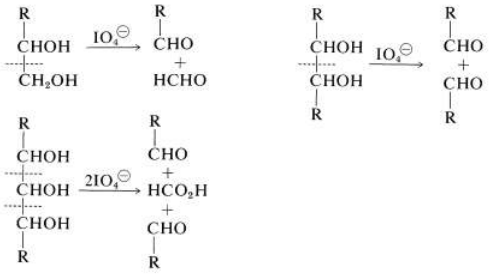


Figure 20-4: Haworth projection formulas showing the formation and reactions of O-methyl derivatives of glucose. The notation (H, OH) in 20 means that the anomeric configuration is unspecified.

The pyranose ring structure of *D*-glucose originally was established by Hirst, in 1926, by converting *D*-glucose to a tetra-O-methyl-*D*-glucose and showing that this substance actually was 2,3,4,6-tetra-O-methyl-*D*-glucose, 20. The key feature of 20 is the fact that all but the two carbons involved hemiacetal formation are protected from oxidation by being substituted with O-methyl groups in place of hydroxy groups. The largest fragment isolated from oxidation of Hirst's tetra-O-methyl-*D*-glucose was a trimethoxypentanedioic acid, 21, and because the two carboxyl carbons must have been the ones originally involved in ring formation, the oxide ring must be between C_1 and C_5:

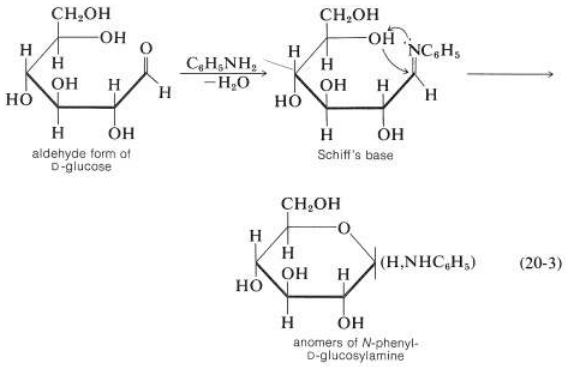


Reagents that specifically oxidize vicinal glycols [e.g., $NaIO_4$, $Pb(O_2CCH_3)_4$, and $NaBiO_3$; Section 16-9A] are quite helpful in determining the cyclic structures of sugars. With periodate, the numbers of moles of oxidant consumed and the moles of methanoic acid and methanal produced are different for each type of ring structure. The cleavage reactions that normally are observed follow:

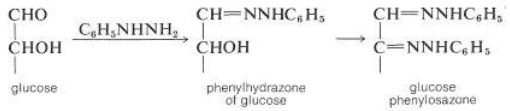


20.5.2: Reactions with Amines and Hydrazines; Osazone Formation

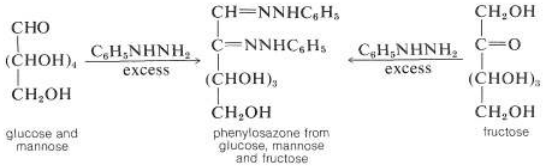
As we stated previously, glucose forms some, but not all, of the common carbonyl derivatives. The amount of free aldehyde present in solution is so small that it is not surprising that no hydrogen sulfite derivative forms. With amines, the product is not a Schiff's base but a glucosylamine of cyclic structure analogous to the hemiacetal structure of glucose, Equation 20-3. The Schiff's base is likely to be an intermediate that rapidly cyclizes to the glucosylamine:



The reaction of glucose with an excess of phenylhydrazine (phenyldiazane) is particularly noteworthy because *two* phenylhydrazine molecules are incorporated into one of glucose. Subsequent to the expected phenylhydrazone formation, and in a manner that is not entirely clear, the –CHOH– group adjacent to the original aldehyde function is oxidized to a carbonyl group, which then consumes more phenylhydrazine to form a crystalline derivative called an **osazone**, or specifically **glucose phenylosazone**:



The sugar osazones usually are crystalline and are useful for characterization and identification of sugars. Fischer employed them in his work that established the configuration of the sugars. The kind of information that can be obtained is illustrated by the following example:



Because the *same* phenylosazone arises from glucose, mannose, and fructose, the configurations of C_3, C_4, and C_5 must be the *same* for all three sugars.

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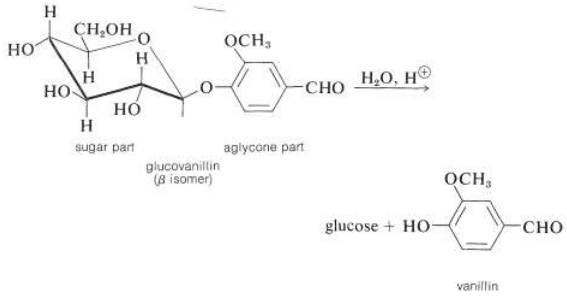
20.6: Glycosides

Although abundant quantities of glucose and fructose are found in the free state, they and less common sugars occur widely in plants and animals combined with various hydroxy compounds. The bonding is through oxygen to the carbonyl carbon, as in the α- and β-methylglucosides discussed in Section 20-4A, to give acetal or ketal structures. These substances are sometimes simply called **glycosides**, but it is desirable to specify that the bonding is through oxygen by using the name O-glycoside. Hydrolysis of an O-glycoside gives the sugar and the hydroxy compound, called the **aglycone** component of the glycoside.

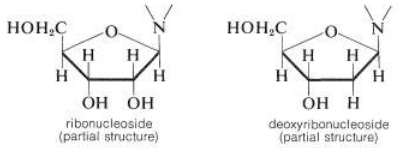
A specific example is glucovanillin, which can be isolated from the green fruit pods of vanilla, a climbing orchid cultivated in several tropical countries. Hydrolysis gives glucose and the aglycone, vanillin, which is the principal ingredient of vanilla flavoring. As the vanilla pods mature, a natural hydrolysis reaction proceeds to the extent that the pods may be covered with small crystals of vanillin.



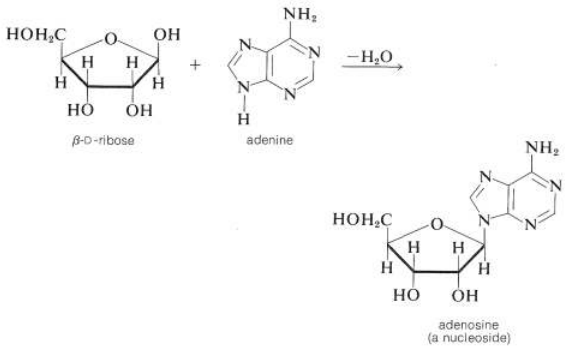
The configurations of glycosides are designated by the same convention used for the sugar anomers. Thus if a glycoside of a *D* sugar has the *D* configuration at the anomeric carbon, it is designated as the α-*D*-glycoside, and if it has the *L* configuration it is called the β-*D*-glycoside (see Section 20-3). If the sugar involved in glycoside formation is glucose, the derivative is a **glucoside**; if fructose, a **fructoside**; if galactose, a **galactoside**; and so on. When the hydroxy compound, or aglycone, is another sugar, then the glycoside is a **disaccharide**, and if the sugar is already a dissacharide, the glycoside is a **trisaccharide**, and so on.

Among the natural products that occur as glycosides (most commonly as β-*D*-glucosides) are many plant pigments (the anthocyanins), the flavorings vanillin and amygdalin, and many steroids (such as the cardiac glycosides and saponins). The structures of some of these substances will be discussed in later chapters.

Not all glycosides are O-glycosides. A group of N-glycosides of special biological importance are derived from heterocyclic nitrogen bases and *D*-ribose and 2-deoxy-*D*-ribose. They commonly are known as *nucleosides*, or more specifically, as **ribonucleosides** and **deoxyribonucleosides**; the N-glycoside linkage is always β:



The N-glycoside of *D*-ribose and the nitrogen heterocycle, adenine, is **adenosine**:



A **nucleotide** is a phosphate ester of a nucleoside. The hydroxyl group at the C_5 position of the pentose is the most common site of esterification. The nucleotides of adenosine are ATP, ADP, and AMP (Section 15-5F).

A **dinucleotide** is a combination of two nucleosides through a common phosphate ester link. Familiar examples are $NAD^{\oplus}$, NADH, FAD, and $FADH_2$ (Section 15-6C). Polynucleotides are polymers of nucleosides linked through phosphate ester bonds. Polynucleotides also are called nucleic acids (RNA and DNA) and are the genetic material of cells, as will be discussed in Chapter 25.

20.6.1: Contributors and Attributions

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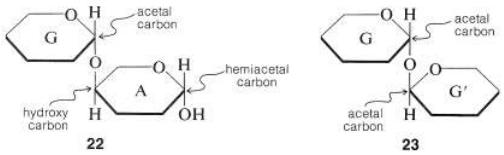
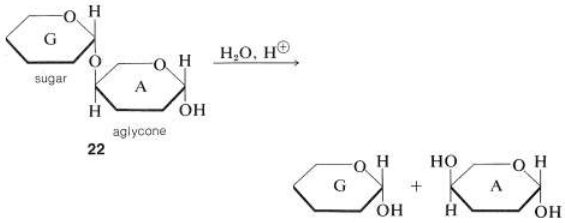
20.7: Disaccharides

20.7.1: General Types and Properties

Combinations of two or more of the simple sugars through glycoside linkages give substances known as **polysaccharides**. They also are called **oligosaccharides** if made from two to ten sugar units. The simplest oligosaccharides are disaccharides made of two molecules of simple sugars that can be joined with O-glycoside links, and it probably is easiest to visualize these as shown in the "stripped-down" formulas, 22 and 23:

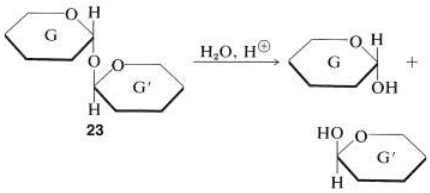


You should look at 22 and 23 carefully to be sure that you recognize the difference between them.[5] In 22, sugar A is acting as a simple hydroxy compound, the aglycone of the sugar G to which it is linked by an O-glycoside linkage.[6] Hydrolysis of 22 at the glycoside link then will proceed as follows:



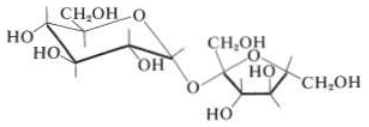
Disaccharides such as 22 are like glucose in being reducing sugars (Section 20-2B), because Component A has the hemiacetal grouping that is opened easily to the aldehyde form in the mildly alkaline conditions used for the Tollen's and Fehling's solution oxidations. Because there is a free hemiacetal group, reducing sugars also form osazones and they mutarotate (Sections 20-4B and 20-2C).

Disaccharides of type 23 are different in that each sugar, G and G', is acting as both a glycoside sugar *and* as an aglycone. The linkage between them is that of a double-barreled acetal, –O–C–O–C–O–, and there is no hemiacetal grouping in the molecule. Therefore these are *nonreducing* sugars as far as the standard tests go. However, hydrolysis of the O-glycoside linkages of 23 does generate reducing sugars with hemiacetal carbons:

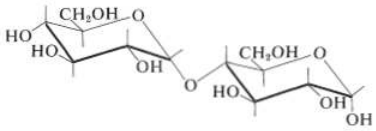


In general, we find that the nonreducing disaccharides give none of the carbonyl reactions observed for glucose, such as mutarotation and osazone formation, except when the conditions are sufficiently acidic to hydrolyze the acetal linkage.

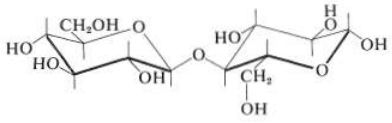
Among the more important disaccharides are sucrose, 24, maltose, 25, cellobiose, 26, and lactose, 27:



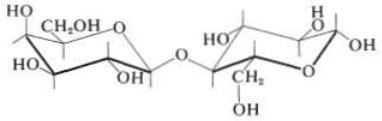
sucrose, **24**



maltose, **25**



cellobiose, **26**



lactose, **27**

Sucrose and lactose occur widely as the free sugars, lactose in the milk of mammals, and sucrose in fruit and plants (especially in sugar cane and sugar beet). Maltose is the product of enzymatic hydrolysis of starch, and cellobiose is a product of hydrolysis of cellulose.

To fully establish the structure of a disaccharide, we must determine (1) the identity of the component monosaccharides; (2) the type of ring junction, furanose or pyranose, in each monosaccharide, as it exists in the disaccharide; (3) the positions that link one monosaccharide with the other; and (4) the anomeric configuration (α or β) of this linkage.

Hydrolysis of disaccharides with enzymes is very helpful in establishing anomeric configurations, because enzymes are highly specific catalysts for hydrolysis of the different types of glycosidic linkages. For instance, α-*D*-glucosidase (maltase) catalyzes hydrolysis of α-*D*-glycosides more rapidly than of β-*D*-glycosides. The enzyme emulsin (found in bitter almonds) in contrast shows a strong preference for β-*D*-glycosides over α-*D*-glycosides. Yeast invertase catalyzes hydrolysis of β-*D*-fructosides.

20.7.2: Structure of Sucrose

We know that sucrose consists of the two monosaccharides glucose and fructose because hydrolysis with acids or enzymes gives equal amounts of each hexose. Further, sucrose is not a reducing sugar, it forms no phenylosazone derivative, and it does not mutarotate. Therefore the anomeric carbons of both glucose and fructose must be linked through an *oxygen bridge* in sucrose. Thus sucrose is a **glycosyl fructoside** or, equally, a **fructosyl glucoside**.

Because sucrose is hydrolyzed by enzymes that specifically assist hydrolysis of both α glycosides (such as yeast α-glucosidase) and β-fructosides (such as invertase), it is inferred that the glucose residue is present as an α *glucoside* and the fructose residue as a β *fructoside*. If so, the remaining uncertainty in the structure of sucrose is the size of the rings in the glucose and fructose residues.

The size of the sugar rings in sucrose has been determined by the reactions shown in Figure 20-5. Methylation of sucrose with dimethyl sulfate in basic solution followed by hydrolysis of the octamethyl derivative gives 2,3,4,6-tetra-O-methyl-*D*-glucopyranose (Section 20-4) and a tetra-O-methyl-*D*-fructose. This establishes the glucose reside in sucrose as a *glucopyranose*. The fructose residue must be a *fructofuranose* because periodate oxidation of sucrose consumes three moles of periodate, whereby one mole of methanoic acid and one mole of a tetraaldehyde are formed. On bromine oxidation followed by acid hydrolysis, the tetraaldehyde gives 3-hydroxy-2-oxopropanoic acid (hydroxypyruvic acid, $HOCH_2COCO_2H$), oxoethanoic acid (glyoxylic acid, $OCHCO_2H$), and *D*-glyceric acid ($HOCH_2CHOHCO_2H$). Sucrose therefore has structure 24, and this structure was confirmed by synthesis (R. Lemieux in 1953).

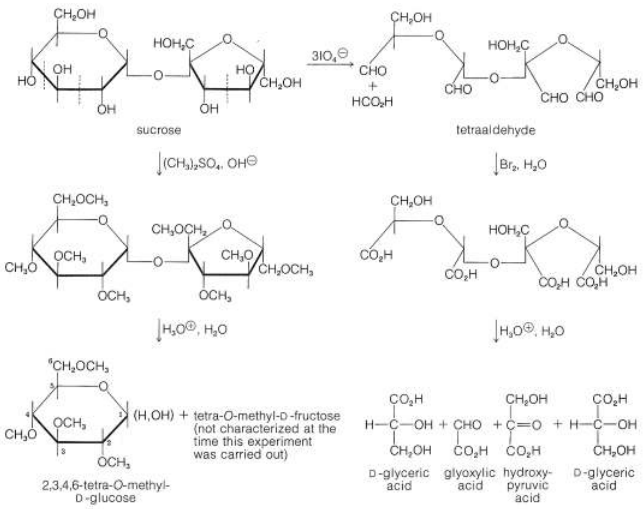


Figure 20-5: Summary of reactions used to establish the ring structure of sucrose.

[5]For now, we will ignore the possibility of different anomers of the disaccharide or their component sugars.

[6]The manner in which sugars are linked together to form oligosaccharides was elucidated by W. N. Haworth, who received the Nobel Prize in chemistry in 1937 for this and other contributions to research on the structures and reactions of carbohydrates.

20.7.3: Contributors and Attributions

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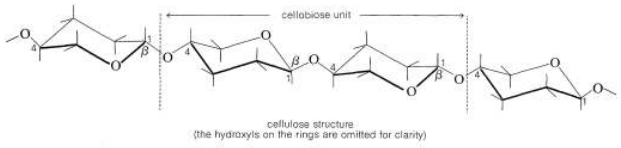
20.8: Polysaccharides

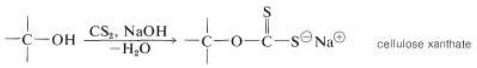
20.8.1: Cellulose

The fibrous tissue in the cell walls of plants contains the polysaccharide **cellulose**, which consists of long chains of glucose units, each of which is connected by a β-glucoside link to the C_4 hydroxyl of another glucose as in the disaccharide **cellobiose** (i.e., β -1,4):

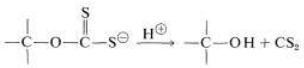


Indeed, enzymatic hydrolysis of cellulose leads to cellobiose. The molecular weight of cellulose varies with the source but is usually high. Cotton cellulose appears to have about 3000 glucose units per molecule.

The natural fibers obtained from cotton, wood, flax, hemp, and jute all are cellulose fibers and serve as raw materials for the textile and paper industries. In addition to its use as a natural fiber and in those industries that depend on wood as a construction material, cellulose is used to make cellulose acetate (for making rayon acetate yarn, photographic film, and cellulose acetate butyrate plastics), nitric acid esters (gun cotton and celluloid[7]), and cellulose xanthate (for making viscose rayon fibers). The process by which viscose rayon is manufactured involves converting wood pulp or cotton linters into cellulose xanthate by reaction with carbon disulfide and sodium hydroxide:



The length of the chains of the cellulose decreases about 300 monomer units in the process. At this point, the cellulose is regenerated in the form of fine filaments by forcing the xanthate solution through a spinneret into an acid bath:

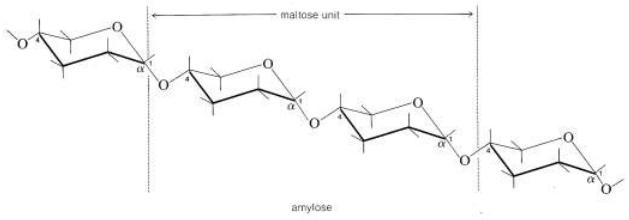


A few animals (especially ruminants and termites) are able to metabolize cellulose, but even these animals depend on appropriate microorganisms in their intestinal tracts to hydrolyze the β-1,4 links; other animals, including man, cannot utilize cellulose as food because they lack the necessary hydrolytic enzymes. However, such enzymes are distributed widely in nature. In fact, deterioration of cellulose materials - textiles, paper, and wood - by enzymatic degradation (such as by dry rot) is an economic problem that is not yet adequately solved. Efforts to turn this to advantage through enzymatic hydrolysis of cellulose to glucose for practical food production have not been very successful (Section 25-12).

20.8.2: Starch and Related Compounds

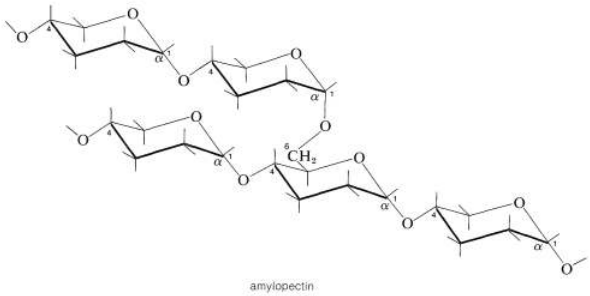
A second, very widely distributed polysaccharide is **starch**, which is stored in the seeds, roots, and fibers of plants as a food reserve - a potential source of glucose. The chemical composition of starch varies with the source, but in any one starch there are two structurally different polysaccharides. Both consist entirely of glucose units, but one is a linear structure (**amylose**) and the other is a branched structure (**amylopectin**).

The amylose form of starch consists of repeating 1,4-glucopyranose links as in cellulose, but unlike cellulose the linkage is α rather than β (i.e., α-1,4):



Hydrolysis by the enzyme diastase leads to maltose.

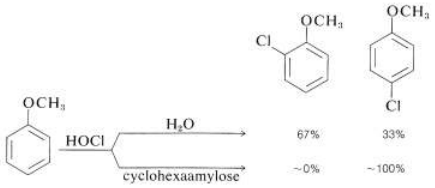
In amylopectin, amylose chains are joined by α-1,6 linkages:



Animals also store glucose in the form of starchlike substances called **glycogens**. These substances resemble amylopectin more than amylose in that they are branched chains of glucose units with α-1,4- and α-1,6-glucoside links.

Starch is used in paper manufacture and in the textile and food industries. Fermentation of grain starches is an important source of ethanol. Hydrolysis of starch catalyzed by hydrochloric acid results in a syrupy mixture of glucose, maltose, and higher-molecular-weight saccharides. This mixture is called **dextrin** and is marketed as corn syrup. The hydrolysis does not proceed all the way to glucose because the α-1,6 glucosidic link at the branch point is not easily hydrolyzed. Enzymes also catalyze hydrolysis of starch, but the enzyme α *amylase* is specific for α-1,4 links and, like acid-catalyzed hydrolysis, gives a mixture of glucose, maltose, and polysaccharides (dextrin). The enzyme α-1,6-*glucosidase* can hydrolyze the α-1,6 links at the branch points and, when used in conjunction with α amylase, completes the hydrolysis of starch to glucose.

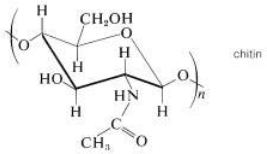
A very interesting group of polysaccharides isolated from cornstarch hydrolysates are known as **cyclodextrins**. One of these compounds, **cyclohexaamylose**, is a large doughnut-shaped molecule with a central cavity that literally can engulf a small, relatively nonpolar organic molecule and hold it in water solution, similar to a micelle (Section 18-2F). As with micelles, unusual reactivity is exhibited by the bound molecules. An example is the change in the ortho-para ratio in electrophilic substitution of methoxybenzene by hypochlorous acid, HOCl, in the presence and absence of cyclohexaamylose:



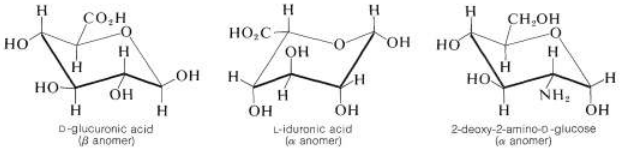
Apparently the cyclohexaamylose wraps around the methoxybenzene in such a way as to protect the ortho carbons from attack by HOCl but to leave the para carbon exposed. It is this kind of specificity that we need to generate in reactions before we can claim to have synthetic reactions under control.

20.8.3: Other Important Polysaccharides

Many polysaccharides besides starch and cellulose are important components of animal tissues, or play a vital role in biochemical processes. One example is **chitin**, a celluloselike material that is the structural component of the hard shells of insects and crustaceans. The difference between chitin and cellulose is that instead of being a polymer of glucose, chitin is a polymer of 2-deoxy-2-N-ethanamidoglucose (N-acetyl-β-*D*-glucosamine):



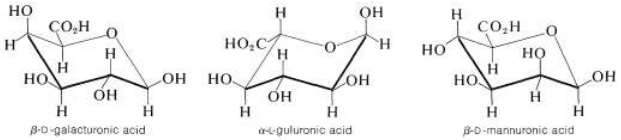
Heparin is a very important and complex polysaccharide derivative that occurs in intestinal walls and has a major use as a blood anticoagulant, especially in connection with artificial kidney therapy. Heparin also has shown great promise in the treatment of patients with extensive burns, by promoting blood circulation to burn-damaged tissue. The structure of heparin can not be defined precisely because its composition depends on the source of supply. The major components of the polysaccharide chain are *D*-glucuronic acid, *L*-iduronic acid, and the same 2-deoxy-2-aminoglucose (*D*-glucosamine) that is a constituent of chitin (although in heparin it occurs as the α anomer):



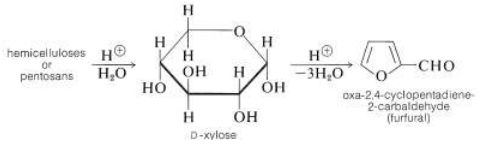
The general construction of heparin involves the linkage of the anomeric carbons of one of the components with the 4-hydroxyl of another. A key feature of the heparin structure is the presence of sulfate groups that occur as hydrogen sulfate esters (Section 15-5B) and as sulfamido groups, $-NHSO_3H$, on the 2-deoxy-2-amino-*D*-glucose units in the chain. Hydrogen sulfate groups also are located on the 2-hydroxyls of the *L*-iduronic acid units of the chain. In addition there are N-ethanoyl groups attached to some of the 2-deoxy-2-amino-*D*-glucose nitrogens that are not connected to $-SO_3H$.

Heparin is clearly an extraordinarily complex substance with many highly polar groups, and its mode of action as an anticoagulant is not clear. At present, because of increases in the use of artificial kidney machines, heparin is in rather short supply.

Among the plant polysaccharides are the **pectins**, which are used as jelling agents in the making of preserves and jellies from fruit. Also important are the **alginates** from seaweeds and **gums** from trees, which are used as stabilizers and emulsifiers in the food, pharmaceutical, cosmetic, and textile industries. The pectins principally are polysaccharides of the methyl ester of *D*-galacturonic acid, whereas the alginates are polysaccharides made up of varying proportions of *D*-mannuronic acid and *L*-guluronic acid. The plant gums are similar materials.



There are other polysaccharides besides cellulose in the cell walls of plants. These are called hemicelluloses, but the name is misleading because they are unrelated to cellulose. Those that are made of pentose sugars (mainly xylose) are most abundant. They accumulate as wastes in the processing of agricultural products, and on treatment with acids that yield a compound of considerable commercial importance, oxa-2,4-cyclopentadiene-2-carbaldehyde (furfural):



[7]Celluloid, one of the first plastics, is partially nitrated cellulose (known as pyroxylin) plasticized with camphor.

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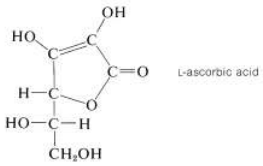
20.9: Vitamin C

The "antiscorbutic" factor of fresh fruits, which prevents the development of the typical symptoms of scurvy in humans, is a carbohydrate derivative known as **vitamin C** or **ascorbic acid**. This substance is not a carboxylic acid, but a lactone, and owes its acidic properties (and ease of oxidation) to the presence of an enediol grouping. It belongs to the *L* series by the glyceraldehyde convention:



L-ascorbic acid

Most animals are able to synthesize vitamin C in their livers but, in the course of evolution, man has lost this capacity.

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20.10: Formation of Carbohydrates by Photosynthesis

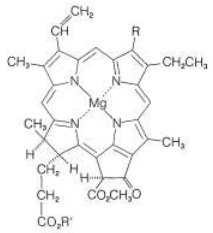
Carbohydrates are formed in green plants by **photosynthesis**, which is the chemical combination, or "fixation", of carbon dioxide and water by utilization of energy from the absorption of visible light. The overall result is the *reduction* of carbon dioxide to carbohydrate and the formation of oxygen:

$$x\mathrm{CO_2} + x\mathrm{H_2O} \xrightarrow[\text{green plants}]{\text{light}} \underset{\text{carbohydrate}}{(\mathrm{C}\cdot\mathrm{H_2O})_x} + x\mathrm{O_2} \quad \left.\begin{matrix}\Delta G^\circ \cong 686\ \text{kcal} \\ \Delta H^\circ \cong 670\ \text{kcal}\end{matrix}\right\} \text{for } x = 6$$

If the carbohydrate formed is cellulose, then the reaction in effect is the reverse of the burning of wood, and obviously requires considerable energy input.

Because of its vital character to life as we know it, photosynthesis has been investigated intensively and the general features of the process are now rather well understood. The principal deficiencies in our knowledge include just how the light absorbed by the plants is converted to chemical energy and the details of how the many complex enzyme-induced reactions involved take place.

The ingredients in green plants that carry on the work of photosynthesis are contained in highly organized, membrane-covered units called **chloroplasts**. The specific substances that absorb the light are the plant pigments, chlorophyll *a* and chlorophyll *b*, whose structures are shown in Figure 20-6. These highly conjugated substances are very efficient light absorbers, and the energy so gained is used in two separate processes, which are represented diagrammatically in Figure 20-7.



R = CH_3 (chlorophyll *a*); —CHO (chlorophyll *b*)

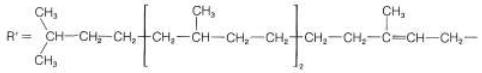


Figure 20-6: The structure of chlorophyll a and chlorophyll b, showing cis-trans relationships of the substituents.

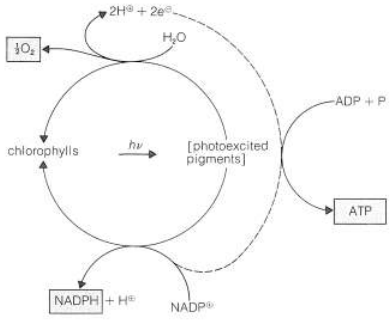
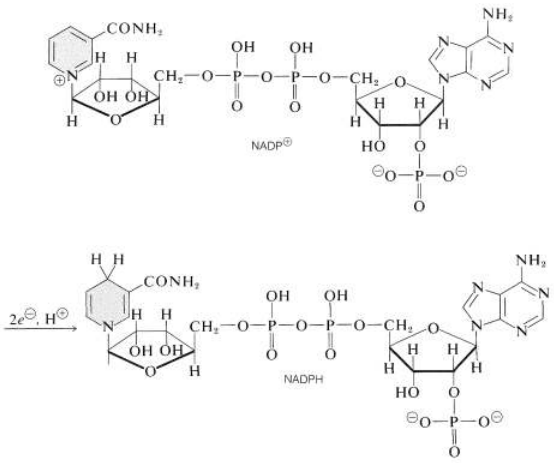


Figure 20-7: Simplified representation of the photoreactions in photosynthesis. The oxidation of water is linked to the reduction of $\mathrm{NADP^{\oplus}}$ by an electron-transport chain (dashed line) that is coupled to ATP formation (photophosphorylation).

One photoprocess reduces *nicotinamide adenine dinucleotide phosphate* $(\mathrm{NADP^{\oplus}})$ to NADPH. These dinucleotides, shown below, differ from $\mathrm{NAD^{\oplus}}$ and NADH (Section 15-6C) in having a phosphate group at $\mathrm{C_2}$ of one of the ribose units. The oxidized form, $\mathrm{NADP^{\oplus}}$, behaves like $\mathrm{NAD^{\oplus}}$ and receives the equivalent of $\mathrm{H^{\ominus}}$ at $\mathrm{C_4}$ of the nicotinamide ring to form NADPH:



The other important photoreaction is oxidation of water to oxygen by the reaction:

$$H_2O \rightarrow 2H^{\oplus} + \frac{1}{2}O_2 + 2e^{\ominus} \tag{20.10.1}$$

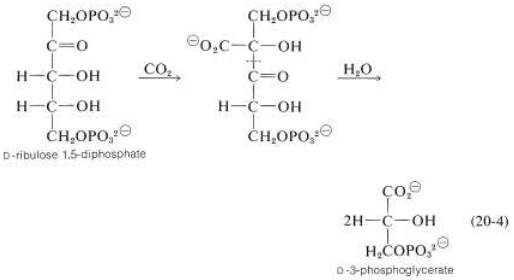
The oxygen formed clearly comes from H_2O and not from CO_2, because photosynthesis in the presence of water labeled with ^{18}O produces oxygen labeled with ^{18}O, whereas carbon dioxide labeled with ^{18}O does not give oxygen labeled with ^{18}O. Notice that the oxidation of the water produces two electrons, and that the formation of $NADPH$ from $NADP^{\oplus}$ requires two electrons. These reactions occur at different locations within the chloroplasts and in the process of transferring electrons from the water oxidation site to the $NADP^{\oplus}$ reduction site, adenosine diphosphate (ADP) is converted to adenosine triphosphate (ATP; see Section 15-5F for discussion between the importance of such phosphorylations). Thus electron transport between the two photoprocesses is coupled to phosphorylation. This process is called **photophosphorylation** (Figure 20-7).

The end result of the photochemical part of photosynthesis is the formation of O_2, $NADPH$, and ATP. Much of the oxygen is released to the atmosphere, but the $NADPH$ and ATP are utilized in a series of dark reactions that achieve the reduction of carbon dioxide to the level of a a carbohydrate (fructose). A balanced equation is

$$6CO_2 + 12NADPH + 12H^{\oplus} \rightarrow C_6H_{12}O_6 + 12NADP^{\oplus} + 6H_2O \tag{20.10.2}$$

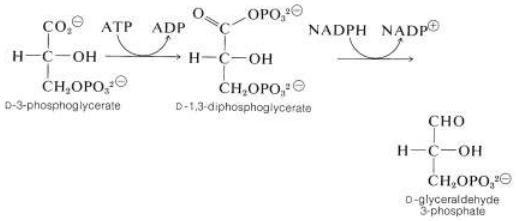
The cycle of reactions that converts carbon dioxide to carbohydrates is called the **Calvin cycle**, after M. Calvin, who received the Nobel Prize in chemistry in 1961 for his work on determining the path of carbon in photosynthesis.

Carbon enters the cycle as carbon dioxide. The key reaction by which the CO_2 is "fixed" involves enzymatic *carboxylation* of a pentose, *D*-ribulose 1,5-phosphate.[8]

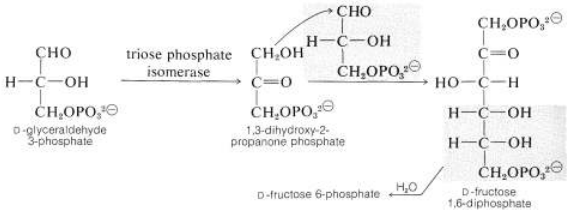


A subsequent hydrolytic cleavage of the C_2-C_3 bond of the carboxylation product (this amounts to a reverse Claisen condensation; Section 18-8B) yields two molecules of *D*-3-phosphoglycerate.[9]

In subsequent steps, ATP is utilized to phosphorylate the carboxyl group of 3-phosphoglycerate to create 1,3-diphosphoglycerate (a mixed anhydride of glyceric and phosphoric acids). This substance then is reduced by $NADPH$ to glyceraldehyde 3-phosphate:



Two glyceraldehyde 3-phosphates are utilized to build the six-carbon chain of fructose by an aldol condensation $(C_3 + C_3 \rightarrow C_6)$, but the donor nucleophile in this reaction is the phosphate ester of dihydroxypropanone, which is an isomer of glyceraldehyde 3-phosphate. Rearrangement of the C_3 aldose to the C_3 ketose (of the type described in Section 20-2D) therefore precedes the aldol addition. (For a discussion of the mechanism of the enzymatic aldol reaction, see Section 17-3F.) The fructose 1,6-diphosphate formed is then hydrolyzed to fructose 6-phosphate:



From what we have described thus far, only one atom of carbon has been added from the atmosphere, and although we have reached fructose, five previously reduced carbons were consumed in the process. Thus the plant has to get back a five-carbon sugar from a six-carbon sugar to perpetuate the cycle. Rather than split off one carbon and use that as a building block to construct other sugars, an amazing series of transformations is carried on that can be summarized by the following equations:

$$C_6 + C_3 \xrightarrow{\text{transketolase}} C_4 + C_5$$
$$C_4 + C_3 \xrightarrow{\text{aldolase}} C_7$$
$$C_7 + C_3 \xrightarrow{\text{transketolase}} C_5 + C_5$$

These reactions have several features in common. They all involve phosphate esters of aldoses or ketoses, and they resemble aldol or reverse-aldol condensations. Their mechanisms will no be considered here, but are discussed more explicitly in Sections 20-10A, 20-10B, and 25-10. Their summation is $C_6 + 3C_3 \rightarrow 3C_5$, which means that fructose 6-phosphate as the C_6 component reacts with a total of three C_3 units (two glyceraldehyde 3-phosphates and one dihydroxypropanone phosphate) to give, ultimately, three ribulose 5-phosphates. Although the sequence may seem complex, it avoids building up pentose or hexose chains one carbon at a time from one-carbon intermediates.

The Calvin cycle is completed by the phosphorylation of *D*-ribulose 5-phosphate with ATP. The resulting *D*-ribulose 1,5-diphosphate then is used to start the cycle again by combining with carbon dioxide. There is one sixth more fructose is used to build other carbohydrates, notably glucose, starch, and cellulose.

[8]All of the reactions we will be discussing are mediated by enzymes, and we will omit henceforth explicit mention of this fact. But it should not be forgotten that these are *all* enzyme-induced processes, for which we have few, if any, laboratory reagents to duplicate on the particular compounds involved.

[9]We will henceforth, in equations, designate the various acids we encounter as the phosphate and the carboxylate anions, although this is hardly reasonable at the pH values normal in living cells. Glyceric and phosphoric acids are only partially ionized at pH 7-8. However, it would be equally unrealistic to represent the acids as being wholly undissociated.

20.10.1: Contributors and Attributions

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20.11: The Generation of Energy from Carbohydrate Metabolism

We will consider here the reverse process of photosynthesis, namely how carbohydrates, especially glucose, are converted to energy by being broken down into carbon dioxide and water.

A general summary of the several stages involved is shown in Figure 20-8. Initially, the storage fuels or foodstuffs (fats, carbohydrates, and proteins) are hydrolyzed into smaller components (fatty acids and glycerol, glucose and other simple sugars, and amino acids). In the next stage, these simple fuels are degraded further to two-carbon fragments that are delivered as the $CH_3C{=}O$ group (ethanoyl, or acetyl) in the form of the thioester of coenzyme A, $CH_3COS\mathbf{CoA}$. The structure of this compound and the manner in which fatty acids are degraded has been considered in Section 18-8F, and amino acid metabolism is discussed briefly in Section 25-5C. This section is concerned mainly with the pathway by which glucose is metabolized by the process known as **glycolysis**.

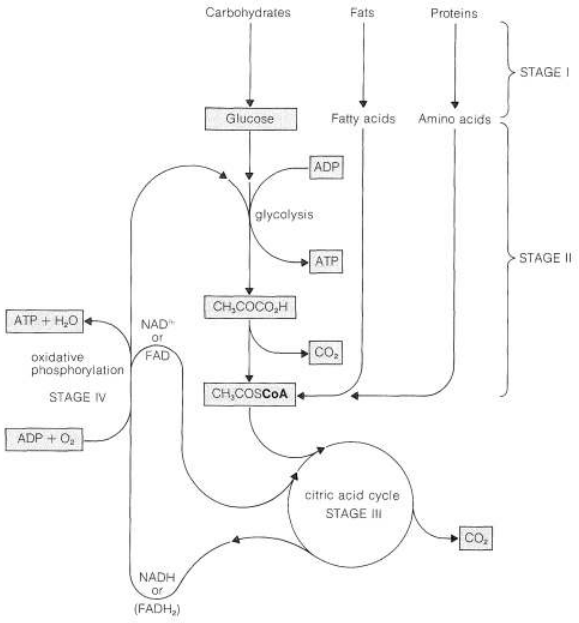


Figure 20-8: Perspective of the metabolic scheme whereby carbohydrates, fats, and proteins in foodstuffs are oxidized to CO_2, showing the link between glycolysis, the citric acid cycle, and oxidative phosphorylation.

In the conversion of glucose to $CH_3COS\mathbf{CoA}$, two carbons are oxidized to carbon dioxide with consumption of two oxygen molecules:

$$C_6H_{12}O_6 + 2\mathbf{CoA}SH + [2O_2] \rightarrow 2CH_3COS\mathbf{CoA} + 4H_2O + 2CO_2 \tag{20-5}$$

For further oxidation to occur, the $CH_3COS\mathbf{CoA}$ must enter the next stage of metabolism, whereby the $CH_3C{=}O$ group is converted to CO_2 and H_2O. This stage is known variously as the citric acid cycle, the tricarboxylic acid cycle, or the Krebs cycle, in honor of H. A. Krebs (Nobel Prize, 1953), who first recognized its cyclic nature in 1937. We can write an equation for the process as if it involved oxygen:

$$2CH_3COS\mathbf{CoA} + [4O_2] \rightarrow 4CO_2 + 2H_2O + 2\mathbf{CoA}SH \tag{20-6}$$

Notice that combination of the reactions of Equations 20-5 and 20-6, glycolysis plus the citric acid cycle, oxidizes glucose completely to CO_2 and H_2O:

$$C_6H_{12}O_6 + [6O_2] \rightarrow 6CO_2 + 6H_2O \tag{20-7}$$

But, as you will see, none of the steps uses molecular oxygen directly. Hence there must be a stage in metabolism whereby molecular oxygen is linked to production of oxidizing agents that are consumed in glycolysis and in the citric acid cycle.

The coupling of oxygen into the metabolism of carbohydrates is an extremely complex process involving transport of the oxygen to the cells by an oxygen carrier such as hemoglobin, myoglobin, or hemocyanin. This is followed by a series of reactions, among

which NADH is converted to $NAD^{\oplus}$ with associated formation of three moles of ATP from three moles of ADP and inorganic phosphate. Another electron-carrier is flavin adenine dinucleotide (FAD; Section 15-6C), which is reduced to $FADH_2$ with an associated production of two moles of ATP from two moles of ADP. These processes are known as **oxidative phosphorylation** and can be expressed by the equations:

$$NADH + \tfrac{1}{2}O_2 + H^{\oplus} \xrightarrow{3ADP\ \ 3ATP} NAD^{\oplus} + H_2O \qquad (20\text{-}8)$$

$$FADH_2 + \tfrac{1}{2}O_2 \xrightarrow{2ADP\ \ 2ATP} FAD + H_2O \qquad (20\text{-}9)$$

Oxidative phosphorylation resembles photophosphorylation, discussed in Section 20-9, in that electron transport in photosynthesis also is coupled with ATP formation.

By suitably juggling Equations 20-7 through 20-9, we find that the metabolic oxidation of one mole of glucose is achieved by ten moles of $NAD^{\oplus}$ and two moles of FAD:

$$C_6H_{12}O_6 + 10\,NAD^{\oplus} + 2FAD + 6H_2O \xrightarrow{34ADP\ \ 34ATP} 6CO_2 + 10\,NADH + 2FADH_2 + 10\,H^{\oplus} \qquad (20\text{-}10)$$

The overall result is production of 36 moles of ATP from ADP and phosphate per mole of glucose oxidized to CO_2 and H_2O. Of these, 34 ATPs are produced according to Equation 20-10 and, as we shall see, two more come from glycolysis.

20.11.1: Glycolysis

Glycolysis is the sequence of steps that converts glucose into two C_3 fragments with the production of ATP. The C_3 product of interest here is 2-oxopropanoate (pyruvate):

$$\underset{\text{glucose}}{C_6H_{12}O_6} \xrightarrow{ADP\ \ ATP} \underset{\text{pyruvate}}{2CH_3\overset{O}{\overset{\|}{C}}CO_2^{\ominus}}$$

There are features in this conversion that closely resemble the dark reactions of photosynthesis, which build a C_6 chain (fructose) from C_3 chains (Section 20-9). For example, the reactants are either phosphate esters or mixed anhydrides, and the phosphorylating agent is ATP:

$$ROH + ATP \rightarrow RO{-}PO_3{}^{2-} + ADP + H^{\oplus} \qquad (20.11.1)$$

Furthermore, rearrangements occur that interconvert an aldose and ketose,

$$R\overset{OH}{\overset{|}{C}}HCHO \rightleftharpoons R\overset{O}{\overset{\|}{C}}CH_2OH$$

and the cleavage of a C_6 chain into two C_3 chains is achieved by a reverse aldol condensation:

$$C{-}C{-}\underset{OH}{\overset{H}{\overset{|}{\underset{|}{C}}}}{-}C{-}\overset{O}{\overset{\|}{C}}{-}C \longrightarrow C{-}C{-}CH{=}O + H{-}C{-}\overset{O}{\overset{\|}{C}}{-}C{-}$$

Also, oxidation of an aldehyde to an acid is accomplished with $NAD^{\oplus}$. There is a related reaction in photosynthesis (Section 20-9) that accomplishes the reduction of an acid to an aldehyde and is specific for NADPH, not NADH:

$$RCHO + NAD^{\oplus} + H_2O \xrightarrow{\text{glycolysis}} RCO_2^{\ominus} + NADH + 2H^{\oplus}$$

$$RCHO + NADP^{\oplus} + H_2O \xleftarrow{\text{photosynthesis}} RCO_2^{\ominus} + NADPH + 2H^{\oplus}$$

Figure 20-9 and each of the steps is identified more specifically in the ensuing discussion.

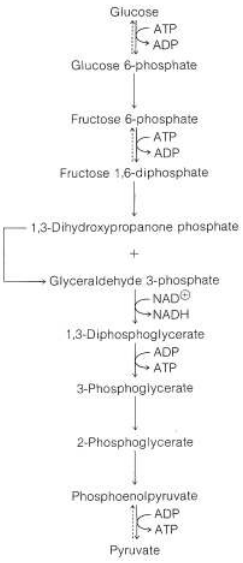
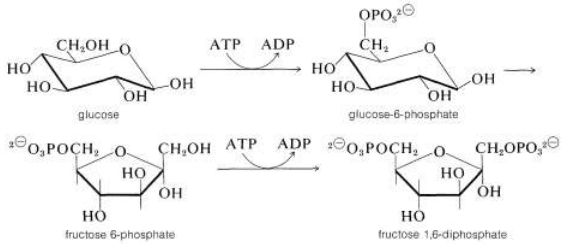
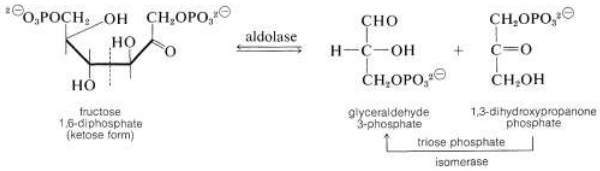


Figure 20-9: The glycolytic sequence. The dashed arrows in the reverse direction indicate the steps in the synthesis of glucose from pyruvate (gluconeogenesis) that differ from those in glycolysis.

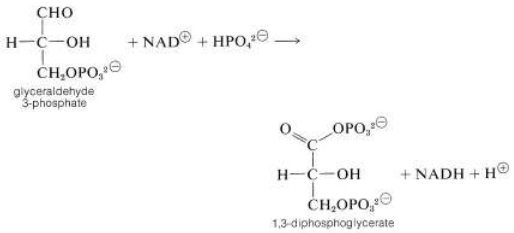
First, glucose is phosphorylated to glucose 6-phosphate with ATP. Then an aldose ⇌ ketose rearrangement converts glucose 6-phosphate into fructose 6-phosphate. A second phosphorylation with ATP gives fructose 1,6-diphosphate:



At this stage the enzyme aldolase catalyzes the aldol cleavage of fructose 1,6-diphosphate. One product is glyceraldehyde 3-phosphate and the other is 1,3-dihydroxypropanone phosphate. Another ketose ⇌ aldose equilibrium converts the propanone into the glyceraldehyde derivative:

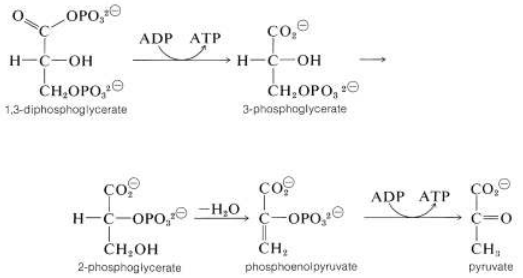


The next step oxidizes glyceraldehyde 3-phosphate with $NAD^{\oplus}$ in the presence of phosphate with the formation of 1,3-diphosphoglycerate:



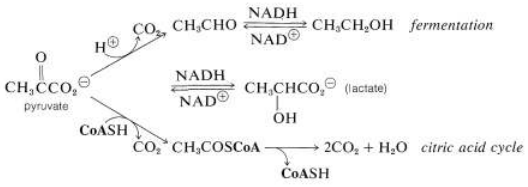
The mixed anhydride of phosphoric acid and glyceric acid then is used to convert ADP to ATP and form 3-phosphoglycerate. Thereafter the sequence differs from that in photosynthesis. The next few steps accomplish the formation of pyruvate by transfer of

the phosphoryl group from C_3 to C_2 followed by dehydration to phosphoenolpyruvate. Phosphoenolpyruvate is an effective phosphorylating agent that converts ADP to ATP and forms pyruvate:



The net reaction at this point produces more ATP than is consumed in the phosphorylation of glucose and fructose.

What happens thereafter depends on the organism. With yeast and certain other microorganisms, pyruvate is decarboxylated and reduced to ethanol. The end result of glycolysis in this instance is *fermentation*. In higher organisms, pyruvate can be stored temporarily as a reduction product (lactate) or it can be oxidized further to give CH_3COS**CoA** and CO_2. The CH_3COS**CoA** then enters the citric acid cycle to be oxidized to CO_2 and H_2O, as discussed in the next section:



20.11.2: The Citric Acid (Krebs) Cycle

Glycolysis to the pyruvate or lactate stage liberates heat, which can help keep the organism warm and produce ATP from ADP for future conversion into energy. However, glycolysis does not directly involve oxygen and does not liberate CO_2, as we might expect from the overall process of the metabolic conversion of glucose to carbon dioxide and water (Equation 20-10). The liberation of CO_2 occurs subsequent to pyruvate formation in a process called variously, the citric acid cycle, the Krebs cycle, or the tricarboxylic acid (TCA) cycle.

Figure 20-10, and it will help to refer to this diagram as each of the steps in it are discussed in more detail.

The initial step, which is not really part of the cycle, is conversion of pyruvate to ethanoyl **CoA** (acetyl **CoA**):

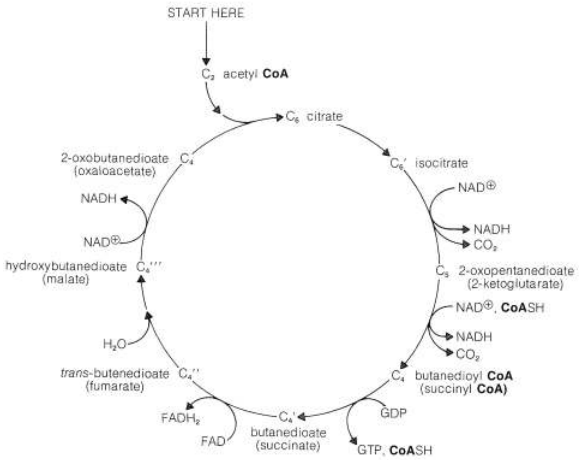
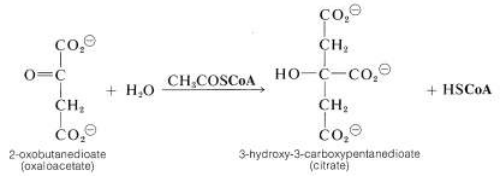


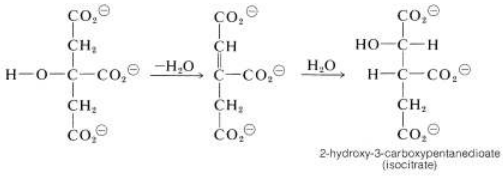
Figure 20-10: The citric acid cycle

To achieve the oxidation of acetyl **CoA** on a continuing basis, intermediates consumed in certain steps must be regenerated in others. Thus we have a situation similar to that in the Calvin cycle (Section 20-9), whereby the first stage of the cycle achieved the desired reaction (CO_2 formation) and the second stage is designed to regenerate intermediates necessary to perpetuate the cycle.

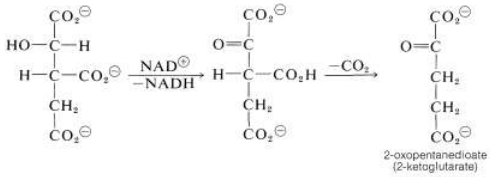
The entry point is the reaction between acetyl **CoA** and a four-carbon unit, 2-oxobutanedioic acid. An aldol-type addition of the CH_3CO group to this C_4 keto acid extends the chain to a branched C_6 acid (as citric acid):



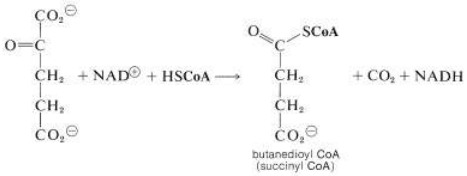
Dehydration-rehydration of citrate converts it to isocitrate:



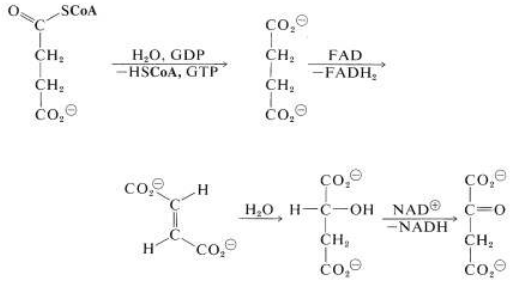
From here, oxidation of the hydroxyl function with $NAD^{\oplus}$ gives a keto acid, which loses CO_2 readily (Section 18-4) and affords 2-oxopentanedioate:



We now have a C_5 keto acid that can be oxidized in the same way as the C_3 keto acid, pyruvic acid, to give a butanedioyl **CoA**:



Two molecules of CO_2 now have been produced and the remaining part of the citric acid cycle is concerned with regeneration of the **CoA** for forming acetyl **CoA** from 2-oxopropanoate, and also with regenerating the 2-oxobutanedioate, which is the precursor of citrate. The steps involved are



The hydrolysis of the acyl **CoA** in the first step is used for energy storage by conversion of guanosine diphosphate (GDP) to guanosine triphosphate (GTP):

The hydration of the *trans*-butenedioate (Section 10-3G) and the final oxidation reaction (Section 15-6C) have been discussed previously.

20.11.3: Alternative Routes in Carbohydrate Metabolism

There is an alternative route, called the *pentose phosphate pathway*, by which glucose enters the glycolytic sequence to pyruvate. This route achieves the oxidative decarboxylation of glucose to give ribose, as the 5-phosphate ester. The essential steps are

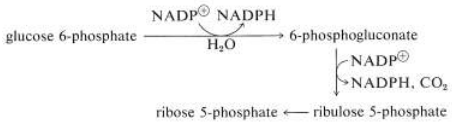
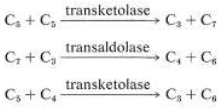


Figure 20-11). The reactions that accomplish this are very similar to those of the Calvin cycle (Section 20-9), only in reverse. They may be summarized as



The net result is that three pentoses are converted into two molecules of fructose and one of glyceraldehyde $(3C_5 \rightarrow 2C_6 + C_3)$.

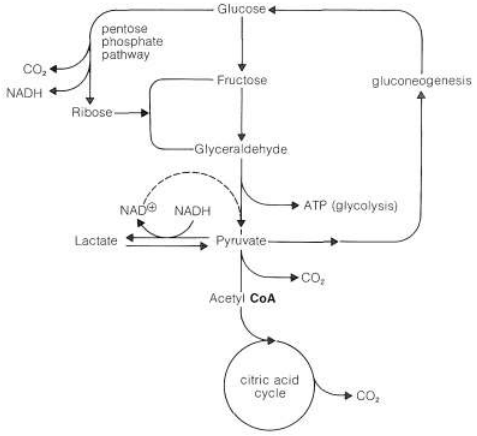


Figure 20-11: Schematic representation of metabolism of glucose by way of glycolysis and citric acid cycle, and the pentose phosphate, lactate, and gluconeogenesis links.

The relationship of the pentose-phosphate pathway to glycolysis is shown in Figure 20-11. The steps involved in the pentose shunt are readily reversible, but there are several steps in glycolysis that are not. These are the phosphorylation steps (Figure 20-9). Yet, there has to be a return route from pyruvate to glucose. This route is called **gluconeogenesis** and, in animals, takes place in the liver. We shall not discuss the steps in gluconeogenesis except to indicate again that they are not all the reverse of glycolysis. For comparison, the steps that differ are indicated in Figure 20-9 by dashed lines.

Why is lactate formed from pyruvate in the metabolism of glucose? Pyruvate $+ \mathrm{NADH} + \mathrm{H}^{\oplus} \rightarrow$ lactate $+ \mathrm{NAD}^{\oplus}$ is a dead-end path, but it does furnish the $\mathrm{NAD}^{\oplus}$ needed for glycolysis in active muscle. This route for forming $\mathrm{NAD}^{\oplus}$ is important, because in circumstances of physical exertion, the rate of production of $\mathrm{NAD}^{\oplus}$ from oxidative phosphorylation may be slower than the demand for $\mathrm{NAD}^{\oplus}$, in which case a temporary supply is available from the pyruvate $\rightarrow$ lactate reduction. The lactate so formed builds up in muscle tissue under conditions of physical exertion and is apt to cause muscles to "cramp". The excess lactate so formed ultimately is removed by being converted back to pyruvate by oxidation with $\mathrm{NAD}^{\oplus}$.

The beauty of the metabolic cycle through pyruvate, shown in summary in Figure 20-11, is the way it can be tapped at various points according to whether the organism requires ATP (from glycolysis), NADH (from pentose shunt), or $\mathrm{NAD}^{\oplus}$ (from the lactate siding).

20.11.4: Contributors and Attributions

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20.E: Carbohydrates (Exercises)

Exercise 20-1 The logic necessary to solve this problem essentially is that used by Fischer in his classic work which established the configurations of glucose, arabinose, and mannose.

a. The projection formulas for all the theoretically possible *D*-aldopentoses, $HOCH_2(CHOH)_3CHO$, are shown in Figure 20-1. One of the *D*-aldopentoses is the naturally occurring *D*-arabinose, which is enantiomeric with the more abundant *L*-arabinose. Oxidation of *D*-arabinose with nitric acid gives an optically active 2,3,4-dihydroxypentanedioic acid. Which of the *D*-aldopentoses could be *D*-arabinose?

b. *D*-Arabinose is converted by the Kiliani-Fischer synthesis[3] to *D*-glucose and *D*-mannose. What do these transformations tell about the relationship between the configurations of mannose and glucose?

c. Oxidation of *D*-glucose and *D*-mannose gives the 2,3,4,5-tetrahydroxyhexanedioic acids, glucaric and mannaric acids, respectively, both are optically active. What are the configurations of the *D*- and *L*-arabinoses?

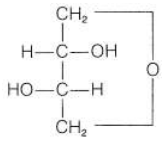
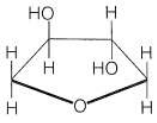
d. *D*-Glucaric acid can form *two different* γ-monolactones, whereas *D*-mannaric acid can form only *one* γ-monolactone. What are the configurations of *D*-glucose and *D*-mannose?

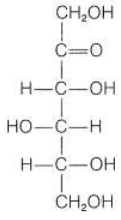
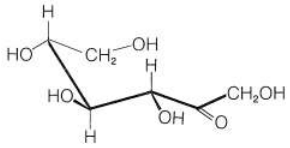
Exercise 20-2

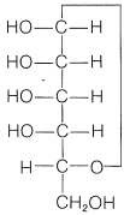
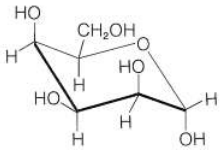
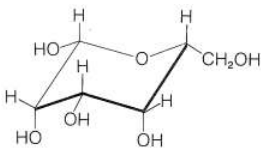
a. Deduce possible configurations of natural galactose from the following observations. Give your reasoning. (1) *D*-Galactose gives a pentose by one Wohl degradation. On nitric acid oxidation this pentose gives an optically active 2,3,4-trihydroxypentanedioic acid. (2) The pentose by a second Wohl degradation followed by nitric acid oxidation gives *D*-tartaric acid.

b. Write reasonable mechanisms for the reactions involved in the Wohl degradation.

Exercise 20-3 Determine each of the following sets of structures whether they correspond to the *same* stereoisomer. The left structure in each example is a Fischer projection formula. Models will be helpful.

a.  and 

b.  and 

c.  and  and 

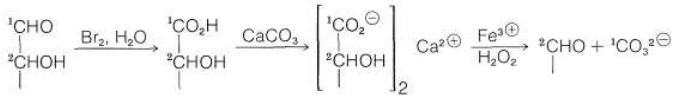
Exercise 20-4 Draw the chair conformation of β-*D*-glucose with all of the substituent groups *axial*. Explain how hydrogen bonding may complicate the usual considerations of steric hindrance in assessing the stability of this conformation relative to the form with all substituent groups equatorial.

Exercise 20-5 Make a sawhorse drawing of what you believe to be the favored conformations of α- and β-*D*-ribopyranose and of α- and β-*D*-idopyranose.

Exercise 20-6 From the following information deduce the ring structures of the sugars. Give your reasoning.

Sugar (as methyl glycoside)	Moles of $IO_4^{\ominus}$ consumed	Moles of HCO_2H formed	Moles of H_2CO formed
methyl α-D-mannoside	2	1	0
methyl α-D-riboside	1	0	0
a methyl glycoside of an aldohexose	3	2	0
a methyl glycoside of an aldohexose	2	0	1

Exercise 20-7 *D*-Arabinose and *D*-ribose give the *same* phenylosazone. *D*-Ribose is reduced to the optically inactive 1,2,3,4,5-pentanepentol, ribitol. *D*-Arabinose can be degraded by the **Ruff** method, which involves the following reactions:



The tetrose, *D*-erythrose, so obtained can be oxidized with nitric acid to *meso*-tartaric acid. Show how this information can be organized to establish the configurations of *D*-arabinose, *D*-ribose, ribitol, and *D*-erythrose.

Exercise 20-8 Work out a mechanism for the acid-induced hydrolysis of N-glycosides. Pay special attention as to where a proton can be added to be most effective in assisting the reaction. Would you expect that adenosine would hydrolyze more, or less, readily than N-methyl-α-ribosylamine? Give your reasoning.

Exercise 20-9

a. Which of the disaccharides, 24 through 27, would you expect to be reducing sugars?

b. Determine the configuration of each of the *anomeric* carbons in 24 through 27 as either α or β.

c. Determine which monosaccharides (neglect the anomeric forms) will be produced on hydrolysis of 24 through 27. Be sure you specify the configurations as *D* or *L*.

Exercise 20-10 Draw Haworth and conformational structures for each of the following disaccharides:

a. 6-O-β-*D*-glucopyranosyl-β-*D*-glucopyranose
b. 4-O-β-*D*-galactopyranosyl-α-*D*-glucopyranose
c. 4-O-β-*D*-xylopyranosyl-β-*L*-arabinopyranose
d. 6-O-α-*D*-galactopyranosyl-β-*D*-fructofuranose

Exercise 20-11 Show how the structure of maltose can be deduced from the following:

(1) The sugar is hydrolyzed by yeast α-*D*-glucosidase to *D*-glucose.

(2) Maltose mutarotates and forms a phenylosazone.

(3) Methylation with dimethyl sulfate in basic solution followed by acid hydrolysis gives 2,3,4,6-tetra-O-methyl-*D*-glucopyranose and 2,3,6-tri-O-methyl-*D*-glucose.

(4) Bromine oxidation of maltose followed by methylation and hydrolysis gives 2,3,4,6-tetra-O-methyl-*D*-glucopyranose and a tetramethyl-*D*-gluconic acid, which readily forms a γ-lactone.

Exercise 20-12 Cellobiose differs from maltose only in its behavior to enzymatic hydrolysis. It is hydrolyzed by yeast β-*D*-glucosidase. What is its structure?

Exercise 20-13 Show how the structure of lactose may be deduced from the following:

(1) The sugar is hydrolyzed by β-*D*-galactosidase to a mixture of equal parts of *D*-glucose and *D*-galactose.

(2) Lactose mutarotates and forms a phenylosazone.

(3) Bromine oxidation of lactose followed by hydrolysis gives *D*-gluconic acid and *D*-galactose.

(4) Methylation and hydrolysis of lactose gives a tetra-O-methyl-*D*-galactose and 2,3,6-tri-O-methyl-*D*-glucose. The same galactose derivative can be obtained from the methylation and hydrolysis of *D*-galactopyranose.

(5) Bromine oxidation of lactose followed by methylation and hydrolysis yields tetra-O-methyl-1,4-gluconolactone and the same galactose derivative as in (4).

Exercise 20-14 Explain how the β-*D*-glucoside units of cellulose produce a polymer with a stronger, more compact physical structure than the α-*D*-glucose units of starch. Models will be helpful.

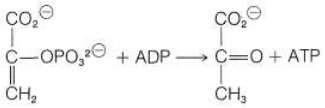
Exercise 20-15 Write Fischer projections, Haworth projections, and sawhorse conformational drawings for the following:

a. α-*D*-glucuronic acid
b. β-*D*-iduronic acid
c. α-*D*-guluronic acid

Exercise 20-16 Explain how you could account for the fact that ascorbic acid is most stable in the enediol form rather than having its C_3 and C_2 carbons arranged either as $-C(=O)-CH(OH)-$ or as $-CH(OH)-C(=O)-$.

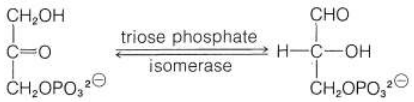
Exercise 20-17* Write mechanisms, supported by analogy insofar as possible, for the carboxylation and cleavage reactions of Equation 20-4 as you would expect them to occur in the *absence* of an enzyme. Both reactions can be reasonably expected to be induced by $OH^{\ominus}$, and it may be helpful to review the properties of enols described in Section 17-1.

Exercise 20-18* From the discussion in Section 15-5F, it should be clear that the reaction of an alcohol phosphate with ADP to give ATP, $ROPO_3^{2-} + ADP \rightarrow ATP + ROH$, is not likely to have a favorable equilibrium constant. Explain why one might expect the following reaction to be more energetically favorable.



Exercise 20-19* The heat of combustion of glucose(s) to $CO_2\,(g)$ and $H_2O\,(l)$ is $670\ \text{kcal mol}^{-1}$, whereas that of 2-oxopropanoic acid (l) is $280\ \text{kcal mol}^{-1}$. Neglecting the heats of solution of the compounds in water, estimate the energy of glucose $(aq) + O_2 \rightarrow 2CH_3COCO_2H\,(aq) + 2H_2O\,(l)$.

Exercise 20-20* The following interconversion is catalyzed by the enzyme *triose phosphate isomerase*:



Explain how you might use bond energies to estimate whether the equilibrium constant, K, for this reaction would be greater, or less, than unity.

Exercise 20-21* Assuming that one molecule of glucose is oxidized to two molecules of 2-oxopropanoic acid (pyruvic acid), how many moles of ATP are formed from ADP in the overall reaction by the sequence of steps given in Figure 20-9?

Exercise 20-22* The reaction $ADP + RCO{-}SR' + PO_4^{3-} \rightarrow ATP + RCO_2H + HSR'$ is substantially more favorable than the corresponding reaction with RCO_2R. On the basis of the valence-bond treatment, explain why this should be so.

Exercise 20-23* Citric acid is prochiral. Nonetheless, if one were to introduce acetyl **CoA** labeled with ^{14}C (radioactive carbon) at the carboxyl group, $CH{-}_3{}^{14}COS\mathbf{CoA}$, into the citric acid cycle, the 2-oxopentanedioate acid (2-ketoglutarate) formed in the fourth step of the cycle would have *all* of the ^{14}C in the carboxylate group *farthest* away from the ketone carbonyl group. For some years, this result was used to argue that citric acid itself could not be an intermediate in the formation of 2-oxopentanedioate. Review Section 19-8 and explain how, in stereospecific enzyme-induced reactions, citric acid could be an intermediate in the formation of 2-oxopentanedioate even if the ^{14}C would *not* appear equally in both carboxylic carbons of the product.

Exercise 20-24* What analogy can you draw from reactions studied in previous chapters to the cleavage $RCOCH_2COS\mathbf{CoA} + HS\mathbf{CoA} \rightarrow RCOS\mathbf{CoA} + CH_3COS\mathbf{CoA}$? What reagents would you expect to cause this reaction to occur in water solution?

Exercise 20-25* A first step in unraveling the mechanism of the metabolism of fatty acids was made in 1904 by F. Knoop, who found that dogs metabolized 4-phenylbutanoic acid to phenylethanoic acid and 3-phenylpropionic acid to benzoic acid. What does this pattern of results indicate about the mechanism of degradation of fatty acids? Give your reasoning.

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Exercise 20-26* A very strong man can lift $225\ \text{kg}\ (500\ \text{lb})$ 2 meters $(6.5\ \text{ft})$. Muscle action gets its energy from the reaction $\text{ATP} + \text{H}_2\text{O} \rightarrow \text{ADP} + \text{H}_2\text{PO}_4^-$, a process with a ΔG^0 of $-7\ \text{kcal}$.

a. Assuming 50% efficiency in the use of the hydrolysis free energy, how many grams of ATP (MW 507) would have to be hydrolyzed to achieve this lifting of the weight? (One kg raised one meter requires $2.3\ \text{cal}$ of energy.)

b. How many grams of glucose would have to be oxidized to CO_2 and water to replenish the ATP used in Part a on the basis of a 40% conversion of the energy of combustion to ATP? (ΔG^0 for combustion of glucose is $-686\ \text{kcal}$.)

Exercise 20-27 A naturally occurring optically active pentose $(\text{C}_5\text{H}_{10}\text{O}_5)$ reduces Tollen's reagent and forms a tetraethanoate with ethanoic anhydride. It gives an optically *inactive* phenylosazone. Write all the possible structures for this pentose that are in accord with each of the experimental observations.

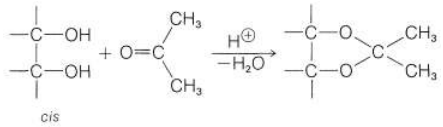
Exercise 20-28 A hexose, $\text{C}_6\text{H}_{12}\text{O}_6$, which we shall call X-ose, on reduction with sodium amalgam gives pure *D*-sorbitol, and upon treatment with phenylhydrazine gives an osazone different from that of *D*-glucose. Write a projection formula for X-ose and equations for its reactions.

Exercise 20-29 Compound A, $\text{C}_5\text{H}_{10}\text{O}_4$, is optically active, forms a diethanoate ester with ethanoic anhydride, but does not give a silver mirror with $\text{Ag}^{\oplus}(\text{NH}_3)_2$. When treated with dilute acid, A yields methanol and B, $\text{C}_4\text{H}_8\text{O}_4$. B is optically active, reduces $\text{Ag}^{\oplus}(\text{NH}_3)_2$, and forms a triethanoate ester with ethanoic anhydride. On reduction, B gives optically inactive C, $\text{C}_4\text{H}_{10}\text{O}_4$. Mild oxidation of B gives D, a carboxylic acid, $\text{C}_4\text{H}_8\text{O}_5$. Treatment of the amide of D with dilute sodium hypochlorite solution gives $(+)$ -glyceraldehyde $(\text{C}_3\text{H}_6\text{O}_3)$. (For a description of this reaction see Section 23-12E.) Use these facts to derive structures and stereochemical configurations for A, B, C, and D. Write equations for all the reactions involved.

Exercise 20-30 Draw Haworth- and conformation-type formulas for each of the following:

a. methyl 2,3,4,6-O-tetramethyl-α-*D*-glucopyranoside
b. β-*D*-arabinofuranosyl-α-*L*-arabinofuranoside
c. *L*-sucrose

Exercise 20-31 Sugars condense with anhydrous 2-propanone in the presence of an acid catalyst to form cyclic ketals known as isopropylidene derivatives:



The reaction of *D*-glucose with 2-propanone and an acid catalyst produces a mono- and a diisopropylidene derivative. Acid hydrolysis of the diisopropylidene derivative gives the monoisopropylidene compound. O-Methylation of the diketal derivative (Section 20-4A) followed by hydrolysis of the ketal groups forms 3-O-methyl-*D*-glucose. O-Methylation of the monoketal derivative followed by hydrolysis of the ketal function forms a tri-O-methyl-*D*-glucose. This tri-O-methyl-*D*-glucose when O-methylated forms an isomer of penta-O-methyl-*D*-glucopyranose. This isomer when subjected to hydrolysis in dilute acid yields an isomer of 2,3,4,6-tetra-O-methyl-*D*-glucopyranose (20, Figure 20-4). Write structures for these cyclic ketals which agree with the experimental evidence. Give your reasoning. (Review Sections 20-2C and 20-4A.)

Figure 20-32 Complete the following sequence of reactions, writing structures for all the products, A-I.

a. α-*D*-glucofuranose $\xrightarrow[\text{HCl}]{\text{1 mol 2-propanone}}$ *A* (see Exercise 20-31)

b. $A \xrightarrow{\text{NaIO}_4} B$

c. $B \xrightarrow{\text{Na}\,^{14}\text{CN}} C + D$

d. $C + D \xrightarrow[\text{2. H}^{\oplus}\textit{plus}, \text{H}_2\text{O}]{\text{1. H}_2\text{O, OH}^{\ominus}} E + F +$ 2-propanone

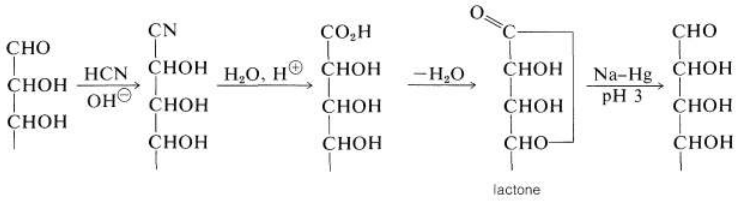
e. $E + F \xrightarrow[-\text{H}_2\text{O}]{\text{heat}} G + H$

f. $G + H \xrightarrow[\text{H}_2\text{O}]{\text{NaBH}_4} i +$ *D*-glucose-6-^{14}C

Exercise 20-33 Write a mechanism for the interconversion of an aldohexose and a ketohexose that is catalyzed by hydroxide ion. What products would you expect starting with *D*-glucose?

Exercise 20-34 The glycoside amygdalin $(C_{20}H_{27}O_{11}N)$ is hydrolyzed with the aid of the enzyme emulsin (but not with the enzyme maltase) to give *D*-glucose, HCN, and benzenecarbaldehyde. O-Methylation of amygdalin, followed by acid hydrolysis, gives 2,3,4,6-tetra-O-methyl-*D*-glucose and 2,3,4-tri-O-methyl-*D*-glucose. Write a structure for amygdalin that fits with these observations.

[3]The steps of the Kiliani-Fischer synthesis are:



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CHAPTER OVERVIEW

21: Resonance and Molecular Orbital Methods

Molecular orbital theory is a method for determining molecular structure in which electrons are not assigned to individual bonds between atoms, but are treated as moving under the influence of the nuclei in the whole molecule. The spatial and energetic properties of electrons within atoms are fixed by quantum mechanics to form orbitals that contain these electrons. While atomic orbitals contain electrons ascribed to a single atom, molecular orbitals, which surround a number of atoms in a molecule, contain valence electrons between atoms. There are two popular approaches to the formulation of the structures and properties of organic compounds based on quantum mechanics - **resonance** and **molecular-orbital** methods. In the past, there has been great controversy as to which of these methods actually is more useful for qualitative purposes and, indeed, the adherents to one or the other could hardly even countenance suggestions of imperfections in their choice. Actually, neither is unequivocally better and one should know and use both - they are in fact more complementary than competitive.

21.1: Prelude to Resonance and Molecular Orbital Methods
21.2: Characteristics of Simple Covalent Bonds
21.3: Comparison of the Resonance and Molecular-Orbital Methods
21.4: The Benzene Problem
21.5: Application of the MO Method to 1,3-Butadiene
21.6: Application of MO Theory to Other Systems
21.7: Which Is Better- MO or VB?
21.8: More on Stabilization Energies
21.9: Bond Lengths and Double-Bond Character
21.10: Hückel's 4n + 2 Rule
21.11: Pericyclic Reactions
21.12: Evidence Bearing on the Mechanism of [2 + 2] Cycloadditions
21.E: Resonance and Molecular Orbital Methods (Exercises)

21.1: Contributors and Attributions

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21.1: Prelude to Resonance and Molecular Orbital Methods

The structural theory of organic chemistry originated and developed from the concepts of valence and the tetrahedral carbon atom. It received powerful impetus from the electronic theory of bonding, as described in Chapter 6. We now express the structures of many organic compounds by simple bond diagrams which, when translated into three-dimensional models, are compatible with most observed molecular properties. Nonetheless, there are many situations for which ordinary structure theory is inadequate. An example is benzene (Section 1-1G), which does not behave as would be expected if it were a cyclic polyene related to alkatrienes, such as $CH_2{=}CH{-}CH{=}CH{-}CH{=}CH_2$.

There are many other substances that do not behave as predicted from the properties of simpler compounds. Some substances are more stable, some more reactive, some more acidic, some more basic, and so on, than we would have anticipated. In this chapter we shall look at the theories that explain some of these apparent anomalies. These theories will be based on quantum-mechanical arguments (Section 1-5).

There are two popular approaches to the formulation of the structures and properties of organic compounds based on quantum mechanics - **resonance** and **molecular-orbital** methods. In the past, there has been great controversy as to which of these methods actually is more useful for qualitative purposes and, indeed, the adherents to one or the other could hardly even countenance suggestions of imperfections in their choice. Actually, neither is unequivocally better and one should know and use both - they are in fact more complementary than competitive.

We have used the concepts of the resonance methods many times in previous chapters to explain the chemical behavior of compounds and to describe the structures of compounds that cannot be represented satisfactorily by a single valence-bond structure (e.g., benzene, Section 6-5). We shall assume, therefore, that you are familiar with the qualitative ideas of resonance theory, and that you are aware that the so-called **resonance** and **valence-bond methods** are in fact synonymous. The further treatment given here emphasizes more directly the quantum-mechanical nature of valence-bond theory. The basis of molecular-orbital theory also is described and compared with valence-bond theory. First, however, we shall discuss general characteristics of simple covalent bonds that we would expect either theory to explain.

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21.2: Characteristics of Simple Covalent Bonds

The simplest kind of bond is that between univalent atoms in diatomic molecules, such as H_2, F_2, and so on. In the gas phase the molecules are in rapid motion, colliding with one another and the walls of the container. The atoms vibrate with respect to one another, and the molecules have rotational energy as well. Despite this activity, we can assign an average equilibrium bond distance (r_e) and an average bond energy (D_e) for normal, unexcited molecules. From *ab initio* calculations (Section 6-6), we learn that the energy of an H_2 molecule is a function of r, the distance between the hydrogens, as shown in Figure 21-1.

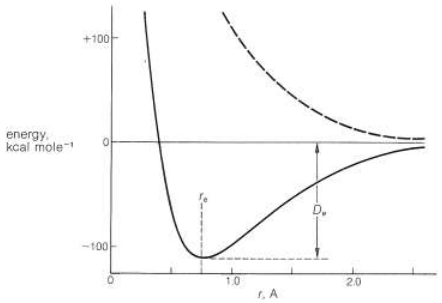

Figure 21-1: Energy of H_2 as a function of the internuclear distance between the hydrogens. The zero of energy is that of two hydrogen atoms at an infinite distance from one another. The corresponding curve for dissociation into $H^{\oplus}$ and $H^{\ominus}$ would reach about $+295$ kcal mol^{-1} at infinite separation. Similar curves are expected for other electron-pair bonds, but the r_e values are much larger. Thus bonds to carbon commonly fall in the range of 1.1 Å (C–H bonds) to 2.2 Å (C–I bonds). The upper dashed cure is for the approach of two hydrogen atoms whose electrons have parallel spins.

When the distance is reduced from r_e, the energy increases very rapidly because of internuclear repulsion. As the separation between the atoms increases, the energy of the system increases more slowly and finally approaches that of the entirely free atoms.

The distance r_e, which corresponds to the bond length at minimum energy, *increases* with atomic number downward in a column of the periodic table as the atoms get larger. It *decreases* across a horizontal row of the periodic table as the electronegativity of the atoms increases and the atomic radius becomes smaller. Other things being equal, the stronger the bond is, the shorter r_e will be, because a strong bond overcomes the repulsive forces between the nuclei and thus permits them to move closer together. For bonds between two carbon atoms, r_e usually ranges between about 1.20 Å and 1.55 Å and, if Figure 21-1 (or anything similar) applies, we should not expect significant C–C bonding at internuclear distances greater than 2 Å.

It is important to recognize that bonding occurs only if the electrons are paired (i.e., have opposite spins). The upper dashed curve of Figure 21-1 shows how the energy changes as two hydrogen atoms will parallel spins approach one another. That there is no net bonding can be understood by the Pauli principle (Section 6-1), which tells us that two electrons cannot be in the same orbital if they are unpaired.

21.2.1: Contributors and Attributions

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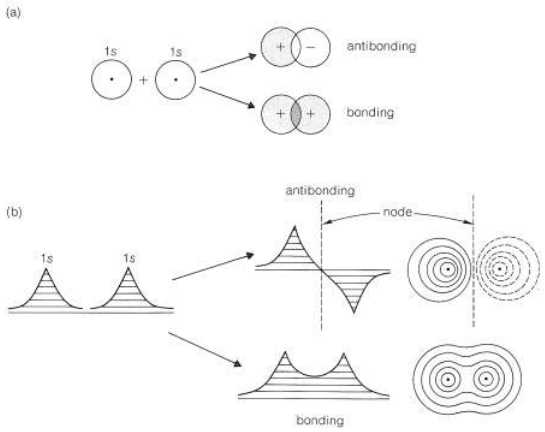
21.3: Comparison of the Resonance and Molecular-Orbital Methods

21.3.1: The Electron-Pair Bond

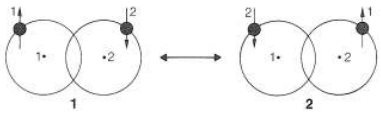
In this section, we will sketch the similarities and differences in the resonance (or valence-bond, VB) and molecular-orbital (MO) approaches for electron-pair bonds. Both methods normally start with atomic orbitals $1s$, $2s$, $2p$, and so on, of the types discussed in Section 6-1. Where the methods differ is in how these orbitals are used. For a bond between two atoms, the **MO procedure** combines (or mixes) *two atomic orbitals*, one from each atom, with proper account of orbital phase (Section 6-2) to obtain *two molecular orbitals*, one of low energy and one of higher energy. The atomic orbitals can be pure or hybrid orbitals (Sections 6-1 and 6-4). In Figure 21-2, we show the results of combining the $1s$ orbitals of hydrogen. The calculation for the most stable state proceeds by determining the energy of the system when two *paired* electrons are in the low-energy molecular orbital. The binding energy is the difference between the energy so calculated and the energies of the separated atoms. Because the molecular orbital extends over *both* atoms, the bonding electrons must be associated with both atoms.



node. (Do not confuse + and − amplitudes with + and − electronic charges.)

Remember, the MO method first combines the atomic orbitals to give molecular orbitals, then populates the molecular orbitals with electrons (no more than two *paired* electrons per orbital). This part of the procedure is similar to the way electrons are allocated to atomic orbitals (Section 6-1).

The **VB treatment** starts with the same atomic orbitals but assigns one electron to each orbital. For an electron-pair bond between two hydrogen atoms, the VB treatment in its simplest form considers two *electronic configurations*. One of these has electron 1 in the orbital of hydrogen 1 and electron 2 in the orbital of hydrogen 2, (1). The other configuration, 2, has electron 2 in the orbital of hydrogen 1 and electron 1 in the orbital of hydrogen 2:



The calculation then proceeds to predict a low-energy state and a high-energy state. These states can be regarded as *hybrids* of 1 and 2. The low-energy state, which is the one of more interest to us, usually is called a *resonance hybrid*.

In the VB method, *each* of the electrons becomes associated with *both* atoms through the mixing of the two configurations. A very important point here is that the calculation that mixes 1 and 2 leads to a six times greater binding energy than calculated for 1 and 2 alone. Thus in the VB treatment we combine *electronic configurations* (here 1 and 2, $\leftrightarrow$ symbolizing mixing), whereas in the MO treatment we combine *atomic orbitals* to get low- and high-energy molecular orbitals.

21.3.2: What is the Glue in These Bonds?

The forces that hold atoms together through chemical bonds are electrostatic, that is, the attraction of positively charged nuclei for negatively charged electrons. But the energy calculated for a single configuration, such as 1, only accounts for about one sixth of

the total binding. In either the VB or the MO method the electrons in an electron pair between two nuclei brought to within bonding distances are equivalent and indistinguishable. That is, we are unable to identify one electron any more than the other with a given atom. The significance of the pairing of the electrons is that is permits each electron to have maximum possible freedom to move through the orbitals of the two-atom system rather than being "localized" on particular atoms. Quantum-mechanical calculations tell us that freedom of motion of the electrons is very important. Thus, using the VB method, we calculate that fully five sixths of the binding of the hydrogen molecule is associated with the "delocalization" of the electrons between the two nuclei.

There are many compounds with structures in which electrons are delocalized over *more than two atoms*. Such molecules should be more stable than would be expected for molecules with the same geometry but with electron pairs constrained to be associated with just one or two atoms. We will shortly discuss some specific examples, but because most of these examples involve the delocalization of π electrons, it is expedient to first discuss ethene as a prototype, using both the MO and VB methods.

21.3.3: The π Bond in Ethene

The atomic-orbital picture of ethene (Figure 6-14) formulates the π bond as resulting from overlap of two adjacent p atomic orbitals, one from each of two sp^2 hybridized carbons. The p orbitals are directed perpendicularly to the plane defined by the hybrid orbitals of the σ bonds, and to a first approximation, we assume that exchange of the π and σ electrons between their respective orbitals does not affect the energy of the molecule. If this assumption is valid, π bonding can be treated independently of σ bonding. Although undoubtedly oversimplified, the VB and MO methods have been remarkably successful using this assumption. In our subsequent discussions, we shall treat the π electrons separately from localized σ electrons.

The π bond of the ethene molecule can be formulated very much like the bond in the hydrogen molecule (Section 21-2A), with the difference that the bonding is achieved by the overlap of two $2p$ atomic orbitals of carbon rather than two $1s$ atomic orbitals of hydrogen.

In the MO method the mixing of the two $2p$ atomic orbitals gives two molecular orbitals. The details of the mathematics of the mixing process to give an optimum set of molecular orbitals are well beyond the scope of this book,[1] but the results are shown in Figure 21-3. The two π electrons of ethene are taken as occupying the low-energy bonding orbital, while the high-energy antibonding orbital normally is empty.

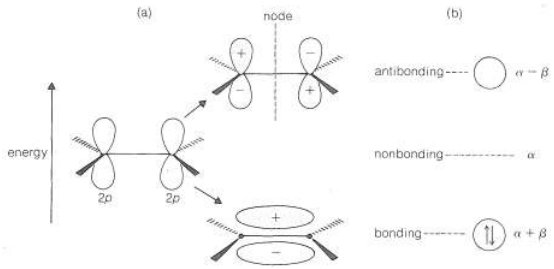
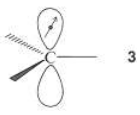


Figure 21-3: *(a) Representation of the bonding and antibonding molecular orbitals formed by the combination of two p atomic orbitals on adjacent sp^2-hybridized carbons, as in ethene. (b) Relative energies of the bonding and antibonding orbitals. The bonding orbital is populated with two paired electrons in the normal (or ground) state of the ethene π bond. The π-electron energy for each electron is $\alpha + \beta$. Therefore the π-electron energy of ethene is $2(\alpha + \beta) = 2\alpha + 2\beta$. The energy terms, α and β, are* negative quantities.

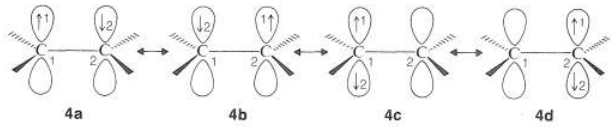
How much more stable is the bonding molecular orbital relative to a pair of noninteracting p atomic orbitals? It is difficult to provide a numerical answer in kcal mol^{-1} that is meaningful, but we can describe the energy in symbolic terms. First, the energy of one electron in the p atomic orbital of an sp^2-hybridized carbon, as in 3, is taken as a standard quantity, α, often called the **Coulomb energy**:



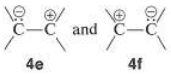
Thus, if there were no π bonding in ethene and no repulsion between the electrons, the energy of the two electrons (one in each of the two adjacent p orbitals of the carbons) would be twice the Coulomb energy, or 2α. This would be the situation for two carbons such as 3 that are widely separated.

The MO calculation shows that the bonding molecular orbital of ethene is more stable (of lower energy) than the nonbonding level, α, by a quantity, β, where β is a *negative* energy term (Figure 21-3). Likewise, the antibonding level is destabilized by an amount $-\beta$. For *two* paired electrons in the bonding molecular orbital, the π-electron energy of ethene is calculated to be $2(\alpha+\beta) = 2\alpha + 2\beta$.

In the valence-bond approach, the π bond of ethene is considered to be a hybrid of all reasonable electronic configurations of two indistinguishable paired electrons distributed between two p orbitals. Each of the configurations that can be written, $4a$, $4b$, $4c$, and $4d$, have identical locations of the atomic nuclei in space:



The four valence-bond structures or configurations, $4a$-d, are combined mathematically to give four hybrid states, and of these, the lowest-energy one corresponds approximately to the normal state of the molecule. The calculation shows that the structures $4a$ and $4b$, which have one electron in each p orbital, are the major contributors to the "hybrid" of ethene. The valence-bond structures, $4c$ and $4d$, are *ionic structures*, which correspond to the conventional formulas, $4e$ and $4f$:



These valence-bond structures are not important to the π bond of the ground state of ethene, although they are important for carbonyl bonds (Section 16-1B).

[1]There are many excellent books that cover this subject in great detail; however, the simplest introductory work is J. D. Roberts; *Molecular Orbital Calculations*, W. A. Benjamin, Inc., Menlo Park, Calif., 1961.

21.3.4: Contributors and Attributions

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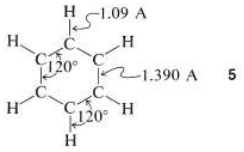
21.4: The Benzene Problem

We already have alluded to the difficulties encountered in the interpretation of the structure of benzene in Sections 1-1G and 6-5. Our task here is to see what new insight the VB and MO treatments can give us about benzene, but first we will indicate those properties of benzene that are difficult to explain on the basis of simple structure theory.

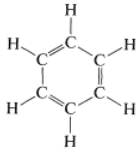
21.4.1: Some of the Unusual Properties of Benzene

From x-ray diffraction and spectroscopic measurements, benzene is known to be a planar molecule with six carbons 1.390 Å apart in a hexagonal ring, 5. Six hydrogen atoms, one associated with each carbon, are located 1.09 Å from those carbons. All $\mathrm{H{-}C{-}C}$ and $\mathrm{C{-}C{-}C}$ bond angles are 120°:



5

The 1,3,5-cyclohexatriene structure, 6, proposed for benzene in 1866 by Kekule, has alternating single and double bonds around the ring, which would be predicted to have bond lengths of 1.48 Å and 1.34 Å, respectively (see Table 2-1):



6

The knowledge that the bond lengths are equal in the ring in benzene is a point against the Kekule formulation, but a more convincing argument is available from a comparison of the chemistry of benzene with that of 1,3,5-hexatriene, 7:

$\mathrm{CH_2{=}CH{-}CH{=}CH{-}CH{=}CH_2}$ 7

1,3,5-hexatriene

Figure 21-4. The reagents that commonly add (in the dark) to the double bonds of alkenes (e.g., $\mathrm{Br_2}$, $\mathrm{Cl_2}$, HOCl, $\mathrm{H_2SO_4}$) attack benzene relatively slowly to substitute for a hydrogen atom rather than to give addition products. Nevertheless, there can be no doubt that benzene is really saturated, because it can be hydrogenated (under forcing conditions compared with simple alkenes) to cyclohexane, and, in sunlight, adds chlorine or bromine to give 1,2,3,4,5,6-hexahalocyclohexanes. Also, benzene is attacked by ozone, and the products are those expected on the basis of Kekule's cyclohexatriene structure.

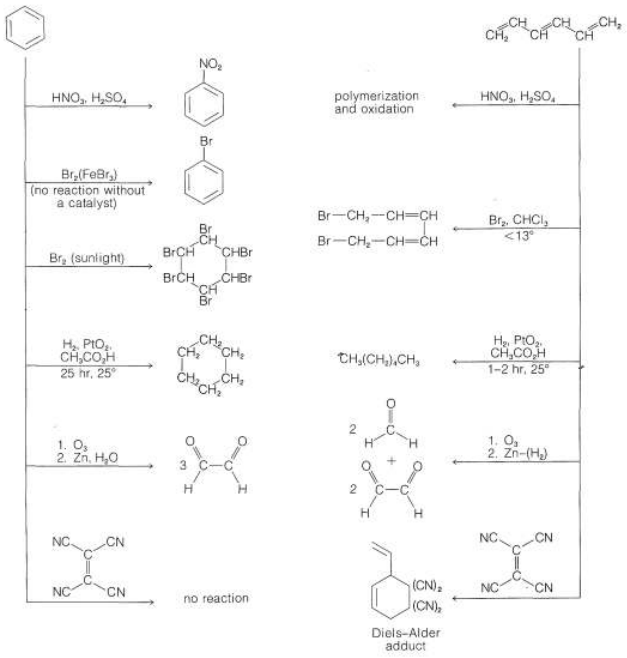


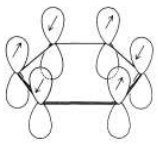
Figure 21-4: Comparative reactions of benzene and 1,3,5-hexatriene.

Benzene also is more stable by about 36-38 kcal mol^{-1} than anticipated for the 1,3,5-cyclohexatriene structure. You will recall from earlier discussions that the heat of combustion of one mole of benzene is 38 kcal *less* than calculated for cyclohexatriene (see Section 6-5A). Also, the heat of hydrogenation of benzene is only 49.8 kcal mol^{1}, which is 36 kcal *less* than expected for 1,3,5-cyclohexatriene; this estimate is based on the assumption that the heat of hydrogenation of 1,3,5-cyclohexatriene (with three double bonds) would be three times that of cyclohexane (28.5 kcal mol^{-1}, for one double bond), or $3 \times 28.2 = 85.5$ kcal mol^{-1}.

The extra stability of benzene relative to the hypothetical 1,3,5-cyclohexatriene can be called its **stabilization energy**. Most (but not all) of this stabilization may be ascribed to resonance or electron delocalization.

21.4.2: The Atomic-Orbital Model of Benzene

In Section 6-5 an atomic model of benzene was discussed in some detail. Each carbon in the ring was considered to form three coplanar sp^2-hybrid σ bonds at 120° angles. These carbon-carbon and carbon-hydrogen σ bonds use three of the four valence electrons of each carbon. The remaining six carbon electrons are in parallel p orbitals, one on each of the six carbons. Each of the π electrons can be regarded as being paired with its immediate neighbors all around the ring, as shown by 8:



8

As mentioned in Section 21-2B, delocalization of the electrons over all six centers in benzene should give a more stable electron distribution than any structure in which the electrons are localized in pairs between adjacent carbons (as in the classical 1,3,5-cyclohexatriene structure).

The simple MO and VB treatments of benzene begin with the *same* atomic-orbital model and each treats benzene as a six-electron π-bonding problem. The assumption is that the σ bonds of benzene should not be very much different from those of ethene and may be regarded as independent of the π system.

21.4.3: The Molecular Orbital Method for Benzene

Extension of the ideas of Section 21-2 for the MO treatment of an electron-pair bond between two nuclei to the π bonding in benzene is fairly straightforward. What is very important to understand is that there must be more than one molecular orbital for the π electrons because there are six π electrons, and the Pauli principle does not allow more than two paired electrons to occupy a

given orbital. In fact, combination (or mixing) os the six $2p$ orbitals of benzene, shown in 8, gives *six* π molecular orbitals. Without exception, *the number of molecular orbitals obtained by mixing is always the same as the number of atomic orbitals mixed*. The details of the mathematics of the mixing process to give an optimum set of molecular orbitals will not be described here,[1] but the results are shown in Figure 21-5. Of the six predicted molecular orbitals, three are bonding and three are antibonding. The six π electrons are assigned to the three bonding orbitals in pairs and are calculated to have a total π-electron energy of $6\alpha + 8\beta$.

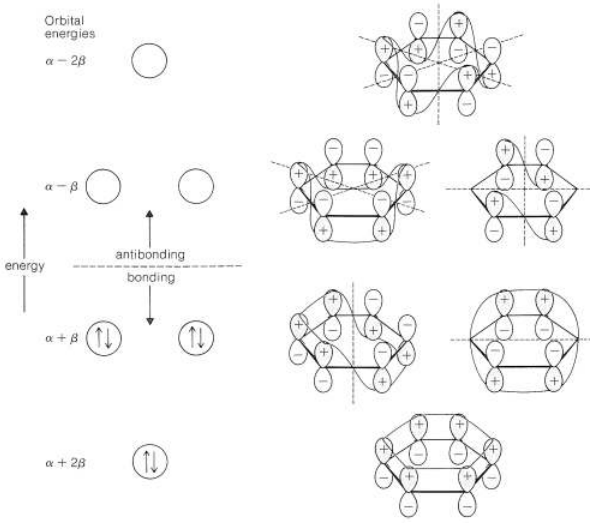


Figure 21-5: Energies and schematic representation of the π molecular orbitals of benzene. If the six π electrons are placed in the three lowest orbitals in three pairs, the π-electron energy is $2(\alpha + 2\beta) + 4(\alpha + \beta) = 6\alpha + 8\beta$, in which α and β are negative energy terms. The schematic representations are drawn to show the phase changes (nodes) of the molecular orbitals. Notice that the more phase changes there are, the less bonding and more antibonding the orbital becomes. Although one could hardly believe it by looking at the schematic representations of the occupied π orbitals, the mathematical form of these is such that benzene is predicted to have its π electrons symmetrically distributed with an average of one per carbon atom. That is, the total π-electron distribution is the same as that suggested by the lowest-energy, nodeless molecular orbital.

The calculation that leads to the results shown in Figure 21-5 is not very sophisticated. It is based on the assumption that the π bonding between each carbon and its immediate neighbors is equal all around the ring and that bonding involving carbons more than 2 Å apart is unimportant.

What happens if we use the MO method to calculate the π-electron energy of classical 1,3,5-cyclohexatriene? The procedure is exactly as for benzene, except that we decree that each carbon p orbital forms a π bond with only *one* of its neighboring p orbitals. The results are shown in Figure 21-6. The π-electron energy turns out to be three times that of ethene, or $6\alpha + 6\beta$ compared to $6\alpha + 8\beta$ for benzene.

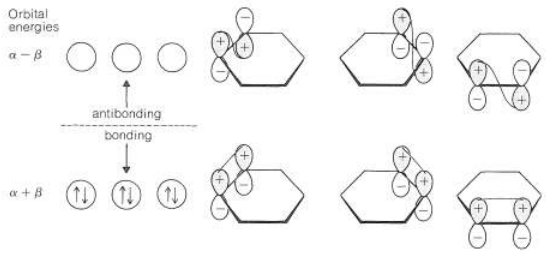
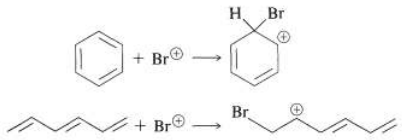


Figure 21-6: Energies and schematic representations of the π molecular orbitals of localized 1,3,5-cyclohexatriene. The molecular orbitals are the π orbitals of three localized ethene bonds and the total π-electron energy is $6(\alpha + \beta) = (6\alpha + 6\beta)$.

The calculated *delocalization energy* for benzene is the difference between these quantities, or $(6\alpha + 8\beta) - (6\alpha + 6\beta) = 2\beta$. That is to say, the calculated delocalization energy is the difference between the energy of benzene with full π bonding and the energy of 1,3,5-cyclohexatriene with alternating single and double bonds. If the electron delocalization energy (2β) is equal to the stabilization energy $(38\ \text{kcal mol}^{-1})$, then $\beta = 19\ \text{kcal mol}^{-1}$. Whether this is a valid method for determining β has been a matter of dispute for many years. Irrespective of this, the results of the calculations do account for the fact that benzene is more stable than would be expected for 1,3,5-cyclohexatriene.

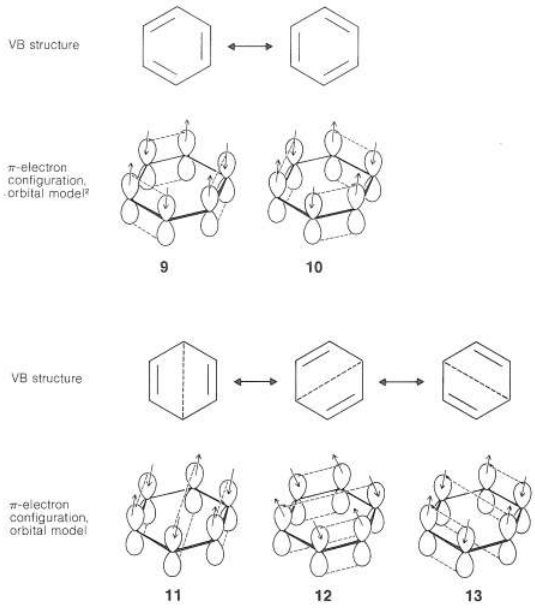
However, do the results also account for the low reactivity toward the various reagents in Figure 214, such as those that donate $Br^{\oplus}$ to double bonds (see Section 10-3A)? To settle this question, we have calculated the changes in π-electron energy that occur in each of the following reactions:



This means calculating the π-electron energies of all four entities and assuming that the differences in the σ-bond energies cancel between the two reactions. The result of this rather simple calculation is that attack of $Br^{\oplus}$ on benzene is thermodynamically *less* favorable than on 1,3,5-cyclohexatriene by about β. If β is $19\ \text{kcal mol}^{-1}$, this is clearly a sizable energy difference, and we can conclude that the simple MO method does indeed account for the fact that benzene is attacked by $Br^{\oplus}$ far less readily than is 1,3,5-cyclohexatriene.

21.4.4: The Valence Bond Method for Benzene

Extension of the basic ideas of the VB treatment described in Section 21-2 to the atomic-orbital model of benzene is straightforward. We can write VB structures that represent pairing schemes of electrons in the atomic orbitals as shown in 9 through 13:



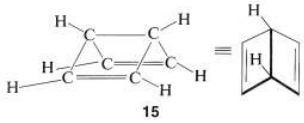
Pairing schemes 9 and 10 correspond to Kekule's structures, whereas 11, 12, and 13 are called "Dewar structures" because J. Dewar suggested, in 1869, that benzene might have a structure such as 14:

The electrons are paired in the configurations represented by 11, 12, and 13, but these pairing schemes are not as energetically favorable as 9 and 10. The reason is that the two electrons paired according to the dashed lines in 11, 12, and 13 are on nuclei separated by 2.8 Å, which is too far apart for effective bonding. The dashed lines between the distant carbons in 11, 12, and 13 are significant *only* in that they define a pairing scheme. Such lines sometimes are said to represent "formal bonds".

We hope that it is clear from what we have said here and previously that the *electron-pairing schemes 9 through 13 do not separately have physical reality or independent existence*; indeed, the energy of the actual molecule is *less* than any one of the contributing structures. The double-headed arrow between the structures is used to indicate that they represent different electron-

pairing schemes for a molecule and *not* different forms of the molecule in equilibrium with one another. When we use the resonance method in a qualitative way, we consider that the contribution of each of the several structures is to be weighted in some way that accords with the degree of bonding each would have, *if* it were to represent an actual molecule with the specified geometry. Thus the Kekule-type electron-pairing schemes, 9 and 10, are to be taken as contributing *equally* and *predominantly* to the hybrid structure of benzene - equally because they are energetically equivalent, and predominantly because they can contribute much more to the overall bonding than 11, 12, and 13.

In using the resonance method, we assume that all the resonance structures contributing to a given resonance hybrid have *exactly* the same spatial arrangements of the nuclei but different pairing schemes for the electrons. Therefore 11, 12, and 13 are not to be confused with bicyclo[2.2.0]-2,5-hexadiene, 15, because 15 is a known (albeit not very stable) molecule with different atom positions and therefore vastly different bond angles and bond lengths from benzene:



15

The electron-pairing schemes 9 and 10 represent the electron pairing that 15 would have if it were grossly distorted, with each carbon at the corner of a regular hexagon and a formal bond in place of a carbon-carbon single bond. Thus 9 and 10 would *not* contribute in a significant way to the resonance hybrid of 15.

Clearly, it is inconvenient and tedious to write the structures of the contributing forms to show the structure of a resonance hybrid. A shorthand notation is therefore desirable. Frequently, dashed rather than full lines are used where the bonding electrons are expected to be delocalized over several atoms. For benzene, 16*a* or 16*b* is quite appropriate:

16a

16b

Unfortunately, although these are clear and explicit renderings, they are tedious to draw. As a result, many authors use (as we will most often) a single Kekule structure to represent benzene, with the understanding that all the C−C bonds are equivalent. Other authors choose to represent benzene as a hexagon with an inscribed circle:

This is a simple notation for benzene, but is quite uninformative and even can be actively misleading with some aromatic ring systems, and thus should be used with this limitation in mind.

In calculations of the resonance energy of benzene, the five electronic configurations (valence-bond structures 9 through 13) are combined mathematically to give five hybrid states, and of these the lowest-energy state is assumed to correspond to the normal state of the molecule. Thus benzene is considered by this approach to be a resonance hybrid of the valence-bond structures 9 through 13. In this simple treatment, 9 and 10 are calculated to contribute about 80% and 11, 12, and 13 about 20% to the hybrid. The actual numerical VB calculations, which are much more difficult to carry through than the corresponding MO calculations, give an energy of $Q + 2.61J$ for benzene and $Q + 1.50J$ for classical 1,3,5-cyclohexatriene.[3] The resonance or delocalization energy then is $(Q + 2.61J) - (Q + 1.50J) = 1.11J$, which makes $J \sim 35\ \text{kcal mol}^{-1}$ if the resonance energy is taken to be equal to the 38 kcal value obtained for the stabilization energy. If one carries through a simple VB calculation of the *relative* energy change associated with attack of $Br^{\oplus}$ on benzene as compared to 1,3,5-cyclohexatriene, the value obtained is $0.63J$, which corresponds to 22 kcal. This is in excellent agreement with the 19 kcal value obtained by the MO method (Section 21-3C).

[1]There are many excellent books that cover this subject in great detail; however, the simplest introductory work is J. D. Roberts, *Molecular Orbital Calculations*, W. A. Benjamin, Inc., Menlo Park, Calif., 1961.

[2] Note that in 9 and also in 10, we show a particular way of pairing the electrons. However, just as $1 \leftrightarrow 2$, and $4a \leftrightarrow 4b$, we also must consider other sets that represent exchanges of electrons across the dashed lines of 9 and also of 10.

^3Q and J are negative VB energy parameters that correspond roughly to the MO parameters α and β.

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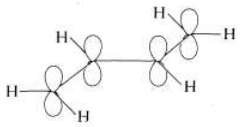
21.5: Application of the MO Method to 1,3-Butadiene

To treat the π-electron system of 1,3-butadiene by simple MO theory, we combine the four p carbon orbitals of an atomic-orbital model, such as 17, to obtain four molecular orbitals:



17

Figure 21-8). Therefore the delocalization energy is $(4\alpha + 4.48\beta) - (4\alpha + 4\beta) = 0.48\beta$ or 9 kcal, assuming that $\beta = 19$ kcal. (The corresponding VB calculation gives the delocalization in good agreement as $0.23J$ or 8 kcal; Section 21-3D.)

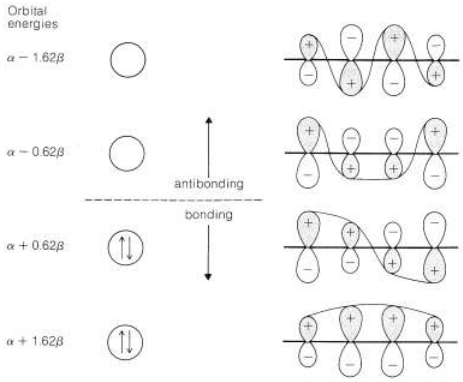


Figure 21-7: Energies and schematic representations of the π molecular orbitals of 1,3-butadiene. If four electrons are placed in the two lowest orbitals, the π-electron energy is $2(\alpha + 1.62\beta) + 2(\alpha + 0.62\beta) = 4\alpha + 4.48\beta$. The schematic representations show the number of phase changes (nodes) in each molecular orbital, and the sizes of the atomic orbitals are drawn to represent crudely the extent to which each contributes to each molecular orbital. Again, the energy of the orbitals increases with increasing number of nodes.

We can estimate a stabilization energy for butadiene from heats of hydrogenation, and it is useful to compare the values obtained with the calculated delocalization energy. Thus the heat of hydrogenation of 1,3-butadiene is 57.1 kcal, whereas that of ethene is 32.8 kcal and of propene 30.1 kcal. If ethene is used as the model alkene, the stabilization energy of 1,3-butadiene is $(2 \times 32.8 - 57.1) = 8.5$ kcal, whereas with propene as the model, it would be $(2 \times 30.1 - 57.1) = 3.1$ kcal. The bond energies (Table 4-3) in combination with the heat of formation at $25°$ $(26.33$ kcal$)$ give a stabilization energy of 5.0 kcal.

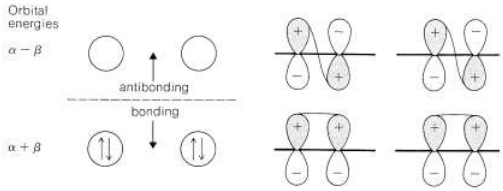


Figure 21-8: Energies and schematic representations of the π molecular orbitals of localized 1,3-butadiene. The orbitals are the π orbitals of two isolated ethene bonds and the total π-electron energy is $4(\alpha + \beta) = 4\alpha + 4\beta$.

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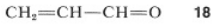
21.6: Application of MO Theory to Other Systems

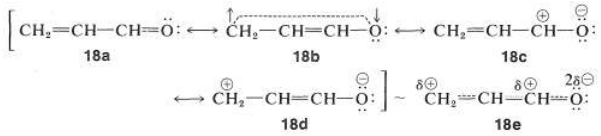
21.6.1: Polar Molecules

Many important molecules have alternating single and double bonds (are conjugated), but have atoms that are more (or less) electron-attracting than carbon. An example is propenal (acrolein), 18:



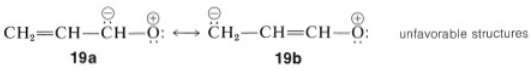
18

With such molecules we need to take into account the fact that the π electrons will be attracted to oxygen from carbon, because oxygen is more electronegative than carbon. With the VB method we can do this by considering ionic electron-pairing schemes, $18c$ and $18d$, along with the dienelike structures, $18a$ and $18b$. The hybrid, $18e$, is drawn to reflect the expected relative contributions of the various forms, with $18a$ being most important.



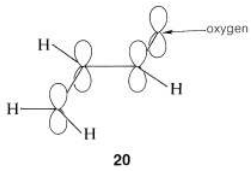
18a 18b 18c 18d 18e

Ionic structures such as $19a$ and $19b$ need not be considered for propenal because carbon is much less electron-attracting than oxygen:



19a 19b

Figure 21-7, but with a greater contribution of the p orbital of oxygen in the lower bonding molecular orbitals:

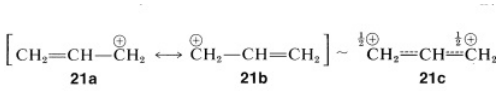


20

Analysis of the electronic configuration resulting from the MO calculations accords generally with the VB hybrid $18e$.

21.6.2: The 2-Propenyl (Allyl) Cation

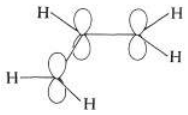
An especially important type of carbocation is represented by the 2-propenyl electron-pairing schemes, $21a$ and $21b$, which correspond to the hybrid $21c$.



21a 21b 21c

Because $21a$ and $21b$ are equivalent and no other single low-energy structure is possible, a sizable delocalization energy is expected. Evidence for this delocalization energy of $21c$ is available from the comparative ease of reactions involving formation of carbocation intermediates. An example is in S_N1 ionizations of alkenyl and alkyl halides. The ionization $CH_2{=}CHCH_2Br \rightarrow CH_2{=}CHCH_2^+ + Br^+$ proceeds *more readily* than $CH_3CH_2CH_2Br \rightarrow CH_3CH_2CH_2^+ + Br^+$ (for which no π-electron delocalization is possible).

MO treatment of the 2-propenyl cation begins with the atomic-orbital model 22:



22

Any π electrons will be delocalized through the orbitals of 22, but it is not so easy to be confident that when two electrons are placed into the lowest molecular orbital the resulting electron distribution will be the same as $21c$ with half of the positive charge on C_1 and half on C_3.

The complete calculation gives the result shown in Figure 21-9. Here the lowest-energy molecular orbital has a higher proportion of the p orbital of C_2 mixed in than the p orbitals of C_1 and C_3 - in fact, just the right amount to have C_2 neutral and C_1 and C_3 each with $\frac{1}{2}^{\oplus}$ when this MO is filled with two paired electrons. The delocalization energy calculated for the cation is $(2\alpha + 2.82\beta) - (2\alpha + 2\beta) = 0.82\beta$ or about $16\ \text{kcal}$ if β is taken to be $19\ \text{kcal}$. Thus in every respect the simple VB and MO methods give the same representation of the 2-propenyl carbocation.

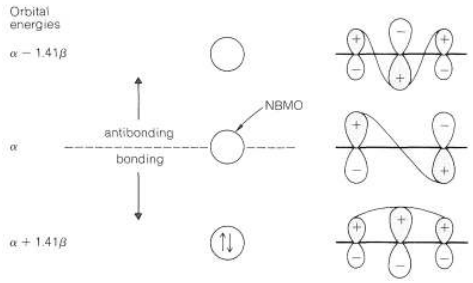


Figure 21-9: Energies and schematic representations of the π molecular orbitals of the 2-propenyl cation, 22. The calculated π-electron energy of the cation is $2(\alpha + 1.41\beta) = 2\alpha + 2.82\beta$. Orbitals with the energy α are neither bonding nor antibonding and are called "nonbonding molecular orbitals" (NBMO). The intermediate energy molecular orbital of the 2-propenyl cation is a NBMO because its component atomic orbitals, being on C_1 and C_3, are too far apart to be bonding or antibonding.

You will notice that the 2-propenyl radical and the 2-propenyl carbanion can be formulated by the same set of π molecular orbitals (Figure 21-9) used for the carbocation by putting one or two electrons into the nonbonding MO. The delocalization energies calculated for the radical and anion are the same as for the cation. Thus $(3\alpha + 2.82\beta) - (3\alpha + 2\beta) = 0.82\beta$ for the radical and $(4\alpha + 2.82\beta) - (4\alpha + 2\beta) = 0.82\beta$ for the anion.

21.6.3: Electronic Spectra by the MO Method

Section 9-9B covers qualitative explanations of how the VB method is used to account for the lower-energy (longer-wavelength) radiation required for electron excitation of conjugated polyenes compared to nonconjugated polyenes. Thus 1,3-butadiene has a λ_{max} for ultraviolet light at $217\ \text{nm}$, whereas 1,5-hexadiene has a corresponding λ_{max} at $185\ \text{nm}$.

We will now consider how the MO approach can be used to understand these differences in excitation energy. The π-energy levels and electronic configurations for delocalized and localized 1,3-butadiene are shown in Figure 21-10 (also see Section 21-4). Because the double bonds are so far apart, the π-electron system of 1,5-hexadiene by the simple MO approach is identical with that of localized 1,3-butadiene. The calculated energy change for the lowest-energy $\pi \rightarrow \pi^*$ transition is $(\alpha - 0.62\beta) - (\alpha + 0.6\beta) = -1.24\beta$ for 1,3-butadiene and $(\alpha - \beta) - (\alpha + \beta) = -2\beta$ for 1,5-hexadiene. In each case the energy of the electron in the *highest occupied* π orbital (the **HOMO orbital**) is subtracted from the energy that an electron would have in the *lowest unoccupied* π^* orbital (the **LUMO orbital**). Other transitions are possible, as of an electron from the lowest occupied orbital of energy $\alpha + 1.62\beta$ to the highest unoccupied orbital of energy $\alpha - 1.62\beta$, but these would have far greater energies.

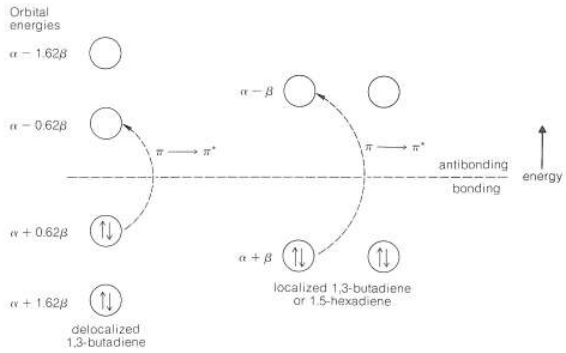


Figure 21-10: The π-molecular-orbital energies and ground-state electronic configurations of (left) delocalized 1,3-butadiene and (right) localized 1,3-butadiene or 1,5-hexadiene.

Qualitatively, the $\pi \rightarrow \pi^*$ transition energy is predicted to be substantially less for 1,3-butadiene than for 1,5-hexadiene. However, any attempt at a quantitative correlation is suspect, because the lowest energy $\pi \rightarrow \pi^*$ transition calculated for 1,3-butadiene is -1.24β and, if β is $19\ \text{kcal}$ (see Section 21-3C), λ_{max} from Equation 9-2 should be $1214\ \text{nm}$ instead of the observed $217\ \text{nm}$.

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21.7: Which Is Better- MO or VB?

The calculated energy of the electron-pair bond of the hydrogen molecule as a function of H−H intermolecular distance r by the *ab initio* (exact), MO, and VB procedures is shown in Figure 21-11. The results show that neither the MO nor the VB calculations come close to the *ab initio* calculation in reproducing the experimental dissociation energy, D_e, or the variation of the energy with the intermolecular distance. The VB method gives a little better energy value at the minimum and the MO method gives poor results at larger values of r. We can say that, as calculated by the MO method, the molecule does not "dissociate properly".

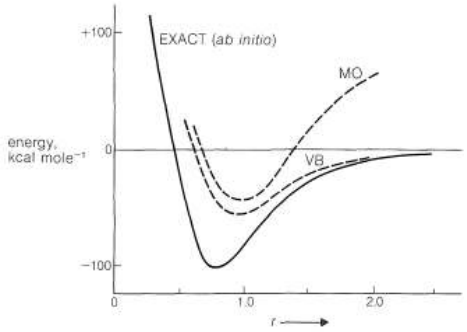

Figure 21-11: Comparison of calculated "exact" ab initio energies of H_2 as a function of internuclear distance, r, with the energies calculated for simple MO and simple VB methods. The dissociation energy calculated by the ab initio procedure is in close agreement with the experimental value of 102 kcal. The zero of the energy scale in this figure is the energy of widely separated hydrogen atoms.

> *Within the calculations of the MO method, the molecule does not "dissociate properly".*

Why do these calculations yield results so far from the *ab initio* curve? There are two reasons. First, atomic orbitals are used that are appropriate for *isolated* atoms, but are hardly expected to be the best orbitals for the electrons when two or more atoms are in close proximity. It is convenient to use atomic orbitals in simple calculations because they are mathematically simple, but more complicated orbitals are known to give better results. Second, neither treatment properly takes into account electron-electron repulsions. For two electrons, a term of the form $\frac{e^2}{r_{12}^2}$ (in which e is the electronic charge and r_{12} is the distance between the electrons) is required to describe the repulsion between electrons. The exact calculations avoid both difficulties but are so complex mathematically as to be devoid of any capability for providing qualitative understanding.

The VB method gives a slightly lower energy than the MO method at the minimum, because in the simple MO method, when we calculate the energy resulting from two electrons going into the lowest molecular orbital, we put no restraints on their being close together. As a result there is a 50% probability for *both* electrons being simultaneously in either half of the molecular orbital. In contrast, the simple VB method combines configurations 1 and 2, each having just *one* electron per atomic orbital, and no account is taken of the possibility of either atomic orbital containing more than one electron. This is equivalent to neglecting the pairing schemes $H^{\ominus}H^{\oplus} \leftrightarrow H^{\oplus}H^{\ominus}$. Neither the VB nor the MO approximation is the best possible; the simple MO method tends to take too little account of interelectronic repulsion, whereas the VB method tends to take too much account of it. However, as can be seen in Figure 21-11, taking too much account of electron repulsion is the better approximation.

Why does an electron-pair bond calculated by the MO method not dissociate properly? We have seen that half of the time both electrons in the low-energy molecular orbital are in the vicinity of just *one* of the nuclei. But as the nuclei move *far apart*, this corresponds to a far greater energy than having only one electron in the vicinity of each nucleus, as the VB method suggests.

There is no unequivocal answer to the question as to which is the better method. Calculations by the VB method are likely to be more reliable than those by the MO method, but in practice are much more difficult to carry out. For many-electron molecules the MO procedure is simpler to visualize because we combine atomic orbitals into molecular orbitals and then populate the lower-energy orbitals with electrons. In the VB method, atomic orbitals are occupied, but the electrons of different atoms are paired to form bonds, a process that requires explicit consideration of many-electron wave functions. To put it another way, it is easier to visualize a system of molecular orbitals containing N electrons than it is to visualize a hybrid wave function of N electrons.

How can the MO and VB methods be improved? The answer depends on what one wants - more accurate calculations or better qualitative understanding. To improve VB calculations we need orbitals that allow the electrons to spread out over more than one

atom. The GVB orbitals discussed in Section 6-6 suit this purpose and give an energy curve only slightly above the exact curve of Figure 21-11. In the GVB treatment the orbitals delocalize less as r increases.

When atomic orbitals are derived for each carbon of the π-electron system of benzene by the GVB method, they are somewhat more spread out than simple carbon p orbitals (Figure 21-12). Use of these orbitals in VB calculations gives excellent results with just the two pairing schemes of benzene, 9 and 10.

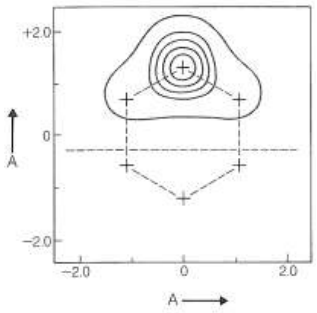

Figure 21-12: Top view of a GVB atomic orbital for the π-electron system of benzene. The contour lines show electron amplitudes, and there is a phase change represented by the dashed line. The crosses show the positions of the carbon nuclei. Six such orbitals are used to make up the electron-pairing schemes, 9 and 10, used in the GVB calculation of the electronic energy of benzene.

Improvement of the MO method involves better orbitals, better account of interelectronic repulsion, and introduction of mixing of different electron configurations in the molecular orbitals ("configuration interaction"). Improved MO calculations give much more accurate energies at the minimum of a plot such as Figure 21-11, but the bonds still do not dissociate properly, for the same reason as with the simple MO method.

We cannot say that either the VB or the MO method is more *correct*; only that one approximation may be more useful than the other in attempting to solve a particular problem. The fact is, the more each is refined, the more they appear to merge into a common procedure; but, unfortunately, in the refinement process the mathematics become so complex that qualitative understanding of what is being done tends to disappear altogether.

> *We cannot say that either the VB or the MO method is more correct; only that one approximation may be more useful than the other in attempting to solve a particular problem.*

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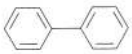
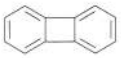
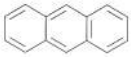
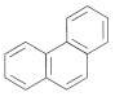
21.8: More on Stabilization Energies

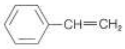
It was shown in Section 21-3 that benzene is 36-38 kcal more stable than the hypothetical molecule 1,3,5-cyclohexatriene on the basis of the differences between experimental heats of combustion, or hydrogenation, and heats calculated from bond energies. We call this energy difference the stabilization energy (SE) of benzene. We have associated most of this energy difference with π-electron delocalization, which is the delocalization energy (DE). The difference between SE and DE will be small only if our bond-energy tables are reliable and steric and strain effects are small.

The problem with bond energies is that we use bond energies that neglect changes in bond strength caused by environment. *Primary*, *secondary*, *tertiary*, *alkenic*, and *alkynic* C_H bonds are assumed to have equal energies; C—C single bonds are assumed to be equal, regardless of whether the *other* bonds to the carbon atoms in question are single or multiple; and differences in energy between double bonds that are mono-, di-, tri-, or tetra-substituted are neglected, as are changes in bond energies associated with steric strain. Bond energies are strictly applicable to molecules in which the bonds are of the normal lengths. In the case of benzene, which has C—C bonds with lengths intermediate between normal single and double bonds, there seems to be no clear agreement as to how to take the bond distances into account in computing the delocalization energy. In spite of these uncertainties the stabilization energies seem to give a good qualitative idea of the importance of electron delocalization in organic molecules.

Tables 21-1 and 21-2 give stabilization energies for several substances that are best represented as hybrid structures.

Table 21-1: *Stabilization Energies (or Approximate Delocalization Energies) from Heats of Formation of Some Aromatic Compounds*

Compound	Structure (as commonly written)	ΔH°_{calc}[a] (kcal mole^{-1})	ΔH°_{obs}[b] (kcal mole^{-1})	SE[c]
benzene		63.0	19.8	43.2
methylbenzene (toluene)		58.5	12.0	46.5
biphenyl		136.6	43.5	93.1
biphenylene		147.2	115.2	32.0
naphthalene		115.6	36.1	79.5
azulene		115.6	66.9	48.7
anthracene		168.2	55.2	113.0
phenanthrene		168.2	49.5	118.7
azabenzene (pyridine)		60.3	33.5	26.8

benzenamine (aniline)		67.6	20.8	46.8
benzenol (phenol)		25.1	−23.1	48.2
ethenylbenzene (styrene)		84.0	35.2	48.8

[a]Heats of formation from the elements in their standard states calculated from bond energies in Table 4-3, and $\Delta H^0 = 171.3$ kcal for $C(s) \longrightarrow C(g)$.

[b]Heats of formation for the gas phase from D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, *The Chemical Thermodynamics of Organic Substances*, John Wiley and Sons, Inc., New York, 1969.

[c]The differences between these numbers and SE values calculated from heats of hydrogenation and combustion probably are due primarily to the difference between values of ΔH^0 for $C(s) \longrightarrow C(g)$ used here (171.3 kcal), and the value of 171.7 kcal used in deriving the bond-energy tables. We give heats of formation here because they are much more useful in other calculations than are heats of combustion.

Table 21-2: *Stabilization Energies (SE) from Heats of Formation* (ΔH^0) *of Some Conjugated Polyenes*

Compound	Structure	ΔH^0_{calc}[a] (kcal mole^{-1})	ΔH^0_{obs}[b] (kcal mole^{-1})	SE[c]
1,3-butadiene	$CH_2{=}CH{-}CH{=}CH_2$	31.4	26.3	5.1
1,3-pentadiene	$CH_2{=}CH{-}CH{=}CHCH_3$	26.9	18.6[d]	8.3[e]
2-methyl-1,3-butadiene (isoprene)	$CH_2{=}CH{-}C(CH_3){=}CH_2$	26.9	18.1	8.8[e]
cyclooctatetraene		84.0	71.2	12.8

[a-b-c]See corresponding footnotes to Table 21-1. [d]For the trans isomer. ΔH^0 for the *cis* isomer is 18.7 kcal. [e]These values include the general stabilization produced by a methyl group substituted on a double bond (Section 11-3).

21.8.1: Contributors and Attributions

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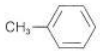
21.9: Bond Lengths and Double-Bond Character

Bond lengths frequently are cited as evidence for, or against, electron delocalization, although some caution should be exercised in this respect. For instance, if the hybrid structure of benzene is considered to be represented by the two possible Kekule structures, then each carbon-carbon bond should be halfway between a single bond and a double bond. In other words, each should possess 50% *double-bond character*. We then may expect the carbon-carbon bond lengths for benzene to be the average of single- and double-bond lengths. However, the average of the $\mathrm{C{-}C}$ bond in ethane $(1.534\ \text{Å})$ and in ethene $(1.337\ \text{Å})$ is 1.436 Å, which does not agree well with the measured $\mathrm{C{-}C}$ bond distance for benzene of 1.397 Å. The discrepancy lies largely in the assumption inherent in this crude calculation that, in the absence of resonance, all $\mathrm{C{-}C}$ single bonds are equal to 1.534 Å. Clearly, this is not a valid assumption because, as we have seen, bond energies depend upon environment, and because the energy of a bond depends upon its length (see Figure 21-1), bond lengths also must vary with environment. This can be seen from the data in Table 21-3, which gives the carbon-carbon *single* bond lengths for several compounds. The single bonds shorten as the other bonds to carbon become progressively unsaturated, that is, as the hybridization of carbon changes from sp^3 to sp. Admittedly, some of this shortening may be ascribed to resonance, but not all.

Table 21-3: *Carbon-Carbon Single-Bond Distances (Å)*

Bond type	Bond length	Bond type	Bond length
sp^3–sp^3		sp^3–sp^2	
$CH_3—CH_3$	1.534	$CH_3—CH{=}CH—CH_3$	1.54
$CH_3—CH_2—CH_3$	1.54	$CH_3—\overset{\overset{O}{\|}}{C}—CH_3$	1.52
diamond	1.544		1.52
sp^3–sp		sp^2–sp^2	
$CH_3—C{\equiv}CH$	1.459	$CH_2{=}CH—CH{=}CH_2$	1.483
$CH_3—C{\equiv}N$	1.458	$CH_3CH{=}CH—\overset{\overset{H}{\|}}{C}{=}O$	1.46
$CH_3—C{\equiv}C—C{\equiv}N$	1.458	$CH_3\overset{\overset{O}{\|}}{C}—\overset{\overset{O}{\|}}{C}CH_3$	1.47
sp^2–sp		sp–sp	
$CH_2{=}CH—C{\equiv}CH$	1.446	$HC{\equiv}C—C{\equiv}CH$	1.379
$CH_2{=}CH—C{\equiv}N$	1.426	$HC{\equiv}C—C{\equiv}N$	1.378
$O{=}CH—C{\equiv}CH$	1.445	$N{\equiv}C—C{\equiv}N$	1.380

If we take 1.48 Å as a reasonable $\mathrm{C{-}C}$ bond distance between two sp^2-hybridized carbons and 1.34 Å for $\mathrm{C{=}C}$ bonds (see Table 2-1), the average is 1.41 Å, which is not much different from the 1.40 Å for the carbon-carbon bonds in benzene.

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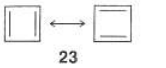
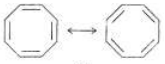
21.10: Hückel's 4n + 2 Rule

21.10.1: Cyclobutadiene and Cyclooctatetraene

More than 100 years ago, Kekule recognized the possible existence of other conjugated cyclic polyalkenes, which at least superficially would be expected to have properties like benzene. The most interesting of these are cyclobutadiene, 23, and cyclooctatetraene, 24:



23



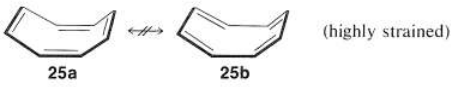
24

For each we can write two equivalent planar VB structures, and the qualitative VB method would suggest that both compounds, like benzene, have substantial electron-delocalization energies. However, the planar structures would have abnormal C−C=C angles, and consequently at least some degree of *destabilization* associated with these bond angles (Section 12-7). Nonetheless, estimation of the strain energies show that while they are substantial, they are not prohibitive. Should then these molecules be stabilized by resonance in the same sense as benzene is postulated to be?

In 1911 a German chemist, R. Willstatter (Nobel Prize 1915), reported an extraordinary thirteen-step synthesis of cyclooctatetraene from a rare alkaloid called pseudopelletierine isolated from the bark of pomegranate trees. The product was reported to be a light-yellow, highly unsaturated compound that absorbed four moles of hydrogen to form cyclooctane. Numerous tries to repeat the Willstatter synthesis were unsuccessful, and in the 1930s the prevailing opinion was that the product had been misidentified. However, during the Second World War, the German chemist W. Reppe found that cyclooctatetraene can be made in reasonable yields by the tetramerization of ethyne under the influence of a nickel cyanide catalyst:

The properties of the product substantiated Willstatter's reports and it became clear that cyclooctatetraene is *not* like benzene.

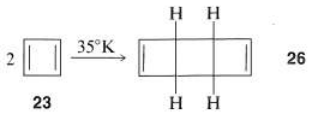
Subsequent studies of the geometry of the molecule revealed further that it is *nonplanar*, with alternating single and double bonds, 25*a*:



25a 25b (highly strained)

This geometry precludes the possibility of two equivalent VB structures, as for benzene, because, as you will see if you try to make a ball-and-stick model, 25*b* is highly strained and not energetically equivalent to 25*a* at all. Thus we can conclude that the delocalization energy of cyclooctatetraene is not large enough to overcome the angle strain that would develop if the molecule were to become planar and allow the π electrons to form equivalent π bonds between all of the pairs of adjacent carbons.

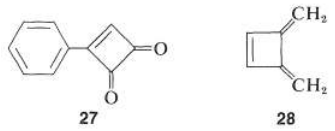
Cyclobutadiene, 23, eluded Kekule, Willstatter, and a host of other investigators for almost 100 years. As more work was done, it became increasingly clear that the molecule, when formed in reactions, was immediately converted to something else. Finally, the will-o'-the-wisp was captured in an essentially rigid matrix of argon at 8 K. It was characterized by its spectral properties (not by combustion analysis). On warming to even 35 K, it dimerizes to yield 26:



23 26

One possibility for the lack of stability[4] of cyclobutadiene is that the angle strain associated with having four sp^2 carbons in a four-membered ring is much greater than estimated. However, the stable existence of many compounds with four such sp^2 carbons, for

example 27 and 28, make this argument weak, if not invalid:



27 28

Why, then, is cyclobutadiene so unstable and reactive? On this point, and also with respect to the nonaromatic character of cyclooctatetraene, the simple qualitative VB method that we have outlined is no help whatsoever. There is no way simply to look at the electron-pairing schemes 23 and 24 and see any difference between them and the corresponding schemes for benzene.[5]

It is in this area that qualitative MO procedures have great success because there are general characteristics of the π molecular orbitals of monocyclic, conjugated polyene systems that predict differences in the properties of cyclobutadiene, benzene, cyclooctatetraene, and other similar compounds that are not obvious from the simple VB method.

As a rule, for N parallel atomic p orbitals overlapping in the π manner in a monocyclic array, there will be just one lowest molecular orbital, with all the atomic orbitals having the same phase. This will be seen for benzene in Figure 21-5. What is harder to understand without going through the calculations is that the higher-energy molecular orbitals for cyclic conjugated polyenes are predicted to come in successive degenerate[6] pairs, as shown in Figure 21-13 for $N = 3$ to 9.

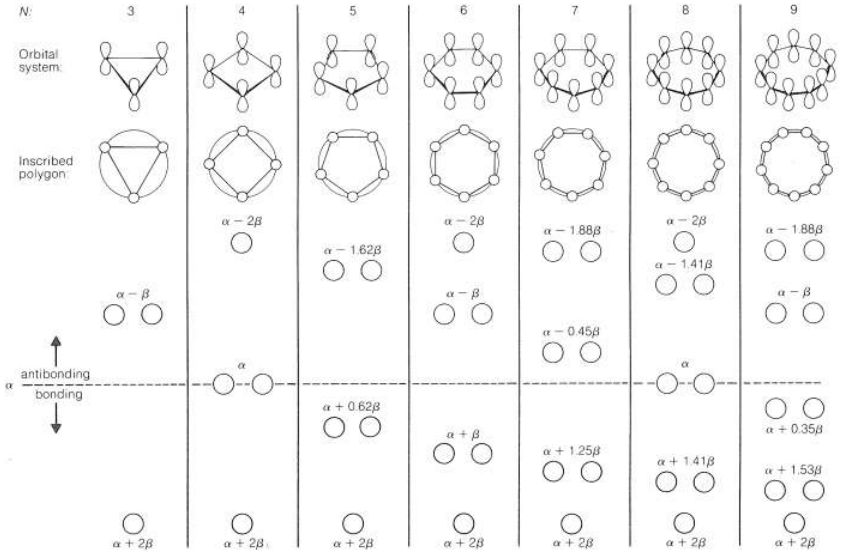
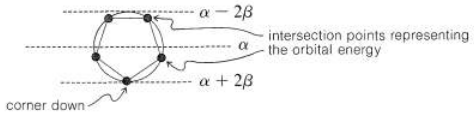


Figure 21-13: Calculated molecular-orbital energies of planar cyclic π-orbital systems made up of N $2p$ carbon atomic orbitals, in units of α and β.

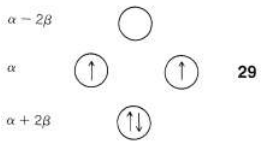
The qualitative ordering and, indeed, the numerical values of the energies of the π molecular orbitals for a cyclic system of N p orbitals can be derived in a very simple way. It is necessary only to inscribe a regular polygon with N sides inside a circle of radius 2β with *a corner down*. For example, for $N = 5$ we get the following:



The molecular orbital energies are in units of β at *the corners of the polygon*. The nonbonding level corresponds to the horizontal dashed line drawn through the *center* of the circle.

The data of Figure 21-13 provide a rationale for the instability of cyclobutadiene and cyclooctatetraene. For cyclobutadiene, we can calculate that four π electrons in the lowest orbitals will lead to a predicted π-electron energy of $2(\alpha + 2\beta) + 2(\alpha) = 4\alpha + 4\beta$, which is just the π-electron energy calculated for *two ethene bonds* (see Figure 21-3). The delocalization energy of the π electrons of cyclobutadiene therefore is predicted to be zero!

Another feature of the π system of cyclobutadiene is that the four π electrons do not suffice to fill the three lowest orbitals and, if we apply Hund's rule (Section 6-1), the best way to arrange the electrons is as in 29, with two *unpaired* electrons, which is known as a **triplet state**:[7]



29

With the MO predictions of zero delocalization energy and an electronic configuration with unpaired electrons, we should not be surprised that cyclobutadiene readily dimerizes to give 26 even at very low temperatures.

The energies of the molecular orbitals calculated for *planar* cyclooctatetraene (Figure 21-13) lead to a predicted delocalization energy of $(8\alpha + 9.64\beta) - (8\alpha + 8\beta) = 1.64\beta\ (\sim 31\ \text{kcal})$, which is smaller than that of benzene, even though there are eight atomic orbitals instead of six through which the electrons are delocalized. Furthermore, the lowest electronic configuration for the planar molecule is, like cyclobutadiene, predicted to be a triplet. Experimental evidence indicates that the positions of the double bonds of cyclooctatetraene shift slowly as the result of formation of the molecule in the unstable planar state. The energy input required to flatten the molecule is about $15\ \text{kcal mol}^{-1}$:

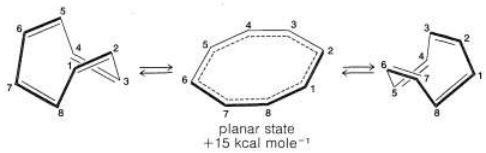
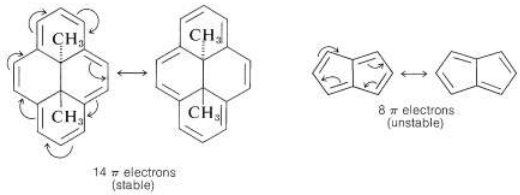
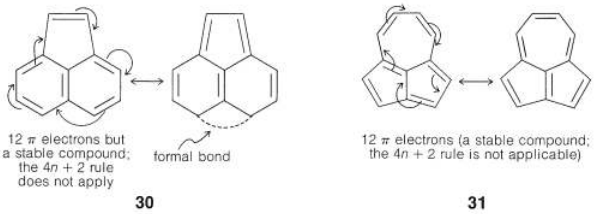


Figure 21-13 will be just filled with 2, 6, or 10 electrons to give singlet states, and 4 or 8 electrons would give triplet states, a $(4n + 2)$ π-electron rule was formulated for stable configurations and a $4n$ π-electron rule for unstable configurations, where n is an integer. Thus 2, 6, 10, 14, $\cdots$ π electrons will be favorable and 4, 8, 12 $\cdots$ π electrons will be unfavorable. This rule is the work of the German theoretician, E. Huckel, who devised the simple form of molecular orbital theory we have described in this chapter. The theory is appropriately called Huckel MO theory, and the rule is Huckel's $4n + 2$ rule.

As Huckel formulated, the $4n + 2$ rule applies only to monocyclic systems. However, as a practical matter it can be used to predict the properties of polycyclic conjugated polyenes, provided the important VB structures involve only the perimeter double bonds, as in the following examples:



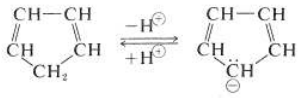
Application of the $4n + 2$ rule to other π systems, such as 30 and 31, is not valid because good VB structures cannot be written that involve changes in the pairing schemes of the perimeter electrons all at once.



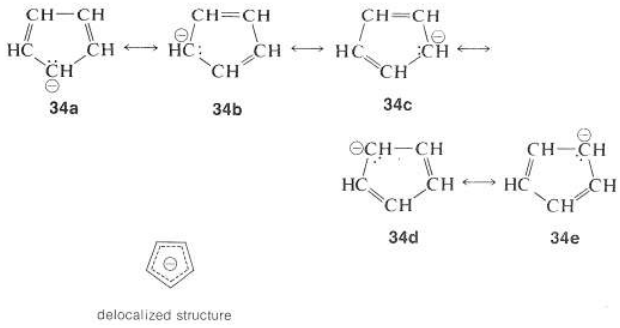
30 31

21.10.2: Application of Resonance and of the $4n + 2$ Rule to Cyclic Ions

The hydrogens of the $-CH_2-$ group of 1,3-cyclopentadiene are acidic. In fact, they are considerably more acidic than the ethyne hydrogens of the 1-alkynes (Section 11-8). This means that 1,3-cyclopentadiene is at least 10^{30} times more acidic than the ordinary alkanes. The reason is that loss of one of the CH_2 protons of cyclopentadiene results in formation of an especially stabilized anion:



The structure of the anion may be described as a hybrid of *five* energetically equivalent structures, 34a through (34e). The unshared electron pair therefore is delocalized over five carbon atoms, and the resulting delocalized anion is much more stable than expected for any *one* of the equivalent localized structures:



This looks very reasonable, although the simple beauty is seemingly destroyed by the fact that the cyclopentadienyl *cation* is not very stable, despite the five structures, 35a through 35e, that may be written for it:

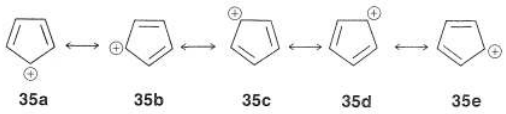
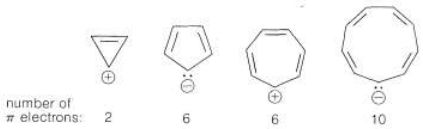
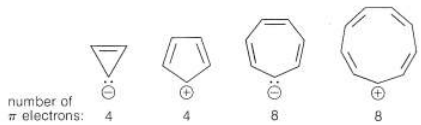


Figure 21-13 for a cyclic system with five p orbitals, and also with the $4n + 2$ rule, because 34 has six π electrons, whereas 35 has only four.

Extension of these ideas to the other ring sizes of Figure 21-13 suggests that all of the following ions, which have $(4n + 2)$ π electrons, should be unusually stable:

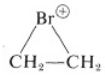


In contrast, the following should be unstable with $4n$ π electrons and triplet electronic configurations:



These predictions indeed are borne out by many experiments, some of which we will discuss later.

[4]It should be recognized that the term "stability" is subject to many interpretations. One criterion of stability would be whether an isolated molecule would fragment spontaneously in interstellar space, such as one would expect for a "molecule" consisting of two neon atoms 1.5 Å apart (see Figure 4-6). A different criterion would be whether a molecule could be preserved in the presence of the same or other kinds of molecules at some specified temperature. The classical criterion would be whether the substance could be isolated, put into a bottle and preserved for at least a short time. All of the existing evidence indicates that cyclobutadiene molecules would not spontaneously decompose in interstellar space, but they do react with each other extremely readily, even at low temperatures, and can be preserved only by being held isolated from one another in a rigid matrix of a very inert material, such as solid argon. "Stability" in the sense of "lack of reactivity" has to be carefully defined in terms of experimental conditions. For

example,  is very *unstable* in the presence of nucleophiles such as water or methanol, whereas it is quite *stable* in "super-acid solutions" where no good nucleophiles are present (Section 10-3B).

[5]A rather simple extension of the VB method by what is called the "orbital-phase continuity principle" does permit the qualitative judgment that cyclobutadiene should be less stable than benzene [see W. A. Goddard III, *J. Amer. Chem. Soc.* **94**, 743 (1972), for applications to many processes for which VB theory generally has been regarded as incapable of giving much insight].

[6]Degenerate orbitals have the same energy; see Section 6-1.

[7]The name "triplet state" is used because a system with two unpaired electrons has *three* different energy states in a magnetic field.

21.10.3: Contributors and Attributions

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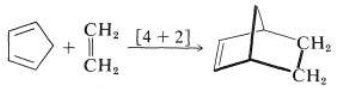
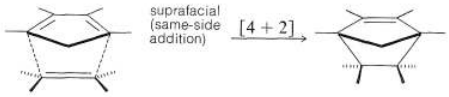
21.11: Pericyclic Reactions

21.11.1: Why are [4 + 2] and [2 + 2] Cycloadditions Different?

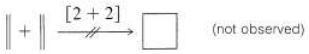
There are numerous reactions in organic chemistry that proceed through cyclic transition states. They may be classified generally as **pericyclic** reactions. An important and familiar example is the Diels-Alder reaction, in which a conjugated diene cycloadds to an alkene or alkyne:



This reaction has been described previously (Section 13-3A) and is an example of a [4 + 2] cycloaddition. Such reactions occur thermally (by simply heating the reactants) and appear to be entirely concerted. By this we mean that the reactants are converted to products *in one step*, without involving the formation of reaction intermediates. The principal evidence for the concertedness of [4 + 2] cycloadditions is the fact that they are highly stereospecific and involve suprafacial addition of both components. The configuration of substituents in the diene and the dienophile is retained in the adduct:



In contrast to the [4 + 2] cycloaddition, thermal [2 + 2] cycloadditions seldom are observed, and when they are observed, they are not stereospecific and evidently are stepwise reactions (see Section 21-11):



Why are the [4 + 2] and [2 + 2] cycloadditions different? Simple molecular orbital theory provides an elegant explanation of this difference based on the $4n + 2$ rule described in Section 21-9. To understand this, we need to look in more detail at how the p orbitals of the double bonds interact in concerted addition mechanisms by suprafacial overlap, as in 36 and 37:

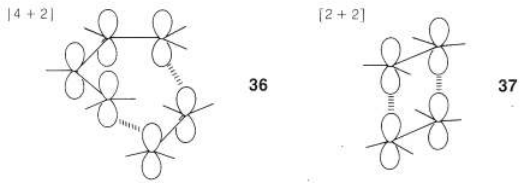


Figure 21-5) and, for 37, a set of four cyclobutadienelike molecular orbitals (29). The $4n + 2$ rule applies to such systems, and a transition state such as 36, which has six electrons, therefore can be very much more favorable than one such as 37, which has four electrons. From this we can conclude that concerted cycloaddition reactions involving $(4n + 2)$ π electrons generally should be more favorable than those involving $4n$ π electrons. Indeed, transition states such as 37 generally are less favorable than transition states for formation of biradicals or ions (Section 21-11).

21.11.2: How Mr. Möbius Beat the $4n + 2$ Rule

There is a way around the $4n + 2$ rule that is not very important for substances analogous to benzene, but is quite important for cycloaddition reactions. Let us see how this works for a cyclic conjugated polyene.

From the molecular-orbital diagrams of Figures 21-5, 21-7, 21-9, and 21-14, you will see that the *lowest*-energy π molecular orbital has *no* nodes (changes of phase). A model of such an orbital, which usually is called a **Hückel orbital**, can be constructed by joining the ends of a ribbon or strip of parallel p orbitals, as represented on the left side of Figure 21-15. However, one could join the orbitals by making *one twist* in the strip, which then would give a lowest-energy orbital with one node, as on the right side of Figure 21-15. A strip with one such twist is called a **Möbius strip**[8] and has the topological property of having only one side.

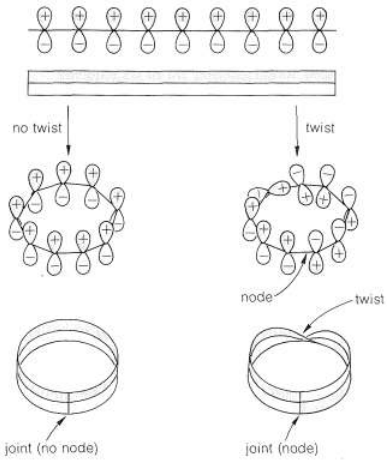


Figure 21-15: Normal (Hückel) and Möbius rings of π orbitals. To clarify the difference between the two rings, visualize a strip of black-red typewriter ribbon, the black representing the $+$ phase, and the red the $-$ orbital phase. Now join the ends together without, or with, one twist in the strip. At the joint there then will be no node (left) or one node (right).

If we now calculate the orbital energies for the Möbius orbitals, as was down for the normal Hückel π orbitals in Figure 21-13, we get the results shown in Figure 21-16. From this, we see that the $4n$ situation now is favored and $4n + 2$ is unfavorable. Whereas the energies of the π molecular orbitals in the Hückel arrangement can be obtained by inscribing a polygon in a circle with a *corner down* (Section 21-9A), in the Möbius arrangement the orbital energies are obtained from the polygon inscribed with a *side down*.

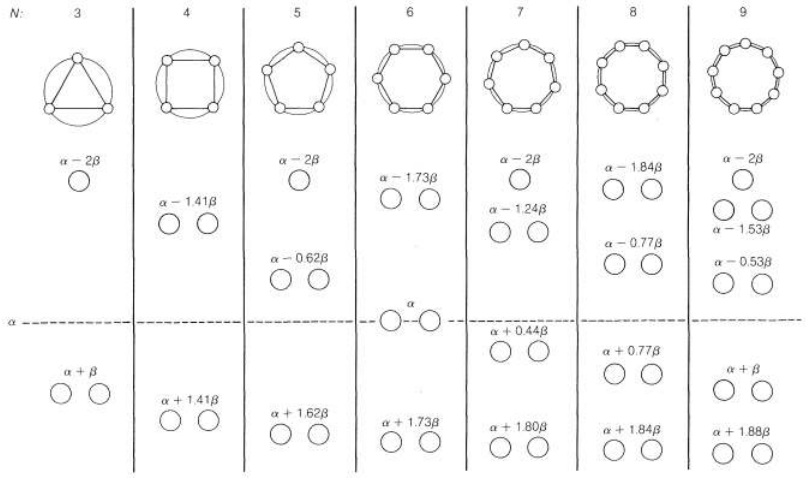


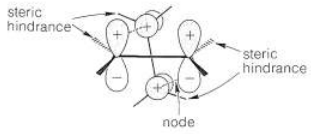
Figure 21-16: Calculated π-molecular orbital energies for N overlapping p orbitals in Möbius cyclic π systems.

If you compare the orbital energies of the Hückel and Möbius cyclic π systems (Figures 21-13 and 21-16), you will see that the Hückel systems have only *one* lowest-energy MO, whereas the Möbius systems have *two*. Hückel systems have an odd number of bonding orbitals (which, when full, accommodate 2, 6, 10, 14, or $4n + 2$ electrons) and the Möbius systems have an even number of bonding orbitals (which, when full, accommodate 4, 8, 12, or $4n$ electrons). The Hückel molecular orbitals have *zero* or an *even number* of nodes (see, for example, the benzene MOs, Figure 21-5); the Möbius molecular orbitals are not shown, but they have *one* or an *odd number* of nodes.

The relevance of all this may seem tenuous, especially because no example of a simple cyclic polyene with a Möbius π system is known. However, the Möbius arrangement is relevant to cycloaddition because we can conceive of alkenes, alkadienes, and so on approaching each other to produce Möbius transition states when $4n$ electrons are involved.

For example, consider two molecules of ethene, which we showed previously would violate the $4n + 2$ rule by undergoing cycloaddition through a transition state represented by 37. There is an alternative transition state, 38, in which the four p orbitals come together in the Möbius arrangement (with one node for minimum energy).

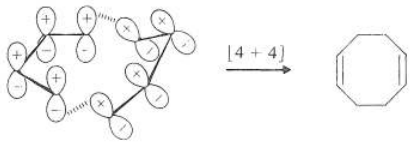
To achieve this arrangement the ethene molecules approach each other in roughly perpendicular planes so that the p orbitals overlap suprafacially in one ethene and antarafacially in the other, as shown in 38:



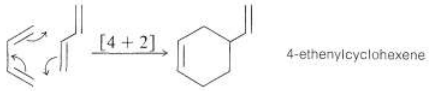
38

This pathway is electronically favorable, but the steric interference between the groups attached to the double bond is likely to be severe. Such repulsions can be relieved if there are no groups sticking out sidewise at one end of the double bond, as with the central carbon of 1,2-propadiene, $CH_2{=}C{=}CH_2$, and ketene, $CH_2{=}C{=}O$. These substances often undergo [2 + 2] cycloadditions rather readily (Section 13-3D), and it is likely that these are concerted additions occurring by the Möbius route.

A much less strained Möbius [4 + 4] transition state can be formed from two *s-cis* molecules of 1,3-butadiene. When 1,3-butadiene is heated by itself, a few percent of 1,5-cyclooctadiene is formed, but it is not known for sure whether the mechanism is that shown:



The principal reaction is a Diels-Alder [4 + 2] cycloaddition, with butadiene acting both as a diene and as a dienophile:

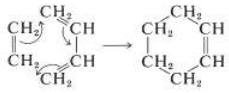


21.11.3: Orbital Symmetry. The Woodward-Hoffmann Rules

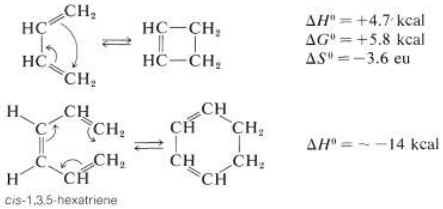
Much of what we have said about the electronic factors controlling whether a cycloaddition reaction can be concerted or not originally was formulated by the American chemists R. B. Woodward and R. Hoffmann several years ago, in terms of what came to be called the **orbital symmetry** principles, or the **Woodward-Hoffmann rules**. Orbital symmetry arguments are too complicated for this book, and we shall, instead, use the $4n + 2$ electron rule for normal Hückel arrangements of π systems and the $4n$ electron rule for Möbius arrangements. This is a particularly simple approach among several available to account for the phenomena to which Woodward and Hoffmann drew special attention and explained by what they call "conservation of orbital symmetry".

21.11.4: Electrocyclic and Sigmatropic Rearrangements

The cycloaddition reactions that we have discussed so far in this chapter ([2 + 2], [4 + 2], etc.) have involved ring formation by bringing two unsaturated molecules together. Thus [4 + 2] addition is represented by the Diels-Alder reaction of ethene and 1,3-butadiene:

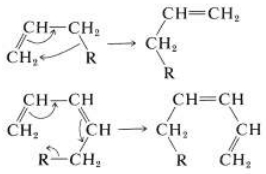


We can conceive of similar cyclizations involving only single molecules, that is, *intramolecular cyclization*. Such reactions are called **electrocyclic rearrangements**. Two examples follow to show cyclization of a diene and a triene:



Cyclization of 1,3,5-hexatriene occurs only when the central double bond has the cis configuration. The reaction is reversible at elevated temperatures because of the gain in entropy on ring opening (see Section 4-4B). The cyclobutene-1,3-butadiene interconversion proceeds much less readily, even in the thermodynamically favorable direction of ring opening. However, substituted dienes and cyclobutenes often react more rapidly.

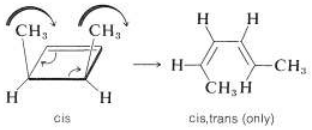
A related group of reactions involves shifts of substituent groups from one atom to another; for example, with H, alkyl, or aryl groups as R:



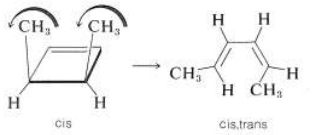
These reactions are called **sigmatropic rearrangements** and, in general, they are subject to the $4n + 2$ rule and the Möbius orbital modification of it. Potential sigmatropic rearrangements can be recognized by the fact that the single bond to the migrating group (R) is "conjugated" with the π bonds, and the group moves from a saturated sp^3 to an sp^2 carbon at a different part of the π system.

21.11.5: The Stereochemistry of Electrocyclic Rearrangements

A striking feature of thermal electrocyclic reactions that proceed by concerted mechanisms is their high degree of stereospecificity. Thus when *cis*-3,4-dimethylcyclobutene is heated, it affords only one of the three possible cis-trans isomers of 2,4-hexadiene, namely, *cis*,*trans*-2,4-hexadiene:

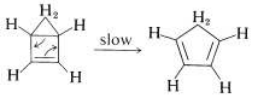


We can see how this can occur if, as the ring opens, the ends of the diene twist in the *same* direction (↷↷ or ↶↶, **conrotatory**) as indicated in the equation. You will notice that with this particular case, if conrotation occurs to the left, rather than the right, the same final product results:



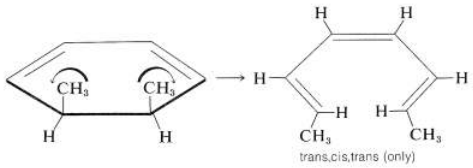
The conrotatory movement of groups is typical of thermal ring openings of cyclobutenes and other rings involving $4n$ electrons.

When a cyclobutene is so constituted that conrotation cannot occur for steric reasons, then the concerted reaction cannot occur easily. Substances that otherwise might be predicted to be highly unstable often turn out to be relatively stable. An example is bicyclo[2.1.0]-2-pentene, which at first sight might seem incapable of isolation because of the possibility of immediate arrangement to 1,3-cyclopentadiene. This rearrangement does occur, but not so fast as to preclude isolation of the substance:

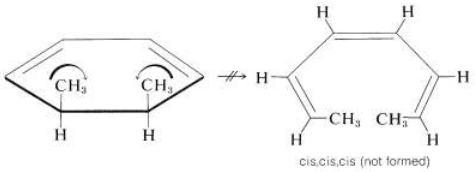


How can we explain the fact that this substance can be isolated? The explanation is that, if the reaction has to be conrotatory, then the product will not be ordinary 1,3-cyclopentadiene, but *cis*,*trans*-1,3-cyclopentadiene - surely a very highly strained substance. (Try to make a ball-and-stick model of it!) This means that the concerted mechanism is not favorable:

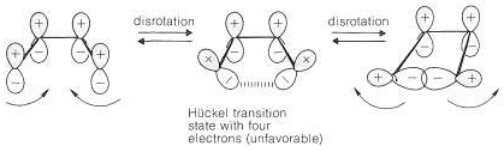
It is of great interest and importance that, with systems of $4n + 2$ electrons, the groups move in *opposite* directions (↶↷ or ↷↶, **disrotatory**). For example,



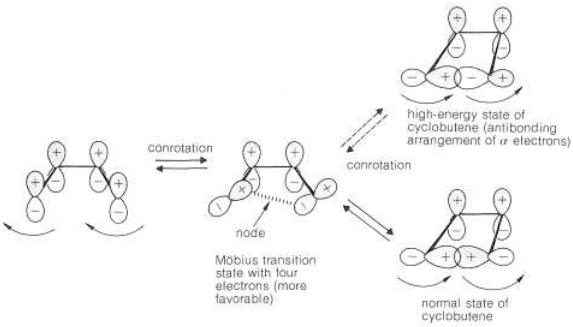
In this case, the disrotation of the groups *toward* one another would lead to the cis,cis,cis product. Because this product is not formed, it seems likely that rotation of the methyl groups toward each other must be sterically unfavorable:



How can we account for the stereoselectivity of thermal electrocyclic reactions? Our problem is to understand why it is that concerted $4n$ electrocyclic rearrangements are conrotatory, whereas the corresponding $4n + 2$ processes are disrotatory. From what has been said previously, we can expect that the conrotatory processes are related to the Möbius molecular orbitals and the disrotatory processes are related to Hückel molecular orbitals. Let us see why this is so. Consider the electrocyclic interconversion of a 1,3-diene and a cyclobutene. In this case, the Hückel transition state (*one having an even number of nodes*) is formed by *disrotation*, but is unfavorable with four (that is, $4n$) electrons:



In contrast, the Möbius transition state (*one having an odd number of nodes*) is formed by *conrotation* and is favorable with four $(4n)$ electrons:

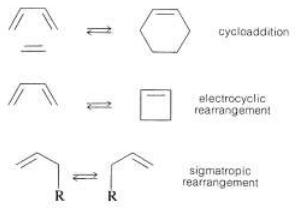


You will notice that the ring closure of a 1,3-diene through the favorable Möbius transition state may appear to be able to form only an *antibonding* arrangement of the overlapping σ orbitals, which would correspond to a high-energy cyclobutene. In fact, the normal cyclobutene would be formed, because on the way down from the transition state, the phases of the orbitals that will become the σ bond change to give the *bonding* arrangement of the σ orbitals expected for the ground state. The reverse occurs in ring opening so that this reaction also can go through the favorable Möbius transition state.

The same reasoning can be extended to electrocyclic reactions of 1,3,5-trienes and 1,3-cyclohexadienes, which involve $4n + 2$ electrons and consequently favor Hückel transition states attained by *disrotation*.

21.11.6: Summary of Rules for Predicting Thermally Favorable Pericyclic Reactions

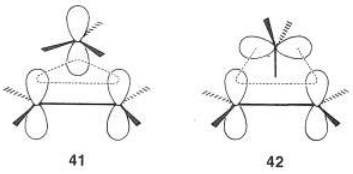
The three principal types of pericyclic reactions are *cycloaddition*, *electrocyclic rearrangement*, and *sigmatropic rearrangement*:



The factors that control if and how these cyclization and rearrangement reactions occur in a concerted manner can be understood from the aromaticity or lack of aromaticity achieved in their *cyclic* transition states. For a concerted pericyclic reaction to be thermally favorable, the transition state must involve $4n + 2$ participating electrons if it is a Hückel orbital system, or $4n$ electrons if it is a Möbius orbital system. A Hückel transition state is one in which the cyclic array of participating orbitals has no nodes (or an even number) and a Möbius transition state has an odd number of nodes.

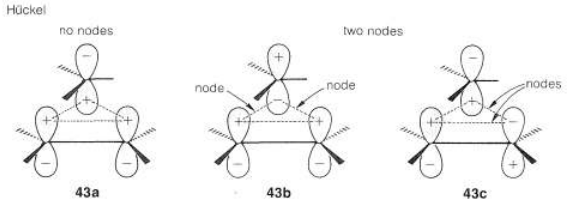
We summarize here a procedure to predict the feasibility and the stereochemistry of *thermally concerted* reactions involving *cyclic transition states*. The 1,2 rearrangement of carbocations will be used to illustrate the approach. This is a very important reaction of carbocations which we have discussed in other chapters. We use it here as an example to illustrate how qualitative MO theory can give insight into how and why reactions occur:

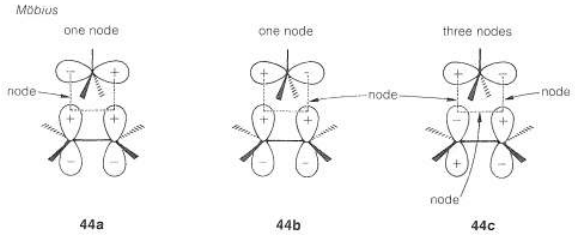
The first step of the procedure is to draw the orbitals as they are expected to be involved in the transition state. There may be several possible arrangements. There are two such arrangements, 41 and 42, for the rearrangement of carbocations; the dotted lines show the regions of bond-making and bond-breaking (i.e., orbital overlap):



The second step is to determine whether the transition states are Hückel or Möbius from the number of nodes. This is readily done by assigning signs to the lobes of the orbitals corresponding to their phases and counting the number of nodes that develop in the circle of overlapping orbitals. An odd number denotes a Möbius transition state, whereas an even number, including zero, denotes a Hückel transition state.

There are alternative ways of node-counting for transition states 41 and 42. Diagrams $43abc$ and $44abc$ represent molecular orbitals of different energies - those with more nodes having the higher energies (cf. Section 21-3C).[9] We show these diagrams with more than one node for the sake of completeness. It is not necessary to draw more than one such diagram to determine whether the transition state is Möbius or Hückel.

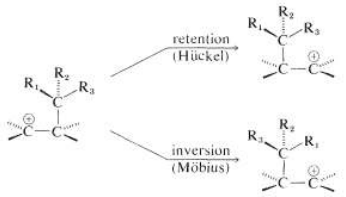




44a 44b 44c

Finally, we evaluate the transition states according to the $4n$ or $4n + 2$ rule. In the example here, because only two electrons occupy the molecular orbitals, the Hückel transition state ($43a$) is the favorable one.

A bonus coming from these formulations is that the stereochemistry of the reaction can be predicted when we have predicted which transition state is the favored one. Thus the migrating group in 1,2-carbocation rearrangements should move with *retention* of configuration by a Hückel transition state - and this has been verified experimentally. The alternative Möbius transition state predicts *inversion* of the configuration of the migrating group:

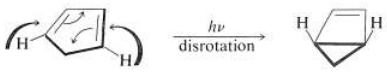


You can use the procedures just outlined to determine whether any thermal reaction with a cyclic transition state is likely to be favorable. A good place to start is the Diels-Alder [4 + 2] cycloaddition, which proceeds thermally by a suprafacial (Hückel) transition state. We suggest that you apply the procedure to the Diels-Alder reaction of 1,3-butadiene and ethene, and following that, show the electrocyclic ring opening of a cyclobutene ring to be thermally favorable only by a conrotatory opening of the C–C bond.

21.11.7: Photochemical Pericyclic Reactions

Many pericyclic reactions take place photochemically, that is, by irradiation with ultraviolet light. One example is the conversion of norbornadiene to quadricyclene, described in Section 13-3D. This reaction would have an unfavorable [2 + 2] mechanism if it were attempted by simple heating. Furthermore, the thermodynamics favor ring opening rather than ring closure. However, quadricyclene can be isolated, even if it is highly strained, because to reopen the ring thermally involves the reverse of some unfavorable [2 + 2] cycloaddition mechanism.

Photochemical activation can be used to achieve forward or reverse cycloadditions and electrocyclic reactions that are thermodynamically unfavorable or have unfavorable concerted thermal mechanisms. Thus the thermodynamically unstable disrotatory [2 + 2] product can be obtained from 1,3-cyclopentadiene by irradiation with ultraviolet light:



The stereochemical results of electrocyclic and cycloaddition reactions carried out photochemically often are opposite to what is observed for corresponding thermal reactions. However, exceptions are known and the degree of stereospecificity is not always as high as in the thermal reactions. Further examples of photochemical pericyclic reactions are given in Section 28-2D.

[8]Named after the mathematician A. F. Möbius.

[9]The assignment of orbital phases must take appropriate account of molecular symmetry, and although this is easy for open-chain systems, it is much less straightforward for cyclic ones. You usually will be able to avoid this problem by always trying to set up the orbitals so that the transition state will have no nodes, or just one node at a point where a bond is being made or broken.

21.11.8: Contributors and Attributions

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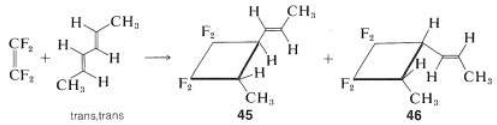
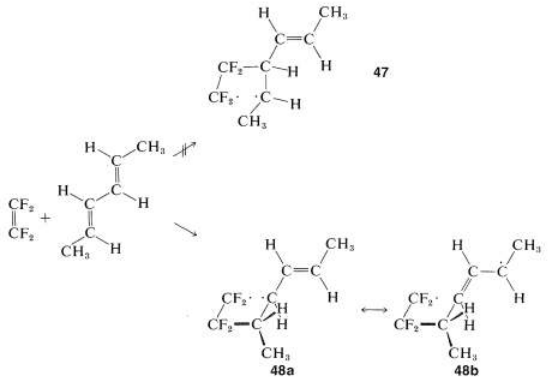
21.12: Evidence Bearing on the Mechanism of [2 + 2] Cycloadditions

We have not given you much evidence to decide why it is that some *thermal* [2 + 2] cycloadditions occur but not others. What is special about fluoroalkenes, allenes, and ketenes in these reactions? One possibility is that Mobius rather than the Huckel transition states are involved, but the Mobius transition states are expected to suffer from steric hindrance (Section 21-10B). It is also possible that [2 + 2] cycloadditions, unlike the Diels-Alder additions, proceed by stepwise mechanisms. This possibility is strongly supported by the fact that these reactions generally are not stereospecific. Thus with tetrafluoroethene and *trans*,*trans*-2,5-hexadiene *two* products are formed, which differ in that the 1-propenyl group is *trans* to the methyl group in one adduct, 45, and *cis* in the other, 46:



A stepwise reaction involving a **biradical intermediate** accounts for the formation of *both* 45 and46. In the biradical mechanism the first step is formation of just one C–C bond between the reactants, and this could occur in two different ways to give 47 or 48*ab*:



Of these, 48*ab* is predicted to have substantial electron delocalization because of the nearly equivalent VB structures 48*a* and 48*b*. By the simple MO theory 48*ab* should have a delocalization energy of 16 kcal mol^{-1} (Section 21-5B). The biradical 47 has no comparable electron delocalization and would be expected to be formed much less readily.

Collapse of 48 through formation of the second C–C bond would give 45 and an overall stereospecific addition. However, rotation around the C–C single bond of 48 forms a different radical conformation, 49, which would collapse to the other stereoisomer, 46:

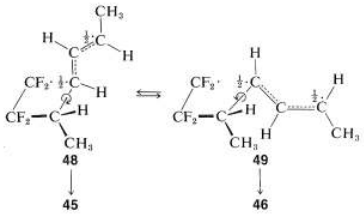


Figure 21-17. The relative energies of the several transition states determine the degree to which 48 and 49 are equilibrated before the ring closes and 45 and 46 are formed; for our purposes it is enough to known that 49 is present and is the precursor of 46.

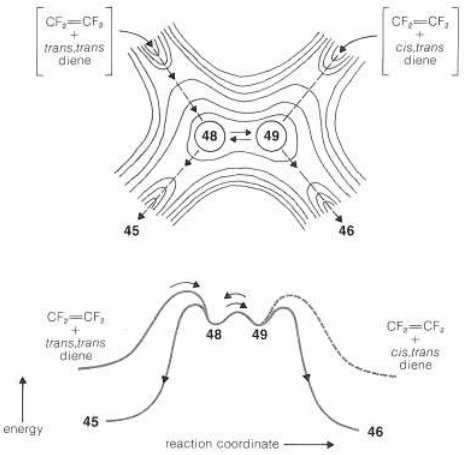


Figure 21-17: Schematic representation of the energy of the stepwise addition of $CH_2{=}CF_2$ to trans,trans-2,4-hexadiene. The lower diagram is a schematic "cross section" that shows everything in two dimensions. If 48 and 49 dissociate to $CF_2{=}CF_2$ and diene, 48 will return the trans,trans isomer, but 49 will go to the cis,trans *diene through the transition state represented by the dashed line. In some [2 + 2] cycloadditions of this type, trans,trans to cis,cis isomerizations are observed in competition with cycloaddition, as expected for breaking apart the intermediate corresponding to* 49. *The upper diagram is an attempt to show the topographical relationship between the reactants and products on an energy-contour diagram. The pathways of minimum energy, which would correspond on a topographical map to trails through mountain passes, are shown by dashed arrows.*

If the reaction is stepwise, why is it stepwise? In the first place, as we have seen (Section 21-10A), there are theoretical reasons why [2 + 2] cycloadditions may not occur in a concerted manner. Second, there are thermodynamic reasons why some alkenes undergo stepwise [2 + 2] additions and others do not. Regarding the second point, we can estimate that $2CH_2{=}CH_2 \rightarrow \cdot CH_2{-}CH_2{-}CH_2{-}CH_2\cdot$ has $\Delta H^0 \sim 37$ kcal, which is too high to achieve at a useful rate at those temperatures where the equilibrium constant is favorable for cyclobutane formation. In other words, when K_{eq} is favorable, the rate is too slow, and when the rate is fast enough, K_{eq} is unfavorable. In contrast, $2CF_2{=}CF_2 \rightarrow \cdot CF_2{-}CF_2{-}CF_2{-}CF_2\cdot$ is estimated to have $\Delta H^0 = -7$ kcal! This tells us that $CF_2{=}CF_2$ has an abnormally low C=C π-bond energy and, in fact, ΔH^0 for addition of hydrogen to one mole of tetrafluoroethene $(-55$ kcal) is 22 kcal more negative than ΔH^0 for ethene $(-33$ kcal). If formation of $\cdot CF_2{-}CF_2{-}CF_2{-}CF_2\cdot$ from $2CF_2{=}CF_2$ actually is exothermic, then it may seem surprising that $CF_2{=}CF_2$ can be kept in a container without immediately reacting with itself. That it can is because fairly high-energy collisions are required to overcome the nonbonded repulsions that resist bringing the carbons close enough together to permit the formation of the biradical. Nonetheless, $CF_2{=}CF_2$ generally is regarded as a hazardous and unpredictable chemical by virtue of its unusually low C=C π-bond strength.

1,2-Propadiene also appears to have the potential for much easier formation of a biradical than does ethene. Not all [2 + 2] cycloadditions proceed by biradical mechanisms, some clearly occur by stepwise reactions involving ionic intermediates.

21.12.1: Contributors and Attributions

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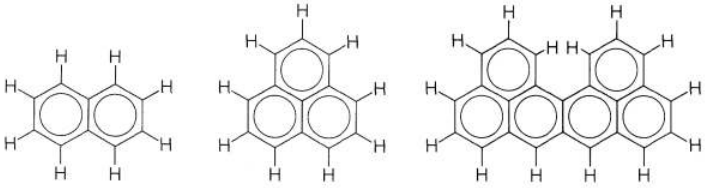
21.E: Resonance and Molecular Orbital Methods (Exercises)

Exercise 21-1 Determine which of the following structures can be represented by one or more specific electron-pairing schemes similar to the Kekulé structures of benzene:



Exercise 21-2 Calculate the heat of formation of 1,3-butadiene in the gas phase at 25° from the bond energies in Table 4-3 and the knowledge that ΔH^0 for $\mathrm{C}\,(s) \rightarrow \mathrm{C}\,(g)$ is $171.3\ \mathrm{kcal}$. The heat of formation is defined as ΔH^0 for $4\mathrm{C}\,(s) + 3\mathrm{H_2}\,(g) \rightarrow \mathrm{C_4H_6}\,(g)$. The experimental value of the heat of formation is $26.3\ \mathrm{kcal}$. Calculate the stabilization energy of 1,3-butadiene.

Exercise 21-3 The heat of formation of propenal by $3\mathrm{C}\,(s) + 2\mathrm{H_2}\,(g) + \frac{1}{2}\mathrm{O_2}\,(g) \rightarrow \mathrm{C_3H_4O}\,(g)$ is $-25.1\ \mathrm{kcal}$. Using the bond energies of Table 4-3 and $\Delta H^0 = +171.3\ \mathrm{kcal}$ for $\mathrm{C}\,(s) \rightarrow \mathrm{C}\,(g)$, calculate a stabilization energy for propenal.

Exercise 21-4 Use the qualitative VB and MO methods to predict whether addition of HCl to 1,3-cyclohexadiene would be favored to give 3-chlorocyclohexene or 4-chlorocyclohexene.

Exercise 21-5 Set up an atomic-orbital model for the enolate anion, $\mathrm{CH_2{=}CH{-}O^{\ominus}}$ and consider how it should be formulated by the VB and MO methods. Write a hybrid structure of the general type of $18e$ and $21c$ for the enolate anion and predict the most likely positions of the atoms for the anion in its most stable configuration.

Exercise 21-6 Use Figure 21-9 to predict the π-electron distribution in the 2-propenyl radical $(\mathrm{CH_2{=}CH{-}CH_2{\cdot}})$ and the 2-propenyl anion $(\mathrm{CH_2{=}CH{-}CH_2{}^{-}{:}})$. Show your reasoning.

Exercise 21-7 1,3-Butadiene has a substantial stabilization energy, whereas ethene has none, yet attack of $\mathrm{Br^{\oplus}}$ on 1,3-butadiene occurs *more readily* than on ethene. Explain how 1,3-butadiene can have a stabilization energy greater than ethene but still be more reactive toward reagents that donate $\mathrm{Br^{\oplus}}$.

Exercise 21-8 The experimental $-\Delta H^0\ (25^{\circ})$ is $707.7\ \mathrm{kcal}$ for combustion of one mole of gaseous 1,3-cyclopentadiene to liquid water and carbon dioxide. From this value compute a stabilization energy for cyclopentadiene with the aid of the heat of vaporization of water $(10\ \mathrm{kcal\ mol^{-1}})$ and any required bond energies. Show your method. Discuss briefly any uncertainties that may arise in estimating a resonance energy for cyclopentadiene that would not be similarly important for 1,3-butadiene.

Exercise 21-9 The heat of combustion of one mole of benzene to carbon dioxide and liquid water is $789\ \mathrm{kcal}$. Calculate values for the stabilization energy of benzene that correspond to (a) the bond energies of Table 4-3 and (b) the ethene $\mathrm{C{-}H}$ bond energy of Section 12-4B, combined with the assumption that the bond energy $(90.6\ \mathrm{kcal})$ of a carbon single bond between two carbon double bonds, $=\mathrm{C{-}C}=$, is $8\ \mathrm{kcal}$ stronger than a normal $\mathrm{C{-}C}$ bond. The point of this exercise is to show how the stabilization energy of benzene is affected when bond energies are taken to depend on the hybridization assumed for carbon, instead of being chosen to give the best possible fit to the heats of combustion of aliphatic compounds.

Exercise 21-10 Suggest reasons why (a) the stabilization energy of biphenylene is less than twice that of benzene, and (b) the heat of combustion of naphthalene is less than that of azulene.

Exercise 21-11 Graphite crystals consist of a network of planar hexagonal rings of carbon atoms arranged in parallel layers. The distance between the layer planes is 3.35 Å and all the $\mathrm{C{-}C}$ bonds within the hexagonal network are equal to 1.421 Å.

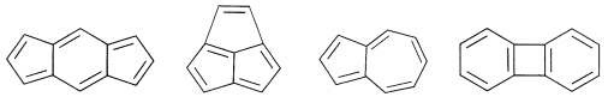
a. Sketch the carbon framework in graphite.
b. What is likely to be the state of hybridization of carbon?
c. Use the VB method to estimate the percentage of double-bond character for the $\mathrm{C{-}C}$ bonds in graphite.
d. Make a plot of double-bond character versus bond length for ethene, benzene, and graphite.
e. From your plot estimate the length of a single bond between sp^2-hybridized carbons. How does this value compare with

the sp^2-sp^2 distances listed in Table 21-3? What conclusion might be drawn from this as to the importance of resonance in 1,3-butadiene?

Exercise 21-12 Draw the possible Kekulé-type structures for biphenylene (five) and naphthalene (three). Assuming the structures may be weighted equally, estimate the double-bond character and bond lengths for both compounds. Indicate which bonds of these hydrocarbons should be attacked preferentially by ozone.

Exercise 21-13 For a regular *polygon* inscribed in a circle with a corner down, use trigonometry to calculate the molecular-orbital energies as in Figure 21-13.

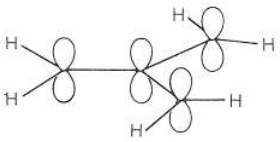
Exercise 21-14* Consider the appropriateness and results from application of the $(4n+2)$ π-electron rule to predict the stability of the following compounds:



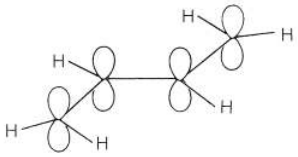
Exercise 21-15 The π-molecular orbitals of tricyclo[5.3.0.$0^{2,6}$]-1,3,5,7,9-decapentaene have the following energies: $\alpha + 2.562\beta$, $\alpha + 1.732\beta$, $\alpha + \beta$, $\alpha + \beta$, $\alpha + 0.414\beta$, α, $\alpha - \beta$, $\alpha - 1.562\beta$, $\alpha - 1.732\beta$, $\alpha - 2.414\beta$. Make an energy diagram of these orbitals, as in Figure 21-13, and calculate the total π-electron energy and the delocalization energy for this hydrocarbon.

Exercise 21-16 Cyclooctatetraene can add two electrons and form a rather stable *planar* dianion, $C_8H_8{}^{2-}$. Use the data of Figure 21-13 to help you write an electronic configuration for this anion and calculate its *total* π-electron energy. Suppose you had planar cyclooctatetraene with four *localized* π bonds of the ethene type. What is the π-electron energy of such a system? Now add two more π electrons to this localized cyclooctatetraene; what will the *localized* total π-electron energy be? What do you calculate for the delocalization energy of the cyclooctatetraene dianion? Is is the same as the delocalization energy of cyclooctatetraene itself? Show your reasoning.

Exercise 21-17 One of the problems with the *qualitative* MO method is that it does not give a good simple answer to whether a four-electron π system, such as 32, is just as stable as the butadiene π system, 33, which we treated in detail in Section 21-4:



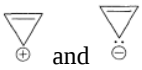
32

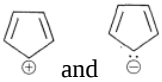


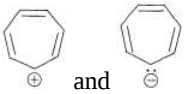
33

What does the qualitative VB method predict about the entity formed when four π electrons are added to the orbitals of 32? Calculation yields the following MO energies for 32: $\alpha \pm 1.73\beta$, α, and α. Arrange the molecular orbitals in order of increasing energy and compare the predicted electronic configuration with that obtained by the VB method. Show your reasoning. (An entity corresponding to 32 with a triplet ground state has been identified as a reaction intermediate.)

Exercise 21-18 Use the orbital energies of Figures 21-9, 21-13, and 21-14 to calculate the delocalization energies of the following ions:

a.  and

b.  and

c.  and

d. $CH_2{=}CH-\overset{\oplus}{C}H_2$ and $CH_2{=}CH-\overset{\ominus}{C}H_2$

e. $CH_2{=}CH{-}CH{=}CH-\overset{\oplus}{C}H_2$ and $CH_2{=}CH{-}CH{=}CH-\overset{\ominus}{C}H_2$

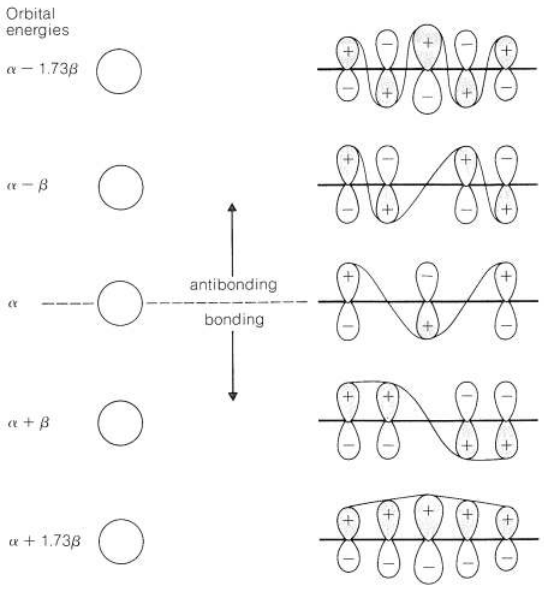
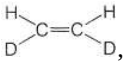
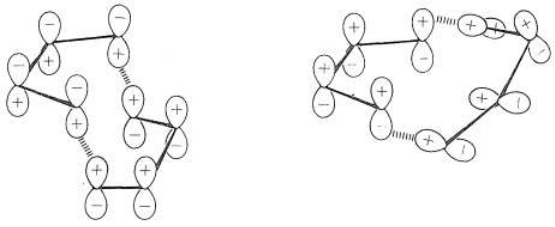


Figure 21-14: *Energies and schematic representations of the π molecular orbitals of the* $CH_2{=}CH{-}CH{=}CH{-}CH_2^+$ *cation (see Exercise 21-18).*

Exercise 21-19* Tetrafluoroethene undergoes a slow [2 + 2] addition to ethene by what appears to be a stepwise biradical mechanism. What would you expect the stereochemistry of the deuteriums in the product to be if one started with *cis*-1,2-dideuterioethene,  , and the reaction proceeded by

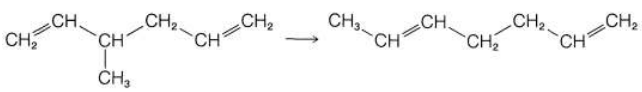
a. a stepwise biradical mechanism?
b. a concerted mechanism with a transition state such as 37?
c. a concerted mechanism with a transition state such as 38?

Exercise 21-20* Use Figures 21-13 and 21-16 to estimate the difference in π-electron energy for the two following transition states (39 and 40) for [4 + 4] cycloaddition of 1,3-butadiene. Show your method.



39 40

Exercise 21-21 The **Cope rearrangement** is a type of sigmatropic rearrangement that occurs with 1,5-dienes. An example is the rearrangement of 3-methyl-1,5-hexadiene to 1,5-heptadiene:



On the basis of this result and the $4n + 2$ rule, work out a mechanism for the reaction and then use this mechanism to predict what product will be formed from the Cope rearrangement of 3,4-dimethyl-1,5-hexadiene. Show your reasoning.

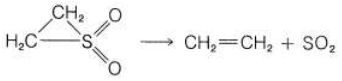
Exercise 21-22 Unlike the conversion of bicyclo[2.1.0]-2-pentene to 1,3-cyclopentadiene, bicyclo[4.1.0]-2,4-heptadiene is transformed to 1,3,5-cycloheptatriene very rapidly at low temperatures by what appears to be a wholly concerted mechanism. Account for this difference.

Exercise 21-23* Show how one can predict the stereochemistry of the electrocyclic rearrangement of *trans*,*cis*,*trans*-2,4,6-octatriene to 5,6-dimethyl-1,3-cyclohexadiene by a favorable concerted thermal mechanism.

Exercise 21-24*

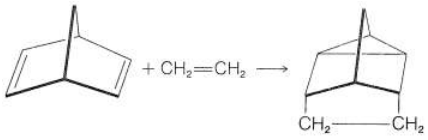
a. Sulfur dioxide is an angular molecule that can be represented as having a nonbonding electron pair in an sp^2 hybrid orbital and one "vacant" p orbital on sulfur. Use this formulation to derive a thermally allowed transition state for the reversible 1,4-cycloaddition of SO_2 to 1,3-butadiene (Section 13-3C).

b. The three-membered ring sulfone, shown below, is very unstable and rapidly dissociations to SO_2 and ethene. This process is used for the synthesis of alkenes by the dissociation of cyclic sulfones (Ramberg-Bäcklund reaction). Determine whether the transition state for the thermally favorable reaction is conrotatory or disrotatory.

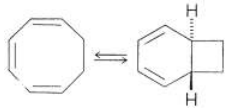


Exercise 21-25* Indicate whether the following reactions are likely to occur thermally by favorable concerted mechanisms:

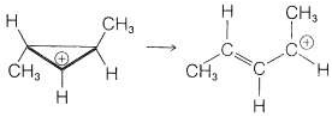
a.



b.

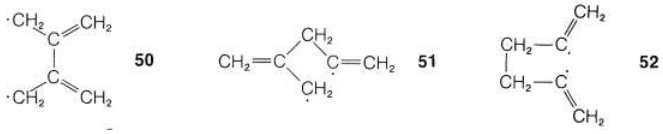


c.



Exercise 21-26* Show how tetracyclo[2.1.1.$0^{5,6}$]-2-hexene may be formed by irradiation of benzene. Would you expect this substance to revert to benzene by a concerted electrocyclic ring opening?

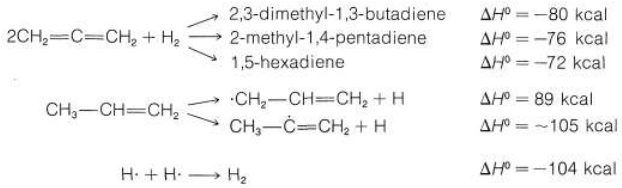
Exercise 21-27* There are three possible biradicals that could be formed by simple combination of two molecules of 1,2-propadiene, 50, 51, and 52:



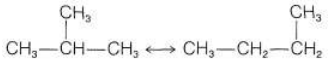
a. Show how each one of these could be formed, and what cyclic product(s) you would expect each to give.

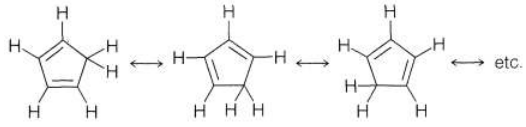
b. Evaluate the degree of electron delocalization expected for 50, 51, and 52 in terms of specific VB structures, and predict qualitatively which biradical you would expect to be formed most easily. Give your reasoning. (As part of your answer you will need to evaluate the importance of electron-pairing schemes for ethenyl-type radicals, such as $R-\dot{C}=CH_2 \longleftrightarrow R-\ddot{C}-\dot{C}H_2$. It is easy to be confused about this; check the rules in Section 6-5B.)

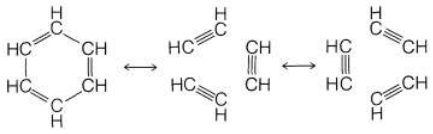
c. By combining the following ΔH^0 values, estimate ΔH^0 for the formation of each of the biradicals 50, 51, and 52. Correlate the results with your predictions in Part b.



Exercise 21-28 Use the VB method in accord with the rules of Section 6-5B to evaluate the contributions of the electron-pairing schemes shown below. (In some cases it will be helpful to use ball-and-stick models to evaluate the relative energies of the VB structure.)

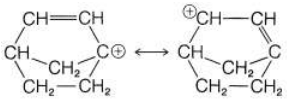
a. 

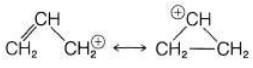
b. 

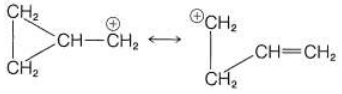
c. 

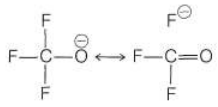
d. $CH_2{=}CH{-}O^{\ominus} \longleftrightarrow {}^{\ominus}CH_2{-}CH{=}O$

e. $CH_2{=}CH-\overset{\oplus}{N}H_3 \longleftrightarrow \overset{\oplus}{C}H_2{-}CH{=}NH_3$

f. 

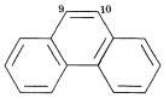
g. 

h. 

i. 

Exercise 21-29 Write three isomeric structures for C_4H_2 with tetravalent carbon and univalent hydrogen. Describe which isomer has the most favorable geometrical configuration and estimate the resonance energy for this isomer.

Exercise 21-30 Write the five Kekulé-type resonance structures of phenanthrene and show how these structures can account for the fact that phenanthrene, unlike benzene, adds bromine, but only across the 9,10-positions.



phenanthrene

Use the data in Tables 4-3 and 21-1 to estimate ΔH^0 for the addition of 1 mole of bromine to phenanthrene. (Don't forget to include the SE of the addition product.)

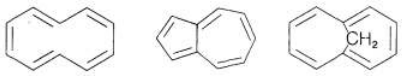
Exercise 21-31 Which compound in each of the following pairs would lose chloride ion more readily and form a carbonium ion? Explain.

$$CH_2{=}CH{-}CH_2{-}CH_2Cl \text{ and } CH_2{=}CH{-}CH_2Cl \tag{21.E.1}$$

$$CH_2{=}CH{-}CHCl{-}CH{=}CH_2 \text{ and } CH_2{=}CH{-}CH{=}CH{-}CH_2Cl \tag{21.E.2}$$

Exercise 21-32 Devise an atomic-orbital model for cyclooctatetraene in accord with the geometry expressed by formula $25a$ (Section 21-9A) and explain why electron delocalization is not likely to be important for a structure with this geometry.

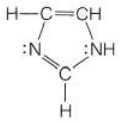
Exercise 21-33 The conjugated 1,3,5,7,9-cyclodecapentaene with the double-bond configuration as in 53 is far less stable than either azulene, 54, or bicyclo[4.4.1]-1,3,5,7,9-undecapentaene, 55. Explain why this is so on the basis of the VB method (molecular models will be helpful).



53 54 55

Exercise 21-34 1,3-Diazole (imidazole) is a planar molecule with substantial delocalization (resonance) energy.

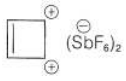
a. Devise an atomic orbital model of imidazole and sketch out the π molecular orbitals you would expect for the molecule on the basis of those in Figure 21-13.



1,3-diazole (imidazole)

b. 1,3-Diazole is relatively acidic and forms the anion $C_3N_2H_3^-$. Which is the acidic hydrogen? Draw valence-bond structures for the anion and indicate which ones should be expected to contribute most to the hybrid structure.

Exercise 21-35 Predict which of the following molecules would have some degree of resonance stability by applying the Hückel $(4n + 2)$ π-electron rule.

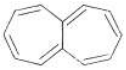
a. 

b.

c.

d.

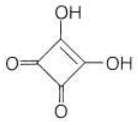
e.*

f.* 

Exercise 21-36 Account for the following experimental observations:

a. 3,4-Dimethylenecyclobutene does not give a Diels-Alder adduct with even the most reactive dienophiles.

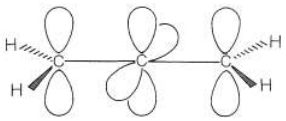
b. Compound 56 is an exceptionally strong *dibasic* organic acid.



56

c. 2,4-Cyclopentadienone is not a stable compound and readily polymerizes.

Exercise 21-37* 1,2-Propadiene is represented in Figure 13-4 as if it were two isolated Hückel ring systems. This molecule also may be represented as a stable Möbius system of 4π electrons. Draw an orbital diagram of 1,2-propadiene to indicate this relationship. If 1,2-propadiene twisted so that the hydrogens on the ends all were in the same plane, 57, would it be a Hückel or a Möbius polyene, or neither?



57

Exercise 21-38 Bicyclo[2.2.0]-1(4)-hexene is highly strained and quite unstable. When it decomposes at room temperature, tetracyclo[6.2.2.$0^{1,8}$.$0^{3,6}$]-3(6)-dodecene is formed.[10]

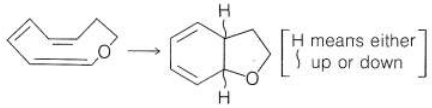
a. Write a structure formula for the product.

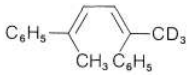
b. Show a reasonable sequence by which it might be formed, with the knowledge that bicyclo[2.2.0]-1(4)-hexene is an extraordinarily reactive dienophile in [4 + 2] cycloadditions.

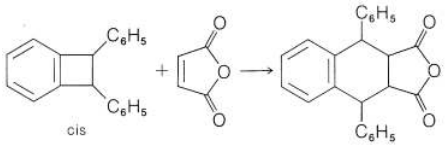
Exercise 21-39 Bicyclo[2.2.0]-2,5-hexadiene is much less stable than its isomer, benzene, yet it does not rearrange to benzene except at elevated temperatures. Give a reason for this observation.

Exercise 21-40 Show the expected stereochemistry of the product of each of the following thermally concerted reactions:

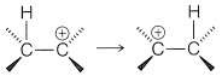
a. 2-*trans*,4-*cis*,6-*cis*,8-*trans*-decatetraene → 7,8-dimethyl-1,3,5-cyclooctatriene

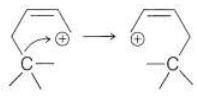
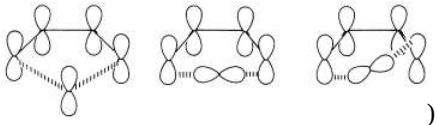
b. 

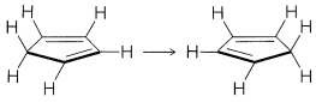
c.  $\overset{124^\circ}{\rightleftharpoons}$ only *one* stereoisomer is formed

d. 

Exercise 21-41* Use the procedure of Section 21-10F to set up transition-state orbitals and determine whether these lead to a favored Hückel or a favored Möbius transition state for the following processes:

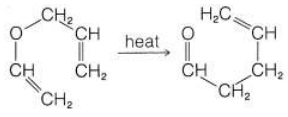
a.  (remember that hydrogen uses 1s orbitals for bonding)

b.  (investigate the orbital systems )

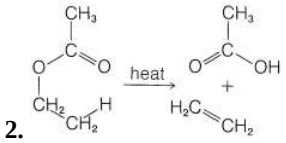
c.  (a 1,3 hydrogen shift)

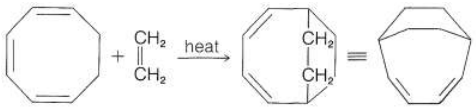
Exercise 21-42

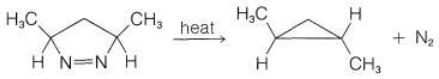
a. Consider each of the following transformations and determine the number of participating orbitals and electrons in each reactant. (Review Section 21-10F if you have trouble.)

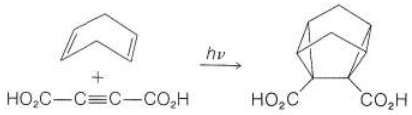
1. 

https://chem.libretexts.org/@go/page/81267









b. Determine whether the reactions in Part a are thermally allowed.

Exercise 21-43* Tetracyanoethene undergoes [2 + 2] cycloaddition with *cis*- and *trans*-1-methoxypropene. The following facts are known about these reactions.

1. Addition is several thousand times faster in CH_3CN (a quite polar solvent) than in cyclohexane.

2. The [2 + 2] addition product becomes *less* stereospecific as the solvent is changed from nonpolar to polar.

3. The *cis*- and *trans*-1-methoxypropene are *interconverted* by tetracyanoethene at a rate *comparable* to the [2 + 2] addition rate with tetracyanoethene.

4. In methanol, only a small amount of [2 + 2] cycloadduct is formed and the principal product is $HC(CN)_2C(CN)_2CH(CH_3)CH(OCH_3)_2$.

a. Write the structures for the [2 + 2] addition.

b. What do Facts 1 and 2 indicate about the mechanism? Write the possible steps involved.

c. Draw an energy diagram for the reaction in a polar solvent as a function of a reaction coordinate in the style of Figure 13-1. This diagram should agree with Fact 3. (Be sure you study the legend of Figure 13-1 before drawing your diagram.)

d. Account for the formation of $HC(CN)_2C(CN)_2CH(CH_3)CH(OCH_3)_2$ along with a [2 + 2] cycloadduct in methanol (a polar solvent). Would you expect any $CH_3OC(CN)_2CH(CH_3)CH_2OCH_3$ to be formed? Explain.

[10]Numbering such as 1(4) means that the double bond comes between carbons 1 and 4 and is used only where necessary to avoid ambiguity.

21.E.1: Contributors

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CHAPTER OVERVIEW

22: Arenes, Electrophilic Aromatic Substitution

Benzene and other aromatic hydrocarbons usually have such strikingly different properties from typical open-chain conjugated polyenes, such as 1,3,5-hexatriene, that it is convenient to consider them as a separate class of compounds called **arenes**. In this chapter we shall outline the essential features of the chemistry of arenes, particularly their reactions with electrophilic reagents which result in the substitution of a ring hydrogen with other functional groups. Some of the important properties of benzene were discussed in Chapter 21 in connection with the valence-bond and molecular-orbital theories, which rationalize the bonding in benzene and account for the remarkable stability and low reactivity of benzene (Section 21-3A). This chapter is especially concerned with chemical properties of benzene and its derivatives as well as related ring systems.

22.1: Nomenclature of Arenes
22.2: Physical Properties of Arenes
22.3: Spectral Properties of Arenes
22.4: Electrophilic Aromatic Substitution
22.5: Effect of Substituents on Reactivity and Orientation in Electrophilic Aromatic Substitution
22.6: Orientation in Disubstituted Benzenes
22.7: IPSO Substitution
22.8: Substitution Reactions of Polynuclear Aromatic Hydrocarbons
22.9: Addition Reactions of Arenes
22.10: Oxidation Reactions
22.11: Sources and Uses of Aromatic Hydrocarbons
22.12: Some Conjugated Cyclic Polyenes
22.13: Fluxional Compounds
22.E: Arenes, Electrophilic Aromatic Substitution (Exercises)

22.1: Contributors and Attributions

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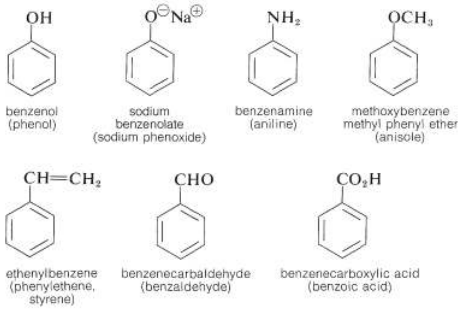
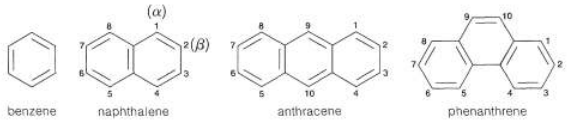
22.1: Nomenclature of Arenes

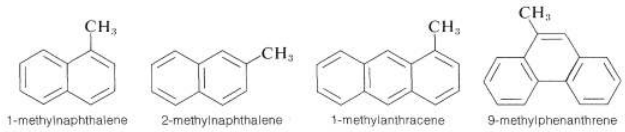
The naming of benzene derivatives was considered in Section 3-5 and is relatively straightforward. However, many benzene derivatives have acquired trivial names, and we draw your attention to a few of these below. The accepted name for the C_6H_5- group as a substituent is **phenyl**.



The more complex ring systems having two or more fused benzene rings have nonsystematic names and illogical numbering systems. They are described as polynuclear aromatic hydrocarbons, the three most important examples being naphthalene, anthracene, and phenanthrene. In anthracene the rings are connected in a *linear* manner, whereas in phenanthrene they are connected *angularly*:



The accepted numbering system for these hydrocarbons is as shown in the structures. The 1- and 2-positions of the naphthalene ring sometimes are designated as α and β, but we prefer not to use these designations. Some illustrative substitution products are:



The names that have been give to these and other more elaborate types of polynuclear aromatic hydrocarbons are for the most part distressingly uninformative with respect to their structures.[1]

[1]A thorough summary of names and numbering systems has been published by A. M. Patterson, L. T. Capell, and D. F. Walker, *Ring Index*, 2nd ed., American Chemical Society, 1960. Less complete but useful summaries are given in various handbooks of chemistry.

22.1.1: Contributors and Attributions

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22.2: Physical Properties of Arenes

The pleasant odors of the derivatives of many arenes is the origin of the name **aromatic** hydrocarbons. The arenes themselves generally are quite toxic; some are carcinogenic and inhalation of their vapors should be avoided. The volatile arenes are highly flammable and burn with a luminous sooty flame, in contrast to alkanes and alkenes, which usually burn with a bluish flame leaving little carbon residue.

The more common arenes and their physical properties are given in Table 22-1. They are less dense than water and are highly insoluble. Boiling points increase regularly with increasing molecular weight, but there is little correlation between melting point and molecular weight. The melting point is highly dependent on the symmetry of the compound; thus benzene melts 100° higher than methylbenzene, and the more symmetrical 1,4-dimethylbenzene (*para*-xylene) has a higher boiling point than either the 1,2- or the 1,3-isomer. This latter fact is utilized in the separation by fractional crystallization of 1,4-dimethylbenzene from mixtures of isomers produced from petroleum.

Table 22-1: *Physical Properties of Arenes*

Compound	Mp, °C	Bp, °C	Density, d_4^{20}
benzene	5.5	80	0.8790
methylbenzene (toluene)	−95	111	0.866
ethylbenzene	−94	136	0.8669
propylbenzene	−99	159	0.8617
isopropylbenzene [(1-methylethyl)benzene]	−96	152	0.8620
tert-butylbenzene [(2,2-dimethylethyl)benzene]	−58	168	0.8658
1,2-dimethylbenzene (*ortho*-xylene)	−25	144	0.8968
1,3-dimethylbenzene (*meta*-xylene)	−47	139	0.8811
1,4-dimethylbenzene (*para*-xylene)	13	138	0.8541
1,3,5-trimethylbenzene (mesitylene)	−45	165	0.8634
1,2,4,5-tetramethylbenzene (durene)	80	197	
naphthalene	80	218	
anthracene	216	340	
phenanthrene	101	340	

22.2.1: Contributors and Attributions

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22.3: Spectral Properties of Arenes

22.3.1: Infrared Spectra

The presence of a phenyl group in a compound can be ascertained with a fair degree of certainty from its infrared spectrum. For example, in Figure 22-1 we see the infrared spectra of methylbenzene, and of 1,2-, 1,3-, and 1,4-dimethylbenzene. That each spectrum is of a benzene derivative is apparent from certain common features. The two bands near $1600\ \mathrm{cm^{-1}}$ and $1500\ \mathrm{cm^{-1}}$, although of variable intensity, have been correlated with the stretching vibrations of the carbon-carbon bonds of the aromatic ring; also, the sharp bands near $3030\ \mathrm{cm^{-1}}$ are characteristic of aromatic C–H bonds. Other bands in the spectra, especially those between $1650\ \mathrm{cm^{-1}}$ and $2000\ \mathrm{cm^{-1}}$, between $1225\ \mathrm{cm^{-1}}$ and $950\ \mathrm{cm^{-1}}$, and below $900\ \mathrm{cm^{-1}}$, have been correlated with the number and position of ring substituents. Although we shall not document all these various bands in detail, each of the spectra in Figure 22-1 is marked to show some of the correlations that have been made.

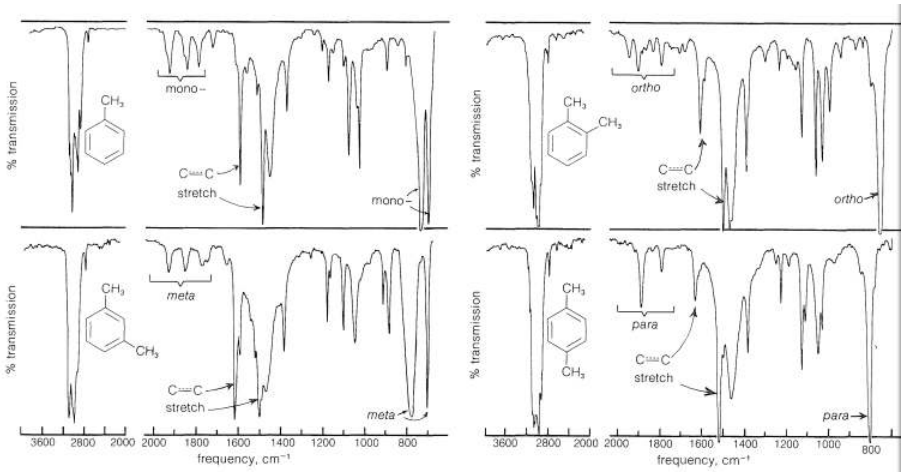
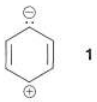


Figure 22-1: Infrared spectra of methylbenzene and the 1,2-, 1,3-, and 1,4-dimethylbenzenes. The number and positions of ring substituents determine the pattern of the low-intensity bands in the region $2000\ \mathrm{cm^{-1}}$ to $1650\ \mathrm{cm^{-1}}$ and the positions of the stronger bands in the region $800\ \mathrm{cm^{-1}}$ to $690\ \mathrm{cm^{-1}}$. The sharp bands near $3030\ \mathrm{cm^{-1}}$ arise from C–H stretching vibrations.

22.3.2: Electronic Absorption Spectra

Compared to straight-chain conjugated polyenes, aromatic compounds have relatively complex absorption spectra with several bands in the ultraviolet region. Benzene and the alkylbenzenes show two bands in which we shall be primarily interested, one near $200\ \mathrm{nm}$ and the other near $260\ \mathrm{nm}$. The 200-nm band is of fairly high intensity and corresponds to excitation of a π electron of the conjugated system to a π^* orbital (i.e., a $\pi \rightarrow \pi^8*$ transition). The excited state has significant contributions from dipolar structures such as 1:



1

This is analogous to the absorption bands of conjugated dienes (Section 9-9B) except that the wavelength of absorption of benzenes is shorter. In fact, the 200-nm absorptions of benzene and the alkylbenzenes are just beyond the range of most commercial quartz spectrometers. However, these absorptions (which we say arise from the benzene **chromophore**[2]) are intensified and shifted to longer wavelengths when the conjugated system is extended by replacement of the ring hydrogens by unsaturated groups (e.g., $-CH{=}CH_2$, $-C \equiv CH$, $-CH{=}O$, and $-C \equiv N$; see Table 22-2). The delocalized π-electron system of the absorbing chromophore now includes the electrons of the unsaturated substituent as well as those of the ring. In the specific case of ethenylbenzene the excited state is a hybrid structure composite of $2a$ and $2b$ and other related dipolar structures:

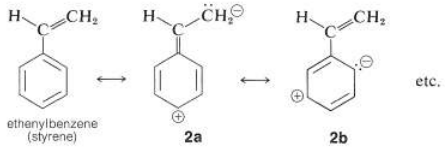
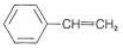
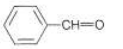
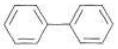
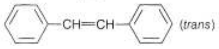
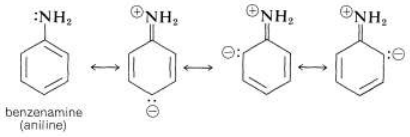


Table 22-2: *Effect of Conjugation on Electronic Absorption by the Benzene Chromophore*

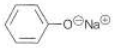
Compound	λ_{max}, nm[a]	ϵ_{max}
	203	8,000
	244	12,000
	244	15,000
	250	18,000
	295	27,000

Similar effects are observed for benzene derivatives in which the substituent has unshared electron pairs that can be conjugated with the benzene ring (e.g., $-NH_2$, $-OH$, $-Cl$). An unshared electron pair is to some extent delocalized to become a part of the aromatic π-electron system in both the ground and excited states, but more importantly in the excited state. This is illustrated for benzenamine (aniline) by the following structures, which contribute to the hybrid structure:



The data of Table 22-3 show the effect on the benzene chromophore of this type of substituent - the substituent often being called an **auxochrome**.[2] This term means that, although the substituent itself is not responsible for the absorption band, it shifts the absorption of the chromophoric group, in this case the benzene ring, toward *longer* wavelengths. The auxochromic groups usually increase the intensity of the absorption also.

Table 22-3: *Effect of Auxochromic Substituents on Electronic Absorption by the Benzene Chromophore*

Compound	λ_{max}, nm[a]	ϵ_{max}
	203	8,000
	210	6,200
	235	9,400
	226	13,000
	230	8,600

[a]In ethanol or water

Figure 22-3, is of relatively low intensity and is found under high resolution to be a composite of several narrow peaks. It appears to be characteristic of aromatic hydrocarbons because no analogous band is found in the spectra of conjugated acyclic polyenes. For this reason it often is called the benzenoid band. The position and intensity of this band, like the one at shorter wavelengths, is affected by the nature of the ring substituents, particularly by those that extend the conjugated system, as may be seen from the date in Table 22-4.

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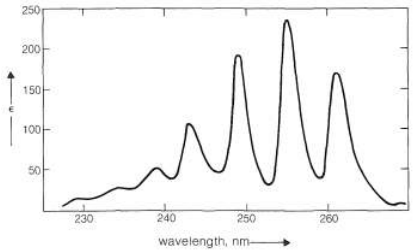
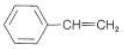
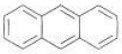
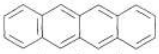
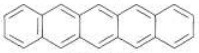


Figure 22-3: Ultraviolet absorption spectrum of benzene (in cyclohexane) showing the "benzenoid" band.

Table 22-4: *Effects of Structure on Electronic Absorption Corresponding to the Benzenoid Band*

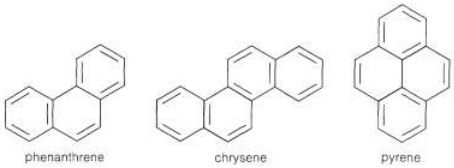
Compound	λ_{max}, nm[a]	ϵ_{max}
	255	230
	261	300
	282	450
	256	800
	280	1,430
	314	316
	380	7,900
 (naphthacene)	480	11,000
 (pentacene)	580	12,600

[a]Mostly in ethanol solution

The benzenoid band corresponds to a low-energy $\pi \rightarrow \pi^*$ transition of the benzene molecules. The absorption intensity is weak because the π^* state involved has the same electronic symmetry as the ground state of benzene, and transitions between symmetrical states usually are forbidden. The transitions are observed in this case only because the vibrations of the ring cause it to be slightly distorted at given instants. In the valence-bond treatment this excited state of benzene is an antibonding state of the π electrons.

The electronic spectra of polynuclear aromatic hydrocarbons such as naphthalene and anthracene, in which aromatic rings are fused together in a linear manner, resemble the spectrum of benzene except that the bands are shifted to longer wavelengths. In fact, with the four linearly connected rings of naphthacene, the benzenoid band is shifted far enough to longer wavelengths to be in the visible region of the spectrum (see Table 22-4). Accordingly, naphthacene is yellow. The next higher member, pentacene, is blue.

Compounds such as phenanthrene, chrysene, and pyrene, in which the aromatic rings are fused in an angular manner, have complex electronic spectra with considerable fine structure. The λ_{max} values normally are at shorter wavelengths than those of their linear isomers.



22.3.3: Nuclear Magnetic Resonance Spectra

The chemical shifts of arene protons (6.5 ppm to 8.0 ppm) characteristically are toward lower magnetic fields than those of protons attached to ordinary double bonds (4.6 ppm to 6.9 ppm). The difference of about 2 ppm cannot be easily explained because the hydrogens in both types of systems are bonded to carbon through sp^2-σ bonds (Sections 6-4C and 6-5A).

At least part of the chemical-shift difference between arene protons and alkene protons is the result of the special property of π electrons in aromatic systems of circulating freely above and below the plane of the carbon nuclei, as shown in Figure 22-4. When a molecule such as benzene is subjected to a magnetic field that has a component *perpendicular* to the plane of the ring, the electrons circulate around the ring in such a way as to produce a local magnetic dipole in the direction *opposite* to the applied field. This *diamagnetic shielding* effect acts to reduce the applied field in the center of the ring. Therefore, if a proton could be located in the center of the ring, the applied field would have to be higher than normal to counteract the local diamagnetic field and bring the proton into resonance. A proton outside the ring is affected in the opposite way (*paramagnetic deshielding* effect) because, as can be seen from the diagram, such protons are located in the return path of the lines of force associated with the local field and thus are in a field greater than that arising from the external magnet alone. When the plane of the molecule is oriented parallel to the field, the diamagnetic circulation is cut off. As a result, as the molecules tumble over and over in the liquid the component of magnetization perpendicular to the plane of the ring varies rapidly. Nonetheless, a substantial *net* paramagnetic effect is experienced by the ring hydrogens. The resonance line positions therefore are shifted to lower magnetic fields.

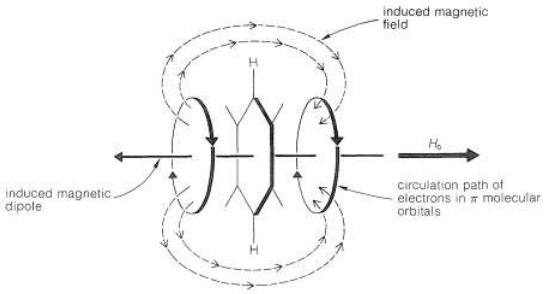
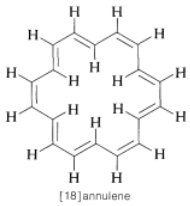


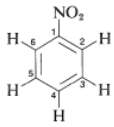
Figure 9-26. The strength of the induced magnetic field, or dipole, is proportional to the applied field.

Strong evidence in confirmation of the above explanation of the chemical shifts of aromatic hydrogens is provided by a study of the cyclic conjugated polyene [18]annulene, which has hydrogens both "inside" and "outside" the ring:



The *inside* hydrogens are strongly deshielded, coming at 1.9 ppm *upfield* from tetramethylsilane, while the *outside* hydrogens are deshielded and come at 8.8 ppm *downfield* from TMS. As we shall see, the ring current effect is quite general and constitutes a widely used test for aromatic character in conjugated polyene ring systems.

In general, the spin-spin splittings observed between the five protons of a phenyl group can be extremely complex. An example is afforded by nitrobenzene (Figure 22-5), which has different chemical shifts for its ortho, meta, and para hydrogens and six different spin-spin interaction constants: J_{23}, J_{24}, J_{25}, J_{26}, J_{34}, J_{35}, (the subscripts correspond to position numbers of the protons):



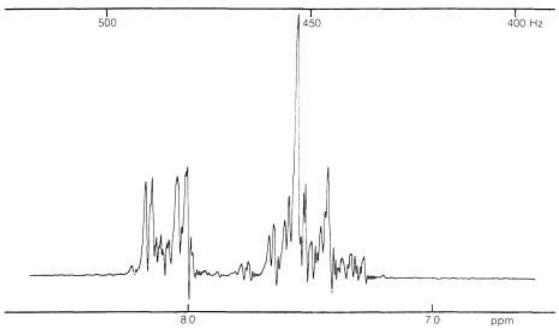
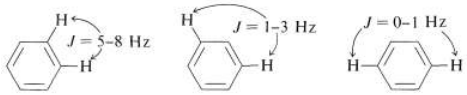


Figure 22-5: Nmr spectrum of nitrobenzene at 60 MHz with reference to TMS at 0.00 ppm.

Such a spectrum is much too complex to be analyzed by any simple procedure. Nonetheless, nuclear magnetic resonance can be useful in assigning structures to aromatic derivatives, particularly in conjunction with integrated line intensities and approximate values of the coupling constants between the ring hydrogens, as shown below:



[2]A chromophore is a grouping of atoms in an organic molecule that gives rise to color, or has the potential of doing so when other groups called **auxochromes** are present (also see Section 28-4).

22.3.4: Contributors and Attributions

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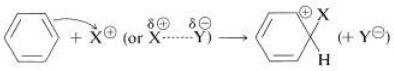
22.4: Electrophilic Aromatic Substitution

22.4.1: Scope and Mechanism

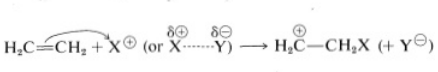
In this section we shall be mainly interested in the reactions of arenes that involve attack on the carbon atoms of the aromatic ring. We shall not elaborate now on the reactions of substituent groups around the ring.

The principal types of reactions involving aromatic rings are substitution, addition, and oxidation. Of these, the most common type is electrophilic substitution. A summary of the more important substitution reactions of benzene is given in Figure 22-7. Many of the reagents used to achieve these substitutions will be familiar to you in connection with electrophilic addition reactions to alkenes (e.g., Cl_2, Br_2, H_2SO_4, and HOCl; Section 10-3). Electrophilic addition to alkenes and electrophilic aromatic substitution are both polar, stepwise processes, and the key step for each is attack of an electrophile at carbon to form a cationic intermediate. We may represent this type of reaction by the following general equations, in which the attacking reagent is represented either formally as a cation, $X^{\oplus}$, or as a neutral but polarized molecule, $\overset{\delta\oplus}{X}\text{---}\overset{\delta\ominus}{Y}$:

electrophilic aromatic substitution (first step)



electrophilic addition to alkenes (first step)



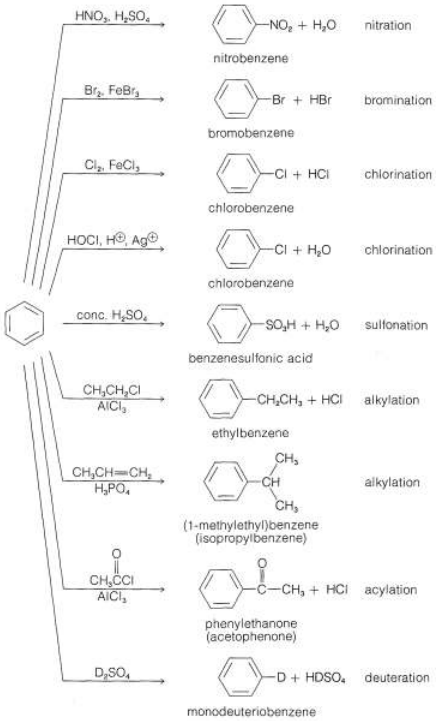
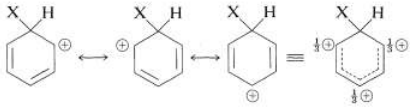


Figure 22-7: Typical benzene substitution reactions.

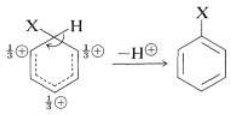
The intermediate shown for aromatic substitution no longer has an aromatic structure; rather, it is a cation with four π electrons delocalized over five carbon nuclei, the sixth carbon being saturated with sp^3-hybrid bonds. It may be formulated in terms of the following contributing structures, which are assumed to contribute essentially equally:



The importance of writing the hybrid structure with the partial charges at these three positions will become evident later. This kind of ion is referred to as a σ *complex* or a *benzenium ion*.

The aromatic ring is regenerated from this cationic intermediate by loss of a proton from the sp^3-hybridized carbon. The electron pair of this $C{-}H$ bond then becomes part of the aromatic π-electron system and a substitution product of benzene, C_6H_5X, is formed.

electrophilic aromatic substitution (second step)



The gain in stabilization attendant on regeneration of the aromatic ring is sufficiently advantageous that this, rather than combination of the cation with $Y^{\ominus}$, normally is the favored course of reaction. Herein lies the difference between aromatic substitution and alkene addition. In the case of alkenes there usually is no substantial resonance energy to be gained by loss of a proton from the intermediate, which tends therefore to react by combination with a nucleophilic reagent.

electrophilic addition to alkenes (second step)

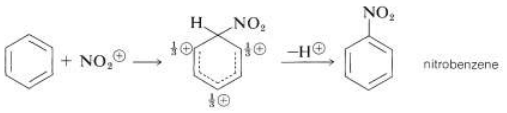
$$\overset{\oplus}{C}H_2{-}CH_2X + Y^{\ominus} \rightarrow YCH_2{-}CH_2X \tag{22.4.1}$$

22.4.2: Nature of the Substituting Agent

It is important to realize that in aromatic substitution the actual electrophilic substituting agent, $\overset{\oplus}{X}$ or $\overset{\delta\oplus}{X} - \overset{\delta\ominus}{Y}$, is not necessarily the reagent that is added to the reaction mixture. For example, nitration in mixtures of nitric and sulfuric acids is not brought about by attack of the nitric acid molecule on the aromatic compound, but by attack of a more electrophilic species, the nitronium ion, $NO_2{}^+$. This ion is formed from nitric acid and sulfuric acid according to the following equation:

$$HNO_3 + 2H_2SO_4 \rightleftharpoons NO_2{}^+ + H_3O^+ + 2_4HSO^- \tag{22.4.2}$$

The nitronium ion attacks the aromatic ring to give first a nitrobenzenium ion and then an aromatic nitro compound:

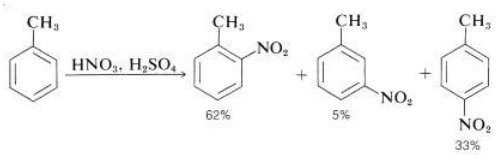


In general, the function of a catalyst (which is so often necessary to promote aromatic substitution) is to generate an electrophilic substituting agent from the given reagents. Thus it is necessary to consider carefully for each substitution reaction what the actual substituting agent may be. This problem does not arise to the same degree in electrophilic additions to alkenes, because alkenes are so much more reactive than arenes that the reagents employed (e.g., Br_2, Cl_2, HCl, HOCl, HOBr, $H_3O^{\oplus}$) themselves are sufficiently electrophilic to react with alkenes without the aid of a catalyst. In fact, conditions that lead to substitution of arenes, such as nitration in mixtures of nitric and sulfuric acid, often will degrade the carbon skeleton of alkenes.

Now we shall consider the individual substitution reactions listed in Figure 22-1 with regard to the nature of the substituting agent and the utility for synthesis of various classes of aromatic compounds.

22.4.3: Nitration

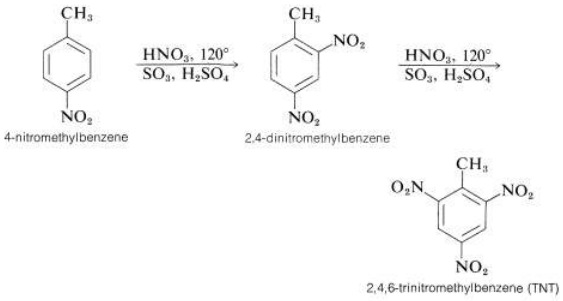
The nitronium ion, $NO_2{}^+$, is the active nitrating agent in nitric acid-sulfuric acid mixtures. The nitration of methylbenzene (toluene) is a typical example of a nitration that proceeds well using nitric acid in a 1:2 mixture with sulfuric acid. The nitration product is a mixture of 2-, 3-, and 4-nitromethylbenzenes:



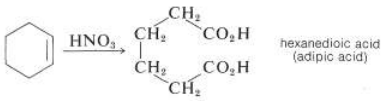
The presence of appreciable amounts of water in the reaction mixture is deleterious because water tends to reverse the reaction by which nitronium ion is formed:

$$NO_2^+ + H_2O \overset{HSO_4^-}{\rightleftharpoons} HNO_3 + H_2SO_4 \qquad (22.4.3)$$

For this reason the potency of a nitric-sulfuric acid mixture can be considerably increased by using fuming nitric and fuming sulfuric acids. With such mixtures nitration of relatively unreactive compounds can be achieved. For example, 4-nitromethylbenzene is far less reactive than methylbenzene, but when heated with an excess of nitric acid in fuming sulfuric acid, it can be converted successively to 2,4-dinitromethylbenzene and to 2,4,6-trinitromethylbenzene (TNT):

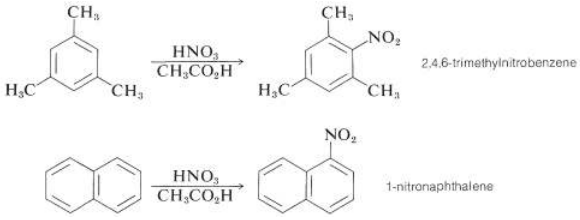


There are several interesting features about the nitration reactions thus far discussed. For instance, the conditions required for nitration of 4-nitromethylbenzene would rapidly oxidize an alkene by cleavage of the double bond:

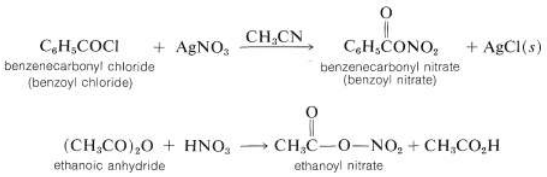


Also the mononitration of methylbenzene does not lead to equal amounts of the three possible products. The methyl substituent apparently orients the entering substituent preferentially to the 2 and 4 positions. This aspect of aromatic substitution will be discussed in Section 22-5 in conjunction with the effect of substituents on the reactivity of aromatic compounds.

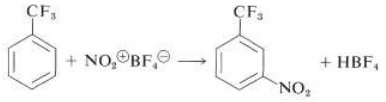
Some compounds are sufficiently reactive that they can be nitrated with nitric acid in ethanoic acid. Pertinent examples are 1,3,5-trimethylbenzene and naphthalene:



Other convenient nitrating reagents are benzoyl nitrate, $C_6H_5COONO_2$, and ethanoyl nitrate, CH_3COONO_2. These reagents provide a source of NO_2^+ and have some advantage over $HNO_3 \cdot H_2SO_4$ mixtures in that they are soluble in organic solvents such as ethanenitrile or nitromethane. Having homogeneous solutions is especially important for kinetic studies of nitration. The reagents usually are prepared in solution as required from the corresponding acyl chloride and silver nitrate or from the acid anhydride and nitric acid. Such reagents are hazardous materials and must be handles with care.

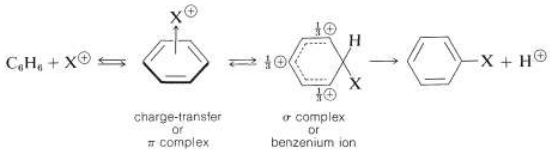


Nitronium salts of the type $NO_2^+X^-$ are very powerful nitrating agents. The counterion, X^-, must be non-nucleophilic and usually is fluoroborate, BF_4^- or SbF_4^-:



22.4.4: Halogenation

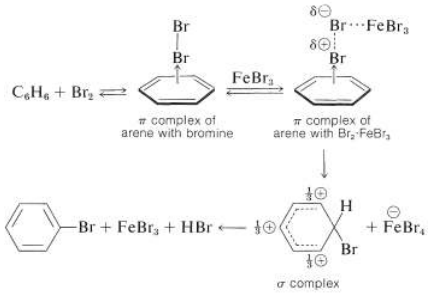
To some degree we have oversimplified electrophilic substitution by neglecting the possible role of the 1:1 charge-transfer complexes that most electrophiles form with arenes (see Section 10-3C for discussion of analogous complexes of alkenes):



With halogens, especially iodine, complex formation is visually evident from the color of solutions of the halogen in arenes. Although complex formation may assist substitution by bringing the halogen and arene in close proximity, substitution does not necessarily occur. A catalyst usually is required, and the catalysts most frequently used are metal halides that are capable of accepting electrons (i.e., Lewis acids such as $FeBr_3$, $AlCl_3$, and $ZnCl_2$). Their catalytic activity may be attributed to their ability to polarize the halogen-halogen bond in the following way:

$$\overset{\delta\oplus}{Br}\cdots\overset{\delta\ominus}{Br}\cdots FeBr_3 \tag{22.4.4}$$

The positive end of the dipole attacks the aromatic compound while the negative end is complexed with the catalyst. We can represent the reaction sequence as follows, with the slow step being formation of a σ bond between $Br^\oplus$ and the aromatic ring:



The order of reactivity of the halogens is $F_2 > Cl_2 > Br_2 > I_2$. Fluorine is too reactive to be of practical use for the preparation of aromatic fluorine compounds and indirect methods are necessary (see Section 23-10B). Iodine usually is unreactive. It has been stated that iodination fails because the reaction is reversed as the result of the reducing properties of the hydrogen iodide that is formed:

$$C_6H_6 + I_2 \overset{\rightarrow}{\leftarrow} C_6H_5I + HI \tag{22.4.5}$$

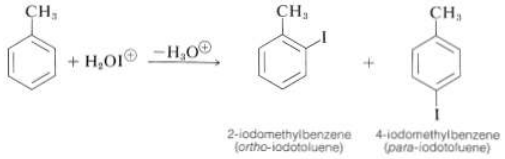
This view is not correct because, as Kekule himself showed, iodobenzene is not reduced by hydroiodic acid except at rather high temperatures.

The way to achieve direct iodination in the absence of powerful activating substituent groups is to convert molecular iodine to some more active species (perhaps $H_2OI^{\oplus}$ or $I^{\oplus}$) with an oxidizing agent such as nitric acid or hydrogen peroxide:

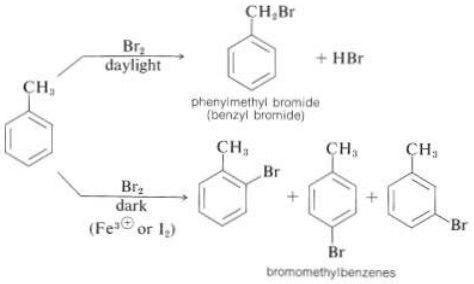
$$I_2 + 4HNO_3 \rightarrow 2H_2O{-}I^+ + 2NO_2 + 2_3NO^- \quad (22.4.6)$$

$$I_2 + H_2O_2 + 2H^+ \rightarrow 2H_2OI^+ \quad (22.4.7)$$

With combinations of this kind good yields of iodination products are obtained:



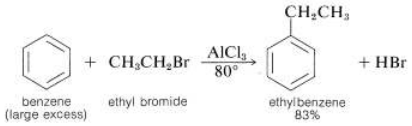
Halogen substitution reactions with chlorine or bromine must be carried out with adequate protection from strong light. If such precautions are not taken, an *alkyl*benzene will react rapidly with halogen by a photochemical process to substitute a hydrogen of the alkyl group rather than of the aromatic ring. The reaction has a light-induced, radical-chain mechanism of the kind discussed for the chlorination of propene (Section 14-3A). Thus methylbenzene reacts with bromine when illuminated to give phenylmethyl bromide; but when light is excluded and a Lewis acid catalyst is present, substitution occurs to give principally the 2- and 4-bromomethylbenzenes. Much less of the 3-bromomethylbenzene is formed:



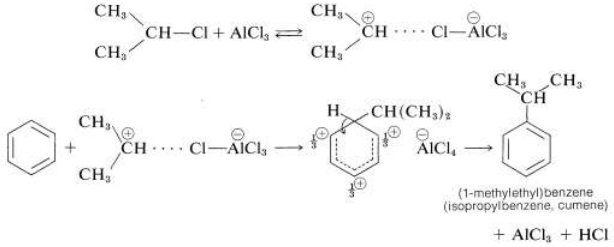
Benzene itself can be induced to *add* halogens on strong irradiation to give polyhalocyclohexanes (see Sections 21-3A and 22-9C):

22.4.5: Alkylation

An important method of synthesis of alkylbenzenes utilizes an alkyl halide as the alkylating agent and a metal halide, usually aluminum chloride, as catalyst:

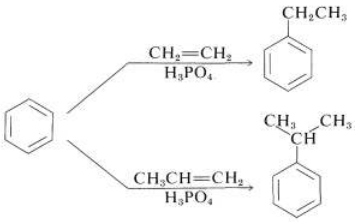


This class of reaction is called **Friedel-Crafts alkylation** in honor of its discoverers, C. Friedel (a French chemist) and J. M. Crafts (an American chemist). The metal-halide catalyst functions much as it does in halogenation reactions to provide a source of a positive substituting agent, which in this case is a carbocation:



Alkylation is not restricted to alkyl halides; alcohols and alkenes may be used to advantage in the presence of acidic catalysts such as H_3PO_4, H_2SO_4, HF, BF_3, or $HF{-}BF_3$. Ethylbenzene is made commercially from benzene and ethene using phosphoric acid as the

catalyst. Isopropylbenzene is made similarly from benzene and propene:

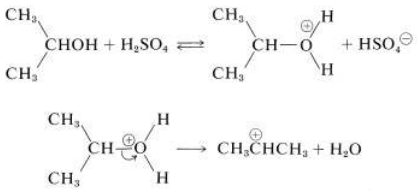


Under these conditions the carbocation, which is the active substituting agent, is generated by protonation of the alkene:

$$CH_2{=}CH_2 + H^+ \rightleftharpoons CH_3CH_2{}^+ \tag{22.4.8}$$

$$CH_3CH{=}CH_2 + H^+ \rightleftharpoons CH_3\overset{+}{C}HCH_3 \tag{22.4.9}$$

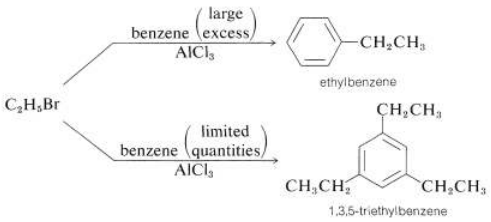
With alcohols the electrophile can be formed by initial protonation by the acid catalyst and subsequent cleavage to a carbocation:



22.4.5.1: Limitations of Alkylation Reactions

Polysubstitution

There are several factors that limit the usefulness of alkylation reactions. First, it may be difficult to limit reaction to monosubstitution because introduction of one alkyl substituent tends to activate the ring towards a second substitution (see Section 22-5). Therefore, to obtain reasonable yields of a monoalkylbenzene, it usually is necessary to use a large excess relative to the alkylating agent:



Rearrangement of the alkylating agent

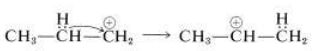
A second limitation is the penchant for the alkylating reagent to give rearrangement products. As an example, the alkylation of benzene with 1-chloropropane leads to a mixture of propylbenzene and isopropylbenzene. We may write the reaction as first involving formation of a propyl cation, which is a *primary* carbocation:

$$CH_3CH_2CH_2Cl + AlCl_3 \rightarrow CH_3CH_2CH_2{}^+ + \bar{A}lCl_4 \tag{22.4.10}$$

This ion either can alkylate benzene to give propylbenzene,

$$C_6H_6 + CH_3CH_2CH_2{}^+ \rightarrow C_6H_5CH_2CH_2CH_3 + H^+ \tag{22.4.11}$$

or it can rearrange to a more stable secondary ion by the transfer of a hydrogen from a neighboring carbon together with its bonding electron pair (i.e., 1,2-hydride shift). The positive charge is thereby transferred from C_1 to C_2:



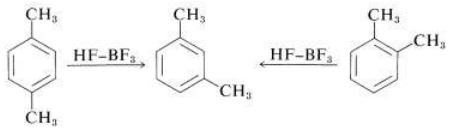
Alkylation of benzene with the isopropyl cation then produces isopropylbenzene:

$$C_6H_6 + CH_3\overset{\oplus}{C}HCH_3 \rightarrow C_6H_5CH(CH_3)_2 + H^{\oplus} \quad (22.4.12)$$

Rearrangements of this type involving carbocation intermediates often occur in Friedel-Crafts alkylations with primary and secondary alkyl groups larger than C_2 and C_3. Related carbocation rearrangements are discussed in Sections 8-9B and 15-5E.

Rearrangement of products

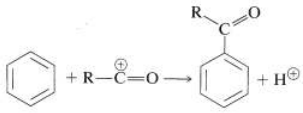
Further complications arise from the fact that the alkylation reactions sometimes are under equilibrium control rather than kinetic control. Products often isomerize and disproportionate, particularly in the presence of large amounts of catalyst. Thus 1,2- and 1,4-dimethylbenzenes (*ortho*- and *para*-xylenes) are converted by large amounts of Friedel-Crafts catalysts into 1,3-dimethylbenzene (*meta*-xylene):



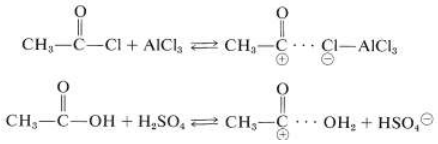
Ethylbenzene disproportionates under the influence of excess $HF{-}BF_3$ to benzene and 1,3-diethylbenzene:

22.4.6: Acylation

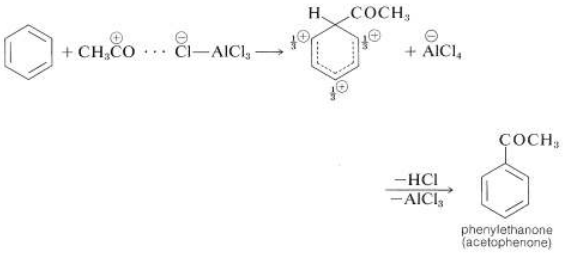
Acylation and alkylation of arenes are closely related. Both reactions were developed as the result of the collaboration between Friedel and Crafts, in 1877. The acylation reaction introduces an acyl group, RCO, into an aromatic ring and the product is an aryl ketone:



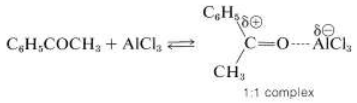
The acylating reagents commonly used are carboxylic acid halides, $RCOCl$, anhydrides, $(RCO)_2O$, or the acid itself, RCO_2H. A strong proton or other Lewis-acid catalyst is essential. The catalyst functions to generate the acyl cation:



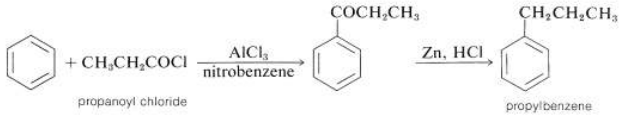
The catalyst most commonly used with acyl halides and anhydrides is aluminum chloride:



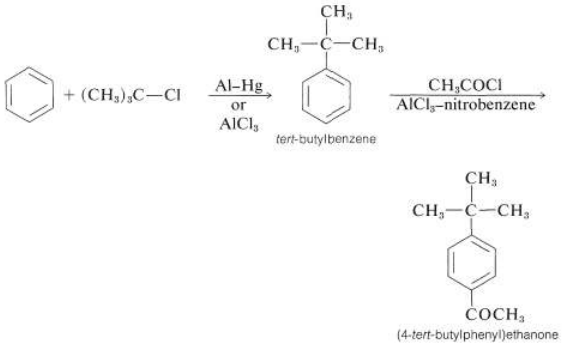
Acylation differs from alkylation in that the reaction usually is carried out in a solvent, commonly carbon disulfide, CS_2, or nitrobenzene. Furthermore, acylation requires more catalyst than alkylation, because much of the catalyst is tied up and inactivated by complex formation with the product ketone:



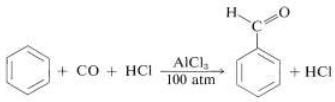
Unlike alkylation, acylation is controlled easily to give monosubstitution, because once an acyl group is attached to a benzene ring, it is not possible to introduce a second acyl group into the same ring. Because of this, a convenient synthesis of alkylbenzenes starts with acylation, followed by reduction of the carbonyl group with zinc and hydrochloric acid (Section 16-6). For example, propylbenzene is prepared best by this two-step route because, as we have noted, the direct alkylation of benzene with propyl chloride produces considerable amounts of isopropylbenzene and polysubstitution products:



In the acylation of alkylbenzene the product almost always is the *para* isomer. The synthesis of (4-*tert*-butylphenyl)ethanone illustrates this as well as the sequential use of alkylation and acylation reactions:



Chemists are inclined to give names to reactions that associate them either with their discoverers or with the products they give. This practice can be confusing because many named reactions (or "name reactions") which once were thought to be quite unrelated, have turned out to have very similar mechanisms. Thus we have two closely related acylation reactions: one is the Friedel-Crafts ketone synthesis, in which the electrophile is $\mathrm{R-\overset{\oplus}{C}{=}O}$; and the other is the **Gattermann-Koch aldehyde synthesis**, in which the electrophile is $\mathrm{H-\overset{\oplus}{C}{=}O}$:

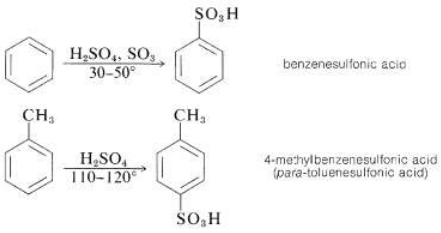


The latter reaction utilizes carbon monoxide and HCl under pressure in the presence of aluminum chloride. The electrophile may be considered to be formed as follows:

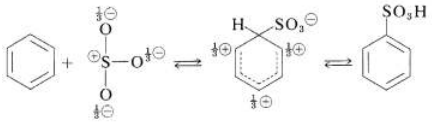
$$\mathrm{C{=}O + HCl + AlCl_3 \rightleftharpoons H-\overset{\oplus}{C}{=}O + \overset{\ominus}{A}lCl_4} \tag{22.4.13}$$

22.4.7: Sulfonation

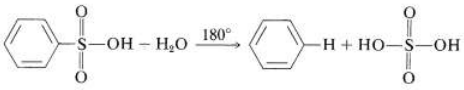
Substitution of the sulfonic acid $(-\mathrm{SO_3H})$ group for a hydrogen of an aromatic hydrocarbon can be carried out by heating the hydrocarbon with a slight excess of concentrated or fuming sulfuric acid:



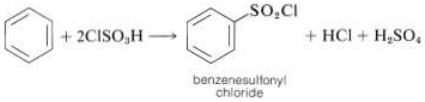
The actual sulfonating agent normally is the SO_3 molecule, which, although neutral, has a powerfully electrophilic sulfur atom:



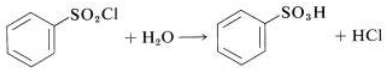
Sulfonation is reversible and the $-SO_3H$ group can be removed by hydrolysis at 180°:



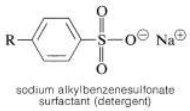
A useful alternative preparation of sulfonyl derivatives is possible with chlorosulfonic acid:



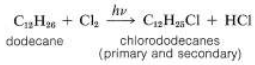
This procedure has an advantage over direct sulfonation in that sulfonyl chlorides usually are soluble in organic solvents and may be easily separated from the reaction mixture. Also, the sulfonyl chloride is a more useful intermediate than the sulfonic acid, but can be converted to the acid by hydrolysis if desired:



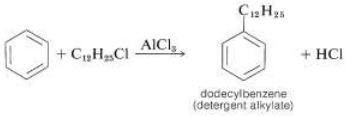
Sulfonation is important in the commercial production of an important class of detergents - the sodium alkylbenzenesulfonates:



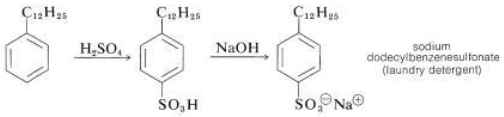
The synthesis illustrates several important types of reactions that we have discussed in this and previous chapters. First, the alkyl group R usually is a C_{12} group derived from the straight-chain hydrocarbon, dodecane, which on photochlorination gives a mixture of chlorododecanes:



This mixture of chlorododecanes is used to alkylate benzene, thereby giving a mixture of isomeric dodecylbenzenes, called *detergent alkylate*:



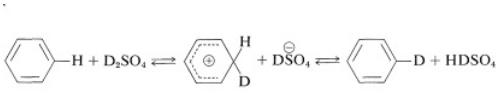
Sulfonation of the detergent alkylate gives exclusively the 4-dodecylbenzenesulfonic acids, which with sodium hydroxide form water-soluble dodecylbenzenesulfonates:



In many countries it is prohibited by law to market detergents of this type, which have highly branched alkyl groups. The reason is that quaternary carbons and, to a lesser extent, tertiary carbons are not degraded readily by bacteria in sewage treatment plants:

22.4.8: Hydrogen Exchange

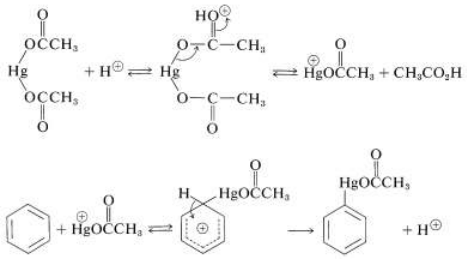
It is possible to replace the ring hydrogens of many aromatic compounds by exchange with strong acids. When an isotopically labeled acid such as D_2SO_4 is used, this reaction is an easy way to introduce deuterium. The mechanism is analogous to other electrophilic substitutions:



Perdeuteriobenzene[3] can be made from benzene in good yield if a sufficiently large excess of deuteriosulfuric acid is used. Deuteration might appear to be competitive with sulfonation, but deuteration actually occurs under much milder conditions.

22.4.9: Aromatic Substitution by Electrophilic Metalation

Because metals are electropositive elements they can be considered potential electrophiles. Their reactions with arenes have been investigated most thoroughly for mercury. Benzene can be substituted with $HgX^{\oplus}$ derived from a mercuric salt, HgX_2, in the presence of an acid catalyst. The salt most commonly used is mercuric ethanoate, $Hg(OOCCH_3)_2$. The catalyst is considered to function by assisting the generation of the active electrophile, $HgX^{\oplus}$. Other metals that may be introduced directly into an aromatic ring in this manner include thallium and lead.



[3]The prefix *per*, as in perdeuterio- or perfluoro-, means that *all* the hydrogens have been replaced with the named substituent, D or F. Perhydro means saturated or fully hydrogenated.

22.4.10: Contributors and Attributions

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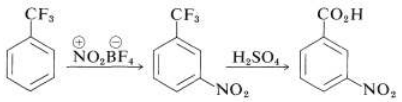
22.5: Effect of Substituents on Reactivity and Orientation in Electrophilic Aromatic Substitution

In planning syntheses based on substitution reactions of substituted benzenes, it is imperative to be able to predict in advance which of the available positions of the ring are likely to be most reactive. This is now possible with a rather high degree of certainty, thanks to the work of many chemists during the past 100 years. Few, if any, other problems in organic chemistry have received so much attention over so many years, and there are now sufficient data on the orientation and reactivity effects of ring substituents in electrophilic substitution to permit the formation of some very valuable generalizations.

Basically, three experimental problems are involved in the substitution reactions of aromatic compounds: (1) proof of structure of the isomers that are formed; (2) determination of the percentage of each isomer formed, if the product is a mixture; and (3) measurement of the reactivity of the compound being substituted relative to some standard substance, usually benzene.

For benzenoid compounds, structures can be established by the historically important substitution method (Section 1-1F) or with the aid of correlations between spectroscopic properties and positions of substitution, as we indicated in Section 22-3. Also, it is often possible to identify the isomers by converting them to compounds of known structure. For example, trifluoromethylbenzene on nitration gives only one product, which has been shown to be the 3-nitro derivative by conversion to the known 3-nitrobenzoic acid by concentrated sulfuric acid:

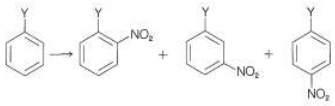


The ratios of isomers formed in substitution reactions can be determined by spectroscopic means or by the analytical separation methods discussed in Section 9-2. We mainly are concerned in this chapter with the reactivity and orientation observed in aromatic substitution.

22.5.1: The Pattern of Orientation in Aromatic Substitution

The reaction most studied in connection with the orientation problem is nitration, but the principles established also apply for the most part to the related reactions of halogenation, sulfonation, alkylation, and acylation. Some illustrative data for the nitration of a number of mono-substituted benzene derivatives are given in Table 22-5. The table includes the percentage of ortho, meta, and para isomers formed, along with their reactivities relative to benzene. We see that there is a wide range of reactivity according to the nature of the substituent, and that the ortho, meta, and para positions are *not* equally reactive. Although these substituent effects may appear complex, they are related closely to substituted alkenes (Section 10-4), as will be explained in the following section.

Table 22-5: *Orientation and Rate Data for Nitration of Some Monosubstituted Benzene Derivatives*[a]



	Orientation			
Substituent, Y	% ortho	% meta	% para	Relative reactivity
—H	–	–	–	1
—CH_3	56.5	3.5	40	24
—$C(CH_3)_3$	12.0	8.5	79.5	15.7
—CH_2Cl	32.0	15.5	52.5	0.302
—Cl	29.6	0.9	68.5	0.033
—Br	36.5	1.2	62.4	0.030
—NO_2	6.4	93.2	0.3	$\sim 10^{-7}$
—$CO_2C_2H_5$	28.3	68.4	3.3	0.003
—CF_3		100		
—$\overset{\oplus}{N}(CH_3)_3$		89	11	

[a]The data are representative but will vary to some extent with the reaction conditions and nature of the substituting agent.

22.5.2: Electronic Effects

It is helpful to construct an energy diagram for substitution by an electrophilic $X^{\oplus}$ of a benzene derivative, C_6H_5Y, in which Y is a substituent group (Figure 22-8). The rate of substitution at any one position (we have arbitrarily chosen in Figure 22-8 to compare the 3 and 4 positions) will depend on the height of the energy barrier between the reactants and the transition state. Effects that act to lower the heights of the barriers increase the rates of substitution. Because the transition state and the positively charged intermediate for aromatic substitution have much the same energy, any effect that stabilizes this intermediate is likely to lower the energy of the transition state and increase the rate of substitution. Thus under conditions of *kinetic control* the preferred arene substitution product, as in alkene addition, will be that derived from the most stable of the possible intermediates. Therefore the problem of predicting relative rates and orientation in aromatic substitution becomes one of deciding what factors are likely to stabilize or destabilize the various possible intermediates relative to one another and to the ground state.

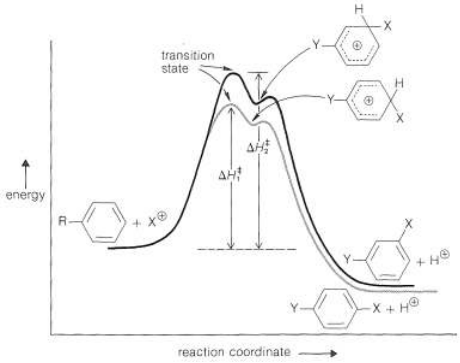
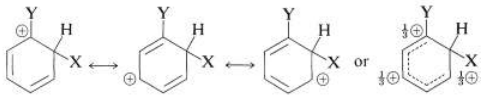


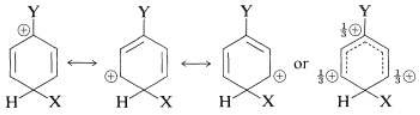
Figure 22-8: Energy diagram for the substitution of a compound C_6H_5Y in the 3 and 4 positions. It is assumed here that the relative rates are determined by differences in $\Delta H^{\ddagger}$ and not in $\Delta S^{\ddagger}$. Because $\Delta H_1^{\ddagger}$ is less than $\Delta H_2^{\ddagger}$, substitution to give the 4-isomer is "kinetically preferred".

We now can examine the structures of the three substitution intermediates with a view to deciding how the substituent might affect their stability. According to the valence-bond method, the positive charge in the ring is dispersed mainly on alternate carbons, as shown below.

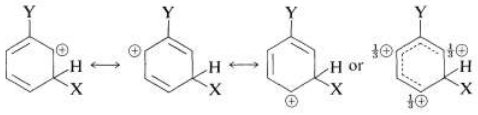
ortho substitution



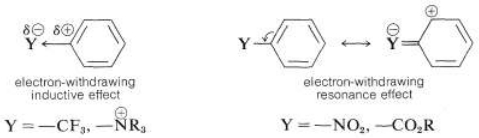
para substitution



meta substitution



The substituent Y should (and does) exert its electronic influence more strongly from the ortho and para positions than from the meta position because Y in the ortho and the para positions is close to a positively charged ring carbon. This electronic influence will be stabilizing if Y has a net electron-donating effect, and destabilizing if Y is electron withdrawing. A group can withdraw electrons relative to hydrogen if it is more electronegative than hydrogen and this is called the electron-withdrawing inductive effect (also see Section 18-2B). A group also can withdraw electrons by the **resonance effect**:



Accordingly, substituents fall into one of the following categories.

22.5.2.1: Meta-directing substituents

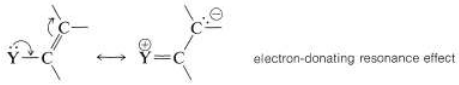
A ring substituent Y that is electron withdrawing relative to hydrogen and has no capacity to donate electrons by a resonance effect will *decrease* the reactivity of C_6H_5Y, especially at the ortho and para positions. The result is a sluggish reaction (**deactivation**) with substitution occurring preferentially at the meta position. Substituents in this category are $-NO_2$, $-CF_3$, $-CO_2R$, $-\overset{\oplus}{N}R_3$, and so on (also see Tables 22-5 and 22-6). No groups are known that direct the electrophile to the meta position and, at the same time, make the phenyl derivative *more* reactive relative to benzene.

Table 22-6: *Orientation and Reactivity Effects of Ring Substituents*

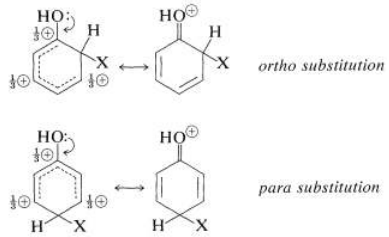
ortho-para-Orientation, with activation	ortho-para-Orientation, with deactivation	meta-Orientation, with deactivation	
—OH	$-CH_2Cl$	$-NO_2$	$-SO_3H$
$-O^{\ominus}$	—F	$-\overset{\oplus}{N}H_3$	$-SO_3R$
—OR	—Cl	$-\overset{\oplus}{N}R_3$	$-CO_2H$
$-OC_6H_5$	—Br	$-\overset{\oplus}{P}R_3$	$-CO_2R$
$-NH_2$	—I	$-\overset{\oplus}{S}R_2$	$-CONH_2$
$-NR_2$	$-CH{=}CHNO_2$	$-\overset{\oplus}{I}C_6H_5$	—CHO
$-NHCOCH_3$		$-CF_3$	—COR
—alkyl (e.g., CH_3)		$-CCl_3$	—C≡N
—aryl (e.g., C_6H_5)			

22.5.2.2: Ortho-para directing substituents

1. A ring substituent, $-Y$, that has an electron pair on the atom adjacent to the ring gives ortho-para substitution in preference to meta substitution. The reason is that the intermediate can be stabilized by an electron-donating resonance effect from Y that is effective from the ortho and para positions only:



This effect is made clear in the valence-bond structures for the ortho-para substitution intermediates from benzenol (phenol):



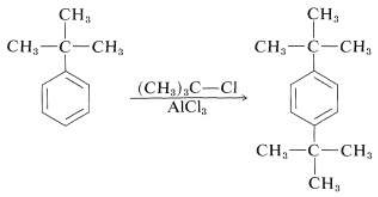
Substituents of the type $-Y$ include $-OH$, $-OR$, $-SR$, $-NH_2$, and halogens. Most of these groups also are electron withdrawing by an inductive effect that opposes their resonance effect. However, as we saw in the case of alkene additions (Section 10-4C), even when $-Y$ is an electronegative group, stabilization of the intermediate cation by donation of unshared electrons of Y to the adjacent positive carbon more than compensates for the polar electron-withdrawing properties of Y. Electron donation thus controls the orientation. If, however, the group is *strongly* electron withdrawing (e.g., $-Y = -F$, $-Cl$, $-Br$, $-I$), the reactivity of the compound C_6H_5Y may be reduced. Groups of this kind are ortho-para directing with deactivation.

But if the polar effect is not pronounced, then substitution can be powerfully assisted by the substituent. This is ortho-para direction with activation and is provided by groups such as $-OH$, $-OR$, $-SR$, and $-NH_2$. A more comprehensive list of substituents and their orientation effects is provided in Table 22-6.

2. When no important π-electron effect is possible, as with alkyl groups, the orientation effect of a substituent is controlled by its polar effect and the degree to which it polarizes the bonding electrons of the ring. Alkyl groups actually are electron donating and therefore are ortho-para directing with activation.

22.5.3: Steric Effects

Thus far we have made no distinction between the reactivities of the ortho and the para positions, yet they clearly are not equal. If they were equal, the ortho:para ratio would be 2:1, thereby reflecting the fact that there are two ortho positions but only one para position in monosubstituted benzenes. Most substitution reactions favor the para product, sometimes by a considerable amount (see Table 22-5). A reasonable explanation is that ortho substitution is subject to steric hindrance between the substituent and the entering group. *tert*-Butylbenzene, for example, gives much less ortho nitration than methylbenzene (Table 22-5), thereby suggesting that the size of the substituent is important. Also, *tert*-butylbenzene gives no ortho alkylation with *tert*-butyl chloride, suggesting that the size of the entering group is also important:



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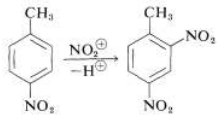
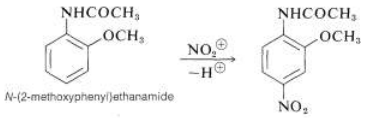
22.6: Orientation in Disubstituted Benzenes

The orientation and reactivity effects of substituents discussed for the substitution of monosubstituted benzenes also hold for disubstituted benzenes, except that the directing influences now come from two groups. Qualitatively, the effects of the two substituents are additive on the reactivity. We therefore would expect 4-nitromethylbenzene to be less reactive than methylbenzene because of the deactivating effect of a nitro group. Also, the most likely position of substiuttion should be, and is, ortho to the methyl group and meta to the nitro group:



When the two substituents have opposed orientation effects, it is not always easy to predict what products will be obtained. For example, N-(2-methoxyphenyl)ethanamide has two powerful *o*,*p*-directing substituents, $-OCH_3$ and $-NHCOCH_3$. Nitration of this compound gives mainly the 4-nitro derivative, which indicates that the $-NHCOCH_3$ exerts a stronger influence than $-OCH_3$:



Seemingly anomalous effects of substituents are known, but such effects may be due to equilibrium control. One example is the aluminum chloride-catalyzed alkylation of benzene, which leads to the formation of a 1,3,5-trialkylbenzene in preference to the expected 1,2,4-isomer (see Section 22-4E). The preferred reaction occurs particularly readily because alkylation is reversible and because alkylation is one of the least selective of the electrophilic aromatic substitutions (considerable meta isomer is formed even under conditions where kinetic control is dominant). Equilibrium control, which favors the 1,3,5-product rather than the less stable 1,2,4-product, becomes most evident when the reaction time, the reaction temperature, and aluminum chloride concentration are increased. Another source of anomalous substituent effects is discussed in the next section.

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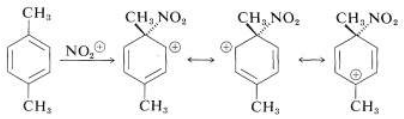
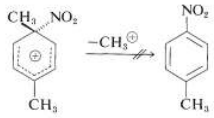
22.7: IPSO Substitution

For all practical purposes, electrophilic aromatic substitution is confined to the substitution of a ring hydrogen. Does this mean that an electrophile such as NO_2^+ only attacks hydrogen-bearing carbons? What about substituted ring carbons?

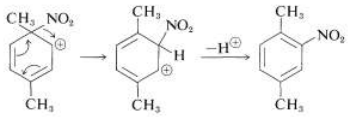
Electrophilic attack at methyl-bearing carbons, particularly in *ortho*- and *para*-dimethylbenzenes, would appear quite reasonable because the electron-donating character of the other methyl group should activate the ring by stabilizing the intermediate ion:



Attack at the substituted (*ipso*) carbon evidently does occur, but it does not lead directly to substitution products because demethylation, unlike deprotonation, does not occur:

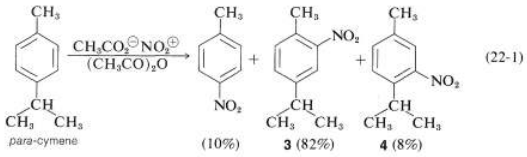


Instead, the nitro group changes positions to the neighboring ring carbon, which then can eliminate a proton to form a substitution product:



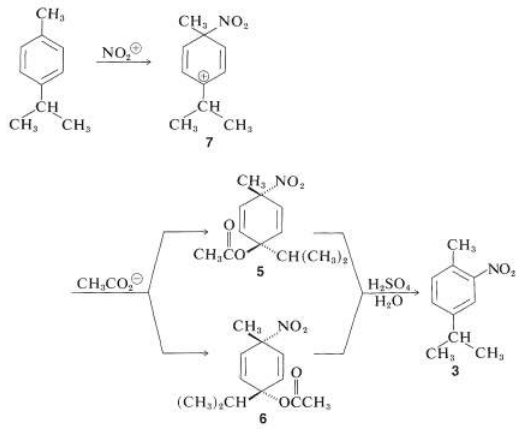
Because the product obtained indirectly (by *ipso* substitution) is indistinguishable from that expected by direct electrophilic attack at C_2, it is not possible to say how much, if any, product is formed by the *ipso* route in this reaction.

In general, orientation effects in the substitution of alkylbenzenes are complicated by *ipso* attack. For example, in the nitration of 4-methylisopropylbenzene (*para*-cymene) about 10% of the nitration product is 4-nitromethylbenzene:



(22-1)

The 4-nitromethylbenzene arises from *ipso* attack of NO_2^+ at the isopropyl-substituted ring carbon. Unlike methyl, the isopropyl group is eliminated rapidly as propene. Can we say that the other products, 3 and 4, arise by direct substitution? Evidently not, because nitration at 0° gives two other products, 5 and 6, which must be formed by *ipso* attack at the *methyl*-bearing carbon. At low temperatures, intermediate ion 7 is attacked by the weakly nucleophilic ethanoate ion to give 5 and 6. Both of these adducts solvolyze rapidly in 78% sulfuric acid to give 3 only:



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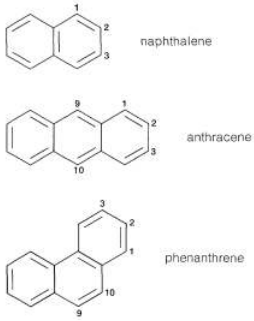
22.8: Substitution Reactions of Polynuclear Aromatic Hydrocarbons

Although naphthalene, phenanthrene, and anthracene resemble benzene in many respects, they are more reactive than benzene in both substitution and addition reactions. This increased reactivity is expected on theoretical grounds because quantum-mechanical calculations show that the net loss in stabilization energy for the first step in electrophilic substitution or addition decreases progressively from benzene to anthracene; therefore the reactivity in substitution and addition reactions should increase from benzene to anthracene.

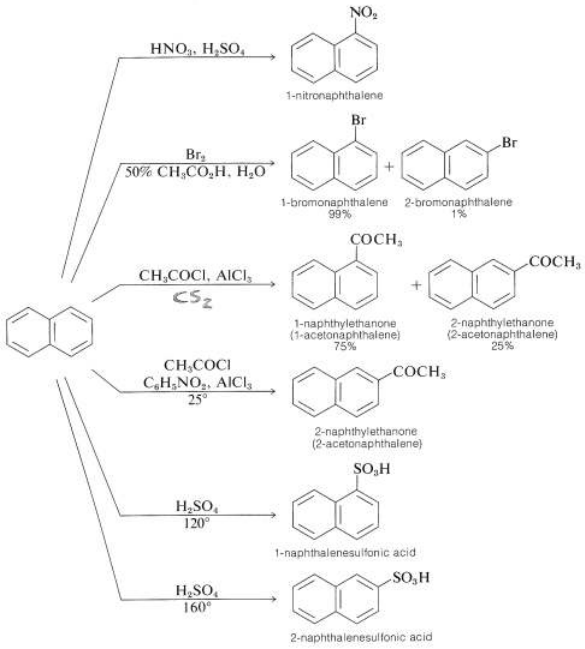
In considering the properties of the polynuclear hydrocarbons relative to benzene, it is important to recognize that we neither expect nor find that all the carbon-carbon bonds in polynuclear hydrocarbons are alike or correspond to benzene bonds in being halfway between single and double bonds.



The 1,2 bonds in both naphthalene and antracene are in fact shorter than the other ring bonds, whereas the 9,10 bond in phenanthrene closely resembles an alkene double bond in both its length and chemical reactivity.

22.8.1: Naphthalene

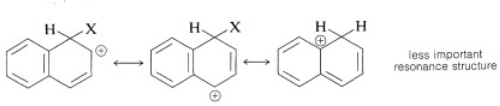
Orientation in the substitution of naphthalene can be complex, although the 1 position is the most reactive. Some examples follow.



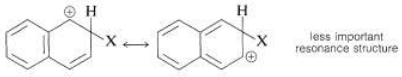
Sometimes, small changes in the reagents and conditions change the pattern of orientation. One example is sulfonation, in which the orientation changes with reaction temperature. Another example is Friedel-Crafts acylation; in carbon disulfide the major product is the 1-isomer, whereas in nitrobenzene the major product is the 2-isomer.

Substitution usually occurs more readily at the 1 position than at the 2 position because the intermediate for 1-substitution is more stable than that for 2-substitution. The reason is that the most favorable resonance structures for either intermediate are those that have *one fully aromatic* ring. We can see that 1-substitution is more favorable because the positive charge can be distributed over two positions, leaving one aromatic ring unchanged. Only one resonance structure is possible for the 2-substitution intermediate that retains a benzenoid-bond arrangement for one of the rings.

1-substitution

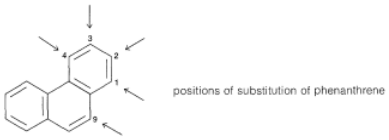


2-substitution

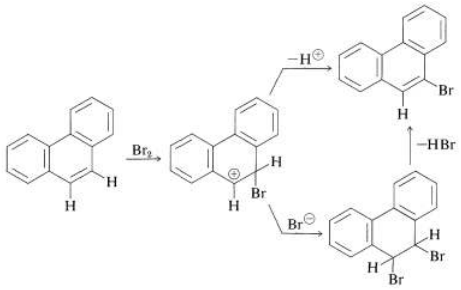


22.8.2: Phenanthrene

The reactions of the higher hydrocarbons with electrophilic reagents are more complex than of naphthalene. For example, phenanthrene can be nitrated and sulfonated, and the products are mixtures of 1-, 2-, 3-, 4-, and 9-substituted phenanthrenes:

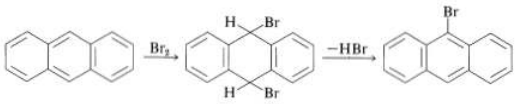


However, the 9,10 bond in phenanthrene is quite reactive; in fact is is almost as reactive as an alkene double bond. Addition therefore occurs fairly readily; halogenation can give both 9,10-addition and 9-substitution products by the following scheme:



22.8.3: Anthracene

Anthracene is even more reactive than phenanthrene and has a greater tendency to add at the 9,10 positions than to substituted. However, the addition products of nitration and halogenation readily undergo elimination to form the 9-substitution products:



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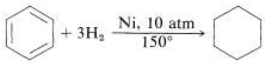
22.9: Addition Reactions of Arenes

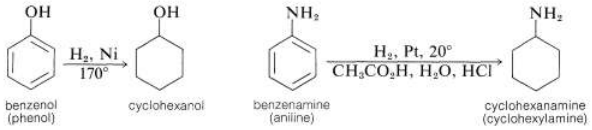
22.9.1: Catalytic Hydrogenation

Benzenoid compounds are not readily converted to cyclohexane derivatives. Nevertheless, several addition reactions are carried out on an industrial scale. Mention was made previously of the hydrogenation of benzene to cyclohexane in the presence of a nickel catalyst:

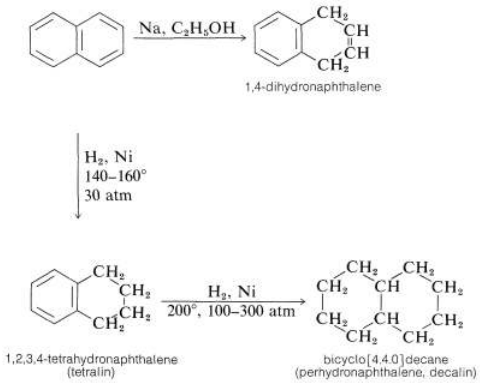


The reaction is very important because cyclohexane is used widely as a solvent and also is oxidized to cyclohexanone, and important intermediate in the synthesis of hexanedioic (adipic) acid and azacycloheptan-2-one (caprolactam), which are used in the preparation of nylon (Section 24-3C).

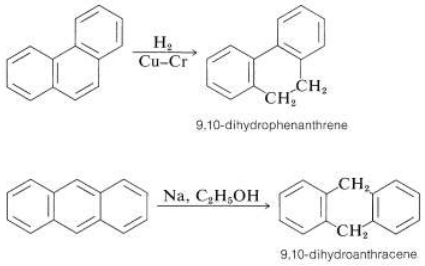
Other cyclohexyl compounds are obtained by catalytic hydrogenation of the corresponding benzene derivatives. Thus cyclohexanol is obtained from benzenol, and cyclohexanamine is obtained from benzenamine (aniline):



Naphthalene can be reduced more easily than benzene. With sodium in alcohol, 1,4-dihydronaphthalene is formed. Catalytic hydrogenation gives tetralin (1,2,3,4-tetrahydronaphthalene). Further reduction to give perhydronaphthalene (decalin) can be achieved on prolonged catalytic hydrogenation at relatively high temperatures and pressures:

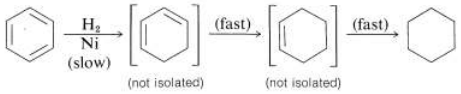


Phenanthrene and anthracene are reduced readily to the dihydro level by addition to the 9,10 positions. Further reduction of the terminal benzene rings is relatively difficult:



22.9.2: Reduction of Arenes with Metals

Catalytic hydrogenation of benzene cannot be stopped at cyclohexane or cyclohexadiene; it proceeds to cyclohexane. This is because the rate of the first addition step is much slower than of the subsequent steps:



However, benzene and its derivatives can be reduced to cyclohexadienes by solutions of metals such as Li, Na, K, Zn, and Hg in a weakly acidic solvent, such as liquid ammonia, amines, or ether-alcohol mixtures. This general type of reaction is known as the **Birch reduction** after the Australian chemist, A. J. Birch. With benzene, reduction with metals leads to 1,4-cyclohexadiene:

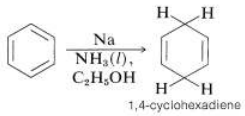
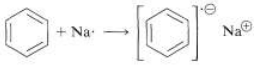
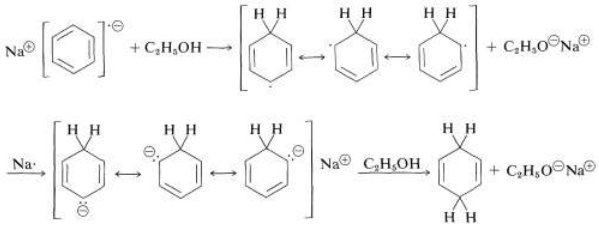


Figure 21-5) to form a radical anion:

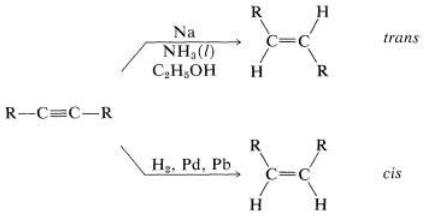


Subsequent steps include a sequence of proton- and electron-transfer steps as follows:



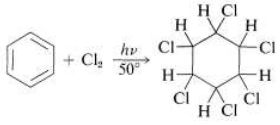
Substituent effects observed for this reaction are entirely consisent with those described for electrophilic substitution and addition - only reversed. That is, the reactivity of an arene in metal reductions is increased by electron-withdrawing groups and decreased by electron-donating groups. Substituents that can stabilize the anion-radical intermediate facilitate the reduction.

Reduction with metals in weakly acidic solvents is not restricted to arenes. A useful related reaction reduces alkynes to *trans*-alkenes, and provides a useful alternative to catalytic hydrogenation, which favors formation of *cis*-alkenes (Section 11-2A):

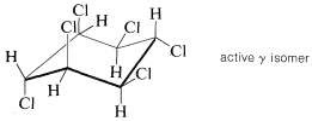


22.9.3: Halogen Addition

Benzene will add chlorine on irradiation with light to give the fully saturated hexachlorocyclohexane as a mixture of stereoisomers:

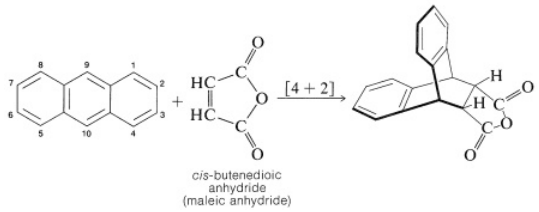


The reaction is commercially important because one of the isomers is a potent insecticide. The product is marketed as a mixture of isomers in which the active isomer (γ) is optimally about 40% by weight. It has a variety of trade names: Fortified, BHC, Lindane, Gammexane, Hexachlor.

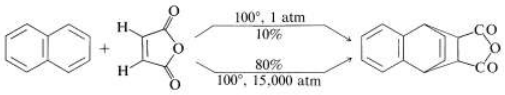


22.9.4: Cycloaddition

In Chapter 13 we encountered the Diels-Aler reaction, which involves addition of a reactive alkene (dienophile) to the 1,4 positions of a conjugated diene. Neither benzene nor naphthalene reacts significantly with dienophiles on simple heating, but anthracene does react. Cycloaddition occurs between the 9,10 positions:



Reactions in which the transition state has a *smaller* volume than the reactants are speeded up by an increase in pressure. This is the case with naphthalene and *cis*-butenedioic anhydride. An 80% yield of adduct is obtained at 100° at 15,000 atmospheres pressure, whereas at one atmosphere and 100°, the yield is only 10%.



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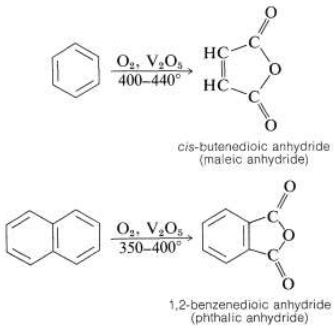
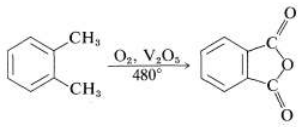
22.10: Oxidation Reactions

The reagents usually employed for the oxidation of alkenes (e.g., CrO_3, $KMnO_4$, H_2O_2, OsO_4) normally do not attack benzene. At high temperatures, benzene can be oxidized to *cis*-butenedioic (maleic) anhydride by air with a vanadium pentoxide catalyst. Naphthalene can be similarly oxidized to 1,2-benzenedioic (phthalic) anhydride:

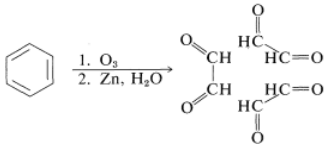


Both anhydrides are prepared in this manner on a large scale for use in the production of ester polymers (Section 29-5A). Phthalic anhydride also is prepared by the oxidation of 1,2-dimethylbenzene:

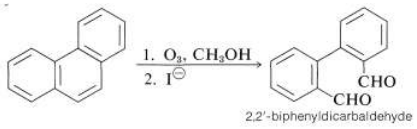


Phthalic anhydride is used to make anthraquinone and to make esters of phthalic acid, which are used widely to plasticize polymers.

Ozonization of aromatic hydrocarbons is possible. Benzene itself gives ethanedial (glyoxal):



The double-bond character of the 9,10 bond in phenanthrene is particularly evident in ozonization. This bond is attacked preferentially, which leads to the formation of a dialdehyde when the ozonide is reduced with iodide ion:



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22.11: Sources and Uses of Aromatic Hydrocarbons

Benzene and many of its derivatives are manufactured on a large scale for use in high-octane gasolines and in the production of polymers, insecticides, detergents, dyes, and many miscellaneous chemicals. Prior to World War II, coal was the only important source of aromatic hydrocarbons, but during the war and thereafter, the demand for benzene, methylbenzene, and the dimethylbenzenes rose so sharply that other sources had to be found. Today, most of the benzene and almost all of the methylbenzene and the dimethylbenzenes produced in the United States are derived from petroleum.

Coal tar, which is a distillate obtained in the coking of coal (Section 4-2), is a source of an amazing number of aromatic compounds. Some of these are listed in Table 22-7, which includes nitrogen, oxygen, and sulfur compounds, as well as hydrocarbons. Although petroleum from some locations contains fairly substantial amounts of aromatic hydrocarbons, it is not a principal source for such compounds. Rather, aromatic compounds are synthesized from the C_6-C_{10} gasoline fraction from petroleum refining by a process referred to in the petroleum industry as **catalytic re-forming** or **hydroforming**. This involves heating a C_6-C_{10} fraction with hydrogen in the presence of a catalyst to modify the molecular structure of its components. Some amazing transformations take place, and the C_6-C_7 alkanes can be converted to cycloalkanes, which, in turn, are converted to arenes. Benzene, methylbenzene (toluene), and the dimethylbenzenes (xylenes) are produced primarily in this way:

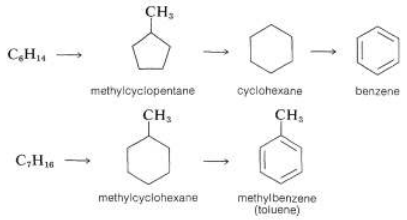
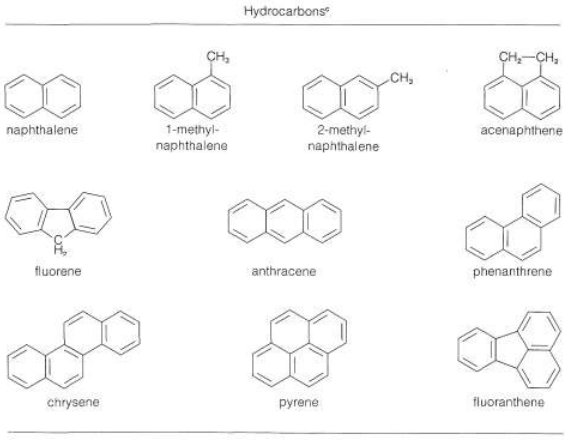
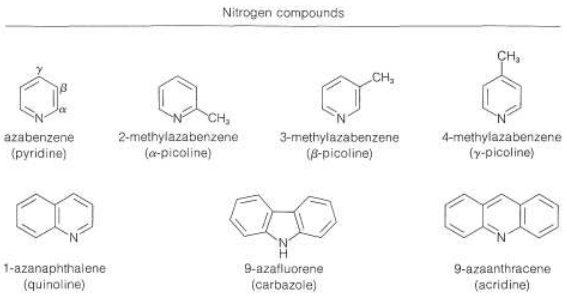
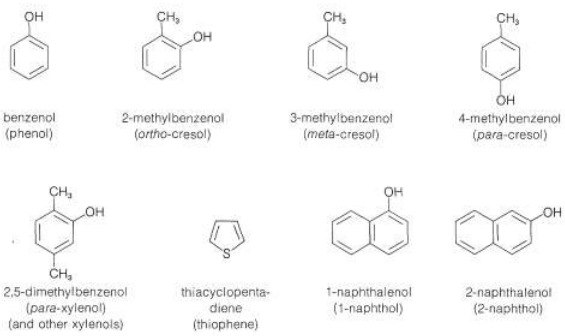


Table 22-7: *Principal Compounds Obtained from Coal Tar*[a,b]





Oxygen and sulfur compounds



[a]Compiled from *Chemistry of Coal Utilization*, National Research Council Committee, H. H. Lowry (Ed.), John Wiley and Sons, Inc., 1945.

[b]None of the compounds listed are very abundant in coal tar. Even naphthalene, which is present in the largest amount, constitutes only 10–11% of coal tar.

[c]Benzene and the mono- and dimethylbenzenes are present in very small amount (0.3% total) in coal tar.

Figures 22-9 and 22-10.

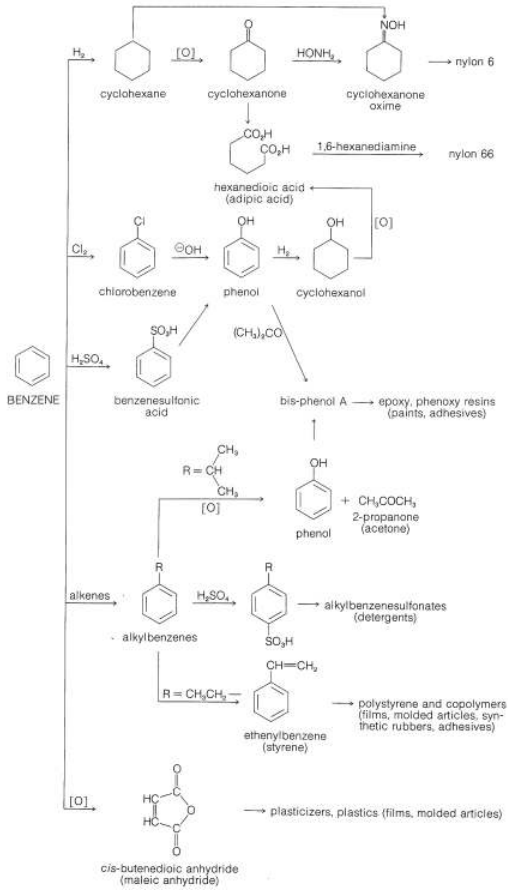


Figure 22-9: Important chemicals derived from benzene.

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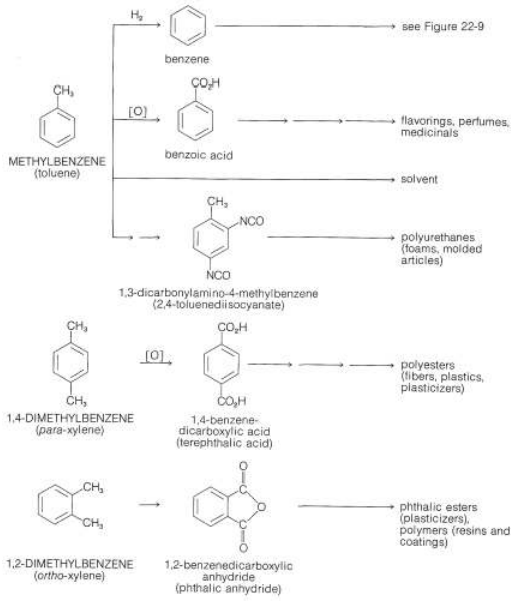

Figure 22-10: Important chemicals derived from methyl-substituted benzenes.

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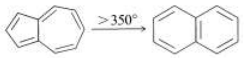
22.12: Some Conjugated Cyclic Polyenes

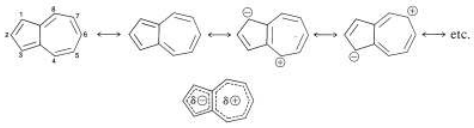
22.12.1: Azulene

There are several compounds that possess some measure of aromatic character typical of benzene, but do not possess a benzenoid ring. Appropriately, they have $(4n + 2)$ π electrons and are classified as nonbenzenoid aromatic compounds (Section 21-9). An example is azulene, which is isomeric with naphthalene and has a five- and a seven-membered ring fused through adjacent carbons:

As the name implies, it is deep blue. It is less stable than naphthalene, to which it isomerizes quantitatively on heating above 350° in the absence of air:

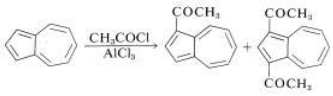


Azulene has a significant polarity, with the five-membered ring negative and the seven-membered ring positive. The structure can be represented as a hybrid of neutral and ionic structures:

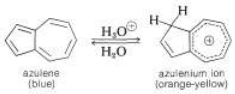


The polarization that has the five-membered ring negative and the seven-membered ring positive corresponds to ionic structures that have *six* (i.e., $4n + 2$) electrons in both the five- and seven-membered rings (Section 21-9B).

In keeping with its aromatic character and unsymmetrical charge distribution, azulene undergoes certain typical electrophilic substitution reactions at the 1 and 3 positions. Thus Friedel-Crafts acylation leads to a mixture of 1-ethanoylazulene and 1,3-diethanoylazulene:

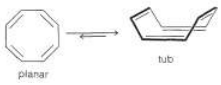


Furthermore, in the presence of strong acids the 1 position is protonated to give a derivative of the relatively stable cycloheptatrienyl (tropylium) ion (Section 21-9B):



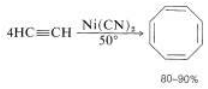
22.12.2: Cyclooctatetraene

1,3,5,7-Cyclooctatetraene (or simply cyclooctatetraene) is a bright-yellow, nonplanar, nonaromatic compound (Section 21-9A). Apparently the resonance energy of a planar structure is insufficient to overcome the unfavorable angle strain of a planar structure would have with its $\mathrm{C{-}C{-}C}$ bond angles of 135°. Cyclooctatetraene normally assumes a "tub" structure with alternating single and double bonds:



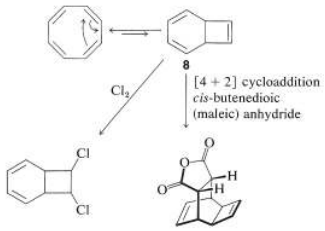
There is, however, nmr evidence that indicates that the tub form is in rapid equilibrium with a very small amount of the planar form at room temperature. There is about a 15-kcal mol^{-1} energy difference between the two forms. The dication, $\mathrm{C_8H_8^{2+}}$, and the dianion of cyclooctatetraene, $\mathrm{C_8H_8^{2-}}$, which have $(4n + 2)$ π electrons, appear to exist in planar conformation.

Cyclooctatetraene can be prepared readily by polymerization of ethyne in the presence of nickel cyanide:

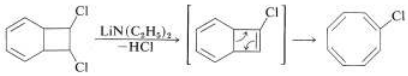


It could be manufactured on a large scale, but no large-scale commercial uses of the substance have yet been developed.

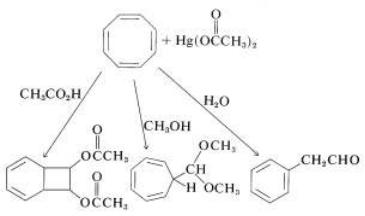
The chemistry of cyclooctatetraene is interesting and unusual. Particularly noteworthy is the way in which it undergoes addition reactions to form products that appear to be derived from the bicyclic isomer, bicyclo[4.2.0]2,4,7-octatriene, 8. In fact, there is an electrocyclic equilibrium between cyclooctatetraene and 8 (Section 21-10D) and, although the position of equilibrium lies far on the side of cyclooctatetraene, 8 is more reactive and leads to the observed addition products:



Treatment of the bridged dichloride with strong bases causes elimination of hydrogen chloride and formation of chlorocyclooctatetraene:



The diverse ways in which cyclooctatetraene can react with a give reagent under different conditions is well illustrated by the variety of products obtained with mercuric ethanoate in ethanoic acid, methanol, and water:

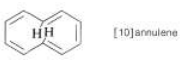


Efforts to prepare "pentalene", a bridged analog of cyclooctatetraene, have not been very successful so far. A substance that appears to be a methylpentalene has been characterized at -180° by its spectral properties. On warming to -105° it forms a dimer.

22.12.3: Annulenes

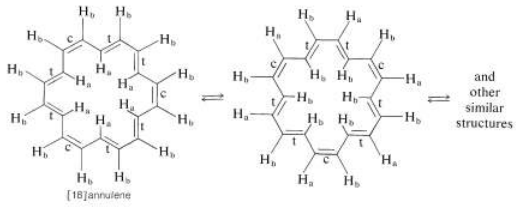
Cyclooctatetraene is nonplanar. One reason is that the angle strain is severe in the planar form. Is it possible that larger-ring conjugated polyalkenes may have strainless planar structures? Models show that a strainless structure can be achieved with two or more of the double bonds only in *trans* configurations, and then only with a large enough ring that the "inside" hydrogens do not interfere with one another.

In discussing compounds of this type, it will be convenient to use the name *[n]annulene* to designate the simple conjugated cyclic polyalkenes, with *n* referring to the number of carbons in the ring - benzene being [6]annulene. The simplest conjugated cyclic polyolefin that could have a strainless planar ring containing trans double bonds, except for interferences between the inside hydrogens, is [10]annulene:



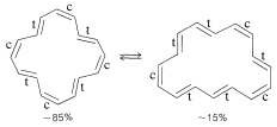
Inside-hydrogen interferences are likely to be of some importancee in all annulenes up to [30]annulene. Many annulenes have been synthesized by F. Sondheimer.

We have mentioned already (Section 22-3C) the large differences in nmr chemical shifts between the inside and outside hydrogens of [18]annulene - a substance which with 18 π electrons should be aromatic by the $4n + 2$ rule. These differences are observed only at low temperatures. The proton nmr spectrum of [18]annulene at room temperature is a single resonance, which indicates that the inside (H_a) and outside (H_b) hydrogens are equilibrating rapidly. This can take place only if cis-trans interconversion occurs about the double bonds (marked c and t):



At low temperatures, this equilibrium is slow enough that separate groups of resonances for the inside and outside hydrogens can be discerned in an nmr experiment (see Sections 9-10C and 27-2).

A theoretical prediction that has been borne out by experiment is that an annulene with $4n$ π electrons should have a *paramagnetic* circulation of electrons - that is, opposite in direction to that shown in Figure 22-4 for benzene. For example, [16]annulene, which has $4n$ electrons, is not very stable and exists as a very rapidly interconverting mixture of two configurational isomers:



At very low temperatures $(-155°)$, the proton nmr spectrum shows the *inner* hydrogens at $\delta 12.9$-10.5 and the outer hydrogens at $\delta 5.7$ -6.4, which is in exactly the opposite order to the shifts with [18]annulene and the other known $[4n + 2]$ π-electron annulenes.

The annulenes generally are not stable compounds, but the $[4n + 2]$annulenes clearly show typical aromatic reactions. For instance [18]annulene has been converted to the nitro, ethanoyl, bromo, and carbaldehyde derivatives by electrophilic substitution reactions.

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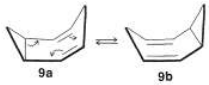
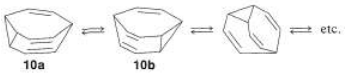
22.13: Fluxional Compounds

A number of compounds are known to rearrange from one structure to an entirely equivalent structure, sometimes with extraordinary facility. Such compounds are said to be **fluxional** to distinguish from tautomers (which usually involve rearrangements between nonequivalent structures). Simple examples are the Cope rearrangement of 1,5-hexadiene,

and the electrocyclic rearrangement of bicyclo[5.1.0]-2,5-octadiene,



If the two methylenes of 9 are bridged with two double-bonded carbons, we get the remarkable structure 10, called "bullvalene", which rapidly interconverts amongst equivalent structures:



Equilibration of fluxional molecules must not be confused with resonance. In each electrocyclic reaction, the nuclei alter their positions as bond lengths and angles change. Interconversion of fluxional molecules also must not be confused with conformational changes (as in the interconversion of two equivalent chair forms of cyclohexane). In the interconversion of fluxional molecules, chemical bonds are broken and made; in conformational changes, no bonds are broken and no bonds are made.

> *Equilibration of fluxional molecules must not be confused with resonance.*

A theoretical prediction is that the very-large-ring annulenes, even those with $[4n+2]$ π electrons, may not have sufficient resonance energy to maintain equal bond lengths between the carbons and hence would be most stable with alternating double and single bonds. These substances then would be as Kekule thought benzene to be - a fluxional, equilibrating mixture of cyclohexatrienes! This does *not* mean that there would be no π-electron delocalization in fluxional cyclic polyenes; it means only that the VB structures would *not* be exactly equivalent and the MO model would have a σ-bond framework with alternating short and long $\mathrm{C{-}C}$ bonds. The theory suggests that if alternation in bond lengths occurs, then neither diamagnetic nor paramagnetic circulation of the π electrons should be important. The synthesis and study of [26]- and [30]annulenes seems to bear out this prediction, in that with these substances there appears to be no ring-current effect on the proton chemical shifts.

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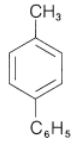
22.E: Arenes, Electrophilic Aromatic Substitution (Exercises)

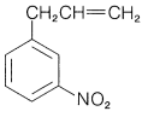
Exercise 22-1 How many structurally different monomethyl derivatives are possible for each of the following compounds? Name each.

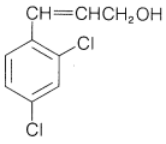
a. naphthalene
b. anthracene
c. phenanthrene

Exercise 22-2 How many isomeric products could each of the dimethylbenzenes give on introduction of a third substituent? Name each isomer, using chlorine as the third substituent.

Exercise 22-3 Name each of the following compounds by the IUPAC system:

a. $(C_6H_5)_2CHCl$
b. $C_6H_5CHCl_2$
c. $C_6H_5CCl_3$
d. 

e. 

f. 

Exercise 22-4 Identify the two compounds with molecular formula C_7H_7Cl from the infrared spectra shown in Figure 22-2.

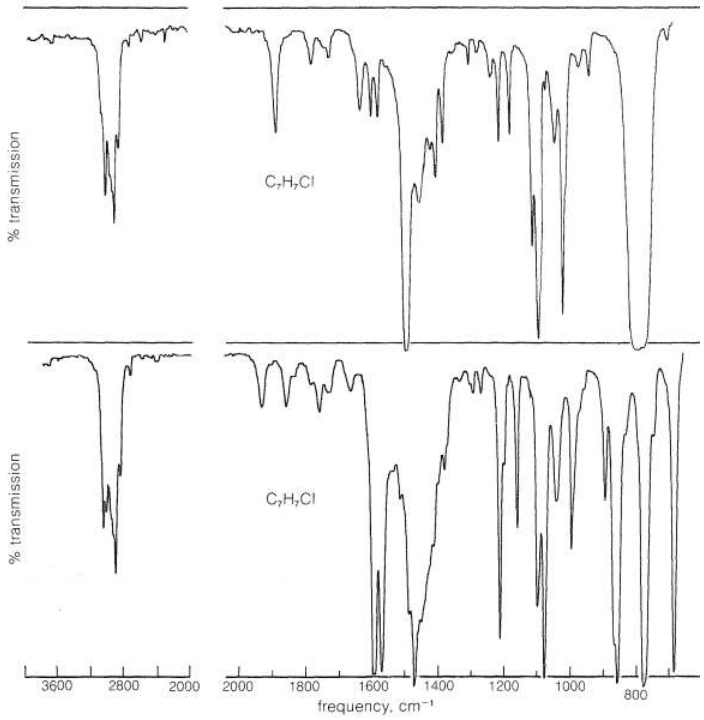
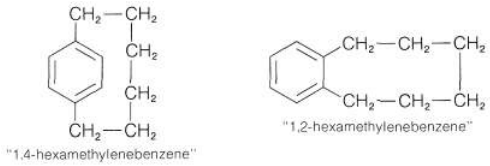


Figure 22-2: Infrared spectra of two isomeric compounds of formula C_7H_7Cl (see Exercise 22-4)

Exercise 22-5 Predict the effect on the ultraviolet spectrum of a water solution of benzenamine when hydrochloric acid is added. Explain why a solution of sodium benzenoxide absorbs at longer wavelengths than a solution of benzenol (see Table 22-3).

Exercise 22-6* Estimate the chemical shifts of the protons of (a) the separate CH_2 of "1,4-hexamethylenebenzene" as compared with "1,2-hexamethylenebenzene"; and (b) cyclooctatetraene (see Section 21-9A).



Exercise 22-7 Establish the structures of the following benzene derivatives on the basis of their empirical formulas and NMR spectra shown in Figure 22-6. Remember that equivalent protons normally do not split each other's resonances.

a. C_8H_{10}
b. C_8H_7OCl
c. $C_9H_{10}O_2$
d. C_9H_{12}

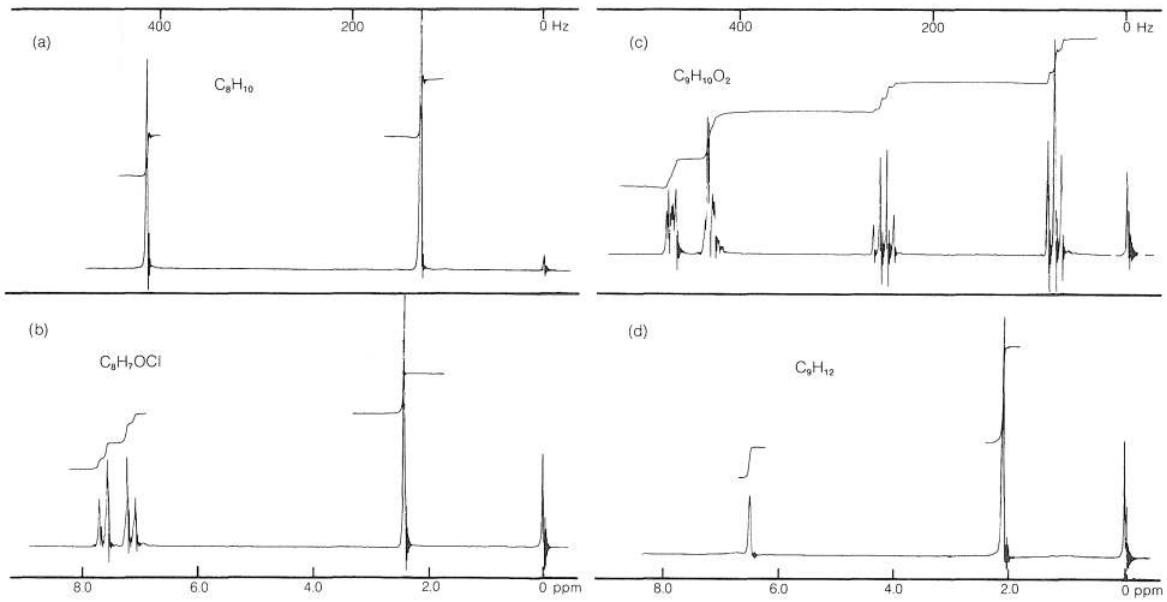
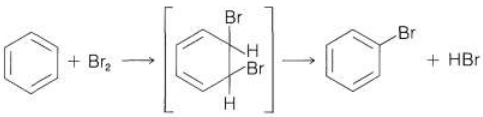


Figure 22-6: Proton NMR spectra of some benzene derivatives at 60 MHz with reference to TMS at 0 ppm (see Exercise 22-7).

Exercise 22-8 Calculate from appropriate bond-energy and stabilization-energy tables (4-3 and 21-1) the heats of chlorine with benzene to give (a) chlorobenzene and (b) 5,6-dichloro-1,3-cyclohexadiene. Your answer should indicate that substitution is energetically more favorable than addition.

Exercise 22-9 Devise an *experimental* test to determine whether the following addition-elimination mechanism for bromination of benzene actually takes place.



Exercise 22-10 Why is nitration with ethanoyl nitrate accelerated by added fluoroboric acid, HBF_4, but retarded by added hydrochloric acid?

Exercise 22-11 Why do fairly reactive arenes, such as benzene, methylbenzene, and ethylbenzene, react with excess nitric acid in nitromethane solution at a rate that is *independent of the concentration of the arene* (i.e., zero order in arene concentration)? Does this lack of dependencies on arene concentration mean that nitration of an equimolar mixture of benzene and methylbenzene would necessarily give an equimolar mixture of nitrobenzene and nitromethylbenzenes? Why or why not?

Exercise 22-12 Reagents, besides the molecular halogens, that effect halogen substitution include hypochlorous and hypobromous acids. They are most effective when a strong acid is present and care is taken to exclude formation of halide ions. Account for the catalytic effect of acid and the anticatalytic effect of halide ions.

Exercise 22-13 Arrange the following bromine-containing species in order of their expected reactivity in achieving electrophilic aromatic bromination: $HOBr$, Br_2, $Br^{\oplus}$, $Br^{\ominus}$, HBr, $H_2OBr^{\oplus}$, $BrCl$.

Exercise 22-14 Aluminum chloride is a much more powerful catalyst than ferric bromide for bromination of benzene. Would you expect the combination of aluminum chloride and bromine to give much chlorobenzene in reaction with benzene? Explain.

Exercise 22-15

a. The bromination of benzene is catalyzed by small amounts of iodine. Devise a possible explanation for this catalytic effect.

b. The kinetic expression for the bromination of naphthalene in ethanoic acid involves a term that is first order in naphthalene and second order in bromine. How can two molecules of bromine and one of naphthalene be involved in the rate-determining step of bromination? Explain why the kinetic expression simplifies to first order in naphthalene and first order in bromine in 50% aqueous ethanoic acid.

Exercise 22-16 Write a mechanism for the alkylation of benzene with 2-propanol catalyzed by boron trifluoride.

Exercise 22-17 Explain how it is possible that the ratio of products isolated from equilibration of 1,2-, 1,3-, and 1,4-dimethylbenzenes is 18:58:24 if the presence of a small amount of $HF{-}BF_3$, but is essentially 0:100:0 in the presence of excess $HF{-}BF_3$. Notice that HBF_4 is an extremely strong acid.

Exercise 22-18 Account for the following observations:

a. 3-Methyl-2-butanol alkylates benzene in HF to give (1,1-dimethylpropyl)benzene.

b. 1-Chloronorbornane will not alkylate in the presence of $AlCl_3$.

1-chloronorbornane

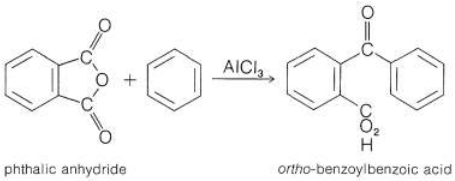
c. 1-Methylcyclopentyl cation is formed from each of the compounds shown below under the indicated conditions at low temperatures (-70°).

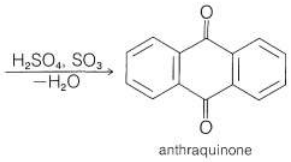
chlorocyclohexane $\xrightarrow{SbF_5-SO_2}$

cyclohexene $\xrightarrow{HF-SbF_5-SO_2}$

cyclohexanol $\xrightarrow{FSO_3H-SbF_5}$

Exercise 22-19 Anthraquinone can be synthesized from phthalic anhydride and benzene in two steps. The first step is catalyzed by $AlCl_3$, the second by fuming sulfuric acid. Write mechanisms for both reactions and suggest why fuming sulfuric is required in the second step but not in the first.





Exercise 22-20 Suggest possible routes for the synthesis of the following compounds:

a. diphenylmethane from benzoic acid and benzene
b. 1-ethyl-4-methylbenzene from methylbenzene

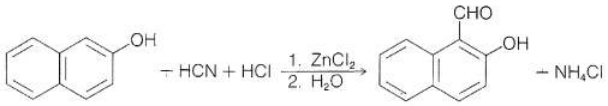
Exercise 22-21

a. Substitution of a chloromethyl group, $-CH_2Cl$, on an aromatic ring is **chloromethylation** and is accomplished using methanal, HCl, and a metal-halide catalyst $(ZnCl_2)$. Write reasonable mechanistic steps that could be involved in this reaction:

$$C_6H_6 + CH_2O + HCl \xrightarrow{ZnCl_2} C_6H_5CH_2Cl + CH_2O \tag{22.E.1}$$

b. Phenylmethyl chloride can be formed from benzene and chloromethyl methyl ether, $ClCH_2OCH_3$, in the presence of stannic chloride, $SnCl_4$. Write reasonable mechanistic steps, again supported by analogy, for this reaction. Notice that $SnCl_4$ is a Lewis acid.

Exercise 22-22 The **Gattermann reaction** (not to be confused with the Gattermann-Koch aldehyde synthesis) introduces the $H-C=O$ function into reactive aromatic compounds such as 2-naphthalenol. The necessary reagents are HCN, HCl, and a metal-halide catalyst ($ZnCl_2$ or $AlCl_3$), and the initial product must be treated with water. Write a mechanism for this reaction that is supported by analogy to other reactions discussed in this chapter.



Exercise 22-23 Show explicitly how an alkyl side chain of alkylbenzenesulfonates could be formed with a quaternary carbon, if the C_{12} alkane used at the start of the synthesis contained any branched-chain C_{12} isomers.

Exercise 22-24 Draw the structures of the intermediate cations for nitration of nitrobenzene in the 2, 3, and 4 positions. Use the structures to explain why the nitro group is meta-orienting with deactivation. Use the same kind of arguments to explain the orientation observed with $-CF_3$, $-CHO$, $-CH_2Cl$, and $-NH_2$ groups in electrophilic aromatic substitution (Table 22-6).

Exercise 22-25* The product distribution in the bromination of methylbenzene (toluene) depends on the nature of the brominating agent. Pertinent information follows:

reagent	% of isomeric bromomethylbenzenes		
	2-	3-	4-
Br_2	33	<1	67
$H_2OBr^{\oplus}$	58	19	23

Explain why the distribution varies with the nature of the substituting agent. Predict the product distribution of isomeric ions if $Br^{\oplus}$ were to add to methylbenzene in the *gas phase*.

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Exercise 22-26 Construct an energy diagram, similar to Figure 22-8, for nitration of phenyltrimethylammonium ion in the meta and para positions.

Exercise 22-27 Using the rationale developed in Section 22-5, predict the major products of nitration of the following compounds. It will help to work out the Lewis structures of the substituent groups.

a. phenylnitromethane, $C_6H_5CH_2NO_2$
b. methylthiobenzene, $C_6H_5SCH_3$
c. nitrosobenzene, C_6H_5NO
d. phenyldimethylphosphine oxide, $C_6H_5PO(CH_3)_2$

Exercise 22-28 The energy diagram in Figure 22-8 represents a two-step reaction in which the first step is slower than the second. This circumstance is found in nitration and halogenation reactions. Show how this diagram would change when (a) the rate-determining step is loss of a proton from the intermediate ion, (b) the reactants rapidly form a π complex prior to the slow step of the electrophilic attack at carbon, and (c) the rate-determining step is π-complex formation.

Exercise 22-29 Predict the favored position(s) of substitution in the nitration of the following compounds:

a. 4-nitro-1-phenylbenzene
b. 4-methylbenzenecarboxylic acid
c. 3-methylbenzenecarboxylic acid
d. 1,3-dibromobenzene
e. 1-fluoro-3-methoxybenzene
f. 1,3-dimethylbenzene

Exercise 22-30*

a. In the nitration of *para*-cymene by ethanoyl nitrate in ethanoic anhydride, the observed product composition at 0° is 41% 5 and 6, 41% 3, 8% 4, and 10% of 4-nitromethylbenzene. Use these results to determine the relative reactivities of the *para*-cymene ring carbons towards NO_2^+. Give your answer relative to C_3 as unity (C_3 is the carbon next to the isopropyl group). determine the relative reactivities based on the data obtained in Equation 22-1. How does neglect of *ipso* substitution affect calculation of relative reactivities of the ring carbons?

b. Write a mechanism for the solvolytic conversion of 5 and 6 to 3.

Exercise 22-31 Draw the Kekulé-type valence-bond structures for napthalene, anthracene, and phenanthrene. Estimate the percentage of double-bond character for the 9,10 bond of phenanthrene, assuming that each of the valence-bond structures contributes equally to the hybrid structure.

Exercise 22-32 Devise an experiment that would establish whether the acylation of naphthalene in the 2 position in nitrobenzene solution is the result of *thermodynamic control* of the orientation.

Exercise 22-33 Predict the orientation in the following reactions:

a. 1-methylnaphthalene $+Br_2$
b. 2-methylnaphthalene $+HNO_3$
c. 2-napthalenecarboxylic acid $+HNO_3$

Exercise 22-34 Show how one can predict qualitatively the character of the 1,2 bond in acenapthylene.

Exercise 22-35* Explain why sodium in liquid ammonia reduces methoxybenzene (anisole) to 1-methoxy-1,4-cyclohexadiene, whereas it reduces sodium benzoate to sodium 2,5-cyclohexadienecarboxylate:

Exercise 22-36 Predict the Birch reduction products of the following reactions:

a. anthracene $\xrightarrow[C_2H_5OH]{Na}$

b. naphthalene $\xrightarrow[NH_3(l)]{Na}$

c.* methylbenzene $\xrightarrow[NH_3(l)]{Na,\ C_2H_5OH}$

Exercise 22-37* A side reaction when reducing benzene derivatives to 1,4-cyclohexadienes with lithium or sodium in liquid ammonia is over-reduction to give cyclohexenes. Addition of ethanol greatly reduces the importance of this side reaction. Explain what role ethanol plays in preventing over-reduction.

Exercise 22-38 Neglecting steric-hindrance effects use the stabilization energies in Table 21-1 to explain why *cis*-butenedioic anhydride adds more readily to anthracene than to benzene and adds across the 9,10 positions but not the 1,4 positions of anthracene.

Exercise 22-39 What products would you expect to be formed in the ozonization of the following substances? Consider carefully which bonds are likely to be most reactive.

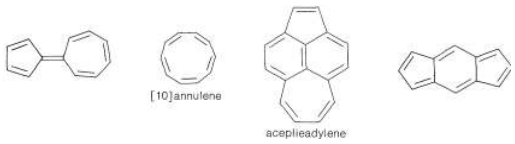
a. 1,2-dimethylbenzene
b. naphthalene
c. acenaphthylene (see Exercise 22-34)

Exercise 22-40* The rate of the Diels-Alder addition between cyclooctatetraene and tetracyanoethene is proportional to the tetracyanoethene concentration, $[C_2(CN)_4]$, at low concentrations of the addends but becomes independent of $[C_2(CN)_4]$ at high concentrations. Write a mechanism that accounts for this behavior.

Exercise 22-41* Write reasonable mechanisms for the different oxidation reactions of cyclooctatetraene with mercuric ethanoate in ethanoic acid, methanol, and water solutions. Notice that compounds of the type $Hg(OR)_2$ appear to act in some cases as $^{\oplus}OR$-donating agents and also that the oxide produced from cyclooctatetraene and peroxyacids (Section 15-11C) rearranges readily in the presence of acids to phenylethanal.

Exercise 22-42* The dianion $C_8H_6{}^{2-}$, which corresponds to pentalene, has been prepared and appears to be reasonably stable. Why may the dianon be more stable than pentalene itself? (See Section 21-9B.)

Exercise 22-43* Predict which of the following compounds may have some aromatic character. Give your reasons.



Exercise 22-44 Write structural formulas for all of the possible isomers of C_8H_{10} that contain one benzene ring. Show how many different mononitration products each could give if no carbon skeleton rearrangements occur but nitration is possible either in the ring or side chain. Name all of the mononitration products by an accepted system.

Exercise 22-45 Write structural formulas (more than one may be possible) for aromatic substances that fit the following descriptions:

a. C_8H_{10}, which can give only one theoretically possible ring nitration product
b. $C_6H_3Br_3$, which can give three theoretically possible nitration products.
c. $C_6H_3Br_2Cl$, which can give two theoretically possible nitration products.
d. $C_8H_8(NO_2)_2$, which can give only two theoretically possible different ring monobromosubstitution products.

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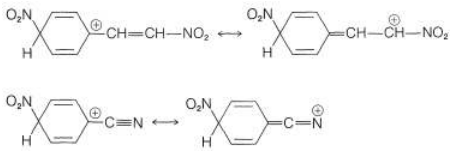
Exercise 22-46 Predict the most favorable position for mononitration for each of the following substances. Indicate whether the rate is greater, or less, than for the nitration of benzene. Give your reasoning in each case.

a. fluorobenzene
b. trifluoromethylbenzene
c. phenylethanone
d. phenylmethyldimethylamine oxide, $C_6H_5CH_2\overset{\oplus}{N}(CH_3)_2\overset{\ominus}{O}$
e. diphenylmethane
f. 4-bromo-1-methoxybenzene
g. phenylsulfinylbenzene, $C_6H_5SOC_6H_5$
h. 1-*tert*-butyl-4-methylbenzene
i. diphenyliodonium nitrate, $(C_6H_5)_2\overset{\oplus}{I}\overset{\ominus}{N}$ \ce{O_3}\)
j. 1,3-diphenylbenzene (*meta*-terphenyl)
k. N-(4-phenylphenyl)ethanamide

Exercise 22-47 Explain why the bromination of benzenamine (aniline) gives 2,4,6-tribromobenzenamine (2,4,6-tribromoaniline), whereas the nitration with mixed acids gives 3-nitrobenzenamine (*meta*-nitroaniline).

Exercise 22-48 Explain how comparison of the following resonance structures for para substitution with the corresponding ones for meta substitution may (or may not) lead to the expectation that ortho-para orientation would be favored for the nitro, cyano, and $-CH{=}CHNO_2$ groups.



Exercise 22-49 Starting with benzene, show how the following compounds could be prepared. Specify the required reagents and catalysts.

a. 1-bromo-4-nitrobenzene
b. 4-isopropyl-3-nitrobenzenesulfonic acid
c. 4-*tert*-butylbenzenecarbaldehyde
d. $C_6H_5COCH_2CH_2CO_2H$
e. 1,2,4,5-tetrachlorocyclohexane

Exercise 22-50 Offer a suitable explanation of each of the following facts:

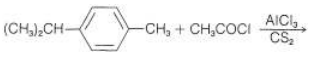
a. Nitration of arenes in concentrated nitric acid is retarded by added nitrate ions and strongly accelerated by small amounts of sulfuric acid.

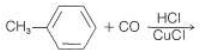
b. Nitrobenzene is a suitable solvent to use in Friedel-Crafts acylation of benzene derivatives.

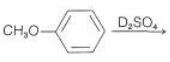
c. Benzene and other arenes usually do not react with *nucleophiles* by either addition or substitution.

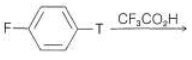
d. Pyridine is almost inert to nitration with mixed nitric and sulfuric acids, a reaction the proceeds readily with benzene.

Exercise 22-51 Indicate the structures of the major product(s) expected in the following reactions:

a. 

b. 

c. 

d.  (T is ^3H, or tritium)

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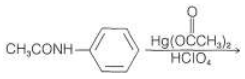
e.



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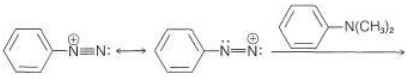

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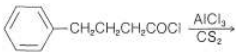
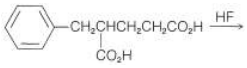
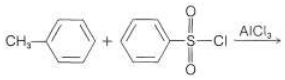


h.

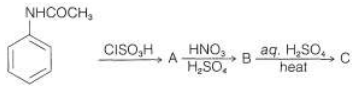


i.

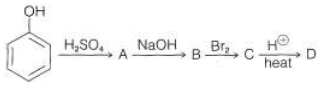


Exercise 22-52 Draw the structures of the products A, B, C, and D in the stepwise reaction sequences shown.

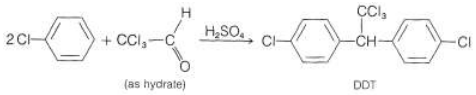
a.



b.

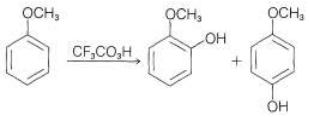


Exercise 22-53 The pesticide DDT is made commercially by the reaction of chlorobenzene with trichloroethanal (chloral) in the presence of an acid catalyst (H_2SO_4). Show the steps that are likely to be involved in this reaction:



Exercise 22-54 Hexachlorophene, the controversial germicide, is prepared from 2,4,5-trichlorobenzenol (2 moles) and methanal (1 mole) in the presence of concentrated sulfuric acid. Show the steps involved and the expected orientation of the substituents in the final product.

Exercise 22-55 Trifluoroperoxyethanoic acid, $CF_3C(O)O{-}OH$ reacts with methoxybenzene to give 2- and 4-methoxybenzenols:



Explain the nature of this reaction. What is likely to be the substituting agent? What products would you expect from trifluoroperoxyethanoic acid and fluorobenzene? Would fluorobenzene be more, or less, reactive than methoxybenzene?

Exercise 22-56 Ethanoic anhydride reacts with concentrated nitric acid to yield the rather unstable ethanoyl nitrate (acetyl nitrate), which is a useful nitrating agent. With mixtures of benzene and methylbenzene, ethanoyl nitrate products a mixture of nitrobenzene and 2- and 4-nitromethylbenzenes. When nitrated separately, each compound reacts at the **same** overall rate, but when mixed together, 25 times more nitromethylbenzene is formed than nitrobenzene.

a. Write equations for the formation of ethanoyl nitrate and its use in nitration of benzene derivatives.

b. Consider possible mechanisms for nitrations with ethanoyl nitrate and show how the above observations with benzene and methylbenzene alone or in mixtures can be rationalized by proper choice of the rate-determining step.

Exercise 22-57 4-Nitromethylbenzene-2,6-D_2 is nitrated by a mixture of nitric and sulfuric acids at the same rate as ordinary 4-nitromethylbenzene under conditions in which the rate of nitration v is given by $v = k\,[\text{nitromethylbenzene}]\,[NO_2{}^+]$. (Review Section 15-6B.)

a. Explain what conclusion may be drawn from this result as to the mechanism of nitration under these conditions.

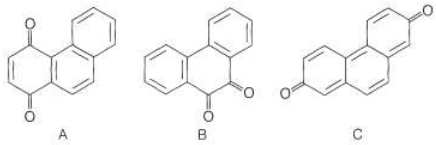
b. What would you expect the nitration rate of C_6D_6 to be as compared with C_6H_6 in the ethanoyl nitrate nitration in Exercise 22-56?

Exercise 22-58

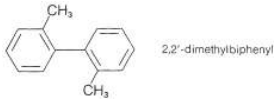
a. From the data of Table 21-1 estimate the overall loss in stabilization energy for the addition of chlorine to the 1,4-positions of naphthalene and to the 9,10 positions of phenanthrene. Which is likely to be the more favorable reaction?

b. Predict whether anthracene is more likely to undergo electrophilic substitution at the 1,2 or 9 position. Show your reasoning.

Exercise 22-59 Phenanthrene is oxidized more easily than benzene or naphthalene. Chromic acid oxidation of phenanthrene forms a substance known as phenanthraquinone. Which structure, A, B, or C, would you expect to be formed most readily by oxidation of phenanthrene? Explain.



Exercise 22-60 Explain why the nitration and halogenation of biphenyl (phenylbenzene) goes with activation at the ortho and para positions but with deactivation at the meta position. Suggest a reason why biphenyl is more reactive than 2,2'-dimethylbiphenyl in nitration.



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CHAPTER OVERVIEW

23: Organonitrogen Compounds I - Amines

A wide variety of organic compounds contain nitrogen. In fact, the types of nitrogen compounds are so numerous and diverse that we shall be unable to consider them all. We shall give most attention to the chemistry of amines and amides in this and the following chapter, because these represent the two largest classes of nitrogen compounds.

23.1: Amines Compared with Alcohols
23.2: Naturally Occurring Amines
23.3: Types and Nomenclature of Amines
23.4: Physical Properties of Amines
23.5: Spectroscopic Properties of Amines
23.6: Stereochemistry of Amines
23.7: Amines as Bases
23.8: Amines as Acids
23.9: Amines as Nucleophiles
23.10: Amines with Nitrous Acid
23.11: Oxidation of Amines
23.12: Synthesis of Amines
23.13: Protection of Amino Groups in Synthesis
23.14: Carcinogenic Nitrogen Compounds
23.E: Organonitrogen Compounds I- Amines (Exercises)

23.1: Contributors and Attributions

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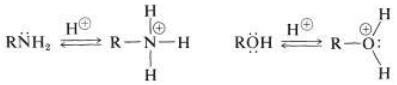
23.1: Amines Compared with Alcohols

As you read the chapter you will realize a similarity between the chemistry of amines and the chemistry of alcohols, which we discussed in Chapter 15. Primary amines (RNH_2) and secondary amines (R_2NH) are much weaker acids than alcohols (ROH) and form strongly basic anions:

Acids

Amines, like alcohols, have nonbonding electrons that impart basic and nucleophilic properties:

Bases



Nucleophiles

Also, amines and alcohols both can behave as carbon electrophiles under appropriate reaction conditions such that cleavage of $C-N$ and $C-O$ bonds occurs in the sense $\overset{\delta\oplus}{C}:\overset{\delta\ominus}{N}$ and $\overset{\delta\oplus}{C}:\overset{\delta\ominus}{O}$. However, because $-NH_2$ and $-OH$ both are poor leaving groups, each must be suitably activated to make this kind of reaction possible (see Section 8-7C). The OH group can be activated by addition of a proton or conversion to a sulfonate ester, RO_3SR', but these processes generally are ineffective for RNH_2. The most effective activation for RNH_2 is through conversion with nitrous acid, $HONO$, to $R-\overset{\oplus}{N}\equiv N$; then N_2 is the leaving group (this reaction is described in more detail in Section 23-10A):

$$R-OH \xrightarrow{HBr} R-Br + H_2O \tag{23.1.1}$$

There is, though a major difference in the way that amines and alcohols behave toward oxidizing agents. Amines genearlly show more complex behavior on oxidation because, as we shall see, nitrogen has a larger number of stable oxidation states than oxygen.

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23.2: Naturally Occurring Amines

A large and widespread class of naturally occurring amines is known as **alkaloids**. These are basic organic nitrogen compounds, mostly of plant origin. The structures of the plant alkaloids are extraordinarily complex, yet they are related to the simple amines in being weak nitrogen bases. In fact, the first investigator to isolate an alkaloid in pure form was F. W. A. Sertürner who, in 1816, described morphine (Figure 23-1) as basic, salt-forming, and ammonia-like. He used the term "organic alkali" from which is derived the name *alkaloid*.

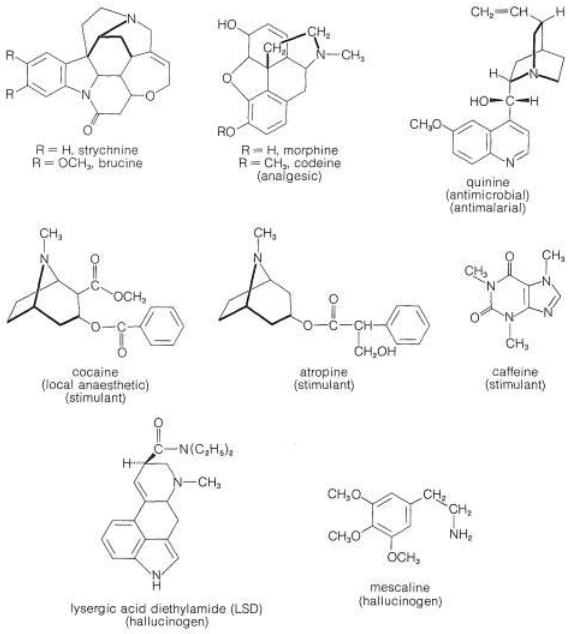

Figure 23-1: Some naturally occurring basic nitrogen compounds (alkaloids).

The structures of some of the better known plant alkaloids are shown in Figure 23-1. You will recognize some of them by name even if you have never seen their structures before. Many of the alkaloids are polycyclic structures and have other functional groups in addition to basic nitrogen. You will see that the nitrogens of alkaloids frequently are tertiary amine functions.

All of the alkaloids shown in Figure 23-1 are substances with very pronounced physiological action. Indeed, alkaloids in general have been used and abused for centuries as medicinals, drugs, and poisons. However, only in this century have their structures become known, and we are still a long way from understanding the chemistry that leads to their pronounced physiological effects. It is not even understood what function, if any, these compounds have in the host plant.

As you can see from Figure 23-1, alkaloids include compounds that may be classified as antimicrobial (quinine), as analgesics (morphine, codeine), as hallucinogens (mescaline, LSD), as stimulants (cocaine, atropine, caffeine), as topical anaesthetics (cocaine). With the possible exception of caffeine, all may be described as potentially poisonous enough to warrant great care in their use. Although some of these compounds are used as natural medicinals, an entire industry has developed in an effort to produce synthetic analogs with similar, but safer, medicinal properties. Some of the better known of these synthetic drugs are shown in Figure 23-2. They include a group of narcotic substances known as barbiturates, which are used widely as sedatives, anticonvulsants, and sleep-inducing drugs. Several representative nitrogen-containing tranquilizing drugs, synthetic stimulants, and antibiotics also are shown.

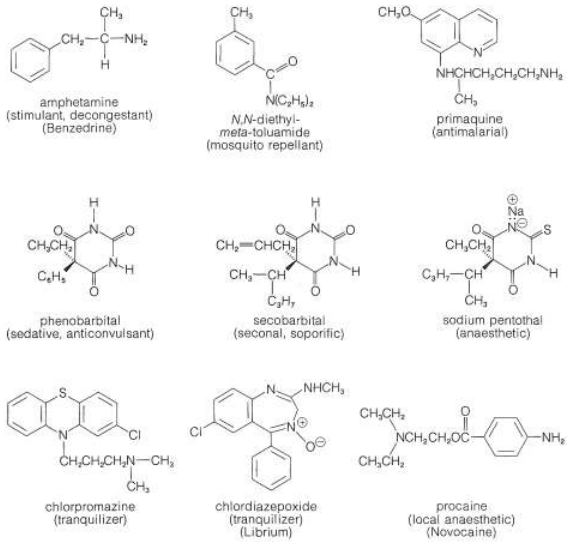

Figure 23-2: Synthetic drugs that are either basic or acidic nitrogen compounds.

Basic nitrogen compounds similar to the plant alkaloids also occur in animals, although the description *animal alkaloid* seldom is used. Certain amines and ammonium compounds play key roles in the function of the central nervous system (Figure 23-3) and the balance of amines in the brain is critical for normal brain functioning. Also, many essential vitamins and hormones are basic nitrogen compounds. Nitrogen bases also are vital constituents of nucleic acid polymers (DNA and RNA) and of proteins (Chapter 25).

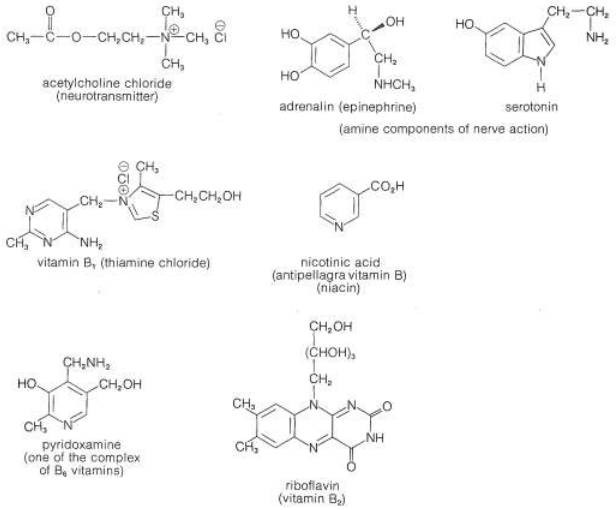

Figure 23-3: Some biologically important amines.

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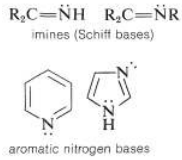
23.3: Types and Nomenclature of Amines

Amine bases are classified according to the number of alkyl or aryl groups attached to nitrogen. This number is important in determining the chemical reactions that are possible at the nitrogen atom:

A further classification exists if the nitrogen is multiply bonded to carbon, as in imines and aromatic nitrogen compounds:



The nomenclature of amines was considered briefly in Section 7-8. We shall give only a short review here to focus on the main points. Amino compounds can be named either as derivatives of ammonia or as amino-substituted compounds:

$HOCH_2CH_2NH_2$	2-hydroxyethan*amine* (2-hydroxyethyl*amine*) or 2-amino*ethanol* (preferred because —OH takes precedence over $—NH_2$; Section 7-1A)

To be consistent and logical in naming amines as substituted ammonias, they strictly should be called *alkanamines* and *arenamines*, according to the nature of the hydrocarbon grouping. Unfortunately, the term *alkylamine* is used very commonly in place of alkanamine, while a host of trivial names are used for arenamines. We shall try to indicate both the trivial and the systematic names where possible. Some typical amines, their names, and their physical properties are listed in Table 23-1. The completely systematic names give in Table 23-1 illustrate in a poignant way the difficulty one gets into by using completely systematic names, and why simpler but less systematic names continue to be used for common compounds. A good example is N,N-dibutylbutamine versus tributylamine. The special ways of naming heterocyclic amines are mentioned previously (Section 15-11A).

Table 23-1: *Typical Amines and Their Properties*

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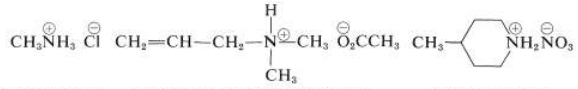
Amine	Name	Bp, °C	Mp, °C	Water solubility, g/100 ml	K_b in water[a]	pK_a[b]
NH_3	ammonia	−33	−77.7	90[0]	1.8×10^{-5}	9.26
CH_3NH_2	methanamine (methylamine)	−6.5	−92.5	1156	4.4×10^{-4}	10.64
$CH_3CH_2NH_2$	ethanamine (ethylamine)	16.6	−80.6	∞	5.6×10^{-4}	10.75
$(CH_3)_3CNH_2$	1,1-dimethylethanamine (*tert*-butylamine)	46	−67.5	∞	2.8×10^{-4}	10.45
$(CH_3CH_2)_2NH$	*N*-ethylethanamine (diethylamine)	55.5	−50	v. sol.	9.6×10^{-4}	10.98
$(CH_3CH_2)_3N$	*N,N*-diethylethanamine (triethylamine)	89.5	−115	1.5[20]	4.4×10^{-4}	10.64
$(CH_3CH_2CH_2CH_2)_3N$	*N,N*-dibutylbutanamine (tributylamine)	214		sl. sol.		
	azacyclohexane (piperidine)	106	−9	∞	1.6×10^{-3}	11.20
	azabenzene (pyridine)	115	−42	∞	1.7×10^{-9}	5.23
	cyclohexanamine	134	−18	sl. sol.	4.4×10^{-4}	10.64
	benzenamine (aniline)	184.4	−6.2	3.4[20]	3.8×10^{-10}	4.58
$H_2NCH_2CH_2NH_2$	1,2-ethanediamine (ethylenediamine)	116	8.5	sol.	8.5×10^{-5}	9.93

[a]Usually at 20–25°. [b]The pK_a values refer to the dissociation of the conjugate acid $RNH_3^{\oplus}$ + $H_2O \overset{K_a}{\rightleftharpoons} RNH_2 + H_3O^{\oplus}$, where $pK_a = -\log K_a = 14 + \log K_b$ (see Sections 8-1 and 23-7).

Salts of amines with inorganic or organic acids are named as *substituted ammonium* salts, except when the nitrogen is part of a ring system. Examples are



methylammonium chloride — 2-propenyldimethylammonium ethanoate — 4-methylazoniacyclohexane nitrate[1]

[1]Note the use of *azonia* to denote the cationic nitrogen in the ring, whereas *aza* is used for neutral nitrogen (see Section 15-11A).

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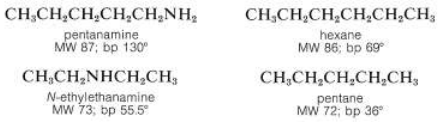
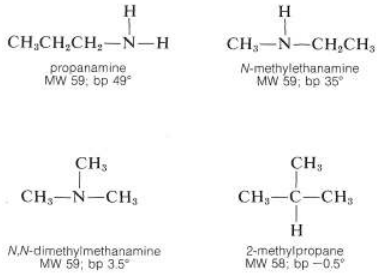
23.4: Physical Properties of Amines

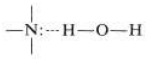
The physical properties of amines depend in an important way on the extent of substitution at nitrogen. Thus primary amines, RNH_2, and secondary amines, R_2NH, are less volatile than hydrocarbons of similar size, weight, and shape, as the following examples show:



This is because the amines are associated through hydrogen bonding of the type $N{-}H\cdots:N$. Generally, $N{-}H\cdots:N$ bonds are somewhat weaker than those of the corresponding types, $O{-}H\cdots:O$ and $F{-}H\cdots:F$, because the electronegativity of nitrogen is *less* than that of oxygen or fluorine thereby making nitrogen a poorer hydrogen *donor*. Even so, association through hydrogen bonding is significant in amines of the type RNH_2 or R_2NH as the boiling-point comparison shows. With tertiary amines, where $N{-}H\cdots:N$ bonding is not possible, the boiling points are much lower and are similar to those of hydrocarbons of similar branching and molecular weights:



The water solubilities of the lower-molecular-weight amines are appreciable, as can be seen from the solubility data in Table 23-1. In fact, amines are more water-soluble than alcohols of similar molecular weights. This is the result of hydrogen bonding, with amine molecules as the hydrogen *acceptors* and water molecules as the hydrogen *donors*:



Hydrogen bonds of this type are stronger than $O{:}\cdots H{-}O{-}H$ bonds.

Amines, especially those with significant volatility, have unpleasant odors. Some of them smell like ammonia, others smell fishy, while others are indescribably revolting. The alkanediamines of structure $H_2N(CH_3)_nNH_2$ are notably wretched and two are aptly called putrescine $(n = 4)$ and cadaverine $(n = 5)$. As you may guess from the names, these compounds are among the amines produced by bacterial decay of organic animal matter (putrefaction of protein) and are poisonous components (ptomaines) thereof.

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23.5: Spectroscopic Properties of Amines

23.5.1: Infrared and Ultraviolet Spectra

A characteristic feature of the infrared spectra of primary and secondary amines is the moderately weak absorption at $3500\ \mathrm{cm^{-1}}$ to $3300\ \mathrm{cm^{-1}}$, which corresponds to $\mathrm{N{-}H}$ stretching vibrations. Primary amines have two such bands in this region, whereas secondary amines generally show only one band. Absorption is shifted to lower frequencies by hydrogen bonding, but because $\mathrm{NH\cdots N}$ bonding is weaker than $\mathrm{OH\cdots O}$ bonding, the shift is not as great and the bands are not as intense as are the absorption bands of hydrogen-bonded $\mathrm{O{-}H}$ groups (see Table 9-2). Bands corresponding to $\mathrm{N{-}H}$ bending vibrations are observed around $1600\ \mathrm{cm^{-1}}$. Absorptions corresponding to $\mathrm{C{-}N}$ vibrations are less easily identifiable, except in the case of arenamines, which absorb fairly strongly near $1300\ \mathrm{cm^{-1}}$. Spectra that illustrate these effects are shown in Figure 23-4.

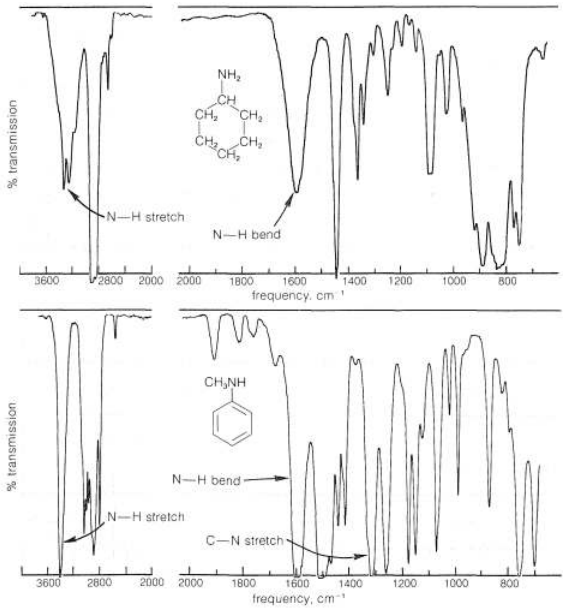

Figure 23-4: Infrared spectra of cyclohexanamine and N-methylbenzenamine (N-methylaniline).

The ultraviolet absorptions of simple saturated amines occur at rather short wavelengths $(\sim 220\ \mathrm{nm})$ and are not particularly useful for identification. These are $n \rightarrow \sigma^*$ transitions that correspond to the antibonding σ orbital of a $\mathrm{C{-}N}$ bond.

23.5.2: NMR Spectra

The proton nmr spectra of amines show characteristic absorptions for $\mathrm{H{-}C{-}N}$ protons around $2.7\ \mathrm{ppm}$. The positions of the resonances of $\mathrm{N{-}H}$ protons show considerable variability as the result of differences in degree of hydrogen bonding (Section 9-10E). Sometimes the $\mathrm{N{-}H}$ resonance has nearly the same chemical shift as the resonances of $\mathrm{CH_3{-}C}$ protons (as with N-ethylethanamine, Figure 23-5).

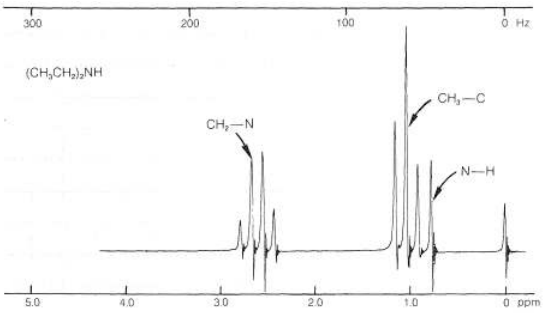

Figure 23-5: Nmr spectrum of N-ethylethanamine (Diethylamine) at $60\ \mathrm{MHz}$ relative to TMS at $0\ \mathrm{ppm}$. Rapid exchange of the $\mathrm{N{-}H}$ protons between different amine molecules causes the $\mathrm{N{-}H}$ resonance to be a single peak (Section 9-10I).

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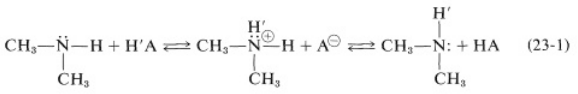
A further complication associated with N–H and H–C–N resonances is their variable chemical shift and line width in the presence of acidic substances because of a chemical exchange process of the type illustrated in Equation 23-1:



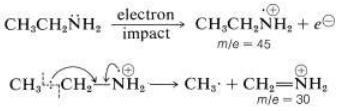
(23-1)

Depending on the rate at which the proton transfers of Equation 23-1 occur and the concentrations of the reactants, the chemical shift of the N–H proton will come between that of pure $(CH_3)_2NH$ and pure HA. Except at high acid concentrations, this exchange eliminates any observable coupling between the N–H proton and the N-methyl protons (H–C–N–H); see Section 9-10I.

In Section 9-10L, we discussed ^{13}C nmr and its many applications to structural problems. The nmr of ^{15}N nuclei has similar possibilities but, because ^{15}N is only 0.37% of natural nitrogen and has an even smaller nuclear magnetic moment than ^{13}C, it is very difficult to detect ^{15}N resonances at the natural abundance level.[2] Indeed, natural ^{15}N has to be observed for about a 6×10^{10} longer time than protons to achieve the same signal-to-noise ratio! Despite this difficulty, natural-abundance ^{15}N spectra can be obtained for many compounds (even enzymes) and, in some cases, provide very useful chemical information (see Figure 24-4).

23.5.3: Mass Spectra of Amines

The most prominent cleavage of the parent molecular ion M^+ derived from amines occurs at the C_β-C_α bond to give an imminium ion which, for ethanamine, has $m/e = 30$:



(23-2)

It is helpful in identifying the molecular ion of an organonitrogen compound to remember that the m/e value of M^+ will be an uneven number if the ion contains one or another odd number of nitrogen atoms. Thus ethanamine, C_2H_7N, gives an M^+ of $m/e = 45$. For all other elemental compositions of C, H, O, or with an even number of nitrogens, the molecular ion will have an even m/e value.

The cleavage reaction of Equation 23-2 reveals other useful generalizations. Whatever its source, a parent molecular ion, M^+, has one unpaired electron and is properly described as an **odd-electron ion** (a radical cation). When a parent molecular ion fragments, it does so *homolytically*, as shown in Equation 23-2, and produces a radical and an ion in which the electrons are paired - an **even-electron ion**. The m/e value of an even-electron ion is an *even* number for any elemental composition of C, H, O in combination with an *odd* number of nitrogens. These generalizations are summarized in Table 23-2 and can be useful in the interpretation of mass spectra.

Composition	Odd-electron parent M^+ molecular ions, m/e	Even-electron ions, from fragmentation of M^+, m/e
C, H, O, even or zero N	even	odd
C, H, O, odd N	odd	even

[2]The abundant nitrogen nucleus, ^{14}N, has a magnetic moment but generally gives very poor nmr spectra with very broad lines. The reason is the ^{14}N usually "relaxes" rapidly, which means that its nuclear magnetic states have short lifetimes (see Section 27-1).

23.5.4: Contributors and Attributions

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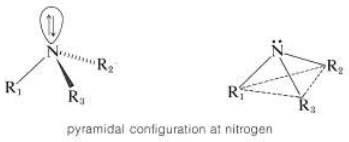
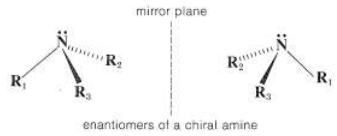
23.6: Stereochemistry of Amines

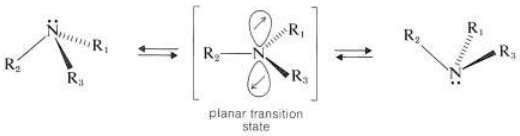
In ammonia and amines, the bonds to nitrogen are pyramidal with bond angles closer to the tetrahedral value of 109.5° than to the 90° value expected for the use of pure p orbitals of nitrogen in bond formation. We consider that the nitrogen in amines is formulated best with hybrid sp^3-type orbitals; three of these orbitals are used in σ-bond formation while the fourth contains the nonbonding electron pair:



A consequence of the pyramidal configuration at nitrogen is that, when the attached groups R_1, R_2, and R_3 are nonidentical, the nitrogen becomes a chiral atom. Under these circumstances, we would expect two enantiomeric configurations:

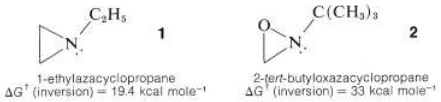


The resolution of an acyclic chiral amine into its separate enantiomers has not been achieved yet, and it appears that the enantiomers are very rapidly interconverted by an inversion process involving a planar transition state:

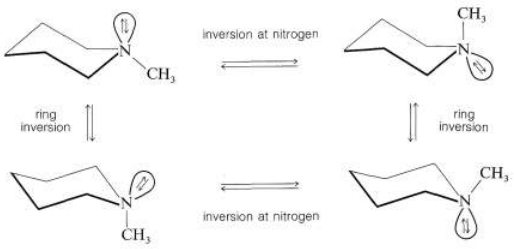


With ammonia, inversion of this type occurs about 4×10^{10} times per second at room temperature, which corresponds to the planar state being less stable than the pyramidal state by about $6\ \text{kcal mol}^{-1}$. With aliphatic tertiary amines, the inversion rate is more on the order of 10^3 to 10^5 times per second. Such rates of inversion are much to great to permit resolution of an amine into its enantiomers by presently available techniques.

When the amine nitrogen is incorporated in a small ring, as in azacyclopropanes, 1, the rate of inversion at nitrogen is markedly slower than in open-chain amines. In fact, with some oxazacyclopropanes, such as 2, inversion does not occur rapidly at ordinary temperatures, which means that the configuration at the nitrogen persists long enough for resolution into enantiomers to be possible:



The stereochemistry of azacyclohexanes is complicated by the fact that there is a conformational change in the ring as well as inversion at the pyramidal nitrogen. Therefore it is difficult to say whether the axial-equatorial equilibrium of, for example, 1-methylazacyclohexane is achieved by ring inversion, or by nitrogen inversion, or both:



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23.7: Amines as Bases

23.7.1: Standard Expressions of Base Strength

Perhaps the most characteristic property of amines is their ability to act as bases by accepting protons from a variety of acids:

$$\mathrm{RNH_2 + HA \rightleftharpoons \overset{\oplus}{R}\overset{\oplus}{N}H_3 + \overset{\ominus}{A}} \tag{23.7.1}$$

When the reference acid, HA is water, we can set up a scale of base strengths from the equilibrium constant, K_b, measured for the proton-transfer reaction shown in Equation 23-3:

$$\mathrm{RNH_2 + H_2O \overset{K_b}{\rightleftharpoons} \overset{\oplus}{R}\overset{\oplus}{N}H_3 + \overset{\ominus}{O}H} \tag{23-3}$$

In many reference works, it is customary to express the strengths of organic bases not as K_b but as the acid-dissociation constants, K_a (or pK_a's) for the corresponding conjugate acids. These K_a values are then the *acid constants* of the corresponding ammonium ions in aqueous solution (Equation 23-4):

$$\mathrm{\overset{\oplus}{R}\overset{\oplus}{N}H_3 + H_2O \overset{K_a}{\rightleftharpoons} RNH_2 + \overset{\oplus}{H_2}O} \tag{23-4}$$

With this convention, the *stronger* the base, $\mathrm{RNH_2}$, the more the equilibrium in Equation 23-4 will lie to the left, and the *smaller* will be K_a. The relationship between K_a and K_b in water solution is

$$K_a \times K_b = 10^{-14} \tag{23.7.2}$$

and in terms of pK values, because by definition $\mathrm{p}K = -\log K$,

$$\mathrm{p}K_a + \mathrm{p}K_b = 14$$

23.7.2: Base Strengths of Alkanamines and Cycloalkanamines

The base strengths of simple alkanamines usually are around $K_b = 10^{-4}$ $(K_a = 10^{-10})$ in water solution, and vary within perhaps a factor of 10 from ammonia to primary, secondary, and tertiary amines, as can be seen from the data in Table 23-1. Cyclohexanamine has about the same base strength as methanamine, whereas the effect on the basic nitrogen of being in a saturated ring, as in azacyclohexane, increases the base strength somewhat.

The trends that are evident, especially from basicities of amines measured in the gas phase, point to increasing basicity with the number and size of alkyl groups on the nitrogen atom.

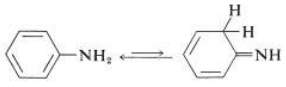
Order of basicity (gas phase): $\mathrm{(CH_3)_3N > (CH_3)_2NH > CH_3NH_2 > NH_3}$

This is reasonable because the conjugate acids, $\mathrm{R_3\overset{\oplus}{N}H}$, are likely to be stabilized by electron-donating and polarizable alkyl groups, thereby making $\mathrm{R_3N}$ a stronger base. That the same trend is not evident in aqueous solution again shows the influence of the solvent on thermochemical properties (see Section 11-8A).

Generally, substituents located on saturated groups attached to nitrogen influence base strengths through their inductive effects in the same way that these substituents influence the strengths of carboxylic acids (see Section 18-2).

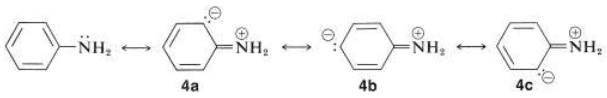
23.7.3: Base Strengths of Arenamines

Alkenamines, or enamines, $\mathrm{R{-}CH{=}CHNH_2}$, usually are not stable and rearrange readily to imines (Section 16-4C). An important exception is benzenamine (aniline), $\mathrm{C_6H_5NH_2}$, which has an amino group attached to a benzene ring. The imine structure is less favorable by virtue of the considerable stabilization energy of the aromatic ring:



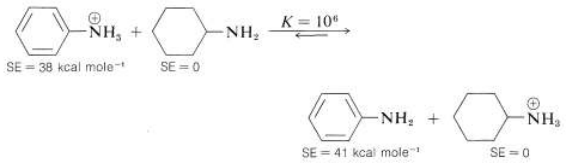
From the heat of combustion of bezenamine we know that it has a $3\ \mathrm{kcal\ mol^{-1}}$ larger stabilization energy than benzene (Table 21-1). This difference in stabilization energies can be ascribed in either valence-bond or molecular-orbital theory to delocalization of

the unshared pair of electrons on nitrogen over the benzene ring. The valence-bond structures are

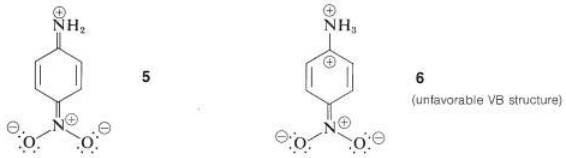


The extra 3-kcal mol^{-1} stabilization energy of benzenamine can be accounted for in terms of the structures $4a$ to $4c$.

Benzenamine is only 1/1,000,000 as strong a base as cyclohexanamine. Most, if not all, of the difference can be accounted for by the decrease in stabilization when the unshared electron pair of nitrogen is localized in forming an N–H bond. Hence, benzenamine is stabilized *more* in the un-ionized state by electron delocalization, relative to cyclohexanamine, than in the ionized state, as expressed by the following equilibrium which lies far to the right:

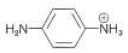
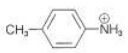
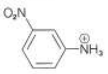


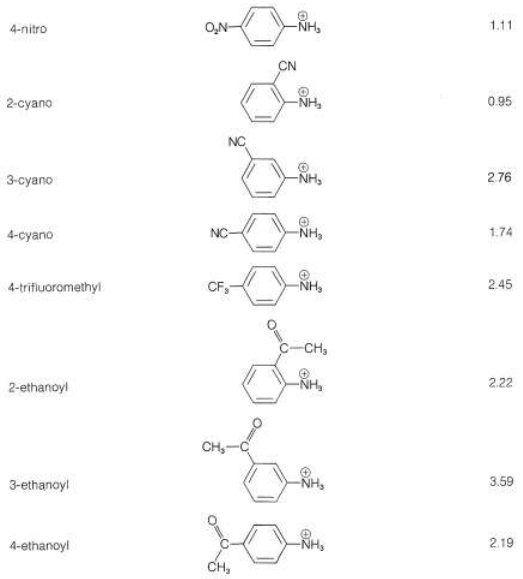
According to the valence-bond structures, $4a$, $4b$, and $4c$, benzenamine has some degree of double-bond character between the nitrogen and the ring, and some degree of negative charge at the ortho and para positions. Accordingly, the ability of the amine nitrogen to add a proton should be particularly sensitive to the electrical effects produced by the presence of substituent groups on the aromatic ring. For example, carbonyl, nitro, cyano, and ethoxycarbonyl substituents, which can delocalize an electron pair on an adjacent carbon (see Sections 17-1A, 17-3E, and 18-8B), are expected to *reduce* the base strength of the amine nitrogen when substituted in the ortho or para positions. The reason is that stabilization by the substituent, as shown by structure 5 for 4-nitrobenzenamine, is important for the free base and *not* for the conjugate acid, 6:



It is simpler and common practice to discuss substituent effects on base strength in terms of the dissociation equilibria of the conjugate acids, $\mathrm{ArNH_3^+ + H_2O \rightleftharpoons ArNH_2 + H_3O^+}$. Substituents that can stabilize the free base by electron delocalization or induction, as in 5, will tend to *increase* the acid dissociation of $\mathrm{ArNH_3^+}$ (decrease base strength of $\mathrm{ArNH_2}$). We see this in the data of Table 23-3 for electron-withdrawing groups ($\mathrm{NO_2}$, CN, $\mathrm{CF_3}$, $\mathrm{CH_3CO-}$), which *increase acid strengths*, and for electron-donating groups ($\mathrm{CH_3}$, $\mathrm{NH_2}$), which *decrease acid strengths*. The effect is most pronounced when the groups are at the ortho or para (2 or 4) positions.

Table 23-3: *Strengths of Conjugate Acids of Monosubstituted Benzenamines in Aqueous Solution at* 25°

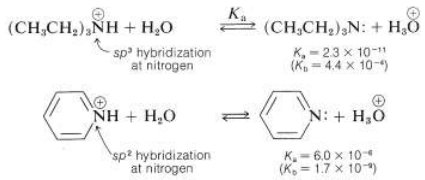
Substituent	Formula	pK_a
H		4.60
4-amino		6.16
4-methyl		5.10
2-nitro		−0.26
3-nitro		2.47



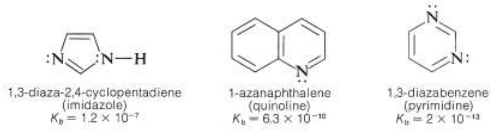
23.7.4: Unsaturated Amines. Azarenes

Substantial differences in base strength are found between alkanamines and unsaturated amines that have the group $-C{=}N-$. An example is azabenzene (pyridine, C_5H_5N), which is a nitrogen analog of benzene:

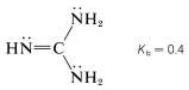
Azabenzene is quite a weak base - in fact, it is 1/100,00 as strong a base as typical alkanamines. This low basicity can be ascribed to the hybridization of the nitrogen orbitals (sp^2) in azabenzene. As we indicated in Section 11-8B in connection with $C{-}H$ acidity, the more s character in the $C{-}H$ bonding orbital, the higher the acidity. The same arguments hold for $N{-}H$ bonds in the conjugate acids, $-C{=}\overset{\oplus}{N}H-$, as the following data show:



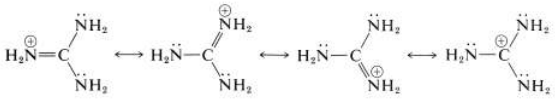
Other examples include:



It is incorrect to assume that the basicity of unsaturated nitrogen in a $C{=}N-$ group is always low. Consider, for example, the base strength of 2,2-diaminoazaethene (guanidine):



This substance is the strongest electrically neutral organonitrogen base known. The basic nitrogen is the imino (sp^2) nitrogen, which on protonation forms a particularly stable conjugate acid in which the three NH_2 groups become identical because of electron delocalization:



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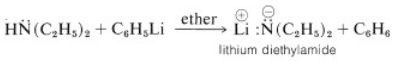
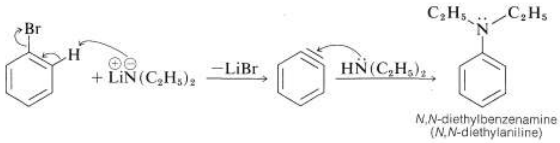
23.8: Amines as Acids

Primary and secondary amines are very weak acids. The lithium salts of such amines can be prepared in ether solution by treatment of the amine with phenyllithium:



The lithium salt of N-ethylethanamine (diethylamine) is called lithium diethylamide,[4] but this nomenclature can lead to confusion with compounds of the type RCO_2NH_2, which are derived from carboxylic acids and also are called amides. We choose to avoid using the name "alkali amide" for $RNHLi$ and accordingly will refer to them as metal salts of the parent amine.

Alkanamines have acid strengths corresponding to K_a values of about 10^{-33}, which means that their conjugate bases are powerfully basic reagents. Therefore they are very effective in causing elimination reactions by the $E2$ mechanism (Section 8-8) and aromatic substitution by the aryne mechanism (Section 14-6C). The following example illustrates this property in a useful synthesis of a benzenamine from bromobenzene:



Salts of alkanamines also are useful for generating enolate salts of carbonyl compounds (Sections 17-4A and 18-8C).

[4]The system used here names these salts as substitution products of NH_2^-. Clearly, to give $LiN(C_2H_5)_2$ the name "lithium N-ethylethanamide" would be totally incorrect because N-ethylethanamide is $CH_3CONHC_2H_5$. Perhaps a better name would be lithium diethylazanide or N,N-diethylaminolithium.

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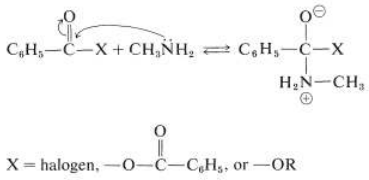
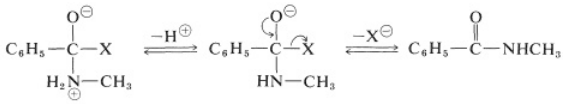
23.9: Amines as Nucleophiles

23.9.1: Acylation of Amines. Synthesis of Amides

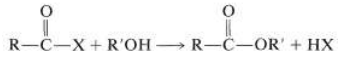
The unshared electrons on nitrogen play a key role in the reactions of amines. In fact, almost all reactions of amines at the nitrogen atom have, as a first step, the formation of a bond involving the unshared electron pair on nitrogen. A typical example is **acylation**, which is amide formation through the reaction of an acyl chloride, an anhydride, or an ester with an amine. The initial step in these reactions with benzenecarbonyl derivatives and methanamine as illustrative reactants is as follows:



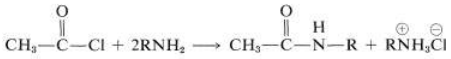
The reaction is completed by loss of a proton and elimination of $X^{\ominus}$:



The reaction is called acylation because an acyl group, $RCO-$, is transferred to the amine nitrogen. It will be seen that these reactions are very similar to the formation of esters by acylating agents, whereby the acyl group is transferred to the oxygen of an alcohol (Section 15-4D):



A serious disadvantage to the preparation of amides through the reaction of an amine with an acyl chloride (or anhydride) is the formation of one mole of amine salt for each mole of amide:



This is especially serious if the amine is the expensive ingredient in the reaction. In such circumstances, the reaction usually is carried on in a two-phase system wit the acyl chloride and amine in the nonaqueous phase and sodium hydroxide in the aqueous phase. As the amine salt is formed and dissolves in the water, it is converted back to amine by the sodium hydroxide and extracted back into the nonaqueous phase:

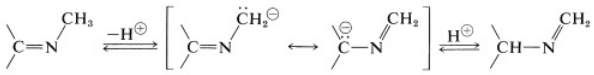
$$\overset{\oplus}{R}\overset{\oplus}{N}H_3\overset{\ominus}{Cl} + \overset{\oplus}{Na}\overset{\ominus}{O}H \rightarrow RNH_2 + \overset{\oplus}{Na}\overset{\ominus}{Cl} + H_2O \tag{23.9.1}$$

This procedure requires an excess of acid chloride because some of it is wasted by hydrolysis.

23.9.2: Imine and Enamine Formation

Amines also add to the carbonyl carbon of aldehydes and ketones, but the reactions take a different course from acylation and, with ammonia or a primary amine, yield *imines*, $-C{=}N-R$, as previously discussed in Section 16-4C.

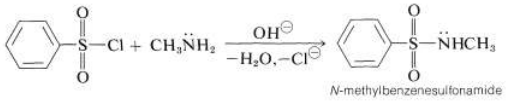
Imines formed from ammonia and aldehydes $(RCH{=}NH)$ are very unstable and readily polymerize (Section 16-4C). However, substitution of an alkyl or aryl group on the nitrogen increases the stability, and N-substituted imines, $-C{=}N-R$, are familiarly known as *Schiff bases*. They are key intermediates in a number of synthetic and biological reactions (see, for example, 17-3F) and are capable of rearrangement by reversible proton transfer that, in some respects, resembles the rearrangement of ketones to enols:



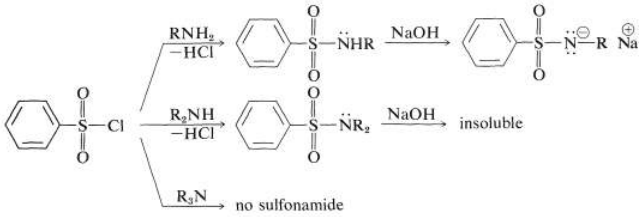
Secondary amines cannot form imines with aldehydes and ketones but may react instead to form *enamines*, $-C{=}C-NR_2$. The formation and synthetic uses of these compounds were discussed previously (Sections 16-4C, 17-4B, and 18-9D).

23.9.3: Sulfonamide Formation from Amines

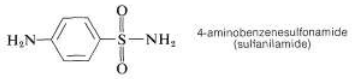
We have seen that amines react with acyl chlorides to give amides. A very similar reaction occurs with sulfonyl chlorides to give *sulfonamides*. An example is benzenesulfonyl chloride reacting with methanamine to give N-methylbenzenesulfonamide:



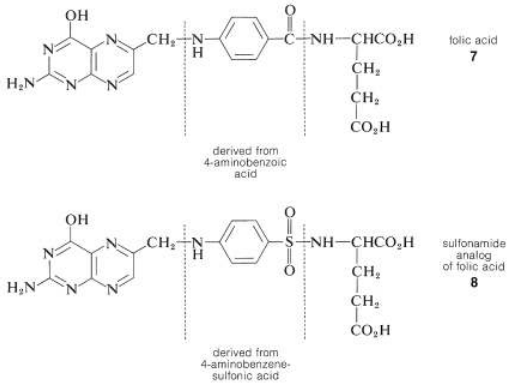
Sulfonylation of amines can be a useful way of differentiating (chemically) between primary, secondary, and tertiary amines by what is known as the **Hinsberg test**. Primary and secondary amines both react with a sulfonyl chloride, but only the sulfonamide from the primary amines has an N–H hydrogen. The sulfonyl group makes this hydrogen relatively acidic and the sulfonamide therefore dissolves readily in sodium hydroxide solutions. The secondary amine does not give a base-soluble amide, whereas the tertiary amine gives no sulfonamide:



Sulfonamides have medicinal value as antibacterial agents. In fact, 4-aminobenzenesulfonamide was the first synthetic antibacterial drug in clinical use, and is effective against a large number of bacterial infections:



This substance inhibits the growth of bacteria by interfering with the synthesis of folic acid, 7, which is an essential substance for bacteria and animals alike. However, animals acquire folic acid from a normal diet, whereas bacteria have to synthesize it. Biosynthesis of folic acid is blocked by 4-aminobenzenesulfonamide, probably because of the structural similarity of the sulfonamide to 4-aminobenzoic acid, which is a normal ingredient in the biosynthesis of folic acid. The enzyme system involved apparently substitutes the sulfonamide for the aminobenzoic acid and creates a sulfonamide-type folic acid instead of the carboxamide derivative (compare structures 7 and 8):



Some 10,000 structurally different sulfonamides have been synthesized as a result of the discovery of the antibacterial properties of sulfanilamide. The practice of synthesizing numerous structurally related compounds in an effort to find some that are more efficient or have fewer side effects than those already available is very important to the pharmaceutical industry. However, as is usually the case, of the many known sulfonamides only about thirty have the proper balance of qualities to be clinically useful.

23.9.4: Alkylation. Synthesis of Alkanamides

Ammonia and amines can function as nucleophiles in S_N2 displacement reactions of alkyl halides (Section 8-7E). Such processes provide syntheses of alkanamines only with those halides that are reactive in S_N2 but not $E2$ reactions. For example,

$$NH_3 + CH_3{-}I \xrightarrow{S_N2} CH_3{-}NH_3{}^+I^- \tag{23-5}$$

The product formed according to Equation 23-5 is an ammonium salt from which the parent amine can be recovered by neutralization with a strong base, such as sodium hydroxide:

$$CH_3NH_3{}^+I^- + Na^{+-}OH \rightleftharpoons CH_3NH_2 + Na^+I^- + H_2O \tag{23-6}$$

Acid-base equilibria similar to Equation 23-6 also occur between an ammonium salt and a neutral amine (Equation 23-7). This can have serious consequences in amine alkylations because it can lead to mixtures of products, whereby more than one alkyl group is bonded to nitrogen:

$$CH_3NH_3{}^+I^- + NH_3 \rightleftharpoons CH_3NH_2 + NH_4{}^+I^- \tag{23.9.2}$$

$$CH_3NH_2 + CH_3{-}I \rightarrow (CH_3)_2CH_2{}^+I^- \tag{23.9.3}$$

Therefore we may expect the reaction of ammonia with methyl iodide to give four possible alkylation products, mono-, di-, and trimethylamines, as well as tetramethylammonium iodide:

$$NH_3 \xrightarrow[-HI]{CH_3I} CH_3NH_2 \xrightarrow[-HI]{CH_3I} (CH_3)_2NH \xrightarrow[-HI]{CH_3I} (CH_3)_3N \xrightarrow{CH_3I} (CH_3)_4N^{\oplus}I^{\ominus} \tag{23.9.4}$$

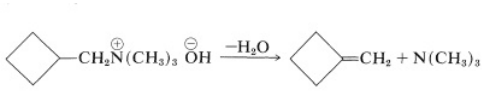
Despite the fact that alkylation reactions of amines generally give mixtures of products, they are of practical value on an industrial scale. The commercial synthesis of methanamines uses methanol as the methylating agent and aluminum oxide as an acidic catalyst; all three amines are formed, and are separated by distillation and extraction. The function of the catalyst is to make OH a better leaving group (Section 8-7D):

$$CH_3OH + NH_3 \xrightarrow[450^\circ,\ 200\ psi]{Al_2O_3} CH_3NH_2 + (CH_3)_2NH + (CH_3)_3N + H_2O \tag{23.9.5}$$

The tetraalkylammonium halides formed by complete alkylation of amines are ionic compounds that resemble alkali-metal salts. When silver oxide is used to precipitate the halide ion, tetraalkylammonium halides are converted to tetraalkylammonium hydroxides, which are strongly basic substances similar to sodium or potassium hydroxide:

$$(CH_3)_4\overset{\oplus}{N}\,\overset{\ominus}{I} \xrightarrow[-AgI]{Ag_2O,\ H_2O} (CH_3)_4\overset{\oplus}{N}\,\overset{\ominus}{OH} \tag{23.9.6}$$

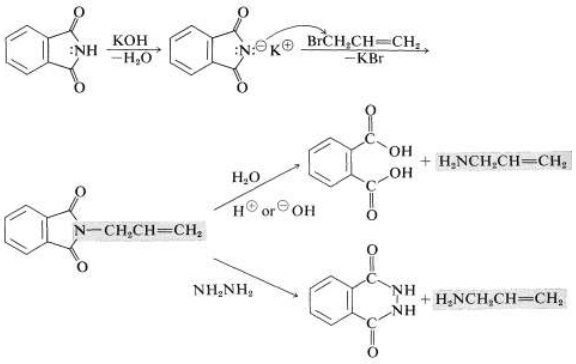
Higher-molecular-weight alkylammonium hydroxides decompose on heating to give alkenes. The reaction is a standard method for the preparation of alkenes and is known as the *Hofmann elimination* (see Section 8-8B):



In principle, the same problems of polyalkylation and $E2$ elimination exist with the amine anion as with the neutral amine - and as far as $E2$ goes, much more so.

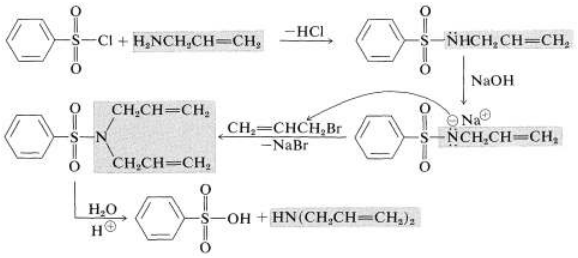
There are nitrogen anions that are useful in alkylation reactions, but they are derived from carboxamides and sulfonamides rather than amines. Two examples are given here to illustrate the synthesis of a primary and a secondary amine (also see Section 18-10C):

Gabriel synthesis of primary amines



The success of the Gabriel synthesis depends on N-alkylation being favored over O-alkylation and S_N2 being favored over $E2$. Polar, aprotic solvents such as methylsufinylmethane, $(CH_3)_2SO$, are useful for the Gabriel synthesis. Hydrolysis of the alkylation product often is difficult and "amide interchange" (analogous to ester interchange, Section 18-7A) with hydrazine can be an effective way to free the amine from the imide.

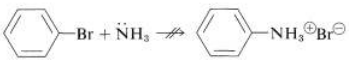
Sulfonamide synthesis of secondary amines



In this synthesis, the acidic properties of sulfonamides of the type $C_6H_5SO_2NHR$ are utilized to form anions capable of alkylation by the S_N2 mechanism.

23.9.5: Arylation. Synthesis of Arenamines

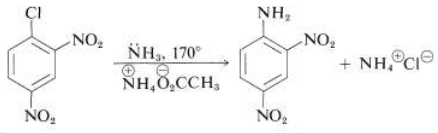
In previous discussions (Section 14-6A) we stated that it is *not* possible to displace halogen from simple aryl halides such as bromobenzene by simple S_N2 reactions using amines or other weakly basic nucleophiles at ordinary temperatures:



However, arylation with such systems will occur with strong bases by the benzyne mechanism (Sections 14-6C and 23-8).

Arylation of amines by the direct displacement of aryl halides is possible when the halogen is activated by strong electron-withdrawing groups in the ortho and para positions. For examples, 2,4-dinitrobenzenamine can be prepared by heating 2,4-

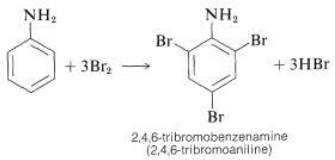
dinitrochlorobenzene with ammonia:



The reasons why this reaction proceeds are discussed in detail in Section 14-6B.

23.9.6: Arenamines as Nucleophiles. Electrophilic Aromatic Substitution

The nitrogen of arenamines is less basic and less nucleophilic than the nitrogen of alkanamines because of electron delocalization of the nitrogen lone pair, as shown for benzenamine in Section 23-7C. The polar valence-bond structures emphasize that the ring atoms, particularly the ortho and para positions, should be more nucleophilic than in benzene. Accordingly, the amino group strongly activates the ring toward attack by electrophiles. In fact, bromine reacts rapidly with benzenamine in aqueous solution to introduce three bromine substituents and form 2,4,6-tribromobenzenamine; no catalyst is required:



Weakly electrophilic reagents that do not normally attack benzene will attack the ring carbons of arenamines. Some of those reactions are described later in the chapter (Sections 23-10C and 23-10D).

23.9.7: Contributors and Attributions

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23.10: Amines with Nitrous Acid

23.10.1: Alkanamines with Nitrous Acid

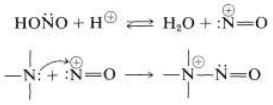
Some of the most important reactions of amines are brought about by nitrous acid (HONO). The character of the products depends very much on whether the amine is primary, secondary, or tertiary. In fact, nitrous acid is a useful reagent to determine whether a particular amine is primary, secondary, or tertiary. With primary amines nitrous acid results in evolution of nitrogen gas; with secondary amines insoluble yellow liquids or solid N-nitroso compounds, $R_2N{-}N{=}O$, separate; tertiary alkanamines dissolve in and react with nitrous acid solutions without evolution of nitrogen, usually to give complex products:

$$RNH_2 + HONO \longrightarrow ROH + H_2O + N_2\uparrow \text{ (evolution of nitrogen)}$$

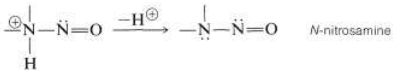
$$R_2NH + HONO \longrightarrow R_2N{-}N{=}O + H_2O \text{ (separation of insoluble yellow } N\text{-nitroso compound)}$$

$$R_3N + HONO \longrightarrow \text{(complex products, but no } N_2 \text{ evolution)}$$

Nitrous acid is unstable and always is prepared as needed, usually by mixing a solution of sodium nitrite, $NaNO_2$, with a strong acid at 0°. These conditions provide a source of $^{\oplus}NO$, which is transferred readily to the nucleophilic nitrogen of the amine:



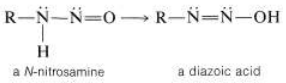
With this common key step, why do amines react differently with nitrous acid depending on their degree of substitution? The answer can bee seen from the reactions that are most easily possible for the $-\overset{\oplus}{N}{-}NO$ intermediate. Clearly, if there is a hydrogen on the positive nitrogen, it can be lost as a proton and a N-nitrosamine formed:



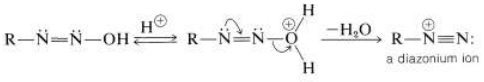
With a *secondary* amine, the reaction stops here, with formation of $R_2N{-}NO$, and because these substances are *very* weak bases, they are *insoluble* in dilute aqueous acids. They are characteristically yellow or orange-yellow solids or oils.

A *tertiary* amine$\cdot\overset{\oplus}{N}O$ complex, $R_3\overset{\oplus}{N}{-}NO$, cannot lose a proton from nitrogen, but instead may lose a proton from carbon and go on to form complex products.

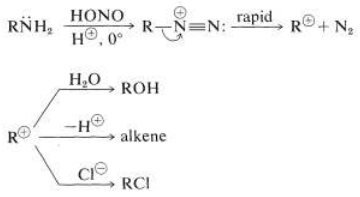
With a *primary* amine, the initially formed N-nitrosamine can undergo a proton shift by a sequence analogous to interconversion of a ketone to an enol. The product is called a **diazoic acid**:



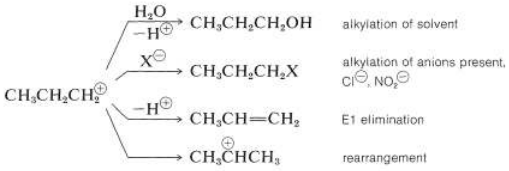
Some diazoic acids form salts that are quite stable, but the acids themselves usually decompose rapidly to diazonium ions:



Diazonium salts can be regarded as combinations of carbocations $R^{\oplus}$ with N_2 and, because of the considerable stability of nitrogen in the form of N_2, we would expect diazonium salts to decompose readily with evolution of nitrogen and formation of carbocations. This expectation is realized, and diazonium salts normally decompose in this manner in water solution. The aliphatic diazonium ions decompose so rapidly that their presence can only be inferred from the fact that the products are typically those of reactions of carbocations:

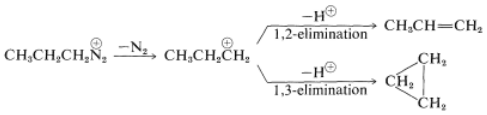


With propanamine, loss of nitrogen from the diazonium ion gives the very poorly stabilized propyl cation, which then undergoes a variety of reactions that are consistent with the carbocation reactions discussed previously (see Sections 8-9B and 15-5E):



The isopropyl cation formed by rearrangement undergoes substitution and elimination like the propyl cation. About half of the products arise from isopropyl cations.

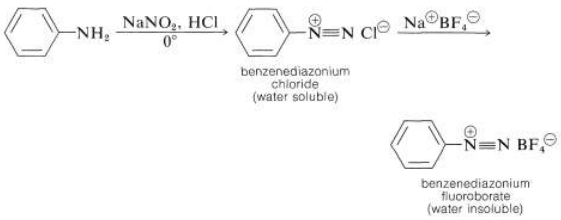
There is one exceptional reaction of the propyl cation that involves *1,3-elimination* and formation of about 10% of cyclopropane:



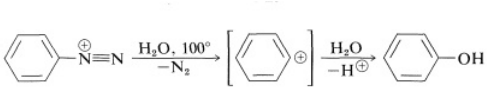
Clearly, the plethora of products to be expected, particularly those resulting from rearrangement, prevents the reaction of the simple primary amines with nitrous acid from having any substantial synthetic utility.

23.10.2: Arenamines with Nitrous Acid. Arenediazonium Salts

Unlike primary alkylamines, primary arenamines react with nitrous acid at 0° to give diazonium salts that, in most cases, are stable enough to be isolated as crystalline BF_4^- salts. Other salts can be isolated, but some of these, such as benzenediazonium chloride, in the solid state may decompose with explosive violence.



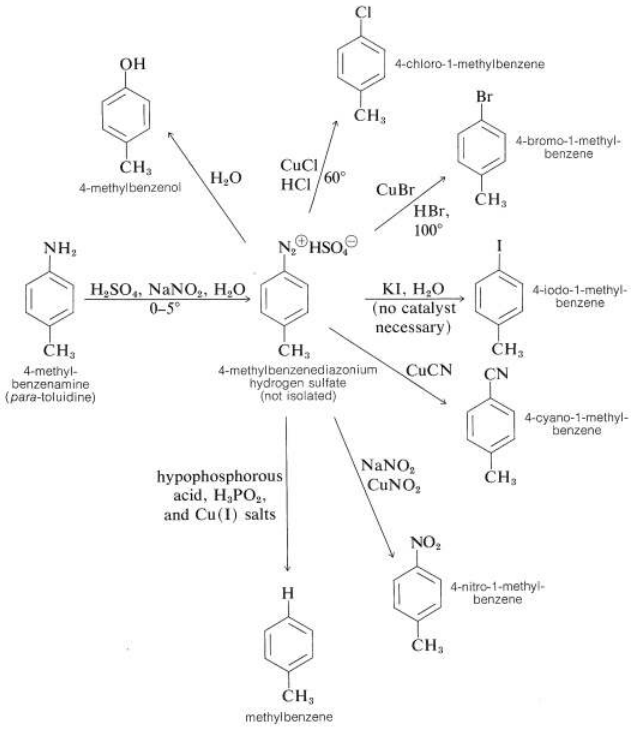
The reason for the greater stability of arenediazonium salts compared with alkanediazonium salts appears to be related to the difficulty of forming aryl carbocations (Section 14-6A). Even the gain in energy associated with having nitrogen as the leaving group is not sufficient to make aryl cations form readily, although solvolysis of arenediazonium ions in water does proceed by an S_N1 mechanism:



This reaction has general utility for replacement of aromatic amino groups by hydroxyl groups. In contrast to the behavior of alkylamines, no rearrangements occur.

Generally, diazonium salts from arenamines are much more useful intermediates than diazonium salts from alkanamines. In fact, arenediazonium salts provide the only substances that undergo nucleophilic substitution reactions on the aromatic ring under mild conditions, without the necessity of having activating groups, such as nitro or cyano, in the ortho or para position. The most

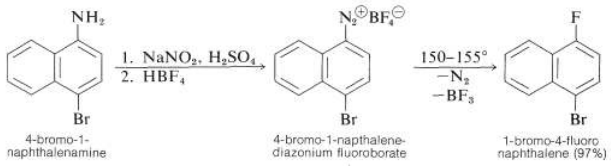
important reactions of this type include the replacement of the diazonium group by nucleophiles such as $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$, $CN^{\ominus}$, NO_2^-, and these reactions lead to the formation of aryl halogen, cyano, and nitro compounds. Most of these reactions require cuprous ions, Cu(I), as catalysts. The method is known as the **Sandmeyer reaction**. The following examples illustrate how a primary arenamine can be converted to a variety of different groups by way of its diazonium salt:



Aryl fluorides also may be prepared from arenamines by way of diazonium salts if the procedure is slightly modified. The amine is diazotized with nitrous acid in the usual way; then fluoroboric acid or a fluoroborate salt is added, which usually causes precipitation of a sparingly soluble diazonium fluoroborate. The salt is collected and thoroughly dried, then carefully heated to the decomposition point - the products being an aryl fluoride, nitrogen, and boron trifluoride:

$$C_6H_5\overset{\oplus}{N}\,\overset{\ominus}{BF_4} \xrightarrow{\text{heat}} C_6H_5F + N_2 + BF_3 \qquad (23.10.1)$$

This reaction is known as the **Schiemann reaction**. An example (which gives a better than usual yield) follows:

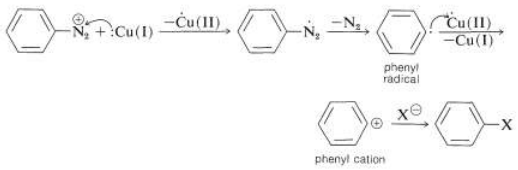


Later in the chapter we shall see that amines can be prepared by the reduction of nitro compounds, which permits the following sequence of reactions:

$$ArH \xrightarrow{HNO_3} ArNO_2 \xrightarrow{[H]} ArNH_2 \xrightarrow{HONO} ArN_2^+ \xrightarrow[-N_2]{CuX} ArX \qquad (23.10.2)$$

This sequence is especially useful to introduce groups or produce orientations of substituents that may not be possible by direct substitution.

The Sandmeyer group of reactions is an example of the production of *nucleophilic substitution by way of radical intermediates* (see Section 14-10A):



This mechanism is supported by the fact that Cu(II) is important in the formation of C_6H_5X. If the concentration of Cu(II) is kept very low so as to slow down conversion of $C_6H_5\cdot$ to $C_6H_5{}^+$, and a compound with a reactive double bond is present, then products are formed by attack of $C_6H_5\cdot$ on the double bond. This is called the **Meerwein reaction**:

$$C_6H_5\overset{\oplus}{N}_2\ \overset{\ominus}{X} + CH_2{=}CHCN \xrightarrow{Cu(I)} C_6H_5CH_2{-}CHXCN + N_2 \tag{23.10.3}$$

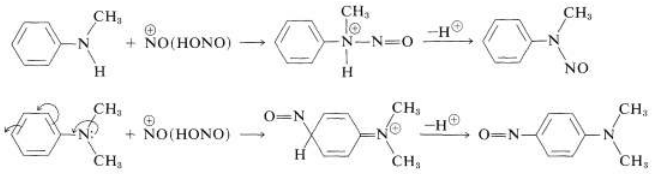
Iodide ion appears to be a good enough reducing agent to form $C_6H_5\cdot$ without the intervention of Cu(I); considerable I_2 usually is formed in the reaction:

$$C_6H_5\overset{\oplus}{N}_2 + \overset{\ominus}{I} \rightarrow C_6H_5\cdot + N_2 + I\cdot \tag{23.10.4}$$

$$C_6H_5\cdot + I\cdot \rightarrow C_6H_5I \tag{23.10.5}$$

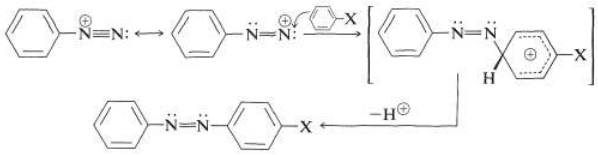
$$2I\cdot \rightarrow I_2 \tag{23.10.6}$$

Secondary arenamines react with nitrous acid to form N-nitroso compounds while tertiary arenamines undergo electrophilic substitution with $NO^{\oplus}$ if they have an unsubstituted *para* position:



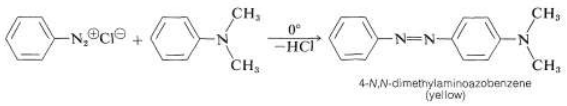
23.10.3: Diazo Coupling Reactions

Not all reactions of diazonium ions involve cleavage of the C−N bond. An important group of reactions of arenediazonium ions involves aromatic substitution by the diazonium ion acting as an *electrophilic* agent to yield azo compounds, Ar−N=N−Ar:



This reaction is highly sensitive to the nature of the substituent X, and coupling to benzene derivatives normally occurs only when X is a strongly electron-donating group such as $-O^{\ominus}$, $-N(CH_3)_2$, and $-OH$. However, coupling with $X = -OCH_3$ may take place with particularly active diazonium ions.

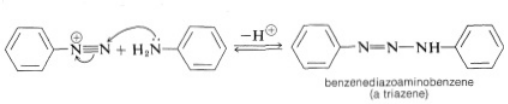
Diazo coupling has considerable technical value, because the azo compounds that are produced are highly colored. Many are used as fabric dyes and for other coloring purposes. A typical example of diazo coupling is formation of 4-N,N-dimethylaminoazobenzene from benzenediazonium chloride and N,N-dimethylbenzenamine:



The product once was used to color edible fats and therefore was known as "Butter Yellow", but its use to color food is prohibited because it is reported to be a potent liver carcinogen for rats.

The pH used for diazo coupling of amines is very important in determining the nature of the products. Under near-neutral conditions the diazonium ion may attack the *nitrogen* of the arenamine rather than a ring carbon. In this event a diazoamino

compound, a triazene, $-N{=}N-N-$, is formed:



The reaction is readily reversed if the pH is lowered sufficiently.

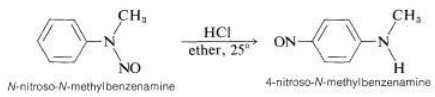
As you see from this brief discussion of arenediazonium salts, their chemistry is complex. It is inappropriate to discuss all of their many reactions here, but a summary of the most important types of reactions is given in Table 23-4.

Table 23-4: *Summary of Reactions of Arenediazonium Salts*

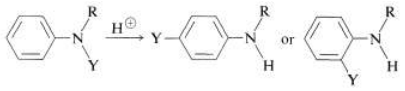
Reaction	Comment
1. *Replacement reactions:* $ArN_2^{\oplus} + X^{\ominus} \longrightarrow ArX + N_2$	Cuprous-catalyzed replacement reactions are called **Sandmeyer reactions**; aryl chlorides, bromides, cyanides, and nitro compounds are prepared in this way; formation of aryl iodides requires no catalyst, fluorides are obtained by heating diazonium fluoroborates (i.e., **Schiemann reaction**); benzenols are obtained by warming aqueous diazonium salt solutions.
a. *aryl halide formation*	
$ArN_2^{\oplus} + Cl^{\ominus} \xrightarrow{Cu(I)} ArCl + N_2$	
$ArN_2^{\oplus}BF_4^{\ominus} \xrightarrow{heat} ArF + N_2 + BF_3$	
b. *arenecarbonitrile formation*	
$ArN_2^{\oplus} + {}^{\ominus}CN \xrightarrow{Cu_2(CN)_2} ArCN + N_2$	
c. *aryl nitro compound formation*	
$ArN_2^{\oplus} + {}^{\ominus}NO_2 \xrightarrow{Cu(I)} ArNO_2 + N_2$	
d. *benzenols by hydrolysis*	
$ArN_2^{\oplus} + H_2O \xrightarrow{-H^{\oplus}} ArOH + N_2$	
e. *aryl azide formation*	
$ArN_2^{\oplus} + {}^{\ominus}N_3 \longrightarrow ArN_3 + N_2$	
2. *Addition to conjugated alkenes*	Cuprous-catalyzed addition of a diazonium salt to activated double bonds of alkenes and related compounds is known as the **Meerwein reaction**; it competes with the Sandmeyer reaction.
$ArN_2^{\ominus}Cl^{\ominus} + C{=}C \xrightarrow[-N_2]{Cu(I)} Ar-C-C-Cl$	
3. *Biaryl formation*	Decomposition of diazonium salts in presence of Cu(I) and ammonia leads to biaryls.
a. $ArN_2^{\oplus} + Cu(I) \xrightarrow[-H^{\oplus}]{NH_3} Ar{-}Ar + Cu(II) + N_2$	
b. $ArN_2^{\oplus}{}^{\ominus}O_3CCH_3 \rightleftharpoons ArN{=}NO_3CCH_3$	Thermal decomposition of diazo ethanoates in an aromatic solvent leads to biaryl formation by attack of aryl radicals on solvent.
$ArN{=}NO_3CCH_3 \xrightarrow[-CH_3CO_2\cdot]{-N_2} Ar\cdot \xrightarrow{Ar'H} Ar{-}Ar'$	
4. *Reduction of diazonium salts*	Reductive replacement of $-N_2^{\oplus}$ by hydrogen is effected by hypophosphorous acid; reduction is initiated with Cu(I).
a. arene formation	
$ArN_2^{\oplus} + H_2O + H_3PO_2 \xrightarrow{Cu(I)} ArH + N_2 + H^{\oplus} + H_3PO_3$	
b. hydrazine formation	Sulfite reduction of diazonium salts leads to hydrazines.
$ArN_2^{\oplus} + 2SO_3^{2\ominus} + HO^{\ominus} + H_2O \longrightarrow ArNHNH_2 + 2SO_4^{2\ominus}$	
5. *Diazo-coupling reactions*	Electrophilic attack of $ArN_2^{\oplus}$ on Ar'X leads to azo compounds; the substituent X must be powerfully activating [e.g., $-O^{\ominus}$, $-N(CH_3)_2$].
a. formation of azo compounds	
$ArN_2^{\oplus} + Ar'X \xrightarrow[0^{\circ}]{-H^{\oplus}} Ar{-}N{=}N{-}Ar'X$	
b. formation of triazenes (diazoamino) compounds	Electrophilic attack of $ArN_2^{\oplus}$ on nitrogen of a *prim*- or *sec*-arylamine in neutral or alkaline solution.
$ArN_2^{\oplus} + Ar'NH_2 \xrightarrow{pH \geq 7} Ar{-}N{=}N{-}NHAr' + H^{\oplus}$	
6. *Diazotate formation*	Diazotate salts are formed reversibly from diazonium salts in basic solution.
$ArN_2^{\oplus}{}^{\ominus}Cl + {}^{\ominus}OH \overset{0^{\circ}}{\rightleftharpoons} Ar{-}N{=}N{-}OH + Cl^{\ominus}$ (diazoic acid)	
$ArN{=}N{-}OH + {}^{\ominus}OH \overset{0^{\circ}}{\rightleftharpoons} ArN{=}N{-}O^{\ominus} + H_2O$ (diazotate)	

23.10.4: Rearrangements of N-Substituted Arenamines

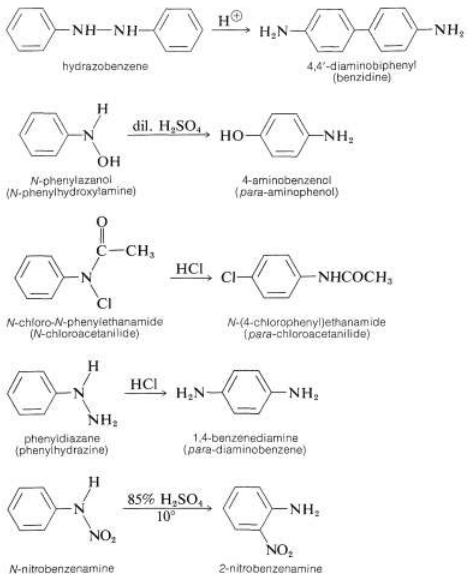
A secondary arenamine behaves like a secondary alkanamine in reacting with nitrous acid to give an N-nitrosamine. However, when treated with an acid the N-nitrosamine rearranges:



This is one example of a group of formally related rearrangements in which a substituent, Y, attached to the nitrogen of a benzenamine derivative migrates to the ortho or para positions of the aromatic ring under the influence of acid:



Rearrangement occurs most readily when Y is a strongly electron-attracting group and the N−Y bond that is broken is not as strong as the C−Y bond that is formed. A few of the many examples of this type of reaction follow:



23.10.5: Contributors and Attributions

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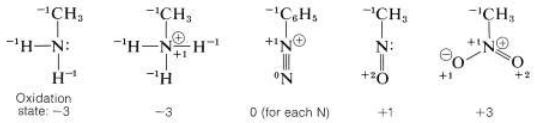
23.11: Oxidation of Amines

23.11.1: Oxidation States of Nitrogen in Organic Compounds

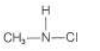
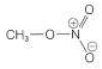
Nitrogen has a wide range of oxidation states in organic compounds. We can arrive at an arbitrary scale for the oxidation of nitrogen in much the same way as we did for carbon (Section 11-1). We simply define elementary nitrogen as the zero oxidation state, and every atom bonded to nitrogen contributes -1 to the oxidation state if it is more electropositive than nitrogen (e.g., H, C, Li, B, Mg) and +1 if it is more electronegative (e.g., O, F, Cl). Doubly bonded atoms are counted twice, and a formal positive charge associated with nitrogen counts as +1.

To illustrate, the oxidation states of several representative compounds are as follows:



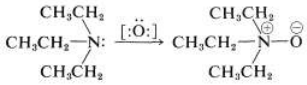
Several types of nitrogen compounds are listed in Table 23-5 to illustrate the range of oxidation states that are possible.

Table 23-5: *Oxidation States of Nitrogen*

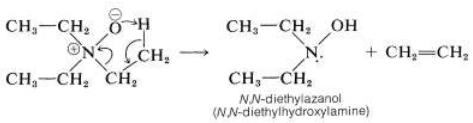
Compound or class of compound	Example	Oxidation state
amine	CH_3NH_2	−3
imine	$CH_2{=}NH$ (unstable)	−3
nitrile	$CH_3C{\equiv}N$	−3
azanol (hydroxylamine)	CH_3NHOH	−1
N-chloroamine		−1
nitrogen	$:N{\equiv}N:$	0
nitroso	$CH_3N{=}O$	+1
nitric oxide	$\cdot N{=}O$	+2
nitro		+3
nitrite ester	$CH_3{-}O{-}N{=}O$	+3
nitrogen dioxide	$\cdot NO_2$	+4
nitrate ester		+5

23.11.2: Oxidation of Tertiary Amines. Amine Oxides

For the oxidation of a tertiary amine by reagents such as hydrogen peroxide, H_2O_2, or peroxycarboxylic acids, RCOOOH, which can supply an oxygen atom with six electrons, the expected product is an azane oxide (amine oxide). Thus N,N-diethylethanamine (triethylamine) can be oxidized to triethylazane oxide (triethylamine oxide):



Amine oxides are interesting for two reasons. First, amine oxides decompose when strongly heated, and this reaction provides a useful preparation of alkenes. With triethylazane oxide (triethylamine oxide), ethene is formed:

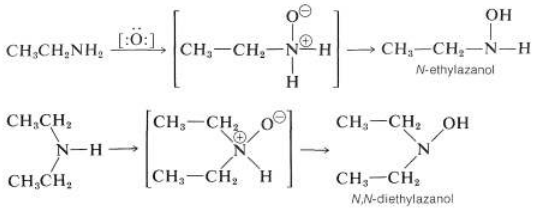


The second interesting point about amine oxides is that, unlike amines, they do not undergo rapid inversion at the nitrogen atom, and the oxides from amines with three different R groups are resolvable into optically active forms. This has been achieved for

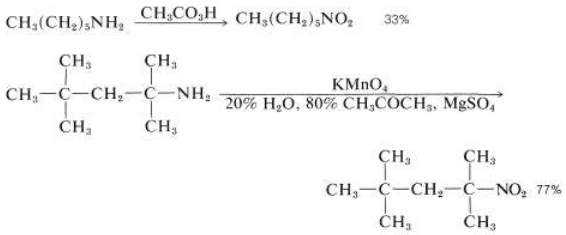
several amine oxides, including the one from N-ethyl-N-methyl-2-propanamine.

23.11.3: Oxidation of Primary and Secondary Alkanamines

Addition of an oxygen atom from hydrogen peroxide or a peroxyacid to a primary or secondary amine might be expected to yield an amine oxide-type intermediate, which then could rearrange to an azanol (hydroxylamine):

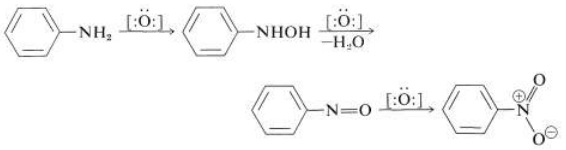


However, these oxidations usually take a more complicated course, because the azanols themselves are oxidized easily, and in the case of primary amines, oxidation occurs all the way to nitro compounds, in fair-to-good yields:

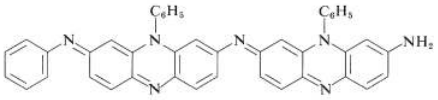


23.11.4: Oxidation of Aromatic Amines

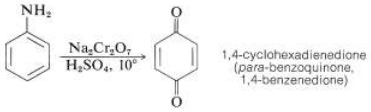
We shall use benzenamine to illustrate some typical oxidation reactions of arenamines. The course of oxidation depends on the nature of the oxidizing agent and on the arenamine. With hydrogen peroxide or peroxycarboxylic acids, each of which functions *to donate oxygen to nitrogen*, oxidation to the azanol, the nitroso, or the nitro compound may occur, depending on the temperature, the pH, and the amount of oxidizing agent:



Oxidizing agents that *abstract a hydrogen atom or hydride ion* lead to more complex reactions, which often result in highly colored products. One of the best black dyes for fabric (Aniline Black) is produced by impregnating cloth with phenylammonium chloride solution and then oxidizing, first with sodium chlorate $(NaClO_3)$ and finally with sodium dichromate $(Na_2Cr_2O_7)$. Aniline Black probably is not a single substance, and its exact structure(s) is not known; but its formation certainly involves addition reactions in which carbon-nitrogen bonds are made. A possible structure is shown in which there are seven aniline units:



Oxidation of benzenamine with sodium dichromate in aqueous sulfuric acid solution produces 1,4-cyclohexadienedione (*para*-benzoquinone), which is the simplest member of an interesting class of conjugated cyclic diketones that will be discussed in more detail in Chapter 26:



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23.12: Synthesis of Amines

23.12.1: Main Types of Synthesis

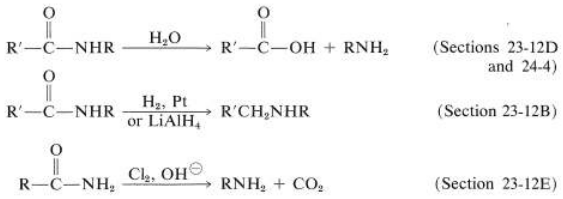
There are seemingly many different ways in which amines can be prepared. However, a careful look at these methods reveals that they fall into three main groups of reactions. The first group starts with a simple amine, or with ammonia, and builds up the carbon framework by alkylation or arylation reactions on nitrogen, as discussed in Section 23-9D:

$$\mathrm{RX + NH_3 \rightarrow RNH_2 + HX} \tag{23.12.1}$$

The second group starts with compounds of the same carbon-nitrogen framework as in the desired amine but with nitrogen in a higher oxidation state. The amine then is obtained from these compounds by catalytic hydrogenation or metal-hydride reduction, as will be described in the next section:

$$\mathrm{RNO_2 + 3H_2 \xrightarrow{Pt} RNH_2 + 2H_2O} \tag{23.12.2}$$

The third group of reactions relies on the fact that amides usually can be converted to amines, either by reduction, hydrolysis, or rearrangement, so that any viable synthesis of amides usually is also a synthesis of amines:

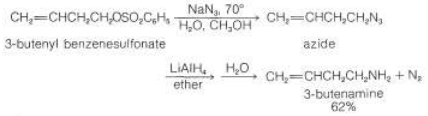


These and related reactions are discussed in further detail in the following sections. For your convenience, a tabular summary of methods for the synthesis of amines appears in Tables 23-6 and 23-7.

Table 23-6: *Practical Examples of the Synthesis of Amines*

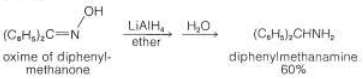
Reaction	Comment
1. *Reduction of nitrogen compounds* a. nitro compounds $CH_3CH_2CHCH_3$ (NO$_2$) —LiAlH$_4$, ether; H$_2$O→ $CH_3CH_2CHCH_3$ (NH$_2$) 2-nitrobutane → 1-methylpropanamine (2-aminobutane) 85% 2,4-dinitromethylbenzene —Fe, HCl→ 4-methyl-1,3-benzenediamine	Lithium aluminum hydride is a convenient reagent for reduction of nitro compounds, nitriles, amides, azides, and oximes to primary amines. Catalytic hydrogenation works also. Aromatic nitro compounds are reduced best by reaction of a metal and aqueous acid or with ammonium or sodium polysulfides (see Section 23-12B). Reduction of *N*-substituted amides leads to secondary amines.
b. nitriles $CH_3CH_2CH_2CN$ —LiAlH$_4$, ether; H$_2$O→ $CH_3CH_2CH_2CH_2NH_2$ butanenitrile → butanamine 57%	See Section 23-12B.
c. amides *N*-methyl-*N*-phenylethanamide (*N*-methylacetanilide) —LiAlH$_4$, ether; H$_2$O→ *N*-ethyl-*N*-methylbenzenamine 91%	See Section 23-12B.

d. azides



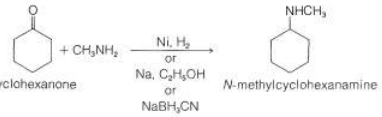
See Section 23-12B.

e. oximes



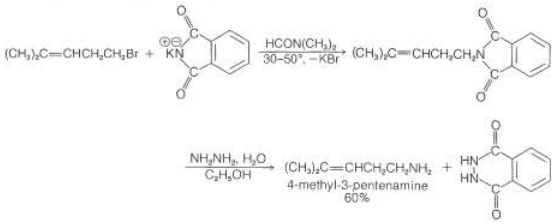
See Section 23-12B.

2. *Reductive alkylation of amines with carbonyl compounds*



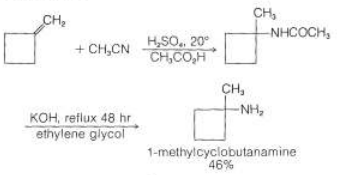
See Section 23-12C. A variety of reducing agents can be used, including hydrogen, sodium in alcohol, and sodium borohydrides.

3. *Gabriel synthesis using potassium phthalimide*



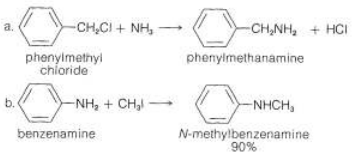
Affords primary amines. Satisfactory for primary and some secondary halides (see Section 23-9D).

4. *Ritter reaction*



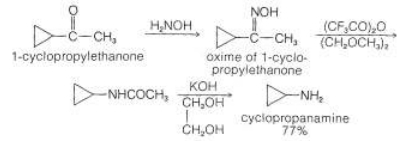
Yields primary amines with tertiary alkyl groups. Satisfactory for alkenes and alcohols that give a tertiary carbocation in strong acid (see Section 24-3B).

5. *Alkylation of ammonia and amines*



Primary amines are obtained from ammonia, and secondary amines from primary amines. Alkylating agent must have good S_N2 reactivity. Limitations are discussed in Section 23-9D.

6. *Beckmann rearrangement of oximes*



See Section 24-3C.

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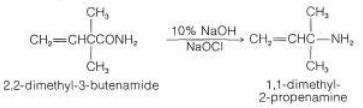
7. *Hofmann degradation of amides*



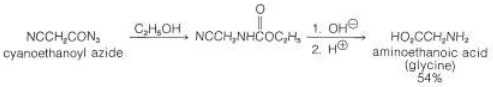
2,2-dimethyl-3-butenamide → 1,1-dimethyl-2-propenamine

See Section 23-12E. Either NaOCl or NaOBr may be used.

8. *Curtius degradation of acyl azides*

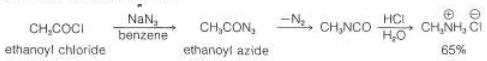
a. acyl azide from hydrazide

ethyl cyanoethanoate → cyanoethanoylhydrazine



cyanoethanoyl azide → aminoethanoic acid (glycine) 54%

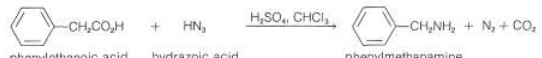
b. acyl azide from acyl chloride



ethanoyl chloride → ethanoyl azide → 65%

Hofmann, Curtius, and Schmidt reactions yield primary amines free of secondary or tertiary amines. The three reactions are closely related but differ in reaction conditions. They apply to alkyl, allyl, and aryl derivatives. See Section 23-12E.

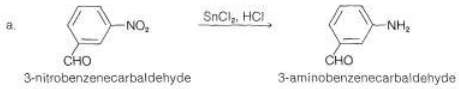
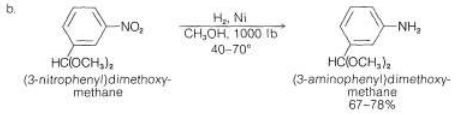
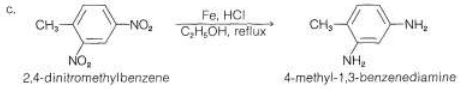
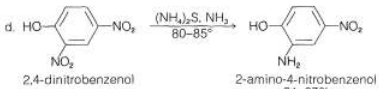
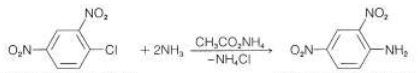
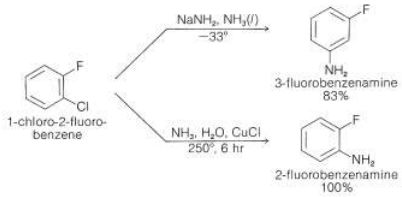
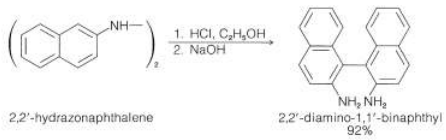
9. *Schmidt degradation of acyl azides* (obtained from carboxylic acids)

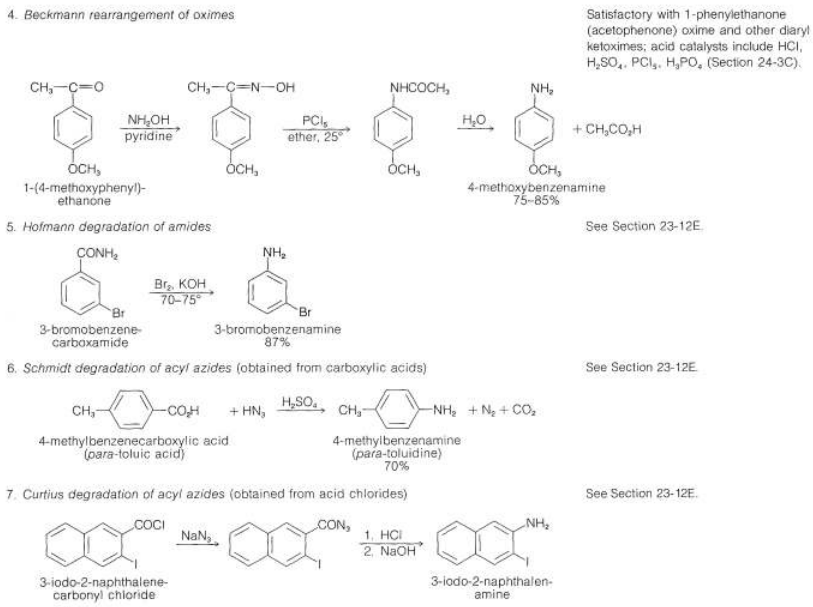


phenylethanoic acid + hydrazoic acid → phenylmethanamine 92%

See Section 23-12E.

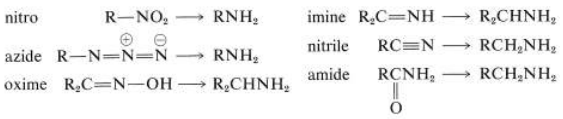
Table 23-7: *Practical Examples of the Synthesis of Aromatic Amines*

Reaction	Comment
1. *Reduction of nitro compounds*	Reducing agents commonly employed are iron, tin, or $SnCl_2$ in hydrochloric acid; and ammonium or alkali-metal sulfides; catalytic hydrogenation and electrolytic reduction also are employed (see Section 23-12B).
a.  3-nitrobenzenecarbaldehyde → 3-aminobenzenecarbaldehyde	
b.  (3-nitrophenyl)dimethoxymethane → (3-aminophenyl)dimethoxymethane 67–78%	Notice, in the example given, that the acetal function is a protecting group for CHO.
c.  2,4-dinitromethylbenzene → 4-methyl-1,3-benzenediamine	
d.  2,4-dinitrobenzenol → 2-amino-4-nitrobenzenol 64–67%	Notice that, with the right conditions and reducing agent, one nitro group can be selectively reduced in the presence of another.
2. *Amination of aryl halides*	Nucleophilic replacement of halogen of aryl halides is discussed in Section 14-6B; ortho and para substituents that activate halogen include NO_2, $N_2^{\oplus}$, SO_3H, NO.
a. activated aryl halides  2,4-dinitrochlorobenzene → 2,4-dinitrobenzenamine 68–76°	
b. nonactivated aryl halides  1-chloro-2-fluorobenzene → 3-fluorobenzenamine 83%; 2-fluorobenzenamine 100%	Elimination-addition reactions of aryl halides with alkali-metal amides are discussed in Section 14-6C; high-temperature copper-catalyzed amination, also effective, usually does not lead to rearrangement.
3. *Benzidine rearrangement of hydrazo compounds*  2,2′-hydrazonaphthalene → 2,2′-diamino-1,1′-binaphthyl 92%	Acid-catalyzed rearrangement of aromatic hydrazo compounds leads to diaminobiaryl compounds (see Section 23-10D).



23.12.2: Formation of Amines by Reduction

Excellent procedures are available for the preparation of primary, secondary, and tertiary amines by the reduction of a variety of nitrogen compounds. Primary amines can be obtained by hydrogenation or by lithium aluminum hydride reduction of nitro compounds, azides, imines, nitriles, or unsubstituted amides [all possible with H_2 over a metal catalyst (Pt or Ni) or with $LiAlH_4$]:



Some care must be exercised in the reduction of nitro compounds because such reductions can be highly exothermic. For example, the reaction of $1\ \text{mol}\ (61\ \text{g})$ of nitromethane with hydrogen to give methanamine liberates sufficient heat to increase the temperature of a 25-lb iron bomb $100°$:

Secondary and tertiary amines, particularly those with different R groups, are prepared easily by lithium aluminum hydride reduction of substituted amides (Section 18-7C).

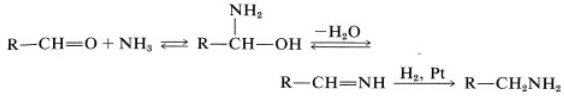
23.12.3: Amines by Reductive Alkylation of Aldehydes and Ketones

A useful synthesis of primary and secondary amines that is related to the reductions just described utilizes the reaction of an aldehyde or a ketone with ammonia or a primary amine in the presence of hydrogen and a metal catalyst:

$$RCHO + NH_3 + H_2 \xrightarrow{Pt} RCH_2NH_2 + H_2O \tag{23.12.3}$$

$$R_2C{=}O + CH_3NH_2 + H_2 \xrightarrow{Pd} R_2CHNHCH_3 + H_2O \tag{23.12.4}$$

It is reasonable to suppose that the carbonyl compound first forms the imine derivative by way of the aminoalcohol (see Section 16-4C), and this derivative is hydrogenated under the reaction conditions:

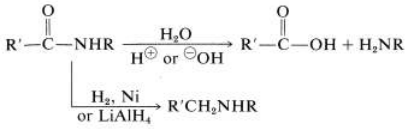


Other reducing agents may be used, and the borohydride salt $Na^{\oplus}\ {}^{\ominus}BH_3(CN)$ is convenient to use in place of H_2 and a metal catalyst.

In a formal sense, the carbonyl compound is reduced in this reaction while the amine is alkylated, hence the term **reductive alkylation** or **reductive amination**.

23.12.4: Amines from Amides by Hydrolysis or Reduction

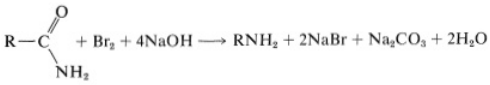
There are a number of ways in which an amide can be transformed into an amine. Two of these ways have been mentioned already and involve hydrolysis or reduction:



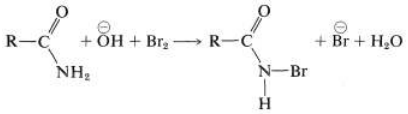
As a means of amine synthesis, both methods depend on the availability or the ease of synthesis of the corresponding amide.

23.12.5: Amines from Amides by the Hofmann Degradation

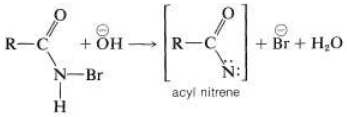
An interesting and general reaction for the preparation of primary amines is the **Hofmann degradation**, in which an unsubstituted amide is converted to an amine by bromine (or chlorine) in sodium hydroxide solution:



The mechanism of this unusual reaction first involves base-catalyzed bromination of the amide on nitrogen to give an N-bromoamide intermediate:

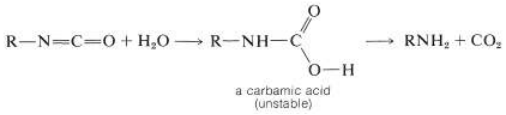


There follows a base-induced elimination of HBr from nitrogen to form a "nitrene" intermediate, which is analogous to the formation of a carbene (Section 14-7B):

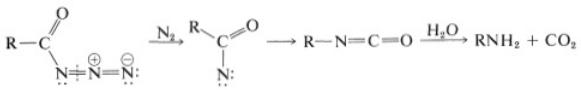


As you might expect from the structure of an acyl nitrene (only six electrons in the valence shell of nitrogen), it is highly unstable but can become stabilized by having the substituent group move as $R^{\ominus}$ from carbon to nitrogen:[5]

The rearrangement is stereospecific and the configuration at the migrating carbon is *retained* (see Section 21-10F). The rearrangement product is called an **isocyanate** and is a nitrogen analog of a ketene ($R_2C{=}C{=}O$); like ketenes, isocyanates readily add water. The products are carbamic acids, which are not very stable, especially in basic solution, and readily lose carbon dioxide to give the amine:



A practical example of this reaction is given in Table 23-6 together with examples of related reactions known as the **Curtius** and **Schmidt** rearrangements. The latter two probably also involve rearrangement of an acyl nitrene, this time formed by decomposition of an acyl azide:



[5]There are several analogies for this kind of rearrangement that involve electron-deficient carbon (Sections 8-9B and 15-5E) and oxygen (Section 16-9E).

23.12.6: Contributors and Attributions

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23.13: Protection of Amino Groups in Synthesis

We have mentioned previously that it may be difficult to ensure selective chemical reaction at one functional group when other functional groups are present in the same molecule. Amino groups are particularly susceptible to reactions with a wide variety of reagents, especially oxidizing reagents, alkylating reagents, and many carbonyl compounds. Therefore, if we wish to prevent the amino group from undergoing undesired reaction while chemical change occurs elsewhere in the molecule, it must be suitably protected. There is more documented chemistry on methods of protecting amino groups than of any other functional group. This is because peptide synthesis has become very important and, as we shall see in Chapter 25, it is not possible to build a peptide of specific structure from its component amino acids unless the amino groups can be suitably protected. Therefore we now will consider the more useful protecting groups that are available - how they are introduced and how they are removed.

23.13.1: Protonation

It should be clear that the reactivity of amines normally involves some process in which a bond is made to the unshared electron pair on nitrogen. Therefore any reaction of an amine that reduces the reactivity of this electron pair should reduce the reactivity of the nitrogen atom. The simplest way to do this would be to convert the amine to an ammonium salt with an acid. Protonation amounts to protection of the amine function:

$$\mathrm{RNH_2 + HX \rightleftharpoons R\overset{\oplus}{N}H_3\ \overset{\ominus}{X}} \tag{23.13.1}$$

Examples are known in which amines indeed can be protected in this manner, but unless the acid concentration is very high, there will be a significant proportion of unprotected free base present. Also, many desirable reactions are not feasible in acid solution.

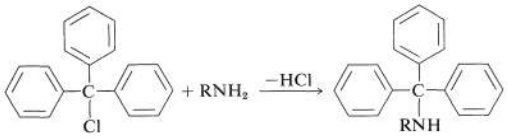
23.13.2: Alkylation

A related protection procedure is alkylation (Equations 23-8 and 23-9), which is suitable for primary and secondary amines:

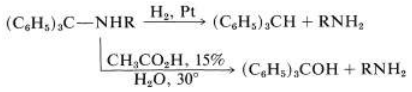
$$\mathrm{R'NH_2 + RX \rightarrow R'NHR + HX} \tag{23-8}$$

$$\mathrm{R'_2NH + RX \rightarrow R'_2NR + HX} \tag{23-9}$$

At first glance, you may not consider that such reactions achieve protection because there is an electron pair on nitrogen in the products. However, it a suitably bulky alkylating agent, RX, is used the reactivity of the resulting alkylated amine can be reduced considerably by a steric effect. The most useful group of this type is the triphenylmethyl group $(\mathrm{C_6H_5})_3\mathrm{C}-$, which can be introduced on the amine nitrogen by the reaction of triphenylmethyl chloride ("trityl" chloride) with the amine in the presence of a suitable base to remove the HCl that is formed:



The triphenylmethyl group can be removed from the amine nitrogen under very mild conditions, either by catalytic hydrogenation or by hydrolysis in the presence of a weak acid:



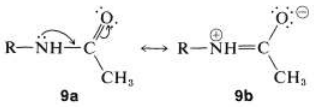
23.13.3: Acylation

One useful way of reducing the basicity and nucleophilicity of an amine nitrogen is to convert it to an amide by treatment with an acid chloride or acid anhydride (Section 18-7):

$$\mathrm{RNH_2 + CH_3COCl \rightarrow RNHCOCH_3 + HCl} \tag{23.13.2}$$

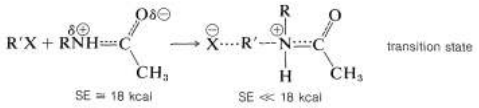
$$\mathrm{RNH_2 + (CH_3CO)_2O \rightarrow RNHCOCH_3 + CH_3CO_2H} \tag{23.13.3}$$

The reduced reactivity is associated with the stabilization produced by the attached carbonyl group because of its ability to accept electrons from the nitrogen atom. This can be seen clearly in valence-bond structures $9a$ and $9b$, which show electron delocalization of the unshared pair of the amide function:



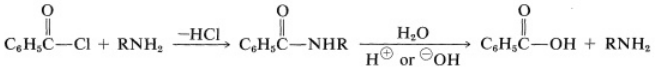
9a **9b**

The stabilization energy (SE) of a simple amide grouping is about $18\ \text{kcal mol}^{-1}$, and if a reaction occurs in which the amide nitrogen acts as an electron-pair donor, almost all of the electron delocalization of the amide group is lost in the transition state:

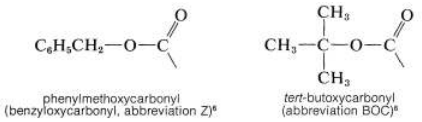


This loss in stabilization energy at the transition state makes an amide far less nucleophilic than an amine.

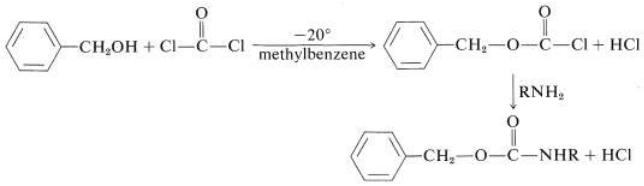
The most common acylating agents are the acyl chlorides and acid anhydrides of ethanoic acid and benzoic acid. The amine can be recovered from the amide by acid- or base-catalyzed hydrolysis:



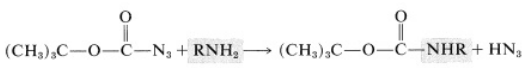
Another useful protecting group for amines has the structure $\text{R}{-}\text{O}{-}\text{CO}{-}$. It differs from the common acyl groups of the type $\text{R}{-}\text{CO}{-}$ in that it has the *alkoxy*carbonyl structure rather than an *alkyl*carbonyl structure. The most used examples are:



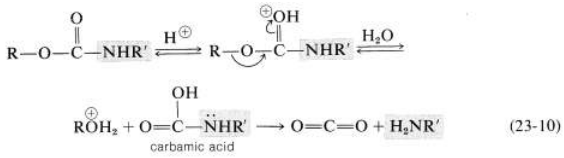
The phenylmethoxycarbonyl (benzyloxycarbonyl) group can be introduced by way of the corresponding acyl chloride, which is prepared from phenylmethanol (benzyl alcohol) and carbonyl dichloride:



The *tert*-butoxycarbonyl group cannot be introduced by way of the corresponding acyl chloride because $(\text{CH}_3)_3\text{COCOCl}$ is unstable. One of several alternative derivatives is the azide, ROCON_3:

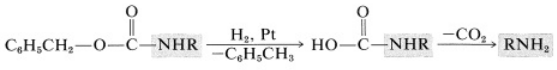


Although these protecting groups may seem bizarre, their value lies in the fact that they can be removed easily by acid-catalyzed hydrolysis under very mild conditions. The sequence of steps is shown in Equation 23-10 and involves proton transfer to the carbonyl oxygen and cleavage of the carbon-oxygen bond by an S_N1 process ($\text{R} = \textit{tert}$-butyl) or S_N2 process ($\text{R} =$ phenylmethyl). The product of this step is a carbamic acid. Acids of this type are unstable and readily eliminate carbon dioxide, leaving only the free amine (also see Section 23-12E):



(23-10)

The benzyloxycarbonyl group, but not the *tert*-butoxycarbonyl group, may be removed by catalytic hydrogenation. Again a carbamic acid is formed, which readily loses CO_2:

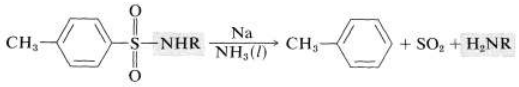


23.13.4: Sulfonylation

A sulfonyl group, RSO_2-, like an acyl group, $R-CO-$ or $RO-CO-$, will deactivate an attached nitrogen. Therefore amines can be protected by transformation to sulfonamides with sulfonyl chlorides (Section 23-9C):

$$C_6H_5SO_2Cl + RNH_2 \rightarrow C_6H_5SO_2NHR + HCl \qquad (23.13.4)$$

However, sulfonamides are much more difficult to hydrolyze back to the amine than are carboxamides. In peptide synthesis (Section 25-7C) the commonly used sulfonyl protecting groups are 4-methylbenzenesulfonyl or 4-bromobenzenesulfonyl groups. These groups can be removed as necessary from the sulfonamide by reduction with sodium metal in liquid ammonia:



[6]This abbreviation is approved by the IUPAC-UIB Commission on Biochemical Nomenclature and is typical of the kind of "alphabet soup" that is making biochemistry almost completely unintelligible without a glossary of approved (and unapproved) abbreviations at hand at all times. We shall make minimum use of such designations. You will remember we already use Z for something else (Section 19-7).

23.13.5: Contributors and Attributions

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23.14: Carcinogenic Nitrogen Compounds

23.14.1: Amines

Everyone who works with organic chemicals should be aware that a number of arenamines are carcinogens. The most dangerous examples (see Figure 23-8) are known to induce human bladder cancer. These chemicals were used widely in the chemical industry (mostly in azo dye manufacture) long before they were recognized as hazardous carcinogens. Voluntary action and appropriate legislation now controls the industrial uses of these substances, and there also are some controls for uses in research and teaching. It is important to be aware of the potential hazards of known carcinogens and to recognize that *all* chemicals, both organic and inorganic, should be treated with great respect if their thermodynamic and physiological properties are not known. Carcinogenic character is just one of many possible hazards.

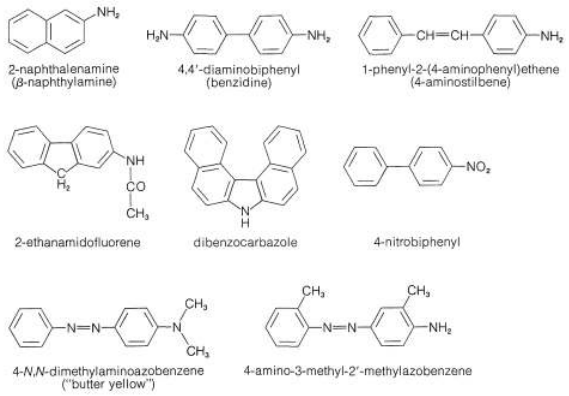


Figure 23-8: Some carcinogenic aromatic nitrogen compounds.

23.14.2: Azo Compounds

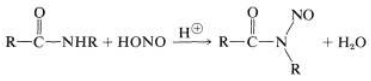
Other nitrogen compounds besides amines are known to be carcinogenic. For example, certain azo dyes (see Figure 23-8) have been found to produce tumors in animals. This fact has caused concern for human health because, as we indicated in Section 23-10C, azo dyes are coloring agents that are used in many products. They certainly are not all carcinogenic, but the structural requirements for a compound to show this property may change completely the toxic properties of a chemical. For example, the N, N-diethylamino analog of "butter yellow" (Figure 23-8) is apparently hazardous.

23.14.3: N-Nitroso Compounds

We have seen that N-nitroso compounds are formed from secondary amines and nitrous acid:

$$R_2NH + HONO \xrightarrow{H^{\oplus}} R_2N{-}NO + H_2O \qquad (23.14.1)$$

N-nitroso compounds also can be formed from carboxamides and nitrous acid:



Some of these nitrosoamines and nitrosoamides are known to be potent carcinogens for some animals, which is reason to suspect they also may be carcinogenic for humans. However, it is clear that there may be very marked differences in carcinogenic properties of a given compound for different animal species.

Why some of these substances have carcinogenic activity is a matter of chemical interest. Recall from Section 23-10 that nitrosation of amines usually leads to cleavage of a C–N bond in the sense C:: N. The carbon fragment ultimately is transferred to some nucleophilic atom. In effect, this means that nitrosamines can function as *alkylating agents* and, in a biological system, the functions that probably would be alkylated are the nucleophilic sites along the polymeric protein or nucleic acid chains. It is not difficult to appreciate that alkylation of these substances may well disrupt the pattern of normal cell growth.

There is an unresolved problem related to the carcinogenic properties of nitroso compounds. You probably are aware (if you read the labels on food packages) that sodium nitrite is added to many packaged meat products. Sodium nitrite prevents the growth of harmful bacteria, thereby retarding spoilage, and it also enhances the appearance by maintaining the red look of fresh meat. There is a possibility that nitrite may have adverse effects on human health by nitrosating the amino and amide functions of proteins in the presence of acids. This possibility has to be balanced against the alternative threat to human health if the use of nitrite were discontinued, that of increased food spoilage. In any case, it seems clear that the amount of sodium nitrite actually used in most processing is in excess of that needed to retard bacterial decay.

There are many other chemicals that are active alkylating agents besides nitrosamines, and some are unquestionably carcinogenic (see Figure 23-9), whereas others apparently are not. In fact, it is a paradox that some of the most useful synthetic drugs in treating certain forms of cancer are alkylating agents. Several of these are shown in Figure 23-10. They all have two or more active centers in the molecule that enable them to form cross-links between protein or nucleic acid molecules.

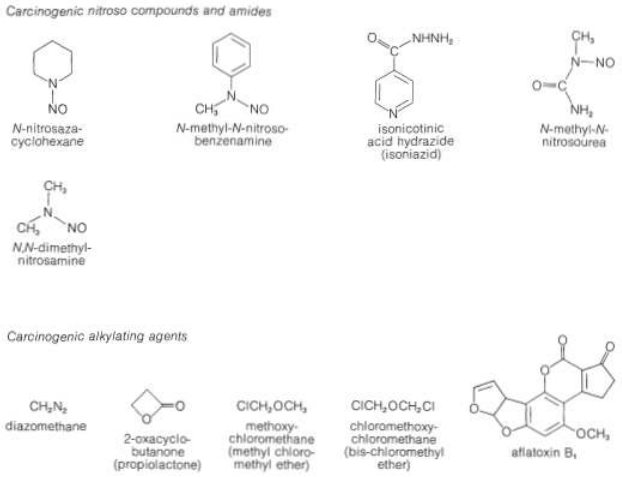


Figure 23-9: Chemical carcinogens (not all of these have been established as carcinogenic for humans).

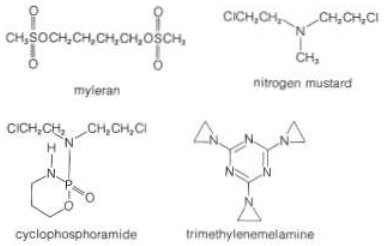


Figure 23-10: Some illustrative antitumor agents (biological alkylating agents).

It should be recognized that not all of the carcinogenic substances loosed on mankind are the result of modern technology. The most potent carcinogens known, which are lethal in test animals at levels of a few parts per billion, are mold metabolites called **aflatoxins**. These substances are complex non-nitrogenous, heterocyclic oxygen compounds, which often are formed by molds growing on cereal grains, peanuts, and so on. (See Figure 23-9)

23.14.4: Contributors and Attributions

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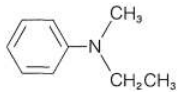
23.E: Organonitrogen Compounds I- Amines (Exercises)

Exercise 23-1 Name the following substances by an accepted system (Section 7-8):

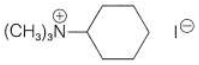
a. $(CH_3)_2N-CH=CH_2$

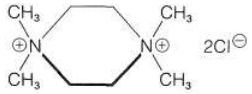
b. 

c. $H_2NCH_2CO_2H$

d. $H_2NCH_2CH_2CH_2CH_2NH_2$

e.

f. 

g. 

Exercise 23-2 How could one show with certainty that the peak at 47 Hz with reference to TMS in the NMR spectrum of N-ethylethanamine (Figure 23-5) is due to the $N-H$ resonance?

Exercise 23-3 Show how structures can be deduced for the isomeric substances of molecular formula $C_8H_{11}N$, whose NMR and infrared spectra are shown in Figure 23-6.

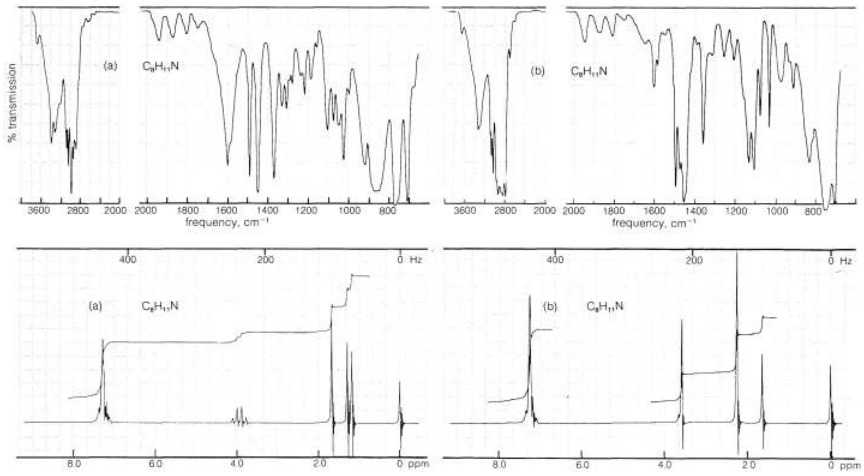


Figure 23-6: *Infrared and NMR spectra of two isomeric compounds, (a) and (b), of formula* $C_8H_{11}N$. *The NMR spectra are at* 60 MHz *relative to TMS. See Exercise 23-3.*

Exercise 23-4 The highest mass peak in the mass spectrum of a certain compound is m/e 73. The most abundant peak has m/e 58. Suggest a structure for the compound and explain how it could form an ion of m/e 58.

Exercise 23-5 Prominent peaks in the mass spectrum of a basic nitrogen compound have m/e values of 87, 72, 57, and 30. The NMR spectrum shows only three proton resonances, having intensity ratios of 9:2:2 at 0.9, 1.3, and 2.3 ppm. Assign a structure to the compound and account for the fragment ions m/e 72, 57, and 30.

Exercise 23-6* Explain why the configuration of the nitrogen in 1-ethylazacyclopropane, 1, is more stable than in triethylamine. Why is the configuration of oxazacyclopropanes, such as 2, exceptionally stable? (Consider the π molecular orbitals of an ethene bond, Figure 21-3, as a model for orbitals of the *adjacent* O and N atoms in the planar transition state for inversion in 2.)

Figure 23-7 The proton NMR spectrum of 1,2,2-trimethylazacyclopropane, 3 at room temperature is shown in Figure 23-7. When the material is heated to 110°, the two lines at 63 Hz and 70 Hz are found to have coalesced to a single line. At the same time, the lines at 50 Hz and 92 Hz coalesce to a single line. When the sample is cooled the spectrum changes back to that of Figure 23-7. Account for all the NMR lines of 3 and explain the effect of temperature on the spectrum. Review Section 9-10C.[3]

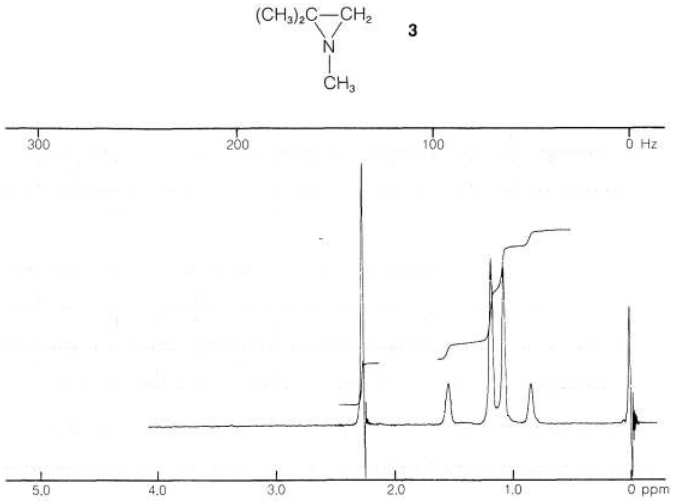


***Figure 23-7:** Proton NMR spectrum of 1,2,2-trimethylazacyclopropane at 60 MHz relative to TMS at 0.0 ppm. See Exercise 23-7.*

Exercise 23-8* The ^{19}F spectrum of 4,4-difluoroazacyclohexane in acetone solution at 25° is a sharp, narrowly spaced 1:4:6:4:1 quintet; at −60° it is a broad quartet with a chemical-shift difference of 960 Hz and J of 235 Hz, and at −90° it is a pair of overlapping quartets with chemical-shift differences and relative intensities of 1050 Hz (75%) and 700 Hz (25%), both with J of 235 Hz. Account for these changes in the ^{19}F spectra with temperature. Review Section 9-10C.[3]

Exercise 23-9 Account for the following observations:

a. The proton NMR spectrum of trimethylamine in nitromethane-D_3 (CD_3NO_2) shows a single resonance near 2.7 ppm. On adding an equivalent of fluoroboric acid, HBF_4, the singlet at 2.7 ppm is replaced by a doublet at 3.5 ppm

b. On adding trace amounts of trimethylamine to the solution described in Part a, the double at 3.5 ppm collapses to a singlet centered at 3.5 ppm. As more trimethylamine is added, the singlet resonance moves progressively upfield.

Exercise 23-10 Decide which member in each of the following pairs of compounds is the stronger base. Give your reasoning.

a. $CH_3CH_2NH_2$ or $(CH_3CH_2)_3N$
b. $(CH_2)_5NH$ or $(CH_2)_2NH$
c. $CF_3CH_2CH_2NH_2$ or $CH_3CH_2CH_2NH_2$
d. $(CH_3)_3\overset{\oplus}{N}CH_2CH_2NH_2$ or $\overset{\ominus}{O}_2CCH_2CH_2NH_2$

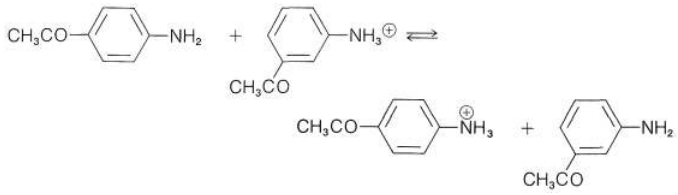
Exercise 23-11 Draw atomic-orbital models for benzenamine and its conjugate acid and describe the features of these models that account for the low base strength of benzenamine relative to saturated amines.

Exercise 23-12 Amidines, $R-C(NH_2)=NH$, are stronger bases than saturated amines. Explain why this should be so, paying special attention to which nitrogen the proton adds to.

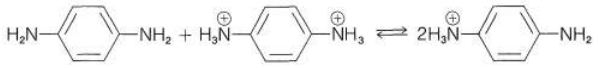
Exercise 23-13 3-Nitrobenzenamine is less than 1/100 as strong a base as benzenamine, but is 23 times stronger than 4-nitrobenzenamine. Remembering that the inductive effect falls of rapidly with the number of intervening bonds, why should 3-nitrobenzenamine be a much weaker base than benzenamine itself, but substantially stronger than 4-nitrobenzenamine?

Exercise 23-14 Indicate whether the following equilibria would have K greater, or less, than unity. This is equivalent to asking which amine is the stronger base. Give a reason for your answer.

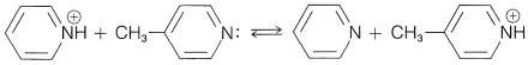
a.



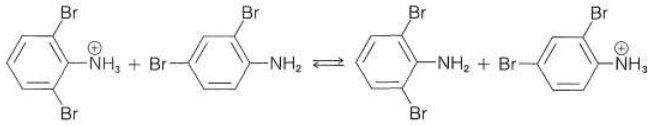
b.



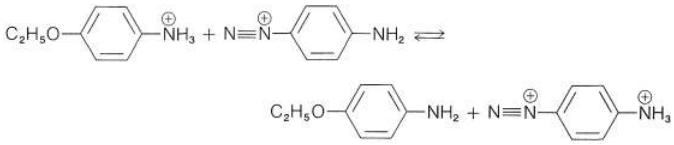
c.



d.

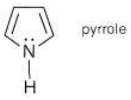


e.

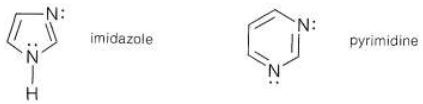


Exercise 23-15 Offer plausible explanations of the following facts:

a. Aza-2,4-cyclopentadiene (pyrrole) is unstable in acid solution and polymerizes. (Consider the effect of adding a proton to this molecule at the nitrogen and at carbon.)



b. 1,3-Diaza-2,4-cyclopentadiene (imidazole) is a much stronger base than 1,3-diazabenzene (pyrimidine).



c. The triaminomethyl cation, $(NH_2)_3\overset{\oplus}{C}$, is an exceptionally weak acid.

Exercise 23-16 The pK_a of the conjugate acid of caffeine (Figure 23-1) is 10.61. Calculate the K_b of caffeine. Write structures for the possible conjugate acids of caffeine in which the added proton is attached to one or the other of the nitrogens of the five-membered ring. Use the resonance method to determine which of these two nitrogens will be the preferred protonation site of caffeine. Give your reasoning.

Exercise 23-17* 2-Amino-1,3-diazabenzene (2-aminopyrimidine) undergoes N-methylation with methyl iodide to give two isomeric products, A and B, of formula $C_5H_7N_3$ (Section 23-9D). At high pH, the major methylation product is A, which is a weakly basic compound with pK_a = 3.82. N-Methylation in neutral conditions produces the more strongly basic compound B with pK_a = 10.75. Draw structures for the two isomers, A and B, and explain why A is a weak base and B is a much stronger base. Why is A the predominant product under basic conditions? Give your reasoning.

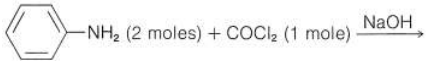
Exercise 23-18* The conjugate acid of N,N-dimethylbenzenamine has pK_a = 5.06, whereas the conjugate acid of diphenyldiazene (azobenzene, $C_6H_5N{=}NC_6H_5$) has pK_a = -2.5. Yet for many years there was considerable controversy about where a proton adds to 4-$(CH_3)_2N{-}C_6H_4N{=}NC_6H_5$. Why is it not an open-and-shut case that a proton would add most favorably to the $(CH_3)_2N-$ nitrogen? Which of the two $-N{=}N-$ nitrogens would you expect to be the more basic? Give your reasoning. (Consider the effect of the $-N{=}N-$ group on the basicity of the $(CH_3)_2N-$ nitrogen and also the effect of the $(CH_3)_2N-$ group on the basicity of each of the $-N{=}N-$ nitrogens.)

Exercise 23-19

a. Explain why 1,3-diazacyclopentadiene (imidazole) is a much stronger *acid* than azacyclopentadiene (pyrrole).

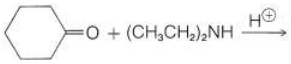
b. Would you expect benzenamine to be a stronger or weaker *acid* than cyclohexanamine? Give your reasoning.

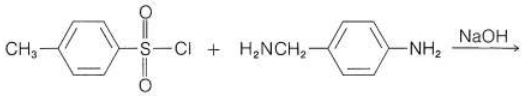
Exercise 23-20 Show the products you would expect to be obtained in each of the following reactions:

a. 

b. $H_2N(CH_2)_4NH_2$ (1 mole) $+C_6H_5SO_2Cl$ (2 moles) $\xrightarrow{NaOH}$

c. $CH_3CH_2CHO + CH_3CH_2NH_2 \xrightarrow{H^{\oplus}}$

d. 

e. 

Exercise 23-21 2,4-Pentanedione reacts with methanamine to give a product of composition $C_6H_{11}NO$ that is an equilibrium mixture of three isomers. The NMR spectrum of the mixture indicates that all three have strong hydrogen bonding. Draw the structures of the three isomers and indicate the nature of the hydrogen bonding.

Exercise 23-22 Write a structural formula (one for each part) that fits the following descriptions. (These descriptions can apply to more than one structural formula.)

a. A liquid basic nitrogen compound of formula C_3H_7N with $C_6H_5SO_2Cl$ and excess $NaOH$ solution gives a clear solution. This solution when acidified gives a solid product of formula $C_9H_{11}O_2NS$.

b. A liquid diamine of formula $C_5H_{14}N_2$ with $C_6H_5SO_2Cl$ and $NaOH$ gives an insoluble solid. This solid dissolves when the mixture is acidified with dilute hydrochloric acid.

Exercise 23-23 Show how the following compounds may be prepared from ammonia and the given starting materials:

a. 1,2-ethanediamine from ethene
b. 2-aminoethanol from ethene
c. benzenamine from chlorobenzene

Exercise 23-24 Show how a mixture of amines prepared from 1-bromobutane and an excess of butanamine may be resolved into its components by reaction with the anhydride of 1,4-butanedioic acid, $(CH_2)_2(CO)_2O$, separation of the products through advantage of their solubility properties in acid or base, and regeneration of the corresponding amines (Section 18-10C). Write equations for the reactions involved.

Exercise 23-25* Assess the possibility of O-alkylation in the reaction of $CH_2{=}CH{-}CH_2Br$ with $C_6H_5SO_2NH^{\ominus}Na^{\oplus}$. Give your reasoning.

Exercise 23-26 The tertiary amine, $C_6H_5CH_2N(CH_3)_2$, reacts with nitrous acid to give benzenecarbaldehyde and N-nitroso-N-methylmethanamine (N-nitrosodimethylamine):

$$2_6CH_5CH_2N(CH_3)_2 + 4HONO \rightarrow 2_6CH_5CHO + 2(CH_3)_2N{-}NO + 3H_2O + N_2O \qquad (23.E.1)$$

A possible reaction sequence that explains the formation of benzenecarbaldehyde involves nitrosation, *E*2 elimination, hydrolysis, and finally nitrosation. Write each of the steps involved in this sequence. Formation of N_2O appears to take place by dimerization of the hypothetical substance HNO $(2HNO \rightarrow N_2O + H_2O)$.

Exercise 23-27

a. Write two valence-bond structures for N-nitroso-N-methylmethanamine and show how these structures explain the fact that the N-nitrosamine is a much weaker base than N-methylmethanamine.

b. N-Nitroso-N-methylmethanamine shows two separate methyl resonances in its proton NMR spectrum. These collapse to a single resonance when the material is heated to 190° and reappear on cooling. Studies of the changes in the line shapes with temperature show that the process involved has an energy barrier of about $23\ \text{kcal mol}^{-1}$. Explain why there should be separate methyl peaks in the NMR and why they should coalesce on heating. (Review Section 9-10C. You also may wish to read Section 27-2.)

Exercise 23-28

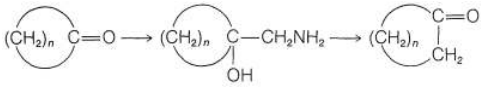
a. When ethyl aminoethanoate $(H_2NCH_2CO_2C_2H_5)$ is treated with nitrous acid in the presence of a layer of diethyl ether, a yellow compound known as ethyl diazoethanoate $(N_2CHCO_2C_2H_5)$ is extracted into the ethyl layer. What is the probable structure of this compound and what is the mechanism by which it is formed?

b. Would you expect the same type of reaction sequence to occur with ethyl 3-aminopropanoate? Explain.

Exercise 23-29 Predict the products expected from the reactions of the following amines with nitrous acid (prepared from $NaNO_2 + HCl$ in aqueous solution):

a. 2-methylpropanamine
b. azacyclopentane
c. 2-butenamine
d. 3-amino-2,3-dimethyl-2-butanol

Exercise 23-30 The following sequence is very useful for expanding the ring size of a cyclic ketone:



List reagents, conditions, and the important intermediates for the sequence, noting that several individual synthetic steps may be required. (Refer to Table 23-6 for amine synthesis.)

Exercise 23-31* The reaction of nitrous acid with 3-butenamine, $CH_2{=}CHCH_2CH_2NH_2$, has been found to give the following mixture of alcohols: 3-buten-1-ol (45%), 3-buten-2-ol (21%), 2-buten-1-ol (7%), cyclobutanol (12%), and cyclopropylmethanol (15%). Show how each of these products may be formed from the 3-butenyl cation.

Exercise 23-32* How could one determine experimentally how much of the propene formed in the reaction of propanamine with nitrous acid arises from the propyl cation and how much from the isopropyl cation?

Exercise 23-33 Benzenediazonium chloride solvolyzes in water to give a mixture of benzenol and chlorobenzene. Some of the facts known about this and related reactions are

1. The ratio C_6H_5Cl/C_6H_5OH increases markedly with $Cl^{\ominus}$ concentration but the rate hardly changes at all.

2. There is no rearrangement observed with 4-substituted benzenediazonium ions, and when the solvolysis is carried out in D_2O, instead of H_2O, no C—D bonds are formed to the benzene ring.

3. 4-Methoxybenzenediazonium chloride solvolyzes about 30 times faster than 4-nitrobenzenediazonium chloride.

4. Benzenediazonium salts solvolyze in $98\%\ H_2SO_4$ at almost the same rate as in $80\%\ H_2SO_4$ and, in these solutions, the effective H_2O concentration differs by a factor of 1000.

Show how these observations support an S_N1 reaction of benzenediazonium chloride, and can be used to argue against a benzyne-type elimination-addition reaction with water acting as the $E2$ base (Section 14-6C) or an S_N2 reaction with water as the nucleophile (Section 8-4, Mechanism B, and Section 14-6).

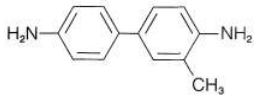
Exercise 23-34 Indicate how you could prepare each of the following compounds, starting with benzene. One of the steps in each synthesis should involve formation of a diazonium salt. (Review Sections 22-4 and 22-5 if necessary.)

a. monodeuteriobenzene
b. 2-cyano-1-isopropylbenzene
c. 4-*tert*-butylbenzenol
d. 3-hydroxyphenylethanone
e. 3-chloronitrobenzene
f. 3-iodobenzenecarboxylic acid
g. 4-chlorophenyl azide
h. 4-methylphenylhydrazine
i. 2-amino-4'-methylazobenzene
j. 2-chloro-1-phenylpropane

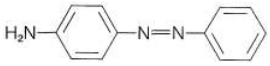
Exercise 23-35* Some of the rearrangements of arenamines, ArNHY, to $\mathrm{Y{-}Ar{-}NH_2}$ shown in Section 23-10D proceed by an intermolecular mechanism involving acid-catalyzed cleavage of the $\mathrm{N{-}Y}$ bond followed by a normal electrophilic substitution of the aromatic ring. Show the steps in this mechanism for $\mathrm{Y = NO}$ and Cl.

Exercise 23-36* Treatment of a mixture of 2,2'-dimethylhydrazobenzene and hydrazobenzene with acid gives *only* 4,4'-diaminobiphenyl and 4,4'-diamino-2,2'-dimethylbiphenyl. What does this tell you about the mechanism of this type of rearrangement? Write a mechanism for the rearrangement of hydrazobenzene that is in accord with the acid catalysis (the rate depends on the *square* of the $\mathrm{H^{\oplus}}$ concentration) and the lack of mixing of groups as described above.

Exercise 23-37* Show how the following substances could be prepared by a suitable ArNRY-type rearrangement.

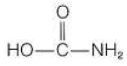
a. 

b. 4-amino-3-methylbenzenol

c. 

d. N-methyl-1,4-benzenediamine

Exercise 23-38 What is the oxidation state of each nitrogen in each of the following substances?

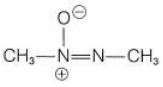
a. 

b. $\mathrm{F_2N{-}NF_2}$

c. $\mathrm{(CH_3)_2C{=}NOH}$

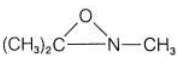
d. $\mathrm{CH_3N_2^+Cl^-}$

e. $\mathrm{CH_3N{=}C{:}}$

f. 

g. $\mathrm{CH_3{-}N{=}\overset{\oplus}{N}{=}\overset{\ominus}{N}}$

h. $\mathrm{CH_3NCl_2}$

i. 

j.

Exercise 23-39 Show how one could synthesize and resolve the oxide from N-ethyl-N-methyl-2-propenamine with the knowledge that amine oxides are somewhat basic substances having K_b values of about 10^{-11} $(K_a \sim 10^{-3})$.

Exercise 23-40 Show how the following transformations may be achieved. List reagents and approximate reaction conditions.

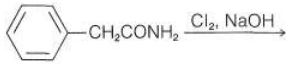
a. 3-bromopropene to 3-butenamine
b. cyclohexanone to cyclohexamine
c. benzenecarboxylic acid to phenylmethanamine (not N-phenylmethanamine)
d. benzenecarbaldehyde to N-methylphenylmethanamine $(C_6H_5CH_2NHCH_3)$

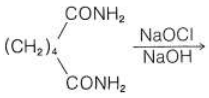
Exercise 23-41 The point of this exercise is to show that reactions of known stereospecificity can be used to establish configuration at chiral centers.

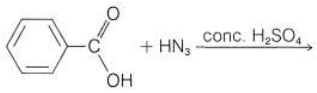
A carboxylic acid of $(+)$ optical rotation was converted to an amide by way of the acyl chloride. The amide in turn was converted to a primary amine of one less carbon atom than the starting carboxylic acid. The primary amine was identified as 2-*S*-aminobutane. What was the structure and configuration of the $(+)$-carboxylic acid? Indicate the reagents you would need to carry out each step in the overall sequence $RCO_2H \rightarrow RCOCl \rightarrow RCONH_2 \rightarrow RNH_2$.

Exercise 23-42 Draw the structures of the products expected to be formed in the following reactions:

a. $(CH_3)_2CHCH_2CONH_2 \xrightarrow[NaOH]{Br_2}$

b. 

c. 

d. 

Exercise 23-43 Cleavage of C–N bonds by catalytic hydrogenation is achieved much more readily with diphenylmethanamine or triphenylmethanamine than with alkanamines. Explain why this should be so on the basis that the cleavage is a *homolytic* reaction.

Exercise 23-44 Write the steps involved in (a) the formation of triphenylmethanamine from triphenylmethyl chloride in *aqueous* ammonia containing sodium hydroxide and (b) the hydrolysis of triphenylmethanamine in aqueous ethanoic acid. (This is an unusually facile heterolytic cleavage of a saturated C–N bonds.)

Exercise 23-45 Explain why the nitration of benzenamine to give 2- and 4-nitrobenzenamines is unsatisfactory with nitric acid-sulfuric acid mixtures. Show how this synthesis could be achieved by suitably modifying the amine function.

Exercise 23-46 Suggest protecting groups and reaction sequences whereby the following transformations could be achieved:

a. 3-amino-1-propanol to 3-aminopropanoic acid
b. 4-(2-aminoethyl)benzenamine to 2-(4-nitrophenyl)ethanamine

Exercise 23-47 Write equations for a practical laboratory synthesis of each of the following compounds from the indicated starting materials. Give reagents and conditions.

a. $(CH_3)_3CCH_2NH$ from $(CH_3)_3CCO_2H$
b. 1,6-hexanediamine from butadiene

Exercise 23-48 Write a structure of at least one substance that fits each of the following descriptions. (Different structures may be written for each part.)

a. a water-insoluble, acid-soluble nitrogen compound that gives no nitrogen gas with nitrous acid
b. a compound that gives off water on heating to 200°
c. a chiral ester that hydrolyzes to give only achiral compounds

Exercise 23-49 Compound A is chiral and is a liquid with the formula $C_5H_{11}O_2N$. A is insoluble in water and dilute acid but dissolves in sodium hydroxide solution. Acidification of a sodium hydroxide solution of chiral A gives *racemic* A. Reduction of chiral A with hydrogen over nickel produces chiral compound B of formula $C_5H_{13}N$. Treatment of chiral B with nitrous acid gives a

mixture containing some chiral alcohol C and some 2-methyl-2-butanol. Write structures for compounds A, B, and C that agree with all the given facts. Write balanced equations for all the reactions involved. Show your reasoning.

In this type of problem, one should work backward from the structures of the final products, analyzing each reaction for the structural information it gives. The key questions to be inferred in the preceding problem are (a) What kind of chiral compound or compounds could give 2-methyl-2-butanol and a chiral alcohol with nitrous acid? (b) What kinds of compounds could give B on reduction? (c) What does the solubility behavior of A indicate about the type of compound that it is? (d) Why does chiral A racemize when dissolved in alkali?

Exercise 23-50 Arrange the following pairs of substances in order of expected base strengths. Show your reasoning.

a. N,N-dimethylmethanamine and trifluoro-N,N-bis(trifluoromethyl)methanamine
b. phenylmethanamine and 4-methylbenzenamine
c. ethanenitrile and azabenzene
d. methamidine $[HC(=NH)NH_2]$ and methanamide (review Exercise 23-12)
e. N-methylazacyclopropane and N-methylazacyclopentane (review Section 11-8B)

Exercise 23-51 What reagents and conditions would you use to prepare 2-methylpropanamine by the following reactions:

a. Hofmann rearrangement
b. Schmidt rearrangement
c. Curtius rearrangement
d. Gabriel synthesis
e. lithium aluminum hydride reaction

Exercise 23-52 Write structural formulas for substances (one for each part) that fit the following descriptions:

a. an aromatic amine that is a stronger base than benzenamine
b. a substituted phenol that would not be expected to couple with benzenediazonium chloride in acid, alkaline, or neutral solution
c. a substituted benzenediazonium chloride that would be a more active coupling agent than benzenediazonium chloride itself
d. methyl *Z*-benzenediazoate
e. the important resonance structures of the ammonium salt of N-nitroso-N-phenylhydroxylamine (Cupferron)

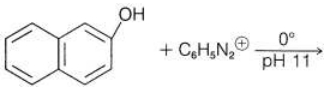
Exercise 23-53 Diazotization of 4-chlorobenzenamine with sodium nitrite and hydrobromic acid yields a diazonium salt solution that couples with N,N-dimethylbenzenamine to give substantial amounts of 4-dimethylamino-4'-bromoazobenzene. Explain.

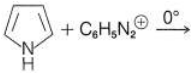
Exercise 23-54* Hypophophorous acid, H_3PO_2, in the presence of copper reduces aryldiazonium salts to arenes (Table 23-4) by a radical-chain mechanism with formation of H_3PO_3. Cupric copper, Cu(II), initiates the chain by reducing H_3PO_2 to $H_2\dot{P}O_2$. Write a chain mechanism for reduction of ArN_2^+ to ArH that involves $H_2\dot{P}O_2$ in the chain-propagating steps.

Exercise 23-55 Give the principal product(s) to be expected from the following reactions:

a. $C_6H_5N_2^+Cl^- + C_6H_5NHCH_3 \xrightarrow[0^\circ]{\text{pH 7}}$

b. $p\text{-}CH_3C_6H_4NHNHC_6H_5 \xrightarrow{H_2SO_4}$

c. 

d. 

Exercise 23-56 Explain why triphenylamine is a much weaker base than benzenamine and why its electronic absorption spectrum is shifted to longer wavelengths compared with the spectrum of benzenamine. Would you expect N-phenylcarbazole to be a stronger, or weaker, base than triphenylamine? Explain.

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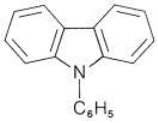

N-phenylcarbazole

[3]You also may wish to read ahead in Section 27-2.

23.E.1: Contributors

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CHAPTER OVERVIEW

24: Organonitrogen Compounds II - Amides, Nitriles, and Nitro Compounds

The properties of the simple amides are relevant to the chemistry of peptides and proteins, substances that are fundamental to all life as we know it. Indeed, the characteristics of peptides and proteins are primarily due to their polyamide structures. For this reason, it is important to know and understand the chemistry of simple amides.

24.1: Structural, Physical, and Spectral Characteristics of Amides

24.2: Amides as Acids and Bases

24.3: Synthesis of Amides

24.4: Hydrolysis of Amides

24.5: Nitriles

24.6: Nitro Compounds

24.7: Some Compounds with N-N Bonds

24.E: Organonitrogen Compounds II- Amides, Nitriles, and Nitro Compounds (Exercises)

24.1: Contributors and Attributions

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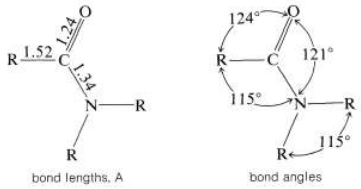
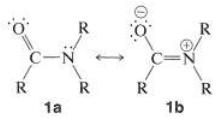
24.1: Structural, Physical, and Spectral Characteristics of Amides

24.1.1: Molecular Structure

The structural parameters of the amide group have been determined carefully and the following diagram gives a reasonable idea of the molecular dimensions:

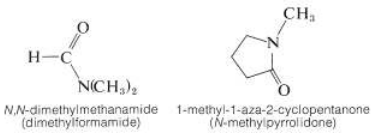


An important feature of the group is that it is *planar* - the carbon, oxygen, nitrogen, and the first atom of each of the R groups on carbon and nitrogen lie in the same plane. The C–N bond distance of 1.34 Å is intermediate between the typical single bond C–N distance of 1.47 Å and the double bond C=N distance of 1.24 Å. This and other evidence indicates that the amide group is a hybrid structure of the valence-bond forms 1*a* and 1*b*, with stabilization energy of about 18 kcal mol^{-1}:

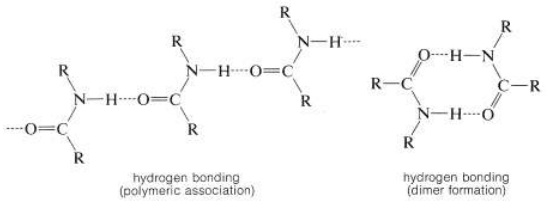


Coplanarity is required if the dipolar structure 1*b* is to be significant. An appreciable dipole moment may be expected of amides and, in fact, simple amides have dipole moments in the range 3.7-3.8 debye. (For reference, the carbonyl group has a moment of about 2.7 debye, Section 16-1B.)

As a consequence of the polarity of the amide group, the lower-molecular-weight amides are relatively high-melting and water-soluble, as compared to esters, amines, alcohols, and the like. The few that are liquids, such as N,N-dimethylmethanamide and 1-methyl-1-aza-2-cyclopentanone, have excellent solvent properties for both polar and nonpolar substances. Therefore they are good solvents for displacement reactions of the S_N type (Table 8-5).

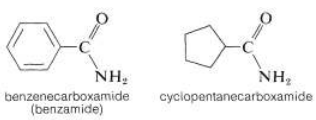


Another very important consequence of amide structure is the extensive molecular association of amides through hydrogen bonding. The relatively negative oxygens act as the hydrogen acceptors while N–H hydrogens serve as the hydrogen donors:

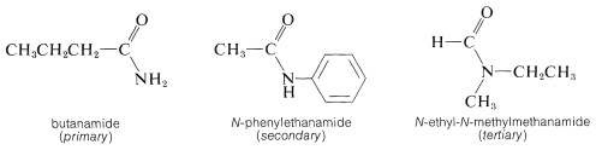


24.1.2: Nomenclature

The naming of amides is summarized in Section 7-7D. The points to remember are that they generally are named either as (i) *alkanamides*, in which the prefix *alkan(e)* is determined by the longest carbon chain that *includes* the carbonyl group ($HCONH_2$ is methanamide), or as (ii) substituted *carboxamides*, $RCONH_2$, in which the name is completed by identifying the R substituent:



The degree of substitution on the amide nitrogen determines whether the amide is *primary*, $\mathrm{RCONH_2}$, *secondary*, RCONHR, or *tertiary*, $\mathrm{RCONR_2}$. When the amide is secondary or tertiary, the symbol N (for nitrogen) must precede the name of *each* different group attached to nitrogen:



24.1.3: Infrared Spectra

Considerable information is available on the infrared spectra of amides. By way of example, the spectra of three typical amides with different degrees of substitution on nitrogen are shown in Figure 24-1.

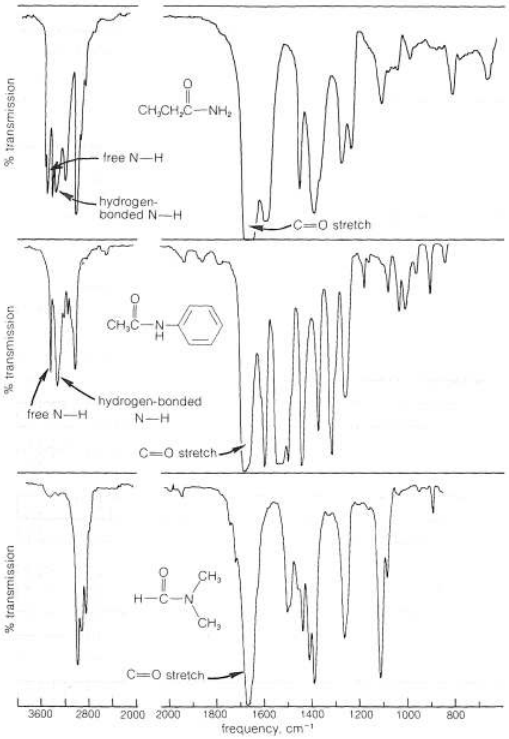
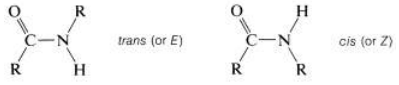
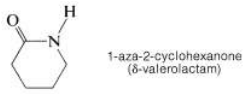


Figure 24-1: Infrared spectra of propanamide, N-phenylethanamide, and N,N-dimethylmethanamide in chloroform solution. Notice the appearance of both free NH bands (sharp, 3300-3500 $\mathrm{cm^{-1}}$) and hydrogen-bonded NH bands (broad, 3100-3300 $\mathrm{cm^{-1}}$) for primary and secondary amides.

A strong carbonyl absorption is evident in the spectra of all amides, although the frequency of absorption varies somewhat with the structure of the amide. Thus primary amides generally absorb near 1680 $\mathrm{cm^{-1}}$, whereas secondary and tertiary amides absorb at slightly lower frequencies. The $\mathrm{N-H}$ stretching frequencies of amides are closely similar to those of amines and show shifts of 100 $\mathrm{cm^{-1}}$ to 200 $\mathrm{cm^{-1}}$ to lower frequencies as the result of hydrogen bonding. Primary amides have two $\mathrm{N-H}$ bands of medium intensity near 3500 $\mathrm{cm^{-1}}$ and 3400 $\mathrm{cm^{-1}}$, whereas secondary amides, to a first approximation, have only one $\mathrm{N-H}$ band near 3440 $\mathrm{cm^{-1}}$. However, a closer look reveals that the number, position, and intensity of the $\mathrm{N-H}$ bands of monosubstituted amides depend on the conformation of the amide, which can be either *cis* or *trans*:



Normally, the trans configuration is more stable than the cis conformation for primary amides. However, for cyclic amides (lactams), in which the ring size is small, the configuration is exclusively cis:



24.1.4: NMR Spectra

The proton NMR resonances of the N–H protons of amides are different from any we have discussed so far. Generally, these will appear at room temperature as a broad singlet absorption, which may turn into a broad triplet at higher temperatures. A typical example is propanamide (Figure 24-2).

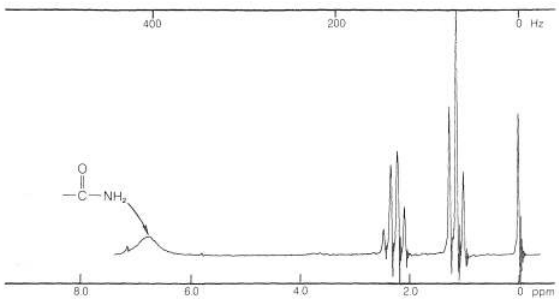


Figure 24-2: Proton NMR spectrum of propanamide, $CH_3CH_2CONH_2$, in chloroform solution (solvent not shown) at 60 MHz relative to TMS at 0.0 ppm.

The broad N–H proton resonance is due to the special nuclear properties of ^{14}N, the predominant natural isotope of nitrogen. This is established beyond question by observation of the proton spectrum of an amide in which the ^{14}N is replaced by the ^{15}N isotope to give $RCO^{15}NH_2$. In this case the proton lines are sharp. The details of the phenomena that lead to the broad resonances of the N–H protons in amides are discussed elsewhere;[1] for our purposes it should suffice to note that the ^{14}N nucleus has much shorter lifetimes for its magnetic states than do protons, and the broad lines result from uncertainties in the lifetimes of the states associated with ^{14}N–H spin-spin coupling (Section 27-1). One should be prepared for absorptions of this character in amides and some other substances with N–H bonds that are not involved in rapid intermolecular proton exchanges, which, when sufficiently rapid, have the effect of averaging the magnetic effects of the ^{14}N atoms to zero:

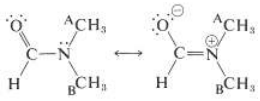
$$R'NH_2 + R\overset{\oplus}{N}H_3 \rightleftharpoons R'\overset{\oplus}{N}H_3 + RNH_2 \tag{24.1.1}$$

or

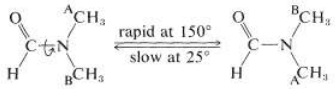
$$R'NH_2 + R\overset{\ominus}{N}H \rightleftharpoons R'\overset{\ominus}{N}H + RNH_2 \tag{24.1.2}$$

The situation here is analogous to that discussed for the splitting of the resonances of O–H protons of alcohols by protons on the α carbons (see Section 9-10I).

The NMR spectra of amides are revealing as to the structure of the amide group. For example, the spectrum of N,N-dimethylmethanamide shows *two* three-proton single resonances at 2.78 ppm and 2.95 ppm, which means that at ordinary temperatures the two methyl groups on nitrogen are not in the same molecular environment:



This is a consequence of the double-bond character of the C–N bond expected from valence-bond structures 1a and 1b, which leads to restricted rotation about this linkage. One of the methyl groups (A) has a different stereochemical relationship to the carbonyl group than the other methyl group (B). Groups A and B therefore will have different chemical shifts, provided that rotation about the C–N bond is slow. However, at 150° the two three-proton lines are found to coalesce to a single six-proton line, which means that at this temperature bond rotation is rapid enough to make the methyl groups essentially indistinguishable (see Section 9-10C):



Most amides do not rotate freely about the $\mathrm{C{-}N}$ bond. The barrier to this kind of rotation is about $19\ \mathrm{kcal\ mol^{-1}}$, which is high enough for the nonequivalence of groups on nitrogen to be observable by spectral techniques, but not quite high enough to allow for actual physical separation of stable E, Z configurational isomers.

[1]J. D. Roberts, *Nuclear Magnetic Resonance, Applications to Organic Chemistry*, McGraw-Hill Book Co., New York, 1959, Chapter 5. Also see the NMR references at the end of Chapter 9 in this book.

24.1.5: Contributors and Attributions

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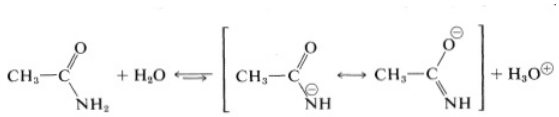
24.2: Amides as Acids and Bases

24.2.1: Acidity

Amides with N—H bonds are weakly acidic, the usual K_a being about 10^{-16}:

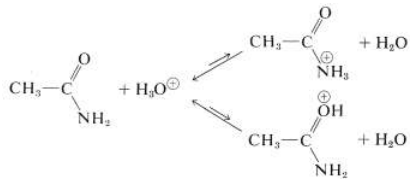


Nonetheless, amides clearly are far more acidic than ammonia $(K_a \sim 10^{-33})$, and this difference reflects a substantial degree of stabilization of the amide anion. However, amides still are very weak acids (about as weak as water) and, for practical purposes, are regarded as neutral compounds.

Where there are *two* carbonyl groups to stabilize the amide anion, as in the 1,2-benzenedicarboximide (phthalimide) anion (Section 18-10C), the acidity increases markedly and imides can be converted to their conjugate bases with concentrated aqueous hydroxide ion. We have seen how imide salts can be used for the synthesis of primary amines. (**Gabriel synthesis**, Section 23-9D and Table 23-6).

24.2.2: Basicity

The degree of basicity of amides is very much less than that of aliphatic amines. For ethanamide, K_b is about 10^{-15} (K_a of the conjugate acid is ~ 10):



The proton can become attached either to nitrogen or to oxygen, and the choice between the assignments is not an easy one. Of course, nitrogen is intrinsically more basic than oxygen; but formation of the N-conjugate acid would cause loss of all the amide stabilization energy. Addition to oxygen actually is favored, but amides are too weakly basic for protonation to occur to any extent in water solution.

24.2.3: Contributors and Attributions

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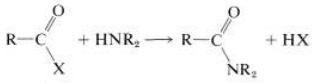
24.3: Synthesis of Amides

24.3.1: From Carboxylic Acids

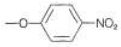
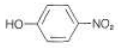
Formation of amides from carboxylic acid derivatives already has been discussed in some detail (Section 23-9A):



The ease of formation of amides by the reaction of Equation 24-1 depends a lot on the nature of the leaving group X. The characteristics of a good leaving group were discussed in Sections 8-7C and 8-7D in connection with S_N reactions, and similar considerations apply here. Some idea of the range of acid derivatives used in amide synthesis can be obtained from Table 24-1, which lists various RCOX compounds and the pK_a values of HX. As a reasonable rule of thumb, the stronger HX is as an acid, the better X is as a leaving group.

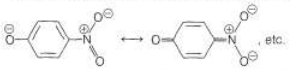
Table 24-1: *Derivatives and Reactivity of Carboxylic Acids Commonly Used in Amide Formation*

$$\mathrm{RCOX + H_2NR' \rightarrow RCONHR' + HX} \tag{24.3.1}$$

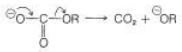
X	HX	pK_a of HX	Reactivity in amide formation
—OH	HOH	16	low[a]
—Cl	HCl	−6	good
—N_3	HN_3	3	good
—OCH_2CH_3	$HOCH_2CH_3$	16	low
		9.89	moderate
		7.15	good[b]
		4.75	moderate
	–	–	good[c]

[a] At ordinary temperatures, requires activation through a coupling agent (Section 23-9A), but on strong heating can give amide directly.

[b] Good leaving group because of stabilization of the type



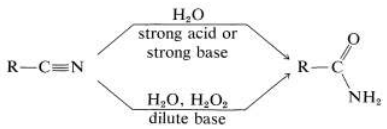
[c] Good leaving group, possibly because of associated decomposition to more stable products



Amides generally are formed from acid chlorides, acid azides, acid anhydrides, and esters. It is not practical to prepare them directly from an amine and a carboxylic acid without strong heating or unless the reaction is coupled to a second reaction that "activates" the acid. Notice that esters of phenols are more reactive toward amines than esters of alcohols because phenols are stronger acids than alcohols.

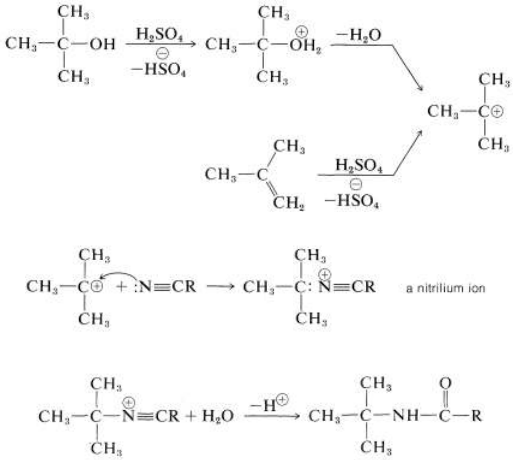
24.3.2: From Nitriles

The hydrolysis of nitriles is a satisfactory method for preparation of unsubstituted amides and is particularly convenient when hydrolysis is induced under mildly basic conditions by hydrogen peroxide:

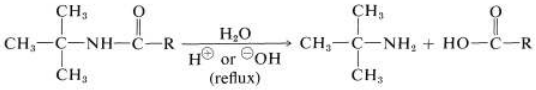


For the preparation of amides of the type $R_3CNHCOR$, which have a tertiary alkyl group bonded to nitrogen, the **Ritter reaction** of an alcohol or alkene with a nitrile or hydrogen cyanide is highly advantageous. This reaction involves formation of a carbocation

by action of strong sulfuric acid on an alkene or an alcohol (Equation 24-2), combination of the carbocation with the unshared electrons on nitrogen of RCN (Equation 24-3), and then addition of water (Equation 24-4). We use here the preparation of an N-*tert*-butylalkanamide as an example; RC ≡ N can be an alkyl cyanide such as ethanenitrile or hydrogen cyanide itself:

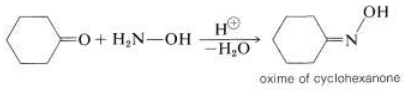


This reaction also is useful for the preparation of primary amines by hydrolysis of the amide. It is one of the relatively few practical methods for synthesizing amines with a tertiary alkyl group on the nitrogen:



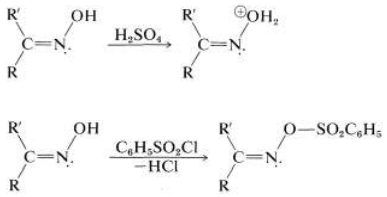
24.3.3: The Beckmann Rearrangement of Oximes

You may recall that ketones react with RNH_2 compounds to give products with a double bond to nitrogen, –C=NR (Section 16-4C). When the RNH_2 compound is azanol (hydroxylamine), $HO–NH_2$, the product is called a **ketoxime**, or oxime:

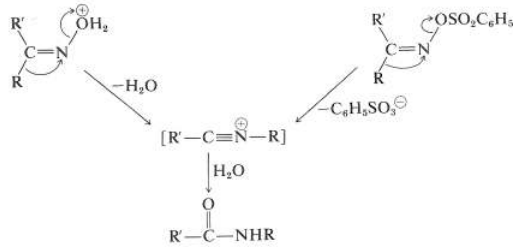


Oximes rearrange when heated with a strong acid, and this reaction provides a useful synthesis of amides:

This intriguing reaction is known as the **Beckmann rearrangement**. It has been the subject of a number of mechanistic studies that have shown the acid or acid halide (PCl_5, $C_6H_5SO_2Cl$) makes the hydroxyl group on nitrogen into a better leaving group by forming $–OH_2^+$ or ester intermediates:

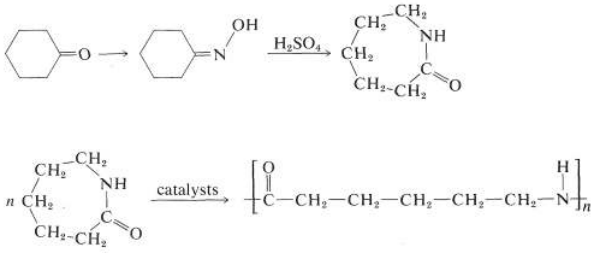


Thereafter, a rearrangement occurs resembling the reactions of carbocations (Sections 8-9B and 15-5E). When the cleavage of the N–O bond occurs, the nitrogen atom would be left with only six valence electrons. However, as the bond breaks, a substituent R on the neighboring carbon moves with its bonding electron pair to the developing positive nitrogen (Equation 24-5):



Oximes with R and R′ as different groups exist as *E* and *Z* isomers (Section 19-7) and you will notice in Equation 24-5 that the group that migrates is the one that is *trans* to the leaving group. To some extent the Beckmann rearrangement is an internal S_N2 reaction with inversion at the nitrogen. Section 21-10F gives a theoretical treatment of this kind of reaction. The rearrangement product is a nitrilium ion, as in the Ritter reaction (Section 24-3B), which adds water to form the amide.

The synthesis of aza-2-cycloheptanone (ε-caprolactam) by the Beckmann rearrangement of the oxime of cyclohexanone is of commercial importance because the lactam is an intermediate in the synthesis of a type of nylon (a polyamide called "nylon-6"[2]):



[2]The number 6 specifies the number of carbons in each monomer unit comprising the polyamide structure. By this code, nylon-6,6 is $(-NH(CH_2)_6NHCO(CH_2)_4CO-)_n$.

24.3.4: Contributors and Attributions

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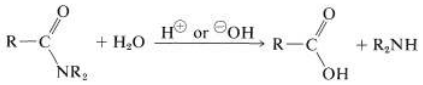
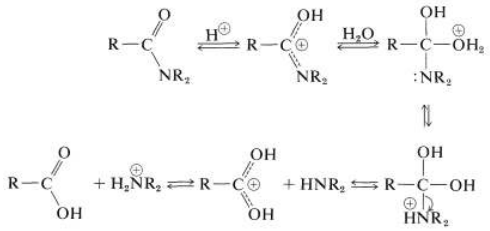
24.4: Hydrolysis of Amides

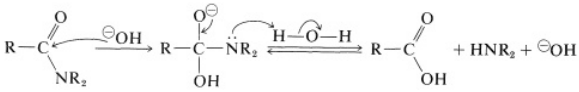
Generally, amides can be hydrolyzed in either acidic or basic solution. The mechanisms are much like those of ester hydrolysis (Section 18-7A), but the reactions are very much slower, a property of great biological importance (which we will discuss later):



As we have indicated in Section 23-12, amide hydrolysis can be an important route to amines. Hydrolysis under acidic conditions requires strong acids such as sulfuric or hydrochloric, and temperatures of about 100° for several hours. The mechanism involves protonation of the amide on oxygen followed by attack of water on the carbonyl carbon. The tetrahedral intermediate formed dissociates ultimately to the carboxylic acid and the ammonium salt:

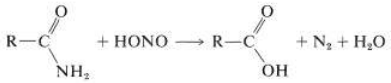


In alkaline hydrolysis the amide is heated with boiling aqueous sodium or potassium hydroxide. The nucleophilic hydroxide ion adds to the carbonyl carbon to form a tetrahedral intermediate, which, with the help of the aqueous solvent, expels the nitrogen as the free amine:

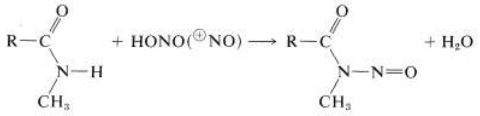


Biological amide hydrolysis, as in the hydrolysis of peptides and proteins, is catalyzed by the proteolytic enzymes. These reactions will be discussed in Chapter 25.

An indirect method of hydrolyzing some amides utilizes nitrous acid. Primary amides are converted easily to carboxylic acids by treatment with nitrous acid. These reactions are very similar to that which occurs between a primary amine and nitrous acid (Section 23-10):



Secondary amides give N-nitroso compounds with nitrous acid, whereas tertiary amides do not react:



A brief summary of important amide reactions follows:

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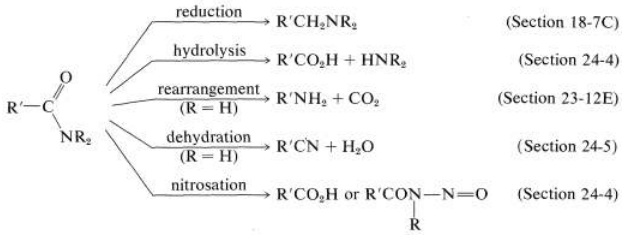

Of the many other types of organonitrogen compounds known, the more important include

nitriles, R—C≡N	(Section 24-5)
isonitriles, R—N=C:	
nitro compounds, R—NO_2	(Section 24-6)
nitroso compounds, R—NO	(Section 24-6C)
nitrile oxides, R—C≡$\overset{\oplus}{N}$—$\overset{\ominus}{O}$ amine oxides, $R_3\overset{\oplus}{N}$—$\overset{\ominus}{O}$	(Section 23-11B)
isocyanates, R—N=C=O	(Section 23-12E)
hydrazines, R_2N—NR_2	(Section 24-7A)
azo compounds, R—N=N—R	(Sections 23-10C and 24-7B)
diazo compounds, R_2C=$\overset{\oplus}{N}$=$\overset{\ominus}{N}$	(Section 24-7C)
azides, R—$\overset{\ominus}{N}$=$\overset{\oplus}{N}$=$\overset{\ominus}{N}$	(Section 23-12E, Table 23-6, and Section 24-7D)
diazonium ions, R—$\overset{\oplus}{N}$≡N	(Section 23-10)
azoxy compounds, R—$\overset{\oplus}{N}$(→$\overset{\ominus}{O}$)=N—R	(Section 24-6C)

Although it is impractical to discuss all of these compounds in detail, we now will discuss briefly several that have not been given much attention heretofore.

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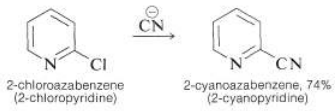
24.5: Nitriles

The carbon-nitrogen triple bond differs considerably from the carbon-carbon triple bond by being stronger ($212\ \text{kcal mol}^{-1}$ vs. $200\ \text{kcal mol}^{-1}$) and much more polar. The degree of polarity of the carbon-nitrogen triple bond is indicate by the high dipole moment ($4.0\ \text{D}$) of the simple nitriles (RCN), which corresponds to about 70% of the dipole moment expected if *one* of the bonds of the triple bond were fully ionic. With this knowledge it is not surprising that liquid nitriles have rather high dielectric constants compared to most organic liquids and are reasonably soluble in water. Ethanenitrile, CH_3CN, is in fact a good solvent for both polar and nonpolar solutes (Table 8-5).

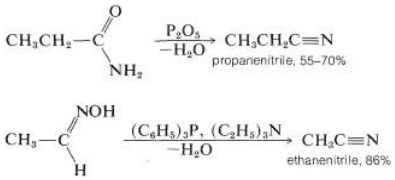
Nitriles absorb with variable strength in the infrared in the region $2000\ \text{cm}^{-1}$ to $2300\ \text{cm}^{-1}$, due to stretching vibrations of the carbon-nitrogen triple bond.

The **preparation of nitriles** by S_N2 reactions between alkyl halides and cyanide ion has been mentioned previously (Section 8-7F) and this is the method of choice when the halide is available and reacts satisfactorily. Activated aryl or azaaryl halides similarly give nitriles with cyanide ion:



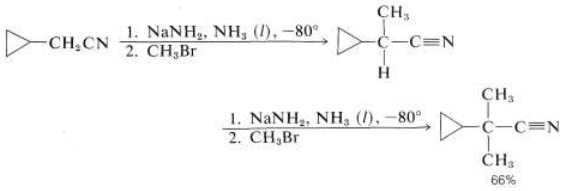
Another practical route to arenecarbonitriles involves the replacement of the diazonium group, $-\overset{\oplus}{\text{N}}\equiv\text{N}$, in arenediazonium ions with cuprous cyanide (Section 23-10B). Other useful syntheses involve cyanohydrin formation (Section 16-4A) and Michael addition to conjugated alkenones (Section 17-5B).

Nitriles also can be obtained by the dehydration of the corresponding amide or aldoxime. This is a widely used synthetic method and numerous dehydrating agents have been found to be effective:



The **reactions of nitriles** include reduction to amines and hydrolysis to acids. Both reactions have been discussed previously (Sections 18-7C and 18-7A).

Hydrogens on the *alpha* carbons of nitriles are about as acidic as the hydrogens alpha to carbonyl groups; accordingly, it is possible to alkylate the α positions of nitriles through successive treatments with a strong base and with an alkyl halide as in the following example:



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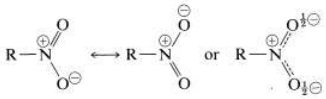
24.6: Nitro Compounds

24.6.1: Physical and Spectroscopic Properties

Nitro compounds are a very important class of nitrogen derivatives. The nitro group, $-NO_2$, like the carboxylate anion, is a hybrid of two equivalent resonance structures:



The hybrid structure has a full positive charge on nitrogen and a half-negative charge on each oxygen. This is in accord with the high dipole moments of nitro compounds, which fall between 3.5 D and 4.0 D, depending upon the nature of R. The polar character of the nitro group results in lower volatility of nitro compounds than ketones of about the same molecular weight; thus the boiling point of nitromethane (MW 61) is $101°$, whereas 2-propanone (MW 58) has a boiling point of $56°$. Surprisingly, the water solubility is low; a saturated solution of nitromethane in water is less than 10% by weight, whereas 2-propanone is completely miscible with water.

Nitro groups of nitroalkanes can be identified by strong infrared bands at about $1550\ \text{cm}^{-1}$ and $1375\ \text{cm}^{-1}$, whereas the corresponding bands in the spectra of aromatic nitro compounds occur at slightly lower frequencies. A weak $n \rightarrow \pi^*$ transition occurs in the electronic spectra of nitroalkanes at around $270\ \text{nm}$; aromatic nitro compounds, such as nitrobenzene, have extended conjugation and absorb at longer wavelengths $(\sim 330\ \text{nm})$.

24.6.2: Preparation of Nitro Compounds

Nitro compounds can be prepared in a number of ways, including the direct substitution of hydrocarbons with nitric acid,

$$RH + HONO_2 \rightarrow RNO_2 + H_2O \tag{24.6.1}$$

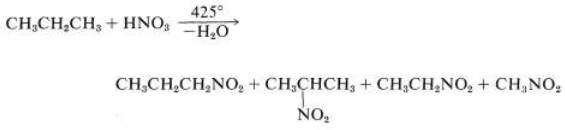
by displacement reactions with nitrite ions,

$$RX + NO_2{}^- \rightarrow RNO_2 + X^- \tag{24.6.2}$$

and by oxidation of primary amines,

$$RNH_2 \xrightarrow{[O]} RNO_2 \tag{24.6.3}$$

Nitration of alkanes is successful only when conducted at high temperatures in the vapor phase. Mixtures of products are invariably obtained (Section 4-6):



In contrast, direct *nitration of aromatic compounds* such as benzene takes place readily in the liquid phase, as discussed in Section 22-4C.

Like other electrophilic substitutions, nitration of a *substituted* benzene, where the substituent is electron withdrawing (NO_2, CO_2H, CN, and so on; Table 22-6), generally produces the 1,3-isomer. To prepare the 1,4-isomer, less direct routes are necessary - the usual stratagem being to use benzene derivatives with substituent groups that produce the desired orientation on nitration and then to make the necessary modifications in these groups to produce the final product. Thus 1,4-dinitrobenzene cannot be obtained by nitration of nitrobenzene but can be prepared from benzenamine by the sequence shown in Figure 24-5. Benzenamine is converted to N-phenylethanamide (acetanilide) which on nitration yields the 1,4-isomer. Hydrolysis of the amide to 4-nitrobenzenamine and replacement of amino by nitro, using nitrite ion in the presence of cuprous salts, gives 1,4-dinitrobenzene (Section 23-10B). Alternatively, the amino group of 4-nitrobenzenamine can be oxidized to a nitro group by trifluoroperoxyacetic acid. In these syntheses, N-phenylethanamide is nitrated in preference to benzenamine itself because, not only is benzenamine easily oxidized by

nitric acid, but the nitration reaction leads to extensive 3-substitution as the result of formation of phenylammonium ion. Another route to 4-nitrobenzenamine is to nitrate chlorobenzene and subsequently replace the chlorine by reaction with ammonia. The nitrations mentioned give mixtures of 2- and 4-isomers, but these usually are easy to separate by distillation or crystallization. The same approach can be used to synthesize 4-nitrobenzoic acid. The methyl group of methylbenzene directs nitration preferentially to the 4 position, and subsequent oxidation with chromic acid yields 4-nitrobenzoic acid:

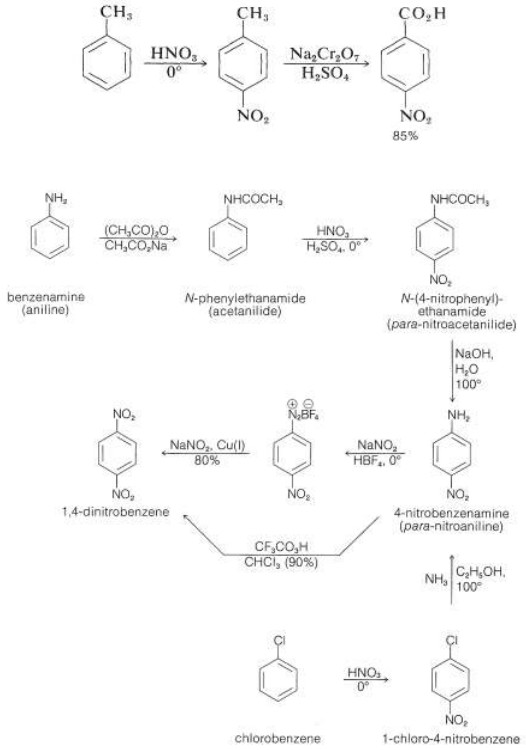
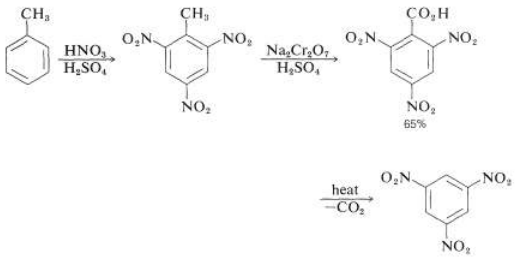


Figure 24-5: Synthetic routes to 1,4-dinitrobenzene.

In some cases it may be necessary to have an activating group to facilitate substitution, which otherwise would be very difficult. The preparation of 1,3,5-trinitrobenzene provides a good example; direct substitution of 1,3-dinitrobenzene requires long heating with nitric acid in fuming sulfuric acid. However, methylbenzene is converted more readily to the trinitro derivative and this substance, on oxidation and decarboxylation (Section 18-4), yields 1,3,5-trinitrobenzene:



Acylamino groups also are useful activating groups and have the advantage that the amino groups obtained after hydrolysis of the acyl function can be removed from an aromatic ring by reduction of the corresponding diazonium salt with hypophosphorous acid, preferably in the presence of copper (I) ions. An example is the preparation of 1-methyl-3-nitrobenzene from N-(4-methyl-phenyl)ethanamide (aceto-*para*-toluidide):

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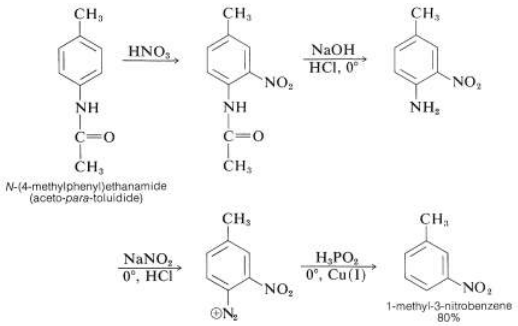
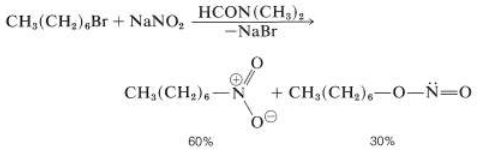


Routes to *aliphatic nitro compounds* include the reaction of an alkyl halide (of good S_N2 reactivity) with nitrite ion. Suitable solvents are methylsulfinylmethane [dimethyl sulfoxide, $(CH_3)_2SO$] and dimethyl methanamide (dimethylformamide). As will be seen from Equation 24-6, formation of the nitrite ester by O- instead of N-alkylation is a competing reaction:



Silver nitrite sometimes is used in preference to sodium nitrite, usually in diethyl ether as solvent:

Nitromethane can be prepared conveniently by the reaction

$$ClCH_2CO_2H + NaNO_2 \xrightarrow[-NaCl]{heat} [O_2NCH_2CO_2H] \xrightarrow[heat]{-CO_2} O_2NCH_3 \tag{24.6.4}$$

Displacement reactions with nitrite ion do not work well with aryl halides. However, displacement of the diazonium group is a practical route to nitroarenes (the **Sandmeyer reaction**), as described in Section 23-10B:

$$ArNH_2 \xrightarrow{HONO} ArN_2^{\oplus} \xrightarrow{CuNO_2} ArNO_2 \tag{24.6.5}$$

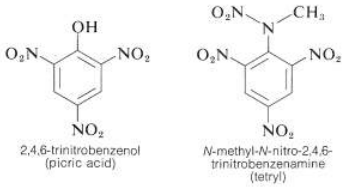
24.6.3: Reactions of Nitro Compounds

Nitro compounds are quite unstable in the thermodynamic sense; for example, the heat of decomposition of nitromethane, according to the following stoichiometry, is $67.4\ \text{kcal mol}^{-1}$.

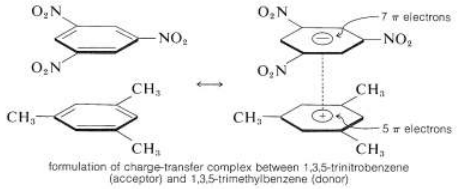
$$CH_3NO_2 \rightarrow \frac{1}{2}N_2 + CO_2 + \frac{3}{2}H_2 \quad \Delta H^0 = -67.4\ \text{kcal mol}^{-1} \tag{24.6.6}$$

Advantage is taken of the considerable energies and rapid rates of reactions such as this in the commercial use of nitro compounds as explosives. With some nitro compounds, such as TNT, there is a further advantage of low shock sensitivity.

TNT is not detonated easily by simple impact and even burns without exploding. However, once detonation starts, decomposition is propagated rapidly. The characteristics of reasonable handling stability and high thermodynamic potential make nitro compounds particularly useful. Other polynitro compounds that are useful as explosives include PETN (Section 17-3C), cyclonite (Section 16-4C), picric acid, and tetryl:

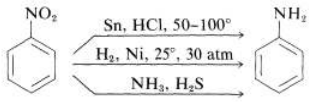


An important characteristic of aromatic polynitro compounds is their ability to form "charge-transfer" complexes with aromatic hydrocarbons, especially those that are substituted with alkyl groups. Complexes of 2,4,6-trinitrobenzenol (picric acid) and aromatic hydrocarbons often are crystalline solids, which are useful for the separation, purification, and identification of aromatic hydrocarbons. These substances are called "hydrocarbon picrates", but the name is misleading because they are not actually salts. Furthermore, similar complexes are formed between aromatic hydrocarbons and trinitrobenzene, which demonstrates that the nitro groups rather than the hydroxyl group are essential to complex formation. The binding in these complexes resembles that in the π complexes of halogens with alkenes and benzene (Sections 22-4D and 10-3C) and results from attractive forces between electron-rich and electron-poor substances. The descriptive name - **charge-transfer complex** - suggests that the complex has VB structures involving transfer of an electron from the donor (electron-rich) molecule to the acceptor (electron-poor) molecule. The name π complex also is used because, usually at least, one component of the complex has a π-electron system. Charge-transfer or π complexes between polynitro compounds and aromatic hydrocarbons appear to give sandwich-type structures with the aromatic rings in parallel planes, although not necessarily centered exactly over one another:



Charge-transfer complexes are almost always more highly colored than their individual components. A spectacular example is benzene and tetracyanoethene, each of which separately is colorless, but which give a bright-orange complex when mixed. A shift toward longer wavelengths of absorption, relative to their components, is to be expected for charge-transfer complexes because of the enhanced possibility for stabilization of the excited state through electron delocalization involving both components.

Reduction of nitro compounds occurs readily with a variety of reducing agents and such reductions afford a particularly useful synthesis of aromatic amines (Section 23-12B):



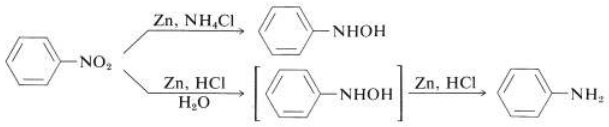
The reduction of a nitro compound to an amine requires six equivalents of reducing agent:

$$\mathrm{R{-}NO_2 + 6H^{\oplus} + 6e^{\ominus} \rightarrow RNH_2 + 2H_2O} \qquad (24.6.7)$$

One would not expect such a reduction to occur in a single step. Indeed, reduction is stepwise and proceeds through a string of intermediates, which, with strong reducing agents in acid solution, have at most a transient existence. The intermediates formed successively from $\mathrm{RNO_2}$ by increments of two equivalents of reducing agent are nitroso compounds, $\mathrm{R{-}N{=}O}$, and N-substituted azanols (hydroxylamines), RNHOH:

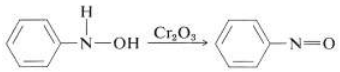
$$\mathrm{RNO_2} \xrightarrow[-\mathrm{H_2O}]{2[\mathrm{H}]} \mathrm{RN{=}O} \xrightarrow{2[\mathrm{H}]} \mathrm{RNHOH} \xrightarrow[-\mathrm{H_2O}]{2[\mathrm{H}]} \mathrm{RNH_2} \qquad (24.6.8)$$

Thus N-aryl-substituted azanols can be obtained directly from the corresponding nitro compounds with zinc and ammonium chloride solution. However, zinc and hydrochloric acid gives the amine:

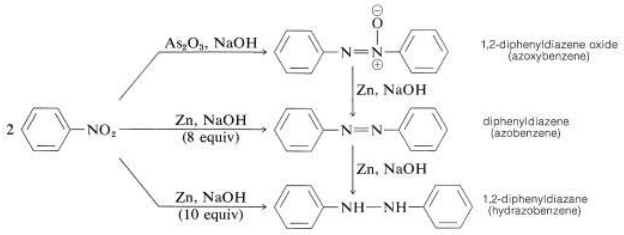


The difference between these reactions is in the reduction rates associated with the *acidity* of the solution. Ammonium chloride is a much weaker acid than HCl; the pH of ammonium chloride solutions is around 6.

Oxidation of the N-arylazanols under controlled conditions yields nitroso compounds. This reaction is not unlike the oxidation of alcohols to ketones (Section 15-6B):



Reduction of aryl nitro compounds with less-powerful reducing agents, especially in alkaline media, gives what may appear to be a mysterious conglomerate of bimolecular reduction products. For example, with nitrobenzene,

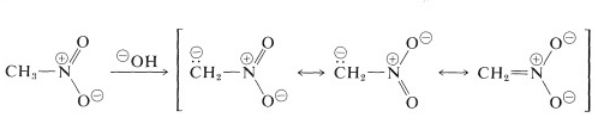


All of these substances can be reduced to benzenamine with tin and hydrochloric acid. As a result, each could be, but not necessarily is, an intermediate in the reduction of nitro compounds to amines. Formation of the bimolecular reduction products is the result of base-induced reactions between nitroso compounds and azanols or amines and possibly further reduction of the initially produced substances.

Several polynitrobenzene derivatives have important herbicidal uses. Examples are N^3, N^3-diethyl-6-trifluoromethyl-2,4-dinitro-1,3-benzenediamine and N,N-dipropyl-4-trifluoromethyl-2,6-dinitrobenzenamine:

These substances when mixed with soil kill weed seedlings but not crop plants such as cotton, soybeans, and peanuts. The activity is high; normally only about $0.08\ \mathrm{g\ m^{-2}}$ is required for good weed control.

The most important reactions of *nitroalkanes* are those involving the α hydrogens of the primary and secondary compounds. For example, nitromethane is sufficiently acidic to dissolve in aqueous hydroxide solutions. The anion so produced has an electronic structure analogous to the nitrate anion:



An interesting property of this ion is that when solutions of it are acidified, an unstable, rather strongly acidic isomer of nitromethane (called the *aci* form) is produced, which slowly reverts to the more stable nitro form:

Similar changes take place in the acidification of the enol salt of a carbonyl compound, the principal difference being the much longer life of the *aci*-nitro compound compared to that of an enol of a simple ketone (see Section 17-1B).

Primary and secondary nitro compounds undergo aldol additions and Michael additions with suitable carbonyl compounds and basic catalysts:

Unfortunately, alkylation reactions analogous to the base-catalyzed alkylation of carbonyl compounds generally are not useful for the synthesis of higher nitro compounds, because C-alkylation of the conjugate bases of primary nitro compounds is slower than O-alkylation.

24.6.4: Contributors and Attributions

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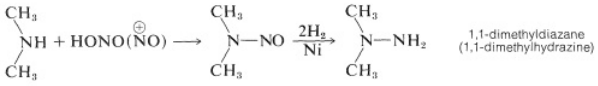
24.7: Some Compounds with N-N Bonds

Among the organic nitrogen compounds having nitrogen above the oxidation level of ammonia are a wide variety of substances with N–N bonds. We shall mention only a very few of the more important of these substances: hydrazines, azo and diazo compounds, and azides.

24.7.1: Hydrazines

Organic hydrazines or diazanes are substitution products of $NH_2–NH_2$ and have many properties similar to those of amines in being basic and forming acyl derivatives as well as undergoing alkylation and condensations with carbonyl compounds (Section 16-4C). Unsymmetrical hydrazines can be prepared by careful reduction of N-nitrosamines. 1,1-Dimethyldiazane is prepared in this way for use as a rocket fuel:



Aromatic hydrazines are best prepared by reduction of aromatic diazonium salts (Table 23-4).

Hydrazines of the type R–NH–NH–R are easily oxidized to the corresponding azo compounds, R–N=N–R. With nitrous acid, monosubstituted hydrazines are converted to azides:

$$R–NH–NH_2 + HONO \rightarrow R–N=\overset{\oplus}{N}=\overset{\ominus}{N} + 2H_2O \tag{24.7.1}$$

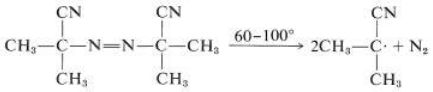
24.7.2: Azo Compounds

Azo or diazo compounds possess the –N=N– grouping. Aliphatic azo compounds of the type R–N=N–H appear to be highly unstable and decompose to R–H and nitrogen. Derivatives of the type R–N=N–R are much more stable and can be prepared as mentioned above by oxidation of the corresponding hydrazines. Aromatic azo compounds are available in considerable profusion from diazo coupling reactions (Section 23-10C) and are of commercial importance as dyes and coloring materials.

A prime characteristic of azo compounds is their tendency to decompose into organic free radicals and liberate nitrogen:

$$R–N=N–R \rightarrow 2R\cdot + N_2 \tag{24.7.2}$$

The ease of these reactions is usually a fairly reliable guide to the stabilities of the free radicals that result. For instance, it is found that dimethyldiazene (azomethane, $CH_3N=NCH_3$) is stable to about 400°, and diphenyldiazene (azobenzene, $C_6H_5N=NC_6H_5$) also is resistant to thermal decomposition; but, when the azo compound decomposes to radicals that have extra stability because of delocalization of the odd electron, the decomposition temperature is greatly reduced. Thus the azo compound, **2**, decomposes to radicals at moderate temperatures (60° to 100°), and for this reason is a very useful agent for generating radicals, such as those required for the initiation of polymerization of ethenyl compounds:

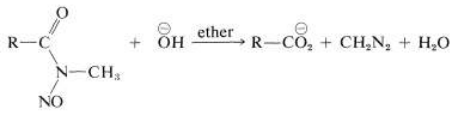


2

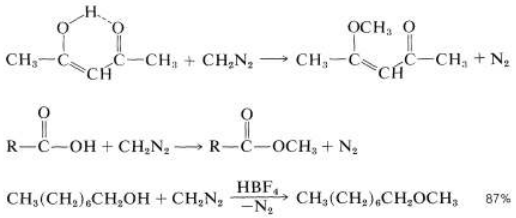
24.7.3: Diazo Compounds

The parent of the diazo compounds, diazomethane, $CH_2=\overset{\oplus}{N}=\overset{\ominus}{N}$, has been mentioned before in connection with ylide reactions for ring enlargement (Section 16-4A) and the preparation of methyl esters from acids (Table 18-7). It is one of the most versatile and useful reagents in organic chemistry, despite the fact that it is highly toxic, dangerously explosive, and cannot be stored without decomposition.

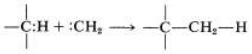
Diazomethane is an intensely yellow gas, bp −23°, which customarily is prepared and used in diethyl ether or dichloromethane solution. It can be synthesized in a number of ways, the most useful of which employs the action of base on an N-nitroso-N-methylamide:



As a methylating agent of reasonably acidic substances, diazomethane has nearly ideal properties. It can be used in organic solvents; reacts very rapidly without need for a catalyst (except with alcohols, which do require an acid catalyst); the coproduct is nitrogen which offers no separation problem; it gives essentially quantitative yields; and it act as as its own indicator to show when reaction is complete. With enols, it gives O-alkylation:

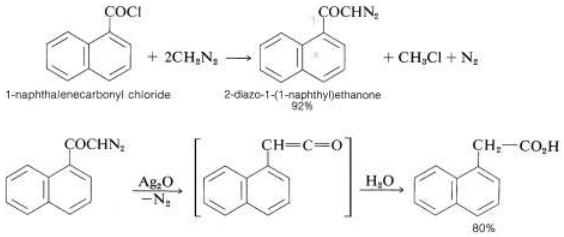


Besides being a methylating agent, diazomethane also is a source of $:CH_3$ when irradiated with light. The carbene formed in this way is highly reactive and even will react with the electrons of a carbon-hydrogen bond to "insert" the carbon of the carbene between carbon and hydrogen. This transforms $-C-H$ to $-C-CH_3$:

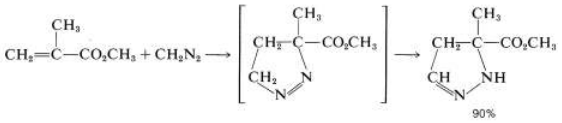


This $:CH_3$ species is one of the most reactive reagents known in organic chemistry. Diazomethane undergoes a wealth of other unusual reactions. Besides those already mentioned are the following two examples:

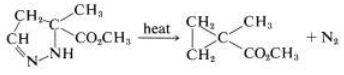
Arndt-Eistert synthesis ($COCl \rightarrow -CH_2CO_2H$, Section 16-4A)



Pyrazoline formation ([2 + 3] cycloaddition)

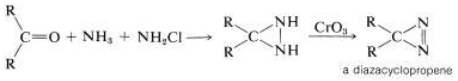


The Arndt-Eistert synthesis is useful for converting an acid to the next higher member of the series. Pyrazolines are important intermediates for the preparation of cyclopropanes:



Diazomethane originally was believed to possess the three-membered 1,2-diazacyclopropene ring structure, but this concept was disproved by electron-diffraction studies, which showed the linear structure to be correct:

Recently, a variety of authentic 1,2-diazacyclopropenes (sometimes called *diazirines*) have been prepared, and these have been found to have very different properties from the diazoalkanes. The simple 1,2-diazacyclopropenes are colorless and do not react with dilute acids, bases, or even bromine. The syntheses of these substances are relatively simple. One of several possible routes follows:



24.7.4: Azides

Organic azides can be prepared from hydrazines and nitrous acid (Section 24-7A) and by the reaction of sodium azide with acyl halides or with alkyl halides having good S_N2 reactivity:

$$\mathrm{RBr} + \mathrm{N_3}^- \xrightarrow[\mathrm{CH_3OH}]{S_N2} \mathrm{R{-}N{=}\overset{+}{N}{=}\overset{-}{N}} + \mathrm{Br}^- \tag{24.7.3}$$

The lower-molecular-weight organic azides often are unpredictably explosive and are best handled in solution.

The use of acyl azides in the preparation of amines by the Curtius rearrangement has been discussed previously (Section 23-12E). Alkyl azides can be reduced readily by lithium aluminum hydride to amines and, if a pure primary amine is desired, the sequence halide → azide → amine may give as good or better results than does the Gabriel synthesis (Section 23-9D).

24.7.5: Contributors and Attributions

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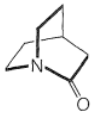
24.E: Organonitrogen Compounds II- Amides, Nitriles, and Nitro Compounds (Exercises)

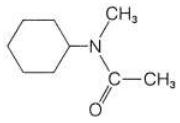
Exercise 24-1 Amides with structures like the following are difficult to prepare and are relatively unstable. Explain.

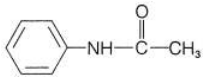


Exercise 24-2

a. Name each of the following compounds by the system described in Section 24-1B:

(i) $CH_2{=}CH{-}CONH_2$

(ii) 

(iii)  (the common name is acetanilide)

b. Write a structure to represent each compound shown:

(i) N-ethylbenzenecarboxamide

(ii) N-cyclohexyl-2-methylpropanamide

Exercise 24-3 Show how structures can be deduced for the two substances with the molecular formulas $C_5H_9NO_3$ and $C_{10}H_{13}NO$ from their infrared and NMR spectra as given in Figure 24-3.

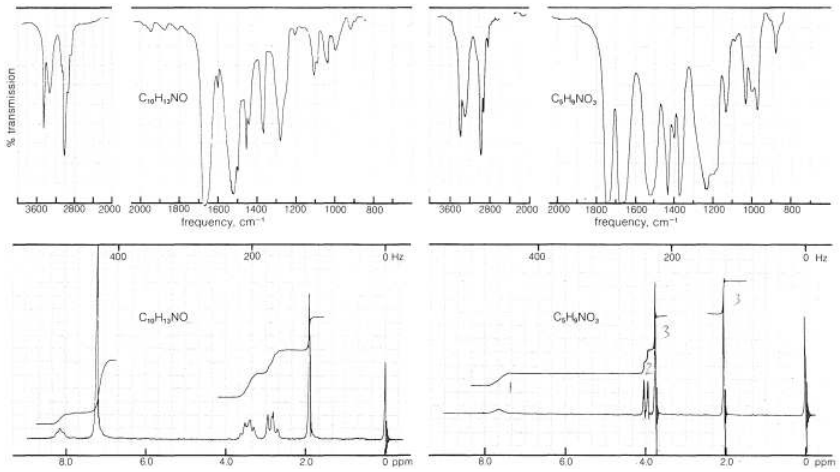


Figure 24-3: *The infrared and proton NMR spectra of a substance* $C_{10}H_{13}NO$ *and a substance* $C_5H_9NO_3 (see Exercise 24-3). The proton spectra were taken at* 60 MHz *with TMS as* 0.0 ppm

Exercise 24-4 Primary amides give a strong peak at m/e 44 in their mass spectra. Indicate the nature of this peak and suggest how it might be formed.

Exercise 24-5*

a. The ^{15}N NMR spectrum *with proton decoupling* (Section 9-10I) of N-methylmethanamide (Figure 24-4) shows two closely spaced signals of unequal height. Explain how these peaks arise and what you would expect the spectrum to look like if it were taken at 150°.

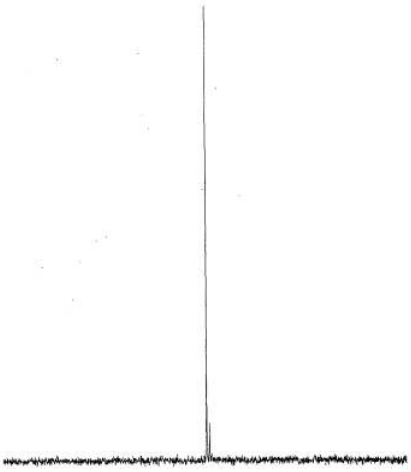


Figure 24-4: *Natural-abundance* $^{15}\mathrm{N}$ *spectrum of* $\mathrm{N}-methylmethanamide, \(HCONHCH_3$, *taken at* $18.2\ \mathrm{MHz}$ *with proton decoupling. The large and small peaks are separated by* $2\ \mathrm{ppm}$. *See Exercise 24-5.*

b. The proton-decoupled $^{15}\mathrm{N}$ spectra of lactams dissolved in $\mathrm{CHCl_3}$ show only one peak when the ring size is 5, 6, 7, 8, 10, and 11, but two unequal peaks when the ring size is 9. Account for this behavior. (Review Section 12-7.)

Exercise 24-6 Explain how the temperature variation of the proton NMR spectrum of N,N-dimethylmethanamide in strongly acidic solution might be used to decide whether amides accept a proton on nitrogen or oxygen. Review Section 24-1D.

Exercise 24-7

a. Draw the two important valence-bond structures for a nitrilium ion $[\mathrm{RCNR}]^{\oplus}$ and write the steps involved in hydration of a nitrilium ion to an amide, RCONHR.

b. Would you expect N-methylethanamide to be formed from methanol and ethanenitrile in $\mathrm{H_2SO_4}$? Explain.

Exercise 24-8 Nitriles are converted readily to amides with hydrogen peroxide in dilute sodium hydroxide solution. The reaction is

$$\mathrm{RC\ \equiv N + 2H_2O_2 \xrightarrow{OH^{\ominus}} RCONH_2 + O_2 + H_2O} \tag{24.E.1}$$

The rate equation is

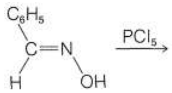
$$v = k\,[\mathrm{H_2O_2}]\left[\overset{\ominus}{\mathrm{O}}\mathrm{H}\right][\mathrm{RC\ \equiv N}] \tag{24.E.2}$$

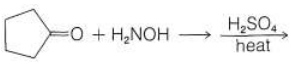
When hydrogen peroxide labeled with $^{18}\mathrm{O}$ $(\mathrm{H_2}\,^{18}\mathrm{_2O})$ is used in ordinary water $(\mathrm{H_2}\,^{16}\mathrm{O})$, the resulting amide is labeled with $^{18}\mathrm{O}$ $(\mathrm{RC}\,^{18}\mathrm{ONH_2})$.

Write a mechanism for this reaction that is consistent with *all* the experimental facts. Notice that hydrogen peroxide is a weak acid $(K_a \sim 10^{-12})$, and in the absence of hydrogen peroxide, dilute sodium hydroxide attacks nitriles very slowly.

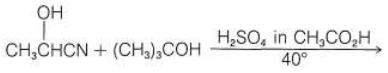
Exercise 24-9 Show how the following transformations could be achieved: $\mathrm{C_6H_5CH_2CO_2CH_3} \rightarrow \mathrm{C_6H_5CH_2C(CH_3)_2OH} \rightarrow \mathrm{C_6H_5CH_2C(CH_3)_2NHCHO}$. Name the product by the system used in Section 24-1B.

Exercise 24-10 Complete the following reactions to show the structures of the products formed:

a. 

b. 

c. \(\ce[C_6H_5CH_2OH} + \ce{CH_2=CHCN} \underset{25^\\text{o}}{\overset{\ce{H_2SO_4} \: \text{(conc)}}{\longrightarrow}}

d. 

Exercise 24-11 Nitriles of the type RCH_2CN undergo a self-addition reaction analogous to the aldol addition in the presence of strong bases such as lithium amide. Hydrolysis of the initial reaction product with dilute acid yields a cyanoketone, $RCH_2COCH(CN)R$. Show the steps that are involved in the mechanism of the overall reaction and outline a scheme for its use to synthesize large-ring ketones of the type $(CH_2)_nC{=}O$ from dinitriles of the type $NC(CH_2)_nCN$.

Exercise 24-12 Show how the following substances can be synthesized from the indicated starting materials:

a. $(CH_3)_3CCN$ from $(CH_3)_3CCl$ (two ways)
b. $CH_3CH{=}CHCN$ from $CH_2{=}CHCH_2Br$
c. $CH_2{=}CHCO_2H$ from CH_3CHO

Exercise 24-13 Propanedinitrile [malononitrile, $CH_2(CN)_2$] reacts with tetracyanoethene in the presence of base to yield a compound of formula $HC_3(CN)_5$, which is a monobasic acid of strength similar to sulfuric acid. What is the structure of this compound and why is it such a strong acid? Write a mechanism for the formation of the compound that is based in part on the Michael addition (Section 17-5B).

Exercise 24-14 Show how the following compounds may be synthesized from the indicated starting materials. (It may be necessary to review parts of Chapters 22 and 23 to work this exercise.)

a. 1-methyl-3,5-dinitrobenzene from methylbenzene
b. 1-methyl-2,6-dinitrobenzene from 4-methylbenzenesulfonic acid (notice that $-SO_3H$ can be removed by hydrolysis; Section 22-4G)
c. 2,4-dinitrobenzenamine from chlorobenzene
d. 1-chloro-3,5-dinitrobenzene from chlorobenzene
e. 1,2,3-trinitrobenzene from 4-chlorobenzenesulfonic acid

Exercise 24-15 Tetracyanoethene in benzene forms an orange solution, but when this solution is mixed with a solution of anthracene in benzene, a brilliant blue-green color is produced, which fades rapidly; colorless crystals of a compound of composition $C_{14}H_{10} \cdot C_2(CN)_4$ then are depositied. Explain the color changes that occur and write a structure for the crystalline product.

Exercise 24-16 Would you expect the dipole moment measured for 1,3,5-trinitrobenzene in 1,3,5-trimethylbenzene solution to be the same as in tetrachloromethane solution? Explain.

Exercise 24-17 Anthracene (mp 217°) forms a red crystalline complex (mp 164°) with 1,3,5-trinitrobenzene (mp 121°). If you were to purify anthracene as this complex, how could you regenerate the anthracene free of trinitrobenzene?

Exercise 24-18* Write the mechanistic steps to show how 1,2-diphenyldiazene oxide and 1,2-diphenyldiazene may be formed by base-induced condensation reactions of nitrosobenzene with N-phenylazanol and benzenamine, respectively. What product would you expect to be formed from nitrosobenzene and N-(4-chlorophenyl)azanol? Give your reasoning.

Exercise 24-19 What kind of properties and reactions would you expect the double bond of nitroethene to have? Consider the ease of electrophilic and nucleophilic addition reactions as well as cycloadditions.

Exercise 24-20 Show how the following compounds can be prepared from the commercially available nitroalkanes obtained from the nitration of propane. (It may be desirable to review the material on aldol and Michael additions in Chapters 17 and 18.)

a. $HOCH_2CH_2NO_2$
b. $CH_2{=}CHNO_2$
c. $(O_2NOCH_2)_3CNO_2$
d. $HOCH_2C(CH_3)_2NH_2$
e. $(N \equiv CCH_2CH_2)_3CNO_2$
f. $H_2NCH_2CH_2C(CH_3)_2NH_2$

Exercise 24-21 Show how 2-methyl-2-nitropropane may be synthesized from (a) *tert*-butyl alcohol and (b) 2,2-dimethylpropanoic acid. (Review Sections 23-12E and 24-3B if necessary.)

Exercise 24-22 Arguing on the basis of mechanistic principles and knowledge of related reactions, work out products that may be expected for the following reactions:

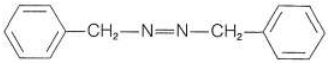
a. $(CH_3)_2NNH_2 + HONO$

b. $(CH_3)_2NNHCH_3 + HONO$

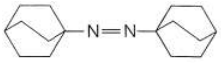
c. $(CH_3)_2NN(CH_3)_2 + HONO$

d. $CH_3CONHNH_2 + Br_2 + NaOH$

Exercise 24-23 Arrange the following azo substances in order of their expected rates of thermal decomposition to produce nitrogen. Give your reasoning.

a. 

b. $(CH_3)_3C{-}N{=}N{-}C(CH_3)_3$

c. 

d. $CH_3{-}N{=}N{-}CH_3$

e.

Exercise 24-24 Devise a synthesis (more than one step may be required) of 2 from 2-propanone, hydrazine, and hydrogen cyanide. What would you expect this substance to yield when heated in (a) a perfluorohydrocarbon solvent and (b) a solution of bromine in carbon tetrachloride?

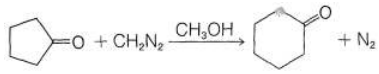
Exercise 24-25 Write the important resonance structures that contribute to the resonance hybrid of diazomethane and show how these can be used to rationalize the formation of methyl ethanoate from diazomethane and ethanoic acid.

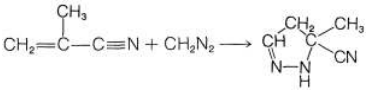
Exercise 24-26* Write reasonable mechanisms based on analogy for the following reaction:

a. $CH_3COCl + 2CH_2N_2 \rightarrow CH_3COCHN_2 + CH_3Cl$

b. $CH_3COCl + CH_2N_2$ \rightarrow \ce{CH_3COCH_2Cl} + \ce{N_2}\)

c. $CH_3COCHN_2 \xrightarrow[\text{heat}]{\text{powdered glass}} CH_3{-}CH{=}C{=}O + N_2$

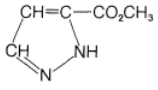
d. 

e. 

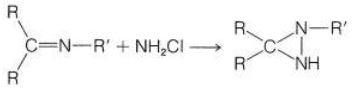
Exercise 24-27 Show how the following substances might be made by synthesis based on diazomethane reactions.

a. hexanedioic acid (from butanedioic acid)

b. 2,2-dimethylcyclopropanone (see Section 17-11)

c. 

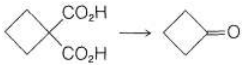
Exercise 24-28* Knowing that ketones and hydrazine react to give hydrazones, show how the combination of ketone, NH_3, and NH_2Cl can react to give diazacyclopropanes. In working out a mechanism, start with the fact that the following reaction occurs in good yield:



Exercise 24-29* Explain why 1,2-diazacyclopropene reacts with acids much more slowly than does diazomethane.

Exercise 24-30 Show how the following transformations may be achieved with the aid of azide derivatives:

a. $CH_2{=}CHCH_2CH_2OH \rightarrow CH_2{=}CHCH_2CH_2NH_2$

b. 

Exercise 24-31 Suggest a route for the synthesis of each of the following compounds from the indicated starting material:

a. 2-methylpropanenitrile from 2-methylpropanal

b. $(CH_3CO_2CH_2)_3C{-}NO_2$ from nitromethane

c. N-*tert*-butylbenzenecarboxamide from benzenecarbonitrile (benzeonitrile)

Exercise 24-32

a. Make a chart of the mp, bp, and solubilities in water, ether, dilute acid, and dilute base of each of the following compounds: octanamine, N-butylbutanamine, 1-nitrobutane, N,N-dimethylethanamide, N,N-dipropylpropanamide, and 2-nitro-2-methylbutane.

b. Outline a practical procedure for separation of an equimolal mixture of each of the compounds in Part a into the *pure components*. Notice that selective reactions are *not* suitable unless the reaction product can be reconverted to the starting material. Fractional distillation will not be accepted here as a practical means of separation of compounds that have boiling points less than 25° apart.

Exercise 24-33 For each of the following pairs of compounds give a chemical test, preferably a test-tube reaction, that will distinguish between the two compounds:

a. $(CH_3)_3CNH_2$ and $(CH_3)_2NC_2H_5$

b. $CH_3CH_2NO_2$ and CH_3CONH_2

c. $CH_3CH_2C \equiv N$ and $HC \equiv C{-}CH_2NH_2$

d. CH_3CH_2NHCl and $CH_3CH_2\overset{\oplus}{N}H_3\overset{\ominus}{Cl}$

e. $CH_3NHCOCH_3$ and $CH_3NHCO_2CH_3$

f. $CH_3OCH_2CH_NH_2$ and $CH_3NHCH_2CH_2OH$

g. $CH_3CH_2CONH_2$ and $CH_3OCH_2CH_2NH_2$

Exercise 24-34 Explain how you would use spectroscopic means to distinguish between the compound pairs in Exercise 24-33. Be specific about what you would expect to observe.

Exercise 24-35 Using spectroscopic methods, how could you distinguish one isomer from the other in the following pairs? Be specific about what you would expect to observe in each case.

a. 2-methylbenzenamine and N-methylbenzenamine

b. propanamide and N,N-dimethylmethanamide

c. nitroethane and ethyl nitrite

d. 3-oxobutanenitrile and 2-butynamide

Exercise 24-36 Compound A of molecular formula $C_6H_{12}O_2$ (which can be obtained resolved into chiral forms) is insoluble in dilute acid and dilute base, but reacts with aqueous nitrous acid to give compound B of formula $C_6H_{10}O_4$, which readily loses water on heating to give C, $C_6H_8O_3$. Compound A reacts with a solution of bromine and sodium hydroxide in water to give D, $C_4H_{12}N_2$, which on treatment with nitrous acid in the presence of perchloric acid gives 2-butanone. Write structures showing configurations for compounds A, B, C, and D and equations for all the reactions involved.

Exercise 24-37 How would you synthesize the following compounds from the indicated starting materials? Write equations for the reactions involved and indicate the reaction conditions.

a. phenylnitroethanoic acid from ethyl phenylethanoate
b. 3-phenylpropanoic acid from phenylethanoic acid

Exercise 24-38 Show by equations how each of the following substances might be synthesized from the indicated materials. Specify reagents and approximate reaction conditions.

a. N-phenylethanamide from benzene
b. 1,2-dinitrobenzene from N-phenylethanamide
c. 4-nitro-1-nitrosobenzene from N-phenylethanamide
d. 1,3,5-trideuteriobenzene from N-phenylethanamide
e. 2,4-dinitrophenyldiazane (2,4-dinitrophenylhydrazine) from benzene

Exercise 24-39 For each of the following pairs of compounds give a chemical test, preferably a test-tube reaction, that will distinguish the two compounds. Write a structural formula for each compound and equations for the reactions involved.

a. 1-methyl-3-nitrobenzene and phenylnitromethane
b. 1-methyl-4-nitrobenzene and benzenecarboxamide
c. benzenamine and cyclohexanamine
d. N-methylbenzenamine and 4-methylbenzenamine
e. N-nitroso-N-methylbenzenamine and 4-nitroso-N-methylbenzenamine

Exercise 24-40 Show how the following substances may be synthesized from benzene, nitrobenzene, and halogenated or alkylbenzenes, using the reactions discussed in this chapter and in Chapters 22 and 23.

a. 3-nitrobenzenamine
b. 1-bromo-4-nitrosobenzene
c. 2-methyl-5-nitrobenzenamine
d. 1-(4-bromophenyl)-2-(4-chlorophenyl)diazane
e. phenyl-(4-nitrophenyl)diazene
f. 1-phenyl-2-(4-methylphenyl)diazene 1-oxide

24.E.0.1: Contributors

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CHAPTER OVERVIEW

25: Amino Acids, Peptides, and Proteins

The chemistry of life is largely the chemistry of polyfunctional organic compounds. The functional groups usually are of types that interact rather strongly as, for example, the hydroxyl and carbonyl functions of carbohydrates (Chapter 20). The interaction between amino and carboxyl functions of amino acids figures greatly in the present chapter. We will approach the very important chemistry of amino acids and their derivatives in three stages. First, simple a-amino acids will be considered with emphasis on how the properties of amine functions and of acid functions are modified in molecules that possess both groups. Then we shall discuss some important properties of peptides and proteins, which are substances made up of amino acids linked together by amide bonds. Attention also will be given to the chemical problems presented by enzymes, which are protein molecules able to act as efficient catalysts for specific chemical reactions, and to the role of nucleic acids in protein synthesis.

25.1: Types of Biologically Important Amino Acids
25.2: Acid-Base Properties of \(\alpha\)-Amino Acids
25.3: Physical and Spectroscopic Properties
25.4: Analysis of Amino Acids
25.5: Reactions of Amino Acids
25.6: Synthesis of α-Amino Acids
25.7: Peptides and Proteins
25.8: Structure and Function of Proteins
25.9: Enzymes
25.10: Coenzymes
25.11: Enzyme Regulation
25.12: Enzyme Technology
25.13: Biosynthesis of Proteins
25.14: Chemical Evolution
25.E: Amino Acids, Peptides, and Proteins (Exercises)

25.1: Contributors and Attributions

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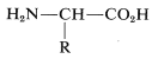
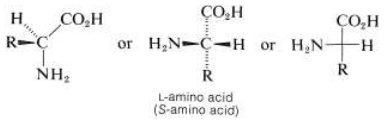
25.1: Types of Biologically Important Amino Acids

25.1.1: Protein Amino Acids

The amino acids that occur naturally as constituents of proteins have an amino group (NH_2) and a carboxylic acid group (CO_2H) attached to the *same* carbon. They are called α-**amino acids** and have the general formula



They differ only in the nature of the R group on the α carbon and, with few exceptions, they are chiral molecules with the *L* configuration at the chiral α carbon:[1]



The structures and names of some particularly important α-amino acids are shown in Table 25-1. You will notice that the names in common use for amino acids are not descriptive of their structural formulas; but at least they have the advantage of being shorter than the systematic names. The abbreviations Gly, Glu, and so on, that are listed in Table 25-1 are particularly useful in designating the sequences of amino acids in proteins and peptides, as will become evident later in the chapter.

Table 25-1: *Amino Acids Important as Constituents of Proteins*

Name	Abbreviations 3-letter	1-letter	Structure[a]	$pK_{A(CO_2H)}$	$pK_{A(\alpha\text{-}NH_3^{\oplus})}$	$pK_{A(R)}$	pI	Solubility[b]	Mp, °C
glycine	Gly	G	$H{-}CH(NH_2)CO_2H$	2.34	9.60		5.97	22.5	292 dec
alanine	Ala	A	$CH_3{-}CH(NH_2)CO_2H$	2.35	9.69		6.02	15.8	297 dec
valine[c]	Val	V	$(CH_3)_2CH{-}CH(NH_2)CO_2H$	2.32	9.62		5.97	6.8	315 dec
leucine[c]	Leu	L	$(CH_3)_2CHCH_2{-}CH(NH_2)CO_2H$	2.36	9.60		5.98	2.4	337 dec
isoleucine[c]	Ile	I	$CH_3CH_2CH(CH_3){-}CH(NH_2)CO_2H$	2.36	9.68		6.02	2.1	285 dec
serine	Ser	S	$HOCH_2{-}CH(NH_2)CO_2H$	2.21	9.15		5.68	4.3	228 dec
threonine[c]	Thr	T	$HOCH(CH_3){-}CH(NH_2)CO_2H$	2.09	9.10		5.60	1.6	253 dec
cysteine	Cys or CySH	C	$HSCH_2{-}CH(NH_2)CO_2H$	1.71	10.8	8.3	5.02	very sol.	–

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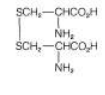
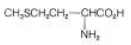
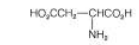
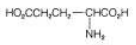
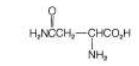
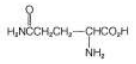
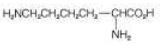
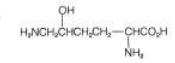
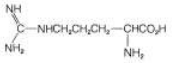
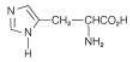
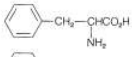
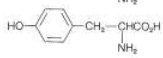
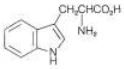
cystine	Cys or Cys	Cy or Cy		1.65 2.26	7.86 9.85		5.06	0.009	258
methionine	Met	M		2.28	9.21		5.06	3.0	283
aspartic acid	Asp	D		2.09	9.82	3.86	2.98	0.4	269
glutamic acid	Glu	E		2.19	9.67	4.25	3.22	0.7	247
asparagine	Asn	N		2.02	8.8		5.41	2.4	236
glutamine	Gln	Q		2.17	9.13		5.70	3.6[b]	184
lysine[c]	Lys	K		2.18	8.95	10.53	9.74	very sol.	224
hydroxylysine	Hyl			2.13	8.62	9.67	9.15	very sol.	–
arginine	Arg	R		2.17	9.04	12.48	10.76	very sol.	230–244 dec
histidine	His	H		1.82	9.17	6.0	7.59	4.0	287
phenylalanine[c]	Phe	F		1.83	9.13		5.48	2.7	283
tyrosine	Tyr	Y		2.20	9.11	10.07	5.67	0.04	342
tryptophan	Trp	W		2.38	9.39		5.88	1.1	283
proline	Pro	P		1.99	10.60		6.30	154.5	220
hydroxyproline[d]	Hyp			1.92	9.73		6.33	34.5	270

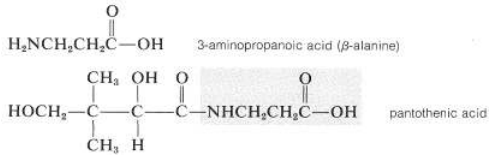
[a]For convenience only, the structures are represented as neutral nonpolar molecules. In reality, ionic and dipolar forms are present in aqueous solution in amounts dependent on the pH (Section 25-2A).
[b]Water solubility at isoelectric point of the L isomer in g/100 g at 20°C. The DL mixtures are usually less soluble.
[c]Must be included in diet for maintenance of proper nitrogen equilibrium in normal adult humans.
[d]Found only in collagen.

The nature of the substituent R varies considerably. In some amino acids, R is a hydrocarbon group, whereas in others it possesses functional groups such as OH, SH, SCH_3, CO_2H, or NH_2. Amino acids that have amine or other basic functions in the R group are called **basic amino acids** (lysine and arginine), whereas those with acidic groups are called **acidic amino acids** (aspartic and glutamic acids). Three of the amino acids listed in Table 25-1 (cysteine, cystine, and methionine) contain sulfur in $-SH$, $-S-S-$, and $-SCH_3$ groups. Cysteine and cystine can be interconverted readily with a wide variety of oxidizing and reducing agents according to the general reaction $2RSH \underset{[H]}{\overset{[O]}{\rightleftharpoons}} RSSR$. This is an important process in the biochemistry of sulfur-containing peptides and proteins (Section 25-8A).

The α-amino function of the common amino acids is primary $-NH_2$ in all except proline and hydroxyproline. Several of the amino acids have aromatic R groups (phenylalanine, tyrosine, tryptophan), while histidine and tryptophan have azarene R groups.

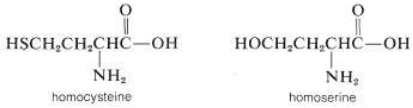
25.1.2: Nonprotein Amino Acids

The most abundant amino acids are those that are protein constituents and these are always α-amino acids. However, there are many other amino acids that occur naturally in living systems that are not constituents of proteins, and are not α-amino acids. Many of these are rare, but others are common and play important roles in cellular metabolism. For example, 3-aminopropanoic acid is a precursor in the biosynthesis of the vitamin, pantothenic acid,[2]



and 4-aminobutanoic acid is involved in the transmission of nerve impulses.

Homocysteine[3] and homoserine are among the important α-amino acids that are not constituents of proteins. These substances are precursors in the biosynthesis of methionine.



[1]A number of *D*-amino acids have been found to be constituents of peptides in the cell walls of bacteria.

[2]Pantothenic acid is in turn a precursor for the synthesis of coenzyme A, which is essential for the biosynthesis of fats and lipids (Sections 18-8F and 30-5A).

[3]The prefix *homo* implies an additional carbon in the longest chain.

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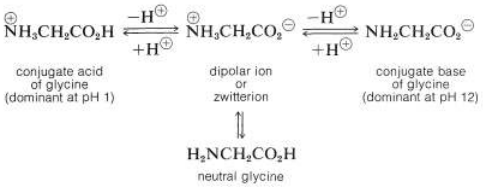
25.2: Acid-Base Properties of α -Amino Acids

The behavior of glycine is reasonably typical of that of the simplest amino acids. Because glycine is neither a strong acid nor a strong base, we shall expect a solution of glycine in water to contain four species in rapid equilibrium. The proportions of these species are expected to change with pH, the cationic conjugate acid being the predominant form at low pH and the anionic conjugate base being favored at high pH:



Spectroscopic measurements show that the equilibrium between neutral glycine and the dipolar ion favors the dipolar ion by at least 100 to 1. This is to be expected because the $H_3\overset{\oplus}{N}-$ group of the dipolar ion will stabilize the $-CO_2^-$ end while the $-CO_2^-$ group will stabilize the $H_3\overset{\oplus}{N}-$ end.

The acid-ionization constant of $H_3\overset{\oplus}{N}CH_2CO_2H$ is 4.5×10^{-3} ($pK_a = 2.34$, Equation 25-1), which is about 25 times greater than K_a for ethanoic acid (Section 18-2). This is expected because of the electron-attracting electrostatic effect of the $H_3\overset{\oplus}{N}-$ group. Ionization of the $H_3\overset{\oplus}{N}-$ group of the dipolar ion ($K_a = 2.0 \times 10^{-10}$; $pK_a = 9.60$; Equation 25-2) is oppositely affected by the electrostatic effect of the $-CO_2^-$ group and is 10 times less than of ethanammonium ion (Section 23-7B). The manner in which the concentrations of the charged glycine species change with pH is shown in Figure 25-1. Notice that, between pH 3 and pH 8, almost all of the glycine is in the form of the dipolar ion. The pH at the center of this range, where the concentration of $H_3\overset{\oplus}{N}CH_2CO_2H$ is equal to the concentration of $H_2NCH_2CO_2^-$, is called the **isoelectric point**, p*I*, and usually corresponds to the pH at which the amino acid has minimum water solubility. Isoelectric points for the amino acids are shown in Table 25-1. The isoelectric points are the average of the pK_a values for dissociation of the monocation and the dipolar ion forms of the amino acid. For glycine, $pI = (2.34 + 9.60)/2$.

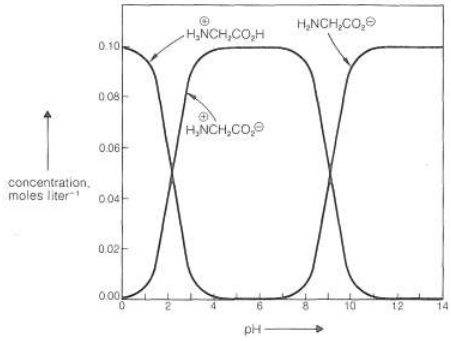
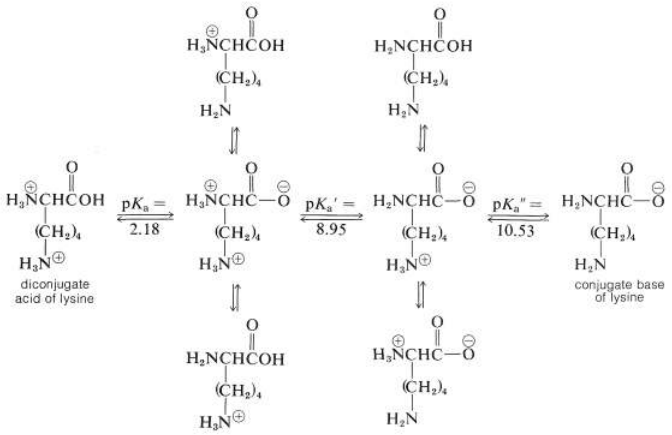


Figure 25-1: Concentrations of $H_3\overset{\oplus}{N}CH_2CO_2H$, $H_3\overset{\oplus}{N}CH_2CO_2^-$, and $H_2NCH_2CO_2^-$ as a function of pH for a 0.1 M solution of glycine in water.

$$pK_a = pH + \log_{10}\frac{\left[H_3\overset{\oplus}{N}CH_2CO_2H\right]}{\left[H_3\overset{\oplus}{N}{}_{22}CHCO^-\right]} = 2.34 \qquad (25\text{-}1)$$

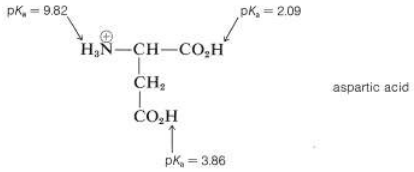
$$pK_a' = pH + \log_{10}\frac{\left[H_3\overset{\oplus}{N}{}_{22}CHCO^-\right]}{[H_3NCH_2CO_2^-]} = 9.60 \qquad (25\text{-}2)$$

The pH behavior of amino acids with either acidic or basic functional groups attached to the side chains is more complicated than of simple amino acids. For example, there are three acid dissociations starting with the diconjugate acid of lysine:

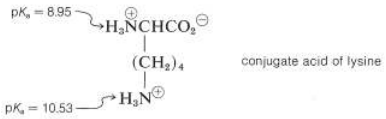


The pK_a values for the side-chain functions of acidic and basic amino acids are given in Table 25-1.

We already mentioned how the $H_3\overset{\oplus}{N}-$ group of the conjugate acid of glycine enhances the acid strength of the carboxyl group compared to ethanoic acid and how the $-CO_2^-$ group reduces the acidity of the $H_3\overset{\oplus}{N}-$ group of the dipolar ion relative to ethanammonium ion. These effects will be smaller the farther away the charged group is from the ionizable group. As a result, one would predict that the carboxyl groups of aspartic acid would have different pK_a values, and indeed this is so:



Similarly, the side-chain ammonium group of lysine is less acidic than that of the ammonium group close to the carboxyl group:



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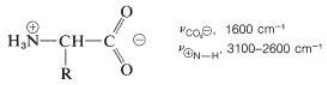
25.3: Physical and Spectroscopic Properties

The α-amino acids crystallize as the dipolar forms, $H_3\overset{\oplus}{N}-CHR-\overset{\ominus}{CO}_2$, and the strong intermolecular electrical forces in the crystals lead to higher melting points than those of simple amines or monocarboxylic acids (see Table 25-1). The melting points are so high that decomposition often occurs on melting. The solubility characteristics of amino acids in water are complex because of the acid-dissociation equilibria involved, but they are least soluble at their isoelectric points. The dipolar structures of amino acids greatly reduce their solubility in nonpolar organic solvents compared to simple amines and carboxylic acids.

The infrared spectra of α-amino acids in the solid state or in solution do not show a carbonyl absorption band at $1720\ \mathrm{cm}^{-1}$ characteristic of a carboxyl group. Rather, they show a strong absorption near $1600\ \mathrm{cm}^{-1}$ typical of the carboxylate anion. the $N-H$ stretch appears as a strong, broad band between $3100\text{-}2600\ \mathrm{cm}^{-1}$:



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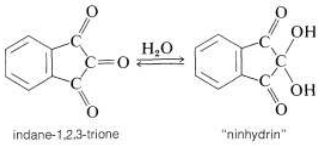
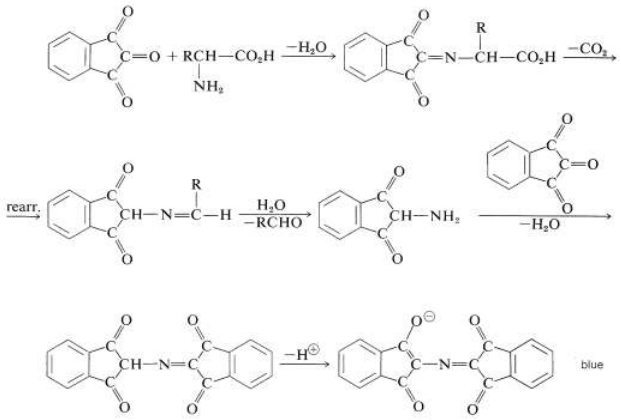
25.4: Analysis of Amino Acids

25.4.1: The Ninhydrin and Related Tests

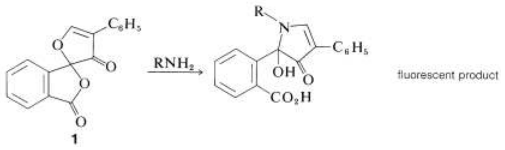
In many kinds of research it is important to have simple and sensitive means for analysis of amino acids, particularly in small quantities. Detection of amino acids can be achieved readily by the "ninhydrin color test", whereby an alcoholic solution of the triketone, "ninhydrin", is heated with an amino acid and produces an intense blue-violet color. The sensitivity and reliability of this test is such that 0.1 micromole of amino acid gives a color intensity reproducible to a few per cent, provided that a reducing agent such as stannous chloride is present to prevent oxidation of the colored salt by dissolved oxygen.



The color-forming reaction is interesting because most α-amino acids give the same color irrespective of their structure.[4] The sequence of steps that leads to the color is as follows:



A new, very sensitive method of detection and analysis of amino acids, which is useful down to the 10^{-12} mole (picomole) level, depends on the formation from $\mathrm{RNH_2}$ and "fluorescamine", 1, of substances that are intensely fluorescent in ultraviolet light:



25.4.2: Paper Chromatography

Ninhydrin (or fluorescamine) is very useful in chromatographic methods for the analysis of amino acids. One of these is paper chromatography, wherein amino acids are separated as the consequence of differences in their partition coefficients between water and an organic solvent. The aqueous phase is held stationary in the pores of the paper because of strong interaction of the water with the hydroxyl functions of the cellulose. The differences in partition coefficients show up as differences in rates of migration on the surface of moist (but not wet) paper over which there is a slow flow of a water-saturated organic solvent. We shall discuss one of several useful modes of operation. In this example, a drop of the solution to be analyzed is placed on the corner of a sheet of moist paper (often filter paper), which is then placed in an apparatus like that of Figure 25-2, arranged so that the organic solvent can migrate upward by capillarity across the paper, carrying the amino acids with it along one edge. The acids that have the greatest solubility in the organic solvent move most rapidly and when the solvent reaches the top of the paper, the paper is removed, dried, and then turned sidewise, and a different solvent allowed to migrate upward. This double migration process gives a better separation of the amino acids than a single migration and results in concentration of the different amino acids in rather well-defined spots. These spots can be made visible by first drying and then spraying the paper with ninhydrin solution. The final result is as

shown in Figure 25-3 and usually is quite reproducible under a given set of conditions. The identities of the amino acids that produce the various spots are established by comparison with the behavior of known mixtures.

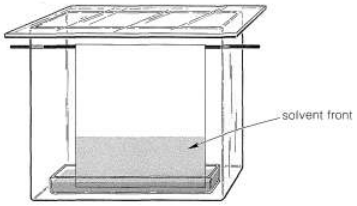


Figure 25-2: Diagram of apparatus used to develop a paper chromatogram. Paper is suspended from its top edge within an airtight container, here a glass box closed with a glass plate, having an atmosphere saturated with solvent vapor, the lower edge of paper dips into a trough containing the liquid solvent.

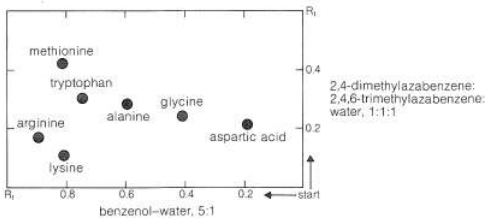
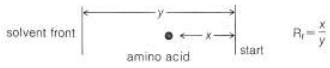


Figure 25-3: Idealized two-dimensional paper chromatogram of a mixture of amino acids. The horizontal and vertical scales represent the distance of travel of a component of the mixture in a given solvent relative to that of the solvent itself. This is known as the R_f value and is fairly constant for a particular compound in a given solvent. A rough identification of the amino acids present in the mixture may therefore be made on the bases of their R_f values:



Analysis by thin-layer chromatography (see Section 9-2B) can be carried out in the same way as paper chromatography. The partitioning is now between a solid stationary phase (the coating on the plate) and the moving solvent front.

25.4.3: Ion-Exchange Chromatography

The advent of ion-exchange chromatography has revolutionized the separation and analysis of amino acids as well as that of many inorganic substances. As the name implies, it involves the exchange of ions between a stationary and a moving phase. The stationary phase is an insoluble polymer (or resin) having chains on which are located ionic functions such as sulfonate groups, $-SO_3^-$ or quaternary ammonium groups, $-\overset{\oplus}{N}R_3$. The counterions to these groups, such as $Na^{\oplus}$ or $Cl^{\ominus}$, are not bound to the resin and can be exchanged for other ions in the mobile phase as the mobile phase travels through the resin. A common application of this principle is in household water softeners, in which the calcium and magnesium ions in ordinary "hard" water are replaced by sodium ions from the resin (Equation 25-3). The resulting "soft" water can be freed of metal ions, if desired, by exchanging the $Na^{\oplus}$ ions for protons (Equation 25-4):

$$2\,(\text{resin}{-}SO_3^-Na^+) + Ca^{2+} \rightleftharpoons 2\,(\text{resin}{-}SO_3^-)\,Ca^{2+} + 2Na^+ \tag{25-3}$$

$$\text{resin}{-}SO_3^-H^+ \rightleftharpoons \text{resin}{-}SO_3^-Na^+ + H^+ \tag{25-4}$$

In strongly acidic solutions (pH ~ 0), the amine and carboxyl groups of an amino acid are completely protonated. This cationic form of the amino acid can be exchanged with the cations associated with the sulfonate groups of the resin:

$$\text{resin}{-}SO_3^-Na^+ + H_3\overset{+}{N}CRHCO_2H \rightleftharpoons \text{resin}{-}SO_3^-H_3\overset{+}{N}CRHCO_2H + Na^+ \tag{25-5}$$

The process is reversible, and the amino acid cations can in turn be exchanged off the columns. However, different amino acids have different affinities for the resin, and these are considerably influenced by the pH of the moving phase (eluent). The basic amino acids (arginine, lysine), which form cations most readily, are more strongly held by cation-exchange resins than are acidic amino acids (aspartic and glutamic acids). There is a spectrum of affinities of the other amino acid cations for the resin between these extremes. Thus a mixture of amino acids can be separated by ion-exchange chromatography by elution with buffered aqueous solutions. The effluent from the column is mixed with ninhydrin solution and the intensity of the blue color is measured and plotted

as a function of time at constant flow rates (Figure 25-4). The identity of an amino acid is determined by the volume of solvent required to elute the amino acid from the column, and the concentration is determined from the intensity of the color developed.

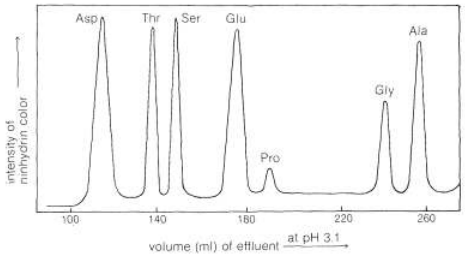


Figure 25-4: Part of amino-acid chromatogram obtained by the method of automatic amino-acid analysis from a hydrolyzed sample of the enzyme ribonuclease. The component amino acids listed are present in the ratio Asp:Thr:Ser:Glu:Pro:Gly:Ala = 15:10:15:12:4:3:12, as determined by peak intensity. The volume of effluent is a measure of the retention time of the amino acids on the column.

[4]Proline and hydroxyproline are exceptions because neither has the necessary primary NH_2 group needed for the reaction. However, these compounds do react with ninhydrin to give yellow compounds, and these colors can be used to identify them satisfactorily.

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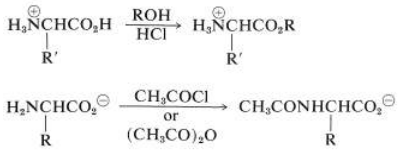
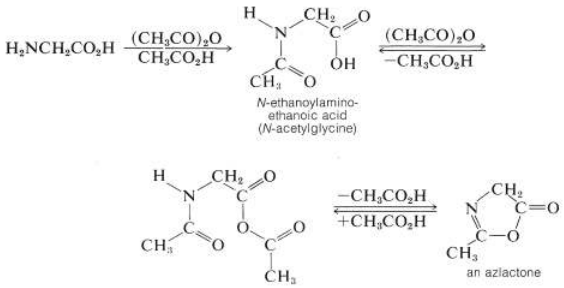
25.5: Reactions of Amino Acids

25.5.1: Ester and Amide Formation

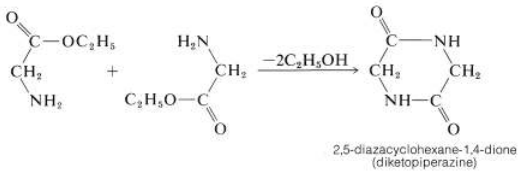
To some degree the reactions of amino acids are typical of isolated carboxylic acid and amine functions. Thus the carboxyl function can be esterified with an excess of an alcohol under acidic conditions, and the amine function can be acylated with acid chlorides or anhydrides under basic conditions:



The products, however, are not indefinitely stable because the functional groups can, and eventually will, react with each other. For example, in the acylation of glycine with ethanoic anhydride, the first-formed product may cyclize to the "azlactone" if the reaction is prolonged or excess anhydride is used:

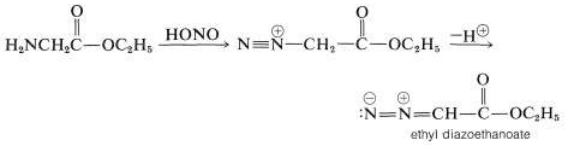


Esters of amino acids also cyclize, but they do so intermolecularly to give "diketopiperazines". These compounds are cyclic amides:



25.5.2: Nitrous Acid Reaction

The amine function of α-amino acids and esters reacts with nitrous acid in a manner similar to that described for primary amines (Section 23-10A). The diazonium ion intermediate loses molecular nitrogen in the case of the acid, but the diazonium ester loses a proton and forms a relatively stable diazo compound known as ethyl diazoethanoate:



This diazo ester is formed because loss of N_2 from the diazonium ion results in formation of a quite unfavorable carbocation.

25.5.3: Amino Acids with Aldehydes

α-Amino acids react with aldehydes to form decarboxylation and/or deamination products. The reaction sequence is shown in Figure 25-5 and closely resembles the ninhydrin reaction (Section 25-4A). In the first step the amine condenses with the aldehyde to give an imine or Schiff base, 2. What happens next depends on the relative rates of proton shift and decarboxylation of 2. Proton shift produces a rearranged imine, 3, which can hydrolyze to the keto acid 4. The keto acid is a deamination product. Alternatively,

decarboxylation can occur (see Section 18-4) and the resulting imine, 5, can either hydrolyze or rearrange by a proton shift to a new imine, 6. Hydrolysis of 5 or 6 gives an aldehyde and an amine.

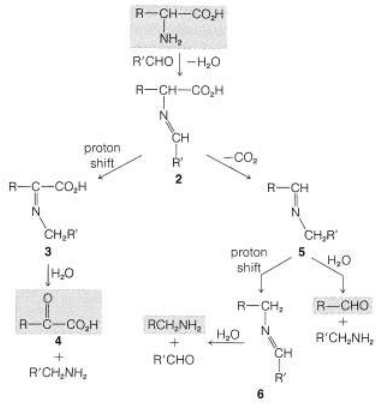
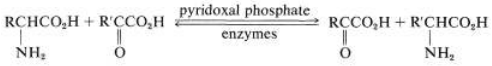
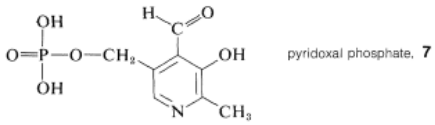


Figure 25-5: Reactions of α-amino acids with an aldehyde, R′CHO. The products are the result of decarboxylation and/or deamination; the fraction of the products formed by each route is determined by the ratio of the rate of proton shift to the rate of decarboxylation of 2.

There is an important biochemical counterpart of the deamination reaction that utilizes pyridoxal phosphate, 7, as the aldehyde. Each step in the sequence is catalyzed by a specific enzyme. The α-amino group of the amino acid combines with 7 and is converted to a keto acid. The resulting pyridoxamine then reacts to form an imine with a different α-keto acid, resulting in formation of a new α-amino acid and regenerating 7. The overall process is shown in Equation 25-6 and is called **transamination**. It is a key part of the process whereby amino acids are metabolized.



The biochemical process occurs with complete preservation of the L configuration at the α carbon. The same reactions can be carried out nonenzymatically using pyridoxal phosphate, but they are nonstereospecific, require metal ions as a catalyst, and give mixtures of products.



pyridoxal phosphate, **7**

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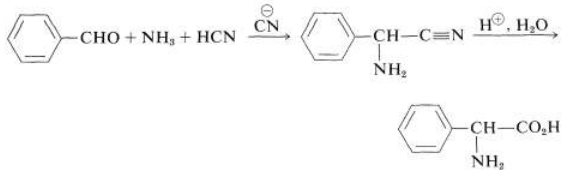
25.6: Synthesis of α-Amino Acids

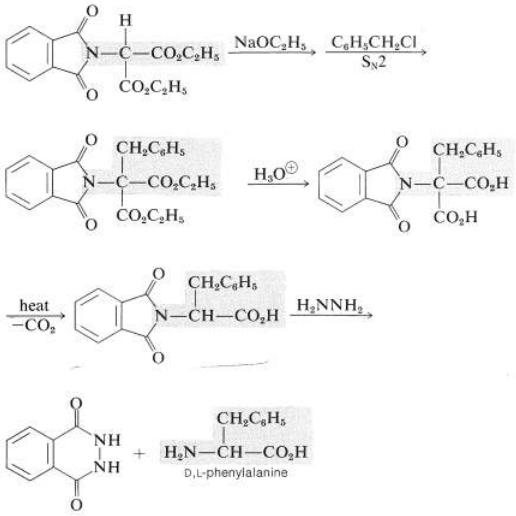
Many of the types of reactions that are useful for the preparation of amino acids have been discussed previously in connection with separate syntheses of carboxylic acids (Chapter 18) and amino compounds (Chapter 23). Examples include the S_N2 displacement of halogen from α-halo acids by ammonia,

and the **Strecker synthesis**, which, in its first step, bears a close relationship to cyanohydrin formation (Section 16-4A):

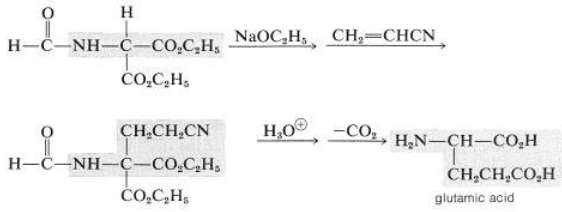


Other general synthetic methods introduce the α-amino acid grouping, $H_2N{-}CH{-}CO_2H$, by way of enolate anions. Two selected examples follow. Notice that in each a carbanion is generated and alkylated. Also the H_2N- group is introduced as a protected amide or imide group.

1. **phthalimidomalonic ester synthesis**



2. N-**formylaminomalonic ester synthesis**



With those amino acids that are very soluble in water, it usually is necessary to isolate the product either by evaporation of an aqueous solution or by precipitation induced by addition of an organic solvent like alcohol. Difficulty may be encountered in obtaining a pure product when inorganic salts are coproducts of the synthesis. The best general method for removal of inorganic salts involves passage of the solutions through columns of suitable ion-exchange resins (Section 25-4C).

The products of laboratory syntheses, starting with achiral reagents, are of course racemic α-amino acids. To obtain the natural amino acids, the D,L mixtures must be resolved (Section 19-3).

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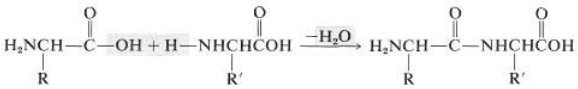
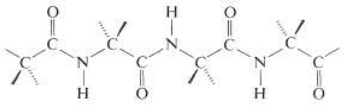
25.7: Peptides and Proteins

25.7.1: Classification

Amino acids are the building blocks of the polyamide structures of peptides and proteins. Each amino acid is linked to another by an amide (or peptide) bond formed between the NH_2 group of one and the CO_2H group of the other:

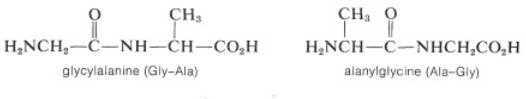


In this manner a polymeric structure of repeating amide links is built into a chain or ring. The amide groups are planar and configuration about the C–N bond is usually, but not always, trans (Section 24-1). The pattern of *covalent* bonds in a peptide or protein is called its **primary structure**:



The distinction between a protein and a peptide is not completely clear. One arbitrary choice is to call proteins only those substances with molecular weights greater than 5000. The distinction might also be made in terms of differences in physical properties, particularly hydration and conformation. Thus proteins, in contrast to peptides, have very long chains that are coiled and folded in particular ways, with water molecules filling the voids in the coils and folds. Hydrogen bonding between the amide groups plays a decisive role in holding the chains in juxtaposition to one another, in what is sometimes called the **secondary** and **tertiary structure**.[5] Under the influence of heat, organic solvents, salts, and so on, protein molecules undergo changes, often irreversibly, called **denaturation**. The conformations of the chains and the degree of hydration are thereby altered, with the result that solubility and ability to crystallize decreases. Most importantly, the physiological properties of the protein usually are destroyed permanently on denaturation. Therefore, if a synthesis of a protein is planned, it would be necessary to duplicate not only the amino-acid sequences but also the exact conformations of the chains and the manner of hydration characteristic of the native protein. With peptides, the chemical and physiological properties of natural and synthetic materials usually are identical, provided the synthesis duplicates all of the structural and configurational elements. What this means is that a peptide automatically assumes the secondary and tertiary structure characteristic of the native peptide on crystallization or dissolution in solvents.

Representation of peptide structures of any length with conventional structural formulas is cumbersome. As a result, abbreviations are universally used that employ three-letter symbols for the component amino acids. It is important that you know the conventions for these abbreviations. The two possible dipeptides made up of one glycien and one alanine are



Notice that in the conventions used for names and abbreviated formulas the amino acid with the free amino group (*the* N-*terminal amino acid*) always is written on the *left*. The amino acid with the free carboxyl group (*the* C-*terminal amino acid*) always is written on the *right*. The dash between the three-letter abbreviations for the acids designates that they are linked together by an *amide* bond.

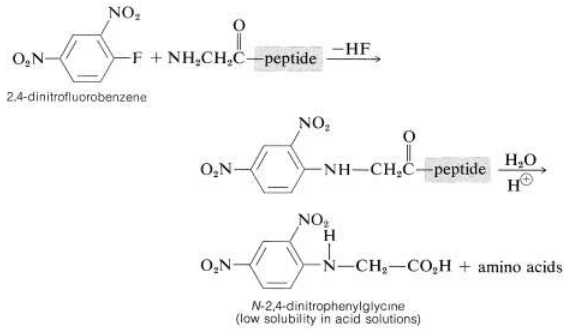
25.7.2: Determination of Amino-Acid Sequences

The general procedure for determining the primary structure of a peptide or protein consists of three main steps. First, the number and kind of amino-acid units in the primary structure must be determined. Second, the amino acids at the ends of the chains are identified, and third, the sequence of the component amino acids in the chains is determined.

The amino-acid composition usually is obtained by complete acid hydrolysis of the peptide into its component amino acids and analysis of the mixture by ion-exchange chromatography (Section 25-4C). This procedure is complicated by the fact that

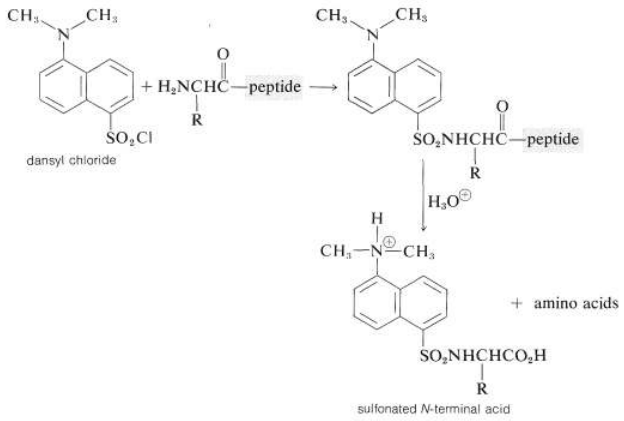
tryptophan is destroyed under acidic conditions. Also, asparagine and glutamine are converted to aspartic and glutamic acids, respectively.

Determination of the N-terminal acid in the peptide can be made by treatment of the peptide with 2,4-dinitrofluorobenzene, a substance very reactive in nucleophilic displacements with amines but not amides (see Section 14-6B). The product is an N-2,4-dinitrophenyl derivative of the peptide which, after hydrolysis of the amide linkages, produces an N-2,4-dinitrophenylamino acid:



These amino-acid derivatives can be separated from the ordinary amino acids resulting from hydrolysis of the peptide because the low basicity of the 2,4-dinitrophenyl-substituted nitrogen (Section 23-7C) greatly reduces the solubility of the compound in acid solution and alters its chromatographic behavior. The main disadvantage to the method is that the entire peptide must be destroyed in order to identify the one N-terminal acid.

A related and more sensitive method makes a sulfonamide of the terminal NH_2 group with a reagent called "dansyl chloride". As with 2,4-dinitrofluorobenzene, the peptide must be destroyed by hydrolysis to release the N-sulfonated amino acid, which can be identified spectroscopically in microgram amounts:



A powerful method of sequencing a peptide from the N-terminal end is the **Edman degradation** in which phenyl isothiocyanate, $C_6H_5N{=}C{=}S$, reacts selectively with the terminal amino acid under mildly basic conditions. If the reaction mixture is then acidified, the terminal amino acid is cleaved from the peptide as a cyclic **thiohydantoin**, 8:

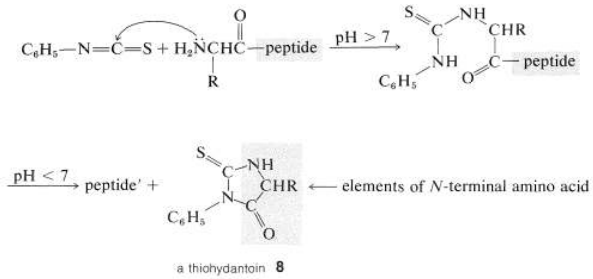


Figure 25-6 illustrates how the procedure works. If the N-terminal nitrogen is not a free amino group, but for example is an ethanoylamide, CH_3CONH-, the Edman degradation does not proceed.

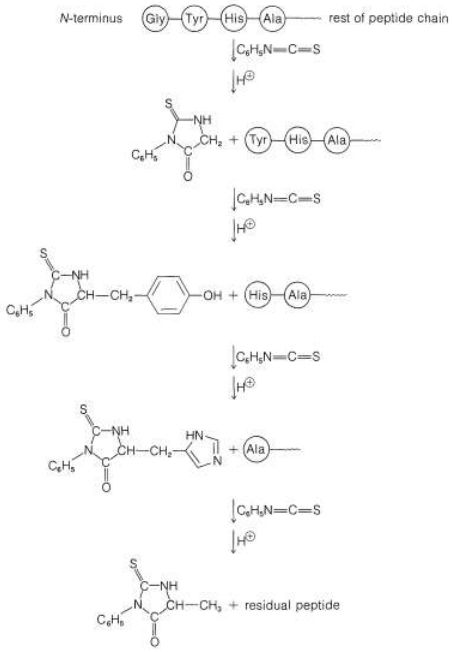


Figure 25-6: *Result of a series of Edman degradations on an N-terminal Gly-Tyr-His-Ala-peptide.*

There are simple reagents that react selectively with the carboxyl terminus of a peptide, but they have not proved as generally useful for analysis of the C-terminal amino acids as has the enzyme *carboxypeptidase A*. This enzyme catalyzes the hydrolysis of the peptide bond connecting the amino acid with the terminal carboxyl groups to the rest of the peptide. Thus the amino acids at the carboxyl end will be removed one by one through the action of the enzyme. Provided that appropriate corrections are made for different rates of hydrolysis of peptide bonds for different amino acids at the carboxyl end of the peptide, the sequence of up to five or six amino acids in the peptide can be deduced from the order of their release by carboxypeptidase. Thus a sequence such as peptide-Ser-Leu-Tyr could be established by observing that carboxypeptidase releases amino acids from the peptide in the order Tyr, Leu, Ser:

$$\text{peptide–Ser–Leu–Tyr} \xrightarrow[H_2O]{\text{carboxypeptidase}} \text{peptide–Ser–Leu} + \text{Tyr}$$

$$\longrightarrow \text{peptide–Ser} + \text{Leu} + \text{Tyr} \longrightarrow \text{peptide} + \text{Ser} + \text{Leu} + \text{Tyr}$$

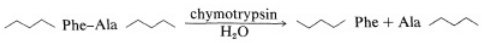
Determining the amino-acid sequences of large peptides and proteins is very difficult. Although the Edman degradation and even carboxypeptidase can be used to completely sequence small peptides, they cannot be applied successfully to peptide chains with several hundred amino acid units. Success has been obtained with long peptide chains by employing reagents, often enzymes, to selectively cleave certain peptide bonds. In this way the chain can be broken down into several smaller peptides that can be separated and sequenced. The problem then is to determine the sequence of these small peptides in the original structure. To do this, alternative procedures for selective cleavages are carried out that produce different sets of smaller peptides. It is not usually necessary to sequence completely all of the peptide sets. The overall amino-acid composition and the respective end groups of each peptide may suffice to show overlapping sequences from which the complete amino-acid sequence logically can be deduced.

The best way to show you how the overlap method of peptide sequencing works is by a specific example. In this example, we will illustrate the use of the two most commonly used enzymes for selective peptide cleavage. One is *trypsin*, a proteolytic enzyme of the pancreas (MW 24,000) that selectively catalyzes the hydrolysis of the peptide bonds of *basic* amino acids, lysine and arginine. Cleavage occurs on the *carboxyl side* of lysine or arginine:

$$\sim\!\text{Lys–Gly}\!\sim \xrightarrow[H_2O]{\text{trypsin}} \sim\!\text{Lys} + \text{Gly}\!\sim$$

$$\sim\!\text{Arg–Gly}\!\sim \xrightarrow[H_2O]{\text{trypsin}} \sim\!\text{Arg} + \text{Gly}\!\sim$$

Chymotrypsin is a proteolytic enzyme of the pancreas (MW 24,500) that catalyzes the hydrolysis of peptide bonds to the aromatic amino acids, tyrosine, tryptophan, and phenylalanine, more rapidly than to other amino acids. Cleavage occurs on the *carboxyl side* of the aromatic amino acid:



Our example is the sequencing of a peptide (P) derived from partial hydrolysis of a protein which, on complete acid hydrolysis, gave Ala, 3 Gly, Glu, His, 3 Lys, Phe, Tyr, 2 Val, and one molar equivalent of ammonia.

1. Treatment of the peptide (P) with carboxypeptidase released alanine, and with 2,4-dinitrofluorobenzene followed by hydrolysis gave the 2,4-dinitrophenyl derivative of valine. These results establish the N-terminus as valine and the C-terminus as alanine. The known structural elements now are

2. Partial hydrolysis of the peptide (P) with trypsin gave a hexapeptide, a tetrapeptide, a dipeptide, and one molar equivalent of lysine. The peptides, which we will designated respectively as M, N, and O, were sequenced by Edman degradation and found to have structures:

$$\begin{array}{ll} \text{Gly} - \text{Ala} & \text{O} \\ \text{Val} - \text{Tyr} - \text{Glu} - \text{Lys} & \text{N} \\ \text{Val} - \text{Gly} - \text{Phe} - \text{Gly} - \text{His} - \text{Lys} & \text{M} \end{array} \tag{25.7.1}$$

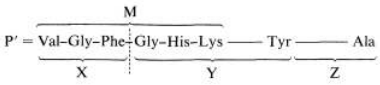
With this information, four possible structures can be written for the original peptide P that are consistent with the known end groups and the fact that trypsin cleaves the peptide P on the *carboxyl* side of the lysine unit. Thus

$$\begin{array}{ll} \text{N} - \text{M} - \text{Lys} - \text{O} & \text{M} - \text{N} - \text{Lys} - \text{O} \\ \text{N} - \text{Lys} - \text{M} - \text{O} & \text{M} - \text{Lys} - \text{N} - \text{O} \end{array} \tag{25.7.2}$$

3. Partial hydrolysis of the peptide P using chymotrypsin as catalyst gave three peptides, X, Y, and Z. These were not sequenced, but their amino-acid composition was determined:

$$\begin{array}{ll} \text{Gly, Phe, Val} & \text{X} \\ \text{Gly, His, Lys, Tyr, Val} & \text{Y} \\ \text{Ala, Glu, Gly, 2 Lys} & \text{Z} \end{array} \tag{25.7.3}$$

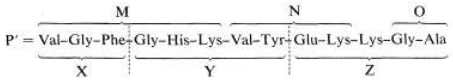
This information can be used to decide which of the alternative structures deduced above is correct. Chymotrypsin cleaves the peptide on the carboxyl side of the phenylalanine and tyrosine units. Only peptide M contains Phe, and if we compare M with the compositions of X, Y, and Z, we see that only X and Y overlap with M. Peptide Z contains the only Ala unit and must be the C-terminus. If we put together these pieces to get a peptide, P' (which differs from P by not having the nitrogen corresponding to the ammonia formed on complete hydrolysis) then P' must have the structure X-Y-Z:



This may not be completely clear, and it will be well to consider the logic in some detail. Peptides M and N both have N-terminal valines, and one of them must be the N-terminal unit. Peptide M overlaps with X and Y, and because X and Y are produced by a cleavage on the *carboxyl* side of Phe, the X and Y units have to be connected in the order X-Y. Because the other Val is in Y, the N-terminus must be M. This narrows the possibilities to

$$\begin{array}{l} \text{M} - \text{N} - \text{Lys} - \text{O} \\ \text{M} - \text{Lys} - \text{N} - \text{O} \end{array} \tag{25.7.4}$$

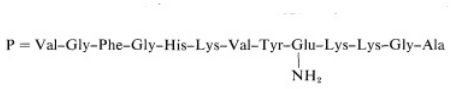
There are two Lys units in Z, and this means that only the sequence M-N-Lys-O is consistent with the sequence X-Y-Z, as shown:



The final piece of the puzzle is the placement of the mole of ammonia released from the original peptide on acid hydrolysis. The ammonia comes from a primary amide function:

$$\mathrm{R{-}CONH_2} \xrightarrow{\mathrm{H_3O^{\oplus}}} \mathrm{RCO_2H + NH_4^-} \tag{25.7.5}$$

The amide group cannot be at the C-terminus because the peptide would then be inert to carboxypeptidase. The only other possible place is on the side-chain carboxyl of glutamic acid. The complete structure may be written as

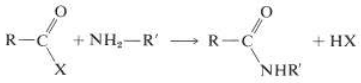


Using procedures such as those outlined in this section more than 100 proteins have been sequenced. This is an impressive accomplishment considering the complexity and size of many of these molecules (see, for example, Table 25-3). It has been little more than two decades since the first amino acid sequence of a protein was reported by F. Sanger, who determined the primary structure of insulin (1953). This work remains a landmark in the history of chemistry because it established for the first time that proteins have definite primary structures in the same way that other organic molecules do. Up until that time, the concept of definite primary structures for proteins was openly questioned. Sanger developed the method of analysis for N-terminal amino acids using 2,4-dinitrofluorobenzene and received a Nobel Prize in 1958 for his success in determining the amino-acid sequence of insulin.

25.7.3: Methods for Forming Peptide Bonds

The problems involved in peptide syntheses are of much practical importance and have received considerable attention. The major difficulty in putting together a chain of say 100 amino acids in a particular order is one of overall yield. At least 100 separate synthetic steps would be required, and, if the yield in each step were equal to $n \times 100\%$, the overall yield would be $(n^{100} \times 100\%)$. If the yield in each step were 90%, the overall yield would be only 0.003%. Obviously, a practical laboratory synthesis of a peptide chain must be a highly efficient process. The extraordinary ability of living cells to achieve syntheses of this nature, not of just one but of a wide variety of such substances, is truly impressive.

Several methods for the formation of amide bonds have been discussed in Sections 18-7A and 24-3A. The most general reaction is shown below, in which X is some reactive leaving group (see Table 24-1):



When applied to coupling two different amino acids, difficulty is to be expected because these same reactions can link two amino acids in a total of four different ways. Thus if we started with a mixture of glycine and alanine, we could generate for dipeptides, Gly-Ala, Ala-Gly, Gly-Gly, and Ala-Ala.

To avoid unwanted coupling reactions a protecting group is substituted on the amino function of the acid that is to act as the acylating agent. Furthermore, all of the amino, hydroxyl, and thiol functions that may be acylated to give undesired products usually must be protected. For instance, to synthesize Gly-Ala free of other possible dipeptides, we would have to protect the amino group of glycine and the carboxyl group of alanine:

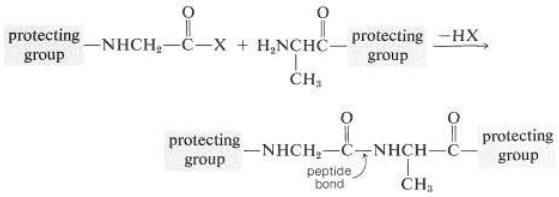


Figure 25-7.

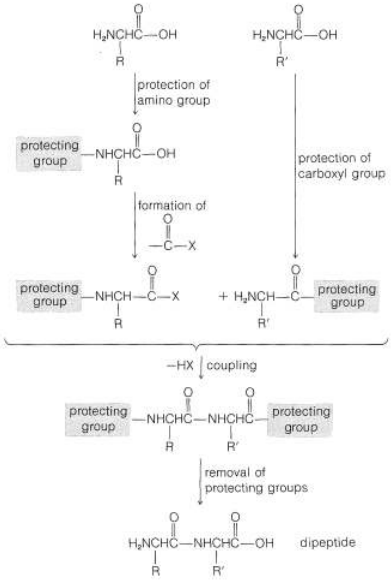


Figure 25-7: Sequence of reactions for forming a peptide bond from two different amino acids. The same type of procedure can be used to make peptide bonds between two peptides or between an amino acid and a peptide.

Some methods of protecting amine and hydroxyl functions were discussed previously in Sections 23-13 and 15-9, respectively. A summary of some commonly used protecting groups for NH_2, OH, SH, and CO_2H functions is in Table 25-2, together with the conditions by which the protecting groups may be removed. The best protecting groups for NH_2 functions are phenylmethoxycarbonyl (benzyloxycarbonyl) and *tert*-butoxycarbonyl. Both groups can be removed by treatment with acid, although the *tert*-butoxycarbonyl group is more reactive. The phenylmethoxycarbonyl group can be removed by reduction with either hydrogen over a metal catalyst or with sodium in liquid ammonia. This method is most useful when, in the removal step, it is necessary to avoid treatment with acid:

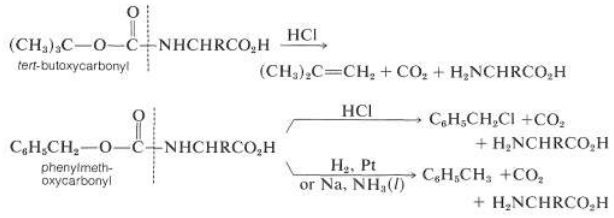


Table 25-2: *Some Amine and Carboxyl Protecting Groups Used in Peptide Syntheses*

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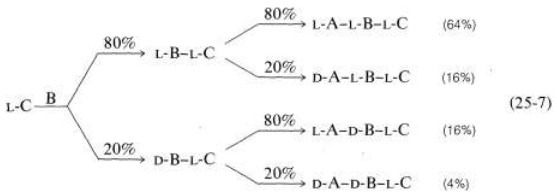
Common name	Structure	Synthesis	Removed by[a]
Amino Protecting Groups			
tert-butoxycarbonyl	$(CH_3)_3COC(=O)-$	$(CH_3)_3COC(=O)Cl + H_2NR$	1, 2, 3
benzyloxycarbonyl	$C_6H_5CH_2OC(=O)-$	$C_6H_5CH_2OC(=O)Cl + H_2NR$	1, 3, 4, 5
para-toluenesulfonyl	$4\text{-}CH_3C_6H_4SO_2-$	$4\text{-}CH_3C_6H_4SO_2Cl + H_2NR$	5
triphenylmethyl (trityl)	$(C_6H_5)_3C-$	$(C_6H_5)_3CCl + H_2NR$	1, 2, 3, 4, 5
Carboxyl Protecting Groups			
ethyl	C_2H_5-	$C_2H_5OH + RCO_2H\ (H^{\oplus})$	6
tert-butyl	$(CH_3)_3C-$	$(CH_3)_2C{=}CH_2 + RCO_2H\ (H_2SO_4)$	1, 2, 3
benzyl	$C_6H_5CH_2-$	$C_6H_5CH_2OH + RCO_2H\ (H^{\oplus})$	1, 3, 4, 5, 6
Hydroxyl and Thiol			
tert-butyl	$(CH_3)_3C-$	$(CH_3)_2C{=}CH_2 + ROH\ (H_2SO_4)$	1, 2, 3
benzyl	$C_6H_5CH_2-$	$C_6H_5CH_2Cl + RSNa$	1, 3, 4, 5

1 = HBr, CH_3CO_2H
2 = CF_3CO_2H
3 = HF
4 = H_2, Pd
5 = Na, NH_3
6 = NaOH

[a]Reagents at room temperature except for Na,NH_3, which is carried out at the bp of $NH_3(l)$, $-33°$.

In most cases, formation of the ethyl ester provides a satisfactory protecting group for the carboxyl function.

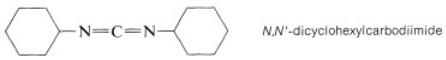
Conversion of the carboxyl group to a more reactive group and coupling are key steps in peptide synthesis. The coupling reaction must occur readily and quantitatively, and with a minimum of racemization of the chiral centers in the molecule. This last criterion is the Achilles' heel of many possible coupling sequences. The importance of nonracemization can best be appreciated by an example. Consider synthesis of a tripeptide from three protected *L*-amino acids, A, B, and C, in two sequential coupling steps, $C \xrightarrow{B} B-C \xrightarrow{A} A-B-C$. Suppose that the coupling yield is quantitative, but there is 20% formation of the *D* isomer in the *acylating* component in each coupling step. Then the tripeptide will consist of a mixture of four diastereomers, only 64% of which will be the desired *L*,*L*,*L* diastereomer (Equation 25-7):



(25-7)

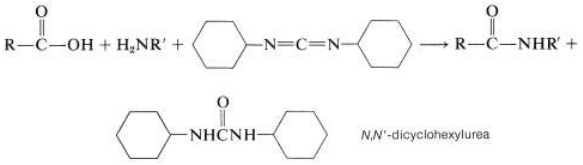
This is clearly unacceptable, especially for longer-chain peptides. Nine coupling steps with 20% of the wrong isomer formed in each would give only 13% of the decapeptide with the correct stereochemistry.

The most frequently used carboxyl derivatives in amide coupling are azides, $RCO-N_3$, mixed anhydrides, $RCO-O-COR'$, and esters of moderately acidic phenols, $RCO-OAr$ (see Table 24-1). It also is possible to couple free acid with an amine group using a diimide, $R-N{=}C{=}N-R$, most frequently N,N′-dicyclohexylcarbodiimide.



N,N′-dicyclohexylcarbodiimide

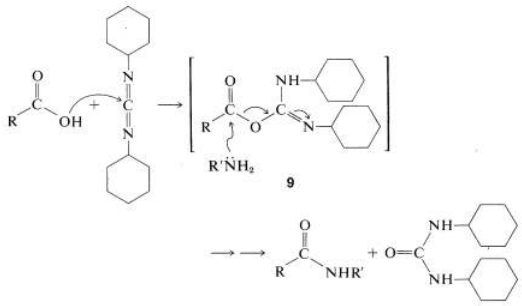
The diimide reagent may be thought of as a dehydrating agent. The "elements of water" eliminated in the coupling are consumed by the diimide to form a substituted urea. The overall reaction is



N,N′-dicyclohexylurea

This reaction takes place because diimides, $-N{=}C{=}N-$, have reactive cumulated double-bond systems like those of ketenes, $-C{=}C{=}O$; isocyanates, $-N{=}C{=}O$; and isothiocyanates, $-N{=}C{=}S$; and are susceptible to nucleophilic attack at the central carbon. In the first step of the diimide-coupling reaction, the carboxyl function adds to the imide to give an acyl intermediate, 9. This

intermediate is an activated carboxyl derivative RCO—X and is much more reactive toward an amino function than is the parent acid. The second step therefore is the aminolysis of 9 to give the coupled product and N,N′-dicyclohexylurea:



After completion of a coupling reaction, and before another amino acid can be added to the N-terminus, it is necessary to remove the protecting group. This must be done by selective reactions that do not destroy the peptide bonds or side-chain protecting groups. This part of peptide synthesis is discussed in Section 23-13, and some reactions useful for removal of the N-terminal protecting groups are summarized in Table 25-2.

In spite of the large number of independent steps involved in the synthesis of even small peptides, each with its attendant problems of yield, racemization, and selectivity, remarkable success has been achieved in the synthesis of large peptides and certain of the smaller peptides. The synthesis of insulin (Figure 25-8) with its 51 amino acid units and 3-disulfide bridges has been achieved by several investigators. Several important hormonal peptides, namely glutathione, oxytocin, vasopressin, and thyrotropic hormone (see Figure 25-9) have been synthesized. A major accomplishment has been the synthesis of an enzyme with ribonuclease activity reported independently by two groups of investigators, led by R. Hirschman (Merck) and R. B. Merrifield (Rockefeller University). This enzyme is one of the simpler proteins, having a linear stricture of 124 amino-acid residues. It is like a peptide, not a protein, in that it assumes the appropriate secondary and tertiary structure without biochemical intervention (Section 25-7A). As a specific example of the strategy involved in peptide synthesis, the stepwise synthesis of oxytocin is outlined in Figure 25-10, using the abbreviated notation in common usage.

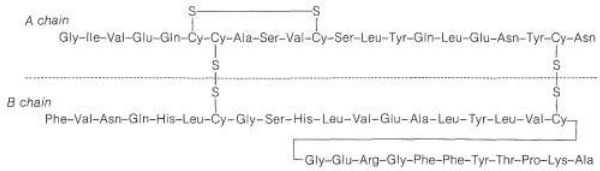
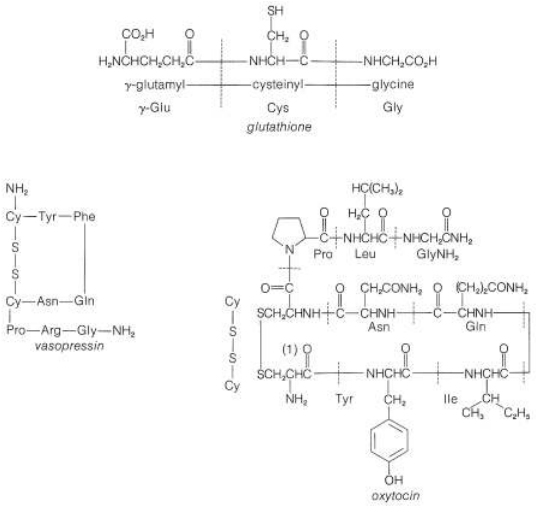


Figure 25-8: Amino-acid sequence in beef insulin. The A chain of 21 amino-acid residues is linked to the B chain of 30 residues by way of two disulfide bridges.



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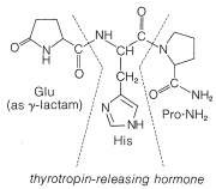


not *to* C_1. *Vasopressin (middle left) and oxytocin (middle right) are peptide hormones from the posterior lobe of the pituitary gland. They function primarily to raise blood pressure (vasopressin), as antidiuretic (vasopressin), and to promote contraction of uterus and lactation muscles (oxytocin). The isolation, identification, and synthesis of these hormones was accomplished by Vincent du Vigneaud, for which he was awarded the Nobel Prize in chemistry in 1965. Thyrotropin-releasing hormone (bottom) is one of several small peptide hormones secreted by the anterior lobe of the pituitary gland. These are the "master" hormones that function to stimulate hormone secretion from other endocrine glands. Thyrotropin stimulates the functioning of the thyroid gland.*

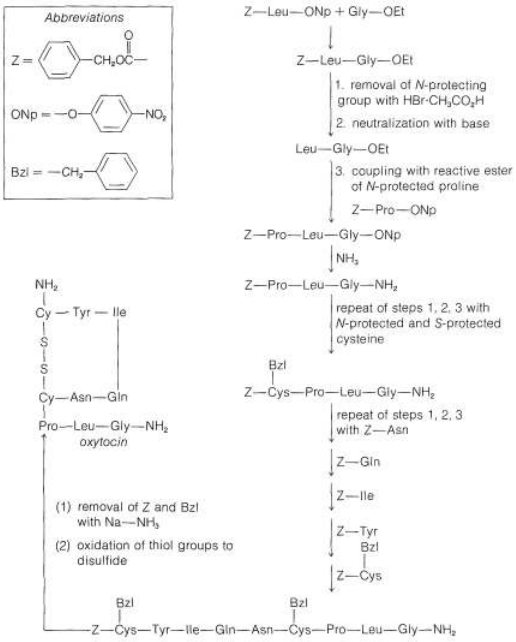
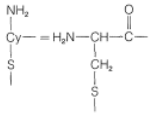


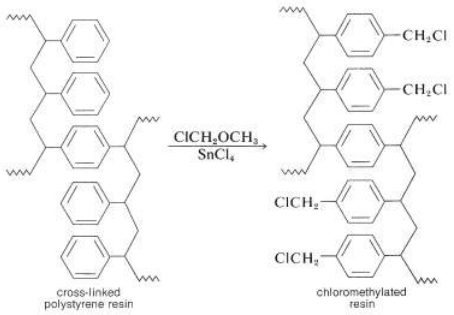
Figure 25-10: *Stepwise synthesis of oxytocin by the reactive ester method. In the abbreviations used here* $-\mathrm{Gly}-\mathrm{NH_2} = -\mathrm{NHCH_2CONH_2}$ *and*



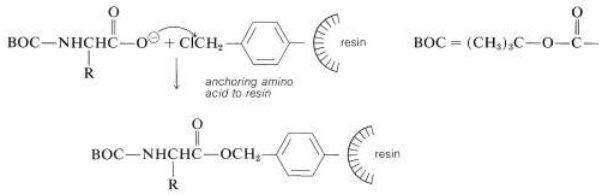
25.7.4: Solid-Phase Peptide Synthesis

The overall yield in a multistep synthesis of a peptide of even modest size is very poor unless each step can be carried out very efficiently. An elegant modification of classical peptide synthesis has been developed by R. B. Merrifield, which offers improved yields by minimizing manipulative losses that normally attend each step of a multistage synthesis. The key innovation is to anchor the C-terminal amino acid to an insoluble support, and then add amino-acid units by the methods used for solution syntheses. After the desired sequence of amino acids has been achieved, the peptide can be cleaved from the support and recovered from solution. All the reactions involved in the synthesis must, of course, be brought to essentially 100% completion so that a homogeneous product can be obtained. The advantage of having the peptide anchored to a solid support is that laborious purification steps are virtually eliminated; solid material is purified simply by washing and filtering without transferring the material from one container to another. The method has become known as **solid-phase peptide synthesis**. More of the details of the solid-phase synthesis follow.

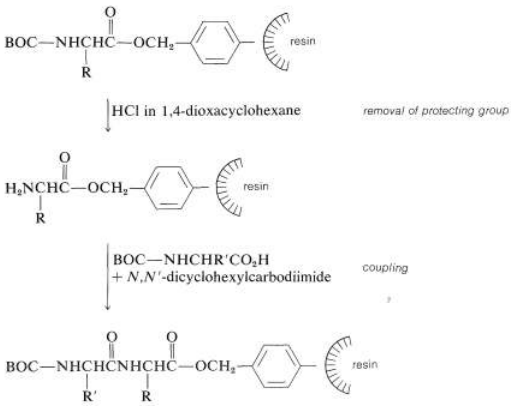
The nature of the polymer support is of great importance for a successful peptide synthesis. One that is widely used is a cross-linked polystyrene resin of the type employed in ion-exchange chromatography (Section 25-4C). It is necessary that the resin be insoluble but have a loose enough structure to absorb organic solvents. Otherwise, the reagents will not be able to penetrate into the spaces between the chains. This is undesirable because the reactions occur on the surface of the resin particles and poor penetration greatly reduces the number of equivalents of reactive sites that can be obtained per gram of resin. Finally, to anchor a peptide chain to the resin, a reactive functional group (usually a chloromethyl group) must be introduced into the resin. This can be done by a Friedel-Crafts chloromethylation reaction, which substitutes the $ClCH_2-$ group in the 4-position of the phenyl groups in the resin:



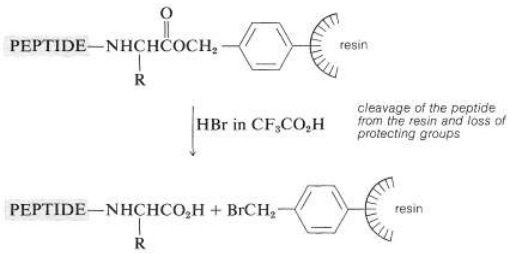
At the start of the peptide synthesis, the C-terminal amino acid is bonded through its carboxyl group to the resin by a nucleophilic attack of the carboxylate ion on the chloromethyl groups. The α-amino group must be suitably protected, as with *tert*-butoxycarbonyl, before carrying out this step:



Next, the amine protecting group must be removed without cleaving the ester bond to the resin. The coupling step to a second N-protected amino acid follows, with N,N′-dicyclohexylcarbodiimide as the coupling reagent of choice:



The peptide-bond-forming steps are repeated as many times as needed to build up the desired sequence. Ultimately, the peptide chain is removed from the resin, usually with HBr in anhydrous trifluoroethanoic acid, CF_3CO_2H, or with anhydrous HF. This treatment also removes the other acid-sensitive protecting groups.



The method lends itself beautifully to automatic control, and machines suitably programmed to add reagents and wash the product at appropriate times have been developed. At present, the chain can be extended by six or so amino acid units a day. It is necessary to check the homogeneity of the growing peptide chain at intervals because if any step does not proceed properly, the final product can be seriously contaminated with peptides with the wrong sequence.

In the synthesis of the enzyme ribonuclease by the Merrifield method, the 124 amino acids were arranged in the ribonuclease sequence through 369 reactions and some 12,000 individual operations of the automated peptide-synthesis machine without isolation of any intermediates.

25.7.5: Separation of Peptides and Proteins

In many problems of peptide sequencing and peptide synthesis it is necessary to be able to separate mixtures of peptides and proteins. The principal methods used for this purpose depend on acid-base properties or on molecular sizes and shapes.

Ultracentrifugation is widely used for the purification, separation, and molecular-weight determination of proteins. A centrifugal field, up to 500,000 times that of gravity, is applied to the solution, and molecules move downward in the field according to their mass and size.

Large molecules also can be separated by **gel filtration** (or gel chromatography), wherein small molecules are separated from large ones by passing a solution over a gel that has pores of a size that the small molecules can penetrate into and be trapped. Molecules larger than the pore size are carried on with the solvent. This form of chromatographic separation is based on "sieving" rather than on chemical affinity. A wide range of gels with different pore sizes is available, and it is possible to fractionate molecules with molecular weights ranging from 700 to 200,000. The molecular weight of a protein can be estimated by the sizes of the pores that it will, or will not, penetrate.

The acid-base properties, and hence ionic character, of peptides and proteins also can be used to achieve separations. **Ion-exchange chromatography**, similar to that described for amino acids (Section 25-4C), is an important separation method. Another method based on acid-base character and molecular size depends on differential rates of migration of the ionized forms of a protein in an electric field (**electrophoresis**). Proteins, like amino acids, have isoelectric points, which are the pH values at which the molecules have no net charge. At all other pH values there will be some degree of net ionic charge. Because different proteins have different ionic properties, they frequently can be separated by electrophoresis in buffered solutions. Another method, which is used for the separation and purification of enzymes, is **affinity chromatography**, which was described briefly in Section 9-2B.

[5] The distinction between secondary and tertiary structure is not sharp. Secondary structure involves consideration of the interactions and spatial relationships of the amino acids in the peptide chains that are *close* together in the primary structure, whereas tertiary structure is concerned with those that are *far apart* in the primary structure.

25.7.6: Contributors and Attributions

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25.8: Structure and Function of Proteins

The biological functions of proteins are extremely diverse. Some act as hormones that regulate various metabolic processes. An example is insulin, which regulates blood-sugar levels. Enzymes act as catalysts for biological reactions, and other proteins serve as biological structural materials - for example, collagen and elastin in connective tissue and keratin in hair. Iron-containing proteins (hemoglobin and myoglobin in mammals) and copper-containing proteins (hemocyanins in shellfish) transport molecular oxygen. Some blood proteins form antibodies, which provide resistance to disease, while the so-called nucleoproteins are important constituents of the genes that supply and transmit genetic information in cell division. Motion by means of muscle contraction and the generation and transmission of nerve impulses also involve proteins.

How can a group of compounds, made from a common basis set of amino acids, be so remarkably heterogeneous and exhibit such varied yet specific functions? Clearly, the primary structure and presence or absence of special functional groups, metals, and so on, are of paramount importance. Of complementary importance are the *three-dimensional structures* of proteins, which are dictated not just by the primary structure but by the way the primary structure is put together biochemically. The polypeptide chains are seldom, if every fully extended, but are coiled and folded into more or less stable conformations. As a result, amino-acid side chains in distant positions in the linear sequence are brought into close proximity, and this juxtaposition often is crucial for the protein to fulfill its specific biological function.

25.8.1: Three-Dimensional Structure of Proteins

The elucidation of the detailed *shape* of protein molecules - in fact, the spatial locations of the individual atoms in a protein - is accomplished primarily by x-ray crystallography. The three-dimensional structures of more than twenty proteins have now been established by this technique. The importance of x-ray crystallography to structural and biological chemistry has been recognized in the award of six Nobel Prizes in this area.[6] A number of important proteins and their properties are listed in Table 25-3.

Table 25-3: *A Few Important Proteins of Known Structure*

Name	Approx. MW	Amino acids	Disulfide bonds	Prosthetic group	Isoelectric point	Occurrence	Function
insulin	5,800	51	3	–	5.4	pancreas	regulation of blood sugar levels
ribonuclease	13,700	124	4	–	7.8	pancreas	enzyme that hydrolyzes RNA
myoglobin	17,800	153	–	heme		muscle	respiratory protein; stores O_2 in muscle tissue
hemoglobin	64,500	α-141[a] β-146	–	heme	6.7	red blood corpuscles	respiratory protein; transports O_2 from lungs; transports CO_2 to lungs
cytochrome *c*	12,800	104	–	heme[b]		all cells	respiratory protein; electron carrier for *oxidative phosphorylation*[c]
lysozyme	14,600	129	4	–	10.7	egg white	enzyme that breaks down the cell walls of bacteria by hydrolysis of $\beta(1 \rightarrow 4)$ glycoside linkages
α-chymotrypsin	24,500	241	5	–	8.4	pancreas	digestive enzyme; hydrolyzes ester and peptide bonds
carboxypeptidase A	34,600	307	–	Zn		pancreas	digestive enzyme; hydrolyzes carboxyterminal peptide bond in proteins

[a]Hemoglobin has four subunits, two α chains and two β chains, each with a heme group.

[b]Cytochrome *c* has two cysteine units covalently bonded to the two ethenyl side chains of the heme group:
protein—SH + CH_2=CH—heme ⟶ protein—S—CH_2CH_2—heme

[c]Oxidative phosphorylation is the process in which ATP is formed as electrons are transferred (by way of the cytochromes) from NADH or $FADH_2$ to O_2. For example, $\frac{1}{2}O_2 + NADH + H^{\oplus} \longrightarrow H_2O + NAD^{\oplus}$, and the energy from this process is used to synthesize ATP (see Section 20-10).

Figure 25-12.

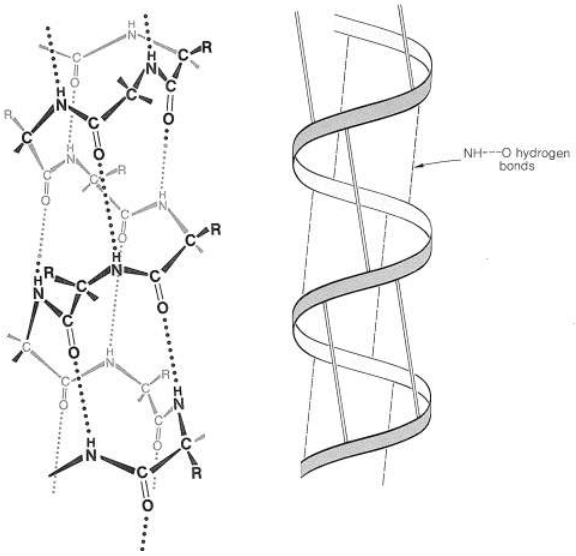

Figure 25-11: Peptide chain of a protein coiled to form a right-handed alpha helix. Configuration of the helix is maintained by hydrogen bonds, shown as vertical dotted (or solid) lines. The helix on the left shows the detailed atom structure of the peptide chain. The helix on the right is a schematic representation without structural detail.

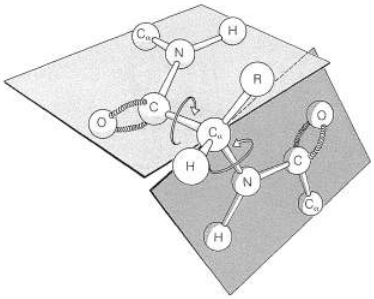

Figure 25-12: Ball-and-stick model of a peptide unit showing the coplanarity of the CNCC atoms of the amide linkage, here in the trans configuration, and the possibility of rotation about the $\mathrm{C{-}C_\alpha}$ and $\mathrm{N{-}C_\alpha}$ bonds.

There are several other points to notice about the α helix shown in Figure 25-11. The amide groups are planar and normally retain the stable *trans* configuration in the helical structure; bond lengths and bond angles are normal, and the $\mathrm{-NH\cdots O{=}C-}$ hydrogen bonds are nearly linear. However, the hydrogen bonds are not quite parallel to the long axis of the coil, so there are 3.6 rather than 4 amino-acid units per helical turn, and the spacing between turns is about 5.4 Å. The α helix in proteins has *right-handed* turns like a right-hand screw thread.

The amino acids of the side chains lie outside the coil of the α helix and are in close proximity to the side chains three and four amino-acid units apart. Because of this proximity, steric hindrance between large side chains can be sufficient to reduce the stability of the normal α helix. When such hindrance occurs, there is a discontinuity in the helical structure, and the peptide chain may assume more random arrangements about the $\mathrm{C{-}C_\alpha}$ and $\mathrm{N{-}C_\alpha}$ bonds (see Figure 25-12), thereby allowing the molecule to fold back on itself and form new hydrogen bonds. The helical structure apparently is always interrupted at proline or hydroxyproline residues because the $\mathrm{N{-}C_\alpha}$ bonds of these amino acids are not free to rotate (they are incorporated in five-membered rings) and also because the proline and hydroxyproline amide nitrogens have no hydrogens to participate in hydrogen bonding to carbonyl groups.

Pauling and Corey recognized a second stable conformation of polypeptide chains - the extended chain or β-pleated sheet (Figure 25-13). In this conformation the chains are fully extended with trans amide configurations. In this arrangement the distance is maximized between adjacent amino-acid side chains. Hydrogen bonding of the type $\mathrm{-N{-}H\cdots O{=}C-}$ is now *between chains* rather than between amino acids in a single chain (as in the α helix). This type of structure is not as common as the α helix and is found extensively only in silk fibroin. However, a number of proteins with a single polypeptide chain can form short sections of "antiparallel" β-pleated sheets by folding back on themselves, as illustrated in Figure 25-14.

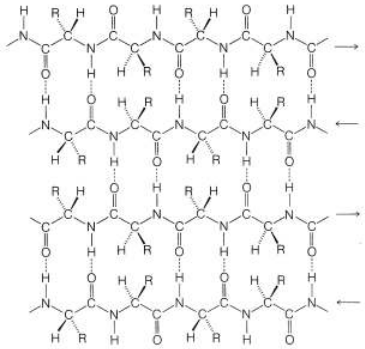

Figure 25-13: Hydrogen-bonded structure of silk fibroin. Notice that the peptides run in different directions in alternate chains. This structure is called an antiparallel β-pleated sheet.

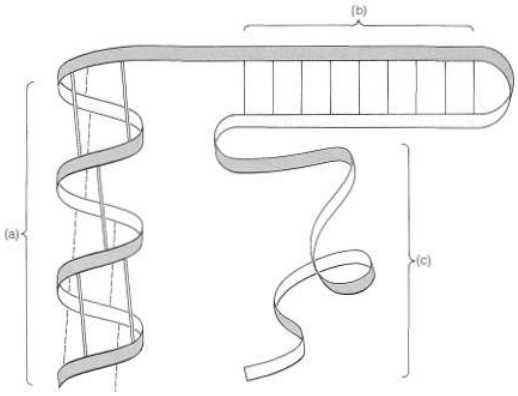

Figure 25-14: Diagrammatic representation of the coiling of a protein chain showing areas of (a) α helix, (b) β-pleated sheet, and (c) random coiling.

Another very important factor in protein architecture is the disulfide $-S-S-$ link. Remote parts of the polypeptide chain can be held close together through the oxidative coupling of two cysteine thiol groups to form a disulfide bridge:

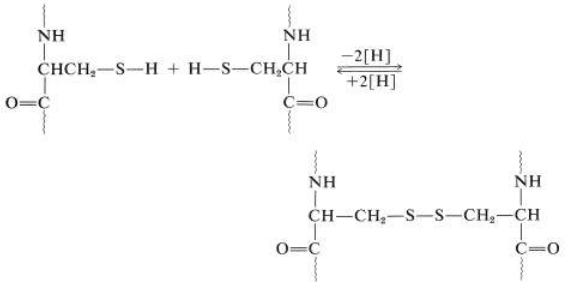

Figure 25-15). It becomes inactive if the disulfide bridges are cleaved or combined in other combinations than the ones shown.

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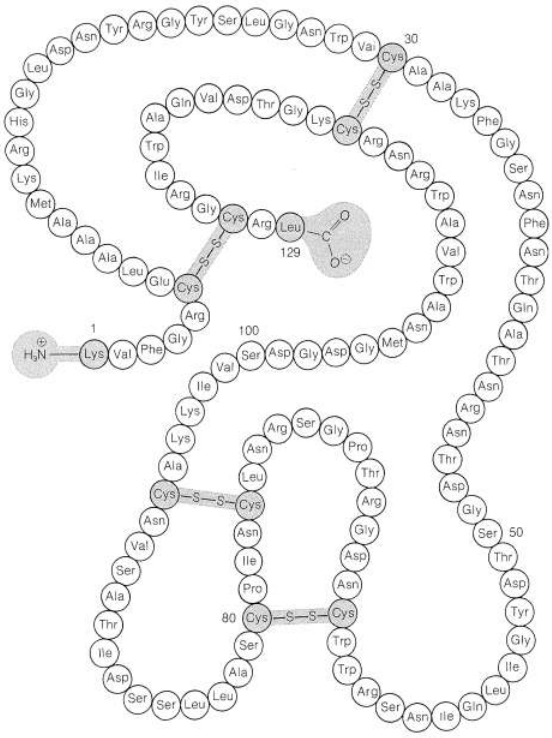


Figure 25-15: Lysozyme from hen egg-white showing the amino-acid sequence (primary structure) and the four intrachain disulfide bridges. [Adapted from D. C. Phillips, Sci. Amer., 5, 215 (1966).]

The disulfide bridges in some proteins are between different peptide chains. Insulin, for instance, has two interchain as well as one intrachain S–S bridges (Figure 25-8).

25.8.2: Myoglobin and Hemoglobin

Some idea of the complexity of protein conformations can be gained from the structure of myoglobin. This protein is responsible for the storage and transport of molecular oxygen in the muscle tissue of mammals. It is a compact molecule of 153 amino-acid units in a chain that is extensively coiled as an α helix. There are eight regions of discontinuity in the helical structure, and in these regions the chain folds on itself as shown in Figure 15-16. Four of the eight nonhelical regions occur at proline residues; the reason for the discontinuity at the other regions is not entirely clear. With the exception of two histidine units, the interior regions of myoglobin accommodate only the nonpolar side chains; the interior, therefore, is mostly hydrocarbonlike and repellant to water and other polar molecules. In contrast, the polar side chains are on the exterior of the protein.

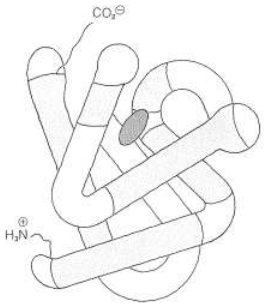
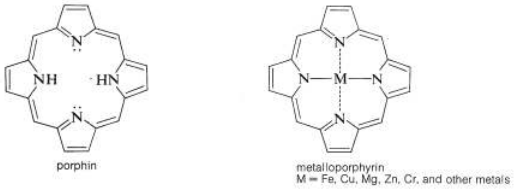


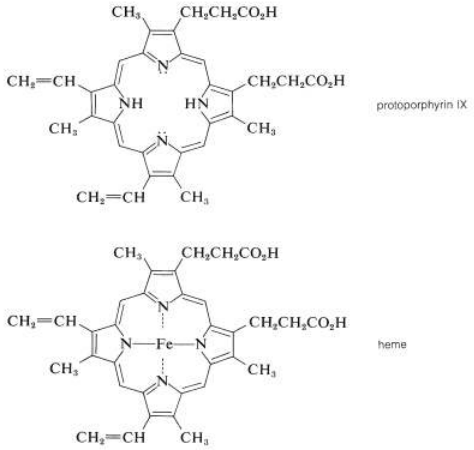
Figure 25-16: A model of myoglobin to show the way in which the polypeptide chain is coiled and folded. The shaded sections correspond to regions in which the chain is coiled into an α helix. Each fold, and the regions near the C-terminus and the N-terminus, represent discontinuities in the helical structure. The position of the heme group is represented by the disclike shape.

A number of proteins, including myoglobin, possess one or more nonpeptide components associated with specific sites on the polypeptide chain. These components are called **prosthetic groups** and are essential to the biological activity. When the prosthetic group is removed, the residual protein is referred to as an **apoprotein**.

In myoglobin the prosthetic group is a molecule of **heme**. The heme group belongs to a class of interesting compounds called **metalloporphyrins**, which are metal complexes of a highly conjugated ring system composed of four azacyclopentadiene (pyrrole) rings linked by $-CH=$ bridges between the 2 and 5 positions. The parent compound is known as **porphin**. Porphyrins have highly stabilized electronic excited states and absorb visible light. As a result they usually are brightly colored compounds (e.g., chlorophyll, Figure 20-6).

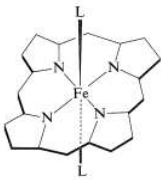


The porphyrin of heme is known as protoporphyrin IX, and the associated metal is iron [as Fe(II) or Fe(III)]. You will notice that the porphyrin ring carries methyl, ethenyl, and propanoic acid side chains:



A major effort on the part of several eminent chemists in the early part of the century led to the elucidation of the structure of heme. The German chemist Hans Fischer successfully synthesized heme in 1929, a feat for which, in 1930, he received the Nobel Prize in chemistry. [Some years earlier (1915), Richard Willstatter received a Nobel Prize for structural studies of chlorophyll and plant pigments.]

A very important question is, how does the particular combination of protein and iron-porphyrin allow myoglobin to reversibly bind molecular oxygen? The answer to this question is not known in all its details, but it is well established that Fe(II)-porphyrins will complex readily and reversibly with oxygen. There are two additional coordination sites around the iron in heme besides the four ring nitrogens. These are indicated below as the general ligands L:



The disclike heme molecule fits into a cleft in the protein structure and is bound to it through one of the L coordination sites to a histidine nitrogen. The remaining coordination site on the other side of the ring is occupied by molecular oxygen. In the absence of the coordination by histidine, the porphyrin iron would be oxidized rapidly to the ferric state, which does not bind oxygen.

A number of model compounds have been synthesized which have Fe(II)-porphyrin rings carrying a side chain with histidine arranged to be able to coordinate with the metal on one side. Several of these substances show promise as oxygen carriers with properties similar to myoglobin.

Hemoglobin is related to myoglobin in both its structure and function. It reversibly binds molecular oxygen which it transports in the red corpuscles of blood rather than in muscle tissue. However, hemoglobin is made up of *four* polypeptide chains, in contrast to myoglobin which has only *one* chain. Two of the hemoglobin chains are of one kind with 141 amino acid residues, called the α chains, and two are of another kind with 146 amino acids, called the β chains. Each chain, or *subunit*, contains one heme group identical with the heme in myoglobin. The subunits are held in the hemoglobin by noncovalent interactions and provide four hemes and hence four binding sites for molecular oxygen. The α and β hemes have different affinities for oxygen but function in a cooperative way to increase oxygen availability to the cells.

In spite of the fact that the α and β chains of hemoglobin are nonidentical with the myoglobin chain, the three-dimensional structures of all three chains are strikingly similar; myoglobins and hemoglobins differ slightly in amino acid composition, depending on the species but the protein shape remains essentially the same.

25.8.3: Quaternary Structures of Proteins

Many factors contribute to the three-dimensional structures of proteins. We already have mentioned hydrogen bonding between amide groups, location and character of prosthetic groups, and disulfide bonds. Other important influences include electrostatic interactions between ionic groups ($-NH_3^+$, $-CO_2^-$), hydrogen-bonding involving side-chain substituents ($-CH_2OH$), and nonbonded interactions. Except for the disulfide linkages, most of these interactions are weak compared to covalent bond strengths, and the conformations of many proteins can be altered rather easily. In fact, several have conformations that clearly are in dynamic equilibrium under physiological conditions. Such structural flexibility may be necessary for the protein to be functional, but if the conformation is altered *irreversibly* - that is, if it is denatured - its biological activity usually is destroyed.

In many cases there are important interactions between protein molecules that may lead to highly organized structures such as the pleated sheet of silk fibroin (Figure 25-13) or the coiling of α helices, as found in α-keratins, the fibrous proteins of hair, horn, and muscles (Figure 25-17). This sort of organization of protein molecules is called **quaternary** structure and is an important feature of many proteins that associate into dimers, tetramers, and so on. The tetrameric structure of hemoglobin is an important example.

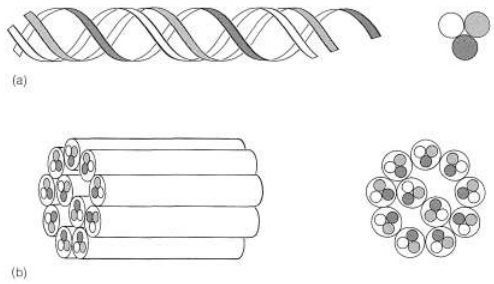


Figure 25-17: Representation of the quaternary structure of α-keratin showing (a) three α-helical polypeptide strands coiled into a rope and (b) eleven units of the three-stranded rope arranged to form one microfibril.

[6]The following Nobel laureates received their awards for contributions to the use of x-ray crystallography for structure determination: 1914, Max von Laue (physics), diffraction of x-rays in crystals; 1915, William Bragg and Lawrence Bragg (physics), study of crystal structure by means of x-rays; 1954, Linus Pauling (chemistry), study of structure of proteins; 1962, Max Perutz and John Kendrew (chemistry), structures of myoglobin and hemoglobin; 1962, Francis Crick, James Watson, and Maurice Wilkins (physiology and medicine), double helix of DNA; 1964, Dorothy Hodgkin (chemistry), determination of structure of vitamin B_{12} and penicillin by x-ray methods. She later determined the three-dimensional structure of insulin.

25.8.4: Contributors and Attributions

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25.9: Enzymes

Virtually all biochemical reactions are catalyzed by proteins called enzymes. The catalytic power and specificity of enzymes is extraordinarily high. The reactions that they catalyze are generally enhanced in rate many orders of magnitude, often as much as 10^7, over the nonenzymatic process. Consequently enzymatic reactions may occur under much milder conditions than comparable laboratory reactions. For example, the simple hydrolysis of an amide proceeds at a practical rate only on heating the amide in either strongly acidic or strongly basic aqueous solution, and even then reaction may not be complete for several hours. In contrast, hydrolysis of amide or peptide bonds catalyzed by typical proteolytic enzymes, such as trypsin, chymotrypsin, or carboxypeptidase A, occurs rapidly as physiological temperatures and physiological pH.[7] It is one of the remarkable attributes of many enzymes that they catalyze reactions that otherwise would require strongly acidic or basic conditions. Enzymes are strictly catalysts, however, and affect only the *rate* of reaction, not the position of equilibrium; they lower the energy of the transition state, not the energies of the reactants or products (see Figure 4-4).

Many enzymes appear to be tailor-made for one specific reaction involving only one reactant, which is called the *substrate*. Others can function more generally with different reactants (substrates). But there is no such thing as a universal enzyme that does all things for all substrates. However, nothing seems to be left to chance; even the equilibration of carbon dioxide with water is achieved with the aid of an enzyme known as carbonic anhydrase.[8] Clearly, the scope of enzyme chemistry is enormous, yet the structure and function of relatively few enzymes are understood in any detail. We can give here only a brief discussion of the mechanisms of enzyme action - first some general principles then some specific examples.

25.9.1: Aspects of the Mechanisms of Enzyme Reactions

An enzyme usually catalyzes a single chemical operation at a very specific position, which means that only a small part of the enzyme is intimately involved. The region of the enzyme structure where key reactions occur as the result of association of the substrate with the enzyme is called the **active site**. The initial association of the enzyme (E) and the substrate (S) is formation of an enzyme-substrate complex (ES):

$$\mathrm{E} + \mathrm{S} \rightleftharpoons \mathrm{ES} \tag{25.9.1}$$

Complexation could occur in many different ways, but for the intimate complexation required for catalysis, the enzyme must have, or must be able to assume, a shape complementary to that of the substrate. Originally, it was believed that the substrate fitted the enzyme somewhat like a key in a lock; this concept has been modified in recent years to the *induced-fit* theory, whereby the enzyme can adapt to fit the substrate by undergoing conformational changes (Figure 25-18). Alternatively, the substrate may be similarly induced to fit the enzyme. The complementarity is three-dimensional, an important factor in determining the specificity of enzymes to the structure and stereochemical configuration of the substrates.

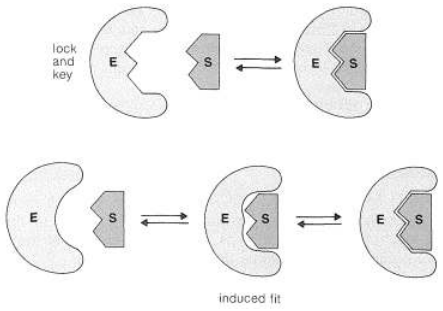


Figure 25-18: Illustration of the lock-and-key concept of enzyme-substrate interaction (top) and of the induced-fit theory, whereby the enzyme molds to the substrate through conformational changes (bottom).

Detailed structures for the active sites of enzymes are difficult to obtain and have been worked out only for a few enzymes that have been studied extensively by both chemical and x-ray methods. Very revealing information has been obtained by x-ray diffraction studies of complexes between the enzyme and *nonsubstrates*, which are molecules similar to actual substrates and complex with the enzyme at the active site, but do not react further. These substances often *inhibit* reaction of the normal substrate by associating strongly with the enzyme at the active site and not moving onward to products. The x-ray studies of enzymes complexed with nonsubstrates show that the active site generally is a cleft or cavity in the folded structure of the enzyme that is

largely hydrophobic in character. The enzyme-substrate complex can be inferred to be held together largely by van der Waals attractive forces between like groups (Section 12-3C), hydrogen-bonding, and by electrostatic attraction between ionic or polar groups. To achieve a stereospecific catalyzed reaction, there must be at least three points of such interactions to align properly the substrate within the cavity of the enzyme.

The reaction of the ES complex may convert the substrate to product (P) directly, and simultaneously free the enzyme (E) to react with more of the substrate:

$$\mathrm{ES} \rightarrow \mathrm{P} + \mathrm{E} \tag{25.9.2}$$

However, the reaction between enzyme and substrate often is much more complex. In many cases, the substrate becomes covalently bound to the enzyme. Then, in a subsequent step, or steps, the enzyme-bound substrate (ES′) reacts to give products and regenerate the active enzyme (E):

$$\mathrm{ES} \rightarrow \mathrm{ES}' \rightarrow \mathrm{P} + \mathrm{E} \tag{25.9.3}$$

25.9.2: Carboxypeptidase A

The considerable detail to which we now can understand enzyme catalysis is well illustrated by what is known about the action of carboxypeptidase A. This enzyme (Section 25-7B and Table 25-3) is one of the digestive enzymes of the pancreas that specifically hydrolyze peptide bonds at the C-terminal end. Both the amino-acid sequence and the three-dimensional structure of carboxypeptidase A are known. The enzyme is a single chain of 307 amino-acid residues. The chain has regions where it is associated as an α helix and others where it is associated as a β-pleated sheet. The prosthetic group is a zinc ion bound to three specific amino acids and one water molecule near the surface of the molecule. The amino acids bound ot zinc are His 69, His 196, and Glu 72; the numbering refers to the position of the amino acid along the chain, with the amino acid at the N-terminus being number 1. The zinc ion is essential for the activity of the enzyme and is implicated, therefore, as part of the active site.

X-ray studies[9] of carboxypeptidase complexed with glycyltyrosine (with which it reacts only slowly) provide a detailed description of the active site, which is shown schematically in Figure 25-19a and is explained below.

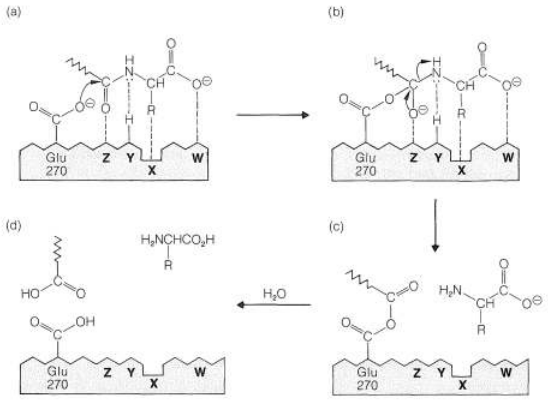
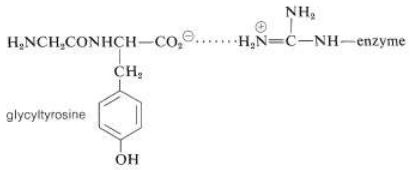


Figure 25-19: Steps in a possible mechanism of carboxypeptidase action. (a) The substrate is shown complexed to the enzyme surface through X, Y, Z, and W; X is a nonpolar pocket; Y is a hydrogen bond, possibly from OH of Tyr 248; Z is the prosthetic group, Zn; and W is an ionic interaction with $=\overset{\oplus}{\mathrm{N}}\mathrm{H}_2$ of Arg 145. The C-terminal amide bond of the substrate is held close to the catalytic site, which is the carboxyl of Glu 270. (b) A tetrahedral intermediate could be formed by attack of Glu 270 carboxylate anion at the amide carbonyl of the substrate. (c) Cleavage of the tetrahedral intermediate of (b) releases the C-terminal amino acid and forms an acyl-enzyme intermediate. (d) The residue of the substrate chain is released from the enzyme by hydrolysis of the acyl-enzyme intermediate. These drawings are deficient in that they try to reproduce a three-dimensional situation in two dimensions. The third dimension is especially important in understanding the stereospecificity of the enzyme.

1. The tyrosine carboxylate group of the substrate is associated by electrostatic attraction with the positively charged side chain of arginine 145 (W):



2. The tyrosine side chain of the substrate associates with a nonpolar pocket in the enzyme (X).
3. Hydrogen bonding possibly occurs between the substrate tyrosine amide unshared pair and the side-chain HO groups of the enzyme tyrosine 248 (Y).
4. The glycyl carbonyl oxygen in the substrate probably is coordinated with the zinc ion (Z), displacing the water molecule coordinated to the zinc in the uncomplexed enzyme.
5. A side-chain carboxylate anion of glutamic acid 270 is so situated with respect to the reaction center that it could well function as a nucleophile by attacking the glycine carbonyl carbon.

The arrangement of the enzyme-substrate complex suggests a plausible reaction mechanism analogous to nonenzymatic mechanisms of amide hydrolysis (Section 24-4). The carboxyl group of Glu 270 can add to the amide carbonyl to form a tetrahedral intermediate that then rapidly dissociates to release the terminal amino acid, leaving the rest of the substrate bound to the enzyme as a mixed anhydride which can be symbolized as $E(CO)OCOR_1$. Reaction of the acyl-enzyme intermediate with water will release the peptide, minus the terminal amino acid, and regenerates the enzyme.

This postulated sequence of events may leave you wondering why the enzyme speeds up the hydrolysis, especially because the sequence proceeds through an energetically unfavorable reaction, the formation of a *carboxylic anhydride* from an *amide* and a *carboxylic acid*:

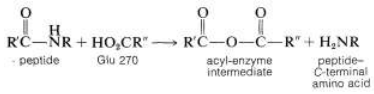


Figure 25-20 is shown with a higher-energy transition state than with water, as would be expected, because CH_3CO_2H is a poorer nucleophile than water.

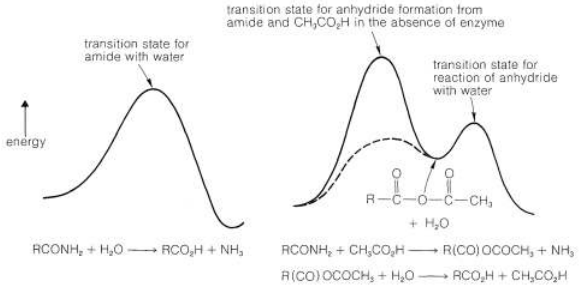
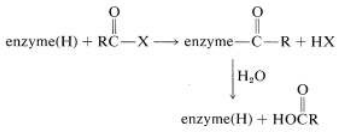


Figure 25-20: Possible energy profiles for different pathways for hydrolysis of a simple amide. The dashed line represents an enzyme-catalyzed formation of $R(CO)OCOCH_3$, which is here hypothesized to have a lower-energy transition state than the reaction of the anhydride with water (see text).

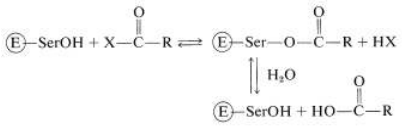
How, then, can we possibly expect that the enzyme could make the anhydride route be faster than the simple water route? The answer is the way in which interactions in the enzyme-substrate complex can stabilize the transition state for the anhydride-forming reaction. Thus for carboxypeptidase the zinc can act as a strong electrophile to facilitate attack on the amide carbonyl. Hydrogen bonding of the amide nitrogen to Tyr 248 both will facilitate attack on the carbonyl group and assist in the breaking of the C–N bond. Furthermore, the nonpolar environment of the alkyl side-chains of the enzyme will increase the nucleophilicity of the $-CO_2^-$ group that forms the anhydride (see Section 8-7F). Inspection of Figure 25-20 shows qualitatively that if the energy of the transition state for formation of the anhydride is lowered greatly, the overall rate will be determined by the rate of hydrolysis of the anhydride! In this circumstance (assuming the anhydride hydrolysis is uncatalyzed), the efficiency of the enzyme in breaking the peptide bond is as great as it can be, at least by this particular pathway of peptide hydrolysis. Such efficiencies have been established for other enzymes.

25.9.3: Participation of Serine in Enzyme Action

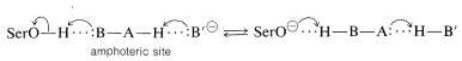
Mechanisms similar to the one described for carboxypeptidase appear to operate in the hydrolysis of amide and ester bonds catalyzed by a number of proteinases and esterases. The substrate, here generalized as RCOX, acts to acylate the enzyme, which subsequently reacts with water to give the observed products:



In the acylation step a nucleophilic group on one of the amino-acid side chains at the active site behaves as the nucleophile. As we have seen in Section 25-9B, the nucleophile of carboxypeptidase is the free carboxyl group of glutamic acid 270. In several other enzymes (chymotrypsin, subtilisin, trypsin, elastase, thrombin, acetylcholinesterase), it is the hydroxyl group of a *serine* residue:

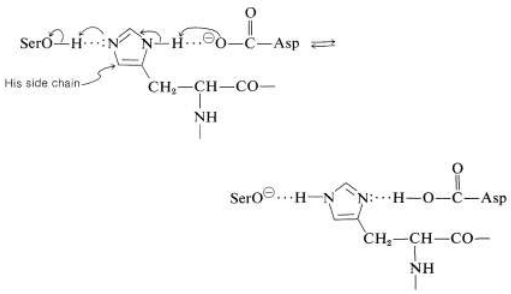


This raises another question. Why is the serine hydroxyl an effective nucleophile when water and other hydroxylic compounds clearly are not similarly effective? Apparently, the nucleophilicity of the serine $-CH_2OH$ is enhanced by acid-base catalysis involving proton transfers between acidic and basic side-chain functions in the vicinity of the active site. The serine is believed to transfer its OH proton to an amphoteric[10] site B–A–H on the enzyme at the same instant that the proton of B–A–H is transferred to another base $B'^{\ominus}$ (Equation 25-8). These proton transfers are, of course, reversible:



Loss of its proton makes the serine hydroxyl oxygen a much more powerful nucleophile, and even though the equilibrium of Equation 25-8 must lie far to the left at physiological pH, it can increase greatly the reactivity of the serine hydroxyl.

In chymotrypsin and subtilisin, this **charge-relay** network system, as it is called, is made up of a specific aspartic acid residue, acting as $B'^{\ominus}$, and a specific histidine residue (acting as the amphoteric B–A–H):



[7]The slowness with which amide bonds are hydrolyzed in the presence of either strong acids or strong bases, and their susceptibility to hydrolysis under the influence of enzymes, clearly is a key advantage in the biological functioning of peptides. Amide hydrolysis in neutral solution has a favorable, but not large, equilibrium constant. Therefore it does not take a great deal of biochemical energy either to form or to hydrolyze peptide bonds. The resistance to ordinary hydrolysis provides needed stability for proteins, and yet when it is necessary to break down the peptide bonds of proteins, as in digestion, this can be done smoothly and efficiently with the aid of the proteolytic enzymes.

[8]Many enzymes are named by adding the suffix *-ase* to a word, or words, descriptive of the type of enzymatic activity. Thus, *esterases* hydrolyze esters, *proteinases* hydrolyze proteins, *reductases* achieve reductions, and *synthetases* achieve synthesis of polypeptide chains, nucleic acid chains, and other molecules.

[9]W. N. Lipscomb, *Accounts of Chemical Research* **3**, 81 (1970); E. T. Kaiser and B. L. Kaiser, *ibid.* **5**, 219 (1972). Lipscomb received the 1976 Nobel Prize in chemistry for structural work on boranes.

[10]Amphoteric means that a substance can act either as an acid or as a base.

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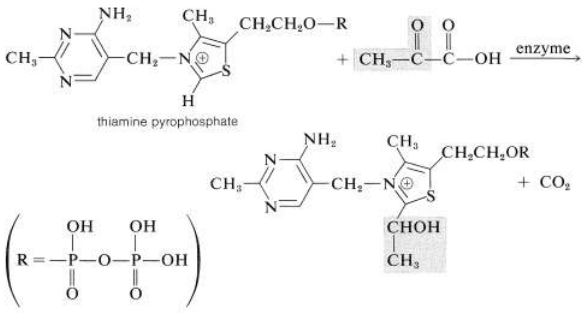
25.10: Coenzymes

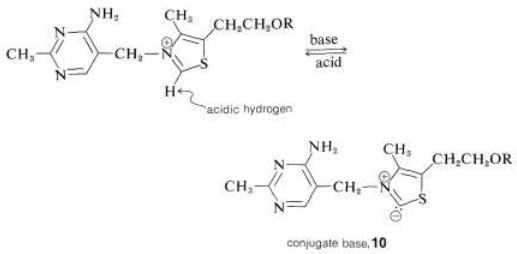
Many enzymes only operate in combination with organic molecules that are actually reagents for the reaction. These substances are called **coenzymes** or **cofactors**. Some coenzymes function with more than one enzyme and are involved in reactions with a number of different substrates.

Several of the B vitamins function as coenzymes or as precursors of coenzymes; some of these have been mentioned previously. Nicotinamide adenine dinucleotide $(NAD^{\oplus})$ which, in conjunction with the enzyme *alcohol dehydrogenase*, oxidizes ethanol to ethanal (Section 15-6C), also is the oxidant in the citric acid cycle (Section 20-10B). The precursor to $NAD^{\oplus}$ is the B vitamin niacin or nicotinic acid (Section 23-2). Riboflavin (vitamin B_2) is a precursor of flavin adenine nucleotide (FAD), a coenzyme in redox processes rather like $NAD^{\oplus}$ (Section 15-6C). Another example of a coenzyme is pyridoxal (vitamin B_6), mentioned in connection with the deamination and decarboxylation of amino acids (Section 25-5C). Yet another is coenzyme A $(CoASH)$, which is essential for metabolism and biosynthesis (Sections 18-8F, 20-10B, and 30-5A).

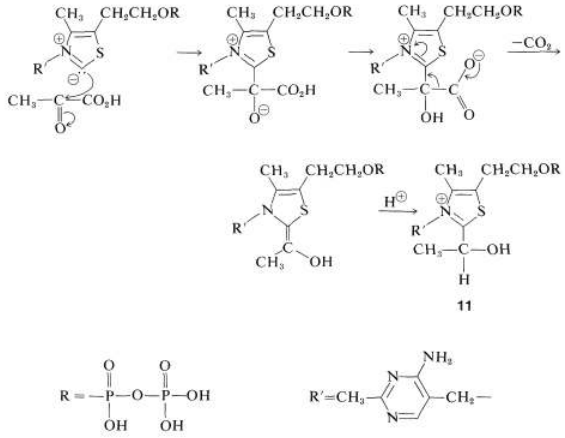
An especially interesting coenzyme is thiamine pyrophosphate (vitamin B_1) which, in conjunction with the appropriate enzyme, decarboxylates 2-oxopropanoic acid (pyruvic acid; Section 20-10B). We can write the overall reaction as follows:



Although we do not know just how thiamine binds to the enzyme, the essential features of the reaction are quite well understood. Thiamine has an acidic hydrogen at the 2-position of the azathiacyclopentadiene ring, and you should recognize that the conjugate base, 10, is both a nitrogen ylide and a sulfur ylide (Section 16-4A):



The acidity of the ring proton of the thiamine ring is a consequence of the adjacent positive nitrogen and the known ability of sulfur to stabilize an adjacent carbanion. Nucleophilic attack of the anionic carbon of 10 on C_2 of 2-oxopropanoic acid is followed by decarboxylation:



The overall reaction introduces a two-carbon chain at the C_2 position of the thiamine ring and the resulting modified coenzyme, 11, functions in subsequent biological reactions as a carrier of a $CH_3{-}CHOH{-}$ group and a potential source of a $CH_3CO{-}$ group. The metabolism of glucose (Section 20-10) requires the conversion of pyruvate to ethanoyl **CoA** by way of 11; and, in fermentation, the hydroxylethyl group of 11 is released as ethanal, which is reduced to ethanol by NADH (see Section 15-6C for discussion of the reverse reaction).

Thiamine pyrophosphate also plays a key role in the biosynthetic reactions that build (or degrade) pentoses from hexoses. We have mentioned these reactions previously in connection with the Calvin cycle (Section 20-9) and the pentose-phosphate pathway (Section 20-10C).

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25.11: Enzyme Regulation

You may have wondered how the proteolytic enzymes such as trypsin, pepsin, chymotrypsin, carboxypeptidase, and others keep from self-destructing by catalyzing their own hydrolysis or by hydrolyzing each other. An interesting feature of the digestive enzymes is that they are produced in an inactive form in the stomach or the pancreas - presumably to protect the different kinds of proteolytic enzymes from attacking each other or other proteins.

The inactive precursors are called trypinogen, pepsinogen, chymotrypsinogen, and procarboxypeptidase. These precursors are converted to the active enzymes by hydrolytic cleavage of a few specific peptide bonds under the influence of other enzymes (trypsin, for example, converts chymotrypsinogen to chymotrypsin). The digestive enzymes do not appear to self-destruct, probably because they are so constructed that it is sterically impossible to fit a part of one enzyme molecule into the active site of another. In this connection, it is significant that chymotrypsin attacks denatured proteins more rapidly than natural proteins with their compact structures of precisely folded chains.

Presumably all enzymes must have some regulatory mechanism that turns them on and off as needed. Less is known about regulation mechanisms than about the enzymatic reactions themselves, but one type of control has been recognized. This occurs when a reaction product inhibits one of the reaction steps producing it by tying up the enzyme as a nonreactive complex (*feedback inhibition*). As the simplest example, suppose that the product (P) as well as the substrate (S) complexes with the enzyme (E); then we can write the following set of equilibria for the net reaction:

$$\mathrm{E} + \mathrm{S} \rightleftharpoons \mathrm{ES} \rightarrow \mathrm{E} + \mathrm{P} \tag{25.11.1}$$

$$\mathrm{E} + \mathrm{P} \rightleftharpoons \mathrm{EP} \tag{25.11.2}$$

Clearly, a reaction of this type will decrease in rate as the product accumulates. It may stop altogether if the active sites are saturated with the product, and it will start again only on removal of the product.

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25.12: Enzyme Technology

Because enzymes function nearly to perfection in living systems, there is great interest in how they might be harnessed to carry on desired reactions of practical value outside of living systems. The potential value in the use of enzymes (separate from the organisms that synthesize them) is undeniable, but how to realize this potential is another matter.

Practical use of separated enzymes is not new. Hydrolytic enzymes isolated from bacteria were widely used for a brief period to assist in removing food stains from clothing, but many people suffer allergic reactions to enzymes used in this way, and the practice was stopped. A major objective in enzyme technology is to develop an enzymatic process for the hydrolysis of cellulose to glucose (Section 20-7A). Some microorganisms do possess the requisite enzymes to catalyze the hydrolysis of the β-1,4 glucoside links in cellulose. If these enzymes could be harnessed for industrial production of glucose from cellulose, this could be an important supplementary food source. Technology already is available to convert glucose into ethanol and ethanoic acid, and from there to many chemicals now derived from petroleum.

A difficult problem in utilizing enzymes as catalysts for reactions in a noncellular environment is their instability. Most enzymes readily denature and become inactive on heating, exposure to air, or in organic solvents. An expensive catalyst that can be used only for one batch is not likely to be economical in an industrial process. Ideally, a catalyst, be it an enzyme or other, should be easily separable from the reaction mixtures and indefinitely reusable. A promising approach to the separation problem is to use the technique of **enzyme immobilization**. This means that the enzyme is modified by making it insoluble in the reaction medium. If the enzyme is insoluble and still able to manifest its catalytic activity, it can be separated from the reaction medium with minimum loss and reused. Immobilization can be achieved by linking the enzyme covalently to a polymer matrix in the same general manner as is used in solid-phase peptide synthesis (Section 25-7D).

Enzymes also have possible applications in organic synthesis. But there is another problem in addition to difficulties with enzyme stability. Enzymes that achieve carbon-carbon bond formation, the **synthetases**, normally require cofactors such as ATP. How to supply ATP in a commercial process and regenerate it continuously from ADP or AMP is a technical problem that has to be solved if the synthetases are to be economically useful. This is a challenging field of biological engineering.

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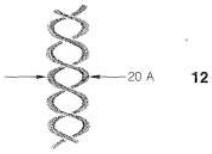
25.13: Biosynthesis of Proteins

One of the most interesting and basic problems connected with the synthesis of proteins in living cells is how the component amino acids are induced to link together in the sequences that are specific for each type of protein. There also is the related problem of how the information as to the amino-acid sequences is perpetuated in each new generation of cells. We now know that the substances responsible for genetic control in plants and animals are present in and originate from the chromosomes of cell nuclei. Chemical analysis of the chromosomes has revealed them to be composed of giant molecules of deoxyribonucleoproteins, which are deoxyribonucleic acids (DNA) bonded to proteins. Since it is known that DNA rather than the protein component of a nucleoprotein contains the genetic information for the biosynthesis of enzymes and other proteins, we shall be interested mainly in DNA and will first discuss its structure. Part or perhaps all of a particular DNA is the chemical equivalent of the Mendelian gene - the unit of inheritance.

25.13.1: The Structure of DNA

The role of DNA in living cells is analogous to that of a punched tape used for controlling the operation of an automatic turret lathe - DNA supplies the information for the development of the cells, including synthesis of the necessary enzymes and such replicas of itself as are required for reproduction by cell division. Obviously, we would not expect the DNA of one kind of organism to be the same as DNA of another kind of organism. It is therefore impossible to be very specific about the structure of DNA without being specific about the organism from which it is derived. Nonetheless, the basic structural features of DNA are the same for many kinds of cells, and we mainly shall be concerned with these basic features in the following discussion.

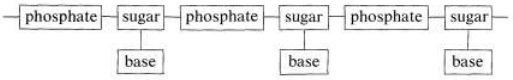
In the first place, DNA molecules are quite large, sufficiently so to permit them to be seen individually in photographs taken with electron microscopes. The molecular weights vary considerably, but values of 1,000,000 to 4,000,000,000 are typical. X-ray diffraction indicates that DNA is made up of two long-chain molecules twisted around each other to form a double-stranded helix about 20 Å in diameter. The arrangement is shown schematically in 12:



12

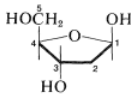
As we shall see, the components of the chains are such that the strands can be held together efficiently by hydrogen bonds. In agreement with this structure, it has been found that, when DNA is heated to about 80° under proper conditions, the strands of the helix unwind and dissociate into two randomly coiled fragments. Furthermore, when the dissociated material is allowed to cool slowly under the proper conditions, the fragments recombine and regenerate the helical structure.

Chemical studies show that the strands of DNA have the structure of a long-chain polymer made of alternating phosphate and sugar residues carrying nitrogen bases, 13:



13

The sugar is *D*-2-deoxyribofuranose, 14, and each sugar residue is bonded to two phosphate groups by way of ester links involving the 3- and 5-hydroxyl groups:



D-2-deoxyribofuranose, 14

The backbone of DNA is thus a *polyphosphate ester of a 1,3-diol:*

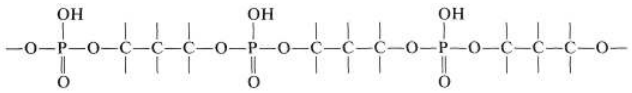


Figure 25-21.

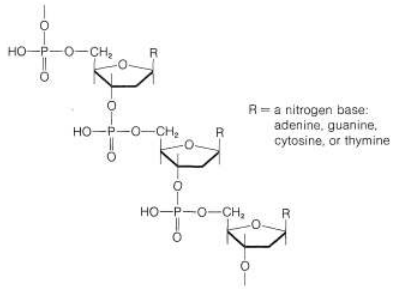
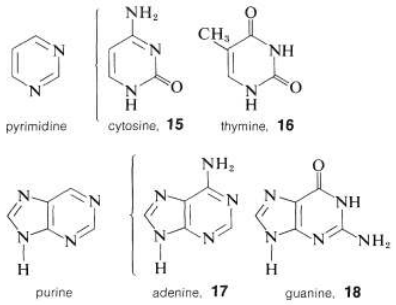
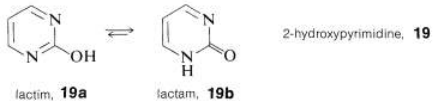


Figure 25-21: Structure of the strands of deoxyribonucleic acid (DNA).

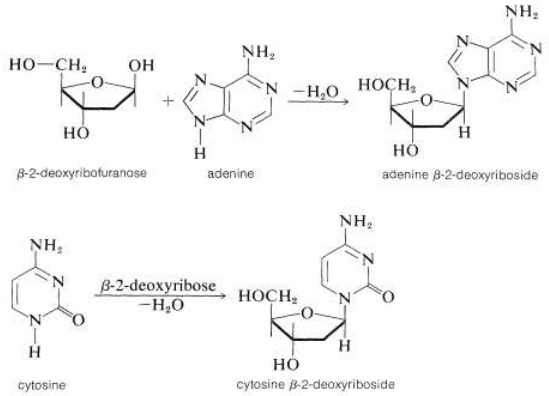
Each of the sugar residues of DNA is bonded at the 1-position of one of four bases: cytosine, 15; thymine, 16; adenine, 17; and guanine, 18. The four bases are derivatives of either *pyrimidine* or *purine*, both of which are heterocyclic nitrogen bases:



Unlike phenols (Section 26-1), structural analysis of many of the hydroxy-substituted aza-aromatic compounds is complicated by isomerism of the keto-enol type, sometimes called **lactim-lactam** isomerism. For 2-hydroxypyrimidine, 19, these isomers are 19*a* and 19*b*, and the lactam form is more stable, as also is true for cytosine, 15, thymine, 16, and the pyrimidine ring of guanine, 18.



For the sake of simplicity in illustrating N-glycoside formation in DNA, we shall show the type of bonding involved for the sugar and base components only (i.e., the deoxyribose nucleoside structure). Attachment of 2-deoxyribose is through a NH group to form the β-N-deoxyribofuranoside (Section 20-5):



Esterification of the 5'-hydroxyl group of deoxyribose *nucleosides*, such as cytosine deoxyriboside, with phosphoric acid gives the corresponding *nucleotides*:[11]

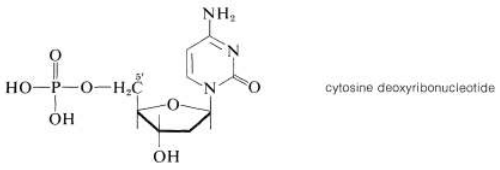


Figure 25-21).

The number of nucleotide units in a DNA chain varies from about 3,000 to 10,000,000 Although the sequence of the purine and pyrimidine bases in the chains are not known, there is a striking equivalence between the numbers of certain of the bases regardless of the origin of DNA. Thus the number of adenine (A) groups equals the number of thymine (T) groups, and the number of guanine (G) groups equals the number of cytosine (C) groups: A = T and G = C. The bases of DNA therefore are half purines and half pyrimidines. Furthermore, although the ratios of A to G and T to C are constant for a given species, they vary widely from one species to another.

The equivalence between the purine and pyrimidine bases in DNA was accounted for by J. D. Watson and F. Crick (1953) through the suggestion that the two strands are constructed so that, when twisted together in the helical structure, hydrogen bonds are formed involving adenine in one chain and thymine in the other, or cytosine in one chain and guanine in the other. Thus each adenine occurs paired with a thymine and each cytosine with a guanine and the strands are said to have complementary structures. The postulated hydrogen bonds are shown in Figure 25-22, and the relationship of the bases to the strands in Figure 25-23.

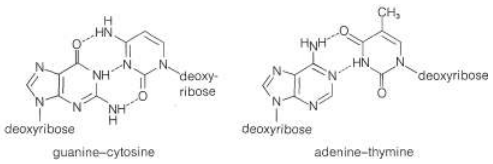


Figure 25-22: Hydrogen bonding postulated between DNA strands involving guanine-cytosine and adenine-thymine. In each case, the distance between the C_1 of the two deoxyribose units is 11 Å and the favored geometry has the rings coplanar.

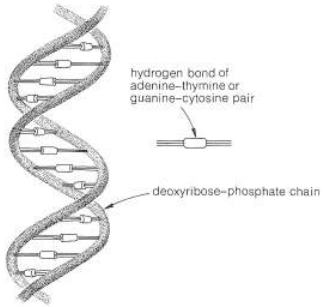


Figure 25-23: Schematic representation of configuration of DNA, showing the relationship between the axes of hydrogen-bonded purine and pyrimidine bases and the deoxyribosephosphate strands. There are 10 pairs of bases per complete 360° twist of the chain. The spacing between the strands is such that there is a wide and a narrow helical "groove" around the molecule. Proteins known as histones coordinate with DNA by winding around the helix, filling one of the other of the grooves. The histone-DNA combination is important in regulating the action of DNA.

25.13.2: Genetic Control and the Replication of DNA

It is now well established that DNA provides the genetic recipe that determines how cells reproduce. In the process of cell division, the DNA itself also is reproduced and thus perpetuates the information necessary to regulate the synthesis of specific enzymes and other proteins of the cell structure. In replicating itself prior to cell division, the DNA double helix evidently separates at least partly into two strands (see Figure 25-24). Each of the separated parts serves as a guide (template) for the assembly of a complementary sequence of nucleotides along its length. Ultimately, *two* new DNA double strands are formed, each of which contains one strand from the parent DNA.

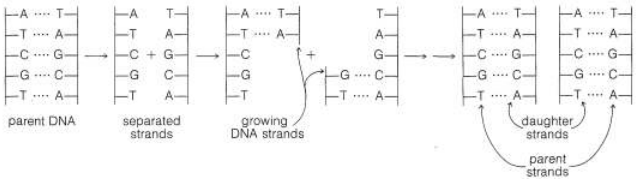


Figure 25-24: Representation of DNA replication.

The genetic information inherent in DNA depends on the arrangement of the bases (A, T, G, and C) along the phosphate-carbohydrate backbone - that is, on the arrangement of the four nucleotides specific to DNA. Thus the sequence A-G-C at a particular point conveys a different message than the sequence G-A-C.

It is quite certain that the code involves a particular sequence of *three* nucleotides for each amino acid. Thus the sequence A-A-A codes for lysine, and U-C-G codes for serine. The sequences or *codons* for all twenty amino acids are known.

25.13.3: Role of RNA in Synthesis of Proteins

It is clear that DNA does not play a direct role in the synthesis of proteins and enzymes because most of the protein synthesis takes place outside of the cell nucleus in the cellular cytoplasm, which does not contain DNA. Furthermore, it has been shown that protein synthesis can occur in the absence of a cell nucleus or, equally, in the absence of DNA. Therefore the genetic code in DNA must be passed on selectively to other substances that carry information from the nucleus to the sites of protein synthesis in the cytoplasm. These other substances are **ribonucleic acids** (RNA), which are polymeric molecules similar in structure to DNA, except that *D*-2-deoxyribofuranose is replaced by *D*-ribofuranose and the base thymine is replace by uracil, as shown in Figure 25-25.

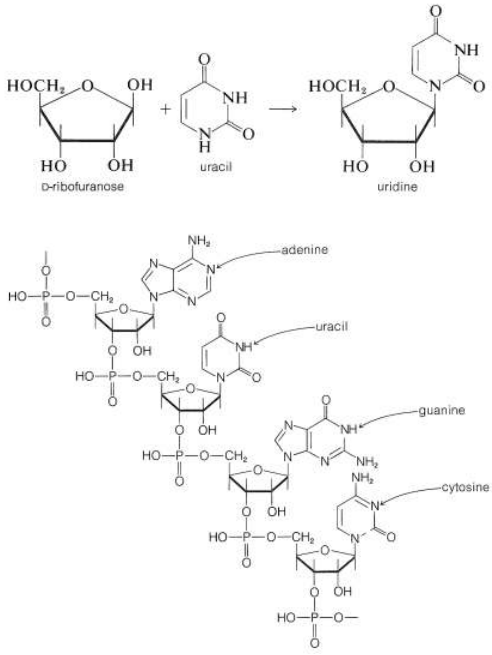


Figure 25-25: Structure of a ribonucleic acid (RNA) chain with the base sequence: adenine, uracil, guanine, cytosine.

RNA also differs from DNA in that there are not the same regularities in the overall composition of its bases and it usually consists of a single polynucleotide chain. There are different types of RNA, which fulfill different functions. About 80% of the RNA in a cell is located in the cytoplasm in clusters closely associated with proteins. These ribonucleoprotein particles specifically are called ribosomes, and the ribosomes are the sites of most of the protein synthesis in the cell. In addition to the **ribosomal RNA** (rRNA), there are ribonucleic acids called **messenger RNA** (mRNA), which convey instructions as to what protein to make. In addition, there are ribonucleic acids called **transfer RNA** (tRNA), which actually guide the amino acids into place in protein synthesis. Much is now known about the structure and function of tRNA.

The principal structural features of tRNA molecules are shown schematically in Figure 25-26. Some of the important characteristics of tRNA molecules are summarized as follows.

1. There is at least one particular tRNA for each amino acid.
2. The tRNA molecules have single chains with 73-93 ribonucleotides. Most of the tRNA bases are adenine (A), cytosine (C), guanine (G), and uracil (U). There also are a number of unusual bases that are methylated derivatives of A, C, G, and U.
3. The clover-leaf pattern of Figure 25-26 shows the general structure of tRNA. There are regions of the chain where the bases are complementary to one another, which causes it to fold into two double-helical regions. The chain has three bends or *loops* separating the helical regions.
4. The 5'-terminal residue usually is a guanine nucleotide; it is phosphorylated at the 5'-OH. The terminus at the 3' end has the same sequence of three nucleotides in all tRNA's, namely, CCA. The 3'-OH of the adenosine in this grouping is the point of attachment of the tRNA to its specific amino acid:

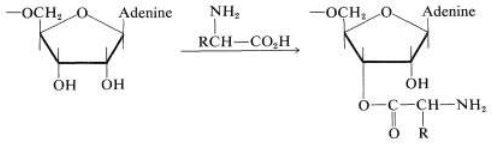


Figure 25-26a) contains a different sequence of bases for each tRNA and it is this sequence that is recognized by the protein-synthesizing apparatus of the ribosomes. The loop is called the anticodon loop.

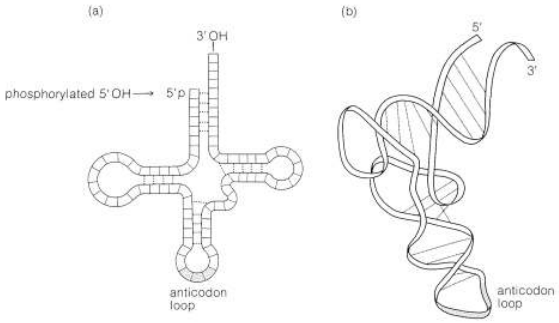


Figure 25-26: (a) Generalized representation of a tRNA molecule. Each segment represents a nucleotide; the actual number and sequence of nucleotides varies with the tRNA. There are regions of intrachain base-pairing (dashed lines). The nucleotide at the long end has a ribose with a free 3'-OH. The nucleotide at the short end is phosphorylated at 5'-OH. The three nucleotides of the anticodon loop pair with the appropriate bases in mRNA. (b) Three-dimensional picture of a tRNA to show the manner in which the chain is coiled. An excellent review article on the determination of the structure of phenylalanine tRNA by x-ray diffraction has been published, J. L. Sussman and S.-H. Kim, Science 192, 853 (1976).

With this information on the structure of tRNA, we can proceed to a discussion of the essential features of biochemical protein synthesis.

The information that determines amino-acid sequence in a protein to be synthesized is contained in the DNA of a cell nucleus as a particular sequence of nucleotides derived from adenine, guanine, thymine, and cytosine. For each particular amino acid there is a sequence of *three* nucleotides called a **codon**.

The information on protein structure is transmitted from the DNA in the cell nucleus to the cytoplasm where the protein is assembled by messenger RNA. This messenger RNA, or at least part of it, is assembled in the nucleus with a base sequence that is complementary to the base sequence in the parent DNA. The assembly mechanism is similar to DNA replication except that thymine (T) is replaced by uracil (U). The uracil is complementary to adenine in the DNA chain (see Figure 25-27). After the mRNA is assembled, it is transported to the cytoplasm where it becomes attached to the ribosomes.

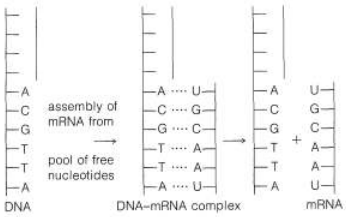


Figure 25-27: Representation of transmittal of information from DNA to RNA.

The amino acids in the cytoplasm will not form polypeptides unless activated by ester formation with appropriate tRNA molecules. The ester linkages are through the 3'-OH of the terminal adenosine nucleotide (Equation 25-9) and are formed only under the influence of a synthetase enzyme that is specific for the particular amino acid. The energy for ester formation comes from ATP hydrolysis (Sections 15-5F and 20-10). The product is called an **aminoacyl-tRNA**.

The aminoacyl-tRNA's form polypeptide chains in the order specified by codons of the mRNA bound to the ribosomes (see Figure 25-28). The order of incorporation of the amino acids depends on the recognition of a codon in mRNA by the corresponding anticodon in tRNA by a complementary base-pairing of the type A ··· U and C ··· G. The first two bases of the codon recognize only their complementary bases in the anticodon, but there is some flexibility in the identity of the third base. Thus phenylalanine tRNA has the anticodon A-A-G and responds to the codons U-U-C and U-U-U, but not U-U-A or U-U-G:

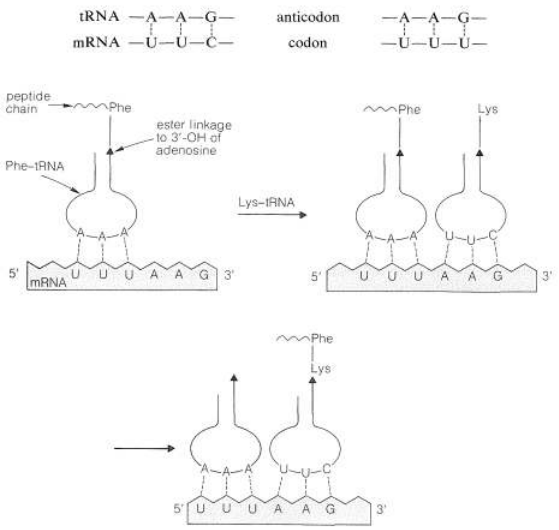


Figure 25-28: Peptide-bond formation in protein biosynthesis showing how the amino-acid sequence is determined by complementary base-pairing between messenger RNA and transfer RNA. The peptide chain is bound to tRNA, which is associated with mRNA through three bases in mRNA (codon) and three bases in tRNA (anticodon). In the diagram, the next codon A-A-G codes for lysine. Hence, Lys-tRNA associates with mRNA by codon-anticodon base-pairing and, under enzyme control, couples to the end of the peptide chain.

The codons of the mRNA on the ribosomes are read from the 5' to the 3' end. Thus the synthetic polynucleotide (5')A-A-A-(A-A-A)$_n$-A-A-C(3') contains the code for lysine (A-A-A) and asparagine (A-A-C); the actual polypeptide obtained using this mRNA in a cell-free system was Lys-(Lys)$_n$-Asn, and not Asn-(Lys)$_n$-Lys.

The start of protein synthesis is signaled by specific codon-anticodon interactions. Termination is also signaled by a codon in the mRNA, although the stop signal is not recognized by tRNA, but by proteins that then trigger the hydrolysis of the completed polypeptide chain from the tRNA. Just how the secondary and tertiary structures of the proteins are achieved is not yet clear, but certainly the mechanism of protein synthesis, which we have outlined here, requires little modification to account for preferential formation of particular conformations.

[11]The positions on the sugar ring are primed to differentiate them from the positions of the nitrogen base.

25.13.4: Contributors and Attributions

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25.14: Chemical Evolution

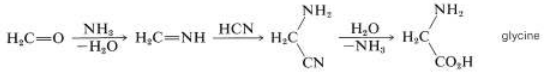
A problem of great interest to those curious about the evolution of life concerns the origins of biological molecules. When and how were the molecules of life, such as proteins, nucleic acids, and polysaccharides, first synthesized?

In the course of geological history, there must have been a prebiotic period when organic compounds were formed and converted to complex molecules similar to those we encounter in living systems. The composition of the earth's atmosphere in prebiotic times was almost certainly very different from what it is today. Probably it was a reducing atmosphere consisting primarily of methane, ammonia, water, and because there was little or no free oxygen, there was no stratosphere ozone layer and little, if any, screening from the sun's ultraviolet radiation. Starting with CH_4, NH_3, and H_2O, it is plausible that photochemical processes would result in formation of hydrogen cyanide, HCN, and methanal, CH_2O, by reactions such as the following:

$$CH_4 + NH_3 \xrightarrow{h\nu} HCN + 3H_2 \tag{25.14.1}$$

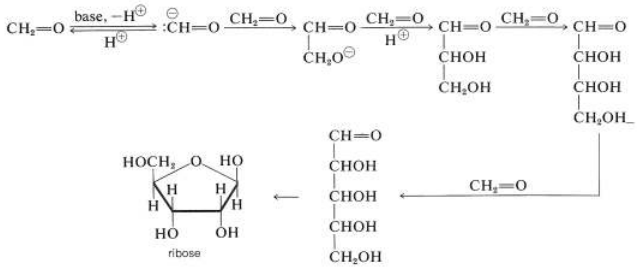
$$CH_4 + H_2O \xrightarrow{h\nu} CH_2{=}O + 2H_2 \tag{25.14.2}$$

Hydrogen cyanide and methanal are especially reasonable starting materials for the prebiotic synthesis of amino acids, purine and pyrimidine bases, ribose, and other sugars. Formation of glycine, for example, could have occurred by a Strecker synthesis (Section 25-6), whereby ammonia adds to methanal in the presence of HCN. Subsequent hydrolysis of the intermediate aminoethanenitrile would produce glycine:

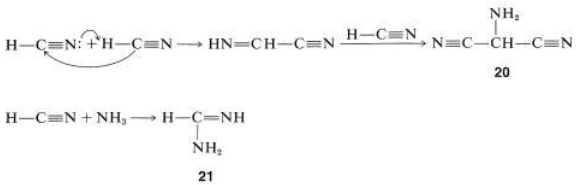


The plausibility of these reactions is strongly supported by the classic experiments of S. Miller (1953), who showed that a mixture of methane or ethane, ammonia, and water, on prolonged ultraviolet irradiation or exposure to an electric discharge, produced a wide range of compounds including racemic α- and β-amino acids.

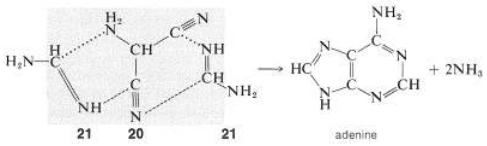
It is not difficult to visualize how sugars such as ribose may be formed. Methanal is known to be converted by bases through a series of aldol-type additions to a mixture of sugarlike molecules called "formose". Formation of racemic ribose along with its stereoisomers could occur as follows:



It is more difficult to conceive how the nucleic acid bases such as adenosine may be achieved in prebiotic syntheses. However, adenine, $C_5H_5N_5$, corresponds in composition to a pentamer of hydrogen cyanide and could result by way of a trimer of HCN, 20, and the adduct of ammonia with HCN, 21:

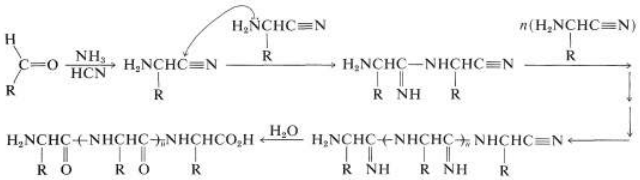


Without worrying about the mechanistic details of how adenine could be formed from 20 and 21, you can see that the adenine ring system is equivalent to 20 plus two 21 minus two NH_3:



How did these small prebiotic organic molecules grow into large polymeric substances such as peptides, RNA, and so on? It is important to recognize that by whatever reactions polymerization occurred, they had to be reactions that would occur in an essentially aqueous environment. This presents difficulties because condensation of amino acids to form peptides, or of nucleotides to form RNA or DNA, is not thermodynamically favorable in aqueous solution.

It is quite possible that primitive polypeptides were formed by the polymerization of aminoethanenitriles produced by the addition of ammonia and HCN to methanal or other aldehydes. The resulting imino polymers certainly would hydrolyze to polypeptides:



There are many other questions regarding the origin of the molecules of life for which we have only partial answers, or no answers at all.

It is difficult to imagine just how these molecules, once formed, somehow evolved further into the extraordinarily complex systems afforded by even the simplest bacterium able to utilize energy from the sun to support and reproduce itself. Nonetheless, synthetic peptides do coil and aggregate rather like natural proteins, and some also have shown catalytic activities characteristic of natural enzymes. One would hope that some kind of life would be found elsewhere in the solar system, the analysis of which would help us to better understand how life began on earth.

25.14.1: Contributors and Attributions

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25.E: Amino Acids, Peptides, and Proteins (Exercises)

Exercise 25-1 Select the amino acids in Table 25-1 that have more than one chiral center and draw projection formulas for all the possible stereoisomers of each which possess the L configuration at the α carbon.

Exercise 25-2 Which of the amino acids in Table 25-1 are *acidic* amino acids and which *basic* amino acids? Which of the structures shown would have the most basic nitrogen? The least basic amino nitrogen? Give the reasons for your choices. (Review Section 23-7.)

Exercise 25-3 How would the general features of the plot of concentration of dipolar ion and charged species versus pH for glycine (Figure 25-1) change for 6-aminohexanoic acid, which has pK_a values of 4.43 and 10.75? Give special attention to the position of the isoelectric point and the width of the pH range over which the dipolar ion is expected to be the most stable species present.

Exercise 25-4 Use Equations 25-1 and 25-2 to show that the isoelectric point of glycine is the average of the two pK_a values for the acid dissociation of glycine.

Exercise 25-5

a. The equations for the acid-base equilibria of lysine in Section 25-2 show possible involvement of three forms of the monocation and three forms of the neutral acid. Arrange the three forms of each set in expected order of stability. Give your reasoning.

b. The conjugate acid of glutamic acid (Table 25-1) has three acid dissociation steps with pK_a values of 2.19, 4.25, and 9.67. Write equations for the equilibria involved and assign pK_a values to each. Do the same for arginine (Table 25-1) with pK_a values of 2.17, 9.04, and 12.48. Calculate the isoelectric point for glutamic acid and for arginine.

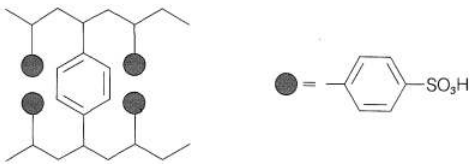
Exercise 25-6 Indicate the approximate positions of C=O and N–H absorptions you would expect in the infrared spectra of (a) $\overset{\ominus}{\mathrm{Cl}}\mathrm{H_3}\overset{\oplus}{\mathrm{N}}\mathrm{CH_2CO_2H}$ and (b) $\mathrm{H_2NCH_2C}\overset{\ominus}{\mathrm{O}}_2\overset{\oplus}{\mathrm{Na}}$.

Exercise 25-7 Sketch the NMR spectrum showing the splitting pattern and chemical shifts you would anticipate for alanine dissolved in an excess of $\mathrm{D_2O}$. Do not neglect H–D exchange (Section 9-10E and 9-10I).

Exercise 25-8 The reactions that lead to the blue color produce between ninhydrin and α-amino acids are examples of reactions discussed previously in the context of carbonyl chemistry (see, for instance, Section 16-4C). Write mechanisms, based insofar as possible on analogy, for each of the steps involved in the ninhydrin test, using glycine as an example. Would you expect ammonia or methanamine to give the blue color? Explain.

Exercise 25-9 Explain why arginine elutes from an ion-exchange column using a buffer at pH 5-6, whereas glutamic acid elutes at pH 3.

Exercise 25-10 A cation-exchange resin can be prepared by radical-addition polymerization of phenylethene (styrene, Section 10-8) in the presence of about 2-10% 1,4-diethenylbenzene (1,4-divinylbenzene), , followed by electrophilic sulfonation of the resulting polymer with $\mathrm{H_2SO_4–SO_3}$ (see Section 22-4G). Explain how these reactions lead to a *three-dimensional* insoluble polymer with linkages as shown below. Indicate the reaction mechanisms involved.



Exercise 25-11 Consider a "hard" water comprised of dilute $\mathrm{MgCl_2}$. Ion exchange with resin–$\mathrm{S}\overset{\ominus}{\mathrm{O}}_3\overset{\oplus}{\mathrm{Na}}$ replaces $\mathrm{Mg^{2+}}$ with $\mathrm{Na^+}$, and with resin–$\mathrm{SO_3H}$, $\mathrm{Na^+}$ is replaced by $\mathrm{H^+}$, thereby producing a dilute HCl solution. What kind of an ion-exchange resin would you need to remove the $\mathrm{Cl^-}$ from the HCl solution and produced "deionized" water? (Consider exchanging $\mathrm{Cl^-}$ for $^-\mathrm{OH}$.)

Exercise 25-12

a. Draw the structure of the azlactone derived from *L*-phenylalanine and ethanoic anhydride.

b. Which of the hydrogens in this azlactone would you expect to be the most acidic? Explain.

c. Why do chiral azlactones derived from amino acids such as *L*-phenylalanine racemize easily on heating in ethanoic acid in the presence of ethanoate ion?

Exercise 25-13 Explain why glycine itself, as the dipolar ion, reacts with nitrous acid to eliminate nitrogen, whereas the ethyl ester of glycine forms ethyl diazoethanoate.

Exercise 25-14 Show how the following amino acids may be prepared from the indicated method and starting materials:

a. glutamic acid from 2-oxopentanedioic acid (α-ketoglutaric acid) by the Strecker method

b. leucine from 2-methyl-1-propanol by the phthalimidomalonic ester synthesis

c. aspartic acid from ethyl chloroethanoate by the N-formylaminomalonic ester synthesis

Exercise 25-15 Suggest a synthetic route to proline from hexanedioic acid (adipic acid) that involves the transformations $-CO_2H- \rightarrow -NH_2$, and $-CH_2CO_2H$ to $-CHBrCO_2H$. Specify the reagents required to accomplish each step.

Exercise 25-16 The structure of the hormonal peptide oxytocin is abbreviated to $\overline{\text{Cys–Tyr–Ile–Gln–Asn–Cys–Pro–Leu–Gly}}NH_2$. Draw its full covalent structure.

Exercise 25-17 What problems might be encountered in using the 2,4-dinitrofluorobenzene method for determination of end groups on Gly-Lys-Ala? Explain.

Exercise 25-18 The tripeptide, eisenine, has only one free carboxyl group, does not react with 2,4-dinitrofluorobenzene, and on complete hydrolysis yields 2 moles of *L*-glutamic acid, 1 mole of *L*-alanine, and 1 mole of ammonia. Alanine is indicated to be the C-terminal amino acid. Write a structure for eisenine that is in accord with the above facts.

Exercise 25-19* Eledoisin is a peptide isolated from the salivary glands of *eledone*, a Mediterranean eight-armed cephalopod. The peptide is a powerful hypotensive agent. Deduce a possible structure from the following information: (1) Complete hydrolysis gives equal amounts of ammonia, Ala, Asp, Glu, Gly, Ile, Leu, Lys, Met, Phe, Pro, and Ser. (2) No free amino N-terminal group or free carboxyl C-terminal group can be detected. (3) Chymotrypsin hydrolysis forms two peptides, L and M. Their compositions are

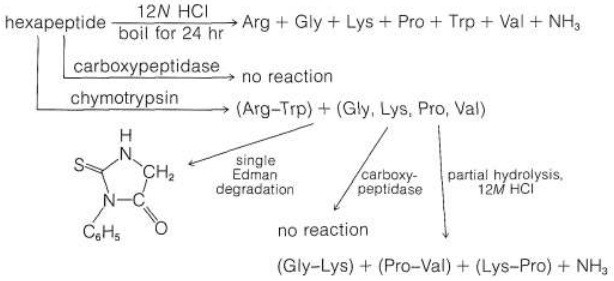
L = Ala, Asp, Glu, Lys, Phe, Pro, Ser (unsequenced)
M = Ile-Gly-Leu-MetNH_2 (sequenced)

(At this point you should be able to deduce the sequence of five amino acids at the C-terminus of eledoisin.) (4) Trypsin hydrolysis gives two peptides, P and Q, with the indicated compositions:

P = Glue, Lys, Pro, Ser
Q = Ala, Asp, Gly, Ile, Leu, Met, Phe

(At this point, you can deduce two possible sequences for Q.) (5) Trypsin hydrolysis of L gives a peptide of composition Ala, Asp, Phe which, with 2,4-dinitrofluorobenzene, gives the 2,4-dinitrophenyl derivative of aspartic acid. (6) Partial acid hydrolysis of eledoisin gives several dipeptides, among them Ser-Lys and Pro-Ser.

Exercise 25-20 A hexapeptide was subjected to the transformations diagrammed below. (The commas between the amino acids indicate the sequence is unknown or unspecified.) Deduce the structure of the hexapeptide.



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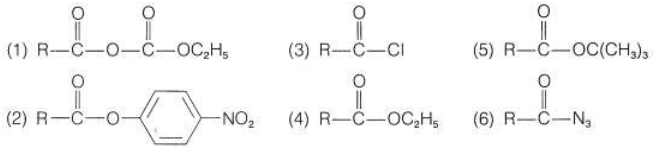
Exercise 25-21 How could an optically pure N-acylamino acid racemize and lead to racemic N-acylpeptides as the result of a peptide coupling reaction wherein the carboxyl group of the amino acid was converted to an anhydride group? (Review Section 25-5A.)

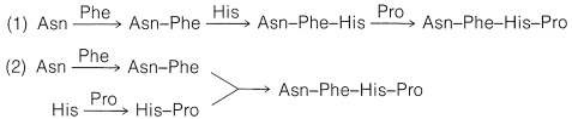
Exercise 25-22 Suppose there is 1% formation in each step of the wrong isomer of the acylating component in an otherwise quantitative 100-step peptide synthesis. What is the yield of the desired polypeptide isomer?

Exercise 25-23* The following are acyl derivatives known to react with amines to give N-acylated amines:



Arrange these reagents in expected order of reactivity with the free amino group of a carboxyl-protected peptide, H_2N–peptide–X, where X is the carboxyl-protecting group. Give your reasoning and indicate what disadvantages each reagent may have as to side reactions, undesirable byproducts, and so on. It may be useful to review Sections 18-7A and 24-3.

Exercise 25-24 Consider two routes to the synthesis of a tetrapeptide:



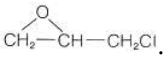
If each coupling step proceeds in 80% yield, which of the two routes would give the highest overall yield?

Exercise 25-25 Indicate the steps that would be necessary to attach each of the amino acids listed to the N-terminus of a peptide chain. Assume that any side-chain functions in the peptide are suitably protected, but do not assume that the amino acids will couple with the peptide without suitable protection of their functional groups.

a. lysine
b. aspartic acid
c. cystine
d. serine

Exercise 25-26 Show how each of the following substances may be synthesized starting with the individual amino acids. Indicate the reagents needed in each step.

a. glutamylglycine (Glu-Gly)
b. Tyr-Ala-Val

Exercise 25-27* A resin known as Sephadex that is useful in gel filtration is prepared from a polysaccharide that is cross-linked into a three-dimensional matrix with "epichlorohydrin",  . The degree of cross-linking determines the pore size of the gel. Write equations, specifying the conditions as closely as possible, for reactions whereby a glucose unit of one polysaccharide chain could be linked to the glucose of another chain through an epichlorohydrin molecule.

Exercise 25-28 Hemoglobin, the protein responsible for carrying oxygen from the lungs to the body tissues, contains 0.355% iron. Hydrolysis of 100 g of hemoglobin gives 1.48 g of tryptophan. Calculate the minimum molecular weight of hemoglobin that is consistent with these results.

Exercise 25-29 Devise a way to use a stereospecific hydrolytic enzyme for resolution of *D*,*L*-alanine.

Exercise 25-30 The proteolytic enzyme, papain, differs from chymotrypsin in having cysteine, or a labile derivative thereof, as part of its active site. The enzyme is deactivated by substances that form complexes with, or react with, –SH groups and the activity is restored by reactions expected to regenerate an –SH group. Work out a schematic mechanism for cleavage of a peptide chain with papain that involves acylation of the critical –SH group of papain.

(One of the most interesting features of papain is that more than 100 of its total of 185 amino-acid residues may be removed with the aid of an aminopeptidase to give a fragment with considerable enzymatic activity.)

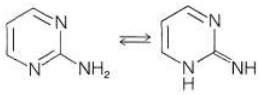
Exercise 25-31 Why would the intermediate addition product of thiamine to pyruvic acid be expected to decarboxylate readily? Support your answer by analogy; see Section 18-4.

Exercise 25-32 Write equations for a base-induced decomposition of the modified thiamine coenzyme, 11, to ethanal and thiamine pyrophosphate.

Exercise 25-33

a. The lactim-lactam equilibrium of 2-hydroxypyrimidine lies on the side of the lactam, yet the benzenol-cyclohexadienone equilibrium lies far on the side of benzenol (Section 26-1). Explain what factors make for the large difference in the positions of these two equilibria. (Bond energies and review of Section 24-1A may help in showing you the differences between these systems.)

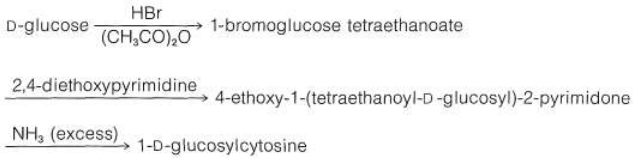
b. Use bond energies to decide whether the following equilibrium with 2-aminopyrimidine is likely to be more, or less, favorably to the right than the corresponding equilibrium 19*a* ⇌ 19*b*. Give your reasoning.



c. Show how the resonance method could be used to predict whether cytosine or 2-hydroxypyrimidine would have the greater tendency to be more stable in the lactam rather than the lactim form.

Exercise 25-34 Write equations for the mechanistic steps involved in hydrolysis of adenine deoxyribonucleoside to deoxyribose and adenine. Would you expect the reaction to occur more readily in acidic, basic, or neutral solution? (Review Section 16-4C).

Exercise 25-35 The following steps have been used in the synthesis of 1-*D*-glucosylcytosine:



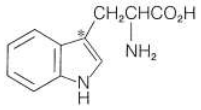
Write the structures of the various substances given, and as detailed a mechanism as you can for the reaction of the bromo compound with 2,4-diethoxypyrimidine. Would you expect the reaction of 1-bromoglucose tetraethanoate with 2,4-diethoxypyrimidine to yield significant amounts of 6-ethoxy-1-(tetraethanoyl-*D*-glucosyl)-2-pyrimidone? Give your reasoning.

Exercise 25-36 The enzyme, *acetoacetate decarboxylase*, converts 3-oxobutanoic (acetoacetic) acid to 2-propanone and carbon dioxide. Investigation of the nature of the catalytically active site has been carried on by F. Westheimer and his coworkers with the following results. First, 3-oxobutanoic acid labeled with ^{18}O at the ketone group and decarboxylated in ordinary water in the presence of the enzyme gives 2-propanone containing no ^{18}O. Second, the enzyme-substrate complex combines with hydrogen cyanide and decarboxylation stops. However, if a solution of the hydrogen cyanide-deactivated enzyme-substrate complex is **dialyzed** (i.e., placed in a cellophane bag immersed in flowing water to permit separation of low-molecular-weight water-soluble materials from the enzyme by diffusion through the cellophane; peptides and proteins having molecular weights greater than 6000 to 10,000 do not diffuse through cellophane), then the enzyme is recovered fully active. Third, the mild reducing agent sodium borohydride, which reacts with C=N but not C—N or amide carbonyl groups, reduces the enzyme-substrate complex made from ^{14}C-labeled 3-oxobutanoic acid to give a product that is not enzymatically active and that retains essentially all the ^{14}C on dialysis without regenerating the enzyme. Sodium borohydride treatment of the enzyme-substrate-hydrogen cyanide complex followed by dialysis regenerates fully active enzyme. Borohydride reduction of the enzyme-substrate complex, prepared from 3-oxobutanoic acid labeled at the 2- and 4-positions with ^{14}C, followed by complete hydrolysis, gives 1 mole of N-(2-propyl-^{14}C-amino)-2-aminohexanoic acid.

Write a stepwise mechanism for the enzyme-induced decarboxylation, clearly indicating the nature of the bonding between the substrate and enzyme. Show how your mechanism can accommodate hydrogen cyanide inhibition and the results of the

borohydride reactions. Utilize the results of the discussion of the ease of decarboxylation of various acids in Section 18-4 to deduce possible structural requirements for the active site so that decarboxylation of the enzyme-substrate complex can occur *more readily* than the uncatalyzed decarboxylation.

Exercise 25-37 Figure 25-29 shows an unusually well-resolved ^{13}C NMR spectrum of the enzyme lysozyme (Table 25-3 and Figure 25-15) taken with proton decoupling. The closely spaced peaks on the left side of the spectrum are of the carbonyl groups. The peaks in the center are of unsaturated and aromatic carbons, while those on the right are of the aliphatic amino acid carbons. The five sharp resonances marked at about 110 ppm with * arise from tryptophan carbons marked with * in 22:



22

a. How many tryptophan residues does the ^{13}C spectrum indicate to be present in lysozyme?

b. Lysozyme contains S–S bonds, and when these S–S bonds are cleaved by reduction, the resonances marked * in Figure 25-29 have much *smaller* chemical-shift differences. Explain why this might be so.

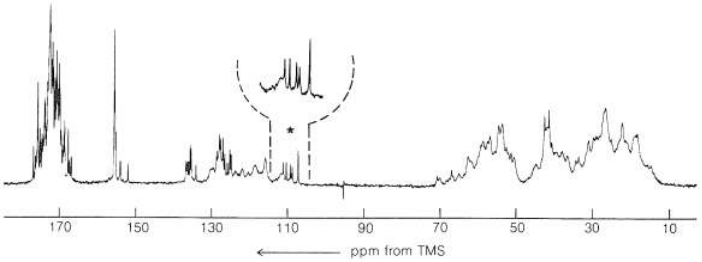


Figure 25-29: *Carbon-13 NMR spectrum at* 45.3 MHz *of lysozyme,* 0.015 M *in water solution, taken with proton decoupling (Section 9-10L).*

25.E.1: Contributors

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CHAPTER OVERVIEW

26: More on Aromatic Compounds

Generally, the reactivity of a substituent on an aromatic ring is greatly modified from that of its aliphatic counterpart. Likewise, the substituent can influence the reactivity of the ring. We have seen this interplay between ring and substituent in the chemistry of aryl halides (Section 14-6), of arenamines (Sections 23-7C and 23-9F), and in electrophilic substitution reactions of aromatic compounds (Section 22-5). It is particularly manifest in the chemistry of substances that have oxygen attached directly to arene rings. We shall discuss aryl oxygen compounds and some of their oxidation products called quinones in this chapter. We also shall discuss aromatic substances that have carbon substituents in the form of alkyl, haloalkyl (such as $-CH_2Cl$, $-CHCl_2$, $-CCl_3$), aldehyde ($-CHO$), and carboxylic acid ($-CO_2H$) groups. We classify such substances as aromatic side-chain derivatives (for want of a better term)

26.1: Aryl Oxygen Compounds

26.2: Quinones

26.3: Tropolones and Related Compounds

26.4: Some Aromatic Side-Chain Compounds

26.5: Natural Occurrence and Uses of Some Aromatic Side-Chain Compounds

26.6: Correlations of Structure with Reactivity of Aromatic Compounds

26.E: More on Aromatic Compounds (Exercises)

26.1: Contributors and Attributions

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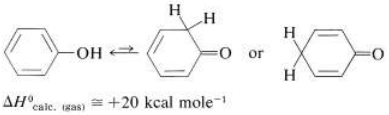
26.1: Aryl Oxygen Compounds

26.1.1: Phenols (Arenols) - Physical Properties

Phenols are enols, and enols normally are unstable with respect to the corresponding carbonyl compounds (Section 17-1D). Thus

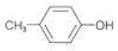
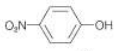
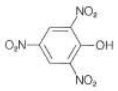
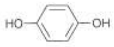
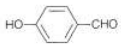
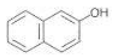
The situation is different for phenols because of the inclusion of the carbon-carbon double bond into the aromatic ring and the associated aromatic stabilization. Phenol (benzenol) exists exclusively in the enol form:



$\Delta H^0_{\text{calc. (gas)}} \cong +20$ kcal mole^{-1}

The *physical properties* of some representative phenols are summarized in Table 26-1. In general, phenols are somewhat more polar than the corresponding saturated alcohols. The magnitudes of the differences are well illustrated by comparison of the physical properties of benzenol and cyclohexanol, shown in Table 26-2. The determining factor appears to be the greater acidity of the phenolic hydroxyl group, which means that, in the undissociated form, the O–H bond is more strongly polarized as $\overset{\delta\ominus}{\text{O}} - \overset{\delta\oplus}{\text{H}}$ than for alcohols. Phenols therefore form stronger hydrogen bonds than alcohols, thereby resulting in higher boiling points, higher water solubility, and increased ability to act as solvents for reasonably polar organic molecules.

Table 26-1: *Physical Properties of Some Representative Phenols*

Name	Formula	Mp, °C	Bp, °C	K_a H_2O, 25°C	λ_{max},[a] nm	ϵ	λ_{max},[b] nm	ϵ
benzenol (phenol)	C_6H_5OH	43	182	1.3×10^{-10}	211	6,200	270	1,450
4-methylbenzenol (*para*-cresol)		34	203	1.5×10^{-10}	225	7,400	280	1,995
4-nitrobenzenol (*para*-nitrophenol)		114		6.5×10^{-8}	318	10,000		
2,4,6-trinitrobenzenol (picric acid)		123			380	13,450		
1,2-benzenediol (catechol)		105	246	3.3×10^{-10}[c]	214	6,300	276	2,300
1,3-benzenediol (resorcinol)		110	280	3.6×10^{-10}[c]	216	6,800	274	1,900
1,4-benzenediol (hydroquinone)		170	285	1×10^{-10}			290	2,800
4-aminobenzenol (*para*-aminophenol)		186		6.6×10^{-9}[c]	233	8,000	280	3,200
2-hydroxybenzenecarbaldehyde (salicylaldehyde)		−7	197		256	12,600	324	3,400
4-hydroxybenzenecarbaldehyde (*para*-hydroxybenzaldehyde)		115	250	2.2×10^{-8}	284	16,000		
1-naphthalenol (1-naphthol)		94	288	1×10^{-9}				
2-naphthalenol (2-naphthol)		123	285					

[a] To be compared with the 200-nm band of benzene (Table 22-3).
[b] To be compared with the 250-nm band of benzene (Table 22-4).
[c] At 18°C.

The wavelengths of the ultraviolet absorption maxima of the arenols shown in Table 26-1 indicate a considerable effect of substituents on these absorptions, which correspond to the 200-nm and 255-nm absorptions of benzene (Section 22-3B).

Table 26-2: *Comparative Physical Properties of Benzenol and Cyclohexanol*

	Benzenol,	Cyclohexanol,
mp, °C	43	25.5
bp, °C	182	161
water solubility, g/100 g, 20°	9.3	3.6
K_a	1.3×10^{-10}	$\sim 10^{-18}$

Substances such as 2-hydroxybenzaldehyde, 2-hydroxybenzoic acid, and 2-nitrobenzenol form *intra*- rather than intermolecular hydrogen bonds. This effectively reduces intermolecular attraction, thereby reducing boiling points and increasing solubility in nonpolar solvents as compared to the meta and para isomers, which only form *inter*molecular hydrogen bonds:

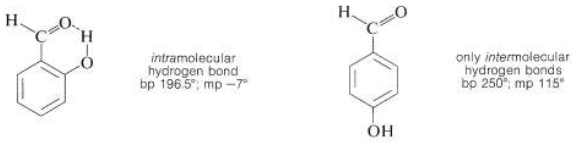
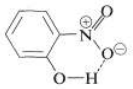


Figure 26-1 shows the proton resonances of the nitrobenzenol isomers, and you will see that the ortho isomer has the OH proton resonance at much lower field than either the meta or para isomer. Only for the ortho isomer are the nitro and hydroxyl groups sufficiently close together to form an intramolecular hydrogen bond:



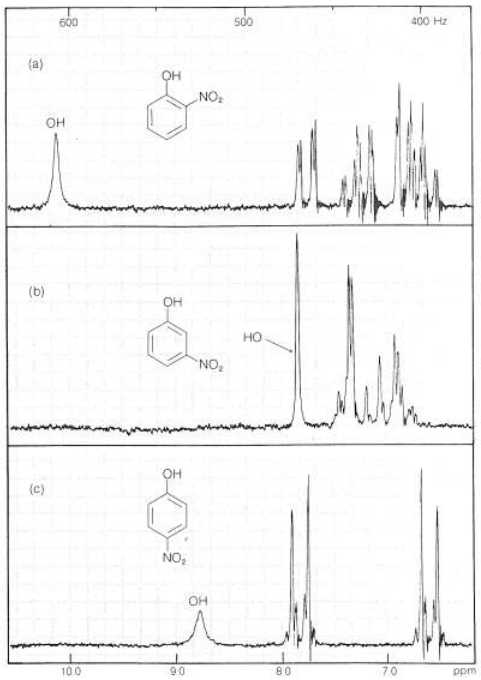
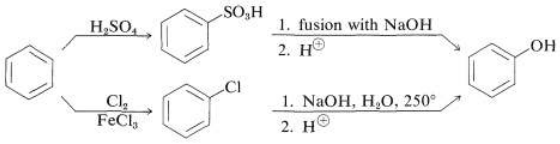


Figure 26-1: Nuclear magnetic resonance spectra at 60 MHz of (a) 2-nitrobenzenol, (b) 3-nitrobenzenol, and (c) 4-nitrobenzenol in ethoxyethane solution (the solvent bands are not shown).

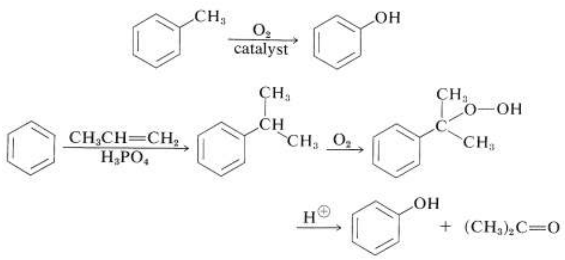
26.1.2: Synthesis of Phenols

Benzenol and the 2-, 3-, and 4-methylbenzenols (cresols) can be isolated from coal tar (Section 22-11). Benzenol itself is used commercially in such large quantities that alternate methods of preparation are necessary and most of these start with benzene or alkylbenzenes. Direct oxidation of benzene is not satisfactory because benzenol is oxidized more readily than is benzene.

At one time, benzenol was made industrially by sulfonating or chlorinating benzene and then introducing the hydroxyl group by nucleophilic substitution with strong alkali:



Current commercial syntheses of benzenol involve oxidation of methylbenzene or isopropylbenzene (Section 16-9E). Oxidation of isopropylbenzene is economically feasible for the production of benzenol because 2-propanone (acetone) also is a valuable product:

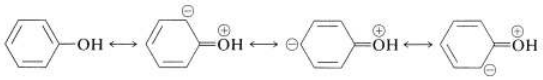


A common laboratory procedure converts an aromatic amine to a phenol by way of the arenediazonium salt, $\mathrm{ArNH_2} \rightarrow \mathrm{ArN_2^+} \rightarrow \mathrm{ArOH}$ (Section 23-10B).

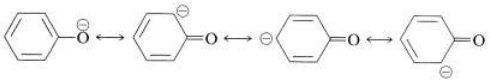
26.1.3: Reactions of Phenols Involving the O−H Bonds

The reactions of the hydroxyl groups of phenols, wherein the O−H bonds are broken, are similar to those of alcohols. Thus phenols are weak acids ($K_a = 10^{-10}$ to 10^{-8}; Table 26-1), intermediate in strength between carboxylic acids and alcohols.

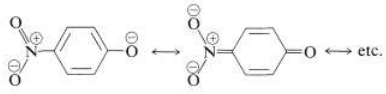
Enols are stronger acids than alcohols because of the increase in electron delocalization in enolate anions as compared to the neutral enols (see Section 15-8A). The stabilization energy of benzenol (Table 21-1) is $48\ \mathrm{kcal\ mol^{-1}}$, $5\ \mathrm{kcal}$ greater than that of benzene. We can ascribe this increase to delocalization of an unshared electron pair from oxygen:



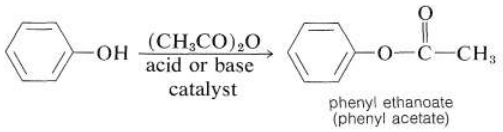
When the OH proton is removed by a base the resulting anion has even greater stabilization, because the corresponding valence-bond structures do not involve charge separation:

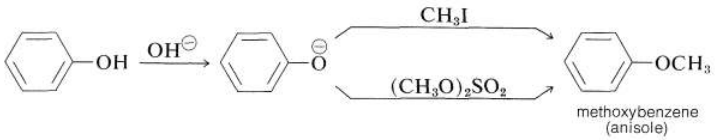


We can be confident that substituent groups that stabilize the anion will increase the acidity. Thus 4-nitrobenzenol is about 500 times stronger as an acid than benzenol, because of the increased delocalization of charge to the nitro group:

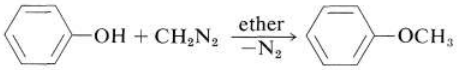


It is possible to prepare esters of phenols with carboxylic acid anhydrides or acid halides, and phenyl ethers by reaction of benzenolate anion with halides, sulfate esters, sulfonates, or other alkyl derivatives that react well by the S_N2 mechanism:





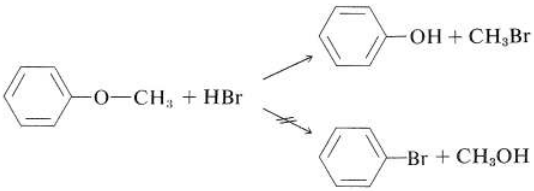
Phenols (like carboxylic acids; Section 24-7C and Table 18-6) are converted to methoxy derivatives with diazomethane:



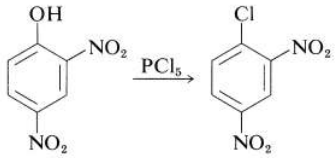
Almost all phenols and enols (such as those of 1,3-diketones) give colors with ferric chloride in dilute water or alcohol solutions. Benzenol itself produces a violet color with ferric chloride, and the methylbenzenols give a blue color. The products apparently are ferric arenolate salts, which absorb visible light to give an excited state having electrons delocalized over both the iron atom and the unsaturated system.

26.1.4: Reactions of Phenols Involving the C–O Bonds

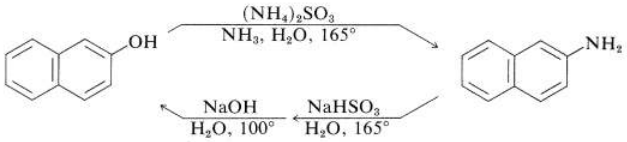
In general, it is very difficult to break the aromatic C–O bond of arenols. Thus concentrated halogen acids do *not* convert simple arenols to aryl halides, and alkoxyarenes are cleaved with hydrogen bromide or hydrogen iodide in the manner ArO–R rather than Ar–OR:



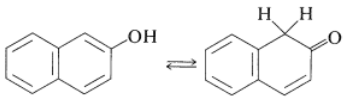
(Diaryl ethers, such as diphenyl ether, do not react with hydrogen iodide even at 200°.) There is no easy way to convert arenols to aryl halides, except where activation is provided by 2- or 4-nitro groups. Thus 2,4-dinitrobenzenol is converted to 1-chloro-2,4-dinitrobenzene with phosphorus pentachloride:



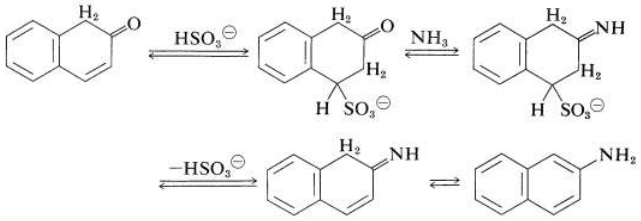
An exception to the generalization that C–O bonds to aromatic systems are difficult both to make and to break is provided by reversible conversion of benzenediols and 1- or 2-naphthalenols to the corresponding amines, usually at elevated temperatures with sodium hydrogen sulfite or an acidic catalyst. The sodium hydrogen sulfite-induced reaction is called the **Bucherer reaction**:



These reactions do not work well with simple benzenols because the key step is formation of the keto isomer of the arenol - a process that is unfavorable for simple benzenols.

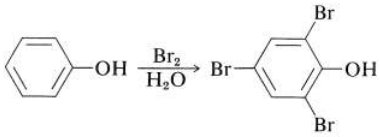


The role of the hydrogen sulfite is participation in a reversible 1,4-addition to the unsaturated ketone to hold it in the ketone form that then is converted to the imine by NH_3 (Section 16-4C) and hence to the arenamine:

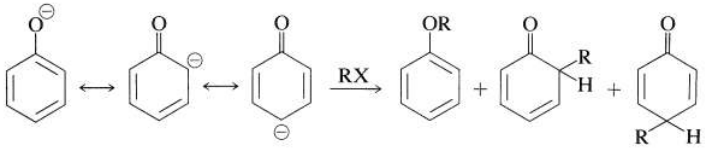


26.1.5: Substitution Reactions at the Ring Carbons of Arenols

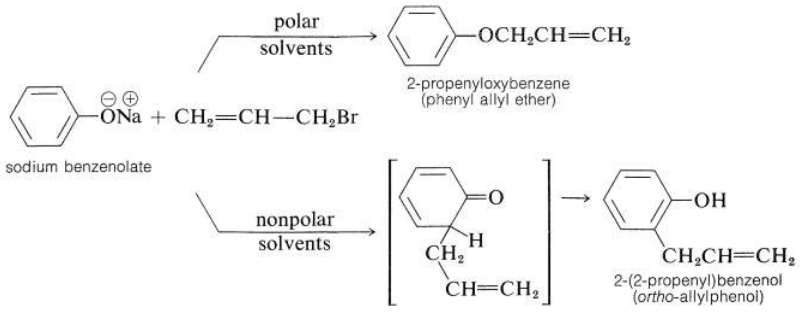
The electron-rich π-orbital systems of arenols and especially of arenolate ions make these compounds very susceptible to electrophilic substitution. Arenols typically react rapidly with bromine in aqueous solution to substituted the positions ortho or para to the hydroxyl group. Benzenol itself gives 2,4,6-tribromobenzenol in high yield:



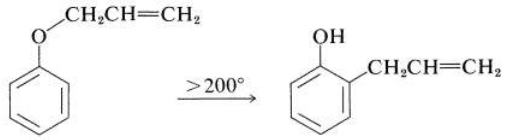
Several important reactions of arenols involve aromatic substitution of arenolate ions with *carbon* electrophiles. In a sense, these reactions are alkylation and acylation reactions as discussed for arenes (Sections 22-4E and 22-4F). In another sense, they are alkylation and acylation reactions of *enolate anions* and therefore could give rise to products by C- and O-alkylation, or C- and O-acylation (Section 17-4). Thus:



In most cases, O-alkylation predominates. However, with 2-propenyl halides either reaction can be made essentially the exclusive reaction by proper choice of solvent. With sodium benzenolate the more polar solvents, such as 2-propanone, lead to 2-propenyloxybenzene, whereas in nonpolar solvents, such as benzene, 2-(2-propenyl)benzenol is the favored product:

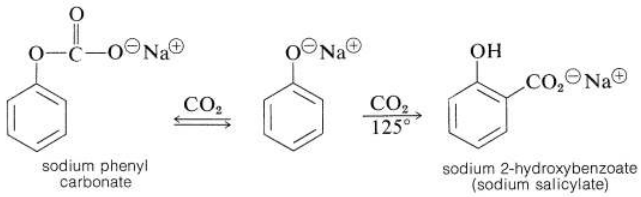


It should be noted that formation of 2-(2-propenyl)benzenol in nonpolar solvents is *not* the result of O-propenylation *followed* by rearrangement, even though the C-propenylation product is thermodynamically more stable. Rearrangement in fact does occur, but at much higher temperatures (above 200°) than required to propenylate sodium benzenolate:

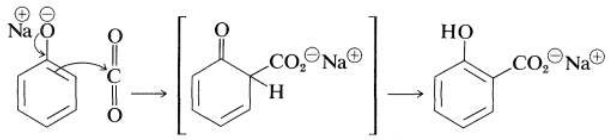


Such rearrangements are quite general for aryl allyl ethers and are called **Claisen rearrangements**. They are examples of the pericyclic reactions discussed in Section 21-10D.

The **Kolbe-Schmitt reaction** produces O- and C-carboxylation through the reaction of carbon dioxide with sodium benzenolate at 125°:



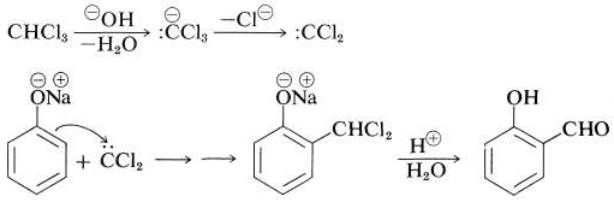
Sodium benzenolate absorbs carbon dioxide at room temperature to form sodium phenyl carbonate (O-carboxylation) and, when this is heated to 125° under a pressure of several atmospheres of carbon dioxide, it rearranges to sodium 2-hydroxybenzoate (sodium salicylate). However, there is no evidence that this reaction is other than a dissociation-recombination process, in which the important step involves electrophilic attack by carbon dioxide on the aromatic ring of the benzenolate ion (C-carboxylation):



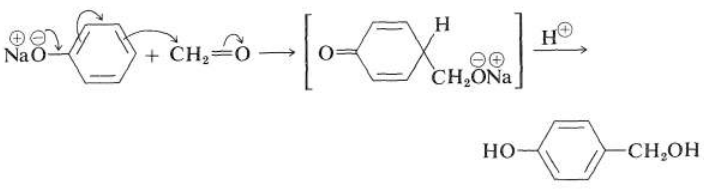
With the sodium benzenolate at temperatures of 125° to 150°, ortho substitution occurs; at higher temperatures (250° to 300°), particularly with the potassium salt, the para isomer is favored.

The Kolbe-Schmitt reaction is related to enzymatic carboxylations as of *D*-ribulose-1,5-diphosphate with carbon dioxide, a key step in photosynthesis (Section 20-9). The overall result is C–C bond formation by addition of CO_2 to an enolate salt or its enamine equivalent.

In the somewhat related **Reimer-Tiemann reaction**, sodium benzenolate with trichloromethane in alkaline solution forms the sodium salt of 2-hydroxybenzenecarbaldehyde (salicylaldehyde). The electrophile in this case probably is dichlorocarbene (Section 14-7B):

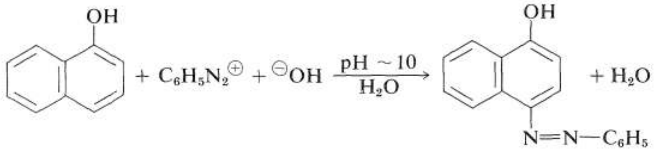


Many phenols undergo aldol-like addition reactions with carbonyl compounds in the presence of acids or bases. Thus benzenol reacts with methanal under mild alkaline conditions to form (4-hydroxyphenyl)methanol:



The use of this type of reaction in the formation of polymers will be discussed in Chapter 29.

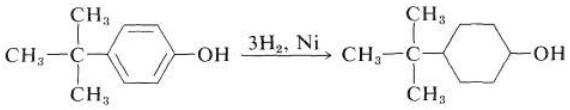
Arenols usually will undergo diazo coupling reactions with aryldiazonium salts at pH values high enough to convert some of the arenol to the more powerfully nucleophilic arenolate anions:



However, if the pH is too high, coupling is inhibited because the diazonium salt is transformed into $ArN{=}N{-}O^{\ominus}$, which is the nonelectrophilic conjugate base of a diazotic acid (Table 23-4).

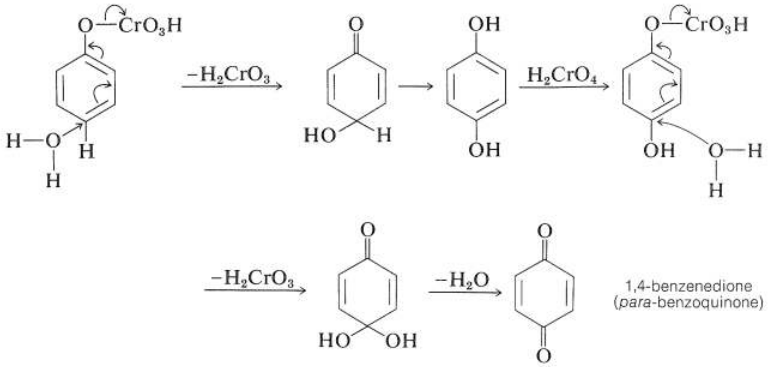
26.1.6: Addition Reactions

Arenols can be reduced successfully with hydrogen over nickel catalysts to the corresponding cyclohexanols. A variety of alkyl-substituted cyclohexanols can be prepared in this way:

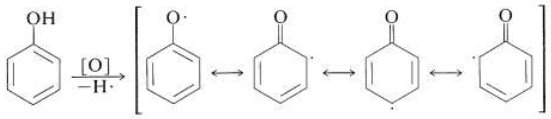


26.1.7: Oxidation of Arenols

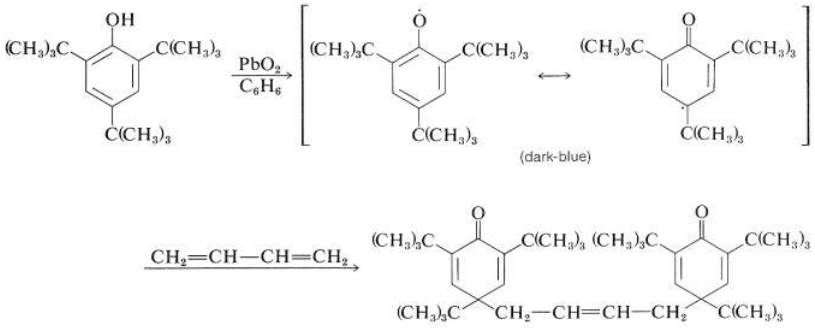
Benzenol can be oxidized to 1,4-benzenedione (*para*-benzoquinone) by chromic acid. The reaction may proceed by way of phenyl hydrogen-chromate (Section 15-6B) as follows:



Oxidation reactions of arenols with other oxidants are complex. Oxidative attack seems to involve, as the first step, removal of the hydroxyl hydrogen to yield a phenoxy radical:

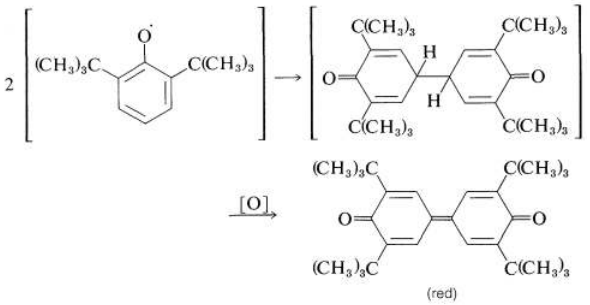


The subsequent course depends upon the substituents on the aromatic ring. With 2,4,6-tri-*tert*-butylbenzenol, the radical is reasonably stable in benzene solution and its presence is indicated by both its dark-blue color and the fact that it adds to 1,3-butadiene:

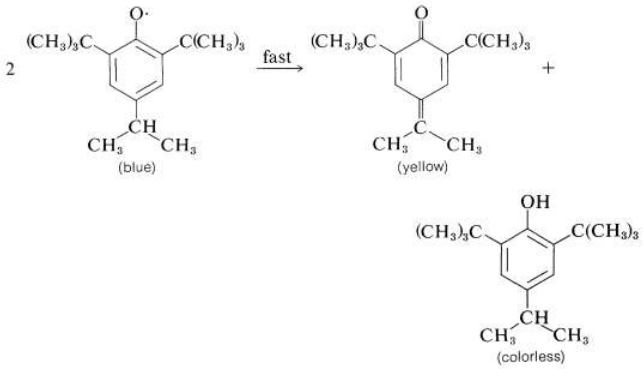


Apparently, dimerization of the above phenoxy radical through either oxygen or the ring is inhibited by the bulky *tert*-butyl groups. With fewer or smaller substituents, the phenoxy radicals may form dimerization or disproportionation products. Examples of these reactions follow.

Dimerization:

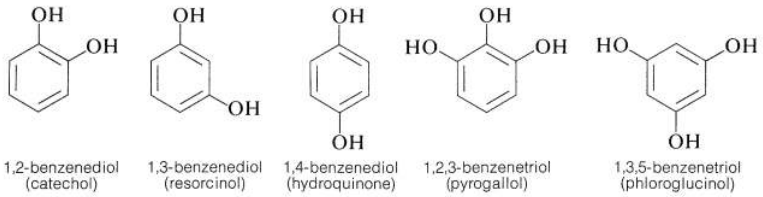


Disproportionation:

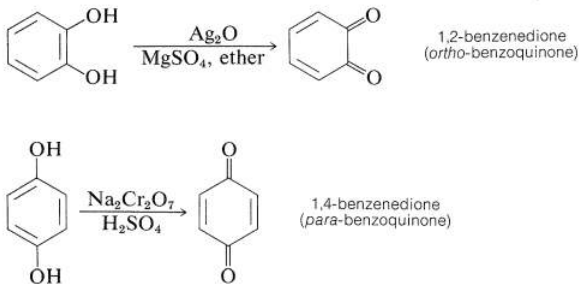


26.1.8: Arene Polyols

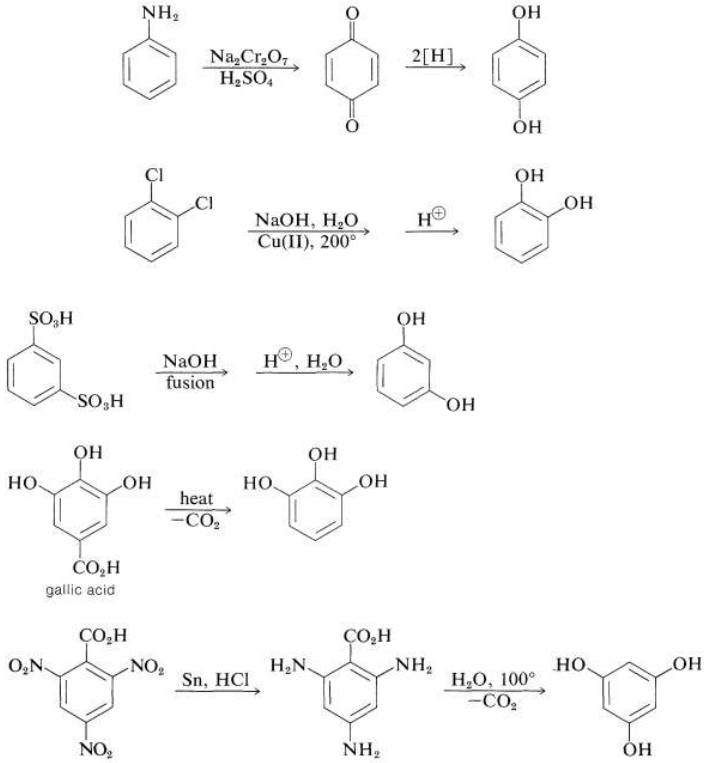
Several important aromatic compounds have more than one arene hydroxyl group. These most often are derivatives of the following dihydric and trihydric arenols, all of which have commonly used (but poorly descriptive) names:



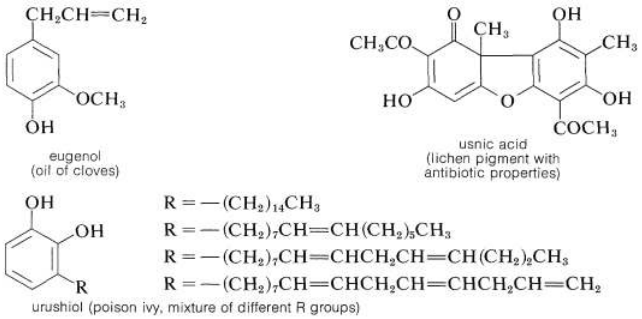
All are exceptionally reactive towards electrophilic reagents, particularly in alkaline solution, and all are readily oxidized. The 1,2- and 1,4-benzenediols, but not 1,3-benzenediol, are oxidized to quinones:



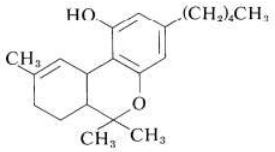
The preparation of these substances can be achieved by standard methods for synthesizing arenols, but most of them actually are made on a commercial scale by rather special procedures, some of which are summarized as follows:



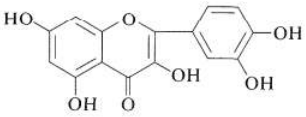
The gallic acid used in the preparation of 1,2,3-benzenetriol can be obtained by microbial degradation of **tannins**, which are complex combinations of glucose and gallic acid obtained from oak bark and gallnuts. A few other representatives of the many types of naturally occurring derivatives of polyhydric arenols are



https://chem.libretexts.org/@go/page/22371



tetrahydrocannabinol
(active constituent of marijuana or hashish)



quercetin
(in the form of glucosides, as
a coloring matter in plants)

26.1.9: Contributors and Attributions

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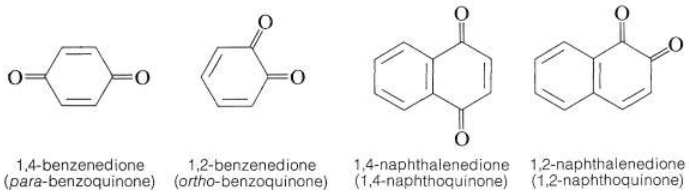
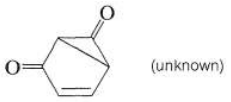
26.2: Quinones

Quinones are not aromatic compounds but are conjugated cyclic diketones. Yet it is convenient to discuss their chemistry at this point because quinones and the related aromatic arenols are readily interconverted, and their chemistry is largely interdependent.

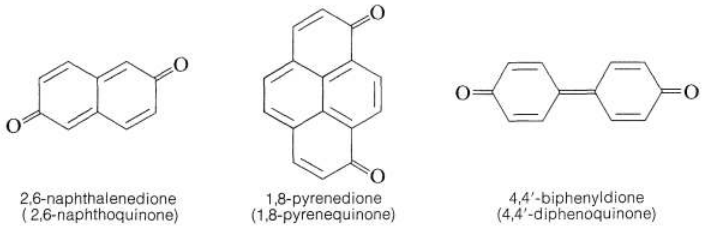
A variety of quinonelike structures have been prepared, the most common of which are the 1,2 - and 1,4-quinones as exemplified by 1,2- and 1,4-benzenediones. Usually the 1,2-quinones are more difficult to make and are more reactive than the 1,4-quinones. A few 1,6- and 1,8-quinones also are known.



No 1,3-quinones are known, possibly because they would have nonplanar, highly strained structures and therefore would be unstable:

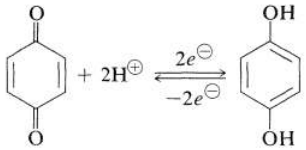


A number of quinones are known in which the quinone arrangement extends over more than one ring. Examples are:



26.2.1: Reduction of Quinones

A characteristic and important reaction of quinones is reduction to the corresponding arenediols. The reduction products of 1,4-quinones are called **hydroquinones**:

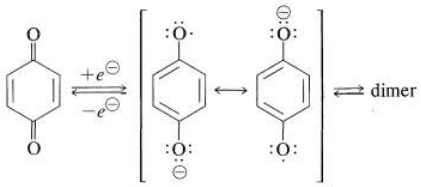


Reduction can be achieved electrochemically and with a variety of reducing agents (metals in aqueous acid, catalytic hydrogenation). Such reductions are unusual among organic reactions in being sufficiently rapid and reversible to give easily reproducible electrode potentials in an electrolytic cell. The position of the 1,4-benzenediol-1,4,-benzenedione equilibrium (Equation 26-2) is proportional to the square of the hydrogen-ion concentration. Therefore the electrode potential is sensitive to pH; a change of one unit of pH in water solution changes the potential of the electrode by 0.059 V. Before the invention of the glass-electrode pH meter, the half-cell potential developed by this equilibrium was used widely to determine pH values of aqueous solutions. The method is not very useful above pH 9 because the quinone reacts irreversibly with alkali.

Numerous studies have been made of the relationship between half-cell reduction potentials and the structures of quinones. As might be expected, the potentials are greatest when the resonance stabilization associated with formation of the aromatic ring is greatest.

When alcohols solutions of hydroquinone and quinone are mixed, a brown-red color develops and a green-black 1:1 complex crystallizes that is known as **quinhydrone**. This substance is a charge-transfer complex (Section 24-6C), with the diol acting as the electron donor and the dione as the electron acceptor. Quinhydrone is not very soluble and dissociates considerably to its components in solution.

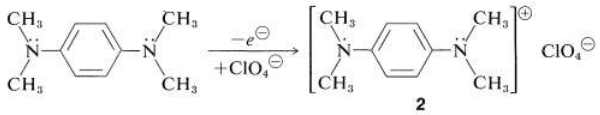
The reduction of a quinone requires two electrons, and it is possible that these electrons could be transferred either together or one at a time. The product of a single-electron transfer leads to what appropriately is called a **semiquinone**, 1, with both a negative charge and an odd electron (a radical anion):



a semiquinone radical anion, **1**

The formation of relatively stable semiquinone radicals by electrolytic reduction of quinones has been established by a variety of methods. Some semiquinone radicals undergo reversible dimerization reactions to form peroxides.

A particularly stable cation-radical of the semiquinone type is formed by mild oxidation of N,N,N′,N′-tetramethyl-1,4-benzenediamine. The cation, which is isolable as a brilliant-blue perchlorate salt, 2, is called "Wurster's Blue":

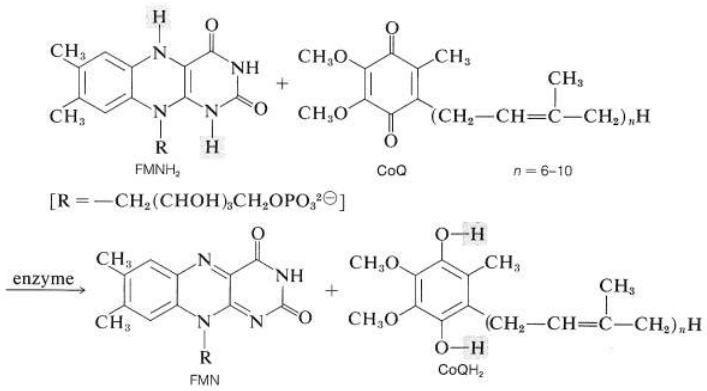


2
Wurster's Blue

26.2.2: Quinones of Biological Importance

Oxidation and reduction in biochemical systems involve many reactions that are similar to the arenediol-arenediol couple. We have mentioned several previously: $NADP^{\oplus} \rightleftharpoons NADPH$ (Section 20-9), and $FADH_2 \rightleftharpoons FAD$ (Section 15-6C).

An important question in metabolic oxidation is just how reduction of oxygen $\left(\frac{1}{2}O_2 + 2H^{\oplus} + 2e \rightarrow H_2O\right)$ is linked to the oxidation of NADH $\left(NADH \rightarrow NAD^{\oplus} + H^{\oplus} + 2e\right)$. The route for transfer of electrons from NADH to oxygen (oxidation plus phosphorylation; Section 20-10) is indirect, complicated, and involves, in an early stage, oxidation of NADH by flavin mononucleotide (FMN) by the reaction $FMN + NADH + H^{\oplus} \rightarrow FMNH_2 + NAD^{\oplus}$. But the reduced form of FMN, $FMNH_2$, does not react directly with oxygen. Instead, it reduces a quinone called **coenzyme Q (CoQ)** to the corresponding arenediol:



FMNH2 CoQ n = 6–10

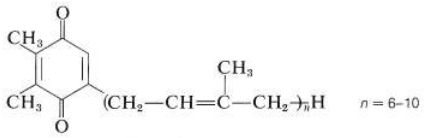
[R = —CH2(CHOH)3CH2OPO3²⊖]

FMN CoQH2

The effect of this step is to form a slightly polar reductant (**CoQ**H_2) from a strongly polar reductant $(FMNH_2)$, and this permits the reduced material to penetrate into a less polar region of the oxidative apparatus. The reduced **CoQ** does not react directly with oxygen but is a participant in a chain of oxidation-reduction reactions involving electron transfer between a number of iron-containing proteins known as *cytochromes*. At the end of this chain of reaction, the reduced form of a copper-containing cytochrome actually reacts with oxygen. The sequence of electron-carriers may be summarized as

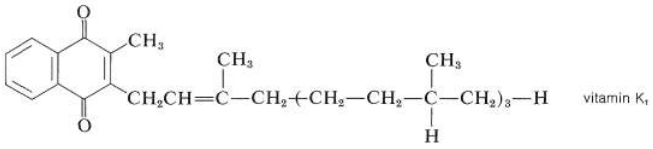
$$\mathrm{NADH} \rightarrow \mathrm{FMNH_2} \rightarrow \mathbf{CoQH_2} \rightarrow \text{cytochromes} \rightarrow \mathrm{O_2} \qquad (26.2.1)$$

A related process occurs in photosynthesis (Section 20-9). You will recall that a critical part of photosynthesis involves the transfer of electrons from the photosystem that oxidizes water $\left(\mathrm{H_2O} \rightarrow \frac{1}{2}\mathrm{O_2} + 2\mathrm{H^{\oplus}} + 2\mathrm{e}\right)$ to the photosystem that reduces $\mathrm{NADP^{\oplus}}$ $\left(\mathrm{NADP^{\oplus}} + 2\mathrm{H^{\oplus}} + 2\mathrm{e} \rightarrow \mathrm{NADPH} + \mathrm{H^{\oplus}}\right)$. As in oxidative phosphorylation, the electron-transfer route is complex. However, one of the electron carriers is a quinone called **plastoquinone** that closely resembles coenzyme Q found in animals. Plastoquinone, like coenzyme Q, is reduced to the hydroquinone form, which is part of an electron-transport chain involving iron- and copper-containing proteins:

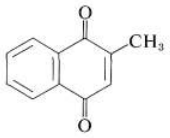


plastoquinone

Among other naturally occurring substances having quinone-type structures, one of the most important is the blood antihemorrhagic factor, vitamin $\mathrm{K_1}$, which occurs in green plants and is a substituted 1,4-naphthalenedione:



The structure of vitamin $\mathrm{K_1}$ has been established by degradation and by synthesis. Surprisingly, the long alkyl side chain of vitamin $\mathrm{K_1}$ is not necessary for its action in aiding blood clotting because 2-methyl-1,4-naphthoquinone is almost equally active on a molar basis.

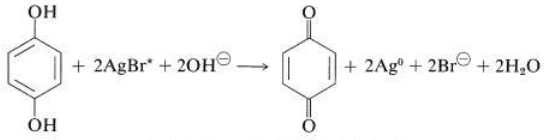


2-methyl-1,4-naphthalenedione (menadione)

Besides playing a vital role in the oxidation-reduction processes of living organisms, quinones occur widely as natural pigments found mainly in plants, fungi, lichens, marine organisms, and insects (see alizarin, Section 28-4A, as representative of a natural anthraquinone-type dye).

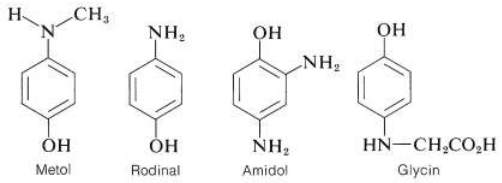
26.2.3: Photographic Developers

Photography makes important practical use of the arenediol-arenediol oxidation-reduction system. Exposure of the minute grains of silver bromide in a photographic emulsion to blue light (or any visible light in the presence of suitably sensitizing dyes) produces a stable activated form of silver bromide, the activation involving generation of some sort of crystal defect. Subsequently, when the emulsion is brought into contact with a developer, which may be an alkaline aqueous solution of 1,4-benzenediol (hydroquinone) and sodium sulfite, the particles of activated silver bromide are reduced to silver metal much more rapidly than the ordinary silver bromide. Removal of the unreduced silver bromide with sodium thiosulfate ("fixing") leaves a suspension of finely divided silver in the emulsion in the form of the familiar photographic negative.

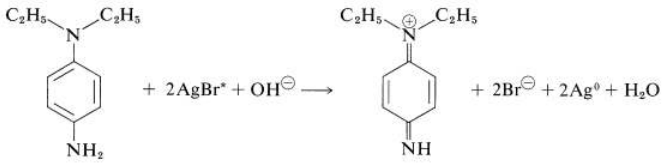


AgBr* = light-activated silver bromide

A variety of compounds are used as photographic developing agents. They are not all arenediols. In fact, most are aromatic aminoalcohols or diamines, but irrespective of their structural differences, they all possess the ability to undergo redox reactions of the type described for 1,4-benzenediol. Structural formulas and commercial names for several important developers are

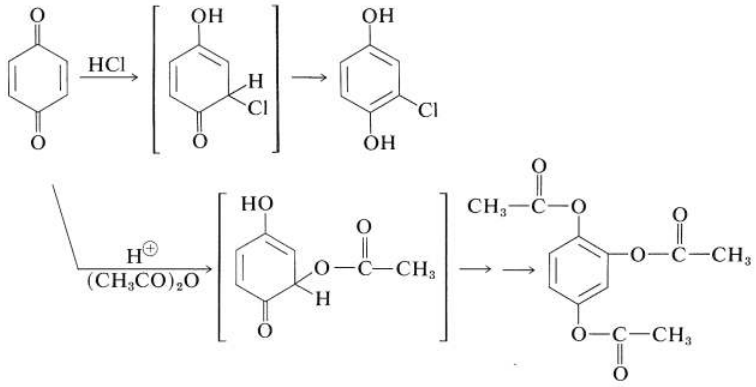


1,4-Benzenediamine also is an effective developing agent, but it may cause dermatitis in sensitive individuals. N,N-Diethyl-1,4-benzenediamine is used as a developer in color photography. These substances react with silver bromide to produce benzenediamine derivatives:

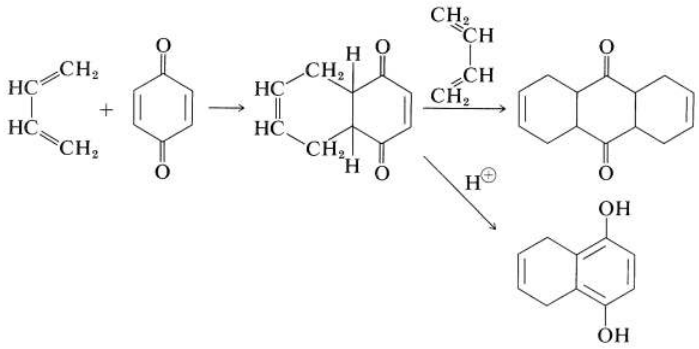


26.2.4: Addition Reactions of Quinones

Being α,β-unsaturated ketones, quinones have the potential of forming 1,4-addition products in the same way as their open-chain analogs (Section 17-5B). 1,4-Benzenedione undergoes such additions rather readily. The products are unstable and undergo enolization to give substituted 1,4-benzenediols. Two examples are the addition of hydrogen chloride and the acid-catalyzed addition of ethanoic anhydride. In the latter reaction, the hydroxyl groups of the adduct are acylated by the anhydride. Hydrolysis of the product yields 1,2,4-benzenetriol:

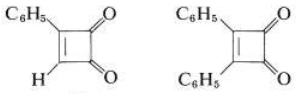


Quinones usually undergo Diels-Alder additions readily, provided that they have at least one double bond that is not part of an aromatic ring. With 1,4-benzenedione and 1,3-butadiene, either the mono- or diadduct can be obtained. The monoadduct enolizes under the influence of acid or base to a 1,4-benzenediol derivative:



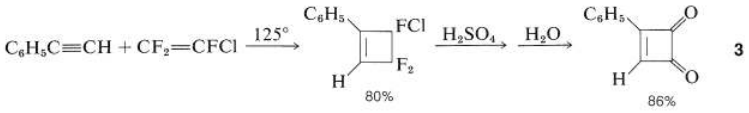
26.2.5: Quinones of Cyclobutadiene

Benzoquinones owe their unusual properties as α,β-unsaturated ketones to the ease by which they are transformed to stable aromatic systems. How would these properties change if the quinone were derived from nonaromatic structures, such as cyclobutadiene, cyclooctatetraene, or pentalene? There is no final answer to this question because few such substances have been prepared, the best known so far being the mono- and diphenylcyclobutenediones:

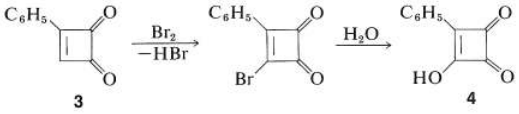


3

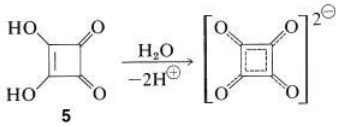
For example, 3 can be prepared from sulfuric acid hydrolysis of the cycloaddition product of ethynylbenzene and trifluorochloroethene (Section 13-3D):



The dione, 3, is a yellow crystalline solid that, despite its strained four-membered ring, is much less reactive than 1,2-benzenedione (*ortho*-benzoquinone). It cannot be reduced to a cyclobutenediol, does not undergo Diels-Alder reactions, and with bromine gives a substitution product rather than addition. The bromo compound so formed hydrolyzes rapidly to a hydroxy compound, 4, which is an extraordinarily strong acid having an ionization constant about 10^9 times that of benzenol:



A related compound, 3,4-dihydroxy-1,2-cyclobutenedione, 5, also has been prepared and is a very strong dibasic acid. It is sometimes called "squaric acid":



From the data so far available, it appears that the quinones corresponding to cyclobutadiene have more aromatic character than do the cyclobutadienes themselves.

26.2.6: Contributors and Attributions

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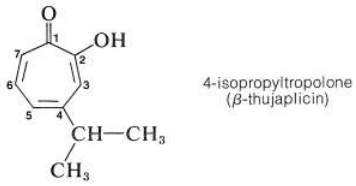
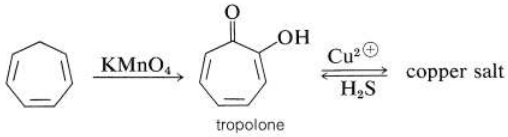
26.3: Tropolones and Related Compounds

The tropolones make up a very interesting class of nonbenzenoid aromatic compound that was discovered first in several quite different kinds of natural products. As one example, the substance called β-thujaplicin or hinokitiol has been isolated from the oil of the Formosan cedar and is 4-isopropyltropolone:



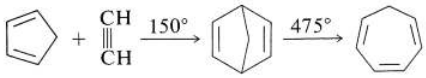
4-isopropyltropolone
(β-thujaplicin)

Tropolone itself can be prepared in a number of ways, the most convenient of which involves oxidation of 1,3,5-cycloheptatriene with alkaline potassium permanganate. The yield is low but the product is isolated readily as the cupric salt:

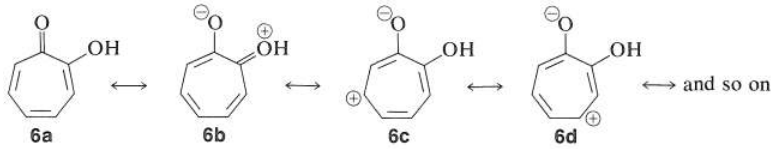


tropolone

The cycloheptatriene for this synthesis can be obtained best by thermal rearrangement of the Diels-Alder addition product of cyclopentadiene and ethyne:

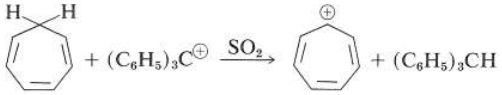


Tropolone is an acid with an ionization constant of 10^{-7}, which is intermediate between the K_a of ethanoic acid and the K_a of benzenol. Like most arenols, tropolones form colored complexes with ferric chloride solution. Tropolone has many properties that attest to its aromatic character - it resists hydrogenation, undergoes diazo coupling, and can be nitrated, sulfonated, and substituted with halogens. The aromaticity of tropolone can be attributed to resonance involving the two nonequivalent VB structures $6a$ and $6b$, and to several dipolar structures, such as $6c$ and $6d$, in which the ring has the stable tropylium cation structure with six π electrons (Section 21-9B):



6a 6b 6c 6d

The tropylium cation is prepared easily by transfer of a hydride ion from cycloheptatriene to triphenylmethyl cation in sulfur dioxide solution. This reaction is related to the hydride ion transfer, $(CH_3)_3C^{\oplus} + RH \rightarrow (CH_3)_3CH + R^{\oplus}$, discussed in Section 10-9:



tropylium cation

Seven equivalent VB structures can be written for the tropylium cation so only one seventh of the positive charge is expected to be on each carbon. Because the cation has six π electrons, it is expected from Huckel's $(4n + 2)$ π-electron rule to be unusually stable for a carbocation.

hybrid structure for
tropylium ion

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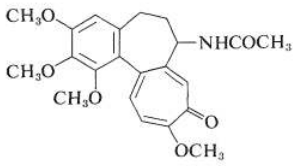
The infrared and Raman spectra of tropylium bromide in hydrobromic acid solution have no common bands, which means that the cation exists in a highly symmetrical form in this solution (see Section 9-8). At higher pH, reversible formation of the hydroxy compound occurs:

$$C_7H_7^+ + OH^- \rightleftharpoons C_7H_7OH \tag{26.3.1}$$

The equilibrium constant for this reaction is such that the cation is half converted to the hydroxy compound at about pH 5.



colchicine

Colchicine is an important naturally occurring tropolone derivative. It is isolated from the autumn crocus and is used in medicine for the treatment of gout. It also has an effect on cell division and is used in plant genetic studies to cause doubling of chromosomes. The structure has been confirmed by total synthesis.

26.3.1: Contributors

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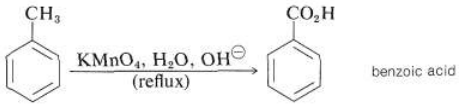
26.4: Some Aromatic Side-Chain Compounds

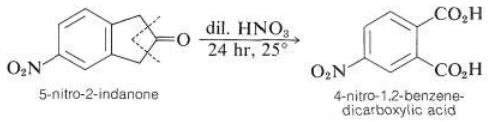
We have discussed in this chapter and in previous chapters how the reactivity of halogen, amino, and hydroxy substituents are modified when linked to aromatic carbons rather than to saturated carbons. Other substituents, particularly those linked to an aromatic ring through a carbon-carbon bond, also are influenced by the ring, although usually to a lesser degree. Examples include $-CH_2OH$, $-CH_2OCH_3$, $-CH_2Cl$, $-CHO$, $-COCH_3$, $-CO_2H$, and $-CN$, and we shall refer to aromatic compounds containing substituents of this type as **aromatic side-chain compounds**. Our interest in such compounds will be directed mainly to reactions at the side chain, with particular reference to the effect of the aromatic ring on reactivity. In this connection, we shall discuss the relatively stable triarylmethyl cations, anions, and radicals, as well as quantitative correlation of rates of organic reactions by what is known as the Hammett equation.

26.4.1: Preparation of Aromatic Side-Chain Compounds

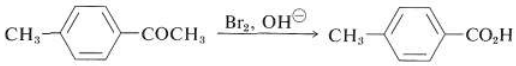
Carboxylic acids can be obtained from most alkylbenzenes by oxidation of the side chain with reagents such as potassium permanganate, potassium dichromate, or nitric acid:



Under the conditions of oxidation, higher alkyl or alkenyl groups are degraded and ring substituents, other than halogen and nitro groups, often fail to survive. As an example, oxidation of 5-nitro-2-indanone with dilute nitric acid leads to 4-nitro-1,2-benzenedicarboxylic acid:

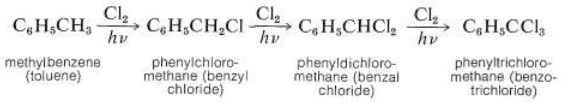


To retain a side-chain substituent, selective methods of oxidation are required. For example, 4-methylbenzoic acid can be prepared from 1-(4-methylphenyl)ethanone by the haloform reaction (Section 17-2B):



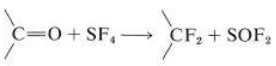
Many side-chain halogen compounds can be synthesized by reactions that also are applicable to alkyl halides (see table 14-5), but there are other methods especially useful for the preparation of arylmethyl halides. The most important of these are the chloromethylation of aromatic compounds (to be discussed later in this section) and radical halogenation of alkylbenzenes.

Light-induced, radical chlorination or bromination of alkylbenzenes with molecular chlorine or bromine was discussed previously (Section 14-3C). Under these conditions, methylbenzene reacts with chlorine to give successively phenylchloromethane, phenyldichloromethane, and phenyltrichloromethane:

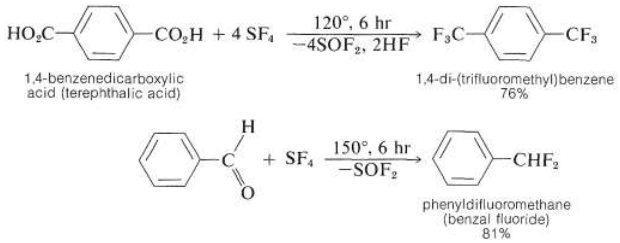


Related reactions occur with other reagents, notably sulfuryl chloride, SO_2Cl_2; *tert*-butyl hypochlorite, $(CH_3)_3COCl$; and N-bromobutanimide, $(CH_2CO)_2NBr$. The α substitution of alkylbenzenes is the result of radical-chain reactions (Section 14-3C).

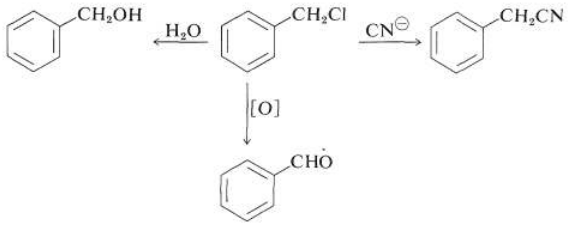
Side-chain fluorine compounds with the groupings $-CHF_2$, $-CF_2-$, and $-CF_3$ are available by the reaction of sulfur tetrafluoride or molybdenum hexafluoride with carbonyl compounds (see Section 16-4D):



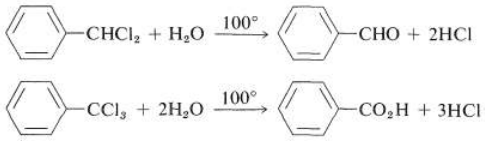
Some specific examples follow:



Arylmethyl chlorides or bromides are quite reactive compounds that are readily available or easily prepared, and as a result they are useful intermediates for the synthesis of other side-chain derivatives. Thus phenylmethyl chloride can be hydrolyzed to phenylmethanol, converted to phenylethanenitrile with alkali-metal cyanides, and oxidized to benzenecarbaldehyde (benzaldehyde):



Phenyldichloromethane hydrolyzes readily to benzaldehyde, and phenyltrichloromethane to benzoic acid:

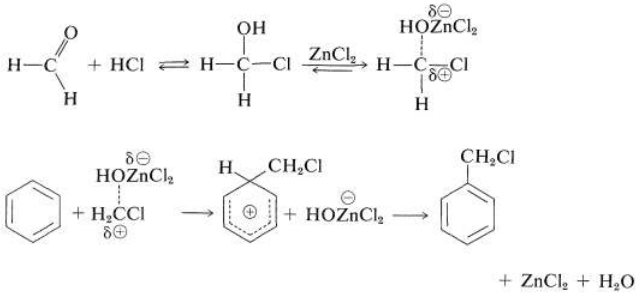


Carbon side chains also may be introduced by direct substitution and several such reactions have been discussed in detail previously. These include Friedel-Crafts alkylation and acylation (Section 22-4E and 22-4F), the Gattermann-Koch reaction for preparation of aldehydes from arenes and carbon monoxide (Section 22-4F), and the Kolbe-Schmitt, Reimer-Tiemann, and Gattermann reactions for synthesis of acids and aldehydes from arenols (Section 26-1E).

Chloromethylation is a useful method for substitution of $-CH_2Cl$ for an aromatic hydrogen, provided one starts with a reasonably reactive arene. The reagents are methanol and hydrogen chloride in the presence of zinc chloride:

$$C_6H_6 + CH_2O + HCl \xrightarrow{ZnCl_2} C_6H_5CH_2Cl + H_2O \qquad (26.4.1)$$

The mechanism of the chloromethylation reaction is related to that of Friedel-Crafts alkylation and acylation and probably involves an incipient chloromethyl cation, $^{\oplus}CH_2Cl$:



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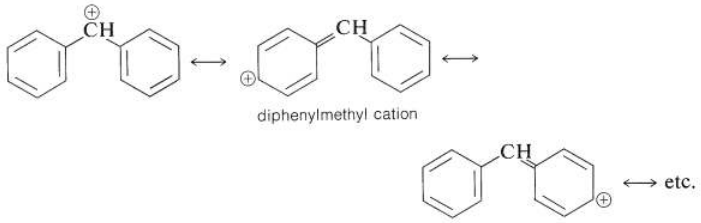
26.4.2: Triarylmethyl Cations

Phenylmethyl halides are similar in S_N1 reactivity to 2-propenyl halides. The S_N1 reactivity of phenylmethyl derivatives can be ascribed mainly to stabilization of the cation by electron delocalization. Diphenylmethyl halides, $(C_6H_5)_2CHX$, are still more reactive and this is reasonable because the diphenylmethyl cation has two phenyl groups over which the positive charge can be delocalized and therefore should be more stable relative to the starting halide than is the phenylmethyl cation:



Accordingly, we might expect triphenylmethyl (or trityl) halides, $(C_6H_5)_3C{-}X$, to be even more reactive. In fact, the C–X bonds of such compounds are extremely labile. In liquid sulfur dioxide, triarylmethyl halides ionize reversibly, although the equilibria are complicated by ion-pair association:

$$(C_6H_5)_3C{-}Cl \xrightleftharpoons{SO_2,\ 0^\circ} \underset{\text{ion pair}}{(C_6H_5)_3C^{\oplus}Cl^{\ominus}} \rightleftharpoons \underset{\text{dissociated ions}}{(C_6H_5)_3C^{\oplus} + Cl^{\ominus}}$$

Triarylmethyl cations are among the most stable carbocations known. They are intensely colored and are formed readily when the corresponding triarylmethanols are dissolved in strong acids:

$$\underset{\substack{\text{triphenylmethanol}\\\text{(colorless)}}}{(C_6H_5)_3C{-}OH} \xrightleftharpoons{H_2SO_4} (C_6H_5)_3C{-}\overset{\oplus}{O}H_2 \xrightleftharpoons{-H_2O} \underset{\substack{\text{triphenylmethyl cation}\\\text{(orange-yellow)}}}{(C_6H_5)_3C^{\oplus}}$$

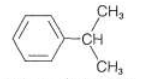
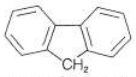
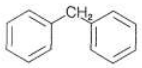
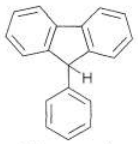
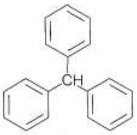
26.4.3: Triarylmethyl Anions

In addition to stable cations, triarylmethyl compounds form stable carbanions. Because of this the corresponding hydrocarbons are relatively acidic compared to simple alkanes. They react readily with strong bases such as sodium amide, and the resulting carbanions, like the cations, are intensely colored:

$$\underset{\substack{\text{triphenylmethane}\\\text{(colorless)}}}{(C_6H_5)_3CH} + Na^{\oplus}NH_2^{\ominus} \xrightleftharpoons{\text{ether}} \underset{\substack{\text{triphenylmethylsodium}\\\text{(blood red)}}}{(C_6H_5)_3C{:}^{\ominus}Na^{\oplus}} + NH_3$$

The acid strengths of arylmethanes are listed in Table 26-3. All are quite weak acids relative to water but vary over many powers of ten relative to one another. The stronger acids form the more stable carbanions, and the carbanion stability generally is determined by the effectiveness with which the negative charge can be delocalized over the substituent aryl groups.

Table 26-3: *Strengths of Some Hydrocarbon Acids*

Compound	K_a	Compound	K_a
 isopropylbenzene (cumene)	10^{-37}	 dibenzocyclopentadiene[a] (fluorene)	10^{-25}
 diphenylmethane	10^{-35}	 5-phenyldibenzocyclopentadiene[a] (9-phenylfluorene)	10^{-21}
 triphenylmethane	10^{-33}	benzocyclopentadiene[a] (indene)	10^{-21}

[a]According to the IUPAC rules for naming polycyclic compounds, when a benzene ring is "ortho-fused" to another ring the prefix "benzo" is attached to the name of the parent ring. This is contracted to "benz" when preceding a vowel, as in benzanthracene.

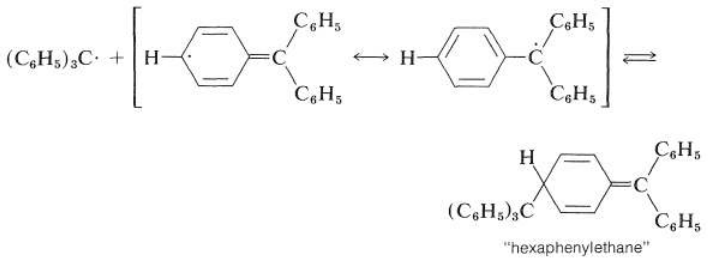
26.4.4: Triarylmethyl Radicals

Triarylmethyl compounds also form rather stable triarylmethyl radicals, and indeed the first stable carbon free radical to be reported was the triphenylmethyl radical, $(C_6H_5)_3C\cdot$, prepared inadvertently by M. Gomberg in 1900. Gomberg's objective was to prepare hexaphenylethane by a Wurtz coupling reaction of triphenylmethyl chloride with metallic silver:

$$2(C_6H_5)_3C{-}C\cdot + 2Ag \xrightarrow{\text{benzene}} \underset{\text{hexaphenylethane}}{(C_6H_5)_3C{-}C(C_6H_5)_3} + 2AgCl$$

However, he found that unless air was carefully excluded from the system, the product was triphenylmethyl peroxide, $(C_6H_5)_3COOC(C_6H_5)_3$, rather than the expected hexaphenylethane.

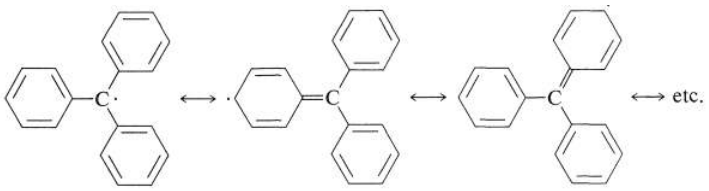
Gomberg believed that the yellow solution obtained from the reaction of triphenylmethyl chloride with silver in benzene in the absence of air contained the triphenylmethyl radical. However, subsequent investigations showed that the molecular weight of the dissolved substance was closer to that for $C_{38}H_{30}$, hexaphenylethane. A bitter battle raged over the nature of the product and its reactions. The controversy finally was though to have been settled by the demonstration that the hydrocarbon $C_{38}H_{30}$ dissociates rapidly, but only slightly, to triphenylmethyl radicals at room temperature in inert solvents ($K = 2.2 \times 10^{-4}$ at 24° in benzene). For many years thereafter, the hydrocarbon $C_{38}H_{30}$ was believed to be the hexaphenylethane. Now it is known that this conclusion was incorrect. The product is a dimer of triphenylmethyl, but it is formed by the addition of one radical to the 4-position of a phenyl ring of the other:



Formation of the peroxide in the presence of oxygen is explained as follows:

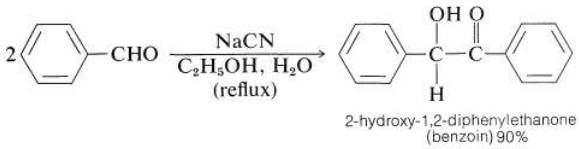
$$(C_6H_5)_3C\cdot + O_2 \longrightarrow (C_6H_5)_3COO\cdot \xrightarrow{(C_6H_5)_3C\cdot} \underset{\text{triphenylmethyl peroxide}}{(C_6H_5)_3COOC(C_6H_5)_3}$$

Although the foregoing reactions involving the triphenylmethyl radical seemed very unreasonable at the time they were discovered, the stability of the radical now has been established beyond question by a variety of methods such as esr spectroscopy (Section 27-9). This stability can be attributed to delocalization of the odd electron over the attached phenyl groups:

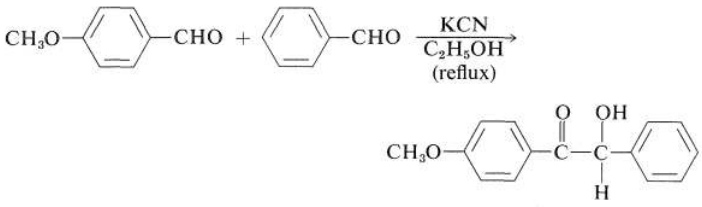


26.4.5: Aromatic Aldehydes. The Benzoin Condensation

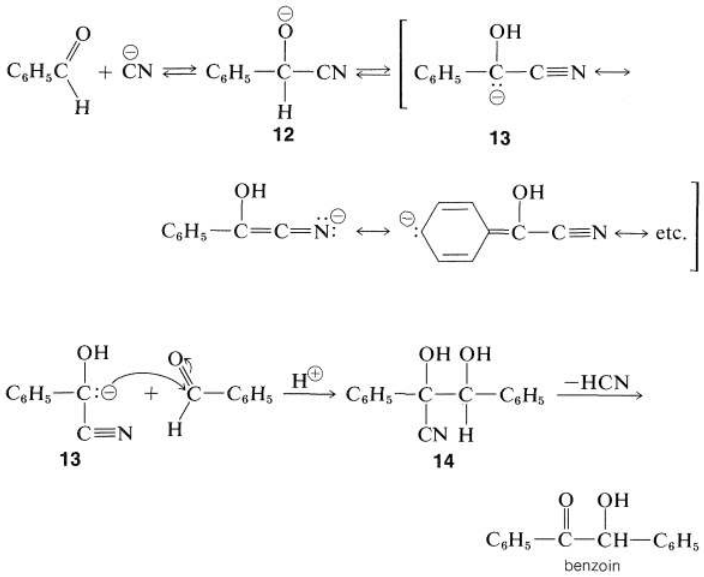
Most of the reactions of aromatic aldehydes, ArCHO, are those expected of aldehydes with no α hydrogens and most of these will not be reviewed here. One reaction that usually is regarded as being characteristic of aromatic aldehydes (although, in fact, it does occur with other aldehydes having no α hydrogens), is known as the **benzoin condensation**. This reaction essentially is a dimerization fo two aldehyde molecules through the catalytic action of sodium or potassium cyanide:



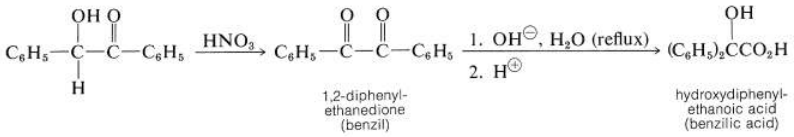
Unsymmetrical or mixed benzoins may be obtained in good yield from two different aldehydes:



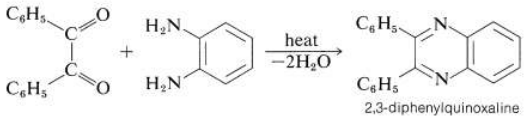
As to the mechanism of benzoin formation, cyanide ion adds to the aldehyde to form 12. This anion is in equilibrium with 13, wherein the negative charge can be delocalized over the phenyl and nitrile groups. A subsequent aldol-type addition of 13 to the carbonyl carbon of a second aldehyde molecule gives the addition product 14, and loss of HCN from 14 leads to the benzoin:



Benzoins are useful intermediates for the synthesis of other compounds because they can be oxidized to 1,2-diones and reduced in stages to various products, depending upon the reaction conditions. The 1,2-diketone known as benzil, which is obtained by nitric acid oxidation of benzoin, undergoes a base-catalyzed hydration rearrangement to form an α-hydroxy acid, commonly called the **benzilic acid rearrangement** (see Section 17-7):



Benzils, like other 1,2-diones, react with 1,2-benzenediamines to form diazaarenes known as quinoxalines. This kind of reaction is an important general procedure for the synthesis of aromatic ring systems containing nitrogen:



26.4.6: Contributors and Attributions

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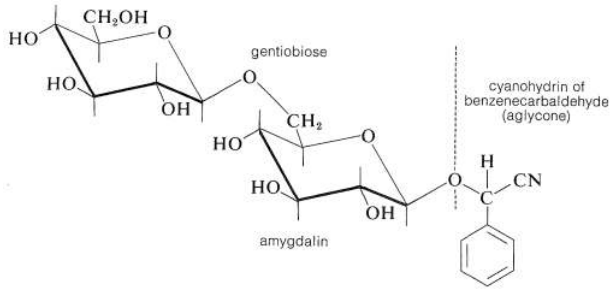
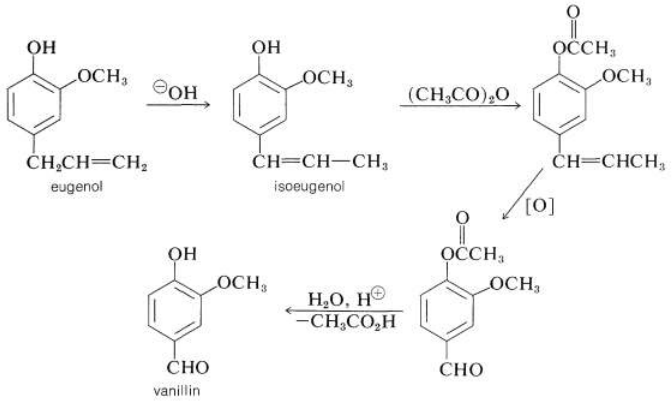
26.5: Natural Occurrence and Uses of Some Aromatic Side-Chain Compounds

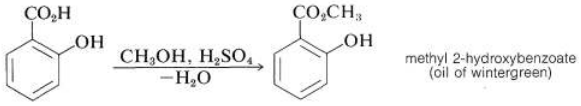
Derivatives of aromatic aldehydes occur naturally in the seeds of plants. For example, amygdalin is a substance occurring in the seeds of the bitter almond. It is a derivative of gentiobiose, which is a disaccharide made up of two glucose units; one of the glucose unites is bonded by a β-glucoside linkage to the OH group of the cyanohydrin of benzenecarbaldehyde:



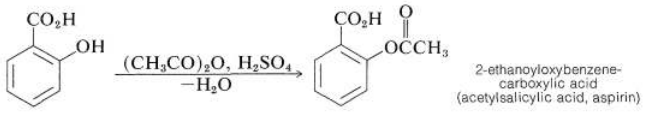
The flavoring vanillin occurs naturally as a glucovanillin (a glucoside) in the vanilla bean (Section 20-5). It is made commercially in several ways. One is from eugenol, itself a constituent of several essential oils:



Methyl 2-hydroxybenzoate (methyl salicylate, oil of wintergreen) occurs in many plants, but it also is readily prepared synthetically by esterification of 2-hydroxybenzoic acid, which in turn is made from benzenol (see Section 26-1E):



The ethanoyl derivative of 2-hydroxybenzoic acid is better known as *aspirin* and is prepared from the acid with ethanoic anhydride, using sulfuric acid as catalyst:



Figures 23-1 through 23-3.

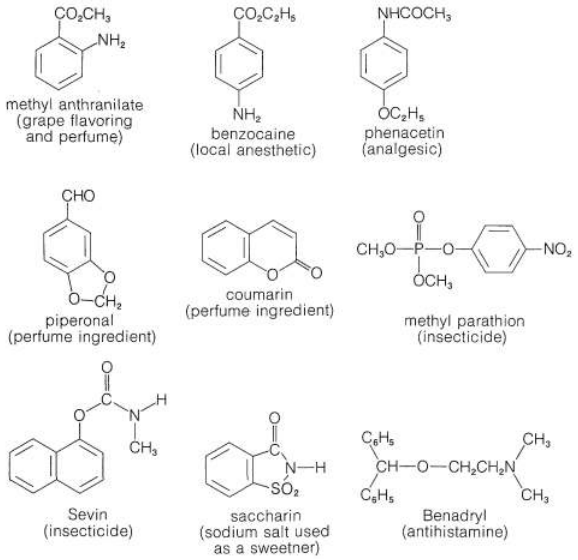


Figure 26-2: Some synthetic and natural aromatic compounds and their uses.

26.5.1: Contributors and Attributions

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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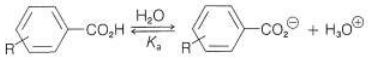
26.6: Correlations of Structure with Reactivity of Aromatic Compounds

This section is concerned with the quantitative correlation of reaction rates and equilibria of organic reactions with the structure of the reactants. We will restrict the discussion to benzene derivatives. The focus is on a remarkably simple treatment developed by L. P. Hammett in 1935, which has been tremendously influential. Hammett's correlation covers chemical reactivity, spectroscopy and other physical properties, and even the biological activity of drugs. Virtually all quantitative treatments of reactivity of organic compounds in solution start with the kinds of correlations that are discussed in this section.

26.6.1: The Hammett Equation

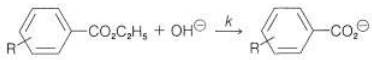
If we compare the acid strengths (K_a) of a series of substituted benzoic acids with the strength of benzoic acid itself (Table 26-4), we see that there are considerable variations with the nature of the substituent and its ring position, ortho, meta, or para. Thus all three nitrobenzoic acids are appreciably stronger than benzoic acid in the order ortho $\gg$ para $>$ meta. A methoxy substituent in the ortho or meta position has a smaller acid-strengthening effect, and in the para position decreases the acid strength relative to benzoic acid. Rate effects also are produced by different substituents, as is evident from the data in Table 26-5 for basic hydrolysis of some substituted ethyl benzoates. A nitro substituent increases the rate, whereas methyl and methoxy substituents decrease the rate relative to that of the unsubstituted ester.

Table 26-4: *Dissociation Constants* $(10^{-5} \times K_a)$ *of Some Substituted Benzoic Acids in Water at* 25°



R	H	CH_3	OCH_3	F	Cl	NO_2
ortho	6.27	12.3	8.06	54.1	114	671
meta	6.27	5.35	8.17	13.6	14.8	32.1
para	6.27	4.24	3.38	7.22	10.5	37.0

Table 26-5: *Specific Rate Constants*[a] *for Alkaline Hydrolysis of Some Substituted Ethyl Benzoates in* 85% *Ethanol-Water Solution at* 30°



R	H	CH_3	OCH_3	F	Cl	NO_2
ortho	81.7	15.8		462	267	912
meta	81.7	57.7			605	5180
para	81.7	38.2	17.5	251	353	8480

[a] $10^5 k$, liter mole^{-1} sec^{-1}.

Figure 26-3). The linear correlation for meta and para substituents is observed for the rates or equilibrium constants for many other reactions. For example, straight lines are obtained on plotting log K for the dissociation of phenylethanoic acids (meta- and para-$RC_6H_4CH_2CO_2H$) against log K' for the dissociation of phenylammonium ions (meta- and *para*-$RC_6H_4\overset{\oplus}{N}H_3$), or against log k for the rate of hydrolysis of phenylmethyl halides (*meta*- and *para*-$RC_6H_4CH_2X$).

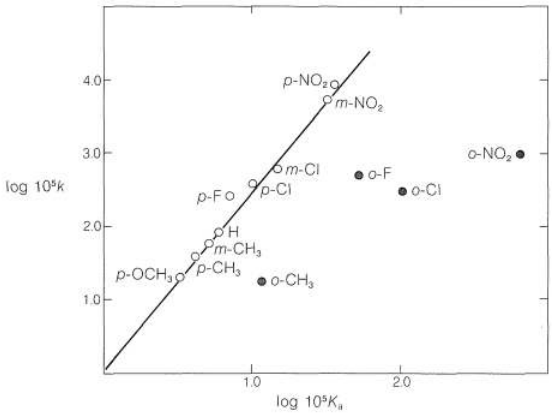


Figure 26-3: Plot of log $10^5\ K_a$ for the dissociation of substituted benzoic acids in water at 25° against log $10^5\ k$ for the rates of alkaline hydrolysis of substituted ethyl benzoates in 85% ethanol-water at 30°.

The straight line in Figure 26-3 can be expressed conveniently by Equation 26-3, in which the two variables are log k and log K, the slope of the line is ρ, and the intercept is C:

$$\log k = \rho \log K + C \tag{26-3}$$

For the particular case for which the ring substituent is hydrogen $(\mathrm{R{=}H})$, Equation 26-3 becomes

$$\log k_0 = \rho \log K_0 + C \tag{26-4}$$

in which K_0 is the dissociation constant of benzoic acid and k_0 is the rate of hydrolysis of ethyl benzoate. Subtracting Equation 26-4 from Equation 26-3 we obtain

$$\log \frac{k}{k_0} = \rho \log \frac{K}{K_0} \tag{26-5}$$

This equation could be tested on the ratios of any rates or equilibrium constants, but it is convenient to reserve log (K/K_0) for the dissociation of benzoic acids in water at 25° (Table 26-4) and correlate the rate or equilibrium constants for all other processes with log (K/K_0). The common procedure is to rewrite Equation 26-5 as Equation 26-6:

$$\log \frac{k}{k_0} = \rho\sigma \tag{26-6}$$

in which σ is defined as:

$$\sigma = \log \frac{K}{K_0} \tag{26-7}$$

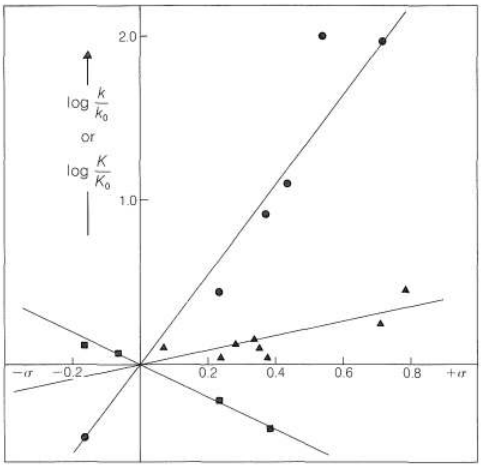
Equation 26-6 is known as the **Hammett equation**, but before we discuss its general applications, it will be helpful to say more about the σ term in Equation 26-7.

The *relative strength* of a substituted benzoic acid and hence the value of σ depends on the *nature* and *position* of the substituent in the ring. For this reason, σ is called the **substituent constant**. Table 26-6 lists several substituent constants and these will be seen to correspond to the polar character of the respective substituents. Thus the more electron-attracting a substituent is, by either resonance or induction, the more acid-strengthening it is, and the more *positive* is its σ value (relative to H as 0.000). Conversely, the more strongly a substituent donates electrons by resonance or induction, the more *negative* is its σ value. We expect that among the more electron-attracting and electron-donating substituents will be those with electric charges, positive and negative respectively. Indeed, a diazonium group $(-\mathrm{N_2}^+)$ in the para position has a very large σ value of +1.91, whereas a para $-\mathrm{O}^\ominus$ group has a σ value of -1.00. In general, meta σ constants correspond to the inductive effect of the substituent while the para σ constants represent the *net* influence of inductive and resonance effects. If there is a substantial resonance effect, and it and the inductive effect operate in the same direction, σ_{para} will have a considerably greater magnitude than σ_{meta}. The converse will be true if the resonance and inductive effects operate in opposite directions.

Table 26-6: *Hammett Substituent Constants*

	σ			σ	
Substituent	Meta	Para	Substituent	Meta	Para
$O^{\ominus}$	−0.71	−1.00	F	+0.34	+0.06
OH	+0.12	−0.37	Cl	+0.37	+0.23
OCH_3	+0.12	−0.27	CO_2H	+0.36	+0.41
NH_2	−0.16	−0.66	$COCH_3$	+0.38	+0.50
CH_3	−0.07	−0.17	CF_3	+0.43	+0.54
$(CH_3)_3Si$	−0.04	−0.07	NO_2	+0.71	+0.78
C_6H_5	+0.06	−0.01	$(CH_3)_3N^{\oplus}$	+0.88	+0.82
H	0.00	0.00	$N_2^{\oplus}$	+1.76	+1.91
SH	+0.25	+0.15	$(CH_3)_2S^{\oplus}$	+1.00	+0.90
SCH_3	+0.15	0.00			

Figure 26-4, which shows plots of log (k/k_0) or of log (K/K_0) against σ for several different reactions. For the examples given, the fit to the Hammett equation is fair. A number of ρ values (slopes) are listed separately in Table 26-7. It can be seen that ρ values vary with the type of reaction and are appropriately called reaction constants. However, the real significance of ρ is that it measures the sensitivity of the reaction to the electrical effects of substituents in meta and para positions. A large ρ constant, positive or negative, means a high sensitivity to substituent influences. Reactions that are assisted by high electron density at the reaction site characteristically have negative ρ values (e.g., Reaction 15, Table 26-7), whereas reactions that are favored by withdrawal of electrons from the reaction site have positive ρ values (e.g., Reaction 16, Table 26-7).

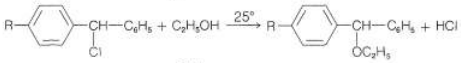
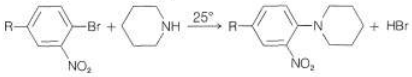


● $RC_6H_4{-}NH_3^{\oplus} + H_2O \overset{25°}{\rightleftharpoons} RC_6H_4{-}NH_2 + H_3O^{\oplus}$

▲ $RC_6H_4{-}COCH_3 + Br_2 \xrightarrow[CH_3CO_2^{\ominus}]{CH_3CO_2H,\ 35°} RC_6H_4{-}COCH_2Br + HBr$

■ $RC_6H_4{-}O^{\ominus} + C_2H_5I \xrightarrow[42.5°]{C_2H_5OH} RC_6H_4{-}OC_2H_5 + I^{\ominus}$

https://chem.libretexts.org/@go/page/22376

No.	Equilibria	ρ
1	$RC_6H_4—CO_2H \xrightleftharpoons[25°]{H_2O} RC_6H_4—CO_2^{\ominus} + H^{\oplus}$	1.00
2	$RC_6H_4—CH_2CO_2H \xrightleftharpoons[25°]{H_2O} RC_6H_4—CH_2CO_2^{\ominus} + H^{\oplus}$	0.49
3	$RC_6H_4—\overset{\oplus}{N}H_3 \xrightleftharpoons[25°]{H_2O} RC_6H_4—NH_2 + H^{\oplus}$	2.77
4	$RC_6H_4—CHO + HCN \xrightleftharpoons[95\%\ C_2H_5OH]{} RC_6H_4—CH(OH)CN$	−1.49
5	$RC_6H_4—OH \xrightleftharpoons[25°]{H_2O} RC_6H_4—O^{\ominus} + H^{\oplus}$	2.11
No.	Reaction rates	ρ
6	$RC_6H_4—CO_2C_2H_5 + OH^{\ominus} \xrightarrow[30°]{85\%\ C_2H_5OH} RC_6H_4—CO_2^{\ominus} + C_2H_5OH$	2.43
7	$RC_6H_4—CO_2H + CH_3OH \xrightarrow[25°]{H^{\oplus}} RC_6H_4—CO_2CH_3 + H_2O$	−0.23
8	$RC_6H_4—OH + C_6H_5COCl \xrightarrow{20°} RC_6H_4—OCOC_6H_5 + HCl$	0.56
9	$RC_6H_4—O^{\ominus} + C_2H_5I \xrightarrow[42.5°]{C_2H_5OH} RC_6H_4—OC_2H_5 + I^{\ominus}$	−0.99
10	$RC_6H_4—CH_2Cl + OH^{\ominus} \xrightarrow[30°]{H_2O} RC_6H_4—CH_2OH + Cl^{\ominus}$	−0.33
11	$RC_6H_4—CH_2Cl + H_2O \xrightarrow[30°]{48\%\ C_2H_5OH} RC_6H_4—CH_2OH + HCl$	−2.18
12		−5.09
13	$RC_6H_4—NH_2 + C_6H_5COCl \xrightarrow[26°]{C_6H_6} RC_6H_4—NHCOC_6H_5 + HCl$	−2.78
14	$RC_6H_4—COCH_3 + Br_2 \xrightarrow[CH_3CO_2^{\ominus}]{CH_3CO_2H,\ 35°} RC_6H_4—COCH_2Br + HBr$	0.42
15	$RC_6H_4—H + NO_2^{\oplus} \xrightarrow[18°]{(CH_3CO)_2O} RC_6H_4—NO_2 + H^{\oplus}$	−5.93
16		4.92

Usually, ρ for a given reaction is influenced by conditions such as the temperature and composition of the solvent. However, the changes normally are not large unless an actual change in mechanism occurs with a change in the reaction conditions.

26.6.2: Scope of the Hammett Equation

The Hammett treatment provides a correlation of much experimental data. Tables 26-6 and 26-7 contain 38 substituent constants and 16 reaction constants. This means that we can calculate relative k or K values for 608 individual reactions. To illustrate, let us suppose that we need to estimate the relative rates of Reaction 16 of Table 2-7 for the para-substituents $\mathrm{R} = \mathrm{OCH_3}$ and $\mathrm{R} = \mathrm{CF_3}$. According to the ρ value of 4.92 for this reaction and the σ values of *p*-$\mathrm{OCH_3}$ and *p*-$\mathrm{CF_3}$ in Table 26-6, we may write

$$\log \frac{k_{\text{p-OCH}_3}}{k_0} = 4.92 \times (-0.27)\text{, and } \log \frac{k_{\text{p-CF}_3}}{k_0} = 4.92 \times (0.54) \tag{26.6.1}$$

Subtracting these two equations gives the result:

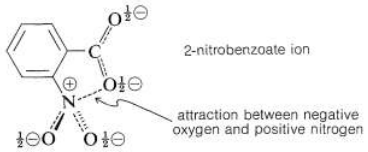
This then is a rate ratio of 1/10,000. If we have a further table of the sixteen k_0 or K_0 values for the reactions listed in Table 26-7, we can calculate actual k or K values for 608 different reactions. It should be recognized that neither Table 26-6 nor Table 26-7 is a complete list; at least 80 substituent constants[1] and several hundred ρ constants are now available.

The Hammett relationship formalizes and puts into quantitative terms much of the qualitative reasoning we have used for reactions involving aliphatic, alicyclic, and aromatic compounds. Considerable effort has been made to extend the Hammett idea to cover reactions other than of meta- and para-substituted benzene derivatives, but these will not be discussed here.[1]

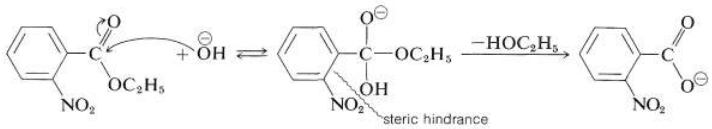
26.6.3: Limitations of the Hammett Equation

The effects of substituents in ortho positions on the reactivity of benzene derivatives do not correlate well with the Hammett equation, as can be seen in Figure 26-3. The problem is that ortho substituents are close enough to the reaction site to exert significant "proximity" effects, which may be polar as well as steric in origin. Thus the enhanced acid strength of 2-nitrobenzoic

acid over the 3- and 4-isomers (see Table 26-4) may be due to a polar stabilization of the acid anion by the neighboring positive nitrogen, which of course is not possible with the 3- and 4-isomers:



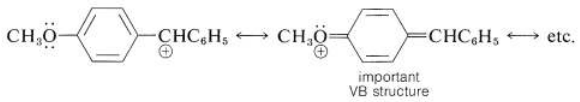
In contrast, the slower rate of alkaline hydrolysis of ethyl 2-nitrobenzoate than of its 3- and 4-isomers is more likely due to a steric hindrance effect of the 2-nitro group (see Table 26-5):



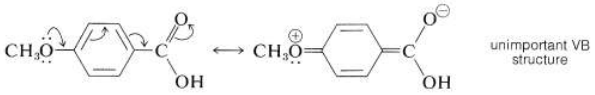
Because the effect of steric hindrance on different types of reactions is not expected to be the same, a given substituent is unlikely to exert the same relative steric effect in one reaction as in another. Consequently we cannot hope to find a very simple relationship such as the Hammett equation that will correlate structure and reactivity of ortho-substituted compounds.

The Hammett equation also fails for open-chain aliphatic derivatives. For example, there is no simple linear relationship between log K for a series of substituted ethanoic acids (RCH_2CO_2H) and log k for the hydrolysis rates of similarly substituted ethyl ethanoates $(RCH_2CO_2C_2H_5)$. The freedom of motion available to a flexible open-chain compound permits a much wider range of variations in steric effects than for meta- and para-substituted aromatic compounds.

The Hammett equation sometimes fails for meta- and para-substituted aromatic compounds. This failure may be expected whenever the opportunity arises for strong electron delocalization between the substituent and the reaction site. Generally, reactions that are strongly assisted by donation of electrons to the reaction site, as in S_N1 reactions and electrophilic aromatic substitution, will be facilitated by electron-delocalization effects of substituents with unshared electron pairs adjacent to the aromatic group (e.g., $-OCH_3$, $-OH$, $-O^{\ominus}$, $-NH_2$, and $-Cl$). Such reactions generally give a poor Hammett correlation. Thus a diphenylmethyl chloride with one 4-methoxy group solvolyzes in ethanol at 25° at a rate much faster than predicted by the Hammett equation, because of the resonance stabilization provided by the substituent to the intermediate carbocation:



The same type of stabilization by a 4-methoxy group does not appear to be important in influencing the ionization of 4-methoxybenzoic acid.



Similarly, those reactions that are strongly assisted by *withdrawal of electrons* from the reaction site, such as nucleophilic aromatic substitution, give a poor fit to a Hammett plot for the substituents that are capable of withdrawing electrons by delocalization ($-NO_2$, $-N_2^+$, $-C\equiv N$, and so on). An example is Reaction 16 in Table 26-7. To correlate reactivity data with structures where strong resonance effects operate, different sets of substituent constants are required.[1]

[1]J. Hine, *Structural Effects on Equilibria in Organic Chemistry*, Wiley-Interscience, New York, 1975, p. 65. This book offers a very broad coverage of quantitative correlations of substituent effects on processes as diverse as radical formation and rates of rotation around single $C-C$ bonds.

26.6.4: Contributors and Attributions

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26.E: More on Aromatic Compounds (Exercises)

Exercise 26-1 Predict which one of the following pairs of compounds will be the stronger acid. Give your reasoning.

a. 3-nitrobenzenol or 4-nitrobenzenol
b. 3,5-dimethyl-4-nitrobezenol or 2,6-dimethyl-4-nitrobenzenol
c. 4-methoxybenzenol or 3-methoxybenzenol
d. azabenzen-4-ol or azabenzen-3-ol

Exercise 26-2* Use bond and stabilization energies to calculate $\Delta H^0\,(g)$ for the reaction of Equation 26-1 on the assumption that the extra stabilization energy of 2-naphthalenol relative to naphthalene is $5\ \text{kcal mol}^{-1}$ (see Tables 4-3 and 21-1). Compare your answer to ΔH^0 calculated for the corresponding reactions of benzenol (Section 26-1A).

Exercise 26-3* Treatment of 1,3-benzenediol (resorcinol) with an ammonia-ammonium chloride solution under pressure at 200° (no sulfite) gives 3-aminobenzenol. Write a reasonable mechanism for this transformation. Would you expect benzenol itself to react similarly? Why?

Exercise 26-4* Explain why benzenol with bromine gives tribromobenzenol readily in water solution but 2- and 4-monobromobenzenol in nonpolar solvents. Notice that 2,4,6-tribromobenzenol is at least a 300-fold stronger acid than phenol in water solution.

Exercise 26-5 When 2-naphthalenol is treated with bromine in ethanoic acid it first gives 1-bromo-2-naphthalenol then 1,6-dibromo-2-naphthalenol. Explain the order of substitution, giving attention to why disubstitution does not lead to 1,3-dibromo-2-naphthalenol.

Exercise 26-6 The herbicide "2,4-D" is (2,4-dichlorophenoxy)ethanoic. Show how this substance could be synthesized starting from benzenol and ethanoic acid.

Exercise 26-7 1,3-Benzenediol (resorcinol) can be converted to a carboxylic acid with carbon dioxide and alkali. Would you expect 1,3-benzenediol to react more, or less, readily than benzenol? Why? Which is the most likely point of monosubstitution? Explain.

Exercise 26-8 Explain how you would use proton NMR spectra to show that the product of oxidation of 2,4,6-tri-*tert*-butylbenzenol in the presence of butadiene links the aromatic rings at the 4-position, not at the 2-position.

Exercise 26-9* Benzenol samples that have been allowed to stand in air always are pink or red because of oxidation. Write a mechanism for the oxidation of benzenol by oxygen that could lead to one or more products that may be expected to be colored.

Exercise 26-10* Explain why gallic acid decarboxylates on heating more readily than benzoic acid. Would you expect 2,5-dihydroxybenzoic acid to decarboxylate as readily as its 2,4 isomer? Explain.

Exercise 26-11* Work out the course of hydrolysis and decarboxylation of 2,4,6-triaminobenzoic acid to 1,3,5-benzenetriol.

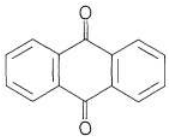
Exercise 26-12* Devise a reasonable sequence of synthetic steps for conversion of eugenol to the flavoring material vanillin, which is 3-methoxy-4-hydroxybenzenecarbaldehyde (Section 26-5).

Exercise 26-13* Reduction of the carbonyl group of quercetin gives a substance that loses water readily to give a brilliant-violet compound. This compound, when treated with hydrochloric acid, is converted reversibly to a red salt. Consider possible ways that the reduction product could dehydrate to give a violet substance and show how addition of a proton to it could occur in such a way as to give a substantial color change.

Exercise 26-14* Natural usnic acid is optically active but racemizes on heating *without need for acid or base catalysts*. Write a mechanism involving a reversible electrocyclic reaction for this racemization that also accounts for the fact that when usnic acid is heated in ethanol, an optically inactive ethyl ester of a *carboxylic acid* is formed. (Review Sections 21-10D and 17-6B.)

Exercise 26-15 Arrange the following quinones in the order of expected increasing half-cell potential for reduction (the larger the potential the greater the tendency for reduction): 1,4-benzenedione, 4,4'-biphenyldione, *cis*-2,2'-dimethyl-4,4'-biphenyldione, 9,10-anthracenedione, and 1,4-naphthalenedione. Your reasoning should be based on differences expected in the stabilization of the arenediones and arenediols, including steric factors, if any.

Exercise 26-16 Reduction of 9,10-anthracenedione with tin and hydrochloric acid in ethanoic acid produces a solid, pale-yellow ketone (mp 156°), which has the formula $C_{14}H_{10}O$. This ketone is not soluble in cold alkali but does dissolve when heated with alkali. Acidification of cooled alkaline solutions of the ketone precipitates a brown-yellow *isomer* of the ketone (mp 120°), which gives a color with ferric chloride, couples with diazonium salts (Section 23-10C), reacts with bromine, and slowly reverts tot he isomeric ketone.



9,10-anthracenedione
(9,10-anthraquinone)

What are the likely structures of the ketone and its isomer? Write equations for the reactions described and calculate ΔH^0 for interconversion of the isomers in the vapor phase. (Review Sections 26-1 and 21-7.)

Exercise 26-17* Write resonance structures that account for the stability of the cation of Wurster's salts, such as Wurster's Blue, 2. Explain why N,N,N′,N′-2,3,5,6-octamethyl-1,4-benzenediamine does not form a similarly stable cation radical.

Exercise 26-18* Acidification of a solution containing semiquinone radicals such as 1 tends to cause the radicals to disproportionate to the arenediol and arenedione. Why should acid cause changes in the relative stabilities of the semiquinones and the corresponding diol-dione pairs?

Exercise 26-19* The biologically important quinone called plastoquinone is similar to **CoQ**, except that the CH_3O- groups of **CoQ** are replaced by CH_3- groups. What differences in properties would you expect between plastoquinone and **CoQ** and their respective reduction products? Consider half-cell potentials (see Exercise 26-15), solubility in polar and nonpolar solvents, and relative acidity.

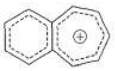
Exercise 26-20* You will see that the natural quinones, vitamin K_1, plastoquinone, and **CoQ**, all have three or four groups on the quinone ring. What kind of possible destructive side reactions would ring substituents tend to prevent? Give your reasoning.

Exercise 26-21* Devise a synthesis of dimethoxy- and dihydroxy-1,2-cyclobutenedione based on the expected dimerization product of trifluorochloroethene (Section 13-3D).

Exercise 26-22 Tropone (2,4,6-cycloheptatrienone) is an exceptionally strong base for a ketone. Explain.

Exercise 26-23 At which position would you expect tropolone to substitute most readily with nitric acid? Explain.

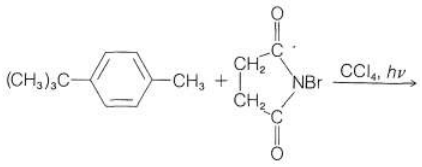
Exercise 26-24 Would you expect benzotropylium ion to form the corresponding OH derivative more readily or less readily than tropylium ion itself in water solution? At which position would you expect the C–O bond to be formed? Explain.



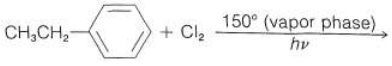
benzotropylium ion

Exercise 26-25 What principal product would you expect from each of the following reactions? Show the steps involved.

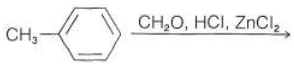
a.



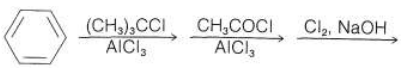
b.



c.



d.



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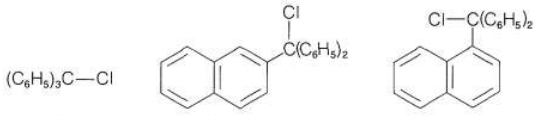
Exercise 26-26 Devise syntheses of the following compounds from the specified starting materials, giving reagents and approximate reactions conditions. (If necessary, review the reactions of Chapter 22 as well as reactions discussed in the sections of this chapter.)

a. 4-aminobenzenecarbaldehyde from methylbenzene
b. 2,2'-biphenyldicarboxylic acid $[C_6H_4\,(2-CO_2H)\,{}_6CH_4\,(2'-CO_2H)]$ from phenanthrene
c. 4-nitrotrifluoromethylbenzene from methylbenzene
d. 9,9,10,10-tetrafluoro-9,10-dihydroanthracene from 1,2-dimethylbenzene and benzene
e. 4-methylphenylethanenitrile from methylbenzene
f. 4-chlorobenzenecarbaldehyde from methylbenzene
g. 2-hydroxy-3-methylbenzenecarbaldehyde from methylbenzene
h. 4-ethylphenylmethanol from benzene, methylbenzene, or ethylbenzene
i. 2-chloro-4-ethoxybenzenecarbaldehyde from benzene or methylbenzene

Exercise 26-27

a. Explain why the energy of ionic dissociation of triarylmethyl chlorides in liquid sulfur dioxide decreases in the order $7 > 8 > 9$. (Review Section 22-8A and also consider possible effects of steric hindrance in the starting material and the cations formed.)



7 8 9

b. Which alcohol would you expect to form a carbocation more readily in sulfuric acid, 10 or 11? Explain.

10 11

c. When triphenylmethanol is dissolved in 100% sulfuric acid, it gives a freezing-point depression that corresponds to formation of *four moles* of particles *per mole* of alcohol dissolved. Explain.

Exercise 26-28 Explain why 9-phenylfluorene is a stronger acid than triphenylmethane.

Exercise 26-29

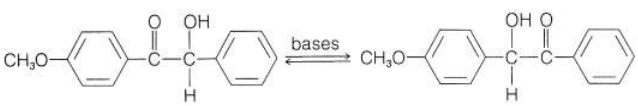
a. Why should 3-phenyl-1-propene be appreciably more reactive than methylbenzene in hydrogen-abstraction reactions?

b. Would you expect 1-phenyl-1-propene $(C_6H_5CH{=}CHCH_3)$ to be more, or less, reactive than 3-phenyl-1-propene $(C_6H_5CH_2CH{=}CH_2)$ if account is taken of the stabilization of the ground state as well as the stabilization of the radicals?

Exercise 26-30 Which of the following pairs of compounds would you expect to be the more reactive under the specified conditions? Give your reasons and write equations for the reactions involved.

a. 4-$NO_2C_6H_4CH_2Br$ or 4-$CH_3OC_6H_4CH_2Br$ on hydrolysis in 2-propanone-water solution
b. $(C_6H_5)_3CH$ or $C_6H_5CH_3$ in the presence of phenyllithium
c. $(C_6H_5)_3C{-}C(C_6H_5)_3$ or $(C_6H_5)_2CH{-}CH(C_6H_5)_2$ on heating
d. $(C_6H_5)_2N{-}N(C_6H_5)_2$ or $(C_6H_5)_2CH{-}CH(C_6H_5)_2$ on heating
e. $(C_6H_5CH_2CO_2)_2$ or $(C_6H_5CO_2)_2$ on heating
f. $C_6H_5COC_6H_5$ or $C_6H_5CH_2C_6H_5$ on reduction with sodium borohydride

Exercise 26-31 The following equilibrium is established readily in the presence of bases:



The mechanism of the reaction could be either a base-induced enolization reaction (Section 17-1) or ionization of the OH proton followed by a Cannizzaro-type reaction (Section 16-4E). Write each mechanism in detail and devise experiments that could be used to distinguish between them.

Exercise 26-32 Devise methods of synthesis of the following compounds based on the given starting materials:

a. 1,2-di-(4-methoxyphenyl)ethane from 4-methoxybenzenecarbaldehyde
b. 4-(2-nitrophenyl)-3-buten-2-one from benzene or methylbenzene
c. 2-methyl-1-azanaphthalene (quinalidine) from 4-(2-nitrophenyl)-3-buten-2-one
d. diphenylmethanone (benzophenone) from benzenecarbaldehyde

Exercise 26-33 Write a mechanism based on analogy for the formation of quinoxalines from benzils and 1,2-benzenediamines. (Review Section 16-4C.)

Exercise 26-34 The ionization constants of 3- and 4-cyanobenzoic acids at 30° are 2.51×10^{-4} and 2.82×10^{-4}, respectively. Benzoic acid has K_a of 6.76×10^{-5} at 30°. Calculate σ_{meta} and σ_{para} for the cyano substituent.

Exercise 26-35 The magnitudes and signs of the σ constants associated with meta and para substituents can be rationalized in terms of inductive and electron-delocalization influences. Show how it is possible, within this framework, to account for the following facts:

a. Fluorine has a sizable positive σ constant when meta but almost zero when para.

b. The σ constant of the methoxy group $(-OCH_3)$ is positive in the meta position an negative in the para position.

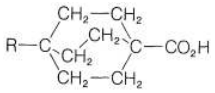
c. The $-\overset{\oplus}{N}(CH_3)_3$ group has a slightly larger positive σ constant in the meta position than in the para position, but the reverse is true for the $-N_2^+$ group.

d.* The σ constant of the $-CF_3$ group is more positive when para than when meta.

Exercise 26-36 Predict whether the meta and para σ constants for the following groups would be positive or negative, and large or small. Give your reasoning.

a. $-C \equiv N$
b. $-CH_2\overset{\oplus}{N}(CH_3)_3$
c. $-OCF_2H$
d. $-CO_2^-$

Exercise 26-37 Would you expect a Hammett type of relationship to correlate data for the dissociation of acids of the following type with rate data for hydrolysis of the corresponding esters? Explain.



Exercise 26-38 Account for the large difference in the ρ values of Reactions 10 and 11 of Table 26-7.

Exercise 26-39 The ρ constant for the ionization of benzoic acid is 1.000 for water solutions at 25°. Would you expect ρ for acid ionization to increase, or decrease, in going to a less polar solvent such as methanol? Explain.

Exercise 26-40 Explain why ρ for ionization of benzoic acids is larger than ρ for phenylethanoic acids. Estimate a value of ρ for the ionization of substituted 4-phenylbutanoic acids. Why should we expect the value of ρ for alkaline hydrolysis of ethyl benzoates to be larger than for acid ionization and to have the same sign?

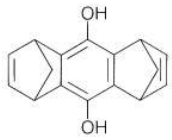
Exercise 26-41 From the data of Tables 26-6 and 26-7 and given that K_a for benzenol at 25° is 1.3×10^{-10}, calculate K_a for 3-nitrobenzenol and 4-nitrobenzenol. The experimental values are 1.0×10^{-8} for 3-nitrobenzenol and 6.5×10^{-8} for 4-nitrobenzenol. Do the calculated and experimental values agree satisfactorily (within a factor of 2 to 3) and, if not, why?

Exercise 26-42 From appropriate ρ values (Table 26-7) and σ values (Table 26-6), calculate the rates of hydrolysis of 4-CH_3-, 4-CH_3O-, 4-NO_2-phenylmethyl chlorides relative to phenylmethyl chloride (a) in water at 30° in the presence of base, and (b) in 48% ethanol at 30°. Explain why there is a greater spread in the relative rates in (b) than in (a).

Exercise 26-43 For each of the following pairs of compounds give a chemical test, preferably a test-tube reaction, that will distinguish between the two compounds. Write a structural formula for each compound and equations for the reactions involved.

a. benzenol and cyclohexanol
b. methyl 4-hydroxybenzoate and 4-methoxybenzoic acid
c. 1,4- and 1,3-benzenediol
d. 1,4-benzenediol and tropolone
e. 9,10-anthracenedione and 1,4-anthracenedione

Exercise 26-44 Show by means of equations how each of the following substances may be synthesized, starting with the indicated materials. Specify reagents and approximate reaction conditions.

a. methyl 2-methoxybenzoate from benzenol
b. 1,3-dibromo-5-*tert*-butyl-2-methoxybenzene from benzenol
c. (4-cyanophenoxy)ethanoic acid from benzenol
d. 2-hydroxy-5-nitrobenzoic acid from benzenol
e. 2-naphthaleneamine from naphthalene
f. tetramethyl-1,4-benzenedione from 1,2,4,5-tetramethylbenzene
g. 2-cyano-1,4-benzenedione from 1,4-benzenediol
h.  from 1,4-benzenedione

Exercise 26-45 Rearrangement of 2-propenyloxybenzene labeled with radioactive carbon (^{14}C) at C_3 of the 2-propenyl group forms 2-propenylbenzenol labeled at C_1 of the 2-propenyl group. Can the rearrangement mechanism involve dissociation into $C_6H_5O\cdot$ and $^{14}CH_2{=}CH{-}CH_2\cdot$ followed by recombination? Can the rearrangement be a concerted pericyclic reaction (Section 21-10)? Where would you expect the ^{14}C label to be found in the rearrangement of 2,6-dimethyl(2-propenyloxy)benzene to 2,6-dimethyl-4-(2-propenyl)benzenol?

Exercise 26-46 Write structural formulas for substances (one for each part) that fit the following descriptions:

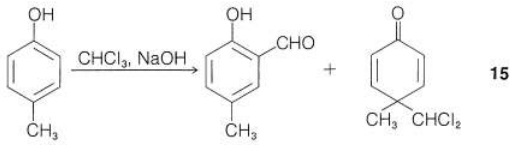
a. an arenol that would be a stronger acid than benzenol itself
b. the dichlorobenzenol isomer that is the strongest acid
c. the Claisen rearrangement product from 1,3-dimethyl-2-(1-methyl-2-propenyloxy)benzene
d. a quinone that would not undergo Diels-Alder addition
e. a quinone that would be a better charge-transfer agent than 1,4-benzenedione
f. the expected product from addition of hydrogen cyanide to 2-cyano-1,4-benzenedione

Exercise 26-47 Predict the positions to which coupling would occur (or whether coupling would occur at all) with benzenediazonium chloride in slightly alkaline solution for the following compounds. Give your reasoning.

a. 2,4,6-trimethylbenzenol
b. 2-naphthalenol
c. 1-methyl-2-naphthalenol
d. 9-phenanthrenol

Exercise 26-48 When 2-hydroxybenzoic acid (salicylic acid) is treated with excess bromine in aqueous solution, it forms 2,4,6-tribromobenzenol. Write a reasonable mechanism for this reaction. Would you expect the same type of reaction to occur with 3-hydroxybenzoic acid?

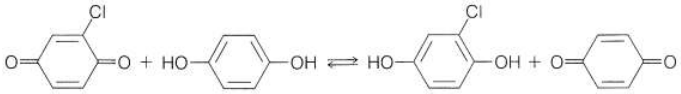
Exercise 26-49 Account for the formation of the byproduct, 15, in the reaction of 4-methylbenzenol with trichloromethane in alkali:



Exercise 26-50 The important polymer intermediate "bis-phenol A" [2,2-bis-(4-hydroxyphenyl)propane] used, among other things, in epoxy resins, is made by an acid-induced condensation of 2-propanone and benzenol. Write a stepwise mechanism for this reaction that is consistent with the nature of the reactants and the products. (Review Section 15-4E on electrophilic reactions of carbonyl compounds, Section 22-4E, and Section 26-1E.)

Exercise 26-51* Devise syntheses from benzene of each of the photographic developers whose structure is shown in Section 26-2C. Some reactions you will need are discussed in Chapters 22 and 23.

Exercise 26-52 Addition of hydrogen chloride to 1,4-benzenedione yields, among other products, 2,3,5,6-tetrachloro-1,4-benzenedione. Explain how this substance might be formed, with the knowledge that equilibria such as the following are established rapidly:



Exercise 26-53 Nitrous acid can substitute the more reactive aromatic derivatives by attack of $NO^{\oplus}$ on the ring and form $Ar{-}N{=}O$ compounds. A product obtained from benzenol by this kind of reaction has the formula $C_6H_5O_2N$. Exactly the same substance is formed from treatment of one mole of 1,4-benzenedione with one mole of azanol (hydroxylamine; Section 16-4C). On the basis of the reactions by which it is formed, write two likely structures for this substance and explain how you would decide which one was correct on the basis of chemical and spectroscopic tests.

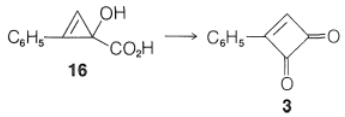
Exercise 26-54 Consider possible benzil-benzilic acid-type rearrangements occurring with 9,10-phenanthrenedione and 9,10-anthracenedione. Give your reasoning as to how easily these rearrangements might occur, relative to rearrangement of benzil itself (Section 26-4E).

Exercise 26-55 The [2 + 2] cycloadduct of tetrafluoroethene and 1,3-cyclopentadiene, when pyrolyzed at 700° to 750° and 5-mm pressure, produces (as the result of a sigmatropic rearrangement; Section 21-10) a mixture of two new substances, each having two double bonds. The pyrolysis mixture, when heated in aqueous ethanoic acid containing potassium ethanoate, forms tropolone in 70% yield. Write equations for the reactions involved, with particular attention to possible structures for the pyrolysis products.

Exercise 26-56 How would you expect the properties of 3- and 4-hydroxy-2,4,6-cycloheptatrienone to compare with those of tropolone? Explain.

Exercise 26-57 Make an atomic-orbital model of benzenol, showing in detail the orbitals and electrons at the oxygen atom. From your model, would you expect one, or both, pairs of unshared electrons on oxygen to be delocalized over the ring? What would be the most favorable orientation of the hydrogen of the hydroxyl group for maximum delocalization of an unshared electron pair?

Exercise 26-58 It has been reported that compound 16 with alkali rearranges to phenyl-1,2-cyclobutenedione, 3 (Section 26-2E). This reaction appears to be the first reported reverse benzil-benzilic acid rearrangement (Section 26-4E). Explain how and why this process occurs.



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CHAPTER OVERVIEW

27: More about Spectroscopy

In Chapter 9, we gave an exposition of the most generally useful and practical spectroscopic methods currently employed in modern organic laboratories. However, in our discussions of NMR spectra, we passed rather quickly over the basis of understanding why some lines are broad and others sharp, why rate effects can cause chemical shifts to be averaged, and how to correlate spin- spin splitting with the energies of NMR transitions. These topics will be discussed in this chapter along with a brief explanation of the remarkable effects on NMR spectra associated with some kinds of chemical reactions, namely, chemically induced dynamic nuclear polarization (CIDNP). In addition to the spectroscopic methods covered in Chapter 9, there are a number of other spectroscopic techniques that are less generally used, but can provide, and have provided, critical information with regard to specialized problems. Because some of these are relatively new and may become more widely used in the next few years, it is important that you be aware of them and their potentialities. However, because they may be peripheral to your present course of study, we have reserved consideration of them to this chapter.

27.1: Prelude to More Spectroscopy
27.2: Line-Width Differences in NMR
27.3: Use of the Uncertainty Principle to Measure the Rates of Chemical Transformations
27.4: Why Spin-Spin Splitting?
27.5: Chemically Induced Dynamic Nuclear Polarization (CIDNP)
27.6: Photoelectron Spectroscopy
27.7: Mössbauer Spectroscopy
27.8: Field- and Chemical-Ionization Mass Spectroscopy
27.9: Ion-Cyclotron Resonance
27.10: Electron-Spin Resonance (ESR) Spectroscopy of Organic Radicals
27.E: More about Spectroscopy (Exercises)

27.1: Contributors and Attributions

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27.1: Prelude to More Spectroscopy

In Chapter 9, we gave an exposition of the most generally useful and practical spectroscopic methods currently employed in modern organic laboratories. However, in our discussions of nmr spectra, we passed rather quickly over the basis of understanding why some lines are broad and others sharp, why rate effects can cause chemical shifts to be averaged, and how to correlate spin-spin splitting with the energies of nmr transitions. These topics will be discussed in this chapter along with a brief explanation of the remarkable effects on nmr spectra associated with some kinds of chemical reactions, namely, *chemically induced dynamic nuclear polarization* (CIDNP).

In addition to the spectroscopic methods covered in Chapter 9, there are a number of other spectroscopic techniques that are less generally used, but can provide, and have provided, critical information with regard to specialized problems. Because some of these are relatively new and may become more widely used in the next few years, it is important that you be aware of them and their potentialities. However, because, they may be peripheral to your present course of study, we have reserved consideration of them to this chapter.

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27.2: Line-Width Differences in NMR

If you look at the NMR spectra of many different kinds of organic compounds, you will notice that some resonances are sharp and others are broad. In a few spectra, all of the peaks may be broad as the result of poor spectrometer performance, but this is not true for the spectra of Figures 9-29 and 24-2 where, within a given spectrum, some resonances will be seen to be sharp and others broad. We can understand these differences by consideration of the *lifetimes* of the magnetic states between which the NMR transitions occur.[1] The lifetimes of the states can be related to the width of the lines by the **Heisenberg uncertainty principle**.

You may have heard of the uncertainty principle, but if you have not studied chemical physics you may have little idea of its possible importance to organic chemistry. The usual statement of the principle is that there are limits to how precisely we can specify the momentum and the position of a particle at the same time. An alternative statement has more relevance to spectroscopy and chemistry, namely, that *the precision with which we can define the energy of a state depends on the lifetime of the state*. The *shorter* the lifetime, the *less the certainty* with which we can define the energy.[2]

Let us consider an example. Suppose a magnetic nucleus in a ground state with a long lifetime and rather precisely defined energy goes to an excited state with a short lifetime, Δt.[3] The uncertainty principle tells us that the energy of the excited state cannot be defined precisely. It will have an inherent uncertainty in its energy so that an *imprecise* ν, having uncertainty in frequency $\Delta\nu$, will take the nucleus from the ground state to the excited state. The imprecision of the energy $\Delta\Delta E$, or the imprecision $\Delta\nu$ in the transition frequency, ν, depends on Δt, and is given approximately by the relationship

$$\Delta\Delta E \sim \frac{h}{2\pi} \times \frac{1}{\Delta t} \sim h\Delta\nu \tag{27-1}$$

in which h is Planck's constant. What this means is that the absorption line corresponding to the transition will have an uncertainty in **line width** that is inversely proportional to Δt (see Figure 27-1).

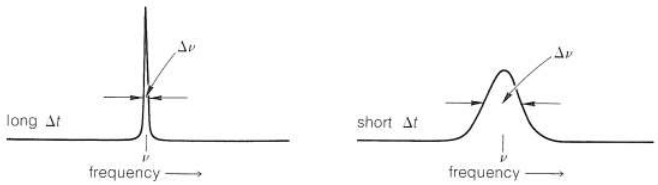

Figure 27-1: Schematic representation of the range of absorption frequencies involved in a transition from a long-lived ground state to an excited state of short (right) and longer (left) lifetime. The line width $\Delta\nu$ can be taken to be the width of the line in frequency units at half maximum height.

It is most convenient to think of line widths in frequency units because most of our spectra are plotted this way. If the scale is wavelength or energy, it can be converted to frequency by the procedures given previously (Section 9-3). Division of Equation 27-1 by h leads to the relationship $\Delta\nu \sim 1/(2\pi \times \Delta t)$. In NMR spectroscopy, we may wish to consider spin-spin splittings or chemical shifts involving lines no farther than 1 Hz apart. However, two lines 1 Hz apart will not be clearly distinguishable unless $\Delta\nu$ of each is less than about 1 Hz, which corresponds to a Δt, the lifetime of the excited state, of $1/(2\pi) \cong 0.16$ sec. If $\Delta\nu$ is ≥ 2 Hz, lines that are 1 Hz apart will be so poorly resolved as to appear as one line (cf. Figure 27-2). A $\Delta\nu$ of 2 Hz corresponds to a Δt of $1/(2 \times 2\pi) \cong 0.08$ sec. Clearly, line separations observed in NMR spectroscopy and, in fact, in all forms of spectroscopy, depend on the lifetimes of the states between which transitions take place. The lifetime of 0.16 sec required for $\Delta\nu$ to be 1 Hz is a *long* time for a molecule! During 0.16 sec, a molecule such as ethanol in the liquid phase may undergo 10^{11} collisions with other molecules, 10^{10} rotations about the C–C bonds, and 10^{12} vibrations of each of the various bonds, and may even undergo a number of chemical changes. The properties of magnetic states that have lifetimes of this order clearly must be an *average* over all of these happenings.

Figure 27-2: Two overlapping NMR resonances separated by 1 Hz and each with a $\Delta\nu$ of (left) 1 Hz and (right) 2 Hz.

It is possible to shorten the lifetime of an excited nuclear magnetic state (or increase its **relaxation rate**) in a number of ways. For a liquid, the simplest way is to dissolve in it paramagnetic metal ions, such as Cu(II), Fe(III), Mn(II), and the like, or other substances

(O_2, NO, and so on) that have *unpaired electrons*. Another way is to reduce the rate of motion of magnetic nuclei in different molecules with respect to one another, which is easily done by *increasing the viscosity*. Without going into details of the mechanisms by which substances with unpaired electrons or increased viscosity shorten the lifetime of excited nuclear magnetic states, it is important to know that dramatic line broadening thereby can be produced. Thus the proton resonance line of water is enormously broadened by adding paramagnetic Mn(II) ions or by freezing (water molecules in ice move much more slowly relative to one another than in liquid water).

27.2.1: Notes

1. It may be helpful to you before proceeding to review the introductions to Section 9-10 and 9-10A in which the general characteristics of the nuclear magnetic states are described.
2. A brief exposition of the basis of the uncertainty principle is given by R. P. Feynman, *Lectures in Physics*, Addison-Wesley, Reading, Mass., 1963, Vol. 1, pp. 6-10.
3. The uncertainty principle will be applied in this section to NMR spectroscopy but, as we will see later, it is applicable to all other forms of spectroscopy.

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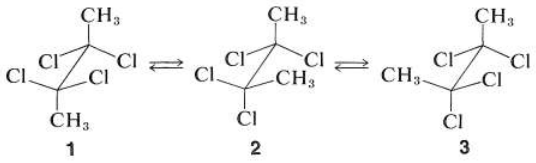
27.3: Use of the Uncertainty Principle to Measure the Rates of Chemical Transformations

We have seen how the uncertainty principle relates the attainable line widths in different kinds of spectroscopy to the lifetimes of the states - the *shorter* the lifetime, the *greater* the spread in energy of the states and the greater the spectroscopic line width. So far we have associated short lifetimes with excited states, but this need not necessarily be so. Short lifetimes also may be associated with chemical or conformational changes. As a specific example, suppose we have a magnetic nucleus in the $+\frac{1}{2}$ state located in a chemical environment whereby it experiences a magnetic field H such that $H = H_0\,(1 - \sigma)$. This nucleus will have a particular magnetic energy, call it E. Now suppose the nucleus has a lifetime Δt before it moves to a different chemical environment where it experiences a different field $H' = H_0\,(1 - \sigma')$ and has a different energy E'. Clearly, there will be an uncertainty in the energy E depending on the lifetime of the $+\frac{1}{2}$ nucleus in the particular chemical environment before it switches to the new environment with a different shielding and a different energy.

Consider a specific example, 2,2,3,3-tetrachlorobutane. This substance can exist in three different conformations, 1, 2, and 3. By reference to the discussions in Section 5-2, you will recognize that 1 is achiral, whereas 2 and 3 are enantiomers:



Clearly, if we could separate 1 from 2 and 3, the protons of its methyl groups would have *different* chemical shifts from those of 2 and 3 (which, as enantiomers, would have their methyl proton resonances at the same frequency).

Now consider a mixture of the conformations 1, 2, and 3 in which the *lifetimes of the conformations* before they convert *one into the other* are Δt. Assuming that the lifetimes of the $+\frac{1}{2}$ and $-\frac{1}{2}$ magnetic states are long compared to Δt, then uncertainty in the transition energies will depend on the lifetimes of the *chemical* states (conformations) with different chemical shifts for the protons. The chemical-shift difference between 1 and 2 or 3 at $-44°$, as shown by Figure 27-3, is about 5 Hz. From Equation 27-1, we can see that 5 Hz also will be the degree of the uncertainty in the frequency when $\Delta t \sim 1/\,(2\pi\Delta\nu) = 1/\,(2\pi \times 5\ \text{Hz}) = 0.03\ \text{sec}$. Thus if 1 has a lifetime much *longer* than 0.03 sec, say 1 sec, before going to 2 or 3, it will give a *sharp* resonance of its own and, of course, 2 and 3 will also. However, if 1, 2, and 3 have lifetimes much *shorter* than 0.03 sec, say 0.001 sec, then we expect *one* average resonance for 1, 2, and 3.

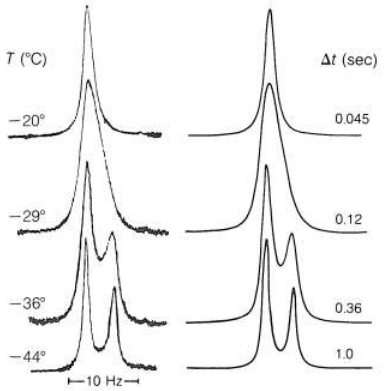


Figure 27-3: Proton nmr spectra of 2,2,3,3-tetrachlorobutane in 2-propanone solution at different temperatures. The curves on the left are experimental curves and those on the right are theoretical spectra calculated in accord with the uncertainty principle for different values of Δt. The large peak at $-44°$ corresponds to 1, the smaller one to the enantiomers 2 and 3. The change of Δt with the temperature indicates that the energy barrier to rotation is about 14 kcal mol^{-1}.

Either condition can be realized for 2,2,3,3-tetrachlorobutane by taking the proton nmr spectrum at different temperatures (Figure 27-3). At $-44°$, at which Δt is 1.0 sec, we see the separate peaks for 1 and for 2 and 3. At $-20°$, at which Δt is 0.045 sec, the uncertainty is such that the lines have coalesced and we no longer can see the separate peaks. When the spectrum is taken at room temperature, at which Δt is about 0.00005 sec, a single very sharp line is observed. We get a sharp line at this temperature because,

for practical purposes, there is no uncertainty about the *average* chemical shift of 1, 2, and 3. The line width now is determined again by the lifetimes of the $+\frac{1}{2}$ and $-\frac{1}{2}$ magnetic states, *not* by the lifetimes of the conformations.

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27.4: Why Spin-Spin Splitting?

In Section 9-10G, we outlined the structural features that lead to observation of spin-spin splitting in the NMR spectra of organic compounds. Rules for predicting the multiplicities and intensities of spin-spin splitting patterns also were discussed. However, we did not discuss the underlying basis for spin-spin splitting, which involves perturbation of the nuclear magnetic energy levels shown in Figure 9-21 by magnetic interaction between the nuclei. You may wish to understand more about the origin of spin-spin splitting than is provided by the rules for correlating and predicting spin-spin splitting given previously, but having a command of what follows is not necessary to the qualitative use of spin-spin splitting in structural analysis. However, it will provide you with an understanding of the origins of the line spacings and line multiplicities. We will confine our attention to protons, but the same considerations apply to other nuclei (^{13}C, ^{15}N, ^{19}F, and ^{31}P) that have the spin $I = \frac{1}{2}$. The main differences between proton-proton splittings and those of other nuclei are in the magnitudes of the splitting constants (J values) and their variation with structure.

Why does splitting occur? Let us start by comparing the two-proton systems of 7 and 8:

The protons in each compound will have the shift differences typical of Cl_2CH- and $-CHO$ and, at 60 MHz, can be expected from the data in Table 9-4 and Equation 9-4 to be observed at about 350 Hz and 580 Hz, respectively, from TMS. Now consider a frequency-sweep experiment[4] arranged so that the $-CH{=}O$ proton will come into resonance first.

For 7 the two protons are separated by seven bonds in all (five carbon-carbon and two carbon-hydrogen bonds), thus we expect spin-spin splitting to be negligible. We can construct an energy diagram (Figure 27-5) for the magnetic energies of the possible states of *two* protons at 60 MHz with the aid of Figure 9-24. (If this diagram is not clear to you, we suggest you review Section 9-10A before proceeding.)

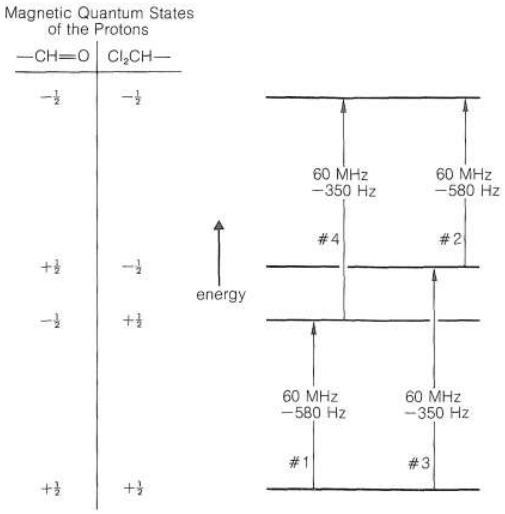


Figure 27-7. The four transitions correspond to chemical shifts of 350 Hz and 580 Hz relative to TMS at exactly 60 MHz.

Now consider $Cl_2CH{-}CH{=}O$, in which the protons are in close proximity to one another, three bonds apart. Each of these protons has a magnetic field and two possible magnetic states that correspond to a compass needle pointing either north or south (see Figure 9-21). The interactions between a north-north set of orientations ($+\frac{1}{2}$, $+\frac{1}{2}$ or $\rightrightarrows$) of the two protons or a south-south set ($-\frac{1}{2}$, $-\frac{1}{2}$ or $\leftleftarrows$) will make these states *less* stable, whereas the interactions between either a north-south ($+\frac{1}{2}$, $-\frac{1}{2}$ or $\rightleftarrows$) or a south-north ($-\frac{1}{2}$, $+\frac{1}{2}$ or $\leftrightarrows$) orientation will make these states more stable. Why? Because north-south or south-north orientations of magnets attract each other, whereas north-north or south-south repel each other.[5] Let us suppose the $+\frac{1}{2}$, $+\frac{1}{2}$ or $-\frac{1}{2}$, $-\frac{1}{2}$ orientations are *destabilized* by 1.25 Hz. The $+\frac{1}{2}$, $-\frac{1}{2}$ or $-\frac{1}{2}$, $+\frac{1}{2}$ states must then be *stabilized* 1.25 Hz. Correction of the energy levels and the transition energies for these **spin-spin magnetic interactions** is shown in Figure 27-6.

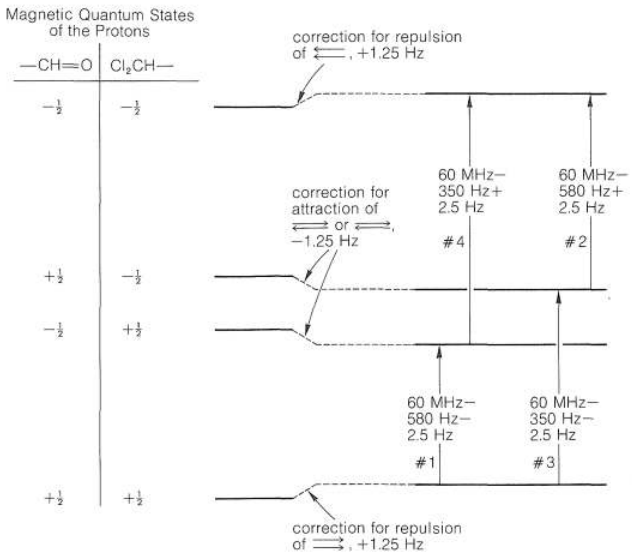
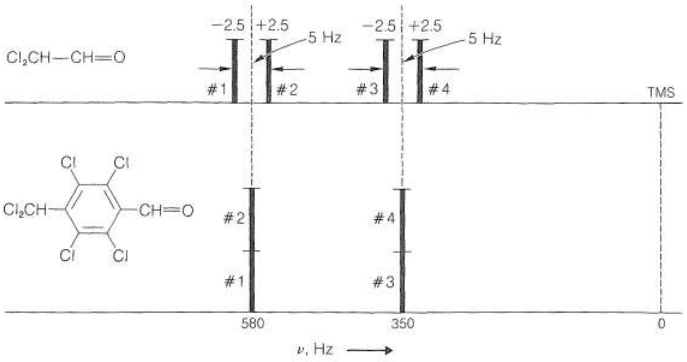


Figure 27-7.

There are four possible combinations of the magnetic quantum numbers of the two protons of $CHCl_2CHO$, as shown in Figure 27-6. Because the differences in energy between the magnetic states corresponding to these four combinations is very small (see Section 9-10A), there will be almost equal numbers of $CHCl_2CHO$ molecules with the $(+\frac{1}{2}, +\frac{1}{2})$, $(-\frac{1}{2}, +\frac{1}{2})$, $(+\frac{1}{2}, -\frac{1}{2})$, and $(-\frac{1}{2}, -\frac{1}{2})$ spin combinations. The transitions shown in Figure 27-6 will be observed for those molecules with the two protons in the $(+\frac{1}{2}, +\frac{1}{2})$ state going to the $(-\frac{1}{2}, +\frac{1}{2})$ state or for the molecules with $(+\frac{1}{2}, +\frac{1}{2})$ to $(+\frac{1}{2}, -\frac{1}{2})$ as well as from $(-\frac{1}{2}, +\frac{1}{2})$ $\rightarrow (-\frac{1}{2}, -\frac{1}{2})$ and $(+\frac{1}{2}, -\frac{1}{2}) \rightarrow (-\frac{1}{2}, -\frac{1}{2})$.[6] It is very important to remember that the transitions shown in Figure 27-6 involve molecules that have protons in *different* spin states, and by the uncertainty principle (Section 27-1) the lifetimes of these spin states must be long if *sharp* resonance lines are to be observed.

Now if we plot the energies of the transitions shown in Figures 27-5 and 27-6, we get the predicted line positions and intensities of Figure 27-7. Four lines in two equally spaced pairs appear for $Cl_CH{-}CH{=}O$, as expected from the naive rules for spin-spin splitting.



Figures 27-5 and 27-6.

A harder matter to explain, and what indeed is beyond the scope of this book to explain, is why, as the chemical shift is decreased at constant spin-spin interactions, the outside lines arising from a system of two nuclei of the type shown in Figure 27-7 become progressively weaker in intensity, as shown in Figure 9-44. Furthermore, the inside lines move closer together, become more intense, and finally coalesce into a single line as the chemical-shift difference, δ, approaches zero. All we can give you here is the proposition that the outside lines become "forbidden" by spectroscopic selection rules as the chemical shift approaches zero. At the same time, the transitions leading to the inside lines become more favorable so that the integrated peak intensity of the overall system remains constant.[7]

In a similar category of difficult explanations is the problem of why second-order splittings are observed, as in Figure 9-32. The roots of the explanation again lie in quantum mechanics which we cannot cover here, but which do permit very precise quantitative

prediction and also qualitative understanding.[7] The important point to remember is that whenever the chemical shifts and couplings begin to be of similar magnitude, you can expect to encounter NMR spectra that will have more lines and lines in different positions than you would expect from the simple treatment we developed in this chapter and in Chapter 9.

In extreme cases, such as with the protons of 4-deuterio-1-buten-3-yne, shown in Figure 27-8, none of the line positions or spacings correspond *directly* to any one chemical shift or spin-spin coupling. However, it is important to recognize that such spectra by no means defy analysis and, as also is seen in Figure 27-8, excellent correspondence can be obtained between calculated and observed line positions and intensities by using appropriate chemical shift and coupling parameters. However, such calculations are numerically laborious and are best made with the aid of a high-speed digital computer.

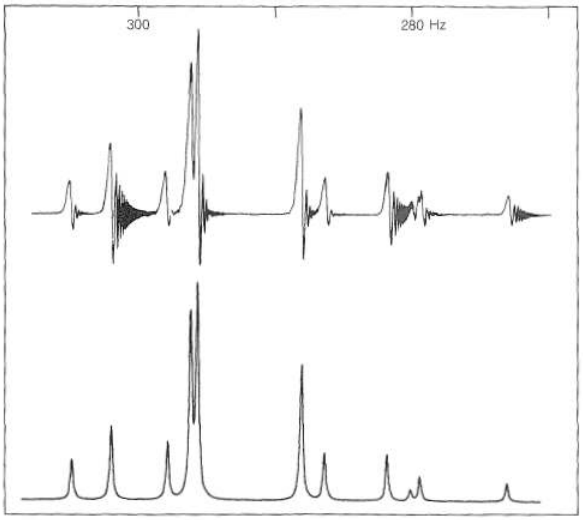


Figure 27-8: Observed (upper) and calculated (lower) NMR spectra of 4-deuterio-1-buten-3-yne ($CH_2{=}CH{-}C \equiv CD$) at 60 MHz. The calculated spectrum is based on chemical shifts of 300, 297, and 283 Hz and coupling constants of 18.0, 11.5, and 2.0 Hz. The deuterium substitution was made to simplify the spectrum by eliminating small long-range couplings involving the double-bond hydrogens and the alkyne hydrogen.

[4]We will use frequency sweep simply because it is easier to talk about energy changes in frequency units. However, the same arguments will hold for a field-sweep experiment.

[5]Such interactions with simple magnets will average to *zero* if the magnets are free to move around each other at a fixed distance. However, when electrons are between the magnets, as they are for magnetic nuclei in molecules, a small residual stabilization (or destabilization) is possible. Because these magnetic interactions are "transmitted" through the bonding electrons, we can understand in principle why it is that the number of bonds between the nuclei, the bond angles, conjugation, and so on, is more important than just the average distance between the nuclei in determining the size of the splittings.

[6]The transitions $(+\frac{1}{2}, +\frac{1}{2}) \rightarrow (-\frac{1}{2}, -\frac{1}{2})$ and $(-\frac{1}{2}, +\frac{1}{2}) \rightarrow (+\frac{1}{2}, -\frac{1}{2})$ are in quantum-mechanical terms known as "forbidden" transitions and are not normally observed. Notice that the *net spin* changes by ± 1 for "allowed" transitions.

[7]A relatively elementary exposition of these matters is available in J. D. Roberts, *An Introduction to Spin-Spin Splitting in High-Resolution Nuclear Magnetic Resonance Spectra*, W. A. Benjamin, Inc., Menlo Park, Calif., 1961.

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27.5: Chemically Induced Dynamic Nuclear Polarization (CIDNP)

One of the most startling developments in NMR spectroscopy since its inception has been the discovery of **chemically induced dynamic nuclear polarization** or CIDNP. An especially dramatic example is provided by irradiation of 3,3-dimethyl-2-butanone with ultraviolet light.

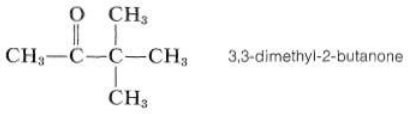


Figure 27-9b). A host of new resonances appear, some inverted (which means emission of radio-frequency energy), and the intensity ratio of the peaks of the ketone itself changes to about 3:18. When the light is turned off, the spectrum rapidly changes to almost exactly its original form. After 20 minutes in the dark, there are no emission lines and only the faintest traces of resonances corresponding to the many resonances observed only after the light was turned on. Similar phenomena are observed in the NMR spectra of many other reacting systems, some induced by light, others not.

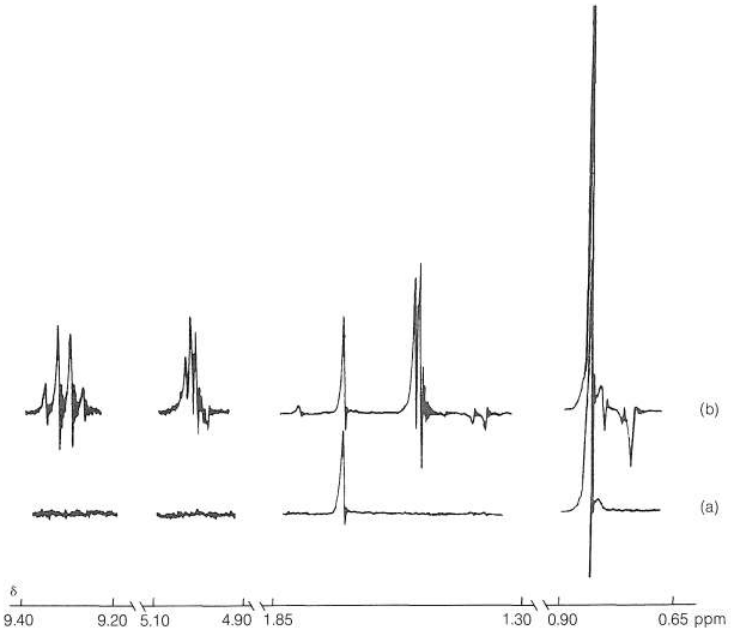
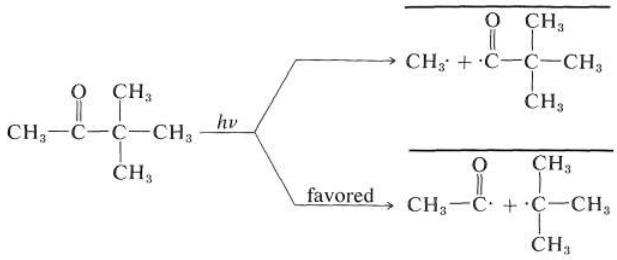


Figure 27-9: Observation of CIDNP-induced enhanced absorption and emission resonances produced by irradiation of 3,3-dimethyl-2-butanone (a) before irradiation and (b) during irradiation. (Courtesy of Professor H. Fischer.)

The CIDNP effect is a complicated one and we will not attempt to explain it in detail. It is observed exclusively for *radical* reactions. However, it is not expected for chain-propagation steps, but only for termination steps. Furthermore, chemically dissimilar radicals have to be involved at some stage in the reaction sequence. Let us now consider how these considerations apply to the irradiation of 3,3-dimethyl-2-butanone.

Absorption of light by a ketone can give several reactions, but an especially important one, which will be discussed in more detail in Chapter 28, is cleavage of C–C=O bonds to give radical pairs. For 3,3-dimethyl-2-butanone there are two possible cleavage reactions of this type:



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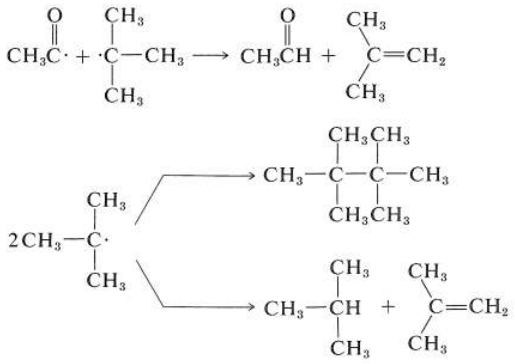
The heavy lines drawn over the radical pairs indicate that the radicals in the pairs are in close proximity to one another. Combination of the radicals in the pairs regenerates the ketone, whereas separation of the radicals can lead to formation of other products. The radicals in a pair can combine with each other *only* if the odd electron on one radical has its spin opposite to the spin of the odd electron on the other radical. This is necessary for formation of an electron-pair bond.

CIDNP arises because the radical combination products have *nonequilibrium* distributions of their proton magnetic states. How can nonequilibrium distributions arise? First, we must recognize that the radicals formed by irradiation of the ketone can have different proton magnetic states. For example, the methyl protons of any given $CH_3CO\cdot$ radical will be in one of the proton states: $+\frac{1}{2}, +\frac{1}{2}, +\frac{1}{2}; -\frac{1}{2}, +\frac{1}{2}, +\frac{1}{2}; \cdots; -\frac{1}{2}, -\frac{1}{2}, -\frac{1}{2}$ states (8 in all; see Section 27-3).

The effect of the different proton magnetic states is to cause the two unpaired electrons of the radical pairs to become unpaired at *different* rates. In other words, $\overline{R\uparrow + R'\downarrow}$ pairs produced by irradiation are converted to $\overline{R\uparrow + R'\uparrow}$ at different rates, depending on the proton magnetic states of $R\uparrow$ and $R'\downarrow$. Thus, a particular pair of proton magnetic states for $R\uparrow$ and $R'\downarrow$ can favor radical-pair recombination over radical-pair separation while another pair of proton magnetic states for $R\uparrow$ and $R'\downarrow$ can favor separation over combination. The result is a "sorting" of proton magnetic states, some appearing preferentially in particular products and others appearing in other products. Thus one product may have more than the normal equilibrium value of a higher-energy magnetic state and hence will emit radio-frequency energy to get back to equilibrium, while another product may have an abnormally low concentration of the higher-energy magnetic states and hence exhibit an enhanced absorption intensity. Figure 27-9 shows that recombination of the radical pairs produced in photolysis of 3,3-dimethyl-2-butanone forms ketone with a higher-than-normal magnetic energy in the protons of the methyl group (reduced absorption) and lower-than-normal magnetic energy in the protons of the *tert*-butyl group (enhanced absorption).

The other CIDNP peaks in Figure 27-9b arise from reactions of the separated radicals first formed, and show both enhanced absorption and enhanced emission. You should try to identify the origin of each of the CIDNP resonances with the expected reaction products:



Because thermodynamic equilibrium usually is established between magnetic states of protons in a few seconds, the enhanced-absorption and enhanced-emission resonances disappear quickly when irradiation is stopped.

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27.6: Photoelectron Spectroscopy

The excitation of electrons to higher energy states through absorption of visible and ultraviolet light (usually covering the range of wavelengths from $200\ \text{nm}$ to $780\ \text{nm}$) is discussed in Sections 9-9 and 28-1. We now will consider what happens on absorption of much shorter wavelength, more energetic, photons.

When radiation of wavelengths on the order of $120\ \text{nm}$ is absorbed by a molecule of ethene, the excited state has just sufficient energy (about $250\ \text{kcal mol}^{-1}$) to cause the most loosely bound electron to be ejected. With radiation of still shorter wavelength, such as the $58.4\ \text{nm}$ $\left(490\ \text{kcal mol}^{-1}\right)$ provided by a helium discharge tube, these electrons will have, by the Einstein law, a kinetic energy of $(490 - 250) = 240\ \text{kcal mol}^{-1}$. More tightly bound electrons also can be ejected by $58.4\ \text{nm}$ radiation, and they will have kinetic energies $E = h\nu - I$, in which $h\nu$ is the energy of the absorbed radiation $\left(490\ \text{kcal mol}^{-1}\right)$ and I is the ionization energy. If we know $h\nu$ and measure the number of ejected electrons as a function of their kinetic energies, we can derive a spectrum that shows how the probability of excitation correlates with the ionization energy. Such spectra, called **photoelectron spectra**, are shown in Figure 27-10 for gaseous ethene, ethyne, and benzene and are quite individualistic. Considerable fine structure is observed as the consequence of a considerable spread in the vibrational levels of the excited state.

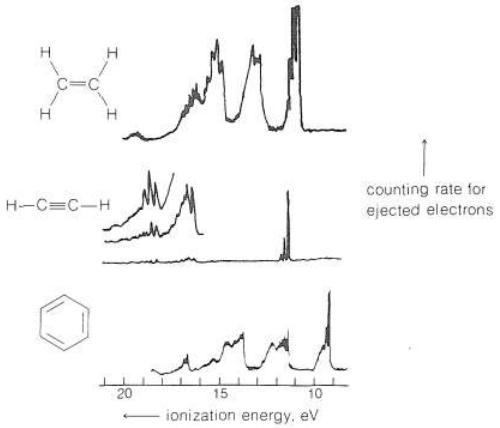

Figure 27-10: Photoelectron spectra of ethene, ethyne, and benzene induced by 58.4-nm radiation from a helium-discharge lamp. For ethyne, the left part of the spectrum is shown with three different sensitivity levels. The horizontal scale here is in units of electron volts (eV), which can be converted to kcal mol^{-1} by multiplying by 23.06. (Published by permission of A. D. Baker and D. W. Turner, and of Accounts of Chemical Research.)

Substitution and conjugation have substantial effects on ionization energies. We have mentioned how methyl groups are able by their electron-donating power to stabilize carbon cations more than hydrogens do (Section 8-7B). The same effect is very prominent in the ionization of alkenes, the lowest energy required to eject an electron from 1-butene being about $11\ \text{kcal mol}^{-1}$ greater than from *cis*- or *trans*-2-butene. The corresponding differences for 1-hexene and 2,3-dimethyl-2-butene are about $27\ \text{kcal mol}^{-1}$. Conjugation produces similar effects. The lowest energy required to eject an electron from 1,4-pentadiene with isolated double bonds is $21\ \text{kcal mol}^{-1}$ greater than for the isomeric 1,3-pentadiene with conjugated double bonds.

Photoelectron spectroscopy also can be carried on with x rays as the source of excitation and in this form often is called "ESCA" (Electron Spectroscopy for Chemical Analysis). The x rays used have wavelengths on the order of $0.9\ \text{nm}$ $\left(32,000\ \text{kcal mol}^{-1}\right)$ and the energies involved are more than ample to cause ejection of electrons form inner shells as well as from valence shells. An x-ray photoelectron spectrum of the carbon $1s$ electrons of ethyl trifluoroethanoate is shown in Figure 27-11. This spectrum is extremely significant in that it shows four different peaks - one for each chemically different carbon present. What this means is that the energy required to eject a $1s$ electron of carbon depends on the chemical state of the carbon. The energy range for this compound is fully $185\ \text{kcal mol}^{-1}$ of the approximately $6700\ \text{kcal mol}^{-1}$ required to eject a $1s$ electron. This form of spectroscopy is especially well suited to the study of solid surfaces and is being used widely for the characterization of solid catalysts.

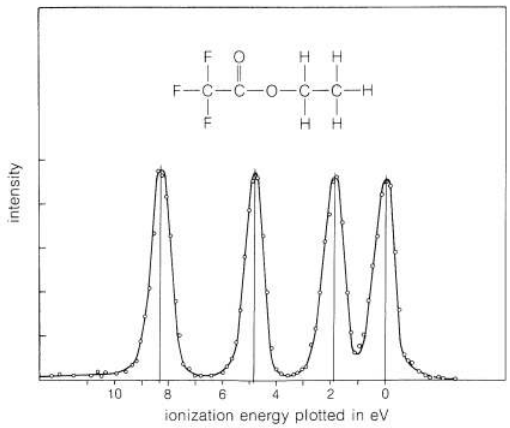

Figure 27-11: Carbon $1s$ x-ray photoelectron spectrum of ethyl trifluoroethanoate. The zero point is 291.2 eV. (Kindly supplied by Professor K. Siegbahn.)

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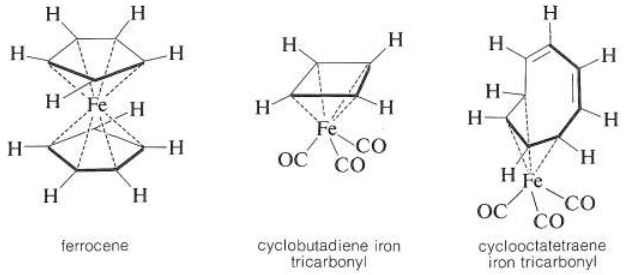
27.7: Mössbauer Spectroscopy

A different form of molecular excitation is that of changes in the energies of the atomic nuclei. In general, enormous energies are involved, and such excitations will not be of interest to the study of organic chemistry unless the atomic energy levels are detectably influenced by the chemical surroundings of the nuclei. Usually this is not so, but there is one form of nuclear spectroscopy, known as **Mössbauer spectroscopy**, which is capable of giving chemical information. The technique would be used widely if there were more nuclei with the proper nuclear properties. For organic chemistry, probably the most important available nucleus is the iron nuclide $^{57}\mathrm{Fe}$ (2.2% of the natural mixture of iron isotopes). Iron occurs in many biologically important substances, such as hemoglobin, myoglobin, cytochromes, the iron storage substance ferritin, and so on, and there are a number of other types of stable organoiron compounds including ferrocene, cyclobutadiene iron tricarbonyl, and cyclooctatetraene iron tricarbonyl, which will be discussed in Chapter 31. These compounds present unusually difficult problems in how to formulate the bonding between carbon and iron. Important information has been obtained for such substances by Mössbauer spectroscopy.



The essence of the Mössbauer technique as applied to $^{57}\mathrm{Fe}$ follows. A radioactive $^{57}\mathrm{Co}$ nucleus captures an electron and is converted to an excited $^{57}\mathrm{Fe}$ nucleus, which then emits a γ ray and becomes an ordinary $^{57}\mathrm{Fe}$ nucleus. If the excited $^{57}\mathrm{Fe}$ nucleus is in a ridig material so that there is no recoil motion associated with the emission of the γ ray, then this ray is extraordinarily monochromatic (has a very small $\Delta\nu$, Section 27-1) even though of great energy $\left(14.4\ \mathrm{KeV} = 3.3 \times 10^{5}\ \mathrm{kcal\ mol^{-1}}\right)$. When such a γ ray passes through a sample containing $^{57}\mathrm{Fe}$ atoms (also held rigidly), the γ ray can be absorbed to produce another excited $^{57}\mathrm{Fe}$ nucleus. The chemical environment of the iron atoms can change the wavelength at which this absorption occurs. The problem is how to vary the wavelength of the γ rays to match the nuclear absorption frequency. The way this is done is almost unbelievably simple - move the sample back and forth a few $\mathrm{mm\ sec^{-1}}$ in the path of the γ rays and measure the velocities at which absorption takes place. The velocity of light is $3 \times 10^{11}\ \mathrm{mm\ sec^{-1}}$. Therefore, a Doppler effect of $1\ \mathrm{mm\ sec^{-1}}$ corresponds to a difference of only one par in 3×10^{11}. However, the selectivity of the recoilless γ rays emitted from excited $^{57}\mathrm{Fe}$ nuclei is on the order of one part in $5 \times 10^{+13}$ (equivalent to about a 7-cm variation in the distance from the earth to the sun!).

A Mössbauer spectrum that has helped to corroborate the structure of cyclooctatetraene iron tricarbonyl is shown in Figure 27-12. The separation of the two absorption peaks in Figure 27-12 corresponds to a sample Doppler velocity of $1.23\ \mathrm{mm\ sec^{-1}}$. This Doppler effect means that there is the very small energy difference of $1.4 \times 10^{-6}\ \mathrm{kcal\ mol^{-1}}$ in the two transitions shown.

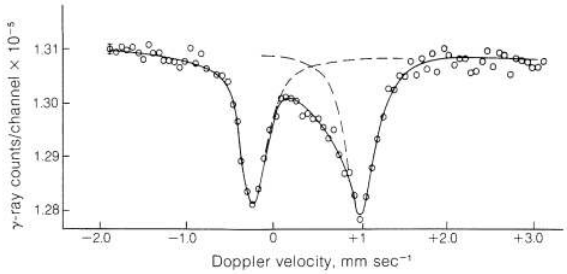


Figure 27-12: Mössbauer spectrum of cyclooctatetraene iron tricarbonyl in octane at $78^{\circ}\mathrm{K}$. Notice that a spread of Doppler velocities of about $3\ \mathrm{mm\ sec^{-1}}$ is enough to give the full spectrum. (Courtesy of Professor R. C. D. Breslow and the Journal of the American Chemical Society.)

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27.8: Field- and Chemical-Ionization Mass Spectroscopy

As we mentioned in connection with our discussion of mass spectroscopy in Section 9-11, one problem with the practical application of mass spectra to structure analysis involving the production of ions by electron impact is that the M^+ peak may be very weak. In many situations we would like to have mass spectra with less intensive fragmentation than that obtainable by electron impact. There are two ways of achieving ion formation without imparting as much energy as by electron impact - in other words, "soft" rather than "hard" ionizations. **Field ionization** is one such method, in which ionization results from passing the molecules through an electric field of 10^7-10^8 V cm^{-1}. This may seem like a practically unattainable electric field. However, it can be achieved easily by impressing a potential of 10^4 volts across a pair of electrodes, one of which has a very sharp radius of curvature $(\sim 10^{-5}\ cm)$, as can be achieved with a very fine metal point, very fine wire, or a sharp edge. Field ionization of a molecule differs from electron-impact ionization in that the electron normally is ejected from the molecule in its ground state. As a result, the parent ion M^+ peak is very strong, even for molecules for which the M^+ is virtually absent on electron impact.

Chemical ionization is, as might be expected from its name, more chemically interesting and is closely allied to ion cyclotron resonance, which will be discussed in the next section. The principle of chemical ionization is simple. The molecule to be studied is injected into the ionizing region of the mass spectrometer in the presence of 0.5-$1.5\ mm\ Hg$ pressure of a gas, usually methane. Electron impact causes ionization of the methane, which is present in relatively large concentration. The ionization products of methane then react with the compound to be analyzed and convert it to ions. The gas mixture then exits into a low-pressure zone $(10^{-4}\ mm)$ and the ions are analyzed according to *m/e* in the usual way.

What happens to CH_4 when it is bombarded with electrons at, say, $1\ mm$ pressure? The simplest reaction is formation of the M^+ ion from $CH_4 + e^- \rightarrow {CH_4}^+ + 2e^-$, but ${CH_3}^+$ and ${CH_2}^+$ also are produced by electron impact. If there is sufficient CH_4, a variety of rapid transformations take place between each of the ions produced by electron impact and the neutral CH_4. The principal ions formed are

Of these, the methonium cation, ${CH_5}^+$, is formed in largest amounts, the ethyl cation, ${C_2H_5}^+$, is next, and there is a smaller amount of the ${C_3H_5}^+$ cation (2-propenyl cation; Section 8-7B). These ions then react with the substance to be analyzed, thereby converting it into ions. Different reactions are possible, but it we have an unsaturated compound, call it RH, then

We then have a strong $(M-1)^+$ peak and weaker $(M+29)^+$ and $(M+41)^+$ peaks. The larger cations probably are similar to those formed in cationic polymerization (Section 10-8B), whereas formation of the $(M-1)^+$ cation corresponds to the hydrogen-transfer reaction discussed in Section 10-9.

With many compounds there is little fragmentation on chemical ionization. An example of a comparison of the spectra resulting from electron impact and chemical ionization is given in Figure 27-13. The simplicity of the spectra makes chemical-ionization mass spectroscopy especially useful for continuous analysis of the effluent from gas-liquid chromatographic columns (Section 9-2).

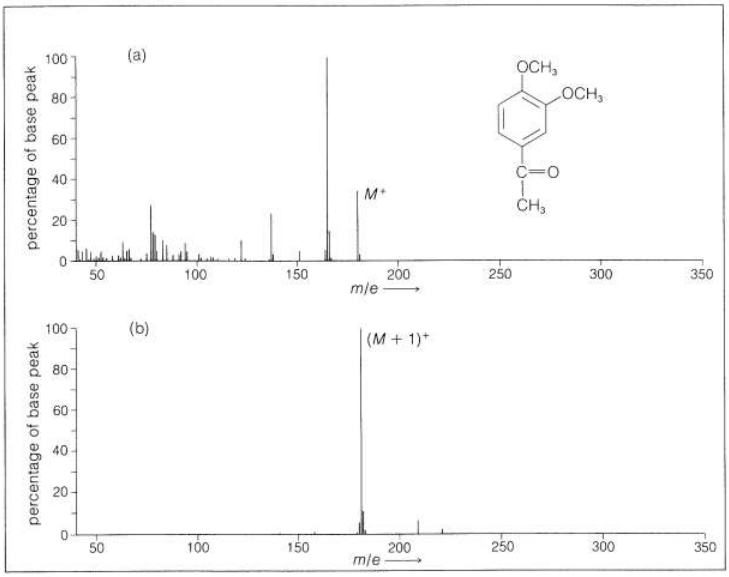

Figure 27-13: Electron-impact (a) and chemical-ionization spectra (b) of 1-(3,4-dimethoxyphenyl)-1-ethanone. (Kindly furnished by the Finnegan Corporation.)

A problem with all mass spectroscopy of large molecules is how to get them into the vapor phase so that they can be ionized and their fragmentation patterns determined. Simple heating may cause excessive degradation and formation of ions not corresponding to the desired substance. Two useful methods that involve only intense short-term local heating of the sample appear to have promise in this connection. One method uses a burst from a powerful infrared laser to volatilize part of the sample, and the other uses bombardment by heavy and energetic particles from fission of californium-252 nuclei to raise the local temperature of the sample to about $10,000^{\circ}$. The latter technique both volatilizes and ionizes the sample molecules.

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27.9: Ion-Cyclotron Resonance

A gaseous ion in a magnetic field moves in a circular orbit with an angular frequency ω_c such that $\omega_c = (e/m)\,(H_0/c)$, in which e/m is the ratio of charge to mass, H_0 is the applied magnetic field, and c is the velocity of light. The frequency ω_c is called the "cyclotron frequency" and is the basis of the cyclotron particle accelerator used in nuclear physics. Now suppose a radio-frequency field is imposed on the ions from a variable oscillator, as shown in Figure 27-15. When the frequency of the oscillator ω equals ω_c, the ions absorb energy and move faster through larger orbits, but at the *same* frequency ω_c.

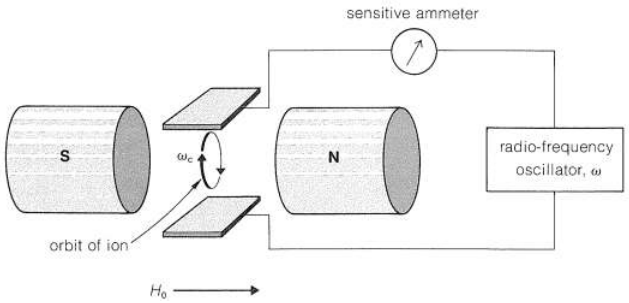

Figure 27-15: Detection of ion-cyclotron resonance. When $\omega = \omega_c$, energy is absorbed by the ions and the ammeter registers a current.

Ion-cyclotron resonance combines features of mass spectroscopy in that the ratio e/m is involved, and of NMR spectroscopy in that detection depends on absorption of energy from a radio-frequency oscillator. The chemical applications depend on reactions between the ions during the time they remain in the cyclotron, which may be many seconds. Suppose then that we generate $OH^{\ominus}$ by electron bombardment of a gaseous mixture of water and 2-methyl-2-propanol (*tert*-butyl alcohol). The $OH^{\ominus}$ ion can be detected by its characteristic frequency $\omega = (e/m)\,(H_0/c)$, in which $e/m = 1/17$. Now, because the reaction $(CH_3)_3COH + OH^{\ominus} \rightarrow (CH_3)_3CO^{\ominus} + H_2O$ occurs, a new ion of $e/m = 1/73$ appears. The reverse reaction, $(CH_3)_3CO^{\ominus} + H_2O \rightarrow (CH_3)_3COH + OH^{\ominus}$, does not occur to a measurable extent. From this we can infer that $(CH_3)_3COH$ is a stronger acid than H_2O *in the gas phase*. These experiments clearly are related to chemical-ionization mass spectroscopy (Section 27-7), and provide the basis for determining the gas-phase acidities of alkynes and water, discussed in Section 11-8. A detailed gas-phase acidity scale has been established by this means.

Many unusual reactions occur between ions and neutral molecules in the gas phase, which can be detected by ion-cyclotron resonance; a few examples are

$$CH_3F^+ \text{ (from electron impact)} + CH_3F \rightarrow CH_3\overset{+}{F}H + \cdot CH_2F \text{ (H} \cdot \text{ atom transfer)} \tag{27.9.1}$$

$$CH_3FH^+ + N_2 \rightarrow CH_3N_2{}^+ + HF \quad \text{(nucleophilic displacement)} \tag{27.9.2}$$

$$CH_3FH^+ + Xe \rightarrow CH_3Xe^+ + HF \quad \text{(nucleophilic displacement)} \tag{27.9.3}$$

Clearly, in gas-phase reactions HF is an extremely good leaving group in being rapidly displaced both by Xe and N_2. From our discussions of leaving groups in Section 8-7C, we can infer that $H_2F^{\oplus}$ must be a very strong acid in the gas phase and the available evidence indicates that this is so.

It is possible to measure the concentrations of the ions as a function of time and thus determine the rates of reaction of ions with neutral molecules in the gas phase. Figure 27-16 shows the results of a typical experiment wherein a sequence of reactions occurs that involves chloromethane as the neutral molecule and begins with the ion $CH_3Cl^{\oplus}$ formed by a short burst (10 msec) of 16 KeV electrons. The originally formed $CH_3Cl^{\oplus}$ ions react with CH_3Cl to yield $CH_3ClH^{\oplus} + \cdot CH_2Cl$. The buildup of $CH_3ClH^{\oplus}$ and the disappearance of $CH_3Cl^{\oplus}$ clearly are coupled. A slower reaction, $CH_3ClH^{\oplus} + CH_3Cl \rightarrow (CH_3)_2Cl^{\oplus} + HCl$, then takes over the action.

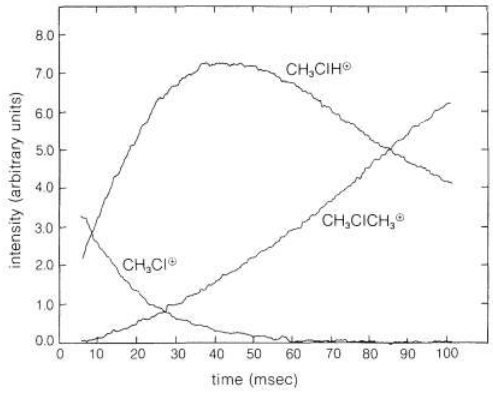

Figure courtesy of Dr. J. L. Beauchamp)

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27.10: Electron-Spin Resonance (ESR) Spectroscopy of Organic Radicals

An important method of studying radicals is **electron-spin resonance** (ESR) spectroscopy. The principles of this form of spectroscopy are much the same as of NMR spectroscopy, but the language used by the practitioners of these two forms of magnetic resonance spectroscopy is different.

First, let us discuss the similarities. The important point is that an *unpaired* electron, like a proton, has a spin and a magnetic moment such that it has two possible orientations in a magnetic field. The two orientations correspond to magnetic quantum numbers $+\frac{1}{2}$ and $-\frac{1}{2}$ that define two energy states. These states differ in energy by $\Delta E = (h\gamma)\, H$, in which γ is the gyromagnetic ratio of the electron. (See Section 9-10A for a discussion of the analogous situation for protons.) Transitions between these states occur with absorption of radiation of frequency $\nu = \gamma H$. Because γ for free electrons is about 1000 times larger than γ for protons, the frequency of absorption nu of electrons is about 1000 times that of protons at the same magnetic field. At magnetic fields of 3600 gauss the absorption frequency of free electrons is about $10,000$ MHz, which falls in the microwave, rather than the radio-wave region.

The basic apparatus for ESR spectroscopy is similar to that shown in Figure 9-22 for NMR spectroscopy, except that the sample is irradiated with a microwave generator. The spectra produced by ESR absorptions of unpaired electrons are similar to those shown in Figure 9-25, except that ESR spectrometers normally are so arranged as to yield a plot of the first derivative of the curve of absorption against magnetic field rather than the absorption curve itself, as shown in Figure 27-17. This arrangement is used because it gives a better signal-to-noise ratio than a simple plot of absorption against magnetic field.

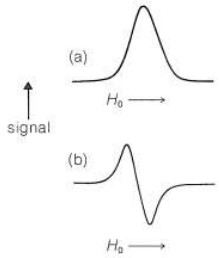


Figure 27-17: Plots of (a) absorption and (b) derivative ESR curves.

The sensitivity of ESR spectroscopy for detection of radicals is very high. Under favorable conditions, a concentration of radicals as low as 10^{-12} M can be detected readily. Identification of simple hydrocarbon radicals often is possible by analysis of the fine structure in their spectra, which arises from spin-spin splittings involving those protons that are reasonably close to the centers over which the unpaired electron is distributed. Methyl radicals, $CH_3\cdot$, generated by x-ray bombardment of methyl iodide at -196° show four resonance lines of intensity 1:3:3:1, as expected for interaction of the electron with $n+1$ protons (see Section 9-10G).

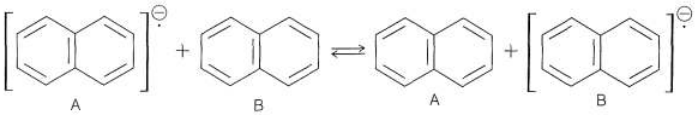
The chemical shift generally is much less important in ESR spectroscopy than in NMR. One reason is that the lifetimes of the electrons in the $+\frac{1}{2}$ and $-\frac{1}{2}$ states generally are very short (10^{-6} sec or less) so ESR lines are quite broad by comparison with NMR lines (Section 27-1). ESR chemical shifts usually are measured in terms of "g factors", which, like NMR δ values, are field-independent. The resonance frequency is given by $\nu = g\mu_0 H_0/h$, in which μ_0 is the magnetic moment of the electron.

Spin-spin splittings arising from *proton-electron* interactions are very large in ESR spectra and usually are reported in gauss, under the heading **hyperfine interactions**. The proton-electron splitting in the methyl radical is 23 gauss $(64.4\,\text{MHz})$, which is vastly larger than the 7-Hz proton-proton splitting in ethanol (Figure 9-23). The large splittings (and broad lines) typical of ESR make it possible to run ESR spectra on solids or highly viscous materials, for which the fine structure typical of high-resolution NMR spectra would be wholly washed out (Section 27-1).

ESR spectra are subject to exchange effects in the same way as NMR spectra. A specific example is provided by *electron* exchange between sodium naphthalenide and naphthalene. Naphthalene has a set of ten π-molecular orbitals, similar to the six π-molecular orbitals of benzene (Figure 21-5). The ten naphthalene π electrons fill the lower five of these orbitals. In a solvent such as 1,2-dimethoxyethane, which solvates small metal ions well, naphthalene accepts an electron from a sodium atom and forms sodium naphthalenide, a *radical anion*:

The additional electron goes into the lowest unoccupied molecular orbital of the napthalene, which means the electron circulates over all of the carbons. The electron resonance is split into a total of 25 lines by electron-proton magnetic interactions. The reason for the complex splitting can be understood if we notice that there are eight protons in two sets of four. One set spits the electron signal into five lines $(n+1)$ of intensity 1:4:6:4:1 with a spacing of 5.0 gauss, while the second set splits *each* of the five lines into another 1:4:6:4:1 quintet with a spacing of 1.9 gauss. So, in all, there are twenty-five lines - five sets of five.

If excess naphthalene is added to a solution of sodium naphthalenide, intermolecular electron exchange occurs:



This means that the electron goes from naphthalene A with a particular set of $+\frac{1}{2}, -\frac{1}{2}$ proton nuclei to naphthalene B with a different set. The result is that the lines broaden and, if the exchange is very fast, the splitting vanishes. Because the splittings area bout 5 gauss $(14\ \text{MHz})$, the mean lifetime before exchange has to be about 10^{-8} sec or less to obscure the splitting (see Sections 27-1 and 27-2).

The most exciting applications of ESR are in the study of radical intermediates in organic reactions. Considerable use has been made of the technique in biochemical reactions and it has been shown that radicals are generated and decay in oxidations brought about by enzymes. Radicals also have been detected by ESR measurements in algae that "fix" carbon dioxide in photosynthesis. The character of the radicals formed has been found to depend upon the wavelength of the light supplied for photosynthesis.

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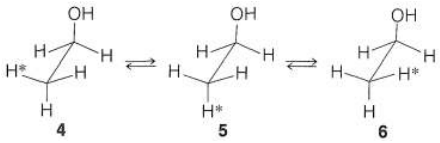
27.E: More about Spectroscopy (Exercises)

Exercise 27-1 The lifetime for rotation about the C−C bond in ethanol is $\sim 10^{-10}$ sec at room temperature. Approximately what (large) chemical-shift difference, in Hz, would a given hydrogen (marked with *) have to have between 4 and either of the conformations 5 and 6 to permit the observation of separate chemical shifts for the CH_3 hydrogens in these conformations? Show your reasoning.



Exercise 27-2 The ^{19}F NMR spectrum of 1,2-difluorotetrachloroethane shows two peaks with unequal areas separated by about 0.90 ppm at -120° but a single sharp resonance at room temperature. Explain this change in the spectrum.

Exercise 27-3 The NMR spectrum of the *tert*-butyl protons of 3,3-dibromo-2,2-dimethylbutane is shown as a function of temperature in Figure 27-4. Explain the two peaks observed at -64°. Calculate the approximate mean lifetime of the process that causes the lines to coalesce at -33°.

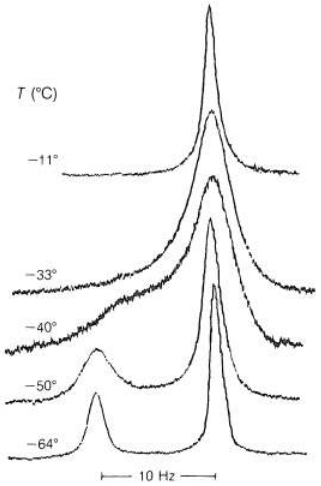


Figure 27-4: *Proton spectra of 3,3-dibromo-2,2-dimethylbutane in CF_2Cl_2 as solvent at various temperatures.*

Exercise 27-4 Referring to Figure 9-8, we see that the microwave spectrum of 1-iodopropane shows separate rotational peaks for the trans and gauche forms. Peaks about 0.35 GHz apart are clearly resolved. What *lower* limit can we then put on Δt for the lifetime of interconversion of the trans and gauche forms of 1-iodopropane? Show your reasoning.

Exercise 27-5 Figure 9-29 shows some rather remarkable changes in the spectrum of ethanol as a function of concentration in CCl_4 solution.

a. Explain the origin of the approximately 5 Hz, 1:2:1 triplet observed for the HO proton at 10% concentration.

b. The washing-out of the triplet splitting of the HO resonance in 100% ethanol is a consequence of intermolecular HO proton exchange ($C_2H_5OH^* + C_2H_5OH \rightleftharpoons C_2H_5OH + C_2H_5OH^*$). Any given proton then experiences a +5 Hz spin-spin interaction on some molecules, a net of *zero* spin-spin interaction on other molecules, and a −5 Hz spin-spin interaction on still others. Notice that the HO resonance in 100% ethanol in Figure 9-29 is quite broad in comparison with that in Figure 9-23, which is of ethanol containing a trace of HCl to make the exchange very fast. Calculate an approximate lifetime before exchange, Δt, for the hydroxyl proton in 100% ethanol that is in accord with the spectrum of Figure 9-29.

c. Explain why the CH_2 resonance in 100% ethanol in Figure 9-29, but not in Figure 9-23, is much less sharp than the CH_3 resonance.

Exercise 27-6* Notice that Figures 27-5 and 27-6 show that the total magnetic energy for the protons in the $+\frac{1}{2}, -\frac{1}{2}$ state is 60 MHz *less* than for those in the $-\frac{1}{2}, +\frac{1}{2}$ state. Why then should we expect the observed transitions from $+\frac{1}{2}, +\frac{1}{2}$ to $+\frac{1}{2}, -\frac{1}{2}$ and the transition from $-\frac{1}{2}, +\frac{1}{2}$ to $-\frac{1}{2}, -\frac{1}{2}$, to have the *same* intensity? (Review Section 9-10A.)

Exercise 27-7* Suppose you have *three* kinds of protons with chemical-shift differences of 100 Hz, 60 Hz, and 40 Hz from TMS. Suppose the $+\frac{1}{2}, +\frac{1}{2}$ state of the $100, 60$ Hz pair is destabilized by a mutual spin-spin magnetic interaction of 5 Hz; the $+\frac{1}{2}, +\frac{1}{2}$ state of the $100, 40$ Hz pair is destabilizing by 3 Hz; and the $+\frac{1}{2}, +\frac{1}{2}$ state of the $60, 40$ Hz pair has zero interaction. Draw energy diagrams analogous to Figures 27-5 and 27-6 showing the total energy for the three nuclei (the levels correspond to $+\frac{1}{2}, +\frac{1}{2}, +\frac{1}{2}$; $-\frac{1}{2}, +\frac{1}{2}, +\frac{1}{2}$; $+\frac{1}{2}, -\frac{1}{2}, +\frac{1}{2}$; $+\frac{1}{2}, +\frac{1}{2}, -\frac{1}{2}$; and so on), first *without* and then *with* correction for the spin-spin interactions. You should have eight energy levels for each diagram. Now calculate and plot the transition energies as in Figure 27-7. What are the resulting J values? What relative intensities would you expect for the lines? (If you work through this problem, you will understand the simple basis of spin-spin splitting. You also will see why it is desirable to carry forward the calculations for more complicated systems with a digital computer.)

Exercise 27-8 Explain why the irradiation of 3,3-dimethyl-2-butanone might be expected to lead to C–C bond cleavage between the C_2 and C_3 carbons rather than between the C_1 and C_2 carbons. What products would you expect to observe in the irradiation of 2-propanone (acetone)? Would CIDNP be expected?

Exercise 27-9* The photoelectron spectrum of ethyne in Figure 27-10 shows vibrational fine structure for the carbon-carbon bond in ionization at about 18.5 eV with spacings of about 0.27 eV. Explain how one could decide whether the observed vibrational spacings are more associated with the ionized *excited* state of ethyne rather than the ground state. Review Section 9-7B.

Exercise 27-10 The purpose of this exercise is to investigate the importance of the uncertainty principle for some kinds of spectroscopy other than NMR, as discussed in Section 27-1. (You may wish to use the wavelength-energy conversion factors given in Sections 9-3 and 9-4.)

a. The lifetime of an excited ^{57}Fe nucleus undergoing γ-ray absorption in a Mössbauer experiment is 9.9×10^{-8} sec. Calculate the range in $\Delta\Delta E$ in frequency units and kcal mol^{-1} that this corresponds to, and also the ratio of the uncertainty of the energy of the quantum absorbed to its total energy $(14,400$ eV$)$.

b. When a sodium atom in the vapor state absorbs radiation of 589.3 nm (sodium D line; Section 9-4) the lifetime of the excited state is 1.5×10^{-8} sec. Calculate the $\Delta\nu$ that corresponds to the lifetime of the excited state and convert this into a $\Delta\lambda$ for the line width of the absorption in nm.

Exercise 27-11 The chemical-ionization mass spectrum produced from octadecane $(C_{18}H_{38})$ by attack of the ions produced by electron impact on CH_4 is shown in Figure 27-14.

a. Why are $M + 29$ and $M + 41$ peaks not visible in this spectrum?

b. Would you expect $C_{17}H_{35}CH_2^+$ or an ion such as $C_{16}H_{33}\overset{\oplus}{C}HCH_3$ to be the most likely $(M-1)^+$ ion formed from $C_{18}H_{38}$ and CH_5^+? Why?

c. Account for the many, but evenly spaced, fragmentation peaks in the spectrum seen at $m/e = 57$, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, 211, 225, and 239 by reasonable decomposition reactions of the $(M-1)^+$ ion(s).

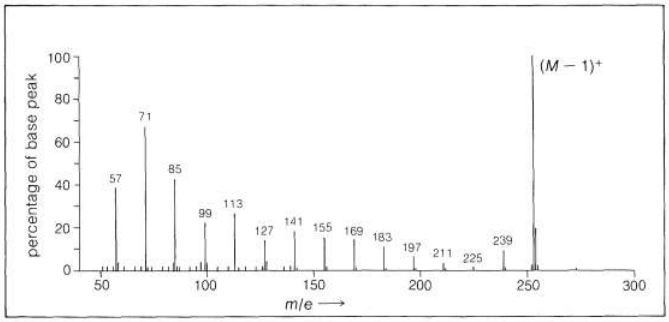


Figure 27-14: *Chemical ionization mass spectrum of octadecane. (Kindly supplied by the Finnegan Corporation.) See Exercise 27-11.*

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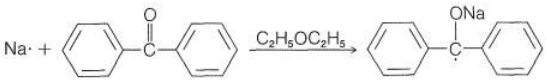
Exercise 27-12 Electron impact on 1,2-dibromoethane produces a positive ion of mass 188, which is converted rapidly to a rather positive ion of mass 108 diminishes in concentration and the equivalent amount of a new positive ion of mass 136 appears. What are the likely structures of these ions? Explain how they are formed and why the one of mass 136 is formed at the expense of the one of mass 108.

Exercise 27-13 The ESR spectrum shown in Figure 27-18 is a first-derivative curve of the absorption of a radical produced by x irradiation of 1,3,5-cycloheptatriene present as an impurity in crystals of naphthalene. Sketch this spectrum as it would look as an absorption spectrum and show the structure of the radical to which it corresponds. Show how at least one isomeric structure for the radical can be eliminated by the observed character of the spectrum.

Figure 27-18: *Electron-spin resonance spectrum of cycloheptatrienyl radical produced by x irradiation of 1,3,5-cycloheptatriene. See Exercise 27-13.*

Exercise 27-14 Diphenylmethanone (benzophenone) in diethyl ether solution adds an electron from a sodium atom and forms a radical anion:



The ESR of the radical anion shows splitting of the electron resonance by the ring protons and a small splitting by sodium ($^{23}\mathrm{Na}$ with $I = \frac{3}{2}$) that gives four lines. When excess diphenylmethanone is added, fast electron exchange occurs. This exchange wipes out the splitting by the protons but *not* the splitting by the $^{23}\mathrm{Na}$ nuclei.

a. What can you say about the degree of ionic dissociation of the $-\mathrm{O}-\mathrm{Na}$ bond $\left(-\mathrm{O}-\mathrm{Na} \rightleftharpoons -\overset{\ominus}{\mathrm{O}} + \overset{\oplus}{\mathrm{Na}}\right)$ in the radical anion in the absence of excess diphenylmethanone? Why? [Notice that there is no $^{23}\mathrm{Na}$ splitting of the electron resonance of sodium naphthalenide in 1,2-dimethoxyethane, but such splittings are observed in oxacyclopentane (tetrahydrofuran); see Sections 8-7F and 15-11E for discussion of possible differences between solvents in their ion-solvating powers.]

oxacyclopentane

b. Write a mechanism for the electron-exchange in diethyl ether that is consistent with the loss of the electron-proton splitting but retention of the electron-sodium splitting. Why does the electron-sodium splitting disappear when 1,2-dimethoxyethane is the solvent?

27.E.1: Contributors

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CHAPTER OVERVIEW

28: Photochemistry

The role of light in effecting chemical change has been recognized for many years. Indeed, the connection between solar energy and the biosynthesis of plant carbohydrates from carbon dioxide and water was known by the early 1800's. Yet organic photochemistry was slow to develop as a well-understood and manageable science. Progress only became rapid following the development of spectroscopy and spectroscopic techniques for structure determination and the detection of transient species. For this reason photochemistry for many years was the domain of physical and theoretical chemists. Their work laid the foundation for modern organic photochemistry, which correlates the nature of excited electronic states of molecules with the reactions they undergo.

Topic hierarchy

28.1: Prelude to Photochemistry
28.2: Light Absorption, Flourescence, and Phosphorescence
28.3: Organic Photochemistry
28.4: Chemiluminescence
28.5: Color and Constitution
28.6: The Sensation of Color
28.7: Color Photography
28.8: Chemistry of Vision
28.E: Photochemistry (Exercises)

28.1: Contributors and Attributions

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28.1: Prelude to Photochemistry

The role of light in effecting chemical change has been recognized for many years. Indeed, the connection between solar energy and the biosynthesis of plant carbohydrates from carbon dioxide and water was known by the early 1800's. Yet organic photochemistry was slow to develop as a well-understood and manageable science. Progress only became rapid following the development of spectroscopy and spectroscopic techniques for structure determination and the detection of transient species. For this reason photochemistry for many years was the domain of physical and theoretical chemists. Their work laid the foundation for modern organic photochemistry, which correlates the nature of excited electronic states of molecules with the reactions they undergo.

Quite apart from the unparalleled importance of photosynthesis, photochemical reactions have a great impact on biology and technology, both good and bad. Vision in all animals is triggered by photochemical reactions. The destructive effects of ultraviolet radiation on all forms of life can be traced to photochemical reactions that alter cellular DNA, and the harmful effects of overexposure to sunlight and the resulting incidence of skin cancer are well established. The technical applications of photochemistry are manifold. The dye industry is based on the fact that many organic compounds absorb particular wavelengths of visible light, and the search for better dyes and pigments around the turn of this century was largely responsible for the development of synthetic organic chemistry. Dye chemistry has helped establish the relationship between chemical structure and color, which also is important in color printing and color photography. We cover these important applications of photochemistry only briefly in this chapter, but we hope to convey some understanding of the fundamentals involved.

Most photochemical reactions can be considered to occur in three stages:

1. *Absorption of electromagnetic radiation* to produce electronically excited states.
2. *Primary photochemical reactions* involving excited electronic states.
3. *Secondary or dark reactions* whereby the products of the primary photochemical reactions are converted to stable products.

We shall begin with a closer look at electronic excitation, some aspects of which were discussed in Section 9-9. Because transfer of electronic energy from one molecule to another is a basic process in photochemistry, we will discuss energy transfer also before giving an overview of representative photochemical reactions. The closely related phenomena of chemiluminescence and bioluminescence then will be described. Finally, there will be a discussion of several important applications of photochemistry.

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28.2: Light Absorption, Flourescence, and Phosphorescence

Electromagnetic radiation in the ultraviolet and visible region spans a wavelength range of about $800\text{-}100\ \text{nm}$ corresponding to energies of $36\text{-}286\ \text{kcal mol}^{-1}$. Absorption of such radiation by molecules is not to be regarded as equivalent to simple excitation by thermal energy of $36\text{-}286\ \text{kcal mol}^{-1}$. Instead, all the energy of the light quantum is taken up in excitation of an electron to a high-energy, usually antibonding, orbital (Section 9-9). An important point about such processes is that they occur more rapidly than the atoms vibrate in the bonds (**Franck-Condon principle**). The short transition time of an electron between ground and excited states is in complete contrast to what happens during absorption of a quantum of radio-frequency energy in nmr spectroscopy, wherein the absorption process may be slow compared to chemical reactions (Section 27-1). Therefore an electronically excited molecule is, in the first instant that it is produced $(< 10^{-13}\ \text{sec})$, just like the ground-state molecule as far as *positions* and *kinetic energies* of the atoms go, but has a very different electronic configuration. What happens at this point depends on several factors, some of which can be best illustrated by energy diagrams of the type used previously (Section 21-1). We shall consider diatomic molecules, but the argument can be extended to more complicated systems.

Consider Figure 28-1, which shows schematic potential-energy curves for a molecule A—B in the ground state (A—B) and in excited electronic states $(\text{A—B})^*$. We have noted previously (Section 6-1) that in the ground states of most molecules all electrons are *paired*; excited states also can have all electrons paired. Such states with paired electrons are called **singlet** states. But, because the bonding is *weaker* in excited states, the average bond length r_e between the nuclei is *greater* in the excited state than in the ground state. For this reason the upper curve (S_1) in Figure 28-1 is displaced toward a larger average bond length relative to the lower or ground-state curve (S_0).

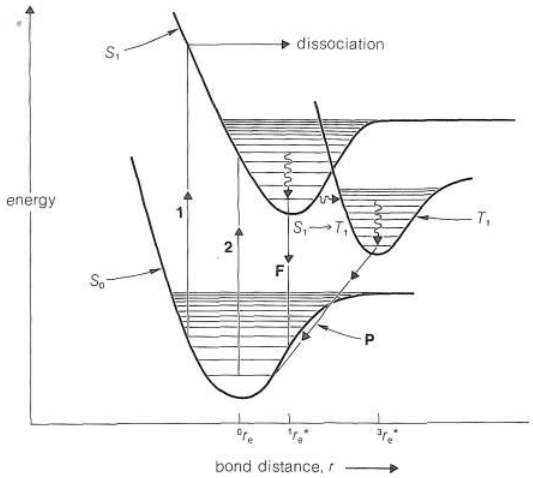


Figure 28-1: Schematic potential-energy diagram for ground and excited electronic states of a diatomic molecule A—B. The horizontal lines represent vibrational energy levels (Section 9-7). Absorption of a photon induces a transition from ground-state singlet to excited singlet $(S_0 \rightarrow S_1)$. Transition 1 leads to dissociation. Transition 2 leads first to vibrational relaxation (wavy line) and then to emission $(S_1 \rightarrow S_0)$ corresponding to transition F (fluorescence). Alternatively, the excited singlet S_1 may cross over to the triplet state nonradiatively ($S_1 \rightarrow T_1$, wavy line). Emission from the triplet state to the ground state $(T_1 \rightarrow S_0)$ corresponds to transition P (phosphorescence). (In this figure the T_1 curve has been displaced to the right for clarity. In a more accurate drawing the P transition would be nearly vertical.)

Excited states also can have *unpaired* electrons. States with two unpaired electrons are called **triplet** states (T) and normally are more stable than the corresponding singlet states because, by Hund's rule, less interelectronic repulsion is expected with unpaired than paired electrons (Sections 6-1 and 21-9A). (For clarity, the potential-energy curve for the excited triplet state (T_1) of A—B is given an unrealistically long equilibrium bond distance, which puts it to the right of the curve for the S_1 state in Figure 28-1.) The electronic configurations for ground singlet (S_0), excited singlet (S_1), and triplet (T_1) states of the σ electrons of a diatomic molecule are shown in Figure 28-2. This diagram will be helpful in interpreting the transitions between S_0, S_1, and T_1 states shown in Figure 28-1, and which we will now discuss in more detail.

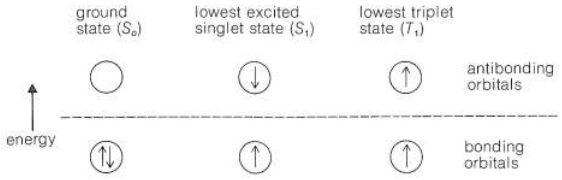


Figure 28-2: Schematic representation of the electronic configurations of ground and lowest excited singlet and triplet states of a diatomic molecule with two σ electrons.

When a molecule absorbs sufficient radiant energy to cause electronic excitation, the *spin* of the excited electron remains *unchanged* in the transition. That is to say, ground-state molecules with paired electrons (S_0) give excited states with paired electrons (S_1), not triplet states (T_1). The transition marked 1 in Figure 28-1 corresponds to a singlet-singlet $(S_0 \rightarrow S_1)$ transition from a relatively high vibrational level of $\mathrm{A{-}B}$. The energy change occurs with no change in r (Franck-Condon principle), and the electronic energy of the $\mathrm{A{-}B^*}$ molecule so produced is seen to be *above* the level required for dissociation of $\mathrm{A{-}B^*}$. The vibration of the excited molecule therefore has no restoring force and leads to dissociation to A and B atoms. In contrast, the transition marked 2 leads to an excited vibrational state of $\mathrm{A{-}B^*}$, which is not expected to dissociate but can lose vibrational energy to the surroundings and come down to a lower vibrational state. This is called "vibrational relaxation" and usually requires about 10^{-12} sec. The vibrationally "relaxed" excited state can return to the ground state with emission of radiation (transition F, $S_1 \rightarrow S_0$); this is known as **fluorescence**, the wavelength of fluorescence being different from that of the original light absorbed. Normally, fluorescence, if it occurs at all, occurs in 10^{-9} to 10^{-7} sec after absorption of the original radiation.

In many cases, the excited state (S_1) can return to the ground state (S_0) by *nonradiative* processes. The most important processes are:

1. By chemical reaction, often with surrounding molecules. This process forms the basis of much organic photochemistry, which will be described in a later section.
2. By transfer of its excess electronic energy to other molecules. This kind of energy transfer also is a very important aspect of photochemistry, and we shall return to it shortly.
3. By decay through a lower energy state. If, for example, the potential-energy curves for the upper and lower singlet states were closer together than shown in Figure 28-1, they may actually cross at some point, thus providing a pathway for S_1 to relax to S_0 without fluorescing. But what about decay of S_1 through the triplet state (T_1)?

Conversion of a singlet excited state to a triplet state $(S_1 \rightarrow T_1)$ is energetically favorable but usually occurs rather slowly, in accord with the spectroscopic selection rules, which predict that spontaneous changes of electron spin should have very low probabilities. Nonetheless, if the singlet state is sufficiently long-lived, the singlet-triplet change, $S_1 \rightarrow T_1$, (often called **intersystem crossing**) may occur for a very considerable proportion of the excited singlet molecules.

The triplet state, like the singlet state, can return to the ground state by nonradiative processes, but in many cases a radiative transition $(T_1 \rightarrow S_0)$ occurs, even though it has low probability. Such transitions result in emission of light of considerably longer wavelength than either that absorbed originally or resulting from fluorescence. This type of radiative transition is called **phosphorescence** (transition P in Figure 28-1). Because phosphorescence is a process with a low probability, the T_1 state may persist from fractions of a second to many seconds. For benzene at -200°, the absorption of light at 254 nm leads to fluorescence centered on 290 nm and phosphorescence at 340 nm. The half-life of the triplet state of benzene at -200° is 7 sec.

28.2.1: The Carbonyl Group

In previous discussions of electronic absorption spectra (Section 9-9), we have identified two different kinds of transitions in the spectra of simple carbonyl compounds such as 2-propanone or methanal. One involves excitation of an electron in a nonbonding n orbital on oxygen to an antibonding (π^*) orbital of the carbon-oxygen double bond (an $n \rightarrow \pi^*$ transition), and the other involves excitation of an electron in the bonding (π) orbital to the corresponding antibonding orbital (a $\pi \rightarrow \pi^*$ transition). These changes are shown for methanal in Figure 28-3. Besides the transitions already discussed, methanal shows strong absorption at 175 nm, which possibly is $n \rightarrow \sigma^*$, or else $\sigma \rightarrow \sigma^*$.

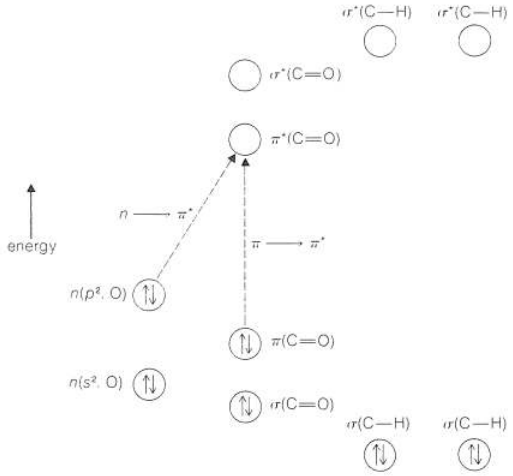
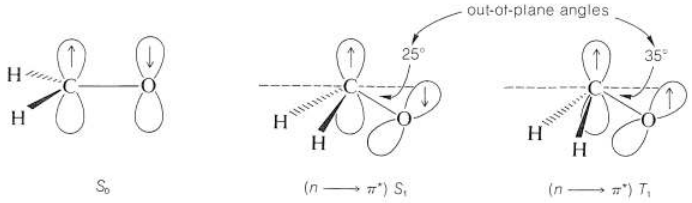


Figure 28-3: Schematic representation of the molecular orbitals and bonding electrons of methanal and the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions. Only the outer-shell electrons are shown for carbon and oxygen.

Although the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions of Figure 28-3 are singlet-singlet transitions, each of the two singlet excited states produced has a corresponding triplet state. Accordingly, there are *four* easily accessible excited states of a carbonyl group - the $n \rightarrow \pi^*$ singlet (S_1), $n \rightarrow \pi^*$ triplet (T_1), $\pi \rightarrow \pi^*$ singlet (S_2), and $\pi \rightarrow \pi^*$ triplet (T_2). The energies of these electronic states for methanal decrease in the order $S_2 > T_2 > S_1 > T_1$, although this ordering may not hold for all carbonyl compounds.

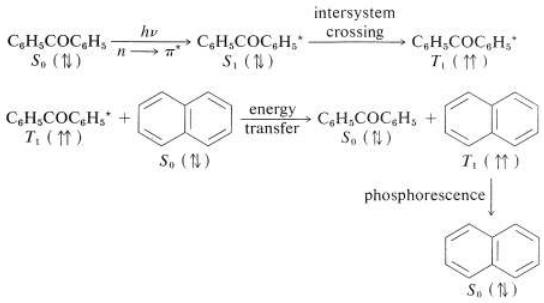
As we shall see, $n \rightarrow \pi^*$ singlet and triplet states of carbonyl compounds play an important role in photochemistry. Aldehydes and ketones display all the characteristics of absorption, fluorescence, phosphorescence, and intersystem crossing $(S_1 \rightarrow T_1)$ illustrated in Figure 28-1. Generally, they are more efficient at intersystem crossing than are unsaturated hydrocarbons, perhaps because the energies of the S and T states involved are not widely different.

Besides the bond lengths being longer in excited states of molecules, the molecular shapes differ from those of the ground states. Although the Franck-Condon principle requires that absorption produce excited states with the same geometry as the ground states, the excited molecules thereafter can relax to more stable shapes, which may be nonplanar and twisted about the erstwhile π bonds. Methanal is planar with a $\mathrm{C{-}O}$ bond length of 1.21 Å in the ground state, but in the $n \rightarrow \pi^*$ singlet (S_1) state, methanal is pyramidal, with a $\mathrm{C{-}O}$ bond length of 1.32 Å. Methanal is even more distorted in the $n \rightarrow \pi^*$ triplet state, although the bond length remains about the same at 1.32 Å.



28.2.2: Indirect Electronic Excitation Energy Transfer

It is possible to produce electronic excited states of molecules indirectly by way of energy transfer from other excited molecules. An example is provided by excitation of naphthalene as the result of energy transfer from excited benzophenone. Benzophenone, $\mathrm{C_6H_5COC_6H_5}$, absorbs ultraviolet light with $\lambda_{\max} = 330\ \mathrm{nm}$ in an $n \rightarrow \pi^*$ transition. Naphthalene does not absorb appreciably in this region. Yet irradiation of a mixture of benzophenone and naphthalene with 330-nm light produces phosphorescent emission from naphthalene. Thus benzophenone absorbs the light and transfers its excess energy to naphthalene, which returns to the ground state by emission. Because the emission is from the triplet state of naphthalene, benzophenone must be involved in exciting the naphthalene to the triplet state. We may write the process as follows:



Energy transfer does not involve a *net* change in electron spin. For this to hold for excitation of naphthalene from S_0 to T_1, the energy transfer must come from triplet (not singlet) benzophenone). The process of producing excited states in this way is called **photosensitization**. Singlet-singlet, as well as triplet-triplet, energy transfers are possible, but in all cases there is no net change in spin. Efficient energy transfer will only be possible if ΔG^0 for the transfer is small or negative.

28.2.3: Contributors and Attributions

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28.3: Organic Photochemistry

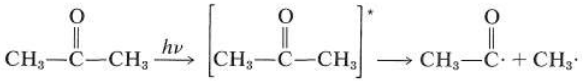
An extraordinary variety of reactions of organic compounds are known to occur under the influence of visible and ultraviolet light. Some of these, such as the photochemical halogenation of alkanes and photosynthesis in green plants, already have been discussed (see Sections 4-4D and 20-9). It is not our purpose here to review organic photochemistry in detail - rather, we shall mention a few types of important photochemical reactions and show how these can be explained by the principles discussed in the preceding section.

Compounds have very different chemical behavior in their excited states compared to their ground states. Not only is the energy much higher, but the molecular geometry and electronic configurations are different. Intuitively, we expect that excited states of molecules, in which two electrons occupy *separate unfilled* orbitals, would have substantial diradical character. This is the case, especially for triplet states, as we shall see.

28.3.1: Photodissociation Reactions

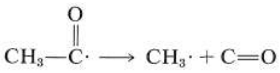
We have mentioned how chlorine molecules dissociate to chlorine atoms on absorption of near-ultraviolet light and thereby cause radical-chain chlorination of saturated hydrocarbons (Section 4-4D). Photochemical chlorination is an example of a photochemical reaction that can have a high *quantum yield* - that is, many molecules of chlorination product can be generated per quantum of light absorbed. The quantum yield of a reaction is said to be unity when $1\ \mathrm{mol}$ of reactant is converted to product(s) per einstein[1] of light absorbed. The symbol for quantum yield is usually Φ.

2-Propanone (acetone) vapor undergoes a photodissociation reaction with $313\text{-}\mathrm{nm}$ light with Φ somewhat less than unity. Absorption of light by 2-propanone results in the formation of an excited state that has sufficient energy to undergo cleavage of a $\mathrm{C{-}C}$ bond (the weakest bond in the molecule) and form a methyl radical and an ethanoyl radical. This is a *primary* photochemical reaction:



The subsequent steps are dark reactions.

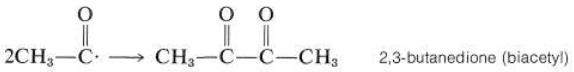
At temperatures much above room temperature, the ethanoyl radical breaks down to give another methyl radical and carbon monoxide:



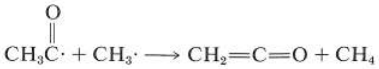
If this reaction goes to completion, the principal reaction products are ethane and carbon monoxide:

$$2\mathrm{CH_3}\cdot \rightarrow \mathrm{CH_3{-}CH_3} \tag{28-3}$$

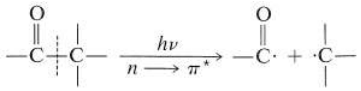
If the ethanoyl radical does not decompose completely, then some 2,3-butanedione also is formed. This reaction is quite important at room temperature or below:



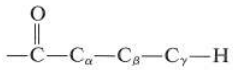
Lesser amounts of methane and ketene also are formed as the result of disproportionation reactions involving hydrogen-atom transfers of the types we have encountered previously in radical reactions (see Section 10-8C):



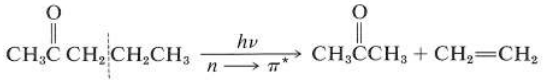
The product-forming reactions, Equations 28-2 through 28-5, all depend on the primary photochemical event, Equation 28-1, which breaks the $\mathrm{C{-}C}$ bond to the carbonyl group. This cleavage has been termed a *Norrish type I process* after the eminent photochemist, R. G. W. Norrish:[2]



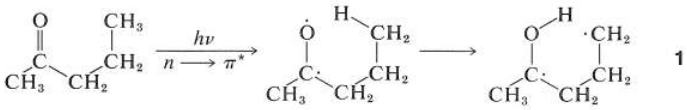
Another photochemical reaction is important for ketones that have at least one γ hydrogen on a chain connected to the carbonyl group, as in



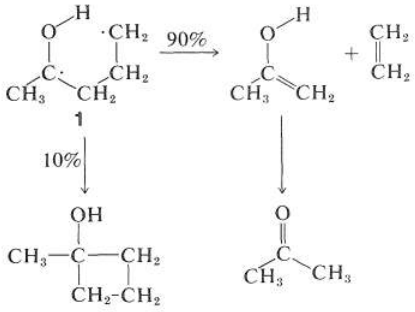
In this pathway (*Norrish type II process*), cleavage occurs at the C_α–C_β bond to give, as the major product, a ketone of shorter chain length and an alkene. Thus for 2-pentanone:



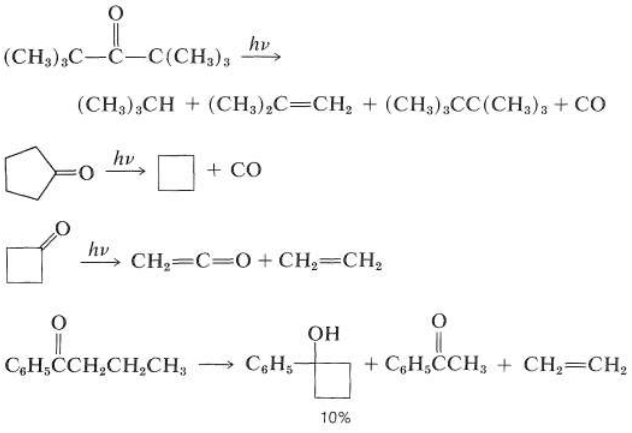
This reaction occurs in an interesting way. Whatever the nature of then $n \rightarrow \pi^*$ excited state, S_1 or T_1, the primary photochemical reaction is the abstraction of a hydrogen atom from the γ carbon by the carbonyl oxygen to give the diradical, 1:



The subsequent dark reactions readily are understood as typical of diradicals. Cleavage of 1 at C_α–C_β gives ethene and an enol, which rearranges to the ketone. Alternatively, 1 can cyclize to a cyclobutanol:



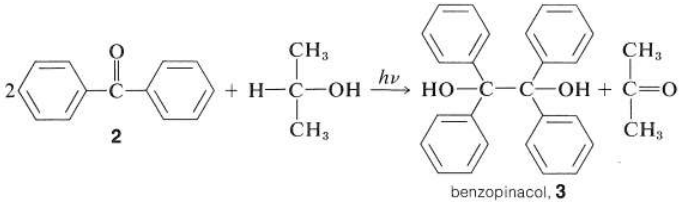
A variety of photodissociation reactions have been found to take place with ketones, but the products almost always can be explained as the result of Norrish type I and/or II cleavage. Examples are:



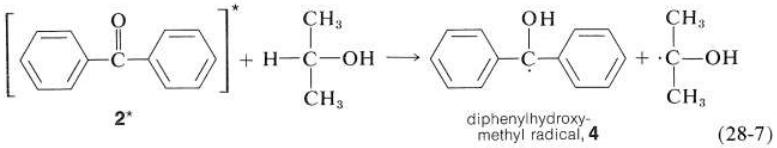
(28-6)

28.3.2: Photoreduction of Diaryl Ketones

Diaryl ketones do not undergo photodissociation in the same way as alkyl ketones, probably because cleavage to phenyl and other aryl radicals is unfavorable (Table 4-6). Nevertheless, aromatic ketones are photochemically reactive in the presence of compounds that can donate a hydrogen atom, with the result that the carbonyl group is reduced. Indeed, one of the classic photochemical reactions of organic chemistry is the formation of 1,1,2,2-tetraphenyl-1,2-ethanediol (3, benzopinacol) by the action of light on a solution of diphenylmethanone (2, benzophenone) in isopropyl alcohol. The yield is quantitative.

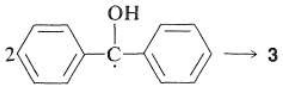


The light is absorbed by 2 and the resulting activated ketone, 2^*, removes a hydrogen from isopropyl alcohol:

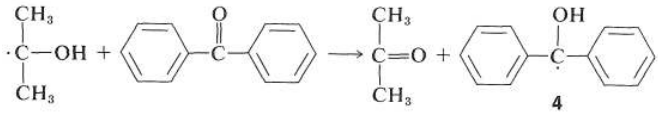


(28-7)

Benzopinacol results from dimerization of the radicals, 4:

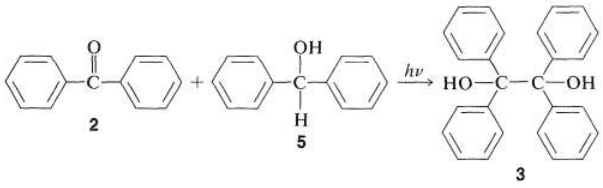


Since the quantum yields of 2-propanone and benzopinacol both are nearly unity when the light intensity is not high, it is clear that two of the radicals, 4, must be formed for each molecule of 2 that becomes activated by light. This is possible if the 2-hydroxy-2-propyl radical formed by Equation 28-7 reacts with 2 to give a second diphenylhydroxymethyl radical:

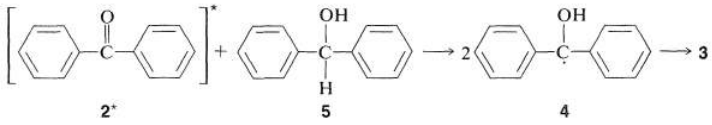


This reaction is energetically favorable because of the greater possibility for delocalization of the odd electron in 4 than in the 2-hydroxy-2-propyl radical.

Photochemical formation of 3 also can be achieved from diphenylmethanone, 2, and diphenylmethanol, 5:



The mechanism is similar to that for isopropyl alcohol as the reducing agent:

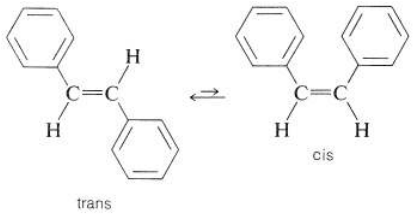


This reduction is believed to involve the triplet state of 2 by the following argument: Formation of 3 is reasonably efficient even when the concentration of the alcohol, 5 is low; therefore, whatever the excited state of the ketone, 2^*, that accepts a hydrogen atom from 5, it must be a fairly long-lived one. Because solutions of 2 show no visible fluorescence, they must be converted rapidly to

another state of longer life than the singlet (S_1). The long-lived state is then most reasonably a triplet state. In fact, if naphthalene is added to the reaction mixture, formation of benzopinacol, 3 is drastically inhibited because the benzophenone triplet transfers energy to naphthalene more rapidly than it reacts with the alcohol, 5 (see Section 28-1A).

28.3.3: Photochemical Isomerization of Cis and Trans Alkenes

An important problem in many syntheses is to produce the desired isomer of a cis-trans pair of alkenes. The problem would not arise if it were possible to isomerize the undesired isomer to the desired isomer. In many cases such isomerizations can be carried out photochemically. A typical example is afforded by *cis*- and *trans*-1,2-diphenylethene (stilbene):



Here the trans form is easily available by a variety of reactions and is more stable than the cis isomer because it is less sterically hindered. However, it is possible to produce a mixture containing mostly cis isomer by irradiating a solution of the trans isomer in the presence of a suitable photosensitizer. This process in no way contravenes the laws of thermodynamics because the input of radiant energy permits the equilibrium point to be shifted from what it would be normally.

Isomerization appears to occur by the following sequence: The sensitizer, usually a ketone such as benzophenone or 1-(2-naphthyl)ethanone, is raised by an $n \rightarrow \pi^*$ transition from the singlet ground state (S_0) to an excited state (S_1) by absorption of light. Intersystem crossing then occurs rapidly to give the triplet state (T_1) of the sensitizer:

$$^1\text{Sens} \xrightarrow[n \longrightarrow \pi^*]{h\nu} {}^1\text{Sens}^* \xrightarrow{\text{intersystem crossing}} {}^3\text{Sens}^*$$

(Sens = $C_6H_5CC_6H_5$; ^{1}Sens = singlet state; ^{3}Sens* = triplet state)

The next step is excitation of the alkene by energy transfer from the triplet state of the sensitizer. Remember, the net electron spin is conserved during energy transfer, which means that the alkene will be excited to the triplet state:

$$^3\text{Sens}^* (\uparrow\uparrow) + {}^1 \text{Alkene} (\uparrow\downarrow) \rightarrow {}^1 \text{Sens} (\uparrow\downarrow) + {}^3 \text{Alkene}^* (\uparrow\uparrow) \tag{28.3.1}$$

The triplet state of the alkene is most stable when the p orbitals, which make up the normal π system of the double bond, are not parallel to one another (Figure 6-17). Therefore, if the energy-transfer process leads initially to a planar triplet, this is converted rapidly to the more stable nonplanar form. The excitation of either the cis or the trans isomer of the alkene appears to lead to a common triplet state, as shown in Figure 28-4.

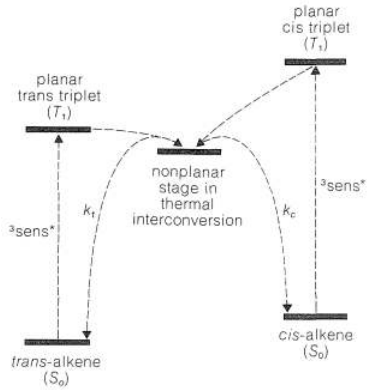


Figure 28-4: Schematic energy levels for cis- and trans-1,2-diphenylethene. The upward transitions are achieved by transfer of energy from triplet sensitizer. The downward transitions from the nonplanar stage marked with the rate constants k_t and k_c involve loss of thermal energy to the solvent, or phosphorescence. The lower energies assigned to the S_0 and T_1 states of trans-*1,2-diphenylethene relative to the S_0 and T_1 states of the cis isomer reflect steric hindrance between the phenyl groups of the cis isomer.*

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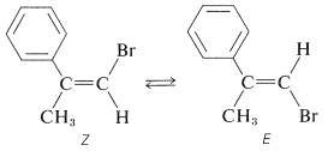
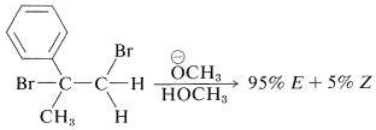
The final step in the isomerization is decay of the alkene triplet to the ground state. This happens either by emission of light (phosphorescence) or by having the triplet energy converted to thermal energy without emission of light. Either way, the cis or trans isomer could be formed and, as can be seen from Figure 28-4, the ratio of isomers produced depends on the relative rates of decay of the alkene triplet to the ground-state isomers, k_c/k_t. This ratio turns out to favor formation of the *less stable* isomer. Therefore, provided both isomers can be photosensitized efficiently, sensitized irradiation of either one will lead ultimately to a mixture of both, in which the thermochemically less stable isomer predominates. The sensitizer must have a triplet energy in excess of the triplet energy of the alkene for energy transfer to occur, and the **photostationary** or equilibrium point is independent of the nature of the sensitizer when the latter transfers energy efficiently to *both* cis and trans isomers. In the practical use of the sensitized photochemical equilibrium of cis and trans isomers, it is normally necessary to carry out pilot experiments to determine what sensitizers are useful.

Another example of how photochemical isomerization can be used is provided by the equilibration of the E and Z form of 1-bromo-2-phenyl-1-propene:



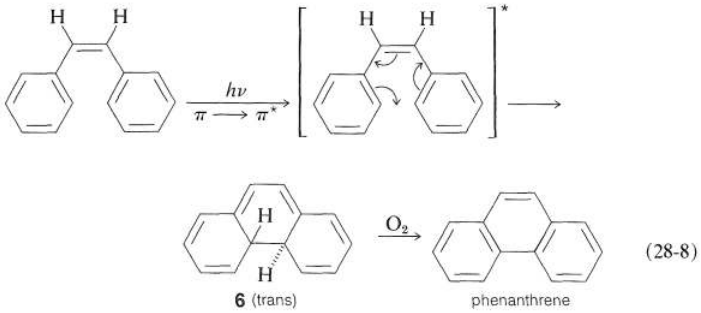
The E isomer is formed to the extent of 95% in the dehydrohalogenation of 1,2-dibromo-2-phenylpropane:



Photoisomerization of the elimination product with 1-(2-naphthyl)ethanone as sensitizer produce a mixture containing 85% of the Z isomer.

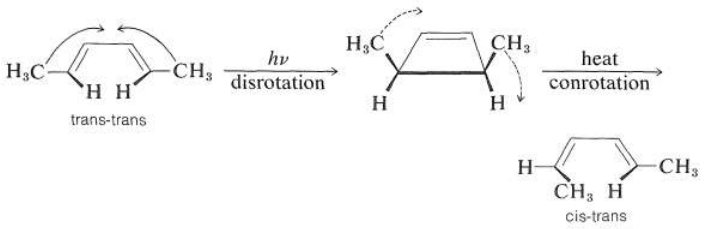
28.3.4: Photochemical Cyclization Reactions

One may well ask why the isomerization of alkenes discussed in the preceding section requires a sensitizer. Why cannot the same result be achieved by direct irradiation? One reason is that a $\pi \rightarrow \pi^*$ singlet excited state (S_1) produced by direct irradiation of an alkene or arene crosses over to the triplet state (T_1) inefficiently (compared to $n \rightarrow \pi^*$ excitation of ketones). Also, the S_1 state leads to *other* reactions beside isomerization which, in the case of 1,2-diphenylethene and other conjugated hydrocarbons, produce cyclic products. For example, *cis*-1,2-diphenylethene irradiated in the presence of oxygen gives phenanthrene by the sequence of Equation 28-8. The primary photoreaction is cyclization to a dihydrophenanthrene intermediate, 6, which, in the presence of oxygen, is converted to phenanthrene:



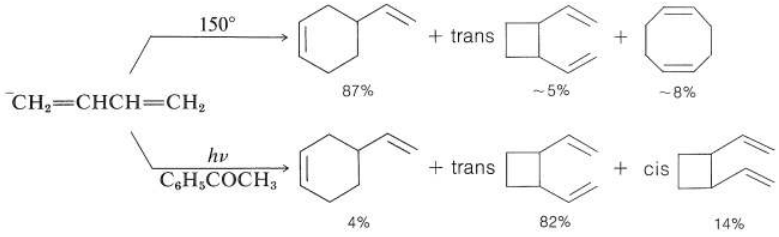
(28-8)

The cyclization step of Equation 28-8 is a photochemical counterpart of the electrocyclic reactions discussed in Section 21-10D. Many similar photochemical reactions of conjugated dienes and trienes are known, and they are of great interest because, like their thermal relatives, they often are stereospecific but tend to exhibit stereochemistry opposite to what is observed for formally similar thermal reactions. For example,



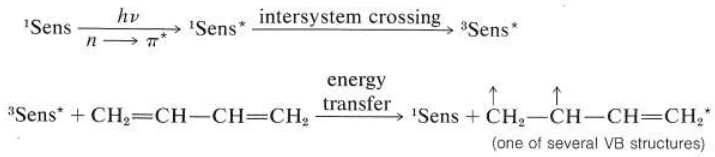
These reactions are $4n$-electron concerted processes controlled by the symmetry of the reacting orbitals. The thermal reaction is most favorable with a Mobius transition state (achieved by conrotation), whereas the photochemical reaction is most favorable with a Huckel transition state (achieved by disrotation).

Conjugated dienes also undergo photochemical cycloaddition reactions. Related thermal cycloadditions of alkadienes have been discussed in Sections 13-3A, 21-10A, and 21-10D, but the thermal and photochemical reactions frequently give different cyclic products. Butadiene provides an excellent example of the differences:

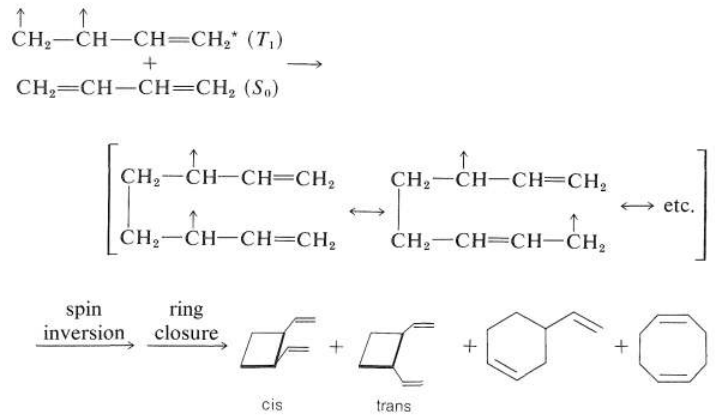


In the thermal reaction the [4 + 2] or Diels-Alder adduct is the major product, whereas in the photochemical reaction [2 + 2] cycloadditions dominate. Because the photochemical additions are sensitized by a ketone, $C_6H_5COCH_3$, these cycloadditions occur through the triplet state of 1,3-butadiene and, as a result, it is not surprising that these cycloadditions are stepwise, nonstereospecific, and involve diradical intermediates.

Excitation:



Cycloaddition:



Direct irradiation of 1,3-butadiene with 254-nm light produces cyclobutene and small amounts of bicyclo[1.1.0]butane along with dimers.

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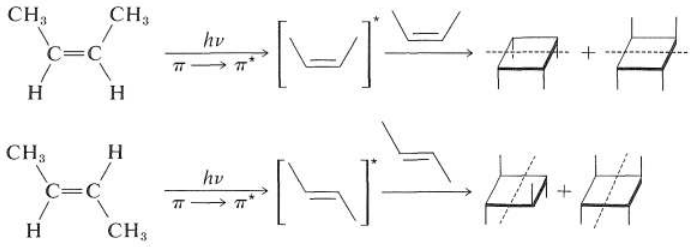
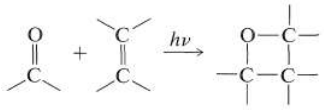
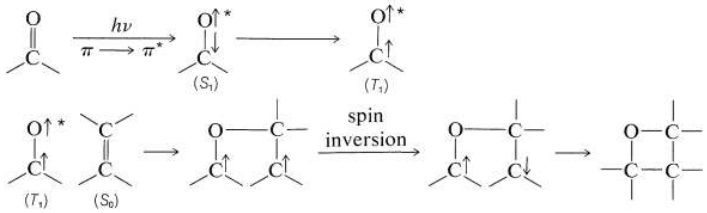
In contrast to conjugated dienes, simple alkenes such as 2-butene do not react easily by photosensitized cycloaddition. But they will form [2 + 2] cycloadducts on direct irradiation. These additions occur by way of a singlet excited state and are stereospecific:



A related reaction, which has no precedent in thermal chemistry, is the cycloaddition of an alkene and an aldehyde or ketone to form an oxacyclobutane:



In this kind of addition the ground-state alkene (S_0) reacts with an excited state (usually T_1) of the carbonyl compound by way of a diradical intermediate:



28.3.5: Singlet Oxygen Reactions

The ground state of molecular oxygen is unusual because it is a triplet state. Two electrons of parallel spin occupy separate π orbitals of equal energy (degenerate), as shown schematically in Figure 28-5,[3] The next two higher electronic states both are singlet states and lie respectively 24 and 37 $\mathrm{kcal\ mol^{-1}}$ above the ground state. From this we can understand why ordinary oxygen has the properties of a diradical and reacts rapidly with many radicals, as in the radical-chain oxidation of hydrocarbons (autoxidation; Sections 15-10 and 16-9E):

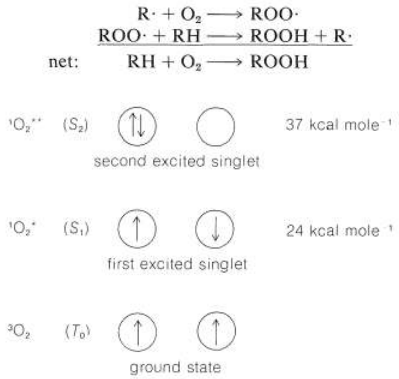
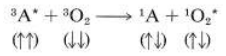
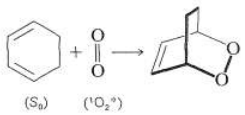


Figure 28-5: Electronic configurations of the two highest occupied (degenerate) π orbitals of oxygen (O_2) in the ground and excited states.

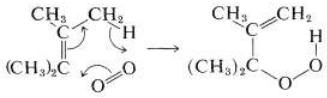
Oxygen also efficiently quenches excited triplet states of other molecules $({}^3A^*)$ and, in accepting triplet energy, is itself promoted to an excited *singlet* state. Notice that the total spin orientation is conserved:



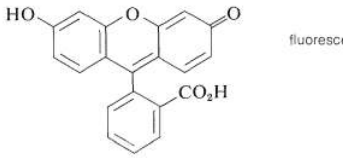
Singlet oxygen is highly reactive toward many organic molecules and will form oxygenated addition or substitution products. As one example, conjugated dienes react with singlet oxygen to give peroxides by [4 + 2] cycloaddition. Because only singlet states are involved, this addition is quite analogous to thermal Diels-Alder reactions (Section 21-10A):

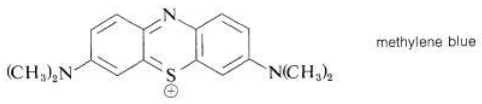


If the alkene or alkadiene has at least one hydrogen on the carbon adjacent to the double bond, reaction with singlet oxygen may give hydroperoxides. The mechanism of this reaction is related to [4 + 2] cycloadditions and is presumed to occur through a Huckel pericyclic transition state (see Section 21-10D):



Many reactions of this type can be achieved by allowing the hydrocarbon to react with oxygen in the presence of a sensitizing dye that strongly absorbs visible light. The dyes most commonly used for this purpose include fluorescein (and its chlorinated analogs, eosin and rose bengal), methylene blue, and porphyrin pigments (such as chlorophyll).





The overall process of photosensitized oxygenation of a substrate (A) proceeds by the following steps:

$$^1\text{Sens} \xrightarrow{h\nu} {}^1\text{Sens}^* \longrightarrow {}^3\text{Sens}^* \tag{28.3.2}$$

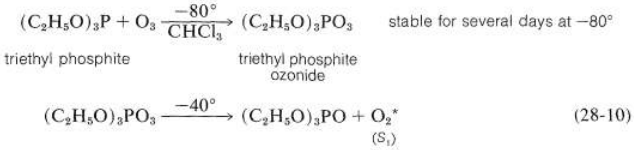
$$^3\text{Sens}^* + {}^3\text{O}_2 \longrightarrow {}^1\text{Sens} + {}^1\text{O}_2* \tag{28.3.3}$$

$$^1\text{O}_2* + \text{A} \longrightarrow \text{AO}_2 \tag{28.3.4}$$

Singlet oxygen can be produced chemically as well as by photochemical sensitization. There are several chemical methods available, one of the best known being the reaction of sodium hypochlorite with peroxide:

$$\text{NaOCl} + \text{H}_2\text{O}_2 \rightarrow \text{NaCl} + \text{H}_2\text{O} + {}^1\text{O}_2 \tag{28-9}$$

An alternative method of formation, which can be used in organic solvents at low temperatures, involves the thermal decomposition of triethyl phosphite ozonide (Equation 28-10):



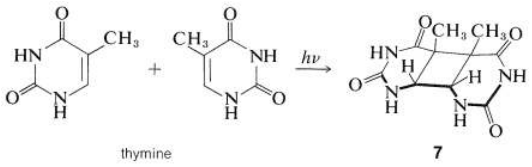
Regardless of whether singlet oxygen is formed chemically or photochemically, it gives similar products in reactions with alkenes.

28.3.6: Photobiology

Photosensitized reactions of oxygen are largely damaging to living organisms. Indeed, singlet oxygen reacts destructively with amino acids, proteins, and nucleic acids. How does an organism protect itself against the damaging effects of oxygen? There are no simple answers, but green plants provide a clue. Chlorophyll is an excellent sensitizing dye for singlet oxygen; yet green plants evidently are not harmed because of it. A reason may be that singlet oxygen is quenched very efficiently by other plant pigments, especially the carotenoid pigments such as β-carotene (Section 2-1). That this is the case is indicated by the fact that mutant plants unable to synthesize carotene are killed rapidly by oxygen and light.

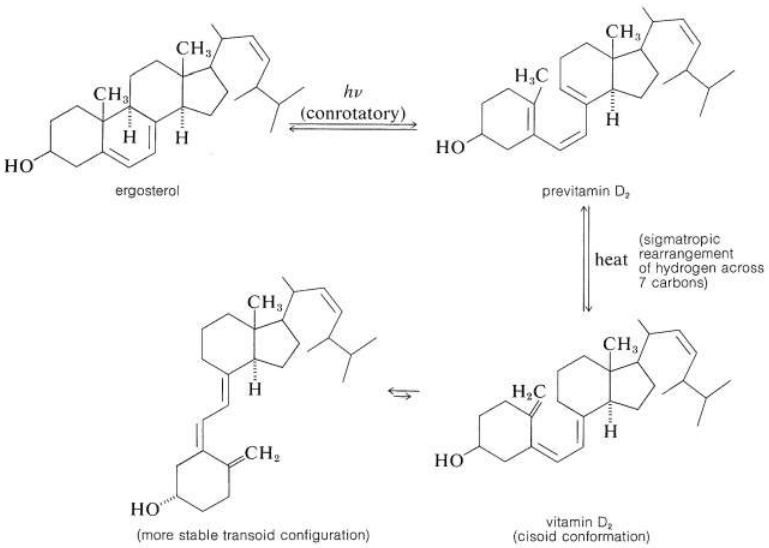
That direct irradiation with ultraviolet light is damaging to single-cell organisms is well known. It also is known that the nucleic acids, DNA and RNA, are the important targets of photochemical damage, and this knowledge has stimulated much research in the field of photobiology in the hope of unravelling the chemistry involved.

An interesting and significant outcome is the finding that the pyrimidine bases of nucleic acids (uracil, thymine, and cytosine) are photoreactive and undergo [2 + 2] cycloadditions on irradiation with ultraviolet light. Thymine, for example, gives a dimer of structure 7:



Comparable experiments with the nucleic acids have confirmed that cycloaddition of their pyrimidine bases also occurs with ultraviolet light and effectively cross-links the chains, a process obviously quite inimical to the functioning of the DNA (Section 25-13B). A remarkable and not well understood aspect of photobiology is the repair and defense mechanism both plants and animals possess to minimize the damaging effects of radiation.

On the positive side, there are photochemical reactions that are essential for human health. One of these is the formation of vitamin D (the antirachitic vitamin) by irradiation of ergosterol. This photochemical reaction is an electrocyclic ring opening of the cyclohexadiene ring of ergosterol of the type described in Section 28-2D. The product, previtamin D_2, subsequently rearranges thermally to vitamin D_2:



[1]The einstein unit is defined in Section 9-4.

[2]Recipient with G. Porter of the Nobel Prize in chemistry in 1967 for work on photochemical reactions.

[3]For a more detailed account of the electronic configuration of molecular oxygen, see M. Orchin and H. H. Jaffe, *The importance of Antibonding Orbitals*, Houghton Mifflin Co., Boston, 1967; or H. B. Gray, *Chemical Bonds*, W. A. Benjamin, Inc., Menlo Park,

Calif., 1973.

28.3.7: Contributors and Attributions

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28.4: Chemiluminescence

The most common means of generating electronically excited states of molecules is by the absorption of electromagnetic radiation. But excited states are accessible by other routes. Indeed, as shown in Section 28-2E, the excited singlet state of molecular oxygen can be produced by chemical reactions (Equations 28-9 and 28-10). Many other reactions are known that generate products in electronically excited states, and this is especially evident when the electronically excited products go to the ground state by the emission of visible light. This behavior is known as **chemiluminescence** and is transduction of chemical energy (ΔH) into radiant energy $(h\nu)$. Chemiluminescence is possible only when the ΔH of the reaction is sufficiently large to allow for production of at least one of the products in an electronically excited state $(^*)$. Chemiluminescence amounts to $\Delta H \rightarrow ^* \rightarrow h\nu$, which is opposite to most photochemistry which involves $h\nu \rightarrow ^* \rightarrow \Delta H$.

A beautiful example of a chemiluminescent reaction is the thermal dissociation of the cyclic peroxide, 8, into two molecules of 2-propanone:

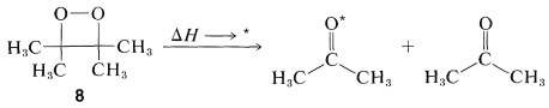


Figure 28-6). Accordingly, half of the 2-propanone molecules can be produced in an excited state and may decay to the ground state by visible emission (luminescence):[4]

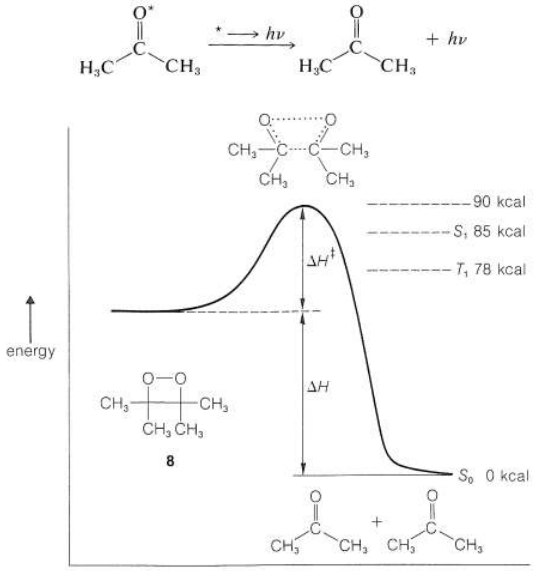


Figure 28-6: Energy profile for the thermal dissociation of 3,3,4,4-tetramethyldioxacyclobutane, 8, to acetone, showing that the transition state is above the threshold required to produce either excited singlet (S_1) or triplet (T_1) acetone.

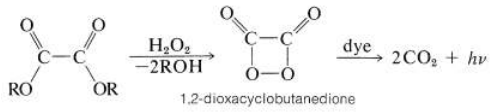
We should not be surprised at the high exothermicity of Reaction 28-11. The peroxide is of high energy (thermochemically unstable) because it combines the strain-energy characteristics of small rings with the weakness of O–O bonds, whereas the product is a stable substance with a strong carbonyl bond.

Chemiluminescence in many reactions is hard to detect because the efficiency of light emission is low. Thus, even though the excited state may be formed in high yield, it may be quenched by other species more efficiently than it loses energy by emission. This fact can be used to advantage by adding a substance that quenches the excited state efficiently and, after energy transfer, gives bright fluorescence or phosphorescence:

$$\Delta H \rightarrow ^* \underset{\text{energy transfer}}{\overset{\text{dye}}{\longrightarrow}} \text{dye}^* \overset{\text{luminescence}}{\longrightarrow} \text{dye} + h\nu \qquad (28.4.1)$$

Chemiluminescence can be greatly amplified by this process and it forms the basis of spectacular demonstrations of "cold light". An example is the *per*hydrolysis of ethanedioic (oxalic) esters with hydrogen peroxide in the presence of a fluorescent substance (Equation 28-12). The reaction is believed to pass through the highly unstable dioxacyclobutanedione, which dissociates into two

moles of carbon dioxide with such exothermicity that electronic excitation occurs, as evident from the intense light produced in the presence of fluorescent dyes:



This reaction has been developed into a commercial product, marketed under the trade name "Coolite", which can be used as an emergency light source by simply shaking a tube to bring the reactants in contact with one another.

Of major interest is the identity of the excited state (singlet or triplet) produced by chemiluminescent reactions. Little is known about excited states produced chemically except in a few cases, as in Reaction 28-11. Here the chemiluminescence dissociation gives a ratio of triplet 2-propanone to excited singlet 2-propanone of 100:1. This is a surprising result because it means that spectroscopic selection rules of electron-spin conservation are not followed in this chemiexcitation. The reaction has generated a triplet state from a singlet state. How can this be? Some idea of what is involved can be obtained from Figure 28-7, in which we see that breaking of the two sigma C–C and O–O bonds gives directly one molecule of ground-state ketone (all spins paired) and one molecule of triplet ketone. In this process, the electrons associated with the orbitals on one of the oxygen atoms appear to interact in such a way as to interchange electrons between orbitals *on the same atoms* with a spin inversion. This is called **spin-orbit coupling**.

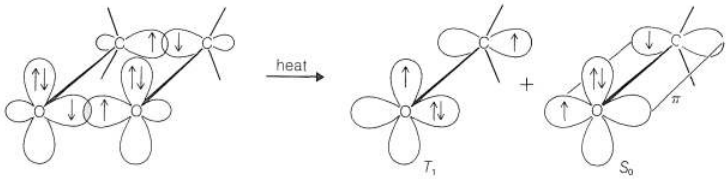


Figure 28-7: Representation of electron configuration changes in dissociation of tetramethyldioxacyclobutane, 8, to T_1 and S_0 2-propanone. Spin-orbit coupling of the nonbinding and the σ-bonding orbital on oxygen (shaded) produces one molecule of ketone in the triplet (T_1) state.

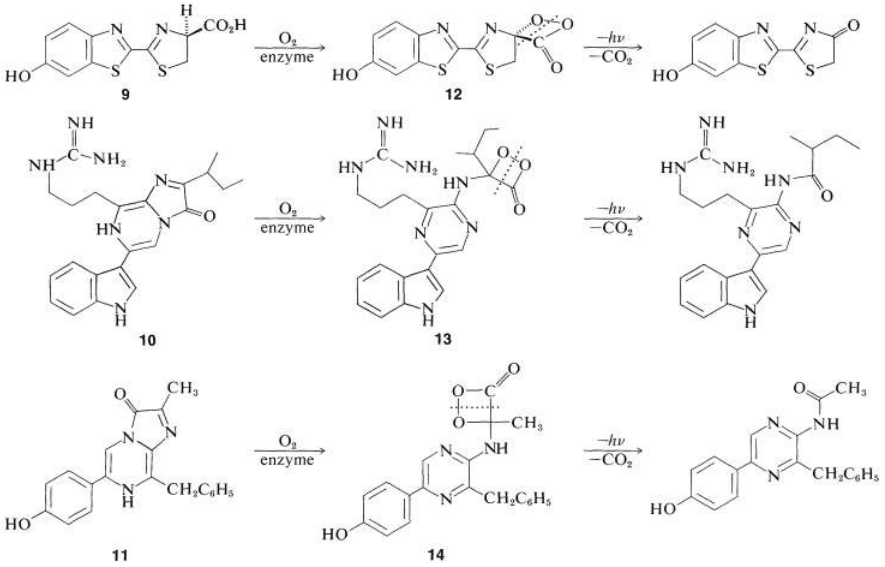
28.4.1: Bioluminescence

The emission of visible light by living organisms is a mysterious and fascinating phenomenon. The magical glow of the firefly and of certain plants and marine animals is a familiar sight and one that has stimulated man's curiosity and imagination for centuries. Despite intense interest in bioluminescence, it is only recently that substantial progress has been made in our understanding of how it occurs.

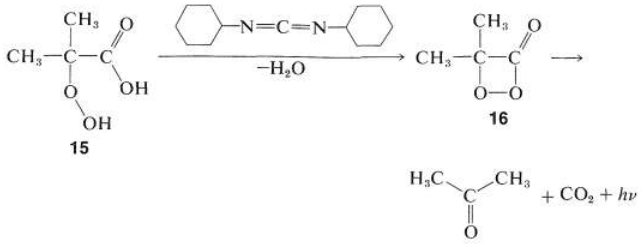
One of the earliest studies of bioluminescence was made by the French scientist R. Dubois toward the end of the nineteenth century. He demonstrated that bioluminescent organisms emitted light as a consequence of chemical change. He succeeded in isolating the active chemical from fireflies (luciferin) and the activating enzyme (luciferase, named by Dubois from the Latin *lucifer*, meaning light bearer). Luciferin and the enzyme in the presence of oxygen were found to reproduce the natural bioluminescence:

$$\text{luciferin} + O_2 \overset{\text{luciferase}}{\longrightarrow} \text{oxyluciferin} + h\nu \tag{28.4.2}$$

Further progress required elucidation of the structures of luciferin and its oxidation product. It turned out that there are several luciferins, depending on the organism. Firefly luciferin has the benzothiazol structure, 9; the luciferins from the marine crustacean *Cypridina hilgendorfii* and the sea pansy *Renilla reformis* have structures 10 and 11, respectively. Their oxidation products 12, 13, and 14 also are shown:



Although the luciferins 9-11 may not seem closely related, each appears to react with oxygen (at the direction of the appropriate enzyme) to give cyclic peroxylacetone intermediates 12-14. Luminescence is the consequence of the energetically favorable dissociation of the dioxacyclobutanone ring system to carbon dioxide and a carbonyl component. This mechanism is suggested by experiments with the peroxy acid, 15, which with N,N-dicyclohexylcarbodiimide gives a very reactive compound presumed to be the peroxylactone, 16. This substance liberates CO_2 rapidly at room temperature with luminescence:



[4]Production of two molecules of excited 2-propanone per molecule of 8 is not possible under the same conditions because this would correspond to a reaction with ΔH^0 of at least 156 kcal above formation of two moles of ground-state ketone.

28.4.2: Contributors and Attributions

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28.5: Color and Constitution

Visible light is electromagnetic radiation having a rather narrow range of wavelengths (400-800 nm). A black substance absorbs *all* wavelengths of visible light. Selective absorption of visible light by a substance imparts color, but the color is not that of the light absorbed but instead of the residual light that the substance transmits or reflects. For example, a compound that absorbs in the region 435-480 nm removes blue light from the visible spectrum, and the residual light is recognized by the eye as being yellow. The relationship of the observed color to wavelength of light absorbed is shown in Table 28-1. It is customary to call the color observed the **complementary color** or the **subtraction color** to that absorbed.

Table 28-1: *Color and Wavelength*

Light absorbed		Complementary (subtraction) color seen
Wavelength (nm)	Color	
400–435	violet	green-yellow
435–480	blue	yellow
480–490	green-blue	orange
490–500	blue-green (cyan)	red
500–560	green	purple (magenta)
560–580	yellow-green	violet
580–595	yellow	blue
595–605	orange	green-blue
605–750	red	blue-green (cyan)

Figure 28-8.

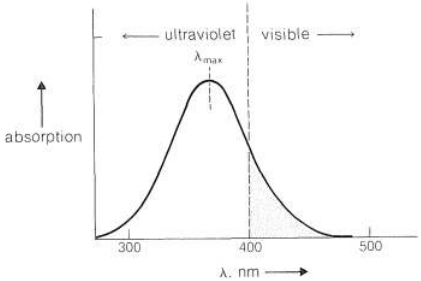


Figure 28-8: Absorption in the visible region by a colored substance that has λ_{max} in the ultraviolet.

Clearly, the color perceived, its brightness and its intensity, depends on the shape of the electronic spectral curve of the absorbing substance, which in turn depends on the chemical structure of the substance. A change in absorption from the blue to the red end of the spectrum corresponds to a *decrease* in the energy of the associated electronic transitions. We know also that this trend is associated with increasing conjugation of multiple bonds. For instance, 1,2-diphenylethene is colorless, whereas 1,10-diphenyl-1,3,5,7,9-decapentaene is yellow-orange:

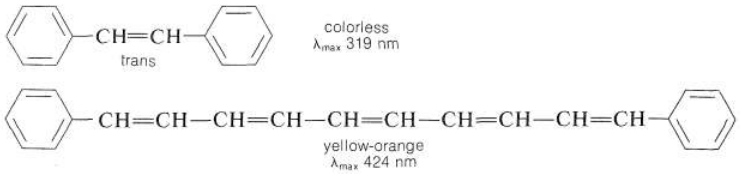


Figure 28-9, from which you can see that conjugation stabilizes both the ground state and the excited state but relatively more so the excited state. Thus the gap between the states narrows with increasing conjugation, and absorption shifts to longer wavelengths (also see Section 9-9B and 21-5C).

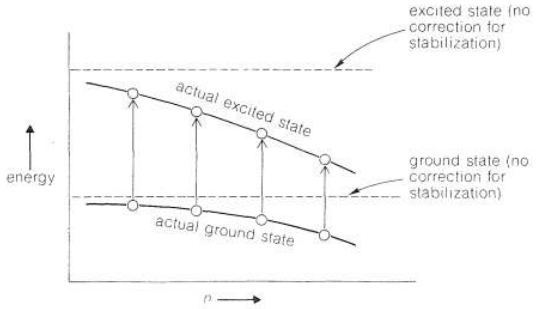


Figure 28-9: Schematic relationship between stabilization of ground and excited states of systems with n conjugated double bonds.

The effect of substituents on colors associated with conjugated systems is of particular interest in the study of dyes, because most dyes have relatively short conjugated systems and would not be intensely colored in the absence of substituent groups. (The plant pigments β-carotene, Section 2-1, and lycopene, often used as food coloring, are exceptions.)

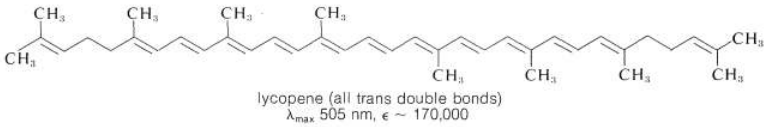
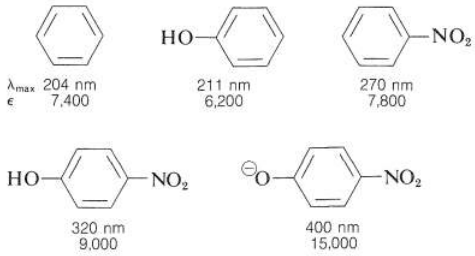


Figure 28-8. Its close relatives are benzene, benzenol, and nitrobenzene:



The conjugated π system common to all four compounds is that of the benzenoid ring, which is described as the absorbing **chromophore** (Section 22-3B). The hydroxyl and nitro substituents can be seen individually to shift the λ_{max} of the chromophore to longer wavelengths. However, the combined effect of the two substituents is much more dramatic, especially if the OH group is converted to the corresponding anion, 4-nitrobenzenolate. Now λ_{max} is shifted into the visible region, giving a yellow color, and because ϵ is large, the color is intense. Thus, properly chosen substituents can shift the main benzenoid absorption band from the ultraviolet into the visible region of the spectrum. Such substituents are often called **auxochromes**. They act by extending the conjugation of the chromophore and are particularly effective in causing large shifts towards the visible when one substituent is a π-electron donor and the other a π-electron acceptor. Thus, with the 4-nitrobenzenolate ion, interaction between the strongly electron-donating $-O^{\ominus}$ group and the strongly electron-accepting $-NO_2$ group provides significant stabilization:

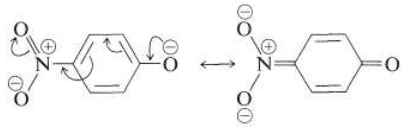
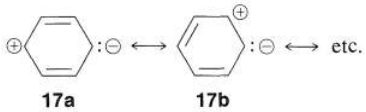


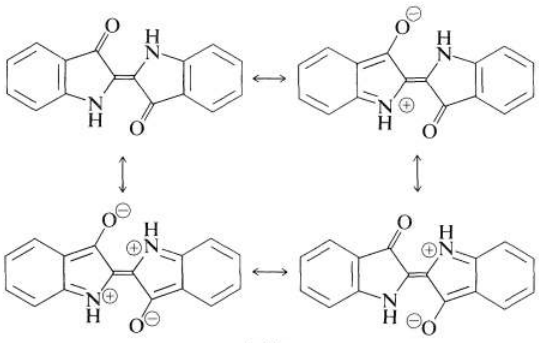
Figure 28-9). The narrowing of the energy gap is expected because excited electronic states have hybrid structures with much more important contributions from dipolar valence-bond forms than does the ground state (see Section 9-9B). Another way to look at the effect of substituents is to recall that excited singlet states of benzene will be stabilized by important contributions from resonance structures such as 17a and 17b:



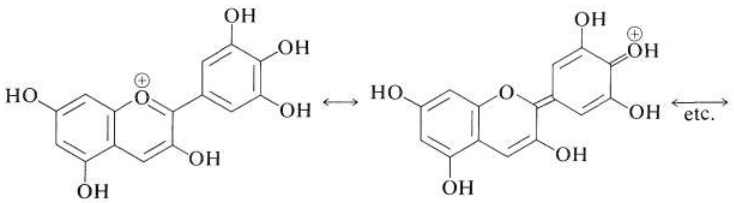
Hence, substitution of an electron-attracting group (such as NO_2) at one end of such a system and an electron-donating group (such as $O^{\ominus}$) at the other end should be particularly favorable for stabilization of the excited state (relative to the ground state, where 17a,

17*b*, etc., are of lesser importance). At the same time, we should *not* expect that two electron-attracting (or two electron-donating) groups at opposite ends would be nearly as effective.

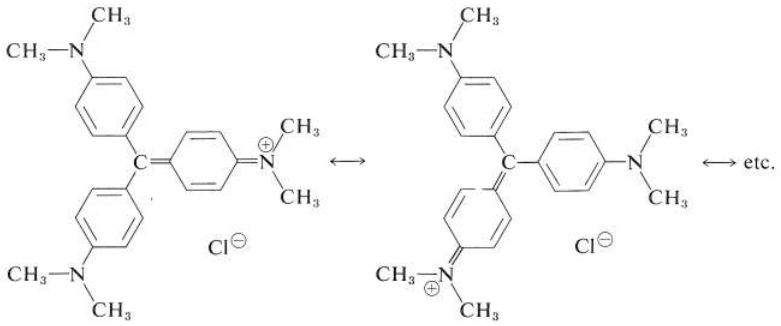
We hope you will understand from the foregoing discussion why it is that many intensely colored substances of natural or synthetic origin have conjugated structures with substituents, often cationic or anionic substituents, that can donate or accept electrons from the conjugated system. Such compounds provide us with many useful dyes, pigments, indicators, and food-coloring agents, as well as conferring color on plants and animals. A few examples follow:



indigo
(a deep-blue dye of natural and synthetic origin)



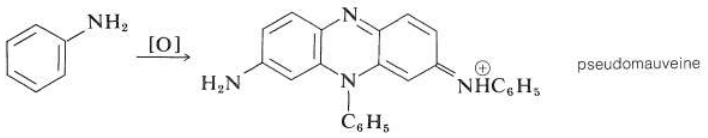
delphinidin
(member of a class of natural compounds, *anthocyanins*, that give color to flowers, leaves, fruits; they occur as glycosides)



Crystal Violet (synthetic dye)

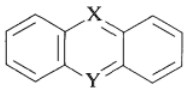
28.5.1: Dyes

Historically, the dye industry has been closely linked with the development of synthetic organic chemistry. Although dyes have been extracted from natural sources for centuries, it was not until 1856 that a synthetic dye was produced commercially. The previous year, William Henry Perkin - at age 17 - oxidized benzenamine (aniline) with potassium dichromate and isolated from the product (which was mostly aniline black; Section 23-11D) a purple compound that was excellent for dyeing silk. Perkin started commercial production of the dye under enormous difficulties. Because there was no organic chemical industry at the time, he had to design and build his own equipment as well as devise efficient syntheses for starting materials. His route to benzenamine stared with crude benzene from coal, which he nitrated and then reduced with iron and acid. He had to make the nitric acid (from nitrate salts and sulfuric acid) because concentrated nitric acid was not available. It was not until 1890 that the structure of Perkin's dye, called mauveine, was established by Otto Fischer. The dye was actually a mixture because the benzene used contained methylbenzene), but the product from the oxidation of benzenamine itself is structurally related to aniline black:

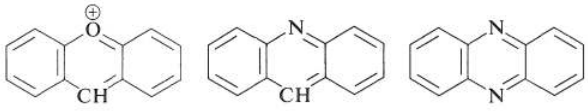


pseudomauveine

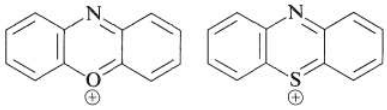
Although the mauveine dyes have been replaced with better dyes, they are representative of a group of useful dyes having the general structure



in which X and Y can be oxygen, nitrogen, sulfur, or carbon. The rings invariably carry substituents (hydroxyl or amino) that provide enhanced stabilization of the excited states. Examples of these ring systems follow:



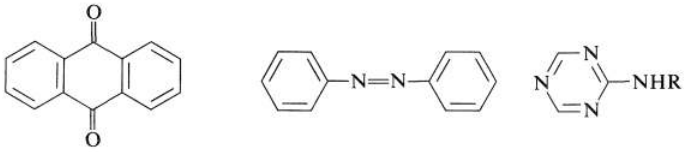
xanthene dyes acridine dyes azine dyes



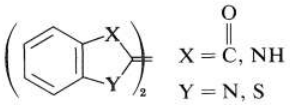
oxazine dyes thiazine dyes

A large number of useful dyes are substituted triphenylmethane derivatives. Crystal Violet (Section 28-4) and phenolphthalein are excellent examples of this kind of dye.

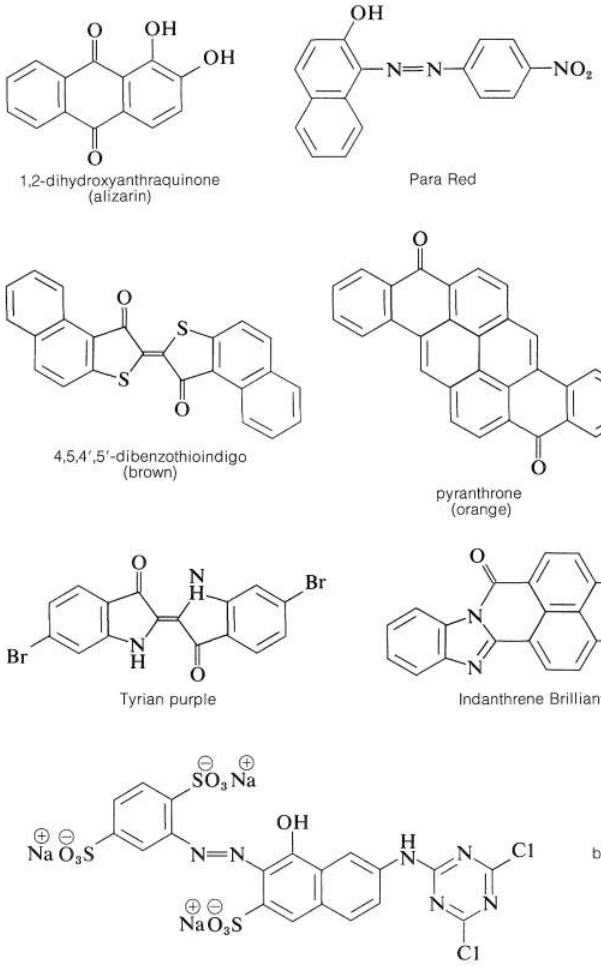
Other important dyes are derivatives of the following types of substances:



anthraquinone azobenzene triazine



Examples are

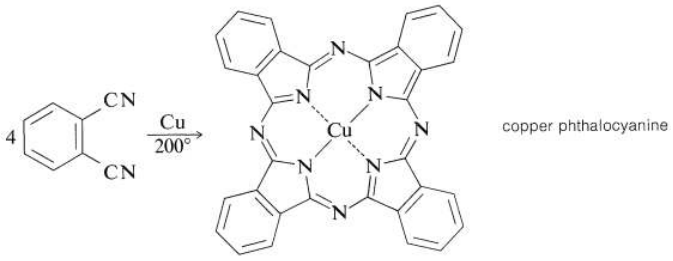


There is more to a successful dye than just an attractive color.[5] If it is to be useful, say for coloring fabrics, some simple means must be available for introducing the color into the fiber and then, usually of greater difficulty and importance, the color must be reasonably permanent - that is, resistant to normal laundry or cleaning procedures (wash-fast) and stable to light (light-fast). Here again, fundamentally important problems are involved. The scientific approach to improving wash-fastness of fabric dyes has to be based on a knowledge of the structural factors bearing on the intermolecular forces that determine solubilities. Light-fastness is connected with the photochemistry of organic compounds.

28.5.2: Pigments

The distinction between a dye and a pigment is that a dye actually is absorbed by the material to be colored, whereas a pigment is applied with a binding material to the surface. Pigments usually are highly insoluble substances. Many insoluble inorganic substances that would be wholly unsatisfactory as dyes are useful pigments.

Copper phthalocyanine is an example of a very important class of organic pigments. These are tetraazatetrabenzo derivatives of the porphyrin compounds discussed in Sections 20-9 and 25-8B. Copper phthalocyanine arises from condensation of four molecules of 1,2-benzenedicarbonitrile in the presence of copper metal at 200°:



[5]For a good account of dyes, see L. F. Fieser and M. Fieser, *Organic Chemistry*, D. C. Health & Co., Lexington, Mass., 1956, Chapter 36.

28.5.3: Contributors and Attributions

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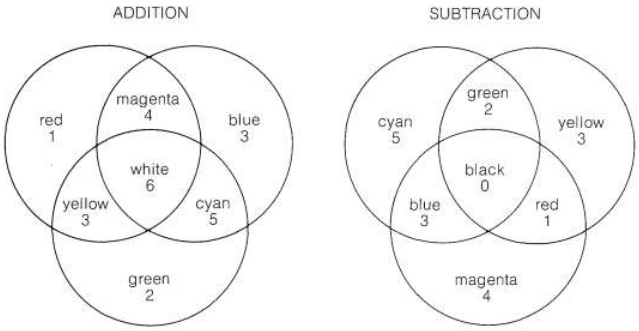
28.6: The Sensation of Color

The sensation of color can be achieved in different ways. According to Table 28-1, which relates wavelength to color, we could recognize a given color, say yellow, by direct perception of light encompassing a narrow band of wavelengths around $580\ \text{nm}$, or by subtraction of blue light (435-$480\ \text{nm}$) from white light.

A third way of producing color is by an additive process. In fact, a wide range of colors can be achieved by the addition of three colors - red, green, and blue - as indicated in Figure 28-10. Mixing all three so-called *primary additive colors*, in the right intensities, gives white light; mixing only red and green gives yellow. It is important to recognize that addition of any two primary colors is equivalent to subtracting the third. This point is amplified in Figure 28-10. Subtraction of the three primary additive colors, red, green, and blue, from white light gives, respectively, the three *primary subtraction colors*, cyan, magenta, and yellow. Application of additive and subtractive processes in color perception is illustrated in the following sections.



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28.7: Color Photography

28.7.1: Subtractive Color Process

Photography is a popular activity for many, but relatively few have an understanding of the chemistry involved, particularly in color photography. This is unfortunate because color photography represents an interesting combination of photochemistry (energy transfer), organic chemistry (dye formation), optics, psychology and physiology (color perception), and engineering (production and development of film).

The sensation of full color in color transparencies produced by photographic means is achieved by *subtraction*. As a simple example, let us suppose that the subject to be photographed is blue. To obtain a blue image by shining white light through a transparency, the transparency is made to subtract (absorb) yellow light - that is, to absorb strongly in the 580-nm region. How a color image of the subject is recorded chemically on the film and how the film is developed into a transparency will become clearer from the following discussion.

28.7.2: Color Film

The emulsion of a typical color film has three silver-bromide layers separately sensitized by suitable dyes to blue, green, and red light (Figure 28-11). When processed (Section 28-6C), the color formed in each layer is *complementary* to the color to which the layer is sensitive. Thus, if *unexposed* film is processed, intense yellow, magenta, and cyan colors are respectively formed in the blue-, green-, and red-sensitive layers. Then, when white light strikes this processed film, the yellow layer subtracts the blue, the magenta subtracts the green, and the cyan subtracts the red, with the result that the film appears black (or nearly so), as corresponds to *no* exposure to light. However, if the film is exposed to strong blue light *before* processing, the blue-sensitive layer responds, and when the film is processed, no yellow dye is formed in the blue-sensitive layer (see Figure 28-11). The transparency then contains only the subtraction colors, magenta and cyan. When white light enters a transparency of superimposed magenta and cyan dyes, only blue light is transmitted, as befits the color of the original sensitizing light. (From the right side of Figure 28-10, we see the overlap of 5 and 4 leads to blue.) Similarly, exposure of the film to strong yellow light (containing no blue), followed by processing, results in formation of yellow dye and no magenta nor cyan. This is because the green- and red-sensitive emulsions both are sensitive to yellow light, while the blue-sensitive emulsion does not respond to yellow light.

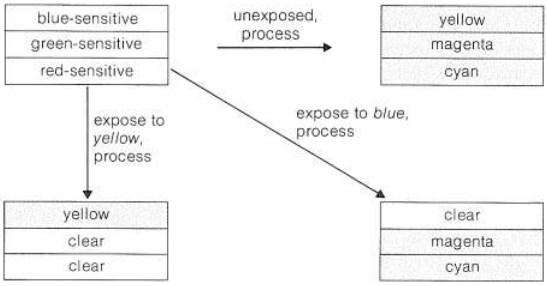


Figure 28-11: Schematic representation of the layer structure of color film and the color changes that occur on development. The actual film also contains a filter below the blue-sensitive layer to remove the blue light passing through this layer (because all emulsions are sensitive to blue), an antihalation layer below the red to prevent scattering of the light back through the emulsion, and a film base, such as cellulose acetate or poly-1,2-ethanediyl 1,4-benzenedioate, to support the emulsion.

In summary, the overall process from color film to the projection of a color image involves two separate conversions of each color into its complement, the net result being an image that has the same colors as the original subject.

28.7.3: Chemistry of Color Developers

We have seen that full color perception can be achieved by subtraction methods using dyes in suitable combinations. We now have to consider how such dyes are formed on exposure and development of color film. First though, you should recognize that a photographic emulsion, whether for color or black-and-white film, is light-sensitive primarily because of the presence of sliver halide. You will recall from previous discussions (Section 26-2C) that the sequence from exposure to development involves the following:

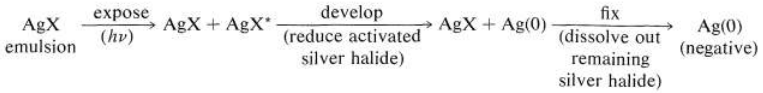


Figure 28-12), but it is directly activated by light only in the first layer. In the other layers, activation is achieved indirectly by a sensitizing dye which, on absorbing light, can transfer energy to the silver halide. The sensitizing dyes are not the same as the color-forming dyes, as we shall see. Among the most important sensitizing dyes are the cyanine dyes, such as the thiacyanines, 21 and 22. Compound 21 is magenta-colored (absorbs green light), and compound 22 is cyan-colored (absorbs red light). Structurally they differ only by one CH=CH unit:

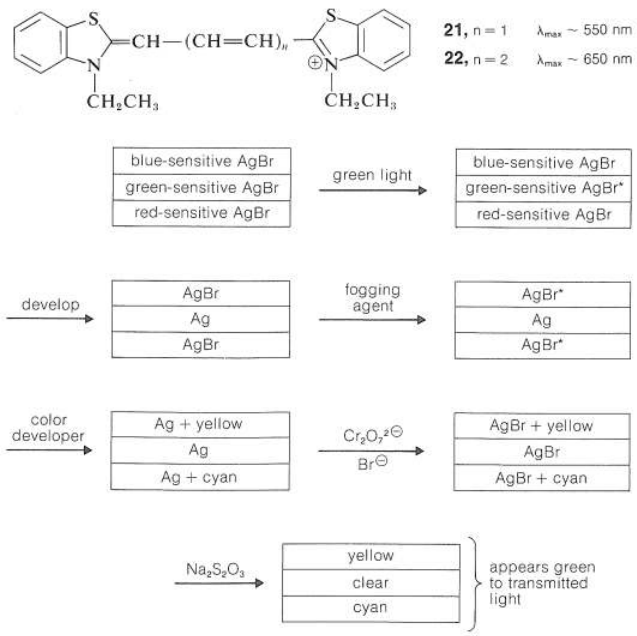
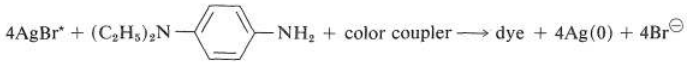


Figure 28-12: Schematic changes in the development of a color film exposed to green light. The color couplers are present in the original sensitized layers.

The chemistry involved in the formation of the dyes in the usual color films is highly ingenious and is achieved through steps shown in Figure 28-12 which, for purposes of illustration, are carried through for an initial exposure to green light. The exposure activates only the green-sensitive emulsion, and development with an ordinary developer such as metol-hydroquinone (Section 26-2C) produces silver metal only in the green-sensitive layer. The film now has the visual appearance of a milky negative. The developer then is washed out and the film is fogged, a process that activates the silver bromide remaining unreduced in the first step. The activated silver bromide so formed then is reduced with a **color developer**, usually 4-amino-N,N-diethylbenzenamine, in the presence of a **color coupler**. Production of dye occurs in direct proportion to the amount of activated silver bromide present, in close conformity with the following equation:



A different color coupler is used for each layer of the emulsion and, although the complete color picture is formed in this step, the film is coal black because of the metallic silver produced at the same time. The silver then is oxidized to silver bromide with dichromate solution containing bromide ion and removed with thiosulfate solution. The final image thus contains no silver.

The color-forming reactions obviously are critical to the success of the overall process and, of necessity, involve some degree of compromise between requirements for yield, reproducibility, suitability of color, and light-fastness. In reactions of the type shown in Equation 28-13, the color coupler is a methylene compound, R_2CH_2, in which the R groups have sufficient electron-attracting character to undergo some degree of formation of $R_2CH^{\ominus}$ in the alkaline medium used for color development. The first two steps in the overall sequence follow:

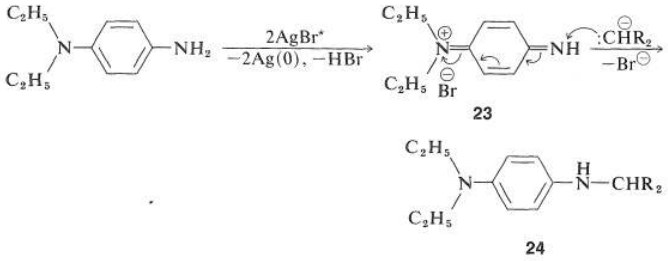
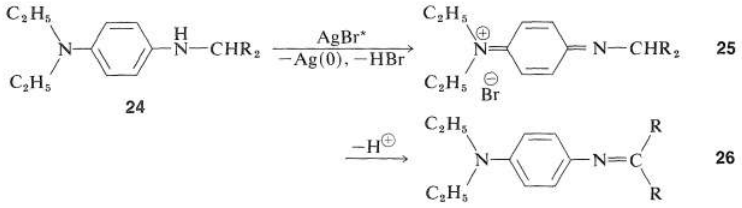
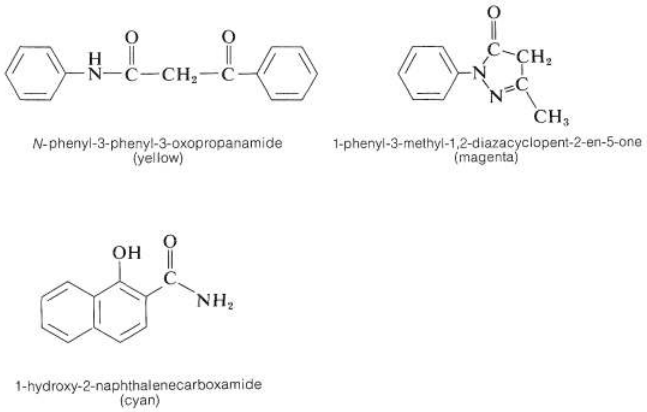


Figure 28-12 to a quinonimmonium salt, 23. This substance readily undergoes a Michael-type conjugate addition (Section 18-9D) with the anion, $R_2CH^{\ominus}$, of the active methylene compound to give an N′-substituted 4-amino-N,N-diethylbenzenamine, 24.

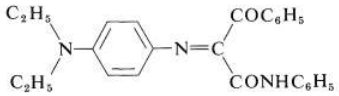
The product 24 is a photographic developer and is oxidized either by activated silver bromide or by 23 to a new quinonimmonium salt, 25:



This substance has an acidic hydrogen at the $-CHR_2$ and, on loss of this proton, a neutral conjugated imine results, 26, which is the actual dye. Color is expected for these molecules because the R groups are electron-attracting and the diethylamino group at the other end of the conjugated system is electron-donating. The remaining important question is how to adjust the R groups to obtain the proper colors in each layer of the film. Compounds that give yellow, magenta, and cyan dyes with 4-amino-N,N-diethylbenzenamine and activated silver bromide are shown below.



In the case of N-phenyl-3-phenyl-3-oxopropanamide, the yellow dye formed has the following structure:



Such dyes often are called **azomethines**. The nature of the exact color couplers used in color film is not well publicized. It is important that the couplers not diffuse out of the layers where they belong and, for this reason, insolubilizing substituent groups are attached to strategic positions on the color couplers.

The "instant" color process pioneered by Polaroid operates by a wonderfully ingenious, subtractive-color, three-layer scheme basically similar to the one shown in Figures 28-11 and 28-12. A very important difference is that the colors are transferred from the emulsion to a layer of white pigment (TiO_2), so the process actually is a printing process. The subtractive dyes (yellow, magenta, and cyan) are present in the emulsion as substituent groups on base-soluble photographic developers, schematically [dye $-(CH_2)_n-$developer]. A copper phthalocyanine derivative (Section 28-4B) is used to provide the cyan color.

What occurs in a given layer of the film is roughly as follows: Activation of the silver bromide in the layer by the light to which it is sensitized, and then development with an alkaline developer solution converts the "dye developer" to a base-insoluble form (Section 26-2C) in proportion to the light absorbed:

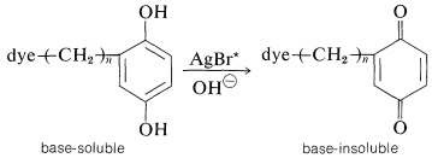


Figure 28-11). The process has the considerable advantage of having no color-forming reactions during development. The emulsion is protected by spreading opaque dye over the surface of the picture. This dye later fades as development becomes complete.

28.7.4: Contributors and Attributions

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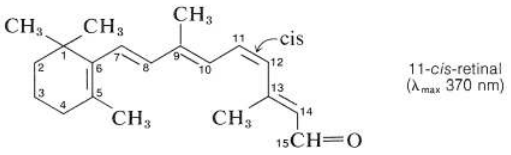
28.8: Chemistry of Vision

Vision is a process in which light is absorbed by a pigment in a photoreceptor cell (by a dye in the eye) and the photochemistry that ensues ultimately produces a transient electrical signal that is transmitted to the brain and interpreted as a visual image. There is much that is not fully understood about this process, but we shall discuss briefly the chemistry involved.

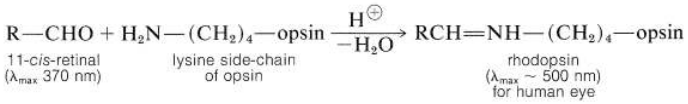
The eye is an extraordinarily sensitive instrument. To be sure, its wavelength response is restricted to $400\text{-}800\ \text{nm}$, but its degree of sensitivity is such that a fully dark-adapted eye can clearly detect objects in light so dim as to correspond to a light input over the retina of only about 10,000 quanta per second - one light quantum per three minutes per receptor cell in the retina!

The retina is made up of two kinds of light-sensitive (photoreceptor) cells, known as rods and cones. The rods are the more sensitive and are responsible for vision in dim light. The cones are much fewer in number than the rods and provide detail and color vision in good light. The part of the retina that corresponds to the center of the visual field contains only cones. A red pigment called **rhodopsin** is the photosensitive substance in the rod cells of the retina. It absorbs most strongly in the blue-green region of the visible spectrum $(\lambda_{\text{max}}\ 500\ \text{nm})$ and is essentially unaffected by the far-red end of the spectrum. Cone vision appears to involve a different pigment called **iodopsin**, which absorbs farther toward the red than does rhodopsin.

Rhodopsin is a combination of a protein called **opsin**, and the highly conjugated aldehyde, 11-*cis*-retinal:



The structure of opsin is unknown, but its prosthetic group (11-*cis*-retinal) is bonded to it through an imine (Schiff base) function formed between the aldehyde group of the retinal and the side-chain amino function of a lysine unit of opsin:



Opsin itself is colorless, whereas 11-*cis*-retinal absorbs strongly at $370\ \text{nm}$. The combination of opsin with 11-*cis*-retinal produces a remarkable shift of λ_{max} to longer wavelengths ($430\ \text{nm}$ to $620\ \text{nm}$, depending on the species). Similar shifts in wavelength for 11-*cis*-retinal in combination with simple amines are observed only up to λ_{max} of $440\ \text{nm}$, and only then for the protonated Schiff base. From this evidence, the chromophore in rhodopsin is believed to be protonated and to be profoundly modified by the structure of the opsin.

Light striking the retina changes the color of rhodopsin from red to yellow. The primary photochemical event in this process was established by G. Wald (Nobel Laureate in Physiology and Medicine, 1967), who showed that light absorption led to a change of configuration about the C_{11}-C_{12} double bond of the retinal chromophore from *cis* to *trans*:

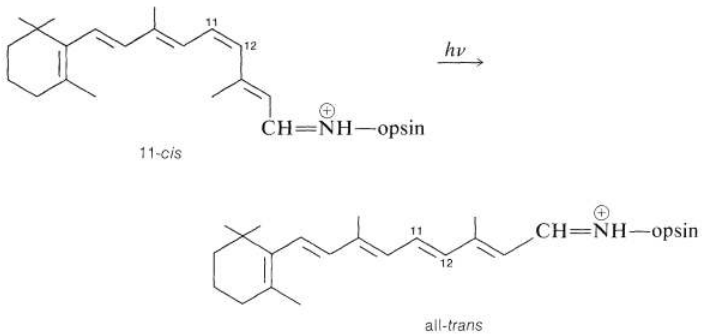


Figure 28-13.

https://chem.libretexts.org/@go/page/22382

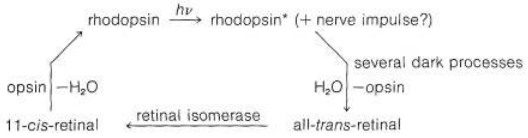


Figure 28-13: Schematic representation of the retinal cycle.

The exact point at which the nerve impulse is transmitted is not established with certainty, but it has to occur *before* the hydrolysis step because hydrolysis is too slow to account for the nerve impulse. One theory suggests that an electrical signal is generated at the instant of light absorption by electron transfer to a $\pi \rightarrow \pi^*$ singlet excited state that has substantially charged carbon atoms.

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28.E: Photochemistry (Exercises)

Exercise 28-1 Suppose absorption of light by a diatomic molecule $\mathrm{A{-}B}$ in the lowest vibrational level of the ground state always resulted in dissociation into A and B atoms. Would this necessarily mean that the molecule could not exist in an excited state in which the atoms were bonded together? Explain.

Exercise 28-2 The π-electron system of ethene has one bonding orbital and one antibonding orbital. Using the general approach of Figure 28-2, show the π-electron configurations for the ground state, two different excited singlet states, and a triplet state of ethene. Suppose the bonding energy of one electron in the bonding orbital is such as to be just canceled by having one electron in the antibonding orbital; would you expect the planar or a nonplanar configuration to be more stable for the excited states of ethene? Explain.

Exercise 28-3 The fluorescence of many substances can be "quenched" (diminished or even prevented) by a variety of means. Explain how concentration, temperature, viscosity, and presence of dissolved oxygen and impurities may affect the degree of fluorescence observed for solutions of a fluorescent material. Would you expect similar effects on phosphorescence? Explain.

Exercise 28-4 Explain qualitatively how temperature could have an effect on the appearance of the absorption spectrum of a diatomic molecule $\mathrm{A{-}B}$ with energy levels such as are shown in Figure 28-1, knowing that most molecules usually are in their lowest vibrational state at room temperature.

Exercise 28-5* Consider a molecule that has a ground state and an excited state which differ from those shown in Figure 28-1 in having potential energy curves with identical shapes, vibrational levels, and r_e values. If we designate the vibrational energy levels of each as $0,\ 1,\ 2, \cdots$ and $0^*,\ 1^*,\ 2^*, \cdots$ (the zeroth level being the lowest), what does the Franck-Condon principle suggest about the relative probabilities of the $0 \rightarrow 0^*$, $0 \rightarrow 1^*$, and $0 \rightarrow 2^*$ transitions? Would the same considerations necessarily hold for the curves of Figure 28-1? Explain.

Exercise 28-6 With reference to the molecular orbital diagram of benzene shown in Figure 21-5, show the electronic configuration of *three* different excited singlet states of benzene corresponding to promotion of an electron from the bonding π orbitals to the antibonding π orbitals. Calculate the energy difference between these states in units of β. Assuming that β is about $20\ \mathrm{kcal}$, calculate the *difference* in $\lambda_{\max}$ between the three absorption bands corresponding to the three states. How many corresponding triplet states are there?

Exercise 28-7 The quantum yield in photochemical chlorination of hydrocarbons such as methane is quite sensitive to the experimental conditions. How would you expect Φ to vary with (a) the *intensity* of the incident light, (b) the wavelength of the incident light from $250\ \mathrm{nm}$ to $450\ \mathrm{nm}$, (c) the presence of oxygen, and (d) the presence of alkenes? Explain.

Exercise 28-8 The vapor-phase photochemical decomposition of 2-propanone proceeds in the presence of iodine vapor, but the amount of carbon monoxide formed becomes very small. Explain how this result argues against one-step process, 2-propanone $\xrightarrow{h\nu}$ $2\mathrm{CH_3}\cdot + \mathrm{CO}$. What do you expect the products to be in the presence of iodine?

Exercise 28-9 Write a reasonable pathway for the photochemical dissociation shown in Equation 28-6. Explain why this reaction is likely to be favored over Norrish type II reactions for this ketone.

Exercise 28-10 Write a mechanism for formation of cyclobutane from the photolysis of cyclopentanone, and ketene from the photolysis of cyclobutanone.

Exercise 28-11 What products would you expect in the photodissociation of 3-methylpentanal?

Exercise 28-12 Irradiation of benzophenone in isopropyl alcohol in the presence of oxygen gives no benzopinacol (the benzophenone is not consumed), but does give 2-propanone (with Φ equal to unity) and hydrogen peroxide (with Φ nearly unity). The reaction does not occur readily in the absence of benzophenone. Explain how benzophenone acts as a *photosensitizer* for the oxidation of isopropyl alcohol by oxygen.

Exercise 28-13 What would you expect to be the quantum yield of 2-propanone in the following sequence of reactions for benzopinacol formation, where B = diphenylmethanone, 2; $\cdot\mathrm{BH}$ = diphenylhydroxymethyl radical, 4; $(\mathrm{BH})_2$ = benzopinacol, 3; A = 2-propanone; $\cdot\mathrm{AH}$ = 2-hydroxy-2-propyl radical; and $\mathrm{AH_2}$ = 2-propanol?

$$\mathrm{B} + h\nu \rightarrow \mathrm{B}^* \tag{28.E.1}$$
$$\mathrm{B}^* + \mathrm{AH_2} \rightarrow \cdot\mathrm{BH} + \cdot\mathrm{AH} \tag{28.E.2}$$
$$2 \cdot \mathrm{BH} \rightarrow (\mathrm{BH})_2 \tag{28.E.3}$$
$$2 \cdot \mathrm{AH} \rightarrow \mathrm{A} + \mathrm{AH_2} \tag{28.E.4}$$

How could this sequence be ruled out if formation of benzopinacol, 3, in the presence of an excess of optically active 2-butanol gave no racemized alcohol?

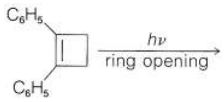
Exercise 28-14* Suppose the rates of the processes marked k_c and k_t in Figure 28-4 were the same. Which isomer would be favored at photoequilibrium if the rate of the reaction represented by k_t^* were greater than the rate represented by k_c^*? On the basis of steric hindrance, would you expect the rate of the k_t^* process or the k_c^* process to be greater, using benzophenone as sensitizer? Explain.

Exercise 28-15

a. Account for the formation of the *trans*-dihydrophenanthrene, 6, in the cyclization of Equation 28-8.

b. Both *cis*- and *trans*-1,2-diphenylethene isomers can be cyclized to phenanthrene. Explain how this is possible for the trans isomer.

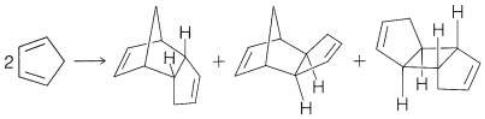
Exercise 28-16 Draw structures for the products expected from the following reactions. Be sure to indicate stereochemistry.

a. 

b. $\mathrm{C_6H_5CH{=}CHCO_2H}$ (trans) $\xrightarrow[[2+2]]{h\nu}$

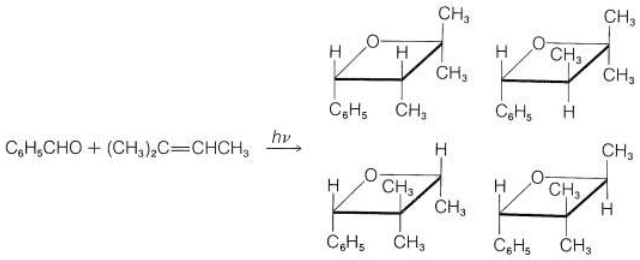
c.

Exercise 28-17 1,3-Cyclopentadiene gives the following substances on irradiation in the presence of a ketone sensitizer:

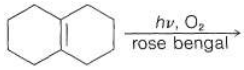


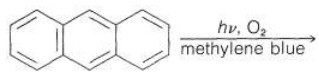
Write reasonable mechanisms for the formation of these substances.

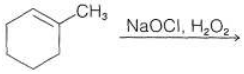
Exercise 28-18 Show the mechanistic steps by which formation of the following reaction products can be explained:



Exercise 28-19 Write structures expected for the products of the following reactions:

a. 

b. 

c. 

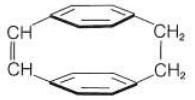
Exercise 28-20* Write at least three possible reaction that β-carotene could undergo as a result of energy transfer from $^1O_2{}^*$.

Exercise 28-21 What color would you expect to perceive if white light were passed through a solution containing a substance that absorbed very strongly but only within the specified wavelength ranges?

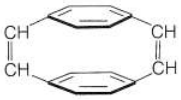
a. 660 ± 30 nm
b. 530 ± 30 nm
c.* 560 ± 300 nm
d.* 480 ± 0.1 nm

Exercise 28-22 What visible color would you expect of the substance having the spectrum shown in Figure 28-8?

Exercise 28-23 How would you expect the spectra of compound 18 and 19 to compare with each other and with the spectra of *cis*- and *trans*-1,2-diphenylethene (stilbene)? Explain.

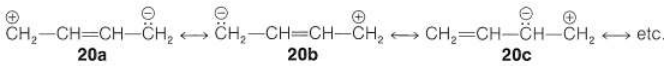


18



19

Exercise 28-24 Why must the resonance forms 20*a*, *b*, *c*, etc. correspond to a singlet state? Formulate the hybrid structure of a triplet state of butadiene in terms of appropriate contributing resonance structures.



20a **20b** **20c**

Exercise 28-25 The $\pi \rightarrow \pi^*$ absorption spectra of *trans*,*trans*- *trans*,*cis*-, and *cis*,*cis*-1,4-diphenylbutadiene show maxima and ε values (in parentheses) at about 330 nm (5.5×10^4), 310 nm (3×10^4), and 300 nm (3×10^4), respectively. What is the difference in energy between the transitions of these isomers in kcal mol^{-1}? Why should the *trans*,*trans* isomer have a different λ_{max} than the other isomers? (It may be helpful to make scale drawings or models.)

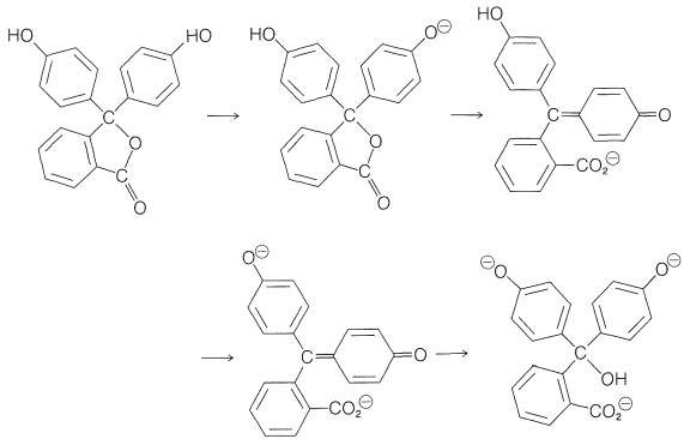
Exercise 28-26 Aqueous solutions of crystal violet turn from violet to blue to green to yellow on addition of successive amounts of acid. The color changes are reversed by adding alkali. What kind of chemical changes could be taking place ot give these color changes?

Exercise 28-27

a. 4-Nitro-N,N-dimethylbenzenamine gives a yellow solution in water which fades to colorless when made acidic. Explain.

b. 4-(N,N-Dimethylamino)azobenzene (Section 23-10C) is bright yellow in aqueous solution (λ_{max} 420 nm) but turns intense red (λ_{max} 530 nm) if dilute acid is added. If the solution is then made very strongly acidic, the red color changes to a different yellow (λ_{max} 430 nm) than the starting solution. Show how one proton could be added to 4-(N,N-dimethylamino)azobenzene to cause the absorption to shift to longer wavelengths and how addition of a second proton could shift the absorption back to shorter wavelengths.

Exercise 28-28 The well-known indicator and laxative, phenolphthalein, undergoes the following changes as a neutral solution is made more and more basic:



Some of these forms are colorless, some intensity colored. Which would you expect to absorb at sufficiently long wavelengths to absorb visible light. Give your reasoning.

Exercise 28-29 Classify the following groups as strong or weak, chromophores or auxochromes:

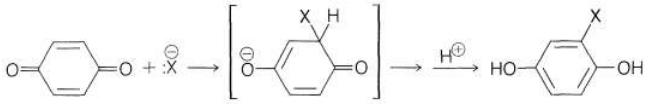
$$-NO_2,\ -CH_3,\ -I,\ -O^{\ominus},\ -\overset{\oplus}{N}(CH_3)_3,\ -N{=}\overset{\oplus}{N}-\overset{\ominus}{O},\text{ and } -C\equiv N$$

Give your reasoning.

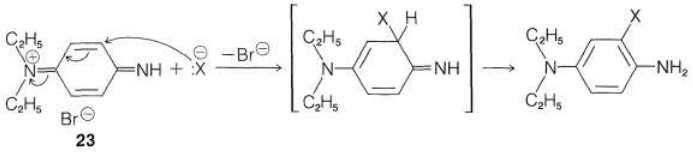
Exercise 28-30 Use Figure 28-10 to determine what colors you would expect in the layers of a processed color film of the type shown in Figure 28-11 if the incident light were (a) white, (b) green, (c) magenta, (d) orange? Explain.

Exercise 28-31* Write a reasonable stepwise mechanism for the formation of a cyan dye from 1-hydroxy-2-naphthalenecarboxamide in the overall reaction expressed by Equation 28-13 (review Section 26-1E).

Exercise 28-32* Quinones react with nucleophilic agents at carbon (Section 26-2D):



However, the quinonimmonium salt, 23, adds preferentially at nitrogen to give 24 rather than by the following path:



23

Explain why nucleophilic addition of 23 to give 24 by attack at nitrogen is more likely than the corresponding addition to a quinone by attack at oxygen. At what position would you expect nucleophilic addition to occur most readily to *para*-xylylene? Explain.

3,6-dimethylidene-1,4-cyclohexadiene
(*para*-xylylene)

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CHAPTER OVERVIEW

29: Polymers

Polymers are substances made up of recurring structural units, each of which can be regarded as derived from a specific compound called a **monomer**. The number of monomeric units usually is large and variable, each sample of a given polymer being characteristically a mixture of molecules with different molecular weights. The range of molecular weights is sometimes quite narrow, but is more often very broad. The concept of polymers being mixtures of molecules with long chains of atoms connected to one another seems simple and logical today, but was not accepted until the 1930's when the results of the extensive work of H. Staudinger, who received the Nobel Prize in Chemistry in 1953, finally became appreciated. Prior to Staudinger's work, polymers were believed to be colloidal aggregates of small molecules with quite nonspecific chemical structures.

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29.2: A Simple Addition Polymerization. The Parts of a Polymer
29.3: Types of Polymers
29.4: Forces Between Polymer Chains
29.5: Correlation of Polymer Properties with Structure
29.6: Condensation Polymers
29.7: Addition Polymers
29.8: Block, Graft, and Ladder Polymers
29.9: Naturally Occurring Polymers
29.10: Preparation of Synthetic Polymers
29.E: Polymers (Exercises)

Thumbnail: Polyethylene terephthalate polymer chain. (Public Domain; Jynto).

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29.1: Prelude

Polymers are substances made up of recurring structural units, each of which can be regarded as derived from a specific compound called a **monomer**. The number of monomeric units usually is large and variable, each sample of a given polymer being characteristically a mixture of molecules with different molecular weights. The range of molecular weights is sometimes quite narrow, but is more often very broad. The concept of polymers being mixtures of molecules with long chains of atoms connected to one another seems simple and logical today, but was not accepted until the 1930's when the results of the extensive work of H. Staudinger, who received the Nobel Prize in Chemistry in 1953, finally became appreciated. Prior to Staudinger's work, polymers were believed to be colloidal aggregates of small molecules with quite nonspecific chemical structures.

The adoption of definite chemical structures for polymers has had far-reaching practical applications, because it has led to an understanding of how and why the physical and chemical properties of polymers change with the nature of the monomers from which they are synthesized. This means that to a very considerable degree the properties of a polymer can be tailored to particular practical applications. Much of the emphasis in this chapter will be on how the properties of polymers can be related to their structures. This is appropriate because we already have given considerable attention in previous chapters to methods of synthesis of monomers and polymers, as well as to the mechanisms of polymerization reactions.

The special technical importance of polymers can be judged by the fact that half of the professional organic chemists employed by industry in the United States are engaged in research or development related to polymers.

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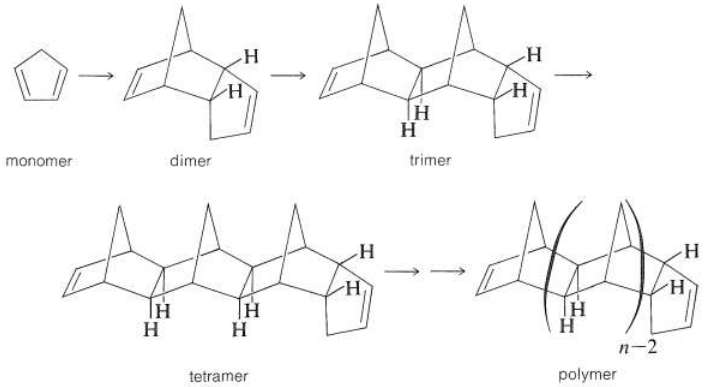
29.2: A Simple Addition Polymerization. The Parts of a Polymer

The thermal polymerization of 1,3-cyclopentadiene by way of the Diels-Alder addition is not an important polymerization, but it does provide a simple concrete example of how a monomer and a polymer are related:



The first step in this polymerization is formation of the dimer, which involves 1,3-cyclopentadiene acting as both diene and dienophile. This step occurs readily on heating, but slowly at room temperature. In subsequent steps, 1,3-cyclopentadiene adds to the relatively strained double bonds of the bicyclo[2.2.1]heptene part of the polymer. These additions to the **growing chain** require higher temperatures (180-200°). If cyclopentadiene is heated to 200° until substantially no further reaction occurs, the product is a waxy solid having a **degree of polymerization** n ranging from two to greater than six.

Polycyclopentadiene molecules have two different kinds of double bonds for **end groups** and a complicated **backbone** of saturated fused rings. The polymerization is reversible and, on strong heating, the polymer reverts to cyclopentadiene.

There are two commonly used and numerically different ways of expressing the *average* molecular weight of a polymer such as polycyclopentadiene. One is the **number-average** molecular weight, $\overline{M_n}$, which is the total weight of a polymer sample, m, divided by the total number of moles of molecules it contains, ΣN_i. Thus

$$\overline{M_n} = \frac{m}{\Sigma N_i} = \frac{\Sigma\left(N_i M_i\right)}{\Sigma N_i} \tag{29.2.1}$$

in which N_i is the number of moles of a single kind of molecular species, i, and M_i is the molecular weight of that species.

An alternative way of expressing the molecular weight is by the **weight average**, $\overline{M_w}$, which can be computed by summing up the contribution (as measured by the weight fraction w_i) of each molecular species i and its molecular weight M_i:

$$\overline{M_w} = \Sigma\left(w_i M_i\right) \tag{29.2.2}$$

The reason for using two different molecular weights is that some properties, such as freezing points, vapor pressure, and osmotic pressure of dilute solutions, are related directly to $\overline{M_w}$, whereas other properties, such as light-scattering, sedimentation, and diffusion constants, are related directly to $\overline{M_n}$.

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29.3: Types of Polymers

Polymers can be classified in several different ways - according to their structures, the types of reactions by which they are prepared, their physical properties, or their technological uses.

From the standpoint of general physical properties, we usually recognize three types of solid polymers: **elastomers**, **thermoplastic** polymers, and **thermosetting** polymers. Elastomers are rubbers or rubberlike elastic materials. Thermoplastic polymers are hard at room temperature, but on heating become soft and more or less fluid and can be molded. Thermosetting polymers can be molded at room temperature or above, but when heated more strongly become hard and infusible. These categories overlap considerably but are nonetheless helpful in defining general areas of utility and types of structures.

The structural characteristics that are most important to determining the properties of polymers are:

1. the degree of rigidity of the polymer molecules,
2. the electrostatic and van der Waals attractive forces between the chains,
3. the degree to which the chains tend to form crystalline domains, and
4. the degree of **cross-linking** between the chains.

Of these, cross-linking is perhaps the simplest and will be discussed next.

Consider a polymer made of a tangle of molecules with long linear chains of atoms. If the intermolecular forces between the chains are small and the material is subjected to pressure, the molecules will tend to move past one another in what is called **plastic flow**. Such a polymer usually is soluble in solvents that will dissolve short-chain molecules with chemical structures similar to those of the polymer. If the intermolecular forces between the chains are sufficiently strong to prevent motion of the molecules past one another the polymer will be solid at room temperature, but will usually lose strength and undergo plastic flow when heated. Such a polymer is thermoplastic. A **cross-link** is a chemical bond between polymer chains other than at the ends. Cross-links are extremely important in determining physical properties because they increase the molecular weight and limit the translational motions of the chains with respect to one another. Only *two cross-links* per polymer chain are required to connect all the polymer molecules in a given sample to produce one gigantic molecule. Only a few cross-links (Figure 29-1) reduce greatly the solubility of a polymer and tend to produce what is called a **gel polymer**, which, although insoluble, usually will absorb (be swelled by) solvents in which the uncross-linked polymer is soluble. The tendency to absorb solvents decreases as the degree of cross-linking is increased because the chains cannot move enough to allow the solvent molecules to penetrate between the chains.

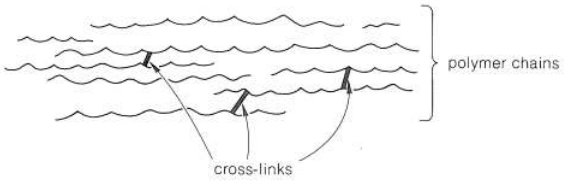


Figure 29-1: Schematic representation of a polymer with a few cross-links between the chains.

Thermosetting polymers normally are made from relatively low-molecular-weight, usually semifluid substances, which when heated in a mold become *highly cross-linked*, thereby forming hard, infusible, and insoluble products having a *three-dimensional network* of bonds interconnecting the polymer chains (Figure 29-2).

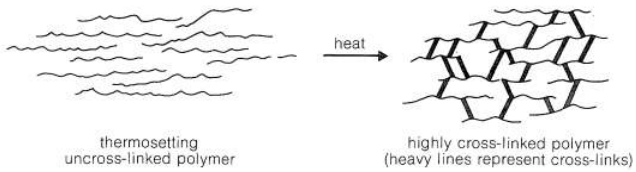
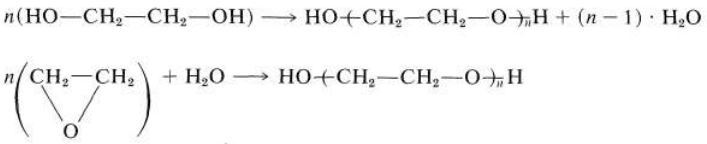


Figure 29-2: *Schematic representation of the conversion of an uncross-linked thermosetting polymer to a highly cross-linked polymer. The cross-links are shown in a two-dimensional network, but in practice three-dimensional networks are formed.*

Polymers usually are prepared by two different types of polymerization reactions - *addition* and *condensation*. In addition polymerization all of the atoms of the monomer molecules become part of the polymer; in condensation polymerization some of the atoms of the monomer are split off in the reaction as water, alcohol, ammonia, or carbon dioxide, and so on. Some polymers can

be formed either by addition or condensation reactions. An example is polyethylene glycol, which, in principle, can form either by dehydration of 1,2-ethanediol (ethylene glycol), which is condensation, or by addition polymerization of oxacyclopropane (ethylene oxide):[1]



Other addition polymerizations were discussed previously, including poly-1,3-cyclopentadiene, alkene polymers (Section 19-8), polyalkadienes (Section 13-4), polyfluoroalkenes (Section 14-7D), and polymethanal (Section 16-4B).

[1]Regardless of whether the *same* polymer would be obtained by polymerization starting with different monomers, the products usually are named to correspond to the starting material. Thus polyethylene glycol and polyethylene oxide would not be used interchangeably for $HO{-}(CH_2CH_2{-}O)_n{-}H$.

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29.4: Forces Between Polymer Chains

Polymers are produced on an industrial scale primarily, although not exclusively, for use as structural materials. Their physical properties are particularly important in determining their usefulness, be it as rubber tires, sidings for buildings, or solid rocket fuels.

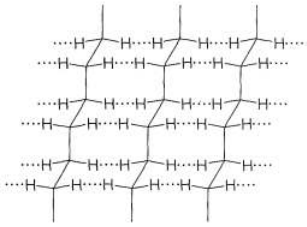


Figure 29-3: Representation of attractive interactions between the hydrogens in a crystallite of polyethene. This drawing is incomplete in that it does not show the interactions of the depicted chains with the other chains in front and behind.

Polymers that are not highly cross-linked have properties that depend greatly on the forces that act between the chains. By way of example, consider a polymer such as polyethene which, in a normal commercial sample, will be made up of molecules having 1000 to 2000 CH_2 groups in continuous chains. Because the material is a mixture of different molecules, it is not expected to crystallize in a conventional way.[2] Nonetheless, x-ray diffraction shows polyethene to have very considerable crystalline character, there being regions as large as several hundred angstrom units in length, which have ordered chains of CH_2 groups oriented with respect to one another like the chains in crystalline low-molecular-weight hydrocarbons. These crystalline regions are called *crystallites* (Figure 29-3). Between the crystallites of polyethene are amorphous, noncrystalline regions in which the polymer chains are essentially randomly ordered with respect to one another (Figure 29-4). These regions constituted crystal defects.

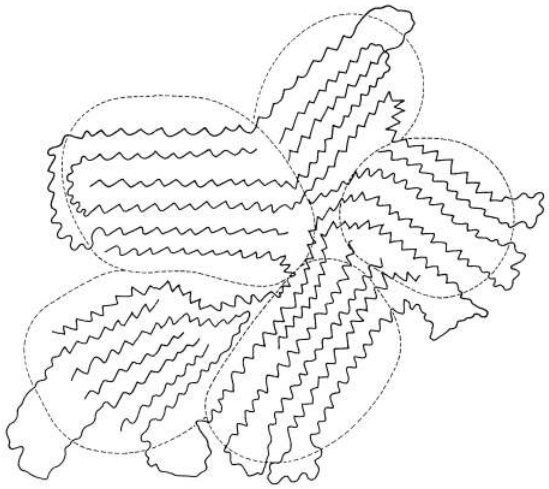


Figure 29-4: Schematic diagram of crystallites (enclosed by dashed lines) in a largely crystalline polymer.

The forces between the chains in the crystallites of polyethene are the so-called **van der Waals** or **dispersion** forces, which are the same forces acting between hydrocarbon molecules in the liquid and solid states, and, to a lesser extent, in the vapor state. These forces are relatively weak and arise through synchronization of the motions of the electrons in the separate atoms as they approach one another. The attractive force that results is rapidly overcome by repulsive forces when the atoms get very close to one another (see Figure 12-9, which shows how the potential energy between a pair of atoms varies with the internuclear distance). The attractive intermolecular forces between pairs of hydrogens in the crystallites of polyethene are only about $0.1\text{-}0.2\ \text{kcal mol}^{-1}$ per pair, but for a crystalline segment of 1000 CH_2 units, the *sum* of these interactions could well be greater than the $C{-}C$ bond strengths. Thus when a sample of the crystalline polymer is stressed to the point at which it fractures, carbon-carbon bonds are broken and radicals that can be detected by esr spectroscopy (Section 27-9) are generated.

In other kinds of polymers, even stronger intermolecular forces can be produced by hydrogen bonding. This is especially important in the polyamides, such as the nylons, of which nylon 66 is most widely used (Figure 29-5).

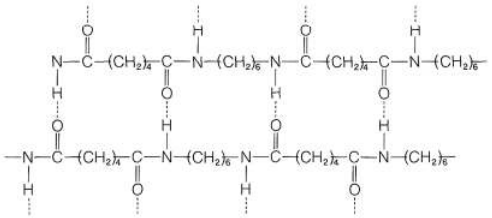


Figure 29-5: Possible hydrogen-bonded structure for crystallites of nylon 66, an amide-type polymer of hexanedioic acid and 1,6-hexanediamine.

The effect of temperature on the physical properties of polymers is very important to their practical uses. At low temperatures, polymers become hard and glasslike because the motions of the segments of the polymer chains with relation to each other are slow. The approximate temperature below which glasslike behavior is apparent is called the **glass temperature** and is symbolized by T_g. When a polymer containing crystallites is heated, the crystallites ultimately melt, and this temperature is usually called the **melting temperature** and is symbolized as T_m. Usually, the molding temperature will be above T_m and the mechanical strength of the polymer will diminish rapidly as the temperature approaches T_m.

Another temperature of great importance in the practical use of polymers is the temperature at which thermal breakdown of the polymer chains occurs. Decomposition temperatures obviously will be sensitive to impurities, such as oxygen, and will be influenced strongly by the presence of inhibitors, antioxidants, and so on. Nonetheless, there will be a temperature (usually rather high, 200° to 400°) at which *uncatalyzed scission* of the bonds in a chain will take place at an appreciable rate and, in general, one cannot expect to prevent this type of reaction from causing degradation of the polymer. Clearly, if this degradation temperature is comparable to T_m, as it is for polypropenenitrile (polyacrylonitrile), difficulties are to be expected in simple thermal molding of the plastic. This difficulty is overcome in making polypropenenitrile (Orlon) fibers by dissolving the polymer in N,N-dimethylmethanamide and forcing the solution through fine holes into a heated air space where the solvent evaporates.

Physical properties such as tensile strength, x-ray diffraction pattern, resistance to plastic flow, softening point, and elasticity of most polymers can be understood in a general way in terms of crystallites, amorphous regions, the degree of flexibility of the chains, cross-links, and the strength of the forces acting between the chains (dispersion forces, hydrogen bonding, etc.). A good way to appreciate the interaction between the physical properties and structure is to start with a rough classification of properties of solid polymers according to the way the chains are disposed in relation to each other.

1. An **amorphous** polymer is one with no crystallites. If the attractive forces between the chains are weak and if the motions of the chain are not in some way severely restricted as by cross-linking or large rotational barriers, such a polymer would be expected to have low tensile strength and when stressed undergo plastic flow in which the chains slip by one another.
2. An **unoriented crystalline** polymer is one which is considerably crystallized but has the crystallites essentially randomly oriented with respect to one another, as in Figure 29-4. When such polymers are heated they often show rather sharp T_m points, which correspond to the melting of the crystallites. Above T_m, these polymers are amorphous and undergo plastic flow, which permits them to be molded. Other things being the same, we expect T_m to be higher for polymers with stiff chains (high barriers to internal rotation).
3. An **oriented crystalline** polymer is one in which the crystallites are oriented with respect to one another, usually as the result of a **cold-drawing** process. Consider a polymer such as nylon, which has strong intermolecular forces and, when first prepared, is in an unoriented state like the one represented by Figure 29-4. When the material is subjected to strong stress in one direction, usually above T_g so that some plastic flow can occur, the material elongates and the crystallites are drawn together and oriented along the direction of the applied stress (Figure 29-6).

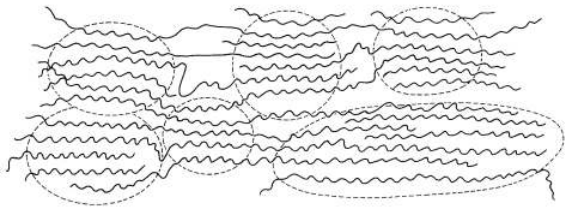


Figure 29-6: Schematic representation of an oriented crystalline polymer produced by drawing the polymer in the horizontal direction. The crystalline regions are enclosed with dashed lines.

> *An oriented crystalline polymer usually has a much higher tensile strength than the unoriented polymer. Cold drawing is an important step in the production of synthetic fibers.*

4. **Elastomers** usually are amorphous polymers. The key to elastic behavior is to have highly flexible chains with either sufficiently weak forces between the chains or a sufficiently irregular structure to be unstable in the crystalline state. The tendency for the chains to crystallize often can be considerably reduced by random introduction of methyl groups, which by steric hindrance inhibit ordering of the chains. A useful elastomer needs to have some kind of cross-linked region to prevent plastic flow and flexible enough chains to have a low T_g. The structure of a polymer of this kind is shown schematically in Figure 29-7; the important difference between this elastomer and the crystalline polymer of Figure 29-4 is the size of the amorphous regions. When tension is applied and the material elongates, the chains in the amorphous regions straighten out and become more nearly parallel. At the elastic limit, a semicrystalline state is reached, which is different from the one produced by cold drawing of a crystalline polymer in that it is stable only while under tension. The forces between the chains are too weak to maintain the crystalline state in the absence of tension. Thus when tension is released, contraction occurs and the original, amorphous polymer is produced. The entropy (Section 4-4B) of the chains is more favorable in the relaxed state than in the stretched state.

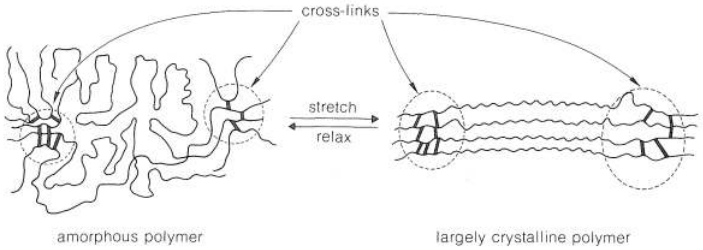
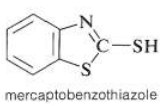


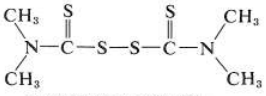
Figure 29-7: Schematic representation of an elastomer in relaxed and stretched configurations. Many elastomers do not crystallize when elongated.

A good elastomer should not undergo plastic flow in either the stretched or relaxed state, and when stretched should have a "memory" of its relaxed state. These conditions are best achieved with natural rubber (*cis*-poly-2-methyl-1,3-butadiene, *cis*-polyisoprene; Section 13-4) by curing (*vulcanizing*) with sulfur. Natural rubber is tacky and undergoes plastic flow rather readily, but when it is heated with 1-8% by weight of elemental sulfur in the presence of an *accelerator*, sulfur cross-links are introduced between the chains. These cross-links reduce plastic flow and provide a reference framework for the stretched polymer to return to when it is allowed to relax. Too much sulfur completely destroys the elastic properties and produces hard rubber of the kind used in cases for storage batteries.

The chemistry of the vulcanization of rubber is complex. The reaction of rubber with sulfur is markedly expedited by substances called **accelerators**, of which those commonly known as mercaptobenzothiazole and tetramethylthiuram disulfide are examples:

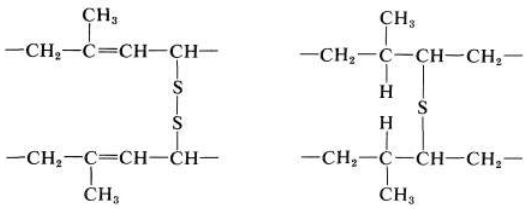


mercaptobenzothiazole



tetramethylthiuram disulfide

Clearly, the double bonds in natural rubber are essential to vulcanization because hydrogenated rubber ("hydrorubber") is not vulcanized by sulfur. The degree of unsaturation decreases during vulcanization, although the decrease is much less than one double bond per atom of sulfur introduced. There is evidence that attack occurs both at the double bond and at the adjacent hydrogen (in a manner similar to some halogenations; Section 14-3A) giving cross-links possibly of the following types:



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The accelerators probably function by acting as sulfur carriers from the elemental sulfur to the sites of the polymer where the cross-links are formed.

[2]Quite good platelike crystals, about 100 Å thick, have been formed from dilute solutions of polyethene. In these crystals, CH_2 chains in the *anti* conformation (Section 5-2) run between the large surfaces of the plates. However, the evidence is strong that when the CH_2 chains reach the surface of the crystal they do not neatly fold over and run back down to the other surface. Instead, the parts of a given chain that are in the crystalline segments appear to be connected at the ends of the crystallites by random loops of disordered CH_2 sequences, something like an old-fashioned telephone switchboard.

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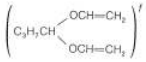
29.5: Correlation of Polymer Properties with Structure

The properties of many of the commercially important thermoplastic and elastic polymers can be understood in terms of their chemical structures by using the concepts developed in the preceding section. Thus the simple linear polymers, polyethene $-(CH_2CH_2)_n-$, polymethanal $-(CH_2-O)_n-$, and polytetrafluoroethene $-(CF_2-CF_2)_n-$, with regular chains and low barriers to rotation about the bonds in the chain tend to be largely crystalline with rather high melting points and low glass temperatures (see Table 29-1). The situation with polychloroethene (polyvinyl chloride), polyfluoroethene (polyvinyl fluoride), and polyethenylbenzene (polystyrene) as usually prepared is quite different. These polymers are much less crystalline and yet have rather high glass temperatures, which suggests that there is considerable attractive force between the chains. The low degree of crystallinity of these polymers is the result of their having a low degree of regularity of the stereochemical configuration of the chiral carbons in the chain. The discovery by G. Natta in 1954 that the stereochemical configurations of chiral centers in polymer chains could be crucial in determining their physical properties has had a profound impact on both the practical and theoretical aspects of polymer chemistry. Natta's work was done primarily with polypropene and this substance provides an excellent example of the importance of stereochemical configurations.

Table 29-1: *Representative Synthetic Thermoplastic and Elastic Polymers and Their Uses*[a]

Monomer(s)	Formula	Type of polymerization	Physical type	T_g, °C	T_m, °C	Trade names	Uses
ethene	$CH_2{=}CH_2$	radical (high pressure)	semi-crystalline	$\ll 0$	110	polyethylene, Alathon,	film, containers, piping, etc.
		Ziegler	crystalline	−120	130	Hi-fax, Dylan	
chloroethene	$CH_2{=}CHCl$	radical	atactic, semi-crystalline	80	180	polyvinyl chloride, Geon	film, insulation, piping, adhesives, etc.
fluoroethene	$CH_2{=}CHF$	radical	atactic, semi-crystalline	45		Tedlar	coatings[b]
chloroethene	$CH_2{=}CHCl$	radical	crystalline	variable		Saran	tubing, fibers, film
1,1-dichloroethene	$CH_2{=}CCl_2$						
chlorotrifluoroethene	$CF_2{=}CFCl$	radical	atactic, semi-crystalline	$\ll 0$	210	Kel-F	gaskets, insulation[c]
tetrafluoroethene	$CF_2{=}CF_2$	radical	crystalline	<-100	330	Teflon	gaskets, valves, insulation, filter felts, film coatings[d]
propene	$CH_2{=}CHCH_3$	Ziegler	isotactic, crystalline	−20	175		fibers, molded articles
ethene	$CH_2{=}CH_2$	Ziegler	amorphous	−55		Nordel	rubber articles
propene	$CH_2{=}CHCH_3$						
1,4-hexadiene	$CH_2{=}CHCH_2CH{=}CHCH_3$						
hexafluoropropene	$CF_2{=}CFCF_3$	radical	amorphous	−23		Viton	rubber articles[e]
1,1-difluoroethene	$CF_2{=}CH_2$						
2-methylpropene	$CH_2{=}C(CH_3)_2$	cationic	amorphous	−70		Vistanex, Oppanol	pressure-sensitive adhesives
2-methylpropene	$CH_2{=}C(CH_3)_2$	cationic	amorphous			butyl rubber	inner tubes
2-methyl-1,3-butadiene	$CH_2{=}C(CH_3)CH{=}CH_2$						

2-chloro-1,3-butadiene	$CH_2{=}C(Cl)CH{=}CH_2$	radical	amorphous	−40		Neoprene	rubber articles[e]
2-methyl-1,3-butadiene	$CH_2{=}C(CH_3)CH{=}CH_2$	Ziegler, Li	amorphous (*cis*-1,4)	−70	28	natural rubber Ameripol, Coral rubber	rubber articles
ethenylbenzene	$CH_2{=}CHC_6H_5$	radical	atactic, semi-crystalline	85	<200	Styron Lustron	molded articles, foam
ethenol	$(CH_2{=}CHOH)^f$	hydrolysis of polyvinyl ethanoate	crystalline		dec.	polyvinyl alcohol	water-soluble adhesives, paper sizing
1,1-diethenoxy-butane		polyvinyl alcohol and butanal	amorphous			polyvinyl butyral	safety-glass laminate
methanal	$CH_2{=}O$	anionic	crystalline		179	Delrin	molded articles
propenenitrile	$CH_2{=}CHCN$	radical	crystalline	100[d]	>200	Orlon	fiber
methyl 2-methyl-propenoate	$CH_2{=}C(CH_3)CO_2CH_3$	radical	atactic amorphous	105		Lucite, Plexiglas	coatings, molded articles
		anionic	isotactic crystalline	115	200		
		anionic	syndiotactic crystalline	45	160		
benzene-1,4-dicarboxylic acid		ester interchange between dimethyl 1,4-benzenedicarboxylate and 1,2-ethanediol	crystalline	56	260	Dacron, Mylar, Cronar, Terylene	fiber, film
1,2-ethanediol	$HOCH_2CH_2OH$						
aza-2-cycloheptanone (caprolactam)		anionic	crystalline	50	225	Perlon	fibers, molded articles
1,6-hexanediamine hexanedioic acid	$NH_2(CH_2)_6NH_2$ $HO_2C(CH_2)_4CO_2H$	anionic condensation	crystalline	50	270	nylon, Zytel	fibers, molded articles

[a]Information on these and related polymers is given in books listed on page 1459.
[b]Exceptional outdoor durability.
[c]Used where chemical resistance is important.
[d]Excellent self-lubricating and electrical properties.
[e]Used particularly where ozone resistance is important.
[f]These monomers are not the starting materials used to make the polymers, which actually are synthesized from polyvinyl alcohol.
[g]T_g is 60° when water is present.

Figure 29-8, we would find that the atactic form has the methyl groups randomly distributed on one side or the other of the main chain. In contrast, isotactic polypropene has a regular structure with the methyl groups all on the same side of the chain. Many other kinds of regular structures are possible and the one of these that has been prepared, although not in quantity, is the syndiotactic form, which has the methyl groups oriented alternately on one side or the other of the polymer chain.

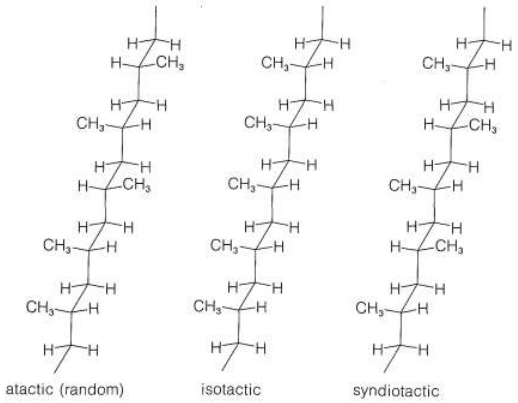


Figure 29-8: Configuration of atactic, isotactic, and syndiotactic polypropene. These configurations are drawn here to show the stereochemical relationships of the substituent groups and are not meant to represent necessarily the stable conformations of the polymer chains.

There are striking differences in physical properties between the atactic and isotactic forms. The atactic material is soft, elastic, somewhat sticky, and rather soluble in solvents such as 1,1,2,2-tetrachloroethane. Isotactic polypropene is a hard, clear, strong crystalline polymer that melts at 175°. It is practically insoluble in all organic solvents at room temperature, but will dissolve to the extent of a few percent in hot 1,1,2,2-tetrachloroethane. That the difference between the atactic and isotactic polymers irises from differences in the configurations of the methyl groups on the chains is shown in a striking way by ^{13}C nmr spectra (Figure 29-9). The differences in these spectra result from differences in the interactions between the methyl groups for the different configurations, in the same way as we have shown you earlier for axial and equatorial methyl groups on cyclohexane rings (Section 12-3D).

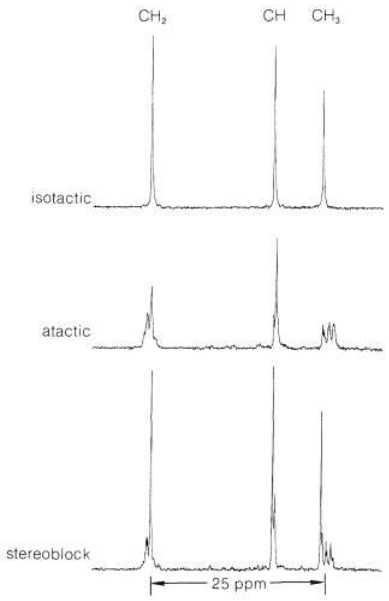
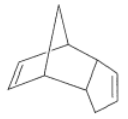


Figure 29-9: Proton-decoupled ^{13}C spectra of different polypropene samples taken in $CHCl_2CHCl_2$ solution at 150° at 15.9 MHz. The upper spectrum is of a highly isotactic polypropene, which shows only the faintest indication of lack of stereoregularity. The middle spectrum is of atactic polypropene, which shows a variety of chemical shifts for the CH_3 groups as expected from the different steric interactions generated by random configurations of the methyl groups. The lower spectrum is of a sample of so-called "stereoblock" polymer, which is very largely isotactic. The ^{13}C spectrum of syndiotactic polypropene looks exactly like that of the isotactic polymer, except that the CH_3- peak is about 1 ppm upfield of the position of the isotactic CH_3 peak and the CH_2 peak is about 1 ppm downfield of the isotactic CH_2 peak.

Why should polypropene melt so much higher than polyethene (175° vs. 110°)? The answer lies in the differences between the way the polymers crystallize. Polyethene crystallites have extended zig-zag chains that have very low barriers to rotation about the $C-C$ bonds. Because of interferences between the methyl groups, polypropene does not crystallize in extended zig-zag chains but instead forms a *helix*, something like the α helix (Section 25-8A), with the chain carbons on the inside and the methyl carbons on the outside. These coils are more rigid than the extended CH_2 chains in polyethene and have stabilizing interchain $H\cdots H$ interactions so that a higher temperature is required for melting. Polypropene can be cold drawn to form fibers that resemble nylon fibers although, as might be expected, these fibers do not match the 270° melting point of nylon and, because of their hydrocarbon character, are much more difficult to dye.

Although both linear polyethene and isotactic polypropene are crystalline polymers, ethene-propene *copolymers* prepared with the aid of Ziegler catalysts are excellent elastomers. Apparently, a more or less random introduction of methyl groups along a polyethene chain reduces the crystallinity sufficiently drastically to lead to an amorphous polymer. The ethene-propene copolymer is an inexpensive elastomer, but having no double bonds, is not capable of vulcanization. Polymerization of ethene and propene in the presence of a small amount of dicyclopentadiene or 1,4-hexadiene gives an unsaturated heteropolymer, which can be vulcanized with sulfur in the usual way.



dicyclopentadiene

$CH_2{=}CH{-}CH_2{-}CH{=}CH{-}CH_3$

1,4-hexadiene

The rationale in using these particular dienes is that only the strained double bond of dicyclopentadiene and the terminal double bond of 1,4-hexadiene undergo polymerization with Ziegler catalysts. Consequently the polymer chains contain one double bond for each molecule of dicyclopentadiene or 1,4-hexadiene that is incorporated. These double bonds later can be converted to cross-links by vulcanization with sulfur (Sections 13-4 and 29-3).

Polychloroethene (polyvinyl chloride), as usually prepared, is atactic and not very crystalline. It is relatively brittle and glassy. The properties of polyvinyl chloride can be improved by copolymerization, as with ethenyl ethanoate (vinyl acetate), which produces a softer polymer ("Vinylite") with better molding properties. Polyvinyl chloride also can be **plasticized** by blending it with

substances of low volatility such as tris-(2-methylphenyl) phosphate (tricresyl phosphate) and dibutyl benzene-1,2-dicarboxylate (dibutyl phthalate) which, when dissolved in the polymer, tend to break down its glasslike structure. Plasticized polyvinyl chloride is reasonably flexible and is widely used as electrical insulation, plastic sheeting, and so on.

Table 29-1 contains information about a number of representative important polymers and their uses. Some similar data on other polymers already have been given (Section 13-4 and Table 10-4). The important use of modified polymers as ion-exchange resins is discussed in Section 25-4C.

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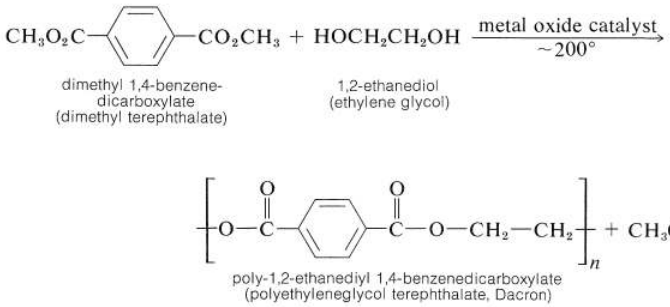
29.6: Condensation Polymers

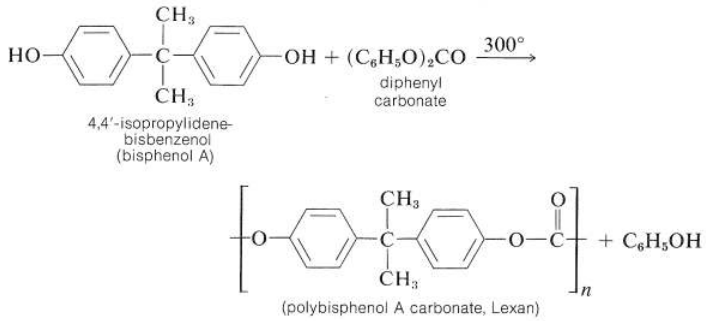
There is a wide variety of condensation reactions that, in principle, can be used to form high polymers. However, high polymers can be obtained only in high-yield reactions, and this limitation severely restricts the number of condensation reactions having any practical importance. A specific example of an impractical reaction is the formation of poly-1,4-butanediol by reaction of 1,4-bromobutane with the disodium salt of the diol:

It is unlikely that this reaction would give useful yields of any very high polymer because $E2$ elimination, involving the dibromide, would give a double-bond end group and prevent the chain from growing.

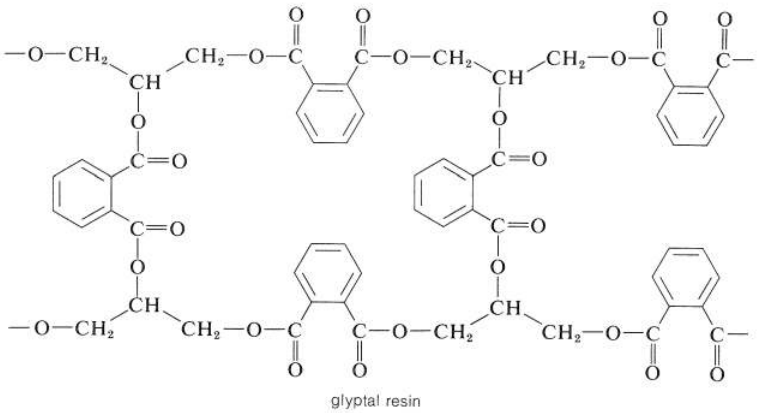
29.6.1: Polyesters

A variety of polyester-condensation polymers are made commercially. Ester interchange (Section 18-7A) appears to be the most useful reaction for preparation of linear polymers:

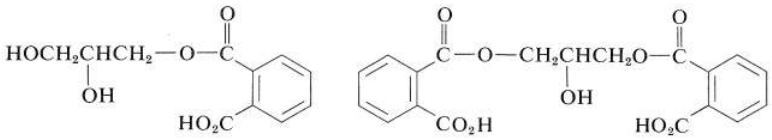




Thermosetting space-network polymers can be prepared through the reaction of polybasic acid anhydrides with polyhydric alcohols. A linear polymer is obtained with a bifunctional anhydride and a bifunctional alcohol, but if either reactant has three or more reactive sites, then formation of a three-dimensional polymer is possible. For example, 2 moles of 1,2,3-propanetriol (glycerol) can react with 3 moles of 1,2-benzenedicarboxylic anhydride (phthalic anhydride) to give a highly cross-linked resin, which usually is called a **glyptal**:

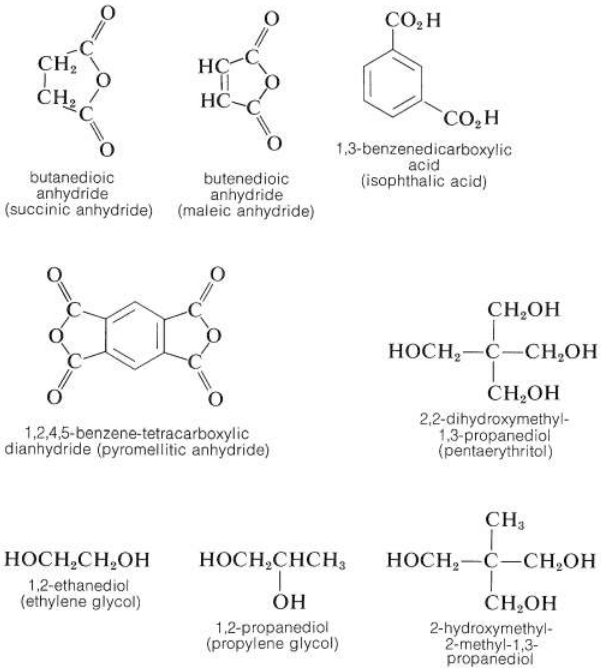


The first stage of the reaction involves preferential esterification of the primary hydroxyl groups with the anhydride to give



In the next stage, in the formation of the resin, direct esterification occurs slowly, particularly at the secondary hydroxyls. Normally, when the resin is used for surface coatings, esterification is carried only to the point where the polymer is not so cross-linked as to be insoluble. It then is applied to the surface in a solvent and baked until esterification is complete. The product is hard, infusible, and insoluble, being cross-linked to the point of being essentially one large molecule.

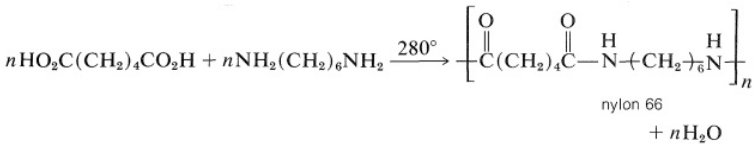
A wide variety of thermosetting polyester (alkyd) resins can be made by similar procedures. The following polybasic acids and anhydrides and polyhydric alcohols are among the other popular ingredients in alkyd formulations:



Articles in which glass fibers are imbedded to improve impact strength often are made by mixing the fibers with an ethenylbenzene (styrene) solution of a linear glycol (usually 1,2-propanediol)-butendioic anhydride polyester and then producing a cross-linked polymer between the styrene and the double bonds in the polyester chains by a peroxide-induced radical polymerization (Section 29-6E).

29.6.2: Nylons

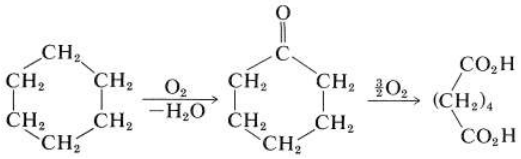
A variety of polyamides can be made by heating diamines with dicarboxylic acids. The most generally useful of these is nylon 66, the designation 66 arising from the fact that it is made from the *six*-carbon diamine, 1,6-hexanediamine, and a *six*-carbon diacid, hexanedioic acid:



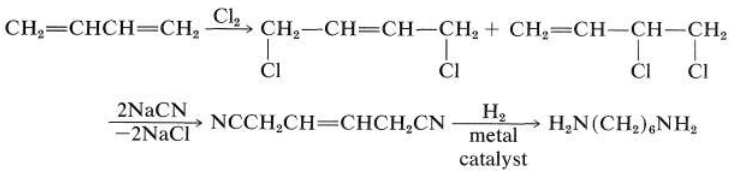
$$n\,HO_2C(CH_2)_4CO_2H + n\,NH_2(CH_2)_6NH_2 \xrightarrow{280^\circ} \text{nylon 66} + n\,H_2O$$

The polymer can be converted into fibers by extruding it above its melting point through spinnerettes, then cooling and drawing the resulting filaments. It also is used to make molded articles. Nylon 66 is exceptionally strong and abrasion resistant.

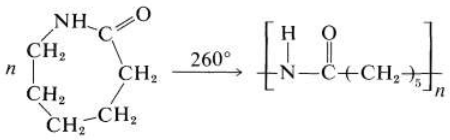
The starting materials for nylon 66 can be made in many ways. Apparently, the best route to hexanedioic acid is by air oxidation of cyclohexane by way of cyclohexanone:



1,6-Hexanediamine can be prepared in many ways. One is from 1,3-butadiene by the following steps:

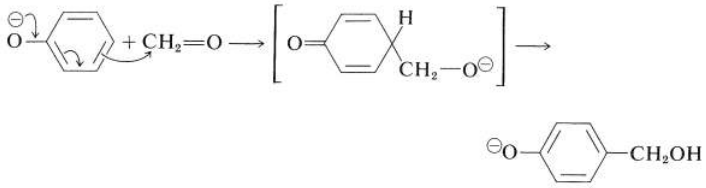


Nylon 6 can be prepared by polymerization of 1-aza-2-cycloheptanone (ε-caprolactam), obtained through the Beckmann rearrangement of cyclohexanone oxime (Section 24-3C):

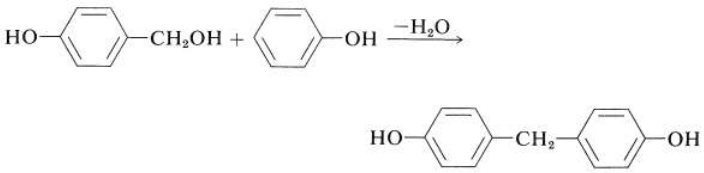


29.6.3: Bakelite Resins

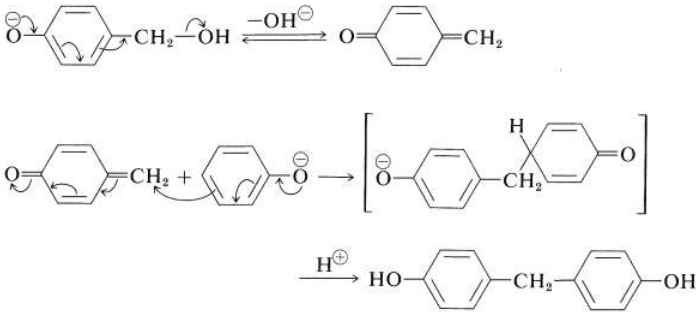
One of the oldest known thermosetting synthetic polymers is made by condensation of phenols with aldehydes using basic catalysts. The resins that are formed are known as **Bakelites**. The initial stage is the base-induced reaction of benzenol and methanal to give a (4-hydroxyphenyl)methanol, and this reaction closely resembles an aldol addition and can take place at either the 2- or the 4-position of the benzene ring:



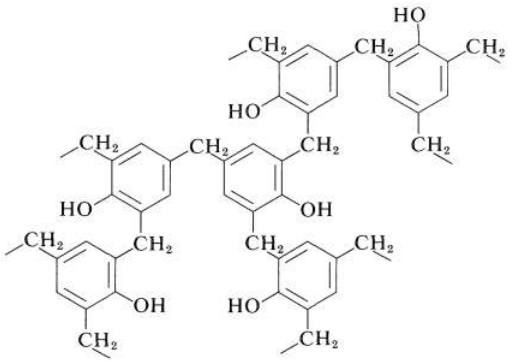
The next step in the condensation is formation of a bis(hydroxyphenyl)methane derivative, which for convenience is here taken to be the 4,4'-isomer:



This reaction is probably a Michael type of addition to a base-induced dehydration product of the (4-hydroxyphenyl)methanol:



Continuation of these reactions at the 2-, 4-, and 6-positions of the benzenol leads to the cross-linked three-dimensional Bakelite resin:

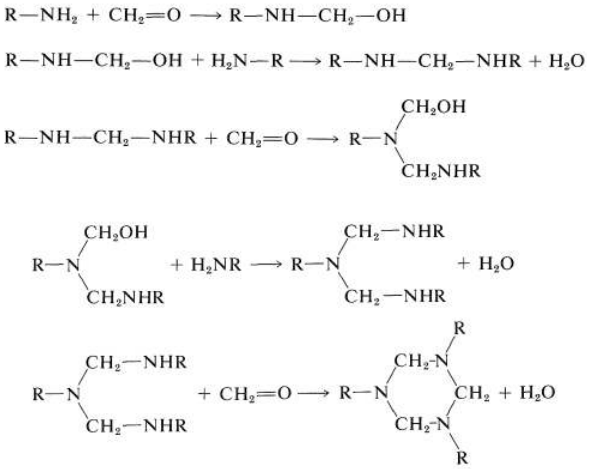


Bakelite resin

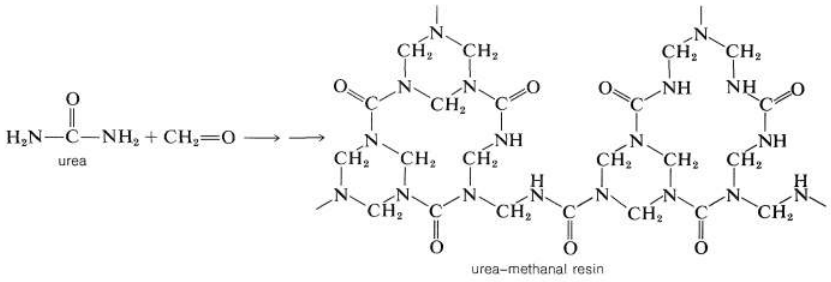
As with the alkyd resins (Section 29-5A), the initial polymerization of a Bakelite resin usually is carried to only a relatively low stage of completion. The low-melting prepolymer (called a **resole**) then is heated in a mold to give the final insoluble, infusible polymer.

29.6.4: Urea-Methanal and Melamine Resins

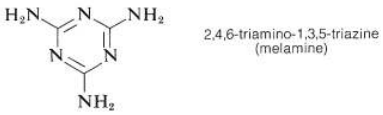
Syntheses of a number of polymers are based on condensation of methanal with amino compounds by mechanisms at least formally analogous to those involved in the preparation of Bakelite resins. The key reactions are:



If the amino compound is urea, these types of reactions will lead to a three-dimensional polymer:

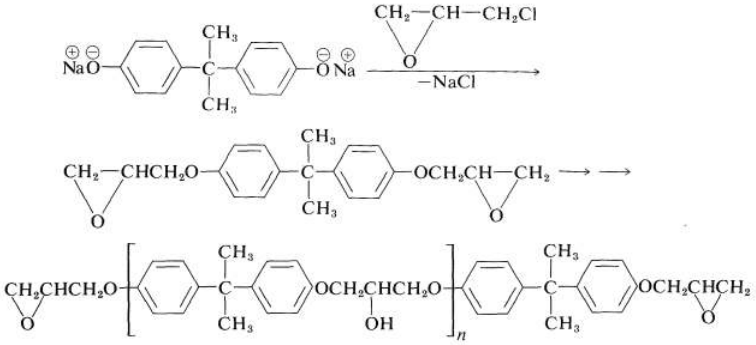


A similar polymer is made from 2,4,6-triamino-1,3,5-triazine (melamine) and methanal. It is used for plastic dishes under the name Melmac.



29.6.5: Epoxy Resins

A very useful group of adhesives and plastics is based on condensation polymers of bisphenol A and chloromethyloxacyclopropane (epichlorohydrin). The first step in the formation of epoxy resins is to form a prepolymer by condensation polymerization of the sodium salt of bisphenol A with the epoxide:



The formation of a prepolymer involves two different kinds of reactions. One is an S_N2-type displacement, and the other is oxide-ring opening of the product by attack of more bisphenol A. Usually, for practical purposes the degree of polymerization n of the prepolymer is small (5 to 12 units).

The epoxy prepolymer can be cured, that is, converted to a three-dimensional network, in several different ways. A trifunctional amine, such as $NH_2CH_2CH_2NHCH_2CH_2NH_2$, can be mixed in and will extend the chain of the polymer and form cross-links by reacting with the oxide rings:

Alternatively, a polybasic acid anhydride can be used to link the chains through combination with secondary alcohol functions and then the oxide rings.

29.6.6: Contributors and Attributions

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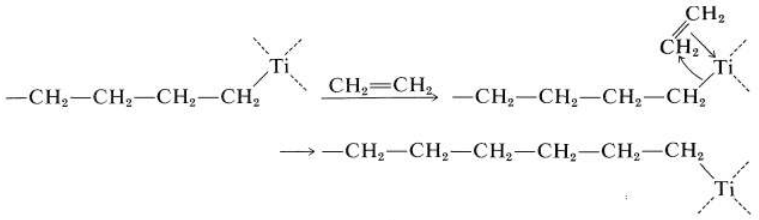
29.7: Addition Polymers

We have discussed the synthesis and properties of a considerable number of addition polymers in this and previous chapters. Our primary concern here will be with some aspects of the mechanism of addition polymerization that influence the character of the polymer formed.

29.7.1: Alkene Polymerization

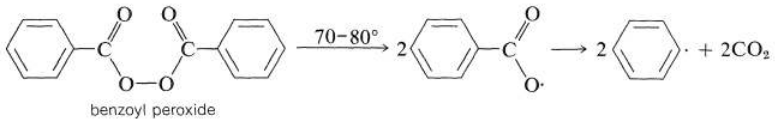
The most important type of addition polymerization is that of alkenes (usually called **vinyl monomers**) such as ethene, propene, ethenylbenzene, and so on. In general, we recognize four basic kinds of mechanisms for polymerization of vinyl monomers - radical, cationic, anionic, and coordination. The elements of the first three of these have been outlined (Section 10-8). The possibility, in fact the reality, of a fourth mechanism is essentially forced on us by the discovery of the Ziegler and other (mostly heterogeneous) catalysts, which apparently do not involve "free" radicals, cations, or anions, and which can and usually do lead to highly stereoregular polymers. With titanium-aluminum Ziegler catalysts, the growing chain has a C–Ti bond; further monomer units then are added to the growing chain by coordination with titanium, followed by an intramolecular rearrangement to give a new growing-chain end and a new vacant site on titanium where a new molecule of monomer can coordinate:



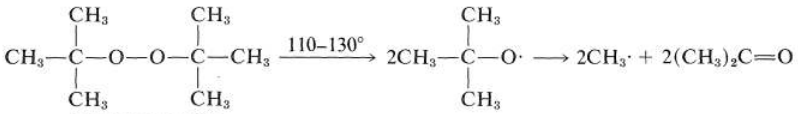
In the coordination of the monomer with the titanium, the metal is probably behaving as an electrophilic agent and the growing-chain end can be thought of as being transferred to the monomer as an anion. Because this mechanism gives no explicit role to the aluminum, it is surely oversimplified. Ziegler catalysts polymerize most monomers of the type $RCH{=}CH_2$, provided the R group is one that does not react with the organometallic compounds present in the catalyst. More reactions of the type that occur in Ziegler polymerizations will be discussed in Chapter 31.

29.7.2: Radical Polymerization

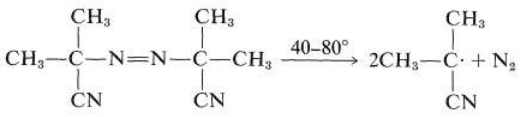
In contrast to coordination polymerizations, formation of vinyl polymers by radical chain mechanisms is reasonably well understood - at least for the kinds of procedures used on the laboratory scale. The first step in the reaction is the production of radicals; this can be achieved in a number of different ways, the most common being the thermal decomposition of an initiator, usually a peroxide or an azo compound:



benzoyl peroxide



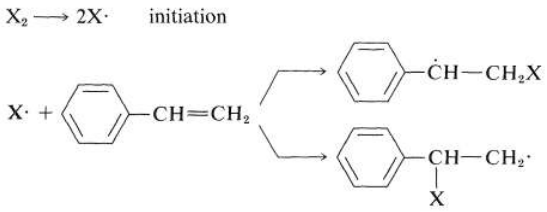
di-*tert*-butyl peroxide



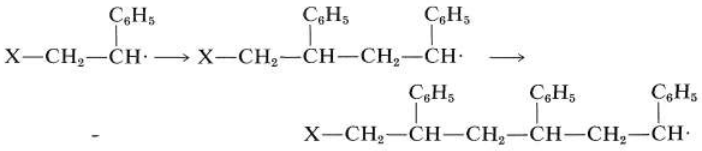
di(1-cyano-1-methylethyl)diazene
(azobisisobutyronitrile)

Many polymerizations are carried out on aqueous emulsions of monomers. For these, water-soluble inorganic peroxides, such as ammonium peroxysulfate, often are employed.

Other ways of obtaining initiator radicals include high-temperature decomposition of the monomer and photochemical processes, often involving a ketone as a photosensitizer. Addition of the initiator radicals to monomer produces a growing-chain radical that combines with successive molecules of monomer until, in some way, the chain is terminated. Addition to an unsymmetrical monomer can occur in two ways. Thus for ethenylbenzenes:

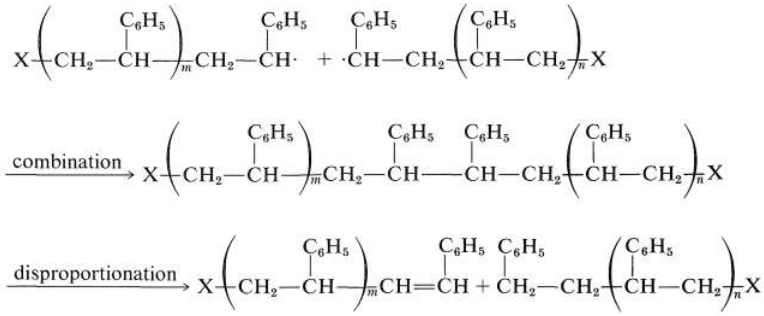


All evidence on addition of radicals to ethenylbenzene indicates that the process by which X· adds to the CH_2 end of the double bond is greatly favored over addition at the CH end. This direction of addition is in accord with the considerable stabilization of the phenylmethyl radicals relative to the alkyl radicals (see Sections 14-3C and 26-4D). Polymerization then will result in the addition of monomer units to give phenyl groups only on alternate carbons (**"head-to-tail"** addition):

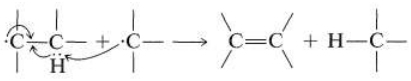


In general, we predict that the direction of addition of an unsymmetrical monomer will be such as to give always the most stable growing-chain radical. Similar considerations were discussed previously (Section 21-11) in respect to how [2 + 2] cycloadditions occur.

The process of addition of monomer units to the growing chain can be interrupted in different ways. One is chain termination by combination or disproportionation of radicals. Explicitly, two growing-chain radicals can combine to form a carbon-carbon bond, or disproportionation can occur with a hydrogen atom being transferred from one chain to the other:



The disproportionation reaction is the radical equivalent of the *E*2 reaction:



Which mode of termination occurs can be determined by measuring the number of initiator fragments per polymer molecule. If there are two initiator fragments in each molecule, termination must have occurred by combination. One initiator fragment per molecule indicates disproportionation. Apparently, ethenylbenzene polymerizations terminate by combination, but with methyl 2-methylpropenoate, both reactions take place, disproportionation being favored.

Another very important way that a growing chain may be terminated is by chain transfer. This stops the chain but starts a new one. Thiols, such as phenylmethanethiol and dodecanethiol, are efficient chain-transferring agents. The reactions involved are as follows

(where M represents monomer and RSH represents the chain-transfer reagent):

$$\mathrm{X{-}M{-}(M)_n{-}M\cdot + RSH \rightarrow X{-}M{-}(M)_n{-}M{-}H + RS\cdot} \quad (29.7.1)$$

$$\mathrm{RS\cdot + M \rightarrow RS{-}M\cdot} \quad (29.7.2)$$

$$\mathrm{RS{-}M\cdot + (n+1)\,M \rightarrow RS{-}M{-}(M)_n{-}M\cdot \ (\text{new growing chain})} \quad (29.7.3)$$

$$\mathrm{RS{-}M{-}(M)_n{-}M\cdot + RSH \rightarrow RS{-}M{-}(M)_n{-}M{-}H + RS\cdot \ \text{etc.}} \quad (29.7.4)$$

Chain transfer reduces the average molecular weight of the polymer without wasting initiator radicals. Dodecanethiol has considerable use in the manufacture of GRS rubber (Section 13-4) as a regulator to hold down the molecular weight in the emulsion polymerization of 1,3-butadiene and ethenylbenzene.

Polymerization inhibitors stop or slow down polymerization by reacting with the initiator or growing-chain radicals. A wide variety of substances can behave as inhibitors: quinones, hydroquinones, aromatic nitro compounds, aromatic amines, and so on. In cases where the inhibitor is a hydrogen donor (symbolized here by InH), then for inhibition to occur, the radical resulting from hydrogen transfer (In·) must be too stable to add to monomer. If it does add to monomer and starts a new chain, chain transfer occurs instead of inhibition. For perfect inhibition, the In· radicals must combine with themselves (or initiator radicals) to give inert products:

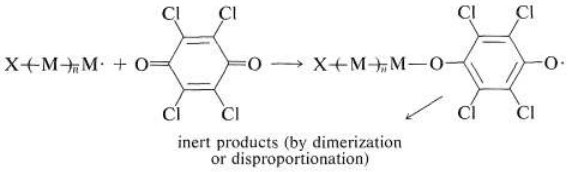
$$\mathrm{X{-}(M)_n{-}M\cdot + InH \rightarrow X{-}(M)_n{-}M{-}H + In\cdot} \quad (29.7.5)$$

$$\mathrm{2In\cdot \rightarrow \text{inert products (inhibition)}} \quad (29.7.6)$$

$$\mathrm{In\cdot + M \rightarrow In{-}M\cdot \ (\text{chain transfer})} \quad (29.7.7)$$

Many compounds are known that fall in the intermediate zone between chain transfer and inhibition reagents.

Some inhibitors such as 2,3,5,6-tetrachloro-1,4-benzenedione (tetrachlorobenzoquinone) act as inhibitors by adding to the growing chain radicals to give radicals too stable to continue the chain:



Again, for inhibition to be effective there must be destruction of the stable radicals by dimerization or disproportionation.

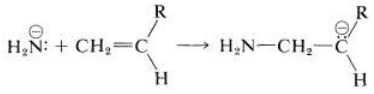
The reactive vinyl monomers usually are stabilized against polymerization, while in storage, by addition of 0.1 to 1% of an inhibitor. 1,4-Benzenediol (hydroquinone), 2,6-di-*tert*-butyl-4-methylbenzenol, and 4-*tert*-butyl-1,2-benzenediol are used for this purpose. These substances are especially effective at scavenging RO· radicals, which are formed by oxidation of the monomer with atmospheric oxygen.

29.7.3: Cationic Polymerization

Polymerization by the cationic mechanism is most important for 2-methylpropene (isobutylene), which does not polymerize well by other methods, and was discussed previously in considerable detail (Section 10-8B).

29.7.4: Anionic Polymerization

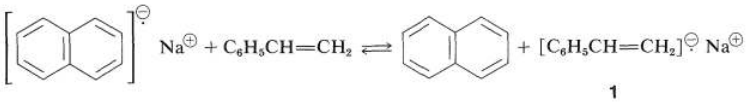
In general, we expect that anionic polymerization will be favorable when the monomer carries substituents that will stabilize the anion formed when a basic initiator such as amide ion adds to the double bond of the monomer:



Cyano and alkoxycarbonyl groups are favorable in this respect and propenenitrile and methyl 2-methylpropenoate can be polymerized with sodium amide in liquid ammonia. Ethenylbenzene and 2-methyl-1,3-butadiene undergo anionic polymerization under the influence of organolithium and organosodium compounds, such as butyllithium and phenylsodium.

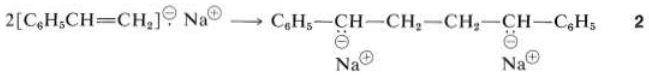
An important development in anionic polymerization has been provided by M. Szwarc's "living polymers". The radical anion, sodium naphthalenide (Section 27-9), transfers an electron reversibly to ethenyl benzene to form a new radical anion, 1, in solvents

such as 1,2-dimethoxyethane or oxacyclopentane:



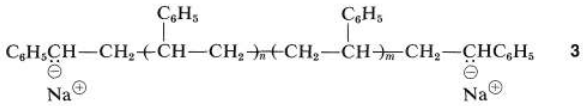
1

Dimerization of the sodium naphthalenide radical anion would result in a loss of aromatic stabilization, but this is not true for 1, which can form a C–C bond and a resonance-stabilized bis-phenylmethyl dianion, 2 (Section 26-4C).



2

The anionic ends of 2 are equivalent and can add ethenylbenzene molecules to form a long-chain polymer with anionic end groups, 3:



3

If moisture and oxygen are rigorously excluded, the anionic groups are stable indefinitely, and if more monomer is added polymerization will continue. Hence the name "living polymer", in contrast to a radical-induced polymerization, which only can be restarted with fresh monomer and fresh initiator, and even then not by growth on the ends of the existing chains.

The beauty of the Szwarc procedure is that the chains can be terminated by hydrolysis, oxidation, carboxylation with CO_2, and so on, to give polymer with the same kind of groups on each end of the chain. Also, it is possible to form chains in which different monomers polymerize well by the anion mechanism and contain no groups or impurities that will destroy the active ends. Thus one can start with ethenylbenzene (S), and when the reaction is complete, add methyl 2-methylpropenoate (M) to obtain a block copolymer of the type

$$M–M–M–M–M–S–S–S–S–S–S–M–M–M–M–M \tag{29.7.8}$$

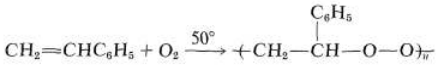
29.7.5: Copolymers

When polymerization occurs in a mixture of monomers there will be competition between the different kinds of monomers to add to the growing chain and produce a copolymer. Such a polymer will be expected to have physical properties quite different from those of a mixture of the separate homopolymers. Many copolymers, such as GRS, ethene-propene, Viton rubbers, and Vinyon plastics are of considerable commercial importance.

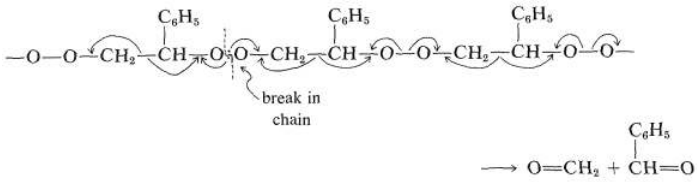
The rates of incorporation of various monomers into growing radical chains have been studied in considerable detail. The rates depend markedly on the nature of the monomer being added and on the character of the radical at the end of the chain. Thus a 1-phenylethyl-type radical on the growing chain reacts about twice as readily with methyl 2-methylpropenoate as it does with ethenylbenzene; a methyl 2-methylpropenoate end shows the reverse behavior, being twice as reactive toward ethylbenzene as toward methyl 2-methylpropenoate. This kind of behavior favors alternation of the monomers in the chain and reaches an extreme in the case of 2-methylpropene and butenedioic anhydride. Neither of these monomers separately will polymerize well with radical initiators. Nonetheless, a mixture polymerizes very well with *perfect alternation* of the monomer units. It is possible that, in this case, a 1:1 complex of the two monomers is what polymerizes.

In general however, in a mixture of two monomers one is considerably more reactive than the other and the propagation reaction tends to favor incorporation of the more reactive monomer, although there usually is some bias toward alternation. Ethenylbenzene and 2-methyl-1,3-butadiene mixtures are almost unique in having a considerable bias toward forming the *separate* homopolymers.

One of the more amazing copolymerizations is that of ethenylbenzene and oxygen gas, which at one atmosphere oxygen pressure gives a peroxide with an average molecular weight of 3000 to 4000 and a composition approaching $C_8H_8O_2$:



When heated rapidly in small portions the product undergoes a mild explosion and gives high yields (80% to 95%) of methanal and benzenecarbaldehyde. The mechanism may be a kind of unzipping process, starting from a break in the chain an spreading toward each end:



Another interesting copolymerization is of ethene and carbon monoxide by the radical mechanism. The polymer contains $-CH_2-CH_2-CO-CH_2-CH_2-$ units, which are broken apart at a $CH_2{:}C{=}O$ bond on absorption of ultraviolet light, thereby giving a polymer that has the possibility of degrading in the environment through the action of sunlight (see Section 28-2A).

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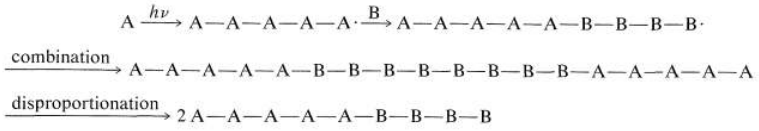
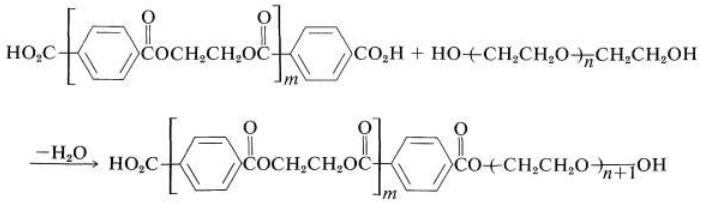
29.8: Block, Graft, and Ladder Polymers

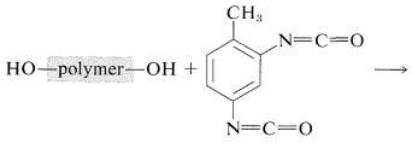
A variation on the usual variety of copolymerization is the preparation of polymer chains made of rather long blocks of different kinds of monomers. A number of ingenious systems have been devised for making such polymers, including the Szwarc method described in Section 29-6D. Another scheme, which will work with monomers that polymerize well by radical chains but not with anion chains, is to irradiate a stream of a particular monomer, flowing through a glass tube, with sufficient light to get polymerization well underway. The stream then is run into a dark flask containing a large excess of a second monomer. The growing chains started in the light-induced polymerization then add the second monomer to give a two-block polymer if termination is by disproportionation, or a three-block polymer if by combination. Thus, with A and B being the two different monomers,

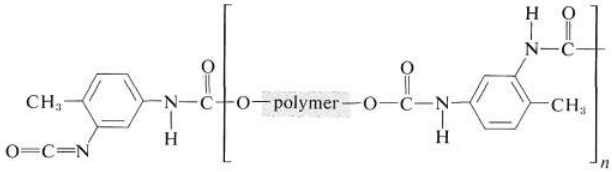


Block polymers also can be made easily by condensation reactions:



The very widely used polyurethane foams can be considered to be either block polymers or copolymers. The essential ingredients are a diisocyanate and a diol. The diisocyanate most used is 2,4-diisocyano-1-methylbenzene, and the diol can be a polyether or a polyester with hydroxyl end groups. The isocyano groups react with the hydroxyl end groups to form initially an addition polymer, which has polycarbamate (polyurethane) links, and isocyano end groups:





A foam is formed by addition of the proper amount of water. The water reacts with the isocyanate end groups to form carbamic acids which decarboxylate to give amine groups:

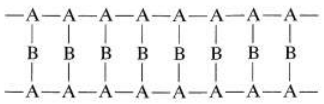
The carbon dioxide evolved is the foaming agent, and the amino groups formed at the same time extend the polymer chains by reacting with the residual isocyano end groups to form urea linkages:

$$R'N{=}C{=}O + RNH_2 \rightarrow R'NHCONHR \qquad (29.8.1)$$

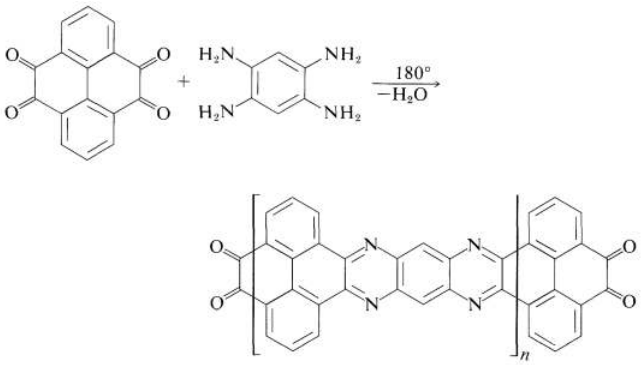
Graft polymers can be made in great profusion by attaching chains of one kind of polymer to the middle of another. A particularly simple but uncontrollable way of doing this is to knock groups off a polymer chain with x-ray or γ radiation in the presence of a monomer. The polymer radicals so produced then can grow side chains made of the new monomer.

A more elegant procedure is to use a photochemical reaction to dissociate groups from the polymer chains and form radicals capable of polymerization with an added monomer.

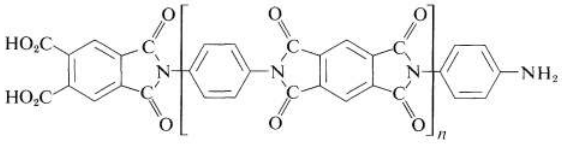
Modern technology has many uses for very strong and very heat-resistant polymers. The logical approach to preparing such polymers is to increase the rigidity of the chains, the strengths of the bonds in the chains, and the intermolecular forces. All of these should be possible if one were to make the polymer molecules in the form of a rigid ribbon rather than a more or less flexible chain. Many so-called **ladder polymers** with basic structures of the following type have been prepared for this purpose:



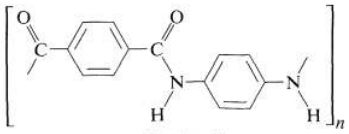
With the proper structures, such polymers can be very rigid and have strong intermolecular interactions. Appropriate syntheses of true ladder polymers in high yield usually employ difficultly obtainable starting materials. An example is



Although there seem to be no true ladder polymers in large-scale commercial production, several **semi-ladder** polymers that have rather rigid structures are employed where high-temperature strength is important. Among these are



aromatic polyimide polymer



aromatic polyamide

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29.9: Naturally Occurring Polymers

There are a number of naturally occurring polymeric substances that have a high degree of technical importance. Some of these, such as natural rubber (Section 13-4), cellulose, and starch (Section 20-7), have regular structures and can be regarded as being made up of single monomer units. Others, such as wool, silk (Section 25-8A), and deoxyribonucleic acid (Section 25-13A) are copolymers. Because we already have considered the chemistry of most of these substances, we shall confine our attention here to wool and collagen, which have properties related to topics discussed previously in this chapter.

29.9.1: Wool

The structure of wool is more complicated than that of silk fibroin (Figure 25-13) because wool, like insulin (Figure 25-8) and lysozyme (Figure 25-15), contains a considerable quantity of cystine, which provides $-S-S-$ (disulfide) cross-links between the peptide chains. These disulfide linkages play an important part in determining the mechanical properties of wool fibers because if the disulfide linkages are reduced, as with ammonium mercaptoethanoate solution, the fibers become much more pliable.

$$\underset{\substack{\text{(wool cystine}\\ \text{cross-link)}}}{RCH_2{-}S{-}S{-}CH_2R} + \underset{\substack{\text{ammonium}\\ \text{mercaptoethanoate}}}{2HSCH_2CO_2^{\ominus}\,NH_4^{\oplus}} \longrightarrow$$

$$RCH_2SH + HSCH_2R + NH_4^{\oplus}\,O_2CCH_2{-}S{-}S{-}CH_2CO_2^{\ominus}\,NH_4^{\oplus}$$

Advantage is taken of this reaction in the curling of hair, the reduction and curling being followed by restoration of the disulfide linkages through treatment with a mild oxidizing agent.

29.9.2: Collagen

The principal protein of skin and connective tissue is called collagen and is primarily constituted of glycine, proline, and hydroxyproline. Collagen is made up of tropocollagen, a substance with very long and thin molecules (14×2900 Å, MW about 300,000). Each tropocollagen molecule consists of three twisted polypeptide strands. When collagen is boiled with water, the strands come apart and the product is ordinary cooking gelatin. Connective tissue and skin are made up of fibrils, 200 Å to 1000 Å wide, which are indicated by x-ray diffraction photographs to be composed of tropocollagen molecules running parallel to the long axis. Electron micrographs show regular bands, 640 Å apart, across the fibrils, and it is believed that these correspond to tropocollagen molecules, all heading in the same direction but regularly staggered by about a fourth of their length (Figure 29-10).

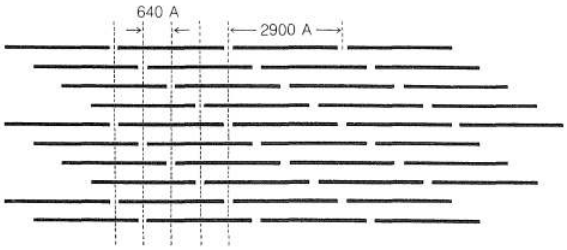

Figure 29-10: Schematic diagram of collagen molecules in a fibril so arranged as to give the 640-Å spacing visible in electron micrographs.

The conversion of collagen fibrils to leather presumably involves formation of cross-links between the tropocollagen molecules. Various substances can be used for the purpose, but chromium salts act particularly rapidly.

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29.10: Preparation of Synthetic Polymers

A prevalent but erroneous notion is that useful polymer, such as those given in Table 29-1, can be, and are, made by slap-dash procedures applied to impure starting materials. This is far from the truth; actually, the monomers used in most large-scale polymerizations are among the purest known organic substances. Furthermore, to obtain uniform commercially useful products, extraordinary care must be used in controlling the polymerization reactions. The reasons are simple - namely, formation of a high-molecular-weight polymer requires a reaction the proceeds in very high yields, and purification of the product by distillation, crystallization, and so on, is difficult, if not impossible. Even a minute contribution of any side reaction that stops polymer chains from growing further will seriously affect the yield of high polymer.

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29.E: Polymers (Exercises)

Exercise 29-1 Write a reasonable mechanism for the thermal *depolymerization* of 1,3-cyclopentadiene tetramer. How could one chemically alter the tetramer to make thermal breakdown more difficult? Explain.

Exercise 29-2 Suppose a bottle of 1,3-cyclopentadiene were held at a temperature at which polymerization is rapid but depolymerization is insignificant. Would the polymerization result in conversion of all the 1,3-cyclopentadiene into essentially one gigantic molecule? Why or why not? How would you carry on the polymerization so as to favor formation of polymer molecules with high molecular weights?

Exercise 29-3* Calculate a number-average and a weight-average molecular weight for a low-molecular-weight sample of poly-1,3-cyclopentadiene having the following composition:

n	Weight %	n	Weight %
2	30	8	4
3	20	9	3
4	15	10	2
5	11	11	1
6	8	≥12	~0
7	6		

Under what circumstances would you expect $\overline{M_n}$ to be equal to $\overline{M_w}$? Suppose one were to determine a molecular weight for a sample of poly-1,3-cyclopentadiene by quantitative hydrogenation of the terminal double bonds. Would the resulting molecular weight be equal to $\overline{M_n}$, $\overline{M_w}$, or neither of these?

Exercise 29-4 Show how each of the following polymer structures may be obtained from suitable monomers either by addition or condensation. More than one step may be required.

a. $-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-$ (three ways)

b. $-N(CH_3)-CH_2-CH_2-N(CH_3)-CH_2-$CH-2-N$(CH_3)-CH_2-CH_2-$

c. $-CH(CH_3)-CH(CH_3)-CH(CH_3)-CH(CH_3)-CH(CH_3)-CH(CH_3)-$

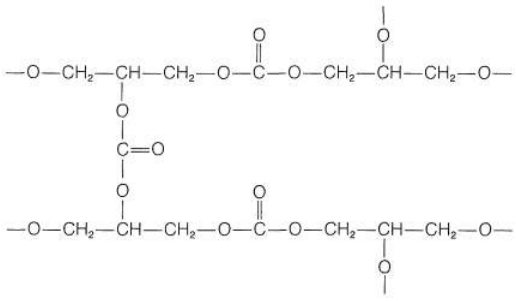
d. $-O-CH_2-CH_2-C(=O)-O-CH_2-CH_2-C(=O)-O-CH_2-CH_2-C(=O)-$

e. $-CH_2-CH(OCOCH_3)-CH_2-CH(OCOCH_3)-CH_2-CH(OCOCH_3)-$

f. $-CH_2-CH(OH)-CH_2-CH(OH)-CH_2-CH(OH)-$

g. $-CH_2-C_6H_4-CH_2-CH_2-C_6H_4-CH_2-CH_2-C_6H_4-CH_2-$

h.



i. $-CH(CCl_3)-O-CH(CCl_3)-O-CH(CCl_3)-O-CH(CCl_3)-O-$

Exercise 29-5 High-pressure polyethene (Section 10-8C) differs from polyethene made with the aid of Ziegler catalysts (Section 10-8D) in having a lower density and lower T_m. It has been suggested that this is due to branches in the chains of the high-pressure material. Explain how such branches may arise in the polymerization process and how they would affect the density and T_m.

Exercise 29-6 Radical-induced chlorination of polyethene in the presence of sulfur dioxide produces a polymer with many chlorine and a few sulfonyl chloride $(-SO_2Cl)$ groups, substituted more or less randomly along the chains. Write suitable mechanisms for these substitution reactions. What kind of physical properties would you expect the chlorosulfonated polymer to have if substitution

is carried to the point of having one substituent group to every 25 to 100 CH_2 groups? How may this polymer be cross-linked? (A useful product of this general type is marketed under the name Hypalon.)

Exercise 29-7 When polyethene (and other polymers) are irradiated with x rays, cross-links are formed between the chains. What changes in physical properties would you expect to accompany such cross-linking? Would the polyethene become more flexible? Explain.

Suppose polyethene were cross-linked by irradiation at a temperature above T_m. What would happen if it were then cooled?

Exercise 29-8 Answer the following questions in as much detail as you can, showing your reasoning:

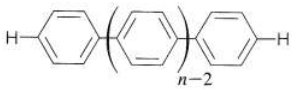
a. Why is atactic polymethyl 2-methylpropenoate not an elastomer?

b. How may one make a polyamide that is an elastomer?

c. What kind of physical properties are to be expected for *isotactic* polyethenylbenzene (polystyrene)?

d. What would you expect to happen if a piece of high-molecular-weight polypropenoic acid, $-(CH_2-CH(CO_2H))_n-$, were placed in a solution of sodium hydroxide?

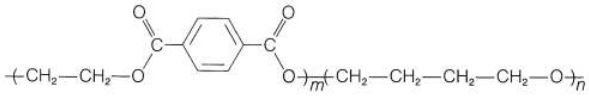
e. What kind of properties would you expect for high-molecular-weight "poly-*para*-phenylene"?



"poly-*para*-phenylene"

f. Are the properties, listed in Table 29-1, of polychloroprene produced by radical polymerization of 2-chloro-1,3-butadiene such as to make it likely that *trans*-1,4-addition occurs exclusively?

g. A very useful oil-resistant commercial polymer called "Hytrel" is a block copolymer, having repeating units of the following basic structure:



The length of the blocks is determined by m and n, and the overall molecular weight by $m + n$. With appropriate average values, the material is a "thermoplastic elastomer", which means that it is elastic and can be stretched without plastic flow at ordinary temperatures but when heated becomes fluid enough to be easily molded. What physical properties would you expect for polymers of this type having $m + n$ large, but with $m = 1$, $n = 200$; $m = 30$, $n = 200$; $m = 200$, $n = 200$; $m = 200$, $n = 30$; and $m = 200$, $n = 1$? Which composition would you expect to correspond to Hytrel?

h. Millions of light, strong soft-drink bottles were made from a recyclable 75% ethenylbenzene-25% propenenitrile copolymer. The mechanical strength of the polymer is increased significantly in the operation of blowing a polymer bubble to fit the mold. Why should this be so?

Exercise 29-9 The material popularly known as "Silly Putty" is a polymer having an $-O-Si(R)_2-O-Si(R)_2-O-$ backbone. It is elastic in that it bounces and snaps back when given a quick jerk, but it rapidly loses any shape it is given when allowed to stand. Which of the polymers listed in Table 29-1 is likely to be the best candidate to have anything like similar properties? Explain. What changes would you expect to take place in the properties of Silly Putty as a function of time if it were irradiated with x rays (see Exercise 29-7)?

Exercise 29-10* Suppose one had a sample of completely isotactic polypropene prepared from nonoptically active substances with the structure $H-[CH(CH_3)-CH_2]_{499}-C(CH_3)=CH_2$.

a. Would the material theoretically cause a net rotation of the plane of polarized light? Explain.

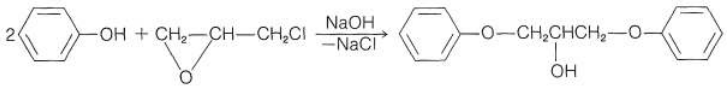
b. Suppose one could make this polypropene with all *D* orientations of the CH_3- groups. Would the resulting material have an optical rotation theoretically? Practically?

Exercise 29-11 What kind of polymer would you expect to be formed if 4-methylbenzenol were used in place of benzenol in the Bakelite process?

Exercise 29-12 Write a reasonable mechanism for the base-catalyzed condensation of urea with methanal to give bis-methyleneurea, $NH_2CONHC_2NHCONH_2$.

Exercise 29-13 Show the reaction whereby butenedioic anhydride would be able to cross-link an epoxy prepolymer with $n = 1$.

Exercise 29-14 The terminal carbon of the epoxide ring of epichlorohydrin generally is quite a bit more reactive toward nucleophilic agents than is the carbon bonded to chlorine. Work out a mechanism for the following reaction that takes account of this fact (review Section 15-11D):



Exercise 29-15 Polymerization of methyl 2-methylpropenoate with benzoyl peroxide labeled with ^{14}C in the aromatic ring gives a polymer from which only 57% of the ^{14}C can be removed by vigorous alkaline hydrolysis. Correlation of the ^{14}C content of the original polymer with its molecular weight shows that, on the average, there are 1.27 initiator fragments per polymer molecule. Write mechanism(s) for this polymerization that are in accord with the experimental data, and calculate the ratios of the different initiation and termination reactions.

Exercise 29-16 The radical polymerization of ethenylbenzene gives atactic polymer. Explain what this means in terms of the mode of addition of monomer units to the growing-chain radical.

Exercise 29-17 Polyvinyl alcohol prepared by hydrolysis of polyethenyl ethanoate (polyvinyl acetate; Table 29-1) does not react with measurable amounts of periodic acid or lead tetraethanoate (Sections 16-9A and 20-4A). However, periodic acid or lead tetraethanoate treatment of the polymer does decrease the number-average molecular weight, for a typical sample from 25,000 to 5000. Explain what these results mean in terms of the polymer structures and the mechanism of the polymerization.

Exercise 29-18 Treatment of polychloroethene with zinc in alcohol removed 85% of the chlorine as zinc chloride without formation of unsaturated polymer. What does this result indicate about the polymer structure? Would you have expected that all of the chlorine would be removed by the zinc treatment? Explain. (See Section 14-10C.)

Exercise 29-19 Ozonizations of natural rubber and gutta-percha, which are both poly-2-methyl-1,3-butadienes, give high yields of $CH_3COCH_2CH_2CHO$ and no $CH_3COCH_2CH_2COCH_3$. What are the structures of these polymers?

Exercise 29-20* What conditions would you choose for producing the highest possible yield of (phenylmethylthio)phenylethane by radical-induced addition of phenylmethanethiol to ethenylbenzene? What structure would you expect the product to have? Explain.

Exercise 29-21* The rate of radical polymerization of ethenylbenzene, induced by benzoyl peroxide in mixtures of tetrachloromethane and benzene, is independent of the concentration of tetrachloromethane. At high concentrations of tetrachloromethane, the average molecular weight of the polymer is greatly reduced and chlorine is found in the polymer. Explain.

Exercise 29-22* 2-Propenyl ethanoate with radical initiators gives a rather short-chain polymer in a relatively slow polymerization. Deuterated 2-propenyl ethanoate of the structure $CH_2{=}CHCD_2O_2CCH_3$. Gives higher-molecular-weight polymer at a faster rate. Explain.

Exercise 29-23 Devise a synthesis of polyethenamine, remembering that ethenamine (vinylamine) itself is unstable.

Exercise 29-24* Write an equation for the dimerization of sodium naphthalenide analogous to dimerization of the ethenylbenzene radical anion 1 to give 2. Show why you may expect that this dimerization would not be as energetically favorable as the dimerization of 1.

Exercise 29-25* How could you use the living-polymer technique to synthesize $HOCH_2CH_2[(C_6H_5)CHCH_2]_2{-}[CH_2CH(C_6H_5)]_2{-}CH_2CH_2OH$?

Exercise 29-26* What physical properties would you expect for a 2-methylpropene-butenedioic anhydride copolymer? (Review Section 29-3.)

Exercise 29-27* What would be the expected structure of a copolymer of ethenylbenzene and propene made by a Ziegler catalyst if the growing chain is transferred to the monomer as a radical? As an anion?

Exercise 29-28* Devise a synthesis of a block polymer with poly-1,2-ethanediol and nylon 66 segments. What kind of physical properties would you expect such a polymer to have?

Exercise 29-29* Suppose one were to synthesize two block copolymers with the following structures:

$$\mathrm{H{-}[CH(C_6H_5){-}CH_2]_{10}{-}(CH_2CH{=}\underset{\text{cis}}{}CHCH_2)_{100}{-}[CH_2{-}(C_6H_5)CH]_{10}{-}H} \tag{29.E.1}$$

$$\mathrm{H{-}(CH_2CH{=}\underset{\text{cis}}{}CHCH_2)_{50}{-}[CH(C_6H_5){-}CH_2]_{20}{-}(CH_2CH{=}\underset{\text{cis}}{}CH{-}CH_2)_{50}{-}H} \tag{29.E.2}$$

What difference in physical properties would you expect for these two materials? (Review Sections 29-3 and 13-4.)

Exercise 29-30* What would you expect for the physical and chemical properties of the following ladder polymer?

Exercise 29-31* Fibers made from aromatic polyamides such as from 1,4-benzenedicarboxylic acid and 1,4-benzenediamine are at least as strong as steel wire with the same ratio of weight to length. What are the structural features of this kind of polyamide that contribute to the strength?

Exercise 29-32 The economically important chain reaction, wool + moths → holes + more moths, has, as a key step, scission of the disulfide linkages of cystine in the polypeptide chains by the digestive enzymes of the moth larva. Devise a method of mothproofing wool that would involve chemically altering the disulfide linkages in such a way as to make it unlikely that they would be attacked by the moth enzymes.

29.E.1: Contributors

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CHAPTER OVERVIEW

30: Natural Products and Biosynthesis

For an organic chemist, a natural product is one that is produced by a living organism. This definition encompasses many compounds already discussed, such as carbohydrates, proteins, lipids, and nucleic acids, all of which play an important and primary role in metabolic reactions. However, there are other organic compounds produced naturally, some of extraordinary complexity, which are not primary metabolites. Organic chemists always have been fascinated by the great diversity of these substances and particularly those that can be isolated from plants or are produced by microorganisms. Many of these compounds, such as the alkaloids and mold metabolites, do not seem to have any obvious metabolic or evolutionary function. In fact, some compounds may be formed as the result of a "metabolic accident" or are by-products of the synthesis machinery of the cellular enzymes. Regardless of their utility to the parent organism, their value to man as drugs, herbs, flavorings, poisons, dyes, and so on is undisputed.

30.1: Classification of Natural Products

30.2: Approaches to the Study of Natural Products

30.3: Isoprenoid Compounds

30.4: Steroids

30.5: Biosynthesis

30.6: Some Nitrogen-Containing Natural Products

30.7: Prostaglandins

30.E: Natural Products and Biosynthesis (Exercises)

30.1: Contributors and Attributions

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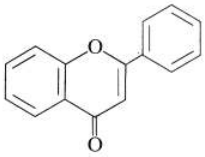
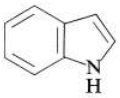
30.1: Classification of Natural Products

There are several ways to categorize natural products. They may be grouped according to a recurring structural feature. *Flavonoid compounds*, for example, are oxygenated derivatives of the aromatic ring structure 1; likewise, alkaloids having an indole ring, 2 are called *indole alkaloids*:



1, flavone



2, indole

Or they may be grouped according to the genus of their plant source (morphine and codeine, Section 23-2, are examples of *opium alkaloids*), or by their physiological effects (antimicrobials, antibiotics, analgesics), or by similarities in the route by which they are synthesized by the organism (biosynthesis). The structural and biosynthetic classifications make the most sense to the chemist and is the organization chosen here.

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30.2: Approaches to the Study of Natural Products

Chemists have a compelling curiosity to discover what compounds Nature provides, but to obtain this information it is necessary to isolate compounds from their natural source and to determine their structures. This is seldom an easy task, especially when the compound of interest is present at low concentrations such that enormous quantities of source material are required to extract even a few micrograms of the desired product. In this circumstance a high degree of skill and technology is required in both the isolation procedures and the subsequent investigations to establish the chemical structure.

A second objective is the total synthesis of the compound from smaller molecules. Indeed, in the classical approach to structure determination, a structure was assigned to a natural product through chemical degradation studies to smaller, identifiable molecules. However, the assigned structure was not regarded as fully confirmed until the compound was synthesized and shown to be identical in all respects (composition, configuration, conformation) with the natural compound. This approach persists, although the enormous impact of modern methods of separation and spectroscopic analysis has made it possible to determine structure beyond a reasonable doubt in almost all cases without recourse to synthesis.

Nevertheless, the synthesis of natural products continues to be important. It provides new methodology, new reactions and techniques. It also provides alternative sources of natural compounds and offers routes to related but unnatural analogs. In the case of a useful drug, the synthetic objective is to find a related structure that is more potent at lower dosages with fewer side effects than the natural compound.

Yet another area of investigation in natural-product chemistry concerns the way in which the compound is synthesized biologically - that is, the *biosynthesis* of the compound. These are experimentally difficult studies and involve first identifying the starting materials (biological precursors). This can be done by feeding the organism isotopically labeled compounds suspected of being precursors and then determining where and how much of the labeled material is incorporated into the natural product. Ultimately, each step in the synthesis should be elucidated and each enzyme isolated and the entire sequence reconstructed in a cell-free system. From experiments of this type we now have a rather good understanding of the biosynthesis of fatty acids, terpenes, and steroids.

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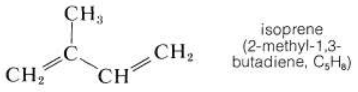
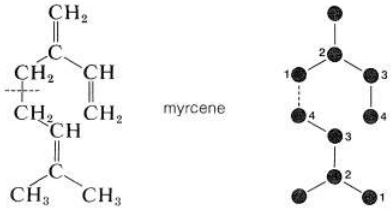
30.3: Isoprenoid Compounds

The odor of a freshly crushed mint leaf, like many plant odors, is due to the presence in the plant of volatile C_{10} and C_{15} compounds, which are called **terpenes**. Isolation of these substances from the various parts of plants, even from the wood in some cases, by steam distillation or ether extraction gives what are known as **essential oils**. These are widely used in perfumery, as food flavorings and medicines, and as solvents. Among the typical essential oils are those obtained from cloves, roses, lavender, citronella, eucalyptus, peppermint, camphor, sandalwood, cedar, and turpentine. Such substances are of interest to use here because, as was pointed out by Wallach in 1887 and reemphasized by Ruzicka in 1935, the components of the essential oils can be regarded as derived from isoprene:



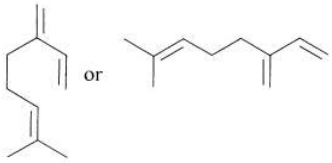
Not only are the carbon skeletons of these substances divisible into isoprene units, but the terpene hydrocarbons are usually exact multiples of C_5H_8. An example is myrcene $(C_{10}H_{16})$, which occurs in the oils of bay and verbena and has a carbon skeleton divisible into two **isoprene units**.



The connection between the isoprene units in myrcene is between the 1- and 4-positions; this turns out to be more common than 1,1 and 4,4 linkages.

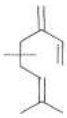
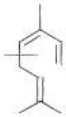
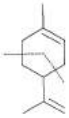
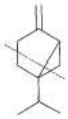
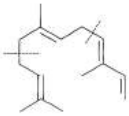
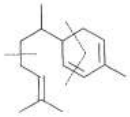
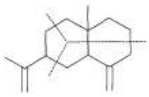
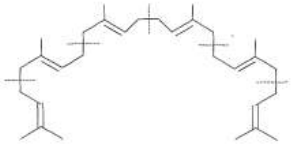
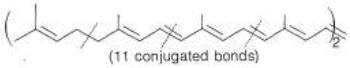
30.3.1: Terpene Hydrocarbons

A wide variety of cyclic terpene hydrocarbons are known and, as multiples of C_5H_8, these have fewer double bonds than the open-chain terpenes. Because it is time consuming to show all the carbon and hydrogen atoms of such substances, the structures often are drawn in a convenient shorthand notation wherein the carbon-carbon bonds are represented by lines, carbon atoms being understood at the junctions or the ends of lines. By this notation, myrcene can be represented by formulas such as the following:



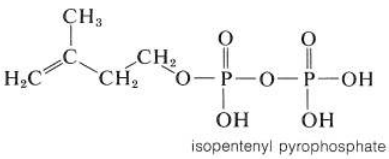
The left semicyclic structural formula is useful to show relationships with the open-chain (acyclic) and cyclic terpene hydrocarbons.

Table 30-1: *Some Isoprenoid Hydrocarbons*[a]

Type	Name and origin	Structure	Name and origin	Structure
terpene, $C_{10}H_{16}$	**myrcene**; bayberry wax; oils of bay, verbena		**ocimene**; oil of *Ocimum basilicum*	
	limonene; oils of lemon, orange		**sabinene**; oil of savin	
	α-pinene; oil of turpentine		**camphene**; oil of ginger, citronella	
sesqui-terpene, $C_{15}H_{24}$	**α-farnesene**; oil of citronella		**zingiberene**; oil of ginger	
	β-selinene; oil of celery		**caryophyllene**; oil of cloves	
triterpene, $C_{30}H_{50}$	**squalene**; shark-liver oil			
tetraterpene, $C_{40}H_{56}$	**lycopene**; plant pigment; tomatoes, pyracantha	 (11 conjugated bonds)		

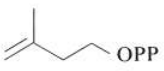
[a]Also see β-carotene (Section 2-1) and natural rubber (Section 13-4).

A number of terpene hydrocarbons are shown in Table 30-1. The designation "terpene" is by custom specifically reserved for the C_{10} compounds, the C_{15} compounds being known as sesquiterpenes, the C_{20} as *diterpenes*, C_{30} as *triterpenes*, and so on. It should be apparent from Table 30-1 that the C_{10} and C_{15} compounds, which are the important components of essential oils, in reality are members of a much larger class of substances with carbon skeletons made up of isoprene units and occurring in both plants *and* animals. It is common to refer to all members of the group as isoprenoid compounds. The so-called *isoprene rule*, which correlates the structures of these substances, speaks for their synthesis in living systems from some common precursor with five carbon atoms. We can characterize the isoprenoid compounds as being *biogenetically* related. Isoprene itself does not occur naturally and appears to play no part in biosynthesis. The actual five-carbon intermediate appears to be isopentenyl pyrophosphate, and the role of this substance in biosynthesis will be discussed later:



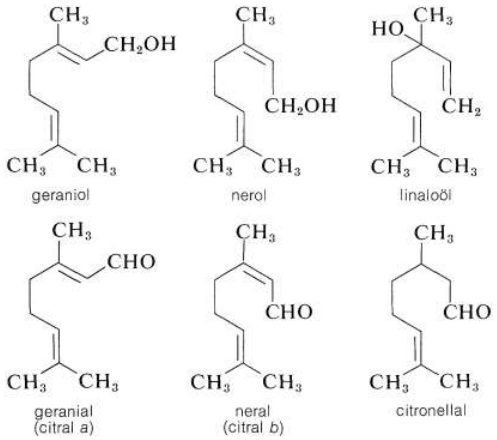
isopentenyl pyrophosphate

or



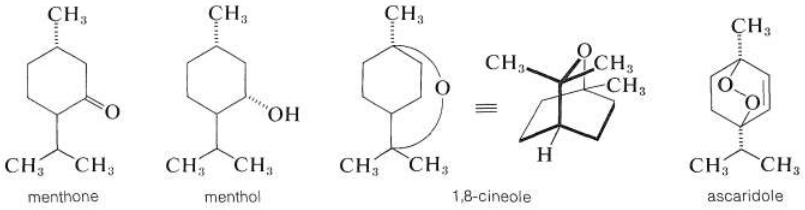
30.3.2: Oxygenated Isoprenoid Compounds

A great profusion of oxygen-containing isoprenoid compounds are known. Of particular importance in the acyclic series are the alcohols geraniol, nerol, and linaloöl, and the aldehydes geranial (citral *a*), neral (citral *b*), and citronellal:

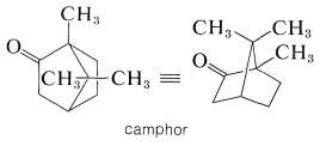


The alcohols occur in oil of rose and other flower essences. They have geranium or rose odors and are important perfume ingredients. The aldehydes have much stronger citruslike odors and occur as major or minor constituents in many essential oils, such as oil of citronella, oil of lemon, and so on.

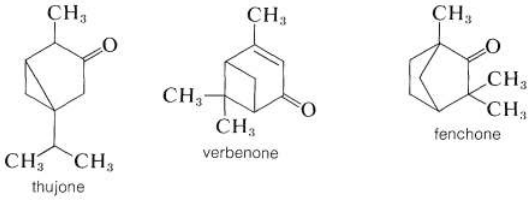
Monocyclic and bicyclic oxygenated terpenes include some familiar and interesting substances such as menthone and menthol from peppermint oil, 1,8-cineole from eucalyptus, and ascaridole, which is a naturally occurring peroxide from chenopodium oil:



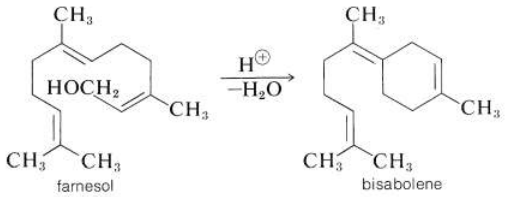
Camphor is a particularly well-known bicyclic terpene ketone, which has uses in medicine and as a plasticizer for nitrocellulose (Section 20-7):



For many years, the principal source of camphor was the Formosan camphor tree. It now can be synthesized on a large scale from α-pinene. Some of the other types of naturally occurring bicyclic ketones follow:

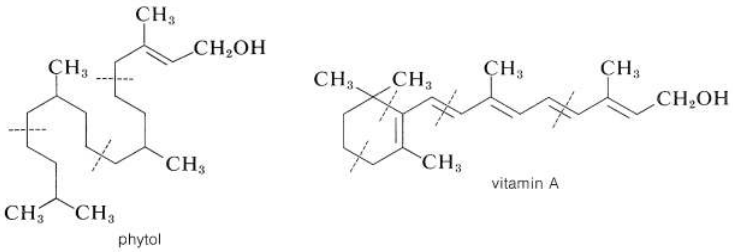


Higher oxygenated terpenes include the sesquiterpene alcohol, farnesol, which has a lily-of-the-valley odor and occurs in ambrette-seed oil. On acid dehydration it gives α-farnesene (Table 30-1) under some conditions, and bisabolene (a component of oil of bergamot) under others:



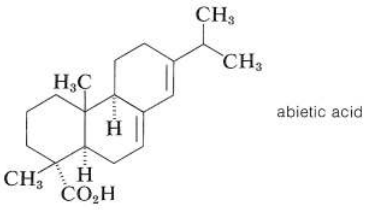
As we shall see, cyclization reactions of this general type seem to be important in terpene biosynthesis. The 6,7-*trans*-farnesol has been shown to have hormone action in some insects. It acts to regulate the changes from caterpillar to cocoon to moth.

Two important *diterpene alcohols* are vitamin A (Section 28-7) and phytol, which occurs as an ester of the propanoic acid side-chain of chlorophyll (Figure 20-6):



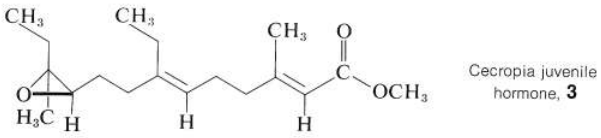
The phytyl group appears also as a side chain in vitamin K_1 (Section 26-2B) and β-Carotene (Section 2-1) has vitamin A activity and apparently is oxidized in the body at the central double bond to give one mole of vitamin A.

The *diterpene acid*, abietic acid, is a major constituent of rosin, which is obtained as a nonvolatile residue in the manufacture of turpentine by steam distillation of pine oleoresin or shredded pine stumps. Abietic acid is used extensively in varnishes and as its sodium salt in laundry soaps.



30.3.3: Isoprenoid Compounds of Animal Origin

A number of compounds important to animal physiology have been identified as isoprenoid compounds. Notable examples are vitamin A, retinal (Section 28-7), and squalene (Table 30-1). Also, terpene hydrocarbons and oxygenated terpenes have been isolated from insects and, like farnesol, show hormonal and pheromonal activity. As one example, the juvenile hormone isolated from *Cecropia* silk moths has the structure shown in 3:



The structure was established by an impressive combination of chemical, spectroscopic, and synthetic methods with about 200 μg of pure compound isolated from the abdomens of a myriad of male moths.[1]

Juvenile hormone plays a critical role in maintaining the juvenile or larval stage of insects, and if its secretion is not controlled, normal development to the adult stage is prevented. Use of hormones or substances with hormonelike activity to control insect populations is an area of intense research interest and activity.[2] The secretion of juvenile hormone is controlled by other hormones originating in the brain (brain hormone) and the phthoracic gland (molting hormone, ecdysone; see Table 30-2).

https://chem.libretexts.org/@go/page/22608

30.3.4: References

- [1]A summary of the structure proof is reported by H. Röller, K. H. Dahn, C. C. Sweely, and B. M. Trost, *Angew. Chem.* (Intl. Ed.) **6**, 179 (1967); B. M. Trost, *Accts. Chem. Res.* **3**, 120 (1970).
- [2]C. E. Berkoff, *J. Chem. Educ*. **48**, 577 (1971).

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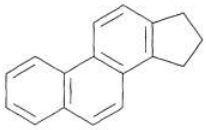
30.4: Steroids

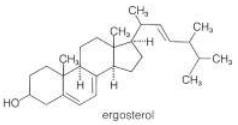
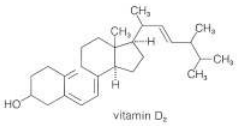
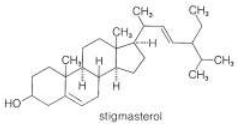
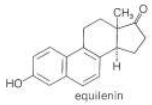
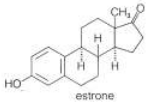
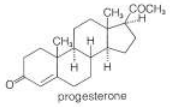
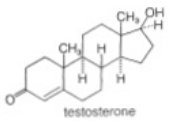
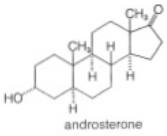
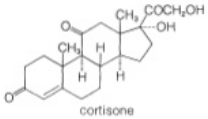
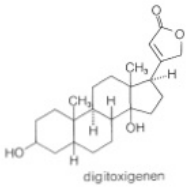
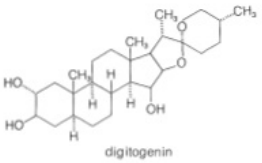
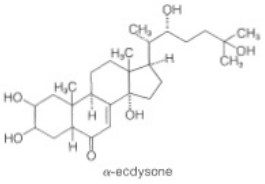
The term **steroid** applies to compounds containing hydrogenated cyclopentanophenanthrene carbon skeleton:



cyclopentanophenanthrene

Most steroids are alcohols, and accordingly are named as **sterols**. Important examples include cholesterol, ergosterol, estradiol, stigmasterol, and other representative sterols given in Table 30-2. As you can see from their structures, most possess the same ring skeleton but vary considerably in their peripheral structural features, stereochemistry, and in the degree of ring unsaturation.

Table 30-2: *Representative Steroids*

Structure and name[a]	Occurrence and physiological properties	Structure and name[a]	Occurrence and physiological properties
 ergosterol	sterol of yeast, gives vitamin D_2 when irradiated (see Section 28-2F)	 vitamin D_2	antirachitic factor, formed by ultraviolet irradiation of ergosterol (Section 28-2F)
 stigmasterol	plant sterol, soybean oil	 equilenin	female sex hormone of horse, regulates sexual cycle
 estrone	human estrogenic hormone, the corresponding C17 alcohol (OH *trans* to the C13 methyl) is even more active (estradiol)	 progesterone	human pregnancy hormone, secreted by the corpus luteum
 testosterone	male sex hormone, regulates development of reproductive organs and secondary sex characteristics	 androsterone	androgenic hormone of less potency than testosterone
 cortisone	hormone of adrenal cortex, once used for treatment of arthritis, 6- and 9-fluoro derivatives have higher activity and fewer side effects	 digitoxigenen	as a complex glycoside at the 3-hydroxyl in digitalis plants, potent cardiac poison, used in small doses to regulate heart action
 digitogenin	a saponin, occurs as a complex glycoside (glucose, galactose, and xylose) in digitalis plants[b]	 α-ecdysone	molting hormone of *Cecropia silk moth*

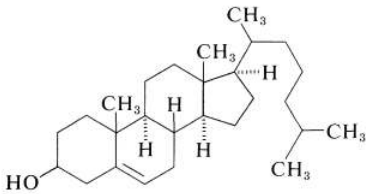
[a]The stereochemistry of the B/C and C/D ring junctions are as in cholesterol and the cholic acids; A/B stereochemistry is indicated where necessary. See p. 1474 for numbering system used for steroids.

[b]Digitogenin as the glycoside, digitonin, has the remarkable property of forming insoluble precipitates with the sterols having the 3-hydroxyl equatorial, but not those in which the hydroxyl is axial.

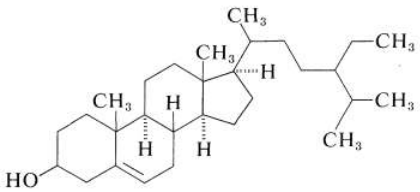
Sterols are widely distributed in both plants and animals. Many are of vital importance to animal physiology, such as cholesterol, the bile acids, vitamin D, sex hormones, and corticoid hormones. Many have value as medicinals, such as the cardiac glycosides, hormones, and steroidal antibiotics. The occurrence and physiological properties of representative steroids are included in Table 30-2.

30.4.1: Cholesterol

Cholesterol is an unsaturated alcohol of formula $C_{27}H_{45}OH$ that has long been known to be the principal constituent of human gall stones and has received notoriety in recent years for its connection with circulatory ailments, particularly hardening of the arteries. Cholesterol, either free or in the form of esters, actually is widely distributed in the body, particularly in nerve and brain tissue, of which it makes up about one sixth of the dry weight. The function of cholesterol in the body is not understood; experiments with labeled cholesterol indicate that cholesterol in nerve and brain tissue is not rapidly equilibrated with cholesterol administered in the diet. Two things are clear: Cholesterol is synthesized in the body and its metabolism is regulated by a highly specific set of enzymes. The high specificity of these enzymes may be judged from the fact that the very closely related plant sterols, such as sitosterol, are not metabolized by the higher animals, even though they have the same stereochemical configuration of all the groups in the ring and differ in structure only near the end of the side chain:

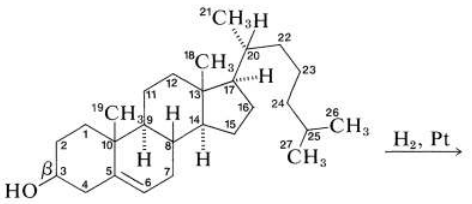


cholesterol

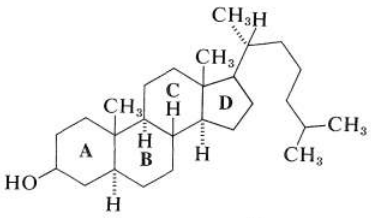


sitosterol

The accepted numbering system for the steroid nucleus and attached side chains is illustrated for cholesterol in 4. The methyl groups at the junction of rings A and B (C_{10}) and rings C and D (C_{13}) are called *angular* methyls. To avoid misinterpretation of structure and stereochemistry, methyl groups and hydrogens at ring junctions should be explicitly written as CH_3 or H. The stereochemistry is specified by a solid line if the atom or group is *above* the ring plane (β), and by a dashed line if *below* the ring plane (α). Thus compound 5, 5α-cholestan-3β-ol, which is obtained by the reduction of cholesterol, implies in the name that the hydroxyl at C_3 is above the ring plane and that the hydrogen at C_5 is below the ring plane (i.e., the A/B rings, have the *trans*-decalin stereochemistry; Section 12-9).



cholesterol, **4**



5α-cholestan-3β-ol, **5**

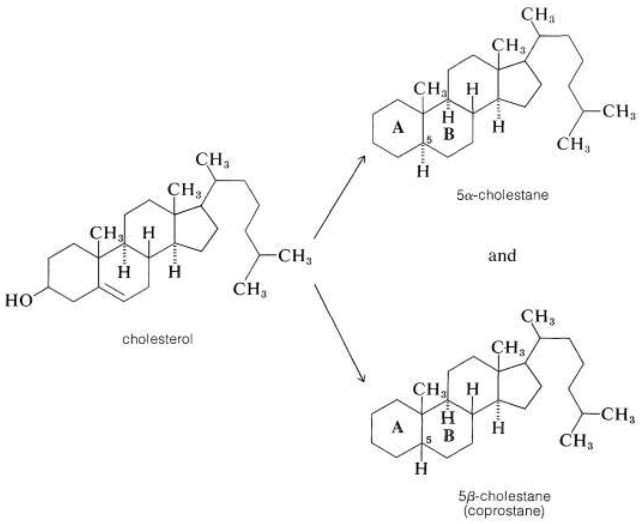
30.4.2: Structure of Cholesterol

Although cholesterol was recognized as an individual chemical substance in 1812, all aspects of its structure and stereochemical configuration were not settled until about 1955. The structural problem was a very difficult one, because most of cholesterol is saturated and not easily degraded. Fortunately, cholesterol is readily available, so that it was possible to use rather elaborate degradative sequences, which would have been quite out of the question with some of the rarer natural products.

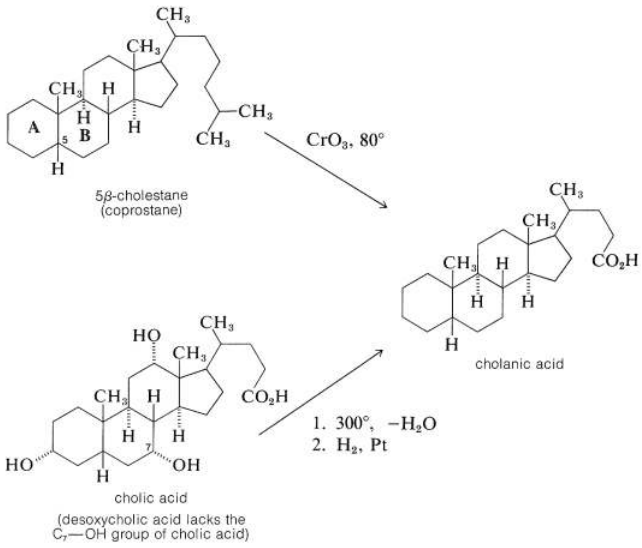
The first step in the elucidation of the structure of cholesterol was the determination of the molecular formula, first incorrectly as $C_{26}H_{44}O$ in 1859 and then correctly as $C_{27}H_{46}O$ in 1888. The precision required to distinguish between these two formulas is quite high, because $C_{26}H_{44}O$ has 83.80% C and 11.90% H, whereas $C_{27}H_{46}O$ has 83.87% C and 11.99% H. Cholesterol was shown in 1859 to

be an alcohol by formation of ester derivatives and in 1868 to possess a double bond by formation of a dibromide. By 1903 the alcohol function was indicated to be secondary by oxidation to a ketone rather than an aldehyde. The presence of the hydroxyl group and double bond when combined with the molecular formula showed the presence of four carbocyclic rings. Further progress was only possible by oxidative degradation.

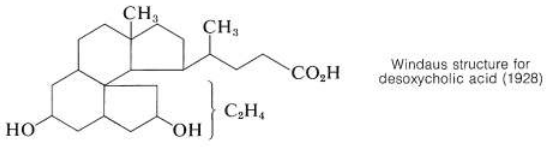
The structure proof for cholesterol paralleled that for two other important steroids, the so-called *bile acids*, cholic and desoxycholic acid, which function to help solubilize fats in the intestinal tract. Proof that cholesterol and the bile acids have the same general ring system was achieved by dehydration and reduction of cholesterol to two different hydrocarbons, *5α-cholestane* and *5β-cholestane* (*coprostane*), which differ only in the stereochemistry of the junction between rings *A* and *B*:



Oxidation of 5β-cholestane, but not 5α-cholestane, gave an acid that turned out to be identical with *cholanic acid* obtained by dehydration of cholic acid at 300° followed by hydrogenation:



Once the connection between cholesterol and the bile acids was established, further work on the structure proof was directed towards degradation experiments on the bile acids which, with their hydroxyl groups on rings *B* and *C*, offered more possible degradation reactions than cholesterol. Outstanding contributions toward the structure proof were made by the German chemists H. Wieland and A. Windaus, both of whom were honored by the award of the Nobel Prize in chemistry. Wieland received the award in 1927 and Windaus in 1928. Despite their many years of effort, the structure proposed by Windaus in 1928 for desoxycholic acid was only tentative and was unspecific as to the location of two carbons.

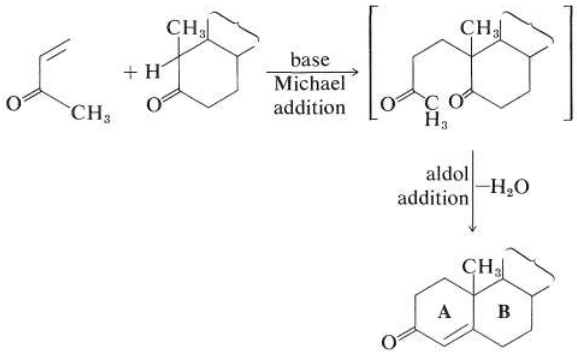


Windaus structure for desoxycholic acid (1928)

Serious doubt as to the correctness of the Windaus structure came as a result of an x-ray study of ergosterol by J. D. Bernal in 1932. He pointed out that the x-ray evidence indicated ergosterol to be a long, rather flat molecule. Steroids with the ring system corresponding to the Windaus structure would have a globular shape. This observation stimulated further work and a re-examination of the evidence that eventually led to the correct structure. The details of this research may be found elsewhere.[3]

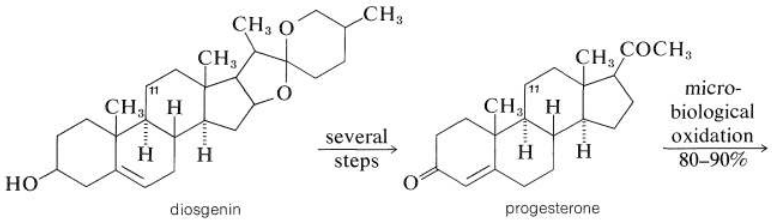
30.4.3: Synthesis of Steroids

One of the most notable achievements of the 1950's was the total synthesis of a number of important steroids, including estrone, cholesterol, cortisone, androsterone, and testosterone. The courses of some of these syntheses are extraordinarily complex and involve large numbers of steps. Although they have not surpassed Nature in providing practical quantities of synthetic steroids, they have led to the development of key reactions of general use in organic synthesis. An especially useful reaction for building fused ring systems is the so-called *Robinson annelation reaction* developed by Sir Robert Robinson (Nobel Prize, 1947) and J. W. Cornforth (Nobel Prize, 1975). The reaction involves a Michael addition to an α,β-unsaturated ketone immediately followed by an aldol addition:

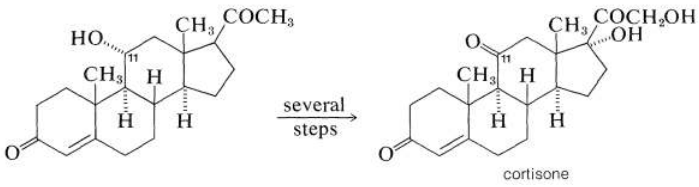


The pharmacological importance of many natural steroids has stimulated much synthetic work in an effort to obtain practical quantities of naturally occurring and unnatural steroids. Oftentimes a combination of biosynthesis and organic synthesis works best. For example, the need for large quantities of cortisone derivatives for therapeutic use in treatment of arthritis and similar metabolic diseases has led to intensive research on synthetic approaches for methods of producing steroids with oxygen functions at C_{11}, which is not a particularly common point of substitution in steroids.

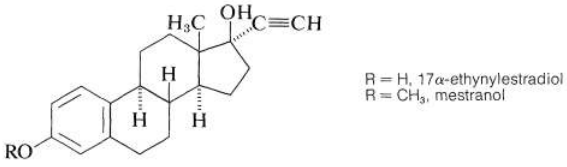
An efficient way of doing this is by microbiological oxidation. Cortisone can be manufactured on a relatively large scale from the saponin, diosgenin, which is isolated from tubers of a Mexican yam of the genus *Dioscorea*. Diosgenin is converted to progesterone, then by a high-yield (80%-90%) oxidation with the mold, *Rhizopus nigricans*, to 11-hydroxyprogesterone and finally to cortisone:



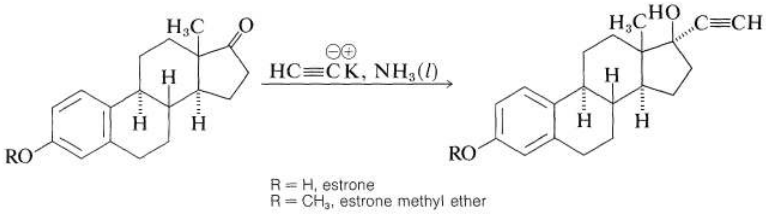
diosgenin progesterone



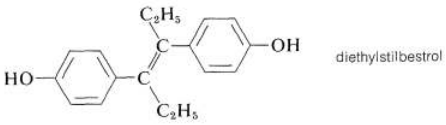
Especially important steroid derivatives in use today are the synthetic estrogens, 17-α-ethynylestradiol and its 3-OCH_3 derivative, mestranol:



Both of these compounds have potent estrogenic activity (inhibit ovulation) and are widely used as oral contraceptives. They are synthesize from the natural estrogen, estrone, by the following reaction:



A compound known as diethylstilbestrol (DES) also exhibits estrogenic activity even though it is unrelated structurally to steroidal estrogens. It has acquired notoriety as a possible cause of uterine cancer. Diethylstilbestrol has been used extensively as an additive in cattle and chicken feed because it gives a greater gain in weight for a given amount of feed.



[3]See, for example, the excellent and authoritative account give by L. F. Fieser and M. Fieser, *Steroids*, Van Nostrand Reinhold Co., New York, 1959, Chapter 3.

30.4.4: Contributors and Attributions

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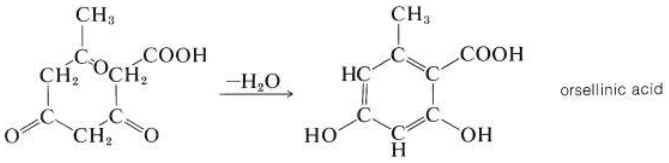
30.5: Biosynthesis

30.5.1: Fatty Acids

The idea that ethanoic acid (acetic acid) is a possible common starting material for the biosynthesis of many organic compounds was first proposed by Collie (1893) on purely structural grounds. He recognized a structural connection between a linear chain of recurring CH_3CO units (a polyketomethylene chain, $CH_3COCH_2COCH_2COCH_2CO-$) and certain cyclic natural products. In the example given below, orsellinic acid is represented as if it were derived from a chain of four CH_3CO units by a condensation-cyclization reaction:



orsellinic acid

Experimental verification of Collie's hypothesis came many years later when isotopic hydrogen and carbon (^2H, ^3H, ^{13}C, and ^{14}C) became available. Tracer studies showed that long-chain fatty acids are made by plants and animals from CH_3CO units by successively linking together the carbonyl group of one to the methyl group of another (K. Bloch and F. Lynen, Nobel Prize, 1964). If ethanoic acid supplied to the organism is labeled at the carboxyl group with ^{14}C $\left(\overset{*}{C}\right)$, the fatty acid has the label at alternate carbons:

$$CH_3\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}O_2H \tag{30.5.1}$$

However, if the carbon of the methyl group is labeled, the product comes out labeled at the other set of alternate carbons:

$$\overset{*}{C}H_3CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CO_2H \tag{30.5.2}$$

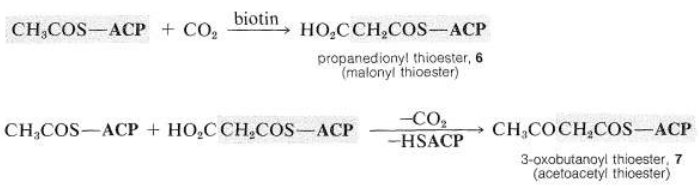
Ethanoic acid is activated for biosynthesis by combination with the thiol, coenzyme A (\textbf{CoA} \ce{SH}\), Figure 18-7) to give the thioester, ethanoyl (acetyl) coenzyme A $(CH_3COSCoA)$. You may recall that the metabolic degradation of fats also involves this coenzyme (Section 18-8F) and it is tempting to assume that fatty acid biosynthesis is simply the reverse of fatty acid metabolism to $CH_3COSCoA$. However, this is not quite the case. In fact, it is a general observation in biochemistry that primary metabolites are synthesized by different routes from those by which they are metabolized (for example, compare the pathways of carbon in photosynthesis and metabolism of carbohydrates in Sectionss 20-9 and 20-10).

A brief description of the main events in fatty-acid biosynthesis follows, and all of these steps must be understood to be under control of appropriate enzymes and their coenzymes even though they are omitted here.

The CH_3CO group of ethanoyl coenzyme A is first transferred to a protein having a free thiol (SH) group to make another thioester, represented here as $CH_3COS-\mathbf{ACP}$, where **ACP** stands for **A**cyl-**C**arrier-**P**rotein. The growing carbon chain remains bound to this protein throughout the synthesis:

$$CH_3COSCoA + HS-\mathbf{ACP} \rightarrow CH_3COS-\mathbf{ACP} + CoASH \tag{30.5.3}$$

Carboxylation of $CH_3COS-\mathbf{ACP}$ yields a propanedioyl thioester, 6, which then undergoes a Claisen condensation with a second mole of $CH_3COS-\mathbf{ACP}$ accompanied by decarboxylation to yield a 3-oxobutanoyl thioester, 7:



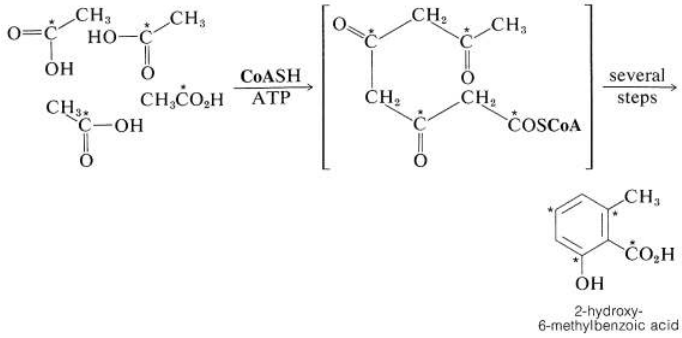
Reduction of the ketone group of the thioester (by NADPH) leads to a thiol ester of a four-carbon carboxylic acid. Repetitive condensations with thioester 6 followed by reduction eventually lead to fatty acids. Each repetition increases the chain length by

two carbons:

The preceding scheme is representative of fatty acid biosynthesis in plants, animals, and bacteria. The major difference is that plant and bacterial fatty acids usually contain more double bonds (or even triple bonds) than do animal fatty acids.

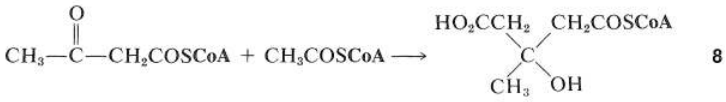
30.5.2: Biosynthesis of Aromatic Rings

Collie's hypothesis that aromatic compounds are made biologically from ethanoic acid was greatly expanded by A. J. Birch to include an extraordinary number of diverse compounds. The generic name "acetogenin" has been suggested as a convenient classification for ethanoate (acetate)-derived natural products, but the name "polyketides" also is used. Naturally occurring aromatic compounds and quinones are largely made in this way. An example is 2-hydroxy-6-methylbenzoic acid formed as a metabolite of the mold *Penicillium urticae*; using ^{14}C-carboxyl-labeled ethanoic acid, the label has been shown to be at the positions indicated below:

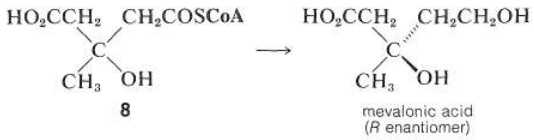


30.5.3: Terpene Biosynthesis

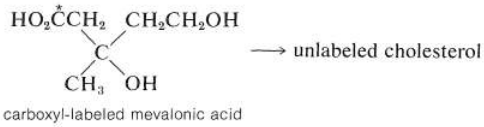
The biosynthesis of terpenes clearly follows a somewhat different course from fatty acids in that branched-chain compounds are formed. One way that this can come about is for 2-oxobutanoyl coenzyme A to undergo an aldol addition at the keto carbonyl group with the ethanoyl coenzyme A to give the 3-methyl-3-hydroxypentanedioic acid derivative, 8:



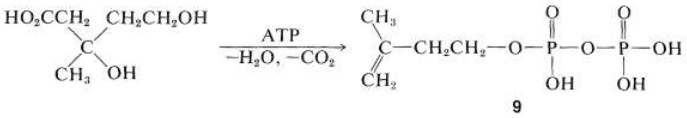
The next step is reduction of one of the carboxyl groups of 8 to give mevalonic acid:



This substance has been shown by tracer studies to be an efficient precursor of terpenes and steroids. Mevalonic acid has six carbon atoms, whereas the isoprene unit has only five. Therefore, if mevalonic acid is the precursor of isoprene units, it must lose one carbon atom at some stage. Synthesis of mevalonic acid labeled at the carboxyl group with ^{14}C, and use of this material as a starting material for production of cholesterol, gives *unlabeled* cholesterol. Therefore, the carboxyl carbon is the one that is lost:

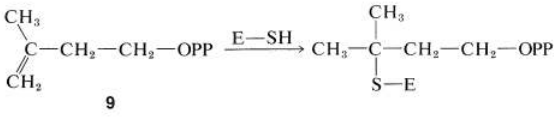


Formation of the "biological isoprene unit" from mevalonic acid has been shown to proceed by stepwise phosphorylation of both alcohol groups, then elimination and decarboxylation to yield 3-methyl-3-butenyl pyrophosphate, 9 (often called Δ^3-isopentenyl pyrophosphate):



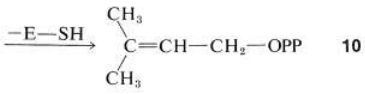
9

The coupling of the five-carbon units, 9, to give isoprenoid compounds has been suggested to proceed by the following steps. First, isomerization of the double bond is effected by an enzyme (E) carrying an SH group:



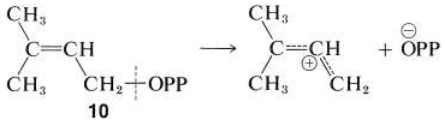
9

[OPP = pyrophosphate]

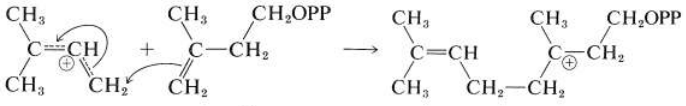


10

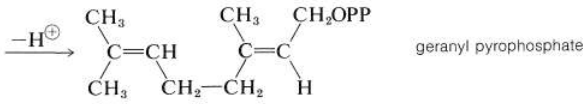
The ester, 10, then becomes connected to the double bond of a molecule of 9, probably in an enzyme-induced carbocation type of polymerization (Section 10-8B):



10

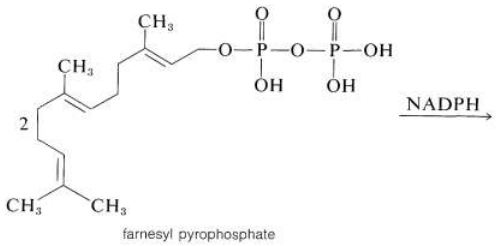


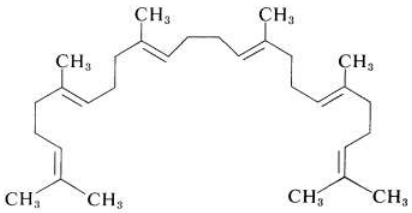
9



The product of the combination of two units of the pyrophosphate, 9, through this sequence is **geranyl pyrophosphate** if, as shown, the proton is lost to give a trans double bond. Formation of a cis double bond would give neryl pyrophosphate (Section 30-3B).

Continuation of the head-to-tail addition of five-carbon units to geranyl (or neryl) pyrophosphate can proceed in the same way to farnesyl pyrophosphate and so to gutta-percha (or natural rubber). At some stage, a new process must be involved because, although many isoprenoid compounds are head-to-tail type polymers of isoprene, others, such as squalene, lycopene, and β- and γ-carotene (Table 30-1), are formed differently. Squalene, for example, has a structure formed from head-to-head reductive coupling of two farnesyl pyrophosphates:





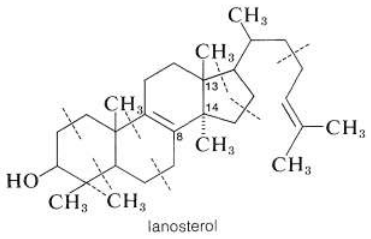
Since squalene can be produced from farnesyl pyrophosphate with NADPH and a suitable enzyme system, the general features of the above scheme for terpene biosynthesis are well supported by experiment.

In summary, the sequence from ethanoate to squalene has been traced as

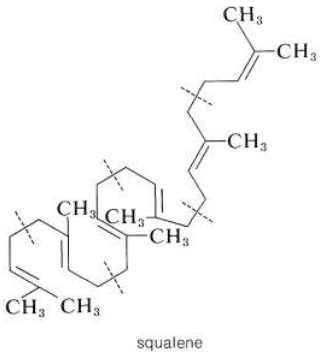
$$\text{ethanoyl coenzyme A} \rightarrow \text{mevalonic acid} \rightarrow \text{isopentenyl pyrophosphate} \rightarrow \text{farnesyl pyrophosphate} \rightarrow \text{squalene} \tag{30.5.4}$$

30.5.4: Cholesterol Biosynthesis

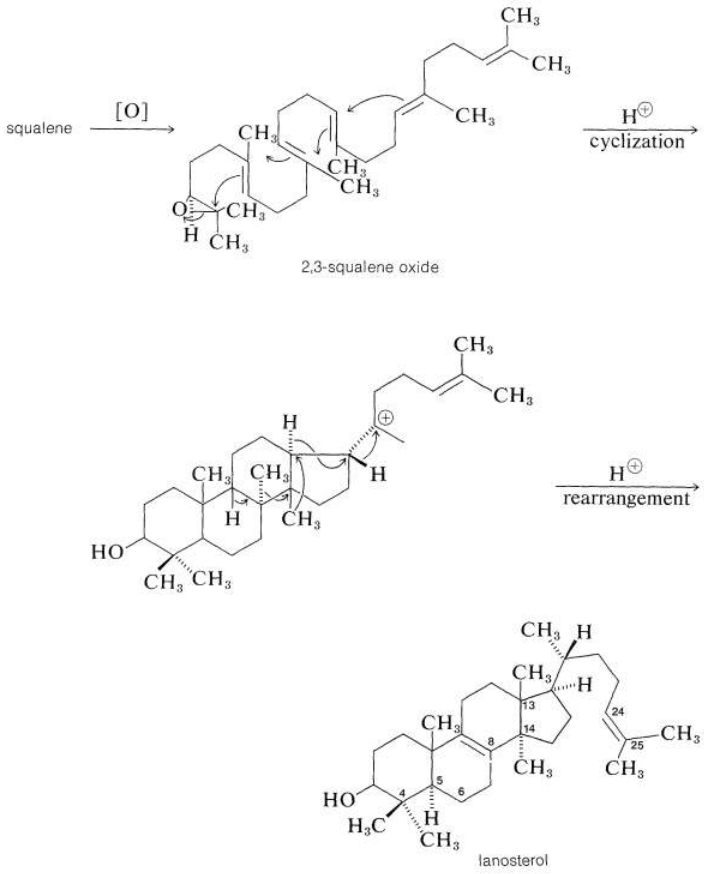
Isotopic labeling experiments show that cholesterol is derived from ethanoate by way of squalene and lanosterol. The evidence for this is that homogenized liver tissue is able to convert labeled squalene to labeled lanosterol and thence to labeled cholesterol. The conversion of squalene to lanosterol is particularly interesting because, although squalene is divisible into isoprene units, lanosterol is not - a methyl being required at C_8 and not C_{13}:



As a result, some kind of rearrangement must be required to get from squalene to lanosterol. The nature of this rearrangement becomes clearer if we write the squalene formula so as to take the shape of lanosterol:



When squalene is written in this form, we see that it is beautifully constructed for cyclization to lanosterol. The key intermediate that initiates the cyclization is the 2,3-epoxide of squalene. Enzymatic cleavage of the epoxide ring is followed by cyclization and then manifold hydride $(H:)$ and methide $(CH_3:)$ shifts to give lanosterol:



The evidence is strong that the biosynthesis of lanosterol actually proceeds by a route of this type. With squalene made from either methyl- or carboxyl-labeled ethanoate, all the carbons of lanosterol and cholesterol are labeled just as predicted from the mechanism. Furthermore, ingenious double-labeling experiments have shown that the methyl at C_{13} of lanosterol is the one that was originally located at C_{14}, whereas the one at C_{14} is the one that came from C_8.

The conversion of lanosterol to cholesterol involves removal of the three methyl groups at the 4,4- and 14-positions, shift of the double bond at the *B*/*C* junction between C_5 and C_6, and reduction of the C_{24}-C_{25} double bond. The methyl groups are indicated by tracer experiments to be eliminated by oxidation to carbon dioxide.

The biosynthetic connection between ethanoyl coenzyme A and the complex natural products briefly discussed is summarized in Figure 30-1.

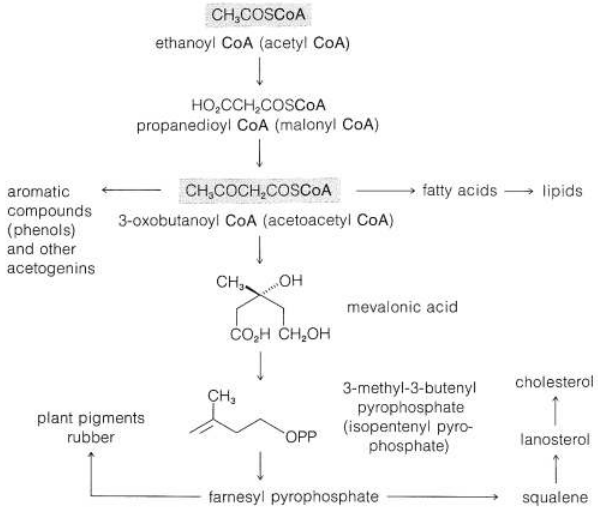


Figure 30-1: Summary of biosynthesis pathways to fatty acids, terpenes, and steroids.

30.5.5: Contributors and Attributions

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30.6: Some Nitrogen-Containing Natural Products

30.6.1: Alkaloids

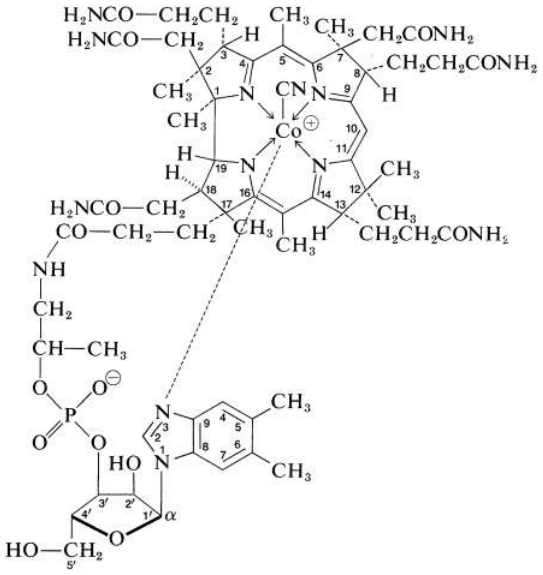
Basic nitrogen compounds in plants are classified as alkaloids. Several examples were given previously of this large and remarkably heterogeneous class of compounds, many of which have very complex structures (Section 23-2). It is difficult to give a coherent account of alkaloid chemistry in the limited space available to us here.

The **biosynthesis of alkaloids** has been extensively studied, and although for a time it was thought that alkaloids arose primarily from amino acid precursors, strong evidence now is available that ethanoate also is involved. The mode of alkaloid biosynthesis is not yet as well understood as that of the terpenes and steroids. One experimental problem is the difficulty of feeding suitably labeled precursors to plants.

30.6.2: Vitamin B_{12}

Vitamin B_{12} is the nutritional factor required for the prevention of pernicious anemia. Its structure was determined in 1956 through the chemical studies of Alexander Todd (Nobel Prize, 1957) and the x-ray diffraction studies of Dorothy Hodgkin (Nobel Prize, 1964). It is one of the most complex natural products known, yet it has features that are not unfamiliar. It is related to the metalloporphyrins discussed previously (Section 25-8B), but the ring system surrounding the cobalt atom has one less carbon bridging two of the nitrogen-containing rings than the porphyrin ring of heme or chlorophyll. The B_{12} ring system is called a **corrin** ring, and the vitamin is a cobalt-corrin complex.

The corrin ring includes methyl, ethanamide, and propanamide groups, and one of these is linked through a nucleotide residue to the cobalt atom. There are five nitrogen ligands around the cobalt, and a sixth ligand is attached through carbon - here a cyano group - so that an alternate name for vitamin B_{12} is *cyanocobalamin*:



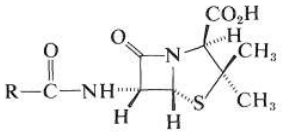
vitamin B_{12} (cyanocobalamin form)

A total synthesis of vitamin B_{12} was announced in 1972, as the result of a collaborative effort between R. B. Woodward (Harvard) and A. Eschenmoser (Zurich). The synthesis was completed after 11 years of effort involving 100 co-workers from 19 countries. A number of important techniques and reactions of synthetic value were developed during the course of this work, including the principle of conservation of orbital symmetry (the Woodward-Hoffman rules, Section 21-10). The biochemical action of vitamin B_{12} is considered in Chapter 31.

30.6.3: Penicillins and Cephalosporins

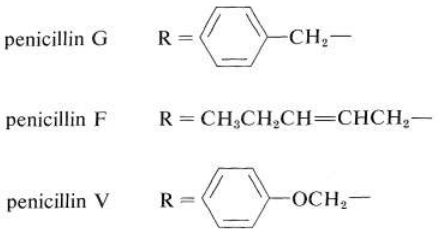
The first antibiotics of medicinal value were discovered by Alexander Fleming in 1929 as metabolites of the microorganism *Penicillium notatum*. They became known as **penicillins**, but their development as useful drugs was slow in coming. However, the

urgent need for nontoxic antibiotics was recognized during World War II, and resulted in a team effort by English and American scientists to develop efficient methods for preparing penicillin by fermentation and to undertake clinical and chemical studies. By 1943, penicillin was available in quantity for the treatment of war wounded. By 1945, the basic structure and stereochemistry was deduced through chemical degradation and x-ray diffraction studies:

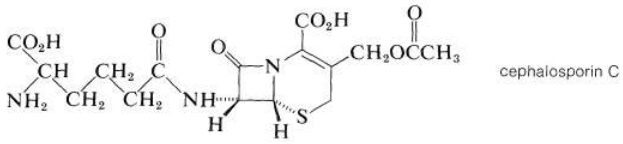


The structure is unusual in that it has a four-membered cyclic amide ring (β-lactam). It was the first example to be discovered of a natural product with this ring structure.

Fermentation can produce penicillins that differ only in the nature of the side-chain group R. The common natural penicillin is penicillin G, in which R = phenylmethyl (benzyl):

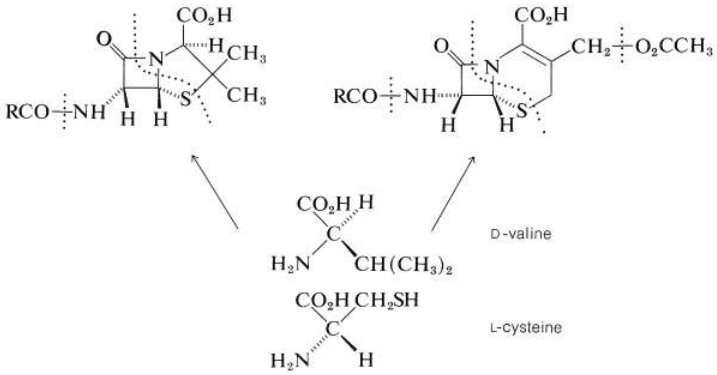


The cephalosporins are antibiotics produced by the bacterial strain *cephalosporium*. They are closely related to the penicillins. Thus cephalosporin C has a β-lactam ring but a six-membered sulfur-containing ring:



Both the cephalosporins and the penicillins owe their antibacterial action to their ability to block bacterial cell-wall biosynthesis. Cephalosporin C is less active than the penicillins, but is less susceptible to enzymatic destruction by β-lactamases, which are enzymes that cleave the lactam ring. In fact, the so-called resistance of *staph* bacteria to penicillins is attributed to the propagation of strains that produce β-lactamase. Numerous semisynthetic penicillins and cephalosporins have been made in the hope of finding new broad-spectrum antibiotics with high activity but with greater β-lactam stability. Several of these are in clinical use.

The total synthesis of penicillin V was achieved by J. C. Sheehan (1957) and of cephalosporin by R. B. Woodward (1966). Biosynthetic routes have been worked out in part, and the precursors to both ring systems are *L*-cysteine and *D*-valine:



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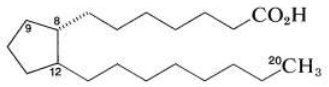
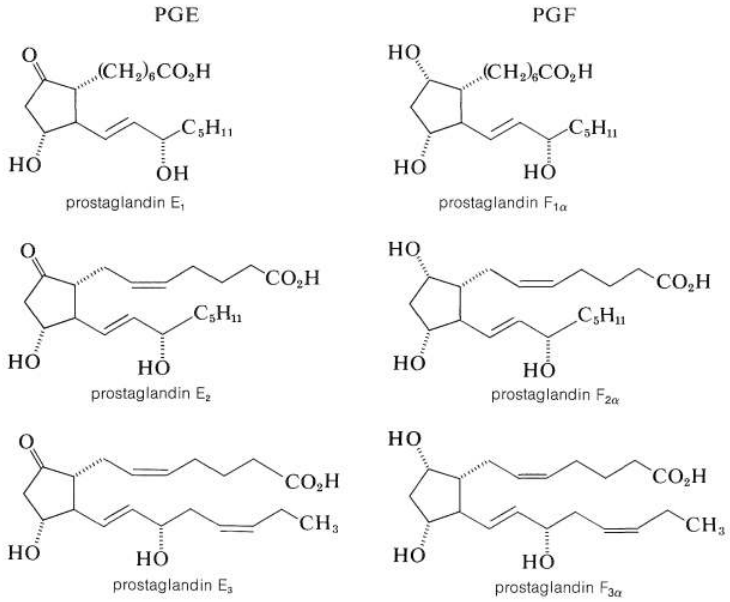
30.7: Prostaglandins

Some of the most recent and exciting developments in the field of natural products are related to the compounds known as **prostaglandins**. All are oxygenated unsaturated derivatives of prostanoic acid, which is a C_{20} fatty acid in which there is a cyclopentane ring formed by connecting the C_8 and C_{12} positions:



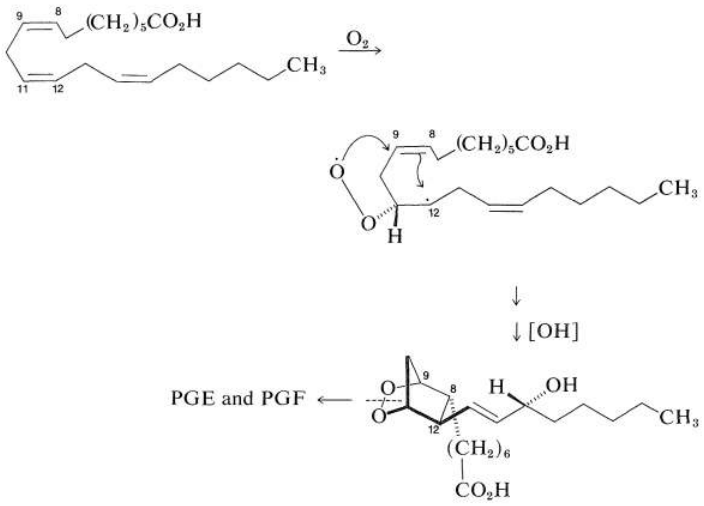
prostanoic acid

There are two main types of prostaglandins that differ in the oxygen function at C_9, which is a carbonyl in Series E (PGE) and hydroxyl in Series F (PGF). Examples follow:



Prostaglandins are found in low concentrations distributed in a large number of organs, tissues, and body fluids of mammals. They exhibit a broad spectrum of physiological activity and are remarkably potent. Their precise biological role is not entirely clear, but they are known to induce strong contractions of smooth muscle tissue (lungs, uterus) and to lower blood pressure and sodium levels. Prostaglandins also have been implicated in the control of pituitary hormones released from the hypothalamus, and in the incidence of "pain" as a response to fever and inflammation. In fact, the analgesic property of aspirin possibly may result from the inhibition of prostaglandin biosynthesis. Although prostaglandins are not yet in extensive clinical use, their wide-ranging physiological effects hold promise that they will become useful drugs for the treatment of high blood pressure, thrombosis, respiratory disease, hypertension, ulcers, and in the regulation of fertility in both men and women.

A number of brilliant total syntheses of natural prostaglandins have been developed and these also have provided a number of interesting prostaglandin analogs. The biosynthesis of prostaglandins proceeds by oxygenation at C_{11} of unsaturated fatty acids. This is followed by cyclization (probably as the result of a radical addition mechanism) to a bicyclic peroxide. Cleavage of the peroxide ring leads to prostaglandins:



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30.E: Natural Products and Biosynthesis (Exercises)

Exercise 30-1

a. Write out all of the possible carbon skeletons for *acyclic* terpene and sesquiterpene hydrocarbons that follow the isoprene rule. Do not consider double-bond position isomers.

b. Do the same for monocyclic terpenes with a six-membered ring.

Exercise 30-2 The terpene known as alloöcimene $(C_{10}H_{16})$ shows λ_{max} at $288\ nm$ and gives among other products 1 mole of 2-propanone and 1 mole of ethanal on ozonization. What is a likely structure for alloöcimene? Show your reasoning.

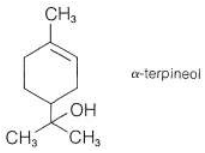
Exercise 30-3 Write structures for each of the optical and cis-trans isomers that would be expected for the following isoprenoid compounds (refer to Table 30-1):

a. myrcene
b. α-farnesene
c. limonene
d. zingiberene
e. sabinene
f. α-pinene
g. camphene
h. selinene
i. caryophyllene

Exercise 30-4* Optically active camphene racemizes on heating with weak acids. Write a mechanism for this racemization that is in harmony with the acid-catalyzed character of the reaction. (We suggest that you review Sections 8-9B and 15-5E.)

Exercise 30-5

a. Nerol and geraniol cyclize under the influence of acid to yield α-terpineol. How could the relative ease of cyclization of these alcohols, coupled with other reactions, be used to establish the configurations at the double bond of geraniol, nerol, geranial, and neral? Write a mechanism for the cyclizations.

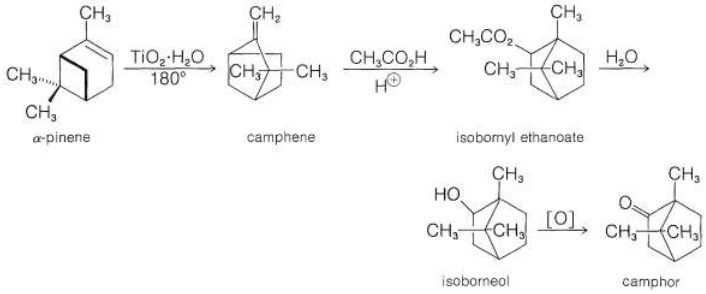


α-terpineol

b. Acidic cyclization of optically active linaloöl produces optically active α-terpineol. Explain how this can come about.

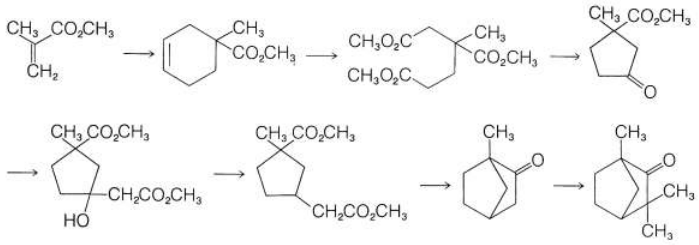
Exercise 30-6 Reduction of the ketone group of $(-)$-menthone, which has its alkyl groups trans to one another, gives two products, known as $(-)$-menthol and $(+)$-neomenthol. These two substances differ considerably in their reactions. $(+)$-Neomenthol undergoes dehydration either in methanoic acid or when treated with phosphorus pentachloride, whereas $(-)$-menthol gives a methanoate ester with methanoic acid and a chloride with phosphorus pentachloride. What is the relationship between neomenthol and menthol, and why do they behave differently with methanoic acid and phosphorus pentachloride? What is the likely structure of the menthene from dehydration of neomenthol? (Review Sections 8-8D, 12-3D, and 12-5.)

Exercise 30-7* Camphor can be made on an industrial scale from α-pinene (turpentine) by the following reactions, some of which involve carbocation rearrangements of a type particularly prevalent in the bicyclic terpenes and the scourge of the earlier workers in the field trying to determine terpene structures.

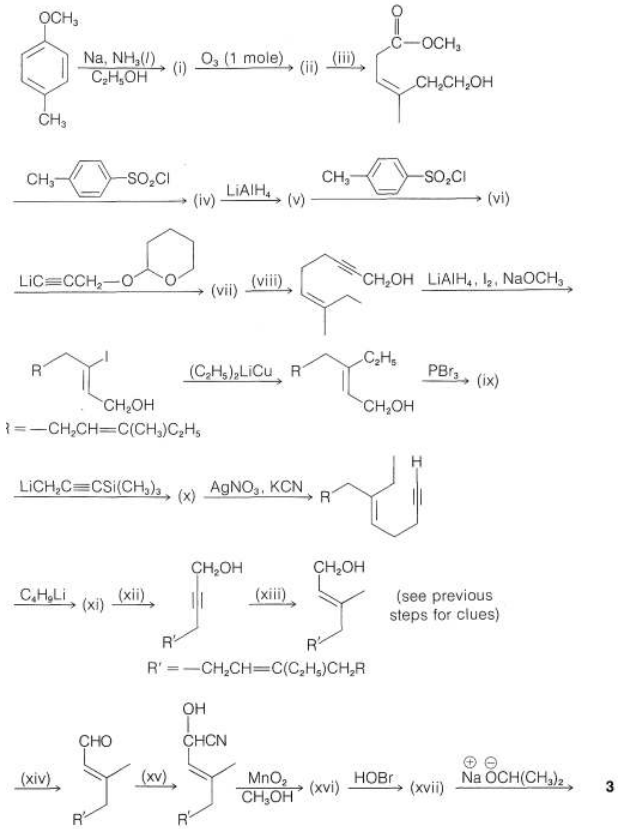


Write mechanisms for the rearrangement reactions, noting that hydrated titanium oxide is an acidic catalyst.

Exercise 30-8 One route for the synthesis of *D*,*L*-fenchone is through the following steps. Show the reagents, conditions, and important reaction intermediates you expect would be successful in achieving each of the indicated transformation, noting that more than one step may be required (all the reactions necessary have been described in previous chapters).



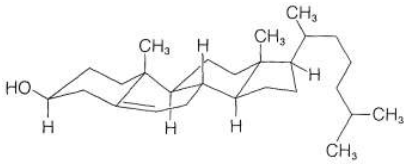
Exercise 30-9 The synthesis of *Cecropia* juvenile hormone outlined below was designed by E. J. Corey and co-workers. Draw in the structure of the product (as i, ii, etc.) at each stage where this has been omitted, and write above the arrows the reagents and conditions necessary to accomplish reactions where these have been omitted. (To save space, the abbreviation R and R′ are used to designate parts of the structure that do not change in later steps.)



https://chem.libretexts.org/@go/page/81276

Exercise 30-10 How many optical isomers are possible for cholic acid?

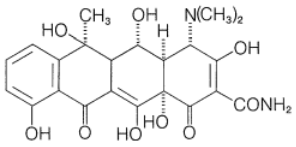
Exercise 30-11 Assuming cholesterol has the following stereochemical configuration, draw a similar configurational structure for cholic acid (including the hydroxyl groups).



Exercise 30-12 Reduction of the double bond of cholesterol can be carried out so as to produce either 5α- or 5β-cholestanol. Equilibration of 5α-cholestanol with a trace of 5α-cholestanone and base (Section 16-4E) gives 90% 5α-cholestanol and 10% of a stereoisomer known as epicholestanol. Similar equilibration of 5β-cholestanol (in the presence of 5β-cholestanone) gives 10% 5β-cholestanol and 90% of a stereoisomer of 5β-cholestanol known as epicoprostanol. Write the configurations of each of these compounds and explain the orders of stabilities that are observed.

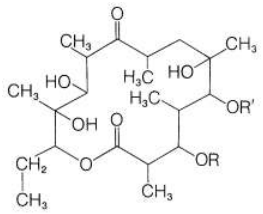
Exercise 30-13

a. The structure of Terramycin (an oxytetracycline antibiotic) is shown below. This substance is a mold metabolite and shows extensive incorporation of ^{14}C when $CH_3{}^{14}CH_2COH$ is introduced into the culture medium. Indicate positions expected for introduction of the ^{14}C-label in Terramycin using $CH_3{}^{14}CH_2COH$.



Terramycin
(oxytetracycline)

b. Erythromycin A is an example of a large group of antibiotics known as **macrolides**. They are medium-ring lactones. Erythromycin A is biosynthesized from propanoate. Show the expected distribution of deuterium and ^{14}C labels in erythromycin grown in a medium containing $CDCH_3{}^{14}CH_2COH$.



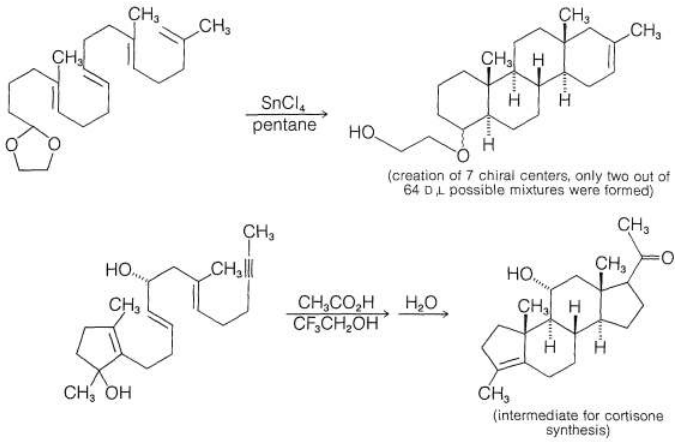
Erythromycin A
(R and R' are sugars)

Exercise 30-14 Show the position(s) of an isotopic carbon label such as ^{14}C in geranyl pyrophosphate biosynthesized from carboxyl-labeled $CH_3C^*O_2H$ by way of 8 and 9.

Exercise 30-15 Show by a reasonable mechanism how myrcene, ocimene, and limonene might arise from CH_3CO_2H by way of the pyrophosphate ester, 9.

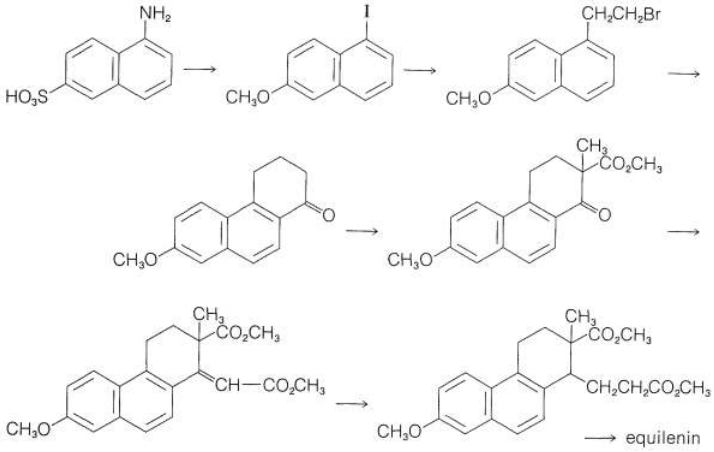
Suppose one started with CH_3CO_2H labeled at the methyl with ^{14}C; where would each product be labeled?

Exercise 30-16 An ingenious and highly practical synthetic procedure for forming the steroid ring system has been developed by W. S. Johnson that closely mimics the squalene cyclization without the need for enzymes. The cyclizations occur by carbocationic intermediates under rather strictly defined conditions that are designed to prevent the reactants from being diverted to nucleophilic substitution or elimination products until the desired additions have occurred. Devise a course for each of the following Johnson reactions:

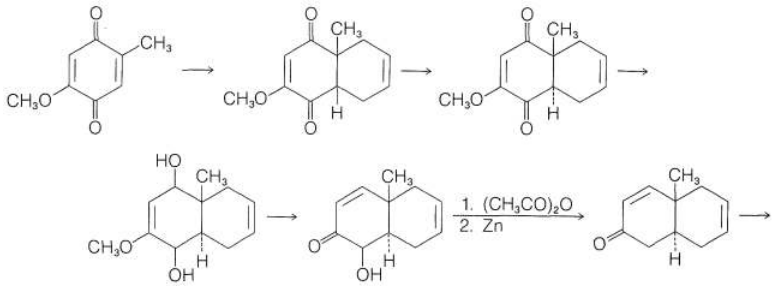


The following problems illustrate the steps taken in several important syntheses of naturally occurring substances. Show the reagents, conditions, and important intermediates you expect to be successful in achieving each of the indicated transformations, noting that more than one step may be required. Except where conditions and reagents already are supplied, all the reactions necessary have been discussed in previous chapters. We suggest that the reasons for the stereospecificity of the reactions (if any) be considered carefully. See Table 30-2 for steroid structures.

Exercise 30-17 Equilenin was synthesized by Bachmann, Cole, and Wilds in 1939. This was the first total synthesis of a steroid. The route follows:



Exercise 30-18 The total synthesis of cortisone has been achieved from an intermediate prepared by Woodward and co-workers in 1951 by the following route:



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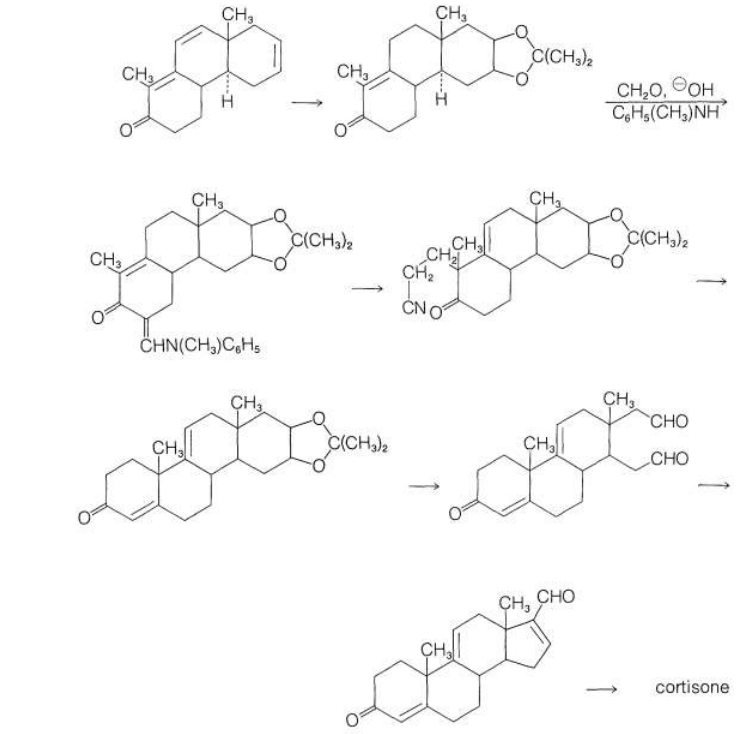
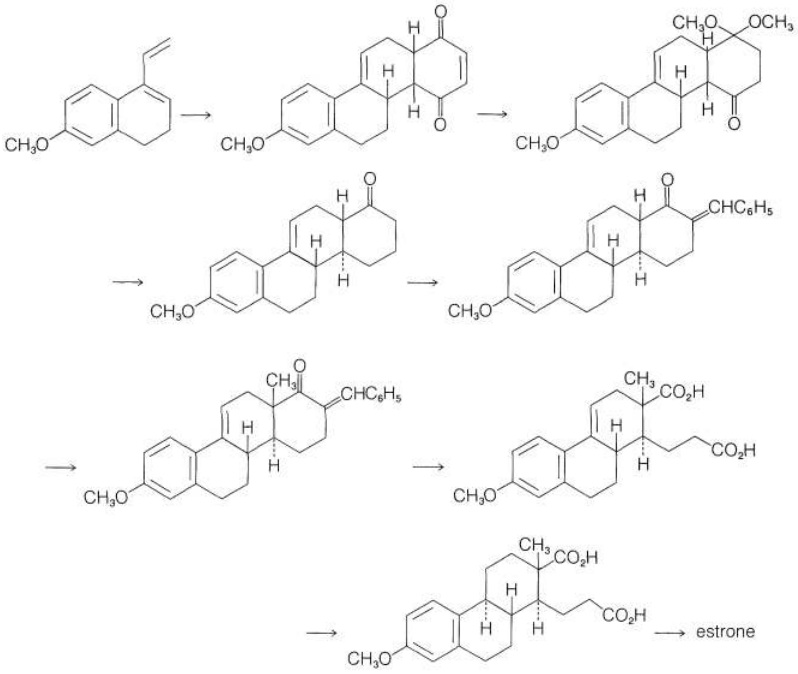


Exercise 30-19 W. S. Johnson and co-workers have produced several elegant syntheses of estrone. One of the shortest and most stereospecific follows:



Exercise 30-20 Cantharidin, a bicyclic "head-to-head" monoterpene (Section 30-3A) that is the irritant principle of the Spanish fly, would seem to be easy to synthesize by hydrogenation of the Diels-Alder adduct of dimethylbutenedioic anhydride and oxacyclopentadiene (furan):

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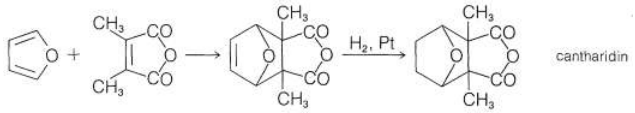
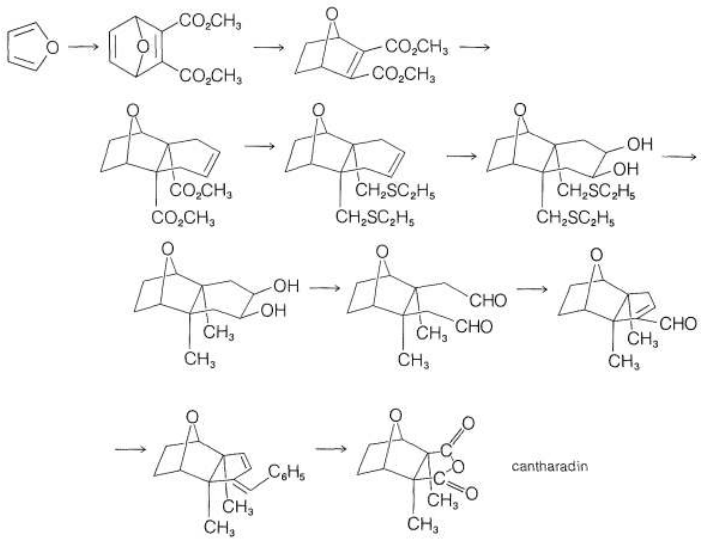


However, this route fails because the Diels-Alder reaction with the particular set of reagents has a very unfavorable equilibrium constant. Even if the addition were successful, it is possible also that the stereochemistry (**exo** or **endo**) of the adduct would not be the same as that of the natural product.

An ingenious synthesis of cantharidin that gives the correct stereochemistry was reported by Stork, van Tamelen, Friedman, and Burgstahler (1953) by way of the following intermediates:



Exercise 30-21 Cedrene (oil of cedar) has been synthesized by Stork and Clarke (1955) by way of the following intermediates:

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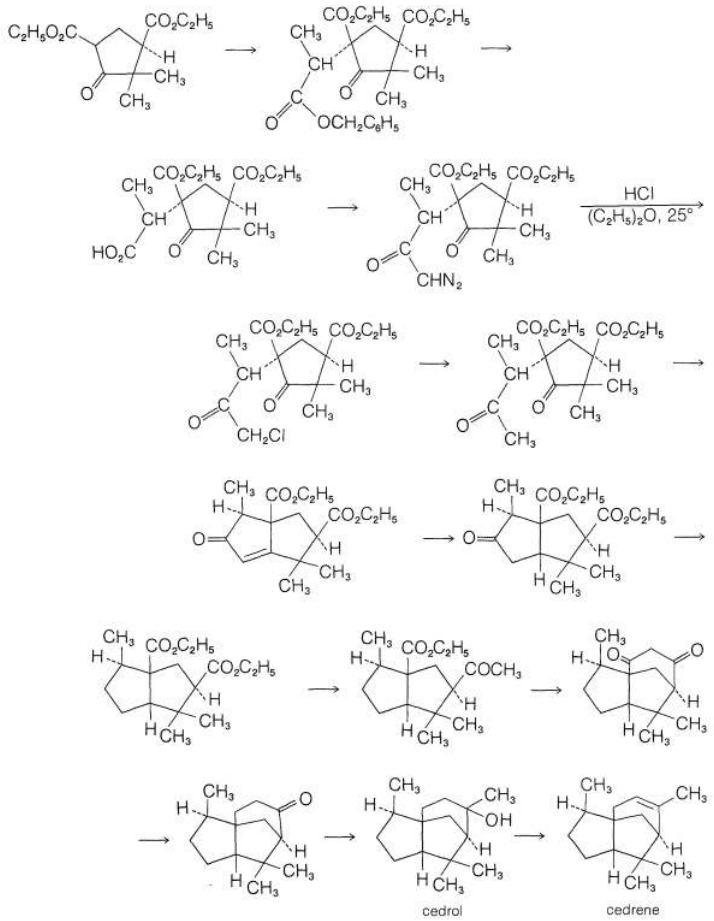

Exercise 30-22 A synthesis of the alkaloid morphine (Section 23-2) was completed by Gates and Tschudi in 1952 by way of the following key intermediates, starting from naphthalene. Show the reagents, conditions, and important reaction intermediates that you expect would be successful in achieving each of the indicated transformations, noting that **more than one** synthetic step may be required between each key compound and considering carefully the order in which the operations should be carried out. Indicate those reactions that may be expected to give mixtures of stereo- or position-isomers. All the reactions involved have analogy in reactions that have been discussed in this or previous chapters, except where conditions and reagents are specified.

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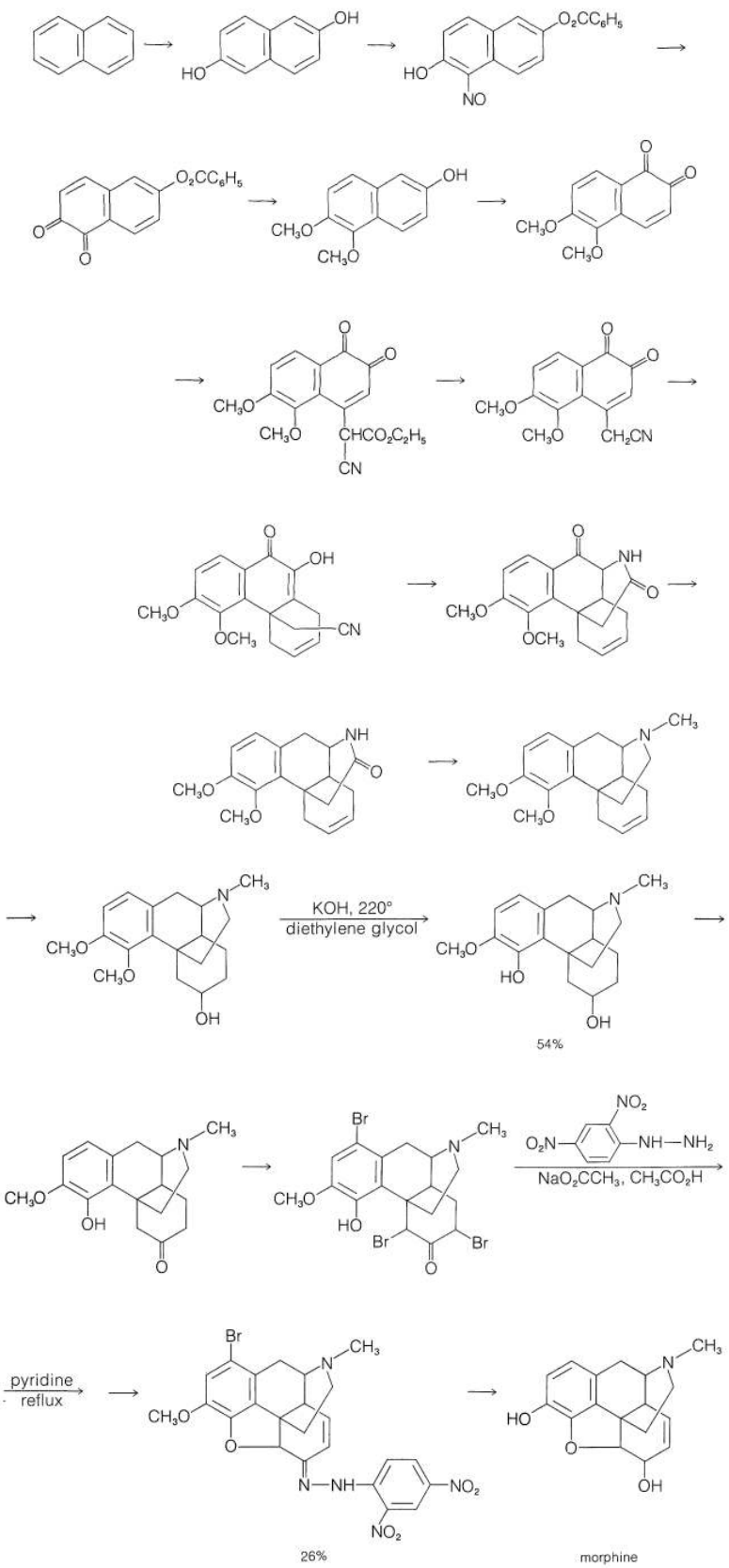

Exercise 30-23 Synthesis of the alkaloid reserpine was reported in 1956 by R. B. Woodward and co-workers through the following intermediates from 2,4-pentadienoic acid. Show the reagents, conditions, and important reaction intermediates that you expect

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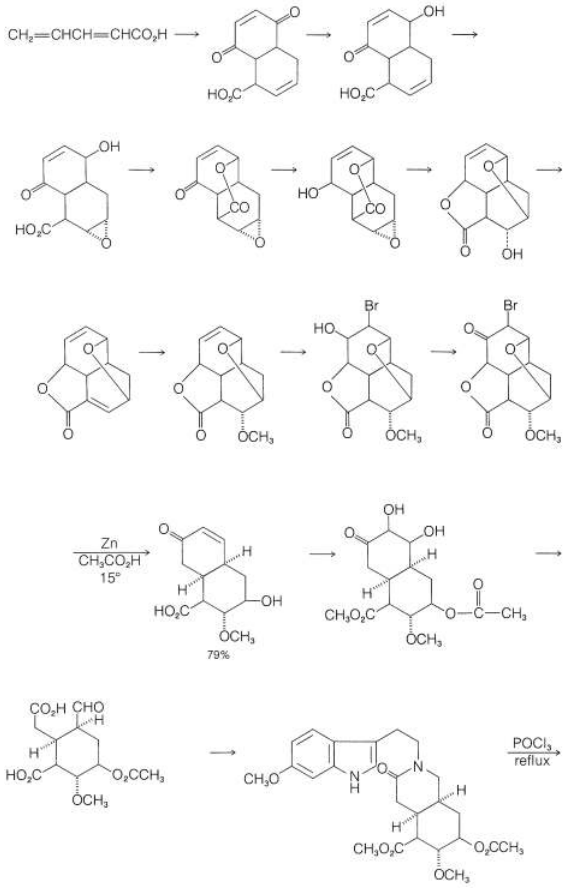
would be successful in achieving each of the indicated transformations, noting that **more than one** synthetic step may be required between each key compound and considering carefully the order in which the operations should be carried out. Indicate those reactions that may be expected to give mixtures of stereo- or position-isomers. All the reactions involved have analogy in reactions that have been discussed in this or previous chapters, except where the reagents and conditions are specified. The beauty of this synthesis lies in the control that it provides over the stereochemistry of the transformations involved, and it is worthwhile to give this detailed attention (with the aid of models, if possible).

Reserpine has important clinical use in the treatment of high blood pressure (hypertension) and also as a tranquilizer for the emotionally disturbed.



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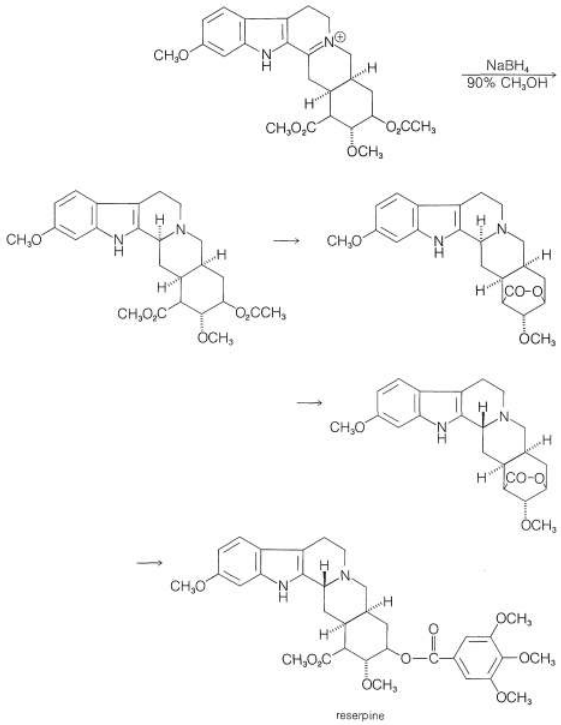

Exercise 30-24 The need for adequate amounts of prostaglandins has led to several total syntheses of these substances. A stereospecific synthesis reported by E. J. Corey and co-workers in 1968 is outlined below. Complete the sequence as in Exercise 30-9 by showing the reagents and conditions needed for each step. Note that ≀ implies a mixture of epimers.

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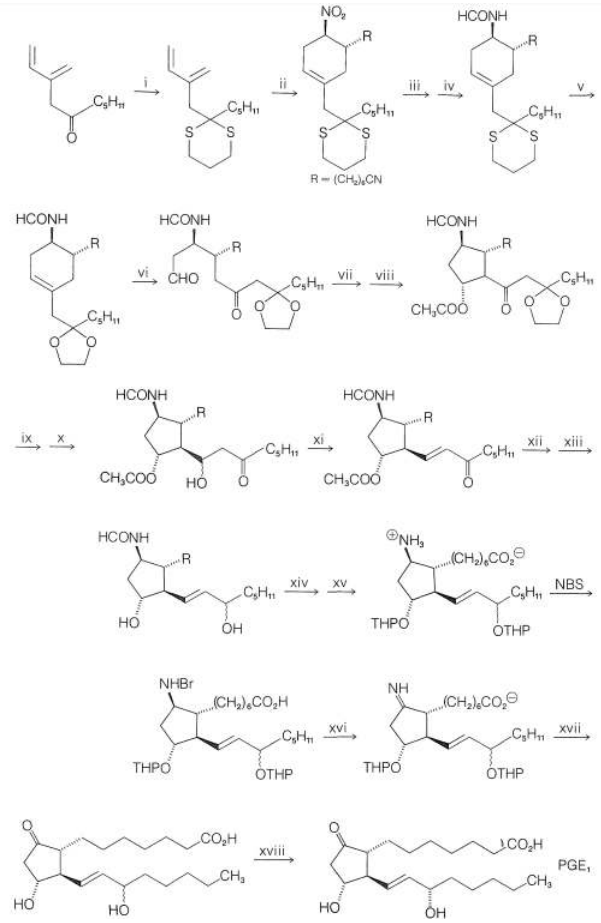

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CHAPTER OVERVIEW

31: Transition Metal Organic Compounds

In the years following Kekulé brilliant proposal for the structure of benzene, organic chemistry underwent a tremendous expansion, and in the process a wide variety of paradigms or working hypotheses were developed about what kinds of compounds could "exist" and what kinds of reactions could occur. In many cases, acceptance of these hypotheses appeared to stifle many possible lines of investigation and caused contrary evidence to be pigeonholed as "interesting but not conclusive." As one example, the paradigm of angle strain was believed to wholly preclude substances that we know now are either stable or important reaction intermediates, such as cubane (Section 12-10), cyclopropanone (Section 17-11), and benzyne (Sections 14-6C and 23-8). No paradigm did more to retard the development of organic chemistry than the notion that, with a "few" exceptions, compounds with bonds between carbon and transition metals (Fe, Co, Ni, Ti, and so on) are inherently unstable. This idea was swept away in 1951 with the discovery of ferrocene ($(C_5H_5)_2Fe$) by P. L. Pauson. Ferrocene has unheard of properties for an organoiron compound, stable to more than 500° and able to be dissolved in, and recovered from, concentrated sulfuric acid! Pauson's work started an avalanche of research on transition metals in the general area between organic and inorganic chemistry, which has flourished ever since and has led to an improved understanding of important biochemical processes.

31.1: Metallocenes

31.2: Other Organometallic Compounds of Transition Metals

31.3: Transition-Metal Compounds as Reagents for Organic Syntheses

31.4: Some Homogeneous Catalytic Reactions Involving Transition-Metal Complexes

31.5: π-Propenyl Complexes of Nickel

31.6: Vitamin B_{12} as an Organometallic Compound

31.E: Transition Metal Organic Compounds (Exercises)

Thumbnail: Ball-and-stick model of a metallocene molecule where the cyclopentadienyl anions are in a staggered conformation. The purple ball in the middle represents the metal cation. (Public Domain; Ben Mills).

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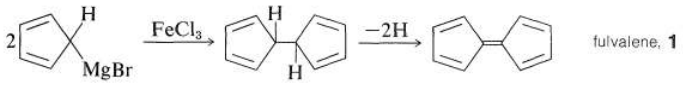
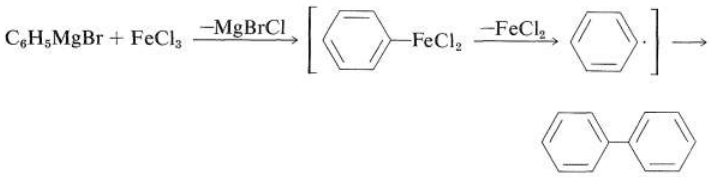
31.1: Metallocenes

The discovery of ferrocene was one of those fortuitous accidents that was wholly unforeseeable - the kind of discovery which, over and over again, has changed the course of science. Pauson was trying to synthesize fulvalene, 1, by first coupling two molecules of cyclopentadienylmagnesium bromide with $FeCl_3$ and then dehydrogenating the product:



fulvalene, **1**

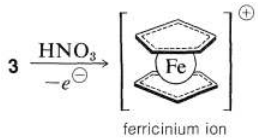
The rationale for the coupling reaction was that phenylmagnesium bromide with $FeCl_3$ gives high yields of biphenyl, presumably by way of an unstable phenyliron compound:



The reaction product was a beautifully crystalline, highly stable orange substance, $C_{10}H_{10}Fe$, which Pauson formulated as a simple combination of two cyclopentadienide anions and *ferrous* ion with two C–Fe bonds, 2. However, the product soon was shown by a variety of physical methods to have the "sandwich" structure, 3:

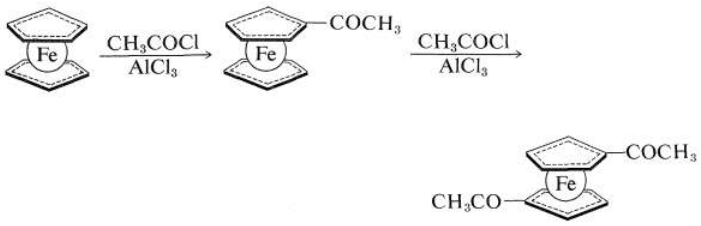
dicyclopentadienyliron, **2** ferrocene, **3** **4**

The bonding between the metal and the cyclopentadiene rings involves the π electrons of the two rings, all carbons being equally bonded to the central ferrous ion. The latter, in accepting a share of 12 π electrons from two cyclopentadienyl anions, achieves the 18 outer-shell electron configuration[1] of the inert gas, krypton. Analysis of the structure of crystalline ferrocene shows that when you look down on the molecule along the ring-iron-ring axis the cyclopentadiene rings are seen to be staggered with respect to one another, as shown in 4. Ferrocene has mp 173° and, although stable to sulfuric acid, it is readily oxidized by nitric acid to the less stable ferricinium ion:



ferricinium ion

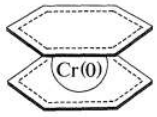
Like benzene, ferrocene does not react easily by addition but does undergo electrophilic substitution. For example, Friedel-Crafts acylation (Section 22-4F) with CH_3COCl gives both a monoethanoylferrocene and a diethanoylferrocene. The two acyl groups become attached to two different rings and, because only one diethanoylferrocene can be isolated, the cyclopentadienyl groups appear to be free to rotate about the axis of the carbon-iron bonds:



Ferrocene is only one of a large number of compounds of transition metals with the cyclopentadienyl anion. Other metals that form sandwich-type structures similar to ferrocene include nickel, titanium, cobalt, ruthenium, zirconium, and osmium. The stability of metallocenes varies greatly with the metal and its oxidation state; ferrocene, ruthenocene, and osmocene are particularly stable

because in each the metal achieves the electronic configuration of an inert gas. Almost the ultimate in resistance to oxidative attack is reached in $(C_2H_5)_2Co^{\oplus}$, cobalticinium ion, which can be recovered from boiling *aqua regia* (a mixture of concentrated nitric and hydrochloric acids named for its ability to dissolve platinum and gold). In cobalticinium ion, the metal has the 18 outer-shell electrons characteristic of krypton.

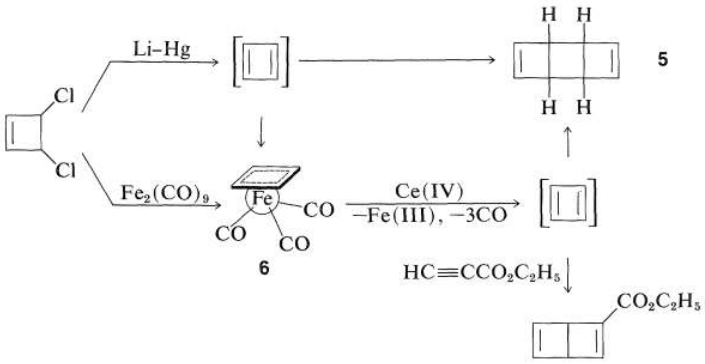
Many other unsaturated organic compounds can form π complexes with transition metals. A substance that is in some ways analogous to ferrocene is the complex of two benzene molecules with chromium metal, called dibenzenechromium. The bonding involves zerovalent chromium and the π electrons of the two benzene rings. In dibenzenechromium, the electronic configuration of the chromium atom is similar to that of krypton:



dibenzenechromium

Although dibenzenechromium is thermally quite stable, it is less so than ferrocene and melts with decomposition at 285° to give benzene and metallic chromium. Furthermore, it appears to lack the aromatic character of either benzene or ferrocene as judged by the fact that it is destroyed by reagents used for electrophilic substitution reactions.

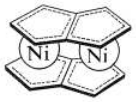
Several transition-metal complexes of cyclobutadiene have been prepared, and this is all the more remarkable because of the instability of the parent hydrocarbon. Reactions that logically should lead to cyclobutadiene give dimeric products instead. Thus, 3,4-dichlorocyclobutene has been dechlorinated with lithium amalgam in ether, and the hydrocarbon product is a dimer of cyclobutadiene, 5. However, 3,4-dichlorocyclobutene reacts with diiron nonacarbonyl, $Fe_2(CO)_9$, to give a stable iron tricarbonyl complex of cyclobutadiene, 6, whose structure has been established by x-ray analysis. The π-electron system of cyclobutadiene is considerably stabilized by complex formation with iron, which again attains the electronic configuration of krypton.



Oxidation of 6 with ceric iron, Ce(IV), releases cyclobutadiene which quickly dimerizes, but can be trapped by good dienophiles such as ethyl propynoate to give a cycloadduct.

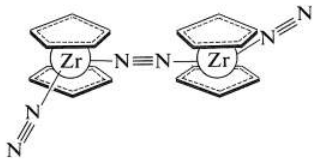
Many metallocene derivatives are known of other conjugated cyclic polyenes. Examples are bis(cyclooctatetraene)uranium (uranocene, 7) and bis(pentalenylnickel), 8 (see Section 22-12B):

uranocene, **7**



bis(pentalenylnickel), **8**

Many of the metallocene compounds display unusual reactivities and reactions, of which none is more startling than the discovery by the Russian chemist, M. E. Vol'pin, of the absorption of dinitrogen, N_2, by titanocene, $(C_2H_5)_2Ti$, to form a complex or complexes that can be reduced easily to form ammonia. The nature of these complexes is in doubt, but very clear evidence has been obtained by J. E. Bercaw for the structure of the complex 9 formed from decamethylzirconocene and dinitrogen:



9 (for clarity, the 20 methyl groups on the rings have been omitted)

This complex treated with acids gives $NH_2{-}NH_2$ and some NH_3.

[1]Figure 6-4 shows that iron(0) has 8 electrons in the $4s$ and $3d$ orbitals. Ferrous iron (Fe^{2+}) then will have 6 outer-shell electrons. This 6 plus the 12 π electrons of the two cyclopentadienide rings makes the 18-electron total and the krypton electronic configuration.

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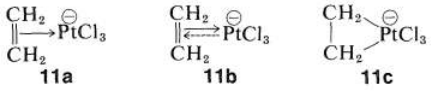
31.2: Other Organometallic Compounds of Transition Metals

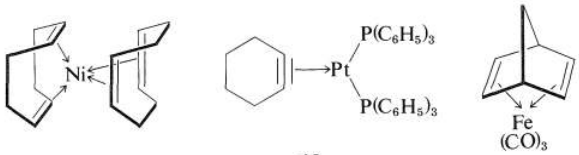
31.2.1: π-Type Alkene and Cycloalkene Complexes

Not all organometallic compounds of transition metals date from the discovery of ferrocene. Many have been known for a long time but their structures were not understood. A conspicuous example is the anion of a substance known as Zeise's salt, which is formed from the reaction of ethanol with chloroplatinic acid, H_2PtCl_6. The anion has the formula $Pt(C_2H_4)Cl_3^-$. Although known since 1830, it finally was shown to have a structure with *both* ethene carbons bonded to platinum. The carbon-to-metal bonding usually is formulated as a π complex, $11a$, or charge-transfer complex (Section 22-4D). Alternatively, we can think of the bonding in $11a$ as between platinum as a Lewis acid (electron-pair acceptor) and ethene as a Lewis base (electron-pair donor):



The arrow in $11a$ symbolizes donation of π electrons. However, because the stability of the ion is much greater than would be expected for either a simple acid-base or charge-transfer complex, it is postulated that unshared d electrons from the metal participate in the bonding. This is symbolized by the dashed arrow in $11b$, which stands for donation of d electrons into the π^* orbital of the double bond or, as it is often called, "back bonding". Perhaps most simple is $11c$, where the $C{-}Pt$ bonding is formulated as a three-membered ring with essentially $C{-}Pt$ (\sigma\) bonds. In this formulation, full participation of a platinum electron pair is assumed.

Many complexes of alkenes, cycloalkenes, alkynes, and cycloalkynes with transition metals are now known. Some examples are:

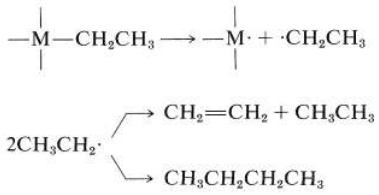


12

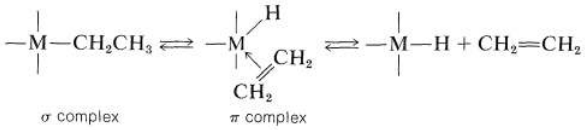
Many substances of this type have potential synthetic usefulness as catalysts or as reagents.

31.2.2: Alkyl-Transition-Metal Bonds

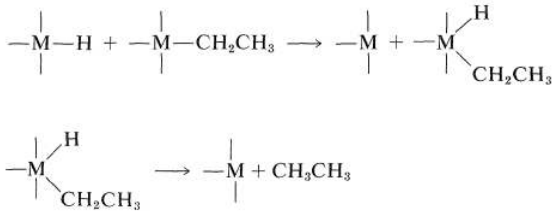
Organometallic compounds of transition metals with alkyl-to-metal bonds for many years were regarded as highly unstable substances and prone to dissociation into radicals that would couple or disproportionate, as illustrated by the following sequence:



The fact is that the stability depends on the character of the attached alkyl groups. Transition-metal compounds with CH_3-, $(CH_3)_3CCH_2-$, and $C_6H_5CH_2-$ groups are in many cases very much more stable than those with CH_3CH_2-, $(CH_3)_2CH-$, and $(CH_3)_3C-$ groups, even though the ease of formation of radicals by dissociation would be expected to be especially favorable with the $C_6H_5CH_2-$ group. Furthermore, decompositions that give alkene and metal hydride or disproportionation products (alkene and alkane) may fail to give coupling products altogether. These facts and many others indicate that an important mode of decomposition of a variety of alkyl-substituted transition-metal compounds does not proceed by a radical mechanism. Instead, there is a transfer of a β hydrogen from the alkyl group to the metal to form a π-type alkene complex and a metal-hydride bond. Decomposition of this complex produces the alkene and the metal hydride. These changes are reversible.

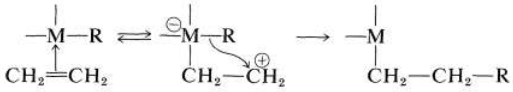


Formation of the alkane then can result from cleavage of an alkyl-metal bond by the metal hydride:



This mechanism but not the sequence of Equation 31-1 makes clear why CH_3-, $(CH_3)_3CCH_2-$, and $C_6H_5CH_2-$ are stable attached to transition metals, because each of these substituents lacks a β hydrogen that would permit formation of a π-bonded complex. The hydride-shift reaction is especially important in hydrogenation and carbonylation reactions, as will be shown in Section 31-3. In fact, the reversible rearrangement of π to σ complexes has wide generality and includes alkyl shifts as well as hydride shifts. An important example of the alkyl-shift mechanism is the polymerization of ethene by Ziegler-Natta catalysts (R_3Al and $TiCl_4$); the chain-building sequence is given in Section 29-6A.

In understanding these reactions, it is helpful to view the metal-alkene π complex as an incipient carbocation (just as π complexes of halogens are incipient carbocations). Alkyl and hydride shifts then bear analogy to carbocation rearrangements. This may be an oversimplification but it makes the chemistry easier to follow.



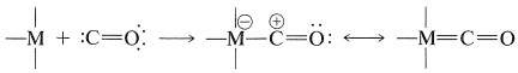
In other reactions, we will see that the metal can act as a nucleophilic reagent.

31.2.3: Carbene-Metal Complexes

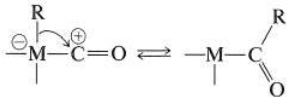
Bonding between a transition-metal atom and one sp^2-hybridized carbon can be represented by the following valence-bond structures:

Stable transition-metal complexes of this type are known and others have been recognized as likely intermediates in a number of reactions. Rightly or wrongly, they are called **carbene-metal complexes**, although they also can be regarded either as metal-stabilized carbocations or as metal-stabilized ylides (Section 16-4A).

Perhaps the most common examples of this type of carbon-metal bonding are the metal carbonyls, in which the carbon monoxide ligand functions as the "carbene":



When represented in this way the chemistry of carbonyl complexes of transition metals becomes easier to understand. Hydroformylation reactions and other carbonylations that are catalyzed by transition-metal complexes frequently involve hydride or alkyl transfers from the metal atom to the "positive" carbonyl carbon (Sections 16-9G, 31-3, and 31-4):



We now proceed to describe some selected reactions that can be understood within this framework of σ-, π-, and carbene-type bonding between the metal and carbon.

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31.3: Transition-Metal Compounds as Reagents for Organic Syntheses

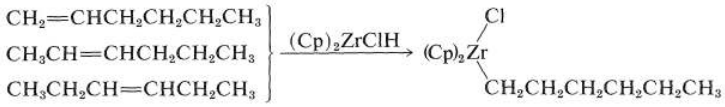
31.3.1: Reactions of Zirconocene Chlorohydride

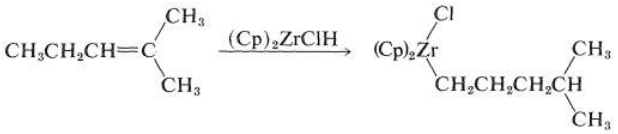
Some transition-metal hydrides show promise as synthetic reagents of the same general applicability as the boron hydrides (Section 11-6). An excellent illustration is provided by the work of J. Schwarz with zirconocene chlorohydride, 13, which is available by reduction of zirconocene dichloride:

13

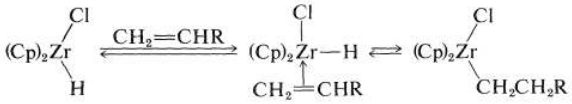
(The cyclopentadienide rings in 13 are shown as being nonparallel and this is in accord with x-ray diffraction studies of metallocenes that have extra substituents on the metal.) Henceforth we will abbreviate the structure 13 by $(Cp)_2ZrClH$.

Alkenes react with $(Cp)_2ZrClH$ to form alkyl-Zr bonds with zirconium becoming attached to the *least-hindered primary carbon*:





The initial step in this kind of reaction is formation of the π-alkene complex followed by hydride transfer:



These reaction must be reversible for an alkene with an *internal* double bond to form an adduct with the metal atom at the *end* of the chain. The process is seen as a series of interconversions between π and σ complexes, which permits the metal atom to move to the least-hindered (primary) carbon:

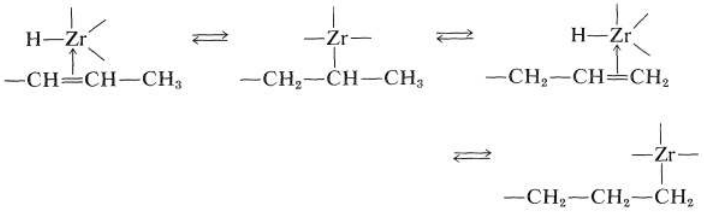


Figure 31-1. Similar reactions also can be carried out with alkynes by way of complexes such as $(Cp)_2Zr(Cl)CH{=}CH_2$.

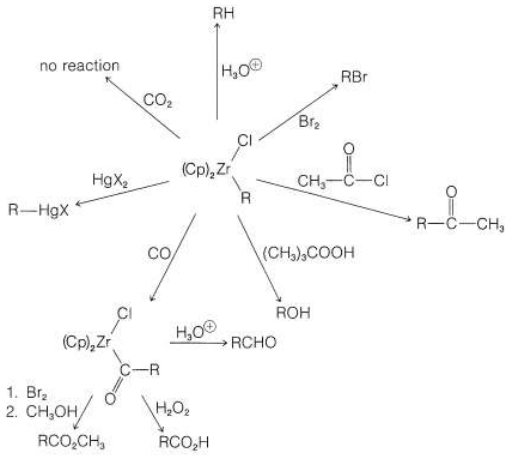


Figure 31-1: Synthetic reactions of alkylzirconocenes. In general, the reactions parallel those of the boranes (Sections 11-6 and 16-9G).

One of the elegant features of these reactions is the formation of crystalline $[(\mathrm{Cp})_2\mathrm{Zr(Cl)}]_2\mathrm{O}$ on treatment of the reaction products with water. This substance can be converted back to zirconocene dichloride with HCl and thence back to $(\mathrm{Cp})_2\mathrm{ZrClH}$:

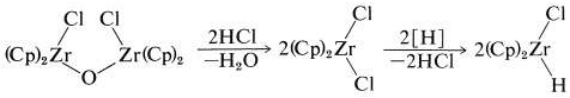
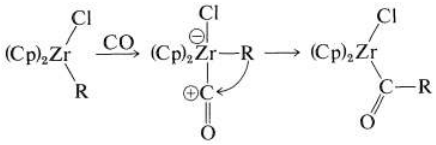


Figure 31-1. This reaction proceeds by way of a carbon-monoxide complex of the metal, which then rearranges by an alkyl shift:



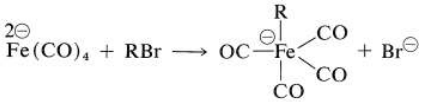
This sequence of steps is an important part of the mechanism of the hydroformylation of alkenes (oxo reaction), to be discussed in Section 31-4B, and also is related to the carbonylation reactions of boranes discussed in Section 16-9G.

31.3.2: A Nucleophilic Transition-Metal Reagent. Sodium Tetracarbonylferrate(-II)

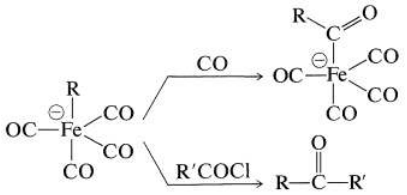
Sodium reacts with iron pentacarbonyl to produce a salt known as sodium tetracarbonylferrate(-II)[2], $\mathrm{Na_2Fe(CO)_4}$, which has been shown by J. P. Collman and co-workers to have considerable potential as a reagent for organic synthesis.

$$2\mathrm{Na} + \mathrm{Fe(CO)_5} \rightarrow \mathrm{Na_2Fe(CO)_4} + \mathrm{CO} \tag{31.3.1}$$

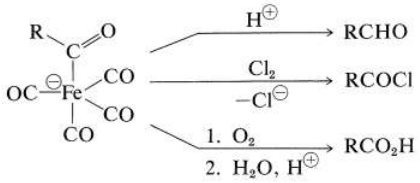
The tetracarbonylferrate dianion is a good nucleophile and reacts with alkyl halides or alkyl sulfonate esters by the S_N2 mechanism (with inversion) to form $\mathrm{C{-}Fe}$ bonds:



The resulting anion undergoes insertion with carbon monoxide or ketone formation with acyl halides in a manner similar to alkylchlorozirconocenes (Section 31-3A):



The product of CO insertion has the potential of transferring $R-\overset{\ominus}{C}=O$, and is converted to RCHO with acids, to RCOX with halogens, or to RCO_2H by oxidation:



[2]The designation (-II) indicates that the iron in this substance can be regarded as being in the -2 oxidation state.

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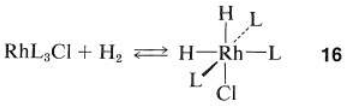
31.4: Some Homogeneous Catalytic Reactions Involving Transition-Metal Complexes

31.4.1: Hydrogenation

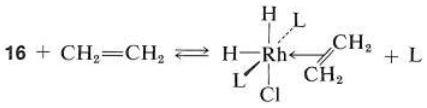
The mechanisms of hydrogenation of alkenes over finely divided metals such as nickel, platinum, and so on (Section 11-2) now are understood in a general way. However, these reactions are extremely difficult to study because they occur on a metallic surface whose structure is hard to define. In contrast, the mechanisms of hydrogenation with homogeneous catalysts are known in considerable detail and provide insight into their heterogeneous counterparts.

Homogeneous hydrogenation catalyzed by the four-coordinated rhodium complex, $\mathrm{Rh[(C_6H_5)_3P]_3Cl}$, has been particularly well investigated. With this catalyst, the first step is formation of the six-coordinated rhodium hydride of known configuration, 16, in which we abbreviate the ligand, triphenylphosphine, $(\mathrm{C_6H_5})_3\mathrm{P}$, as L:



16

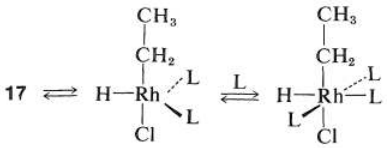
The next step is coordination of the alkene (here ethene) with 16 with loss of L to give the π complex, 17, also of known configuration:



17

Stable ethene complexes of Rh similar to 17 have been isolated and shown to have the π-complex structure. Formation of 17 must be an equilibrium process because addition of extra L reduces the rate of hydrogenation by shifting the equilibrium to the left.

Hydrogenation proceeds by hydride rearrangement of 17 to a five-coordinated ethyl-rhodium complex, 18. This complex regains a ligand molecule to replace the one lost previously, thereby giving the six-coordinated complex, 19:



Stable complexes with $\mathrm{Rh{-}CH_2CH_3}$ bonds similar to 19 have been well characterized. The final step is formation of ethane from 19 with regeneration of $\mathrm{RhL_3Cl}$:

$$19 \rightleftharpoons \mathrm{RhL_3Cl + CH_3CH_3} \tag{31.4.1}$$

Although we abbreviate $(\mathrm{C_6H_5})_3\mathrm{P}$ as L and show little role for it or for the Cl attached to rhodium in the reaction, these ligands play a very important role in providing the electronic and steric environment around the rhodium, which makes efficient catalysis possible. A useful diagram of how the catalyst functions in the overall reaction is shown in Figure 31-2.

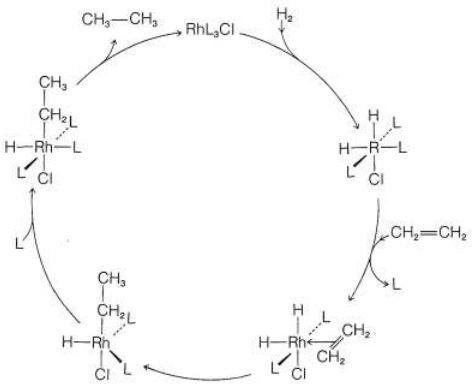


Figure 31-2: Merry-go-round diagram that summarizes the steps in the hydrogenation of ethene by $\mathrm{Rh[(C_6H_5)_3P]_3Cl}$. The key features are the flow of reagents into and the products out of the cycle, the loss and regaining of the ligand, and the regeneration of the catalyst. The ligand triphenylphosphine is represented by L.

31.4.2: Hydroformylation of Alkenes (Oxo Reaction)

The conversion of alkenes to aldehydes with carbon monoxide and hydrogen in the presence of a cobalt catalyst is an important reaction (Section 16-9F):

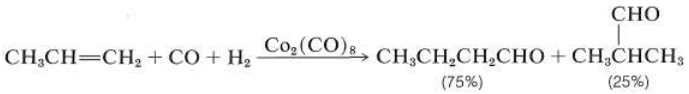
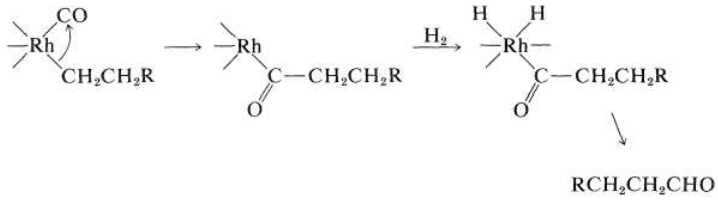


Figure 31-2. The new steps are



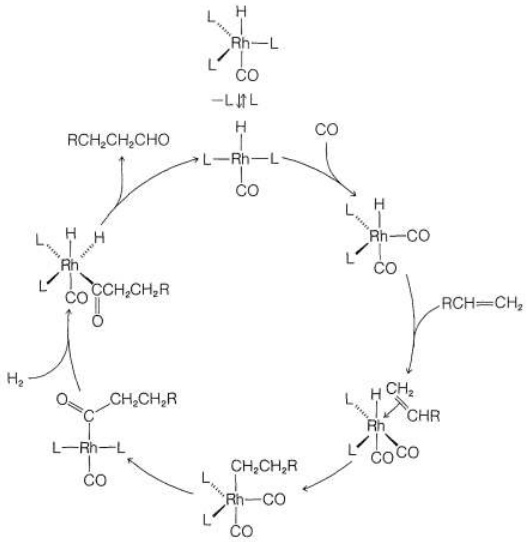


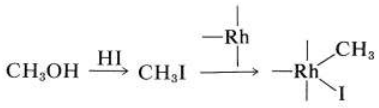
Figure 31-3: Catalytic cycle for the hydroformylation of alkenes as developed by G. Wilkinson. The stereochemical configurations of the participants in the cycle are uncertain.

31.4.3: Carbonylation of Methanol

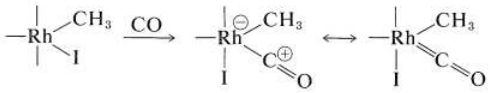
A successful commercial synthesis of ethanoic acid starts with methanol and carbon monoxide in the presence of a rhodium catalyst and hydrogen iodide:

$$CH_3OH + CO \xrightarrow[175^\circ,\ 400\ psi]{RhCl_3 \cdot 3H_2O,\ HI} CH_3CO_2H \qquad (31.4.2)$$

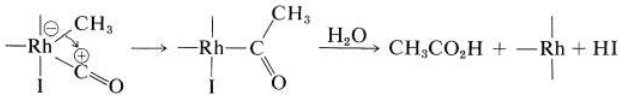
The reaction has some similarity to the hydroformylation reaction described in Section 31-4B. The hydrogen iodide is required to transform methanol to methyl iodide. The rhodium catalyst then reacts with the methyl iodide as a *nucleophilic reagent*:



Complexation with carbon monoxide follows:

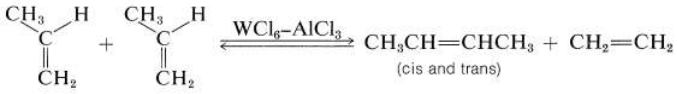


A shift of the methyl group from rhodium to carbon and then hydrolysis gives the acid and regenerates HI and the rhodium catalyst:



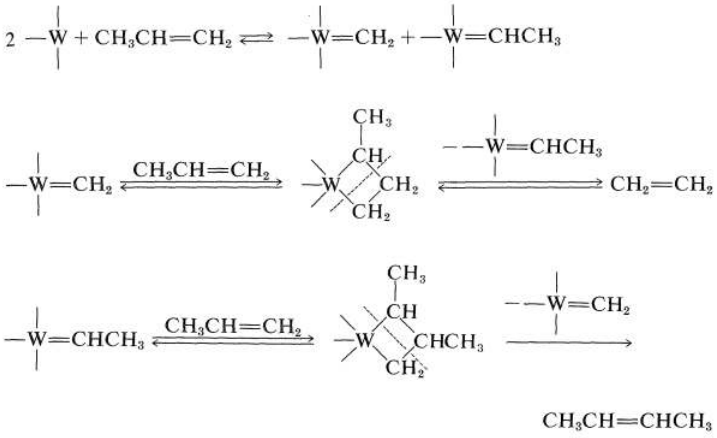
31.4.4: The Alkene Metathesis Reaction

One of the most curious catalytic reactions of alkenes ever discovered is **alkene metathesis** or **alkene dismutation**, in which two alkenes exchange alkylidene groups, usually over a tungsten catalyst. The essence of the reaction is illustrated by a commercial process for converting excess propene to a mixture of ethene and butenes:



The reaction products are those expected if cyclobutanes were intermediates, but formation and cleavage of cyclobutanes is not the correct mechanism because cyclobutanes generally are not converted to alkenes over alkene-metathesis catalysts.

After a great deal of research on the mechanism of this reaction, it now appears likely that the crucial step is the formation of carbene metal complexes and that the products are formed by recombination of the carbenes with alkene in the various possible ways:



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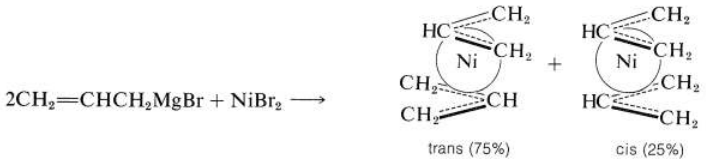
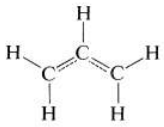
31.5: π-Propenyl Complexes of Nickel

A considerable body of highly useful chemistry based on nickel has been developed, largely by the German chemist, G. Wilke. Many of these reactions involve what are called π-propenyl (π-allyl) complexes and their formation has a close analogy in the formation of ferrocene from cyclopentadienylmagnesium compounds and ferric chloride (Section 31-1). Treatment of $NiBr_2$ with two moles of 2-propenylmagnesium bromide gives a stable (albeit oxygen sensitive) substance of composition $(C_3H_5)_2Ni$:

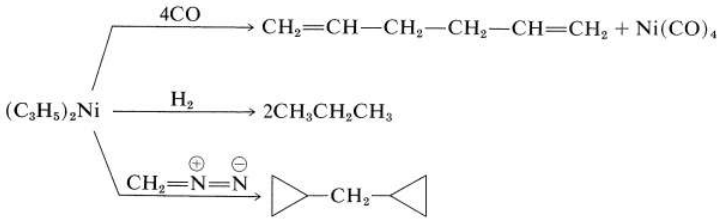


20

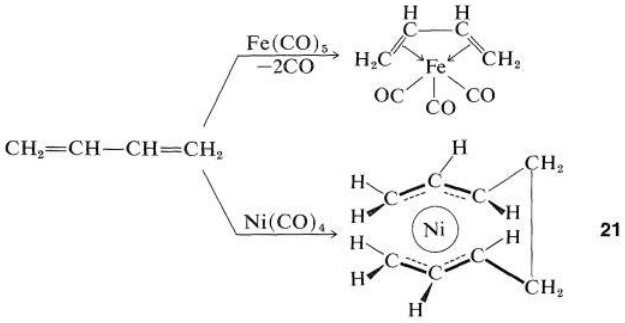
Unlike C_3H_5MgBr, the metal compound has a very complex proton NMR spectrum. Analysis of the spectrum indicates it arises from a mixture (75:25) of two $(C_3H_5)_2Ni$ isomers with each isomer having its C_3H_5 groups in a rigid planar arrangement as follows:



These facts can be accommodated by the *trans*- and *cis*-di-π-propenylnickel structures, 20. Di-π-propenylnickel has many interesting reactions, among which are the following examples:

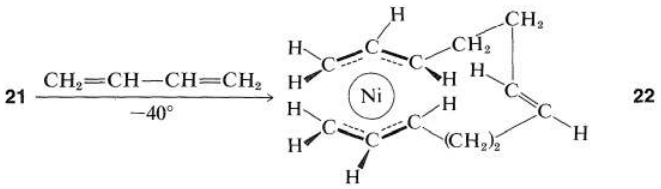


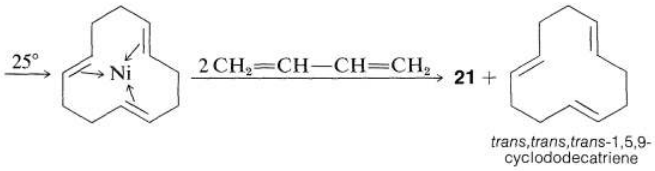
The π-propenyl-type structures are more stable for nickel than for other metals such as iron. With 1,3-butadiene, $Fe(CO)_5$ forms a double π complex, whereas $Ni(CO)_4$ produces a bis-π-propenyl-type structure, 21:



21

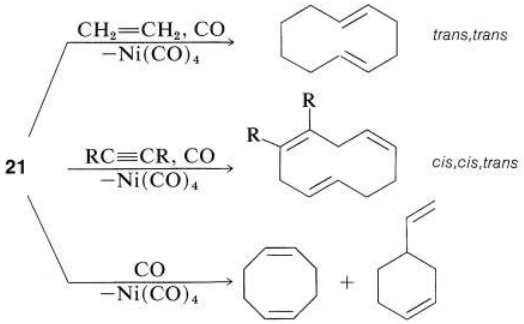
With more 1,3-butadiene, 21 is converted first to 22, which after rearrangement reacts with 1,3-butadiene to give back 21 with liberation of *trans*,*trans*,*trans*-1,5,9-cyclododecatriene:





The overall sequence thus provides a catalytic route for the *cyclic trimerization of* 1,3-butadiene.

Ethene and alkynes react with 21 in the presence of excess carbon monoxide to give ten-membered ring compounds, whereas the reaction of 21 with excess carbon monoxide results in formation of a mixture of six- and eight-membered rings:



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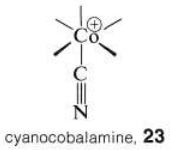
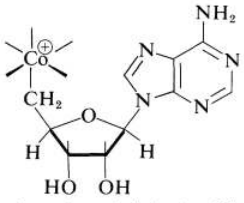
31.6: Vitamin B_{12} as an Organometallic Compound

The structure of vitamin B_{12} shown in Section 30-6B with a cyanide ion coordinated with cobalt is not the active form of the vitamin but is a particularly stable form, convenient to isolate and handle. The active form is a coenzyme that is remarkable in having a carbon-cobalt bond to an essentially alkyl-type carbon. The carbon-cobalt bond is to a 5'-deoxyadenosyl group, and if we abbreviate vitamin B_{12} coordinated to cyanide as 23, the coenzyme can be written, in the same style, as 24. (You will notice that 23 is an abbreviation of the formula of Section 30-6B turned 180°.)

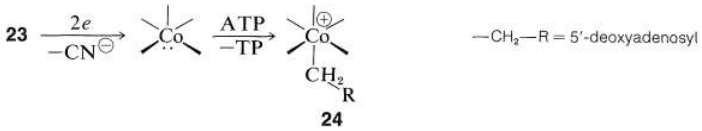


cyanocobalamine, **23**



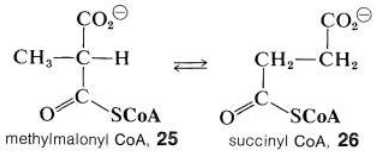
deoxyadenosylcobalamine, **24**

Both 23 and the B_{12} coenzyme, 24, are compounds of Co(III) and both substances have all electrons paired. B_{12} can be reduced to a form with Co(II) which has an unpaired electron and gives an ESR signal (Section 27-9). The cobalt-carbon bond of 24 appears to be formed from 23 by removal of the cyano group and a *two-electron* reduction to Co(I). The reduced cobalt is powerfully *nucleophilic* and probably is alkylated with adenosine triphosphate (ATP, Section 15-5F) to form 24:



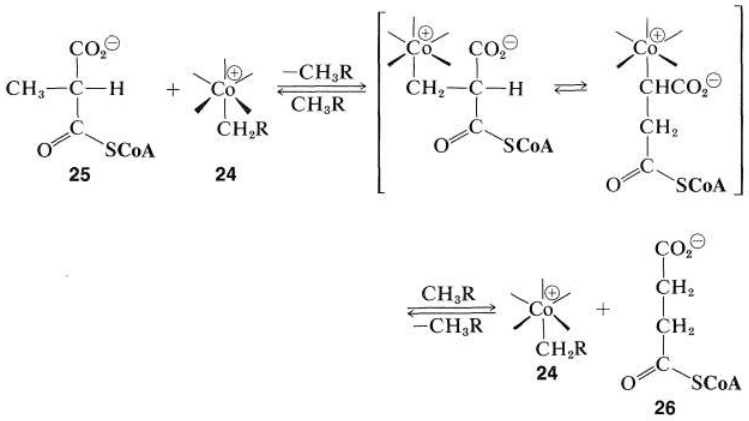
24

Vitamin B_{12} coenzyme participates in several biological reactions but none is more unusual, or as hard to rationalize, as its role in the interconversion of methylpropanedioyl **CoA** (methylmalonyl **CoA**, 25) to butanedioyl **CoA** (succinyl **CoA**, 26):[3]



methylmalonyl CoA, **25** succinyl CoA, **26**

This rearrangement, which is important in the biochemical utilization of propanoic acid, has been shown to involve transfer of a hydrogen from the CH_3- group of 25 to the $-CH_2R$ group of 24. Then rearrangement and formation of 26 occurs along with reformation of 24:



25 **24** **24** **26**

We formulate the intermediate oxidized forms of 25 and 26 with cobalt-to-carbon bonds, but there is no definitive evidence that this is correct. The overall reaction involves attack on the CH_3- of 25, not an easy reaction to carry out in the laboratory, except with

reagents such as $Cl\cdot$, because this CH_3 is not adjacent to a double bond or other activating group. Furthermore, there is no very good analogy for the rearrangement step. At present, although it is known that 24 is reduced to give $CH_3{-}R$, the details of this important biochemical mechanism remain to be elucidated by further research.

[3]For the structure of **CoA**, see Section 18-8F.

31.6.1: Contributors and Attributions

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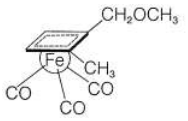
31.E: Transition Metal Organic Compounds (Exercises)

Exercise 31-1 If the ferrocene rings in 3 were *not* free to rotate, how many different dichloroferrocene isomers would be expected (including chiral forms)? How could the substitution method (Section 1-1F) be used to determine which of the isomers was which?

Exercise 31-2 The cyclobutadiene iron complex, 10, has been prepared *optically active*, and when oxidized with Ce(IV) in the presence of tetracyanoethene gives a mixture of *cyclobutadiene* cycloadducts, all of which are optically *inactive*.



10 (one chiral form)

a. Draw the other chiral form of 10.

b. Write structures for the cycloadducts that would be expected to be formed if 10 were oxidized with Ce(IV) in the presence of tetracyanoethene

c. How does formation of optically inactive products indicate that the cycloadducts are formed from the cyclobutadiene corresponding to 10?

d. Is cycloaddition of an alkene to cyclobutadiene best regarded as a [2 + 2] or a [4 + 2] reaction?

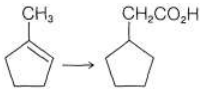
Exercise 31-3* Assuming the molecular formula of 9 is established as $C_{40}H_{60}N_6Zr_2$, explain how the proposed structure is consistent with ^{15}N NMR spectra as follows. Made with $N \equiv {}^{15}{}^{14}N$, 9 shows three widely separated resonance lines of equal intensity. However, when 9 is made with $N \equiv {}^{15}{}^{15}N$, two of the peaks become doublets with a spacing of 6 Hz.

Exercise 31-4 The diphenylethyne complex with Pt(0), analogous to 12, has been shown by x-ray diffraction analysis to have $C-C \equiv C$ bond angles of about 140° and a central $C-C$ bond distance of 1.32 Å. Explain which of the formulations, 11*a*, 11*b*, or 11*c*, seems most reasonable to account for the x-ray data for this complex.

Exercise 31-5 Write the sequence of steps whereby $(Cp)_2ZrClH$ reacts with 2-methyl-2-pentene to form $(Cp)_2Zr(Cl)CH_2CH_2CH_2CH(CH_3)_2$. Why is there no appreciable amount of $(Cp)_2Zr(Cl)CH_2CH(CH_3)CH_2CH_2CH_3$ in the product?

Exercise 31-6 Show how $(Cp)_2ZrClH$ could be used to achieve the following conversions:

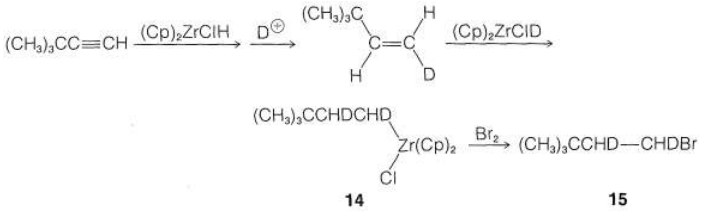
a.



b. $CH_3CH_2CH_2CH_2C \equiv CH \rightarrow CH_3CH_2CH_2CH_2CH{=}CHCHO$

c.* $(CH_3)_3CC \equiv CH \rightarrow (CH_3)_3CCH_2CH_2COCH_3$

Exercise 31-7* The stereochemistry of reactions in which $Zr-C$ bonds are formed and cleaved can be deduced from the results of the following reactions, where D is hydrogen of mass 2.



14 **15**

The $CH-CH$ coupling constants in the proton NMR spectra of 14 and 15 are about 13 Hz. Work out the favorable conformations and the likely configurations of 14 and 15 and the stereochemistry of the addition and cleavage reactions. (Review Section 9-10H.)

Exercise 31-8 Explain how 2-methylpropanal could be formed in substantial amount in the cycle of Figure 31-3 with propene as the starting alkene.

Exercise 31-9 Explain how an alkene-metathesis catalyst might convert a cycloalkene into (a) a long-chain unsaturated polymer, (b) a mixture of large-ring polymers, and (c) a catenane (interlocking carbon rings like two links in a chain).

Exercise 31-10 The NMR spectrum of 2-propenylmagnesium bromide in ether is shown in Figure 31-4. With the aid of the discussion in Sections 9-10C and 9-10E and the knowledge that the CH_2 resonance of ethylmagnesium bromide comes at 38 Hz *upfield* from tetramethylsilane, sketch the NMR spectrum you would expect for $CH_2{=}CHCH_2MgBr$. Consider possible ways of reconciling your expected spectrum with the actual spectrum shown in Figure 31-4. (Review Section 27-2.)

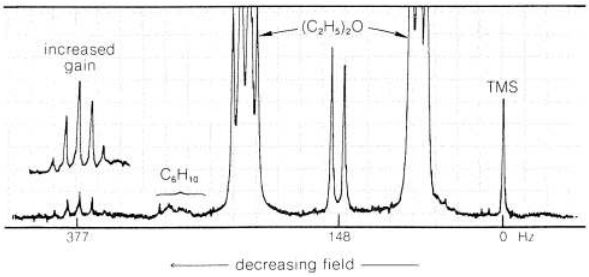
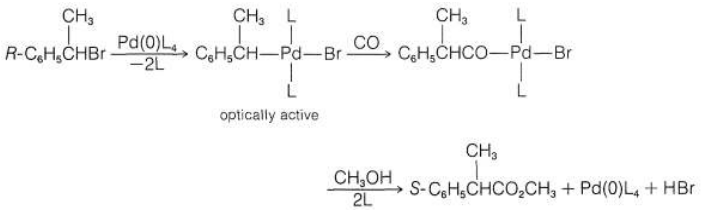


Figure 31-4: *NMR spectrum of 2-propenylmagnesium bromide in diethyl ether solution at* 60 MHz *with reference to tetramethylsilane at* 0 Hz. *The off-scale bands are due to the diethyl ether, and the signals designated* C_6H_{10} *are due to 1,5-hexadiene (coupling product resulting during formation of the Grignard reagent).*

Exercise 31-11 When one mole of azabenzene (pyridine), which is a good ligand, is added to a solution of one mole of 20 in diethyl ether, a complex of composition $(C_3H_5)_2NiNC_5H_5$ is formed in which the very complex proton spectrum of the C_3H_5 groups of 20 becomes greatly simplified and essentially like that of Figure 31-4. Explain how complexation of one mole of azabenzene with nickel in 20 could so greatly simplify the proton NMR spectrum.

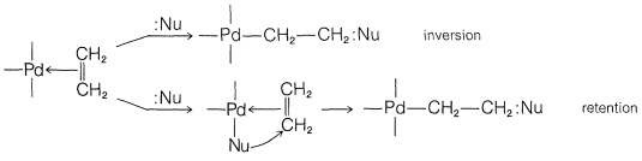
Exercise 31-12* π-Propenyl(ethyl)nickel decomposes at -70° to give propene and ethene. If the ethyl group is labeled with deuterium as $-CH_2CD_3$, the products are C_3H_5D and $CD_2{=}CH_2$. If it is labeled as $-CD_2{-}CH_3$, the products are $C_3H_6 + CD_2{=}CH_2$. Are these the products expected of a radical decomposition, or of a *reversible* hydride-shift followed by decomposition as in the mechanism of Section 31-2B? Suppose the hydride-shift step were not reversible, what products would you expect then?

Exercise 31-13 Palladium has many interesting uses in organic syntheses. The following sequence of reactions also could be achieved by forming and carbonating a Grignard reagent, but would *not* be stereospecific as it is with palladium. Devise mechanistic steps for the reaction that account for the stereochemical result [L is $(C_6H_5)_3P$]. Review Sections 31-2, 31-3, and 31-4.



Exercise 31-14*

a. When a metal is complexed with an alkene, there are two possible ways for nucleophiles to become attached to carbon, as illustrated here with palladium:



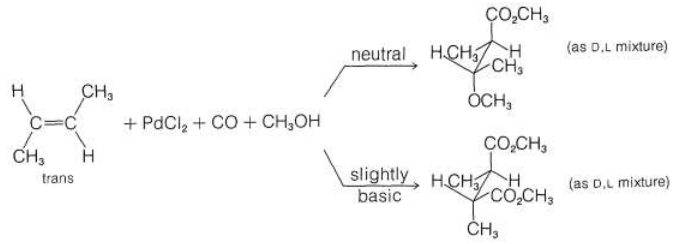
Show how these mechanisms in combination with others described in this chapter can explain how $PdCl_2$ can convert $CH_2{=}CH_2$ to CH_3CHO (Wacker process). Your mechanism must be in accord with the fact that, when the reaction is carried out in D_2O, there is *no* deuterium in the ethanal formed.

$$CH_2{=}CH_2 + PdCl_2 + H_2O \rightarrow CH_3CHO + 2HCl + Pd\,(0) \qquad (31.E.1)$$

[This reaction is used for large-scale production by oxidizing the Pd(0) back to Pd(II) with Cu(II). Thus $Pd\,(0) + 2Cu\,(II) \rightarrow Pd\,(II) + 2Cu\,(I)$, and then the Cu(I) is converted back to Cu(II) with O_2. The overall result is $CH_2{=}CH_2 + \frac{1}{2}O_2$

$\rightarrow CH_3CHO.]$

b. The balance between the competitive nucleophilic reactions described in Part a is a delicate one as judged from the following results:



Write mechanistic steps that will account for the difference in stereochemical results of these reactions, noting that in one case there is a single carbonylation reaction and in the other a dicarbonylation reaction.

31.E.1: Contributors

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