CHM 223 CHEMISTRY III: ORGANIC CHEMISTRY (2024)

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About the Authors

This text has many contributors. Some of the key authors and content creators include:

Dr. Layne Morsch is a Professor of Organic Chemistry and leads the Center for Faculty Excellence at the University of Illinois Springfield. He received his PhD in Organic Chemistry from the University of Illinois Chicago in 2002. Layne has received several distinguished teaching awards including Apple Distinguished Educator (class of 2015), UIS College of Liberal Arts and Sciences Faculty Excellence Award in Teaching (2017), the Burks Oakley II Distinguished Online Teaching Award (2018) and the UIS Pearson Faculty Award for Outstanding Teaching (2019). He has been a faculty fellow and senior faculty fellow with the Center for Online Learning Research and Service at UIS and is currently a mentor to Faculty Fellows in Teaching. His research interests in chemistry education focus on international collaborative learning between student partners and disciplinary language development through organic chemistry courses.

Dr. Steven Farmer is a Professor of Organic Chemistry at Sonoma State University (SSU). He received his Ph.D. in Organic Chemistry from the University of California, Davis in 2002. Dr. Farmer has received multiple teaching awards including the SSU Sarlo Excellence in Teaching Award (2011), the Santa Rosa Chamber of Commerce Excellence in Education Award (2012), the SSU Educational Experience Enhancement Award, and the inaugural SSU Affordable Learning Hero Award (2019). His research and scholarship interests focus on Chemical Education, Affordable Learning, and Public Outreach. He is the author of the book, *Strange Chemistry: The Stories Your Chemistry Teacher Wouldn't Tell You*, which discusses the many fascinating ways chemistry shows up in everyday life.

Dr. Krista Cunningham

Dr. Zachary Sharrett

Dietmar Kennepohl, BSc(Hons) PhD FCIC is Professor of Chemistry and former Associate Vice President Academic at Athabasca University. Most of his teaching experience has been in a distributed and online setting. He holds university, national, and

international teaching awards and is a Society for Teaching and Learning in Higher Education 3M National Teaching Fellow. He is a well-published and sought-after presenter on topics including learning design, learning outcomes, assessment, PLAR, transfer credit, distance and online education, and emerging educational technologies. His research in chemistry education concentrates on the use of online course access including innovative distance delivery methods for undergraduate laboratory work. He has edited several books including *Teaching Science Online: Practical Guidance for Effective Instruction and Lab Work* (2016) and *Accessible Elements: Teaching Science Online and at a Distance* (2010). The latter was winner of the 2010 Charles A. Wedemeyer Award and is a freely available publication.

CHM 223 Chemistry III: Organic Chemistry (2023)

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Licensing

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CHAPTER OVERVIEW

1: Alkynes - An Introduction to Organic Synthesis

Learning Objectives

After you have completed this chapter, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. solve road-map problems involving any of the reactions introduced to this point.
3. design multistep syntheses using any of the reactions introduced to this point, and determine the viability of a given synthesis.
4. define, and use in context, the key terms introduced.

Addition reactions not only dominate the chemistry of alkenes, they are also the major class of reaction you will encounter for alkynes. This chapter discusses an important difference between (terminal) alkynes and alkenes, that is, the acidity of the former; it also addresses the problem of devising organic syntheses. Once you have completed this chapter you will have increased the number of organic reactions in your repertoire, and should be able to design much more elaborate multistep syntheses. As you work through this chapter, you should notice the many similarities among the reactions described here and those from the alkene reactions chapters.

Chapter Video

This video provides an overview of some important alkyne reactions: hydrogenation (3 versions), hydration (2 versions), and C-C bond formation.

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1.1: Chapter Objectives

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1.2: Naming Alkynes (reference only)

Objectives

After completing this section, you should be able to

1. provide the correct IUPAC name of an alkyne, given its Kekulé, condensed or shorthand structure.
2. provide the correct IUPAC name of a compound containing both double and triple bonds, given its Kekulé, condensed or shorthand structure.
3. draw the structure of a compound containing one or more triple bonds, and possibly one or more double bonds, given its IUPAC name.
4. name and draw the structure of simple alkynyl groups, and where appropriate, use these names as part of the IUPAC system of nomenclature.

Study Notes

Simple alkynes are named by the same rules that are used for alkenes (see Section 7.3), except that the ending is *-yne* instead of *-ene*. Alkynes cannot exhibit *E*,*Z* (cis-trans) isomerism; hence, in this sense, their nomenclature is simpler than that of alkenes.

Alkynes are organic molecules made of the functional group carbon-carbon triple bonds and are written in the empirical formula of C_nH_{2n-2}. They are unsaturated hydrocarbons. Like alkenes have the suffix –ene, alkynes use the ending –yne; this suffix is used when there is only one alkyne in the molecule.

$$HC{\equiv}CH$$

Introduction

Here are the molecular formulas and names of the first ten carbon straight chain alkynes.

Name	Molecular Formula
Ethyne	C_2H_2
Propyne	C_3H_4
1-Butyne	C_4H_6
1-Pentyne	C_5H_8
1-Hexyne	C_6H_{10}
1-Heptyne	C_7H_{12}
1-Octyne	C_8H_{14}
1-Nonyne	C_9H_{16}
1-Decyne	$C_{10}H_{18}$

The more commonly used name for ethyne is acetylene, which used industrially.

Naming Alkynes

Like previously mentioned, the IUPAC rules are used for the naming of alkynes.

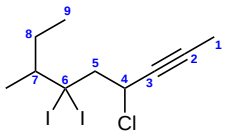
Rule 1

Find the longest carbon chain that includes both carbons of the triple bond.

Rule 2

Number the longest chain starting at the end closest to the triple bond. A 1-alkyne is referred to as a terminal alkyne and alkynes at any other position are called internal alkynes.

For example:

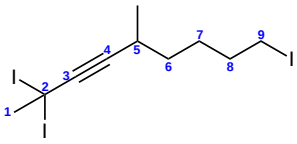


4-chloro-6,6-diiodo-7-methylnon-2-yne

Rule 3

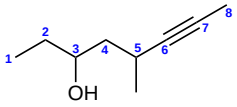
After numbering the longest chain with the lowest number assigned to the alkyne, label each of the substituents at its corresponding carbon. While writing out the name of the molecule, arrange the substituents in alphabetical order. If there are more than one of the same substituent use the prefixes di, tri, and tetra for two, three, and four substituents respectively. These prefixes are not taken into account in the alphabetical order.

For example:



2,2,9-triiodo-5-methylnon-3-yne

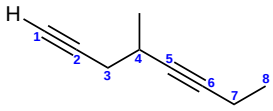
If there is an alcohol present in the molecule, number the longest chain starting at the end closest to it, and follow the same rules. However, the suffix would be –ynol, because the alcohol group takes priority over the triple bond.



5-methyl-6-octyn-3-ol

When there are two triple bonds in the molecule, find the longest carbon chain including both the triple bonds. Number the longest chain starting at the end closest to the triple bond that appears first. The suffix that would be used to name this molecule would be –diyne.

For example:

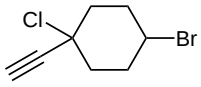


4-methyl-1,5-octadiyne

Rule 4

Substituents containing a triple bond are called alkynyl.

For example:



4-bromo-1-chloro-1-ethynylcyclohexane

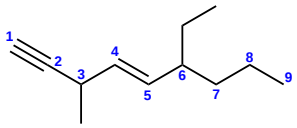
Here is a table with a few of the alkynyl substituents:

Name	Molecule

Name	Molecule
Ethynyl	-C≡CH
2- Propynyl	$-CH_2C{\equiv}CH$
2-Butynyl	$-CH_3C{\equiv}CH_2CH_3$

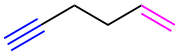
Rule 5

A molecule that contains both double and triple bonds is called an alkenyne. The chain can be numbered starting with the end closest to the functional group that appears first. For example:



(*E*)-6-ethyl-3-methyl-non-4-en-1-yne

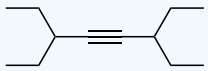
If both functional groups are the exact same distance from the ending of the parent chain, the alkene takes precedence in the numbering.



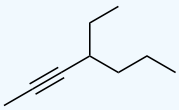
hex-1-en-5-yne

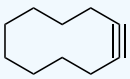
Exercise 1.2.1

1) Name the following compounds:

a) 

b)

c) 

d) 

2) How many isomers are possible for C_5H_8? Draw them.

3) Draw the following compounds:

a) 4,4-dimethyl-2-pentyne

b) 3-octyne

c) 3-methyl-1-hexyne

d) *trans* 3-hepten-1-yne

4) Do alkynes show cis-trans isomerism? Explain.

Answer

1)

A – 3,6-diethyl-4-octyne

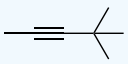
B – 3-methylbutyne

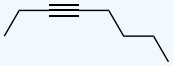
C – 4-ethyl-2-heptyne

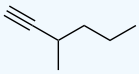
D – cyclodecyne

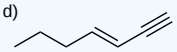
2) 2 possible isomers

3)

a) 

b) 

c) 

d) 

4) No. A triply bonded carbon atom can form only one other bond and has linear electron geometry so there are no "sides". Allkenes have two groups attached to each inyl carbon with a trigonal planar electron geometry that creates the possibility of cis-trans isomerism.

Reference

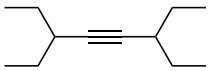
1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

Exercises

Questions

Q9.1.1

Name the following compounds:

a) 

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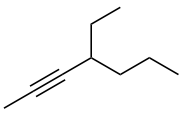
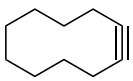
c) 

d) 

Q9.1.2

How many isomers are possible for C_5H_8? Draw them.

Q9.1.3

Draw the following compounds:

A) 4,4-dimethyl-2-pentyne

B) 3-octyne

C) 3-methyl-1-hexyne

D) *trans* 3-hepten-1-yne

Q9.1.4

Do alkynes show cis-trans isomerism? Explain.

Solutions

S9.1.1

A – 3,6-diethyl-4-octyne

B – 3-methylbutyne

C – 4-ethyl-2-heptyne

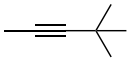
D – cyclodecyne

S9.1.2

2 possible isomers

S9.1.3

a)



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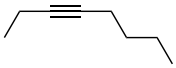
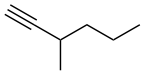


c)



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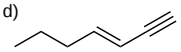

S9.1.4

No. A triply bonded carbon atom can form only one other bond and has linear electron geometry so there are no "sides". Allkenes have two groups attached to each inyl carbon with a trigonal planar electron geometry that creates the possibility of cis-trans isomerism.

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1.3: Preparation of Alkynes - Elimination Reactions of Dihalides (reference only)

Objectives

After completing this section, you should be able to

1. write an equation to describe the preparation of an alkyne by the dehydrohalogenation of a vicinal dihalide or vinylic halide.
2. identify the alkyne produced from the dehydrohalogenation of a given vicinal dihalide or vinylic halide.
3. write a reaction sequence to show how the double bond of an alkene can be transformed into a triple bond.
4. identify the vicinal dihalide (or vinylic halide) needed to synthesize a given alkyne by dehydrohalogenation.

Key Terms

Make certain that you can define, and use in context, the key terms below.

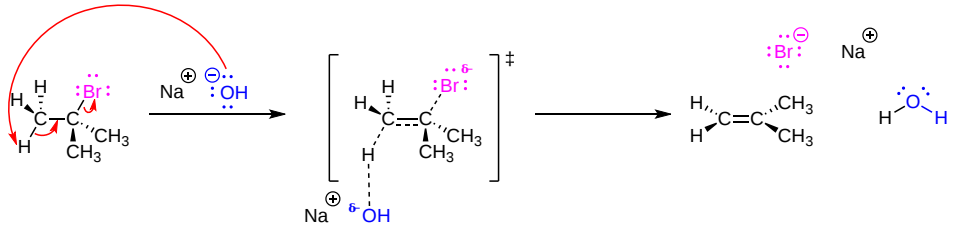
- vicinal dihalide
- vinylic halide

Alkynes can be a useful functional group to synthesize due to some of their antibacterial, antiparasitic, and antifungal properties. One simple method for alkyne synthesis is by double elimination from a dihaloalkane.

E2 Mechanism

Section 8.2 discussed that alkenes can be formed through an elimination reaction. In particular, the synthesis of alkynes will utilize the E2 elimination reaction. During the mechanism of an E2 reaction, a strong base removes a hydrogen adjacent to a halogen. The electrons from the broken C-H bond move to form the C=C double bond. Doing this causes the halogen to be ejected from the compound. Overall, a hydrogen and a halogen are eliminated from the compound to form an alkene. During this mechanism there is a stereoelectronic requirement that the adjacent hydrogen and the halogen be adjacent to each other.

E2 reaction will be discussed in greater detail in **Section 11.10**.

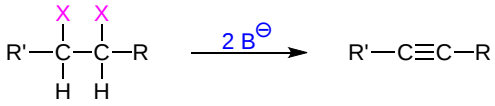


1. The base will deprotonate the haloalkane.
2. The leaving group will depart from the molecule.
3. The deprotonated carbon will rehybridize from sp^3 to sp^2.

Alkyne Formation Through Dihaloalkane Elimination

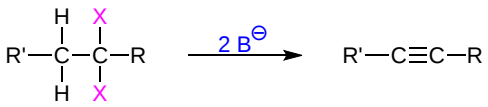
Alkynes are frequently prepared through a double E2 reaction using 2 halides that are vicinal (meaning on adjacent carbons) or geminal (meaning on the same carbon). Because the E2 reaction takes place twice 2 π bonds are formed thus creating an Alkyne. Although hydroxide and alkoxide bases could be used for the strong base required for an E2 reaction, their used opens the possibility of position rearrangement in the alkyne product. Because of this, the stronger base sodium amide in ammonia ($NaNH_2/NH_3$) is commonly used.

General Reaction



Vicinal dihalide converted to an alkyne

or

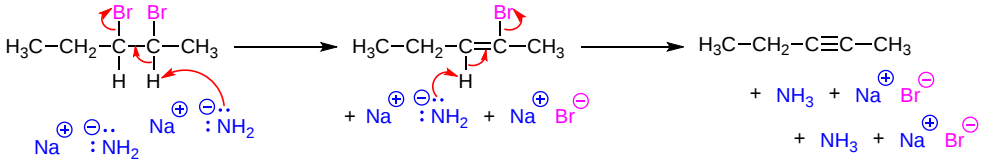


Geminal dihalide converted to an alkyne

Note! If a terminal alkyne is formed during the reaction, 3 equivalents of base are required instead of 2 as discussed below.

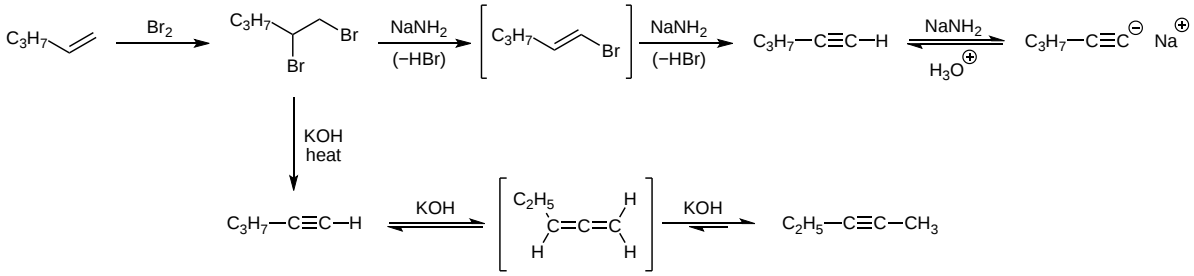
Mechanism

The following mechanism represents the reaction between 2,3-Dibromopentane with sodium amide in liquid ammonia to form pent-2-yne. During this mechanism an intermediate alkene is formed. Notice that in the alkene intermediate, the remaining hydrogen and halogen are anti to each other due to the stereoelectronic requirements of the E2 mechanism. The intermediate alkene is converted to an alkyne by a second E2 elimination of a hydrogen and halogen.



Terminal Alkynes

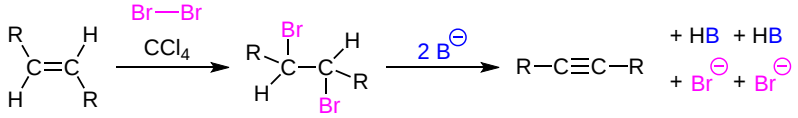
The acidity of terminal alkynes also plays a role in product determination when vicinal (or geminal) dihalides undergo base induced dielimination reactions. The following example illustrates eliminations of this kind starting from 1,2-dibromopentane, prepared from 1-pentene by addition of bromine. The initial elimination presumably forms 1-bromo-1-pentene, since base attack at the more acidic and less hindered 1°-carbon should be favored. The second elimination then produces 1-pentyne. If the very strong base such as sodium amide is used, the terminal alkyne is trapped as its sodium salt, from which it may be released by mild acid treatment. However, if the weaker base KOH with heat is used for the elimination, the terminal alkyne salt is not formed, or is formed reversibly, and the initially generated 1-pentyne rearranges to the more stable 2-pentyne via an allene intermediate. Even though terminal alkynes can be generated using sodium amide as a base, most chemists will prefer to use S_N2 nucleophilic substitution instead of elimination when trying to form a terminal alkyne.



Preparation of Alkynes from Alkenes

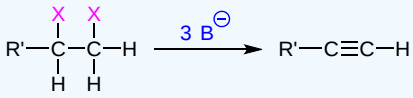
An simple method for the preparation of alkynes utilizes alkenes as starting material. The process begins with the electrophilic addition of a halogen to the alkene bond to form the dihaloalkane. Then the double E2 elimination process is used to form the 2 π bonds of an alkyne.

This first process is gone over in much greater detail in the page on halogenation of an alkene. In general, chlorine or bromine is used with an inert halogenated solvent like chloromethane to create a vicinal dihalide from an alkene. The vicinal dihalide formed is the reactant needed to produce the alkyne using double elimination, as covered previously on this page.



Exercise 1.3.1

1) Why would we need 3 bases for every terminal dihaloalkane instead of 2 in order to form an alkyne?

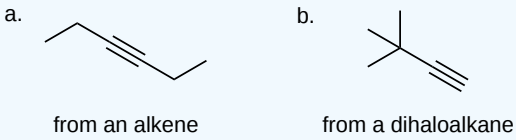


2) What are the major products of the following reactions:

a.) 1,2-Dibromopentane with sodium amide in liquid ammonia

b.) 1-Pentene first with Br_2 and chloromethane, followed by sodium ethoxide (Na^+ $^-O\text{-}CH_2CH_3$)

3) What would be good starting molecules for the synthesis of the following molecules:



4) Use a 6 carbon diene to synthesize a 6 carbon molecule with 2 terminal alkynes.

5) Identify the vinyl halide or halides and the vicinal dihalide or dihalides that could be used in the synthesis of:

a) 2,2,5,5-Tetramethyl-3-hexyne.

b) 4-Methyl-2-hexyne.

Answer

1) Remember that hydrogen atoms on terminal alkynes make the alkyne acidic. One of the base molecules will pull off the terminal hydrogen instead of one of the halides like we want.

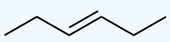
2)

a) 1-Pentyne

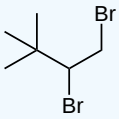
b) 1-Pentyne

3)

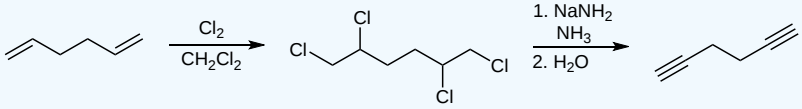
a.



b.

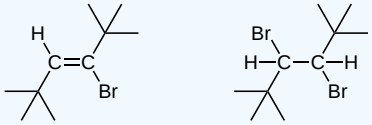


4) Bromine or chlorine can be used with different inert solvents for the halogenation. This can be done using many different bases. Liquid ammonia is used as a solvent and needs to be followed by an aqueous work-up.

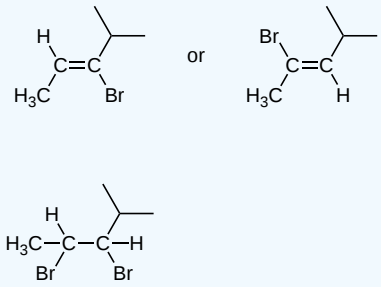


5)

a)



b)



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1. Vollhardt, Peter, and Neil Shore. Organic Chemistry: Structure and Function. 5th. New York: W.H. Freeman and Company, 2007.
2. Daley, Richard, and Sally Daley. "13.8 Elimination of Organohalogens." Organic Chemistry. Daley. 5 July 2005. 21 Feb. 2009. <https://studylib.net/doc/8721401/13-elimination-reactions>.

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1.4: Reactions of Alkynes - Addition of HX and X_2

Objectives

After completing this section, you should be able to

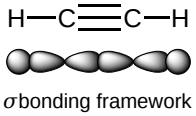
1. describe the bonding and geometry of the carbon-carbon triple bond in terms of the *sp*-hybridization of the carbon atoms involved.
2. explain the reactivity of alkynes based on the known strengths of carbon-carbon single, double and triple bonds.
3. write equations for the reaction of an alkyne with one or two equivalents of halogen (chlorine or bromine) or halogen acid (HCl, HBr or HI).
4. draw the structure of the product formed when an alkyne reacts with one equivalent of the halogens and halogen acids listed in Objective 3.
5. identify the alkyne which must have been used in an addition reaction with a halogen or halogen acid, given the product of such a reaction.

Study Notes

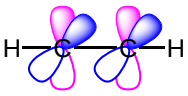
You might find it useful to review your notes from alkene reactions before you begin work on this chapter. If necessary, construct a molecular model of a simple alkyne. Notice the similarity between the behaviour of alkenes and that of alkynes. It might be helpful to review the Chapter on Alkene Reactions.

The Alkyne Triple Bond

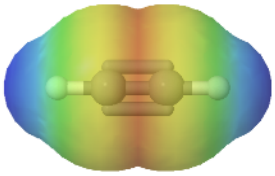
The carbon-carbon triple bonds of alkynes are created by the the overlap of orbitals on two sp hybridized carbon atoms. The molecule acetylene (HCCH) is said to contain three sigma bonds and two pi bonds. The C-C sigma bond of acetylene is formed by the overlap an *sp* hybrid orbital from each of the carbon atoms. The two C-H sigma bonds are formed by the overlap of the second *sp* orbital on each carbon atom with a 1*s* orbital from a hydrogen. Each carbon atom still has two half-filled P orbitals, which are perpendicular both to each other and to the line formed by the sigma bonds. These two perpendicular pairs of *p* orbitals form two pi bonds between the carbons, resulting in a triple bond overall (one sigma bond plus two pi bonds). The electrostatic potential map of acetylene shows that the pi electrons of the triple bond form a negative belt (shown in red) around the center of the molecule.



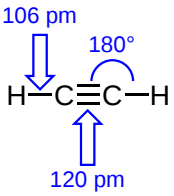
σ bonding framework



π overlap



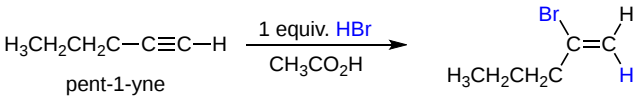
Acetylene is linear, as predicted by VSEPR, with all four atoms lying in a straight line and both H-C-C bond angles being 180°. The triple bond in acetylene is the shortest (120 pm) and the strongest (964 kJ/mol) carbon-carbon bond known.



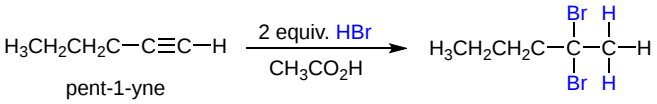
Electrophilic Addition of HX to Alkynes

Alkynes undergo electrophilic addition in much the same manner as alkenes, however, the presence to two pi bonds allows for the possibly of the addition happening twice. The addition of one equivalent of hydrogen chloride or hydrogen bromide converts alkynes to haloalkenes. The addition of two or more equivalents of HCl or HBr converts alkynes to geminal dihalides through an haloalkene intermediate. These additions are regioselective and follow Markovnikov's rule. The double bonds formed during the reaction with internal alkynes tend to have Z stereochemistry although not always.

HBr Addition to a Terminal Alkyne

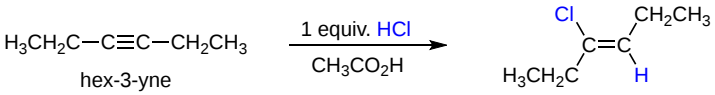


pent-1-yne → 2-bromopent-1-ene

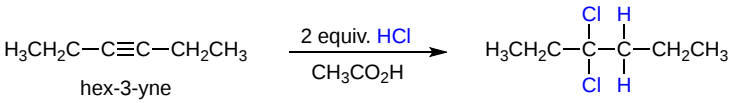


pent-1-yne → 2,2-dibromopentane

HCl Addition to a Symmetrical Internal Alkyne



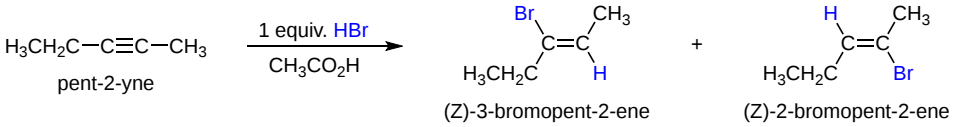
hex-3-yne → (Z)-4-chlorohex-3-ene



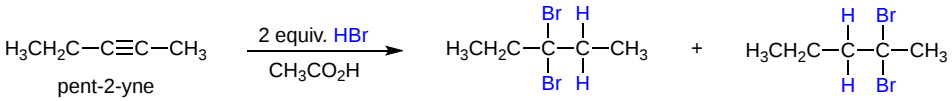
hex-3-yne → 3,3-dichlorohexane

HBr Addition to an Asymmetrical Internal Alkyne

The addition of HX to an asymmetrical internal alkyne tend to make a mixture of isomers as products.



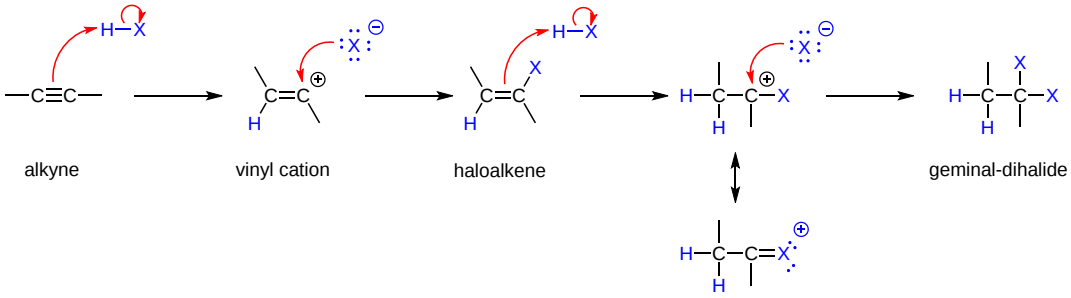
pent-2-yne → (Z)-3-bromopent-2-ene + (Z)-2-bromopent-2-ene



pent-2-yne → 3,3-dibromopentane + 2,2-dibromopentane

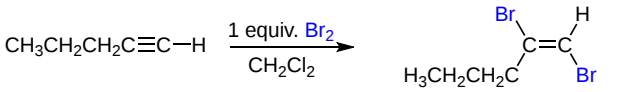
Mechanism

The mechanism for the electrophilic addition of HX to an alkyne is analogous to the HX addition to an alkene. The presence of two pi bonds in the alkyne allows for the addition of HX to occur twice. The addition of H^+ to the alkyne forms a vinyl cation will preferably form on the more substituted side of the alkyne following Markovnikov's rule. The subsequent addition of Br^- forms a haloalkene which undergoes electrophilic addition to a second H^+. The carbocation form will preferably form on the carbon attached to the halogen already in place. The carbocation is stabilized by the halogen through the creation of a resonance structure which obeys the octet rule. This stabilizing effect ensures that a geminal-dihalide is the sole product and no vicinal-dihalide is formed.

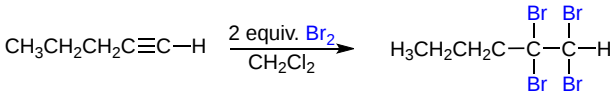


Electrophilic Addition of X_2 to Alkynes

Alkynes undergo the same type of electrophilic addition with chloride and bromine as alkenes. However, with alkynes the halogen addition can occur once or twice depending on the molar equivalents of halogen used in the reaction. If one molar equivalent of halogen is used, a dihaloalkene is formed. The anti addition of the reaction mechanism causes the halogens to be trans in the resulting alkene. The addition of two or more molar equivalents of halogen converts the alkyne to a tetrahaloalkane through a dihaloalkene intermediate.



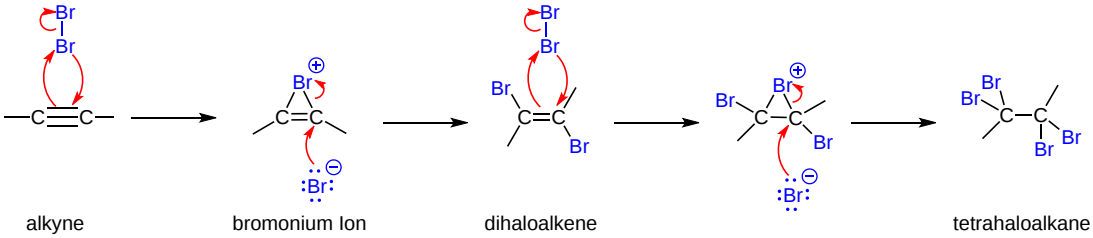
pent-1-yne (*E*)-1,2-dibromopent-1-ene



pent-1-yne 1,1,2,2-tetrabromopentane

Mechanism

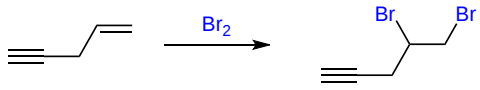
The alkyne undergoes electrophilic addition with bromine to form a bromonium ion in a three-membered ring. The ejected bromide ion performs an S_N2 reaction with the bromonium ion causing the ring to open and the bromines in the resulting alkene to be in a *trans* configuration. The process is repeated with a second pi bond creating a tetrahaloalkane as a product.



alkyne bromonium Ion dihaloalkene tetrahaloalkane

Relative Reactivity of Alkynes and Alkenes to Electrophilic Reagents

When the addition reactions of electrophilic reagents, such as strong Brønsted acids and halogens, to alkynes are studied there is a curious paradox. The reactions of alkynes are even more exothermic than the additions to alkenes, and yet the rate of addition to alkynes is slower by a factor of 100 to 1000. This concept is shown in the reaction of one equivalent of bromine with 1-penten-4-yne to produce 4,5-dibromopent-1-yne as the chief product.

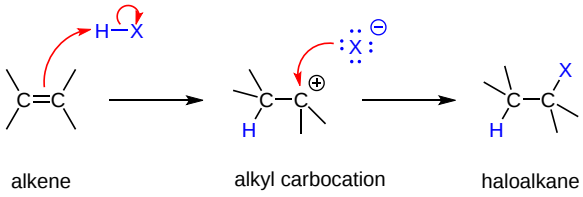


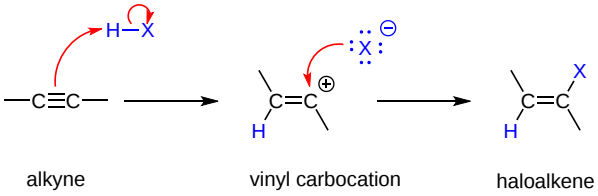
1-penten-4-yne 4,5-dibromopent-1-yne

Why are the reactions of alkynes with electrophilic reagents more sluggish than the corresponding reactions of alkenes? Typically, addition reactions to alkynes are more exothermic than additions to alkenes, and there would seem to be a higher pi-electron density about the triple bond (two pi-bonds versus one). Two factors are significant in explaining this apparent paradox. First, although there are more pi-electrons associated with the triple bond, the sp-hybridized alkyne carbons are more electronegative than the sp^2-hybridized alkene carbons. The alkyne carbons exert a strong attraction for their pi-electrons, which are consequently bound more tightly to the functional group than are the pi-electrons of a double bond. This is seen in the ionization potentials of ethylene and acetylene. Remember an **ionization potential** is the minimum energy required to remove an electron from a molecule of a compound. Since the initial interaction between an electrophile and an alkene or alkyne involves the donation of electrons, the relatively slower reactions of alkynes becomes understandable.

Acetylene	$HC{\equiv}CH + Energy \rightarrow [HC{\equiv}CH\ \bullet^{(+)} + e^{(-)}$	$\Delta H = +264$ kcal/mole
Ethylene	$H_2C{=}CH_2 + Energy \rightarrow [H_2C{=}CH_2]\ \bullet^{(+)} + e^{(-)}$	$\Delta H = +244$ kcal/mole

A second factor is presumed to be the stability of the carbocation intermediate generated by sigma-bonding of a proton or other electrophile to one of the triple bond carbon atoms. When comparing the mechanism for the addition of HBr to an alkene and an alkyne, the alkyne reaction creates a vinyl carbocation which is less stable than the alkyl carbocation made during the alkene reaction.

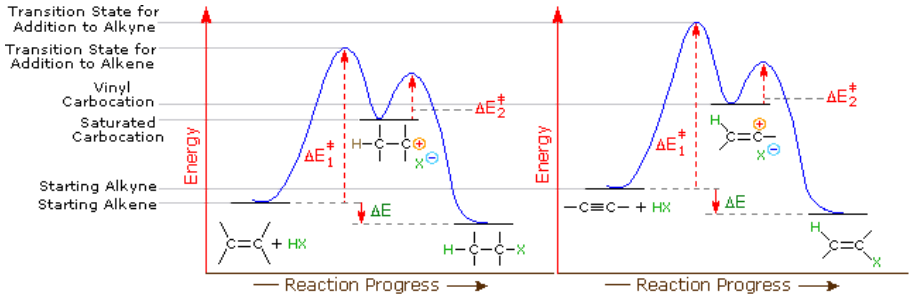




Indeed, we can modify our earlier ordering of carbocation stability to include these vinyl cations in the manner shown below.

Substitution		**Methyl**		**1°-Vinyl**		**1°**		**2°-Vinyl**		**2°**		**1°-Allyl**		**3°**
Stability	$CH_3^{(+)}$	≈	$RCH=CH^{(+)}$	<	$RCH_2^{(+)}$	≈	$RCH=CR^{(+)}$	<	$R_2CH^{(+)}$	≈	$CH_2=CH-CH_2^{(+)}$	<	$R_3C^{(+)}$

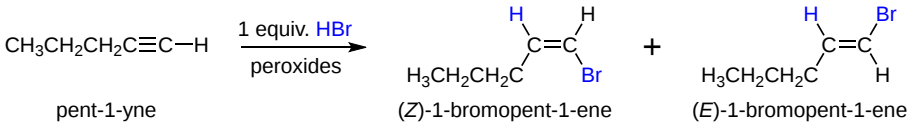
Application of the Hammond postulate indicates that the activation energy for the generation of a vinyl cation intermediate would be higher than that for a lower energy intermediate. Thus, electrophilic reactions with alkenes have a lower activation energy and process faster than the corresponding reaction with an alkyne. This is illustrated for alkenes versus alkynes by the following energy diagrams. Despite these differences, electrophilic additions to alkynes have emerged as exceptionally useful synthetic transforms.



A Comparison of Energy Profiles for Electrophilic Addition to Alkenes and Alkynes

Electrophilic Addition of HX with Peroxides to Alkynes

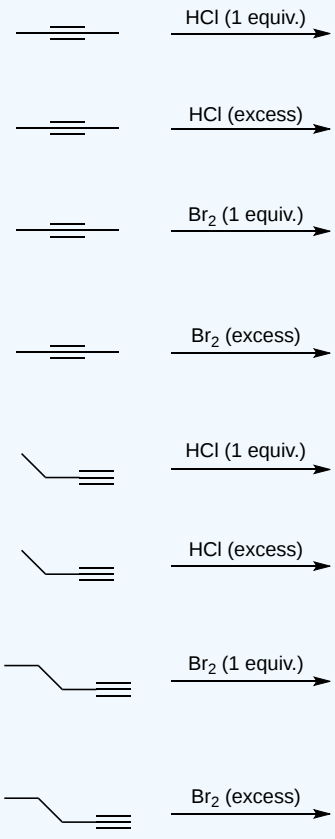
When 1 equivalent of HBr is reacted with alkynes in the presence of peroxides and Anti-Markovnikov addition occurs. The use of peroxides causes the reaction to occur via a free radical mechanism. The bromine adds to the less substituted alkyne carbon while the hydrogen adds to the more substituted creating a haloalkene. Typically, H and Br are added in a syn or anti manner creating a mixture of products.



pent-1-yne (*Z*)-1-bromopent-1-ene (*E*)-1-bromopent-1-ene

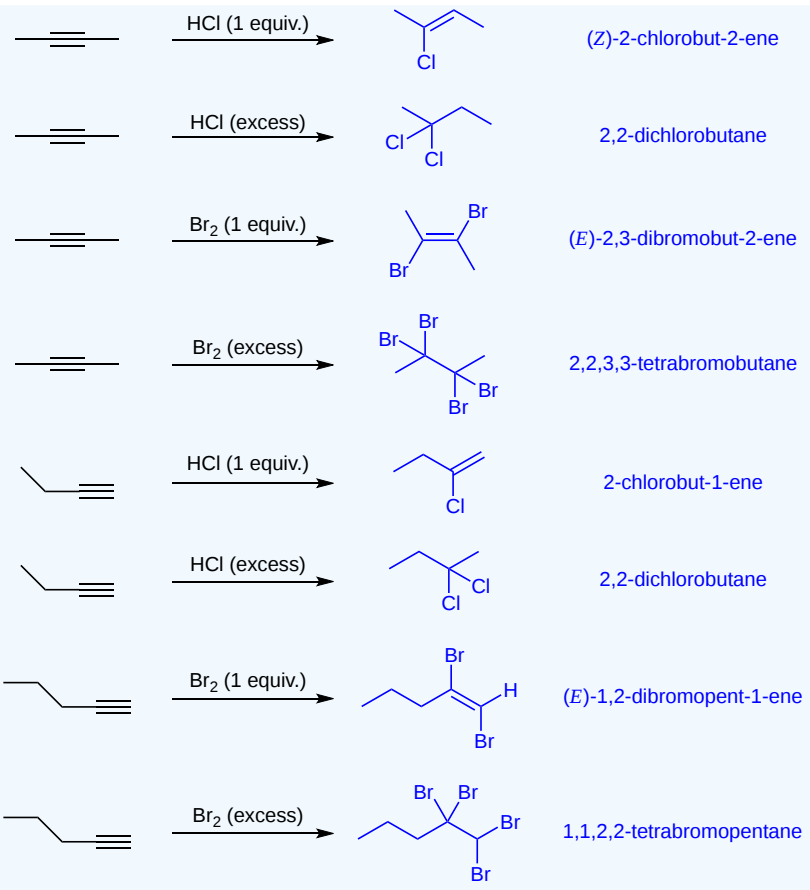
Exercise 1.4.1

Draw the structure of the product formed in each of the reactions listed below:



Answer

https://chem.libretexts.org/@go/page/443753



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1.5: Hydration of Alkynes

Objectives

After completing this section, you should be able to

1. write the equation for the reaction of water with an alkyne in the presence of sulfuric acid and mercury(II) sulfate.
2. describe keto-enol tautomerism.
3. predict the structure of the ketone formed when a given alkyne reacts with sulfuric acid in the presence of mercury(II) sulfate.
4. identify the reagents needed to convert a given alkyne to a given ketone.
5. identify the alkyne needed to prepare a given ketone by hydration of the triple bond.
6. write an equation for the reaction of an alkyne with borane.
7. write the equation for the reaction of a vinylic borane with basic hydrogen peroxide.
8. identify the reagents, the alkyne, or both, needed to prepare a given ketone or a given cis alkene through a vinylic borane intermediate.
9. identify the ketone produced when a given alkyne is reacted with borane followed by basic hydrogen peroxide.
10. explain why it is necessary to use a bulky, sterically hindered borane when preparing vinylic boranes from terminal alkynes.
11. predict the product formed when the vinylic borane produced from a terminal alkyne is treated with basic hydrogen peroxide.
12. identify the alkyne needed to prepare a given aldehyde by a vinylic borane.

Key Terms

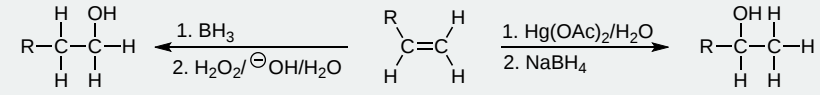
Make certain that you can define, and use in context, the key terms below.

- enol
- keto-enol tautomeric equilibrium
- tautomerism
- tautomers

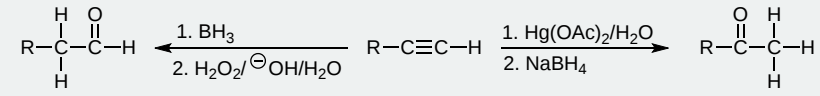
Study Notes

Rapid interconversion between tautomers is called *tautomerism*; however, as the two tautomers are in equilibrium, the term *tautomeric equilibrium* may be used. This section demonstrates the equilibrium between a ketone and an enol; hence, the term *keto-enol tautomeric equilibrium* is appropriate. The term “enol” indicates the presence of a carbon-carbon double bond and a hydroxyl (i.e., alcohol) group.

Notice how hydroboration complements hydration in the chemistry of both alkenes and alkynes.



a primary alcohol — a terminal alkene — a secondary alcohol

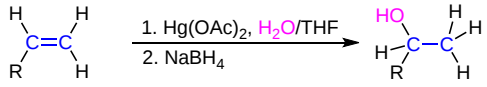


an aldehyde — a terminal alkyne — a ketone

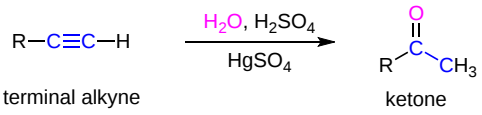
Mercury(II)-Catalyzed Hydration of Alkynes

As with alkenes, hydration (addition of water) of alkynes requires a strong acid, usually sulfuric acid, and is facilitated by the mercuric ion (Hg^{2+}). However, the hydration of alkynes gives ketone products while the hydration of alkenes gives alcohol

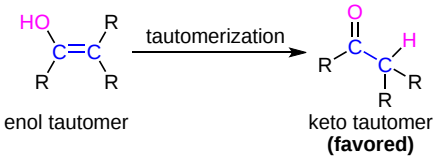
products. Notice that the addition of oxygen in both reactions follows Markovnikov rule.



During the hydration of an alkyne, the initial product is an enol intermediate (a compound having a hydroxyl substituent attached to a double-bond), which immediately rearranges to the more stable ketone through a process called **enol-keto tautomerization**.

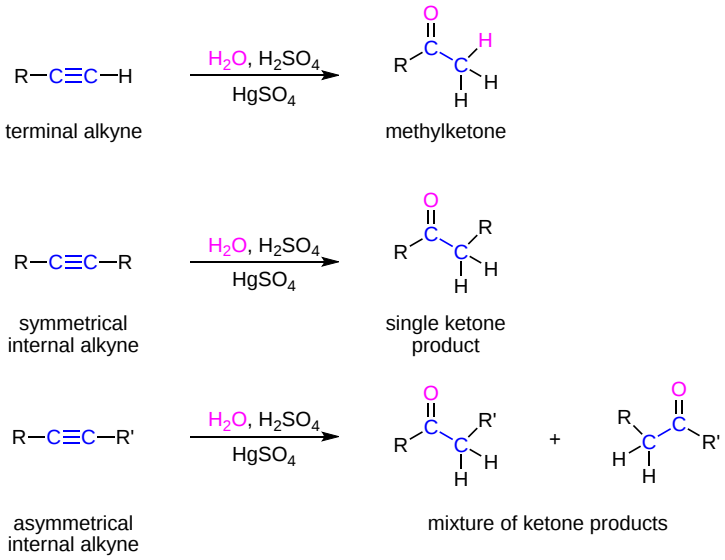


Tautomers are defined as rapidly inter-converted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom and a differently located double bond. The keto and enol tautomers are in equilibrium with each other and with few exceptions the keto tautomer is more thermodynamically stable and therefor favored by the equilibrium. This mechanism for tautomerization will be discussed in greater detail in **Section 6-2**.



General Reaction

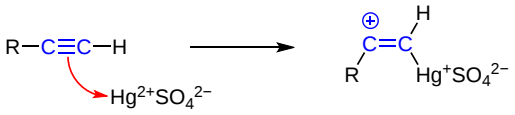
For terminal alkynes, the addition of water follows the Markovnikov rule, and the final product is a methyl ketone. For internal alkynes the addition of water is not regioselective. Hydration of symmetrical internal alkynes produces a single ketone product. However, hydration of asymmetrical alkynes, (i.e. if R & R' are not the same) produces two isomeric ketone products.



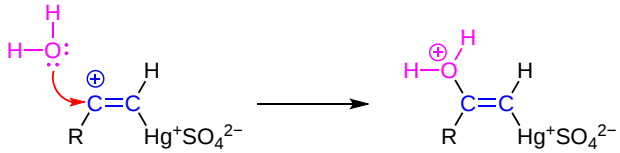
Mechanism

The mechanism starts with the eletrophilic addition of the mercuric ion (Hg^{2+}) to the alkyne producing a mercury-containing vinylic carbocation intermediate. Nucleophilic attack of water on the vinylic carbocation forms a C-O bond to produce a protonated enol. Deprotonation of the enol by water then produces a organomurcury enol. The murcury is substituted with H^+ to produced a neutral enol and regenerate the Hg^{2+} catalyst. The enol is converted to the ketone product through keto-enol tautomerization the mechanism of which is provided in the Carbonyl alpha-Substitution Chapter.

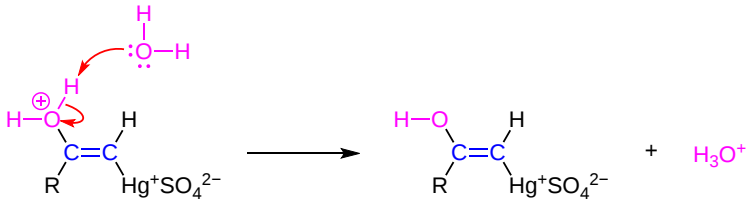
1) Electrophilic addition of Hg^{2+}



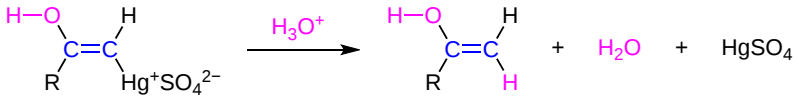
2) Nucleophilic attack by water



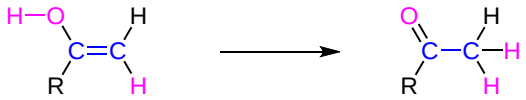
3) Deprotonation



4) Substitution

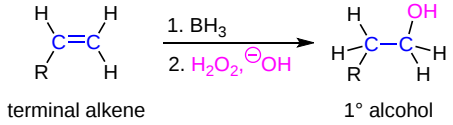


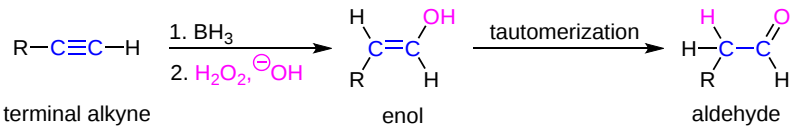
5) Tautomerization



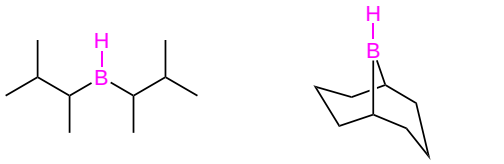
Hydroboration–Oxidation of Alkynes

The hydroboration-oxidation of alkynes is analagous to the reaction with alkenes. However, where alkenes for alcohol products, alkynes for aldehyde or ketone products. In both cases the addition is anti-Markovnikov and an oxygen is placed on the less alkyl substituted carbon. With the hydroboration of an alkyne the presences of a second pi bond allows the initial product to under tautomerization to become the final aldehyde product.





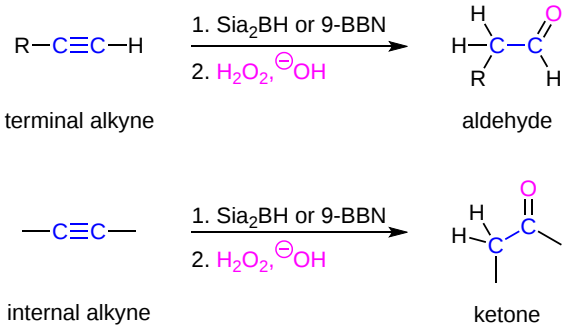
Alkynes have two pi bonds both of which are capable of reacting with borane (BH_3). To limit the reactivity to only one alkyne pi bond, a dialkyl borane reagent (R_2BH) is used. Replacing two of the hydrogens on the borane with alkyl groups also creates steric hindrance which enhances the anti-Markovnikov regioselective of the reaction. Disiamylborane (Sia_2BH) and 9-borabicyclo[3.3.1]nonane (9-BBN) are two common reagents for this hydroboration reaction. The oxidation reagents (a basic hydrogen peroxide solution) are the same for both alkenes and alkynes.



disiamylborane (Sia_2BH) | 9-borabicyclo[3.3.1]nonane (9-BBN)

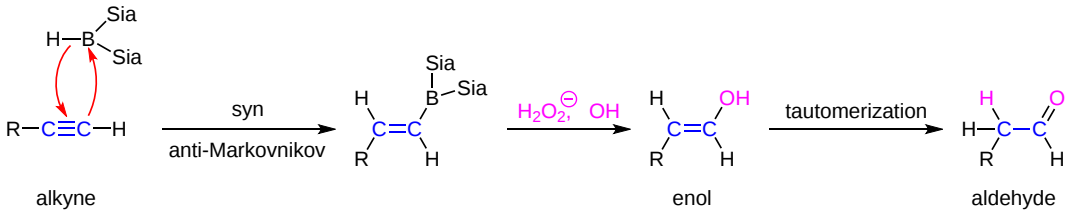
General Reaction

The hydroboration of terminal alkynes produces aldehyde products while internal alkynes produce ketone products. The hydroboration of symmetrical alkynes produces one ketone product and asymmetrical alkynes produce a mixture of product ketones.



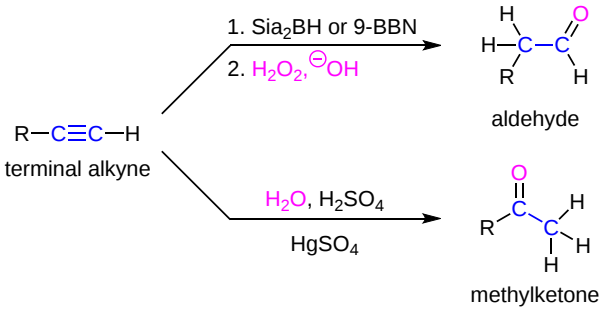
Mechanism

The mechanism starts with the electrophilic addition of the B-H bond of the borane. The hydrogen atom and the borane all on the same side of the alkyne creating a syn addition configuration in the alkene product. Also, the addition is anti-Markovnikov regioselective which means the borane adds to the less substituted carbon of the alkyne and the hydrogen atom adds to the more substituted. The oxidative work-up replaces the borane with a hydroxy group (-OH) creating an enol intermediate. The enol immediately tautomerizes to the product aldehyde for terminal alkynes and the product ketone for internal alkynes.

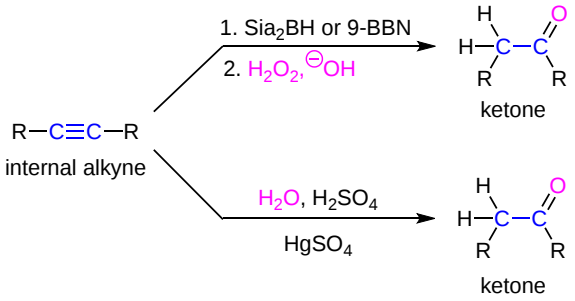


Comparison of Mercury(II)-Catalyzed Hydration and Hydroboration–Oxidation of Alkynes

These two reactions are complementary for the reaction of a terminal alkyne because the produce distinctly different products. The mercury(II) catalyzed hydration of a terminal alkyne produces a methyl ketone, while the hydroboration-oxidation produces an aldehyde.

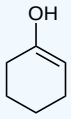


For internal alkynes, the regioslectivity of these reactions are rendered ineffective. The reactions are redundant in that they both produce the same ketone products.



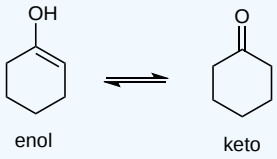
Exercise 1.5.1

Draw the structure of the keto form of the enol compound below. Which form would you expect to be the most stable? Draw the mechanism for the enol to keto transformation under both acidic and basic conditions.



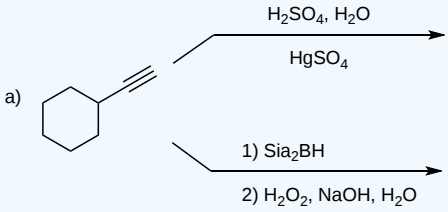
Answer

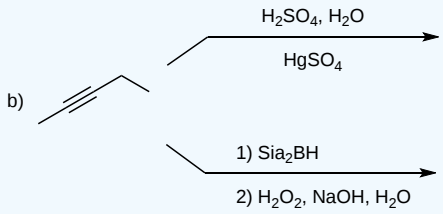
Our prediction is that the keto form will be the most stable. (This will be true unless the enol form is part of a highly conjugate system, like a benzene ring.) Check out Section 6-2 for the enol to keto tautomerization mechanism.



Exercise 1.5.2

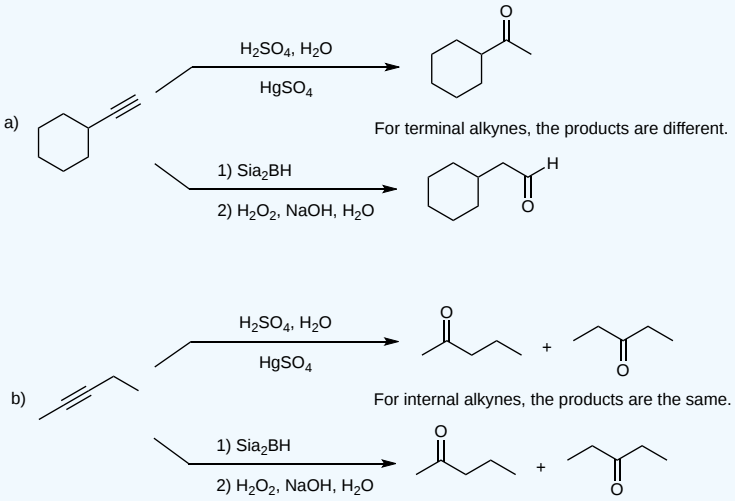
Draw the product(s) of the following reactions.





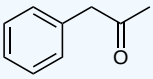
Answer

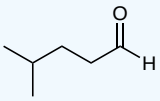
Terminal alkynes will yield ketones upon acidic hydration and aldehydes upon hydroboration-oxidation. Internal alkynes will yield the same ketone products regardless of the reaction conditions.



Exercise 1.5.3

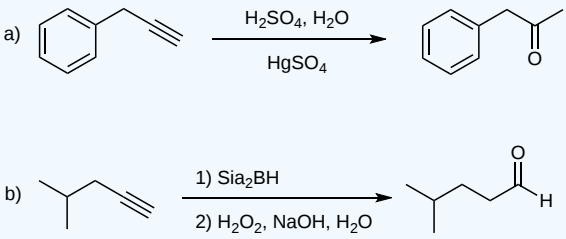
What alkyne starting material would you use to synthesize the following targets?

a) 

b) 

Answer

Remember, using a terminal alkyne to make a ketone avoids generating a mixture of ketones products.



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1.6: Reduction of Alkynes

Objectives

After completing this section, you should be able to

1. write equations for the catalytic hydrogenation of alkynes to alkanes and cis alkenes.
2. identify the reagent and catalyst required to produce a given alkane or cis alkene from a given alkyne.
3. identify the product formed from the reaction of a given alkyne with hydrogen and a specified catalyst.
4. identify the alkyne that must be used to produce a given alkane or cis alkene by catalytic hydrogenation.
5. write the equation for the reduction of an alkyne with an alkali metal and liquid ammonia.
6. predict the structure of the product formed when a given alkyne is reduced with an alkali metal and liquid ammonia.
7. identify the alkyne that must be used to produce a given alkene by reduction with an alkali metal and ammonia.

Key Terms

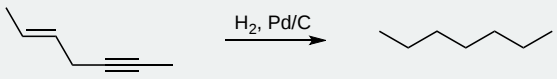
Make certain that you can define, and use in context, the key terms below.

- anion radical
- Lindlar catalyst

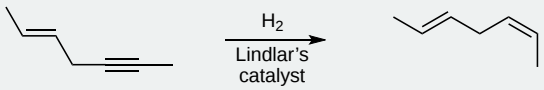
Study Notes

The Lindlar catalyst allows a chemist to reduce a triple bond in the presence of a double bond.

Thus

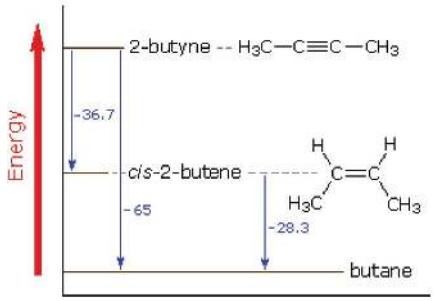


but



Hydrogenation and the Relative Stability of Hydrocarbons

Like alkenes, alkynes readily undergo catalytic hydrogenation partially to **cis**- or *trans*- alkenes or fully to alkanes depending on the reaction employed.

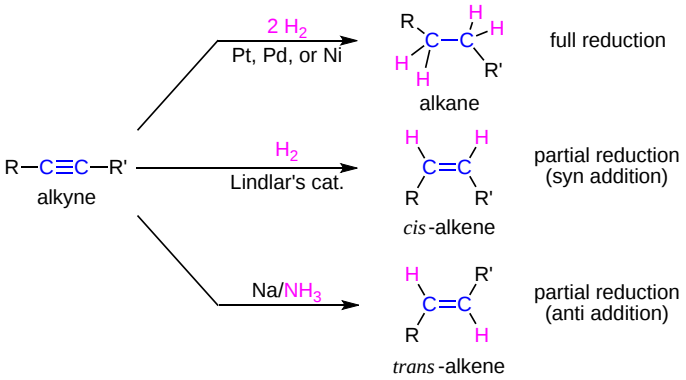


The catalytic addition of hydrogen to 2-butyne provides heat of reaction data that reflect the relative thermodynamic stabilities of these hydrocarbons, as shown above. From the heats of hydrogenation, shown in blue in units of kcal/mole, it would appear that alkynes are thermodynamically less stable than alkenes to a greater degree than alkenes are less stable than alkanes. The standard bond energies for carbon-carbon bonds confirm this conclusion. Thus, a double bond is stronger than a single bond, but not twice as strong. The difference (63 kcal/mole) may be regarded as the strength of the π-bond component. Similarly, a triple bond is

stronger than a double bond, but not 50% stronger. Here the difference (54 kcal/mole) may be taken as the strength of the second π-bond. The 9 kcal/mole weakening of this second π-bond is reflected in the heat of hydrogenation numbers (36.7 - 28.3 = 8.4).

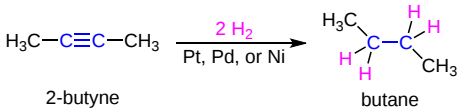
Overview of Reduction of Alkynes

Alkynes can undergo reductive hydrogenation reactions similar to alkenes. With the presence of two pi bonds within alkynes, the reduction reactions can be partial to form an alkene or complete to form an alkane. Since partial reduction of an alkyne produces an alkene, the stereochemistry provided by the reaction's mechanism determines whether a *cis*- or *trans*- alkene is formed. The three most significant alkyne reduction reactions are summarized below:



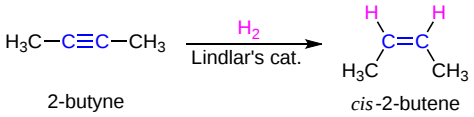
Catalytic Hydrogenation of an Alkyne

Much like alkenes, alkynes can be fully hydrogenated into alkanes with the help of a platinum, palladium, or nickel catalyst. Because the reaction is catalyzed on the surface of the metal, it is common for these catalysts to dispersed on carbon (Pd/C) or finely dispersed as nickel (Raney-Ni). The presence of two pi bonds in the alkyne cause two equivalents of H_2 to be added during the reaction. During the reaction an alkene intermediate is form but not isolated.

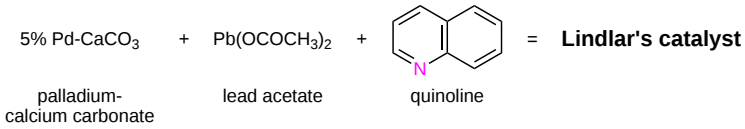


Hydrogenation of an Alkyne to a *Cis*-Alkene

For catalytic hydrogenation, the Pt, Pd, or Ni catalysts are so effective in promoting addition of hydrogen to both double and triple carbon-carbon bonds that the alkene intermediate formed by hydrogen addition to an alkyne cannot be isolated. A less efficient catalyst, **Lindlar's catalyst** permits alkynes to be converted to alkenes without further reduction to an alkane. Lindlar's Catalyst transforms an alkyne to a *cis*-alkene because the hydrogenation reaction is occurring on the surface of the metal. Both hydrogen atoms are added to the same side of the alkyne as shown in the syn-addition mechanism for hydrogenation of alkenes in the previous chapter.

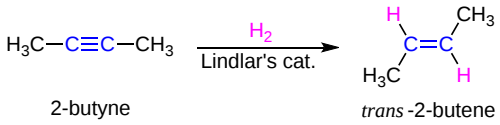


Lindlar's catalyst is prepared by deactivating (or poisoning) a conventional palladium catalyst. Lindlar's catalyst has three components: palladium-calcium carbonate, lead acetate, and quinoline. The quinoline serves to prevent complete hydrogenation of the alkyne to an alkane.



Hydrogenation of an Alkyne to a *Trans*-Alkene

The anti-addition of hydrogen to an alkyne pi bond occurs when reacted with sodium or lithium metal dissolved in ammonia. This reaction, also called dissolving metal reduction, involves radicals in its mechanism and produces a *trans*-alkene as it product.

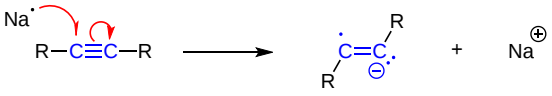


2-butyne — *trans* -2-butene

Mechanism

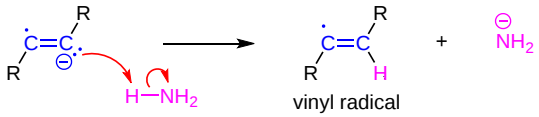
Sodium metal is a powerful reducing agent due to the presence of a $3s^1$ electron in its valence. Sodium metal easily gives up this electron to become Na^+. The mechanism start with a sodium atom donating an electron to the alkyne creating an intermediate with a negative charge and an unpaired electron called a radical anion. Next the amine solvent protonates the anion to create a vinyl radical. A second sodium atom then donates an electron to pair the radical converting it to a vinyl anion. This vinyl anion intermediate rapid interconverts between *cis* and *trans* conformations and determines the stereochemistry of the reaction. The *trans*-vinyl anion is more stable due to reduced steric crowding and is preferentially formed. Finally, the protonation of the *trans*-vinyl anion creates the *trans*-alkene product.

1) Electron Donation



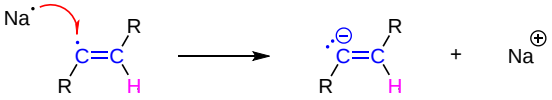
radical anion

2) Protonation



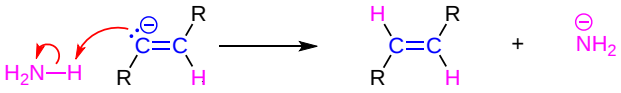
vinyl radical

3) Electron Donation



trans -vinyl anion

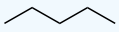
4) Protonation

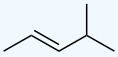


trans -alkene

? Exercise 1.6.1

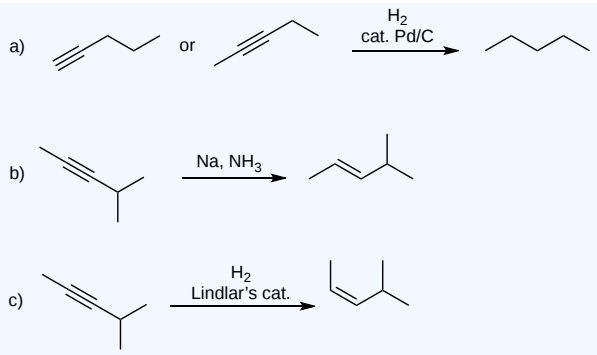
Propose a synthesis for each of the following targets starting with any alkyne.

a) 

b) 

c)

Answer



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1.7: Oxidative Cleavage of Alkynes

Objectives

After completing this section, you should be able to

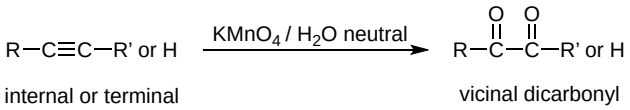
1. write an equation to represent the oxidative cleavage of an alkyne with potassium permanganate or ozone.
2. identify the products that result from the oxidative cleavage of a given alkyne.
3. identify the reagents needed to carry out the oxidative cleavage of an alkyne.
4. use the results of an oxidative cleavage to determine the identity of an alkyne of unknown structure.

Study Notes

Compare the oxidative cleavage of alkynes with the oxidative cleavage of alkenes.

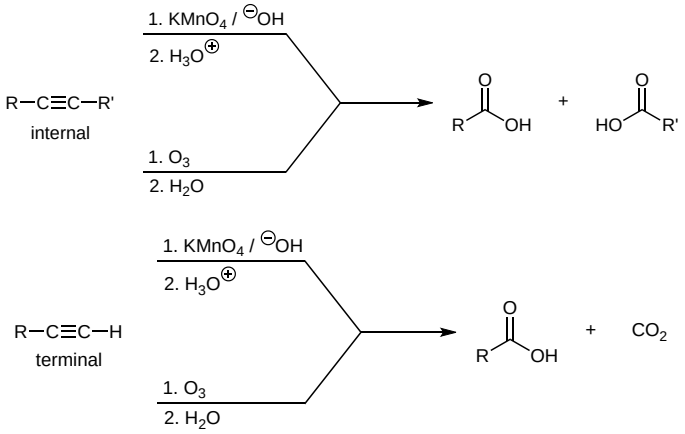
Alkynes, similar to alkenes, can be oxidized gently or strongly depending on the reaction environment. Since alkynes are less stable than alkenes, the reaction conditions can be gentler. For example, alkynes form vicinal dicarbonyls in neutral permanganate solution.

Gentle Alkyne Oxidation



Strong Alkyne Oxidation - Oxidative Cleavage

During strong oxidation with ozone or basic potassium permanganate, the alkyne is cleaved into two products. Because at least one of the reaction products is a carboxylic acid, it is important to consider the acid-base chemistry of the product in the reaction solution. Carboxylic acids are deprotonated in basic solutions to carboxylates. A second reaction step is required to protonate the carboxylate to the neutral form of the carboxylic acid.



Exercise

1. Draw the structures for the product(s) of the following reactions.

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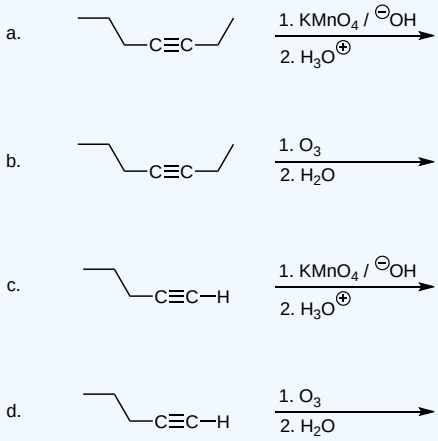
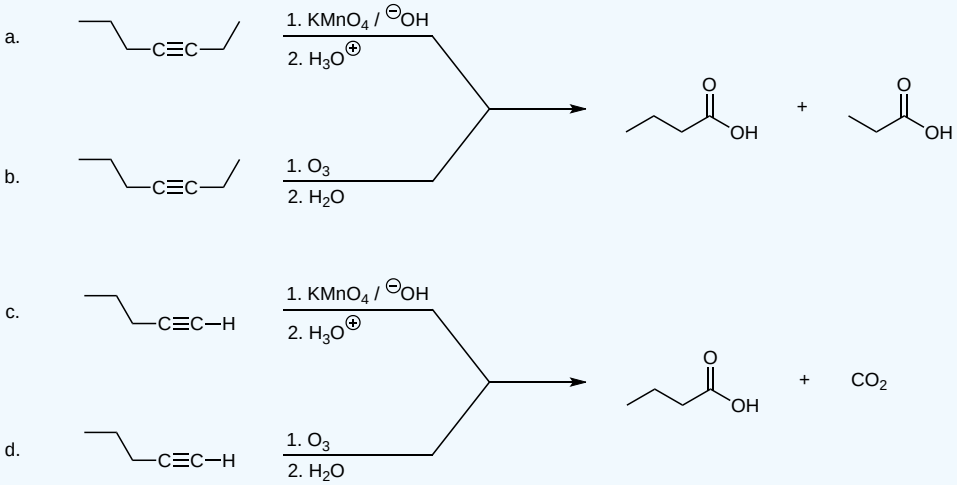


Answer

1.



Oxidative cleavage of alkynes produces carboxylic acids and/or carbon dioxide. Aldehydes are not produced.

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1.8: Alkyne Acidity - Formation of Acetylide Anions

Objectives

After completing this section, you should be able to

1. write an equation for the reaction that occurs between a terminal alkyne and a strong base, such as sodamide, $NaNH_2$.
2. rank a given list of compounds, including water, acetylene and ammonia, in order of increasing or decreasing acidity.
3. rank a given list of hydrocarbons, such as acetylene, ethylene and ethane, in order of increasing or decreasing acidity.
4. describe a general method for determining which of two given compounds is the stronger acid.
5. provide an acceptable explanation of why terminal alkynes are more acidic than alkanes or alkenes.

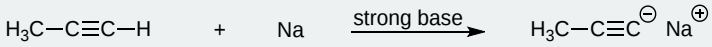
Key Terms

Make certain that you can define, and use in context, the key terms below.

- acetylide anion
- acidity order

Study Notes

An *acetylide anion* is an anion formed by removing the proton from the end carbon of a terminal alkyne:



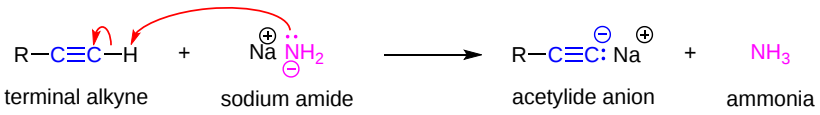
An *acidity order* is a list of compounds arranged in order of increasing or decreasing acidity.

The general ideas discussed in this section should already be familiar to you from your previous exposure to acid-base chemistry. A slightly different account of why terminal alkynes are stronger acids than are alkenes or alkanes is given below. However, the argument is still based on the differences between *sp*-, sp^2- and sp^3-hybrid orbitals.

The carbons of a triple bond are *sp*-hybridized. An *sp* hybrid orbital has a 50% *s* character and a 50% *p* character, whereas an sp^2 hybrid orbital is 33% *s* and 67% *p*, and an sp^3 hybrid orbital is 25% *s* and 75% *p*. The greater the *s* character of the orbital, the closer the electrons are to the nucleus. Thus in a C(*sp*)-H bond, the bonding electrons are closer to the carbon nucleus than they are in a C(sp^2)-H bond. In other words, compared to a C(sp^2)-H bond (or a C(sp^3)-H bond), a C(*sp*)-H bond is very slightly polar: $C^{\delta-}$-$H^{\delta+}$. This slight polarity makes it easier for a base to remove a proton from a terminal alkyne than from a less polar or non-polar alkene or alkane.

Acidity of Terminal Alkynes: Formation of Acetylide Anions

Terminal alkynes are much more acidic than most other hydrocarbons. Removal of the terminal proton leads to the formation of an acetylide anion, $RC{\equiv}C{:}^-$.



As discussed in CHM 222 (**Acids and Bases**), acidity typically increases with the stability of the corresponding conjugate base. The origin of the enhanced acidity of terminal alkynes can be attributed to the stability of the acetylide anion, which has the unpaired electrons in an sp hybridized orbital. The hybridization of an orbital affects its electronegativity. Within a shell, the s orbitals occupy the region closer to the nucleus than the p orbitals. Therefore, the spherical s orbitals are more electronegative than the lobed p orbitals. The relative electronegativity of hybridized orbitals increases as the percent s character increases and follows the order sp > sp^2 > sp^3. This trend indicates the sp hybridized orbitals of the acetylide anion are more electronegative and better able to stabilize a negative charge than sp^2 or sp^3 hybridized orbitals. There is a strong correlation between s-character in the orbital containing the non-bonding electrons in the anion and the acidity of hydrocarbons. The table below shows how orbital

hybridization compares with the identity of the atom when predicting relative acidity. Remember that as the pK_a of a compound decreases its acidity increases.

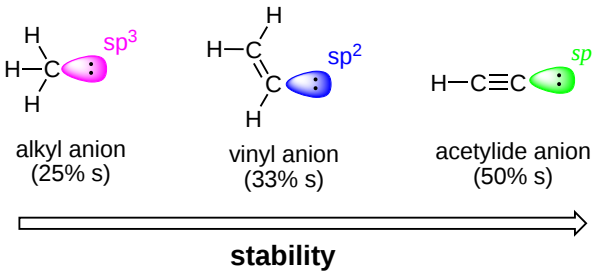
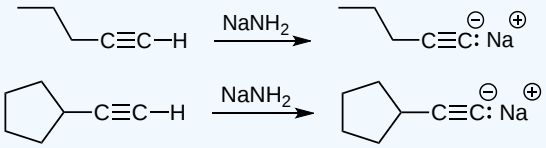


Table 9.7.1: Akynes

Compound	Conjugate Base	Hybridization	"s Character"	pKa	C-H BDE (kJ/mol)
CH_3CH_3	$CH_3CH_2^-$	sp^3	25%	50	410
CH_2CH_2	CH_2CH^-	sp^2	33%	44	473
HCCH	HCC^-	sp	50%	25	523

Acetylene, with a pK_a of 25 is shown to be much more acidic than ethylene (pK_a = 44) or ethane (pK_a = 50). Consequently, acetylide anions can be readily formed by deprotonation of a terminal alkynes with a sufficiently strong base. The amide anion (NH_2^-), in the form of sodium amide ($NaNH_2$), is commonly used for the formation of acetylide anions. Another useful base for this deprotonation is the diisopropyl amide anion (iPr_2N^-) which is commercially available as lithium diisopropyl amide (LDA).

Example 1.8.1



Exercise 1.8.1

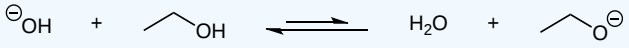
Given that the p*K*a of water is 14.00, would you expect hydroxide ion to be capable of removing a proton from each of the substances listed below? Justify your answers, briefly.

a. ethanol (p*K*a = 16)
b. acetic acid (p*K*a = 4.72)
c. acetylene (p*K*a = 25)

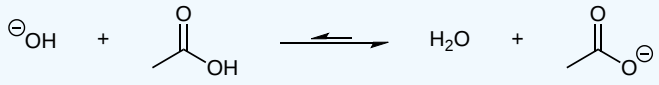
Answer

1.

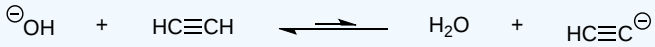
a. No, not very well. The p*K*a of ethanol is greater than that of water, thus the equilibrium lies to the left rather than to the right.



b. Yes, very well. There is a difference of 11 p*K*a units between the p*K*a of water and the p*K*a of acetic acid. The equilibrium lies well to the right.



c. No, hardly at all. The hydroxide ion is too weak a base to remove a proton from acetylene. The equilibrium lies well to the left.



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1.9: Alkylation of Acetylide Anions

Objectives

After completing this section, you should be able to

1. write an equation to describe the reaction of an acetylide ion with an alkyl halide or an epoxide.
2. discuss the importance of the reaction between acetylide ions and alkyl halides or epoxides as a method of extending a carbon chain.
3. identify the alkyne (and hence the acetylide ion) and the alkyl halide or epoxide needed to synthesize a given alkyne.
4. determine whether or not the reaction of an acetylide ion with a given alkyl halide or epoxide will result in substitution or elimination, and draw the structure of the product formed in either case.

Key Terms

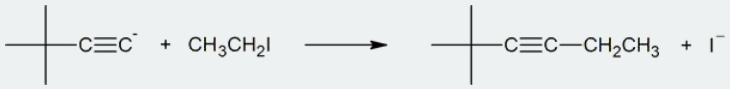
Make certain that you can define, and use in context, the key term below.

- alkylation

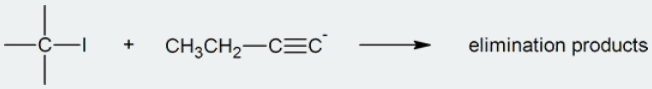
Study Notes

The alkylation of acetylide ions is important in organic synthesis because it is a reaction in which a new carbon-carbon bond is formed; hence, it can be used when an organic chemist is trying to build a complicated molecule from much simpler starting materials.

The alkyl halide used in this reaction must be primary. Thus, if you were asked for a suitable synthesis of 2,2-dimethyl-3-hexyne, you would choose to attack iodoethane with the anion of 3,3- dimethyl-1-butyne



rather than to attack 2-iodo-2-methylpropane with the anion of 1-butyne.



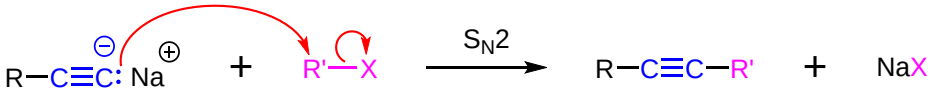
The reasons will be made clear in Chapter 3.

Nucleophilic Substitution Reactions of Acetylides

The presence of lone pair electrons and a negative charge on a carbon means acetylide anions are strong bases and strong nucleophiles. Therefore, acetylide anions can attack electrophiles such as alkyl halides or epoxides to cause a substitution reaction. These substitution reactions will be discussed in detail in **Chapter 2**.

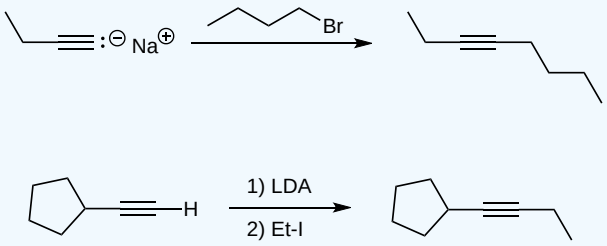
Mechanism

The C-X bonds in 1° alkyl halides are polarized due to the high electronegativity of the halogen. The electrons of the C-X sigma bond are shifted towards the halogen giving it a partial negative charge. This also causes electrons to be shifted away from the carbon giving it a partial positive and making it electrophilic. During this reaction, the lone pair electrons on the acetylide anion attack the electrophilic carbon in the 1° alkyl halide forming a new C-C bond. The formation of this new bond causes the expulsion of the halogen as what is called a leaving group. Overall, this reaction forms a C-C bond and converts a terminal alkyne into a internal alkyne. Because a new alkyl group is added to the alkyne during this reaction, it is commonly called an alkylation.

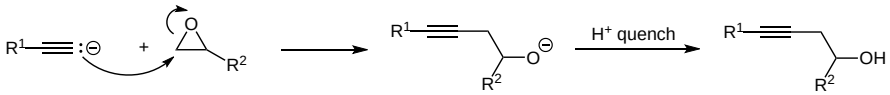


This substitution reaction is often coupled with the acetylide formation, discussed in the previous section, and shown as a single reaction.

Example 1.9.1

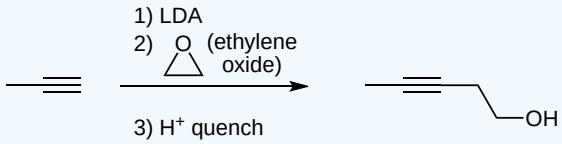


Similar reactions occur with epoxides. Since substitution reactions of acetylide anions are controlled by sterics, substitution occurs at the less substituted side of the epoxide. Ethylene oxide is a very useful two-carbon electrophile that is often used in synthesis. For a broader discussion of epoxide reactions, see Chapter 3.7.

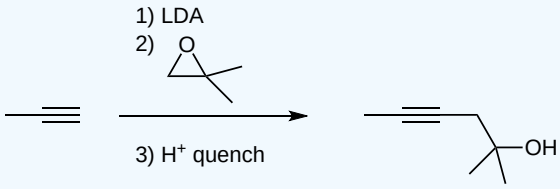


Example 1.9.2

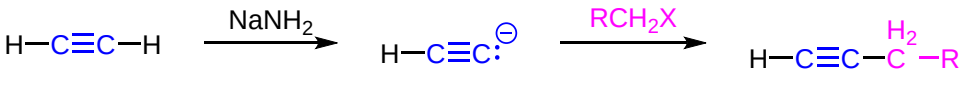
Acetylide reaction with ethylene oxide - synthesis of a primary alcohol



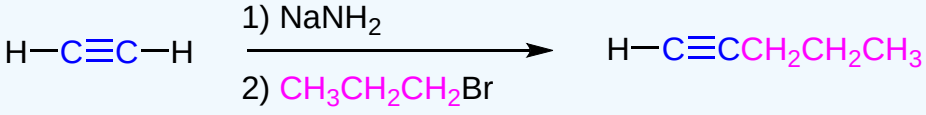
Acetylide reaction with gem-disubstituted epoxide - synthesis of a tertiary alcohol



Terminal alkynes can be generated through the reaction of acetylene and a 1º alkyl halide.



Example 1.9.3



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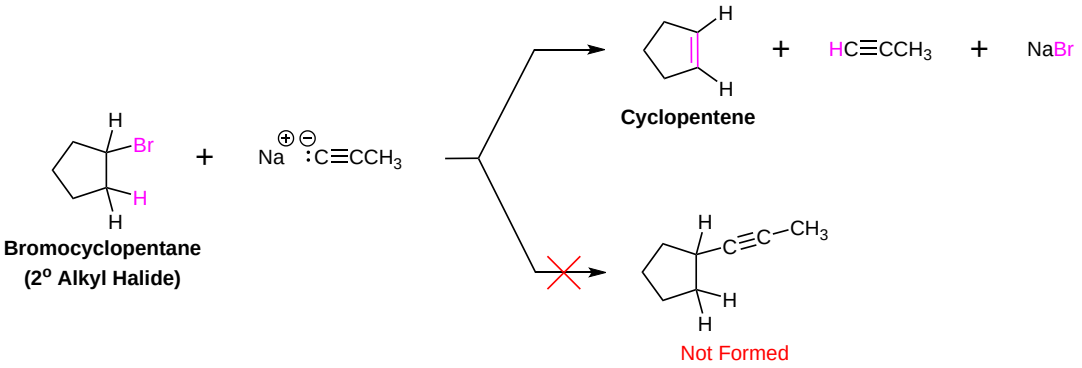
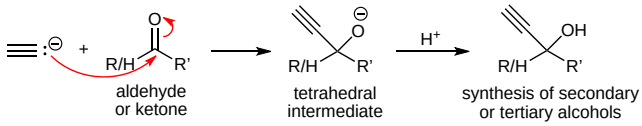
Because the acetylide anion is a very strong base, this substitution reaction is most efficient with methyl or primary halides. Secondary, tertiary, or even bulky primary halogens will give alkenes by the E2 elimination mechanism discussed in Section 2.8. An example of this effect is seen in the reaction of bromocyclopentane with a propyne anion. The reaction produces the elimination product cyclopentene rather than the substitution product 1-propynylcyclopentane.



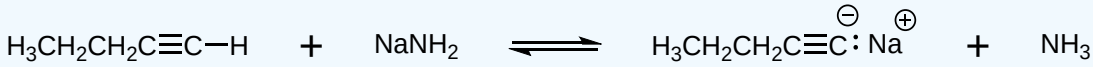
Nucleophilic Addition of Acetylides to Carbonyls

Acetylide anions also add to the electrophilic carbon in aldehydes and ketones to form alkoxides, which, upon protonation, give propargyl alcohols. With aldehydes and non-symmetric ketones, in the absence of chiral catalyst, the product will be a racemic mixture of the two enantiomers. This is similar to what you learned in CHM 222 for addition reactions of Grignard and organolithium reagents to aldehydes and ketones.



Exercise 1.9.1

The pK_a of ammonia is 35. Estimate the equilibrium constant for the deprotonation of pent-1-yne by sodium amide, as shown below.

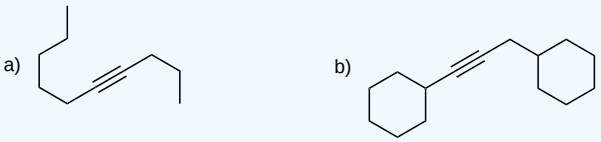


Answer

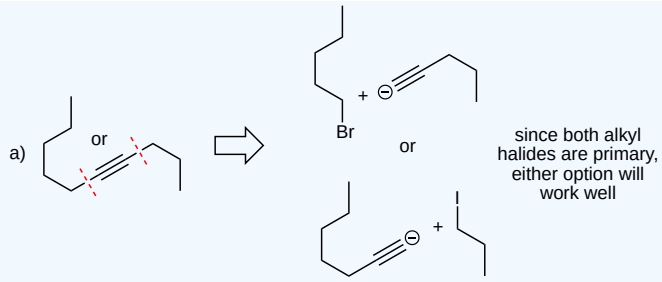
Assuming the pK_a of pent-1-yne is about 25, then the difference in pK_as is 10. Since pentyne is more acidic, the formation of the acetylide will be favored at equilibrium, so the equilibrium constant for the reaction is about 10^{10}.

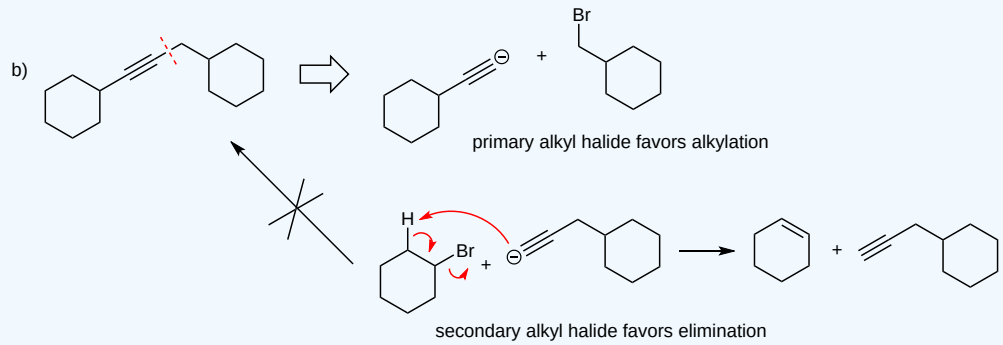
Exercise 1.9.2

Synthesize each of the following molecules using an acetylide alkylation reaction.



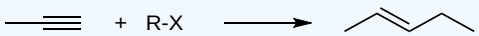
Answer



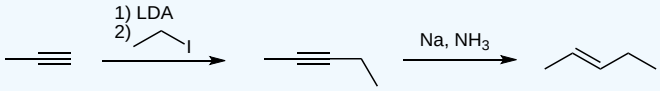


Exercise 1.9.3

Propose a synthetic route to produce trans 2-pentene from propyne and an alkyl halide.

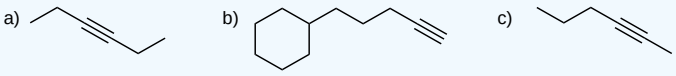


Answer

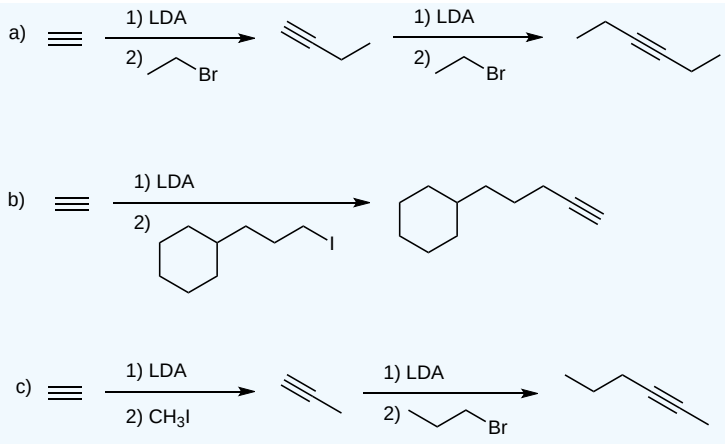


Exercise 1.9.4

Using acetylene as the starting material, show how you would synthesize the following compounds.

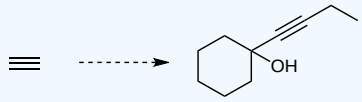


Answer

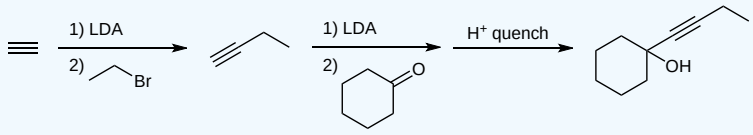


Exercise 1.9.5

Complete the following synthesis.



Answer



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1.10: An Introduction to Organic Synthesis

Objective

After completing this section, you should be able to design a multistep synthesis to prepare a given product from a given starting material, using any of the reactions introduced in the textbook up to this point.

Study Notes

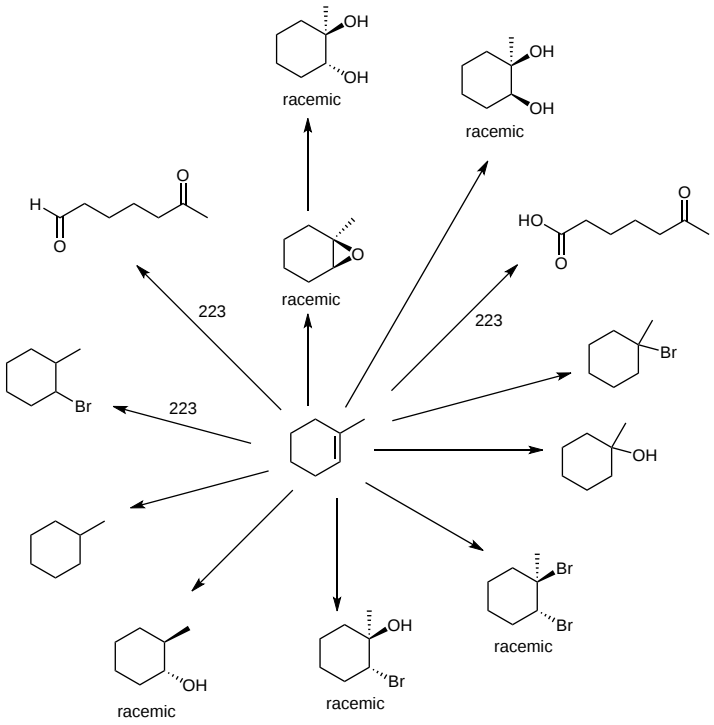
You should have noticed that some of the assigned problems have required that you string together a number of organic reactions to convert one organic compound to another when there is no single reaction to achieve this goal. Such a string of reactions is called an “organic synthesis.” One of the major objectives of this course is to assist you in designing such syntheses. To achieve this objective, you will need to have all of the reactions described in the course available in your memory. You will need to recall some reactions much more frequently than others, and the only way to master this objective is to practice. The examples given in this chapter will be relatively simple, but you will soon see that you can devise some quite sophisticated syntheses using a limited number of basic reactions.

Introduction

The study of organic chemistry introduces students to a wide range of interrelated reactions. Alkenes, for example, may be converted to structurally similar alkanes, alcohols, alkyl halides, epoxides, glycols and boranes; cleaved to smaller aldehydes, ketones and carboxylic acids; and enlarged by carbocation and radical additions as well as cycloadditions. Most of these reactions are shown in the Alkene Reaction Map below. All of these products may be subsequently transformed into a host of new compounds incorporating a wide variety of functional groups. Consequently, the logical conception of a multi-step synthesis for the construction of a designated compound from a specified starting material becomes one of the most challenging problems that may be posed. Functional group reaction maps like the one below for alkenes can be helpful in designing multi-step syntheses. It can be helpful to build and design your own reaction maps for each functional group studied.

Alkene Reaction Map

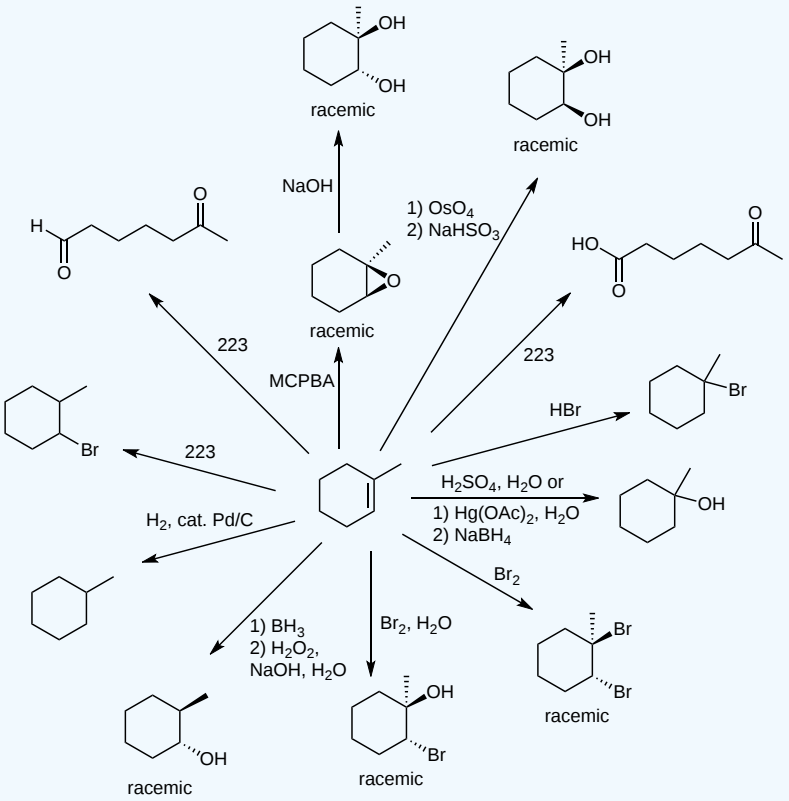
Please note: 1) The reagents for each chemical transformation have been intentionally omitted so that this map can be used as a study tool. 2) We will learn about the three reactions labeled as "223" later this semester (in the sections on oxidation reactions and radical reactions).



Exercise 1.10.1

Fill in the reagents for the Alkene Reaction Map shown above.

Answer



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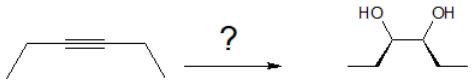
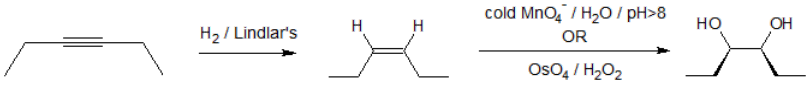
Simple Multi-Step Syntheses

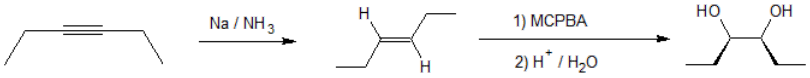
A one or two step sequence of simple reactions is not that difficult to deduce. For example, the synthesis of meso-3,4-hexanediol from 3-hexyne can occur by more than one multi-step pathway.



One approach would be to reduce the alkyne to cis or trans-3-hexene before undertaking glycol formation. Permanaganate or osmium tetroxide dihydroxylation of cis-3-hexene would form the desired meso isomer.



From trans-3-hexene, it would be necessary to first epoxidize the alkene with a peracid followed by ring opening with acidic or basic hydrolysis.

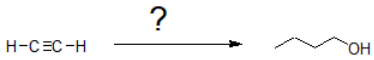


Longer multi-step syntheses require careful analysis and thought, since many options need to be considered. Like an expert chess player evaluating the long range pros and cons of potential moves, the chemist must appraise the potential success of various possible reaction paths, focusing on the scope and limitations constraining each of the individual reactions being employed. The skill is acquired by practice, experience, and often trial and error.

Thinking it Through with 2 Examples

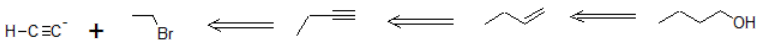
The following two examples illustrate strategies for developing multi-step syntheses from the reactions studied in the first ten chapters of this text. It is helpful to systematically look for structural changes beginning with the carbon chain and brainstorm relevant functional group conversion reactions. Retro-synthesis is the approach of working backwards from the product to the starting material.

In the first example, we are asked to synthesize 1-butanol from acetylene.

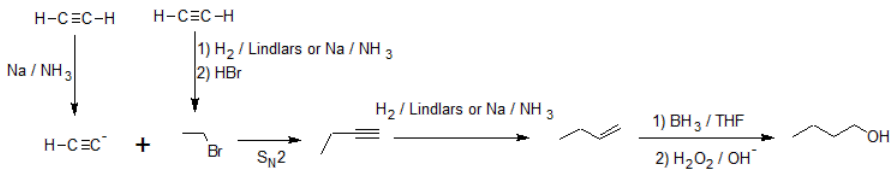


The carbon chain doubles in size indicating an acetylide S_N2 reaction with an alkyl halide. Primary alcohol formation from an anti-Markovnikov alkene hydration reaction (hydroboration-oxidation) is more likely than a substitution reaction. Applying retro-synthesis, we work backwards from the alcohol to the alkene to the alkyne from an acetylide reaction that initially builds the carbon chain.

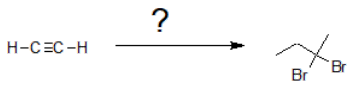
Retro-Synthesis



Working forwards, we specify the reagents needed for each transformation identified from the retro-synthesis. The ethylbromide must also be derived from acetylene so multiple reaction pathways are combined as shown below.

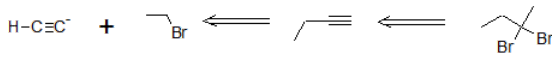


In the second example, we are asked to synthesize 1,2-dibromobutane from acetylene.

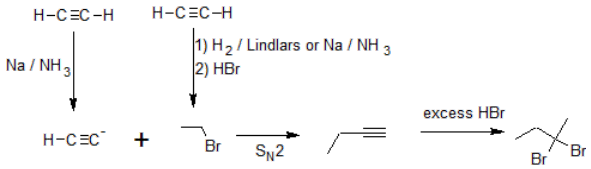


Once again there is an increase in the carbon chain length indicating an acetylide S_N2 reaction with an alkyl halide similar to the first example. The hydrohalogenation can be subtle to discern because the hydrogen atoms are not shown in bond-line structures. Comparing the chemical formulas of 1-butyne with 1,2-dibromobutane, there is a difference of two H atoms and two Br atoms indicating hydrohalogenation and not halogenation. The addition of both bromine atoms to the same carbon atom also supports the idea that hydrohalogenation occurs on an alkyne and not an alkene. The formation of the geminal dihalide also indicates hydrohalogenation instead of halogenation because halogenation produces vicinal dihalides. With this insight, the retro-synthesis indicates the following series of chemical transformations.

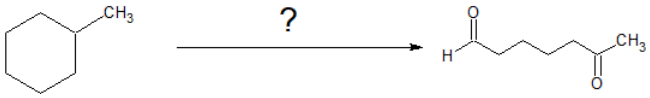
Retro-Synthesis



Working forwards, we specify the reagents needed for each transformation.

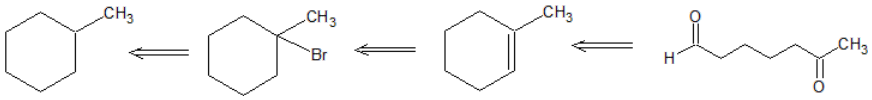


In the third example, we are asked to produce 6-oxoheptanal from methylcyclohexane.



Counting the carbons, the starting material and product both contain seven carbon atoms and there is a cleavage reaction of an alkene under reductive conditions. One important missing aspect of this reaction is a good leaving group (LG). Alkanes are chemically quite boring. We can burn them as fuel or perform free-radical halogenation to create alkyl halides with excellent leaving groups. With these observations, the following retro-synthesis is reasonable.

Retro-Synthesis



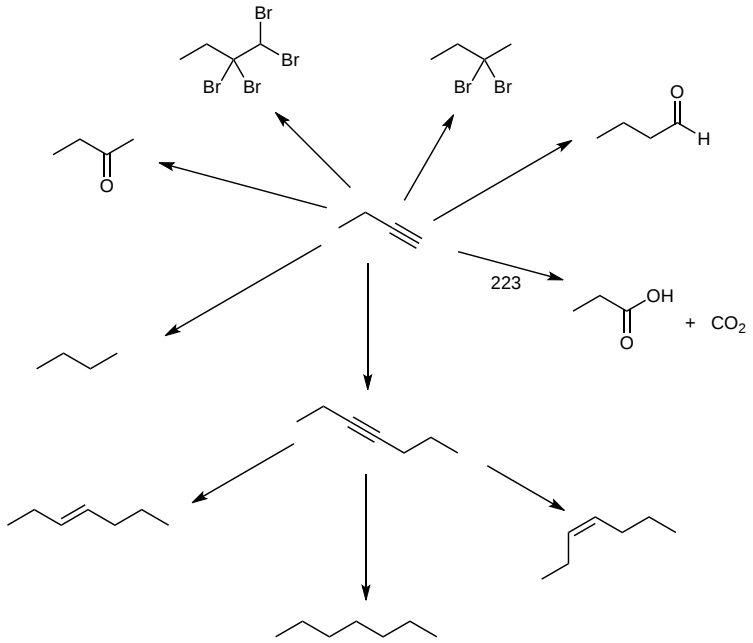
Working forwards, we specify the reagents needed for each reaction. For the initial free-radical halogenation of the alkane, we have the option of chlorine (Cl_2) or bromine (Br_2). Because methylcyclohexane has several different classifications of carbons, the selectivity of Br_2 is more important than the faster reactivity of Cl_2. A strong base with heat can be used for the second step to follow an E2 mechanism and form 1-methylcyclohexene. The aldehyde group on the final product indicates gentle oxidative cleavage by any of several reaction pathways. These reactions can be combined in to the following multi-step synthesis.

Reaction Maps to Build Functional Group Conversion Mastery

After working through the examples above, we can see how important it is to memorize all of the functional group reactions studied in CHM 222. We can apply the knowledge of these reactions to the wisdom of multi-step syntheses.

Alkyne Reaction Map

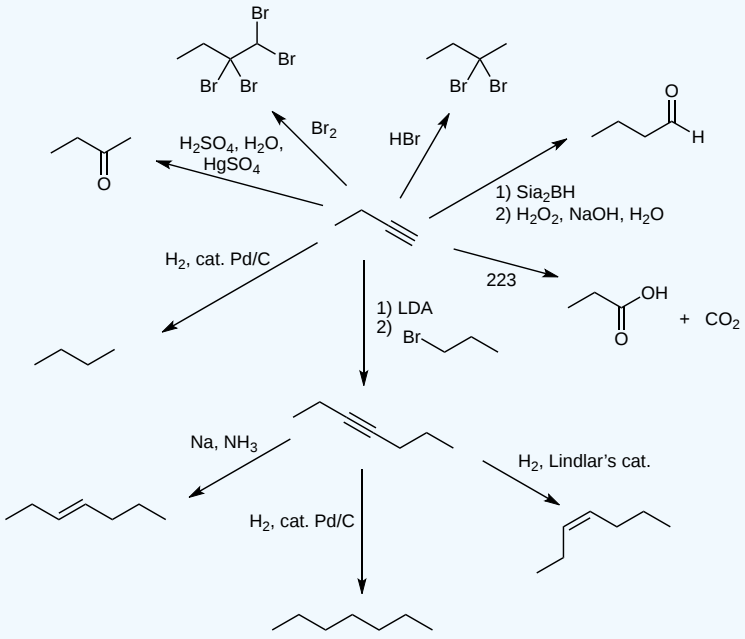
Please note: The reagents for each chemical transformation have been intentionally omitted so that these maps can be used as a study tools. We will learn the reaction labeled "223" later this semester as part of the oxidation reactions section.



Exercise 1.10.2

Add the reagents to the Alkyne Reaction Map shown above.

Answer



Exercise 1.10.3

Starting with 3-hexyne propose synthetic routes to make:

a) trans-3-hexene

b) 3,4-dibromohexane

c) 3-hexanol

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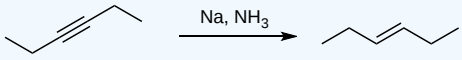
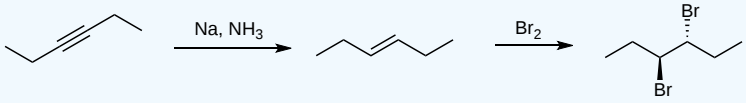
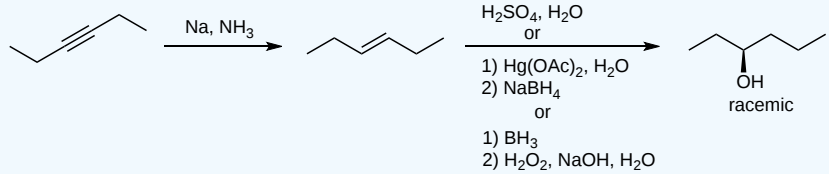
Answer

a) 

b) 

c) 

Exercise 1.10.4

Starting with acetylene and any alkyl halides propose syntheses to make:

a) pentanal

b) hexane

Answer

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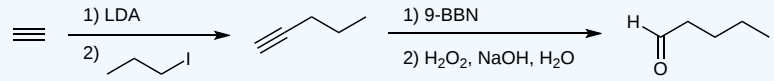
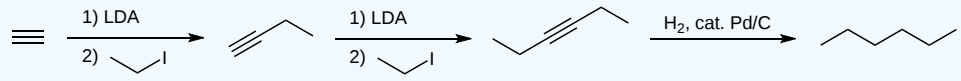
a) 

b) 

Exercise 1.10.5

Show how you would accomplish the following synthetic transformations.

a)

b)

Answer

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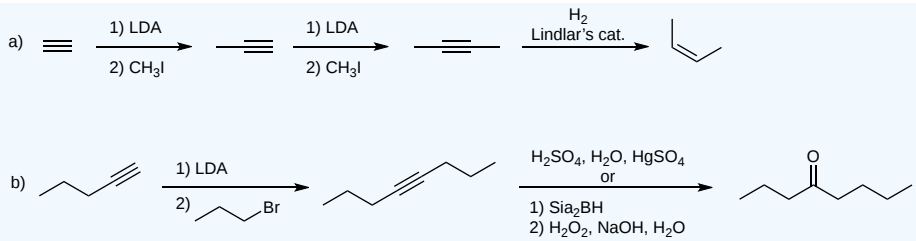

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1.S: Alkynes - An Introduction to Organic Synthesis (Summary)

Concepts & Vocabulary

1.1 Naming Alkynes (reference only)

- Follow IUPAC rules in naming alkynes.

1.2 Preparation of Alkynes - Elimination Reactions of Dihalides (reference only)

- **Vicinal** describes two groups on adjacent carbon atoms.
- **Geminal** describes two groups on the same carbon atom.
- Alkynes can be prepared by two successive eliminations of HX from either **vicinal** or **geminal** dihalides.

1.3 Reactions of Alkynes - Addition of HX and X_2

- **Alkynes** undergo addition reactions similarly to alkenes yielding Markovnikov products.

1.4 Hydration of Alkynes

- Enols have a hydroxyl group bonded to a sp^2 hybrid carbon (double-bonded carbon).
- Enols are usually not stable and undergo **keto-enol tautomerization** to form a ketone or aldehyde.
- Hydration of alkynes leads to an enol product which then rapidly tautomerizes into a ketone or aldehyde.

1.5 Reduction of Alkynes

- Alkynes can be hydrogenated with hydrogen gas and strong catalysts to yield alkanes.
- Alkynes can be hydrogenated with hydrogen gas and Lindlar's catalyst to yield Z alkenes.
- Alkynes can be hydrogenated with sodium metal and liquid ammonia to yield E alkenes.

1.6 Oxidative Cleavage of Alkynes

- Oxidative cleavage of internal alkynes forms two molecules of carboxylic acids.
- Oxidative cleavage of terminal alkynes forms one molecule of carbon dioxide and one carboxylic acid.

1.7 Alkyne Acidity - Formation of Acetylide Anions

- Terminal alkynes are relatively acidic compared to alkene and alkane carbon-hydrogen bonds.
- Deprotonation of a terminal alkyne forms an acetylide ion, which is a good nucleophile.

1.8 Alkylation of Acetylide Anions

- Acetylide ions can be alkylated by adding to alkyl halides and carbonyl compounds.

1.9 An Introduction to Organic Synthesis

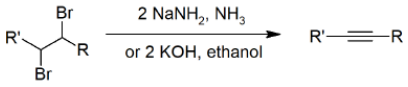
- Desired products cannot always be made from available starting materials through one reaction. Formation of these materials may require multiple reactions completed in sequence. This type of reaction sequence is termed synthesis.

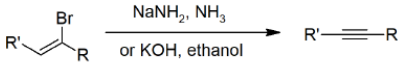
Skills to Master

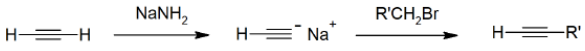
- Skill 1.1 Draw addition mechanisms to alkynes incorporating carbocation intermediates.
- Skill 1.2 Draw addition mechanisms to alkynes incorporating halonium intermediates.
- Skill 1.3 Describe relative stability of enols to ketones and aldehydes.
- Skill 1.4 Draw keto-enol tautomerism mechanism.
- Skill 1.5 Draw products that differentiate between multiple reduction reactions of alkynes.
- Skill 1.6 Draw products of oxidative cleavage of alkynes.
- Skill 1.7 Draw mechanism for deprotonation of terminal alkynes.
- Skill 1.8 Compare acidity of terminal alkynes with other organic compounds.
- Skill 1.9 Draw reaction mechanisms using acetylide ions as nucleophiles.
- Skill 1.10 Describe schemes to accomplish synthesis of organic products given a starting material.

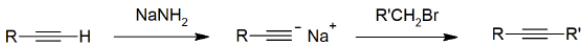
Summary of Reactions

Preparation of Alkynes (The first two options are much less important than the two that form a new C-C single bond.)

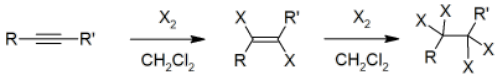


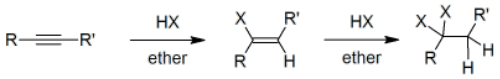


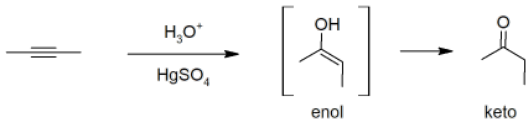


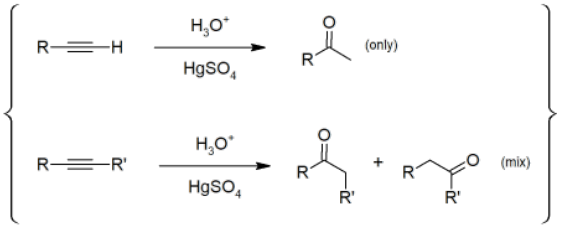


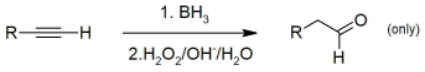
Reactions of Alkynes

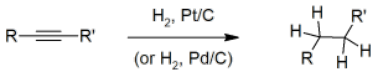


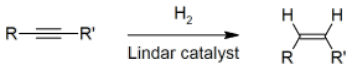


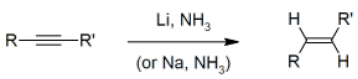












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CHAPTER OVERVIEW

2: Reactions of Alkyl Halides- Nucleophilic Substitutions and Eliminations

Learning Objectives

After you have completed Chapter 2, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- use the reactions studied in this chapter with those from earlier ones when designing multistep syntheses.
- use the reactions and concepts discussed in this chapter to solve road map problems.
- define, and use in context, the key terms introduced.

In this course, you have already seen several examples of nucleophilic substitution reactions; now you will see that these reactions can occur by two different mechanisms. You will study the factors that determine which mechanism will be in operation in a given situation, and examine possible ways for increasing or decreasing the rates at which such reactions occur. The stereochemical consequences of both mechanisms will also be discussed. Elimination reactions often accompany nucleophilic substitution; so these reactions are also examined in this chapter. Again you will see that two different mechanisms are possible, and, as in the case of nucleophilic substitution reactions, chemists have learned a great deal about the factors that determine which mechanism will be observed when a given alkyl halide undergoes such a reaction.

Chapter Videos

This video focuses on S_N1 and E1 reactions with alkyl halides.

This video focuses on S_N2 and E2 reactions with alkyl halides.

This video highlights strategies for solving problems involving S_N1 and S_N2 reactions.

This video focuses on substitution and elimination reactions of alcohols.

This video highlights synthetic applications of substitution and elimination reactions.

2.1: Introduction
2.2: The Discovery of Nucleophilic Substitution Reactions (for reference)
2.3: The SN2 Reaction
2.4: Characteristics of the SN2 Reaction
2.5: The SN1 Reaction
2.6: Characteristics of the SN1 Reaction
2.7: Biological Substitution Reactions (reference only)
2.8: Elimination Reactions- Zaitsev's Rule
2.9: The Mechanism of the E2 Reaction

2.10: The E2 Reaction and Cyclohexane Conformation
2.11: The E1 and E1cB Reactions
2.12: Biological Elimination Reactions (reference only)
2.13: A Summary of Reactivity - SN1, SN2, E1, E1cB, and E2
2.S: Reactions of Alkyl Halides - Nucleophilic Substitutions and Eliminations (Summary)

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2.1: Introduction

Objective

After completing this section, you should be able to identify substitution and elimination as being the two most important reactions of alkyl halides.

Study Notes

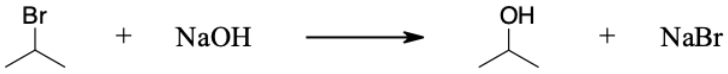
Alkyl halides are electrophiles, which means they can undergo nucleophilic substitution and base-induced elimination reactions. These reaction types offer a large and useful range of reactions for organic synthesis in the laboratory.

The Reactions

Two reactions are shown here with both involving heating a halooalkane under reflux with sodium or potassium hydroxide solution. Two different reactions can occur.

Nucleophilic substitution

The hydroxide ions present are good nucleophiles, and one possibility is a replacement of the halogen atom by an -OH group to give an alcohol via a nucleophilic substitution reaction.



In the example, 2-bromopropane is converted into propan-2-ol.

Elimination

Hydroxide ions are also strong bases, therefore haloalkanes also undergo elimination reactions in the presence of sodium or potassium hydroxide.

In this reaction, the 2-bromopropane has reacted to form an alkene - propene.

Notice that a hydrogen atom has been removed from one of the end carbon atoms together with the bromine from the central one. In all simple elimination reactions the things being removed are on adjacent carbon atoms, and a double bond is added between those carbons.

What decides whether you get substitution or elimination?

The reagents you are using are the same for both substitution or elimination - the haloalkane and either sodium or potassium hydroxide solution. In all cases, you will get a mixture of both reactions happening - some substitution and some elimination. What you get most of depends on a number of factors.

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2.2: The Discovery of Nucleophilic Substitution Reactions (for reference)

Objectives

After completing this section, you should be able to

1. write an equation to represent the Walden inversion.
2. write a short paragraph describing the Walden inversion.
3. describe, using equations, a series of reactions interconverting two enantiomers of 1-phenyl-2-propanol which led to the conclusion that nucleophilic substitution of primary and secondary alkyl halides proceeds with inversion of configuration.

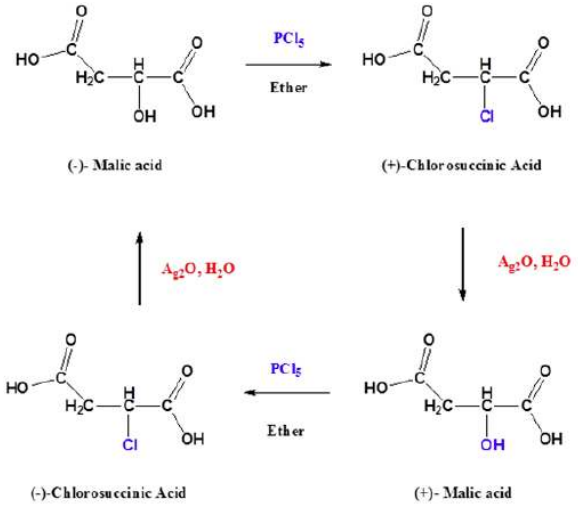
Study Notes

The IUPAC name for malic acid is 2-hydroxybutanedioic acid. This acid is produced by apples, a fact which seems to have been appreciated by the British novelist Thomas Hardy in *The Woodlanders*:

Up, upward they crept, a stray beam of the sun alighting every now and then like a star on the blades of the pomace-shovels, which had been converted to steel mirrors by the action of the malic acid.

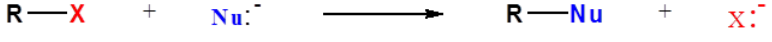
In 1896, the German chemist Paul Walden discovered that he could interconvert pure enantiomeric (+) and (-) malic acids through a series of reactions. This conversion meant that there was some kind of change in the stereochemistry made during the series of reactions. First, (−)-malic acid was reacted with **phosphorus pentachloride (PCl_5)** to provide (+)-chlorosuccinic acid.

This was reacted with **silver(I)oxide (Ag_2O)** to provide (+)-malic acid. These two combined steps caused an inversion of stereochemistry of (−)-malic acid to (+)-malic acid. The reaction series was then continued to convert (+)-malic acid back into (−)-malic acid by further reaction with PCl_5 and Ag_2O.

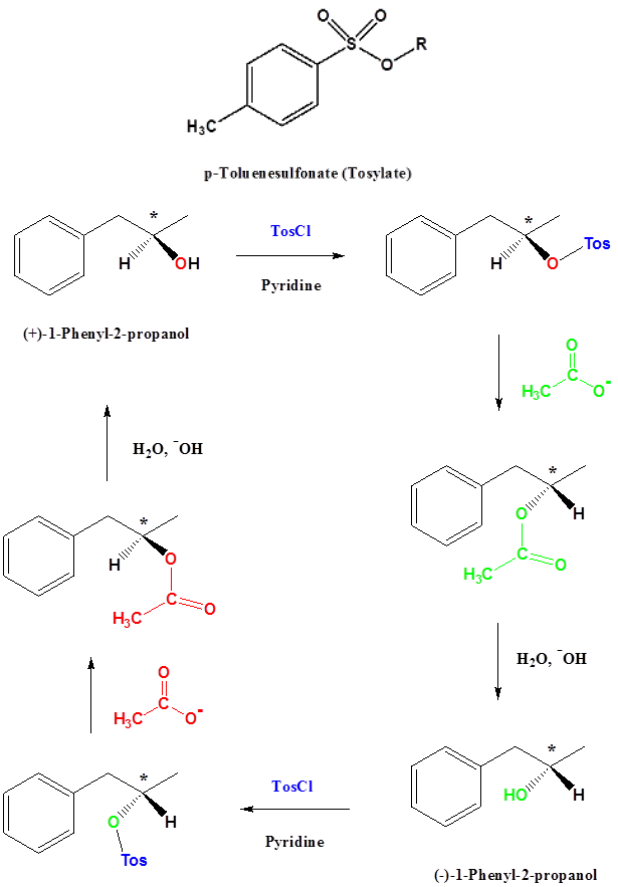


These results were considered astonishing. The fact that (−)-malic acid was converted into (+)-malic acid meant that the configuration of the chiral center has somehow been changed during the reaction series.

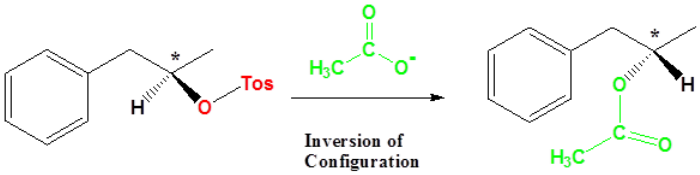
These reactions are currently referred to as nucleophilic substitution reactions because each step involves the substitution of one nucleophile by another. These are among the most common and versatile reaction types in organic chemistry.



Further investigations into these reaction were undertaken during the 1920's and 1930's to clarify the mechanism and clarify how the inversion of configurations occur. These reactions involved nucleophilic substitution of an alkyl p-toluenesulfonate (called a tosylate group). For this purpose the tosylate groups act similarly to a halogen substituent. In the series of reactions (+)-1-phenyl-2-propanol is interconverted with (-)-1-phenyl-2-propanol.



Somewhere in this three-step series of reactions the configuration at a chiral center is being inverted. In the first step the tosylate is formed without breaking the C-O bond of the chiral center, which means the configuration is unchanged. Similarly, the cleavage of the ester in step three occurs without breaking the C-O bond of the chiral center, which also means the configuration of the chiral carbon is unaffected. It was determined that the second step where acetate nucleophile undergoes a substitution with tosylate was causing the stereochemical configuration to be inverted.

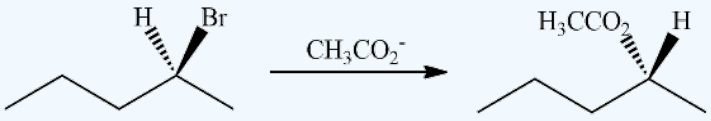


Exercise 2.2.1

1) Predict the product of a nucleophilic substitution of (S)-2-bromopentane reacting with $CH_3CO_2^-$, Show stereochemistry.

Answer

1)



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2.3: The SN2 Reaction

Objectives

After completing this section, you should be able to

1. write an expression relating reaction rate to the concentration of reagents for a second-order reaction.
2. determine the order of a chemical reaction from experimentally obtained rate data.
3. describe the essential features of the S_N2 mechanism, and draw a generalized **transition state** for such a reaction.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- bimolecular
- kinetics
- rate coefficient
- rate equation
- reaction rate
- second-order reaction
- S_N2

Study Notes

Some of the key terms introduced in this section might already be familiar to you from a previous general chemistry course.

Reaction rate refers to the change in concentration of a reactant or product per unit of time. Using strict SI units, reaction rates are expressed in mol · L^{-1} · s^{-1}, but in some textbooks you will find this value written as M/s. In general, the reaction rate of a given reaction changes with time, as it is dependent on the concentration of one or more of the reactants.

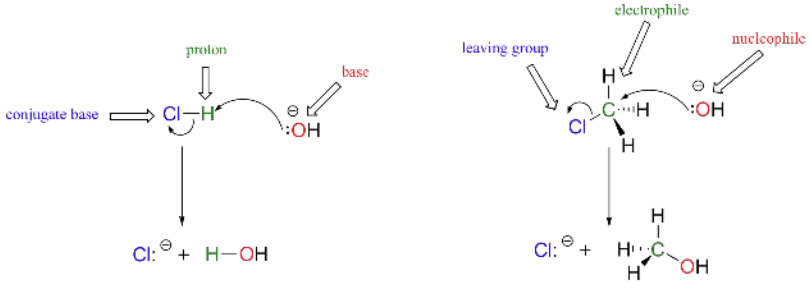
An equation which shows the relationship between the reaction rate and the concentrations of the reactants is known as the rate equation. All rate equations contain a proportionality constant, usually given the symbol *k*, which is known as the rate coefficient. Some textbooks refer to this value as the "rate constant," but this name is a little misleading as it is not a true constant. The rate coefficient of a given reaction depends on such factors as temperature and the nature of the solvent.

S_N2 is short for "bimolecular nucleophilic substitution." You will encounter abbreviations for other types of reactions later in this chapter.

If you are unclear on the point about the inversion of configuration during an S_N2 reaction, construct a molecular model of a chiral alkyl halide, the **transition state** formed when this substance reacts with a nucleophile in an S_N2 process, and the product obtained from this reaction.

Brønsted-Lowry acid-base reactions

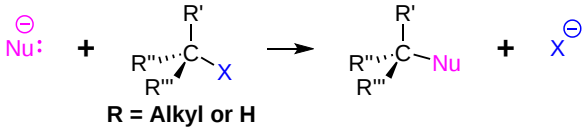
In many ways, the proton transfer process in a Brønsted-Lowry acid-base reaction can be thought of as a special kind of nucleophilic substitution reaction, one in which the electrophile is a hydrogen rather than a carbon.



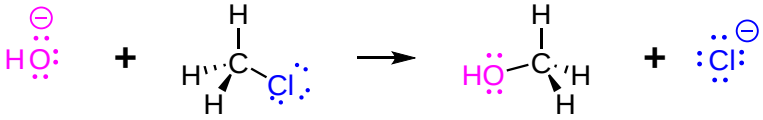
acid-base reaction **nucleophilic substitution**

In both reaction types, we are looking at very similar players: an electron-rich species (the nucleophile/base) attacks an electron-poor species (the electrophile/proton), driving off the leaving group/conjugate base. Instead of showing a specific nucleophile like hydroxide, we will simply refer to the nucleophilic reactant as 'Nu'. In a similar fashion, we will call the leaving group 'X'. We will see as we study actual reactions that leaving groups are sometimes negatively charged, sometimes neutral, and sometimes positively charged. We will also see some examples of nucleophiles that are negatively charged and some that are neutral. Therefore, in this general picture we will not include a charge designation on the 'X' or 'Nu' species. We will generalize the three other groups bonded on the electrophilic central carbon as R_1, R_2, and R_3: these symbols could represent hydrogens as well as alkyl groups. Here, then, is the generalized picture of a concerted (single-step) nucleophilic substitution reaction.

General S_N2 Reaction

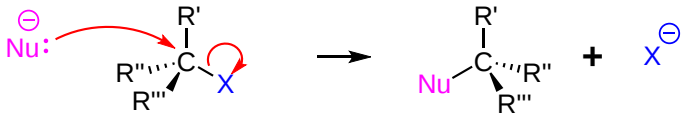


Example

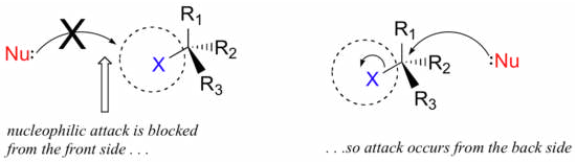


The S_N2 Mechanism

Bimolecular nucleophilic substitution (S_N2) reactions are **concerted**, meaning they are a **one step process**. This means that the process whereby the nucleophile attacks and the leaving group leaves is simultaneous. Hence, the bond-making between the nucleophile and the electrophilic carbon occurs at the same time as the bond-breaking between the electrophilic carbon and the halogen. This is called an '**S_N2**' mechanism. In the term S_N2, S stands for 'substitution', the subscript N stands for 'nucleophilic', and the number 2 refers to the fact that this is a **bimolecular reaction**: the overall rate depends on a step in which two separate molecules (the nucleophile and the electrophile) collide. The mechanism starts when lone pair electrons from the nucleophile attack the electrophilic carbon of the alkyl halide to form a C-Nu sigma bond. Simultaneously, the X-C bond is broken when the electrons are pushed onto the leaving group. Overall during this mechanism, a set of lone pair electrons are transferred from the nucleophile to the leaving group.



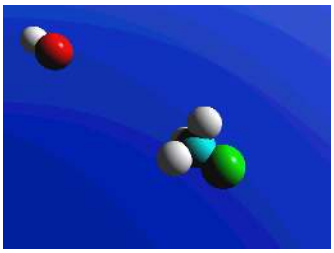
If you look carefully at the progress of the S_N2 reaction, you will realize something very important about the outcome. The nucleophile, being an electron-rich species, must attack the electrophilic carbon from the *back side* relative to the location of the leaving group. Approach from the front side simply doesn't work: the leaving group - which is also an electron-rich group - blocks the way.



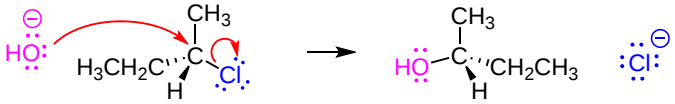
The result of this backside attack is that the stereochemical configuration at the central carbon *inverts* as the reaction proceeds. In a sense, the molecule is turned inside out. S_N2 reactions that begin with the R enantiomer as the substrate will form the S enantiomer as the product. Those that begin with the S enantiomer as the substrate will form the R enantiomer as the product. This concept also

applies to substrates that are *cis* and substrates that are *trans*. If the *cis* configuration is the substrate, the resulting product will be *trans*. Conversely, if the *trans* configuration is the substrate, the resulting product will be *cis*.

What this means is that S_N2 reactions whether enzyme catalyzed or not, are inherently stereoselective: when the substitution takes place at a stereocenter, we can confidently predict the stereochemical configuration of the product. Below is an animation illustrating the principles we have just learned, showing the S_N2 reaction between hydroxide ion and methyl iodide. Notice how backside attack by the hydroxide nucleophile results in inversion at the tetrahedral carbon electrophile.



Example



(S)-2-Chlorobutane **(R)-2-Butanol**

Bimolecular Nucleophilic Substitution Reactions and Kinetics

In the term S_N2, (as previously stated) the number two stands for bimolecular, meaning there are two molecules involved in the rate determining step. The rate of bimolecular nucleophilic substitution reactions depends on the concentration of both the haloalkane and the nucleophile. To understand how the rate depends on the concentrations of both the haloalkane and the nucleophile, let us look at the following example. The hydroxide ion is the nucleophile and methyl iodide is the haloalkane.

$$HO^- + CH_3-I \longrightarrow CH_3OH + I^-$$

$$\text{Rate} = k[CH_3-I][HO^-]$$

If we were to double the concentration of either the haloalkane or the nucleophile, we can see that the rate of the reaction would proceed twice as fast as the initial rate.

$$\text{Rate}_1 = k[CH_3-I][HO^-]$$
$$\text{Rate}_2 = 2k[CH_3-I][HO^-]$$
$$\text{Rate}_2 = 2\,\text{Rate}_1$$

If we were to double the concentration of both the haloalkane and the nucleophile, we can see that the rate of the reaction would proceed four times as fast as the initial rate.

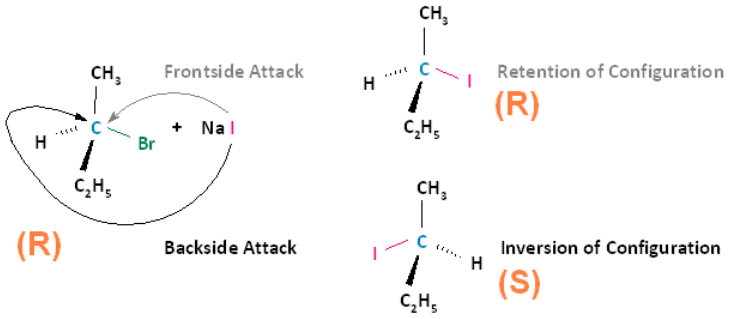
$$\text{Rate}_1 = k[CH_3-I][HO^-]$$
$$\text{Rate}_2 = 4k[CH_3-I][HO^-]$$
$$\text{Rate}_2 = 4\,\text{Rate}_1$$

The bimolecular nucleophilic substitution reaction follows second-order kinetics; that is, the rate of the reaction depends on the concentration of two first-order reactants. In the case of bimolecular nucleophilic substitution, these two reactants are the haloalkane and the nucleophile. For further clarification on reaction kinetics, the following links may facilitate your understanding of rate laws, rate constants, and second-order kinetics:

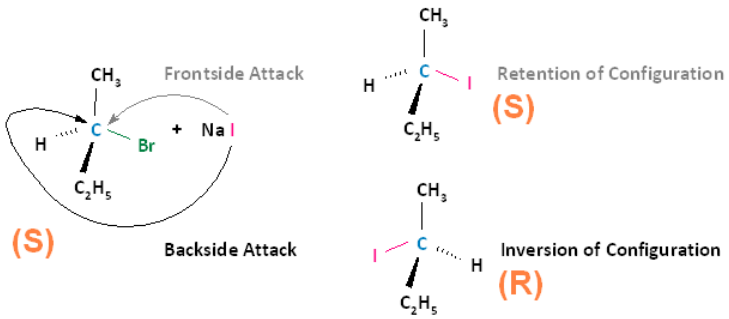
- Definition of a Reaction Rate
- Rate Laws and Rate Constants
- The Determination of the Rate Law
- Second-Order Reactions

S_N2 Reactions Are Stereospecific

The S_N2 reaction is stereospecific. A stereospecific reaction is one in which different stereoisomers react to give different stereoisomers of the product. For example, if the substrate is an R enantiomer, a frontside nucleophilic attack results in retention of configuration, and the formation of the R enantiomer. A backside nucleophilic attack results in inversion of configuration, and the formation of the S enantiomer.



Conversely, if the substrate is an S enantiomer, a frontside nucleophilic attack results in retention of configuration, and the formation of the S enantiomer. A backside nucleophilic attack results in inversion of configuration, and the formation of the R enantiomer.



In conclusion, S_N2 reactions that begin with the R enantiomer as the substrate will form the S enantiomer as the product. Those that begin with the S enantiomer as the substrate will form the R enantiomer as the product. This concept also applies to substrates that are *cis* and substrates that are *trans*. If the *cis* configuration is the substrate, the resulting product will be *trans*. Conversely, if the *trans* configuration is the substrate, the resulting product will be *cis*.

? Exercise 2.3.1

The reaction below follows the S_N2 mechanism.

$$CH_3Cl + NaOH \longrightarrow CH_3OH + NaCl$$

a) Write the rate law for this reaction.

b) Determine the value of the rate coefficient, k, if the initial concentrations are 0.01 M CH_3Cl, 0.01 M NaOH, and the initial reaction rate is 6×10^{-10} M/s.

c) Calculate the initial reaction rate if the initial reactant concentrations are changed to 0.02 M CH_3Cl and 0.0005 M NaOH.

Answer

a) rate = k $[CH_3Cl]$ $[OH^-]$

b) substitute the data into the rate expression above and apply algebra to solve for k

$k = 6 \times 10^{-6}$ $Lmol^{-1}s^{-1}$

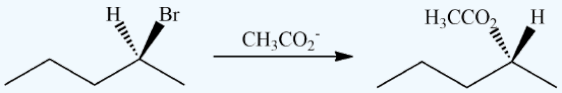
c) Using the rate law above, substitute the value for k from the previous question along with the new concentrations to determine the new initial rate.

rate = 6 x 10^{-10} M/s

Exercise 2.3.2

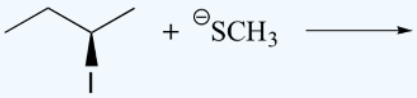
Predict the product of a nucleophilic substitution of (S)-2-bromopentane reacting with $CH_3CO_2^-$. Show stereochemistry.

Answer

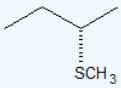


Exercise 2.3.3

Predict the structure of the product in this S_N2 reaction. Be sure to specify stereochemistry.



Answer



Exercise 2.3.4

Since everything is relative in chemistry, one reaction's nucleophile can be another reaction's leaving group. Some functional groups can only react as a nucleophile or electrophile, while other functional groups can react as either a nucleophile or electrophile depending on the reaction conditions. Classify the following compounds as nucleophile, electrophile, or leaving groups. More than one answer may be possible.

a) bromoethane

b) hydroxide

c) water

d) chlorocyclohexane

e) ethanol

f) bromide

Answer

a) electrophile (Alkyl halides are always electrophiles - one reason they are an o-chem student's best friend.)

b) strong nucleophile

c) weak nucleophile and good leaving group

d) electrophile (Alkyl halides are always electrophiles - one reason they are an o-chem student's best friend.)

e) weak nucleophile, a poor electrophile without clever chemistry (stay tuned for future chapters), good leaving group

f) good nucleophile and a good leaving group

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2.4: Characteristics of the SN2 Reaction

Objectives

After completing this section, you should be able to

1. discuss the role of steric effects in S_N2 reactions.
2. arrange a given series of alkyl halides in order of increasing or decreasing reactivity towards nucleophilic substitution through the S_N2 mechanism.
3. suggest a reason why vinyl halides and aryl halides do not undergo S_N2 reactions.
4. discuss how the nature of the nucleophile affects the rate of an S_N2 reaction.
5. arrange a given series of common nucleophiles (e.g., CN^-, I^-, Br^- Cl^-, H_2O) in order of increasing or decreasing nucleophilicity.
6. discuss how the nature of the leaving group affects the rate of an S_N2 reaction.
7. arrange a given series of leaving groups in order of increasing or decreasing ability to leave during an S_N2 reaction.
8. discuss the role played by the solvent in an S_N2 reaction.
9. give examples of the solvents which are commonly used for S_N2 reactions, and identify those that promote a high reaction rate.
10. predict which of two given S_N2 reactions will proceed faster, by taking into account the structure of the substrates, the nucleophiles involved, leaving-group ability, solvent effects, or any combination of these factors.

Key Terms

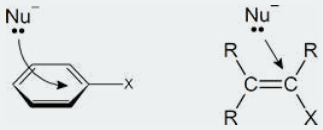
Make certain that you can define, and use in context, the key terms below.

- leaving group
- polar aprotic solvent
- solvation

Study Notes

You may wish to review the discussion of acid-base theory from CHM 222.

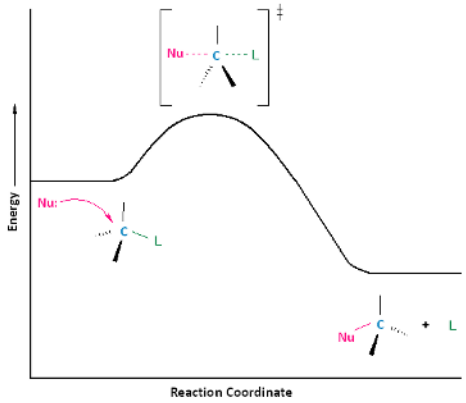
Both aryl and vinylic halides are relatively unreactive in S_N2 displacement mechanisms, mostly because during the backside attack of the molecule the incoming nucleophile is sterically hindered by both substituents and electron density from any double bonds present. Also, leaving groups on sp^2-hybridized carbons tend to be held tighter than sp^3-hybridized carbons.



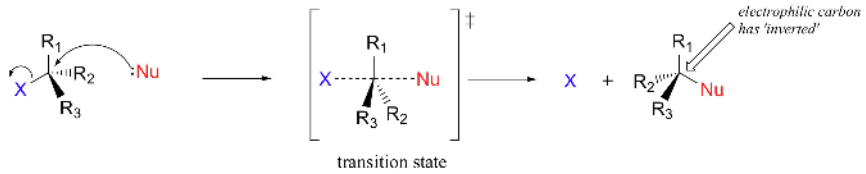
Solvation may be defined as the interaction between molecules of solvent and particles of solute. The result of solvation is to stabilize (i.e., lower the energy of) the solute particles. Solvents with lone pairs of electrons are good at solvating cations. Protic (i.e., hydroxylic) solvents are able to solvate anions through hydrogen bonding. As water has two lone pairs of electrons and is also protic, it is good at solvating both anions and cations.

Potential Energy Diagram for an S_N2 Reaction

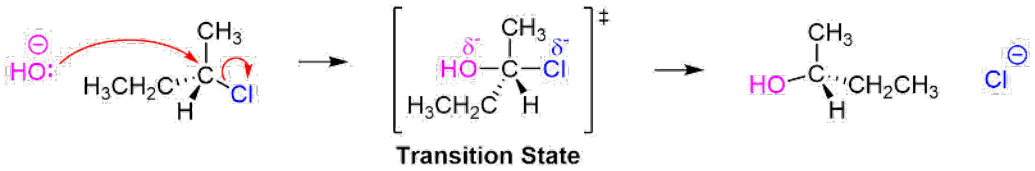
The potential energy diagram for an S_N2 reaction is shown below. This is a single-step, concerted process so a single transition state is formed. A transition state, unlike a reaction intermediate, is a very short-lived species that cannot be isolated or directly observed. For an S_N2 reaction the transition state directly determines the energy of activation which must be overcome for the reaction to occur. Factors which affect the stability of the transition state affect the rate of the S_N2 reaction.



For an S_N2 reaction, the transition state represents the half way point of the reaction. The C-Nu bond is in the process of forming and is represented by a dashed bond. The X-C bond is in the process of breaking and is also represented by a dash bond. The negative charge of the nucleophile is in the process of being transferred to the leaving group. This is represented by both the nucleophile and the leaving group having a partial negative charge. The electrophilic carbon and the three 'R' substituents all lie on the same plane. Brackets and a double-dagger are placed around the structure to represent that it is a transition state.

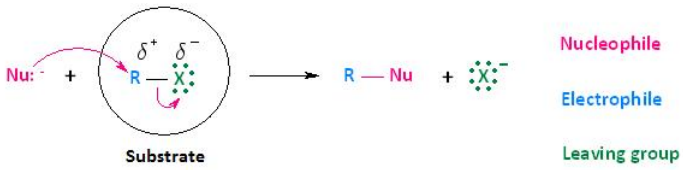


Example

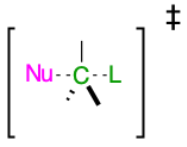


Sterically Hindered Substrates Will Reduce the S_N2 Reaction Rate

Steric hindrance about the electrophilic carbon, is one of the most important factors determining the rate of S_N2 reactions. Although the substrate, in the case of nucleophilic substitution of haloalkanes, is considered to be the entire molecule circled below we are most interested in the electrophilic carbon that bears the leaving group.



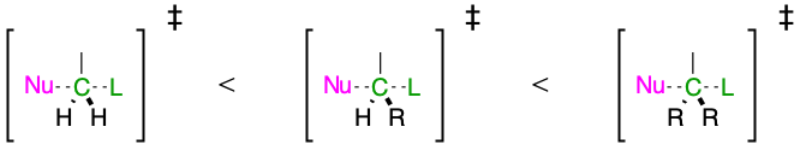
The S_N2 **transition state** is very crowded. Recall that there are a total of five groups around the electrophilic center, the nucleophile, the leaving group, and three substituents.



S_N2 Transition State

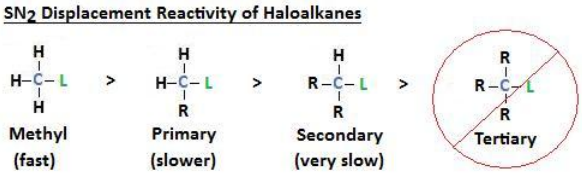
If each of the three substituents were hydrogen atoms, as illustrated in the first example below, there would be little steric repulsion created in the planar portion of the transition state thereby increasing the ease at which the nucleophilic substitution reaction occurs. If one of the hydrogens, however, were replaced with an R group, such as a methyl or ethyl group, there would be an increase in steric repulsion created in the planar portion of the transition state. If two of the hydrogens were replaced by R groups, there would be an even greater increase in steric repulsion in the transition state.

Steric repulsion of S_N2 Transition States

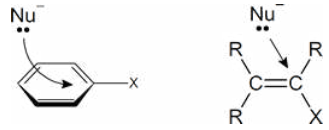


How does steric hindrance affect the rate at which an S_N2 reaction will occur? As each hydrogen is replaced by an R group, the rate of reaction is significantly diminished. The increases steric hindrance destabilizes the transition state causing it to become higher in energy. This in turn increases the energy of activation and decreases the reaction rate.

The diagram below illustrates this concept, showing that electrophilic carbons attached to three hydrogen atoms results in faster nucleophilic substitution reactions, in comparison to primary and secondary haloalkanes, which result in nucleophilic substitution reactions that occur at slower or much slower rates, respectively. Notice that a tertiary haloalkane, that which has three R groups attached, does not undergo nucleophilic substitution reactions at all. The addition of a third R group to this molecule creates a carbon that is entirely blocked.



Vinyl and aryl halides are unreactive toward S_N2 displacement due to extreme steric factors. To perform an S_N2 reaction, the incoming nucleophile would have to enter the plane of the C-C double bond and move through the molecule to achieve the backside displacement required.



In addition to alkyl groups being added to the electrophilic carbon, it turns out that the addition of substitutes on neighboring carbons will slow nucleophilic substitution reactions as well.

In the example below, 2-methyl-1-bromopropane differs from 1-bromopropane in that it has a methyl group attached to the carbon that neighbors the electrophilic carbon. The addition of this methyl group results in a significant decrease in the rate of a nucleophilic substitution reaction.

If R groups were added to carbons farther away from the electrophilic carbon, we would still see a decrease in the reaction rate. However, branching at carbons farther away from the electrophilic carbon would have a much smaller effect.

The Nucleophile

Nucleophilic functional groups are those which have electron-rich atoms able to donate a pair of electrons to form a new covalent bond. In both laboratory and biological organic chemistry, the most relevant nucleophilic atoms are oxygen, nitrogen, and sulfur, and the most common nucleophilic functional groups are water, alcohols, phenols, amines, thiols, and occasionally carboxylates.

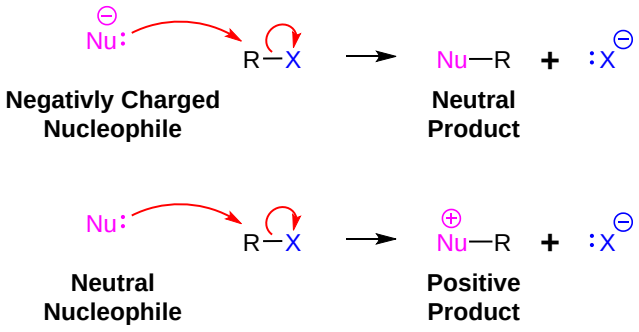
When thinking about nucleophiles, the first thing to recognize is that, for the most part, the same quality of 'electron-richness' that makes something nucleophilic also makes it basic: *nucleophiles can be bases, and bases can be nucleophiles*. It should not be surprising, then, that most of the trends in basicity that we have already discussed also apply to nucleophilicity.

Some confusion in distinguishing basicity (base strength) and nucleophilicity (nucleophile strength) is inevitable. Since basicity is a less troublesome concept; it is convenient to start with it. Basicity refers to the ability of a base to accept a proton. Basicity may be related to the pK_a of the corresponding conjugate acid, as shown below. The strongest bases have the weakest conjugate acids and vice versa. The range of basicities included in the following table is remarkable, covering over fifty powers of ten! In general, as the pKa of the conjugate acid increases the base becomes a stronger nuclophile. This, however, is not always the case.

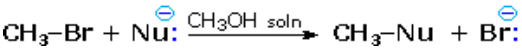
Base	$I^{(-)}$	$Cl^{(-)}$	H_2O	$CH_3CO_2^{(-)}$	$RS^{(-)}$	$CN^{(-)}$	$RO^{(-)}$	$NH_2^{(-)}$	$CH_3^{(-)}$
Conj. Acid	HI	HCl	$H_3O^{(+)}$	CH_3CO_2H	RSH	HCN	ROH	NH_3	CH_4
pK_a	-9	-7	0.0	4.8	8	9.1	16	33	48

Increasing base strength

Nucleophilicity is a more complex property. Any compound, neutral or charged, which has lone pair electrons can act a neuclophile. After an S_N2 reaction neutral nucleophiles make a positively charged products and negatively charged nucleophiles make neutral products. In general, negatively charged compounds tend to make better nucleophilies.



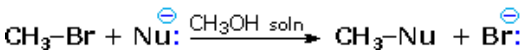
Specifically, nucleophilicity refers to the rate of substitution reactions at the halogen-bearing **carbon atom** of a reference alkyl halide, such as CH_3-Br. The nucleophilicity of the $Nu:^{(-)}$ reactant in the following substitution reaction varies as shown in the chart below:



Nucleophilicity: $H_2O < CH_3CO_2^{(-)} < NH_3 < Cl^{(-)} < Br^{(-)} < HO^{(-)} < CH_3O^{(-)} < I^{(-)} < CN^{(-)} < CH_3S^{(-)}$

Increasing nucleophile strength

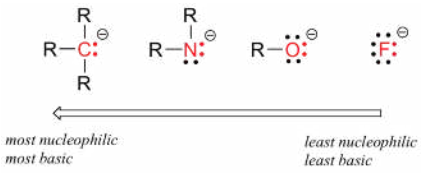
The versatility of the S_N2 reaction is shown by the wide variety of functional groups which can be formed.



Nucleophile		Products		
Formula	**Name**	**Formula**	**Name**	**Functional Group**
$CH_3S^{(-)}$	Methanethiolate	CH_3SCH_3	Dimethylsulfide	Sulfide
$CN^{(-)}$	Cyanide	CH_3CN	Acetonitrile	Nitrile
$I^{(-)}$	Iodide	CH_3I	Iodomethane	Alkyl Halide
$CH_3O^{(-)}$	Methoxide	CH_3OCH_3	Diethylether	Ether
$HO^{(-)}$	Hydroxide	CH_3OH	Methanol	Alcohol
$Br^{(-)}$	Bromide	CH_3Br	Bromomethane	Alkyl Halide
$Cl^{(-)}$	Chloride	CH_3Cl	Chloromethane	Alkyl Halide
NH_3	Ammonia	$CH_3NH_3^{(+)}$	Methylammonium ion	Ammonium
$CH_3CO_2^{(-)}$	Acetate	$CH_3O_2CH_3$	Methyl acetate	Ester
H_2O	Water	$CH_3OH_2^{(+)}$	Methylhydronium ion	Protonated Alcohol

Periodic Trends in Nucleophilicity

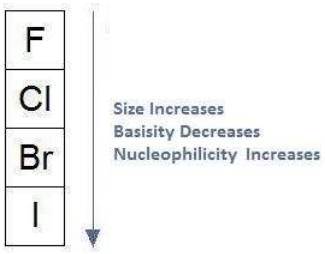
There are predictable periodic trends in nucleophilicity. Moving horizontally across the second row of the table, the trend in nucleophilicity parallels the trend in basicity:



The reasoning behind the horizontal nucleophilicity trend is the same as the reasoning behind the basicity trend: more electronegative elements hold their electrons more tightly, and are less able to donate them to form a new bond. This horizontal trend also tells us that amines are more nucleophilic than alcohols, although both groups commonly act as nucleophiles in both laboratory and biochemical reactions.

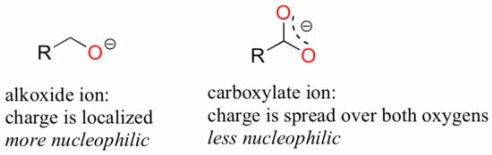
Recall that the basicity of atoms decreases as we move vertically down a column on the periodic table: thiolate ions are less basic than alkoxide ions, for example, and bromide ion is less basic than chloride ion, which in turn is less basic than fluoride ion. Recall also that this trend can be explained by considering the increasing size of the 'electron cloud' around the larger ions: the electron density inherent in the negative charge is spread around a larger area, which tends to increase stability (and thus reduce basicity).

As Size Increases, Basicity Decreases: In general, if we move from the top of the periodic table to the bottom of the periodic table as shown in the diagram below, the size of an atom will increase. As size increases, basicity will decrease, meaning a species will be less likely to act as a base; however, the species will be **more likely** to share its electrons and act as a nucleophile.

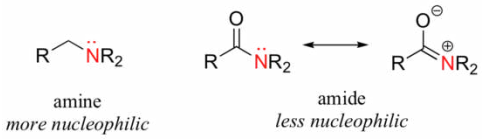


Resonance Effects on Nucleophilicity

Resonance effects also come into play when comparing the inherent nucleophilicity of different molecules. The reasoning involved is the same as that which we used to understand resonance effects on basicity. If the electron lone pair on a heteroatom is delocalized by resonance, it is inherently less reactive - meaning less nucleophilic, and also less basic. An alkoxide ion, for example, is more nucleophilic and more basic than a carboxylate group, even though in both cases the nucleophilic atom is a negatively charged oxygen. In the alkoxide, the negative charge is localized on a single oxygen, while in the carboxylate the charge is delocalized over two oxygen atoms by resonance.



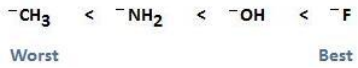
The nitrogen atom on an amide is less nucleophilic than the nitrogen of an amine, due to the resonance stabilization of the nitrogen lone pair provided by the amide carbonyl group.



The Leaving Group

As Electronegativity Increases, The Ability of the Leaving Group to Leave Increases

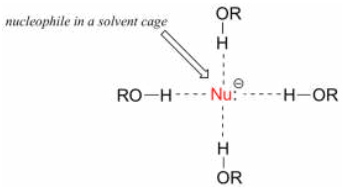
As mentioned previously, if we move from left to right on the periodic table, electronegativity increases. With an increase in electronegativity, basicity decreases, and the ability of the leaving group to leave increases. This is because an increase in electronegativity results in a species that wants to hold onto its electrons rather than donate them. The following diagram illustrates this concept, showing $^{-}CH_3$ to be the worst leaving group and F^- to be the best leaving group. This particular example should only be used to facilitate your understanding of this concept. In real reaction mechanisms, these groups are not good leaving groups at all. For example, fluoride is such a poor leaving group that S_N2 reactions of fluoroalkanes are rarely observed.



As Size Increases, The Ability of the Leaving Group to Leave Increases: Here we revisit the effect size has on basicity. If we move down the periodic table, size increases. With an increase in size, basicity decreases, and the ability of the leaving group to leave increases. The relationship among the following halogens, unlike the previous example, is true to what we will see in upcoming reaction mechanisms.

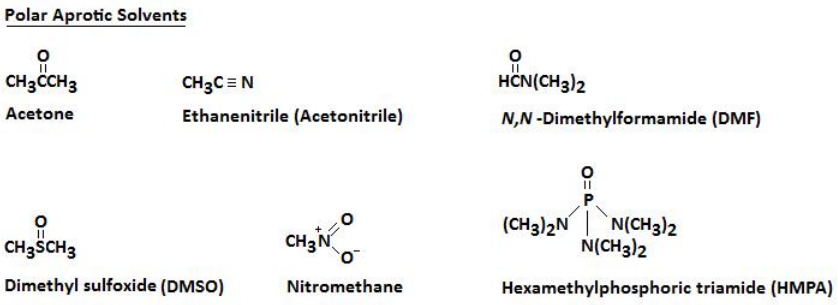
Influence of the Solvent in an S_N2 Reaction

The rate of an S_N2 reaction is significantly influenced by the solvent in which the reaction takes place. The use of **protic solvents** (those, such as water or alcohols, with hydrogen-bond donating capability) decreases the power of the nucleophile, because of strong hydrogen-bond interactions between solvent protons and the reactive lone pairs on the nucleophile. Protic solvent molecules form very strong ion-dipole interactions with the negatively-charged nucleophile, essentially creating a 'solvent cage' around the nucleophile. In order for the nucleophile to attack the electrophile, it must break free, at least in part, from its solvent cage. A less powerful nucleophile in turn means a slower S_N2 reaction. S_N2 reactions are faster in **polar, aprotic solvents:** those that lack hydrogen-bond donating capability.

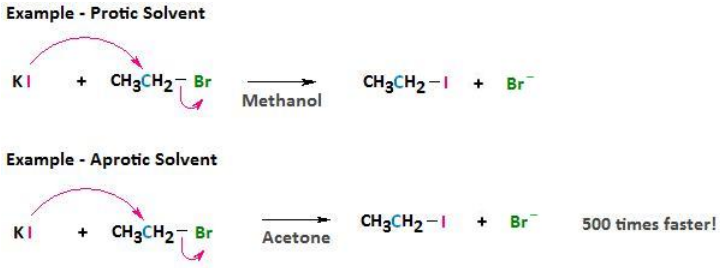


Why not use a completely nonpolar solvent, such as hexane, for this reaction, so that the solvent cage is eliminated completely? The answer to this is simple - the nucleophile needs to be in solution in order to react at an appreciable rate with the electrophile, and a solvent such as hexane will not solvate a charged (or highly polar) nucleophile at all. That is why chemists use polar aprotic solvents for nucleophilic substitution reactions in the laboratory: they are polar enough to solvate the nucleophile, but not so polar as to lock it away in an impenetrable solvent cage. In addition to acetone, three other commonly used polar aprotic solvents are acetonitrile, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO).

Below are several polar aprotic solvents that are commonly used in the laboratory:



These aprotic solvents are polar but, because they do not form hydrogen bonds with the anionic nucleophile, there is a relatively weak interaction between the aprotic solvent and the nucleophile. By using an aprotic solvent we can raise the reactivity of the nucleophile. This can sometimes have dramatic effects on the rate at which a nucleophilic substitution reaction can occur. For example, if we consider the reaction between bromoethane and potassium iodide, the reaction occurs 500 times faster in acetone than in methanol.



Summary of Factors in Affecting S_N2 Reactions

There are four main factors which affect S_N2 reaction:

1) The structure of the alkyl portion of the substrate: S_N2 reactions are affected by steric hindrance around the electrophilic carbon. As steric hindrance increases the rate of S_N2 reactions decrease. Methyl and primary substrates work well for S_N2 reactions, secondary substrates react slowly, and teritary substrates do not undergo S_N2 reactions at all.

2) The reactivity of the nucleophile: The rate of S_N2 reaction is increased when strong nucleophiles are used. Strong nucleophiles tend to be negatively charged and good bases. Also, being of an increased size tends to increase the nucleophilicity of an atom.

3) The nature of the leaving group: The rate of an S_N2 reaction is increased when good leaving groups are used in the substrate. Good leaving groups tend to stabilize the electrons gained during an S_N2 reaction. High electronegativity, resonance, and an increased size all can stabilize electrons.

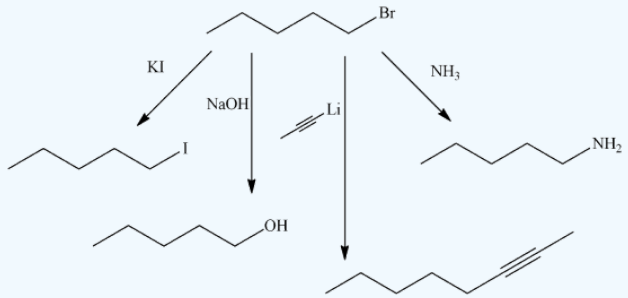
4) The solvent: S_N2 reactions are severely hindered when a polar protic solvent is used for the reaction. Instead, polar aprotic solvents tend to be used for S_N2 reactions.

Exercise 2.4.1

1) What product(s) do you expect from the reaction of 1-bromopentane with each of the following reagents in an S_N2 reaction?

a) KI b) NaOH c) $CH_3C{\equiv}C\text{-}Li$ d) NH_3

Answer



Exercise 2.4.2

Which of the following molecules in each pair is a better nuceophile?

a) $(CH_3CH_2)_2N^-$ or $(CH_3CH_2)_2NH$

b) $(CH_3CH_2)_3N$ or $(CH_3CH_2)_3B$

Answer

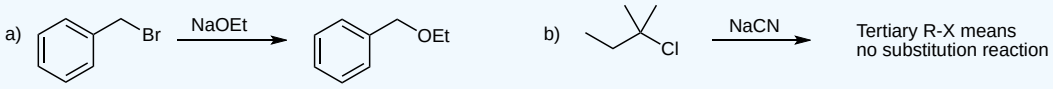
a) $(CH_3CH_2)_2N^-$ since there is a charge present on the nitrogen.

b) $(CH_3CH_2)_3N$ because a lone pair of electrons is present.

Exercise 2.4.3

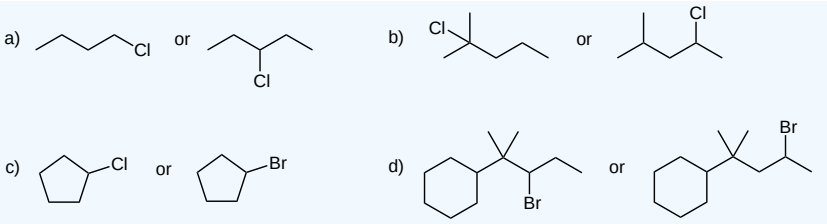
Predict the products of these nucleophilic substitution reactions, including stereochemistry when appropriate.

Answer

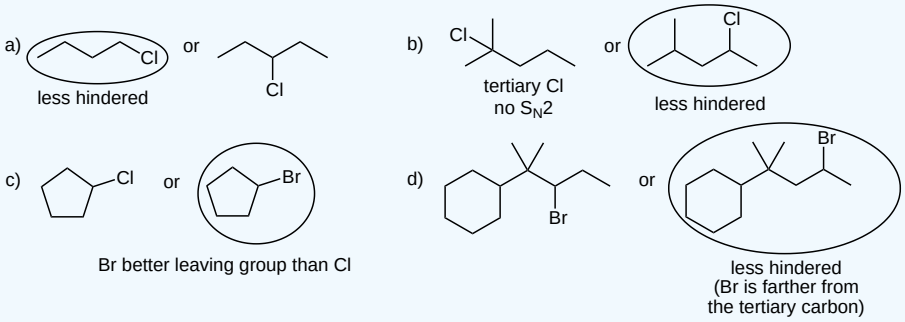


Exercise 2.4.4

Predict which compound in each pair would undergo an S_N2 reaction faster.



Answer



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2.5: The SN1 Reaction

Objectives

After completing this section, you should be able to

1. write an expression relating reaction rate and reactant concentration for a first-order reaction.
2. compare the kinetics of S_N1 and S_N2 reactions.
3. identify the rate-limiting step for a reaction, given the reaction energy diagram.
4. sketch a reaction energy diagram for a reaction, given the mechanism and sufficient information to identify the rate-limiting step.
5. write the mechanism of a typical S_N1 reaction, and discuss the important features of the mechanism.
6. discuss the stereochemistry of an S_N1 reaction, and explain why a racemic mixture is expected when substitution takes place at the chiral carbon atom of an optically pure substrate.
7. explain why unimolecular nucleophilic substitution at the chiral carbon atom of an optically pure substrate does not result in complete racemization.
8. compare the stereochemical consequences of the S_N1 mechanism with those of the S_N2 mechanism.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- first-order reaction
- rate-limiting step
- S_N1

Study Notes

You should recognize that certain compounds (notably tertiary alkyl halides) which react very slowly by the S_N2 mechanism can undergo rapid nucleophilic substitution by an alternative mechanism.

The abbreviation S_N1 refers to "unimolecular nucleophilic substitution." In a *first-order reaction*, the rate of the reaction depends on the concentration of only one of the reactants. Thus, when an alkyl halide reacts by an S_N1 mechanism, the rate of reaction is dependent on the concentration of the alkyl halide, but is independent of the concentration of the attacking nucleophile.

Note: In many textbooks the "rate-limiting step" is called the "rate-determining step."

Racemization problems can be a potential source of confusion. Most students entering an introductory organic chemistry course have a reasonable background in mathematics, and feel comfortable if they have a formula or equation they can use in this type of situation. Thus, we recommend that you consider the following approach.

1. In a given mixture of enantiomers, let x = the fraction of the (+)-enantiomer, and $1 - x$ = the fraction of the (−)-enantiomer. [Remember that the fraction can be obtained by dividing the percentage by 100%.]
2. The observed $[\alpha]_D$ of the mixture is then given by:

   Observed $[\alpha]_D = x$ ($[\alpha]_D$ of the (+)-enantiomer)

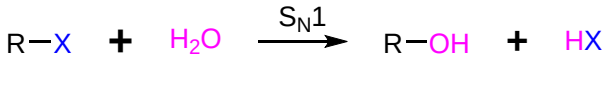
   + $(1 - x)$($[\alpha]_D$ of the (−)-enantiomer)

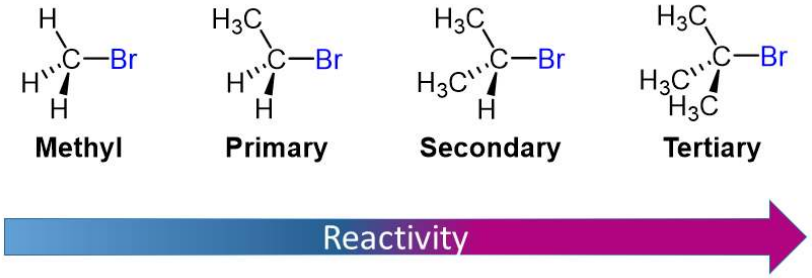
Another source of confusion is the way in which the terms "percentage racemization" and "percentage inversion" are used. You must be clear in your mind that 80% racemized means that we have 40% of the original configuration and 60% (40% + 20%) of the inverted configuration.

General S_N1 Reaction

When looking at the following substitution reaction it would be expected to be extremely slow. The reaction represents a worst case scenario based off the rules of an S_N2 reaction. The substrate is sterically hindered, the nucleophile is relatively weak, and the

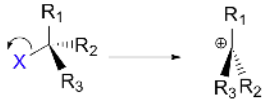
solvent is polar protic. However, the reaction proceeds quickly and prefers tertiary substrates over methyl, which is opposite to the trend seen in S_N2 reactions. It makes sense that this substitution reaction occurs using a different mechanism than S_N2.



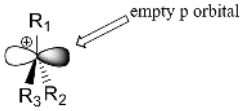


The S_N1 mechanism

A second model for a nucleophilic substitution reaction is called the '**dissociative**', or '**S_N1**' mechanism. In the S_N1 reaction, the bond between the substrate and the leaving group is broken when the leaving group departs with the pair of electrons that formerly composed the bond.

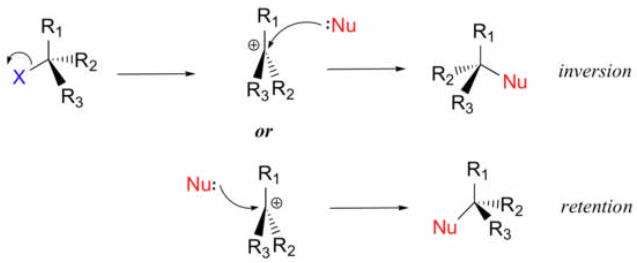


This results in the formation of a **carbocation** (from "carbon" and "cation") the word for a positively charged carbon atom. Because the carbocation has only three bonds, it bears a formal charge of +1. Recall that a carbocation is sp^2 hybridized, with trigonal planar geometry. The positive charge is contained in an empty, unhybridized *p* orbital perpendicular to the plane formed by the three sigma bonds. The formation of a carbocation is not energetically favored, so this step in the reaction is the slowest step and determines the overall rate of the reaction. The step which controls the overall rate of a reaction is called the **rate-determining step**.

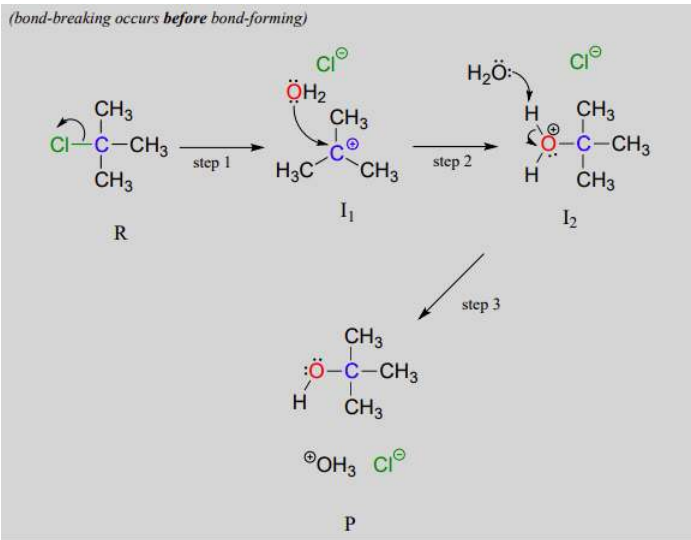


Like alkene reactions with acid that form carbocations, rearrangements are possible for S_N1 reactions. Always consider if a hydride or alkyl shift from an adjacent carbon will enable formation of a more stable carbocation before proceeding with the mechanism. For a review of rearrangement details, please refer to the Alkene Reactivity Chapter.

In the second step of this two-step reaction, the nucleophile attacks the empty, 'electron hungry' *p* orbital of the carbocation to form a new bond and return the carbon to tetrahedral geometry. Since the nucleophile attacks the carbocation only after the leaving group has departed, there is no need for back-side attack. The carbocation and its substituents are all in the same plane, meaning that the nucleophile can attack from either side. As a result, both enantiomers are formed in an the S_N1 reaction, leading to a **racemic mixture** of both enantiomers.

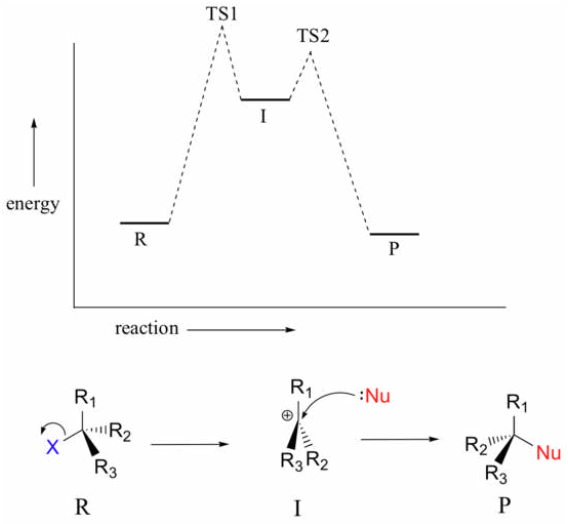


Because S_N1 reactions almost exclusively involve neutral nucleophiles the product of this second step of the mechanism is often positively charged. The neutral substitution product is usually formed after a third, deprotonation step.



Reaction Coordinate Diagrams and S_N1 Mechanism

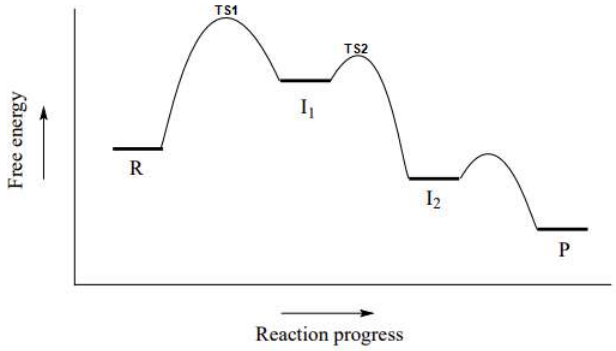
During the S_N1 reaction we see an example of a reaction intermediate, a very important concept in the study of organic reaction mechanisms that was introduced earlier in the module on organic reactivity. Recall that many important organic reactions do not occur in a single step; rather, they are the sum of two or more discreet bond-forming / bond-breaking steps, and involve transient intermediate species that go on to react very quickly. In the S_N1 reaction, the carbocation species is a reaction intermediate. A potential energy diagram for an S_N1 reaction shows that the carbocation intermediate can be visualized as a kind of valley in the path of the reaction, higher in energy than both the reactant and product but lower in energy than the two transition states. The following reaction coordinate diagram shows an example of a an S_N1 reaction with a negatively charged nucleophile.



There are several important consequences to the **unimolecular** nature of the rate-determining step in the the S_N1 reaction. The first step (dissociation) is the rate determining step, so the rate is controlled only by the loss of the leaving group and does not involve any participation of the nucleophile. Therefore, the rate of the reaction is dependent only on the concentration of the substrate, not on the concentration of the nucleophile.

This can also be shown for the reactions with a neutral nucleophile which includes an extra step of deprotonation. A potential energy diagram for this mechanism shows that each of the two positively-charged intermediates (I_1 and I_2) can be visualized as a valley in the path of the reaction, higher in energy than both the reactant and product but lower in energy than the transition states.

The first, bond-breaking step is the slowest, rate-determining step - notice it has the highest activation energy and leads to the highest-energy species, I_1, the carbocation intermediate. Step 2 is rapid: a new covalent bond forms between a carbocation and a water nucleophile, and no covalent bonds are broken. The third step represents a Bronsted-Lowry proton transfer which is rapid, with low activation energy.



Because the first step of the mechanism is the rate determining step, the first transition state will be the most important. During the first step, a carbon-leaving group bond in a neutral substrate is broken to form a carbocation intermediate and a leaving group anion. The breaking bond is represented as a dashed-partial bond in the transition state. A partial positive charge is shown on the carbon to represent the formation of a carbocation and a partial negative charge is shown on the leaving group to represent the formation of an anion.

Transition State 1 (TS1)

S_N1 Reaction Kinetics

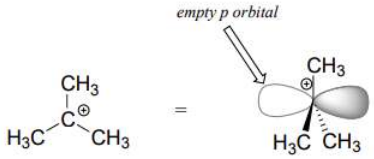
In the first step of an S_N1 mechanism, two charged species are formed from a neutral molecule. This step is much the slower of the three steps, and is therefore rate-determining. In the reaction energy diagram, the activation energy for the first step is higher than that for the second step indicating that the S_N1 reaction has *first order*, *unimolecular* kinetics because the rate determining step involves one molecule splitting apart, not two molecules colliding. It is important to remember that first order refers to the rate law expression where the generic term substrate is used to describe the alkyl halide.

$$\text{rate} = k\,[\text{substrate}]$$

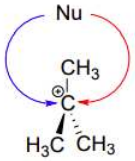
Because an S_N1 reaction is first order overall the concentration of the nucleophile does not affect the rate. Since the nucleophile is not involved in the rate-limiting first step, the nature of the nucleophile does not affect the rate of an S_N1 reaction.

Stereochemical Considerations

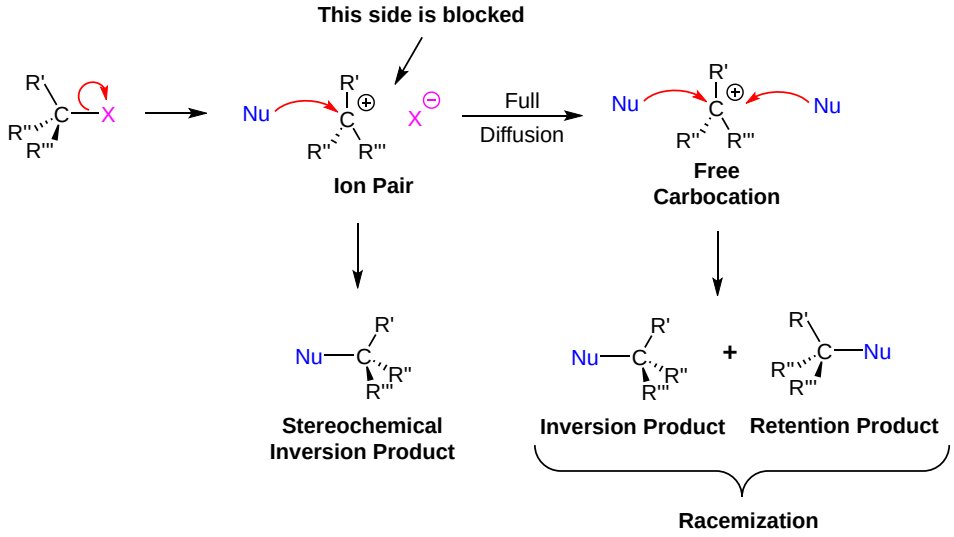
We saw that S_N2 reactions result in inversion of stereochemical configuration at the carbon center. The difference in mechanisms means the stereochemical outcome of S_N1 can be different than S_N2. Recall that a carbocation intermediate produced during an S_N1 reaction is sp^2-hybridized, with an empty p orbital perpendicular to the plane formed by the three sigma bonds:



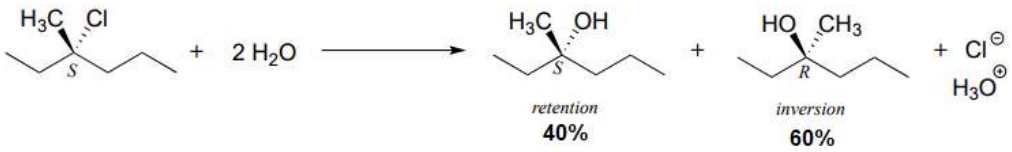
Because the nucleophile is free to attack from either side of the carbocation electrophile, the reaction leads to a 50:50 mixture of two stereoisomeric products. In other words: the S_N1 reaction occurs with both retention or inversion of configuration at the electrophilic carbon, leading to racemization if the carbon is chiral after the substitution.



However, often chemical reactions are more complicated than the mechanisms that represent limiting cases like S_N1 and S_N2. Experimental data has shown that the inversion product is favored over racemization due to the formation of **ion pairs**. After dissociation during the rate determining step the carbocation and the leaving group are still electrostatically associated. The leaving group anion is temporarily held in place which provides a shield to one side of the carbocation. If substitution occurs before the leaving group anion fully diffuses away the stereochemical inversion substitution product is created. Only after the leaving group fully diffuses away can racemization occur. Overall, the product of an S_N1 reaction shows an excess of the stereochemical inversion product.

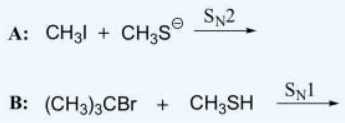


For an example, consider the hydrolysis of (S)-3-chloro-3-methylhexane.



Exercise 2.5.1

Consider the two nucleophilic substitution reactions below. Assume that reaction A is S_N2, and reaction B is S_N1. Predict, in each case, what would happen to the rate of the reaction if the concentration of the nucleophile were doubled, while all other conditions remained constant.



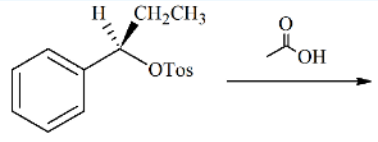
Answer

For Reaction A, the rate law is rate = $k[CH_3I][CH_3S^-]$. Therefore, if the concentration of the nucleophile, CH_3S^-, is doubled and the concentration of the alkyl halide remains the same, then the reaction rate will double.

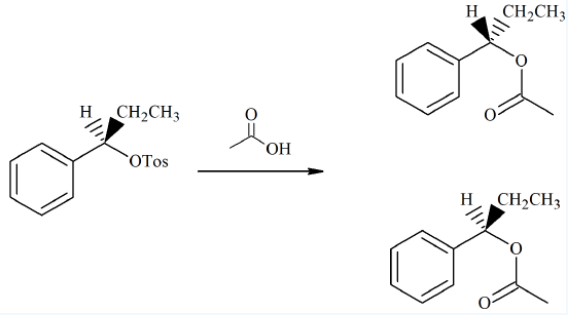
For Reaction B, the rate law is rate = $k[(CH_3)_3Br]$. Therefore, if the concentration of the nucleophile, CH_3SH, is doubled and the concentration of the alkyl halide remains the same, then reaction rate stays the same.

Exercise 2.5.2

Give the products of the following S_N1 reaction. Show stereochemistry. (Remember OTos is the abbreviation for a tosylate. It behaves like an iodine atom.)

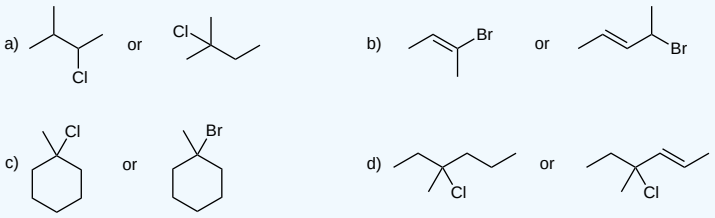


Answer



Exercise 2.5.3

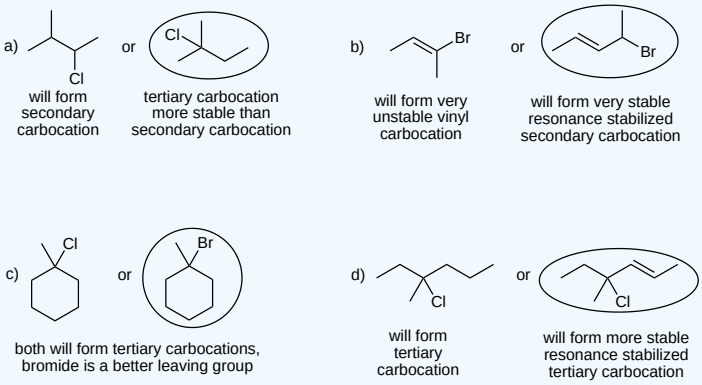
Predict with compound in each pair will undergo an S_N1 reaction more quickly.



Answer

It's almost always about the stability of the carbocation that forms when the leaving group leaves. (In one problem, it's about the two different leaving groups.) The more stable carbocation will form faster and the reaction will occur more

quickly.



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2.6: Characteristics of the SN1 Reaction

Objectives

After completing this section, you should be able to

1. discuss how the structure of the substrate affects the rate of a reaction occurring by the S_N1 mechanism.
2. arrange a given list of carbocations (including benzyl and allyl) in order of increasing or decreasing stability.
3. explain the high stability of the allyl and benzyl carbocations.
4. arrange a given series of compounds in order of increasing or decreasing reactivity in S_N1 reactions, and discuss this order in terms of the Hammond postulate.
5. discuss how the nature of the leaving group affects the rate of an S_N1 reaction, and in particular, explain why S_N1 reactions involving alcohols are carried out under acidic conditions.
6. explain why the nature of the nucleophile does not affect the rate of an S_N1 reaction.
7. discuss the role played by the solvent in an S_N1 reaction, and hence determine whether a given solvent will promote reaction by this mechanism.
8. compare the roles played by the solvent in S_N1 and in S_N2 reactions.
9. determine which of two S_N1 reactions will occur faster, by taking into account factors such as the structure of the substrate and the polarity of the solvent.
10. determine whether a given reaction is most likely to occur by an S_N1 or S_N2 mechanism, based on factors such as the structure of the substrate, the solvent used, etc.

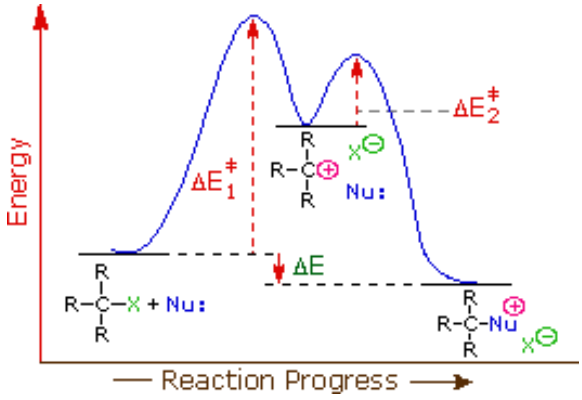
Key Terms

Make certain that you can define, and use in context, the key terms below.

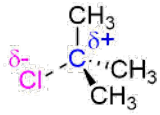
- benzylic
- dielectric constant
- polarity

The Substrate in S_N1Reactions

As discussed in the previous section, S_N1 reactions follow first order kinetics due to a multi-step mechanism in which the rate-determining step consists of the ionization of the alkyl halide to form a carbocation.

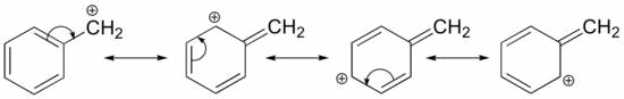


The transition state for the rate determining step shows the transition of an alkyl halide to a carbocation. Because the rate determining step is endothermic, the Hammond postulate says that the transition state more closely resembles the carbocation intermediate. Factors which stabilize this intermediate will lower the energy of activation for the rate determining step and cause the rate of reaction to increase. In general, a more stable carbocation intermediate formed during the reaction allows for a faster S_N1 reaction rate.

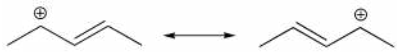


Transition State 1
(TS1)

In CHM 222, we saw that the stability of alky carbocations was $3^o > 2^o > 1^o >$ methyl. Two special cases of resonance-stabilized carbocations, allyl and benzyl, must be considered and added to the list. The delocalization of the positive charge over an extended p orbital system allows for allyl and benzyl carbocations to be exceptionally stable. The resonance hybrid of an allyic cation is made up of two resonance forms while the resonance hybrid of the benzylic carbocation is made up of four.

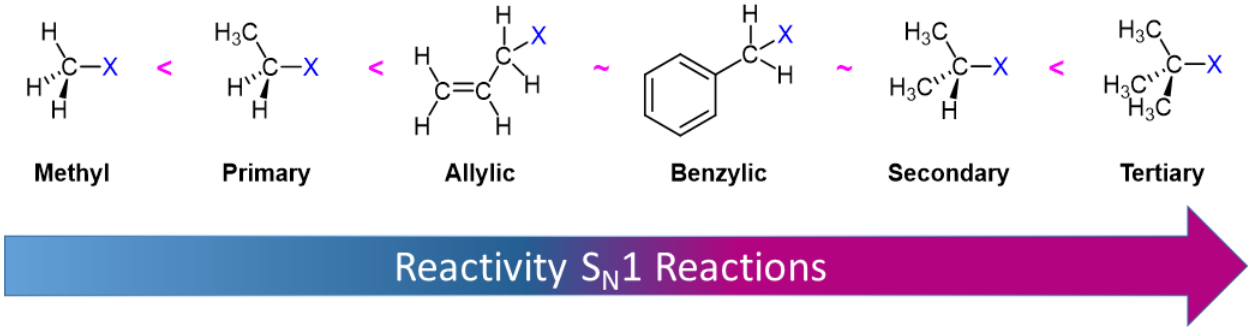


Benzyl Carbocation



an allylic carbocation

Carbocation Stability	$CH_3CH_2^{(+)}$	<	$(CH_3)_2CH^{(+)}$	≈	CH_2=CH-$CH_2^{(+)}$	≈	$C_6H_5CH_2^{(+)}$	<	$(CH_3)_3C^{(+)}$



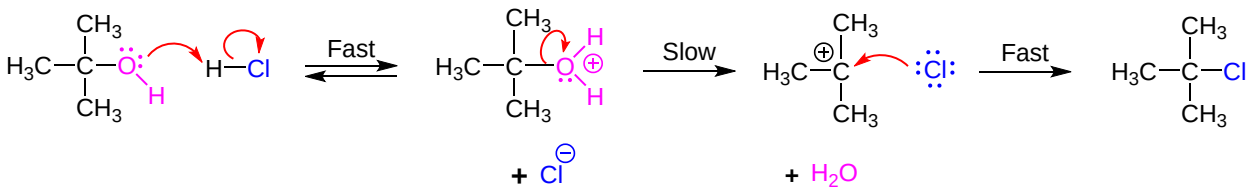
Also, don't forget about the importance of spotting rearrangements. The table above will help you determine if a rearrangement is energetically favorable.

Effects of Leaving Group

Since leaving group removal is involved in the rate-determining step of the S_N1 mechanism, reaction rates increase with a good leaving group. A good leaving group can stabilize the electron pair it obtains after the breaking of the C-Leaving Group bond faster. Once the bond breaks, the carbocation is formed and the faster the carbocation is formed, the faster the nucleophile can come in and the faster the reaction will be completed.

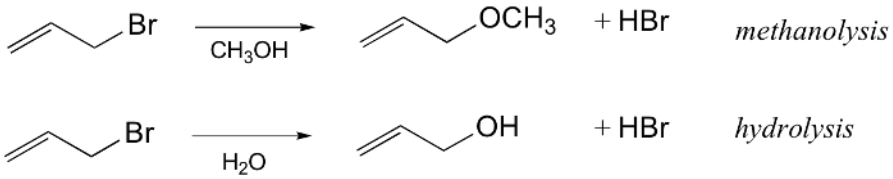
Because weak bases tend to strongly hold onto their electrons, they are lower energy molecules and they tend to make good leaving groups. Strong bases, on the other hand, donate electrons readily because they are high energy, reactive molecules. Therefore, they are not typically good leaving groups. As you go from left to right on the periodic table, electron donating ability decreases and thus ability to be a good leaving group increases. Halides are an example of a good leaving group whose leaving-group ability increases as you go down the halogen column of the periodic table.

Under acidic conditions, the -OH group of an alcohol can be converted into a neutral water leaving group through protonation. As discussed in Section 5-6, this occurs during the conversion of a tertiary alcohol to an alkyl halide through reaction with HCl or HBr. Because the -OH group itself is a poor nucleophile, the mechanism starts with protonation to form a hydronium ion. Neutral water is then lost as a leaving group to create the carbocation intermediate which then reacts with the halide ion nucleophile to provide the alkyl halide product. This reaction works best when a tertiary alcohol is used because it produces a stable carbocation intermediate.

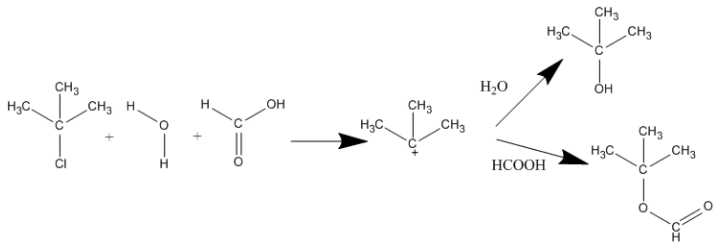


The Nucleophile

Since nucleophiles only participate in the fast second step, their relative molar concentrations rather than their nucleophilicities should be the primary product-determining factor. If a nucleophilic solvent such as water is used, its high concentration will assure that alcohols are the major product. While recombination of the halide anion with the carbocation intermediate can occur, it simply reforms the starting compound. Also, this is less likely since there are fewer molecules of the leaving group in solution than there are of the solvent. Note that S_N1 reactions in which the nucleophile is also the solvent are commonly called **solvolysis** reactions. The S_N1 reaction of allyl bromide in methanol is an example of what we would call **methanolysis**, while if water is the solvent the reaction would be called **hydrolysis**:

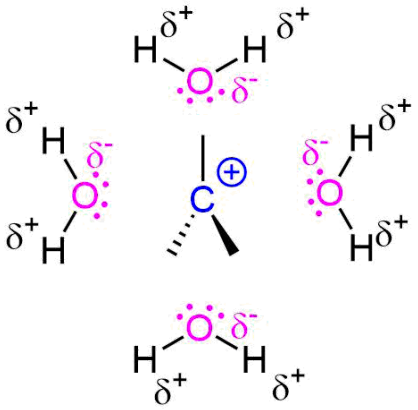


The strength of the nucleophile does not affect the reaction rate of S_N1 because, as described previously, the nucleophile is not involved in the rate-determining step. However, if you have more than one nucleophile competing to bond to the carbocation, the strengths and concentrations of those nucleophiles affects the distribution of products that you will get. For example, if you have $(CH_3)_3CCl$ reacting in water and formic acid where the water and formic acid are competing nucleophiles, you will get two different products: $(CH_3)_3COH$ and $(CH_3)_3COCOH$. The relative yields of these products depend on the concentrations and relative reactivities of the nucleophiles.



Solvent Effects on the S_N1 Reaction

Since the hydrogen atom in a polar protic solvent is highly positively charged, it can interact with the anionic nucleophile which would negatively affect an S_N2 reaction which depends on nucleophilic attack during the rate-determining step of the reaction. However, this does not affect an S_N1 reaction because the nucleophile is not a part of the rate-determining step. Polar protic solvents actually speed up the rate of the unimolecular substitution reaction because the large dipole moment of the solvent helps to stabilize the carbocation-like transition state. Since the carbocation is unstable, anything that can stabilize this even a little will speed up the reaction.



The polarity and the ability of the solvent to stabilize the intermediate carbocation is very important as shown by the relative rate data for a solvolysis (see table below). The dielectric constant of a solvent roughly provides a measure of the solvent's polarity. A dielectric constant below 15 is usually considered non-polar. Basically, the dielectric constant can be thought of as the solvent's ability to reduce the internal charge of the solvent. So for our purposes, the higher the dielectric constant the more polar the substance and in the case of S_N1 reactions, the faster the rate.

Solvent	Dielectric Constant	Relative Rate
• CH_3CO_2H • CH_3OH • H_2O	• 6 • 33 • 78	• 1 • 4 • 150,000

(note that even though acetic acid is a highly polar molecule, it tends to make a dimer with itself greatly reducing its dielectric constant)

Predicting S_N1 vs. S_N2 mechanisms

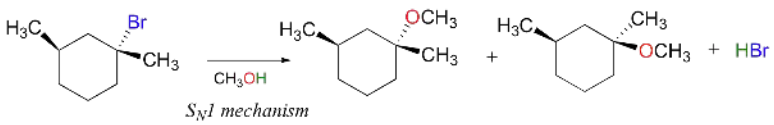
When considering whether a nucleophilic substitution is likely to occur via an S_N1 or S_N2 mechanism, we really need to consider three factors:

1) **The electrophile:** when the leaving group is attached to a methyl group or a primary carbon, an S_N2 mechanism is favored (here the electrophile is unhindered by surrounded groups, and any carbocation intermediate would be high-energy and thus unlikely). When the leaving group is attached to a tertiary, allylic, or benzylic carbon, a carbocation intermediate will be relatively stable and thus an S_N1 mechanism is favored.

2) **The nucleophile**: powerful nucleophiles, especially those with negative charges, favor the S_N2 mechanism. Weaker nucleophiles such as water or alcohols favor the S_N1 mechanism.

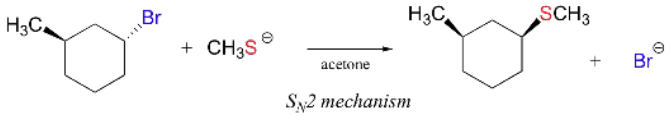
3) **The solvent**: Polar aprotic solvents favor the S_N2 mechanism by enhancing the reactivity of the nucleophile. Polar protic solvents favor the S_N1 mechanism by stabilizing the carbocation intermediate. S_N1 reactions are frequently solvolysis reactions.

For example, the reaction below has a tertiary alkyl bromide as the electrophile, a weak nucleophile, and a polar protic solvent (we'll assume that methanol is the solvent). Thus we'd confidently predict an S_N1 reaction mechanism. Because substitution occurs at a chiral carbon, we can also predict that the reaction will proceed with racemization.



S_N1 mechanism

In the reaction below, on the other hand, the electrophile is a secondary alkyl bromide – with these, both S_N1 and S_N2 mechanisms are possible, depending on the nucleophile and the solvent. In this example, the nucleophile (a thiolate anion) is strong, and a polar aprotic solvent is used – so the S_N2 mechanism is heavily favored. The reaction is expected to proceed with inversion of configuration.



S_N2 mechanism

Exercise 2.6.1

Which solvent would an S_N1 reaction occur faster in? H_2O or CH_3CN?

Answer

An S_N1 reaction would occur faster in H_2O because it's polar protic and would stailize the carbocation. CH_3CN is polar aprotic and would favor an S_N2 reaction.

Exercise 2.6.2

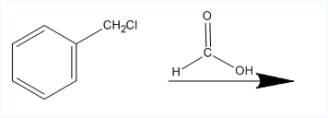
What kind of conditions disfavor S_N1 reactions?

Answer

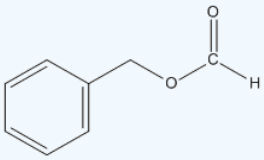
Basic conditions, polar aprotic solvents, poor leaving groups, and primary substrates disfavor S_N1 reactions.

Exercise 2.6.3

Draw the expected product and explain why it occurs via S_N1 instead of S_N2.



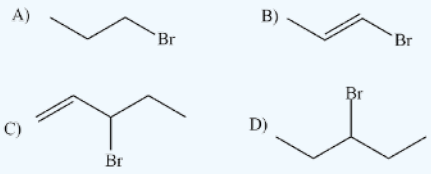
Answer



This reaction occurs via S_N1 because a resonance stabilized carbocation can form, there is not a strong nucleophile present, and the solvent is polar protic. This is an example of a solvolysis reaction because the nucleophile is also the solvent.

Exercise 2.6.4

Rank the following by increasing reactivity in an S_N1 reaction.



https://chem.libretexts.org/@go/page/443778

Answer

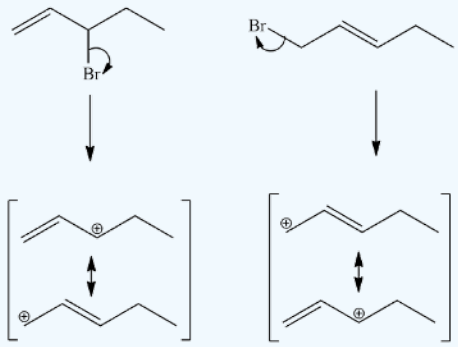
Again, it's all about carbocation stability. The most reactive is C (resonance stabilized secondary carbocation). The next most reactive is D (secondary carbocation). A (primary carbocation) and B (vinyl carbocation) are unreactive since their carbocations are too high energy to form.

Exercise 2.6.5

3-Bromo-1-pentene and 1-bromo-2-pentene undergo S_N1 reaction at almost the same rate, but one is a secondary halide while the other is a primary halide. Explain.

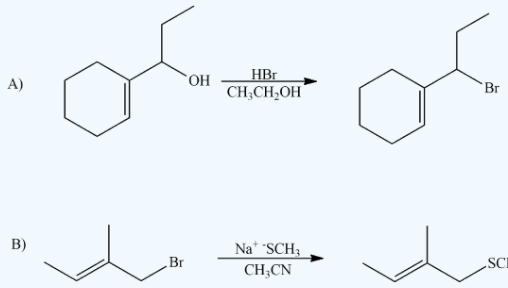
Answer

They form the same intermediate when you look at the resonance structures.



Exercise 2.6.6

Label the following reactions as most likely occuring by an S_N1 or S_N2 mechanism. Suggest why.



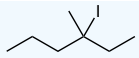
Answer

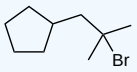
A – S_N1 resonance stabilized secondary carbocation intermediate, no strong nucleophile, acid protonates alcohol to make water as leaving group, polar protic solvent

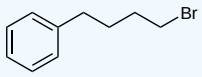
B – S_N2 primary alkyl bromide, strong nucleophile, polar aprotic solvent

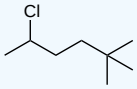
Exercise 2.6.7

Give the solvolysis product expected when the compound is heated in methanol.

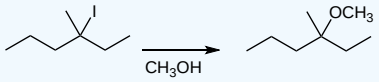
a) 

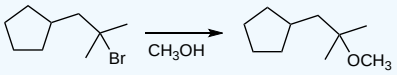
b) 

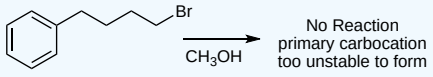
c) 

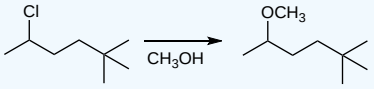
d) 

Answer

a) 

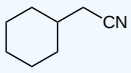
b) 

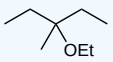
c) 

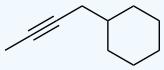
d) 

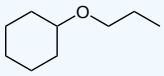
Exercise 2.6.8

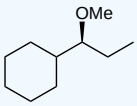
Show how each compound can be synthesized using a nucleophilic substitution reaction.

a) 

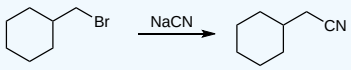
b) 

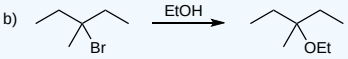
c) 

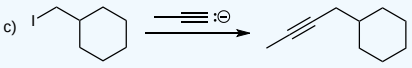
d) 

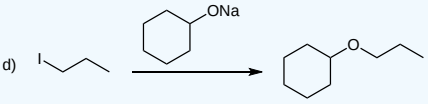
e) 

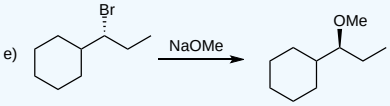
Answer

a) 

b) 

c) 

d) 

e) 

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2.7: Biological Substitution Reactions (reference only)

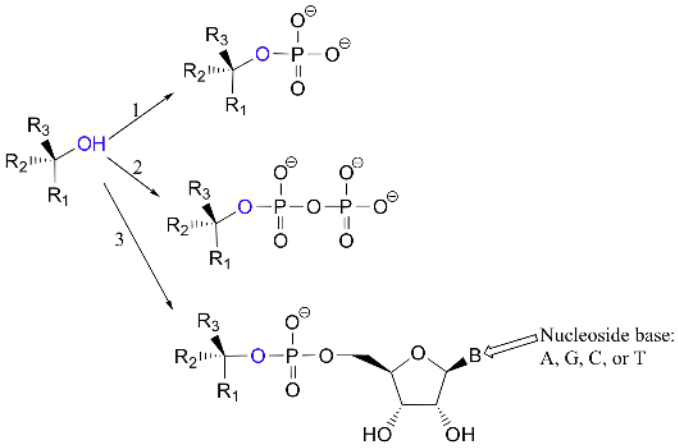
Objective

After completing this section, you should have an appreciation that S_N1 and S_N2 mechanisms exist and are well-known in biological chemistry.

Leaving Groups in Biochemical Reactions

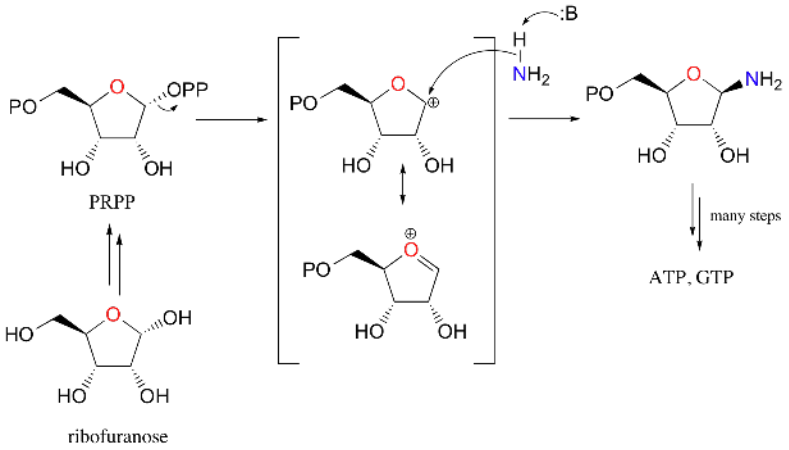
In biological reactions, we do not often see halides serving as leaving groups (in fact, outside of some marine organisms, halogens are fairly unusual in biological molecules). More common leaving groups in biochemical reactions are phosphates, water, alcohols, and thiols. In many cases, the leaving group is protonated by an acidic group on the enzyme as bond-breaking occurs. For example, hydroxide ion itself seldom acts as a leaving group – it is simply too high in energy (too basic). Rather, the hydroxide oxygen is generally protonated by an enzymatic acid before or during the bond-breaking event, resulting in a (very stable) water leaving group.

More often, however, the hydroxyl group of an alcohol is first converted enzymatically to a phosphate ester in order to create a better leaving group. This phosphate ester can take the form of a simple monophosphate (arrow 1 in the figure below), a diphosphate (arrow 2), or a nucleotide monophosphate (arrow 3).



Due to resonance delocalization of the developing negative charge, phosphates are excellent leaving groups.

Here's a specific example (from DNA nucleotide biosynthesis) that we will encounter in more detail in section 11.5:

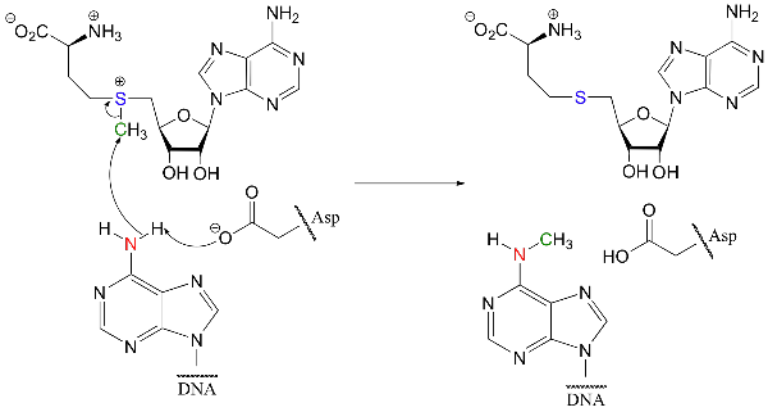


Here, the OH group on ribofuranose is converted to a diphosphate, a much better leaving group. Ammonia is the nucleophile in the second step of this S_N1-like reaction.

We will learn much more about phosphates in chapter 10. What is important for now is that in each case, an alcohol has been converted into a much better leaving group, and is now primed for a nucleophilic substitution reaction.

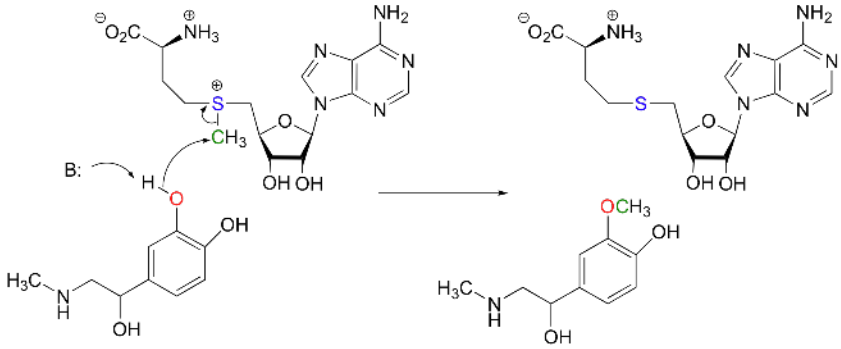
SAM Methyltransferases

Some of the most important examples of S_N2 reactions in biochemistry are those catalyzed by S-adenosyl methionine (SAM) – dependent methyltransferase enzymes. We have already seen, in chapter 6 and again in chapter 8, how a methyl group is transferred in an S_N2 reaction from SAM to the amine group on the nucleotide base adenosine:



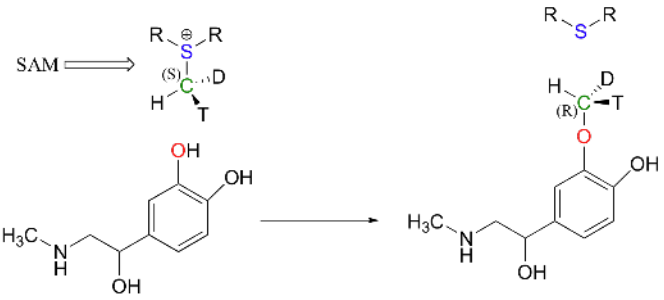
(*Nucleic Acids Res*. **2000**, *28*, 3950).

Another SAM-dependent methylation reaction is catalyzed by an enzyme called catechol-O-methyltransferase. The substrate here is epinephrine, also known as adrenaline.



Notice that in this example, the attacking nucleophile is an alcohol rather than an amine (that's why the enzyme is called an O-methyltransferase). In both cases, though, a basic amino acid side chain is positioned in the active site in just the right place to deprotonate the nucleophilic group as it attacks, increasing its nucleophilicity. The electrophile in both reactions is a methyl carbon, so there is little steric hindrance to slow down the nucleophilic attack. The methyl carbon is electrophilic because it is bonded to a positively-charged sulfur, which is a powerful electron withdrawing group. The positive charge on the sulfur also makes it an excellent leaving group, as the resulting product will be a neutral and very stable sulfide. All in all, in both reactions we have a reasonably good nucleophile, an electron-poor, unhindered electrophile, and an excellent leaving group.

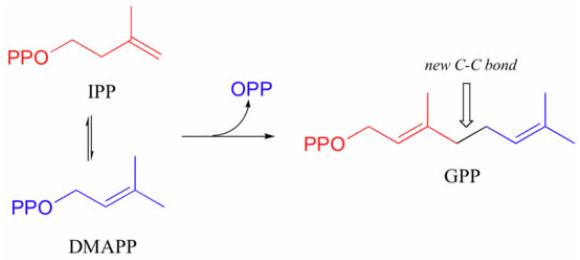
Because the electrophilic carbon in these reactions is a methyl carbon, a stepwise S_N1-like mechanism is extremely unlikely: a methyl carbocation is very high in energy and thus is not a reasonable intermediate to propose. We can confidently predict that this reaction is S_N2. Does this S_N2 reaction occur, as expected, with inversion of stereochemistry? Of course, the electrophilic methyl carbon in these reactions is achiral, so inversion is not apparent. To demonstrate inversion, the following experiment has been carried out with catechol-O-methyltransferase:



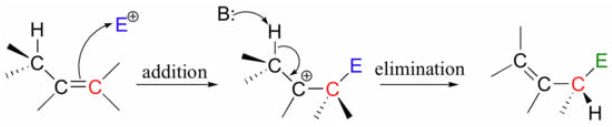
Here, the methyl group of SAM was made to be chiral by incorporating hydrogen isotopes tritium (^{3}H, T) and deuterium (^{2}H, D). The researchers determined that the reaction occurred with inversion of configuration, as expected for an S_N2 displacement (*J. Biol. Chem.* **1980,** *255,* 9124).

Substitution by Electrophilic Addition/Elimination

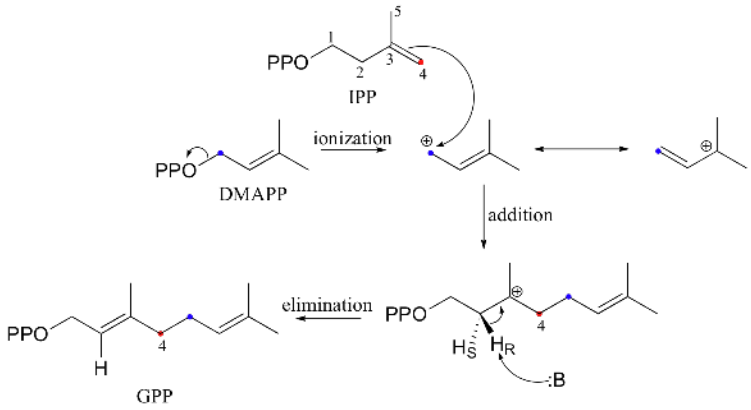
The electrophilic double bond isomerization catalyzed by IPP isomerase is a highly reversible reaction, with an equilibrium IPP:DMAPP ratio of about 6:1. In the next step of isoprenoid biosynthesis, the two five-carbon isomers condense to form a 10-carbon isoprenoid product called geranyl diphosphate (GPP).



This is a nice example of an electrophilic addition/elimination mechanism, which we saw in general form in section 15.1:

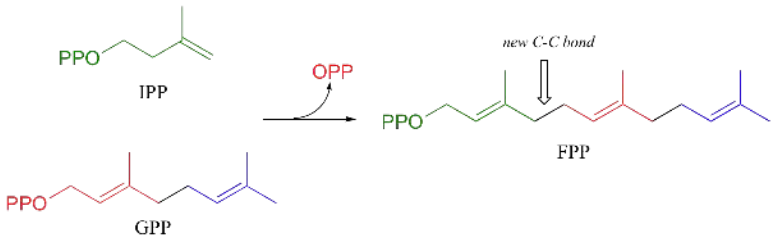


The first step is ionization of the electrophile - in other words, the leaving group departs and a carbocation intermediate is formed. In this case, the pyrophosphate group on DMAPP is the leaving group, and the electrophilic species is the resulting allylic carbocation.

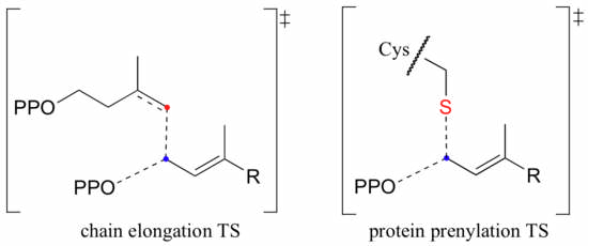


In the condensation (addition) step, the C_3-C_4 double bond in IPP attacks the positively-charged C_1 of DMAPP, resulting in a new carbon-carbon bond and a second carbocation intermediate, this time at a tertiary carbon. In the elimination phase, proton abstraction leads to re-establishment of a double bond in the GPP product. Notice that the enzyme specifically takes the *pro-R* proton in this step.

To continue the chain elongation process, another IPP molecule can then condense, in a very similar reaction, with C_1 of geranyl diphosphate to form a 15-carbon product called farnesyl diphosphate (FPP).

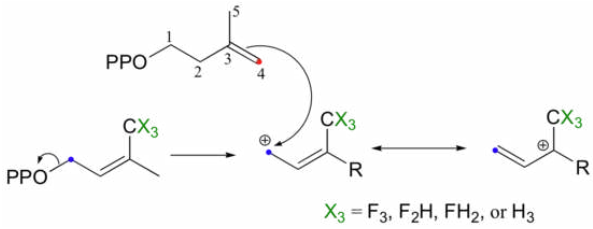


How do we know that these are indeed S_N1-like mechanisms with carbocation intermediates, rather than concerted S_N2-like mechanisms? First of all, recall that the question of whether a substitution is dissociative (S_N1-like) or associative (S_N2-like) is not always clear-cut - it could be somewhere in between, like the protein prenyltransferase reaction (section 9.3). The protein prenyltransferase reaction and the isoprenoid chain elongation reactions are very similar: the electrophile is the same, but in the former the nucleophile is a thiolate, while in the latter the nucleophile is a pi bond.



This difference in the identity of the nucleophilic species would lead one to predict that the chain elongation reaction has more S_N1-like character than the protein prenylation reaction. A thiolate is a very powerful nucleophile, and thus is able to *push* the pyrophosphate leaving group off, implying some degree of S_N2 character. The electrons in a pi bond, in contrast, are only weakly nucleophilic, and thus need to be *pulled* in by a powerful electrophile - *ie*. a carbocation.

So it makes perfect sense that the chain elongation reaction should more S_N1-like than S_N2-like. Is this in fact the case? We know how to answer this question experimentally - just run the reaction with fluorinated DMAPP or GPP substrates and observe how much the fluorines slow things down (see section 9.3B).



If the reaction is S_N1-like, the electron-withdrawing fluorines should destabilize the allylic carbocation intermediate and thus slow the reaction down considerably. If the mechanism is S_N2-like, the fluorine substitutions should not have a noticeable effect, because a carbocation intermediate would not be formed. When this experiment was performed with FPP synthase, the results were dramatic: the presence of a single fluorine slowed down the rate of the reaction by a factor of about 60, while two and three fluorines resulted in a reaction that was 500,000 and 3 million times slower, respectively (*J. Am. Chem. Soc*. **1981**, *103*, 3926.) These results strongly suggest indicate the formation of a carbocation intermediate in an S_N1-like displacement.

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2.8: Elimination Reactions- Zaitsev's Rule

Objective

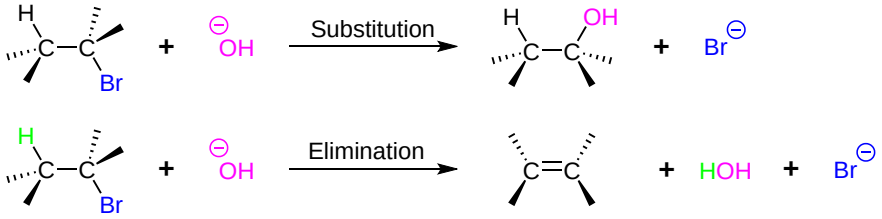
After completing this section, you should be able to apply Zaitsev's rule to predict the major product in a base-induced elimination of an unsymmetrical halide.

Key Terms

Make certain that you can define, and use in context, the key term below.

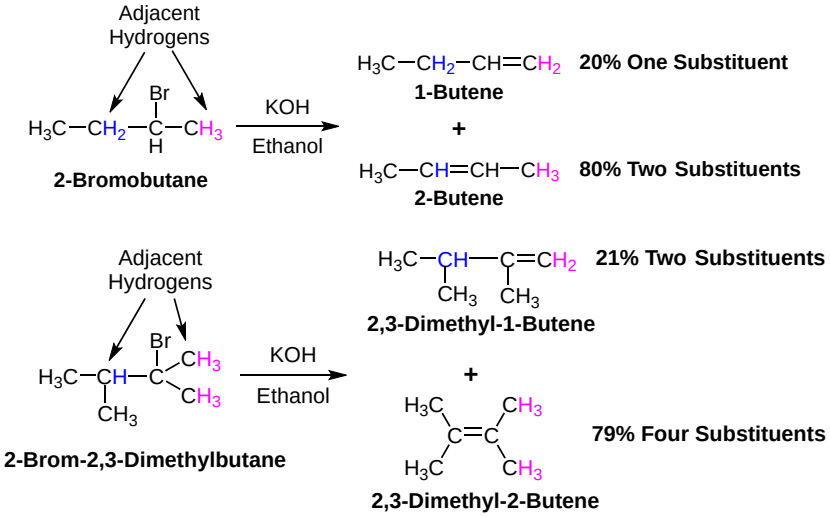
- Zaitsev's rule

When an alkyl halide is reacted with a nucleophile/Lewis base two major types of reaction can occur. Thus far in this chapter, we have discussed substitution reactions where a nucleophile displaces a leaving group at the electrophilic carbon of a substrate. Alternatively, the nucleophile could act as a Lewis base and cause an elimination reaction by removing a hydrogen adjacent to the leaving group. These reaction are similar and are often in competition with each other.



Introduction

The prefix "regio" indicates the interaction of reactants during bond making and/or bond breaking occurs preferentially by one orientation. If two or more structurally distinct groups of adjacent hydrogens are present in a given reactant, then multiple constitutionally isomeric alkenes may be formed by an elimination. **Zaitsev's rule** is an empirical rule used to predict the major products of elimination reactions. It states that in an elimination reaction the major product is the more stable alkene with the more highly substituted double bond. This situation is illustrated by the 2-bromobutane and 2-bromo-2,3-dimethylbutane elimination examples given below.



By using the strong base hydroxide, we direct these reactions toward elimination (rather than substitution). In both cases there are two different sets of adjacent hydrogens available to the elimination reaction (these are colored pink and blue). If the rate of each possible elimination was the same, we might expect the amounts of the isomeric elimination products to reflect the number of hydrogens that could participate in that reaction. For example, since there are three 1º-hydrogens (pink) and two 2º-hydrogens

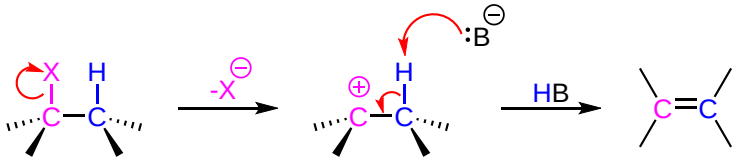
(blue) on beta-carbons in 2-bromobutane, statistics would suggest a 3:2 ratio of 1-butene and 2-butene in the products. This is not observed, and the latter predominates by 4:1. This departure from statistical expectation is even more pronounced in the second example, where there are six adjacent 1º hydrogens compared with one 3º-hydrogen. These results point to a strong favoring the more highly substituted product double bond predicted by **Zaitsev's Rule**.

The E1, E2, and E1cB Reactions

Elimination reaction take place by three common mechanism, E1, E2, and E1cB, all of which break the H-C and X-C bonds at different points of their mechanism. In addition, the different mechanisms will have subtle effects on the reaction products which will be discussed later in this chapter.

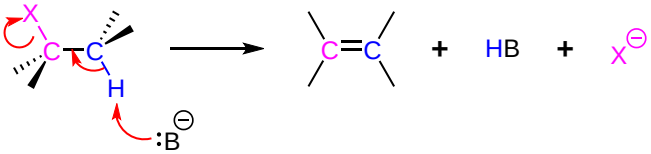
E1 Mechanism

This mechanism starts the breaking of the C-X to provide a carbocation intermediate. A base removes a hydrogen adjacent to the original electrophilic carbon. The electrons from the broken H-C bond move to form the pi bond of the alkene. In much the same fashion as the S_N1 mechanism, the first step of the mechanism is slow making it the rate determining step. This means that the reaction kinetics are unimolecular and first-order with respect to the substrate.



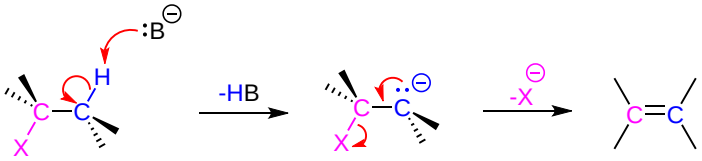
E2 Mechanism

The E2 mechanism takes place in a single concerted step. The rate at which this mechanism occurs follows second order kinetics, and depends on the concentration of both the base and alkyl halide. The base removes a hydrogen from a carbon adjacent to the leaving group. The electrons of the broken H-C move to form the pi bond of the alkene. In doing this the C-X bond is broken causing the removal of the leaving group.



E1cB Mechanism

The E1cB mechanism starts with the base deprotonating a hydrogen adjacent to the leaving to form a carbanion. In the second step of the mechanism the lone pair electrons of the carbanion move to become the pi bond of the alkene. This causes the C-X bond to break and the leaving group to be removed.



Predicting the Products of an Elimination Reaction

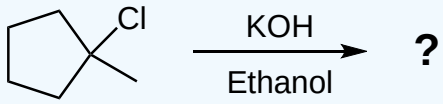
For most elimination reactions, the formation of the product involves the breaking of a C-X bond from the electrophilic carbon, the breaking of a C-H bond from a carbon adjacent to the electrophilic carbon, and the formation of a pi bond between these two carbons. Which elimination mechanism is being followed has little effect on these steps. The limitations of each elimination mechanism will be discussed later in this chapter.

To determining the possible products, it is vital to first identify the electrophilic carbon in the substrate. Next identify all hydrogens on carbons directly adjacent to the electrophilic carbon. Each unique adjacent hydrogen has the possibility of forming a unique elimination product. Break a C-H bond from each unique group of adjacent hydrogens then break the C-X bond. Finally connect

the adjacent carbon and the electrophilic carbon with a double bond. Repeat this process for each unique group of adjacent hydrogens. Finally, compare all of the possible elimination products. The product whose double bond has the most alkyl substituents will most likely be the preferred product.

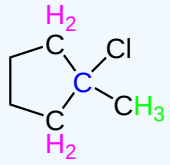
Worked Example 2.8.1

What would be the expected products of the following reaction? Which would be expected to be the major product?



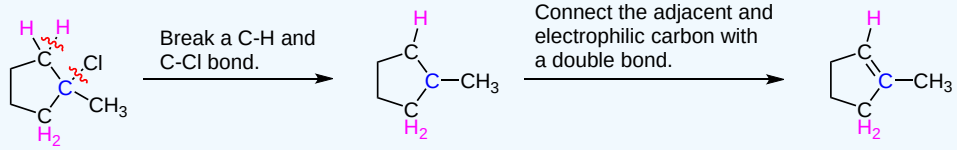
Solution

To solve this problem, first find the electrophilic carbon in the starting compound. This carbon is directly attached to the chlorine leaving groups and is shown in blue in the structure below. Next, identify all unique groups of hydrogens on carbons directly adjacent to the electrophilic carbon. In the starting compound, there are two distinct groups of hygrogens which can create a unique elimination product if removed. They are shown as pink and green in the structure below.



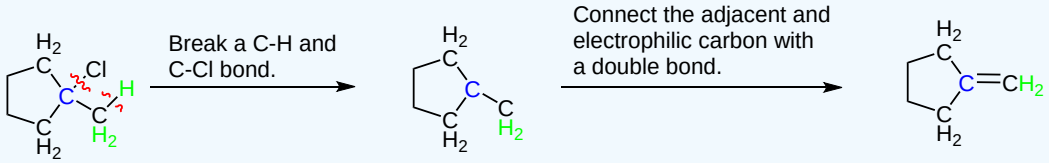
Create the possible elimination product by breaking a C-H bond from each unique group of adjacent hydrogens then breaking the C-Cl bond. Then connect the adjacent carbon and the electrophilic carbon with a double bond to create an alkene elimiation product. Repeat this process for each unique group of adjacent hydrogens. Because the starting compound in this example has two unique groups of adjacent hydrogens, two elimination products can possibly be made.

Product 1



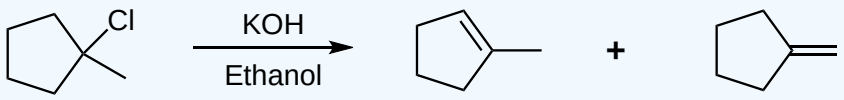
Elimination Product

Product 2



Elimination Product

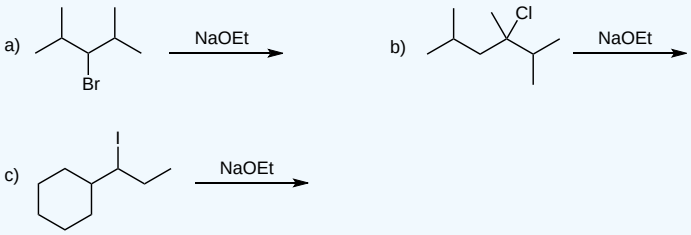
Finally, compare the possible elimination products to determine which has the most alkyl substituents. This product will most likely be the preferred. For this example product 1 has three alkyl substituents and product 2 has only two. This means product 1 will likely be the preferred product of the reaction.



Major Product (3 Alkyl Substituents) **Minor Product (2 Alkyl Substituents)**

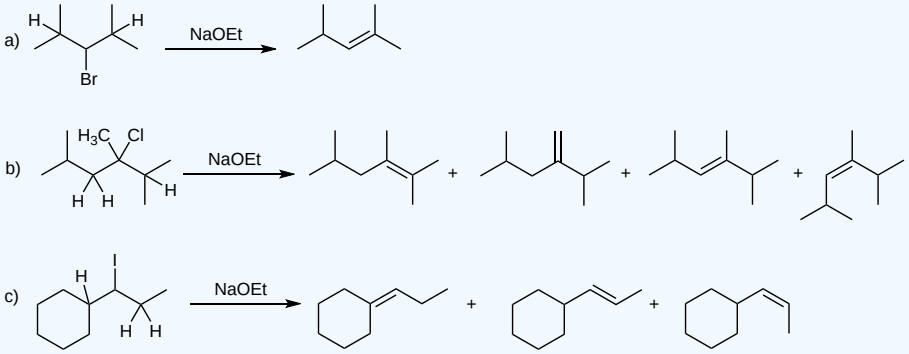
Exercise 2.8.1

Show the elimination products of the following alkyl halides.



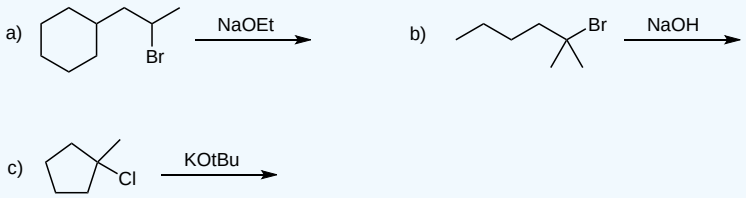
Answer

The beta Hs (Hs available for elimination) are drawn in below. Since a in symmetrical, elimination of either beta H yields the same product. For b, there are beta Hs at three different positions. Elimination of an H from the methyl group yields a disubstituted product, elimination of the tertiary H yields a tetrasubstituted product (the major product), and elimination of the secondary Hs produces both the E and Z-isomers of the trisubstituted alkene product. For c, the major trisubstituted product results from elimination of the tertiary H. Elimination of the CH_2 Hs yields the cis and trans disubstituted products.

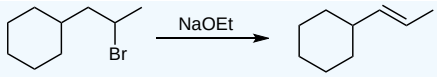


Exercise 2.8.2

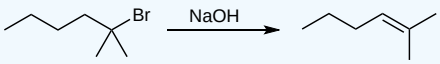
Predict the major product for each of the following reactions.



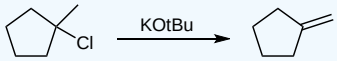
Answer

a) 

Secondary alkyl bromide with a strong base will favor E2. The trans disubstituted alkene is the most stable possible product.

b) 

Tertiary alkyl bromide with a strong base will favor E2. The trisubstituted alkene is the most stable possible product.

c) 

This one is tricky. The tertiary alkyl chloride plus a strong base will favor E2. However, the less substituted alkene is the major product. This results from the use of a very hindered base that selectively removes an H from the least hindered carbon, in this case the methyl group.

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2.9: The Mechanism of the E2 Reaction

Objectives

After completing this section, you should be able to

1. write the mechanism of a typical E2 reaction.
2. sketch the transition state of a typical E2 reaction.
3. discuss the kinetic evidence that supports the proposed E2 mechanism.
4. discuss the stereochemistry of an E2 reaction, and explain why the anti periplanar geometry is preferred.
5. determine the structure of the alkene produced from the E2 reaction of a substrate containing two chiral carbon atoms.
6. describe the deuterium isotope effect, and discuss how it can be used to provide evidence in support of the E2 mechanism.

Key Terms

Make certain that you can define, and use in context, the key terms below.

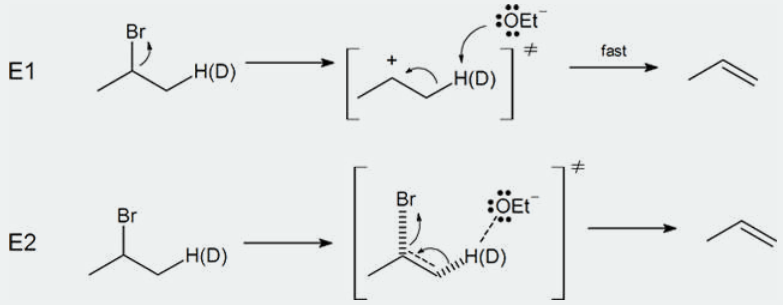
- anti periplanar
- deuterium isotope effect
- E2 reaction
- periplanar
- syn periplanar

Study Notes

An *E2 reaction* is a bimolecular elimination reaction; thus, two molecules are involved in the rate-limiting step. In this section, we are concerned with E2 reactions involving an alkyl halide and a base.

Use molecular models to assist you to understand the difference between syn periplanar and anti periplanar, and to appreciate why E2 eliminations are stereospecific.

Note that when deuterium is used the kinetic isotope effect (KIE) is referred to as the deuterium isotope effect. A C–H bond is about 5 kJ/mol weaker than a C–D bond. So if the rate-limiting step involves a breaking of this bond as it does at the E2 transition state there will be a substantial difference in reaction rates when comparing deuterated and non-deuterated analogues. Indeed, the reaction of 2-bromopropane with sodium ethoxide (NaOEt) is 6.7 times faster than its deuterated counterpart, providing evidence consistent with an E2 mechanism.

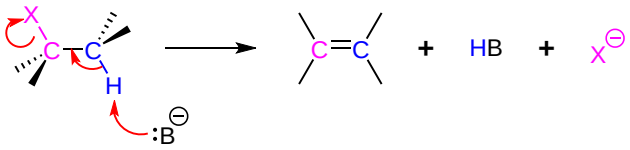


Introduction

E2, bimolecular elimination, was proposed in the 1920s by British chemist Christopher Kelk Ingold. E2 reactions are typically seen with secondary and tertiary alkyl halides, in the presence of a base (OH-, RO-, R_2N-). For a primary halide to undergo an E2 reaction a strong sterically hindered base is usually required. The products of an E2 reaction follow Zaitsev's rule, the most substituted alkene is usually the major product. The exception to this rule is that the least substituted alkene becomes the major product when using sterically hindered bases like NaOtBu or KOtBu.

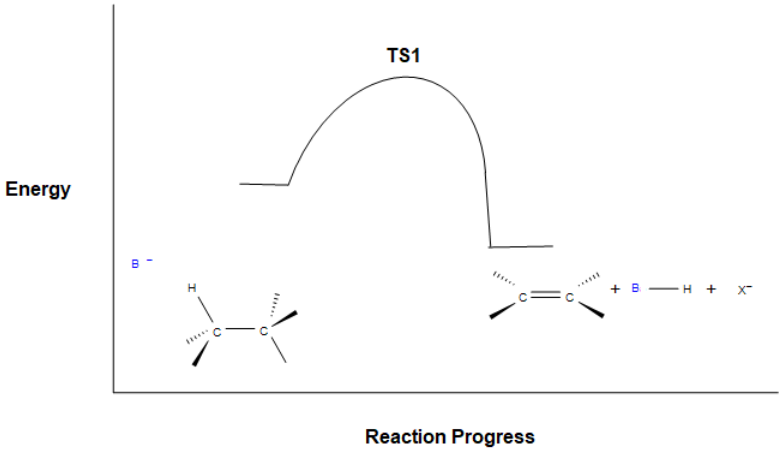
E2 Mechanism

The E2 mechanism takes place in a single concerted step. The rate at which this mechanism occurs follows second order kinetics, and depends on the concentration of both the base and alkyl halide. The base removes a hydrogen from a carbon adjacent to the carbon with the leaving group. The electrons of the broken H-C bond move to form the pi bond of the neutral product alkene. In doing this, the C-X bond is broken causing the removal of the leaving group. Overall during this reaction an electron pair is transferred from the base to the leaving group.

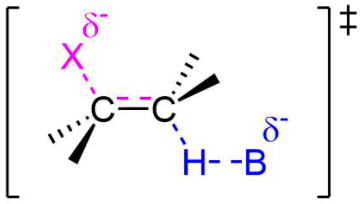


E2 Reaction Transition State

Because the E2 reaction is predicted to follow a concerted mechanism only one transition state is expected in its energy coordinate diagram.



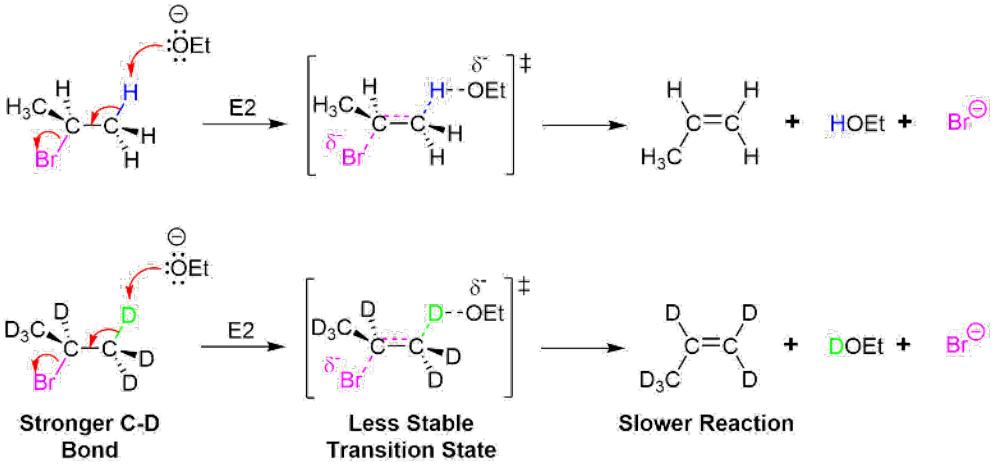
As the base begins to remove a hydrogen adjacent to the leaving group an H-B is starting to form and an H-C bond is in the process of breaking. Simultaneously, a C=C pi bond forms and the C-X bond breaks. During this reaction a set of electrons and a negative charge are transferred from the base to the leaving group. This is represented by a partial negative charge being present on both the base and the leaving group in the transition state.



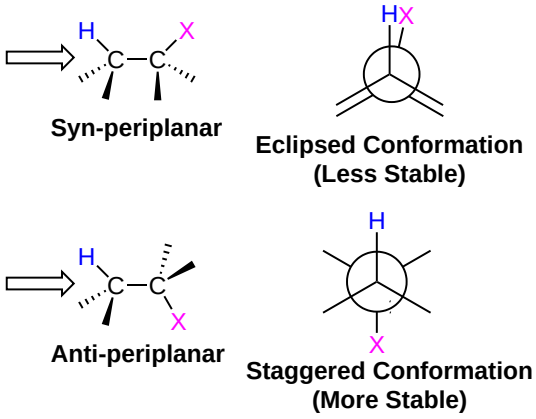
Evidence for the E2 Mechanism and Transition State

Kinetic studies of E2 reactions show that they are second order overall and follow the rate law: rate = k[RX][Base]. This data is consistent with the predicted bimolecular E2 mechanism that includes both the alkyl halide and the base participating in the mechanism's rate-determining step.

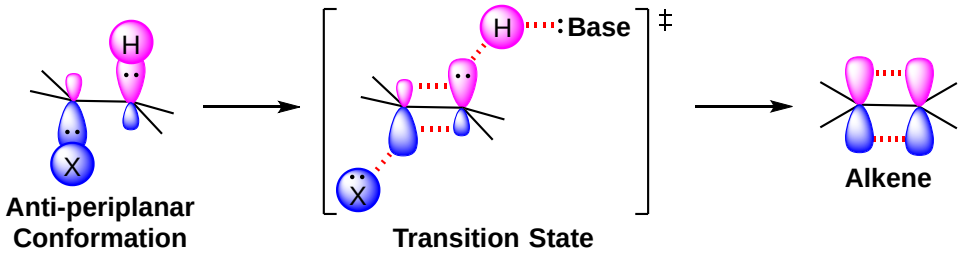
Further evidence for the predicted mechanism for the E2 reaction was provided by experiments involving the **deuterium isotope effect** (DIE). The **deuterium isotope effect** (DIE) is a phenomenon associated with molecules which have had hydrogen (H) atoms isotopically substituted with deuterium (D) atoms, exhibiting different reaction rates. The bond dissociation energy for C-D bonds is about 5 kJ/mol stronger than the bond dissociation energy of C-H bonds. This difference in energy results in a reduction in the rate of reaction, if the deuterium replacement occurs at a site of bond breaking in the rate determining step of a reaction. So if the rate-limiting step involves a breaking of this bond, as it does at the E2 transition state, there will be a substantial decrease in reaction rates when comparing deuterated and non-deuterated analogues. Indeed, the reaction of 2-bromopropane with sodium ethoxide (NaOEt) is 6.7 times faster than its deuterated counterpart, providing evidence that the C-H bond is broken during the rate determining step of the E2 mechanism. This is consistent with the predicted mechanism of the E2 reaction consisting of a single concerted step. If the rate-determining step was the leaving group bond breaking first (as in an E1 reaction) the deuterium substitution would not have caused an observable change in reaction rate.



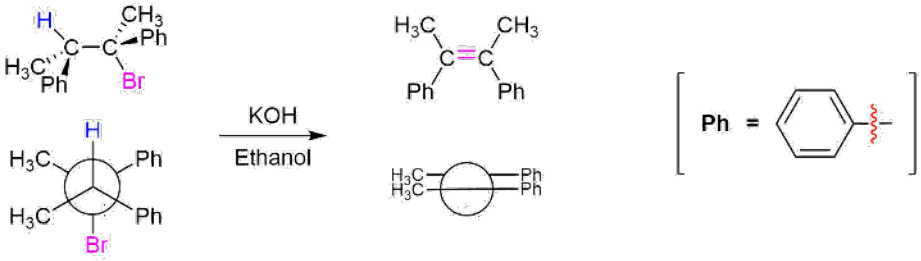
Yet another piece of evidence which supports the E2 mechanism comes when considering the stereochemistry of the elimination products. In the transition state of the E2 mechanism there are two carbons rehybridizing from sp^3 to sp^2 while forming a pi-bond. For good orbital overlap to occur during this change all the atoms involved in the reaction, the two carbons, the hydrogen, and the leaving group need to all lie in the same plane or **periplanar**. There are two possible ways this geometry can be achieved: **syn-periplanar** where the hydrogen and the leaving group are on the same side of the C-C bond and **anti-periplanar** where the hydrogen and the leaving group are on opposite sides of the C-C bond. To obtain a syn-periplanar geometry the substituents attached to the C-C bond must adopt an energetically unfavorable eclipsed conformation. The energy barrier to syn-orientation is such that syn-elimination is rarely observed in E2 reactions. E2 eliminations typically take place from the anti-periplanar conformation, as this is the most stable conformation due to the substituents attached to the C-C bond being staggered.



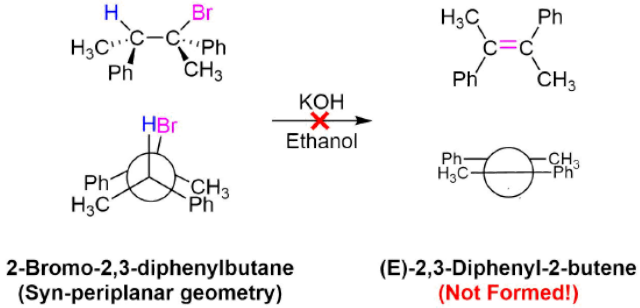
When viewing the transition state of the E2 mechanism when in the anti-periplanar conformation, the two sp^3 hybridized orbitals making up the C-H and C-X sigma bonds are in the same plane. When these two carbons rehybridize from sp^3 to sp^2, the p orbitals forming the pi-bond will also have good overlap.



The stereochemical consequences of reactant molecules obtaining anti-periplanar geometry prior to E2 reactions has been observed in numerous experiments and provides further evidence of the proposed mechanism. For example, (2S, 3R)-2-bromo-2,3-diphenylbutane only forms (Z)-2,3-diphenyl-2-butene as a product of E2 elimination. To form the Z alkene isomer, the starting material must obtain the anti-periplanar geometry preferred for E2 reactions.



No isomeric E alkene product is formed because the starting materials would need to obtain an eclipsed, syn-periplanar geometry. The syn-periplanar geometry would be transferred to the transition state making it higher in energy and harder to form. The fact that only the Z alkene isomer forms provides further evidence that the E2 mechanism takes place by a single bimolecular step.



Predicting the Stereochemical Product of E2 Reactions

E2 reactions have the requirements of a leaving group and a hydrogen on a carbon adjacent to the leaving group carbon. For non-ringed compounds, the C-C can usually undergo free rotation to place the C-X and C-H bonds anti-periplaner to each other. Stereochemical considerations usually come into play when both of the carbons in the C-C bond are chiral. When these carbons are achiral but contain the other requirements for an E2 reaction, products lacking stereochemistry are usually produced.

When both of the carbons in the C-C bond are chiral, one carbon will have a leaving group and the other carbon will have a single hydrogen. To consider the stereochemistry of an E2 product, start by creating a Newman projection looking down the C-C bond. Then rotate the C-C bond until the C-X and C-H bonds are in the anti position. The Newman projection now shows the relative positioning of the substituents on the C-C bond as they will appear in the double bond formed. It should be noted that if syn elimination was possible, a positional isomer of the double bond will be created. Consider the elimination products for (2R, 3R)-2-bromo-3-methylpentane.

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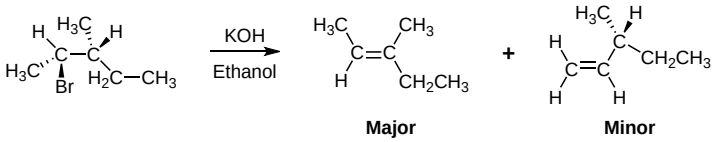
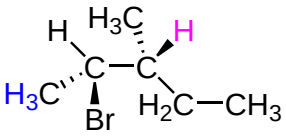
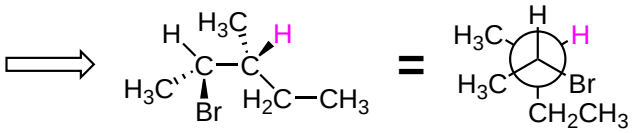


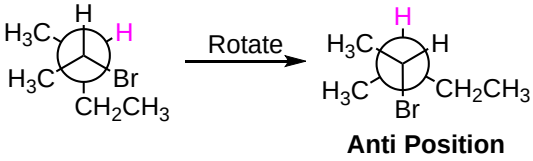
First, locate hydrogens on carbons adjacent to the leaving group. The compound used in this example has two unique sets of hydrogens.



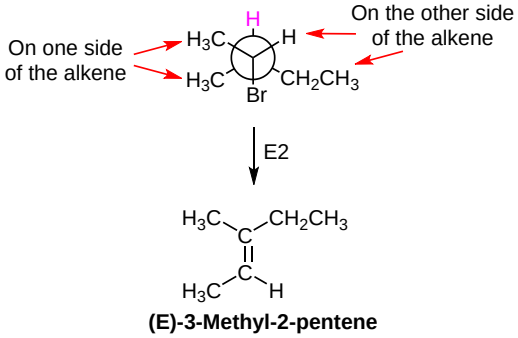
Because the adjacent hydrogen colored fuchsia is attached to a chiral carbon it require special consideration. Convert the structure into a Newman projection along the C-C bond that will for the alkene elimination product. The C-C bond can be view down either direction and still product the correct product.



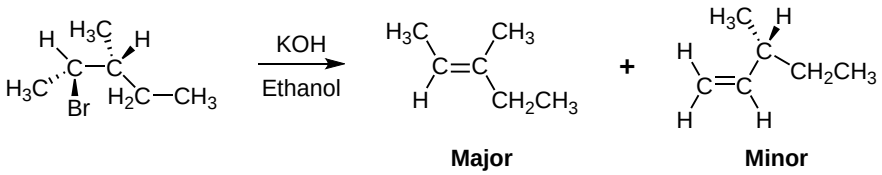
Then rotate such the the adjacent H and the leaving group are in the anti position.



This Newman projection shows the relative positioning of the substituents on the double bond formed. Note, none of the Z isomer is formed because it would require syn orientation of the H and Br.

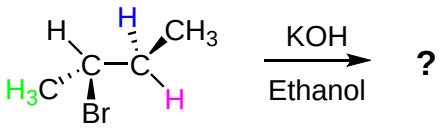


Lastly, consider the products made by other adjacent hydrogens and apply Zaitsev's rule to predict the preferred product.

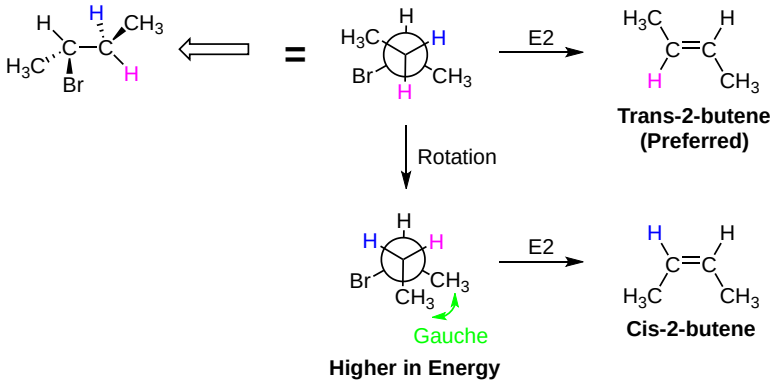


Determining *Cis* and *Trans* Products in Elimination Reaction

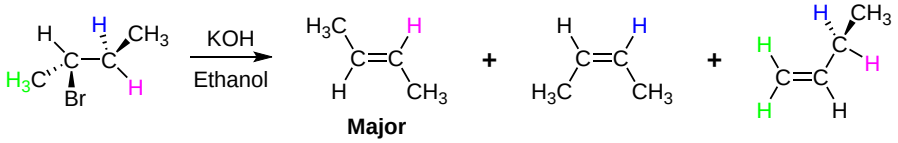
Understanding that E2 reactions require an anti-periplanar geometry can explain cis and trans alkene isomers can form as products. This occurs as an important exception to the rule that stereoisomers only form as elimination products when both of the carbons in the C-C bond forming the alkene are chiral. When considering the E2 reaction products of (R)-2-butane, there are two groups of hydrogens on carbons adjacent to the leaving group a CH_3 and a CH_2.



The carbon in the CH_2 group is achiral so both the H's appear to be equivalent. However, when the anti-periplanar geometry requirement is applied each hydrogen will produce its own unique product. Once the reactant is converted into a Newman projection it can be seen that the Br leaving group and the hydrogen colored blue are in the anti orientation and are ready to be eliminated. It should also be noted that the two CH_3 groups are also in the anti position which gives them the least amount of steric interaction possible. Because the CH_3 groups are on opposite sides of the Newman projection the CH_3 groups will be on opposite sides of the alkene thus creating the product *trans*-2-butene. When the Newman projection is rotated such that the fuchsia colored hydrogen is anti to the Br leaving group, the two CH_3 groups are now on the same. This orientation creates the isomer *cis*-2-butene. However, to obtain this orientation the two CH_3 groups must overcome the steric strain associated with a gauche conformation. This makes the transition state leading the cis isomer higher in energy and more difficult to form. Because of this, the trans isomer will be the major product. It is clear that the two hydrogens of the CH_2 group are not equivalent despite their not being attached to a chiral carbon.

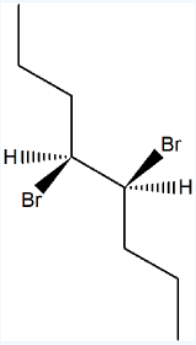


After considering all the products made during this E2 reaction the preferred product can be determined. The *cis* and *trans* isomer both have two alkene substituents while the third product only has one. Of the *cis* and *trans* isomer, the *trans* isomer is expected to be easier to form. Zaitsev's rule says that trans-2-butene will be the major product of this reaction.



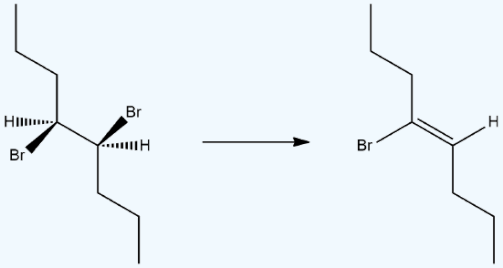
Exercise 2.9.1

1) What is the product of the following molecule in an E2 reaction? What is the stereochemistry?



Answer

The stereochemistry is (*Z*) for the reaction.



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2.10: The E2 Reaction and Cyclohexane Conformation

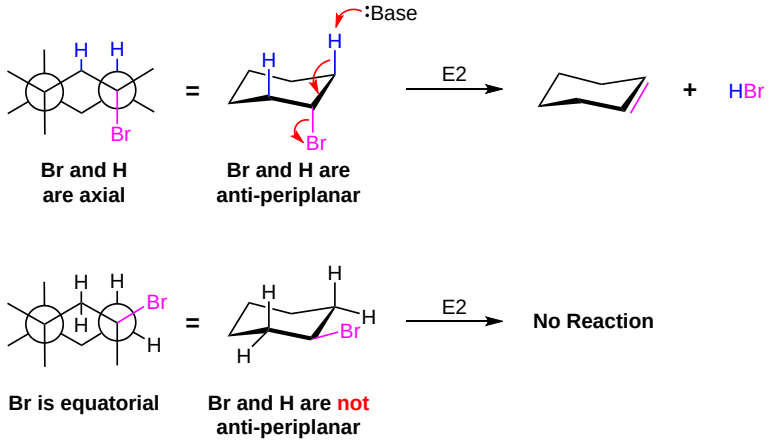
Objectives

After completing this section, you should be able to

1. identify anti periplanar arrangements of atoms in substituted cyclohexanes.
2. determine which cyclohexane conformation will generate a specific anti periplanar arrangement.

Stereochemical Requirements of the E2 Reaction

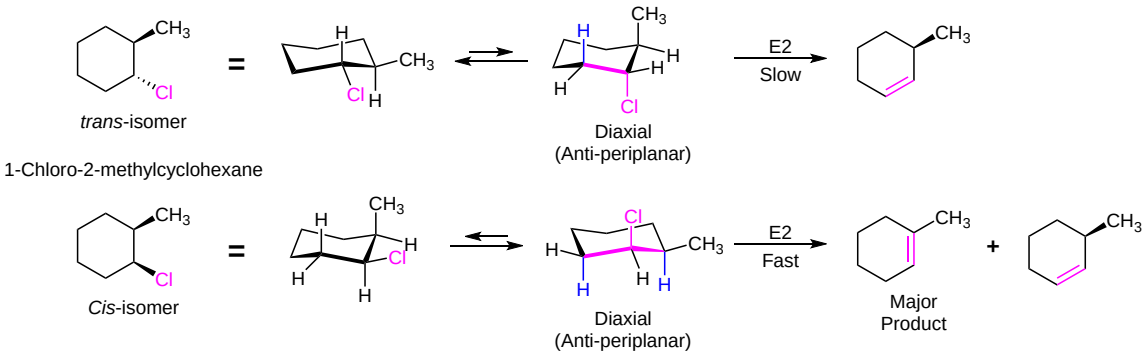
E2 elimination reactions of certain isomeric cycloalkyl halides show unusual rates and regioselectivity which can provide important supporting evidence that anti-periplanar is the preferred orientation of reactant species in the E2 transition state. Unlike open chain structures, cyclic compounds generally restrict the spatial orientation of ring substituents to relatively few arrangements. The compounds used here all have six-membered rings, so to achieve the anti-periplanar orientation required for the E2 reaction both the halogen and the adjacent hydrogen much assume an axial conformation.



For the compound, 2-methyl-1-chlorocyclohexane, the *cis* to the *trans* isomers have distinctly different reaction rates and form different preferred products. For example, *trans*-2-methyl-1-chlorocyclohexane reacts with alcoholic KOH at a much slower rate than does its *cis*-isomer. For trans-methyl-1-chlorocyclohexane, to obtains a chair conformation which places the chlorine substituent in the axial orientation required for E2 elimination, the methyl substituents is also forced into an axial position. Having both substituents in the axial position makes this chair conformer of the *trans*-isomer much less stable and presents an energy barrier that must be overcome for an E2 reaction to occur. When *cis*-2-methyl-1-chlorocyclohexane obtains a chair conformation which places its chlorine substituent in an axial orientation, the methyl substituent is forced into an equatorial orientation. Having one substituent axial and one equatorial makes this chair conformation of the cis-isomer lower in energy and thus easier to form. Consequently, the E2 reaction rates with the *trans*-isomer are slower than with the *cis*-isomer.

Furthermore, the product from E2 elimination of the *trans*-isomer is 3-methylcyclohexene (not predicted by Zaitsev's rule), whereas the *cis*-isomer gives the 1-methylcyclohexene as the preferred product (as predicted by Zaitsev's rule). The trans-isomer only has one adjacent hydrogen which can obtain an axial orientation along with the chlorine. The adjacent hydrogen which would lead to a 1-methylcyclohexene product cannot obtain the diaxial, anti-periplanar orientation with chlorine so an E2 reaction cannot occur. This makes 3-methylcyclohexene the preferred E2 elimination product of the *trans*-isomer showing that the anti-periplanar orientation requirement of E2 reactions is more important in determining products for this reaction than Zaitsev's rule.

In the *cis*-isomer the smaller chlorine atom assumes an axial position in the more stable chair conformation, and here there are two adjacent axial hydrogens. Removing one hydrogen forms the product, 3-methylcyclohexene, while removing the other hydrogen forms 1-methylcyclohexene. Here Zaitsev's rule determines that the more substituted alkene, 1-methylcyclohexene, is the preferred product.

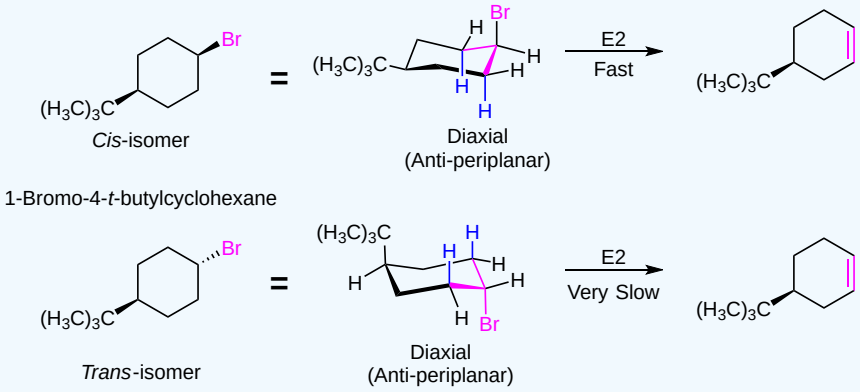


Exercise2.10.1

Which isomer would be expected to undergo E2 elimination quicker cis or trans-1-bromo-4-tert-butylcyclohexane? Explain your answer.

Answer

In the case of the 1-bromo-4-tert-butylcyclohexane isomers, the tert-butyl group is so large that **it will always assume an equatorial orientation**, leaving the bromine to be axial in the *cis*-isomer and equatorial in the *trans*-isomer. Because of symmetry, the two axial adjacent hydrogens in the *cis*-isomer react equally with base, resulting in rapid elimination to the same alkene (actually a racemic mixture). This reflects the fixed anti orientation of these hydrogens to the bromine atom. To assume a conformation having an axial bromine, the *trans*-isomer must tolerate serious crowding distortions. Such conformers are therefore present in extremely low concentration, and the rate of elimination is very slow. Indeed, **substitution by hydroxide anion predominates in this situation**.



Exercise 2.10.2

Which of the following compounds will react faster in an E2 reaction; *trans*-1-bromo-2-isopropylcyclohexane or *cis*-1-bromo-2-isopropylcyclohexane?

Answer

The *cis* isomer will react faster than the *trans*. The *cis* isomer has two possible antiperiplanar hydrogens that can eliminate, and, more importantly, the most stable conformation of the cis isomers has the larger isopropyl group equatorial and the Br axial, ready for elimination.

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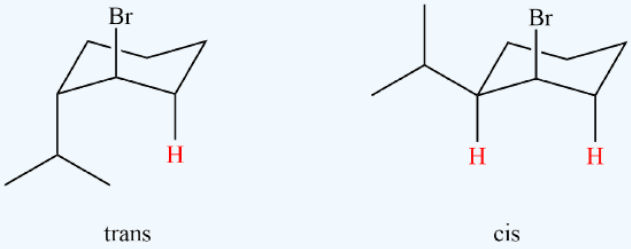

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2.11: The E1 and E1cB Reactions

Objectives

After completing this section, you should be able to

1. write the mechanism for a typical E1 reaction.
2. explain why E1 elimination often accompanies S_N1 substitution.
3. write an equation to describe the kinetics of an E1 reaction.
4. discuss the stereochemistry of E1 reactions.
5. account for the lack of a deuterium isotope effect in E1 reactions.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- E1 reaction
- E1cB reaction

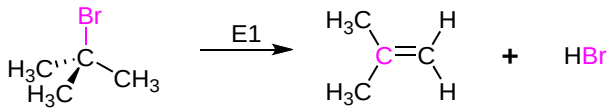
Study Notes

The abbreviation E1 stands for “unimolecular elimination”; that is, an E1 reaction is an elimination reaction in which only one species is involved in the rate-limiting step.

Unimolecular Elimination (E1) is a reaction in which the removal of an HX substituent results in the formation of a double bond. It is similar to a unimolecular nucleophilic substitution reaction (S_N1) in various ways. One being the formation of a carbocation intermediate. Also, the only rate determining (slow) step is the dissociation of the leaving group to form a carbocation, hence the name unimolecular. Thus, since these two reactions behave similarly, they compete against each other. Many times, both these reactions will occur simultaneously to form different products from a single reaction. However, one can be favored over another through thermodynamic control.

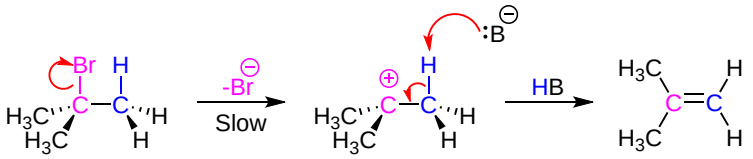
General E1 Reaction

An E1 reaction involves the removal of the halogen leaving group followed by the deprotonation of an adjacent hydrogen to produce an alkene product. In order to accomplish this, a Lewis base is required.



Mechanism

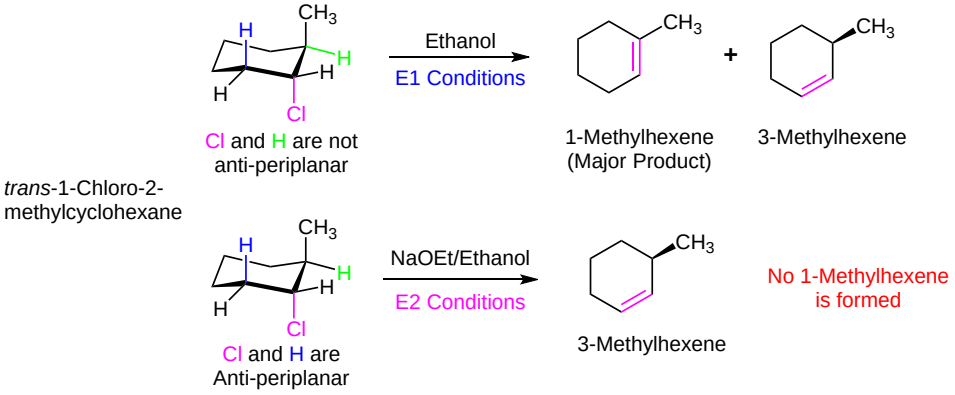
This mechanism starts with the spontaneous removal of the leaving group. The leaving group also removes the electrons from the C-Br bond, making the attached carbon a carbocation. In much the same fashion as the S_N1 mechanism, the first step of the E1 mechanism is slow thus making it the rate determining step. This makes E1 reaction kinetics unimolecular and first-order with respect to the substrate. Next, a Lewis Base (B^-) deprotonates an adjacent hydrogen from the carbocation. The electrons of the C-H bond are donated to the adjacent C-C bond, forming a double bond. Unlike E2 reactions, which require the adjacent proton to be *anti* to the leaving group, E1 reactions only require a neighboring hydrogen. This is due to the fact that the leaving group has left the molecule to form an achiral, trigonal planar carbocation.



Evidence for the E1 Mechanism

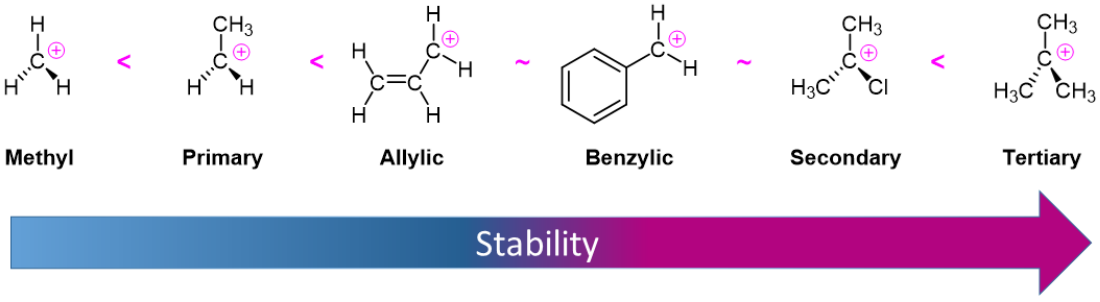
The primary evidence in support of the E1 mechanism is the fact that E1 reactions follow first-order kinetics which is consistent with the reaction mechanism containing a unimolecular dissociation as the rate determining step. Another piece of evidence is seen in the fact that E1 reactions show no deuterium isotope effect. Experiments have shown that there is no difference in reaction rate when deuterated and nondeuterated substrates are used. This is consistent with the E1 mechanism because a C-H bond is not broken in the rate determining step.

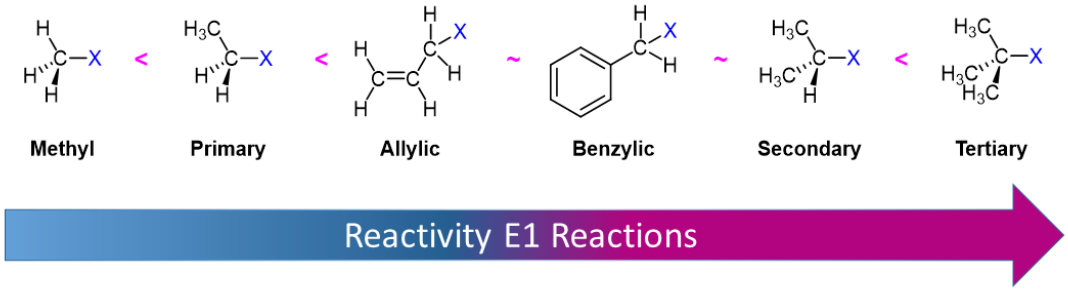
Lastly, because the halogen and hydrogen are removed in different steps, the mechanism of E1 reactions predicts that they will not require the anti-periplanar geometry required for E2 reactions. E1 reactions do not have the geometric constraints of E2 reactions discussed in **Sections 2-9** and **2-10**. In Section 2-10 an example showed that trans-1-Chloro-2-methylcyclohexane was capable of only forming the product 3-methylhexene during an E2 reaction due to the anti-periplanar constraints. When the same substrate is reacted under E1 conditions, two elimination products (1-methylhexene and 3-methylhexene) are produced. In the substrate, the hydrogen marked as green cannot obtain anti-periplanar geometry with the Cl leaving group. Under E2 conditions this hydrogen and the Cl cannot be eliminated to form an elimination product. However, under E1 conditions the hydrogen and the Cl eliminate, despite the lack of anti-periplanar geometry, to form 1-methylhexene.



Alkyl Halide Reactivity in E1 Reactions

Due to the fact that E1 reactions create a carbocation intermediate, reactivity of alkyl halides toward E1 reaction mirror those present in S_N1 reactions.



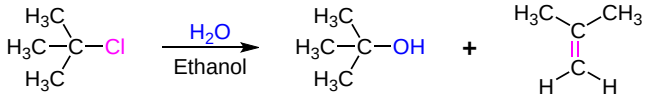


As expected, tertiary carbocations are favored over secondary, primary and methyl carbocations. This is due to the phenomena of hyperconjugation, which essentially allows a nearby C-C or C-H bond to interact with the p orbital of the carbon to bring the electrons down to a lower energy state. Thus, this has a stabilizing effect on the molecule as a whole. In general, **primary and methyl carbocations do not proceed through the E1 pathway** for this reason, unless there is a means of carbocation rearrangement to move the positive charge to a nearby carbon that is more stable. Secondary and Tertiary carbons form more stable carbocations, thus E1 reactions occur quite rapidly at these atoms.

Secondary carbocations can be subject to the E2 reaction pathway, but this generally occurs in the presence of a good/strong base. Adding a weak base to the reaction disfavors E2, essentially pushing towards the E1 pathway. In many instances, solvolysis occurs rather than using a base to deprotonate. This means heat is added to the solution, and the solvent itself deprotonates a hydrogen. The medium can effect the pathway of the reaction as well. Polar protic solvents may be used to hinder nucleophiles, thus disfavoring E2/S_N2 from occurring.

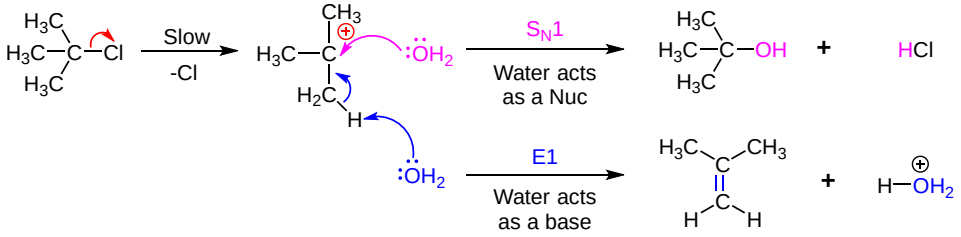
The Connection Between S_N1 and E1 Reactions

The E1 and S_N1 mechanisms both begin with the rate-determing step, the unimolecular removal of a leaving group to form a carbocation intermediate. Sharing the rate-determining step causes alkyl halides to produce both S_N1 substitution and E1 elimination products whenever they are reacted with nonbasic nucleophiles in a protic solvent. For example, the hydrolysis of *tert*-butyl chloride in a solution of water and ethanol gives a mixture of 2-methyl-2-propanol (60%) and 2-methylpropene (40%) at a rate independent of the water concentration.



2-Chloro-2-methylpropane | **2-Methyl-2-propanol (60%)** | **2-Methylpropene (40%)**

To produce the alcohol product, water attacks the carbocation as a nucleophile as part of an S_N1 reaction. To produce the alkene product, water acts as a base and deprotonates an adjacent hydrogen as part of an E1 reaction. As expected, the mechanism of the two reactions have similar characteristics. They both show first order kinetics; neither is much influenced by a change in the nucleophile/base; and both are relatively non-stereospecific.



To summarize, when carbocation intermediates are formed one can expect them to react further by one or more of the following modes:

1. The cation may bond to a nucleophile to give a substitution product.
2. The cation may transfer a adjacent proton to a base, giving an alkene product.
3. The **cation may rearrange to a more stable carbocation**, and then react by mode #1 or #2. In any reaction that forms a carbocation (alkene reactions with acid, S_N1, or E1), always beware of rearrangement. If a hydride or alkyl shift from an adjacent carbon will generate a more stable carbocation, it will occur. To review specifics of rearrangements, refer back to the reactivity of alkenes.

Comparing E1 and E2 Mechanisms

When considering whether an elimination reaction is likely to occur via an E1 or E2 mechanism, we really need to consider three factors:

1) **The base:** strong bases favor the E2 mechanism, whereas, E1 mechanisms only require a weak base.

2) **The solvent**: good ionizing solvents (polar protic) favor the E1 mechanism by stabilizing the carbocation intermediate.

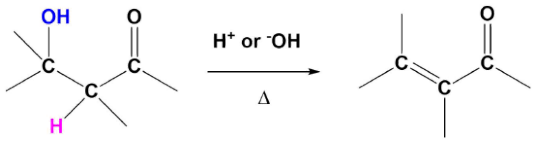
3) **The alkyl halide:** primary alkyl halides have the only structure useful in distinguishing between the E2 and E1 pathways. Since primary carbocations do not form, only the E2 mechanism is possible.

Reaction Parameter	E2	E1
alkyl halide structure	tertiary > secondary > primary	tertiary > secondary >>>> primary
nucleophile	high concentration of a strong base	weak base
mechanism	1-step	2-step
rate limiting step	bimolecular transition state	carbocation formation
rate law	rate = k[R-X][Base]	rate = k[R-X]
solvent	not important	polar protic

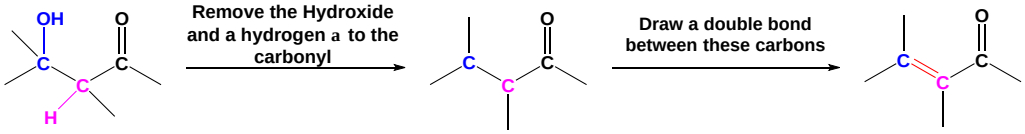
The E1cB Reaction

Although E1 reactions typically involve a carbocation intermediate, the E1cB reaction utilizes a carbanion intermediate. A proton adjacent to a carbonyl group is removed using a strong base. This proton is acidic because the resulting conjugate base anion is stabilized by delocalization on to the carbonyl group. This anion causes the expulsion of an adjacent leaving group to create an alkene which is conjugated with the carbonyl which is called an enone. This reaction is generally utilized when a poor leaving group, such as a hydroxide, is involved. This poor leaving group makes the direct E1 or E2 reactions difficult. This reaction is used later in a reaction called an aldol condensation.

General Reaction



Predicting the Product of an E1cB Reaction



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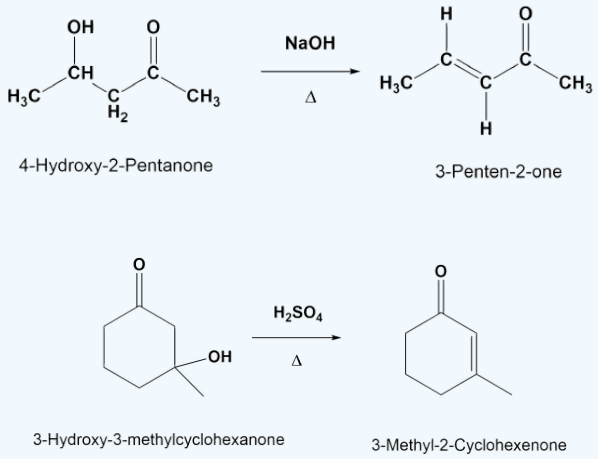
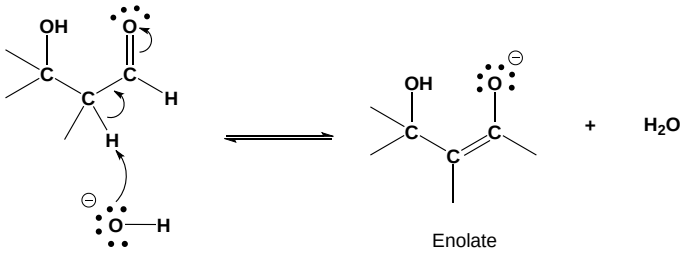
Example 11.10.1



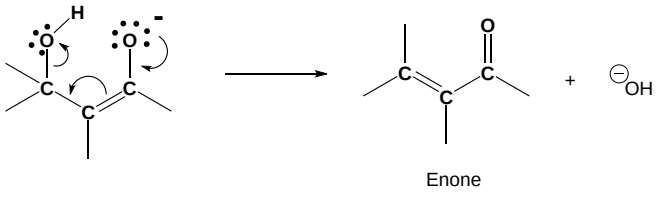
E1cB Mechanism

The mechanism starts with the base removing a hydrogen to form an enolate. The enolate reforms the carbonyl C=O bond promoting the elimination of alcohol OH as a leaving group which also reforms the base catalyst. Although the base catalyzed elimination of alcohols is rare, it happens in this case in part due to the stability of the conjugated enone product.

1) Deprotonation to form the anion



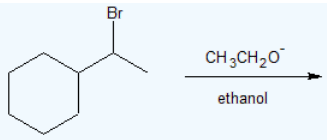
2) Leaving Group Removal

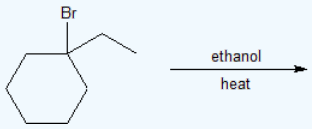


Note! The double bond always forms in conjugation with the carbonyl.

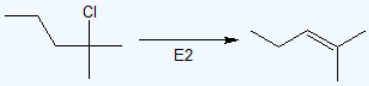
Exercise 2.11.1

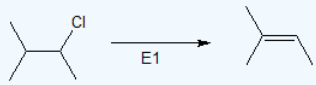
1. Predict the dominant elimination mechanism (E1 or E2) for each reaction below. Explain your reasoning.

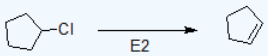
a) 

b) 

2) Specify the reaction conditions to favor the indicated elimination mechanism.

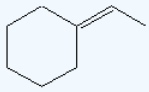
a) 

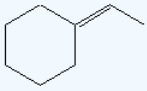
b) 

c) 

Answer

1)

a)  E2 reaction b/c secondary alkyl halide with a strong base.

b)  E1 reaction b/c tertiary alkyl halide with a weak base.

2)

a) strong base, such as hydroxide, an alkoxide, or equivalent

b) water or alcohol or equivalent weak base with heat

c) strong base, such as hydroxide, an alkoxide, or equivalent

---

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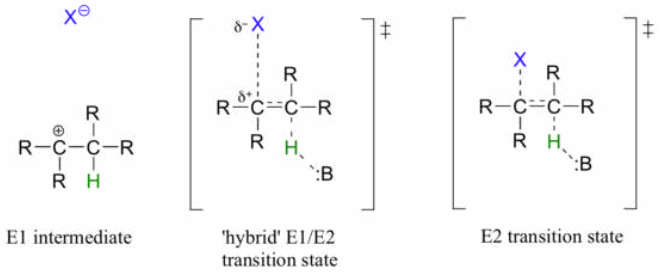
2.12: Biological Elimination Reactions (reference only)

Objective

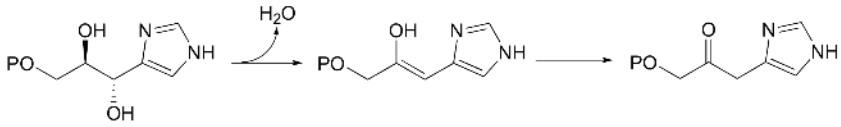
After completing this section, you should have an appreciation that E1, E2 and E1cB mechanisms exist and are well-known in biological chemistry.

Enzymatic E1 and E2 reactions

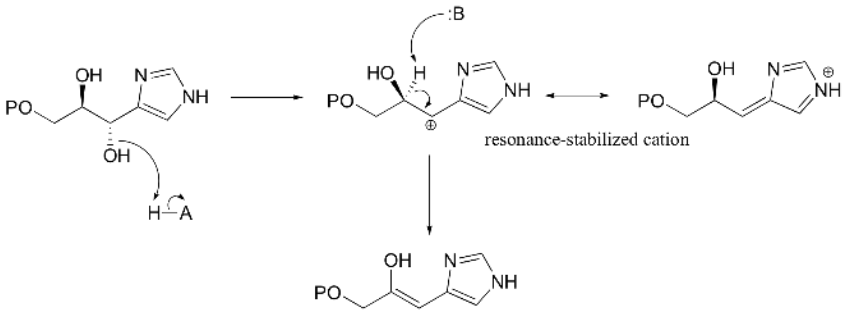
While most biochemical b-elimination reactions are of the E1cb type, some enzymatic E2 and E1 reactions are known. Like the enzymatic S_N2 and S_N1 substitution mechanisms discussed in chapters 8 and 9, the E2 and E1 models represent two possible mechanistic extremes, and actual enzymatic elimination reactions may fall somewhere in between. In an E1/E2 hybrid elimination, for example, C_β-X bond cleavage may be quite advanced (but not complete) before proton abstraction takes place - this would lead to the build-up of transient *partial* positive charge on C_β, but a discreet carbocation intermediate would not form. The extent to which partial positive charge builds up determines whether we refer to the mechanism as 'E1-like' or 'E2-like'.



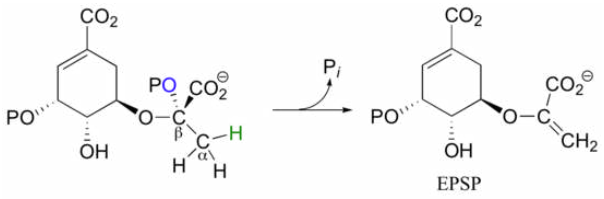
A reaction in the histidine biosynthetic pathway provides a good example of a biological E1-like elimination step (we're looking specifically here at the first, enol-forming step in the reaction below - the second step is simply a tautomerization from the enol to the ketone product (section 13.1A)).



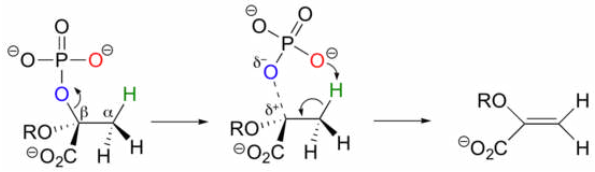
Notice in this mechanism that an E1cb elimination is not possible - there is no electron-withdrawing group (like a carbonyl) to stabilize the carbanion intermediate that would form if the proton were abstracted first. There is, however, an electron-*donating* group (the lone pair on a nitrogen) that can stabilize a positively-charged intermediate that forms when the water leaves.



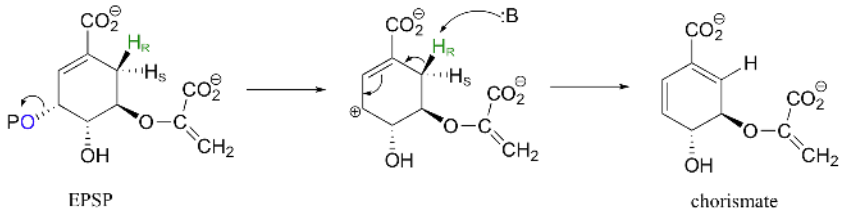
Another good example of a biological E1-like reaction is the elimination of phosphate in the formation of 5-enolpyruvylshikimate-3-phosphate (EPSP), an intermediate in the synthesis of aromatic amino acids.



Experimental evidence indicates that significant positive charge probably builds up on C_β of the starting compound, implying that C-O bond cleavage is advanced before proton abstraction occurs (notice the parallels to the Cope elimination in the previous section):

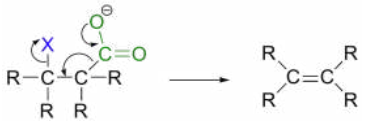


The very next step in the aromatic acid biosynthesis pathway is also an elimination, this time a 1,6-conjugated elimination rather than a simple beta-elimination.

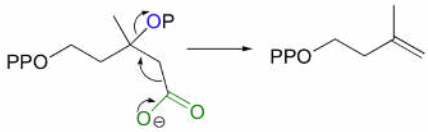


An E1-like mechanism (as illustrated above) has been proposed for this step, but other evidence suggests that a free-radical mechanism may be involved.

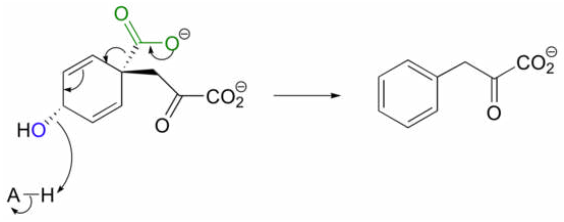
While most E1 and E2 reactions involve proton abstraction, eliminations can also incorporate a decarboxylation step.



Isopentenyl diphosphate, the 'building block' for all isoprenoid compounds, is formed from a decarboxylation-elimination reaction.



Phenylpyruvate, a precursor in the biosynthesis of phenylalanine, results from a conjugated 1,6 decarboxylation-elimination.



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2.13: A Summary of Reactivity - SN1, SN2, E1, E1cB, and E2

Objectives

After completing this section, you should be able to

1. determine whether a specified substrate is most likely to undergo an E1, E2, S_N1 or S_N2 reaction under a given set of conditions.
2. describe the conditions under which a given substrate is most likely to react by a specified mechanism (E1, E2, S_N1 or S_N2).

Study Notes

This section summarizes much of what has been discussed in the chapter. It focuses on how a given substrate will behave under certain conditions, but does not deal with the stereochemistry of the products.

Having discussed the many factors that influence nucleophilic substitution and elimination reactions of alkyl halides, we must now consider the practical problem of predicting the most likely outcome when a given alkyl halide is reacted with a given nucleophile. As we noted earlier, there are multiple variables to be considered, **the most important being the substitution of the alkyl halide**. S_N2 reactions favor alkyl halides with little steric hindrance such as methyl halides and primary halides. In general, in order for an S_N1 or E1 reaction to occur, the relevant carbocation intermediate must be relatively stable such as with tertiary halides, secondary allylic halides, and secondary benzylic halides.

The next most import variable for predicting the outcome of a reaction is **the nature of the nucleophilic reactant**. Strong nucleophiles favor S_N2 substitution, and strong bases, especially strong hindered bases (such as tert-butoxide) favor E2 elimination. Weak nucleophiles that are also weak bases tend to favor S_N1 and E1 reactions.

- **Good Nucleophiles Which are Weak Bases:** I^-, Br^-, SCN^-, N_3^-, $CH_3CO_2^-$, RS^-, CN^-, Amines, etc.
- **Good Nucleophiles Which are Strong Bases:** HO^-, RO^-.
- **Poor Nucleophiles which are Weak Bases:** H_2O, ROH, RSH.

General Rules For Predicting a Reaction

Consider these in the order listed.

Methyl Halides

- An S_N2 substitution occurs regardless if a good or poor nucleophile is used.

Primary Alkyl Halides

- An E2 elimination occurs if a strong, sterically hindered base is used.
- An E1cB elimination occurs if a strong base is used and the leaving group is two carbons away from a carbonyl group.
- An S_N2 substitution occurs if a good nucleophile is used.

Secondary Alkyl Halides

- An E1cB elimination occurs if a strong base is used and the leaving group is two carbons away from a carbonyl group.
- An E2 elimination occurs if a strong base is used.
- An S_N2 reaction occurs if a good nucleophile that is a weak bases is used in a polar aprotic solvent.
- An S_N1 reaction along with an E1 reaction occurs if a poor nucleophile that is a weak bases is used in a protic solvent.

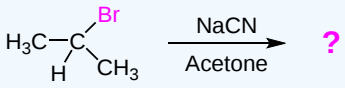
Tertiary Alkyl Halides

- An E1cB elimination occurs if a strong base is used and the leaving group is two carbons away from a carbonyl group.
- An E2 elimination occurs if a strong base is used.
- An S_N1 reaction along with an E1 reaction occurs if a poor nucleophile that is a weak bases is used in a protic solvent.

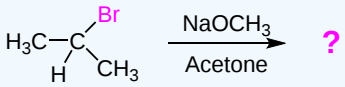
Exercise 2.13.1

For the following, please determine what kind of reaction is occurring and predict the product(s).

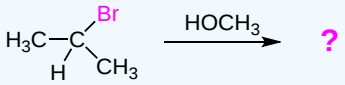
a)



b)

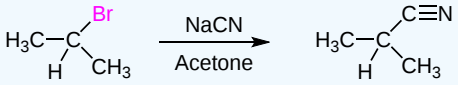


c)

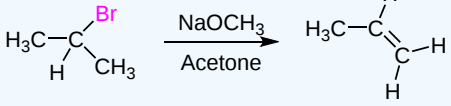


Answer

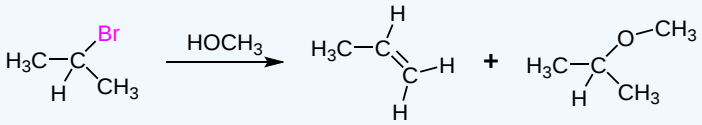
a) The substrate is a secondary halide so the product is determined by the nature of the nucleophile used in the reaction. Cyanide ($^{-}$CN) is a good nucleophile which is a weak base. The fact that the nucleophile is a weak base means that an E2 reaction is not favored. Also, the fact that cyanide is a good nucleophile means that S_N2 substitutions are favored over S_N1. When a secondary halide is reacted with a good nucleophile which is a weak base, the preferred reaction is S_N2. After S_N2 substitution the product is a nitrile.



b) The substrate is a secondary halide so the product is determined by the nature of the nucleophile used in the reaction. Methoxide ($^{-}$OCH$_3$) is a strong base so it could prefer to remove a hydrogen from the substrate. This makes an E2 elimination the preferred reaction and an alkene the product.

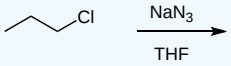


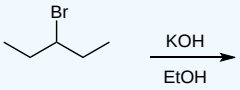
c) The substrate is a secondary halide so the product is determined by the nature of the nucleophile used in the reaction. Methanol (HOCH$_3$) is a weak nucleophile that is a weak base. Being a weak base means that methanol is not capable of actively removing a hydrogen to cause an E2 reaction. Also, because methanol is a weak nucleophile is not capable of attacking the substrate and causing an S_N2 reaction. For the methanol nucleophile to react the substrate must first eject it leaving group to form the highly reactive carbocation intermediate. Formation of the carbocation is the rate determine step for both the S_N1 and E1 reactions so they each form a separate product.

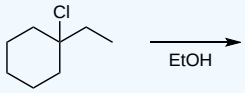


Exercise 2.13.2

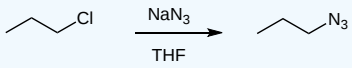
Identify the dominant reaction mechanism (S_N1, S_N2, E1, or E2) and predict the major product for the following reactions.

a) 

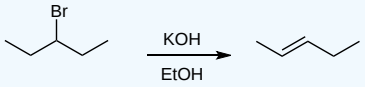
b) 

c) 

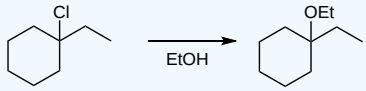
Answer

a) 

S_N2 because primary alkyl halide and strong nonbasic nucleophile

b) 

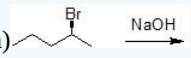
E2 because secondary alkyl halide and strong base

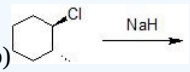
c) 

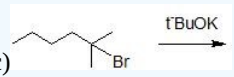
S_N1 because tertiary alkyl halide and solvent as weak nucleophile

Exercise 2.13.3

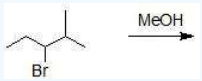
Identify all the products of the following reactions and specify the major product.

a) 

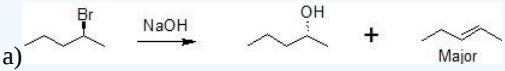
b) 

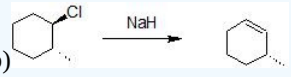
c) 

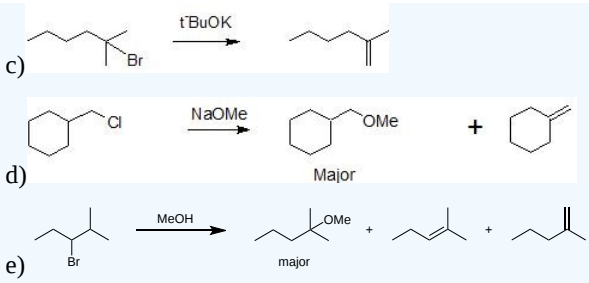
d)

e) 

Answer

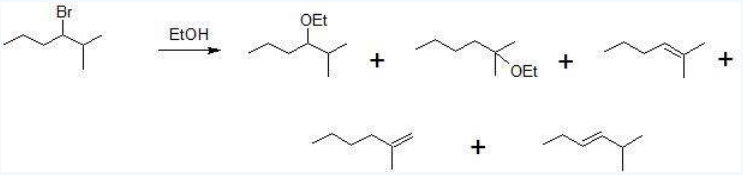
a) 

b) 

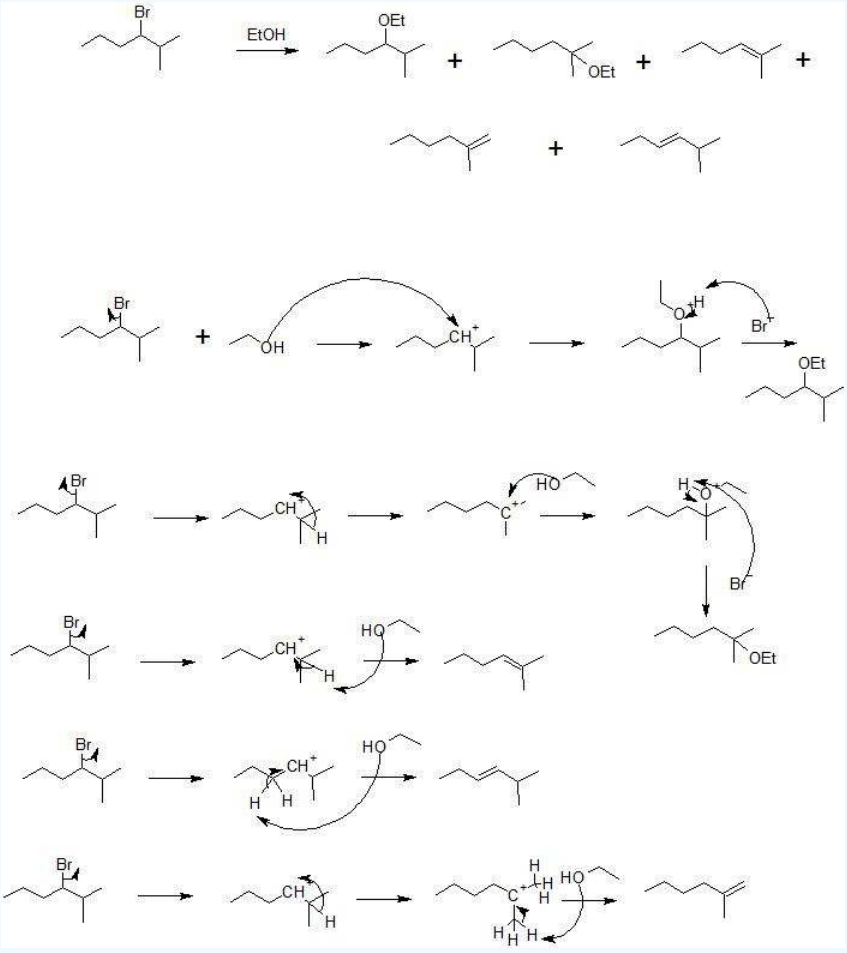


Exercise 2.13.4

The following reaction yields five different products. Provide mechanisms to show how each is formed.



Answer



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2.S: Reactions of Alkyl Halides - Nucleophilic Substitutions and Eliminations (Summary)

Concepts & Vocabulary

11.1 Introduction

- Alkyl halides react as electrophiles and undergo nucleophilic substitution and elimination reactions.

11.2 The Discovery of Nucleophilic Substitution Reactions

- Some nucleophilic substitution reactions invert stereochemistry at the reactive carbon.

11.3 The S_N2 Reaction

- Reaction steps with two molecules involved in the rate determining step are called bimolecular.
- A substitution mechanism that has the nucleophile entering at the same time the leaving group leaves, in a concerted step, is called S_N2 - substitution nucleophilic bimolecular.
- Concerted substitution mechanisms (S_N2) occur via backside attack, which causes inversion of the carbon where the reaction occurs.
- Rates of S_N2 reactions depend on concentration of nucleophile and alkyl halide.

11.4 Characteristics of the S_N2 Reaction

- S_N2 reactions are concerted.
- Sterically hindered substrates reduce S_N2 reaction rate.
- A **transition state** in a reaction mechanism is the highest energy point on a pathway from reactants to an intermediate or products.
- Larger groups (such as alkyl vs. hydrogen) cause greater steric repulsion in S_N2 **transition states**, reducing rates of S_N2 reactions.
- Groups that have electron-rich atoms are typically good nucleophiles.
- In general, stronger bases are better nucleophiles.
- Polar aprotic solvents increase rates of S_N2 reactions.
- Polar protic solvents decrease rates of S_N2 reactions.
- As basicity of leaving groups decreases, their ability to leave increases.

11.5 The S_N1 Reaction

- A substitution mechanism that occurs with the leaving group leaving in the first step, creating a carbocation intermediate, followed by the nucleophile entering is called S_N1 - substitution nucleophilic unimolecular.
- S_N1 reactions occur through a stepwise mechanism.
- The first step (dissociation) of an S_N1 mechanism is rate limiting.
- In S_N1 reactions the nucleophile is not involved in the rate limiting step, therefore nucleophile strength or concentration do not affect the rate.
- The intermediate for S_N1 mechanisms contains a planar carbocation. The nucleophile can then enter from either side of the molecule giving racemic products with no additional stereocenters in the molecule.
- Since a carbocation intermediate is formed, always beware of rearrangements.

11.6 Characteristics of the S_N1 Reaction

- Polar solvents increase rates of S_N1 reactions.
- Better leaving groups increase rates of S_N1 and S_N2 reactions.
- Predicting whether a reaction will follow an S_N1 or S_N2 mechanism requires analysis of:
  - Electrophile - primary favor S_N2, tertiary (and allyl or benzyl) favor S_N1, secondary depends on other factors
  - Nucleophile - strong favor S_N2, weak favor S_N1
  - Solvent - polar aprotic favor S_N2, polar protic favor S_N1

11.7 Biological Substitution Reactions

- When biological substitution reactions occur, the electrophiles are often different though the mechanisms are primarily the same.

11.8 Elimination Reactions - Zaitsev's Rule

- The major product of Elimination reactions is the product with the more substituted double bond. This is known as Zaitsev's rule.

11.9 The E2 Reaction and Deuterium Isotope Effect

- The E2 mechanism is concerted with the base removing a proton and the leaving group leaving at the same time.
- Since E2 mechanisms are concerted, both the base and the electrophile are present in the rate equation.
- E2 reactions require strong bases and polar aprotic solvents.
- Kinetic Isotope Effects can provide evidence for E2 mechanisms since they can show when breaking of the C-H bond is part of the rate-determining step.

11.10 The E2 Reaction and Cyclohexane Conformation

- E2 reactions of cyclic structures show necessity for anti orientation of the proton being removed and the leaving group.

11.11 The E1 and E1cB Reactions

- E1 mechanisms begin with a leaving group leaving which forms a carbocation intermediate, which is then deprotonated in a second step.
- E1 mechanisms are step-wise.
- More substituted electrophiles are more reactive in E1 reactions.
- Zaitsev products are preferred, similarly to E2 reactions.
- E1 and S_N1 proceed via the same carbocation intermediate and the same rate-determining step so typically happen concurrently. Again, since a carbocation is formed, rearragnements are always possible.
- E1cB reactions begin with deprotonation (usually resulting in a resonance stabilized carbanion), followed by loss of the leaving group in the second step.

11.12 Biological Elimination Reactions

- There are many important examples of biological elimination reactions.

11.13 A Summary of Reactivity - S_N1, S_N2, E1, E1CcB, and E2

Skills to Master

- Skill 11.1 Draw S_N1/S_N2 mechanisms showing appropriate stereochemistry.
- Skill 11.2 Explain when S_N1/S_N2 mechanisms are likely to occur.
- Skill 11.3 Describe/draw the intermediate for an S_N1 mechanism and transition state(s) for S_N1/S_N2 mechanisms.
- Skill 11.4 Write out rate laws for S_N1/S_N2 mechanisms.
- Skill 11.5 Differentiate between which mechanism is more likely between S_N1/S_N2.
- Skill 11.6 Draw reaction coordinate diagrams for S_N1/S_N2 mechanisms.
- Skill 11.7 Explain how the electrophile, nucleophile, leaving group, and solvent affect S_N1/S_N2 mechanisms.
- Skill 11.8 Recognize use of nucleophilic substitution and elimination reactions in biological systems.
- Skill 11.9 Draw E1/E2 mechanisms showing appropriate stereochemistry.
- Skill 11.10 Explain when E1/E2 mechanisms are likely to occur.
- Skill 11.11Describe/draw the intermediate for an E1 mechanism and transition state(s) for E1/E2mechanisms.
- Skill 11.12 Write out rate laws for E1/E2 mechanisms.
- Skill 11.13 Differentiate between which mechanism is more likely between E1/E2.
- Skill 11.14 Draw reaction coordinate diagrams for E1/E2 mechanisms.
- Skill 11.15 Explain how kinetic isotope effects can be used to support or refute a proposed mechanism.
- Skill 11.16 Draw an E1cB mechanism and explain when it is a viable option.
- Skill 11.17 Differentiate between which mechanism is more likely between S_N1/S_N2 and E1/E2.

Memorization Tasks (MT)

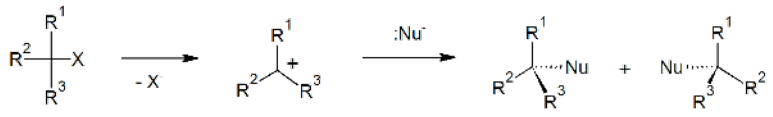
MT 11.1 Memorize the order of good leaving groups.

MT 11.2 Memorize which solvents are polar protic and polar aprotic.

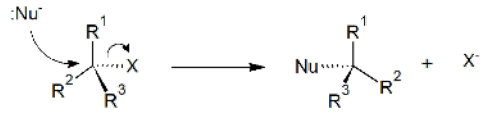
MT 11.3 Memorize the stability order of carbocations.

Summary of Reactions

Nucleophilic Substitutions

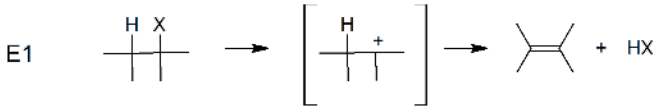


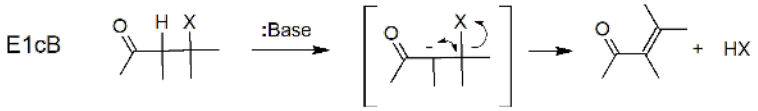
S_N1 (racemic mix of *R* and *S* products)

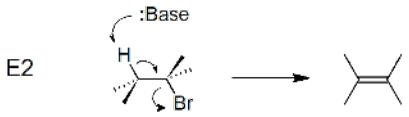


S_N2 (inverted product)

Eliminations







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CHAPTER OVERVIEW

3: Ethers and Epoxides; Thiols and Sulfides

We shall begin in a very traditional manner, with a discussion of the nomenclature of ethers. We will then describe how ethers may be prepared in the laboratory, and discuss the relative inertness of these compounds. A discussion of the chemistry of cyclic ethers follows, with particular emphasis on the preparation and reactions of epoxides (cyclic ethers containing a three-membered ring). We will then introduce crown ethers—compounds that consist of large rings containing several oxygen atoms and the spectroscopic properties of ethers. The unit will close with a description of the chemistry of thiols and sulfides, the sulfur-containing analogues of alcohols and ethers.

3.1: Introduction
3.2: Names and Properties of Ethers (reference only)
3.3: Preparing Ethers
3.4: Reactions of Ethers- Acidic Cleavage
3.5: Reactions of Ethers- Claisen Rearrangement (reference only, covered in CHM 321)
3.6: Cyclic Ethers - Epoxides
3.7: Reactions of Epoxides- Ring-opening
3.8: Crown Ethers (reference only)
3.9: Thiols and Sulfides (reference only)
3.10: Spectroscopy of Ethers (reference only, covered in CHM 222)
3.11: Interchapter- A Preview of Carbonyl Chemistry (reference only, most of this covered in CHM 222)
3.S: Ethers and Epoxides; Thiols and Sulfides (Summary)

Learning Objectives

- fulfill all of the detailed objectives listed under each individual section.
- design a multi-step synthesis using one or more of the reactions introduced in this chapter, along with any number of the reactions you have studied to date.
- solve “road-map” problems that may require a knowledge of the chemistry of ethers, epoxides, thiols and sulfides, in addition to any of the material you have studied up to this point in organic chemistry.
- define, and use in context, the key terms introduced in this chapter.

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3.1: Introduction

Objectives

After completing this section, you should be able to use the terms “ether,” “diethyl ether ” and “ethyl ether ” appropriately in context.

Key Terms

Make certain that you can define, and use in context, the key terms below.

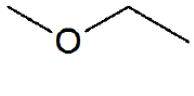
- ether ($\mathrm{R-O-R'}$)
- sulfide ($\mathrm{R-S-R'}$)
- thiol ($\mathrm{R-S-H}$)

Study Notes

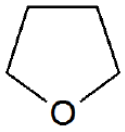
As defined in the textbook, an “ether” is a substance with the general formula ($\mathrm{R-O-R'}$) where R and $\mathrm{R'}$ are alkyl, aryl, vinyl or allyl groups. However, the word “ether” is also commonly used to refer to the specific compound, $\mathrm{CH_3-CH_2-O-CH_2-CH_3}$, which is correctly called “diethyl ether.” Further confusion can arise because some chemists refer to “diethyl ether ” as “ethyl ether.” In this course, “ether ” will be used to refer to the class of compounds with the structure ($\mathrm{R-O-R'}$); diethyl ether will refer to the compound, $\mathrm{CH_3-CH_2-O-CH_2-CH_3}$; and “ethyl ether ” will not be used.

Ethers and Epoxides

While the general formula for ethers is R-O-R′, keep in mind that there also cyclic ethers like tetrahydrofuran (a common organic solvent) or even epoxides which you first encounter in Section 8.7 in synthesizing diols from alkenes.



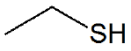
ethyl methyl ether



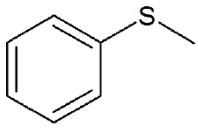
tetrahydrofuran

Thiols and Sulfides

Thiols (thio alcohols or mercaptans) and sulfides (thioethers) are the sulfur analogues of alcohols and ethers and have the general formulas of R-S-H and R-S-R′, respectively.



ethanethiol



methyl phenyl sulfide

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3.2: Names and Properties of Ethers (reference only)

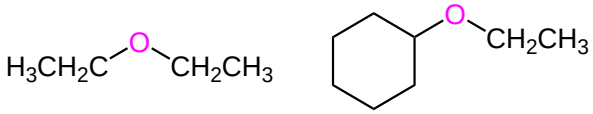
Objectives

After completing this section, you should be able to

1. write two acceptable names for a simple dialkyl ether, given its Kekulé, shorthand or condensed structure.
2. name a complicated ether by the IUPAC system, given its Kekulé, shorthand or condensed structure.
3. draw the Kekulé, condensed or shorthand structure of an ether, given an acceptable name.
4. explain why the boiling point of an ether is generally higher than that of an alkane of similar molecular mass.

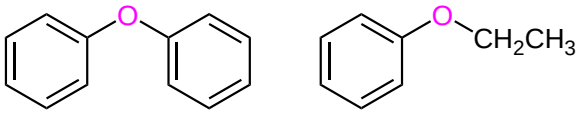
Structure of Ethers

Ethers are a class of organic compounds that contain an sp^3 hybridized oxygen between two alkyl groups and have the formula R-O-R'. These compounds are used in dyes, perfumes, oils, waxes and other industrial uses. Aliphatic ethers have no aryl groups directly attached to the ether oxygen.



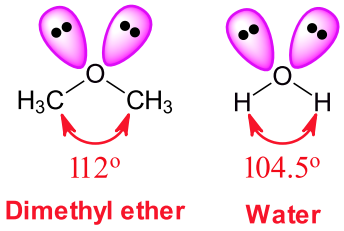
Examples of Aliphatic Ethers

Aromatic ethers have at least one aryl ring directly attached to the ether oxygen. In aryl ethers, the lone pair electrons on oxygen are conjugated with the aromatic ring which significantly changes the properties of the ether.

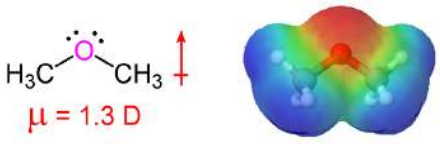


Example of Aromatic Ethers

The sp^3 hybridization of oxygen gives ethers roughly the same geometry as alcohols and water. The R-O-R' bond angle is close to what is expected in a tetrahedral geometry. The bond angle of dimethyl ether is 112° which is larger than the H-O-H bond angle in water (104.5°) due to the steric repulsion of the methyl groups.



The presence of an electronegative oxygen atom gives ethers a small dipole moment with the electron density primarily on oxygen (red and orange in the electrostatic potential map).



Comparisons of Physical Properties of Alcohols and Ethers

Ethers, unlike alcohols, have no hydrogen atom on the oxygen atom (that is, no OH group). Therefore, there is no intermolecular hydrogen bonding between ether molecules, which makes their boiling points much lower than an alcohol with similar mass.

Despite the presence of a small dipole moment, ethers have boiling points that are about the same as alkanes of comparable molar mass. (Table 18.1.2).

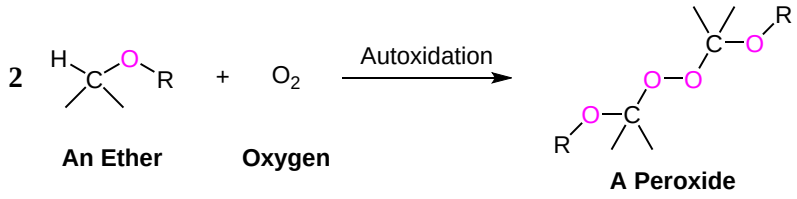
Table 18.1.2: Comparison of Boiling Points of Alkanes, Alcohols, and Ethers

Condensed Structural Formula	Name	Molar Mass	Boiling Point (°C)	Intermolecular Hydrogen Bonding in Pure Liquid?
$CH_3CH_2CH_3$	propane	44	–42	no
CH_3OCH_3	dimethyl ether	46	–25	no
CH_3CH_2OH	ethyl alcohol	46	78	yes
$CH_3CH_2CH_2CH_2CH_3$	pentane	72	36	no
$CH_3CH_2OCH_2CH_3$	diethyl ether	74	35	no
$CH_3CH_2CH_2CH_2OH$	butyl alcohol	74	117	yes

Ether molecules do have an oxygen atom, however, and engage in hydrogen bonding with water molecules. Consequently, an ether has about the same solubility in water as the alcohol that is isomeric with it. For example, dimethyl ether and ethanol (both having the molecular formula C_2H_6O) are completely soluble in water, whereas diethyl ether and 1-butanol (both $C_4H_{10}O$) are barely soluble in water (8 g/100 mL of water).

Peroxide Formation

Many ethers can react with oxygen to form explosive peroxide compounds n a free radical process called autoxidation. For this reason ethers should not be stored for long periods of time and should not be stored in glass bottles. The danger is particularly acute when ether solutions are distilled to near dryness. The hydroperoxides can become more concentrated during a distillation because they tend to have a slightly higher boiling point than the corresponding ether. Before performing an ether distillation great care should be taken to test for the presence of peroxides.

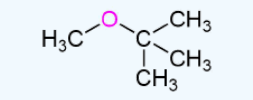


An Ether **Oxygen** **A Peroxide**

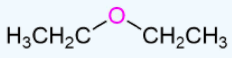
Naming Ethers

When no other functional group is present, simple ethers are often given common functional class names. Both alkyl groups attached to the oxygen atom are named as substituents (in alphabetical order) and then the word *ether* is added. The common names for alkyl substituents discussed in **Section 3.3** are often used.

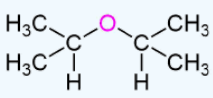
Example 3.2.1



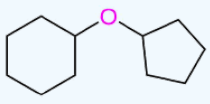
Methyl *tert*-butyl ether



Diethyl ether



Diisopropyl ether



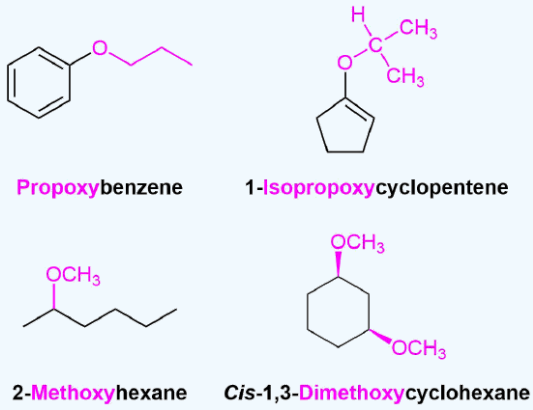
Cyclohexyl cyclopentyl ether

IUPAC nomenclature for ethers should be used for complicated ethers, compounds with more than one ether linkage, and compounds where other functional groups are present with an ether. In these cases, an RO group of the ether is named as an alkoxy substituent. Common alkoxy substituents are given names derived from their alkyl component. The suffix *-yl* is replaced with *-oxy*. (Table 18.1.1):

Table 18.1.1: Common Alkyl and Alkoxy Groups

Alkyl Group	Name		Alkoxy Group	Name
CH_3–	Methyl		CH_3O–	Methoxy
CH_3CH_2–	Ethyl		CH_3CH_2O–	Ethoxy
$(CH_3)_2CH$–	Isopropyl		$(CH_3)_2CHO$–	Isopropoxy
$(CH_3)_3C$–	tert-Butyl		$(CH_3)_3CO$–	tert-Butoxy
C_6H_5–	Phenyl		C_6H_5O–	Phenoxy

Example 3.2.2

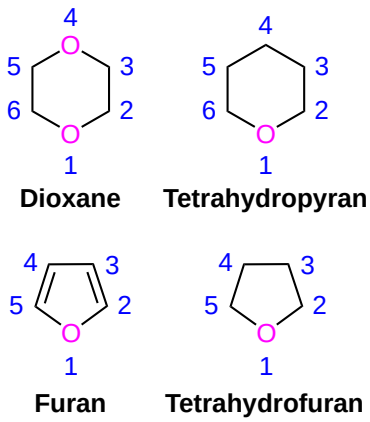


Propoxybenzene **1-Isopropoxycyclopentene**

2-Methoxyhexane ***Cis*-1,3-Dimethoxycyclohexane**

Cyclic Ethers

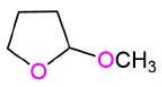
Cyclic ethers are a type of heterocycle with one or more oxygens located in the ring. Many cyclic ethers have common names and are often used as solvents due to their inert nature. These ring structures are also found in many biological molecules such as sugars and DNA. The rings are numbered so that an oxygen gets position 1.



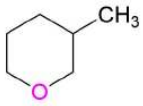
Dioxane **Tetrahydropyran**

Furan **Tetrahydrofuran**

Example 3.2.3



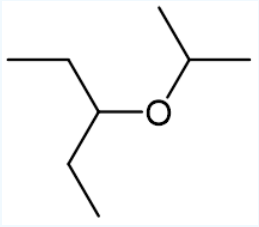
2-Methoxytetrahydrofuran



3-Methyltetrahydropyran

Exercise 3.2.1

Name the following ethers:



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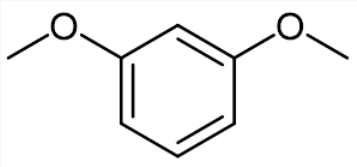

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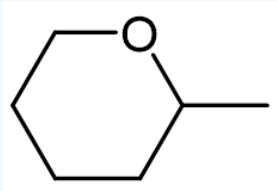
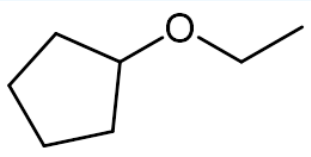
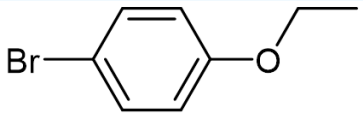


d)



e)



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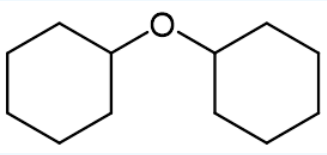

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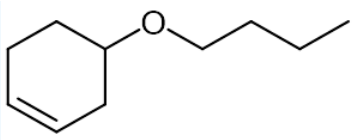

Answers

a) 3-Isopropoxypentane

b) 1,3-Dimethoxybenzene

c) 2-Methyltetrahydropyran

d) Cyclopentyl ethyl ether

e) 4-Bromo-1-ethoxybenzene

f) Dicyclohexyl ether

g) 4-Butoxycyclohexene

Contributors and Attributions

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-

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

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3.3: Preparing Ethers

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the industrial preparation of simple symmetrical ethers.
2. write an equation to illustrate the Williamson synthesis of ethers.
   a. identify the ether obtained from the reaction of a given alkyl halide with a given alkoxide ion.
   b. identify the reagents needed to prepare a given ether through a Williamson synthesis.
   c. identify the limitations of the Williamson synthesis, and make the appropriate choices when deciding how best to synthesize a given ether.
   d. write an equation to describe the formation of an alkoxide from an alcohol.
   e. identify silver(I) oxide as a reagent which can be used in a Williamson synthesis.
3. write an equation to show how an ether can be prepared by the alkoxymercuration-demercuration of an alkene.
   a. identify the product formed from the alkoxymercuration-demercuration of a given alkene.
   b. identify the alkene, the reagents, or both, needed to prepare a given ether by the alkoxymercuration-demercuration process.
   c. write the detailed mechanism of the reaction between an alkene, an alcohol and mercury(II) trifluoroacetate.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- alkoxymercuration
- oxymercuration
- Williamson ether synthesis

Study Notes

We studied oxymercuration as a method of converting an alkene to an alcohol in the Alkene Reactions Chapter. "Alkoxymercuration" is a very similar process, except that we are now converting an alkene into an ether. The two processes are compared below.

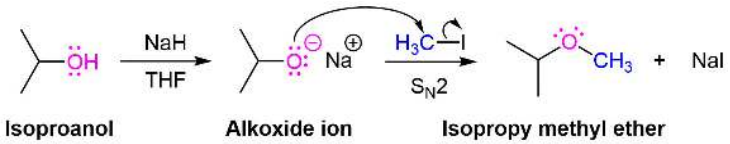
Description	oxymercuration	alkoxymercuration
we react an	alkene	alkene
with	water	an alcohol
in the presence of	$Hg(O_2CCH_3)_2$	$Hg(O_2CCF_3)_2$
followed by treatment with	$NaBH_4$	$NaBH_4$
to produce an	alcohol	ether

Review the mechanism of the oxymercuration reaction in Section 8.5, paying particular attention to the regiochemistry and the stereochemistry of the reaction. The mechanism is identical to alkoxymercuration.

Williamson Ether Synthesis

One important procedure, known as the **Williamson Ether Synthesis**, proceeds by an S_N2 reaction of an alkoxide nucleophile with a primary alkyl halide or tosylate. Alkoxides are commonly created by deprotonating an alcohol with a strong base, such as sodium

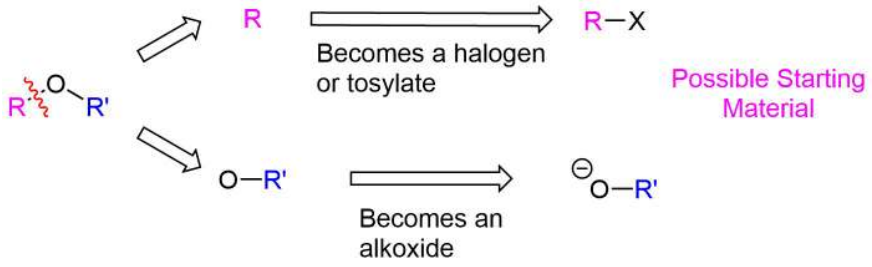
hydride (NaH). Simple alcohols can be used a solvent during a Williamson ether synthesis and with their alkoxide created through the addition of sodium metal ($Na_{(s)}$).



Planning a Williamson Ether Synthesis

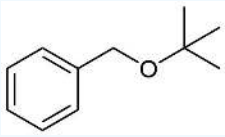
The Williamson ether synthesis has the same limitations as other S_N2 reactions, as discussed in the previous chapter. Since alkoxide anions are strong bases, utilizing 2° or 3° halogen leaving groups could possibly produce an E2 elimination product. When considering the synthesis of an unsymmetrical ether, there are two different combinations of reactants possible and each should be carefully considered. In general, the pathway which utilizes the least sterically hindered halogen will be preferred.

The key bond cleavage in the target molecule involves a C-O bond. Because unsymmetrical ethers have two unique C-O bonds, each can be broken to provide a unique set of reactants. After cleavage, the fragment with the oxygen will become an alkoxide. The other fragment will become a halogen or tosylate.



? Worked Example 3.3.1

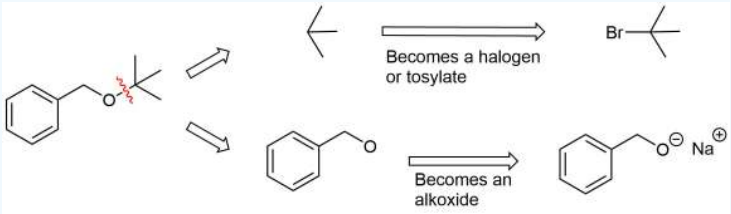
How would you prepare the following molecule using a Williamson Ether Synthesis?



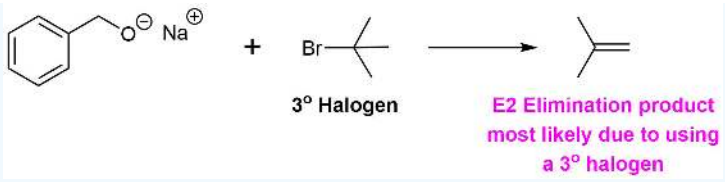
Answer

Analysis: The ether is asymmetrical so each of the C-O bonds can be broken to create a different set of possible reactants. After cleavage of the C-O bond, pathway 1 shows a 3° halogen as the starting material. This reaction will most likely not be effective due to alkoxides reacting with 3° halogens to preferable form an alkenes by E2 elimination. Pathway 2 shows a 1° halogen as a starting material which is favorable for S_N2 reactions.

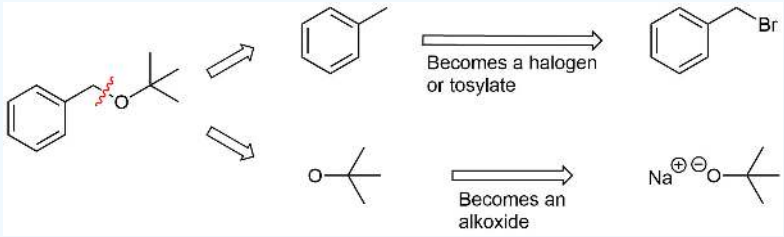
Pathway 1



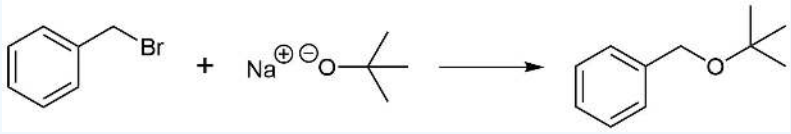
Solution 1



Pathway 2

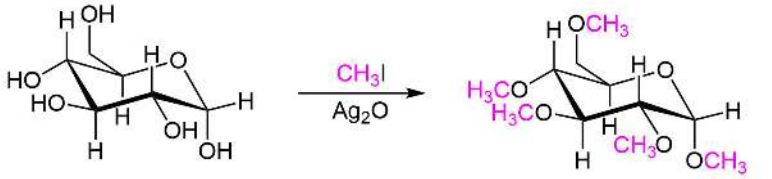


Solution 2



Ether Synthesis Using Silver Oxide

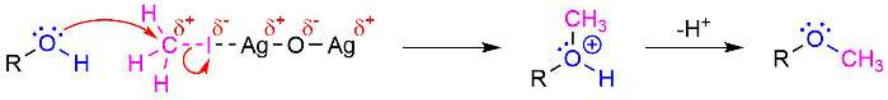
A variation of the Williamson ether synthesis uses silver oxide (Ag_2O) in the place of the strong base. The conditions of this variation are milder than the typical Willamson synthesis because a strong base and the formation of an alkoxide intermediate are not necessary. This reaction is particually useful when converting the -OH groups on a sugar into ethers.



α-D-Glucopyranose — Methyl 2,3,4,6-tetra-*O*-methyl-α-D-Glucopyranoside

Mechanism

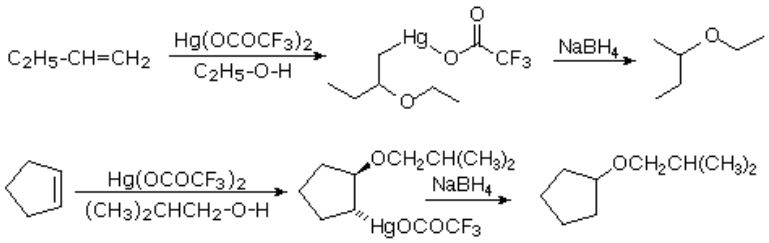
During this reaction a partial positively charged silver in Ag_2O gives draws electron density from the iodine in CH_3I. This correspondingly removes electron density from the adjacent carbon increasing its partial positive charge which increases its electrophlicity. This allows the alcohol to act as a nucleophile in the subsequent S_N2 reaction.



Alcohol — Polarized C-I Bond — Ether

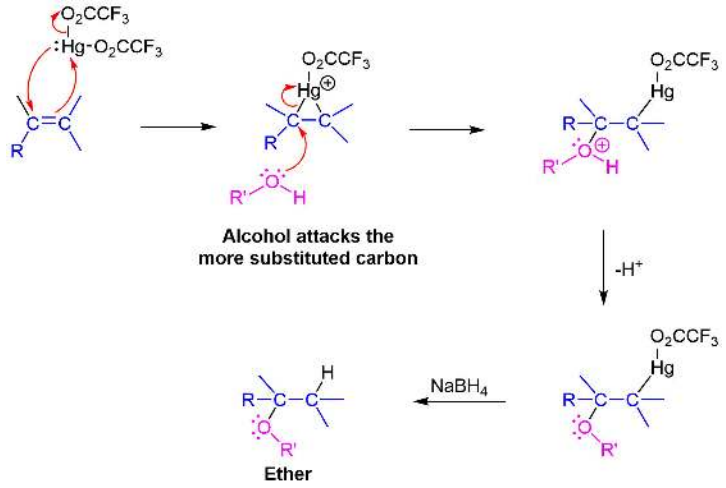
Ether Synthesis Using Alkoxymercuration

Alkoxymercuration, is patterned after the oxymercuration reaction discussed in the Alkene Reactions Chapter. Reaction of an alkene with an alcohol in the presence of a trifluoroacetate mercury (II) salt [$(CF_3CO_2)_2Hg$] prodcues an alkoxymercuration product. Demercuration using sodium borohydride ($NaBH_4$) yields an ether product. Overall, this reaction allows for the Markovnikov addition of an alcohol to an alkene to create an ether. Note that the alcohol reactant is used as the solvent, and a trifluoroacetate mercury (II) salt is used in preference to the mercuric acetate (trifluoroacetate anion is a poorer nucleophile than acetate). Most 1°, 2°, 3° alcohols can be successfully used for this reaction.



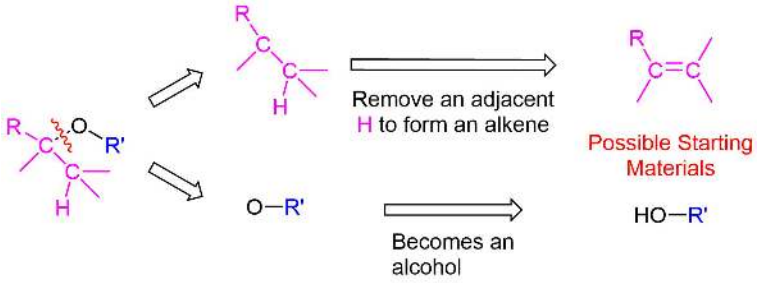
Mechanism

The mechanism of alkoxymercuration is similar to that of oxymercuration, with electrophillic addition of the mercuric species to the alkene. The alcohol nucleophile attacks the more substituted carbon of the three-membered ring via a S_N2 reaction. Finally, sodium borohydride ($NaBH_4$) provides a reductive demercuration to form the ether product.



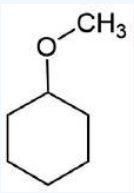
Planning the Synthesis of an Ether using Alkoxymercuration

The key bond cleavage in the target molecule involves a C-O bond. Because unsymmetrical ethers have two unique C-O bonds, each can be broken to provide a unique set of reactants. After cleavage, the fragment with the oxygen will become an alcohol. The alkyl fragment will lose a hydrogen from a adjacent carbon to form an alkene. The main point to consider when choosing a possible synthesis pathways is the ability of the alkyl fragment to form an alkene.



? Worked Example 3.3.2

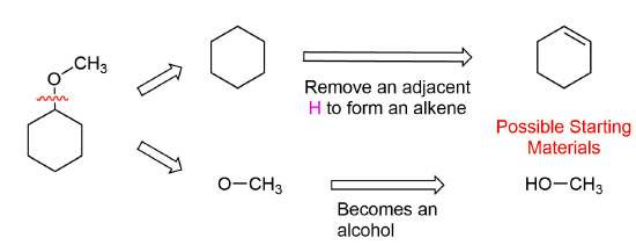
How would you prepare the following molecule using a alkoxymercuration?



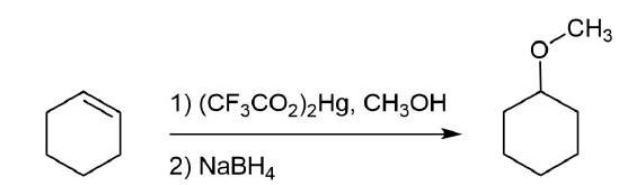
Answer

Analysis: The ether is symmetrical so each C-O bond of the ether can be cleaved to produce a set of starting materials for consideration. Pathway one shows a set of starting material which should work well for this reaction. The alcohol, methanol, can easily be used as a solvent. Although the alkene does not have a defined more and less substituted side, its symmetry will prevent a mixture of product from forming. The fragmentation for pathway 2 shows starting material which are not viable for this reaction. The alkyl fragment only has one carbon which cannot be used to form an alkene starting material. This means pathway 2 is not a viable method for the synthesis of the target molecule.

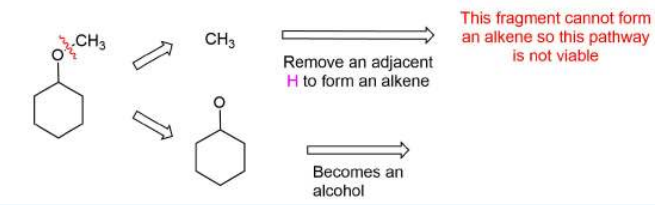
Pathway 1



Solution 1



Pathway 2



Exercises

Exercise 3.3.1

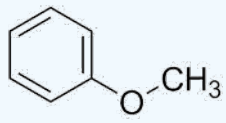
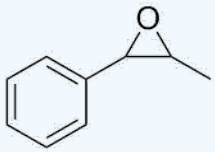
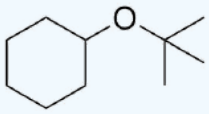
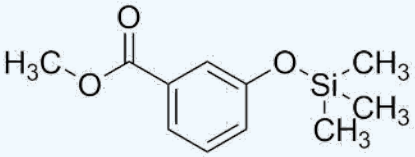
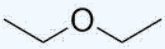
When preparing ethers using the Williamson ether synthesis, what factors are important when considering the nucleophile and the electrophile?

Answer

The nucleophile ideally should be very basic, yet not sterically hindered. This will minimize any elimination reactions from occurring. The electrophile should have the characteristics of a good S_N2 electrophile, preferably primary to minimize any elimination reactions from occurring.

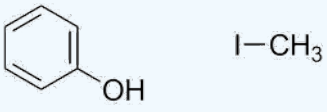
Exercise 3.3.2

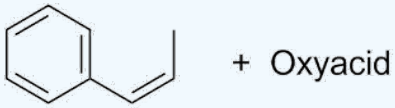
How would you synthesize the following ethers? Keep in mind there are multiple ways. The Williamson ether synthesis, alkoxymercuration of alkenes, and also the acid catalyzed substitution.

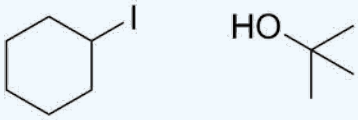
(a)  (b)  (c)  (d)  (e) 

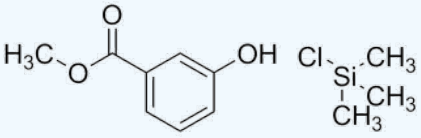
Answer

The Williamson ether syntheses require added catalytic base. Also, most of the halides can be interchanged, say for example for a -Br or a -Cl. Although, typically -I is the best leaving group.

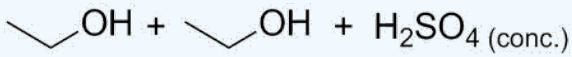
(a) 

(b) 

(c) 

(d) 

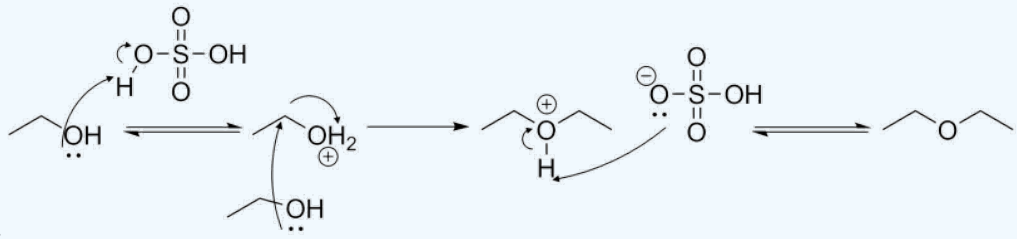
Note, there is only one ether (also called a silyl ether, and often used as an alcohol protecting group.) The other group is an ester.

(e) 

Exercise 3.3.3

Draw the electron arrow pushing mechanism for the formation of diethyl ether in the previous problem.

Answer



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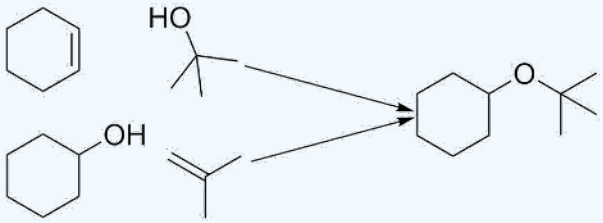
Exercise 3.3.4

t-butoxycyclohexane can be prepared two different ways from an alkene and an alcohol, draw both possible reactions.

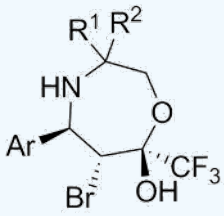
Answer



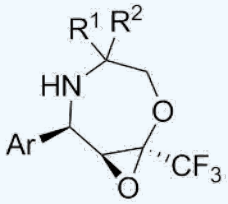
While both are possible, the top route is likely easier because both starting materials are a liquid.

Exercise 3.3.5

Epoxides are often formed intramolecularly. Take for example this large ring, in a publication from 2016 [*J. Org. Chem.*, **2016**, *81 (20)*, pp 10029–10034]. If subjected to base, what epoxide would be formed? (Include stereochemistry)



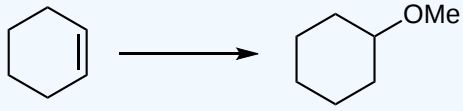
Answer



Exercise 3.3.6

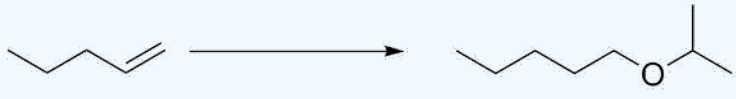
What reagents would you use to perform the following transformations?

(a)



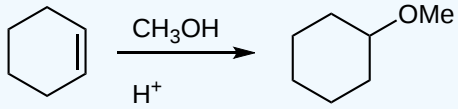
(b)

(c)

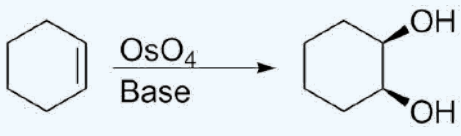


Answer

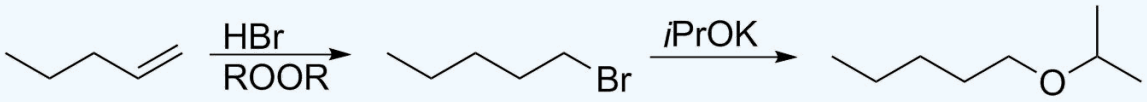
(a)



Note: This is also possible using alkoxymercuration. However, with a simple substrate like cyclohexene, acid and methanol is simpler and works well.

(b) 

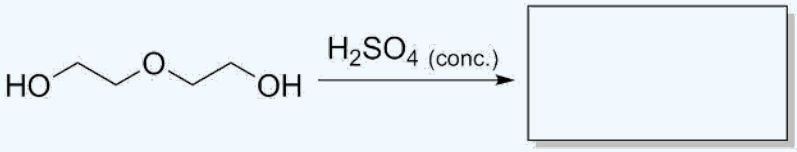
Note the cis addition

(c) 

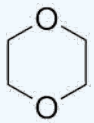
An oxidation to an alcohol through hydroboration, and subsequent substitution with 2-bromopropane could also work, but this route provides the least likelihood of an elimination reaction occurring.

Exercise 3.3.7

Predict the product of the following.



Answer



The result is the production of dioxane, a common solvent.

Contributors and Attributions

-
-
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Layne Morsch (University of Illinois Springfield)

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3.4: Reactions of Ethers- Acidic Cleavage

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the acidic cleavage of an ether.
2. identify the products formed when a given ether is cleaved by a strong acid.
3. identify the reagent needed to bring about cleavage of a given ether.
4. deduce the structure of an unknown ether, given the products of acidic cleavage of the ether.
5. write the detailed mechanism for the acidic cleavage of a given ether.

Study Notes

There are a number of points in this section that require additional explanations.

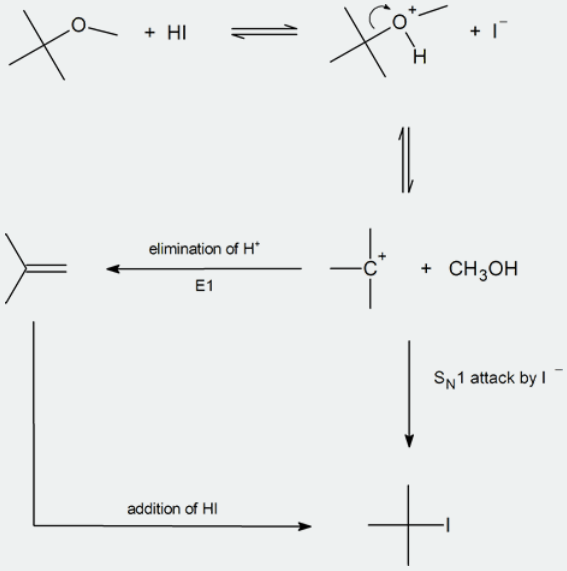
First, if an excess of HI (or HBr) is used in the cleavage reaction, the alcohol formed is converted by a nucleophilic substitution reaction to the appropriate alkyl halide:

$ROH + HI \rightarrow RI + H_2O$

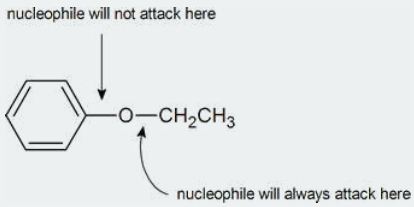
In view of this substitution, some textbooks simplify the overall cleavage process as:

$R\text{-}O\text{-}R' + 2HI \rightarrow RI + R'I + H_2O$

Second, we should consider in detail how certain ethers (those containing tertiary alkyl, benzyl or allyl groups) cleave by an S_N1 mechanism:



Finally, notice that an aryl alkyl ether will always produce a phenol and an alkyl halide, never an aryl halide and an alcohol. This is because we rarely see a nucleophile attacking an aromatic ring carbon in preference to an aliphatic carbon:

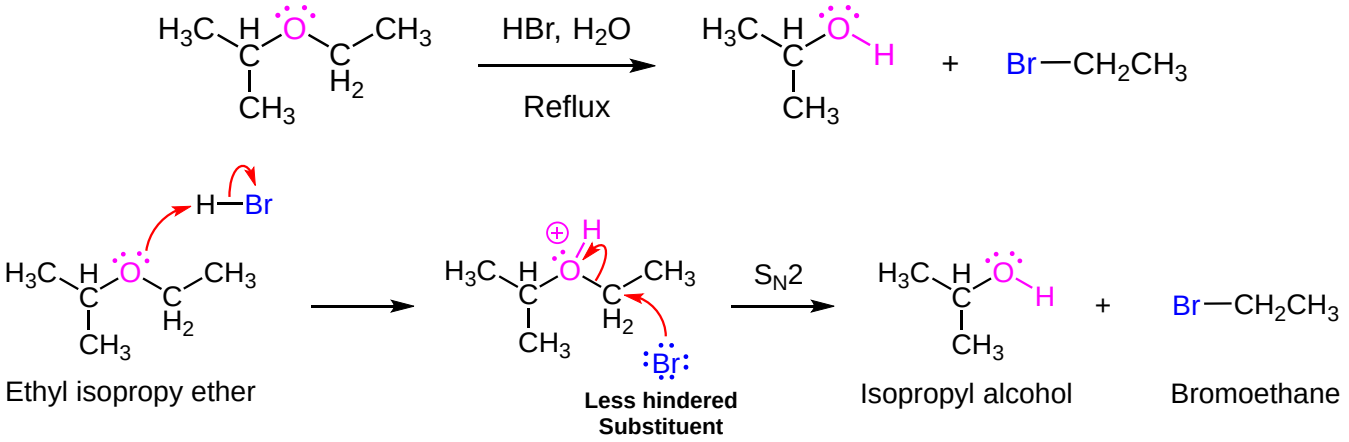


As phenols do not undergo nucleophilic substitution reactions, even if an excess of HX is used, the products from the cleavage of an aryl alkyl ether are a phenol and an alkyl halide. Diaryl ethers are not cleaved by acids.

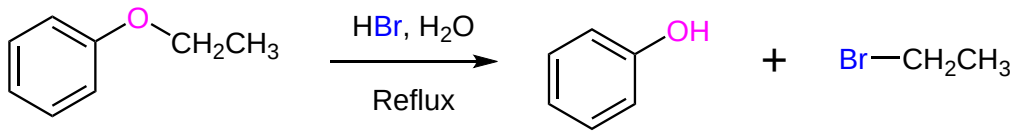
Ethers are known to be unreactive towards most reagents which makes them excellent reaction solvents. The most common reaction of ethers is cleavage of the C–O bond by using strong acids. During acidic cleavage the ether oxygen is protonated to form a good leaving groups which can be eliminated as part of an S_N2, S_N1, or E1 reaction mechanism. The mechanistic pathway is primarily determined by the strong acid used and the type of substituents attached to the ether.

Acidic Cleavage of Ethers

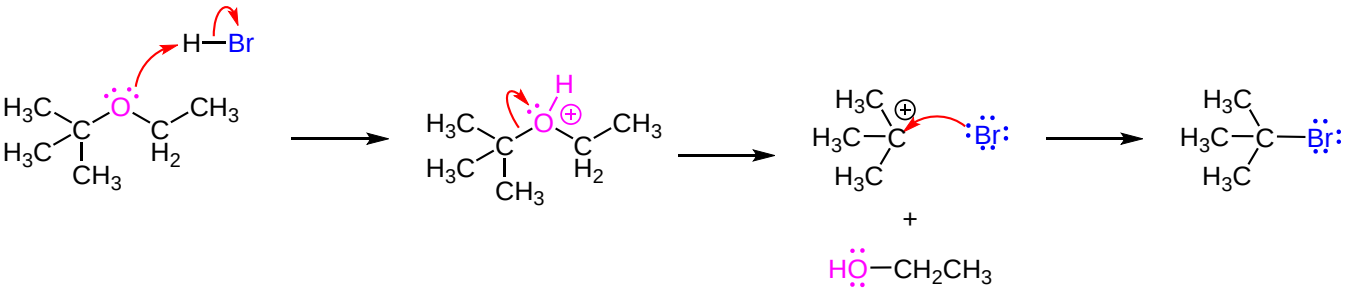
Aqueous solutions of HBr or HI (but not HCl) tend to cleave ethers into alcohol and an alkyl halide product by either an S_N2 or S_N1 mechanism. If the ether is attached to only primary, secondary, or methyl alkyl groups, a selective cleavage will typically take place using an S_N2 mechanism. First, the strong acid protonates the ether oxygen. Then resulting halide conjugate base attacks the protonated ether at the less sterically hindered alkyl substituent forming a halogen product. The ether's more sterically hindered alkyl substituent is ejected as a leaving group and forms an alcohol product. The example below shows that when ethyl isopropyl ether is cleaved with hydrobromic acid the products isopropyl alcohol and bromoethane are produced. The bromide nucleophile preferably attacks the ether's ethyl substituent because it is less hindered (1°) than the isopropyl substituent (2°).



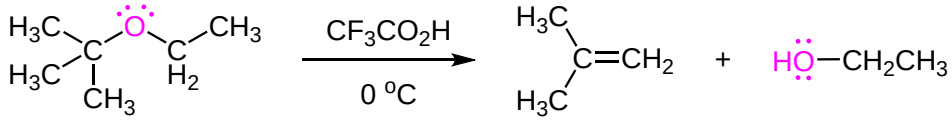
It is important to note that a phenyl substituent on an ether is not capable of participating in the S_N2 reaction of an acidic cleavage. If a phenyl group is present it will become a phenol in the product due to the halide nucleophile preferably attacking the other alkyl substituent.



When using HBr or HI, the acidic cleavage of ethers with tertiary, benzylic, or allylic substituents tend to occur by an S_N1 mechanism. The ability of these substituents to produce relatively stable carbocations promotes the S_N1 mechanism. The change in mechanism causes the tertiary, benzylic, or allyic group to preferably become the halogen product of the acidic cleavage. This makes the ether's other alkyl substituent become the alcohol product.

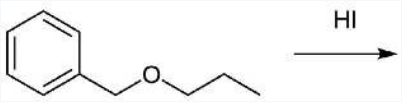


When using a strong acid whose conjugate base is a poor nucleophile, such as trifluoroacetic acid (CF_3CO_2H), for the the acidic cleavage of an ether with a tertiary alkyl substituent, the mechanism will often be E1. In this case the tertiary alkyl substituent will lose an adjacent hydrogen to form an alkene product. The ether's other alkyl substituent will form an alcohol product.



Worked Example 3.4.1

Predict the products of the following reaction:



Answer

Analysis: When considering the acidic cleavage of ethers it is important to realize that S_N2, S_N1, or E1 reactions are possible depending on the conditions. First, identify if the ether has a substituent which can easily form a carbocation: tertiary, benzylic, or allylic substituents. If none of these substituents are present the reaction will most likely be S_N2. However, if one of the substituents is present the reaction will most likely be S_N1 or E1. Next, identify if the reaction conditions will allow for an E1 reaction. These are the presence of a tertiary alkyl substituent on the ether along with the use of a strong acid which has a poor nucleophile as a conjugate base. If this set of conditions is not present the reaction will most likely be S_N1.

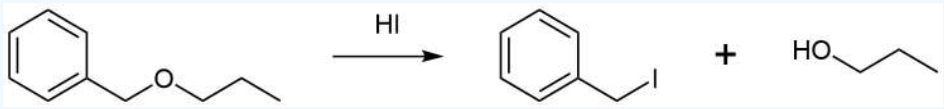
For a S_N2 reaction: The less hindered alkyl substituent of the ether will become a halogen. The other alkyl substituent will become an alcohol.

For a S_N1 reaction: The substituent which easily forms a carbocation will become a halogen and the other alkyl substituent will become an alcohol.

For an E1 reaction: The tertiary alkyl substutent will form an alkene and the other alkyl substiutent will become an alcohol.

For the reaction proposed above, the reactant contains a benzylic substituent so the reaction will most likely be S_N1. Consequently, the benzylic substituent will become and Iodide product and the propyl substituent will become an alcohol.

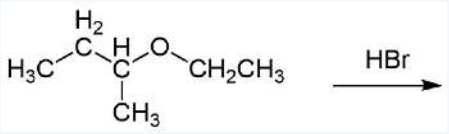
Solution



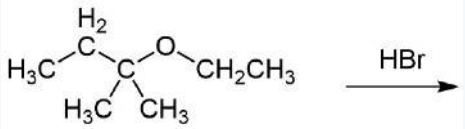
Exercises 3.4.1

1) Predict the product of the following reactions:

a)



b)



2) Please draw the mechanism for the following reaction:

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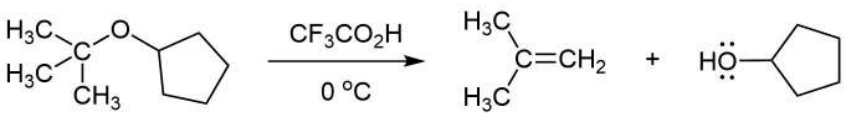
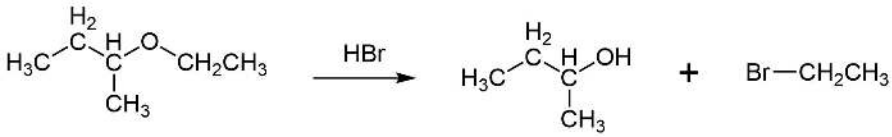


3) Why is HCl less effective at cleaving ethers than HBr or HI?

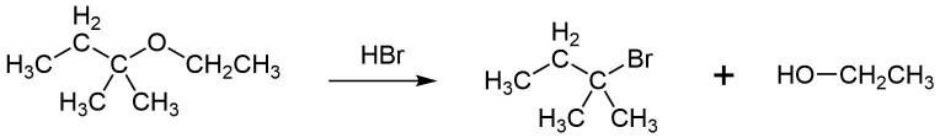
Answer

1)

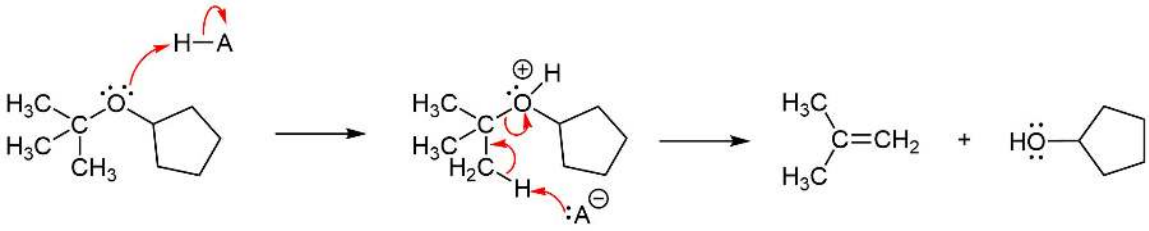
a)



b)



2)



3) HCl's conjugate base Cl^- is a poor nucleophile when compared to Br^- and I^-. The chloride anion is not a strong enough nucleophile to promote the acidic cleavage of ethers.

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3.5: Reactions of Ethers- Claisen Rearrangement (reference only, covered in CHM 321)

Objectives

After completing this section, you should be able to

1. write an equation to represent the Claisen rearrangement of allyl phenyl ester.
2. account for the formation of a specific product from a Claisen rearrangement, without giving mechanistic details.

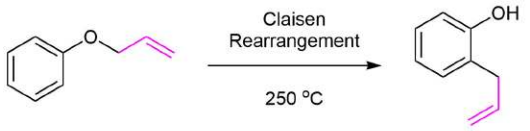
Key Terms

Make certain that you can define, and use in context, the key term below.

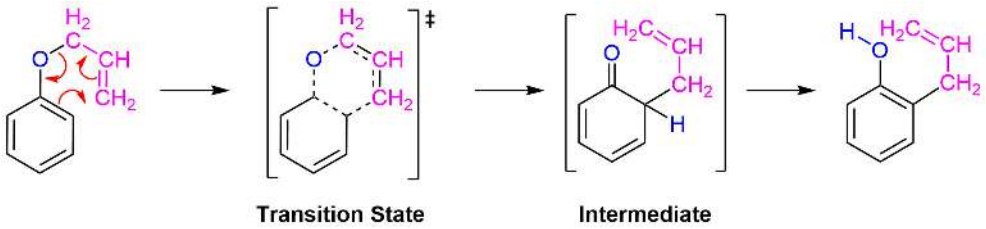
- Claisen rearrangement

Claisen Rearrangements

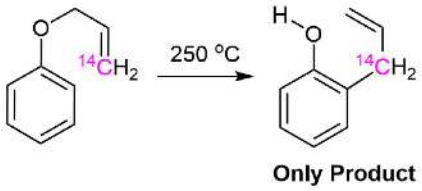
A Claisen rearrangement is a reaction which is specific to ally aryl ethers and allyl vinyl ethers. Heating an allyl aryl ether to 250 ^{o}C causes an intramolecular rearrangement to produce an *o*-allylphenol.



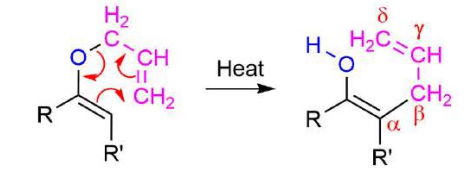
The Claisen rearrangement takes place through a concerted mechanism in which a C-C bond forms between the C3 of the allyl group and the ortho position of the benzene ring at the same time that the C-O bond of the ether breaks. This rearrangement initially produces the non-aromatic 6-allyl-2,4- cyclohexadienone intermediate which quickly undergoes a proton shift to reform the aromatic ring in the *o*-allylphenol product. Claisen rearrangement occurs in a six-membered, cyclic transition state involving the concerted movement of six bonding electrons in the first step. The presence of six electrons in a ring suggests that the transition state may have aromatic characteristics. The Claisen rearrangement is part of a broader class of reactions called sigmatropic rearrangements which will be discussed in more detail in **Section 30-8**.



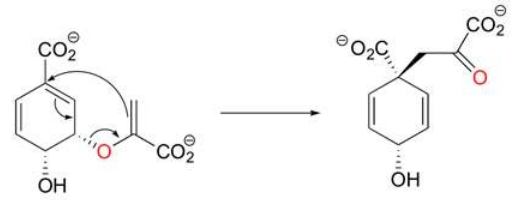
Evidence for this mechanism was provided by performing the rearrangement with allyl group with a ^{14}C label at C3. The product of this reaction was shown to have the ^{14}C labeled carbon exclusively bonded to the ring.



Allyl vinyl ethers can also undergo a Claisen rearrangement when heated to form gamma, delta -unsaturated ketones or aldehydes.



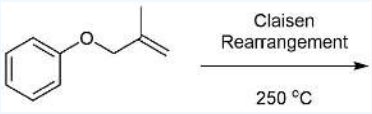
Claisen rearrangements are rare in biological chemistry. One example is the chorismate mutase catalyzed Claisen rearrangement of chorismate (a allylic vinyl ether) to form prephenate. Prephenate is a precursor in the biosynthetic pathway of aromatic amino acids phenylalanine and tyrosine.



Exercise 3.5.1

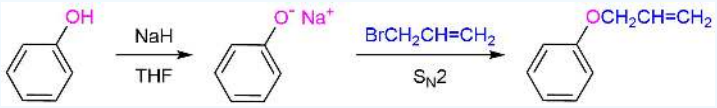
1) Show how you could synthesize allyl phenyl ether from allyl bromide and phenol.

2) What would be the expected product of the following Claisen rearrangement?

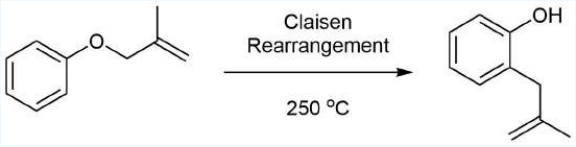


Answer

1)



2)



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3.6: Cyclic Ethers - Epoxides

Objectives

After completing this section, you should be able to

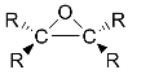
1. write an equation to describe the industrial preparation of ethylene oxide.
2. list two important industrial uses of ethylene oxide.
3. write an equation to describe the normal laboratory preparation of an epoxide.
4. identify the epoxide produced from the reaction of a given alkene with a peroxyacid.
5. identify the alkene, the reagent, or both, needed to prepare a given epoxide.
6. write an equation to describe the preparation of an epoxide from an alkene via a halohydrin.

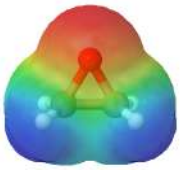
Key Terms

Make certain that you can define, and use in context, the key term below.

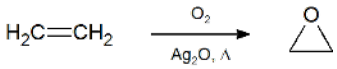
- epoxide (oxirane)

Epoxides (also known as **oxiranes**) are three-membered ring structures in which one of the vertices is an oxygen and the other two are carbons. Epoxides behave differently than other ethers due to the strain created by the three-membered ring.





The most important and simplest epoxide is ethylene oxide which is prepared on an industrial scale by catalytic oxidation of ethylene by air. Ethylene oxide is used as an important chemical feedstock in the manufacturing of ethylene glycol, which is used as antifreeze, liquid coolant and solvent. In turn, ethylene glycol is used in the production of polyester and polyethylene terephthalate (PET) the raw material for plastic bottles.

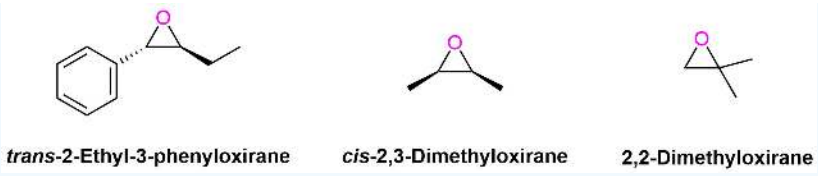


Nomenclature of Epoxides

The name ethylene oxide is not systematic but common. Epoxides are systematically named as an oxirane ring system much like the other cyclic ethers discussed in **Section 18.1**. The oxygen is numbered in the 1 position.

Oxirane

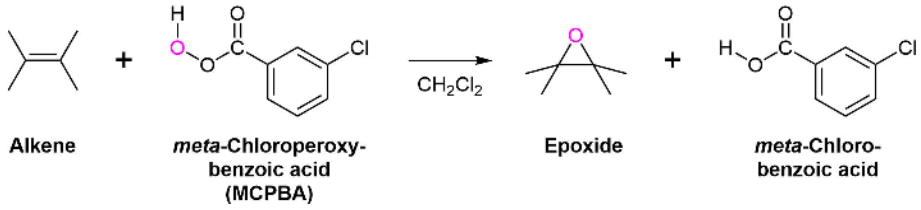
Example 3.6.1



Synthesis of Epoxides

As discussed in the Alkene Reactions Chapter, epoxides are typically prepared by the reaction of an alkene and a peroxycarboxylic acid (RCO_3H), such as *meta*-chloroperbenzoic acid (MCPBA). The peroxycarboxylic acid has the unique property of having an electropositive oxygen atom on the CO_3H group. The reaction is initiated by the electrophilic oxygen atom reacting with the nucleophilic carbon-carbon double bond. The mechanism involves a concerted reaction with a four-part, circular transition state. The result is that the originally electropositive oxygen atom ends up in the oxacyclopropane ring and the CO_3H group becomes CO_2H.

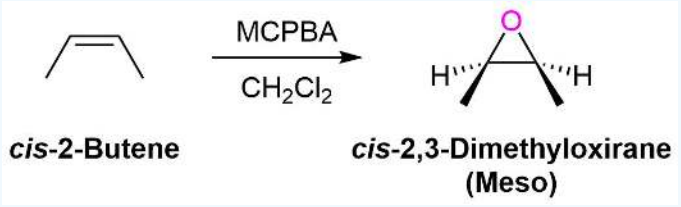
General Reaction

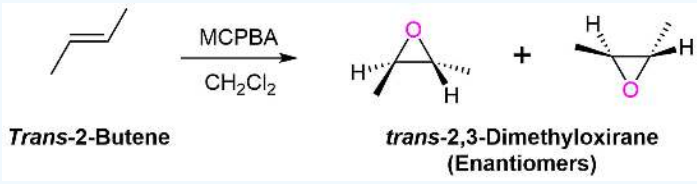


Stereochemical Consideration

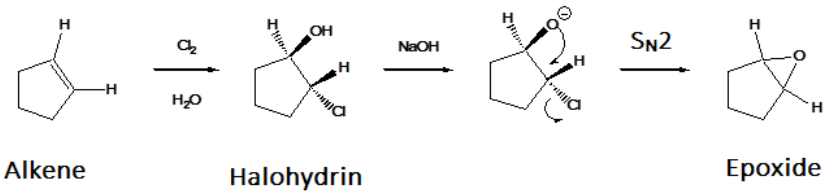
The oxygen addition to the alkene is a syn addition and is stereospecific. The substituents of a *cis*-alkene will appear in the *cis* configuration on the epoxide ring. Likewise, Substituents of a *trans*-alkene will appear in the *trans* configuration on the epoxide ring. During this reaction the sp^2 hybridized carbons of the alkene are converted to sp^3 hybridized carbons in the epoxide. Thus, there is the possibility of two new chiral carbons forming in the epoxide product. In most cases, epoxidation of an alkene will product a mixture of enantiomers in the product, due to the electrophilic oxygen being able to attack from above or below the plane of the alkene. One major exception is the epoxidation of symmetrical cis-alkene which produces a meso compound product.

Example 3.6.2



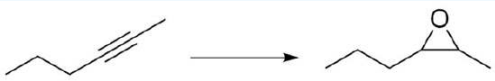


Treatment of an alkene with X_2 & H_2O creates a halohydrin (Alkene Reactions Chapter). When a halohydrin is treated with a base the alcohol is deprotonated to from an alkoxide. This causes an intramolecular Williamson ether synthesis to produce an epoxide along with the elimination of HX. Note, that this reaction generally forms a mixture of enantiomeric products unless a meso compound is produced.



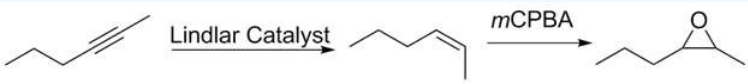
Exercise 3.6.1

What reagents would you use to perform the following transformation?



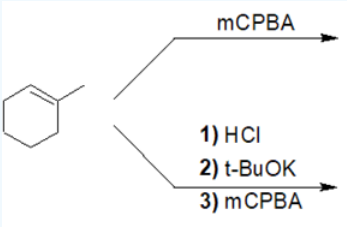
Answer

Lindlar's catalyst reduces alkynes to cis/Z alkenes. This stereochemistry is retained after epoxidation.

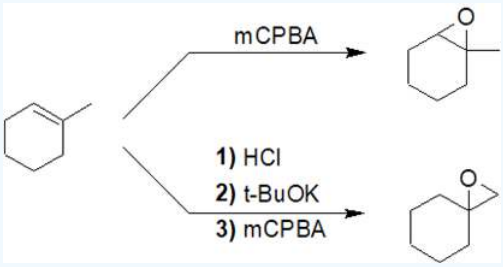


Exercise 3.6.2

Predict the products of the following reactions:

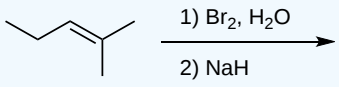


Answer



Exercise 3.6.3

Predict the product of the following reaction. Be sure to include proper stereochemistry.



Answer

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3.7: Reactions of Epoxides- Ring-opening

Objectives

After completing this section, you should be able to

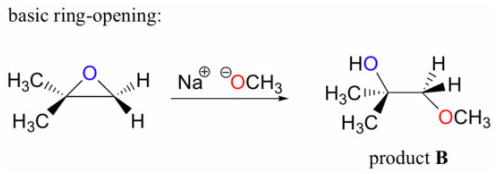
1. write an equation to describe the opening of an epoxide ring under mildly acidic conditions.
    a. identify the product formed from the hydrolysis of an epoxide.
    b. write the mechanism for the opening of an epoxide ring by an aqueous acid, paying particular attention to the stereochemistry of the product.
    c. identify the product formed when an epoxide ring is opened by a hydrogen halide under anhydrous conditions.
2. predict the major product from the acidic cleavage of a given unsymmetrical epoxide.
3. write an equation to illustrate the cleavage of an epoxide ring by a base.
    a. identify the product formed from the reaction of a given epoxide with given base.
    b. explain why epoxides are susceptible to cleavage by bases, whereas other cyclic ethers are not.

Study Notes

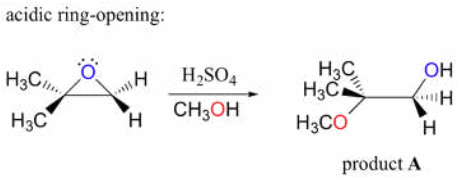
In the discussion on base-catalyzed epoxide opening, the mechanism is essentially S_N2. While oxygen is a poor leaving group, the ring strain of the epoxide really helps to drive this reaction to completion. Indeed, larger cyclic ethers would not be susceptible to either acid-catalyzed or base-catalyzed cleavage under the same conditions because the ring strain is not as great as in the three-membered epoxide ring.

Epoxide Ring-Opening by Alcoholysis

The ring-opening reactions of epoxides provide a nice overview of many of the concepts discussed in earlier chapters of this book. Ring-opening reactions can proceed by either S_N2 or S_N1 mechanisms, depending on the nature of the epoxide and on the reaction conditions. If the epoxide is asymmetric, the structure of the product will vary according to which mechanism dominates. When an asymmetric epoxide undergoes alcoholysis in basic methanol, ring-opening occurs by an S_N2 mechanism, and the *less* substituted carbon is the site of nucleophilic attack, leading to what we will refer to as product B:



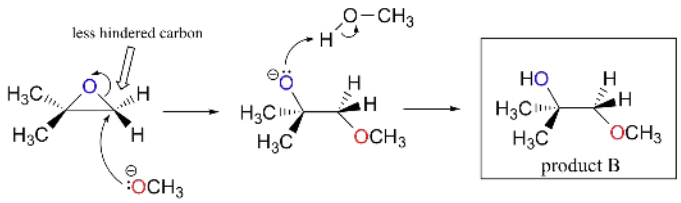
Conversely, when solvolysis occurs in acidic methanol, the reaction occurs by a mechanism with substantial S_N1 character, and the *more* substituted carbon is the site of attack. As a result, product A predominates.



These are both good examples of **regioselective reactions**. In a regioselective reaction, two (or more) different constitutional isomers are possible as products, but one is formed preferentially (or sometimes exclusively).

Basic Epoxide Ring-Opening by Alcoholysis

In the basic, S_N2 reaction, the leaving group is an alkoxide anion, because there is no acid available to protonate the oxygen prior to ring opening. An alkoxide is a poor leaving group, and thus the ring is unlikely to open without a 'push' from the nucleophile.

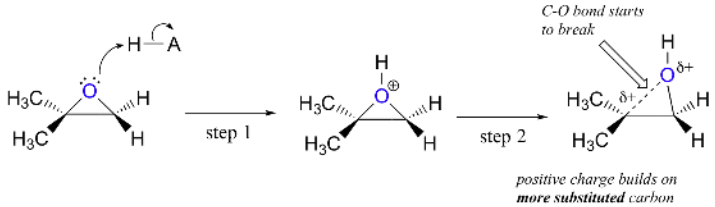


The nucleophile itself is important: a deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an S_N2 mechanism.

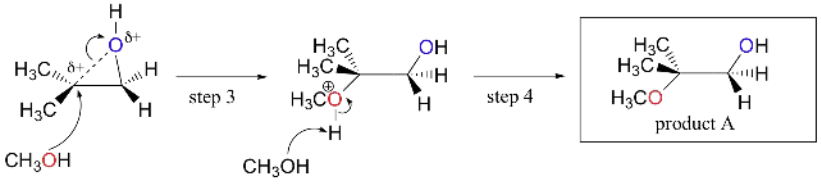
There are two electrophilic carbons in the epoxide, but the best target for the nucleophile in an S_N2 reaction is the carbon that is *least hindered*. This accounts for the observed regiochemical outcome. Like in other S_N2 reactions, nucleophilic attack takes place from the backside, resulting in inversion at the electrophilic carbon.

Acid-Catalyzed Epoxide Ring-Opening by Alcoholysis

The best way to depict the acid-catalyzed epoxide ring-opening reaction is as a hybrid, or cross, between an S_N2 and S_N1 mechanism. First, the oxygen is protonated, creating a good leaving group (step 1 below). Then the carbon-oxygen bond begins to break (step 2) and positive charge begins to build up on the more substituted carbon. Recall that alkyl substituents can donate electron density through hyper conjugation and stabilize a positive charge on a carbon.



Unlike in an S_N1 reaction, the nucleophile attacks the electrophilic carbon (step 3) before a complete carbocation intermediate has a chance to form.

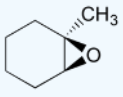


Attack takes place preferentially from the backside (like in an S_N2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks attack from the front side. Notice, however, how the regiochemical outcome is different from the base-catalyzed reaction: in the acid-catalyzed process, the nucleophile attacks the more substituted carbon because it is this carbon that holds a greater degree of positive charge.

Example 18.6.1

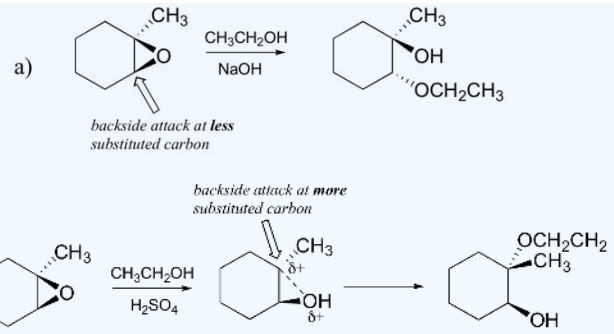
Predict the major product(s) of the ring opening reaction that occurs when the epoxide shown below is treated with:

a. ethanol and a small amount of sodium hydroxide
b. ethanol and a small amount of sulfuric acid



Hint: be sure to consider both regiochemistry ***and*** *stereochemistry!*

Answer



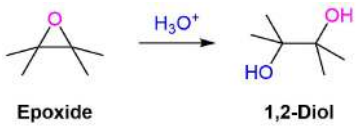
Epoxide Ring-Opening by Hydrolysis

Epoxides may be cleaved by hydrolysis to give ***trans*-1,2-diols** (1,2 diols are also called **vicinal diols or vicinal glycols)**. The reaction can be preformed under acidic or basic conditions which will provide the same regioselectivity previously discussed.

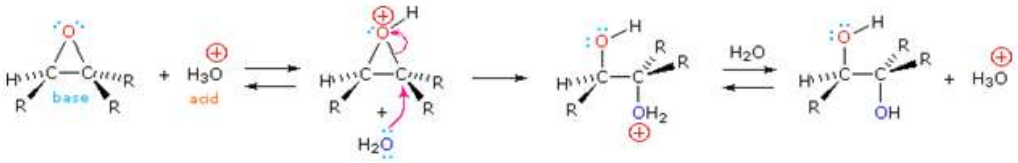
Acid Catalyzed Hydrolysis

Under aqueous acidic conditions the epoxide oxygen is protonated and is subsequently attacked by a nucleophilic water. After deprotonation to reform the acid catalyst a 1,2-diol product is formed. If the epoxide is asymmetric, the incoming water nucleophile will preferably attack the more substituted epoxide carbon. The epoxide ring is opened by an S_N2 like mechanism so the two -OH groups will be *trans* to each other in the product.

General Reaction



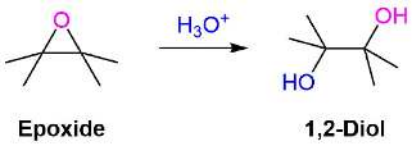
Mechanism



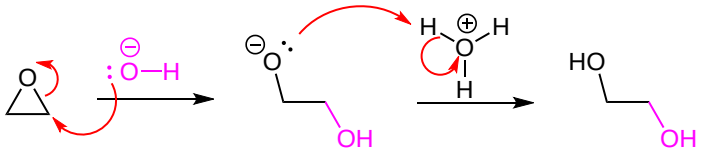
Basic Hydrolysis

Under aqueous basic conditions the epoxide is opened by the attack of hydroxide nucleophile during an S_N2 reaction. The epoxide oxygen forms an alkoxide which is subsequently protonated by water forming the 1,2-diol product. If the epoxide is asymmetric the incoming hydroxide nucleophile will preferable attack the less substituted epoxide carbon. Because the reaction takes place by an S_N2 mechanism the two -OH groups in the product will be *trans* to each other.

General Reaction



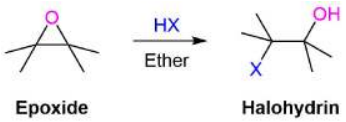
Mechanism



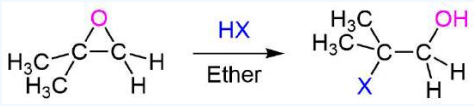
Epoxide Ring-Opening by HX

Epoxides can also be opened by anhydrous acids (HX) to form a trans halohydrin. When both the epoxide carbons are either primary or secondary the halogen anion will attack the less substituted carbon through an S_N2 like reaction. However, if one of the epoxide carbons is tertiary, the halogen anion will primarily attack the tertiary carbon in an S_N1 like reaction.

General Reaction

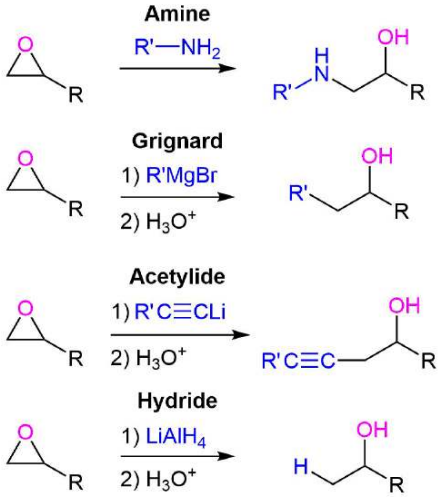


Example 18.6.2

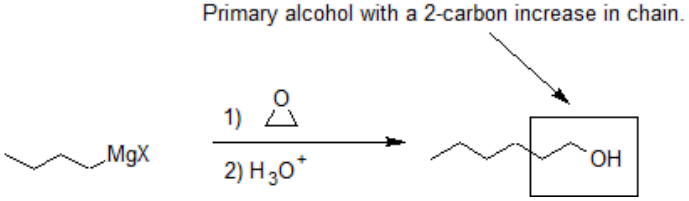


Epoxide Ring-Opening by Other Basic Nucleophiles

A wide variety of basic nucleophiles can be used for the ring opening of an epoxide including, amines, hydrides, Grignard reagents, acetylide anions, and hydride. These ring openings generally take place by an S_N2 mechanism.

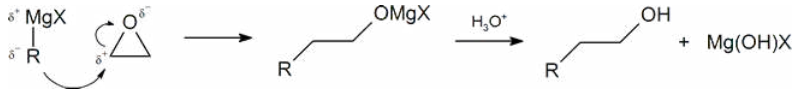


Reacting Grignard reagents with ethylene oxide is a particularly useful reaction because it produces a primary alcohol containing two more carbon atoms than the original Grignard reagent.



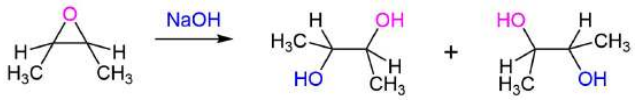
This reaction follows the same S_N2 mechanism as the opening of epoxide rings under basic conditions since Grignard reagents are both strong nucleophiles and strong bases. The first step of the mechanism of this reaction involves the S_N2 attack of the Grignard

reaction to open the epoxide to form an alkoxide. The second step of the mechanism involves the protonation of the alkoxide to form an alcohol.



Additional Stereochemical Considerations of Ring-Opening

During the ring-opening of an asymmetrical epoxide, the regiochemical control of the reaction usually allows for one stereoisomer to be produced. However, if the epoxide is symmetrical, each epoxide carbon has roughly the same ability to accept the incoming nucleophile. When this occurs the product typically contains a mixture of enantiomers.



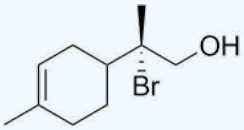
Symmetrical Epoxide **Enantiomers**

Exercises

Exercise 3.7.1

Given the following, predict the product assuming only the epoxide is affected. (Remember to show stereochemistry)

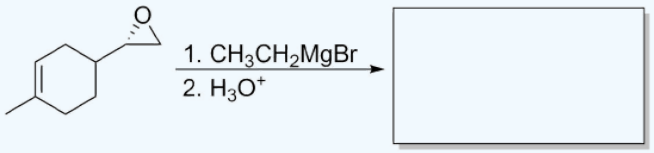
Answer



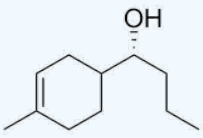
Note that the stereochemistry has been inverted

Exercise 3.7.2

Predict the product of the following, similar to above but a different nucleophile is used and not in acidic conditions. (Remember stereochemistry)

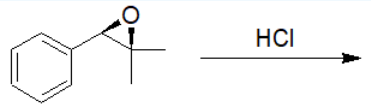


Answer

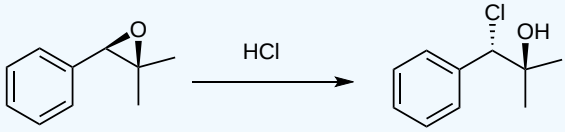


Exercise 3.7.3

Provide the structure of the product of the following reaction. Be sure to include proper stereochemistry.



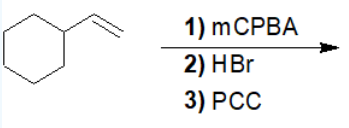
Answer



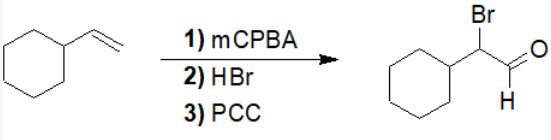
The ring side of the protonated epoxide intermediate will better stabilize a partial positive charge, so would be the more likely carbon for the chloride ion to attack.

Exercise 3.7.4

Predict the product of the following reaction.

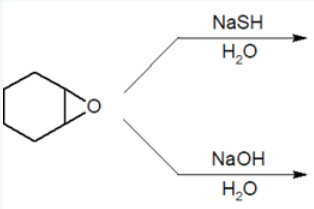


Answer

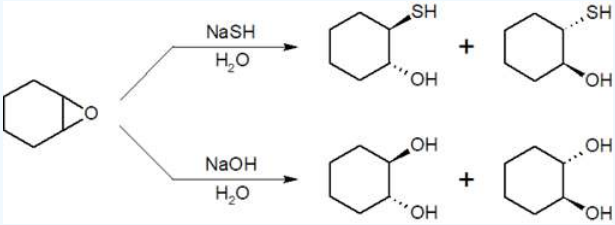


Exercise 3.7.5

Provide the final products of the following reactions.



Answer



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Contributors and Attributions

- Layne Morsch (University of Illinois Springfield)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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3.8: Crown Ethers (reference only)

Objectives

After completing this section, you should be able to

1. write the normally accepted name for a crown ether, given its structure.
2. draw the structure of a crown ether, given its normally accepted name.
3. describe, briefly, the uses of crown ethers.

Key Terms

Make certain that you can define, and use in context, the key term below.

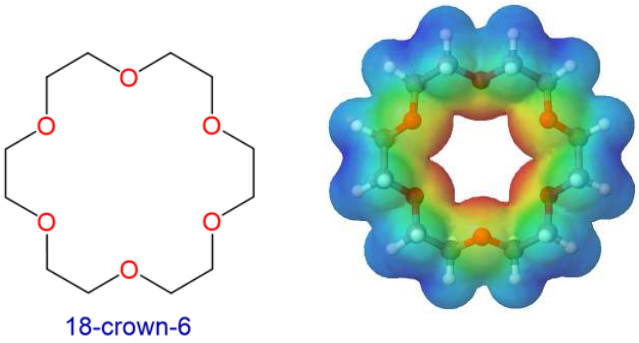
- crown ether

Study Notes

A “crown ether ” is a cyclic ether containing several (i.e., 4, 5, 6 or more) oxygen atoms. As we have indicated in the objectives above, a detailed knowledge of these compounds is not required in this course.

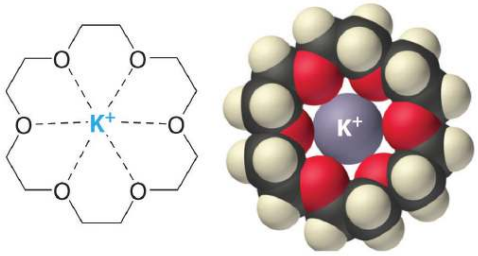
Crown Ethers

Crown ethers are cyclic polyethers with four or more oxygen atoms each separated by two or three carbon atoms. Crown ethers have the general formula of $(OCH_2CH_2)_n$ or $(OCH_2CH_2CH_2)_n$ and are named using both the total number of atoms in the ring and the number of oxygen atoms. Thus 18-crown-6 is an 18-membered ring with six oxygen atoms. All crown ethers have a cavity in the center this is lined with oxygen atoms and can accommodate a alkali metal ion, such as K^+. The cation is stabilized by interacting with lone pairs of electrons on the surrounding oxygen atoms. The negative character of center cavity of 18-crown-6 can be seen by looking at its electrostatic potential map shown below. The presence of high electron density is shown by a red color.



18-crown-6

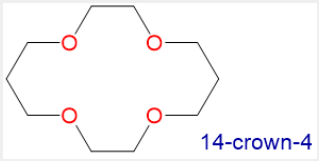
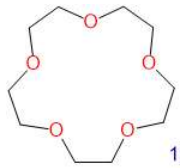
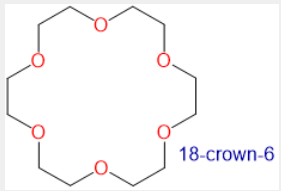
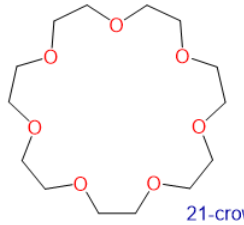
Crown ethers are useful for dissolving ionic substances in organic solvents, such as $KMnO_4$ dissolving in toluene, by sequestering the cations inside a hydrophilic cavity, whereas the outer shell, consisting of C–H bonds, is hydrophobic.



Potassium complex of the crown ether 18-crown-6

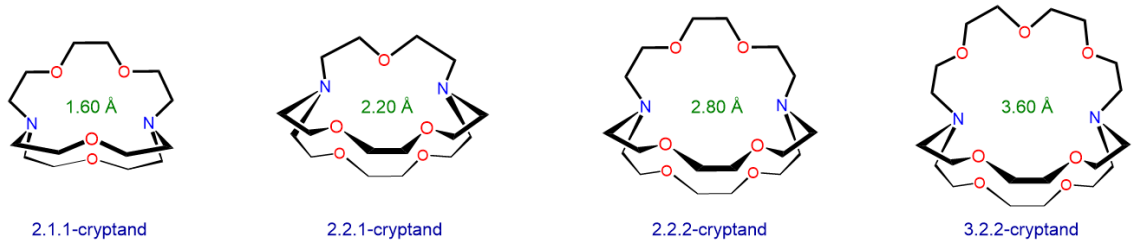
The availability of crown ethers with cavities of different sizes allows specific cations to be solvated with a high degree of selectivity. Crown ethers prefer to bind alkali metal cations with sizes that match that of their binding cavity. For instance, as shown in **Table-18.7.1**, 14-crown-4 preferentially binds to Li^+, 15-crown-5 preferentially binds to Na^+, 18-crown-6 preferentially binds to K^+, and 21-crown-7 preferentially binds to Cs^+.

Table 18.7.1: Crown ethers preferentially bind cations with sizes that match the cavity size of their crown-shaped conformers.

Crown Ether	Cavity Diameter (A˚)	Preferred Cation	Cation Diameter (A˚)
 14-crown-4	**1.2-1.5**	**Li^+**	**1.36**
 15-crown-5	**1.7-2.2**	**Na^+**	**1.94**
 18-crown-6	**2.6-3.2**	**K^+**	**2.66**
 21-crown-7	**3.4-4.3**	**Cs^+**	**3.34**

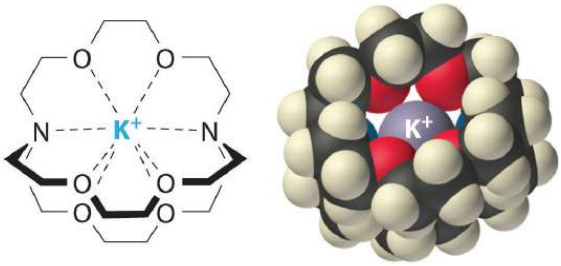
Cryptands

Cryptands (from the Greek *kryptós*, meaning “hidden”) are variations of crown ethers comprised of two nitrogens connected by three polyether strands. A common nomenclature is used where the numbers preceding the word cryptan indicate the number of oxygen atoms in each strand of the molecule.



Structures and approximate binding cavity diameters for several cryptands

Like crown ethers, cryptands are compounds that contains a central cavity that can completely surround a cation with lone pair electrons from oxygen and nitrogen atoms. Also, cryptands can be used to prepare solutions of ionic compounds in solvents that are otherwise too nonpolar to dissolve them. Similar to crown ethers, cryptands prefer to bind with alkali metal cations whose diameter matches the size of their binding cavity.



Potassium complex of 2,2,2-cryptand

? Exercise 3.8.1

Cryptand ligands also preferentially bind alkali metal ions with sizes that match the size of their binding cavities. The structure and approximate cavity sizes of several cryptands are shown above. Use the information in **Table 18.7.1** to predict which alkali metal ion each cryptand will preferentially bind.

Answer

The cryptands might be expected to selectively bind the largest ion which fits within the cavity. Predicted selectivity of crown ethers for alkali metal cations based on the hypothesis that they will selectively bind the largest ion which fits their bindng cavity are listed below.

Cryptand	Cavity Diameter of (Å)	Preferred Cation	Cation Diameter (Å)
2.1.1-cryptand	**1.60**	**Li^+**	**1.36**
2.2.1-cryptand	**2.20**	**Na^+**	**1.96**
2.2.2-cryptand	**2.80**	**K^+**	**2.66**
3.2.2-cryptand	**3.60**	**Cs^+**	**3.34**

Contributors and Attributions

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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Stephen Contakes, Westmont College

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3.9: Thiols and Sulfides (reference only)

Objectives

After completing this section, you should be able to

1. a. write the IUPAC name of a thiol, given its Kekulé, condensed or shorthand structure.
   b. draw the structure of a thiol, given its IUPAC name.
   c. write an equation to represent the formation of a thiol by the reaction of hydrosulfide anion with an alkyl halide.
   d. write an equation to illustrate the preparation of a thiol by the reaction of thiourea with an alkyl halide.
2. write an equation to show the interconversion between thiols and disulfides.
3. a. write the name of a sulfide, given its structure.
   b. draw the structure of a sulfide, given its name.
   c. write an equation showing how a sulfide may be prepared by the reaction of a thiolate anion on an alkyl halide.
   d. identify the product from the reaction of a given alkyl halide with a given thiolate anion.
   e. identify the reagents necessary to prepare a given sulfide.
   f. write an equation to illustrate the formation of a trialkylsulfonium salt from a sulfide and an alkyl halide.

Key Terms

Note: All of these terms are defined in the "Study Notes," below.

- disulfide
- mercapto group
- (organic) sulfide
- sulfone
- sulfoxide
- thiol
- thiolate anion
- trialkylsulfonium ion (trialkylsulfonium salt)

Study Notes

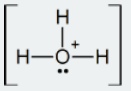
The chemistry of sulfur-containing organic compounds is often omitted from introductory organic chemistry courses. However, we have included a short section on these compounds, not for the sake of increasing the amount of material to be digested, but because much of the chemistry of these substances can be predicted from a knowledge of their oxygen-containing analogues.

A thiol is a compound which contains an SH functional group. The SH group itself is called a mercapto group. A disulfide is a compound containing an S-S linkage.

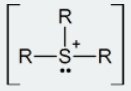
(Organic) sulfides have the structure R-S-R′, and are therefore the sulfur analogues of ethers. The nomenclature of sulfides can be easily understood if one understands the nomenclature of the corresponding ethers. Notice that the term "thio" is also used in inorganic chemistry. For example, SO_4^{2-} is the sulfate ion; while $S_2O_3^{2-}$, in which one of the oxygen atoms of a sulfate ion has been replaced by a sulfur atom, is called thiosulfate.

Thiolate anions, RS^-, are analogous to alkoxy anions, RO^-. Thiolate anions are better nucleophiles than are alkoxy anions.

If you have trouble understanding why trialkylsulfonium ions are formed, think of them as being somewhat similar to the hydronium ions that are formed by protonating water:



hydronium ion



trialkylsulfonium ion

Later we shall see examples of tetraalkylammonium ions, R_4N^+, which again may be regarded as being similar to hydronium ions.

Sulfoxides and sulfones are obtained by oxidizing organic sulfides. You need not memorize the methods used to carry out these oxidations.

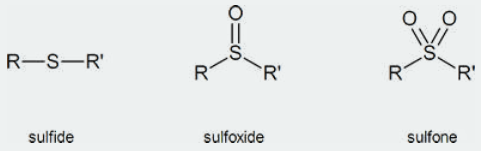


Table 18.1, below, provides a quick comparison of oxygen-containing and sulfur-containing organic compounds.

Table 18.1 Comparison of compounds containing oxygen and sulfur

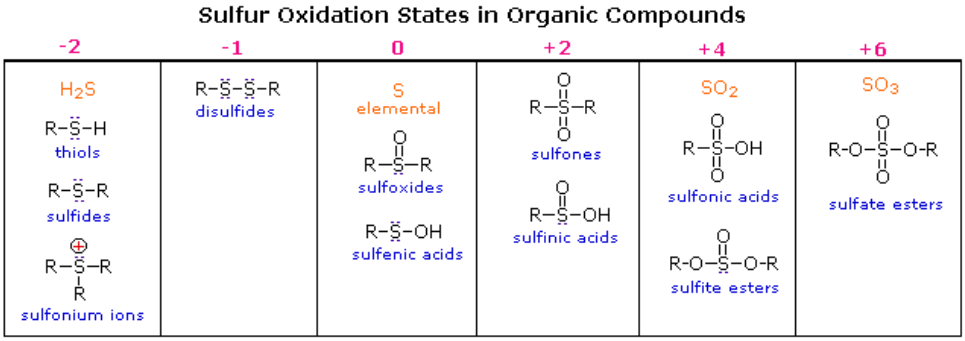
Oxygen-containing Compound	Sulfur Analogue
ether, R-O-R′	sulfide, R-S-R′
alkoxy anion, RO^-	thiolate anion, RS^-
alcohol, ROH	thiol, RSH
hydroxy group, OH^-	mercapto group, SH^-
peroxide, R-O-O-R′	disulfide, R-S-S-R′

Note that when we name thiols, we include the “e” of the alkane name. Thus, CH_3CH_2SH is called “ethanethiol,” not “ethanthiol.”

Thiols and sulfides are the "sulfur equivalent" of alcohols and ethers. You can replace the oxygen atom of an alcohol with a sulfur atom to make a thiol; similarly, you can replace the oxygen atom in an ether with S to make the corresponding alkyl sulfide. This is because thiols contain the C-S-H functional group, while sulfides contain the C-S-C group.

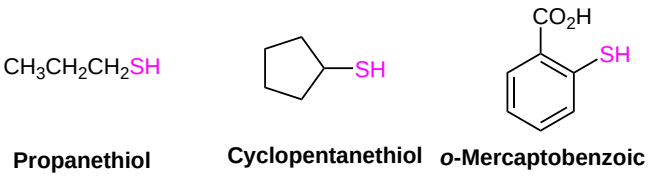
Oxidation States of Sulfur Compounds

Oxygen assumes only two oxidation states in its organic compounds (–1 in peroxides and –2 in other compounds). Sulfur, on the other hand, is found in oxidation states ranging from –2 to +6, as shown in the following table (some simple inorganic compounds are displayed in orange).



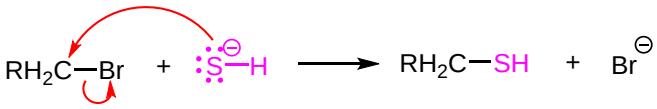
Thiols

Thiols are often called “mercaptans,” a reference to the Latin term mercurium captans (capturing mercury), since the -SH group forms strong bonds with mercury and its ions. Thiols are analogous to alcohols. Thiols are weakly acidic (pK_a ~ 10) and are much stronger acids than alcohols (pKa ~ 16). However, thiols usually do not form hydrogen bonds due to the sulfur atom not have sufficient electronegativity. Thiols named using the same rules as alcohols except the parent chain is named as alkane with the suffix -thiol added. As a substituent the -SH group is called a **mercapto** group.



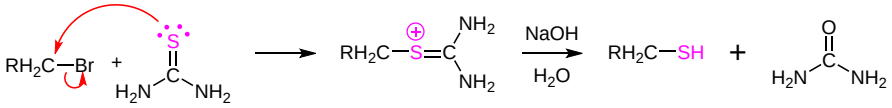
Propanethiol **Cyclopentanethiol** ***o*-Mercaptobenzoic acid**

Thiols are usually prepared by using the hydrosulfide anion (-SH) as a nucleophile in an S_N2 reaction with alkyl halides.



Hydrosulfide ion **Thiol**

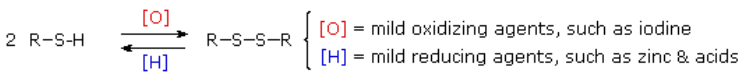
One problem with this reaction is that the thiol product can deprotonate and undergo a second S_N2 reaction with an additional alkyl halide to produce a sulfide side product. This problem can be solved by using thiourea, $(NH_2)_2C=S$, as the nucleophile. The S_N2 reaction first produces an alkyl isothiourea salt as an intermediate. This salt is then hydrolyzed to form the thiol by a reaction with aqueous base.



Thiourea **Thiol** **Urea**

Disulfides

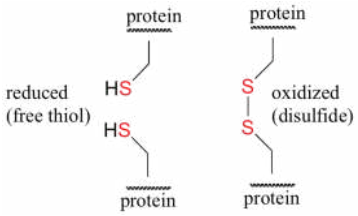
Thiols (R-S-H) can be oxidized to form disulfides (R-S-S-R') through reaction with Br_2 or I_2. Note, an equivalent oxidation of alcohols (R-O-H) to peroxides (R-O-O-R') is not normally observed. The reasons for this different behavior becomes clear when looking at bond strengths. The S–S single bond in disulfides is nearly twice as strong as the O–O bond in peroxides. Also, the O–H bond in alcohols is more than 25 kcal/mole stronger than the S–H bond in thiols. Thus, thermodynamics favors disulfide formation over peroxide. Disulfides can easily be reduced back to a thiols through reaction with zinc and acid.



Thiol **Disulfide**

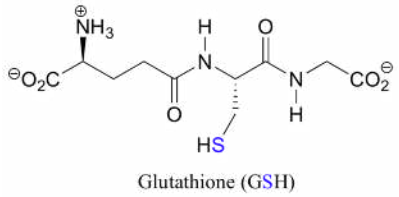
Disulfide bridges in proteins

Disulfide (sulfur-sulfur) linkages between two cysteine residues are an integral component of the three-dimensional structure of many proteins. The interconversion between thiols and disulfide groups is a redox reaction: the thiol is the reduced state, and the disulfide is the oxidized state.



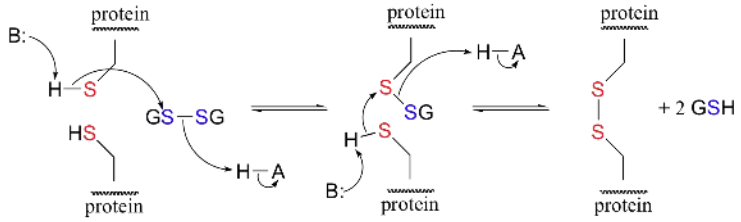
Notice that in the oxidized (disulfide) state, each sulfur atom has lost a bond to hydrogen and gained a bond to a sulfur - this is why the disulfide state is considered to be oxidized relative to the thiol state. The redox agent that mediates the formation and

degradation of disulfide bridges in most proteins is glutathione, a versatile coenzyme. Recall that the important functional group in glutathione is the thiol, highlighted in blue in the figure below. In its reduced (free thiol) form, glutathione is abbreviated 'GSH'.



Glutathione (GSH)

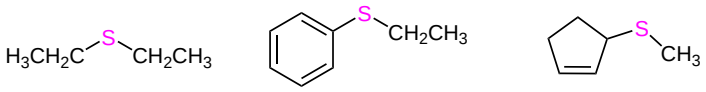
In its oxidized form, glutathione exists as a dimer of two molecules linked by a disulfide group, and is abbreviated 'GSSG'. A new disulfide in a protein forms via a 'disulfide exchange' reaction with GSSG, a process that can be described as a combination of two S_N2-like attacks. The end result is that a new cysteine-cysteine disulfide forms at the expense of the disulfide in GSSG.



In its reduced (thiol) state, glutathione can reduce disulfides bridges in proteins through the reverse of the above reaction.

Sulfides

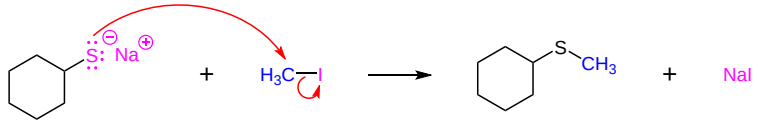
Sulfides are named using the same rules as ethers except *sulfide* is used in the place of *ether*. For more complex substances, alkylthio is used in place of alkoxy.



Diethyl sulfide **Ethyl phenyl sulfide** **3-(Methylthio)cyclopentene**

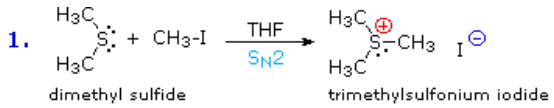
Sulfur analogs of ethers are called **sulfides**. Sulfides are less common than thiols as naturally occurring compounds. However, sulfides—especially disulfides (C-S-S-C)—have important biological functions, mainly in reducing agents (antioxidants).

Since thiols are weakly acidic their conjugate bases, called thiolate ions, can be easily formed through reaction with a strong base such as NaH. Thiolates have proven to be excellent nucleophiles and easily undergo S_N2 reactions with primary and secondary alkyl halides to form sulfides. The reaction is analogous to the Williamson ether synthesis previously discussed in this chapter (**Section 18-2**)



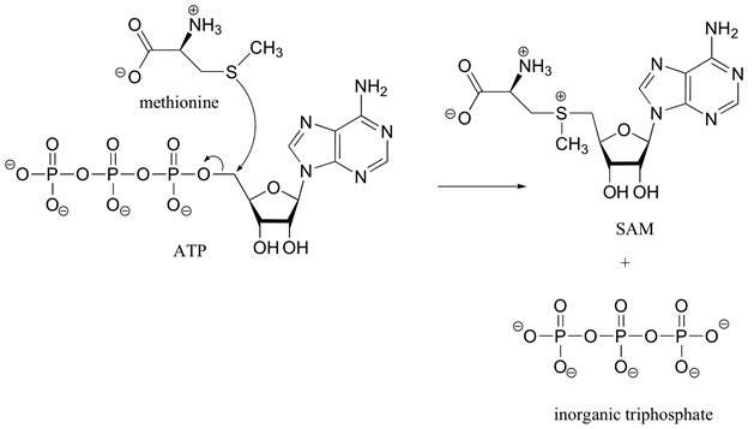
Cyclohexanethiolate **Cyclohexyl methyl sulfide**

The chemical behavior of sulfides contrasts with that of ethers in some important ways. Because sulfur's valence electrons involve 3P orbitals they are further away and less tightly held than the valence electrons on oxygen which involve 2P orbitals. This makes the nucleophilicity of sulfur atoms much greater than that of oxygen, leading to a number of interesting and useful electrophilic substitutions of sulfur that are not normally observed for oxygen. For instance, sulfides, unlike ethers, easily react with primary alkyl halides through an S_N2 mechanism to give ternary sulfonium ions (R_3S^+) in the same manner that 3º-amines can be alkylated to form quaternary ammonium salts. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive.

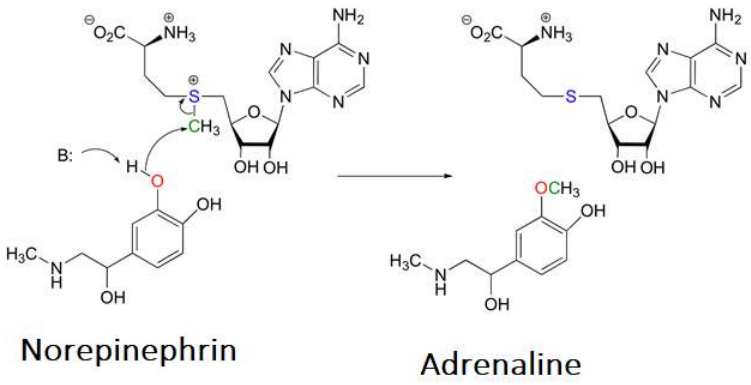


Biological Sulfonium Ion Formation

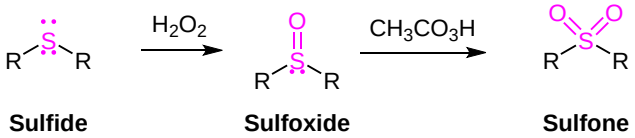
In biological systems the sulfonium ion, *S*-adenosylmethionine (SAM), is formed by a S_N2 reaction between the nucleophilic sulfur atom of the amino acid methionine and the electrophilic methene (CH_2) carbon of adenosine triphosphate (ATP). This reaction is unusually in that the triphosphate ion is removed from ATP as a leaving group. In most cases biological nucleophiles attack an electrophilic phosphorus on ATP causing a diphosphate ion to be removed as the leaving group.



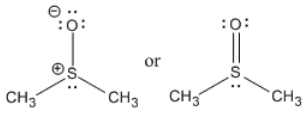
The sulfonium ion in SAM is an effective methylating agent. Through an S_N2 reaction, biological nucleophiles can attack the electrophilic methyl group bonded to the positively charged sulfonium ion and cause the removal of a neutral sulfide as a leaving group. An example of this reaction is the catechol-O-methyltransferase catalyzed O-methylation of norepinephrin by SAM to produce adrenaline.



Sulfides can be easily oxidized. Reacting a sulfide with hydrogen peroxide, H_2O_2, as room temperature produces a sulfoxide (R_2SO). The oxidation can be continued by reaction with a peroxyacid, such as peracetic acid (CH_3CO_3H), to produce the sulfone (R_2SO_2).



A common example of a sulfoxide is the solvent dimethyl sulfoxide (DMSO). DMSO is considered a polar aprotic solvent.

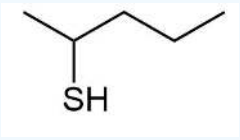


DMSO is a very polar, aprotic solvent

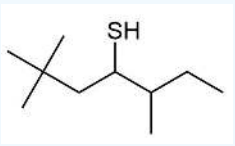
Exercise 3.9.1

Give IUPAC names the following compounds:

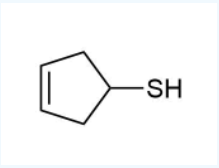
a)



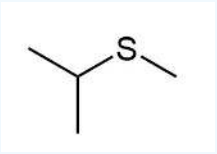
b)



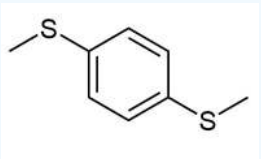
c)



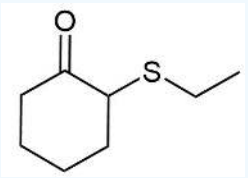
d)



e)



f)



Answer

a) 2-Pentanethiol

b) 2,2,5-Trimethyl-4-heptanethiol

c) 3-Cyclopentene-1-thiol

d) Methyl isopropyl sulfide

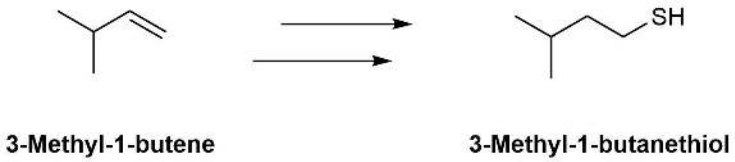
e) *p*-Di(methylthio)benzene

f) 2-(Ethylthio)cyclohexanone

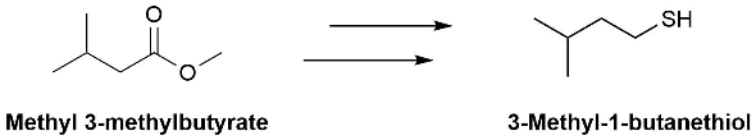
? Exercise 3.9.2

The molecule 3-methyl-1-butanethiol has been shown to be one of the components of skunk spray. How would make the following conversions?

a)



b)



Answers

a) 1) HBr & Peroxides, 2) $(NH_2)_2C=S$, 3) NaOH & H_2O

b) 1) $LiAlH_4$, 2) PBr_3, 3) $(NH_2)_2C=S$, 4) NaOH & H_2O

Contributors and Attributions

-
-
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

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3.10: Spectroscopy of Ethers (reference only, covered in CHM 222)

Objectives

After completing this section, you should be able to

1. use the ^{1}H NMR spectrum of an unknown ether or epoxide to determine its identity.
2. identify the approximate chemical shift expected for protons attached to the carbon atoms that are bonded to oxygen in an ether or an epoxide.

Infrared Spectroscopy

Ethers and epoxides typically have a strong C-O stretch between 1000 and 1300 1/cm. Because this absorption appears in the fingerprint region of the IR is can be difficult to assign. In addition to the C-O peak, it is helpful to note if an IR spectrum has no C=O or O-H stretch peaks to confirms it is not aldehyde, ketone, or alcohol.

If you look at an IR spectrum of dibutyl ether, you will see:

- there are the usual sp^3 C-H stretching and CH_2 bending modes at 2900 and 1500 cm^{-1}.
- there is a strong peak near 1100 cm^{-1}. This peak is due to the C-O stretching vibration.

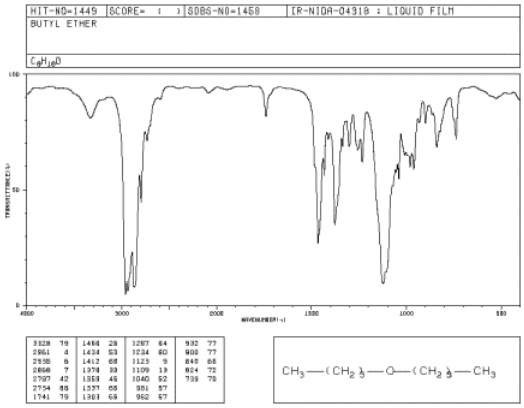
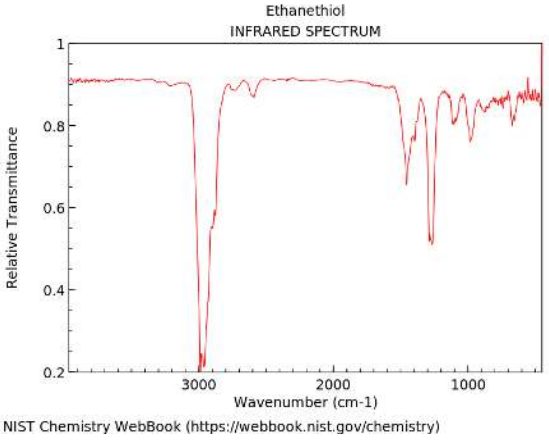


Figure IR7. *IR spectrum of dibutyl ether. Source: SDBSWeb: http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 14 July 2008)*

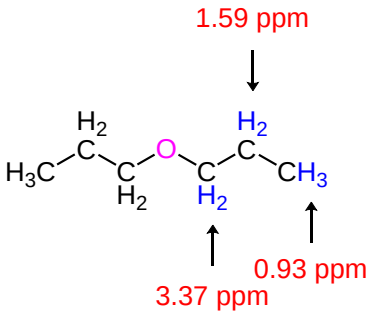
Although thios and sulfides do have a weak C-S stretch between 710 and 570 1/cm, the absorption is very difficult to assign. In addition thios have a weak S-H stretch at 2600-2550 1/cm.



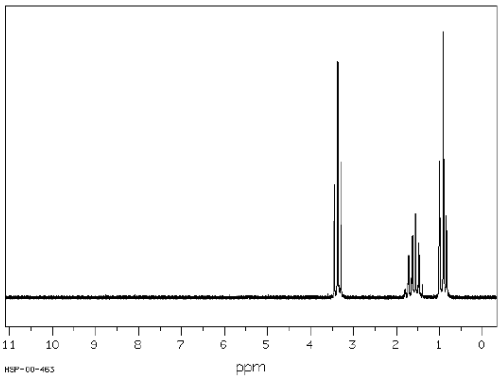
^{1}H NMR Spectroscopy

- Hydrogens on carbon adjacent to the ether show up in the region of 3.4-4.5 ppm.
- Similar peaks in epoxides are shifted to a slightly higher field than other ethers. Hydrogens on carbons in and epoxide appear in the region of 2.5 to 3.5 ppm.
- Hydrogens on carbons adjacent to the sulfur in sulfides and thiols appear in the region of 2.0 to 2.5 ppm.
- The SH hydrogen of a thiol typically appears in the region of 1.3-1.5 ppm.

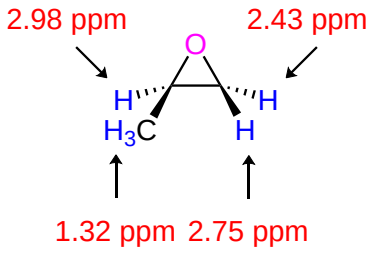
The ^{1}H NMR spectrum of dipropyl ether shows three signals with the triplet at 3.37 ppm assigned to the -CH_2- beside the ether and the other two signals upfield (1.59 and 0.93 ppm). Notice the protons closer to the electron withdrawing oxygen atom are further downfield indicating some deshielding. Protons at (A) and (C) are each coupled to two equivalent (B) protons. So, each of these signals appears as a triplet. The (B) protons in turn are coupled to a set of two and three equivalent protons and appears as a sextet. Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 28 June 2017).



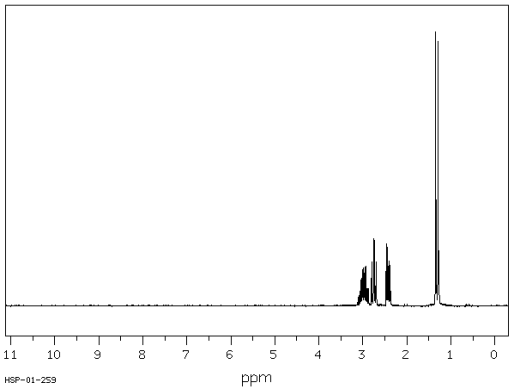
Dipropyl ether



Source: SDBSWeb : http://sdbs.db.aist.go.jp

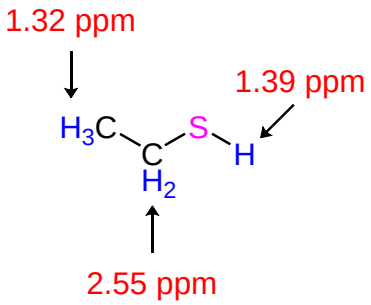


2-Methyloxirane

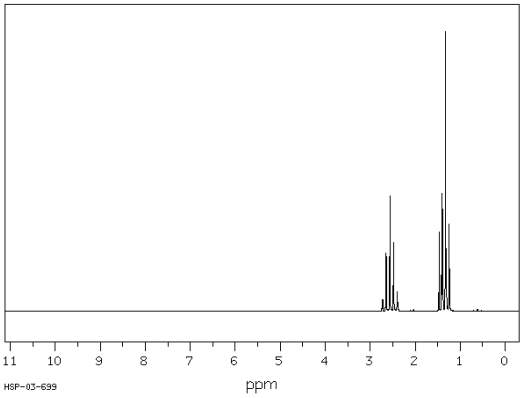


Source: SDBSWeb : http://sdbs.db.aist.go.jp

The methylene protons of this epoxide are diastereotopic and appear as two separate peak. When looking at the 3D structure of 2-methyloxirane it is clear that each methylene hydrogen is distinctly different. Also, hydrogens attached to the carbons in eposxides tend to display complex splitting patterns (Sections **13-7 and 13-8**).



Ethanethiol

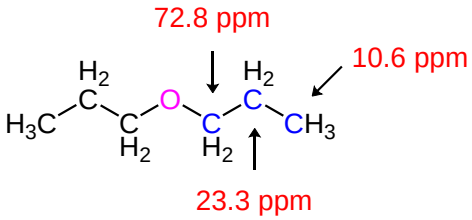


Source: SDBSWeb : http://sdbs.db.aist.go.jp

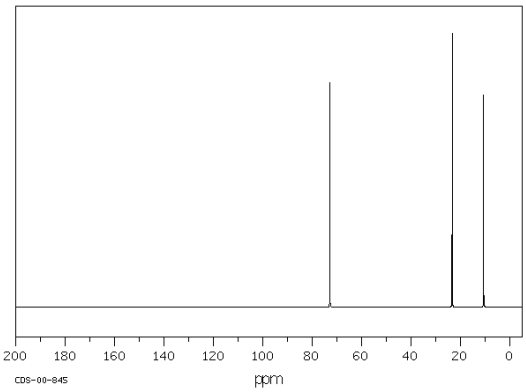
Note that in this ^{1}H NMR spectra the SH proton is actively involved in splitting. The SH proton peak at 1.39 ppm is split into a triplet and the methylene peak at 2.55 ppm is split into a quintet.

^{13}C NMR Spectra

- Carbons adjacent to the ether appear in the region of 50-80 ppm.
- Carbons that are part of the epoxide appear in the region of 40-60 ppm.
- Carbons adjacent to the sulfur in sulfides and thiols appear in the region of 20-40 ppm.



Dipropyl ether



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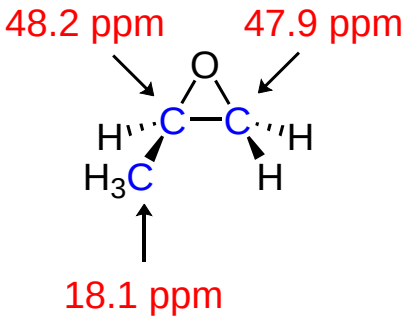
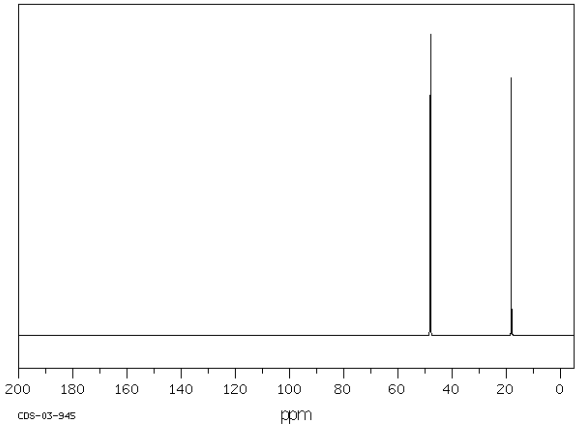


2-Methyloxirane



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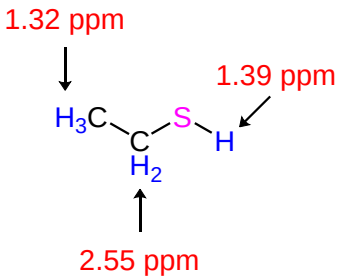
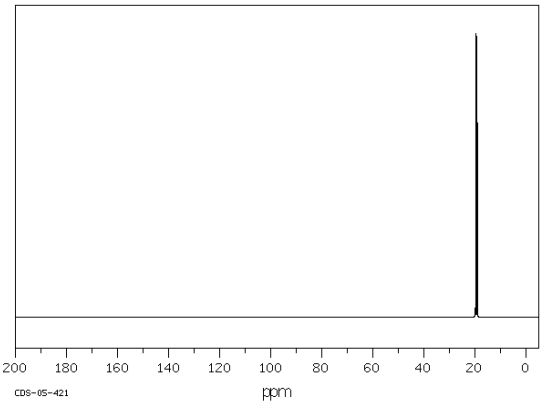


Ethanethiol



Source: SDBSWeb : http://sdbs.db.aist.go.jp

Mass Spectra

Ethers, sulfides, and epoxides all have similar fragmentation patterns in mass spectra with a few subtle variations.

Ethers

- The M^+ is typically weak or absent
- They primarily undergo alpha-cleavage to produce $[H_2C{=}O\text{-}R]^+$
- They can also undergo an inductive cleavage to produce R^+

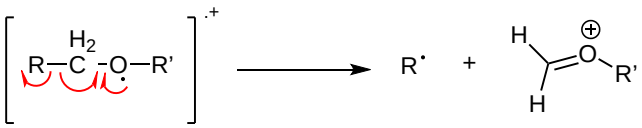
Epoxides

- The M^+ is typically weak or absent
- They primarily undergo alpha-cleavage to produce an alkyl radical

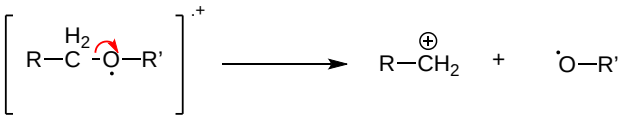
Sulfides

- The M^+ is typically stronger than the corresponding ether
- They primarily undergo alpha-cleavage to produce an alkyl radical
- They can also undergo an inductive cleavage to produce R^+

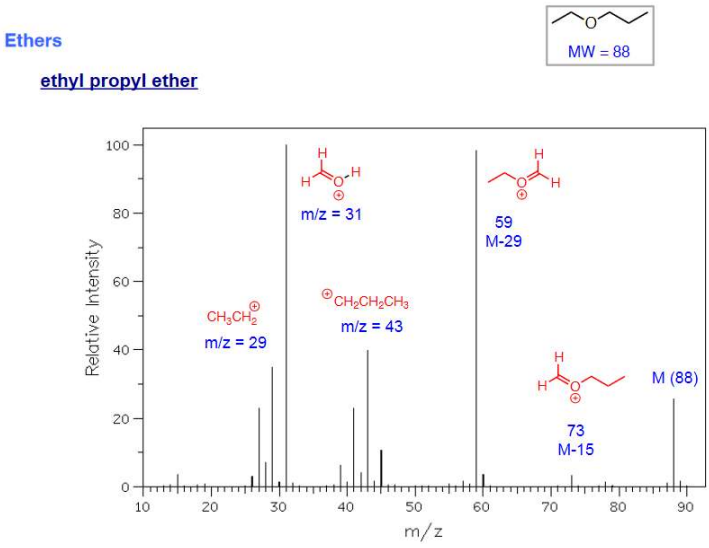
Fragmentation Patterns



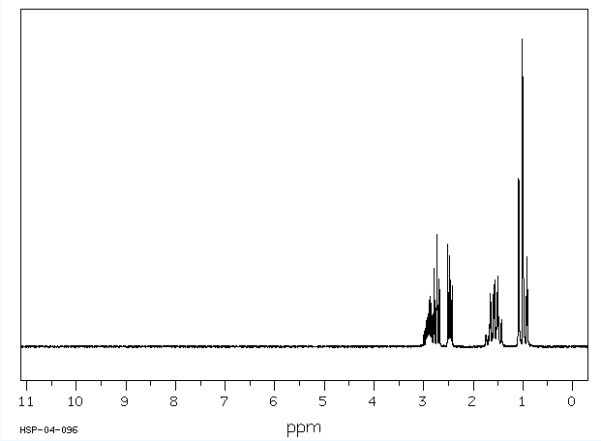
alpha-cleavage



inductive cleavage



Exercise 3.10.1



Source: SDBSWeb : http://sdbs.db.aist.go.jp

Answer

2-Ethyloxirane

Contributors and Attributions

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-

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3.11: Interchapter- A Preview of Carbonyl Chemistry (reference only, most of this covered in CHM 222)

So far, in our survey of the oxygen-containing organic compounds, we have studied the chemistry of ethers and alcohols. Now we turn our attention to a much larger group of compounds—those containing a carbonyl group:

The variety of carbonyl compounds is so wide, and their chemistry so extensive, that we shall need the next five chapters to discuss them thoroughly. One advantage of this course is that we have divided up the discussion of carbonyl compounds so that this large amount of factual material can be studied in small, readily digestible blocks.

The purpose of this chapter is to provide a general outline of what is to follow in the next five chapters: the various types of carbonyl compounds are introduced, the nature of the carbonyl group is explained, and the four most common mechanisms by which carbonyl groups react are described in general terms.

Chapter Objectives

When you have completed this chapter, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. identify the various types of carbonyl compounds.
3. write the mechanism of each of the four general types of reactions discussed in the chapter.
4. define, and use in context, the key terms introduced in this chapter.

Introduction

Objectives

After completing this section, you should be able to give examples of the wide variety of biologically important, pharmaceutical and industrial compounds that contain one or more carbonyl groups.

Key Terms

Make certain that you can define, and use in context, the key term below.

- carbonyl group

Study Notes

A “carbonyl group” consists of an sp^2-hybridized carbon atom that is joined to an oxygen atom by a double bond.

Natural Occurrence of Aldehydes and Ketones

Aldehydes and ketones are widespread in nature and are often combined with other functional groups. Examples of naturally occurring molecules which contain a aldehyde or ketone functional group are shown in the following two figures. The compounds in the figure 1 are found chiefly in plants or microorganisms and those in the figure 2 have animal origins. Many of these molecular structures are chiral.

When chiral compounds are found in nature they are usually enantiomerically pure, although different sources may yield different enantiomers. For example, carvone is found as its levorotatory (R)-enantiomer in spearmint oil, whereas, caraway seeds contain the dextrorotatory (S)-enantiomer. In this case the change of the stereochemistry causes a drastic change in the perceived scent. Aldehydes and ketones are known for their sweet and sometimes pungent odors. The odor from vanilla extract comes from the molecule vanillin. Likewise, benzaldehyde provides a strong scent of almonds and is this author’s favorite chemical smell. Because of their pleasant fragrances aldehyde and ketone containing molecules are often found in perfumes. However, not all of the fragrances are pleasing. In particular, 2-heptanone provides part of the sharp scent from blue cheese and (R)-Muscone is part of the musky smell from the Himalayan musk deer. Lastly, ketones show up in many important hormones such as progesterone (a female

sex hormone) and testosterone (a male sex hormone). Notice how subtle differences in structure can cause drastic changes in biological activity. The ketone functionality also shows up in the anti-inflammatory steroid, Cortisone.

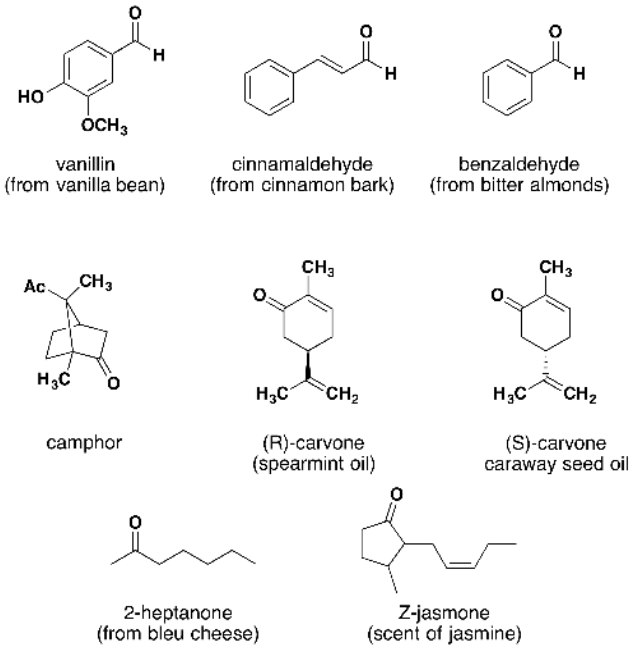


Figure 1. Aldehyde and ketone containing molecules isolated from plant sources.

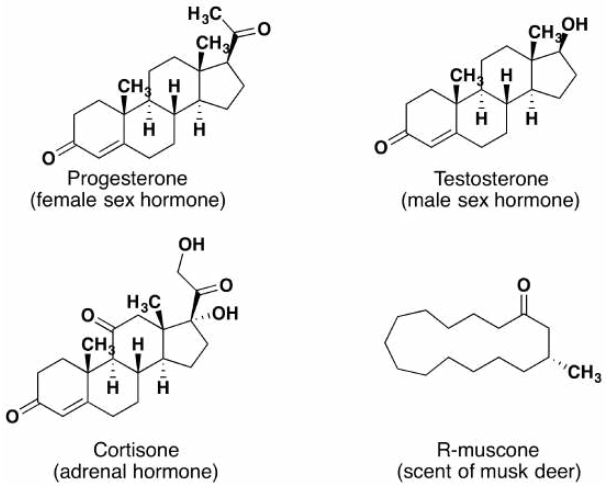


Figure 2. Aldehyde and ketone containing molecules isolated from animal sources.

I Kinds of Carbonyl Compounds

Objectives

After completing this section, you should be able to

1. identify the following types of compounds as containing carbonyl groups: aldehydes, ketones, carboxylic acids, acid chlorides, acid anhydrides, esters, lactones, amides and lactams.
2. identify the important difference between aldehydes and ketones, and the other types of compounds listed under Objective 1, above.

Key Terms

Make certain that you can define, and use in context, the key term below.

- acyl fragment or acyl group

Study Notes

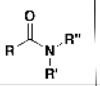
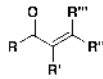
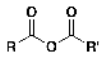
The idea of an “acyl group”

is not really new. Recall that in Chapter 16 we discussed the introduction of acyl groups into benzene rings by means of the Friedel-Crafts acylation reaction.

Note the use of the word “moiety” as an alternative to “group” or “fragment.”

Study the different types of carbonyl compounds listed in the table so that you can immediately recognize to which type a given compound belongs.

Some Carbonyl Compounds

Compound	Aldehyde	Ketone	Formaldehyde	Carboxylic Acid	Ester	Amide	Enone	Acyl Halide	Acid Anhydride
Structure									
General Formula	RCHO	RCOR'	CH_2O	RCOOH	RCOOR'	RCONR'R''	RC(O)C(R')CR''R'''	RCOX	$(RCO)_2O$

One should also add to this list lactones (cyclic esters) and lactams (cyclic amides).

II Nature of the Carbonyl Group

Objectives

After completing this section, you should be able to describe the electronic structure, polarity, and geometry of the carbonyl group.

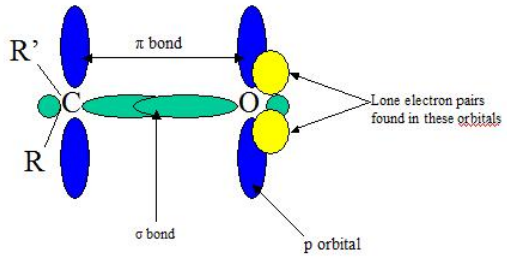
A carbonyl group is a chemically organic functional group composed of a carbon atom double-bonded to an oxygen atom --> [**C=O**] The simplest carbonyl groups are aldehydes and ketones usually attached to another carbon compound. These structures can be found in many aromatic compounds contributing to smell and taste.

Introduction

Before going into anything in depth be sure to understand that the **C=O** entity itself is known as the "Carbonyl group" while the members of this group are called "carbonyl compounds" --> **X**-C=O. The carbon and oxygen are usually sp^2 hybridized and planar.

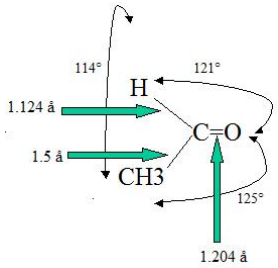
Carbonyl Group Double Bonds

The double bonds in alkenes and double bonds in carbonyl groups are VERY different in terms of reactivity. The C=C is *less* reactive due to C=O electronegativity attributed to the oxygen and its two lone pairs of electrons. One pair of the oxygen lone pairs are located in 2s while the other pair are in 2p orbital where its axis is directed perpendicular to the direction of the pi orbitals. The Carbonyl groups properties are directly tied to its electronic structure as well as geometric positioning. For example, the electronegativity of oxygen also polarizes the pi bond allowing the single bonded substituent connected to become electron withdrawing.



**Note: Both the pi bonds are in phase (top and botom blue ovals)*

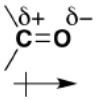
The double bond lengths of a carbonyl group is about 1.2 angstroms and the strength is about 176-179 kcal/mol). It is possible to correlate the length of a carbonyl bond with its polarity; the longer the bond meaing the lower the polarity. For example, the bond length in C=O is larger in acetaldehyde than in formaldehyde (this of course takes into account the inductive effect of CH_3 in the compound).



Polarization

As discussed before, we understand that oxygen has two lone pairs of electrons hanging around. These electrons make the oxygen more electronegative than carbon. The carbon is then partially postive (electrophillic) and the oxygen partially negative (nucleophillic). The polarizability is denoted by a lowercase delta and a positive or negative superscript depending. For example, carbon would have d+ and oxygen delta^(-). The polarization of carbonyl groups also effects the boiling point of aldehydes and ketones to be higher than those of hydrocarbons in the same amount. The larger the carbonyl compound the less soluble it is in water. If the compound exceeds six carbons it then becomes insoluble.

**For more information about carbonyl solubility, look in the "outside links" section*



**Amides are the most stable of the carbonyl couplings due to the high-resonance stabilization between nitrogen-carbon and carbon-oxygen.*

III General Reactions of Carbonyl Compounds

Objectives

After completing this section, you should be able to

1. list the four general reaction mechanisms that dominate the chemistry of carbonyl compounds.
2. discuss nucleophilic addition reactions of aldehydes and ketones (Chapter 19).
    a. write a general mechanism for nucleophilic addition to a carbonyl compound.
    b. write a detailed mechanism for the addition of a given nucleophile (e.g., a Grignard reagent) to an aldehyde or ketone.
3. discuss nucleophilic acyl substitution reactions of carboxylic acid derivatives (Chapter 21).
    a. write a general mechanism to illustrate nucleophilic acyl substitution reactions.
    b. write a detailed mechanism for the reaction of a given carbonyl-containing compound with a given nucleophile through a nucleophilic acyl substitution.

4. discuss alpha substitution reactions (Chapter 22).
    a. write a general mechanism to illustrate alpha-substitution of a carbonyl compound through the formation of an enol or enolate anion.
    b. explain the stability and ease of formation of enolate anions.
    c. write the detailed mechanism for the formation of an alpha-substituted carbonyl compound from the overall reaction of a carbonyl compound with a primary alkyl halide.
5. discuss carbonyl condensation reactions (Chapter 23).
    a. write a general mechanism to illustrate the condensation reaction that can occur between two molecules of a carbonyl compound; for example, the reaction of two molecules of acetaldehyde to form one molecule of aldol.

Key Terms

Note: All of these terms are defined in the "Study Notes," below.

- aldol reaction
- alkylation
- alpha substitution
- carbonyl condensation
- enol
- enolate anion
- nucleophilic acyl substitution
- nucleophilic addition reaction

Study Notes

A "nucleophilic addition reaction" (of a carbonyl compound) involves the initial attack of a nucleophile on the slightly positive carbonyl-carbon atom to form a tetrahedral intermediate.

In a "nucleophilic acyl substitution reaction," a nucleophile attacks the carbonyl carbon of a carboxylic acid derivative

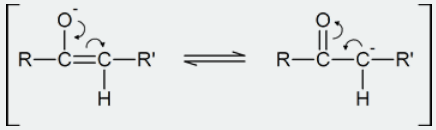
and initially produces a tetrahedral intermediate. The intermediate then reacts by expelling the leaving group, X, thereby forming a new carboxylic acid derivative.

In an "alpha substitution reaction" of a carbonyl compound, one of the hydrogen atoms attached to a carbon atom adjacent to the carbonyl group is removed and replaced by some other group.

Alpha substitution reactions of carbonyl compounds involve the "enol" form of the compound. Keto-enol tautomerism was briefly introduced in Section 9.4. Review this section if necessary.

keto form enol form

As you can see from the above diagram, the enol form has a hydroxyl group attached to one of the sp^2 hybridized carbon atoms of a carbon-carbon double bond. Removal of the proton from the hydroxyl group produces a resonance-stabilized "enolate anion":



A “carbonyl condensation reaction” is one in which two carbonyl- containing molecules condense together (i.e., join together), often with the elimination of water. The reaction involves the formation of an enolate anion from one carbonyl-containing molecule, followed by the subsequent nucleophilic attack by this enolate anion on the carbonyl carbon atom of the second molecule.

Nucleophilic Addition to a Carbonyl Group

C=O is prone to additions and nucleophillic attack because or carbon's positive charge and oxygen's negative charge. The resonance of the carbon partial positive charge allows the negative charge on the nucleophile to attack the Carbonyl group and become a part of the structure and a positive charge (usually a proton hydrogen) attacks the oxygen. Just a reminder, the nucleophile is a good acid therefore "likes protons" so it will attack the side with a positive charge.

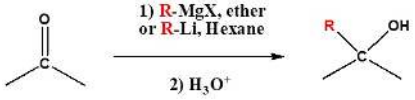
**Remember: due to the electronegative nature of oxygen the carbon is partially positive and oxygen is partially negative*

1 2 3

1. The Nucleophile (Nu) attacks the positively charged carbon and pushes one of the double bond electrons onto oxygen to give it a negative charge.
2. The Nucleophile is now a part of the carbon structure with a negatively charged oxygen and a Na^+ "floating" around.
3. The negatively charged oxygen attacks the proton (H^+) to give the resulting product above.

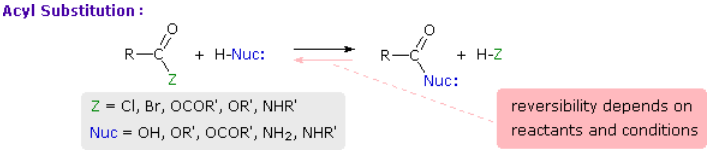
An Organometallic Example

Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. The basic reaction involves the nucleophilic attack of the carbanionic carbon in the organometallic reagent with the electrophilic carbon in the carbonyl to form alcohols.

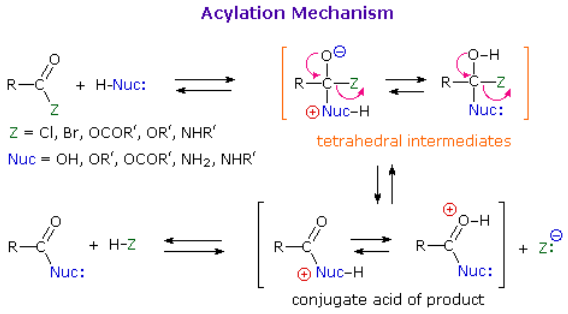


Nucleophilic Acyl Substitution

This is probably the single most important reaction of carboxylic acid derivatives. The overall transformation is defined by the following equation, and may be classified either as **nucleophilic substitution at an acyl group** or as **acylation of a nucleophile**. For certain nucleophilic reagents the reaction may assume other names as well. If Nuc-H is water the reaction is often called **hydrolysis**, if Nuc–H is an alcohol the reaction is called **alcoholysis**, and for ammonia and amines it is called **aminolysis**.



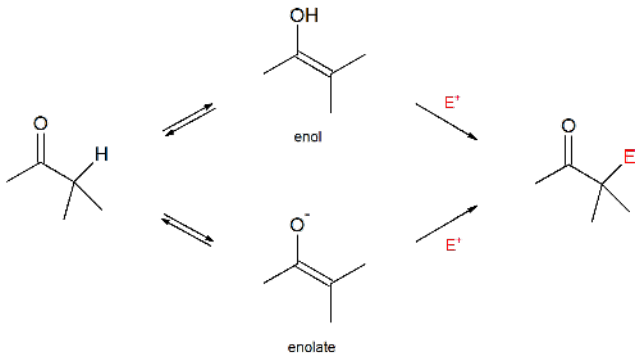
As illustrated in the following diagram, acylation reactions generally take place by an **addition-elimination process** in which a nucleophilic reactant bonds to the electrophilic carbonyl carbon atom to create a tetrahedral intermediate. This tetrahedral intermediate then undergoes an elimination to yield the products. In this two-stage mechanism bond formation occurs before bond cleavage, and the carbonyl carbon atom undergoes a hybridization change from sp^2 to sp^3 and back again. The facility with which nucleophilic reagents add to a carbonyl group was noted earlier for aldehydes and ketones.



Mechanism Toggle

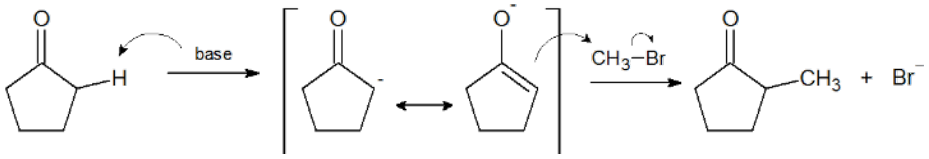
Alpha-Substitution Reactions

Now we will investigate reactions which occur a the carbon alpha to the carbonyl groups. These reactions involve two new nucleophilic species the enol and the enolate.



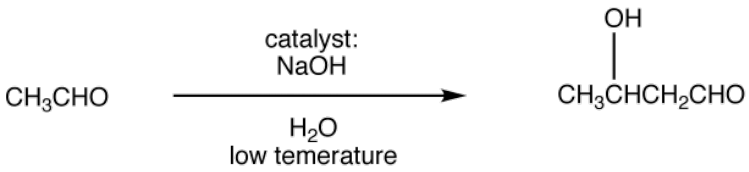
Note! The electrophile replaces the hydrogen on the alpha carbon.

The following is a specific example of this type of reaction. Here we methylate the carbon alpha to the carbonyl group through an enolate intermediate. The hydrogen on the alpha carbon is acidic because of the presence of the C=O group and is therefore preferentially abstracted by the base.



Carbonyl Condensation Reactions

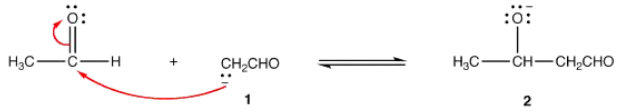
Enolizable aldehydes and enolizable ketones, in the presence of an acid or base catalyst usually in aqueous medium at low temperature, undergo a reaction, giving an aldol as the major product. This reaction is known as aldol reaction. The base-catalyzed aldol reaction, in which the catalyst is usually the hydroxide ion, is more common. Careful control of reaction temperature is critical because high temperatures promote aldol condensation. The optimum temperature depends on the nature of the aldehyde or ketone. Typically, heating the reaction mixture results in aldol condensation. For example:



Mechanism:

Step 1: The hydroxide ion deprotanates the aldehyde reversibly.

Step 2: Enolate ion 1 adds to the unreacted aldehyde.



Step 3: Alkoxide ion 2 is protonated by water.

Since all three steps are reversible, the overall reaction is reversible and its equilibrium constant depends on the nature of the aldehyde or ketone. The reactions of aldehydes in which the α-carbon is a secondary carbon usually have large equilibrium constants; those of other aldehydes and ketones have small equilibrium constants. These observations suggest that the equilibrium constant of aldol reaction is sensitive to steric hindrance at the carbonyl carbon in the aldehyde or ketone.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

-
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Sharleen Agvateesiri
- Gamini Gunawardena from the OChemPal site (Utah Valley University)
-

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3.S: Ethers and Epoxides; Thiols and Sulfides (Summary)

Concepts & Vocabulary

3.0 Introduction

- Ethers are molecules containing oxygen which is bonded to two carbon groups.
- Thiols are sulfur analogues of alcohols with an SH group instead of OH.
- Sulfides are sulfur analogues of ethers with sulfur bonded to two carbon groups instead of oxygen.

3.1 Names and Properties of Ethers

- Ether groups are named as alkoxy groups.
- Ethers do not have intramolecular hydrogen bonding (unlike alcohols), therefore ethers have significantly reduced intermolecular forces causing boiling points that are much lower than similar sized alcohols.

3.2 Preparing Ethers

- Alkoxymercuration can be used to prepare an ether from an alkene.

3.3 Reactions of Ethers: Acidic Cleavage

- The carbon-oxygen bonds of ethers can be cleaved with strong acids through either nucleophilic substitution or elimination reactions.

3.4 Reactions of Ethers: Claisen Rearrangement

- The Claisen rearrangement is a [3, 3] sigmatropic rearrangement reaction that converts aryl or enol ethers into carbonyl compounds (though the aromatic version rearranges into a phenol to re-establish aromaticity.

3.5 Cyclic Ethers: Epoxides

- Epoxides, also called oxiranes, have a three-membered ring structure with one oxygen and two carbon atoms.
- Epoxides can be formed from alkenes by reaction with peroxy acids (MCPBA for example).
- Epoxides can be formed from halohydrin molecules by reaction with a base, which causes an intramolecular Williamson ether synthesis.

3.6 Reactions of Epoxides: Ring Opening

- When epoxides are ring opened under basic conditions, they follow S_N2 mechanism leading to the nucleophile adding to the less substituted side of the epoxide.
- When epoxides are ring opened under acidic conditions, they follow S_N1 mechanism leading to the nucleophile adding to the more substituted side of the epoxide.
- When epoxides are ring opened in aqueous reactions, the result is an anti-diol.
- Halo acids can be added to epoxides to form anti-halohydrins.

3.7 Crown Ethers

- Crown ethers are cyclic ethers containing several oxygen atoms.
- Crown ethers are named by the number of total atoms in the ring, followed by the word crown and finally the number of oxygen atoms (18-crown-6 for example).

3.8 Thiols and Sulfides

- Thiols can be prepared from alkyl halides through reaction with hydrosulfide ion (SH^-) or through a more complicated series of reactions including thiourea.
- Thiols can be oxidized with mild oxidizing agents to form disulfides.
- Disulfide bridges link cysteine residues in protein structures.
- Sulfides are sulfur analogues of ether, though are much better nucleophiles with sulfur in place of oxygen.

3.9 Spectroscopy of Ethers

- Ethers show standard C-H stretches and bends in IR along with a strong C-O stretch around 1000 cm^{-1}.
- In ^1H NMR, hydrogens on carbons adjacent to the oxygen typically appear between 3.4-4.5 ppm.

- Hydrogens on carbons of an epoxide ring typically appear between 2.5-3.5 ppm in ^{1}H NMR.

3.10 Interchapter: A Preview of Carbonyl Chemistry

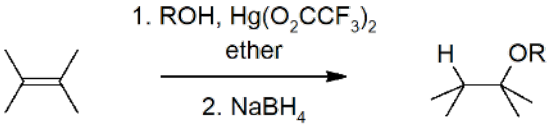
- Carbonyl groups are one of the most important features in organic chemistry and consist of a sp^2 carbon double-bonded to oxygen.
- Carbonyl groups are present in ~10 different functional groups.
- Carbonyl groups are polarized with a partial positive charge on carbon and partial negative charge on oxygen. This makes the carbon atom an electrophile, while the oxygen can act as a nucleophile.
- Carbonyl groups can react through several mechanisms including nucleophilic addition and nucleophilic acyl substitution, alpha substitution and condensation.

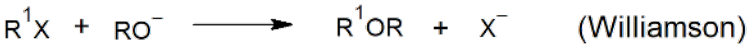
Skills to Master

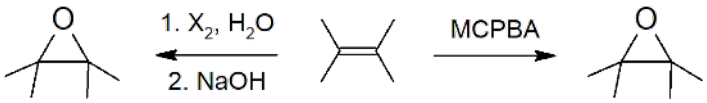
- Skill 3.2 Write reaction equations for preparation of ethers.
- Skill 3.3 Write mechanisms for reactions of ethers with strong halogen acids.
- Skill 3.5 Draw mechanisms for ring-opening epoxides under acidic and basic conditions.

Summary of Reactions

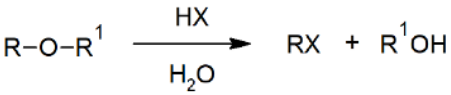
Ether and Epoxide Preparation







Ether Reactions



Epoxide Reactions

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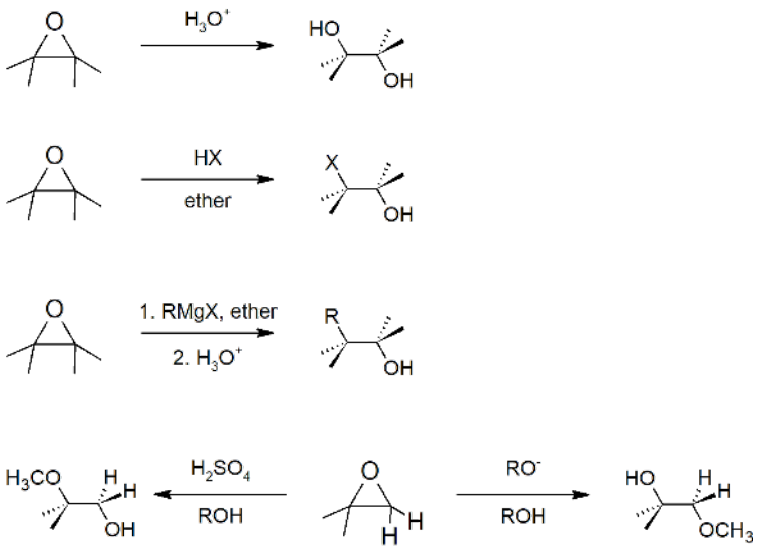

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CHAPTER OVERVIEW

4: Oxidation Reactions

4.1: Introduction
4.2: Oxidation of Alcohols (review from CHM 222)
4.3: Oxidation of Alkenes- Epoxidation and Dihydroxylation (review from CHM 222)
4.4: Oxidation of Alkenes- Oxidative Cleavage Reactions
4.5: Oxidation of Alkynes- Oxidative Cleavage Reactions
4.6: Oxidation of Aldehydes and Ketones- The Baeyer-Villager Oxidation

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4.1: Introduction

Chapter Videos

This video focuses on the mechanisms for the oxidation of alcohols to carbonyls.

This video focuses on ozonolysis and the Baeyer-Villager oxidation.

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4.2: Oxidation of Alcohols (review from CHM 222)

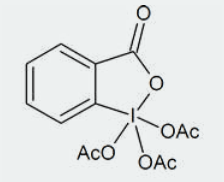
Objectives

After completing this section, you should be able to

1. write an equation to represent the oxidation of an alcohol.
2. identify the reagents that may be used to oxidize a given alcohol.
3. identify the specific reagent that is used to oxidize primary alcohols to aldehydes rather than to carboxylic acids.
4. identify the product formed from the oxidation of a given alcohol with a specified oxidizing agent.
5. identify the alcohol needed to prepare a given aldehyde, ketone or carboxylic acid by simple oxidation.
6. write a mechanism for the oxidation of an alcohol using a chromium(VI) reagent.

Study Notes

The reading mentions that pyridinium chlorochromate (PCC) is a milder version of chromic acid that is suitable for converting a primary alcohol into an aldehyde without oxidizing it all the way to a carboxylic acid. This reagent is being replaced in laboratories by **Dess-Martin periodinane (DMP)**, which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous reaction conditions. DMP is named after Daniel Dess and James Martin, who developed it in 1983.



Dess–Martin periodinane (DMP)

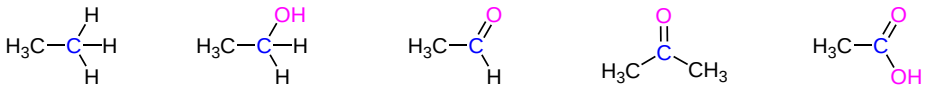
Oxidation States of Carbon

The general idea of oxidation and reduction reactions learned in general chemistry is that when a compound or atom is oxidized it loses electrons, and when it is reduced it gains electrons. In order, to keep track of electrons in organic molecules a oxidation state formalism is used. Oxidation states to not represent the actual charge but it will allow the number of electrons being gained or lost by a particular atom during a reaction.

To calculate the oxidation state of a carbon atom the following rules are used:

1. A C-C bond does not affect the oxidation state of a carbon. So a carbon attached to 4 carbons has an oxidation state of zero.
2. Every C-H bond will **decrease** the oxidation state of the carbon by 1.
3. Each C-X bond will **increase** the oxidation state of the carbon by 1. Where X is an electronegative, such as nitrogen, oxygen, sulfur, or a halogen.

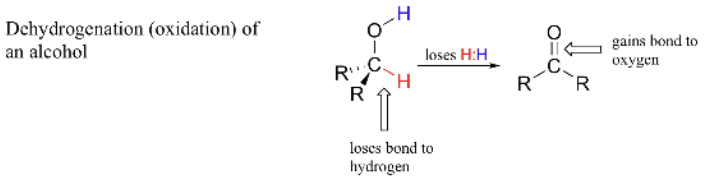
When looking at the oxidation states of carbon in the common functional groups shown below it can be said that carbon loses electron density as it becomes more oxidized.



	Ethane	Ethanol	Ethanal	Propanone	Ethanoic Acid
Oxidation State:	**3(-1) + O = -3**	**2(-1) +1 +0 = -1**	**2(+1) -1 +0 = +1**	**2(+1) + 2(0) = +2**	**3(+1) +0 = +3**

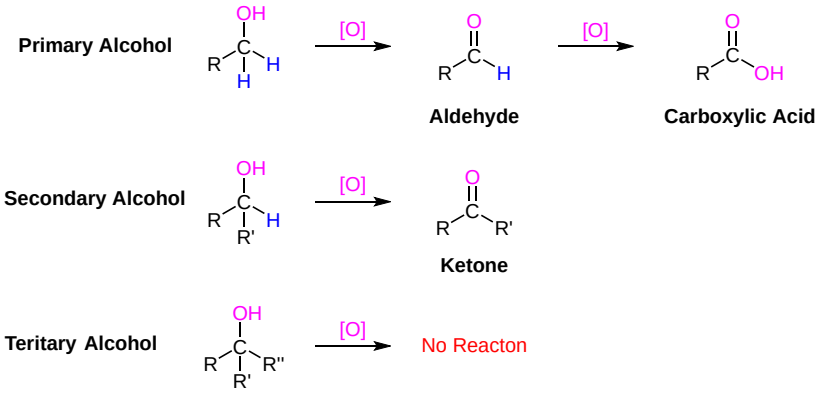
Most Reduced ⟶ **Most Oxidized**

For this section, a simpler way to consider this process is to say that when a carbon atom in an organic compound loses a bond to hydrogen and gains a new bond to a oxygen it has been oxidized. A very commonly example is the oxidation of an alcohol to a ketone or aldehyde. Notice that during this process the carbon atom loses a hydrogen and gains a bond to oxygen.



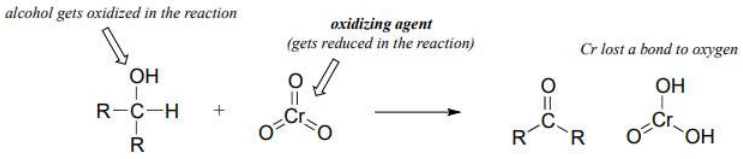
Oxidation of Alcohols

On of the most important reactions of alcohols is their oxidation to carbonyl containing compounds such as aldehyde, ketones, and carboxylic acid. Typically primary alcohols, depending on the reagent used, produce aldehydes or carboxylic acids during oxidations. Secondary alcohols are oxidized to produce ketones, and tertiary alcohols are usually not affected by oxidations.



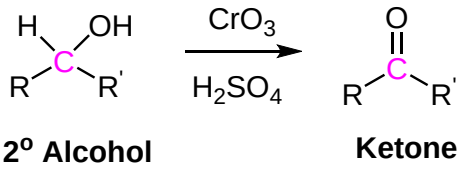
Alcohol Oxidizing Agents

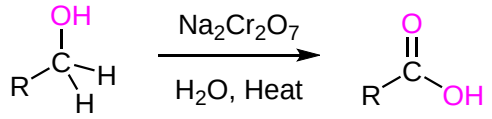
Oxidation and reduction reactions always occurs in tandem: when one compound is oxidized, another compound must be reduced. For an alcohol to be oxidized in a reaction there must also be a compound being reduced. This reduced compound is also called the oxidizing agent. For example, chromium trioxide (CrO_3) is a common oxidizing agent used by organic chemists to oxidize a secondary alcohol to a ketone. During this reaction CrO_3 is being reduced to form H_2CrO_3. A common method for oxidizing secondary alcohols to ketones uses **chromic acid (H_2CrO_4)** as the oxidizing agent. Chromic acid, also known as **Jones reagent**, is prepared by adding chromium trioxide (CrO_3) to aqueous sulfuric acid.



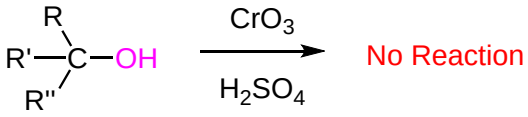
There is a wide selection of oxidizing agents available for use in the organic chemistry laboratory, each with its own particular properties and uses. In addition to CrO_3, other commonly used oxidizing agents include potassium permanganate ($KMnO_4$) and sodium dichromate ($Na_2Cr_2O_7$). Any of these reagents can be used to oxidize secondary alcohols to form ketones and primary alcohols to form carboxylic acids. Tertiary alcohols remain unreactive to oxidation.

General Reactions



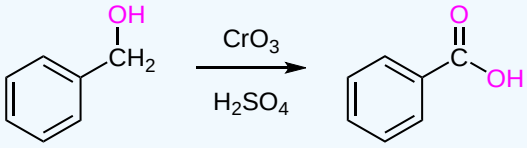


1° Alcohol **Carboylic Acid**

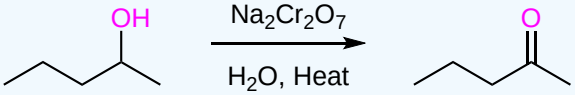


3° Alcohol

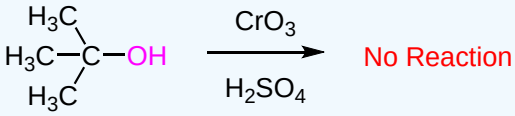
Example 4.2.1



Oxidation of Benzyl Alcohol to Benzoic Acid

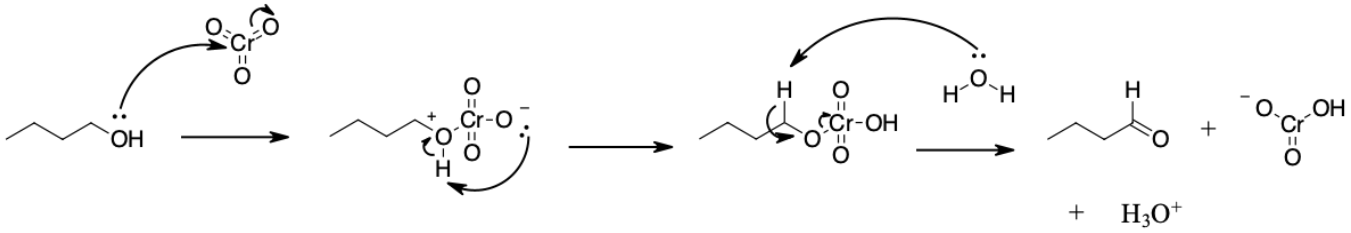


Oxidation of 2-Pentanol to 2-Pentanone



Mechanism

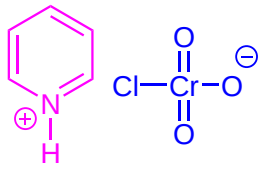
During this reaction mechanism the chromium atom is being reduced from Cr(VI) in the CrO_3 starting material to Cr(IV) in the H_2CrO_3 product. Also, notice the the C=O bond is formed in the third step of the mechanism through an E2 reaction. Although E2 reaction are generally know for forming C=C double bonds thought the elimination of a halide leaving group, in this case they are use to generate a C=O through the elimination of a reduced metal as a leaving group.



Examples

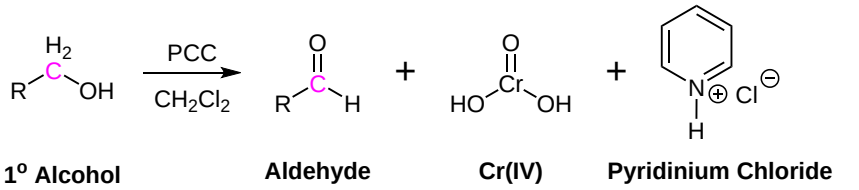
Oxidation of 1° Alcohols with PCC to form Aldehydes

Pyridinium chlorochromate (PCC) is a milder version of chromic acid. PCC oxidizes 1° alcohols one rung up the oxidation ladder, turning primary alcohols into aldehydes and secondary alcohols into ketones. Unlike chromic acid, PCC will not oxidize aldehydes to carboxylic acids. Cr(IV) as well as pyridinium chloride are produced as byproducts of this reaction.

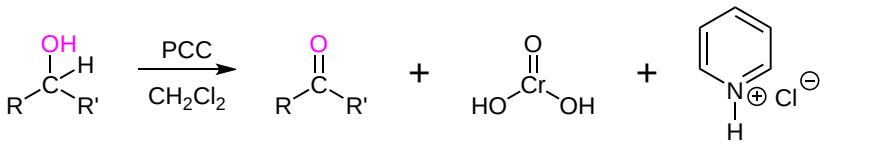


Pyridinium chlorochromate (PCC)

General Reactions

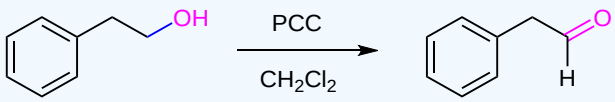


1° Alcohol **Aldehyde** **Cr(IV)** **Pyridinium Chloride**

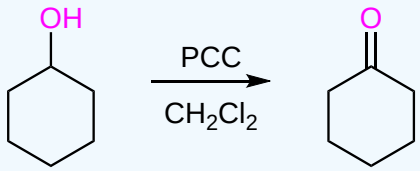


2° Alcohol **Ketone** **Cr(IV)** **Pyridinium Chloride**

? Example 4.2.2



Oxidation of 2-Phenylethanol to Phenylacetaldehyde

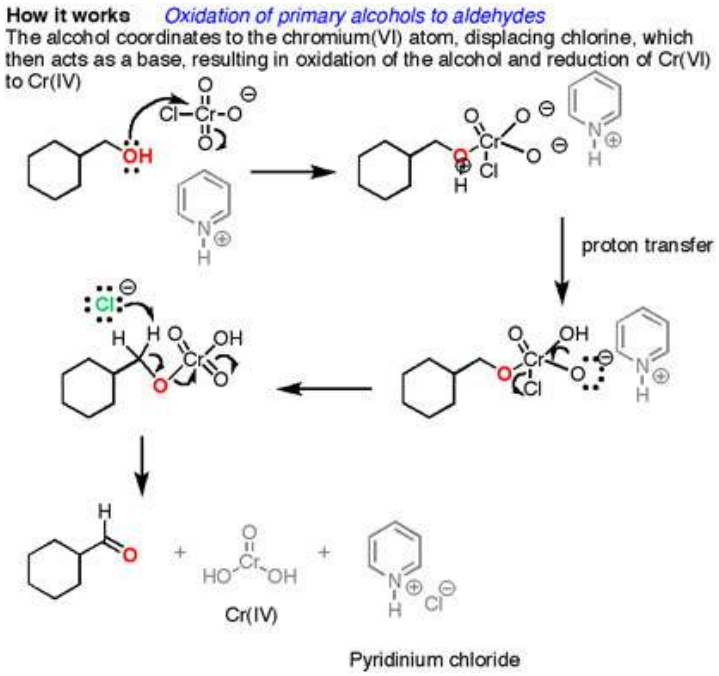


Oxidation of Cyclohexanol to Cyclohexanone

Mechanism

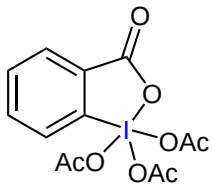
The first step of the mechanism is attack of alcohol oxygen on the chromium atom to form the Cr-O bond. Secondly, a proton on the (now positive) OH is transferred to one of the oxygens of the chromium, possibly through the intermediacy of the pyridinium salt. A chloride ion is then displaced, in a reaction reminiscent of a 1,2 elimination reaction, to form what is known as a chromate ester.

The C-O double bond is formed when a base removes the proton on the carbon adjacent to the oxygen. It is also possible for pyridine to be used as the base here, although only very low concentrations of the deprotonated form will be present under these acidic conditions. In an E2 reaction, the electrons from the C-H bond move to form the C=O bond, and in the process break the O-Cr bond. During this step Cr(VI) gains two electrons to become Cr(IV) (drawn here as $O{=}Cr(OH)_2$).



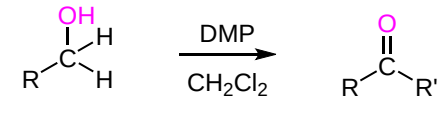
Oxidation of 1° Alcohols with Dess-Martin Periodinane (DMP) to form Aldehydes

PCC is being replaced in laboratories by **Dess-Martin periodinane (DMP)** in dichloromethane solvent, which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous conditions (lower reaction temperature and a nonacidic medium). DMP is named after Daniel Dess and James Martin, who developed it in 1983.

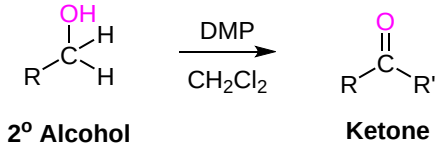


Dess-Martin periodinane (DMP)

General Reactions

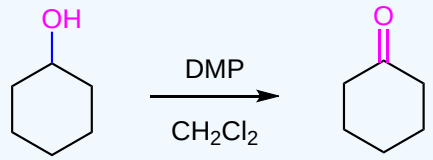


2° Alcohol **Ketone**

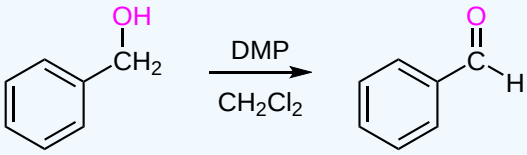


2° Alcohol **Ketone**

✔ Example 4.2.3



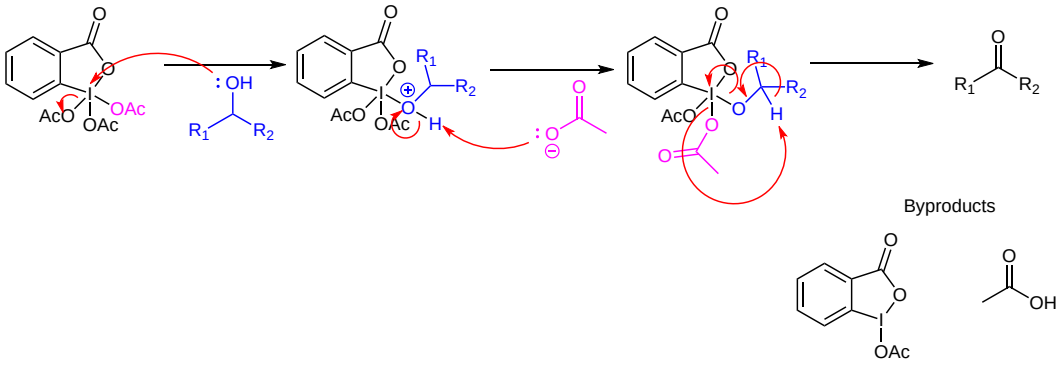
Oxidation of Cyclohexanol to Cyclohexanone



Oxidation of Benzyl Alcohol to Benzaldehyde

Mechanism

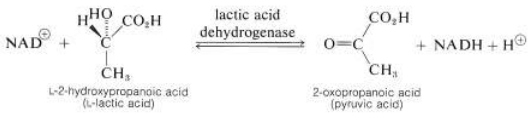
The first step of the mechanism involves the reactant alcohol attacking the Iodine (V) atom and eliminating an acetate (Ac^-) leaving group to form a periodinate intermediate. The next step is a concerted E2-like reaction where a hydrogen is removed from the alcohol, the C=O bond is formed, an acetate group is eliminated from the iodine atom, and the iodine (V) atom gains two electrons to be reduced to iodine (III).

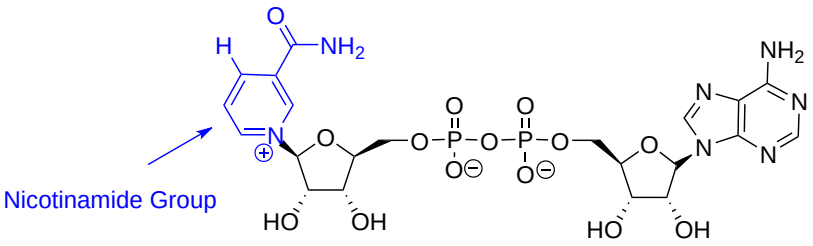


Biological Alcohol Oxidations

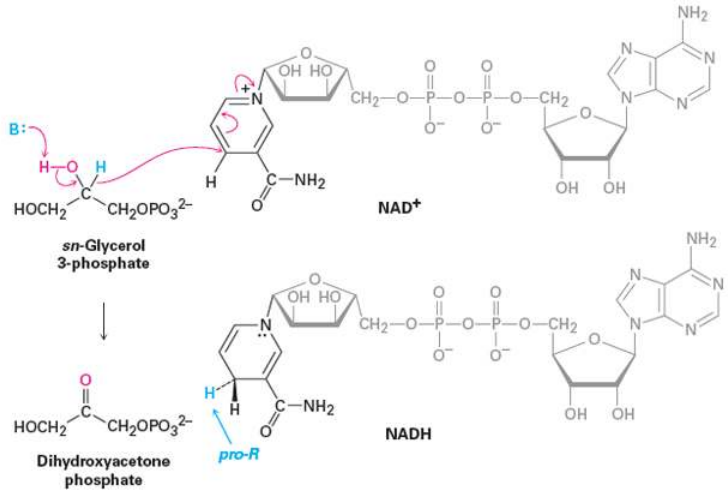
There are many biological oxidations that convert a primary or secondary alcohol to a carbonyl compound. These reactions cannot possibly involve the extreme pH conditions and vigorous inorganic oxidants used in typical laboratory oxidations. Rather, they occur at nearly neutral pH values and they all 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^+) is an example. This very complex molecule functions to accept hydride ($H:^-$) or the equivalent ($H^+ + 2e^-$) from the α carbon of an alcohol. The reduced form of NAD^+ is abbreviated as NADH and the $H:^-$ is added at the 4-position of the pyridine ring. It is important to note that the hydride adds exclusively to the *Re* face of the pyridine ring giving NADH a *pro*-R stereochemistry.

An example of the remarkable specificity of this kind of redox system. One of the last steps in the metabolic breakdown of glucose 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. During this reaction a base removes the alcohol hydrogen. The resulting alkoxide ion then forms the C=O bond causing a hydride ion to transfer to NAD^+.



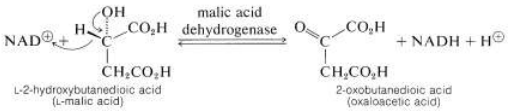


The Structure of NAD+



From an outside source. Convert mechanism to use lactic acid.

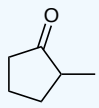
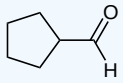
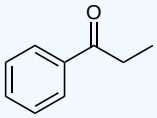
Another example is provided by one of the steps in metabolism by way of the Krebs citric acid cycle, is the oxidation of L-2-hydroxy-butanedioic (L-malic) acid to 2-oxobutanedioic (oxaloacetic) acid. This enzyme functions only with L-malic acid:



Exercises

Exercise 4.2.1

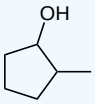
Draw the alcohol that the following ketones/aldehydes would have resulted from if oxidized. What oxidant could be used?

a)  b)  c) 

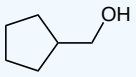
Answer

1)

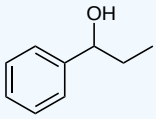
a) Any oxidant capable of oxidizing an alcohol to a ketone would work, such as the Jones reagent (CrO_3, H_2SO_4, H_2O), PCC, or Dess-Martin periodinane.



b) Since this is a primary alcohol, there are some precautions necessary to avoid formation of the carboxyllic acid. Milder oxidants such as the Dess-Martin periodinane, and also PCC (there is no water to form the carboxyllic acid) would work



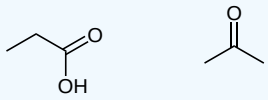
c) Any oxidant capable of oxidizing an alcohol to a ketone would work, such as the Jones reagent (CrO_3, H_2SO_4, H_2O), PCC, or Dess-Martin periodinane.



Exercise 4.2.2

Show the products of the oxidation of 1-propanol and 2-propanol with chromic acid in aqueous solution.

Answer



Exercise 4.2.3

Show the products of the oxidation of 1-propanol and 2-propanol with Dess-Martin periodinane.

Answer

4.2: Oxidation of Alcohols (review from CHM 222) is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

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4.3: Oxidation of Alkenes- Epoxidation and Dihydroxylation (review from CHM 222)

Objectives

After completing this section, you should be able to

1. write the equation for the epoxidation of an alkene using meta-chloroperoxybenzoic acid.
2. identify the alkene, reagents, or both, that must be used to prepare a given epoxide.
3. write the equation for the hydroxylation of an alkene using osmium tetroxide, and draw the structure of the cyclic intermediate.
4. draw the structure of the diol formed from the reaction of a given alkene with osmium tetroxide.
5. identify the alkene, the reagents, or both, that must be used to prepare a given 1,2-diol.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- diol
- glycol
- hydroxylation

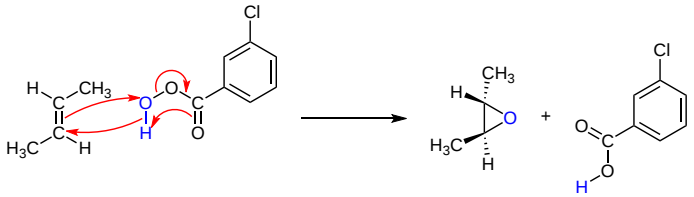
The previous section discussed the reduction of a double bond, so adding hydrogen to the the double bond. This section will discuss oxidation. In organic chemistry, this is a reaction that where the carbon atom loses electron density, which happens when new bond to a more electronegative atom occurs or when a double bond is broken between a carbon and a less electronegative atom. A simplified to say this is in organic chemistry a reduction is more bonds to hydrogen and oxidation is more bonds to oxygen often.

Oxacyclopropane Synthesis by Peroxycarboxylic Acid

One way to oxidized a double bond is to produce an oxacyclopropane ring. Oxacyclopropane rings, also called epoxide rings, are useful reagents that may be opened by further reaction to form anti vicinal diols. One way to synthesize oxacyclopropane rings is through the reaction of an alkene with peroxycarboxylic acid. Oxacyclopropane synthesis by peroxycarboxylic acid requires an alkene and a peroxycarboxylic acid as well as an appropriate solvent. The peroxycarboxylic acid has the unique property of having an electropositive oxygen atom on the COOH group. The reaction is initiated by the electrophilic oxygen atom reacting with the nucleophilic carbon-carbon double bond. The mechanism involves a concerted reaction with a four-part, circular transition state. The result is that the originally electropositive oxygen atom ends up in the oxacyclopropane ring and the COOH group becomes COH.

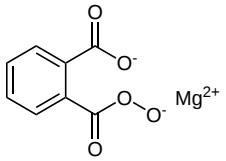
Mechanism

Peroxycarboxylic acids are generally unstable. An exception is meta-chloroperoxybenzoic acid, shown in the mechanism above. Often abbreviated MCPBA, it is a stable crystalline solid. Consequently, MCPBA is popular for laboratory use. However, MCPBA can be explosive under some conditions.



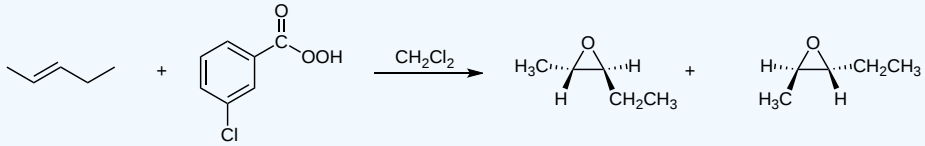
Peroxycarboxylic acids are sometimes replaced in industrial applications by monoperphthalic acid, or the monoperoxyphthalate ion bound to magnesium, which gives magnesium monoperoxyphthalate (MMPP). In either case, a nonaqueous solvent such as chloroform, ether, acetone, or dioxane is used. This is because in an aqueous medium with any acid or base catalyst present, the epoxide ring is hydrolyzed to form a vicinal diol, a molecule with two OH groups on neighboring carbons. (For more explanation of how this reaction leads to vicinal diols, see below.) However, in a nonaqueous solvent, the hydrolysis is prevented and the

epoxide ring can be isolated as the product. Reaction yields from this reaction are usually about 75%. The reaction rate is affected by the nature of the alkene, with more nucleophilic double bonds resulting in faster reactions.



magnesium monoperoxyphthalate, MMPP

Example 8.7.1



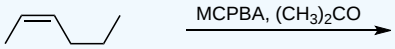
trans-2-pentene MCPBA mixture of enantiomers of *trans*-3-ethyl-2-methyloxacyclopropane

Since the transfer of oxygen is to the same side of the double bond, the resulting oxacyclopropane ring will have the same stereochemistry as the starting alkene. A good way to think of this is that the alkene is rotated so that some constituents are coming forward and some are behind. Then, the oxygen is inserted on top. (See the product of the above reaction.) One way the epoxide ring can be opened is by an acid catalyzed oxidation-hydrolysis. Oxidation-hydrolysis gives a vicinal diol, a molecule with OH groups on neighboring carbons. For this reaction, the dihydroxylation is *anti* since, due to steric hindrance, the ring is attacked from the side opposite the existing oxygen atom. Thus, if the starting alkene is trans, the resulting vicinal diol will have one *(S)* and one (*R*) stereocenter. But, if the starting alkene is cis, the resulting vicinal diol will have a racemic mixture of (*S*,*S*) and (*R*,*R*) enantiomers.

Epoxidation exercises

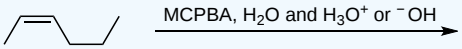
1. Predict the product of the reaction of cis-2-hexene with MCPBA (meta-chloroperoxybenzoic acid)

a) in acetone solvent.



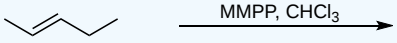
cis-2-hexene

b) in an aqueous medium with acid or base catalyst present.



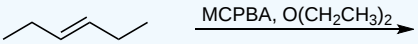
cis-2-hexene

2. Predict the product of the reaction of trans-2-pentene with magnesium monoperoxyphthalate (MMPP) in a chloroform solvent.



trans-2-pentene

3. Predict the product of the reaction of trans-3-hexene with MCPBA in ether solvent.

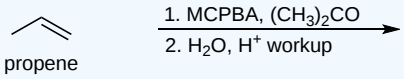


trans-3-hexene

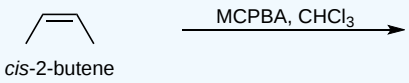
4. Predict the reaction of propene with MCPBA.

a) in acetone solvent

b) after aqueous work-up.

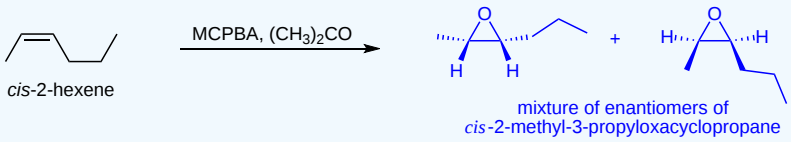


5. Predict the reaction of cis-2-butene in chloroform solvent.

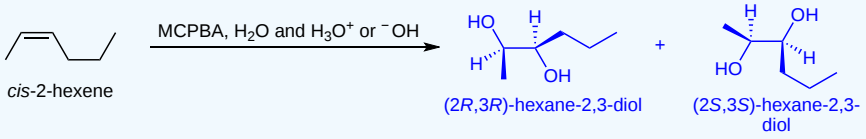


Answers

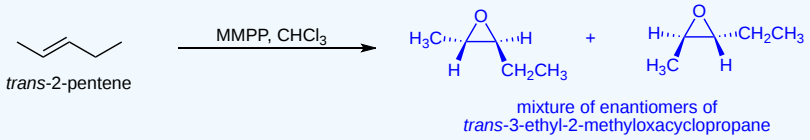
1. a) *Cis*-2-methyl-3-propyloxacyclopropane



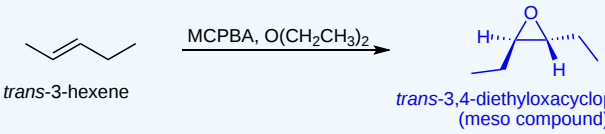
b) Racemic (2*R*,3*R*)-2,3-hexanediol and (2*S*,3*S*)-2,3-hexanediol



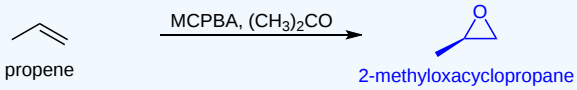
2. *Trans*-3-ethyl-2-methyloxacyclopropane.



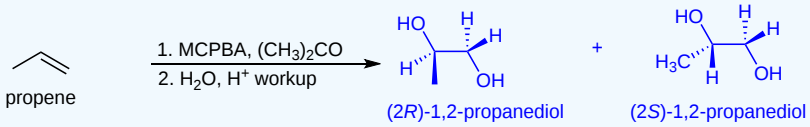
3. *Trans*-3,4-diethyloxacyclopropane.



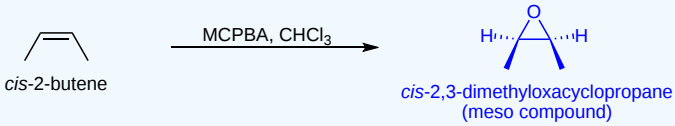
4. a) 2-methyl-oxacyclopropane



b) Racemic (2*S*)-1,2-propandiol and (2*R*)-1,2-propanediol

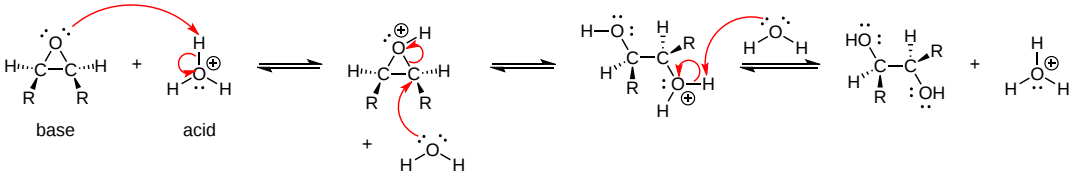


5. *Cis*-2,3-dimethyloxacyclopropane



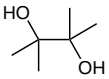
Anti Dihydroxylation

Epoxides may be cleaved by aqueous acid to give glycols that are often diastereomeric with those prepared by the syn-hydroxylation reaction described above. Proton transfer from the acid catalyst generates the conjugate acid of the epoxide, which is attacked by nucleophiles such as water in the same way that the cyclic bromonium ion described above undergoes reaction. The result is **anti-hydroxylation** of the double bond, in contrast to the syn-stereoselectivity of the earlier method. In the following equation this procedure is illustrated for a cis-disubstituted epoxide, which, of course, could be prepared from the corresponding cis-alkene. This hydration of an epoxide does not change the oxidation state of any atoms or groups.



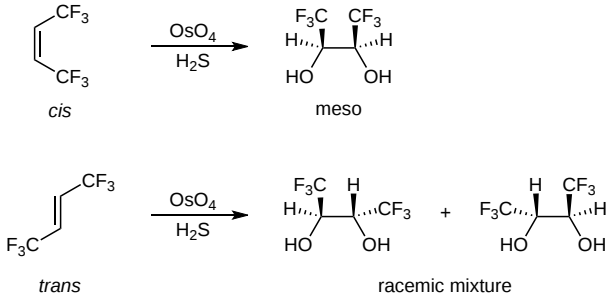
Syn Dihydroxylation

Osmium tetroxide oxidizes alkenes to give glycols through syn addition. A glycol, also known as a vicinal diol, is a compound with two -OH groups on adjacent carbons.



Introduction

The reaction with OsO_4 is a concerted process that has a cyclic intermediate and no rearrangements. Vicinal syn dihydroxylation complements the epoxide-hydrolysis sequence which constitutes an *anti* dihydroxylation of an alkene. When an alkene reacts with osmium tetroxide, stereocenters can form in the glycol product. Cis alkenes give meso products and trans alkenes give racemic mixtures.



OsO_4 is formed slowly when osmium powder reacts with gasoues O_2 at ambient temperature. Reaction of bulk solid requires heating to 400 °C:

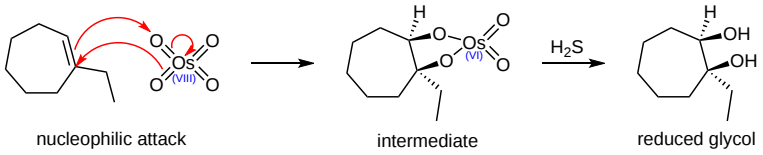
$$Os_{(s)} + 2O_{2\ (g)} \rightarrow OS_4$$

Since Osmium tetroxide is expensive and highly toxic, the reaction with alkenes has been modified. Catalytic amounts of OsO_4 and stoichiometric amounts of an oxidizing agent such as hydrogen peroxide are now used to eliminate some hazards. Also, an older reagent that was used instead of OsO_4 was potassium permanganate, $KMnO_4$. Although syn diols will result from the reaction of $KMnO_4$ and an alkene, potassium permanganate is less useful since it gives poor yields of the product because of *overoxidation*.

Mechanism

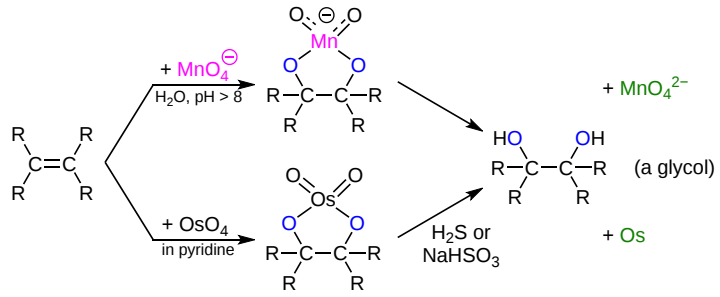
- Electrophilic attack on the alkene
  - Pi bond of the alkene acts as the nucleophile and reacts with osmium (VIII) tetroxide (OsO_4)
  - 2 electrons from the double bond flows toward the osmium metal
    - In the process, 3 electron pairs move simultaneously
  - Cyclic ester with Os (VI) is produced
- Reduction
  - H_2S reduces the cyclic ester
    - $NaHSO_4$ with H_2O may be used
  - Forms the syn-1,2-diol (glycol)

Example: Dihydroxylation of 1-ethyl-1-cycloheptene



Hydroxylation of alkenes

Dihydroxylated products (glycols) are obtained by reaction with aqueous potassium permanganate (pH > 8) or osmium tetroxide in pyridine solution. Both reactions appear to proceed by the same mechanism (shown below); the metallocyclic intermediate may be isolated in the osmium reaction. In basic solution the purple permanganate anion is reduced to the green manganate ion, providing a nice color test for the double bond functional group. From the mechanism shown here we would expect syn-stereoselectivity in the bonding to oxygen, and regioselectivity is not an issue.



When viewed in context with the previously discussed addition reactions, the hydroxylation reaction might seem implausible. Permanganate and osmium tetroxide have similar configurations, in which the metal atom occupies the center of a tetrahedral grouping of negatively charged oxygen atoms. How, then, would such a species interact with the nucleophilic pi-electrons of a double bond? A possible explanation is that an empty d-orbital of the electrophilic metal atom extends well beyond the surrounding oxygen atoms and initiates electron transfer from the double bond to the metal, in much the same fashion noted above for platinum. Back-bonding of the nucleophilic oxygens to the antibonding π*-orbital completes this interaction. The result is formation of a metallocyclic intermediate, as shown above.

Chemical Highlight

Antitumor drugs have been formed by using dihydroxylation. This method has been applied to the enantioselective synthesis of ovalicin, which is a class of fungal-derived products called antiangiogenesis agents. These antitumor products can cut off the blood supply to solid tumors. A derivative of ovalicin, TNP-470, is chemically stable, nontoxic, and noninflammatory. TNP-470 has been used in research to determine its effectiveness in treating cancer of the breast, brain, cervix, liver, and prostate.

Outside links

- http://en.Wikipedia.org/wiki/Osmium_tetroxide
- http://www.chm.bris.ac.uk/motm/oso4/oso4v.htm

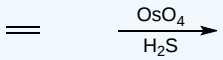
- http://www.organic-chemistry.org/chemicals/oxidations/osmiumtetroxide.shtm

References

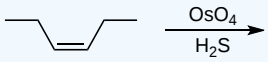
1. Dehestani, Ahmad et al. (2005). Ligand-assisted reduction of osmium tetroxide with molecular hydrogen via a [3+2] mechanism. *Journal of the American Chemical Society, 2005, 127 (10)*, 3423-3432.
2. Sorrell, Thomas, N. Organic Chemistry. New York: University Science Books, 2006.
3. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

? Dihydroxylation Exercises

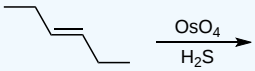
1. Give the major product.



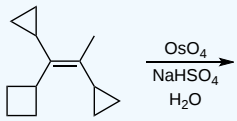
2. What is the product in the dihydroxylation of (Z)-3-hexene?



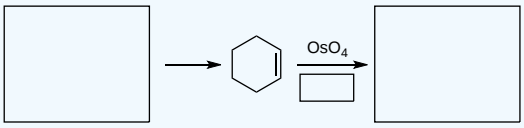
3. What is the product in the dihydroxylation of (E)-3-hexene?



4. Draw the intermediate of this reaction.

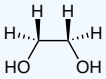


5. Fill in the missing reactants, reagents, and product.

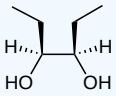


Answers

1. A syn-1,2-ethanediol is formed. There is no stereocenter in this particular reaction. The OH groups are on the same side.

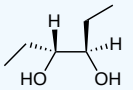


2. Meso-3,4-hexanediol is formed. There are 2 stereocenters in this reaction.

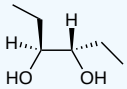


(3*S*,4*R*)

3. A racemic mixture of 3,4-hexanediol is formed. There are 2 stereocenters in both products.

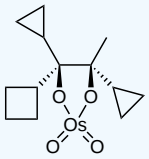


(3*R*,4*R*)

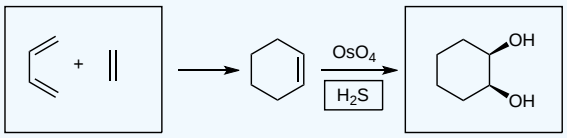


(3*S*,4*S*)

4. A cyclic osmic ester is formed.



5. The Diels-Alder cycloaddition reaction is needed in the first box to form the cyclohexene. The second box needs a reagent to reduce the intermediate cyclic ester (not shown). The third box has the product: 1,2-cyclohexanediol.



4.3: Oxidation of Alkenes- Epoxidation and Dihydroxylation (review from CHM 222) is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

- **8.7: Oxidation of Alkenes - Epoxidation and Hydroxylation** by Dietmar Kennepohl, Krista Cunningham, Kristen Perano, Lauren Reutenauer, Layne Morsch, Steven Farmer is licensed CC BY-SA 4.0.

4.4: Oxidation of Alkenes- Oxidative Cleavage Reactions

Objective

After completing this section, you should be able to

1. write an equation to describe the cleavage of an alkene by ozone, followed by reduction of the ozonide so formed with either dimethyl sulfide or zinc and acetic acid.
2. write an equation to describe the cleavage of an alkene by ozone, followed by oxidation of the ozonide so formed with hydrogen peroxide.
3. predict the products formed from the ozonolysis-reduction or ozonolysis-oxidation of a given alkene.
4. use the results of ozonolysis-reduction or ozonolysis-oxidation to deduce the structure of an unknown alkene.
5. identify the reagents that should be used in the oxidative cleavage of an alkene to obtain a given product or products.

Key Terms

Make certain that you can define, and use in context, the key terms below.

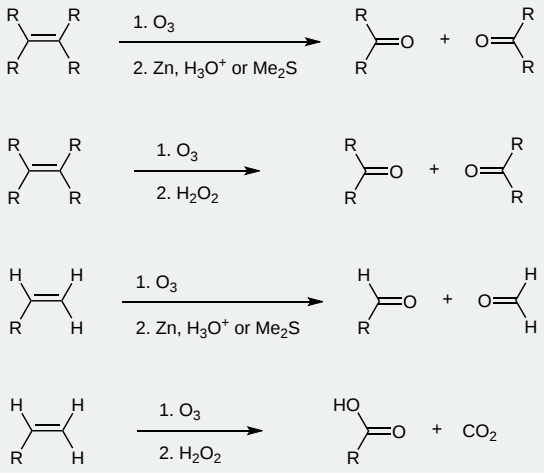
- molozonide
- ozonide
- ozonolysis

Study Notes

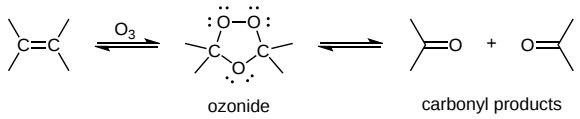
Ozonolysis refers to the treatment of an alkene with ozone followed by a suitable reducing or oxidizing agent to break down complex double-bond-containing compounds into smaller, more easily identified products. From the identity of the products formed, it may be possible to deduce the structure of the original double-bond-containing substance. Ozonolysis will feature prominently in many of the road-map problems that you will encounter in this course.

A *molozonide* is an unstable, cyclic intermediate that is initially formed when an alkene reacts with ozone.

Note within the summary of the following reactions that ozonolysis produces aldehydes and ketones (reductive workup) or carboxylic acids, ketones, and carbon dioxide (oxidative workup).



Ozonolysis is a method of oxidatively cleaving alkenes or alkynes using ozone (O_3), a reactive allotrope of oxygen. The process allows for carbon-carbon double or triple bonds to be replaced by double bonds with oxygen. This reaction is often used to identify the structure of unknown alkenes by breaking them down into smaller, more easily identifiable pieces. Ozonolysis also occurs naturally and breaks down repeat units used in rubber and other polymers. On an industrial scale, azelaic acid and pelargonic acids are produced from ozonolysis.

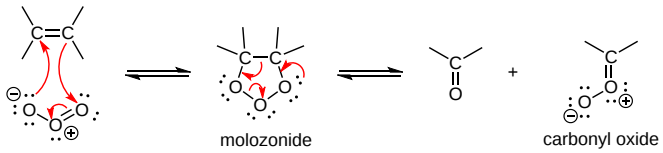


Introduction

The gaseous ozone is first passed through the desired alkene solution in either methanol or dichloromethane. The first intermediate product is an ozonide molecule which reacts further to produce carbonyl products. This results in the breaking of the Carbon-Carbon double bond and is replaced by a Carbon-Oxygen double bond instead.

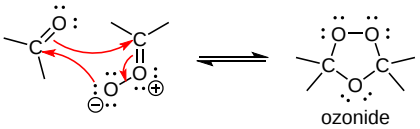
Reaction Mechanism

Step 1:



The first step in the mechanism of ozonolysis is a cycloaddition (we will learn about this type of reaction later in the semester) between ozone and the Carbon-Carbon double bond, which forms the molozonide intermediate. Due to the high energy of the molozonide, it breaks apart to form a carbonyl and a carbonyl oxide molecule.

Step 2:



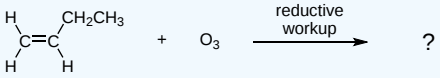
The carbonyl and the carbonyl oxide reorient (molecular rotation) and react again to create the stable ozonide intermediate. Since some ozonides are explosive, it is immediately reacted with a reductive or oxidative workup to then convert the ozonide molecule into the desired carbonyl products. A typical reductive workup is either zinc metal in acetic acid or dimethyl sulfide (DMS). A typical oxidative workup is hydrogen peroxide. A variety of carbonyl products could result depending on the starting alkene. For example, a tetrasubstituted alkene would yield two ketone products (with either a reductive or oxidative workup), while a trisubstituted alkene would yield one ketone product and one aldehyde product with a reductive workup or one ketone product and one carboxylic acid product (oxidative workup).

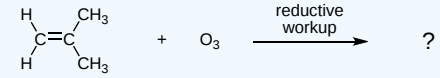
While there are other options for oxidative cleavage of the double bond, this is the most commonly used reaction.

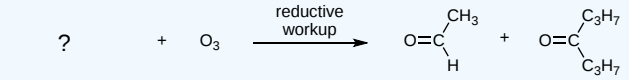
References

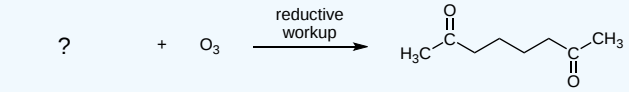
1. Vollhardt, K., Schore, N. Organic Chemistry: Structure and Function. 5th ed. New York, NY: W. H. Freeman and Company, 2007.
2. Shore, N. Study Guide and Solutions Manual for Organic Chemistry. 5th ed. New York, NY: W.H. Freeman and Company, 2007.

? Exercise 4.4.1

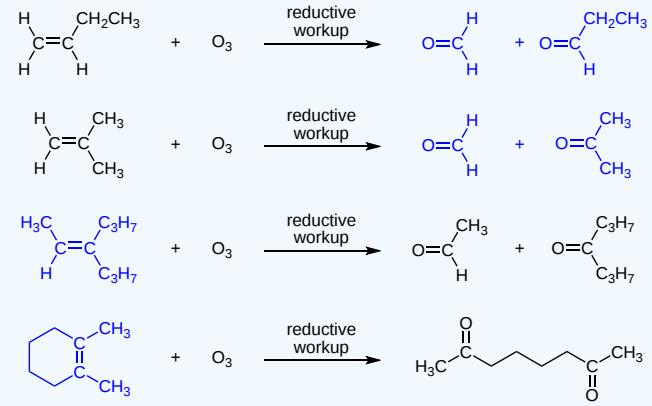
1. 

2. 

3. 

4. 

Answer



Exercise 4.4.2

Draw the structure of the product or products obtained in each of the following reactions:

a. *cis*-2-butene $\xrightarrow[2.\ Zn/H_3O^+]{1.\ O_3}$

b. *trans*-2-butene $\xrightarrow[2.\ Zn/H_3O^+]{1.\ O_3}$

c. 2-methylpropene $\xrightarrow[2.\ Zn/H_3O^+]{1.\ O_3}$

Answer

a.

b.

c.

Exercise 4.4.3

Draw the structure of the product or products obtained in each of the following reactions:

a) cis- or trans-2-butene $\xrightarrow[2.\ H_2O_2]{1.\ O_3}$

b) 2-methylpropene $\xrightarrow[2.\ H_2O_2]{1.\ O_3}$

Answer

a) cis- or trans-2-butene $\xrightarrow[2.\ H_2O_2]{1.\ O_3}$ 2

b) 2-methylpropene $\xrightarrow[2.\ H_2O_2]{1.\ O_3}$

+ CO_2

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- **8.8: Oxidation of Alkenes - Cleavage to Carbonyl Compounds** by Dietmar Kennepohl, Krista Cunningham, Lauren Reutenauer, Steven Farmer, Tim Soderberg is licensed CC BY-SA 4.0.

4.5: Oxidation of Alkynes- Oxidative Cleavage Reactions

Objectives

After completing this section, you should be able to

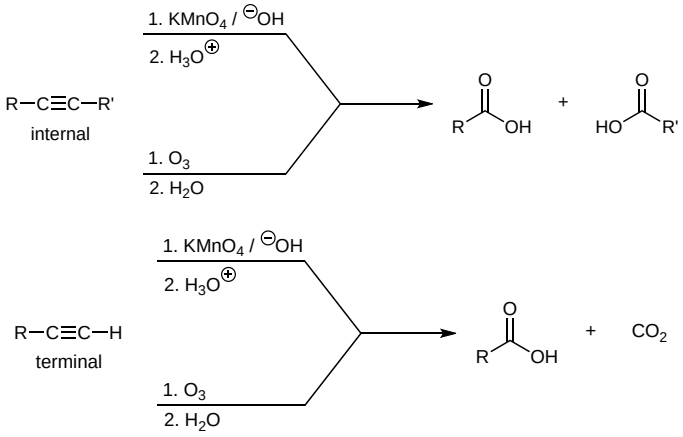
1. write an equation to represent the oxidative cleavage of an alkyne with potassium permanganate or ozone.
2. identify the products that result from the oxidative cleavage of a given alkyne.
3. identify the reagents needed to carry out the oxidative cleavage of an alkyne.
4. use the results of an oxidative cleavage to determine the identity of an alkyne of unknown structure.

Study Notes

Compare the oxidative cleavage of alkynes with the oxidative cleavage of alkenes, discussed in Section 4.4.

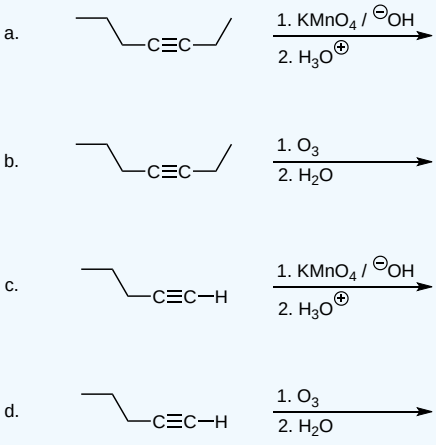
Strong Alkyne Oxidation - Oxidative Cleavage

During strong oxidation with ozone or basic potassium permanganate, the alkyne is cleaved into two products. Because at least one of the reaction products is a carboxylic acid, it is important to consider the acid-base chemistry of the product in the reaction solution. Carboxylic acids are deprotonated in basic solutions to carboxylates. A second reaction step is required to protonate the carboxylate to the neutral form of the carboxylic acid.



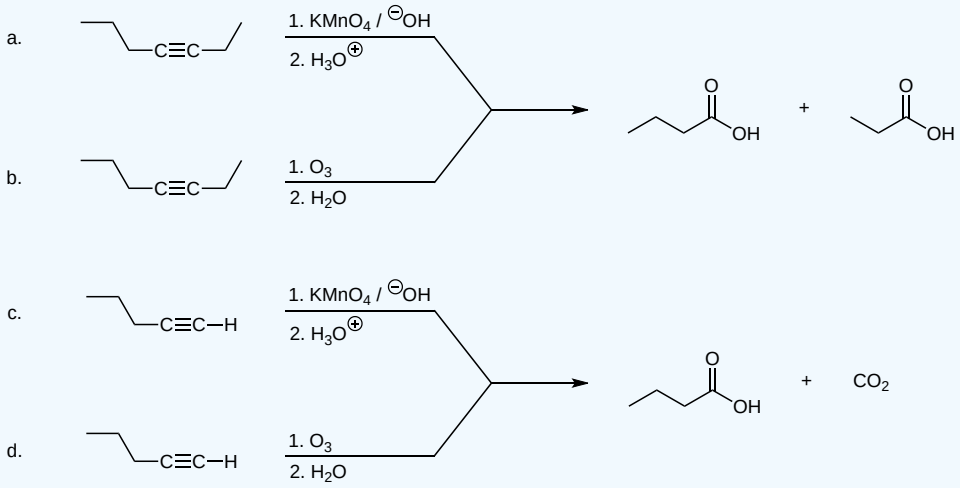
Exercise

1. Draw the bond-line structures for the product(s) of the following reactions.



Answer

1.



Oxidative cleavage of alkynes produces carboxylic acids and/or carbon dioxide. Aldehydes are not produced.

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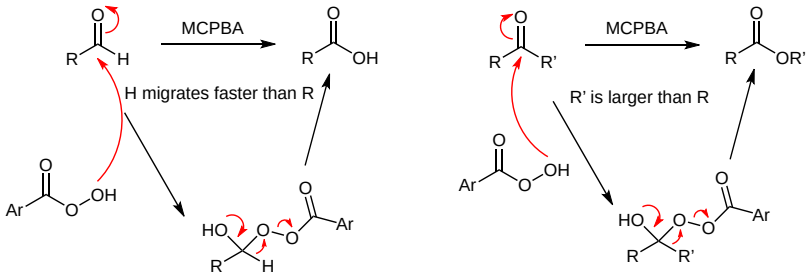
4.6: Oxidation of Aldehydes and Ketones- The Baeyer-Villager Oxidation

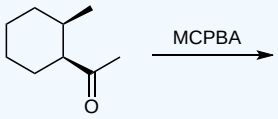
Baeyer-Villager Rearrangement

The Baeyer-Villager rearrangement is the reaction of a peracid with an aldehyde or ketone to yield a carboxylic acid or ester, respectively. There are two possible products for ketones with selectivity generally favoring migration of the larger group. The most common peracid used synthetically is meta-chloroperoxybenzoic acid (MCPBA) which also reacts with alkenes to form epoxides (Chapter 4.3). Beware of this dual reactivity when planning syntheses. The Baeyer-Villager rearrangement mechanism is shown below. The peracid adds to the aldehyde or ketone to produce a tetrahedral intermediate. Reforming the carbonyl promotes the rearrangement with H migrating exclusively in the aldehyde substrate to yield the carboxylic acid product. A similar intermediate is formed in the ketone reaction. In this case, the larger alkyl group migrates (related to which group can better stabilize a partial carbocation on the carbonyl carbon in the transition state) to yield the ester product.



Exercise 4.6.10

Propose a product for the following Baeyer-Villager rearrangement.

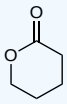


Answer

The left side of the ketone is larger than the methyl group, so this alkyl group migrates onto the new O in the mechanism to yield the product ester. Note that no bonds were formed or broken to the chiral carbon on the cyclohexane ring so this stereochemistry does not change.

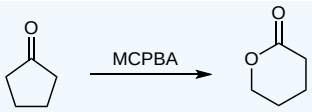
Exercise 4.6.11

Propose a Baeyer-Villager rearrangement that would yield the target lactone.



Answer

Thinking about the ketone that led to the formation of the six-membered ring lactone, we should realize that we just need to remove the O in the ring from the product to yield the all-carbon starting material. In this case, it's cyclopentanone. This reaction highlights the ability of the Baeyer-Villager rearrangement to promote a ring expansion reaction.



4.6: Oxidation of Aldehydes and Ketones- The Baeyer-Villager Oxidation is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

CHAPTER OVERVIEW

5: Radical Reactions

5.1 Introduction - Radical Mechanism Overview
5.2 Radical Bromination of Alkenes Part 1: HBr with peroxides
5.3 Radical Bromination of Alkenes Part II: Allylic Bromination with NBS
5.4 Carbon-Carbon Bond Forming Radical Reactions

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5.1 Introduction - Radical Mechanism Overview

Chapter Videos

This video is an overview of all of the radical reactions we will learn this semester.

Objectives

After completing this section, you should be able to

1. give an example of a radical substitution reaction.
2. identify the three steps (initiation, propagation and termination) that occur in a typical radical substitution reaction.
3. write out the steps involved in a simple radical substitution reaction, such as the chlorination of methane.
4. explain why the halogenation of an alkane is not a particularly useful method of preparing specific alkyl halides.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- chain reaction
- initiation step
- propagation step
- radical substitution
- termination step

Study Notes

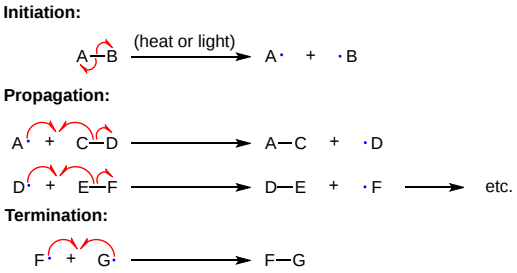
A *radical substitution reaction* is a reaction which occurs by a free radical mechanism and results in the substitution of one or more of the atoms or groups present in the substrate by different atoms or groups.

The *initiation step* in a radical chain reaction is the step in which a free radical is first produced. A *termination step* of a radical chain reaction is one in which two radicals react together in some way so that the chain can no longer be propagated.

While radical halogenation of very simple alkanes can be an effective synthetic strategy, it cannot be employed for larger more complex alkanes to yield specific alkyl halides, since the reactive nature of radicals always leads to mixtures of single- and multiple-halogenated products.

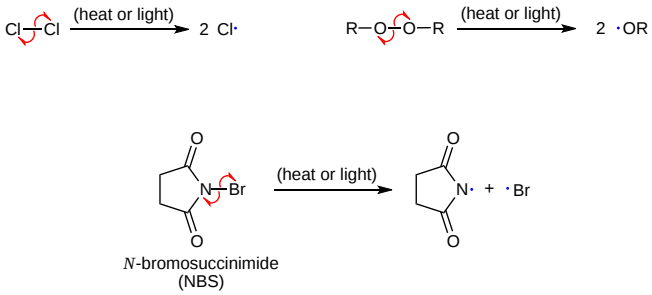
The Three Phases of Radical Chain Reactions

Because of their high reactivity, free radicals have the potential to be both extremely powerful chemical tools and extremely harmful contaminants. Much of the power of free radical species stems from the natural tendency of radical processes to occur in a chain reaction fashion. **Radical chain reactions** have three distinct phases: initiation, propagation, and termination.



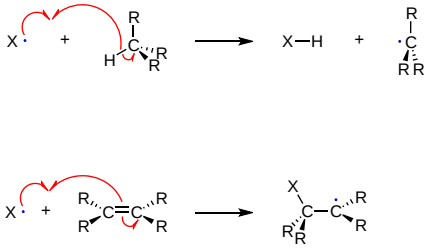
The **initiation phase** describes the step that initially creates a radical species. In most cases, this is a homolytic cleavage event, and takes place very rarely due to the high energy barriers involved. Often the influence of heat, UV radiation, or a metal-containing catalyst is necessary to overcome the energy barrier.

Molecular chlorine and bromine will both undergo homolytic cleavage to form radicals when subjected to heat or light. Other functional groups which also tend to form radicals when exposed to heat or light are chlorofluorocarbons, peroxides, and the halogenated amide N-bromosuccinimide (NBS).



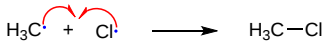
The **propagation phase** describes the 'chain' part of chain reactions. Once a reactive free radical is generated, it can react with stable molecules to form new free radicals. These new free radicals go on to generate yet more free radicals, and so on. Propagation steps often involve hydrogen abstraction or addition of the radical to double bonds.

Propagation steps generate the desired product of the reaction and regenerate the chain propagating radical, usually Br radical or Bu_3Sn radical.



Chain termination occurs when two free radical species react with each other to form a stable, non-radical adduct. Although this is a very thermodynamically downhill event, it is also very rare due to the low concentration of radical species and the small likelihood of two radicals colliding with one another. In other words, the Gibbs free energy barrier is very high for this reaction, mostly due to entropic rather than enthalpic considerations. The active sites of enzymes, of course, can evolve to overcome this entropic barrier by positioning two radical intermediates adjacent to one another.

In radical chain reactions, termination steps do not produce the desired product. Instead, they produce undesired byproducts that must be removed from the target molecule by some type of purification.



Exercises

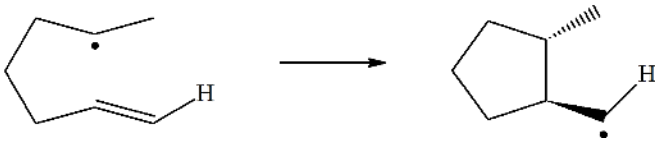
Questions

Q6.3.1

Radical chlorination of alkanes are not useful due to uncontrolled substitution. Draw the mono-substituted products of Cl_2 reacting with 2-methylbutane.

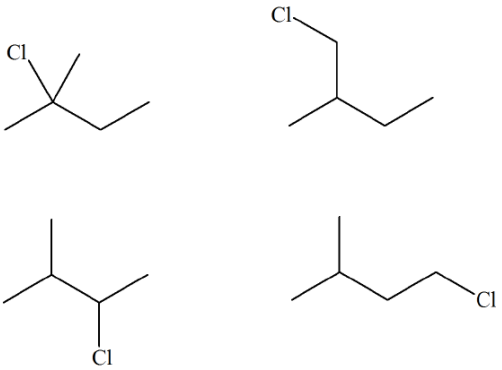
Q6.3.2

Propose a radical mechanism for the following reaction:



Solutions

S6.3.1



S6.3.2

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5.2 Radical Bromination of Alkenes Part 1: HBr with peroxides

Objectives

After completing this section, you should be able to

1. write the reaction for the bromination of an alkene using HBr in the presence of peroxides.
2. predict the product formed when a given alkene is treated with HBr and peroxides (and contrast this to the polar HBr reaction).
3. identify the starting alkene needed to produce a given bromide by radical alkene bromination.

Key Terms

Make certain that you can define, and use in context, the key term below.

- peroxide

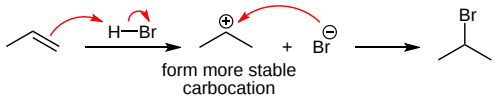
Study Notes

In CHM 222, we learned about the electrophilic (polar) addition of HX to alkenes. The mechanism for these reactions proceeds via the most stable carbocation and results in X minus adding to the more substituted side of the starting alkene. In this section, we will see that it is possible to reverse that regiochemistry and directly synthesize the less substituted bromide by using a radical mechanism.

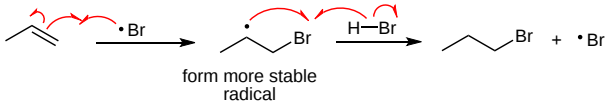
Radical Alkene Bromination

In CHM 222, we learned that reaction of HCl, HBr, or HI with an alkene promotes halogen addition to the more substituted position of the alkene because the reaction forms the most stable carbocation. Due to the unique reactivity of HBr, it is possible for this reagent to participate in a radical reaction to provide the opposite regiochemistry. In this reaction, Br radical adds to the alkene to generate the most stable radical (most highly substituted). The final product is synthesized upon reaction with HBr which also regenerates the chain propagating Br radical.

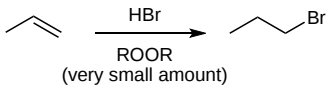
Polar HBr Reaction



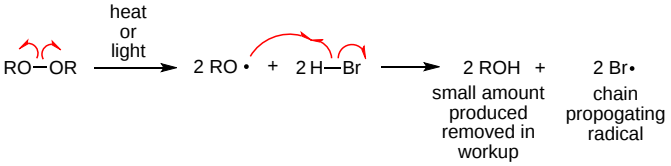
Radical HBr Reaction



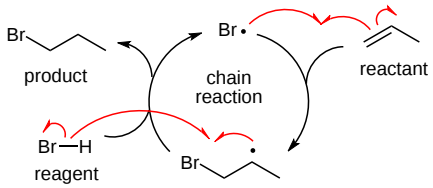
This radical reaction is only possible with HBr. HCl and HI have different bond energies that are not able to support the reaction rates required for a radical chain process. The complete mechanism with HBr is shown below. Remember, the key different in conditions between this reaction and the polar HBr reaction is the presence of peroxides that initiate the radical chain process. The peroxide is often written as ROOR to indicate that any peroxide can serve as the initiator. So, you might see MeOOMe, $(tBuO)_2$, MeOOtBu, or another similar reagent when doing these types of problems. As always, the initiator is present in very small amounts, usually around 1 mol percent.



Initiation



Propogation - product producing steps



5.2 Radical Bromination of Alkenes Part 1: HBr with peroxides is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

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5.3 Radical Bromination of Alkenes Part II: Allylic Bromination with NBS

Objectives

After completing this section, you should be able to

1. write the equation for the bromination of a symmetrical alkene using N-bromosuccinimide.
2. predict the product formed when a given symmetrical alkene is treated with N-bromosuccinimide.
3. identify the reagent, the symmetrical alkene, or both, needed to produce a given allyl halide by allylic bromination.
4. list the following radicals in order of increasing or decreasing stability: allyl, vinyl, primary alkyl, secondary alkyl, tertiary alkyl, methyl.
5. explain the ease of forming an allyl radical, and the difficulty of forming a vinyl radical, in terms of relative C–H bond dissociation energies.

Key Terms

Make certain that you can define, and use in context, the key term below.

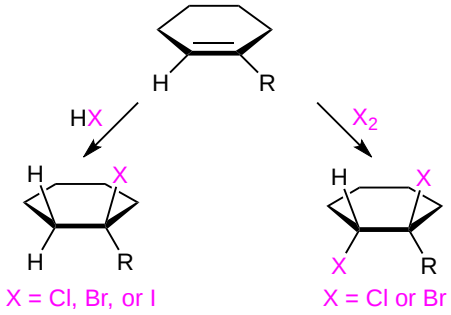
- allylic carbon

Study Notes

We have discussed the electrophilic addition of X_2 and HX to alkenes as a route to forming alkyl halides in CHM 222. In this section we introduce bromination at the allyic position with N-bromosuccinimide (NBS). Notice that at the moment we are restricting our studies to the allylic bromination of symmetrical alkenes, such as cyclohexene. When we introduce an element of asymmetry, we find that more than one allyl radical can be formed; therefore, we must assess the relative stability of each radical when trying to predict which product will predominate. The method of doing this assessment is described in the next section.

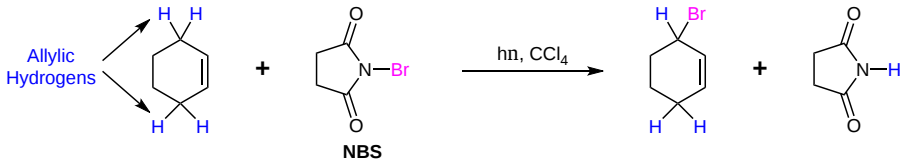
Allylic Bromination

Previously, alkyl halides have been produced though reactions with alkenes. Hydrogen halides (HCl, HBr, and HI) react with alkenes in an electrophilic addition reaction to yield alkyl halides as products. Also, Bromine (Br_2) and chlorine (Cl_2) can react with alkenes to provide dihalogenated products.



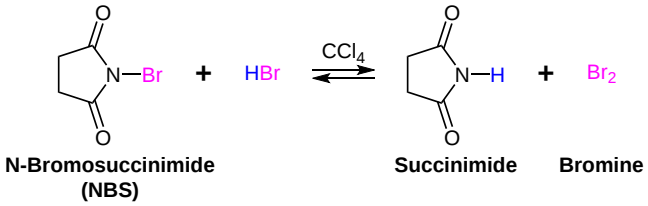
Another method for preparing alkyl halides from alkenes is with **N-bromosuccinimide (NBS)** in carbon tetrachloride (CCl_4) solution with the presence of light. The reaction specifically causes the substitution of bromine with a hydrogen attached to a carbon adjacent to the double bond - the allylic position.

General Reaction

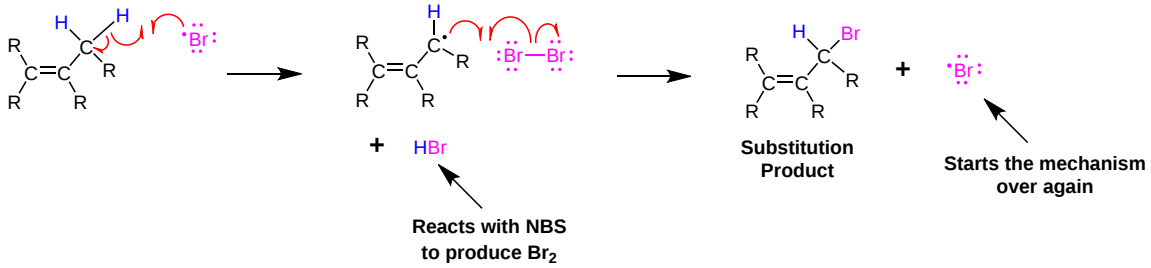


Mechanism

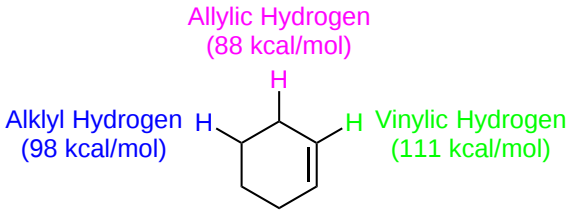
The allylic bromination with NBS occurs as a radical chain reaction. NBS is the most commonly used reagent to produce low concentrations of bromine. When suspended in tetrachloride (CCl_4), NBS reacts very rapidly with the HBr formed during the reaction mechanism to provide bromine (Br_2) which is required for the reaction to continue. Under the correct conditions, NBS provides a constant but very low concentration of Br_2 in the reaction mixture. The low concentration of Br_2 helps to prevent the formation of unwanted side-products.



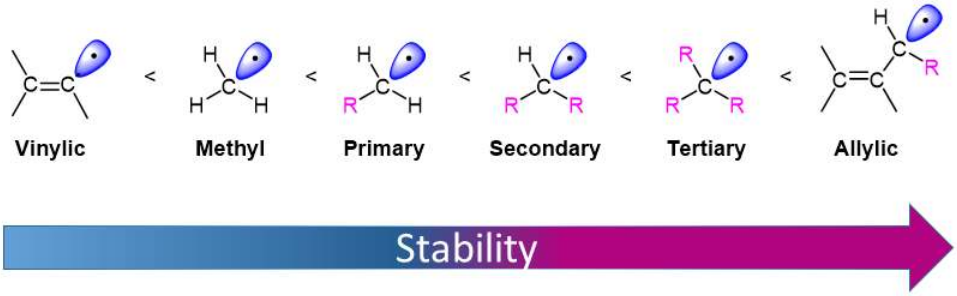
The mechanism starts with the formation of a small amount of bromine radical which then abstracts an allylic hydrogen to form an allylic radical and HBr. The HBr can then react with NBS to form the Br_2 required for the reaction. The allylic radical then abstracts a bromine atom from Br_2 to form the allyl halide product and a bromine radical. The bromine radical produced allows the reaction to continue.



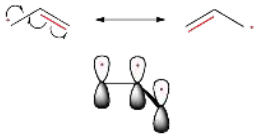
The predominance of allylic substitution over other positions is based on bond dissociation energies. An allylic C-H bond has a strength of about 88 kcal/mol which is much weaker than a typical alkyl C-H bond (98 kcal/mol) or vinylic C-H bond (111 kcal/mol). Therefore, an allylic C-H bond is most likely to form a free radical and react.



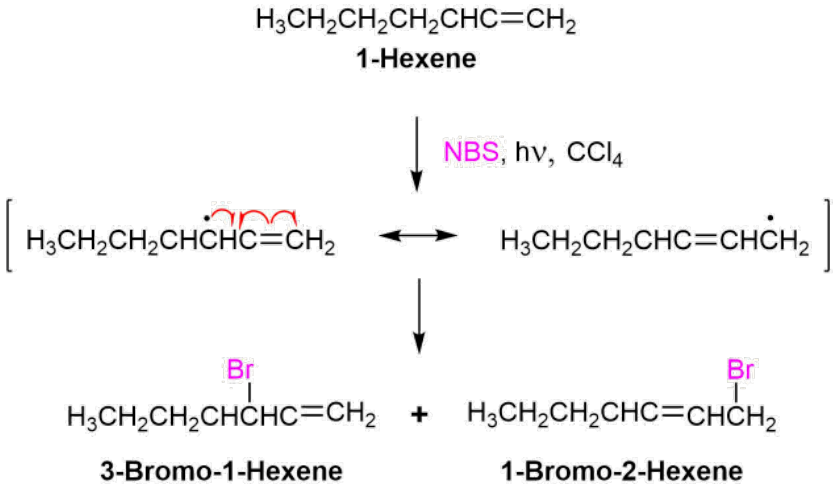
Because a allylic C-H bond requires less energy to undergo homolytic cleavage than even a tertiary C-H bond, it can be inferred that a allylic radical is more stable than a tertiary radical. The ordering of stability in radicals can be expanded to include vinylic and allylic radicals. The enhanced stability of allyl radicals can be attributed to resonance stabilization which will be discussed in the next section.



Benzylic and allylic radicals are more stable than alkyl radicals due to resonance effects - an unpaired electron can be delocalized over a system of conjugated pi bonds. An allylic radical, for example, can be pictured as a system of three parallel $2p_z$ orbitals sharing three electrons. With two resonance forms, the allylic radical is electronically symmetrical. Due to resonance hybrid theory, neither structure is correct, but instead the structure lies somewhere between the two resonance forms. Another way to phrase this is that the unpaired electron is delocalized across all the carbon atoms through the pi system and not localized on one site. The more resonance structures, the more stable the molecule. This is why the allylic radical is more stable than the alkyl radical.

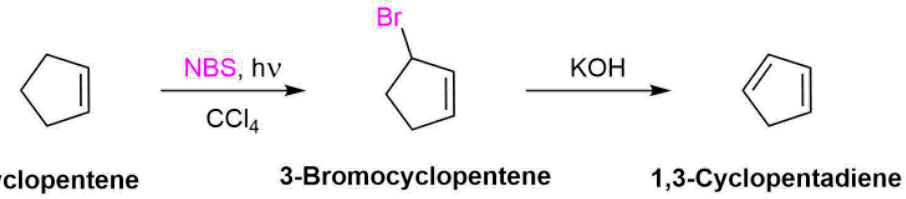


Because the allylic radical is symmetrical, a reaction can occur on either side. Therefore if reacting with bromine, the bromination could occur on either end of the allylic radical. When the allyl radical is symmetrical, this yields the same product. However, if you have an unsymmetrical allyl radical, it would lead to a mixture of products and not necessarily in equal amounts. This is because the intermediate radical is unsymmetrical. The reaction will occur at the less hindered site. An example would be 1-octene as a starting material in a bromination. The products the reaction would yield would be 3-bromo-1-octene and 1-bromo-2-octene.



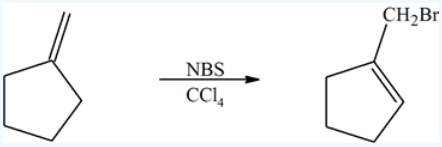
Further Reactions

The products from allylic bromination reactions can easily be converted into dienes by elimination using a base.

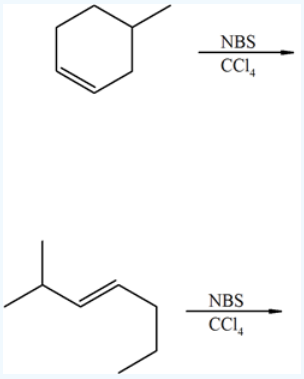


Exercise 5.3 *Radical Bromination of Alkenes Part II*. 1

1) The following reaction shows the major product. Explain why this would be the final product and why the 2° bromo product is not the major product.

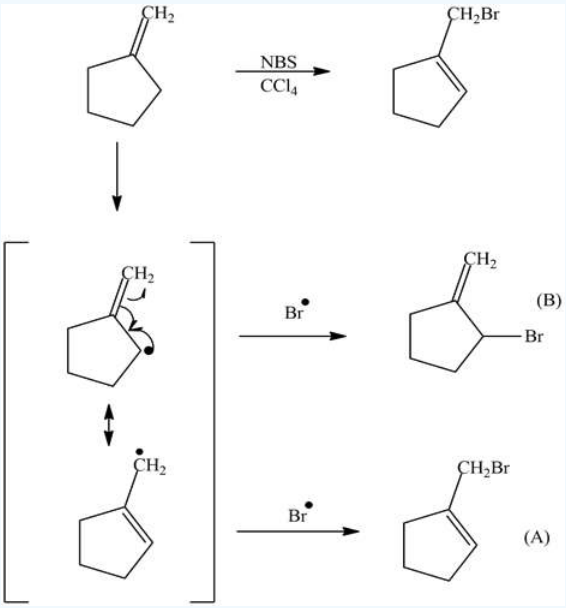


2) Predict the products of the following reactions:

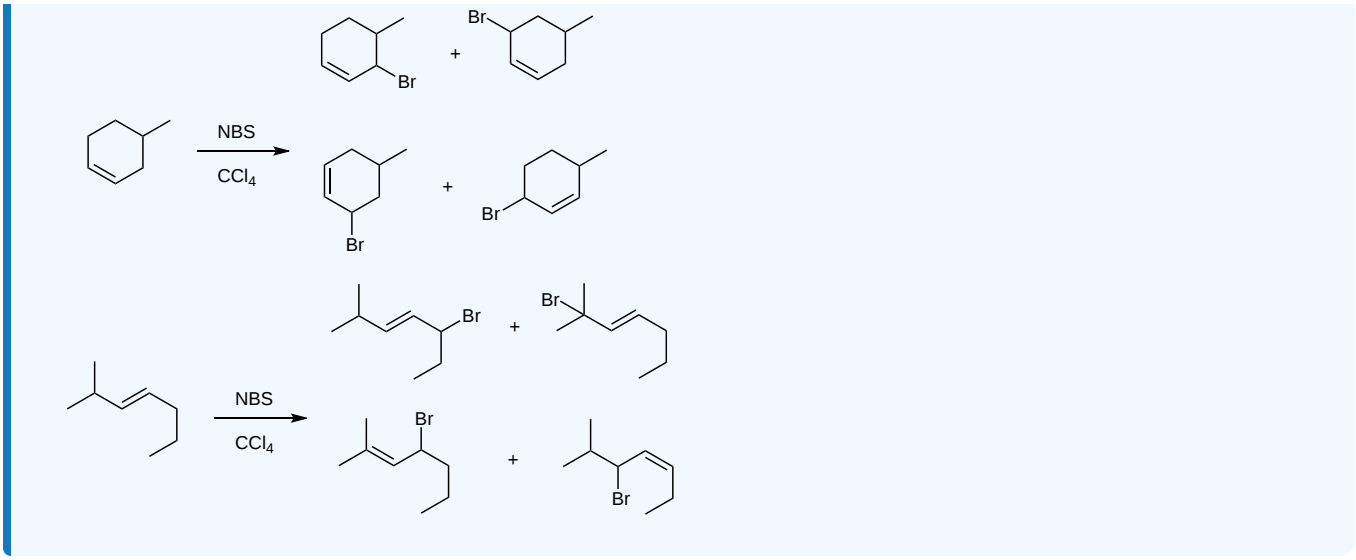


Answer

1) The product (A) is a 1° halogen which is more predominant product even though the (B) had a better transition state with a 2° radical. The 1° radical intermediate is not as sterically hindered.



2)



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- **16.9: Oxidation of Aromatic Compounds** by Dietmar Kennepohl, James Kabrhel, Steven Farmer, William Reusch is licensed CC BY-SA 4.0.
- **10.4: Stability of the Allyl Radical - Resonance Revisited** by Dietmar Kennepohl, Liza Chu, Sharon Wei, Steven Farmer is licensed CC BY-SA 4.0.

5.4 Carbon-Carbon Bond Forming Radical Reactions

Objectives

After completing this section, you should be able to:

1. Understand radical reactions involved in carbon-carbon bond formation
2. Draw mechanisms incorporating radicals to explain reaction outcomes
3. Plan syntheses using radical reactions

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Radical initiation
- AIBN
- Radical propagation
- Bu_3SnH
- Radical termination

Study Notes

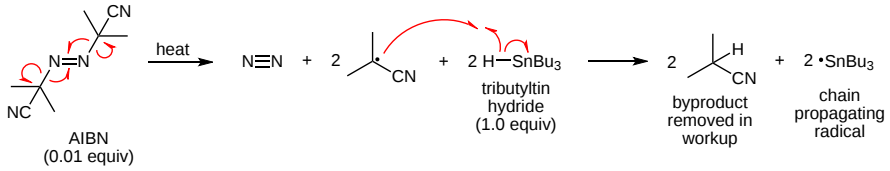
Don't forget that all mechanisms in this chapter involve the movement of single electrons (radicals!), so we will use **single-headed arrows** in our mechanisms.

Content

Initiation and Propagation Steps

Before getting into the actual radical reactions, we first need to comment on two key reagents: AIBN (AzobisIsoButyroNitrile) and Bu_3SnH (tributyltin hydride). We will use AIBN as our radical initiator and Bu_3SnH as the precursor for our chain propagating radical, tributyltin radical. Upon heating, AIBN cleaves to form nitrogen gas and two radicals that react with Bu_3SnH to yield two tributyltin radicals, as shown below. Tributyltin is our chain propagating radical, so these two radicals can each start a radical chain process (the propagation steps) resulting in the production of our desired molecule. Please remember a few key points about initiation and propagation steps: 1) We only need a small amount of the initiator to begin the chain process. Generally, 1 mol% of AIBN (0.01 equivalents) is sufficient to generate enough tributyltin radicals for the propagation steps. Although not a true catalyst, you can think about AIBN like the catalyst that must be present to make the chain reaction possible. 2) The chain propagating radical, tributyltin radical, must be a reactant in your first propagation step and a product in your last propagation step. Tributyltin radical looks a bit like a catalyst but it is different in a key way. Tributyltin hydride is consumed in the reaction and must be present in a stoichiometric amount (at least 1.0 equivalents) or the chain will be broken before all of the starting material reacts. Don't forget, the propagation steps are the only productive steps in a chain reaction. This is where your product is formed. 3) Termination steps break the chain and are undesired. In radical chain reactions, combining two radicals to form a new bond is never a productive reaction. Your product will never come from a termination step. These molecules are undesired byproducts and their formation must be very limited for the radical chain reaction to be synthetically useful.

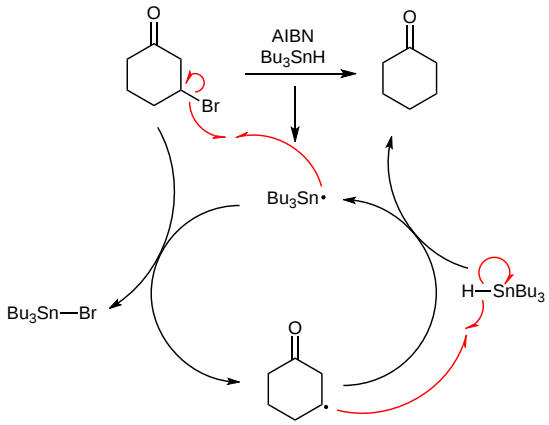
Initiation Steps with AIBN and Bu_3SnH



Dehalogenation Reactions

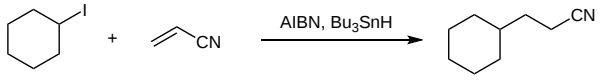
Tributyltin hydride is a useful reagent for the dehalogenation (reduction) of alkyl halides. This illustrates a radical chain mechanism using tributyltin as the chain propagating radical. (As always, AIBN and tributyltin hydride combine in the initiation steps shown above to produce tributyltin radical.) Once the tributyltin radical is formed, it reacts to form a new Sn-Br bond by cleaving the C-Br bond to generate a carbon radical. This forms tributyltin bromide, a byproduct that must be removed after the reaction, and the new carbon radical that is part of our chain process. The carbon radical reacts with tributyltin hydride (remember, we have a very small

amount of AIBN, just enough to start the process, and at least 1 equivalent of Bu_3SnH to react completely with the alkyl bromide starting material) to form the new C-H bond in the product and another molecule of tributyltin radical that can participate in another cycle of the chain process.

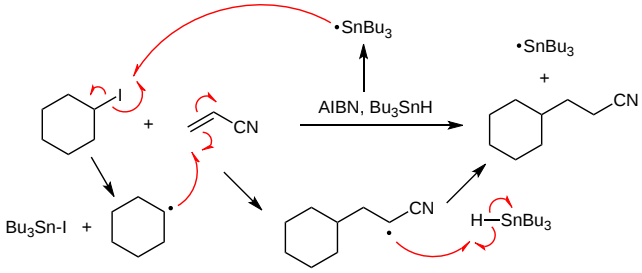


Carbon-Carbon Bond Forming Reactions

Radical chain reactions mediated by Bu_3SnH can also promote the formation of carbon-carbon bonds. These are among the most important radical reactions in synthetic chemistry since they provide us with another option in our toolbox of methods to make critical molecular connections. Key components in these reactions are a carbon-halogen bond that can react with the chain propagating tributyltin radical to generate a carbon radical that combines with an alkene or alkyne to form the new carbon-carbon bond. These reactions occur both inter- and intramolecularly with the latter being favored for higher yields and better regioselectivity. Radical reactions are kinetically controlled so they provide a very useful strategy for the synthesis of 5-membered rings. This is even true for most instances when selecting between the formation of 5- versus 6-membered rings in intramolecular cyclization reactions. (The smaller ring forms faster and, thus, is favored.) In intermolecular reactions, it is often helpful to have an electron poor alkene or alkyne as the radical partner to help favor regioselectivity with the (generally) more substituted radical formed in the first step. An example reaction and mechanism are shown below for a standard intermolecular carbon-carbon bond forming reaction. An intramolecular example is shown in the following problem.

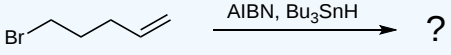


Mechanism



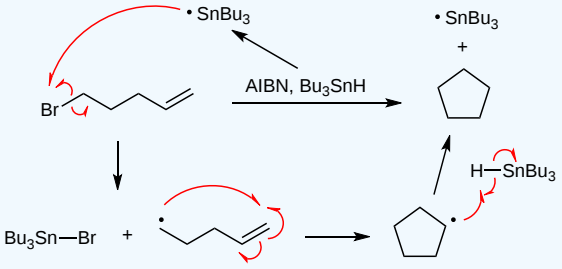
? Exercise 1

For the following intramolecular C-C bond forming reaction, predict the product and propose a mechanism for its formation.



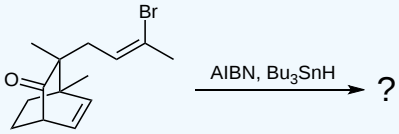
Answer

Like in our intermolecular example above, the tributyltin radical attacks the carbon-halogen bond to yield a carbon radical. This new radical participates in an intramolecular C-C bond forming reaction to form a 5-membered ring radical that reacts in the final step to form the product and regenerate the chain propagating radical. Note, because of ring strain, we won't form the 4-membered ring resulting from addition to the other side of the alkene.



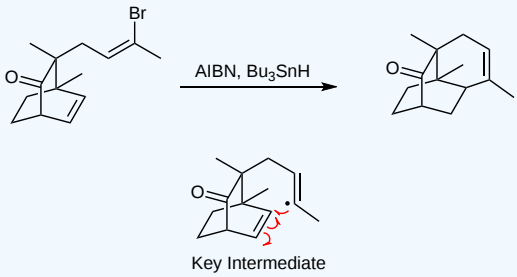
? Exercise 2

Predict the product of the following reaction.



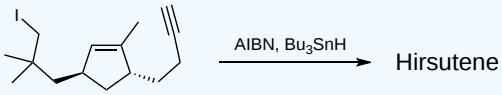
Answer

This problem highlights that radicals can easily form on sp^2 carbons and is a reminder that bond rotation is always important to consider. The key intermediate forms and reacts to yield the new 6-membered ring which forms faster than the 7-membered ring alternative.



? Exercise 3

One of the most powerful examples of the utility of carbon-carbon bond forming radical reactions in synthesis is Curran's synthesis of hirsutene published in 1985. The reaction below is the final step in the synthesis. Propose the structure of hirsutene and a mechanism for its formation.

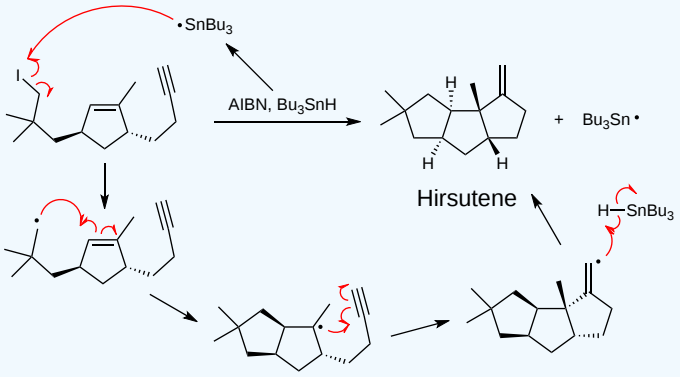


Answer

DOI - https://doi.org/10.1021/ja00291a077

This follows the pattern we observed previously. The tin radical reacts with the iodide to form a carbon radical that reacts with the alkene to form a new 5-membered ring. The resulting tertiary radical reacts with the alkyne to form the third 5-membered ring in hirsutene. Note that the stereochemistry in the starting material determines the stereochemistry in the

product. The alkyl chain coming out forms a new bond from above the initial 5-membered ring. The alkyl chain going back forms a new bond from beneath the initial 5-membered ring.



Contributors

- Prof. Kevin Shea (Smith College)

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CHAPTER OVERVIEW

6: Carbonyl Alpha-Substitution Reactions

Learning Objectives

When you have completed this Chapter, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design multistep syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
3. solve road map problems that require a knowledge of carbonyl alpha substitution reactions.
4. define, and use in context, the key terms introduced.

Chapter Video

This video focuses on enolate alkylation and decarboxylation reaction.

Chapter Introduction

Alpha substitution reactions are the third major type of reaction that you will study in your investigation of the chemistry of carbonyl compounds. As you will see, these reactions proceed through the formation of the enol form of the carbonyl compound.

After a brief review of keto-enol tautomerism, we begin our discussion of alpha substitution reactions by looking at the methods in which the enol form of the carbonyl compound is directly involved. After discussing the factors that influence the formation and stability of enolate anions, we will examine some halogenation reactions in which an enolate ion is formed as an intermediate.

The chapter concludes with a study of the alkylation of enolate anions. These reactions are of tremendous use in organic syntheses, as they provide a method of forming new carbon-carbon bonds, and hence facilitate the laboratory preparation of increasingly complex compounds.

6.1: Chapter Objectives and Introduction to Carbonyl Alpha-Substitution Reactions
6.2: Keto-Enol Tautomerism
6.3: Reactivity of Enols- The Mechanism of Alpha-Substitution Reactions
6.4: Alpha Halogenation of Aldehydes and Ketones (reference only)

6.5: Alpha Bromination of Carboxylic Acids (reference only)
6.6: Acidity of Alpha Hydrogen Atoms- Enolate Ion Formation
6.7: Reactivity of Enolate Ions (haloform reaction is reference only)
6.8: Alkylation of Enolate Ions
6.S: Carbonyl Alpha-Substitution Reactions (Summary)

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6.1: Chapter Objectives and Introduction to Carbonyl Alpha-Substitution Reactions

Objectives

After completing this section, you should be able to write a general mechanism for an alpha substitution reaction of a carbonyl compound.

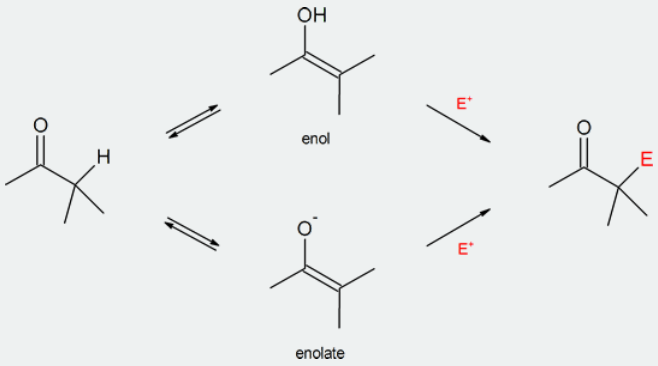
Key Terms

Make certain that you can define, and use in context, the key terms below.

- alpha (α) position
- alpha substitution reaction

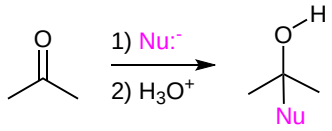
Study Notes

An “alpha substitution reaction” of a carbonyl compound is a reaction in which one of the hydrogen atoms on the carbon adjacent to the carbonyl group is substituted by some other atom or group. Attack by the electrophile (E^+) can occur on the enol or enolate intermediate.



There are four common types of reactions involving compounds containing a carbonyl bond. The first two, nucleophilic addition and nucleophilic acyl substitution, have been discussed in CHM 222.

Nucleophilic addition occurs due to the electrophilic nature of the carbonyl carbon. After addition of a nucleophile, the carbonyl becomes a tetrahedral alkoxide intermediate which is usually protonated to become an -OH group.



Nucleophilic Addition to a Carbonyl

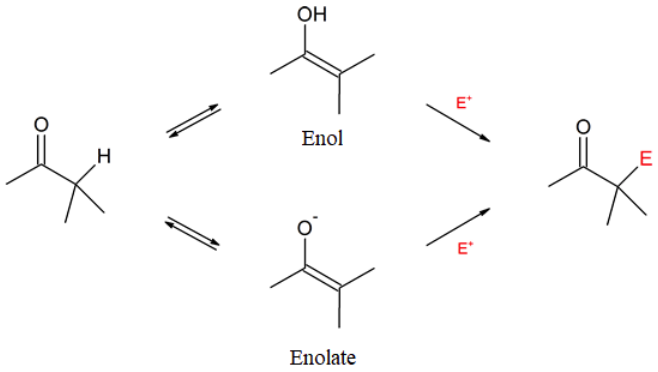
Nucleophilic acyl substitution is similar in that a tetrahedral alkoxide intermediate is formed after nucleophilic addition to the carbonyl. However, subsequent removal of the leaving group allows for the C=O (carbonyl) bond to reform. Overall, there is a substitution of the leaving group with the incoming nucleophile.

L = Leaving Group

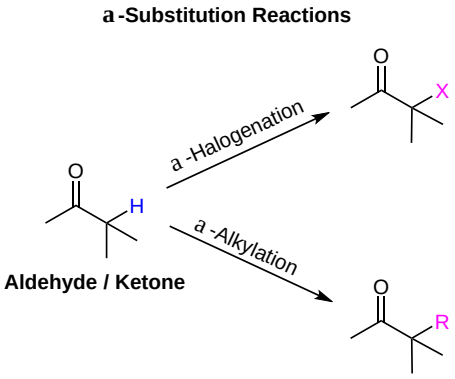
Nucleophilic Acyl Substitution Involving a Carbonyl

Reactions at The Alpha Carbon

The remaining common carbonyl reaction types are α-substitutions and carbonyl condensations. Both utilize the special properties of carbons directly adjacent to carbonyls which are called **α-carbons**. These reactions, which can be regarded as the backbone of much synthetic organic chemistry, usually result in the replacement of a hydrogen attached to an α-carbon with some type of electrophile. These reactions involve two new nucleophilic species called the enol and the enolate.



This chapter will focus on α-substitutions reactions. Although there are many carbonyl containing functional groups, the initial investigation in this chapter will focus on α-substitutions reactions using aldehydes and ketones. Important examples considered in this chapter include α-halogenation and α-alkylation.



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6.2: Keto-Enol Tautomerism

Objectives

After completing this section, you should be able to

1. write an equation to illustrate keto-enol tautomerism.
2. write a detailed mechanism for acid catalyzed keto-enol tautomerism.
3. write a detailed mechanism for base catalyzed keto-enol tautomerism.
4. draw the structure of the enol form of a given carbonyl compound.

Key Terms

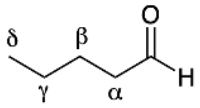
Make certain that you can define, and use in context, the key terms below.

- enol
- keto
- tautomerism
- tautomers
- enolate ion

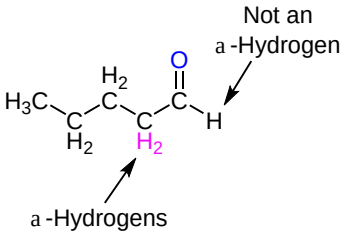
Study Notes

Keto-enol tautomerism was first introduced in the Alkyne Chapter, in the discussion of the hydration of alkynes. You may wish to review this section before proceeding.

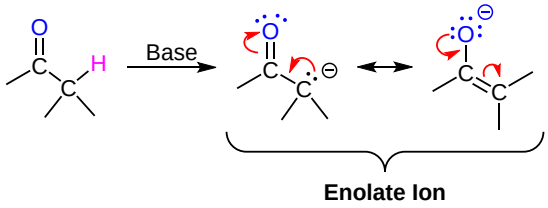
Often, the position of a carbon atom near a carbonyl group is designated using Greek letters. The atom adjacent to the carbonyl is alpha, the next removed is beta and so on. The carbon in the carbonyl group is used as reference point and is not assigned a Greek letter. Likewise, hydrogens bare the same Greek letter as the carbon atoms to which they are attached. α-Hydrogens are bonded to α-carbons and β-hydrogens are bonded to β-carbons etc.



The presence of α-hydrogens in a molecule provides the possibility of certain chemical reactions, which will be discussed in this chapter and the next chapter. Because of this, the ability to identify α-hydrogens is an important skill. As shown below, pentanal has two α-hydrogens. Note that aldehyde hydrogens are not given a Greek letter, they are simply referred to as an aldehyde hydrogen.

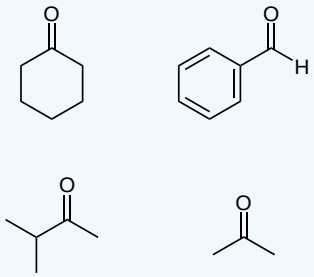


α-hydrogens, which are attached to a carbon directly adjacent to a carbonyl group, display unusual acidity. This is almost exclusively due to the resonance stabilization of the carbanion conjugate base, called an enolate, as illustrated in the diagram below. The effect of the the stabilizing C=O is seen when comparing the pK_a for the α-hydrogens of aldehydes (~16-18), ketones (~19-21), and esters (~23-25) to that of a typical alkyl C-H bond (~40-50).

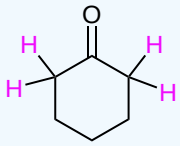


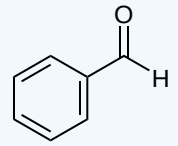
? Exercise 6.2.1

Indicate any α-hydrogens contained in the following molecules:

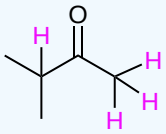


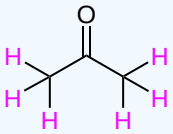
Answer





No a-Hydrogens

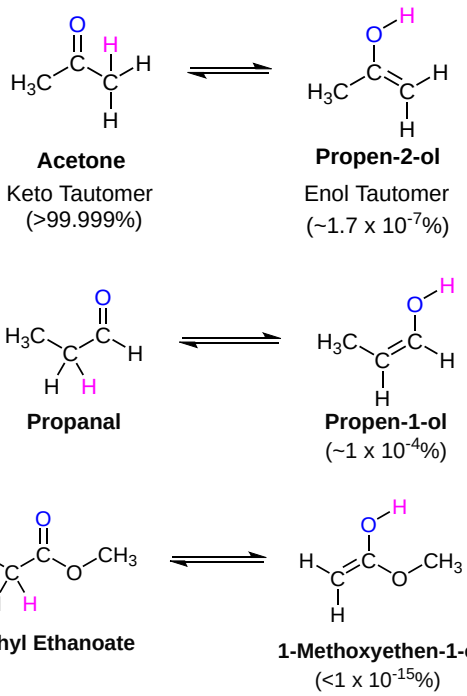




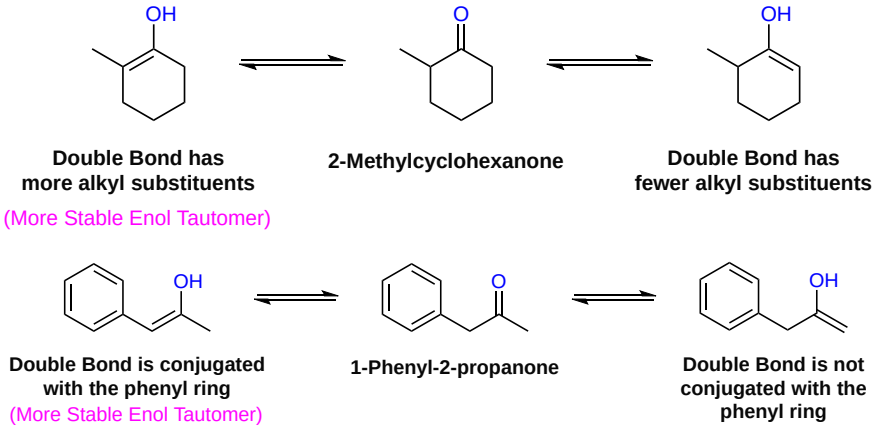
Keto-enol Tautomerization

Because of the acidity of α-hydrogens, many carbonyl containing compounds undergo a proton-transfer equilibrium called tautomerism. Tautomers are readily interconverted constitutional isomers, usually distinguished by a different location for an atom or a group. Because tautomers involve the rearrangement of atoms, they are distinctly different than resonance forms, which only differ in the position of bonds and lone pair electrons. This discussion focuses on carbonyl groups with α-hydrogens, which undergo keto-enol tautomerism. Keto implies that the tautomer contains a carbonyl bond while enol implies the presence of a double bond and a hydroxyl group.

The keto-enol tautomerization equilibrium is dependent on stabilization factors of both the keto tautomer and the enol tautomer. For simple carbonyl compounds under normal conditions, the equilibrium usually strongly favors the keto tautomer (acetone, for example, is >99.999% keto tautomer). The keto tautomer is preferred because it is usually more stable than the enol tautomer by about 45–60 kJ/mol, which is mainly due to the C=O double bond (-749 kJ/mol) being stronger than the C=C double bond (-611 kJ/mol). Because ketones have two alky groups donating electron density into the carbonyl carbon, they tend to be more stable and therefore less apt to form the enol tautomer than aldehydes. For example, propanal is 1000 times more likely to be in its enol tautomer than acetone. With carboxylic acid derivatives, the leaving group tends to stabilize the carbonyl through electron donation which makes the formation of the enol tautomer much less likely. In general, ketones are over 100,000,000 times more likely to be in an enol tautomer form than esters.

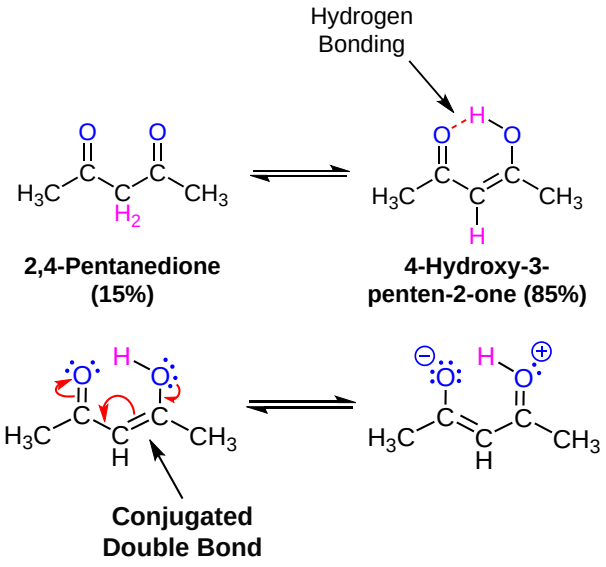


Aldehydes and symmetrical ketones typically only have one possible enol tautomer while asymmetrical ketones can have two or more. The preferred enol tautomer formed can be often be predicted by considering effects which can stabilize alkenes, such as conjugation and alkyl group substitution. The asymmetrical ketone, 2-methylcyclohexanone has two possible enol tautomers. Of the two tautomers, 2-methyl-1-cyclohexen-1-ol, is the more stable and therefore preferred due to the presence of an additional alkyl substituent. Likewise, 1-phenyl-1-propen-2-ol is the more stable enol tautomer of 1-phenyl-2-propanone due to conjugation with the phenyl ring.

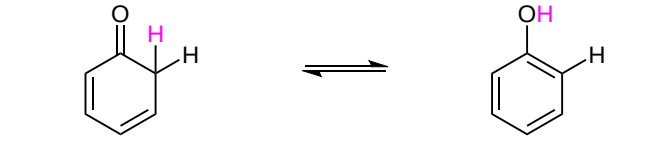


1,3-Dicarbonyls

In certain cases additional stabilizing effects allow the enol tautomer to be preferred in the tautomerization equilibrium. In particular, the 1,3 arrangement of two carbonyl groups can work synergistically to stabilize the enol tautomer, increasing the amount present at equilibrium. The diketone, 2,4-pentanedione, is in its enol form 85% of the time under normal conditions. The positioning of the carbonyl groups allows for the formation of a stabilizing intramolecular hydrogen bond between the hydroxyl group of the enol and the carbonyl oxygen. The alkene group of the enol tautomer is also conjugated with the carbonyl double bond which provides additional stabilization. Both of these stabilizing effects are not possible in the keto tautomer.



Another effect which can stabile an enol tautomer is aromaticity. When considering the molecule 2,4-cyclohexadienone, the enol tautomer is the aromatic molecule phenol. The stabilization gained by forming an aromatic ring is sufficient to make phenol the exclusive tautomer present in the equilibrium.



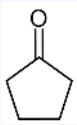
2,4-Cyclohexandienone
(Keto form, Non-aromatic)

Phenol
(Enol form,aromatic)

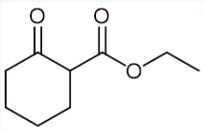
? Exercise 6.2.2

Please draw all of the possible enol tautomers for the following compounds. If more than one is possible then indicate which is the most stable and why.

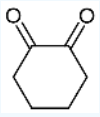
a)



b)



c)



Answer

a)

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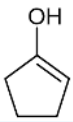
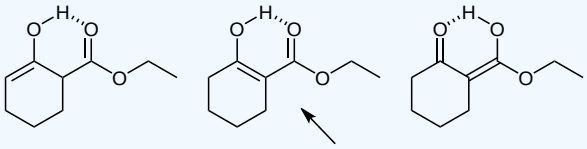
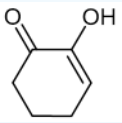


b)



This enol tautomer is the most stable due to hydrogen bonding, conjugation, and the ketone being in the enol form rather than the ester.

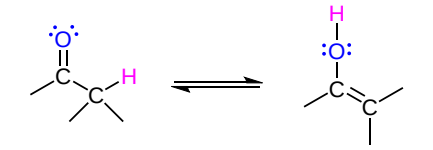
c)



Mechanism for Catalyzed Keto-Enol Tautomerization

The enol tautomer has valuable nucleophilic characteristics. In neutral media, tautomerization is slow but it can be speed up by catalysis with acids or bases. Both pathways involve two separate proton transfer steps. Because enols are a key reactive intermediate, these mechanistic steps will be used repeatedly in later reactions. The following mechanistic steps represent the continuous interconversion between the keto and enol tautomers.

Overall Process



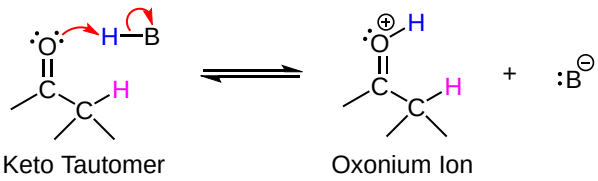
Keto Tautomer **Enol Tautomer**

Acidic Conditions

Keto Tautomer → Enol Tautomer

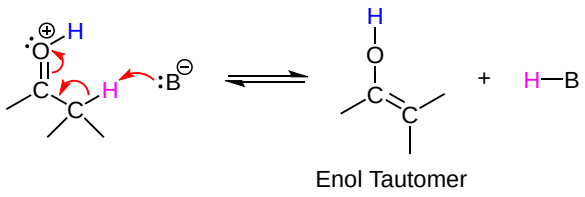
In the first step, the carbonyl oxygen is protonated by an acid to form an intermediate oxonium ion. A base removes an α-hydrogen during the second step forming a double bond by an E2 type reaction. This causes the pi electrons of the protonated carbonyl to move to the oxygen to form the hydroxyl group of the enol product and regenerating the acid catalyst.

1) Protonation of the carbonyl to form an oxonium ion



Keto Tautomer Oxonium Ion

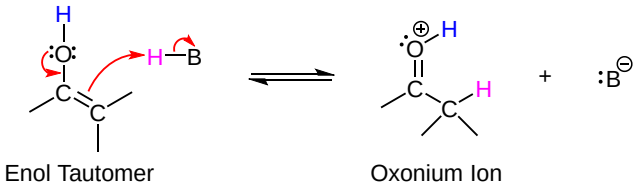
2) Deprotonation of an α-hydrogen to form an enol



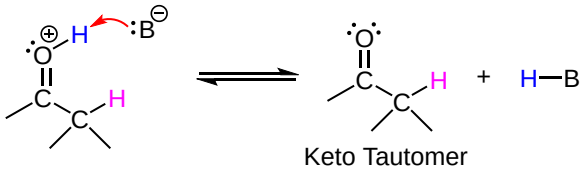
Enol Tautomer → Keto Tautomer

First, one of the lone pairs of electrons on the enol oxygen moves to form a pi bond with the adjacent carbon to create a oxonium ion. This also causes the pi bond electrons from the enol double bond to attack the electrophilic H^+ provided by acid catalyst forming a C-H bond in the α-position. This produced oxonium ion intermediate is subsequently deprotonated to form the neutral ketone and regenerate the acid catalyst.

1) Protonation at the α-carbon



2) Deprotonation

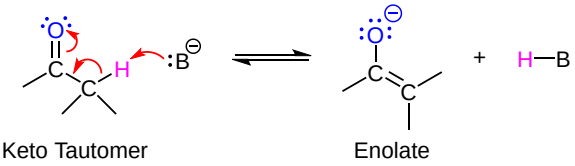


Under Basic Conditions

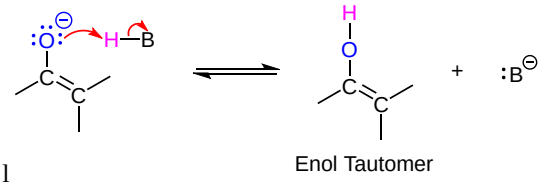
Keto Tautomer → Enol Tautomer

In the first step, a base removes an α-hydrogen from a carbonyl containing compound to form an alkene by an E2 like process. The causes the pi electrons of the carbonyl bond to move onto the carbonyl oxygen to form an enolate anion. The oxygen of the enolate anion is protonated in the second step to create a neutral enol and regenerate the base catalyst.

1) Deprotonation of a *α*-hydrogen to form an enolate ion



2) Protonation the enolate ion to form an enol



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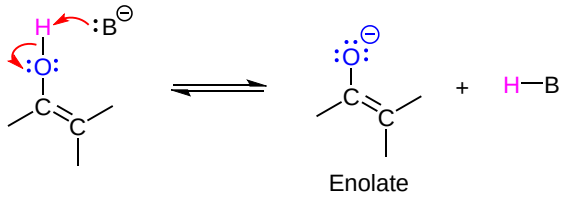
Enol Tautomer → Keto Tautomer

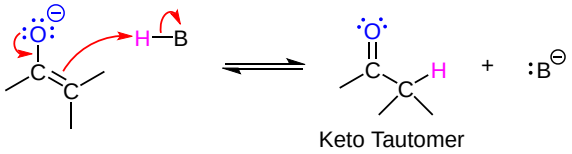
The mechanistic return to the keto tautomer begins with deprotonation of the hydroxyl hydrogen to produce an enolate ion. Then lone pair electrons from the enolate anion attack an electrophilic H^+ through conjugation with the double bond. This simultaneously

forms the carbonyl double bond, adds an alpha hydrogen, and regenerates the base catalyst.

1) Deprotonation of the enol hydrogen

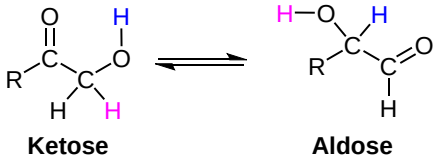


2) Protonation of the α-carbon



Biological Enol Forming Reactions

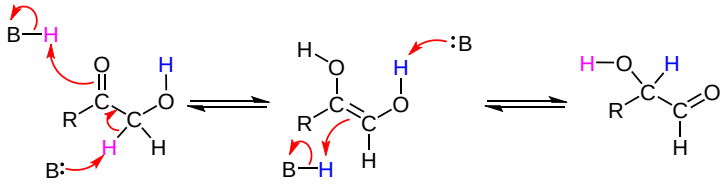
One very important family of isomerase enzymes catalyzes the shifting of a carbonyl group in sugar molecules using a process called an carbonyl isomerization. Carbonyl isomerization often involves converting between a ketose and an aldose. (recall that the terms ketose and aldose refer to sugar molecules containing ketone and aldehyde groups, respectively).



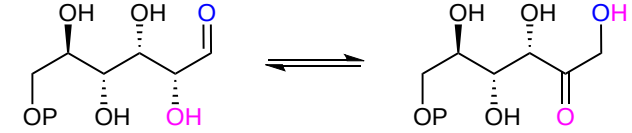
Carbonyl Isomerization

Mechanism

Carbonyl isomerization can only occur if there is an OH group adjacent to the carbonyl. Isomerization forms an ene-diol intermediate which has both OH hydrogens available to be removed to form a carbonyl. If the hydrogen from the original OH group is removed a new carbonyl bond is formed.



Carbonyl isomerization is involved in the metabolism of carbohydrates (starches and sugars) to their eventual conversion to CO_2 and H_2O. First, starches are broken down into glucose in the digestive tract. In the cells, the first step of the glycolysis pathway involves an enzyme converting glucose to glucose-6-phosphate. This is followed by the enzyme-catalyzed tautomerization of glucose-6-phosphate (an aldose) to fructose-6-phosphate (a ketose) through an enediol intermediate. Notice how the carbonyl has moved from the 1-carbon (terminal) to the 2-carbon.



Exercise 6.2.3

Draw the enol forms of the following molecules.

a. 4-methylcyclohexanone
b. Methyl acetate
c. Butanal
d. 1-phenyl-2-butanone

Answer

(a)

(b)

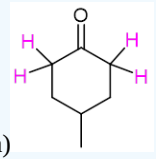
(c)

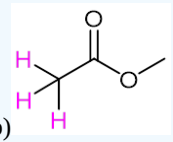
(d)

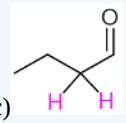
Exercise 6.2.4

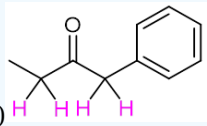
How many α-hydrogens do each of the molecules from the previous question have? Label them.

Answer

(a) 

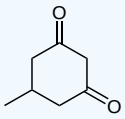
(b) 

(c) 

(d) 

Exercise 6.2.5

Draw all of the mono-enol forms for the following molecule. Which ones are most stable? Why?



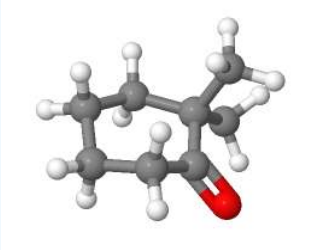
Answer

Additional resonance forms stabilizes this enol. Another explanation is that the enol alkene is conjugated to the carbonyl.

This enol has fewer resonance forms and is therefore less stable. There is no conjugation between the enol and the ketone.

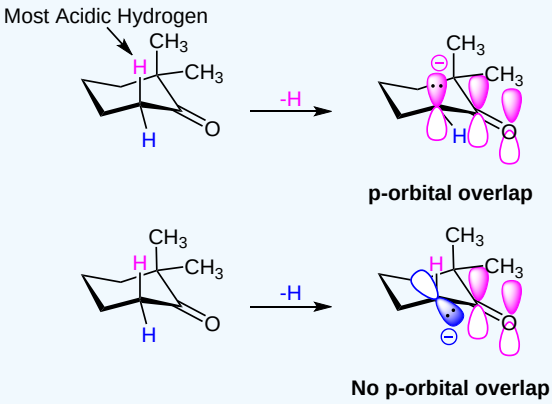
Exercise 6.2.6

For the following compound please identify the most acidic hydrogen atom. Remember that for an enolate conjugate base to be stabilized through conjugation, the lone pair electrons need to be contained in a p orbital which is parallel to the p orbitals which form the C=O pi bond.



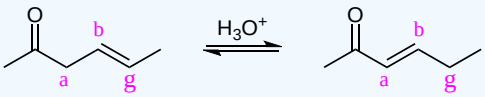
Answer

The presence of two methyl groups on one of the α-carbons of the carbonyl means that the two hydrogens on the other α-carbon may be deprotonated to form an enolate. When the indicated axial hydrogen is deprotonated the p-orbital formed is parallel with the carbonyl p-orbitals and can participate in overlap. If the equatorial hydrogen were to be deprotonated, the p-orbital formed would be perpendicular with the carbonyl p-orbitals and prevented from participating in overlap.

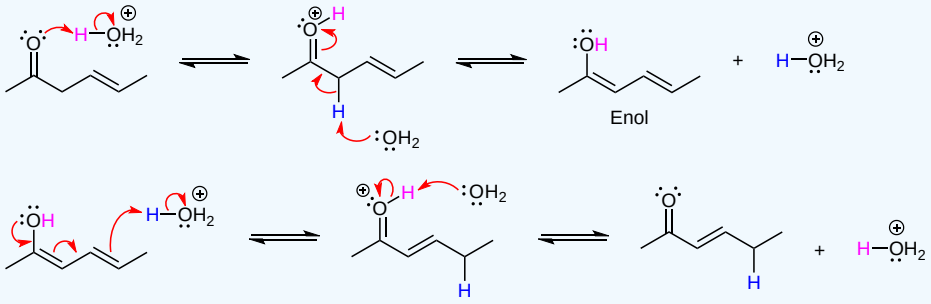


Exercise 6.2.7

Nonconjugated ß, gamma-unsaturated ketones, such as 2-hexen-4-one, can be converted to their α, ß-unsaturated isomers by treatment with an acid catalyst. Please propose a mechanism for this isomerization.



Answer



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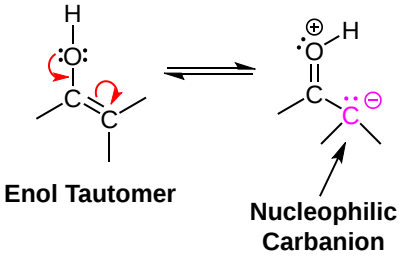
6.3: Reactivity of Enols- The Mechanism of Alpha-Substitution Reactions

Objectives

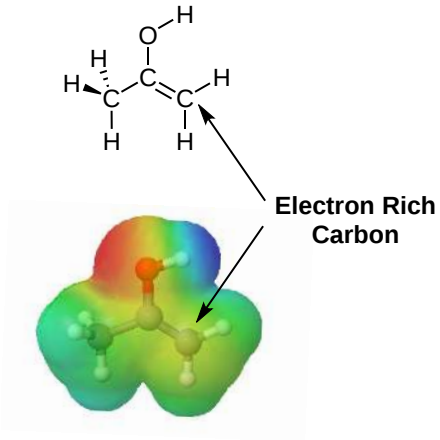
After completing this section, you should be able to write a detailed mechanism for an acid catalyzed, alpha substitution reaction of a carbonyl compound.

How Enols React

The oxygen of an enol can donate electron density into its double bond making it electron-rich and more reactive than typical alkenes.



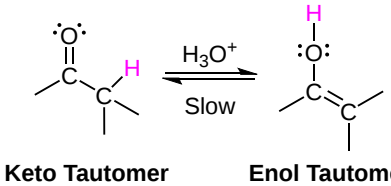
As seen in the electrostatic potential map for propen-2-ol ($CH_3COH{=}CH_2$), the enol tautomer of acetone, shows an increased electron density on the α-carbon (yellow) especially when compared to the -CH_3 carbon (blue/green). One of the resonance forms of an enol places a lone pair of electrons and a negative charge on the α-carbon forming a carbanion nucleophile. Enols react with electrophiles in a similar fashion as other carbanion nucleophiles, such as Grignard reagents.



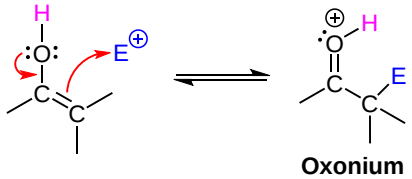
Mechanism of Alpha Substitution Reactions Using an Enol

The mechanism begins with the acid-catalyzed tautomerization to form an enol via the mechanism discussed in **Section 6.2**. Lone pair electrons on the enol oxygen move to become a C=O pi bond thus creating a positively charged oxonium ion. This also causes electrons from the C=C enol pi bond to attack an electrophile forming a C-E sigma bond. These two electron movements in concert represent the enol acting as a nucleophile. In the last step, an H^+ is removed from the carbonyl oxygen, regenerating the acid catalyst, and forming an *α*-substituted carbonyl .

1) Acid catalyzed tautomerization to form an enol

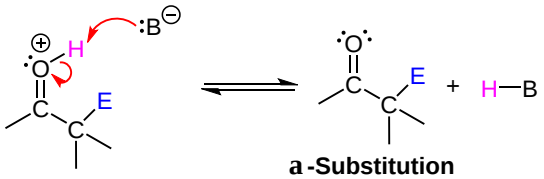


2) The nucleophilic enol attacks the electrophile



Oxonium Ion

3) Deprotonation of the carbonyl to produce an *α*-substituted product

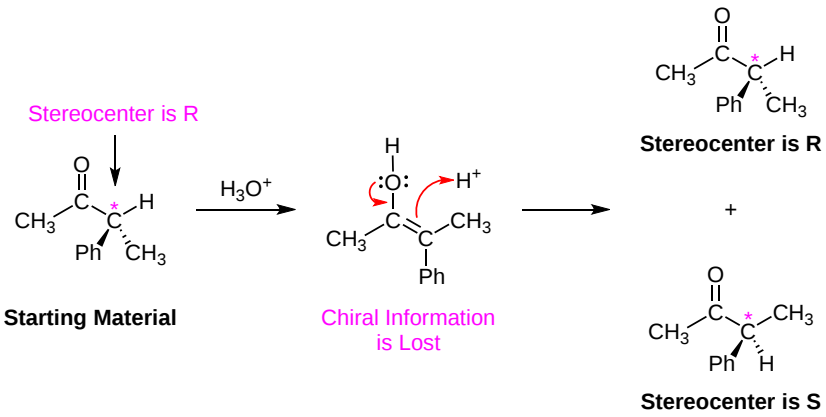


a -Substitution

Stereochemical Implication of Enol Formation

During an acid-catalyzed enol formation, an α-hydrogen is removed to form a sp^2-hybridized, trigonal planar C=C bond which removes any chiral information from the original alpha carbon. Because the enol alkene is planar the incoming electrophile can attack from either the top or the bottom of the molecule. If the α-carbon of the starting material has a defined stereochemistry or if a new stereocenter if formed during the reaction, the product will typically be a racemic mixture of enantiomers at the site of substitution.

One of the easiest ways of displaying this process is through acid-catalyzed racemization. If a carbonyl compound has an α-carbon with a defined stereochemisty and an α-hydrogen, a racemic mixture can be formed simply through tautomerization. The addition of acid promotes the formation of the enol tautomer which removes the chiral information of the α-carbon. The enol then attacks an H^+ electrophile to reform the keto tautomer which then contains a racemic mixture of enantiomers.



Starting Material

Chiral Information is Lost

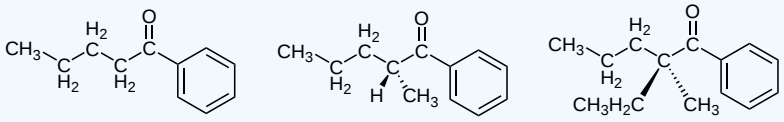
Stereocenter is R

Stereocenter is S

Example of Acid-Catalyzed Racemization

? Exercise 6.3.1

Which of the following ketones would undergo acid-catalyzed racemization? Explain.



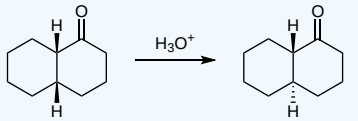
A **B** **C**

Answer

Molecule A would not because the alpha carbon is not a stereocenter. Molecule B would because the alpha carbon is a stereocenter and contains a hydrogen. Molecule C would not because it does not contain an alpha hydrogen.

Exercise 6.3.2

When *cis*-Decalone is treated with an acid it almost exclusively becomes *trans*-Decalone. Explain.



***Cis*-Decalone** ***Trans*-Decalone**

Answer

This change involves a process call epimerization. Epimers are diastereomers which differ at only one chiral carbon. Epimerization is a process where only one of multiple chiral carbons is changed. In this example, the stereocenter in questions is a chiral carbon. The addition of an acid promotes this carbon becoming part of an enol thereby losing its chiral information. When the enol tautomer converts back the ketone tautomer the a mixture of both *cis* and *trans* epimers should form. However, the *trans* isomer of the decalin ring system is more stable than the *cis*. Because there is a defined difference in stability, the trans isomer of decalone is preferred.

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6.4: Alpha Halogenation of Aldehydes and Ketones (reference only)

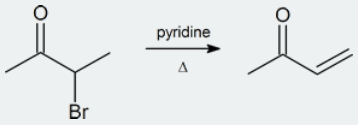
Objectives

After completing this section, you should be able to

1. write an equation to illustrate the alpha halogenation of aldehydes and ketones.
2. identify the product formed from the alpha halogenation of a given aldehyde or ketone.
3. identify the carbonyl compound, the reagents, or both, needed to prepare a given α-halogenated aldehyde or ketone.
4. illustrate the importance of the alpha halogenation of carbonyl compounds as an intermediate step in the synthesis of α,β-unsaturated aldehydes and ketones.
5. write a detailed mechanism for the acid catalyzed halogenation of a ketone.
6. describe the evidence provided by kinetic experiments supporting the suggestion that the acid catalyzed, alpha halogenation of ketones proceeds via the rate determining formation of an enol.

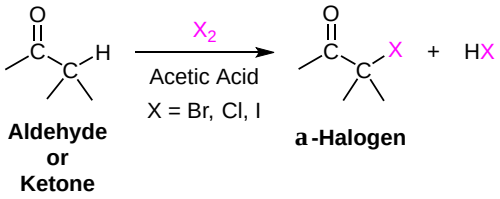
Study Notes

Note: α-bromo ketones are a good starting materials to generate α,β-unsaturated ketones by dehydrobromination.

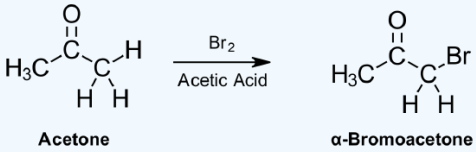


Aldehydes and ketones can substitute an α-hydrogen for a halogen atom in the presence of an acid. This reaction takes place using acid catalyzed tautomerization to form a nucleophilic enol, which then reacts with an electrophilic halogen (Cl_2, Br_2 or I_2). Because an enol intermediate is used, a racemic mixture of products can be produced. A particularly useful variation of this reaction uses bromine in an acetic acid solvent. The α-bromo substituted product can then be readily transformed into an α,β-unsaturated carbonyl through reaction with pyridine and heat.

General Reaction (*alpha* substitution)



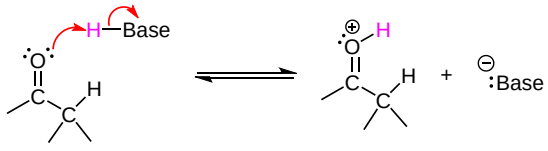
Example 6.4.1



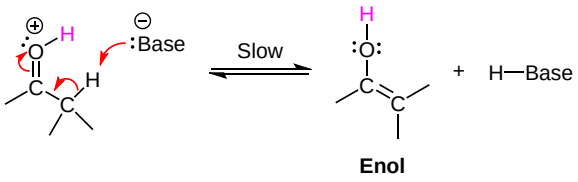
Acid Catalyzed Mechanism

The mechanism begins with protonation of the carbonyl oxygen followed by removal of an α-hydrogen to form the enol. Lone pair electrons from the enol oxygen move to form a carbonyl while the pi electrons from the double bond attack the halogen forming an oxonium ion intermediate with a C-X sigma bond in the α-position. Deprotonation of the oxonium ion intermediate provides the α-halogen substituted product and regenerates the acid catalyst.

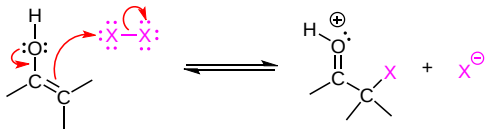
1) Protonation by the acid catalyst



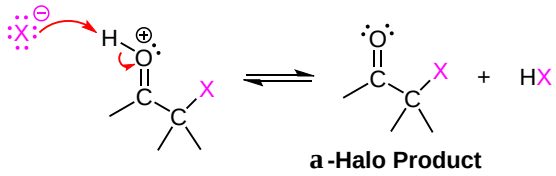
2) Removal of an α-hydrogen to form the enol. This step is slow and represents the rate determining step.



3) Nucleophilic attack on the halogen



4) Deprotonation



Experimental Evidence of the Enol Intermediate

This reaction was the focus of one of the first mechanistic investigations in organic chemistry. In the early 1900's chemist Arthur Lapworth showed that the rates of chlorination, bromination, and iodination of acetone were all the same. Also, it was shown that the rates for all three halogenation reactions were first-order with respect to acetone and the acid catalyst but independent of the halogen concentration (overall second-order for the mechanism). The rate law expression for the α-halogenation of a ketone can be given by:

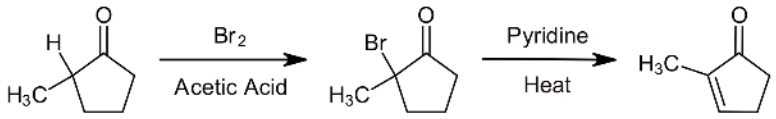
$$\text{rate} = k\,[\text{ketone}]\,[H^+]$$

This implies that the halogen participates in the mechanism through a fast step which occurs after the rate-determining step. These observations led Lapworth to theorize that the rate-determining step of the mechanism involves converting acetone to a more reactive form. The fact that the substitution occurs on the α-carbon led Lapworth to propose that the more reactive form was an enol tautomer of acetone.

Synthetic Uses for α-Halogenated Carbonyls

The product of an α-bromination can be converted to an α,β-unsaturated carbonyl by reaction with pyridine and heat which causes the elimination of H and Br. This reaction takes place by an E2 elimination mechanism and creates a C=C double bond which is conjugated with the carbonyl. In order to promote an E2 reaction, a sterically hindered base, pyridine, is often used.

An example of this reaction involves the α-bromination of 2-methylcyclopentanone to form 2-bromo-2-methylcyclopentanone. Because enol tautomers prefer to form on the more substituted α-carbon, α-bromination also occurs on the more substituted α-carbon. Although the enol intermediate causes a racemic mixture of the α-brominated compound to form, it is irrelevant because the chiral carbon is subsequently converted to an achiral alkene. Subsequent reaction with pyridine and heat forms the α,β-unsaturated ketone, 2-methyl-2-cyclopentenone.

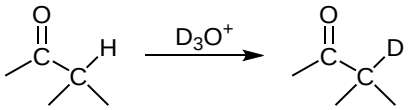


2-Methylcyclopentanone **(Racemic Mixture)** **2-Methyl-2-cyclopentenone**

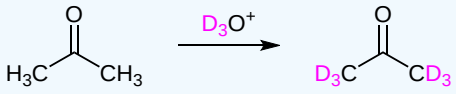
Deuterium Exchange

More evidence for the formation of an enol intermediate was provided using a reaction called deuterium exchange. Deuterium is an isotope of hydrogen which contains one proton and one neutron. Due to the acidic nature of α-hydrogens, they can be exchanged with deuterium by reaction with the isotopic form of water, D_2O (deuterium oxide-heavy water). The process is accelerated by addition of the deuterium equivalent of a strong acid, such as deuterium chloride (DCl), which quickly reacts with D_2O to form D_3O^+, the deuterium equivalent of hydronium (H_3O^+). If an excess of D_2O is used, the exchange process continues to the end result of all α-hydrogens present in a given compound being replaced with deuterium. Deuterium exchange is an effective method for introducing an isotopic label into a molecule. Also, deuterium does not appear in ^1H NMR, so deuterium exchange can help determine peak assignments.

General Reaction (Deuterium exchange)



Example 6.4.2



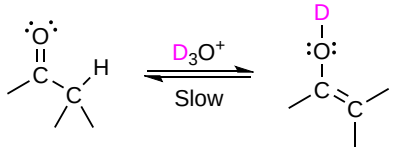
Acetone

Hexadeuteroacetone
Acetone-d6
Deuterated Acetone

Mechanism in Acidic Conditions

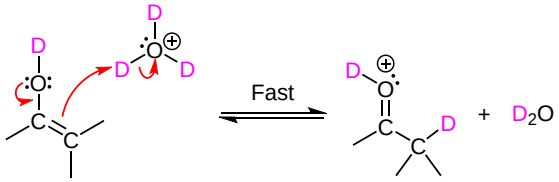
The mechanism for deuterium exchange is virtually the same as keto-enol tautomerism under acidic conditions, as shown in **Section 6.3**. The only difference is that when the keto tautomer is reformed a deuterium is placed in the *α*-position.

1) Formation of an enol

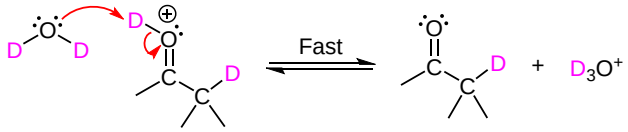


Aldehyde or Ketone **Enol**

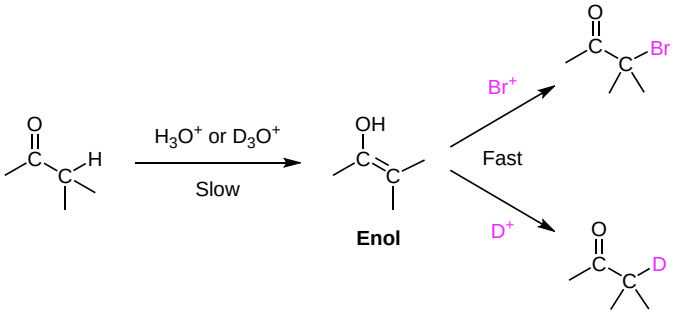
2) *α*-Deuteration



3) De-deuteration to form the keto tautomer

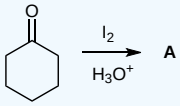


Kinetic investigations into the mechanism of this reaction provided further evidence for the formation of a reactive enol intermediate. It was shown that the rate of deuterium exchange was the same as the rate of halogenation for ketones. This implies that both reactions have a common intermediate involved in the rate determining step of their mechanism, an enol.

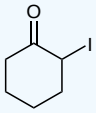


Exercise 6.4.1

Please draw the product of the following reaction.



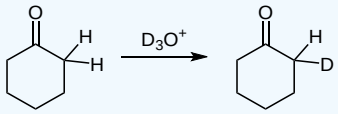
Answer



A

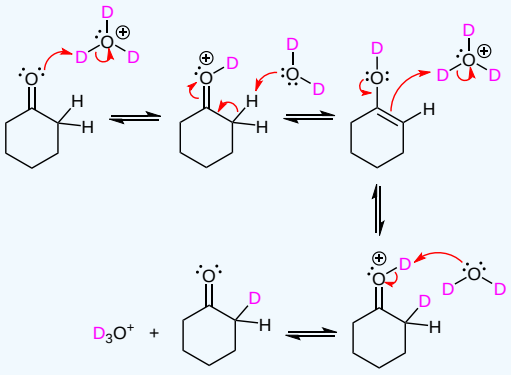
Exercise 6.4.2

Draw out the mechanism for the following reaction.



Answer

https://chem.libretexts.org/@go/page/443804



Exercise 6.4.3

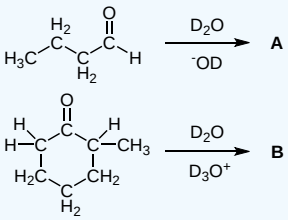
How might you form 2-hepten-4-one from 4-heptanone?

Answer

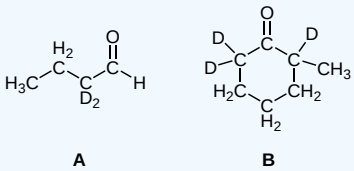
1) Br_2, H_3O^+; 2) Pyridine, Heat

Exercise 6.4.4

Show the products of the following reactions:



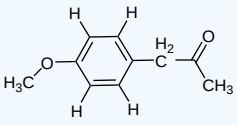
Answer



A B

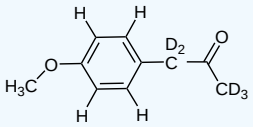
Exercise 6.4.5

The following compound was reacted with D_3O^+. The only signals that could be found in the ^1H NMR spectrum of the product were at 3.9 ppm (3H) and 6.6-6.9 ppm (4H). Please explain the results of the NMR.



Answer

A deuterium exchange reaction occurred. All of the alpha-hydrogens in the molecule have been exchanged with deuterium. Because detueriums do not appear in a typical ^1H NMR, only the remaining hydrogens appear.



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6.5: Alpha Bromination of Carboxylic Acids (reference only)

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the Hell-Volhard-Zelinskii reaction.
2. identify the product formed from the reaction of a given carboxylic acid with bromine and phosphorus tribromide.
3. identify the carboxylic acid, the reagents, or both, needed to synthesize a given α-bromo carboxylic acid.
4. outline the stereochemical implications of the fact that the Hell-Volhard-Zelinskii reaction proceeds through the formation of an acid bromide enol.

Key Terms

Make certain that you can define, and use in context, the key term below.

- Hell-Volhard-Zelinskii reaction

Study Notes

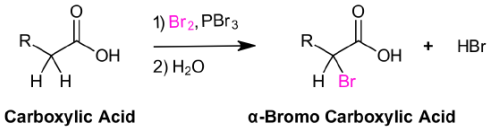
The reagents for the Hell-Volhard-Zelinskii reaction are given as bromine and phosphorus tribromide. In some questions, you may observe that only bromine and phosphorus are listed as reagents. Really there is no difference, as phosphorus tribromide would be formed *in situ* by the combination of bromine and red phosphorus:

$3Br_2 + 2P \rightarrow 2PBr_3$

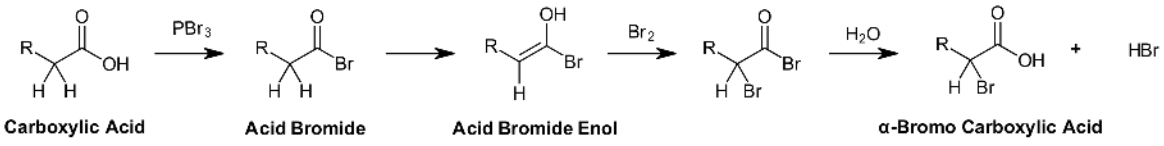
Excess bromine is required to ensure that enough reagent is available for the reaction with the enol.

Hell-Volhard-Zelinskii Reaction

Although the α-bromination of some carbonyl compounds, such as aldehydes and ketones, can be accomplished with Br_2 under acidic conditions, the reaction will generally not occur with carboxylic acids, esters, and amides. Carboxylic acids do not enolize to a sufficient extent since the carboxylic acid proton is preferably removed before an α-hydrogen. However, carboxylic acids, can be brominated in the α-position with a mixture of Br_2 and phosphorus tribromide (PBr_3) in what is called the Hell-Volhard-Zelinskii reaction.

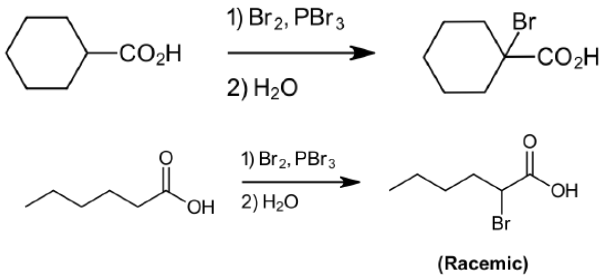


Mechanism



This reaction is the combination of three separate reaction mechanisms all of which have been previously discussed. The mechanism starts with the reaction of the carboxylic acid with PBr_3 to form an acid bromide and HBr. Formation of an acid bromide is vital to this reaction because they lack the acidic carboxylic acid proton and can enolize much more readily making α-bromination possible. Next, HBr catalyzes the tautomerization of the acid bromide into its enol tautomer, acid bromide enol, which subsequently reacts with Br_2 to give α-bromination. Lastly, the product undergoes nucleophilic acyl substitution which causes the hydrolysis of the acid bromide to reform the carboxylic acid and the HBr catalyst. Because an enol intermediate is formed, this reaction will form a racemic mixture at the α-carbon.

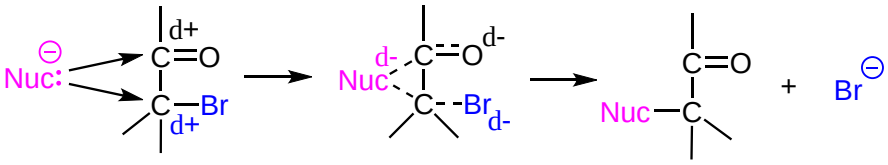
Examples



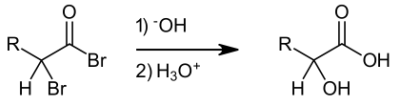
(Racemic)

Further Reactions of α-Bromo Carboxylic Acids

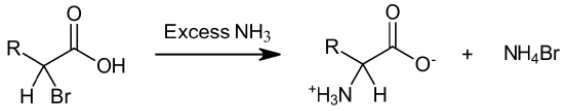
α-Bromo carboxylic acids are extremely useful synthetic intermediates because the halogen is highly reactive towards S_N2 reactions. Having the electrophilic carbon of the carbonyl adjacent to the electrophilic α-carbon attached to the bromine allows an incoming nucleophile to share its charge between the two. This stabilizes the transition state of the S_N2 reaction, lowering the energy of activation, and increasing reaction rates. Primary α-Halogenated carbonyls have S_N2 reaction rates which are much greater than the corresponding primary aliphatic halogens.



Because bromides are capable of reacting with a wide variety of nucleophiles, α-bromo carboxylic acids serve as important intermediates. Reaction of α-bromo carboxylic acids with an aqueous basic solution followed by an acidic work-up produces α-hydroxy carboxylic acids. Reaction of α-bromo carboxylic acids with an excess of ammonia provides α-amination, which provides a possible route to amino acids.

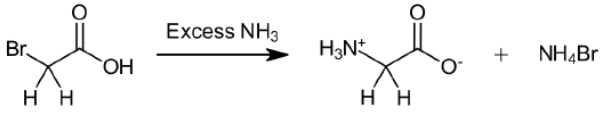


α-Bromo Carboxylic Acid **α-Hydroxy Carboxylic Acid**



α-Amino Carboxylic Acid

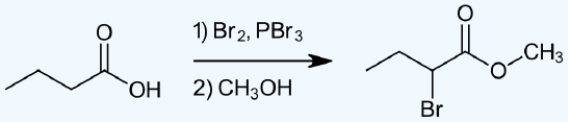
Example



Bromoacetic acid **Glycine**

? Exercise 6.5.1

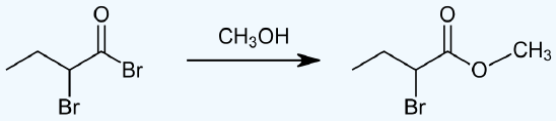
Explain why the following reaction occurs.



Answer

https://chem.libretexts.org/@go/page/443805

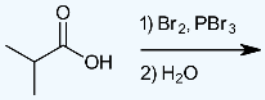
The first step represents the beginning of the Hell-Volhard-Zelinskii reaction which provides a-bromination and creates and acid bromide intermediate. The second step adds methanol which reacts with the acid bromide to produce an ester.



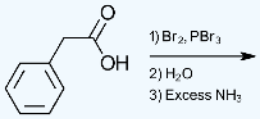
Exercise 6.5.2

Draw the products of the following reactions:

a)

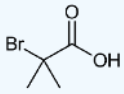


b)

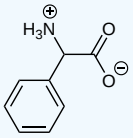


Answer

a)



b)



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6.6: Acidity of Alpha Hydrogen Atoms- Enolate Ion Formation

Objectives

After completing this section, you should be able to

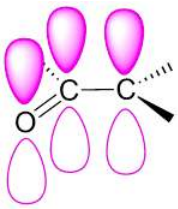
1. explain why the alpha hydrogens of carbonyl compounds are more acidic than the hydrogens in a typical hydrocarbon.
2. list the properties that make lithium diisopropylamide a suitable reagent for converting a wide range of carbonyl compounds into their enolate anions.
3. arrange a given list of carbonyl compounds in order of increasing or decreasing acidity.
4. determine whether a given carbonyl containing compound is more or less acidic than selected other compounds, such as water, ammonia, alcohols, alkanes, alkenes, alkynes and amines.
5. explain why dicarbonyl compounds, such as β-diketones, are more acidic than compounds that contain only a single carbonyl group.

Key Terms

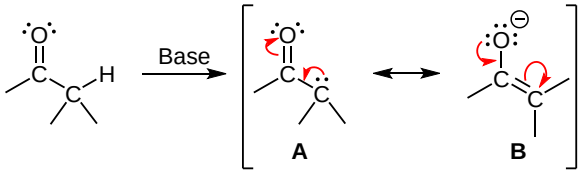
Make certain that you can define, and use in context, the key terms below.

- β-diketone
- β-keto ester

α-hydrogens are weakly acidic because their conjugate base, called an enolate, is stabilized though conjugation with the pi orbitals of the adjacent carbonyl. Removal of an α-hydrogen creates an sp^2 hybridized carbon anion. The negative charge and lone pair electrons of the carbon anion are contained in an unhybridized p orbital. Orbital overlap with p orbitals from the adjacent carbonyl pi bond allows for the lone pair electrons and negative charge to be shared with the electronegative carbonyl oxygen, stabilizing the negative charge of the enolate ion.

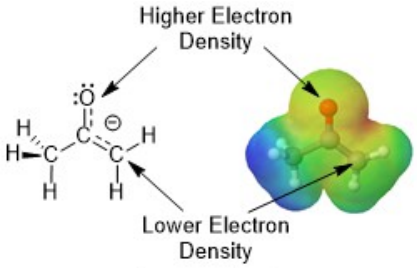


Enolate conjugation can be represent by two major resonance forms represented by structures A and B which share the negative charge (Shown Below). In resonance form A, the negative charge is on a carbon while in resonance form B the negative change is on an oxygen.



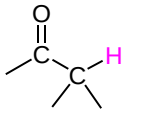
Enolate Ion

Resonance form B is preferred because oxygen is highly electronegative and better able to stabilize the negative charge. Both resonance form contribute to an overall resonance hybrid but not equally. Due to its stability, resonance form B makes a greater contribution to the resonance hybrid structure. Form B's increased contribution to the hybrid is seen when considering the electrostatic potential map of an acetone enolate. The red/yellow color shows there is a high electron density around the oxygen. The yellow/green color around the enolate carbon shows that there is a lower but still significant electron density present. Notice that the electron density on the enolate carbon is much larger than the non-enolate carbon (blue color).



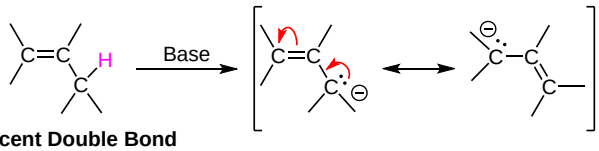
Acetone Enolate Resonance Hybrid

The effect of an adjacent carbonyl on the acidity of α-hydrogens is seen when comparing the pK_a of aldehydes (~16-18) and ketones (~19-21) to the pK_a of an alkane (~50). The ability of the electronegative oxygen to stabilize a negative charge can be seen by considering the pK_a of an allyl C-H bond (~42). Having a C-H bond adjacent to a C=C double bond allows the conjugate base created by deprotonating an allyl C-H bond to be stabilized by conjugation. However, the stability gained only provides a 10^8 increase in acidity when compared to an alkane. In comparison, the presence of an electronegative oxygen allows the acidity of an α-hydrogen to be 10^{30} times greater than that of an alkane.



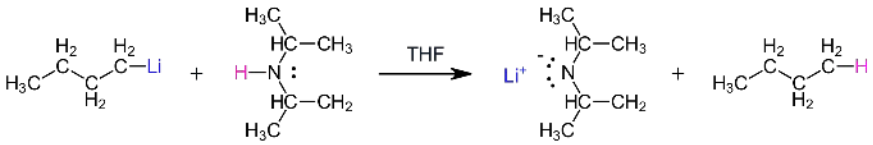
Aldehydes and Ketones (pK_a ~ 20)

Alkanes (pK_a ~ 50)



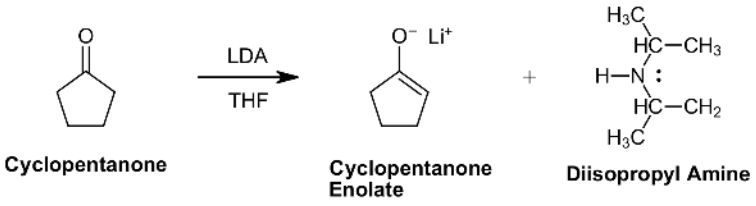
Adjacent Double Bond (pK_a ~ 42)

Although α-hydrogens are weakly acidic, typical strong bases such as a hydroxide or alkoxides are only capable of forming the enolate ion in very low concentrations. This can leave a significant concentration of the electrophilic carbonyl carbon remaining, which can react with the bases or the enolate. To achieve the complete deprotonation of aldehyde or ketone reactants to their enolate conjugate bases, a very strong base such as LDA (lithium diisopropylamide) must be used. Complete deprotonation removes the carbonyl groups of the starting material from the reaction mixture and prevents their ability to form unwanted products. Also, the large alkyl substituents sterically hinder the ability of LDA and its corresponding amine (diisopropyl amine) to undergo nucleophilic addition to the carbonyl. In addition to aldehydes and ketones, LDA readily deprotonates a wide variety of carbonyl containing functional groups including esters, amides and nitriles. Ether solvents like tetrahydrofuran (THF) are commonly used for enolate formation reactions using LDA. Certain other strong bases, such as alkyl lithium and Grignard reagents, cannot be used to make enolate anions because they rapidly and irreversibly add to the carbonyl groups. Nevertheless, these very strong bases are useful in the preparation of LDA. By reacting *n*-butyllithium with diisopropylamine (pK_a 36), LDA can be easily formed.

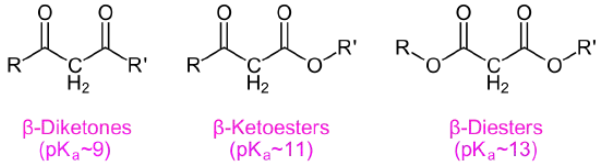


n-Butyllithium **Diisopropyl Amine** **Lithium Diisopropyl Amide (LDA)** **Butane**

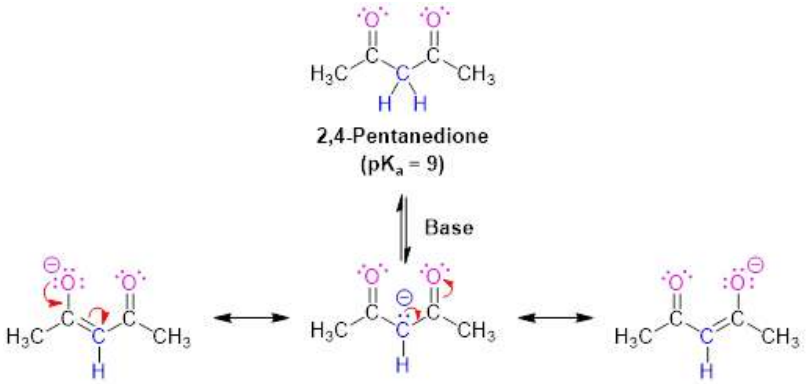
Example



Hydrogen atoms with two or more adjacent carbonyl groups are more acidic than typical α-hydrogens.



The enolate ions of compound such as *β*-diketones, *β*-keto-esters, and *β*-diesters are stabilized through additional resonance forms which share the negative charge with multiple carbonyl oxygens. The acidity of these compounds is increased to the point where weaker bases, such as sodium ethoxide ($NaOCH_2CH_3$) can be used to form the enolate.



The pK_a and acidic hydrogens of multiple functional groups are shown in the table below.

* = a functional group with two ketones.

Functional Group	Structure	pK_a
carboxylic acid	HO–(C=O)R	5
nitro	$RCH_2–NO_2$	9
β-diketone *	R(O=C)–CH_2–(C=O)R	9
β-ketoester *	R(O=C)–CH_2–(C=O)OR	11
β-diester *	RO(O=C)–CH_2–(C=O)OR	13
amide	RNH–(C=O)R	15
alcohol	$RCH_2–OH$	16
aldehyde	RCH_2–(C=O)H	17
ketone	RCH_2–(C=O)R	20
thioester	RCH_2–(C=O)SR	21
ester	RCH_2–(C=O)OR	25
nitrile	$RCH_2–C≡N$	25

Functional Group	Structure	pK_a
sulfone	$RCH_2–SO_2R$	25
amide	$RCH_2–(C=O)N(CH_3)_2$	30
alkane	$CH_3–R$	50

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6.7: Reactivity of Enolate Ions (haloform reaction is reference only)

Objectives

After completing this section, you should be able to

1. identify the two possible ways in which a given enolate anion could conceivably react with an electrophile.
2. write an equation to illustrate the haloform reaction.
3. identify the products formed from the reaction of a given methyl ketone with a halogen and excess base.
4. identify the methyl ketone, the reagents, or both, needed to obtain a specified carboxylic acid through a haloform reaction.

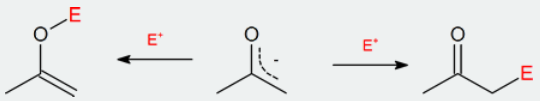
Key Terms

Make certain that you can define, and use in context, the key terms below.

- haloform
- haloform reaction

Study Notes

Because the negative charge on an enolate ion is delocalized, there are two reactive sites and therefore two potential products. The *α*-substituted product is much more common.



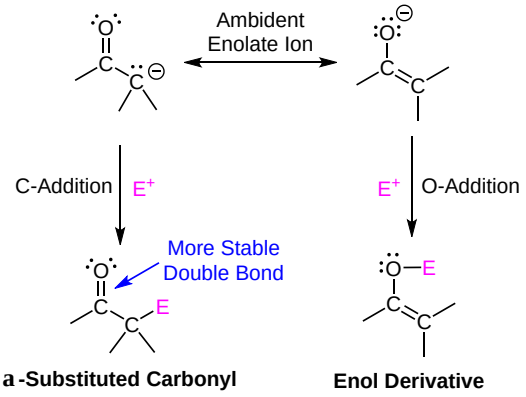
A “haloform” is any compound of the type CHX_3, where X = Cl, Br or I. Of these three compounds, chloroform is the most common.

The haloform reaction described in the reading is usually carried out with iodine. This reaction is called the “iodoform test,” and is one of the reactions carried out in the laboratory as a simple qualitative test for methyl ketones.

How Enolates React

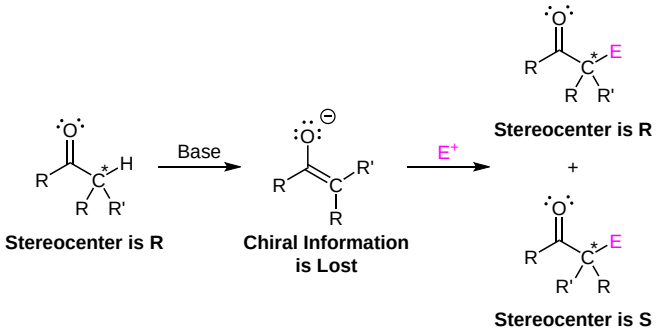
Due to their negative charges, enolates are better and more versatile nucleophiles than enols. The increased reactivity of enolates makes them capable of a wider range of reactions than enols. Also, α-hydrogen containing compounds can be completely converted to an enolate by reaction with a strong base. Whereas enols can only be created in small amounts through manipulating their equilibrium.

Since the negative charge of an enolate anion is delocalized between the α-carbon and an oxygen, electrophiles may bond to either atom. Reactants having two or more reactive sites are called ambident, so this term applies to enolate anions. Either the C of the O reactive site in an enolate may act as a nucleophile depending on the reaction conditions. Reactions with the oxygen would create a new O-E bond and produce an enol derivative. Reactions with the α-carbon creates a new C-E bond and creates an α-substituted carbonyl compound. Although reactions with the nucleophilic oxygen are possible, reactions involving the nucleophilic α-carbon are much more common, partially due to the thermodynamic stability of the C=O bonds in the final products. Also, the enolate counter ion, such as Li^+ or Na^+, is more tightly associated with the negatively charged enolate oxygen which can then block incoming electrophiles, reducing their chance of reaction at the oxygen.



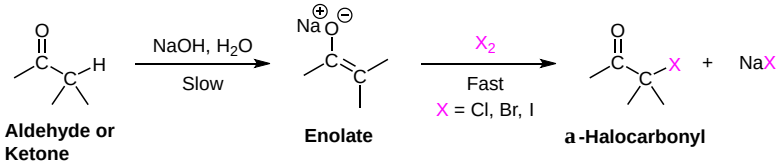
Stereochemical Implication of Enolate Formation

During enolate formation, an α-hydrogen is removed to form a sp^2-hybridized, trigonal planar C=C bond which removes any chiral information from the original α-carbon. Because the enolate alkene is planar, the incoming electrophile can attack from either the top or the bottom. If the α-carbon of the starting material has a defined stereochemistry or if a new stereocenter is formed during the reaction, the product will be a racemic mixture of enantiomers.



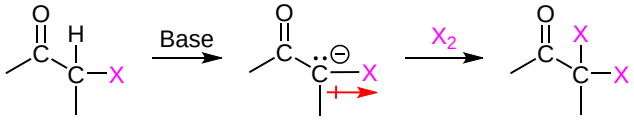
Base Promoted α-Halogenation

An enolate reacts rapidly with a halogen to produce α-halogenated carbonyl products. This reaction has the tendency to overreact and create polyhalogenated products. If a monohalogenated product is sought, the acid catalyzed halogenation reaction discussed in Section 6.4 is preferred. Because complete formation to the enolate is not necessary, weak bases, such as the hydroxide anion, are sufficient to produce this reaction. Once a small amount of enolate is formed, it quickly reacts with the halogen. This removes the enolate and shifts the equilibrium toward forming more enolate by Le Chatelier's principle.



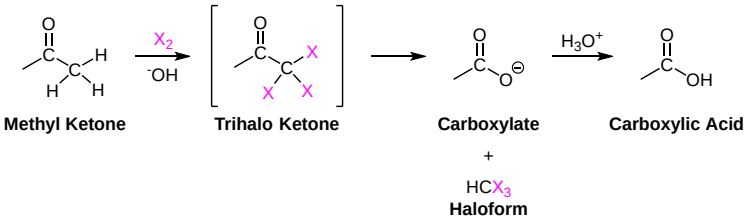
Overreaction During Base Promoted α-Halogenation

The α-hydrogens of halogenated carbonyl products are usually more acidic than the corresponding non-halogenated compounds. The inductive electron withdrawing effect of the electronegative halogen stabilizes the negative charge of the enolate ion. This promotes further enolate formation and also further halogenation of the α-carbon. Monohalogenated carbonyls form an enolate over 100 times faster than their non-halogenated counterparts making multiple halogenations of the α-carbon frequent. This effect is exploited to cause the haloform reaction.

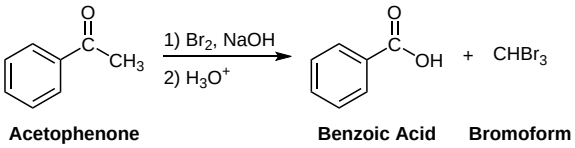


The Haloform Reaction

Overall, the haloform reaction represents a method for the conversion of methyl ketones to carboxylic acids. Due to the increased reactivity of α-halogenated products, methyl ketones typically undergo base promoted halogenation three times to give a trihalo-ketone. A halomethyl ion leaving group is then substituted with a hydroxide ion during nucleophilic acyl substitution. The resulting carboxylate can then be protonated to form a carboxylic acid.



Example

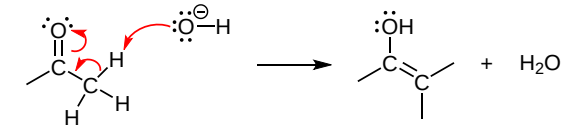


Mechanism

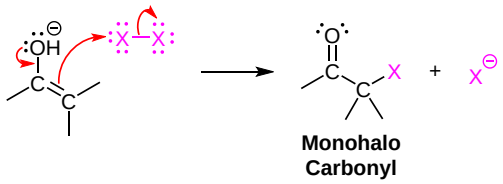
Note! This reaction is considered to be base promoted and not base catalyzed because an entire equivalent of base is required for each α-halogenation. Deprotonation of an α-hydrogen with hydroxide produces the nucleophilic enolate ion which subsequently reacts with the halogen. The increasing acidity of α-halogenated ketone causes this reaction to occur two more times. Once formed, the -CX_3 group attached to the carbonyl can act as a leaving group. Nucleophilic acyl substitution with a hydroxide anion causes C-C bond cleavage and eventually produces a haloform ($CHCl_3$, $CHBr_3$, CHI_3) and a carboxylate anion. The carboxylate ion is easily protonated with acid to form a carboxylic acid functional group. Often, this reaction is performed using iodine (I_2) because the subsequent iodoform (CHI_3) side-product is a bright yellow solid which is easily filtered off.

This reaction represents one of the few examples of a carbanion leaving group. The trihalomethyl ion ($^-:CX_3$) is particularly stabilized due to the inductive electron-withdrawing effects of the three halogens. The stability of the carbanion can be seen when considering the pK_a corresponding conjugate acid. In particular, bromoform ($CHBr_3$) has a pK_a of 13.7 which is more than 10^{36} times more acidic than a typical alkane C-H bond.

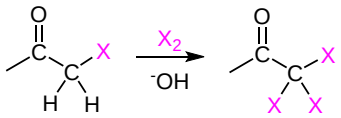
1) Enolate formation



2) Nucleophilic attack on the halogen

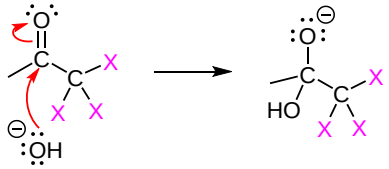


3) Repeat the halogenation two more times

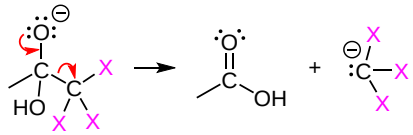


Trihalo Ketone

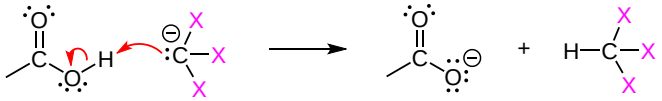
4) Nucleophilic attack on the electrophilic carbonyl carbon



5) Nucleophilic acyl substitution

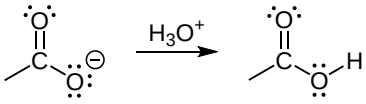


6) Deprotonation



Carboxylate **Haloform**

7) Protonation of the carboxylate

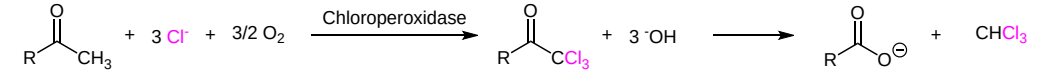


Carboxylic Acid

Biological Haloform Reaction

Interest in the haloform reaction has increased since the discovery that certain plants and marine algae can biosynthize chloroform, bromoform, and other small halocarbons through an analogous process. Previously it was assumed that these toxic compounds were present in the environment as a man-made pollutants.

The likely starting material of the biosynthesis are biogenic methyl ketones, a halogen anion, and oxygen. The enzyme, chloroperoxidase, catalyzes the polyhalogenation of the methyl groups. As in the haloform reaction, the final biosynthesis step involves a nucleophilic acyl substitution with a hydroxide anion to create a haloform and a carboxylate anion.



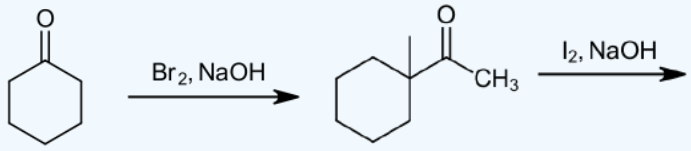
Methyl Ketone **Trichloromethyl Ketone** **Carboxylate anion** **Chloroform**

? Exercise 6.7.1

Please predict the expected products of the following reactions:

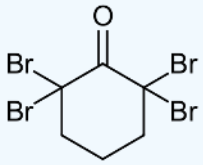
a)

b)

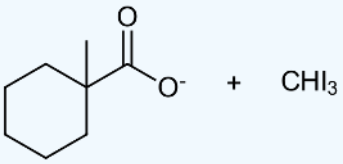


Answer

a)



b)



6.7: Reactivity of Enolate Ions (haloform reaction is reference only) is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer, Dietmar Kennepohl, Layne Morsch, & Layne Morsch.

- **22.6: Reactivity of Enolate Ions** by Dietmar Kennepohl, Layne Morsch, Steven Farmer is licensed CC BY-SA 4.0.

6.8: Alkylation of Enolate Ions

Objectives

After completing this section, you should be able to

1. write a general mechanism for the attack of an enolate anion on an alkyl halide.
2. write a reaction sequence to illustrate the preparation of carboxylic acids via the malonic ester synthesis.
3. identify the product formed, and all the intermediates, in a given malonic ester synthesis.
4. identify all of the compounds needed to prepare a given carboxylic acid by a malonic ester synthesis.
5. write a detailed mechanism for each of the steps involved in a malonic ester synthesis.
6. write a reaction sequence to illustrate the preparation of ketones through the acetoacetic ester synthesis.
7. identify the product formed, and all the intermediates, in a given acetoacetic ester synthesis.
8. identify all of the compounds needed to prepare a given ketone by an acetoacetic ester synthesis.
9. write a detailed mechanism for each of the steps involved in an acetoacetic ester synthesis.
10. identify the product or products formed when a given lactone, ester, nitrile or ketone is treated with lithium diisopropylamide followed by an alkyl halide.
11. identify the compounds needed to prepare a given α-substituted ketone, ester, lactone or nitrile by a method involving the alkylation of an enolate anion.

Key Terms

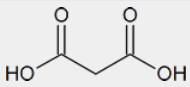
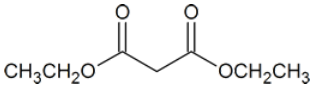
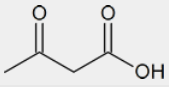
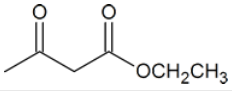
Make certain that you can define, and use in context, the key terms below.

- alkylation
- malonic ester synthesis

Study Notes

The two syntheses discussed in this section provide routes to a wide variety of carboxylic acids and methyl ketones. You may wish to review the factors influencing S_N2 reactions (Section 2.4) in conjunction with this section.

You should try to memorize the structures of malonic ester and ethyl acetoacetate. The IUPAC names of these compounds are shown in the table below.

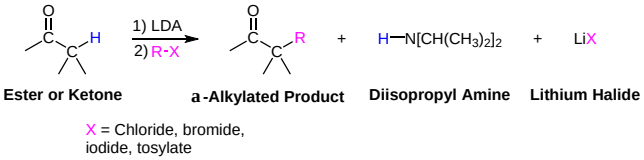
Structure	Common name	IUPAC name
	malonic acid	propanedioic acid
	malonic ester or diethyl malonate	diethyl propanedioate
	acetoacetic acid	3-oxobutanoic acid
	ethyl acetoacetate or acetoacetic ester	ethyl 3-oxobutanoate

Alkylation of Enolates

Enolates can be alkylated in the alpha position through an S_N2 reaction with alkyl halides. During this reaction an α-hydrogen is replaced with an alkyl group and a new C-C bond is formed. The limitations of S_N2 reactions still apply. This includes preferring a good primary or secondary leaving group, X = chloride, bromide, iodide, tosylate. Tertiary leaving groups cannot be used in this reaction and typically give undesired E2 elimination products. A very strong base, such as LDA, is often used because of its ability

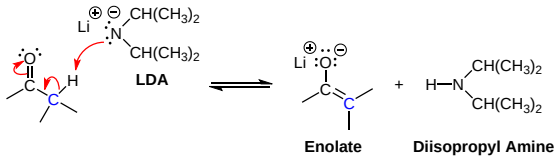
to form the enolate completely. Removal of the carbonyl starting material from the reaction mixture makes it unavailable for nucleophilic addition by the enolate. Aldehydes are usually not directly alkylated because their enolates prefer to undergo the carbonyl condensation reactions discussed later in **Section 7.1**. In addition, the acidic hydrogen on carboxylic acids inhibits the formation of an enolate, and makes their direct alkylation difficult. Esters, including lactones, and symmetrical ketones readily undergo direct alkylation. However, direct alkylations, like all enolate-based reactions, can form a racemic mixture if the alkylated α-carbon produced is chiral.

General Reaction

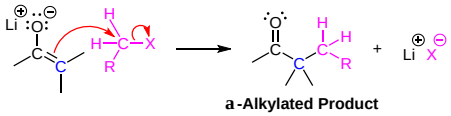


Mechanism

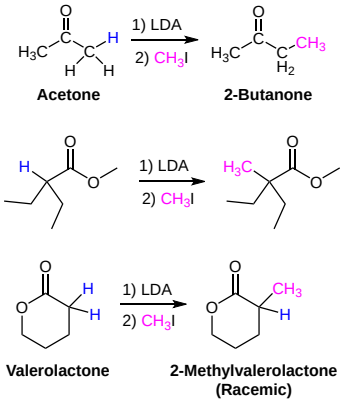
1) Enolate formation



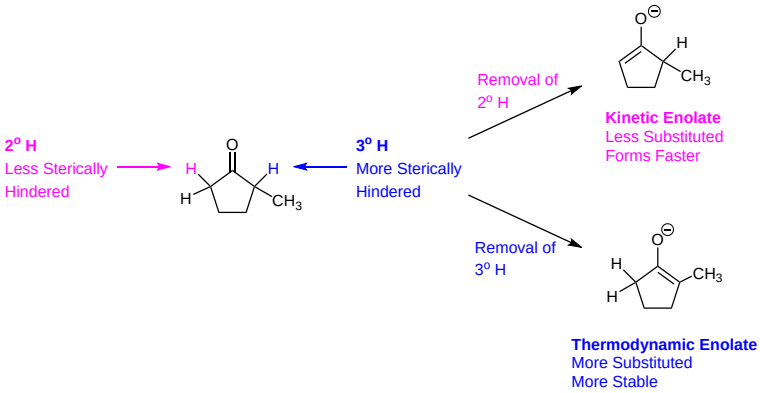
2) S_N2 attack



Examples



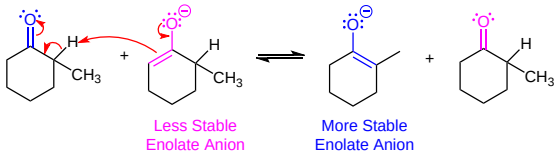
When an unsymmetrical ketone with two sets of non-equivalent α-hydrogens is treated with a base, two possible enolates can form. Regioselective enolate formation is possible under the proper conditions. The main determinant is whether the reaction is under kinetic control (rate) or thermodynamic control (equilibrium). Although a predominant product can be produced, a mixture of products is usually formed causing a reduction in product yield.



Thermodynamic Enolates

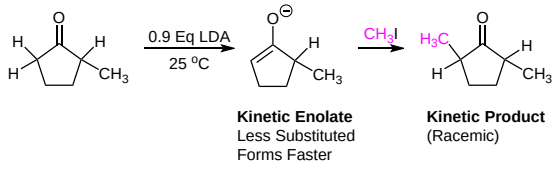
The thermodynamic enolate is formed when the more substituted α-hydrogen is removed. This leads to the more alkyl substituted, therefore the more stable, enolate to be formed. The presence of additional alkyl groups causes the formation of the thermodynamic enolate to be sterically hindered and kinetically slow, especially when a bulky base like LDA is used. Thermodynamic enolates are favored by conditions which allow for equilibration between the possible enolates. When the ketone starting material is not completely deprotonated, equilibrium between the possible enolates and the α-hydrogens of the ketone can occur. During equilibrium, interconversion between the enolates allows the lower energy of the thermodynamic enolate to dominate. Other conditions can also promote the formation of the thermodynamic enolate, such as higher reaction temperatures, or the use of a smaller less sterically hindered base such as sodium hydride (NaH). Weaker bases, such as sodium ethoxide, do not completely deprotonate the ketone starting material which also allows for enolate equilibrium to occur.

Example of enolate equilibration



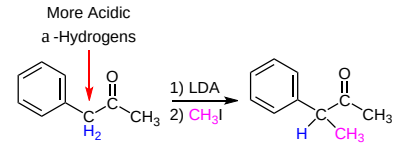
Kinetic Enolates

Kinetic enolates are favored under conditions which do not allow for equilibration between the enolates, such as the use of a strong bulky base, like LDA, in a molar equivalent to the ketone starting material. Kinetic enolates are formed when the less substituted α-hydrogen is deprotonated. Being less sterically hindered allows this α-hydrogen to be deprotonated faster even though it forms a less thermodynamically stable enolate. Using a molar equivalent of LDA completely converts the ketone starting material to an enolate, removing it from the reaction mixture and preventing equilibration between the possible enolates. Low reaction temperatures (-78 ºC) prevent enolate equilibration and promote the formation of the kinetic enolate.



When and enolate of an asymmetric ketone is stabilized through additional resonance forms there is no competition between possible enolates despite kinetic or thermodynamics conditions. The resonance stabilized enolate will be preferentially alkylated to the point that formation of the alkylated products of other possible enolates will be minimal.

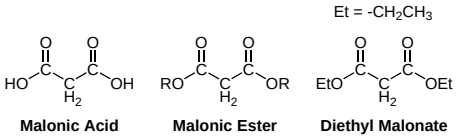
Example



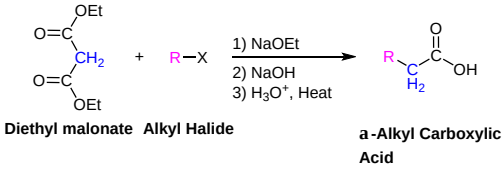
Malonic Ester Synthesis

The malonic ester synthesis is a series of reactions which converts an alkyl halide to a carboxylic acid with two additional carbons. One important use of this synthesis pathway is that it allows for the creation of α-alkylated carboxylic acids which cannot be created by direct alkylation.

The starting material of this reaction is a malonic ester: a diester derivative of malonic acid. Diethyl propanedioate, also known as diethyl malonate, is the malonic ester most commonly used in pathway. Since it is a 1,3-dicarbonyl compound, diethyl malonate has relatively acidic α-hydrogens (pK_a = 12.6) and can be transformed to its enolate using sodium ethoxide as a base. Other alkoxide bases are not typically used given the possibility of a transesterification reaction.

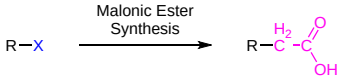


General Reaction



Predicting the Product of a Malonic Ester Synthesis

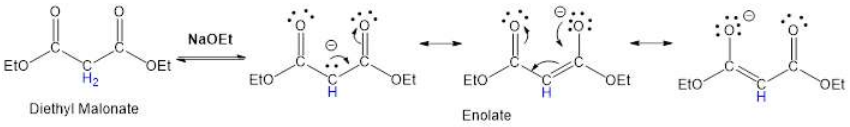
The product of a Malonic Ester Synthesis can be created by simply replacing the halogen on the alkyl halide with a $-CH_2CO_2H$ group.



Malonic ester synthesis takes place in four steps:

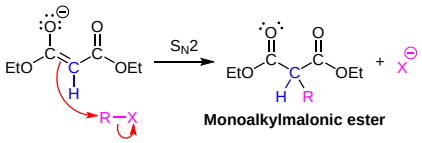
1) Enolate Formation

Reacting diethyl malonate with sodium ethoxide (NaOEt) forms a resonance-stabilized enolate.



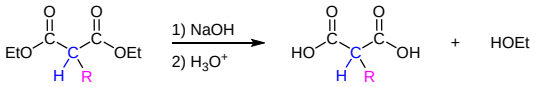
2) Alkylation

The enolate is alkylated via an S_N2 reaction to form an monoalkylmalonic ester.



3) Ester hydrolysis and protonation

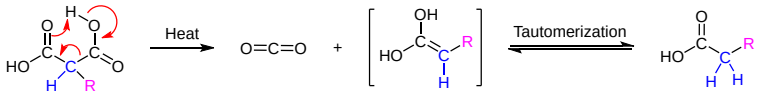
After alkylation, the diester undergoes hydrolysis with sodium hydroxide to form a dicarboxylate. Subsequent protonation with acid forms a monoalkyl malonic acid.



Monoalkyl Malonic Acid

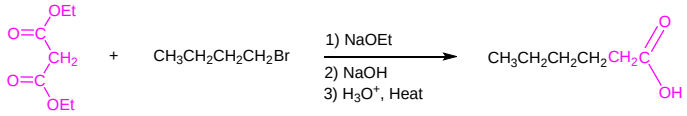
4) Decarboxylation & Tautomerization

Monoalkyl malonic acids decarboxylate when heated, forming an α-alkyl carboxylic acid and carbon dioxide (CO_2). Decarboxylation can only occur in compounds with a second carbonyl group two atoms away from carboxylic acid such as in malonic acids and β-keto acids. The mechanism occurs via a concerted mechanism involving a proton transfer between the carboxyl acid hydrogen and the nearby carbonyl group to form the enol of a carboxylic acid and CO_2. The enol undergoes tautomerization to form the carboxylic acid.



Carbon Dioxide **Carboxylic Acid Enol** **a -Alkylated Carboxylic acid**

Example

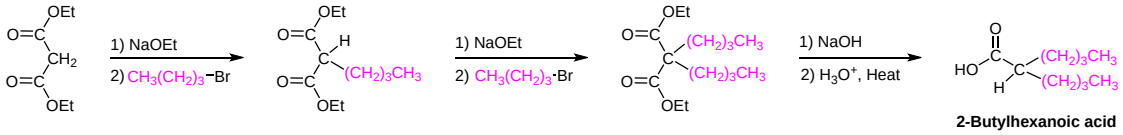


Diethyl malonate **1-Bromobutane** **Hexanoic Acid**

Dialkylation

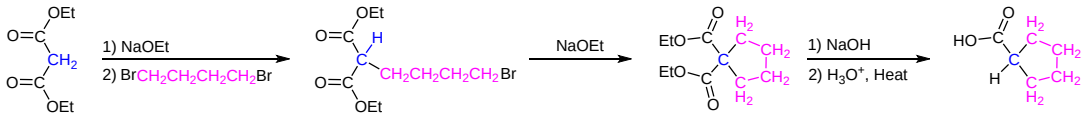
The presence of two α-hydrogens in malonic esters allows for a second alkylation to be performed prior to decarboxylation. This leads to dialkylated carboxylic acids. Due to the lack of stereochemical control inherent in enolate based reactions, if the two added alkyl groups are different, a racemic mixture of products will result.

Examples



2-Butylhexanoic acid

In a variation of the dialkylation reaction - if one molar equivalent of malonic ester is reacted with one molar equivalent of a dihaloalkane and two molar equivalents of sodium ethoxide, a cyclization reaction occurs. By changing the dihaloalkane, three, four, five, and six-membered rings can be created.

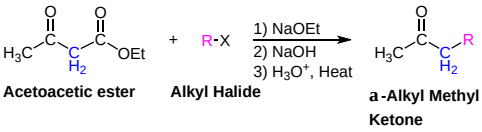


Cyclopentanecarboxylic acid

The Acetoacetic Ester Synthesis

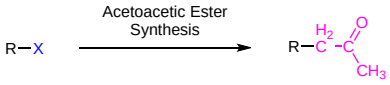
The acetoacetic ester synthesis is a series of reactions which converts alkyl halides into a methyl ketone with three additional carbons. This reaction creates an α-substituted methyl ketone without side-products. The starting reagent for this pathway is ethyl 3-oxobutanoate, also called ethyl acetoacetate, or acetoacetic ester. Like other 1,3-dicarbonyl compounds, ethyl acetoacetate is more acidic than ordinary esters being almost completely converted to an enolate by sodium ethoxide.

General Reaction



Predicting the Product of an Acetoacetic Ester Synthesis

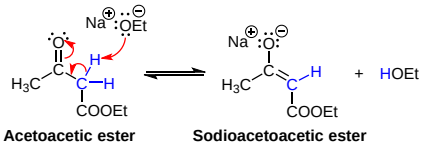
The product of a acetoacetic ester synthesis can be created by replacing halogen on the alkyl halide with a -CH_2COCH_3 group.



Reaction Steps

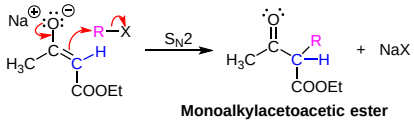
1) Formation of the enolate

As previously described, the α-hydrogens of acetoacetic ester are rather acidic (pK_a = 10.7) allowing the enolate to be easily formed when sodium ethoxide is used as a base.



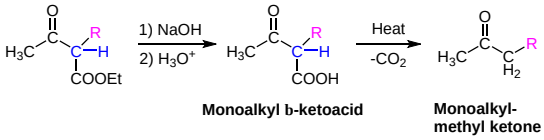
2) Alkylation via an S_N2 Reaction

Subsequent reaction with an alkyl halide produces a monoalkylacetoacetic ester.

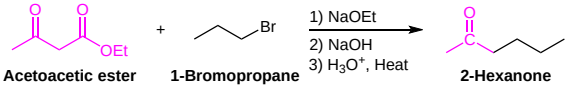


3) Ester hydrolysis and decarboxylation

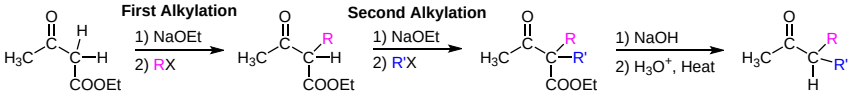
Hydrolysis with NaOH followed by protonation produces an alkylated beta-ketoacid. β-ketoacids are easily decoboxylated to form an α-alkyl substituted methyl ketone and carbon dioxide (CO_2) using a similar mechanism as the malonic ester synthesis.



Examples

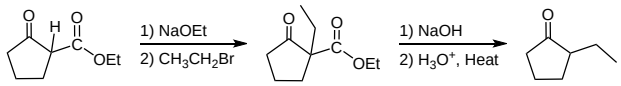


Much like the malonic ester synthesis, a second alkyl group can added before the decarboxylation step.



The reaction steps of the acetoacetic ester synthesis can also be applied to other β-keto esters with acidic α-hydrogens. Because the α-hydrogens between the two carbonyls are the most acidic, they are preferentially deprotonated allowing for a single enolate to be formed. Even cyclic beta-keto esters can be alkylated and subsequently decarboxylated to give an α-alkylated cyclic ketone.

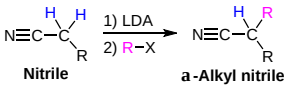
Examples



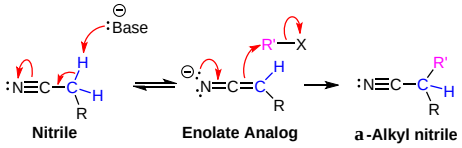
Direct Alkylation of Nitriles

The presence of acidic α-hydrogens in nitriles gives them the ability to form an enolate equivalent which can be also be directly alkylated.

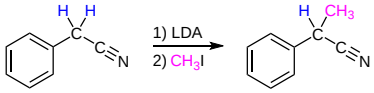
General Reaction



Mechanism



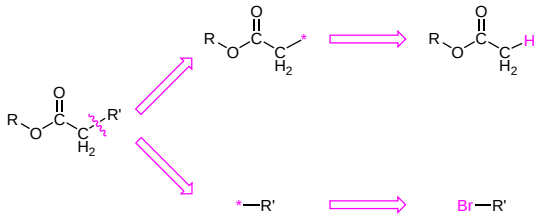
Example



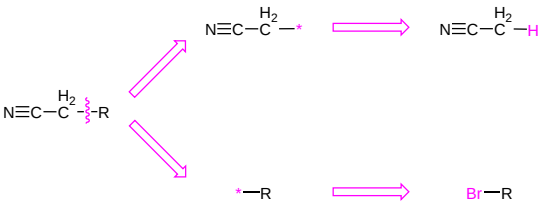
Planning a Synthesis Using Enolate Alkylations

When planning a synthesis that could involve enolates, the key is to recognize the functionality which can form an enolate. During retrosynthetic analysis a C-C bond is broken between the α-carbon and the β-carbon away from this functionality. It is also important to be able to identify specific groups of atoms which indicate if a malonic ester or an acetoacetic ester synthesis can be used. Having multiple C-C bonds which can be broken allows for multiple synthetic pathways.

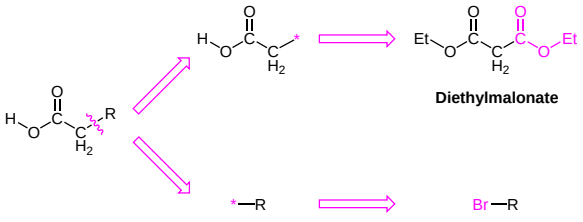
After retrosynthetically breaking the C-C bond, the fragment with the functionality will gain a hydrogen and the other fragment will gain a halogen. Sometimes the fragment with the functionality will become diethyl malonate or acetoacetic ester.

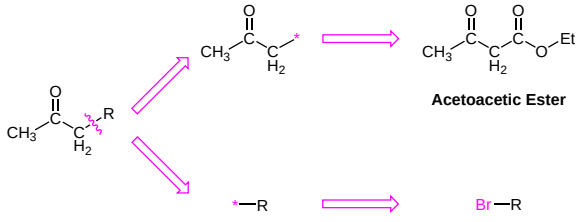


Direct Alkylation of an Ester



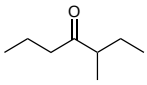
Direct Alkylation of a Nitrile



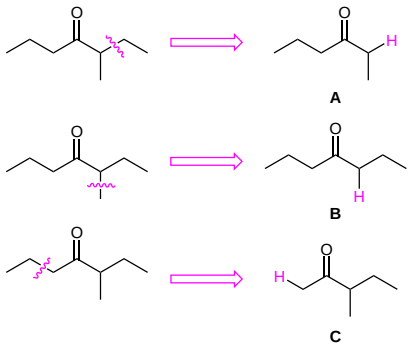


Worked out example:

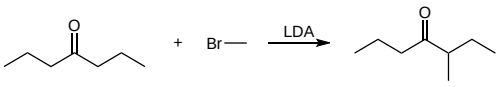
Plan a synthesis of the following molecule using an alkylation of an enolate. Consider multiple pathways and explain which is preferable.



The target molecule does not contain the appropriate fragments to utilize either the malonic ester or acetoacetic acid synthesis so direct alkylation of a ketone will likely be used. When analyzing this molecule, there are three α-β C-C bonds which could be cleaved to create a possible starting material. When looking at the possible starting materials, A and C are asymmetrical ketones and therefore can create multiple products during alkylation. B is a symmetrical ketone and should be the most likely to create the target molecule in high yield.

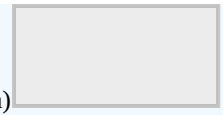


Possible Synthesis

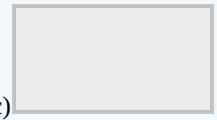


? Exercise 6.8.1

Propose a synthesis for each of the following molecules from this malonic ester.

(a) 

(b)

(c) 

Answer

(a) 1) Malonic Ester, NaOEt, 2) 4-Methylbenzyl Bromide, 3) Base, 4) Acid, Heat

(b) 1) Malonic Ester, NaOEt, 2) 3-bromohexane, 3) Base, 4) Acid, Eat

(c) 1) Malonic Ester, NaOEt, 2) 1-Bromo-2,3,3-trimethylbutane, 3) Base, 4) Acid, Heat

Exercise 6.8.2

Why can't you prepare tri substituted acetic acids from a malonic ester?

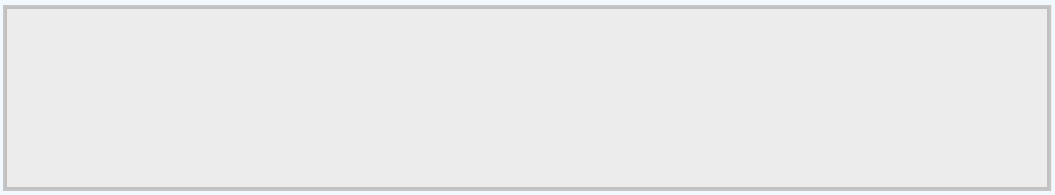
Answer

Malonic esters only contain two acid protons.

Exercise 6.8.3

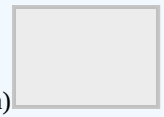
Propose a synthesis for the following molecule via a malonic ester.

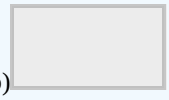
Answer

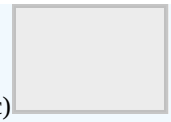


Exercise 6.8.4

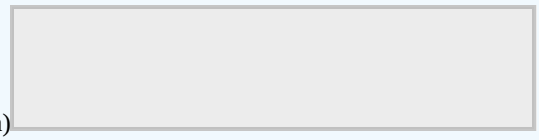
How might you prepare the following compounds from an alkylation reaction?

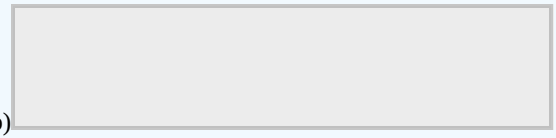
(a) 

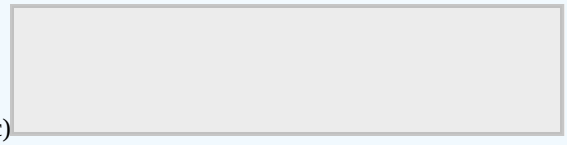
(b) 

(c) 

Answer

(a) 

(b) 

(c) 

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6.S: Carbonyl Alpha-Substitution Reactions (Summary)

Concepts & Vocabulary

- Four common types of reactions involving carbonyl reactions: 1) nucleophilic addition; 2) nucleophilic acyl substitution; 3) alpha substitution; 4) carbonyl condensations. The first two were previously discussed and the second two involve the properties of the carbon directly adjacent to the carbonyls, **α carbons**.
- Alpha-substitution reactions results in the replacement of an H attached to the alpha carbon with an electrophile.
- The nucleophile in these reactions are new and called enols and enolates.
- In this chapter, the focus is on α substitutions reactions with aldehydes and ketones.

6.1 Keto-Enol Tautomerization

- Greek letters are used to denote the carbon atoms near carbonyls.
- The carbon in the carbonyl is the reference point and the alpha carbon is adjacent to the carbonyl carbon.
- Hydrogen atoms attached the these carbons denoted with Greek letters will have the same designation, so an alpha hydrogen is attached to an alpha carbon.
- Aldehyde hydrogens not given Greek leters.
- α hydrogens display unusual acidity, due to the resonance stabilization of the carbanion conjugate base, called an enolate.
- Tautomers are readily interconverted constitutional isomers, usually distinguished by a different location for an atom or a group, which is different than resonance.
- The tautomerization in this chapter focuses on the carbonyl group with alpha hydrogen, which undergo keto-enol tautomerism.
- Keto refers to the tautomer containing the carbonyl while enol implies a double bond and a hydroxyl group present in the tautomer.
- The keto-enol tautomerization equilibrium is dependent on stabilization factors of both the keto tautomer and the enol tautomer, though the keto form is typically favored for simple carbonyl compounds.
- The 1,3 arrangement of two carbonyl groups can work synergistically to stabilize the enol tautomer, increasing the amount present at equilibrium.
- The positioning of the carbonyl groups in the 1,3 arrangement allows for the formation of a stabilizing intramolecular hydrogen bond between the hydroxyl group of the enol and the carbonyl oxygen as well as the alkene group of the enol tautomer is also conjugated with the carbonyl double bond which provides additional stabilization.
- Aromaticity can also stabilize the enol tautomer over the keto tautomer.
- Under neutral conditions, the tautomerization is slow, but both acid and base catalysts can be utilized to speed the reaction up.
- Biological enol forming reactions use isomerase enzymes to catalyze the shifting of a carbonyl group in sugar molecules, often converting between a ketose and an aldose in a process called carbonyl isomerization.

6.2 Reactivity of Enols: The Mechanism of Alpha-Substitution Reactions

- The oxygen of the enol donates electron density to the double bond making it more electron rich and thus more reactive than a typical alkene.
- The mechanism starts with an acid-catalyzed tautomerization to form an enol.
- The double bond is then able to act as a nucleophile and attack an electrophile.
- The final product is an alpha-substituted carbonyl after the deprotonation of the carbonyl to also regenerate the acid-catalyst.
- The enol formed has planar geometry, which means the electrophile can attach on the top or bottom of the alpha-carbon.
- A racemic mixture can result if a sterocenter is created at the site of substitution.

6.3 Alpha Halogenation of Aldehydes and Ketones (reference only)

- Aldehydes and ketons can undergo a substitution of an alpha hydrogen to a halogen.
- An acid-catalyzed tautomerization starts the mechanism followed by the enol attacking molecular halogens.
- The nucleophile in this reaction is the enol and the electrophile is the halogen.
- Mechanistic studies showed that the reaction was a first-order in the ketone.
- The halogen is part of a fast step after the rate-determing step.
- The formation of an enol intermediate was provided using a reaction called deuterium exchange.
- Due to the acidic nature of α hydrogens they can be exchanged with deuterium by reaction with the isotopic form of water, D_2O.

- The mechanism for deuterium exchange is virtually the same as that of keto-enol tautomerism under acidic conditions, the difference being a deuterium is placed in the α-position.
- Both alpha halogenation and deuterium exhange reactions were found to have a common intermediate involved in the rate determining step of their mechanism, an enol.

6.4 Alpha Bromination of Carboxylic Acids (reference only)

- The α-bromination of some carbonyl compounds, such as aldehydes and ketones, can be accomplished with Br_2 under acidic conditions, but the reaction will generally not occur with more stable carboxylic acid derivatives.
- Carboxylic acids do not enolize to a sufficient extent since the carboxylic acid proton is preferably removed before an α-hydrogen.
- Carboxylic acids, can be brominated in the α position with a mixture of Br_2 and phosphorus tribromide (PBr_3) in what is called the Hell-Volhard-Zelinskii reaction.
- α-Bromo carboxylic acids are extremely useful synthetic intermediates because the halogen is highly reactive towards S_N2 reaction.
- Reaction of a α-bromo carboxylic acids with an excess of ammonia provides α-amination, which is a possible route to amino acids.

6.5 Acidity of Alpha Hydrogen Atoms: Enolate Ion Formation

- α hydrogens are weakly acidic because the conjugate base, called an enolate, is stabilized though conjugation with the π orbitals of the adjacent carbonyl.
- The enolate has two resonance structures to contribute to the resonance hybrid.
- While α-hydrogens are weakly acidic, typical strong bases such as hydroxide or alkoxide are only capable of forming the enolate ion in very low concentrations.
- To achieve complete deprotonation of aldehyde or ketone reactants to their enolate conjugate bases, a very strong base such as LDA (lithium diisopropylamide) must be used.
- Hydrogen atoms with two or more adjacent carbonyl groups are more acidic than typical α hydrogens, such as β-diketones, β-keto-esters, and β-diesters, which create enolates that are stabilized through additional resonance forms which share the negative charge with multiple carbonyl carbons.
- The acidity of these compounds is increased to the point where typical strong bases such as hydroxide and alkoxide can be used to form the enolate.

6.6 Reactivity of Enolate Ions (halogorm reaction is reference only)

- Enolates are better nucleophlies than enols.
- α-hydrogen containing compounds can be completely converted to an enolate by reaction with a strong base whereas enols can only be created in small amounts through manipulating their equilibrium.
- Either the C of the O reactive site in an enolate may act as a nucleophile depending on the reaction conditions, but reactions involving the nucleophilic α-carbon are more common, partially due to the thermodynamic stability of the C=O bonds in the final products.
- An enolate reacts rapidly with a halogen to produce α-halogenated carbonyl products.
- The α-hydrogens of halogenated carbonyl products are usually more acidic than the corresponding non-halogenated compounds, which promotes polyhalogenated products.
- The Haloform reaction represents a method for the conversion of methyl ketones to carboxylic acids.
- This reaction is considered a base promoted and not base catalyzed because an entire equivalent of base is required for each α-halogenation.
- Deprotonation of an α-hydrogen with hydroxide produces the nucleophilic enolate ion which subsequently reacts with the halogen.
- The increasing acidity of α-halogenated ketone causes this reaction to occur two more times.
- Once formed, the CX_3 group attached to the carbonyl can act as a leaving group, eventually produces a haloform ($CHCl_3$, $CHBr_3$, CHI_3) and a carboxylate anion.

6.7 Alkylation of Enolate Ions

- Enolates can be alkylated in the alpha position through an S_N2 reaction with alkyl halides.
- An α hydrogen is replaced with an alkyl group and a new C-C bond is formed.

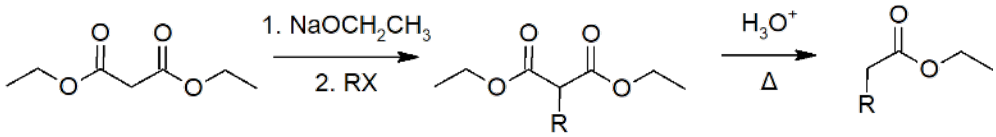
- Very strong bases like LDA are often used to fully deprotonate the carbonyl and completely form the enolate.
- Direct alkylations, like all enolate-based reactions, will form a racemic mixture if the alkylated alpha carbon is chiral.
- When an unsymmetrical ketone with two sets of nonequivalent alpha hydrogens is treated with a base, two possible enolates can form.
- The main determinant for which enolate is formed is whether the reaction is under kinetic control (rate) or thermodynamic (equilibrium) control.
- The thermodynamic enolate is formed when the more substituted alpha hydrogen is removed, yielding the more alkyl substituted, therefore the most stable, enolate.
- Formation of the thermodynamic enolate is sterically hindered and is kinetically slow, especially with a bulky base like LDA.
- Kinetic enolates are formed when the less substituted alpha hydrogen is deprotonated, being less sterically hindered allows this alpha hydrogen to be deprotonated faster even though it forms a less thermodynamically stable enolate.
- The malonic ester synthesis is a series of reactions which converts an alkyl halide to a carboxylic acid with two additional carbons.
- The importance of this synthesis pathways is that it allows for the creation of alpha alkylated carboxylic acids which cannot be created by direct alkylation.
- The acetoacetic ester synthesis is a series of reaction which converts alkyl halides into a methyl ketone with three additional carbons.
- This reaction creates an alpha substituted methyl ketone without side-products.
- In retrosynthetic analysis, a C-C bond is broken between the alpha carbon and the beta carbon away from this functionality.

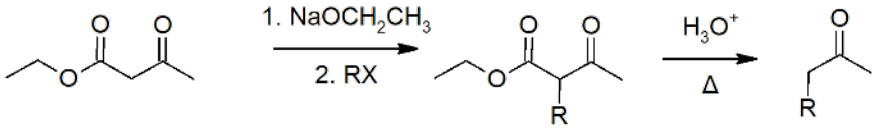
Skills to Master

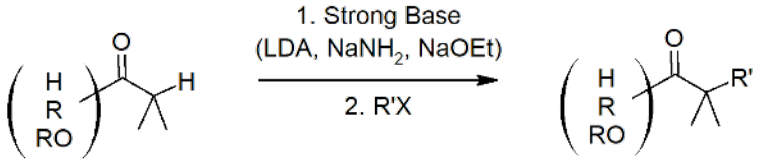
- Skill 6.1 Determine alpha carbons and alpha hydrogens.
- Skill 6.2 Draw the enols formed from carbonyl derivatives.
- Skill 6.3 Provide the mechanism for the keto-enol tautomerization under neutral, acidic and basic conditions.
- Skill 6.4 Provide the mechanism for the enol-keto tautomerization under neutral, acidic and basic conditions.
- Skill 6.5 Explain why the alpha hydrogen of carbonyl compounds are more acidic than a typical hydrogen.
- Skill 6.6 Explain why dicarbonyl protons are more acidic than compounds that contain a single carbonyl.
- Skill 6.7 Provide a mechanism for an alkylation reaction with an enolate.
- Skill 6.8 Provide a mechanism for malonic ester synthesis.
- Skill 6.9 Propose synthesis for alkylated carboxylic acids.
- Skill 6.10 Provide a mechanism for acetoacetic acid synthesis.
- Skill 6.11 Propose a synthesis for alkylated methyl ketones.

Summary of Reactions

Alkylation







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CHAPTER OVERVIEW

7: Carbonyl Condensation Reactions

Learning Objectives

When you have completed Chapter 7, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- design multistep syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
- solve road map problems that require a knowledge of carbonyl condensation reactions.
- define, and use in context, any of the key terms introduced.

In this chapter, we consider the fourth and final general type of reaction that carbonyl compounds undergo—the carbonyl condensation reaction. Carbonyl condensation reactions take place between two carbonyl containing reactants, one of which must possess an alpha hydrogen atom. The first step of the reaction involves the removal of an alpha hydrogen atom by a base. In the second step, the enolate anion that results from this removal attacks the carbonyl carbon of the second reacting molecule. In the final step of the reaction, a proton is transferred to the tetrahedral intermediate formed in the second step, although in some cases the product that results may subsequently be dehydrated.

Chapter Videos

This video provides an overview of enolate reaction.

This video provides an overview of how to use retrosynthetic analysis when thinking about enolate reactions.

This video provides an introduction to conjugate addition reactions that form carbon-carbon bonds.

7.1: Chapter Objectives
7.2: Carbonyl Condensations - The Aldol Reaction
7.3: Carbonyl Condensations versus Alpha Substitutions
7.4: Dehydration of Aldol Products - Synthesis of Enones
7.5: Using Aldol Reactions in Synthesis
7.6: Mixed Aldol Reactions
7.7: Intramolecular Aldol Reactions
7.8: The Claisen Condensation Reaction
7.9: Mixed Claisen Condensations

7.10: Intramolecular Claisen Condensations - The Dieckmann Cyclization
7.11: Conjugate Carbonyl Additions - The Michael Reaction
7.12: Carbonyl Condensations with Enamines - The Stork Reaction (reference only)
7.13: The Robinson Annulation Reaction
7.14: Some Biological Carbonyl Condensation Reactions (reference only)
7.S: Carbonyl Condensation Reactions (Summary)

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7.1: Chapter Objectives

The importance of carbonyl condensation reactions to synthetic organic chemistry arises from the large number of combinations of carbonyl compounds that can be used in such reactions. Aldehydes or ketones can be used in a simple aldol condensation to produce β-hydroxy aldehydes, β-hydroxy ketones, or their dehydration products. Mixtures of aldehydes, ketones, or both, can be used in a mixed aldol condensation. Intramolecular aldol condensations can occur in compounds containing two suitable carbonyl groups. Aldol-like condensations can be brought about between aldehydes and a variety of compounds containing acidic alpha hydrogen atoms, including diethyl malonate, acetic anhydride, nitriles and nitro compounds. Esters can be used in Claisen condensations and 1,6- and 1,7-diesters can give rise to internal condensations, called Dieckmann cyclizations. Related reactions include the Michael reaction, in which an α,β-unsaturated carbonyl compound is reacted with an enolate anion; and the Stork enamine reaction, where an enamine adds to an α,β-unsaturated ketone.

The chapter concludes with a look at how condensation reactions can be used in the synthesis of complex ring containing organic compounds, and at the role played by carbonyl condensation reactions in biological systems.

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7.2: Carbonyl Condensations - The Aldol Reaction

Objectives

After completing this section, you should be able to

1. write a general mechanism for carbonyl condensation reactions.
2. write an equation to illustrate the aldol condensation reaction.
3. identify the product formed when an aldehyde or ketone having an alpha hydrogen atom is treated with base in a protic medium.
4. identify the aldehyde or ketone, and other reagents required to produce a given *β*-hydroxy carbonyl compound by an aldol reaction.
5. determine whether a given aldehyde or ketone will undergo an aldol reaction.
6. write the detailed mechanism of the aldol reaction.

Key Terms

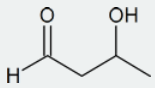
- aldol
- aldol reaction
- carbonyl condensation reaction

Study Notes

It is important that you understand the general mechanism of carbonyl condensation described in this section: once you grasp this mechanism, you will see that all the reactions that follow are very similar.

The aldol reaction is sometimes referred to as the aldol condensation. However, a condensation reaction is often regarded as a reaction in which two molecules join together with the elimination of a molecule of water (or some other compound of low molar mass). Thus, the aldol reaction described here is not a true condensation; the true aldol condensation is described later, in Section 7.3. It is perhaps unfortunate that the reactions discussed in this unit are all described as condensation reactions whether or not water is eliminated.

The term “aldol” (from "aldehyde alcohol") is used both to describe the specific compound 3-hydroxybutanal:

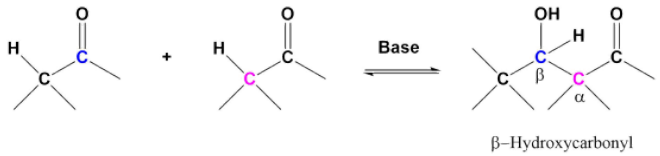


and to describe *β*-hydroxy aldehydes in general.

A useful carbon-carbon bond-forming reaction known as the Aldol Reaction is another example of electrophilic substitution at the alpha carbon in enolate anions. This reaction requires the formation of an enolate so at least one of the reactants must have an α-hydrogen. Due to the carbanion like nature of enolates, they can add to carbonyls through nucleophilic addition much like Grignard reagents.

The aldol reaction takes advantage of a carbonyl compound’s ability to undergo both alpha substitution and nucleophilic addition reactions. The fundamental transformation in the aldol reaction is a dimerization of an aldehyde (or ketone) to form a beta-hydroxy aldehyde (or ketone). A C-C bond is formed between the alpha carbon of one reactant molecule and the carbonyl carbon of a second reactant molecule. In the reaction’s product, the formed C-C bond links a carbon in the alpha position and a carbon in the beta position away from the carbonyl.

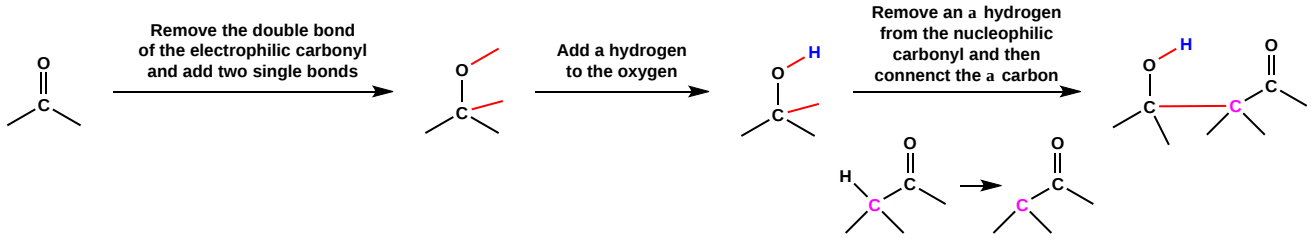
General Aldol reaction



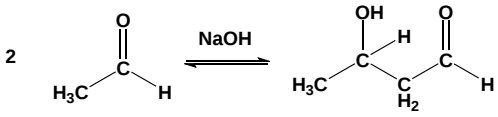
A typical example involves two molecules of acetaldehyde (ethanal) reacting to form beta-hydroxybuteraldehyde (3-hydroxybutanal). This product and other beta-hydroxy aldehydes are generically called “aldols” because they contain both an aldehyde and an alcohol functional group.

An aldol reaction, like many carbonyl addition reactions, is an equilibrium reaction and is reversible. The presence of an equilibrium means weaker bases, such a hydroxides or alkoxides, can be used to perform this reaction. The reaction equilibrium favors the products when aldehydes with little steric hindrance around the carbonyl are used. However, the reaction equilibrium for ketones and sterically hindered aldehydes favors the reactants. To provide good reaction yields when using these reactants, the equilibrium must be pushed towards the products. Typically, this is done by utilizing a method to remove the product as it is formed during the reaction.

Predicting the Product of an Aldol Reaction

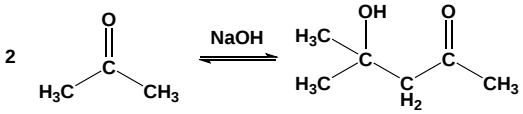


Examples



Ethanal — 3-Hydroxybutanal

Aldol

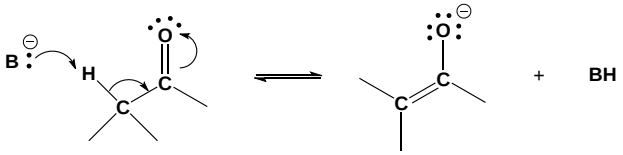


Acetone — 4-Hydroxy-4-methyl-2-pentanone

Mechanism of Aldol Reaction

1) Enolate formation

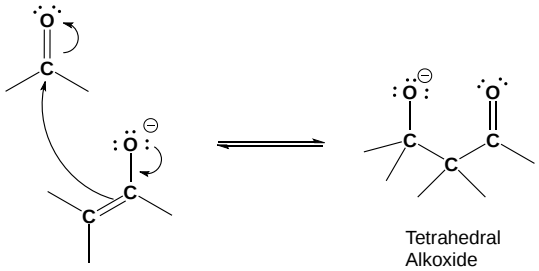
The reaction starts with a base removing an alpha hydrogen to form a nucleophilic enolate.



Aldehyde or Ketone — Enolate

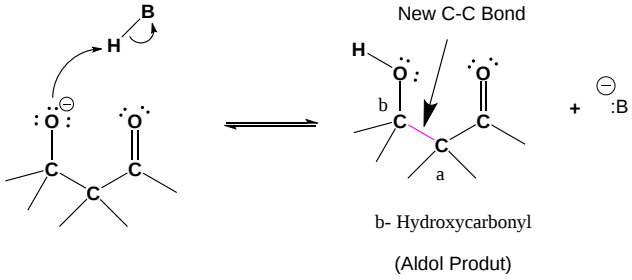
2) Nucleophilic attack by the enolate

Through nucleophilic addition, the enolate adds to the electrophilic carbonyl group on a second molecule. As with other nucleophilic addition reaction a tetrahedral alkoxide intermediate is formed.



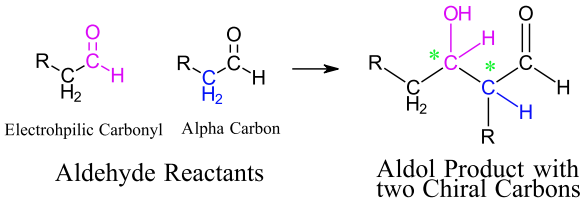
3) Protonation

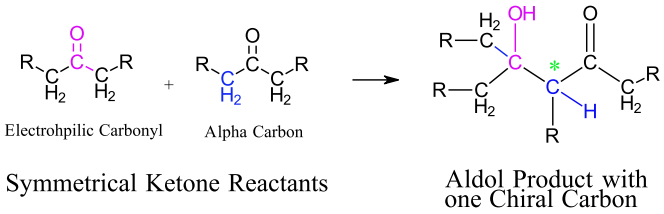
Protonation of the alkoxide forms the neutral aldol product and regenerates the base.



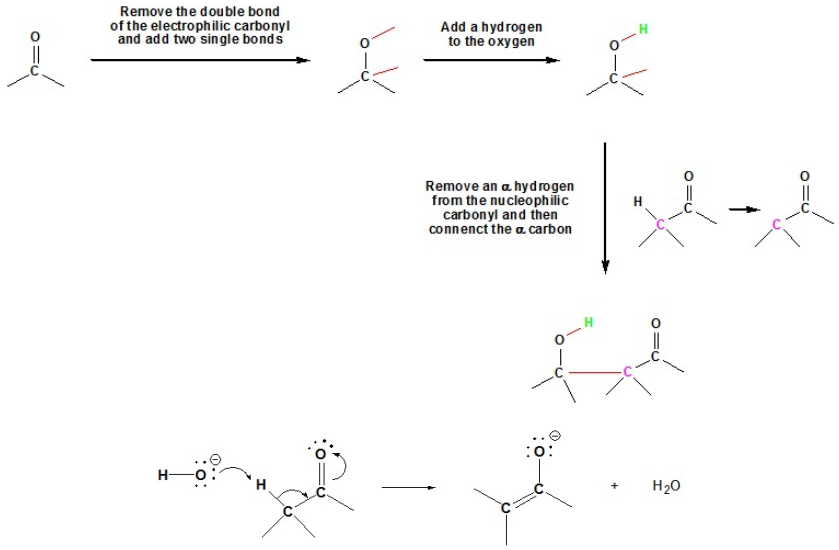
Stereochemical Ramifications of the Aldol Reaction

As previously discussed, both nucleophilic addition and alpha-substitution reactions have the possibility of creating chiral carbons. The alpha carbon and the electrophilic carbon of the reactants should be identified in the aldol product to assess their possible chirality. Most aldehydes produce chirality in both of these carbons. Most symmetrical ketones create a chiral carbon from the alpha-carbon of the reactant.



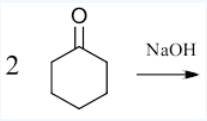


Going from reactants to products simply



Exercise 7.2.1

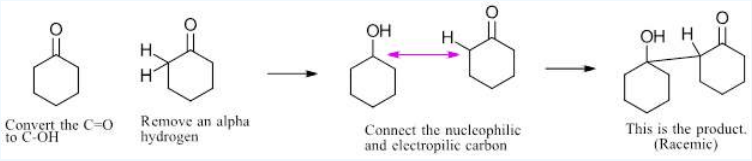
What would be the expect product of the following aldol reaction?



Answer

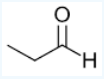
When considering the product of an aldol reaction it is vital to consider each reactant molecule separately. Also,

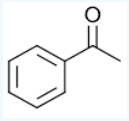
Identify electrophilic carbonyl carbon and any alpha hydrogens present.

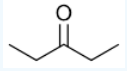


Exercise 7.2.2

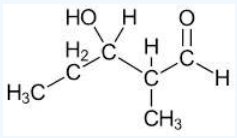
Predict the product of an aldol reaction with the following molecules:

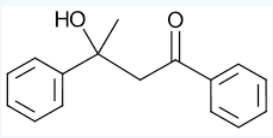
a) 

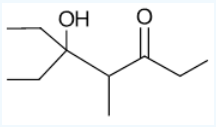
b) 

c) 

Answer

a) 

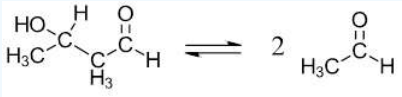
b) 

c) 

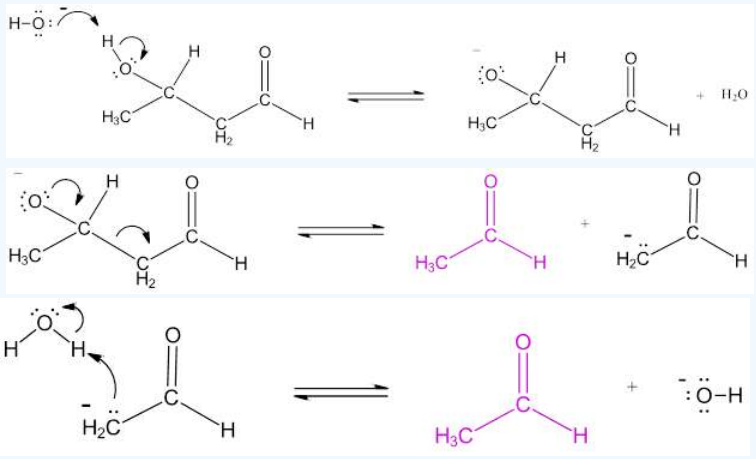
https://chem.libretexts.org/@go/page/443812

Exercises 7.2.3

Because the aldol reaction is reversible it is possible for a beta-hydroxy carbonyl compound to undergo a retro-aldol reaction. Please draw the mechanism or the based catalyzed retro-aldol reaction shown below.



Answers



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7.3: Carbonyl Condensations versus Alpha Substitutions

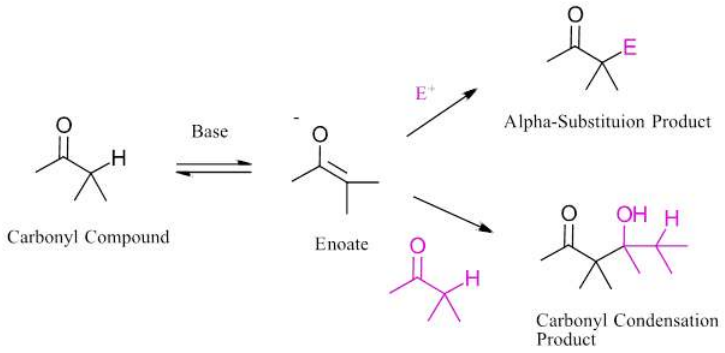
Objectives

After completing this section, you should be able to describe the difference between a carbonyl condensation reaction and an alpha substitution reaction, and determine which of these two types of reactions is most likely to occur, given the appropriate experimental data.

Study Notes

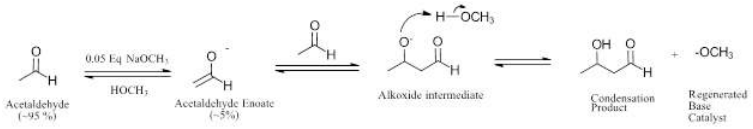
So far we have discussed three of the four general reactions of carbonyl compounds: nucleophilic additions of aldehydes and ketones (CHM 222), nucleophilic acyl substitution reactions of carboxylic acid derivatives (CHM 222) and alpha substitution reactions (Chapter 6). The fourth general reaction, carbonyl condensation, is similar to the alpha substitution reaction, so you need to appreciate how it differs from the other three and the conditions under which it occurs.

Carbonyl condensation and alpha-substitution reactions both involve the formation of a reactive enolate ion intermediate. How is it possible to generate an enolate ion for a alpha substitution reaction without a carbonyl condensation also occurring? What reaction conditions are required to cause one reaction and not the other?



In a carbonyl condensation a catalytic amount of base is used to generate only a small amount of the the enolate ion. Most of the carbonyl compound is unreacted and can react with the enolate. During the reaction the base catalyst is regenerated which can then produce more enolate ion and continue the cycle.

If acetaldehyde was reacted with 0.05 equivalents of sodium methoxide in a methanol solvent only a small amount (~5%) of the enolate would form. The majority of the acetaldehyde would be unchanged and capable of undergoing a condensation reaction with the enolate present. The alkoxide intermediate produced is protonated by methanol to the neutral condensation product and regenerates the methoxide base catalyst. Methoxide can then deprotonate a new acetaldehyde molecule to create another enolate allowing the reaction cycle to continue.

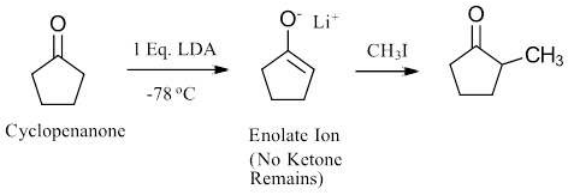


These steps are all reversible and it should be noted that reactants and products that are close in energy level can potentially undergo the reverse reaction if conditions change enough. While from a synthetic point of view in the laboratory this may mean increasing yields by driving the reaction to completion (e.g. adding heat, removing product), in biological systems it can have more drastic consequences. Indeed, depending on metabolic conditions, retro-aldol reactions (the reverse of aldol condensations, in which carbon-carbon bonds are broken) can occur.

In contrast, the alpha-substitution reaction is often more directional by design. To reduce unwanted competition from carbonyl condensation, the enolate ion intermediate is generated all at once with a full equivalent of strong base at low temperature. This effectively removes the carbonyl from the reactive mixture making it difficult for a carbonyl condensation to occur. The reactive enolate intermediate then is quickly quenched by rapid addition of the electrophile to complete the substitution reaction. As

discussed in Section 6.8, for direct alkylation, strong bases like $NaNH_2$ and LDA were used to generate the enolate intermediate followed by addition of an alkylhalide.

An example is shown with the alpha-alkylation reaction of cyclopentanone. During this reaction, one equivalent of lithium diisopropyamide (LDA) is added to the reactant at -78 ºC which completely converts cyclopenanone to the corresponding enolate ion. This leaves none of the ketone carbonyl remaining to undergo a condensation reaction. Methyliodide is quickly added to react with enolate ion forming the alpha-alkylated product.



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7.4: Dehydration of Aldol Products - Synthesis of Enones

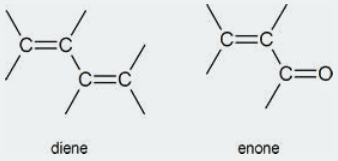
Objectives

After completing this section, you should be able to

1. write an equation to illustrate the formation of a conjugated enone from a β-hydroxy aldehyde or ketone.
2. write a detailed mechanism for the basic or acidic elimination of water from a β-hydroxy aldehyde or ketone.
3. explain why β-hydroxy aldehydes and ketones undergo elimination reactions much more readily than most other alcohols.
4. identify the enone products from the aldol condensation of a given aldehyde or ketone.

Study Notes

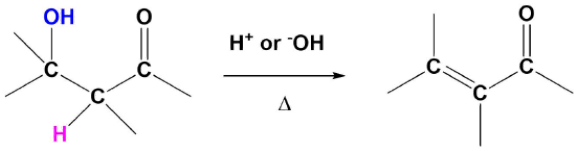
Conjugated enones, like conjugated dienes, have more inherent stability compared with their non-conjugated counterparts. You may wish to preview Section 8.2 on dienes, which gives a molecular orbital description showing pi electron distribution over four atoms.



Note that both of the elimination mechanisms described here (acidic and basic) involve either the enol form or the enolate anion of the β-hydroxy carbonyl compound.

Aldol Condensation

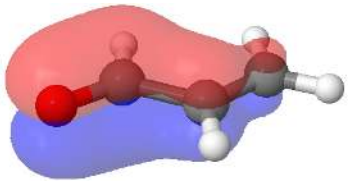
Reactions in which a larger molecule is formed from smaller components, with the elimination of a very small by-product such as water are termed Condensations. Hence the following examples are properly referred to as aldol condensations.

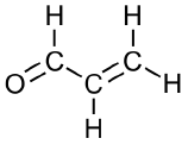


Dehydration of Aldol Products to Synthesize α, β Unsaturated carbonyl (enones)

The products of aldol reactions, with heating, often undergo a subsequent elimination of water, made up from an alpha-hydrogen and the beta-hydroxyl group. The product of this acid or base-catalyzed E1cB elimination reaction (Section 2-11) is an α,β-unsaturated aldehyde or ketone (conjugated enones). Although there may be multiple positions where the alkene may form, it will always prefer to be in conjugation with the carbonyl.

Conjugated enone products are more stable than non-conjugated due to extended P orbital overlap. Conjugation of the p electrons of the alkene and carbonyl bonds provide a molecular-orbital description showing the interaction of p electrons of all four atoms. The additional stability provided by the conjugated carbonyl system of the product makes many aldol reactions thermodynamically favorable.



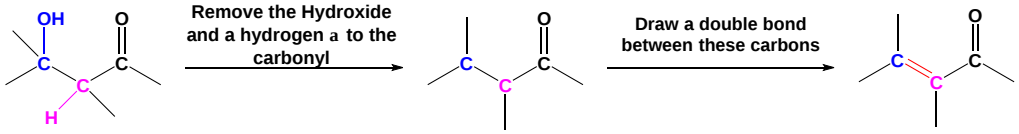


Propenal

A representation of pi bonding molecular orbitals of the conjugated enone, propenal, are delocalized through p-orbital overlap

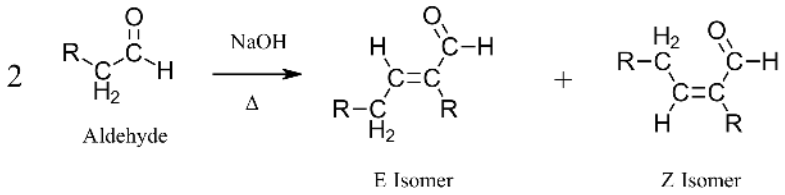
The elimination of water from the reaction mixture can be used to drive the equilibrium towards the products by Le Chatelier's principal. This coupled with the thermodynamic stability of the conjugated product allow for good reaction yields when the formation of the initial aldol intermediate is unfavorable (ketones & sterically hindered aldehydes).

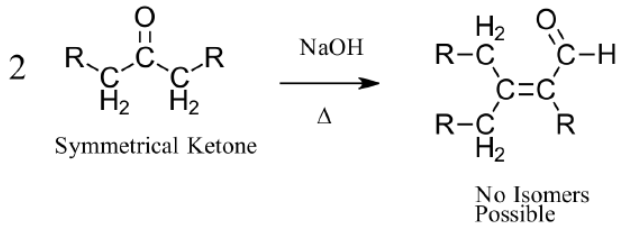
Predicting the Product of an Enone Formation



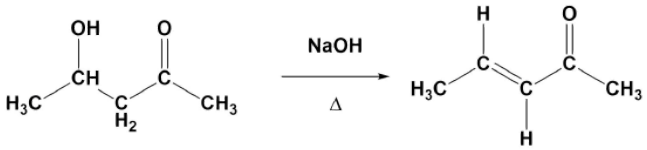
Stereochemical Considerations

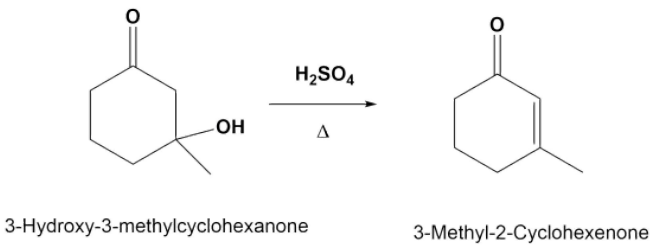
When aldehyde starting materials are used for an aldol condensation, there is the possibility of forming both E and Z alkene isomers. When symmetrical ketones are used, the alkene formed lacks the ability to form isomers so a single product is made.





Examples



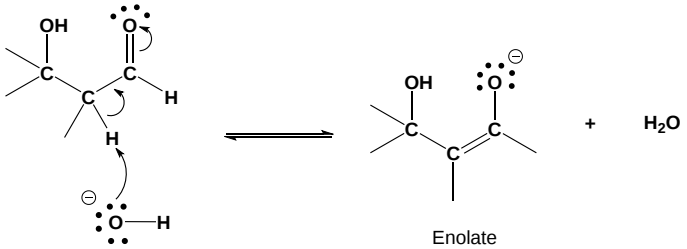


Mechanism

Base Catalyzed Mechanism

1) Form an enolate

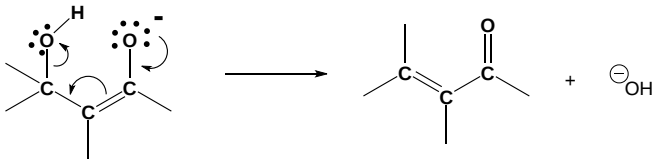
The mechanism starts with the base removing an alpha-hydrogen to form an enolate ion.



Enolate

2) Form the enone

The alkoxide reforming the carbonyl C=O bond promotes the elimination of alcohol OH as a leaving group which reforms the base catalyst. Although the base catalyzed elimination of alcohols is rare, it happens in this case in part due to the stability of the conjugated enone product.

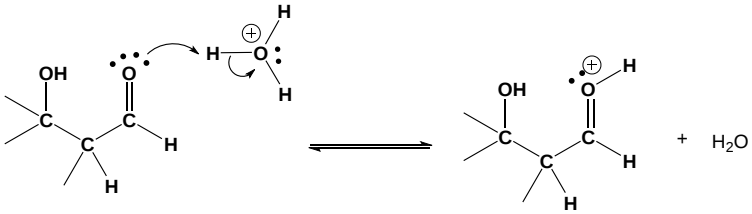


Enone

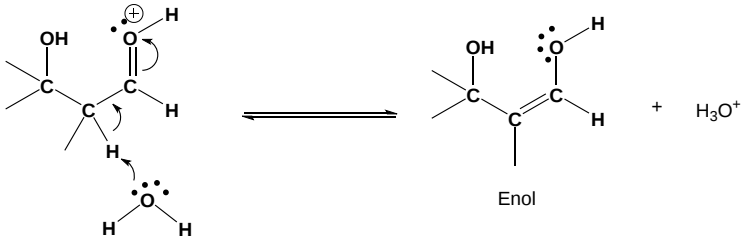
Acidic Conditions Mechanism

1) Protonation

The mechanism starts with the two step tautomerization process to form an enol.



2) Form an enol



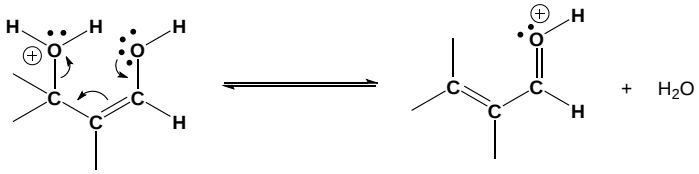
Enol

3) Protonation

Protonation of the alcohol OH increases its ability to act as a leaving group.

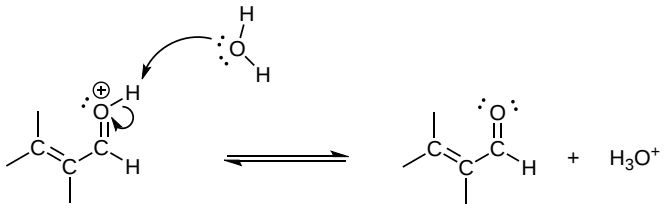
4) Elimination

Lone pair electrons from the enol reform the carbonyl C=O bond and promote the elimination of water as a leaving group.



5) Deprotonation

Deprotonation by water in the final step creates the neutral enone product and regenerates the acid catalyst.

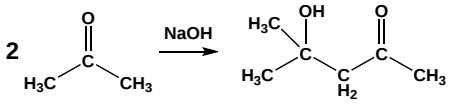


Aldol Condensation

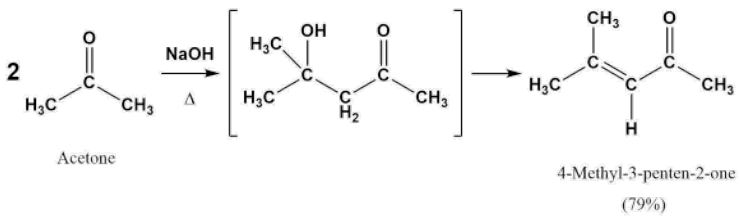
Whether an aldol reaction or an aldol condensation product is formed during a reaction largely depends on the reaction conditions. Typically, a reaction with a base at room temperature provides the aldol reaction product. However, if the reaction mixture is heated the aldol product is quickly converted into the aldol condensation product. If the condensation product is desired the aldol intermediate is usually not isolated.

Examples

Aldol Reaction

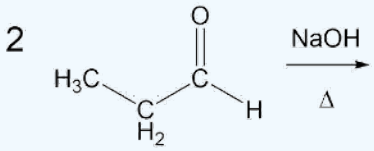


Aldol Condensation



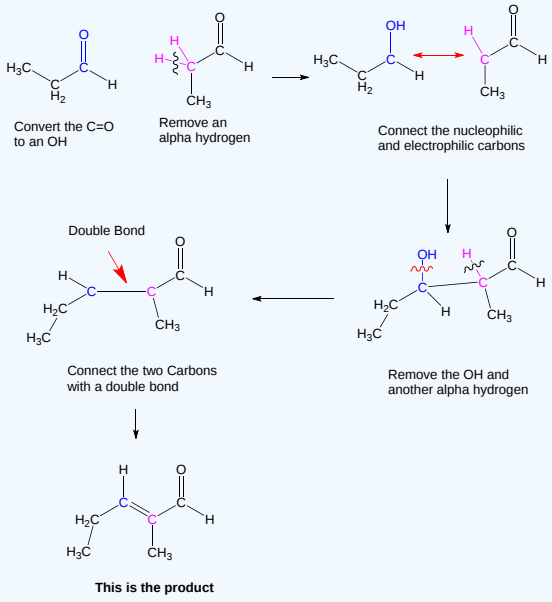
Worked Example

Draw the product of an aldol condensation with the following molecule:



Answer

The overall reaction is a combination of two major steps, an aldol reaction followed by a dehydration to form the enone. In this situation it is best to consider the aldol product first (as discussed in Section 7.3, then convert it to the enone. Note! The double bond always forms in conjugation with the carbonyl.



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7.5: Using Aldol Reactions in Synthesis

Objectives

After completing this section, you should be able to identify the aldehyde or ketone and other necessary reagents that should be used to prepare a given enone by an aldol condensation.

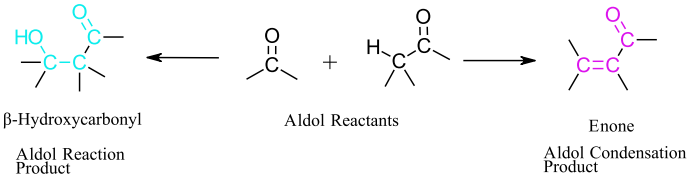
Study Notes

This section stresses the importance of being able to think logically.

The experience that you have already gained through designing multi step syntheses and solving road map problems should help you to recognize when an aldol reaction may have been one of the steps in the synthesis of a given compound.

It is important that you recognize that the aldol condensation is an important part of a synthetic chemist's repertoire, both because it involves the formation of a new carbon-carbon bond, and also because it yields a product containing two functional groups.

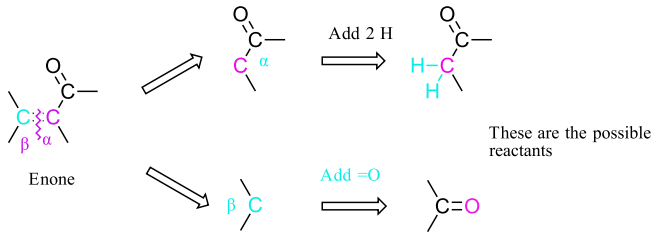
Aldol reactions are excellent methods for the synthesis of many enones or beta-hydroxy carbonyls. Because of this, being able to predict when an aldol reaction might be used in a synthesis in an important skill. This can be accomplished by identifying these combinations of atoms and bonds and then, working backwards, theoretically breaking the target molecule apart into possible reactants.



Fragments which are easily formed by an aldol reaction

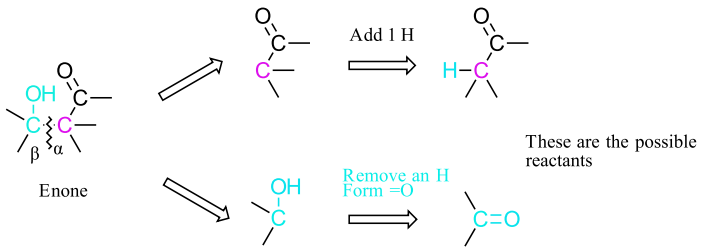
Determining the Reactants for an Aldol Condensation

During an aldol condensation a C-C sigma and a C-C pi bond are formed. This makes the key bond cleavage in the target molecule the C=C bond between the carbons alpha and beta away from the carbonyl. After the cleavage, the carbon that was in the alpha position (on the fragment with the carbonyl) gains two hydrogens. The carbon that was in the beta gains a =O to form a carbonyl.



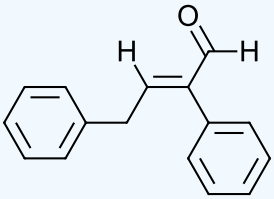
Determining the Reactants for an Aldol Reaction

During an aldol condensation a C-C sigma bond is formed. This makes the key bond cleavage in the target molecule the C-C bond between the carbons alpha and beta away from the carbonyl. After the cleavage, the carbon that was in the alpha position (the fragment with the carbonyl) gains one hydrogen. The fragment loses a hydrogen from the OH and then forms a C=O carbonyl bond.



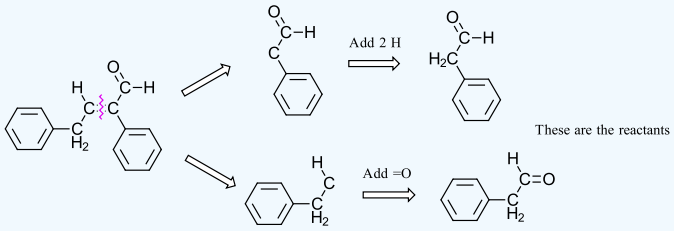
Worked Example

Show how the following molecule could be made using an aldol condensation?

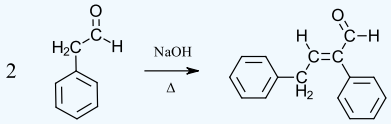


Answer

Analysis: The C=C bond in the target molecule is cleaved to form two fragments. The fragment with the carbonyl gains two alpha hydrogens. The other fragment gains a =O to form a carbonyl. Both fragments end up producing the same reactant which is typical for an aldol condensation.

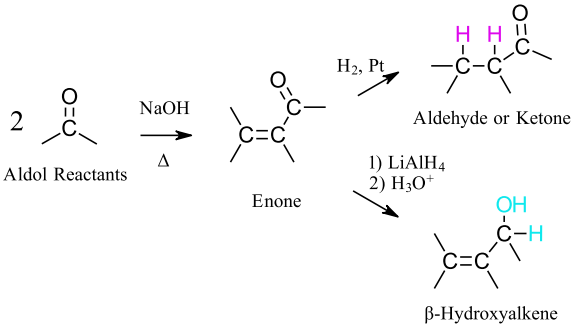


Solution



Additional Synthetic Considerations

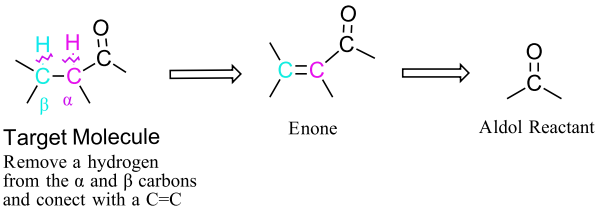
The enone product of an aldol condensation is versatile because it contains two functional groups (alkene & carbonyl) which can be subject to further reactions. Among many possible reactions, an enone can undergo hydrogenation to produce an aldehyde or ketone. Also, the carbonyl group can undergo hydride reduction to produce a beta-hydroxyalkene.



These additional reactions can be applied with the consideration of using an aldol reaction in the synthesis of a target molecule. A similar analysis can be extrapolated to the other reactions possible with the alkene and carbonyl present in an enone.

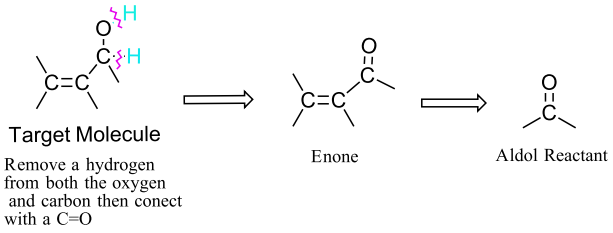
Analysis for Hydrogenation

To consider a hydrogenation, remove a hydrogen from a carbon in both the alpha and beta positions relative to the carbonyl. Then connect these two carbons with a C=C double bond. This create a possible enone which can be broken apart further using the analysis described above. Target molecules can have often have multiple alkyl chains which can be used to form a double bond.



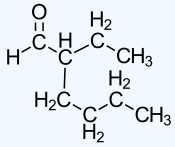
Analysis for Hydride Reduction

To consider a hydride reduction remove a hydrogen from the alcohol oxygen then a hydrogen from the adjacent carbon. Connect the oxygen and carbon with a double bond to form a C=O carbonyl. This provides an enone which can undergo further analysis.



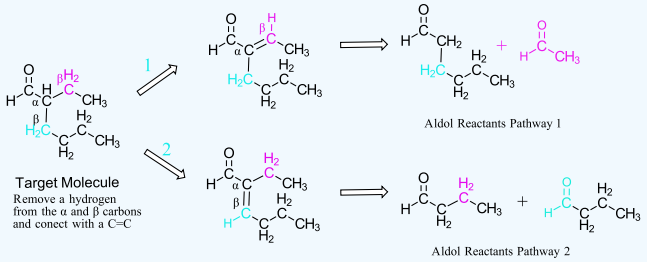
? Exercise 7.5.1

Please devise a synthesis pathway for the following molecule using an aldol reaction:

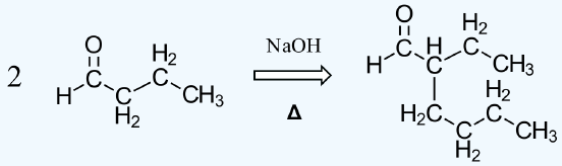


Answer

Analysis: Because the target molecule has two beta-carbons with hydrogens there are two possible synthesis pathways. Both should be considered for their effectiveness. Because a carbonyl is already present fragmentations will first be performed to create two possible enone intermediates. These enones will both be broken into their aldol reactants. When looking a possible aldol reactants produced by each pathway it is clear that pathway 2 is preferred. Because both fragments are the same they will react to form on major product.

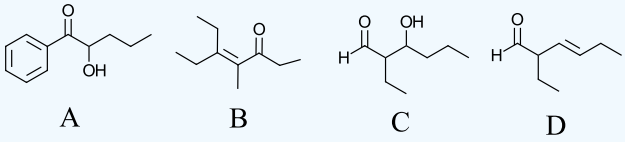


Solution



Exercises 7.5.2

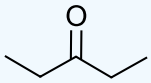
Which of the following molecules could be made using an aldol reaction or condensation. Please show the starting material for the reactions that are possible.



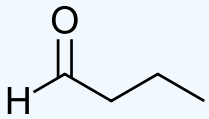
Answers

Molecules A and C are possible.

Solution for molecule A

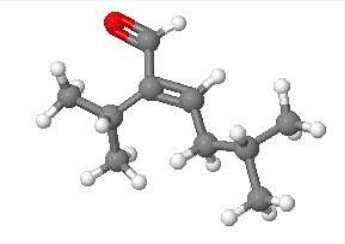


Solution for molecule C

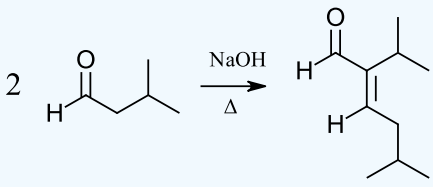


Exercise 7.5.3

Please design a synthesis for the following molecule: Red = Oxygen, Grey = Carbon, White = Hydrogen



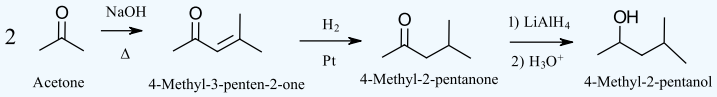
Answer



Exercise 7.5.4

Please show the reaction steps required to make 4-methyl-2-pentanol using an aldol condensation as one of your synthetic steps.

Answer



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7.6: Mixed Aldol Reactions

Objectives

After completing this section, you should be able to

1. write an equation to illustrate a mixed aldol reaction.
2. identify the structural features necessary to ensure that two carbonyl compounds will react together in a mixed aldol reaction to give a single product rather than a mixture of products.
3. determine whether a given mixed aldol reaction is likely to produce a single product or a mixture of products.
4. identify the product or products formed in a given mixed aldol reaction.
5. identify the carbonyl compounds needed to produce a given enone or β-hydroxy aldehyde or ketone by a mixed aldol reaction.

Study Notes

You should satisfy yourself that you understand how four products arise from the condensation of 2-propanone and 2-phenylacetaldehyde.

Mixed Aldol Reaction and Condensations

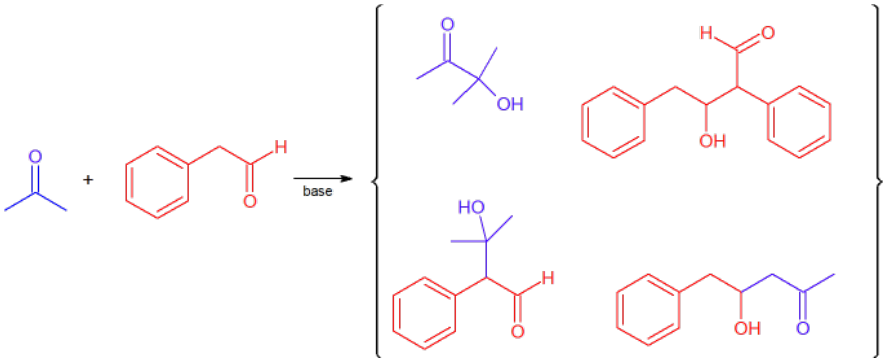
The previous examples of aldol reactions and condensations used a common reactant as both the enolate donor and the electrophilic acceptor. The product in such cases is always a dimer of the reactant carbonyl compound. Aldol condensations between different carbonyl reactants are called crossed or mixed reactions, and under certain conditions such crossed aldol condensations can be effective.

Mixed aldols in which both reactants can serve as donors and acceptors generally give complex mixtures of both dimeric (homo) aldols and crossed aldols. Because of this, most mixed aldol reactions are usually not performed unless one reactant has no alpha Hs.

The following abbreviated formulas illustrate the possible products in such a case, red letters representing the acceptor component and blue the donor. If all the reactions occurred at the same rate, equal quantities of the four products would be obtained. Separation and purification of the components of such a mixture would be difficult.

$$\mathbf{A}CH_2CHO + \mathbf{B}CH_2CHO + NaOH \longrightarrow A\text{–}A + B\text{–}B + A\text{–}B + B\text{–}A$$

Products of a Uncontrolled Mixed Aldol Reaction

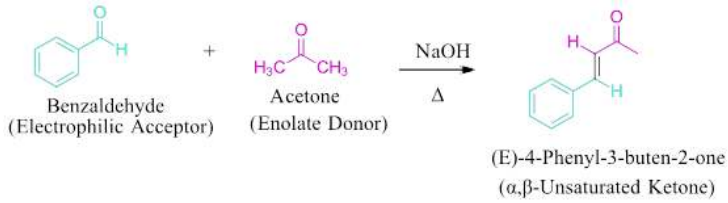


To avoid complex reaction mixtures the reactants should be chosen to favor one particular donor/acceptor reaction. Successful mixed aldol reactions usually use one of two combination of factors.

1) A reaction of an aldehyde with no alpha-hydrogens with a ketone that has alpha hydrogens: Aldehydes lacking alpha-hydrogens cannot form an enolate so they can only function as electrophilic acceptor reactants. This reduces the number of possible products by half. Although it would be possible for the ketone to react with itself, it is unlikely. Aldehydes are more reactive acceptor electrophiles than ketones. This makes the preferred reaction one with the ketone as an enoloate donor and the aldehyde as an electrophilic acceptor.

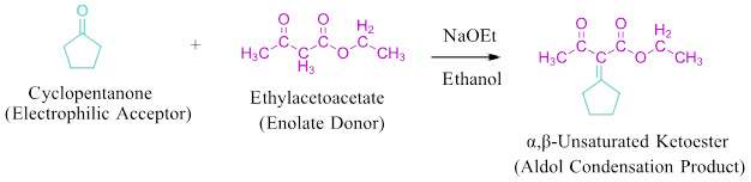
The aldol condensation between an aromatic aldehyde with no α-hydrogens and an aliphatic aldehyde or ketone with α-hydrogen is called a **Claisen–Schmidt condensation**. The reaction product is a highly conjugated α,β-unsaturated aldehyde or ketone which forms in the more stable (E)-alkene isomer.

Example: Claisen–Schmidt Condensation



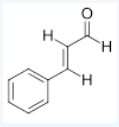
2) One of the reactants has alpha-hydrogens which are highly acidic: The acidic compound will be preferably converted into an enolate donor which removes the possibility of its carbonyl acting as an electrophilic acceptor. An example is the aldol condensation of ethylacetoacetate and cyclopentanone. Ethylacetoacetate has α-hydrogens which are particularly acidic due to their conjugate base being stabilized by two carbonyl bonds. Upon reaction with base, ethylacetoacetate is converted to the enolate donor leaving cyclopentanone to be the electrophilic acceptor. This provides one predominant aldol condensation product. In this reaction sodium ethoxide is used as a base to prevent hydrolysis side-reactions with the ester of ethylacetoacetate.

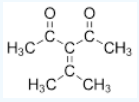
Example

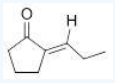


Exercises 7.6.1

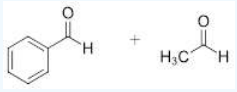
1) Show the reactants required to make the following using a mixed aldol condensation. Indicate those which would be likely to produce a mixture of products.

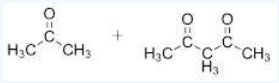
a) 

b) 

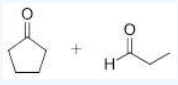
c) 

Answers

a) 

b) 

c) Because both reactants have αlpha-hydrogens and neither are particularly acidic, the reaction probably will produce a mixture of condensation products.



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7.7: Intramolecular Aldol Reactions

Objectives

After completing this section, you should be able to

1. write an equation to illustrate an intramolecular aldol reaction.
2. identify the product formed when a given dicarbonyl compound undergoes an intramolecular aldol condensation.
3. identify the dicarbonyl compound which, when treated with a suitable base, could be used to prepare a given cyclic enone by an intramolecular aldol condensation.

Study Notes

"Intramolecular " means "within the same molecule." You have already seen some examples of intramolecular reactions in previous chapters. Another term for intramolecular aldol reaction is "internal aldol reaction."

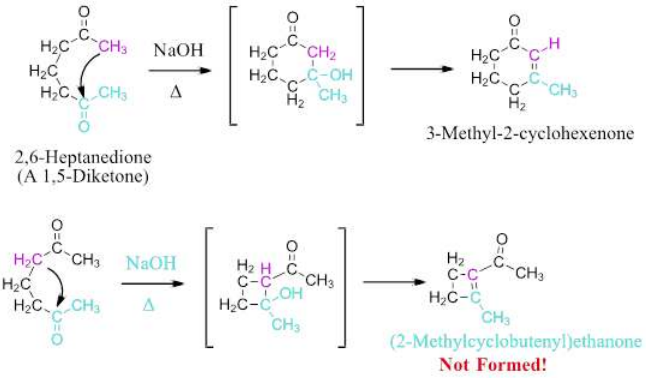
Intramolecular aldol reaction

Molecules which contain two carbonyl functionalities have the possibility of forming a ring through an intramolecular aldol reaction. The term "Intramolecular" means "within the same molecule." In this case, it means that the enolate donor and the electrophilic acceptor of an aldol reaction are contained in the same molecule such as dialdehydes, keto aldehydes, or diketones. In these cases, the small distance between the donor and acceptor leads to faster reaction rates for intramolecular condensations making intermolecular condensations (which require two molecules to collide in solution) less favorable.

In most cases multiple sets of α-hydrogens need to be considered when determining the donor/acceptor roles for the reaction, which might lead to a mixture of products. The intramolecular aldol reaction of a 1,5-diketone, 2,6-heptanedione, could possibly yield either the six-membered ring product, 3-methyl-2-cyclohexenone, or the four-membered ring product, (2-methylcyclobutenyl)ethanone. However, the cyclohexanone product is exclusively formed.

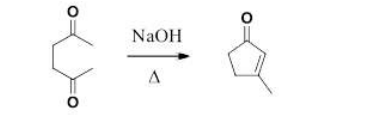
This product selectivity is possible due to all of the steps of the mechanism being reversibly, which tends to produce the most stable product. As with most ring forming reactions, five and six membered rings are preferred due to their relative lack of ring strain compared to other sized rings (See Section on Cycloalkanes). Once equilibrium is reached, the relatively strain free and therefore more thermodynamically stable, cyclohexanone product will be preferably formed.

Example



Similar analysis can be used to predict the products of other intramolecular aldol reactions. In a similar reaction, 1,4-diketones, such as 2,5-hexanedione, only form the five-membered ring product, ex. 3-methyl-2-cyclopentenone, without any of the possible cyclopropane product forming.

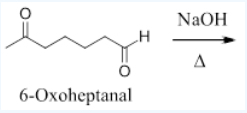
Example



2,5-Hexanedione 3-Methyl-2-cyclopentenone

Worked Example

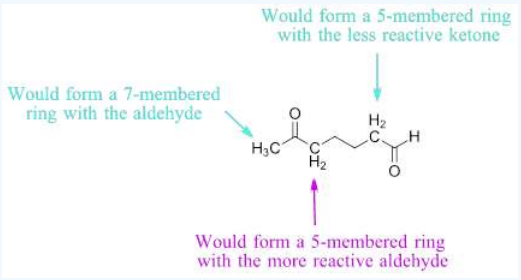
Please draw the expected product of an intramolecular aldol condensation with the following molecule:



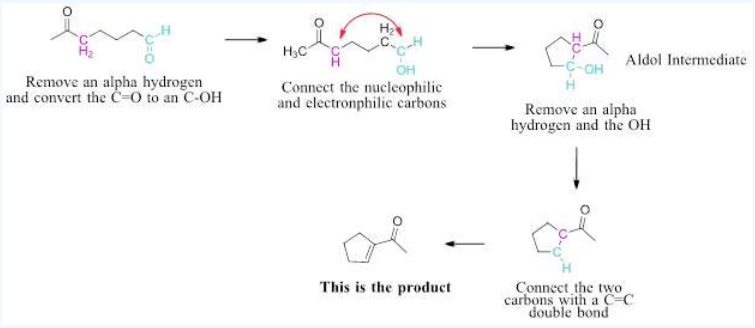
6-Oxoheptanal

Answer

Analysis: 6-Oxoheptanal has three unique sets of alpha-hydrogens which could be deprotonated to form an enolate. Selecting the correct set involves analyzing the carbonyl reactivity's along with the possible ring sizes of the products.



Solution: Once the preferred alpha-hydrogens are determined go through the steps discussed in the previous sections to determine the aldol condensation product. Remember to form the aldol intermediate first.

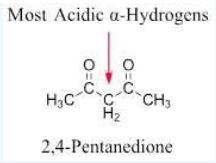


Exercises 7.7.1

Briefly explain why the molecule, 2,4-pentanedione, when reacted with a base would mostly likely not produce an intramolecular aldol condensation product.

Answers

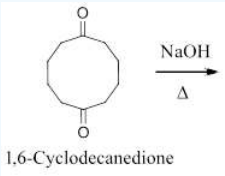
2,4-Pentanedione like other 1,3-Diketones have particularly acidic alpha-hydrogens between the two carbonyl. When base is applied these will be the first to deprotonate and form an enolate. For an intramolecular aldol condensation to occur an alpha-hydrogen one of the methyl groups would have to be removed which would be difficult.



2,4-Pentanedione

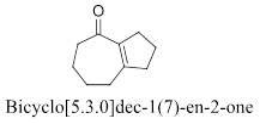
? Exercise 7.7.2

Draw the product of the following aldol condensation:



1,6-Cyclodecanedione

Answer



Bicyclo[5.3.0]dec-1(7)-en-2-one

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7.8: The Claisen Condensation Reaction

Objectives

After completing this section, you should be able to

1. write an equation to illustrate a Claisen condensation reaction.
2. write a detailed mechanism for a Claisen condensation reaction or its reverse.
3. identify the product formed in a given Claisen condensation reaction.
4. identify the ester and other reagents needed to form a given β-keto ester by a Claisen condensation reaction.

Key Terms

- Claisen condensation reaction

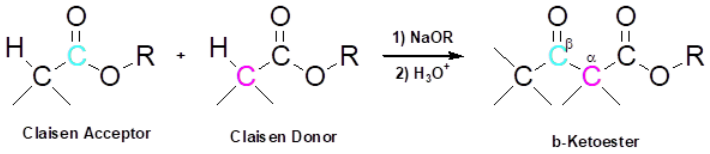
Study Notes

You have already seen that ethyl acetoacetate-type compounds are very useful in organic syntheses, see Section 6.8. Any reaction which results in the formation of these compounds will also be of importance. In the next section, you will see how the range of β-keto esters that can be prepared by this method is extended through the use of two different esters as starting materials.

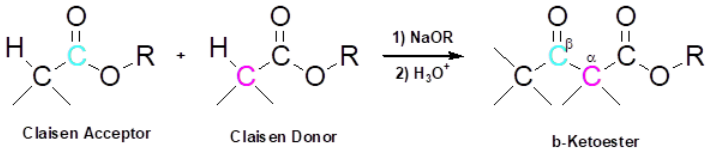
Claisen Condensation

Because esters commonly contain both α-hydrogens and a carbonyl bond, they can undergo a reversible condensation similar to the aldol reaction called a Claisen Condensation. In a fashion similar to the aldol reaction, one ester acts as a Claisen enolate donor (nucleophile) while a second ester acts as the Claisen acceptor (electrophile). During the reaction a new carbon-carbon bond is formed to produce a β-keto ester product. This reaction is considered a condensation because it eliminates a small alcohol as an unwanted side-product.

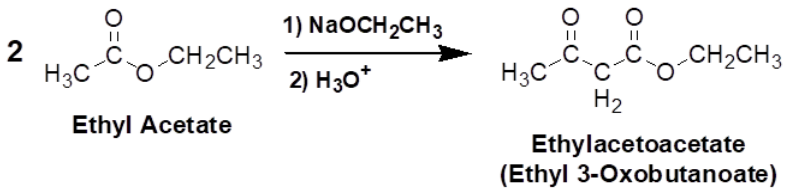
General Reaction



Predicting the Product of a Claisen Condensation



Example

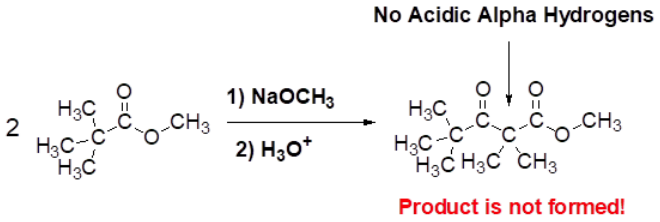


Although they may appear similar, there are a number of fundamental differences between an aldol and Claisen condensation. During the mechanism of the reaction, the formed tetrahedral alkoxide intermediate is not protonated to from an “aldol” type

product. Rather, the alkoxide intermediate will reform the C=O carbonyl bond and eliminate a (-OR) leaving group to produce a nucleophilic acyl substitution product.

Claisen condensations cannot use a hydroxide for the reaction base due to the possibility of ester hydrolysis. Also, to prevent transesterification side products, the alkoxide base typically has the same alkyl group as alkoxy group present in the ester starting material.

Lastly, the β-keto ester products of Claisen condensation can be acidic enough to be deprotonated by the reaction's base during the final steps of the mechanism. This means the base is not catalytically regenerated during the reaction and a full equivalent of base is required. The β-keto ester condensation products are removed from the equilibrium by this deprotonation, which causes the reaction to be driven forward by Le Chatelier's principle. This concept is so important that a Claisen product will not form unless it contains an alpha hydrogen acidic enough to react completely with the reaction base. This requires that the ester starting materials have at least two alpha-hydrogens for a Claisen condensation product to form. One is removed to form an ester enolate and the second is removed to drive the reaction forward.

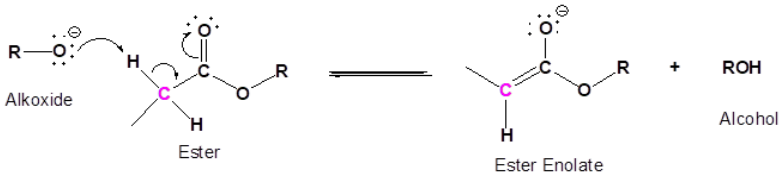


Mechanism

The Claisen condensation mechanism is analogous to the ester saponification reaction seen here.

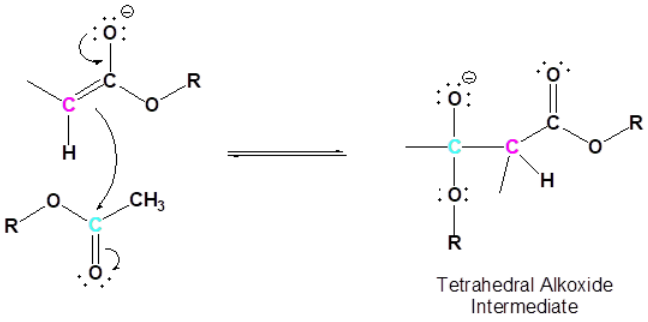
1) Enolate formation

The mechanism starts with the alkoxide base removing an alpha-hydrogen from the ester to form a nucleophilic ester enolate ion.



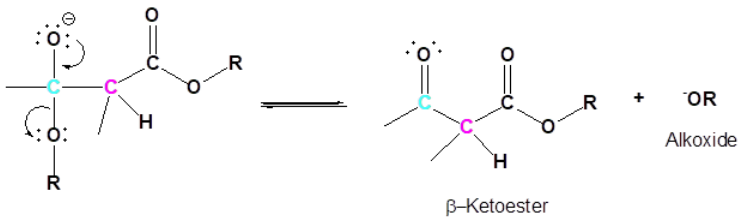
2) Nucleophilic attack

The enolate nucleophile adds to carbonyl carbon of a different ester, forming a tetrahedral alkoxide intermediate.



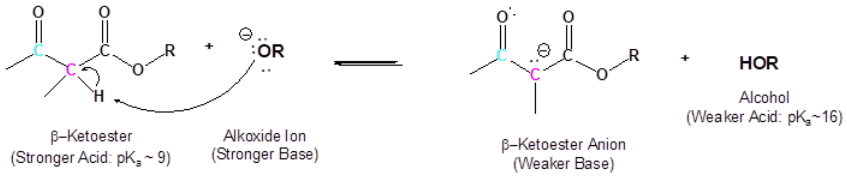
3) Removal of leaving group

The alkoxide then reforms the carbonyl, eliminating the –OR leaving group to form a beta-ketoester.



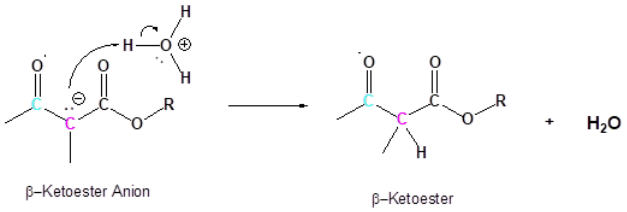
4) Deprotonation

The acidity of beta-ketoesters (pK_a ~9) is high enough to allow them to be completely deprotonated by alkoxide bases (pK_a of an alcohol ~16) to form a second enolate. This makes the equilibrium of this step very favorable, which is enough to drive the whole reaction towards the product.



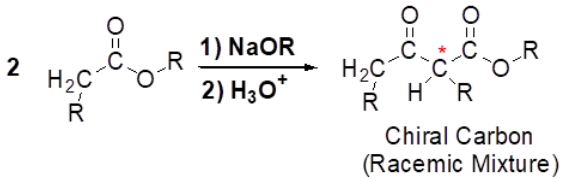
5) Protonation

The enolate is protonated in an acid work-up to form the neutral beta-ketoester product.



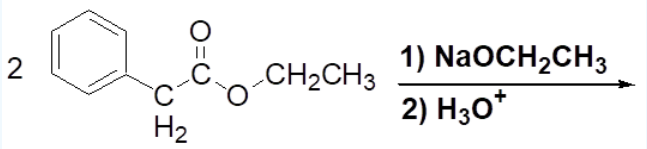
Stereochemical Considerations

The alpha-carbon gains a substituent during the reaction which means it will can form a chiral carbon. The fact that the alpha-carbon is temporarily converted to an enolate in the last step of the mechanism means that a racemic mixture of enantiomers will form.



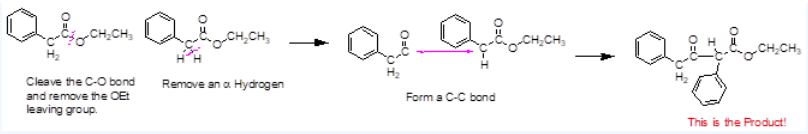
? Worked Example

Draw the products of the following reaction:



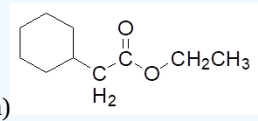
Answer

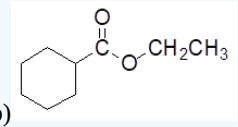
Analysis: Remember to consider each start ester separately.

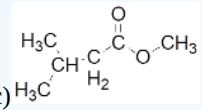


Exercise 7.8.1

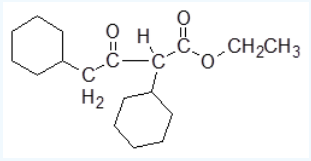
Please draw the products if the following molecules were to undergo a Claisen condensation.

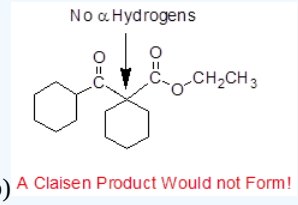
a) 

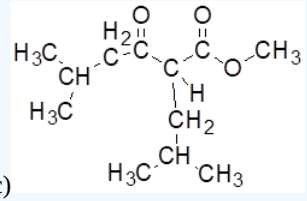
b) 

c) 

Answers

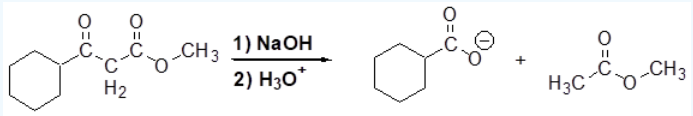
a) 

b) 

c) 

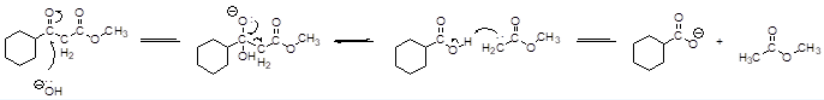
Exercise 7.8.2

The beta-keto ester product of a Claisen condensation can undergo hydrolysis with sodium hydroxide as shown in the reaction below. Please draw a curved arrow mechanism to explain how the products are formed. Also, explain why the ketone functional group preferably reacts with hydroxide instead of the ester.



Answer

The carbonyl of the ketone is more likely to be attacked by the hydroxide nucleophile because is more reactive than the ester carbonyl.



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7.9: Mixed Claisen Condensations

Objectives

After completing this section, you should be able to

1. write an equation to illustrate a mixed Claisen condensation.
2. identify the structural features that should be present in the two esters if a mixed Claisen condensation is to be successful.
3. determine whether a given pair of esters is likely to produce a good yield of a single product when subjected to a mixed Claisen condensation.
4. identify the product formed when a given pair of esters is used in a mixed Claisen condensation.
5. identify the esters that should be used to produce a given β-keto ester by a mixed Claisen condensation.
6. write an equation to illustrate the formation of a β-diketone through a mixed Claisen-type condensation between an ester and a ketone.
7. identify the β-diketone formed as the result of a mixed Claisen-type condensation between a given ester and a given ketone.
8. identify the reagents necessary to synthesize a given β-diketone by a mixed Claisen-type condensation between an ester and a ketone.
9. write detailed mechanisms for mixed Claisen reactions and reactions that are related to the mixed Claisen reaction, including those in which both reacting moieties are present in the same compound.

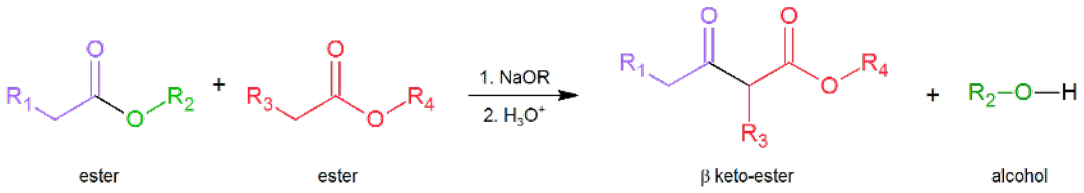
Study Notes

Just as we can react together two different aldehydes or ketones in a mixed aldol condensation, so can we react together two different esters in a mixed (or "crossed") Claisen condensation. Again, by carefully selecting our substrates we can obtain a good yield of the desired product and minimize the number of possible byproducts. Note that even if we replace one of the esters with a ketone, the reaction is still referred to as Claisen condensation. The important thing to realize as you study these reactions is that they all take place by essentially the same mechanism—attack by an enolate anion on a carbonyl group.

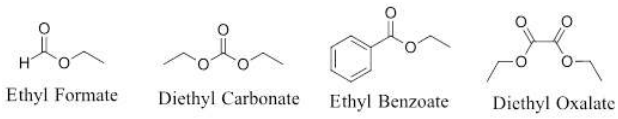
Crossed Claisen Condensation

Claisen condensations between different ester reactants are called **Crossed Claisen** reactions. Crossed Claisen reactions in which both reactants can serve as Claisen donors and Claisen acceptors generally give complex mixtures which are difficult to separate.

General Reaction

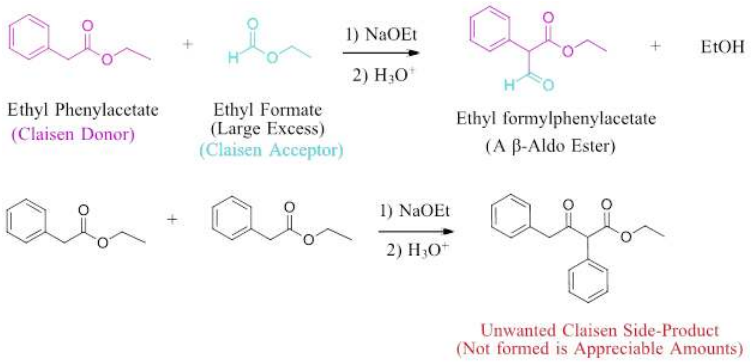


To avoid complex mixtures most Crossed Claisen reactions are usually not successful unless one of the two esters has no alpha-hydrogens as in the following examples.



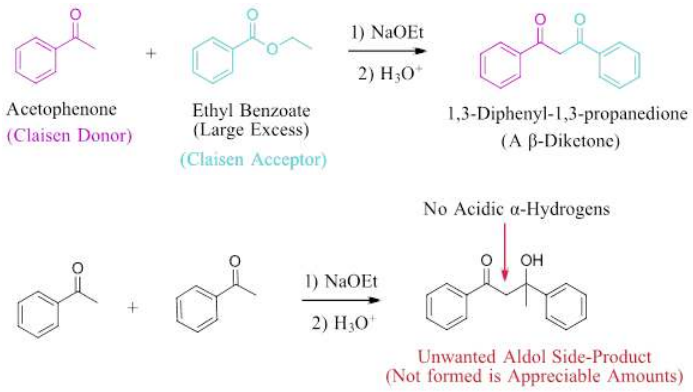
This forces the ester with alpha-hydrogens to be the Claisen donor (enolate) and the ester without alpha-hydrogens to be the Claisen acceptor (electrophile). Even with this differentiation, it is possible for the ester with alpha-hydrogens to undergo a Claisen Condensation with itself to produce an unwanted side-product. This is typically partially prevented by using the ester without alpha-hydrogens in a large excess.

Example - no alpha hydrogens



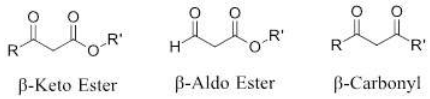
Another type of crossed Claisen condensation occurs when a ketone is reacted with an ester. The use of an ester without alpha-hydrogens is not necessary due to the greater reactivity of the ketone. The alpha-hydrogens of the ketone are much more acidic (pKa~20) than those of the ester (pKa~25). The alpha hydrogens of ketone will be preferably deprotonated to make it the enolate Claisen donor. The ester will therefore be the electrophilic Claisen acceptor and is likewise commonly used in a large excess. There is still a possibility of the ketone reacting with itself to form the product of an aldol reaction however the equilibrium is unfavorable. Also, the formation of the aldol product is reversible due to its lack of an acidic alpha hydrogen. The beta-diketone Claisen product can be irreversibly deprotonated due to its more acidic alpha-hydrogens, making it the reaction's main product.

Example - ester with ketone



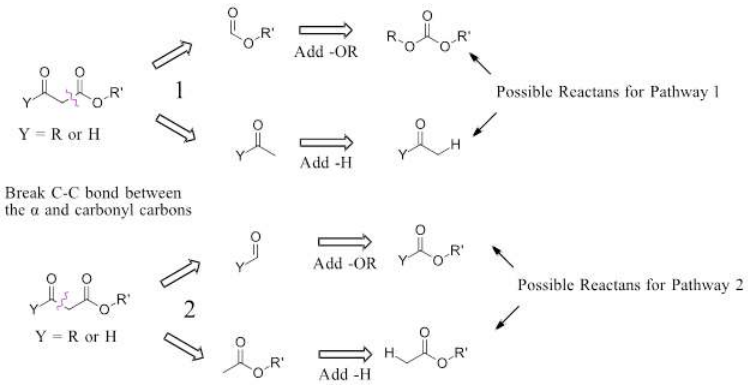
Planing a Synthesis using a Claisen or Crossed Claisen-like Reaction

A Claisen reaction should be considered for a synthesis pathway if the target molecule contains a beta-keto esters, a beta-aldo ester or a beta-dicarbonyl.



A beta-keto ester or a beta-aldo ester could possibly be made by a Claisen condensation of two esters. A beta-dicarbonyl could possibly be made by a Claisen-like condensation between a ketone and an ester. Here, the key bond cleavage is a C-C bond between one of the carbonyls and the alpha-carbon which lies between the carbonyl. In each of these situations there are two such C-C bonds so there will be two possible pathways to consider. After the C-C bond cleavage the fragment with the alpha-carbon will gain a hydrogen. The fragment with the bare carbonyl will gain an –OR group to become an ester. The –OR group added will be the same as any ester present in the target molecule. If none are present $–OCH_2CH_3$ is typically used.

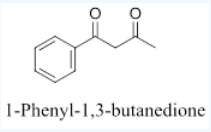
Analysis for Beta-Keto and Aldo Esters



A similar analysis can be performed on a 1,3-diketone and will be presented in the worked example below.

Worked Example

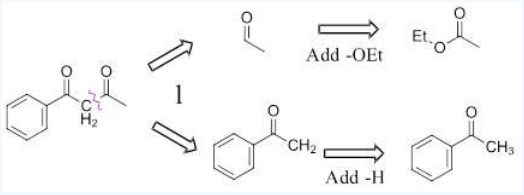
Show how the following molecule can be made using a Claisen-like condensation.



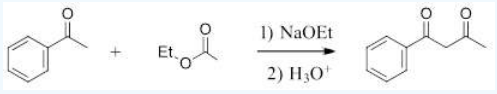
1-Phenyl-1,3-butanedione

Answer

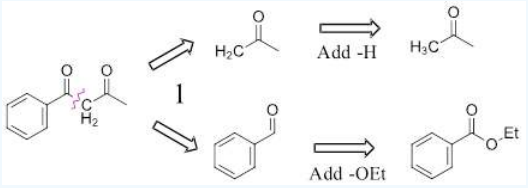
Pathway 1



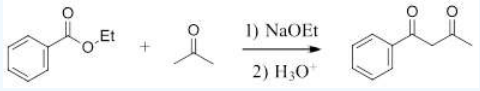
Solution 1



Pathway 2



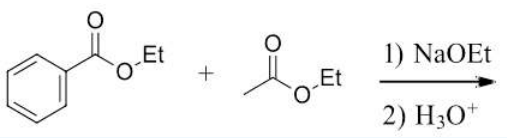
Solution 2



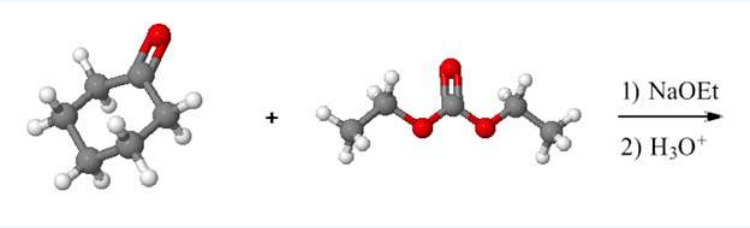
Exercises 7.9.1

Draw the product of the following reactions:

a)

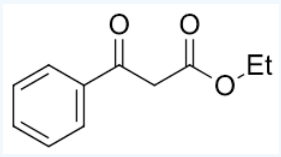


b)

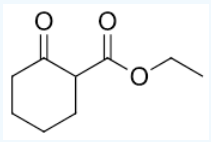


Answers

a)



b)



7.9: Mixed Claisen Condensations is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer, Dietmar Kennepohl, Layne Morsch, & Layne Morsch.

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7.10: Intramolecular Claisen Condensations - The Dieckmann Cyclization

Objectives

After completing this section, you should be able to

1. write an equation to illustrate an internal Claisen condensation, that is, a Dieckmann cyclization.
2. identify the product formed when a 1,6- or 1,7-diester undergoes an internal Claisen condensation.
3. identify the diester needed to prepare a given cyclic β-keto ester by an internal Claisen condensation.
4. identify the structural features present in a diester that lead to the formation of more than one product in an internal Claisen condensation.

Key Terms

- Dieckmann cyclization

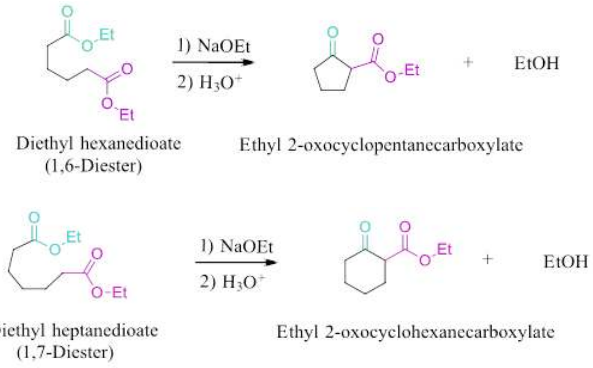
Study Notes

Essentially no new material is introduced in this section; Dieckmann cyclizations are intramolecular Claisen condensations. These reactions occur for 1,6- and 1,7-diesters, as these substances result in the formation of compounds containing five- and six-membered rings, respectively. You may recall that the formation of such ring systems is favored because they are relatively free of strain.

The Dieckmann Cyclization

Diesters can undergo an intramolecular reaction, called the Dieckmann condensation, to produce cyclic beta-keto esters. This reaction works best with 1,6-diesters, which produce five-membered rings, and 1,7-diesters which produce six membered rings.

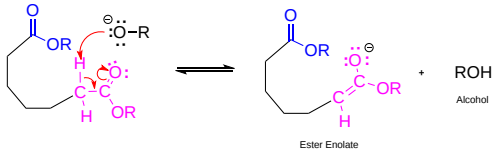
Examples



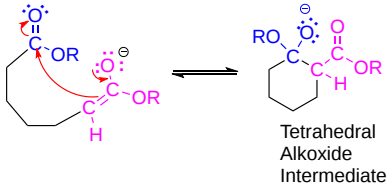
Mechanism

The mechanism of the Dieckmann condensation is the same as a Claisen condensation. An alkoxide base removes an alpha-hydrogen from one of the esters to form an ester enolate. The enolate then adds to the carbonyl carbon of the other ester to form a tetrahedral alkoxide intermediate. The alkoxide reforms the carbonyl bond which causes the elimination of the –OR leaving group and forms a cyclic beta-keto ester. The high acidity of the beta-keto ester allows it to be deprotonated by the reaction's base to form a second enolate. Like the Claisen condensation, this deprotonation step drives the equilibrium towards the products and is required for the reaction to occur. A full equivalent of base is necessary during this reaction.

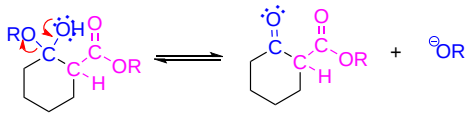
1) Enolate formation



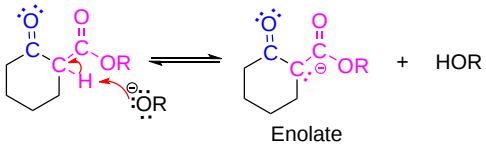
2) Nucleophilic attack



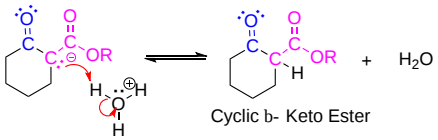
3) Removal of leaving group (note the OH is a typo, it should be O minus)



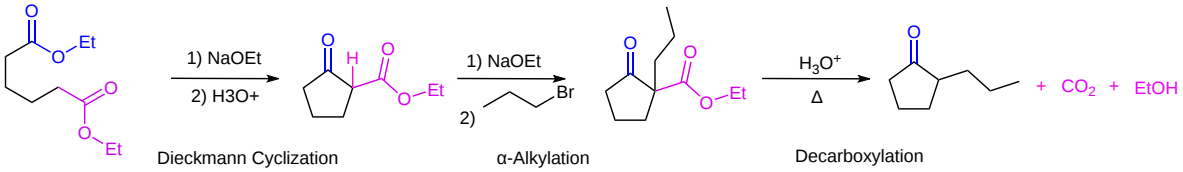
4) Deprotonation



5) Protonation



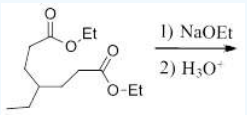
Further Reactions of the Dieckmann Cyclization Product



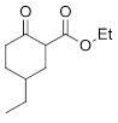
The cyclic beta-keto ester product of a Dieckmann cyclization can be modified by reactions similar to those used in the acetoacetic ester synthesis. The acidic alpha-hydrogens of the beta-keto ester allow it to easily be deprotonated and alkylated in an alpha-substitution reaction. Having a carbonyl group in the beta position allows the ester to be removed through decarboxylation. The combination of these three reactions (1) Dieckmann cyclization, (2) alpha alkylation, and (3) decarboxylation provides an efficient method for preparing 2-substituted cyclopentanones and cyclohexanones.

? Exercises 7.10.1

1) Draw the expected product for the following reaction:

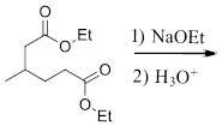


Answers

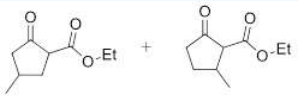


Exercise 7.10.2

The Dieckmann cyclization of the following molecule is expected to give a mixture of two cyclized products. Draw the structure of the two products and briefly explain why a mixture is formed.



Answer



Each has the ability to act as a Claisen donor and a Claisen acceptor. The reaction should produce a roughly 50/50 mixture where each ester acts as a Claisen acceptor.

7.10: Intramolecular Claisen Condensations - The Dieckmann Cyclization is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer, Dietmar Kennepohl, Layne Morsch, Gamini Gunawardena, & Gamini Gunawardena.

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7.11: Conjugate Carbonyl Additions - The Michael Reaction

Objectives

After completing this section, you should be able to

1. explain how the carbonyl group which is present in α, β-unsaturated aldehydes and ketones activates the carbon-carbon double bond so that it is susceptible to attack by nucleophiles.
2. write equations to illustrate the addition of lithium diorganocopper reagents to α, β-unsaturated aldehydes and ketones.
3. identify the product formed from the reaction of a given α, β-unsaturated aldehyde or ketone with a given lithium diorganocopper reagent.
4. identify the α, β-unsaturated aldehyde or ketone, the lithium diorganocopper reagent, or both, needed to prepare a given product through a conjugate addition reaction.
5. write an equation to illustrate the Michael reaction.
6. write a detailed mechanism for a given typical Michael reaction.
7. identify the product formed in a given Michael reaction.
8. identify the reagents necessary to synthesize a given compound by a Michael reaction.

Key Terms

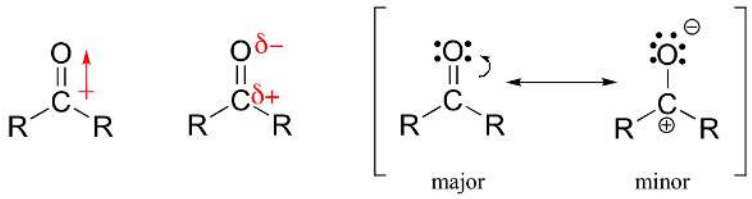
- Michael reaction

Study Notes

Notice the wide variety of compounds that can take part in conjugate addition/Michael reactions. As usual, you should not feel overwhelmed by the number of different compounds that can be used, just keep in mind that in all cases the mechanism is essentially the same.

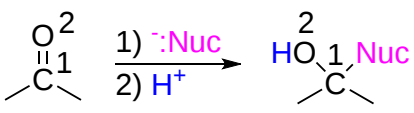
You may be confused about the designation of the product from the conjugate addition to an α, β-unsaturated aldehyde or ketone as a 1,4 adduct. You can more clearly understand this name if you recognize that the proton added in the second step of the reaction first adds to the oxygen of the enolate ion to produce an enol. The latter then tautomerizes to the more stable keto form.

One of the largest and most diverse classes of reactions involves nucleophilic additions to a carbonyl group. As you learned in CHM 222, carbonyl carbons are electrophilic due to bond polarity created by resonance.



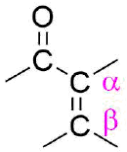
We have discussed a nucleophilic addition to carbonyl carbons called a **1,2 addition**. During 1,2 addition the nucleophile adds to the carbonyl carbon which is defined as the one position. Subsequently, hydrogen adds to the carbonyl oxygen which considered the two position. Overall an atom is added in both the 1 and 2 position justifying the reaction name, 1,2 addition.

Basic Reaction of 1,2 Addition

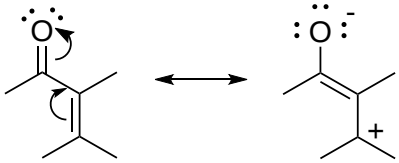


An important functional group is created when an alkene is placed in conjugation with a carbonyl. These conjugated carbonyl are called enones or **α, β-unsaturated carbonyls**. The term α commonly refers to the carbon adjacent to a carbonyl and β referrers to

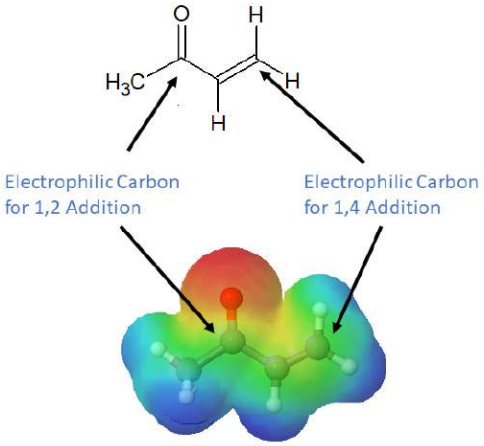
the next carbon in the chain.



Conjugation transmits the electrophilic character of the carbonyl carbon to the β-carbon of the **α, β-unsaturated carbonyl** double bond. The resonance structure shown below shows that the electronegative oxygen atom in α, β-unsaturated carbonyls pulls electrons away from the β carbon making it more electrophilic than a typical alkene carbon.

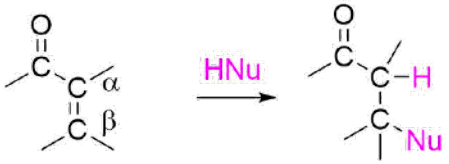


From this resonance form, it should be clear that nucleophiles may attack either at the carbonyl carbon or at the β-alkene carbon. These two modes of reaction are referred to as 1,2-addition and **1,4-addition** respectively. A 1,4-addition is also called a **conjugate addition**.



Basic Reaction of 1,4 Conjugate Addition

In 1,4 addition, a nucleophile is added to the carbon β to the carbonyl while a hydrogen is added to the carbon α to the carbonyl. Overall, the carbonyl is unaffected by the nucleophilic addition. It is important to note that **this reaction only occurs because the alkene is conjugated with a carbonyl**. The utility of 1,4 conjugate addition is shown below by the nucleophiles that enable carbon-carbon bond formation via this addition to α,β-unsaturated carbonyls.

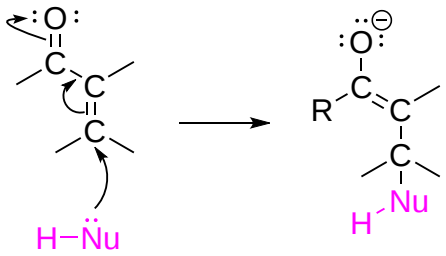


General Mechanism for 1,4 Conjugate Addition

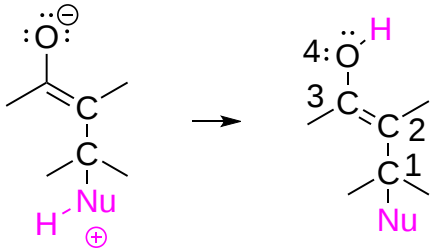
The mechanism starts with the nucleophile attacking the electrophilic β carbon forming a single bond. The two electrons from the alkene pi bond are pushed onto the electronegative carbonyl oxygen creating an enolate. In the next step the the enolate is protonated to form an enol. If the original nucleophile was neutral, this addition will cause it to become positively charge. A proton transfer will occur making the nucleophile neutral and turning the enolate into an enol. If the original nucleophile was negatively

charged this protonation is accomplished by the subsequent addition of a proton source. The product of the second step of the mechanism shows why the reaction is called a 1,4 addition. The nucleophile bonds to the β alkene carbon which is considered the one position and the hydrogen adds to the carbonyl oxygen which is in the four position. Overall, addition occurs in the one and four position. In the final step of the mechanism, the enol undergoes a rearranges to form a carbonyl during a process called tautomerization. Tautomerization causes the hydrogen to move from the oxygen to the β-carbon.

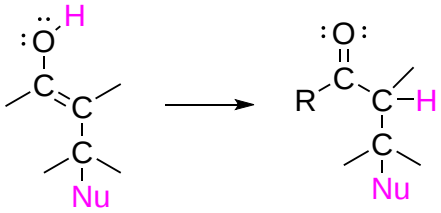
1) Nucleophilic attack (Note: The Nu in the product should have a positive charge.)



2) Protonation

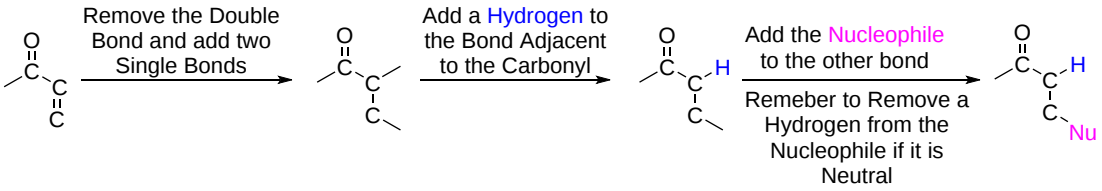


3) Tautomerization



Predicting the Products of a 1,4 Conjugate Addition.

In total, 1,4 addition occurs across the alkene bond of the α,β-unsaturated carbonyl. The alkene pi bonds is broken to form two single bonds, one on the α-carbon and one on the β-carbon. During 1,4 addition, the α-carbon of the α,β-unsaturated carbonyl forms a bond with a hydrogen while the β-carbon forms a bond to the nucleophile. Remember that neutral nucleophiles typically lose a hydrogen during 1,4 addition.



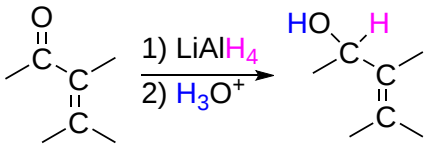
1,2 Vs. 1,4 Addition

Whether 1,2 or 1,4-addition occurs to a α,β-unsaturated carbonyl depends on multiple variables but is mostly determined by the nature of the nucleophile. During the addition of a nucleophile there is a competition between the formation 1,2 and 1,4 addition products. If the nucleophile is a strong base, such as Grignard reagents or metal hydrides, both the 1,2 and 1,4 reactions are irreversible and therefor are under kinetic control. Since 1,2-additions to the carbonyl group are fast, we would expect to find a predominance of 1,2-products from these reactions. If the nucleophile is a weak base, such as, water, alcohols or amines, then the

possible 1,2 addition is usually reversible. This means the competition between 1,2 and 1,4 addition is under thermodynamic control. In this most cases, the 1,4-addition product dominates because the stable carbonyl group is retained.

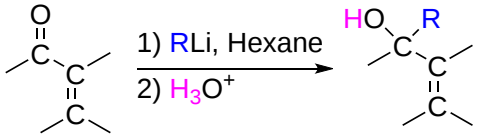
Nucleophiles Which add 1,2 to α, β-Unsaturated Carbonyls

Metal Hydrides ($LiAlH_4$)

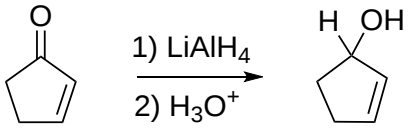


Grignard Reagents

Organolithium Reagents

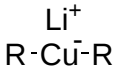


Example



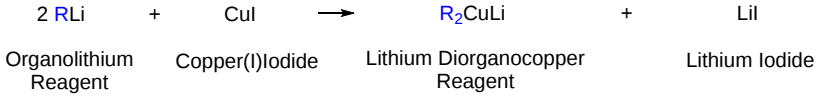
Gilman Reagents

Another important reaction exhibited by organometallic reagents is metal exchange. Organolithium reagents react with cuprous iodide to give a **lithium diorganocopper reagent**, which often is referred to as a **Gilman reagent**. Remember that organolithium reagents are formed by a reaction of lithium metal with an organohalide. Lithium diorganocopper reagents are considered a source of carbanion like nucleophiles similar to Grignard and organolithium reagents. However, the reactivity of lithium diorganocuprate reagents is slightly different and this difference will be exploited in different situations. Diorganocuprate reagents are made from the reaction of two equivalents of an organolithium reagent and copper (I) iodide (CuI). The created lithium diorganocuprate reagent acts as a source of $R:^-$

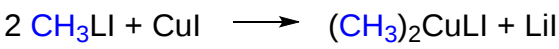


Lithium Diorganocopper (Gilman Reagent)

General Reaction



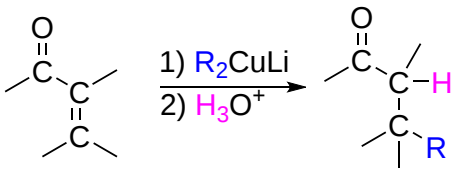
Example



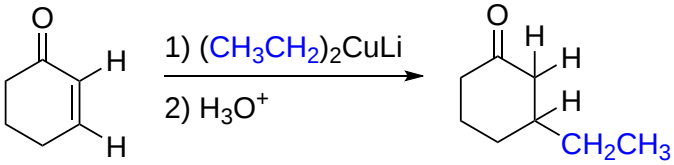
Formation of Lithium Dimethylcopper

Reaction of 1,4 Conjugate Addition of Gilman Reagents to α, β Unsaturated Ketones

Lithium diorganocopper reagents, R_2CuLi, undergo 1,4 conjugate addition when reacted with α,β-unsaturated ketones. Using lithium diorganocopper reagents allows for a wide range of organic groups to undergo this 1,4 conjugate addition including alkyl, aryl, and alkenyl groups. Because a C-C single bond is formed this reaction is an excellent method for adding to the carbon framework of a ketone.

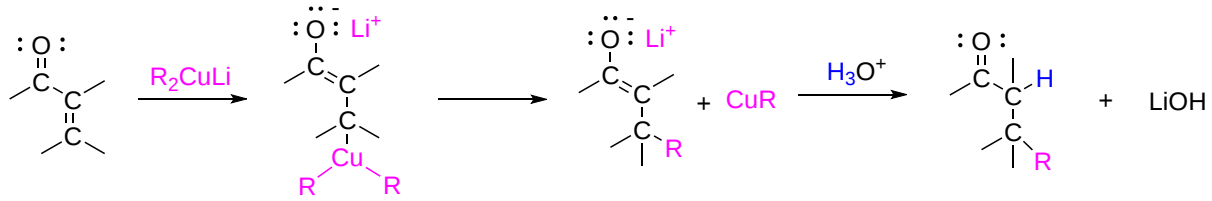


Example



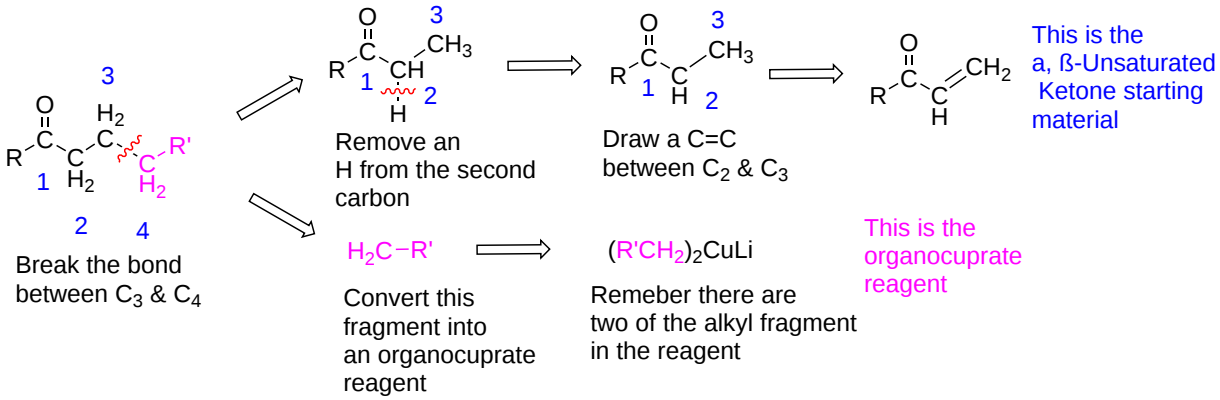
Mechanism for the 1,4 Conjugate Addition of Lithium Diorganocopper Reagents to α, β-Unsaturated Ketone

This mechanism is only slightly different than the general mechanism for 1,4 conjugate addition described above. The mechanism starts with the nucleophilc diorganocopper anion (R_2Cu^-) adding to the electrophilc β alkene carbon forming a Cu-C bond. The R group from the diorganocopper is then transferred to the β alkene carbon with elimination of a neutral organocopper species (RCu). Protonation of the enolate ion followed by tautomerization creates the final 1,4 addition product.



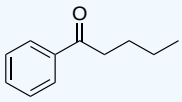
Synthesis of Ketones using 1,4 Conjugate Addition of Lithium Diorganocopper Reagents to α, β Unsaturated Ketones

When using retrosynthetic analysis to plan the synthesis of a ketone, remember this reaction allows for the formation of a C-C bond between third and fourth carbon away from a ketone. The carbonyl group in the target molecule will become an α,β-unsaturated carbonyl in the probable reactant. To determine the structure of a possible reactant, start by cleaving the C-C between the third and fourth carbon away from the carbonyl to create two fragments. The take the fragment which retains the carbonyl and remove a hydrogen from the second carbon and connect the second and third carbon with a double bond. The creates the required α,β-unsaturated carbonyl reactant. The other fragment will become the lithium diorganocopper reagent. Remember the lithium diorganocopper reagent contains two of the required R group. Note! If the fourth carbon away from the ketone in the target molecule is tertiary or quarternary there may be multiple bonds which could be retrosynthetically cleaved.

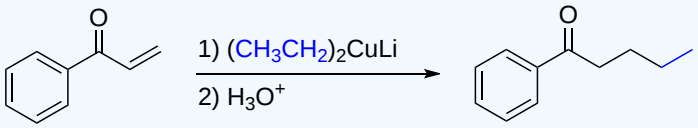


? Exercise 7.11.1

How would you make the following molecule using a conjugate addition of a Gilman reagent to an α,β-unsaturated ketone?



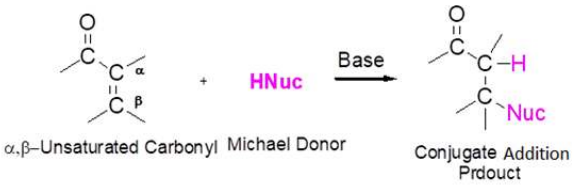
Answer



Michael Reaction

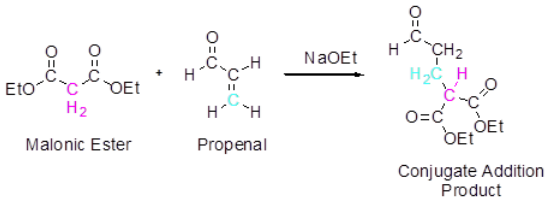
Certain nucleophiles undergo conjugate addition with the alkene of an α,β-unsaturated carbonyl compounds rather than undergo direct nucleophilic addition with the carbonyl. During conjugate addition, a nucleophile adds to the electrophilic β-alkene carbon to from a C-Nuc bond. If the starting materials contains an ester the corresponding alkoxide is used as the base in the reaction. Otherwise a hydroxide base, such as sodium or potassium hydroxide, is commonly used.

General Reaction



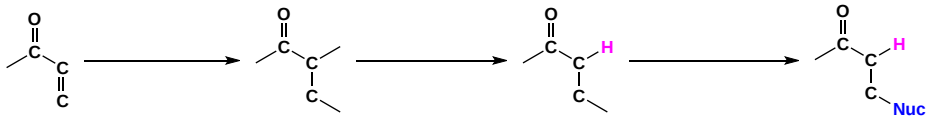
When enolate nucleophiles undergo conjugate addition with an α, β-unsaturated carbonyl the process is called a Michael Reaction. The Michael reaction works best with particularly acidic enolate donors such as malonic esters, β-keto esters, etc. Enolates which are weaker acids tend to undergo nucleophilic addition to the carbonyl rather than conjugate addition. For example, malonic ester's acidic alpha-hydrogens can be easily deprotonated by sodium ethoxide to form an enolate. The enolate adds to propenal to form the conjugate addition product.

Example



Predicting the Product of a Michael Reaction

During the is reaction the C=C pi bond of the α,β-unsaturated carbonyl is broken. An C-H bond is formed on the carbon in the α-position from the carbonyl. An acidic hydrogen is removed from the nucleophile and then it is used to form a C-C bond with the carbon in the beta position from the carbonyl.



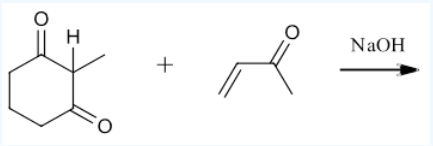
a. In the first step, remove the double bond and add two single bonds

b. Add a hydrogen to the bond adjacent to the carbonyl

c. Add the nucleophile to the other end of the double bond (remember to remove a hydrogen from the nucleophile)

? Worked Example 7.11.1

What would be the product of the following conjugate addition?



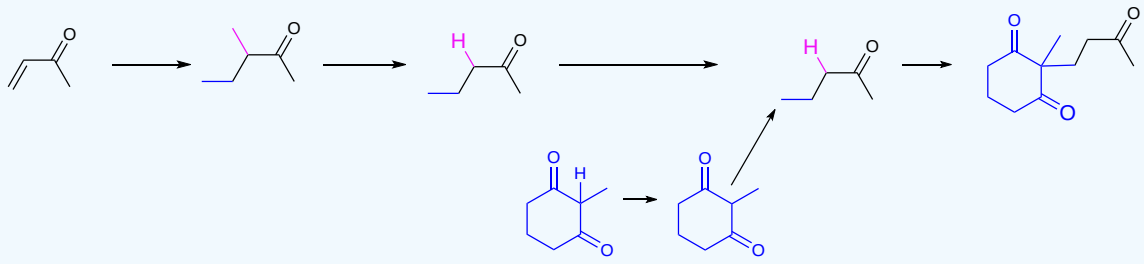
Answer

1. break the double bond and add two single bonds

2. Add a hydrogen to the bond adjacent to the carbonyl

3. Remove a hydrogen from the nucleophile.

4. Add the nucleophile to the other end of the double bond.



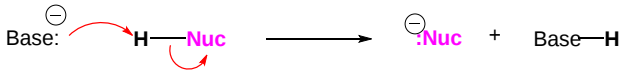
Mechanism of Michael reaction

During a Michael reaction the enolate acts as a nucleophilic donor and the α, β-unsaturated carbonyl acts as the electrophilic acceptor. The mechanism is a mixture of an alpha-substitution for the enolate and a conjugate addition for the α, β-unsaturated carbonyl.

Notice that the Michael Reaction does not require the deprotonation of the product to push the reaction towards completion. The reaction is thermodynamically favorable because the C-C bond formed in the product is stronger than the C=C bond in the starting material. This means that, unlike the Claisen condensation, this reaction only requires a catalytic amount of reaction base.

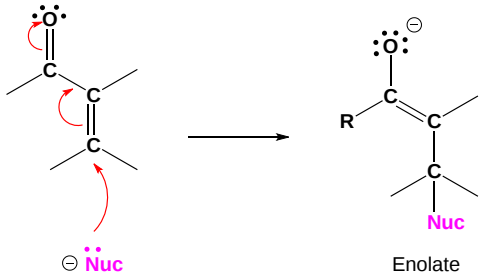
1) Deprotonation

The alkoxide base removes an alpha-hydrogen to from an enolate nucleophile.



2) Nucleophilic attack on the carbon β to the carbonyl

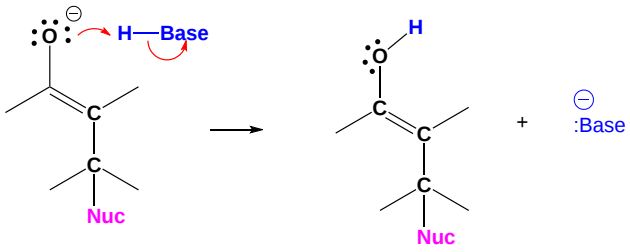
The enolate nucleophile then adds to the electrophilic β-carbon of the α, β-unsaturated carbonyl. Conjugation pushes the C=C pi bond electrons onto the carbonyl oxygen, forming a new enolate enolate.



Enolate

3) Protonation

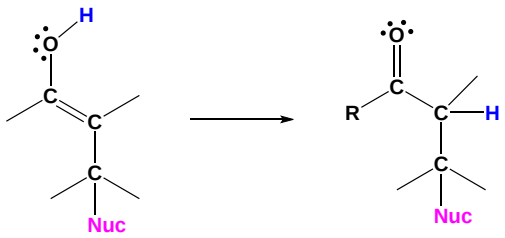
The alkoxide is protonated, forming an enol.



Enol

4) Tautomerization

Tautomerization converts the enol back into a carbonyl forming the neutral conjugate addition product.



The Michael reaction can be performed with a wide variety of α, β-unsaturated carbonyl electrophilic acceptors and enolate donors. Michael acceptors such as α, β-unsaturated ketones, aldehydes, esters, amides, and nitro compounds can all participate in this reaction. Michael donors with particularly acidic α-hydrogens, such as β-diketones, β-keto esters, β-keto nitriles, α-nitro ketones, malonic esters, and nitro compounds can be used.

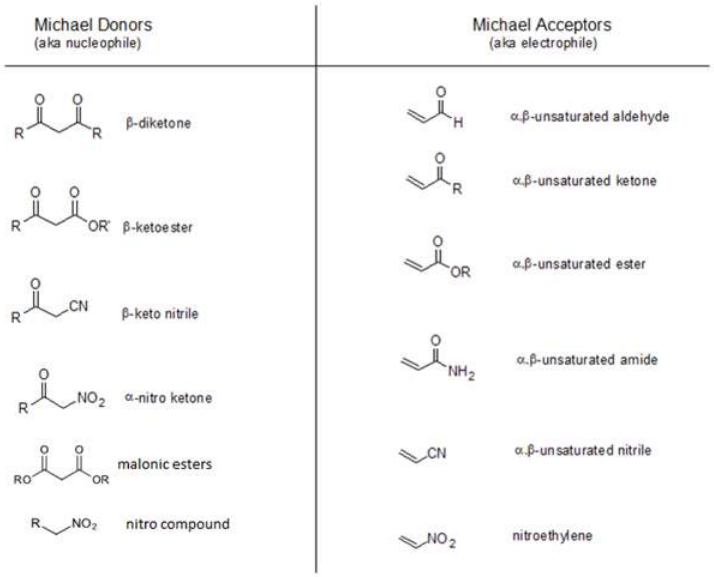
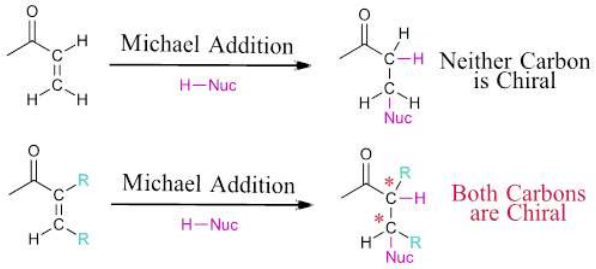


Table 7.1: Possible Donors and Acceptors Which can be used in a Michael Reaction

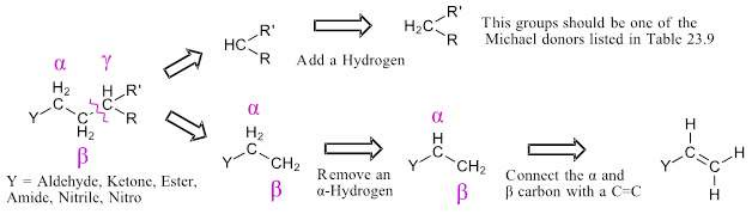
Stereochemical Consideration of Micheal Reactions

During a Michael reaction two sp^2 hybridized carbons are both converted to sp^3 hybridization. Both of them have the possibility of creating a chiral carbon. Michael reactions are often performed using an α, β-unsaturated carbonyl with only hydrogen substituents on the alkene to prevent the formation of chiral carbons. If either carbon in the alkene has an alkyl substituent it will likely form a chiral carbon in the Michael reaction product. The α-carbon of the enolate donor also has the possibility of forming a chiral carbon.



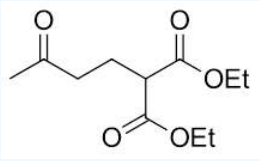
Planning a Synthesis Using a Michael Reaction

The true utility of the Michael reaction is seen when considering it use in a synthesis. The reaction can be used to prepare aldehydes, ketones, esters, amides, nitriles, and nitro compounds. A target molecule can possibly be made using a Michael reaction if it contains one of these functional groups and an alkyl chain at least three carbons long. The key bond cleavage is a C-C bond between β and gamma carbons from a carbonyl-like group. The fragment with the Y group loses an α-hydrogen and then forms a C=C bond between the α and beta carbon. The carbon of the other fragment gains a hydrogen. This fragment should possess an acidic α-hydrogen and should be made up of Michael donor fragments such as those listed in **Table 7.1**. In some cases, there may be more than one fragmentation variation. Each variation should be investigated and the possible starting materials compared for viability.



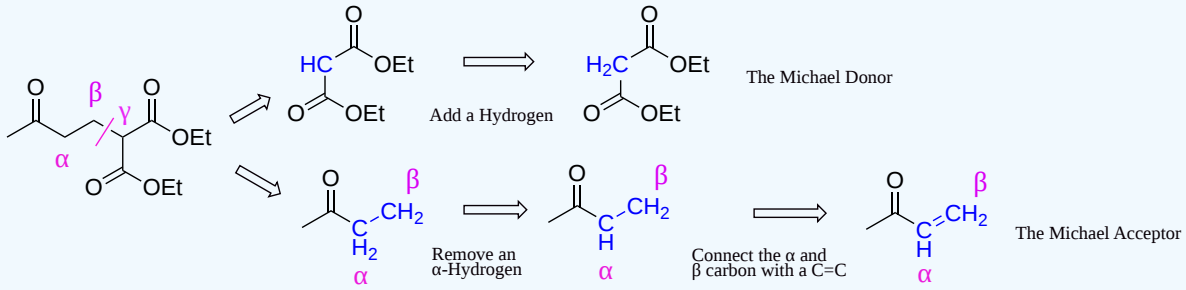
Worked Example

How could the following molecule be synthesized using a Michael Reaction?



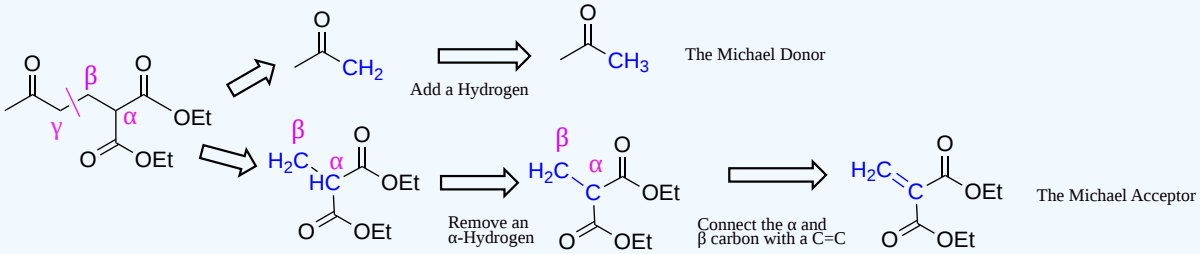
Answer

Pathway 1

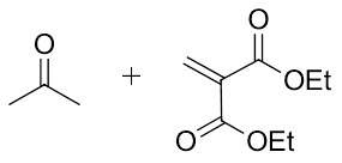


Starting Materials 1

Pathway 2

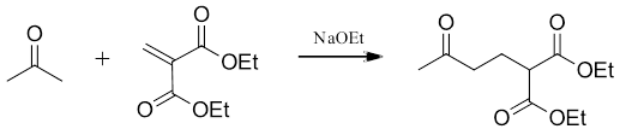


Starting Material 2



Solution

When comparing the two sets of possible starting materials of pathway 1 are preferred. The Michael enolate donor is particularly acidic because its conjugate base is stabilized by two carbonyls. The Michael enolate donor for pathway 2 does not have the same acidity. Consequently, the enolate would preferably undergo nucleophilic addition rather than conjugate addition. The makes the starting materials of pathway 1 preferred for the synthesis of the starting material.



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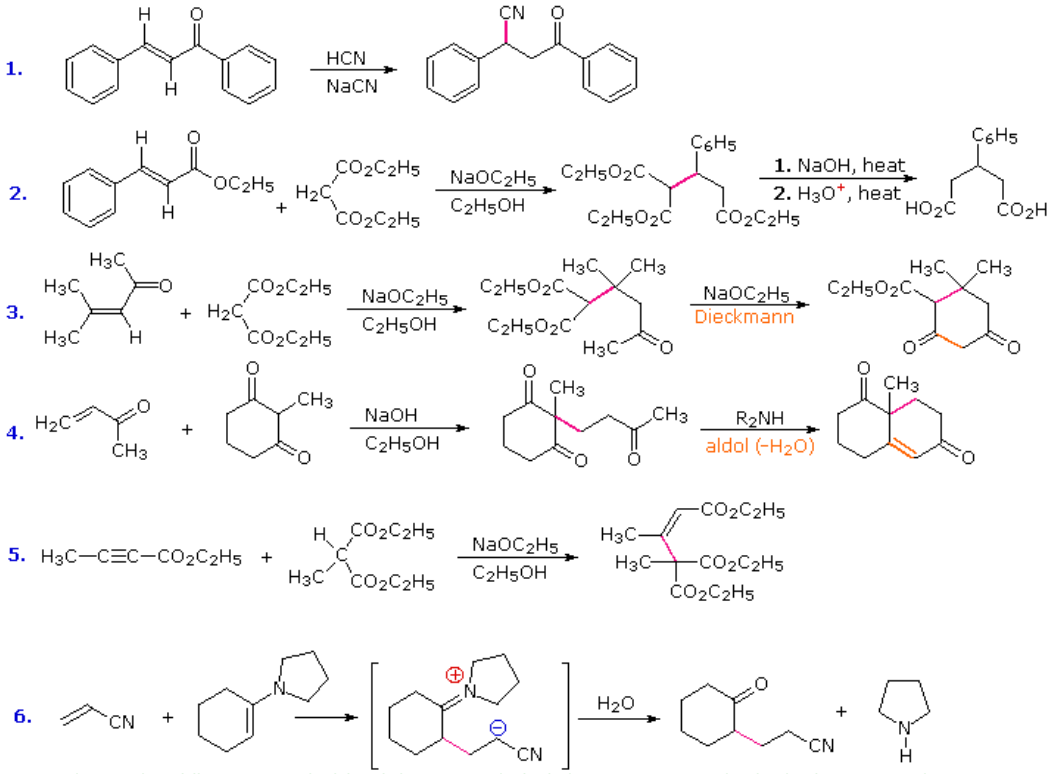
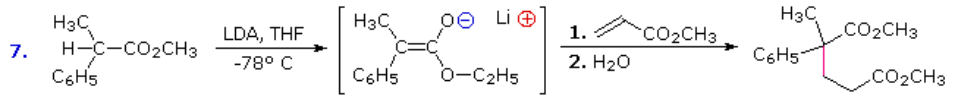
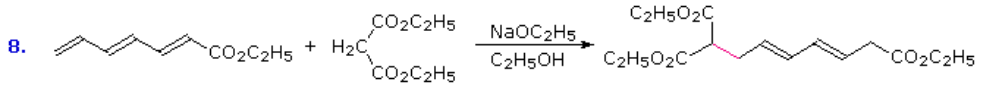
In combination with alkylations and condensations, the Michael reaction may be used to construct a wide variety of complex molecules from relatively simple starting materials. The carbon nucleophiles used in the following examples include cyanide ion, sodium diethylmalonate and the conjugate base of cyclohexane-1,3-dione. These anions are sufficiently stable that their addition reactions may be presumed reversible. If this is so, the thermodynamic argument used for hetero-nucleophile additions would apply here as well, and would indicate preferential formation of 1,4-addition products. Cyanide addition does not always follow this rule, and aldehydes often give 1,2-products (cyanohydrins). In each case the initial reaction is a Michael addition, and the new carbon-carbon bond is colored magenta. Any subsequent bonds that are formed by other reactions are colored orange.



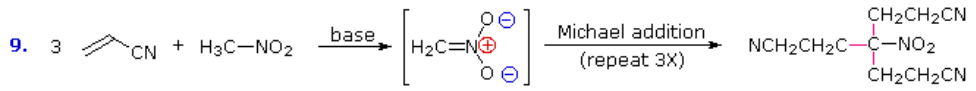
Enamine nucleophiles are good Michael donors. Hydrolysis is necessary to obtain the ketone product.



Weak carbon acids may be converted to their enolate anions prior to addition of the Michael acceptor.



Extended vinylagous Michael acceptors have been used. This is a 1,6-addition (1,8 if the enol is counted).



Nitroalkanes have acidic α-hydrogens and make excellent Michael donors.

? Exercise 7.11.2

Provide the products of the following Michael additions:

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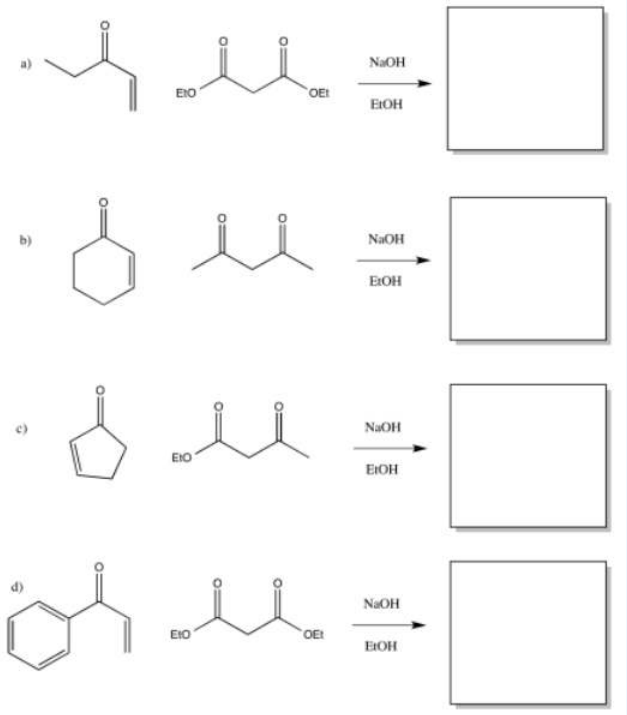
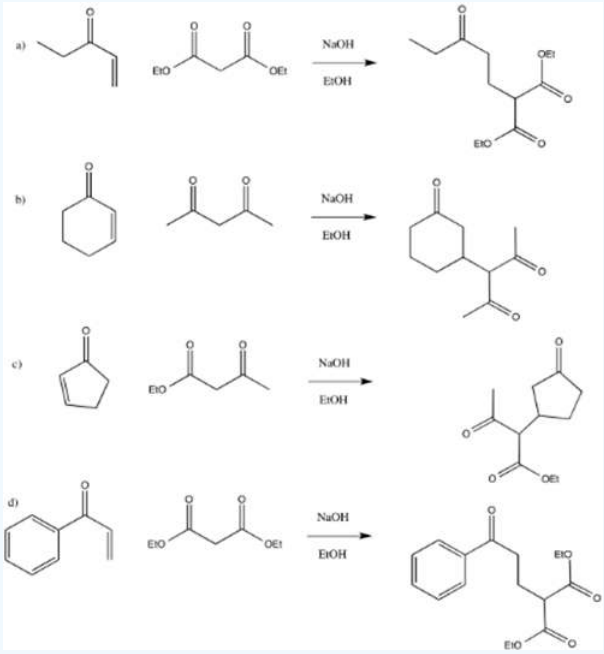
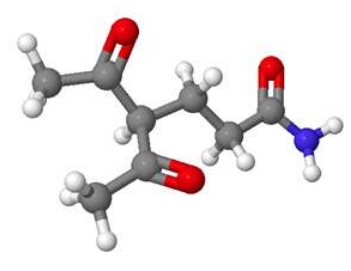


Answer

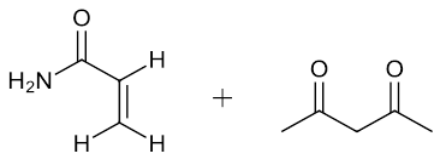


Exercises 7.11.3

What would be the starting materials required to make the following molecule using a Michael reaction? Red = Oxygen, Grey = Carbon, White = Hydrogen, Blue = Nitrogen.



Answers



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- **19.13: Conjugate Nucleophilic Addition to α, β-unsaturated Aldehydes and Ketones** by Dietmar Kennepohl, Layne Morsch, Steven Farmer is licensed CC BY-SA 4.0.

7.12: Carbonyl Condensations with Enamines - The Stork Reaction (reference only)

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the 3-step Stork enamine reaction.
2. write a detailed mechanism for each of the three steps of the Stork enamine reaction.
3. identify the product formed, and the various intermediates (i.e., the enamine, the Michael-type adduct), in a given Stork enamine reaction.
4. identify the reagents needed to synthesize a given compound by a Stork enamine reaction.

Key Terms

- Stork enamine reaction

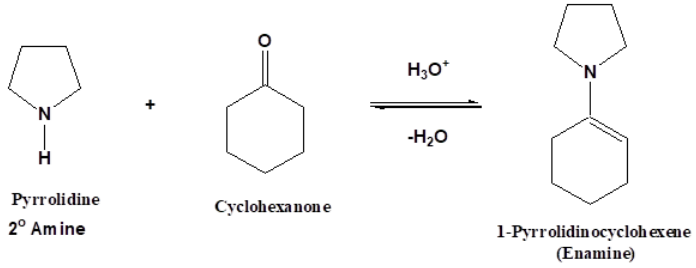
Study Notes

If we try to use a monoketone as a donor molecule in a Michael reaction, we will obtain a poor yield. An alternative route to the product that would be expected from such a synthesis is via the Stork enamine reaction. You may wish to review the formation of enamines (from ketones and secondary amines) before you proceed with this section.

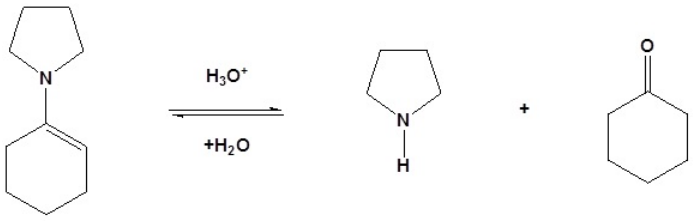
Synthesis of Enamines

As previously seen in **CHM 222**, aldehydes and ketones react with 2° amines to reversibly form enamines. Enamines can add to acid halides to form 1,3-diketones and α, β-unsaturated Michael acceptors to from 1,5-dicarbonyls.

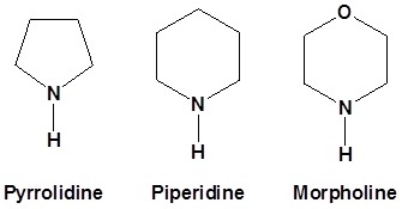
Example



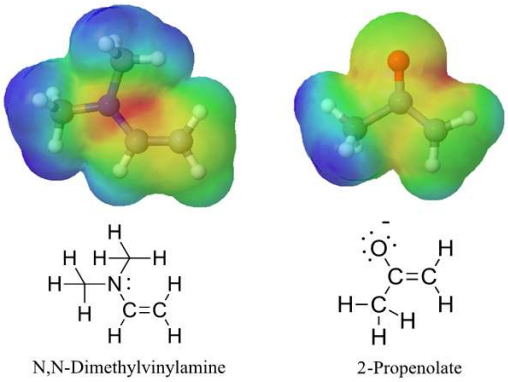
Reversibility



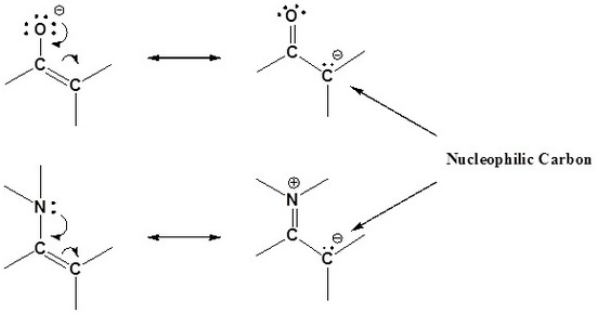
Typically the following 2° amines are used for enamine reactions



Enamines have resonance structures similar to enolates. The lone pair electrons on the nitrogen are conjugated with the double bond and can donate electron density to the α-carbon. This allows the α-carbon of enamines to be nucleophilic in much the same fashion as enolates. The increased electron density of the α-carbon enamine, N,N-dimethylaminoethylene, is shown as a yellow/green color in its electrostatic map. This is analogous to the increased electron density of the α-carbon of an enolate.

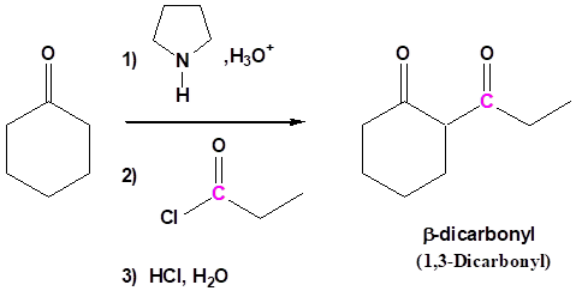


Enamines act as nucleophiles in a fashion similar to enolates. Because of this enamines can be used as synthetic equivalents as enolates in many reactions. This process requires a three steps: 1) Formation of the enamine, 2) Reaction with an electrophile to form an iminium salt, 3) Hydrolysis of the iminium salt to reform the aldehyde or ketone. Some of the advantages of using an enamine over an enolate are enamines are neutral, easier to prepare, and usually prevent the overreaction problems plagued by enolates. Also, enamine are more effective at the Michael reaction compared to a mono-carbonyl enolate.



Acylation of Enamines

Example



Mechanism on Enamine Acylation

1) Formation of the enamine

The mechanism starts with the formation of an enamine.

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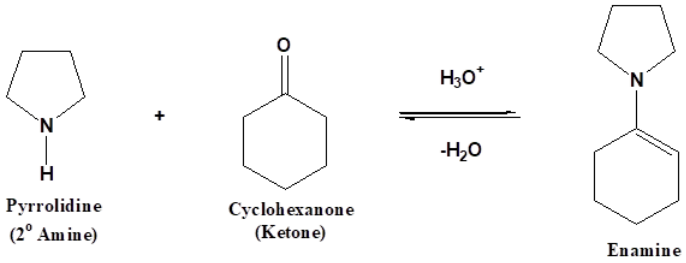
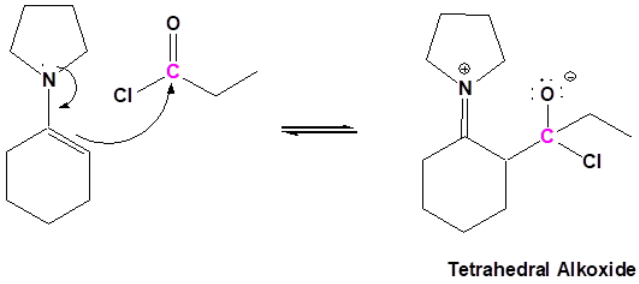


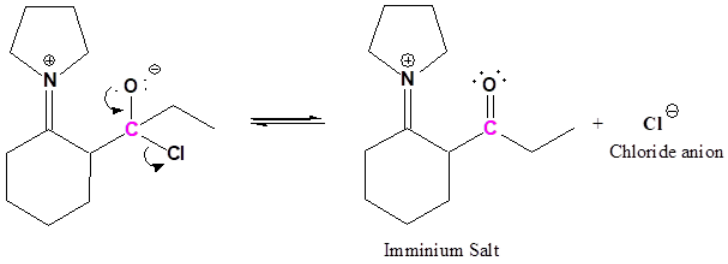
2) Nucleophilic attack

The enamine adds to the electrophilic carbonyl carbon of the acid halide to form an iminium bond with tetrahedral alkoxide as an intermediate.



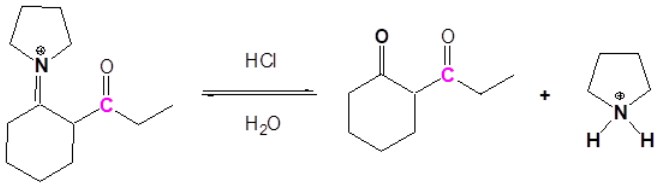
3) Leaving group removal

The alkoxide reforms the carbonyl bond and eliminate a halide anion as a leaving group.



4) Reform the carbonyl by hydrolysis

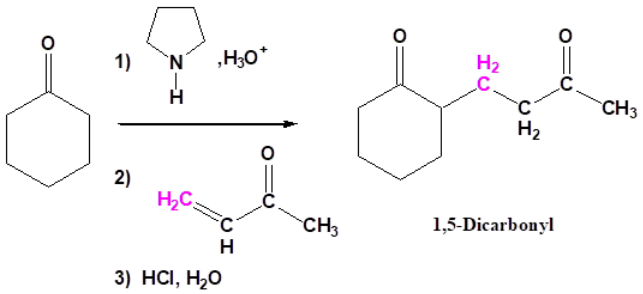
The iminium bond is then hydrolyzed to reform the carbonyl to create a 1,3-dicarbonyl compound as the product of a nucleophilic acyl substitution.



Michael Reaction Using Enamines: The Stork Reaction

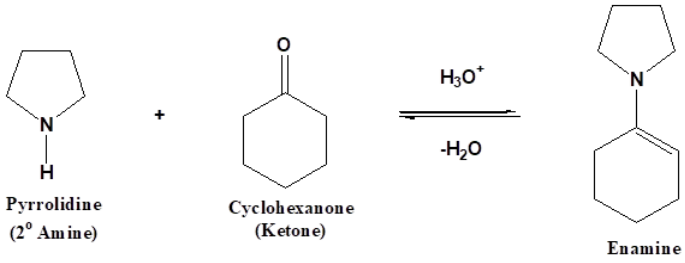
Enamines add to α, β-unsaturated carbonyls in a Michael-like reaction. The net reaction is the addition of a ketone to a α,β-unsaturated carbonyl to product a 1,5 dicarbonyl compound as the end product. This reaction is commonly known as the Stork enamine reaction after Gilbert Stork of Columbia University who originated the work.

Example



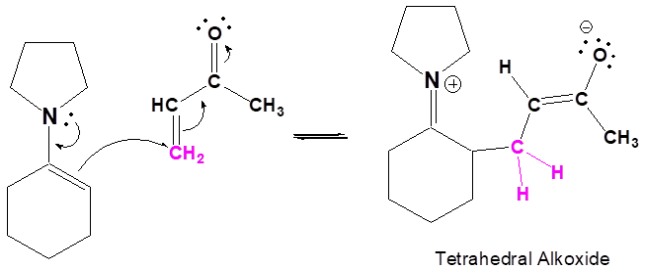
Mechanism of the Stork Reaction

1) Formation of the enamine



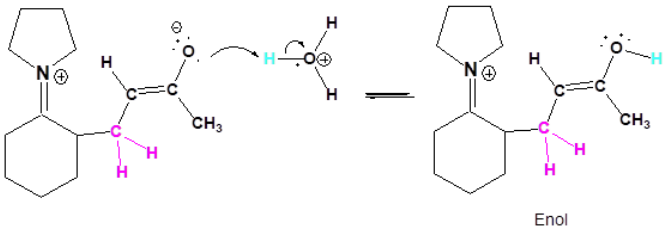
2) Nucleophilic attack on the carbon β to the carbonyl

After formation, the enamine adds to the electrophilic alkene carbon of the a α, β-unsaturated carbonyl form an iminium bond. The pi electrons of the alkene are pushed onto the oxygen through conjugation to form an alkoxide as an intermediate.



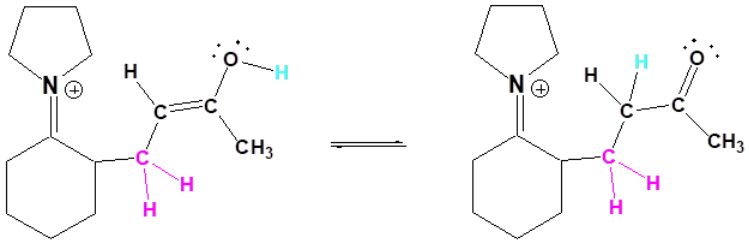
3) Protonation

Protonation of the alkoxide forms an enol.



4) Tautomerization

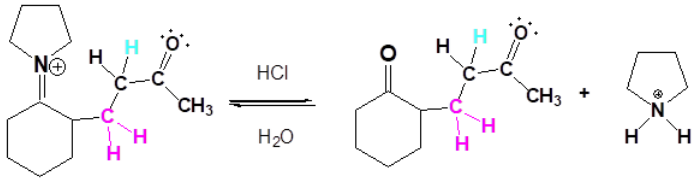
The enol undergoes tautomerization to reform the ketone.



Conjugate Additon Product

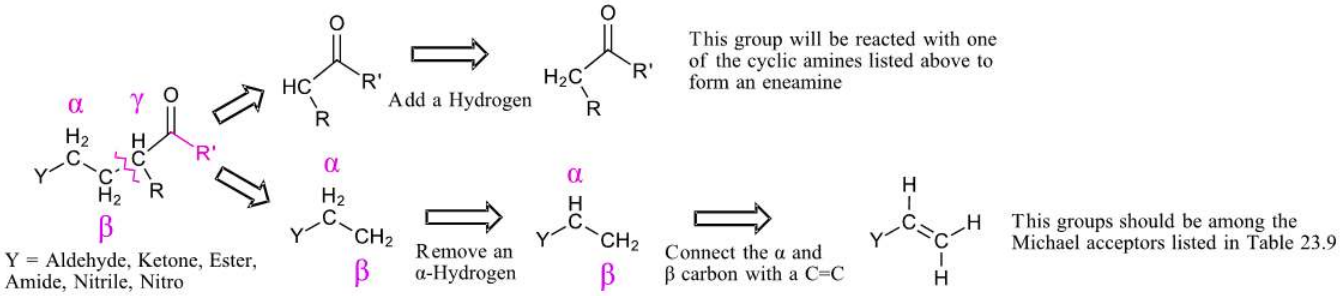
4) Reform the carbonyl by hydrolysis

In the last step of the mechanism, the iminium bond is hydrolyzed to reform the carbonyl to create a 1,5-dicarbonyl compound as the product of a Michael-like reaction.



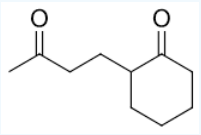
Planning a Synthesis Using the Stork Enamine Synthesis

Planning a synthesis using a Stork enamine reaction is very similar to that of a Michael reaction. A target molecule can possibly be made using a Stork enamine reaction if it contains a 1,5-dicarbonyl. Like the Michael reaction, the key bond cleavage is a C-C bond between beta and gamma carbons from a carbonyl-like group. The fragment with the Y group loses an alpha-hydrogen and then forms a C=C bond between the alpha and beta carbon. The carbon of the other fragment gains a hydrogen. This fragment should possess an acidic alpha-hydrogen and should be made up of Michael donor fragments.



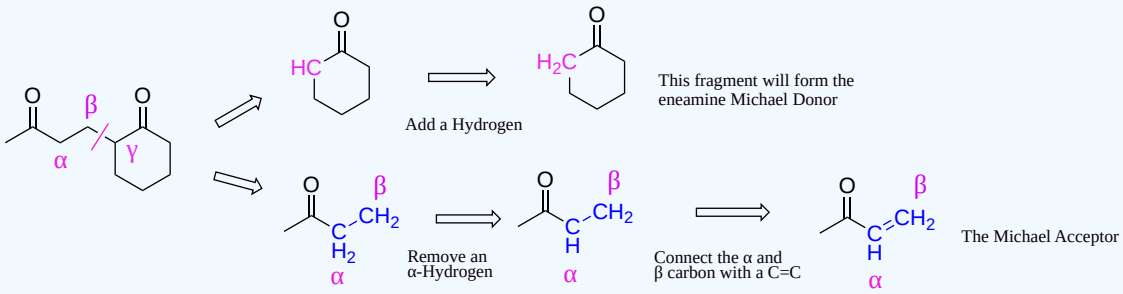
? Worked Example

How could the following molecule be made using a Michael Reaction?

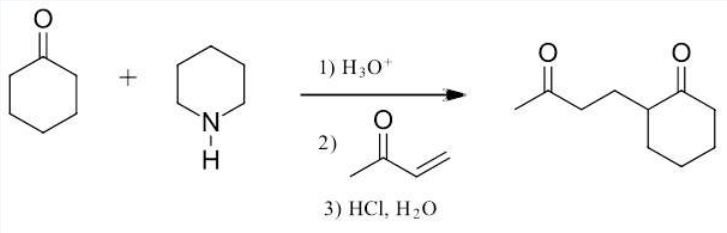


Answer

Pathway 1



Solution

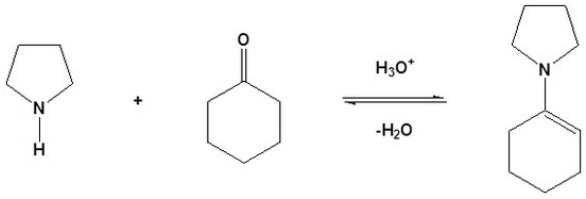


Alkylation of an Enamine

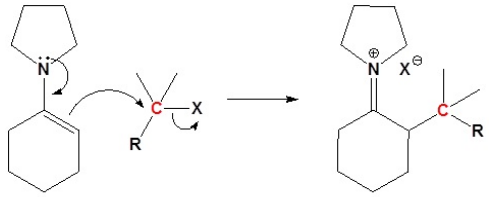
Enamines undergo an S_N2 reaction with reactive alkyl halides to give the iminium salt. The iminium salt can be hydrolyzed back into the carbonyl.

Individual steps

1) Formation of an enamine

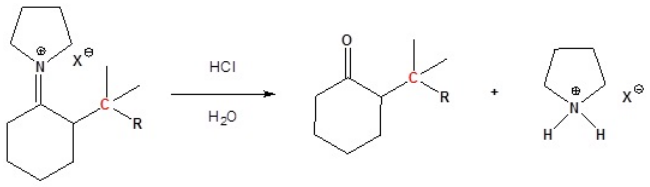


2) S_N2 Alkylation



Iminium Salt

3) Reform the carbonyl by hydrolysis



All three steps together:

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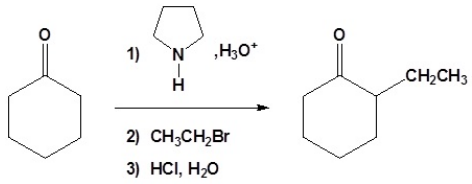
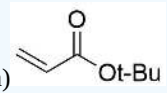
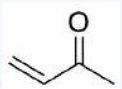
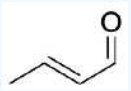


Exercise 7.12.1

Draw the product of the reaction with the enamine prepared from cyclopentanone and pyrrolidine, and the following molecules.

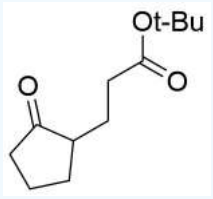
a) 

b) 
c) 

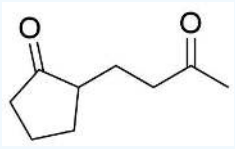
Answer

1)

a)



b)



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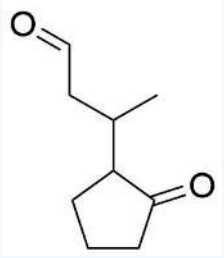
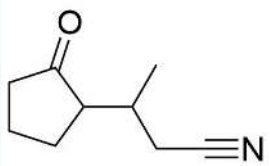


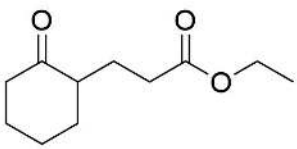
Exercises 7.12.2

What would be the starting materials necessary to make the following molecules during a Stork enamine reaction.

a)



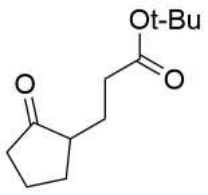
b)



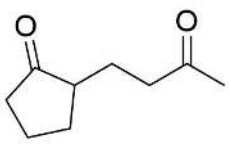
Answers

1)

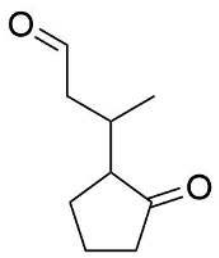
a)



b)

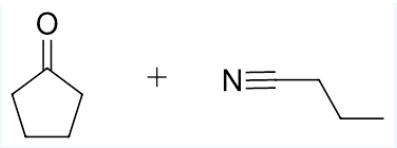


c)

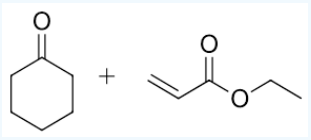


2)

a)



b)



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7.13: The Robinson Annulation Reaction

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the Robinson annulation reaction.
2. identify the cyclic product formed when a 1,5-diketone is treated with base.
3. identify the carbonyl compounds and any other reagents needed to synthesize a given cyclic compound by a series of reactions, one of which is a Robinson annulation.

Key Terms

- Robinson annulation reaction

Study Notes

The building of a cyclic compound from acyclic starting materials can present an interesting challenge to the synthetic organic chemist. One route by which such a synthesis can be achieved is through the use of the Robinson annulation reaction. This reaction, which may at first look very complex, can be readily understood once you realize that it simply involves a Michael reaction followed by an intramolecular aldol condensation. Both of these steps involve attack by enolate anions.

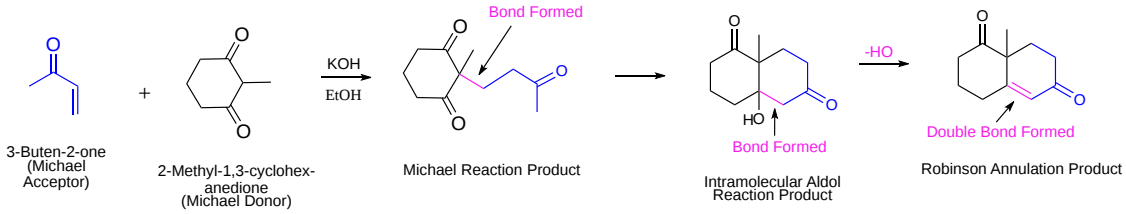
As in some of the other syntheses that you have studied, when you are simply given the structure of a compound and asked how it could have been prepared, it can be difficult to recognize which reactions might have been used. In this instance, keep in mind that you have studied relatively few reactions which have resulted in the formation of a cyclic compound. Thus, when asked how such a compound might be prepared, you should keep the possibility of using a Robinson annulation reaction in mind when the target is a 6-membered ring.

The Robinson Annulation

Many times the product of a Michael addition produces a dicarbonyl which can then undergo an intramolecular aldol reaction. These two processes together in one reaction create two new carbon-carbon bonds and also create a ring. Ring-forming reactions are called annulations after the Latin work for ring, annulus. The reaction is named after English chemist Sir Robert Robinson (1886-1975) who developed it. He received the Nobel prize in chemistry in 1947. Remember that during annulations five- and six-membered rings are preferred.

The nucleophilic enolate donor is typically an enolate ion or enamine of a cyclic ketone, β-keto ester or β-diketone. The electrophilic acceptor is usually an α, β-unsaturated ketone. In the example below, 2-methyl-1,3-cyclohexanedione is deprotonated to form an enolate which affects a Michael reaction addition on 3-buten-2-one forming a C-C bond. The product contains a 1,5-diketone fragment which can undergo an intramolecular aldol condensation. This occurs through creation of a new enolate at the methyl ketone which undergoes an intramolecular aldol reaction. A new C-C bond is formed to one of the ring carbonyls, creating a new six-membered ring. In the last step, the resulting alcohol is eliminated to form a α, β-unsaturated ketone as the final Robinson annulation product.

Example



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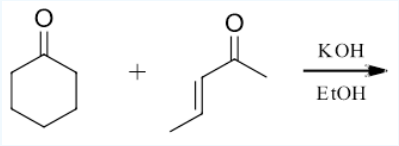
Worked Example

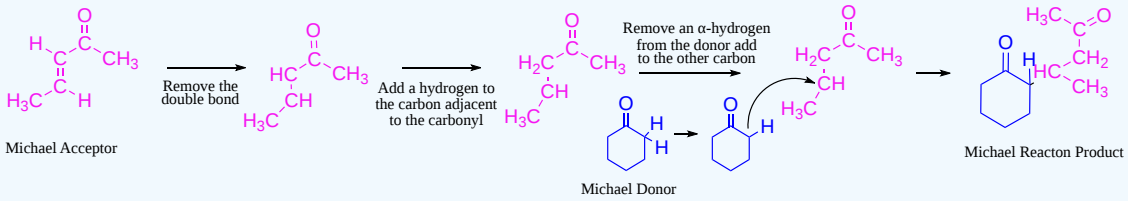
Draw the product of the following Robinson Annulation.



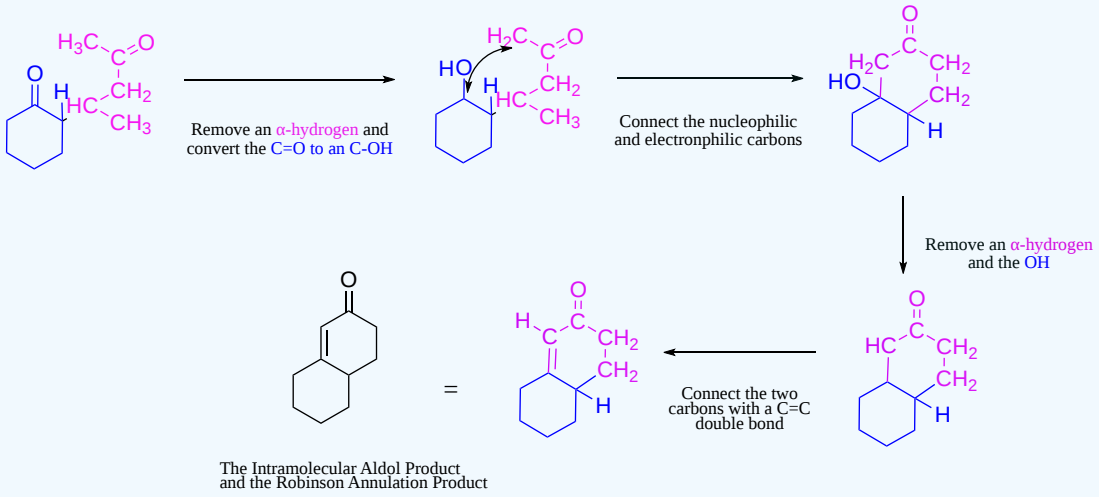
Answer

Analysis: When considering the product of a Robinson annulation it is usually best to consider each reaction individually. Use the steps discussed in Section 7.11 to convert the starting materials into the product of a Michael reaction, then into the product of an intramolecular aldol condensation. If the starting materials are drawn in a skeletal structure it may be helpful to convert to a condensed formula to better keep track of carbons and hydrogens.

Formation of the Michael reaction product

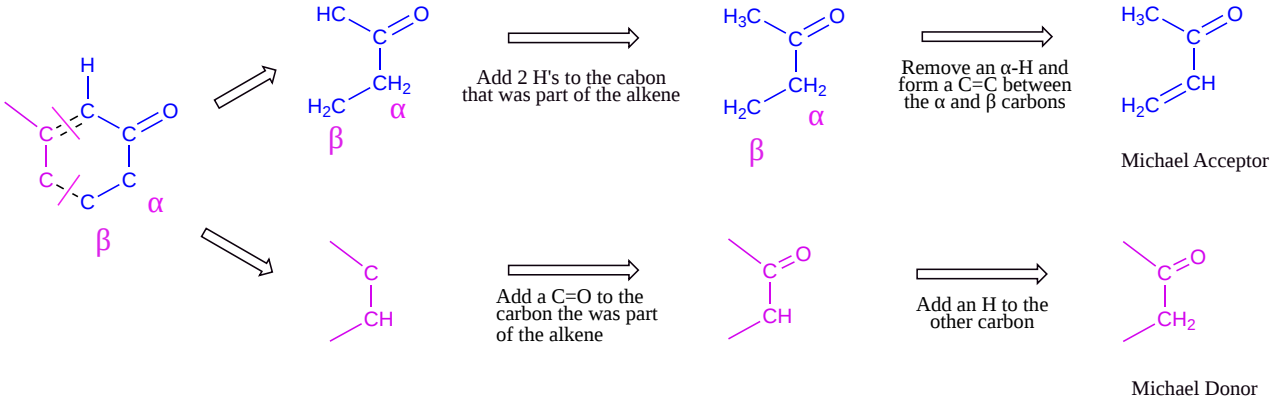


Formation of the intramolecular Aldol condensation product



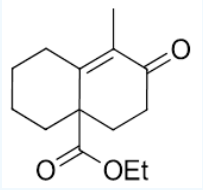
Planning a Synthesis Using a Robinson Annulation

The presence of a cyclic, six-membered α, β-unsaturated ketone in a target molecule suggest that a Robinson Annulation may be utilized in its synthesis. The key bond cleavages are the C=C bond of the α, β-unsaturated ketone and the C-C bond between carbons in the a and g on the opposite alkyl chain of the ketone.



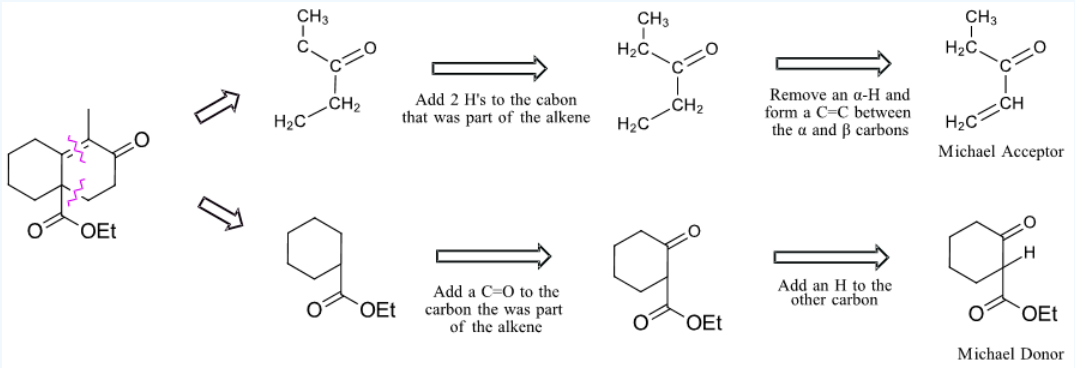
Worked Example

What would be the starting materials used if the following molecule was made using a Robinson annulation?



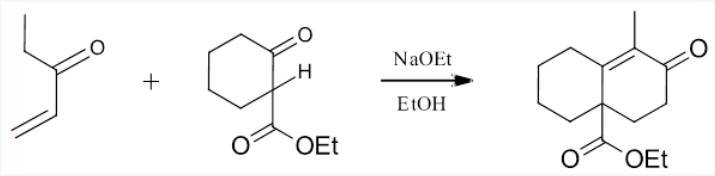
Answer

Analysis



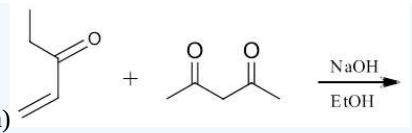
Solution

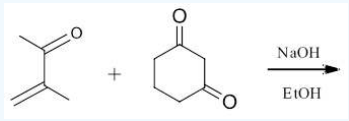
It is necessary to use sodium ethoxide as the reaction base due to the presence of an ester.



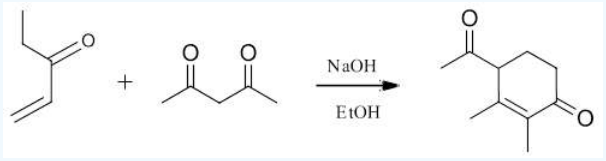
Exercise 7.13.1

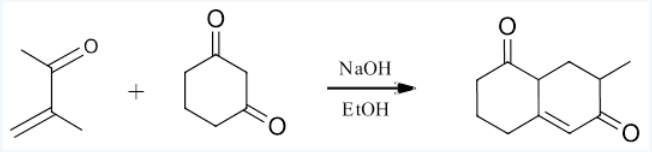
1) Provide products of the following Robinson annulations.

a) 

b) 

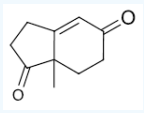
Answers

a) 

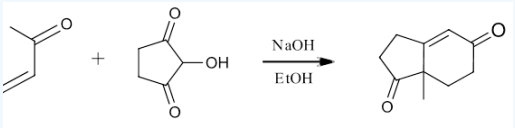
b) 

Exercise 7.13.2

What would be the starting materials required to make the following molecule using a Robinson annulation?



Answer



Note: The OH in the starting material is a typo. That should be a methyl group.

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7.14: Some Biological Carbonyl Condensation Reactions (reference only)

Objectives

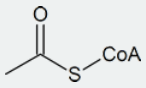
After completing this section, you should be able to

1. identify acetyl coenzyme A as an important biomolecule which undergoes carbonyl condensation reactions.
2. identify aldoases as enzymes that catalyze aldol reactions in biological systems.
3. identify the steps in which a carbonyl condensation reaction has occurred, given a general outline of a specific biosynthesis.

Study Notes

Carbonyl condensation reactions occur in biological systems; for example, in the biosynthesis of citric acid.

You first met acetyl coenzyme A in Section 21.8. Again, we stress that it is not essential that you know the detailed structure of this compound (or other large biochemical stuctures discussed), but you should know that it may be represented as



and that it has the ability to behave just as any other acetyl-containing compound.

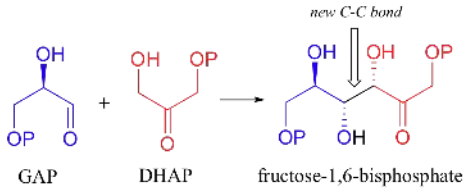
Aldol Reactions in Nature

So far, we have examined the non-enzymatic reaction of an aldehyde or ketone with itself (a so-called 'self-condensation' reaction, where 'condensation' means the formation of one larger molecule from two smaller ones). However, aldol reactions occur in several biological pathways, most commonly in the metabolism of carbohydrates (sugars). The enzymes that catalyze aldol reactions are called, not surprisingly, '**aldolases**'. They occur in all organisms, but note that **Class I aldoases** are usually found in animals and higher plants, while **Class II aldoases** normally appear in bacteria and fungi.

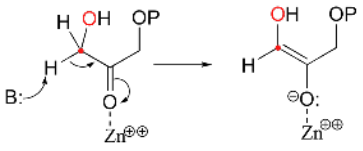
Typical aldolase reactions - three variations on a theme

The first step in an aldolase reaction is the deprotonation of an alpha-carbon to generate a nucleophilic carbanion. Nature has evolved several distinct strategies to stabilize the intermediate that results. Some aldolases use a metal ion to stabilize the negative charge on an enolate intermediate, while others catalyze reactions that proceed through neutral Schiff base or enol intermediates.

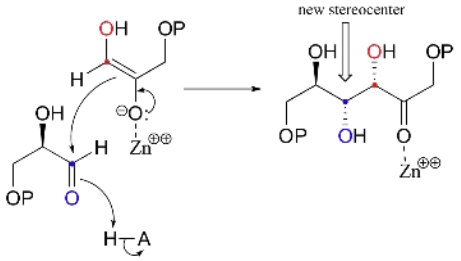
Let's examine first a reaction catalyzed by a so-called '**Class II' aldolase**, in which a metal cation - generally Zn^{2+} - bound in the active site serves to stabilize the negative charge on an enolate intermediate. Fructose 1,6-bisphosphate aldolase is an enzyme that participates in both the glycolytic (sugar burning) and gluconeogenesis (sugar building) biochemical pathways. For now, we will concentrate on its role in the gluconeogenesis pathway, but we will see it again later in its glycolytic role. The reaction catalyzed by fructose 1,6-bisphosphate aldolase is a condensation between two 3-carbon sugars, glyceraldehyde-3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP), forming a six-carbon product (which leads, after three more enzymatic steps, to glucose).



In the first step of the condensation, an alpha-carbon on DHAP is deprotonated, leading to an enolate intermediate. The strategy used to stabilize this key intermediate is to coordinate the negatively-charged enolate oxygen to an enzyme-bound zinc cation.

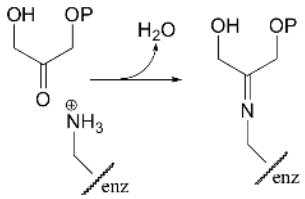


Next, the deprotonated a-carbon attacks the carbonyl carbon of GAP in a nucleophilic addition reaction, and protonation of the resulting alcohol leads directly to the fructose 1,6-bisphosphate product.

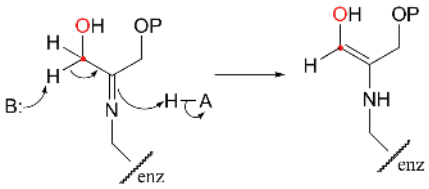


As with many other nucleophilic carbonyl addition reactions, a new stereocenter is created in this reaction, as a planar, achiral carbonyl group is converted to a tetrahedral, chiral alcohol. The enzyme-catalyzed reaction, not surprisingly, is completely stereospecific: the DHAP substrate is positioned in the active site so as to attack the *re* (front)face of the GAP carbonyl group, leading to the *R* configuration at the new stereocenter.

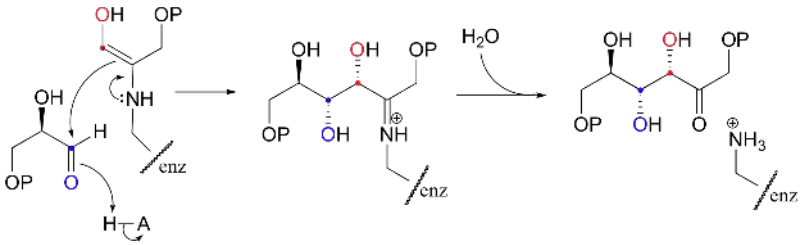
Interestingly, it appears that in bacteria, the fructose bisphosphate aldolase enzyme evolved separately from the corresponding enzyme in plants and animals. In plants and animals, the same aldol condensation reaction is carried out by a significantly different mechanism, in which the key intermediate is not a zinc-stabilized enolate but an enamine. The nucleophilic substrate (DHAP) is first linked to the enzyme through the formation of an imine (also known as a Schiff base) with a lysine residue in the active site.



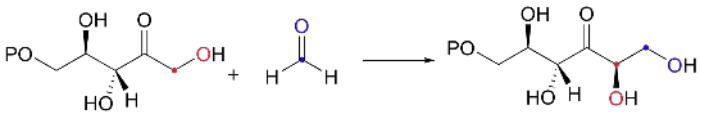
The alpha-proton is then abstracted by an active site base to form an enamine.



In the next step, the alpha-carbon attacks the carbonyl carbon of GAP, and the new carbon-carbon bond is formed. In order to release the product from the enzyme active site and free the enzyme to catalyze another reaction, the imine is hydrolyzed back to a ketone group.



There are many more examples of **'Class I' aldolase** reactions in which the key intermediate is a lysine-linked imine. Many bacteria are able to incorporate formaldehyde, a toxic compound, into carbohydrate metabolism by condensing it with ribulose monophosphate. The reaction proceeds through imine and enamine intermediates.



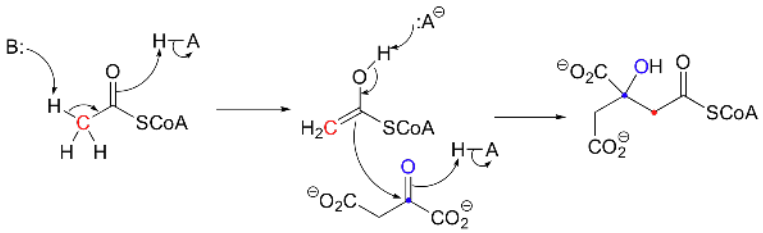
ribulose-5-phosphate formaldehyde hexulose-6-phosphate

Example 23.13.1

a. Propose a complete mechanism for the condensation reaction shown above.
b. Propose a complete mechanism for the conversion of hexulose-6-phosphate (formed from the condensation of ribulose-5-phosphate and formaldehyde) into fructose-6-phosphate.

Solution

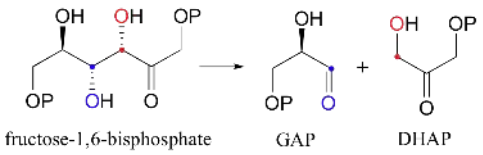
Along with aldehydes and ketones, esters and thioesters can act as the nucleophilic partner in aldol condensations. In the first step of the citric acid (Krebs) cycle, acetyl CoA condenses with oxaloacetate to form (S)-citryl CoA.



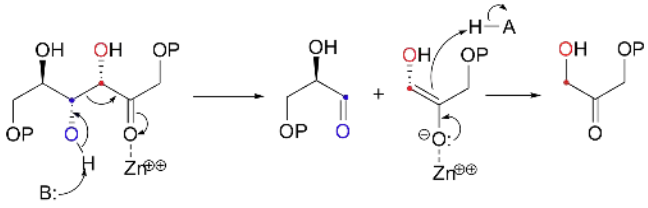
Notice that in this aldol reaction, the nucleophilic intermediate is stabilized by protonation, rather than by formation of an imine (as in the Class I aldolases) or by a metal ion (as in the Class II aldolases).

Going backwards: the retroaldol reaction

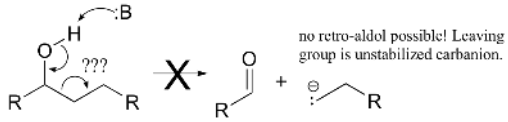
Although aldol reactions play a very important role in the formation of new carbon-carbon bonds in metabolic pathways, it is important to emphasize that they are also highly reversible: in most cases, the energy level of starting compounds and products are very close. This means that, depending on metabolic conditions, aldolases can also catalyze **retro-aldol** reactions (the reverse of aldol condensations, in which carbon-carbon bonds are *broken*). Recall that fructose 1,6-bisphosphate aldolase (section 13.3B) is active in the direction of sugar breakdown (glycolysis) as well as sugar synthesis (gluconeogenesis). In the glycolytic direction, the enzyme catalyzes - either by zinc cation or by imine/enamine mechanisms, depending on the organism - the retro-aldol cleavage of fructose bisphosphate into DHAP and GAP.



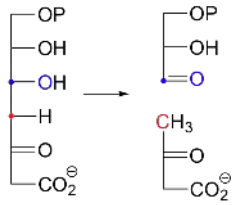
The mechanism is the exact reverse of the condensation reaction. Shown below is the mechanism for a Zn^{2+} - dependent (Type II) retroaldol cleavage. Notice that in the retroaldol reaction, the enolate intermediate is the *leaving group*, rather than the nucleophile.



The key thing to keep in mind when looking for a possible retro-aldol mechanism is that, when the carbon-carbon bond breaks, the electrons must have some place to go, where they will be stabilized by resonance. Generally, this means that there *must* be a carbonyl or imine group on the next carbon. If there is no adjacent carbonyl or imine group, the carbon-carbon bond is not free to break.



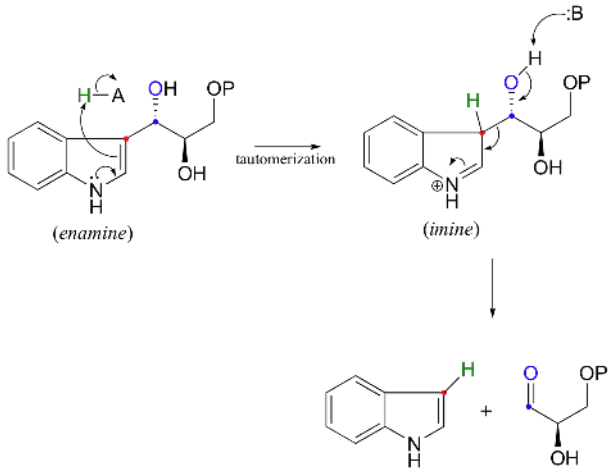
Here are two more examples of retro-aldol reactions. Bacterial carbohydrate metabolism involves this reversible, class I retro-aldol cleavage: (*Proc. Natl. Acad. Sci* **2001**, *98*, 3679).



Example 23.13.2

Draw the structure of the enamine intermediate in the retroaldol reaction shown above.

Another interesting example is the retro-aldol cleavage of indole-3-glycerol phosphate, a step in the biosynthesis of tryptophan.



Look carefully at this reaction - how is the leaving group stabilized? There is an imine group involved, but no participation by an enzymatic lysine. The imine is 'built into' the starting compound, available from the initial tautomerization of the cyclic enamine group in indole-3-glycerol phosphate.

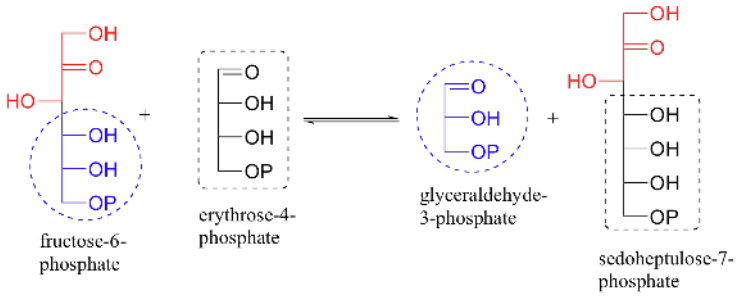
Example 23.13.3

Draw the reverse (aldol condensation) direction of the reaction above.

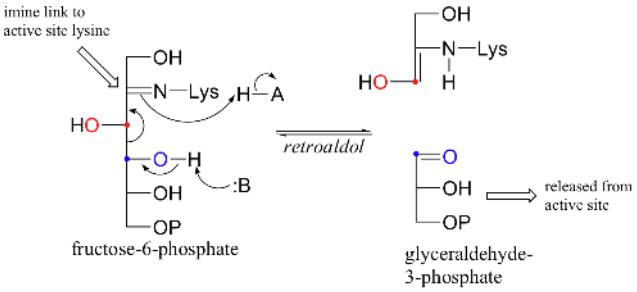
Solution

Going both ways: transaldolase

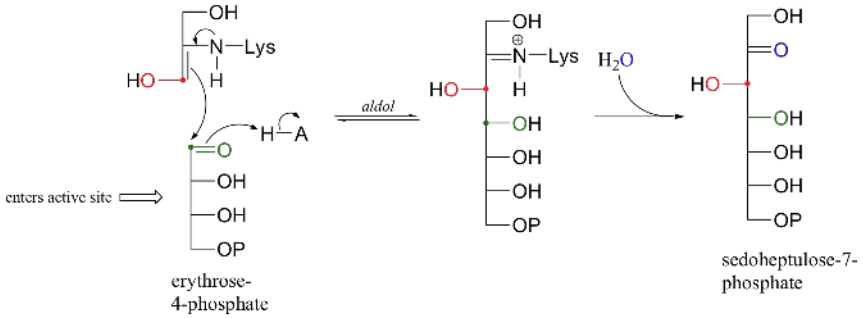
An enzyme called transaldolase, which is part of the 'pentose phosphate pathway' of carbohydrate metabolism, catalyzes an interesting combination of class I aldol and retro-aldol reactions. The overall reaction, which can proceed in either direction depending on metabolic requirements, converts 3- and 7-carbon sugars into 6- and 4-carbon sugars. Essentially, a 3-carbon unit breaks off from a ketone sugar (ketose) and then is condensed directly with an aldehyde sugar (aldose).



Let's follow the progress of the reaction in the left-to-right direction as depicted above. Because this is a class I aldolase, the first step is the formation of an imine linkage between the ketone carbon of fructose-6-phosphate (F6P) and a lysine group from the enzyme. The enzyme-substrate adduct then undergoes a retro-aldol step to free glyceralde-3-phosphate (GAP), which leaves the active site.



The second substrate, erythrose 4-phosphate (E4P), enters the active site, and an aldol condensation occurs between E4P and the 3-carbon fragment remaining from the cleavage of fructose-6-phosphate.



The final step is hydrolysis of the imine and subsequent dissociation of sedoheptulose 7-phosphate from the active site.

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7.S: Carbonyl Condensation Reactions (Summary)

Concepts & Vocabulary

- Design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
- Solve road-map problems that require a knowledge of carbonyl condensation reactions.
- Define, and use in context, any of the key terms introduced.

23.1 Carbonyl Condensations - The Aldol Reaction

- A carbon-carbon bond forming reaction at the alpha carbon through an enolate nucleophile.
- The Aldol Reaction proceeds by first making an enolate nucelophile on an aldehyde (or ketone).
- The enolate nucleophile then dimerizes by attacking the carbonyl of the same aldehyde (or ketone).
- The final product is a beta-hydroxy aldehyde (or ketone).

23.2 Carbonyl Condensations versus Alpha Substitutions

- Carbonyl condensation reactions are a type of alpha substitution reaction.
- Both involve an enolate nucleophile and end with an alpha substitution product.
- In carbonyl condensations, the electrophile is another carbonyl compound.
- Carbonyl condensations are reversible and use a catalytic amount of base.
- The electrophile is already present in the reaction as the enolate is formed in carbonyl condensations.
- Alpha substitution reactions are more directional by design, since a full equivalent of base is used to generate the enolate.
- The electrophile is introduced after the enolate is generated.

23.3 Dehydration of Aldol Products - Synthesis of Enones

- The aldol reaction can undergo a dehydration (loss of water) to yield an α,β-unsaturated aldehyde or ketone.
- The additional stability provided by the conjugated carbonyl system makes some of the products thermodynamically driven.
- The of small products, such as water in this case, are termed condensations, so this reaction is aldol condesation.
- Heat promotes the condensation reactions.
- Under basic conditions, the β-elimination occurs through an E1cb mechanism.
- Under acidic conditions, the β-elimination occurs through an E1 or E2 mechanism.

23.4 Using Aldol Reactions in Synthesis

- If the target contains a β-hydroxy carbonyl compound or an α,β-unsaturated carbonyl compound, then synthetically think aldol reaction or condensation.
- To reverse the aldol condensation, break the enone at the double bond.
- To reverse the aldol reaction, break the C-C bond between the alpha carbon and the carbon attached to the hydroxy group.

23.5 Mixed Aldol Reactions

- Aldol condensations between different reactants are called mixed or crossed Claisen reactions.
- Multiple products are possible, so the success of the mixed aldol reactions depends on two things:
  - The electrophile (or acceptor) is an aldehyde.
  - The aldehyde acceptor has no alpha protons.
- Mixed aldols in which both reactants can serve as donors and acceptors generally give complex mixtures of both dimeric (homo) aldols and crossed aldols.
- The aldol condensation of ketones with aryl aldehydes to form α,β-unsaturated derivatives is called the Claisen-Schmidt reaction.

23.6 Intramolecular Aldol Reactions

- Molecules which contain two carbonyl functionalities have the possibility of forming a ring through an intramolecular aldol reaction.
- In these intramolecular reactions, two sets of α-hydrogens need to be considered and most ring forming reaction five and six membered rings are preferred.

23.7 The Claisen Condensation Reaction

- Esters can contain α hydrogens, so can undergo a condensation reaction similar to the aldol reaction called a Claisen Condensation.
- One ester reacts as a nucleophile while the other reacts as an electrophile.
- A new C-C bond is formed in the reaction to form a β-keto ester product.
- An alkoxide that matches the ester group is used to help prevent side reactions in the Claisen Condensation.
- There is a thermodynamic driving step forming an enolate, which is followed by a protonation to obtain the neutral product.

23.8 Mixed Claisen Condensation Reactions

- Claisen condensations between different ester reactants are called Crossed Claisen reactions.
- Crossed Claisen reactions in which both reactants can serve as donors and acceptors generally give complex mixtures.
- Because of this most Crossed Claisen reactions are usually not performed unless one reactant has no alpha hydrogens.

23.9 Intramolecular Claisen Condensation Reactions - The Dieckmann Cyclization

- A diester can undergo an intramolecular reaction called a Dieckmann condensation.

23.10 Conjugate Carbonyl Additions - The Michael Reaction

- In 1,4 additions the nucleophile is added to the carbon β to the carbonyl while the hydrogen is added to the carbon α to the carbonyl.
- Enolates undergo 1,4 addition to α, β-unsaturated carbonyl compounds (product of the Aldol condensation) is a process called a Michael addition.
- A new C-C bond is formed between an enolate and the 4-C of the α, β-unsaturated carbonyl compound.
- The product is a 1,5-dicarbonyl species.

23.11 Carbonyl Condensations with Enamines - The Stork Reaction (reference only)

- Aldehydes and ketones react with 2° amines to reversibly form enamines.
- Enamines act as nucleophiles similar to enolates.
- This process requires a three steps:
  - Formation of the enamine
  - Reaction with an eletrophile to form an iminium salt
  - Hydrolysis of the iminium salt to reform the aldehyde or ketone
- Advantages of using an enamine over an enolate
  - Neutral
  - Easier to prepare
  - Prevent overreaction issue that occurs when using enolates.
- Enamines undergo an S_N2 reaction with alkyl halides to yield the iminium salt.
- Enamines can react with acid halides to form β-dicarbonyls.
- Enamines can also be used as a nucleophile in a Michael reaction.

23.12 The Robinson Annulation Reaction

- Forms a cyclic product from acyclic starting materials by first creating a new C-C bond followed by ring formation.
- The Robinson Annulation reaction starts with a Michael reaction followed by an intramolecular Aldol condensation.
- The formation of 5 or 6 membered rings is preferred.

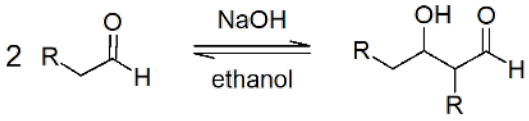
23.13 Some Biological Carbonyl Condensation Reactions (reference only)

- Aldol reactions occur in several biological pathways.
- Enzymes that catalyze aldol reactions are called, not surprisingly, 'aldolases'.
- The first step in an aldolase reaction is the deprotonation of an alpha-carbon to generate a nucleophilic carbanion.
- Nature has evolved several distinct strategies to stabilize the intermediate that results.
  - Some aldolases use a metal ion to stabilize the negative charge on an enolate intermediate.
  - Others catalyze reactions that proceed through neutral Schiff base or enol intermediates.

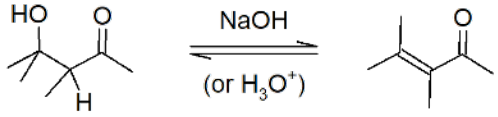
Skills to Master

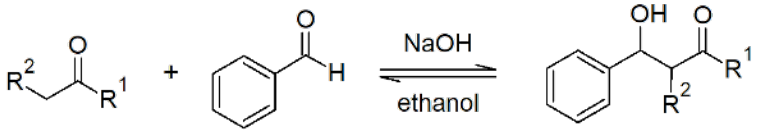
- Skill 23.1 Identify the product of an aldol reaction.
- Skill 23.2 Write the detailed mechanism for the aldol reaction.
- Skill 23.3 Describe the difference between a carbonyl condensation reaction and an alpha-substitution reaction.
- Skill 23.4 Know what an enone is.
- Skill 23.5 Write a detailed mechanism for the aldol condensation under basic conditions.
- Skill 23.6 Write a detailed mechanism for the aldol condensation under acidic conditions.
- Skill 23.7 Determine the products of an aldol condensation reaction.
- Skill 23.8 Provide the reactants for a target aldol condensation product.
- Skill 23.9 Write an equation to illustrate a mixed aldol reaction.
- Skill 23.10 Identify the structural features necessary to ensure that two carbonyl compounds will react together in a mixed aldol reaction to give a single product rather than a mixture of products.
- Skill 23.11 Determine whether a given mixed aldol reaction is likely to produce a single product or a mixture of products.
- Skill 23.12 Identify the carbonyl compounds needed to produce a given enone or β-hydroxy aldehyde or ketone by a mixed aldol reaction.
- Skill 23.13 Write a detailed mechanism for the intramolecular aldol condensation.
- Skill 23.14 Write an equation to illustrate a Claisen condensation reaction.
- Skill 23.15 Write a detailed mechanism for a Claisen condensation reaction or its reverse.
- Skill 23.16 Identify the ester and other reagents needed to form a given β-keto ester by a Claisen condensation reaction.
- Skill 23.17 Write an equation to illustrate a mixed Claisen condensation.
- Skill 23.18 Identify the structural features that should be present in the two esters if a mixed Claisen condensation is to be successful.
- Skill 23.19 Identify the product formed when a given pair of esters is used in a mixed Claisen condensation.
- Skill 23.20 Identify the esters that should be used to produce a given β-keto ester by a mixed Claisen condensation.
- Skill 23.21 Write detailed mechanisms for mixed Claisen condensation.
- Skill 23.22 Write a detailed mechanism for an intramolecular Claisen condensation.
- Skill 23.23 Write a detailed mechanism for a given typical Michael reaction.
- Skill 23.24 Identify the product formed in a given Michael reaction.
- Skill 23.25 Identify the reagents necessary to synthesize a given compound by a Michael reaction.
- Skill 23.26 Write a detailed mechanism for the Robinson Annulation reaction.
- Skill 23.29 Identify the product from an enone and an dicarbonyl under basic conditions.

Summary of Reactions

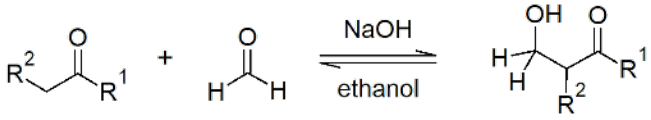


(Aldol)

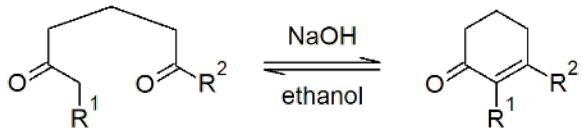




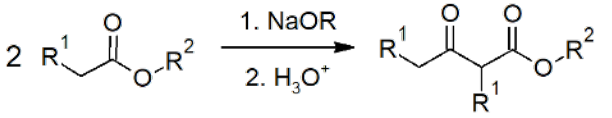
(mixedAldol)



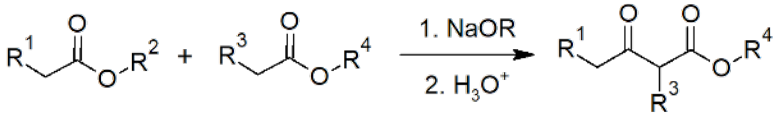
(mixedAldol)



(intramolecular Aldol)



(Claisen)



(mixed Claisen)

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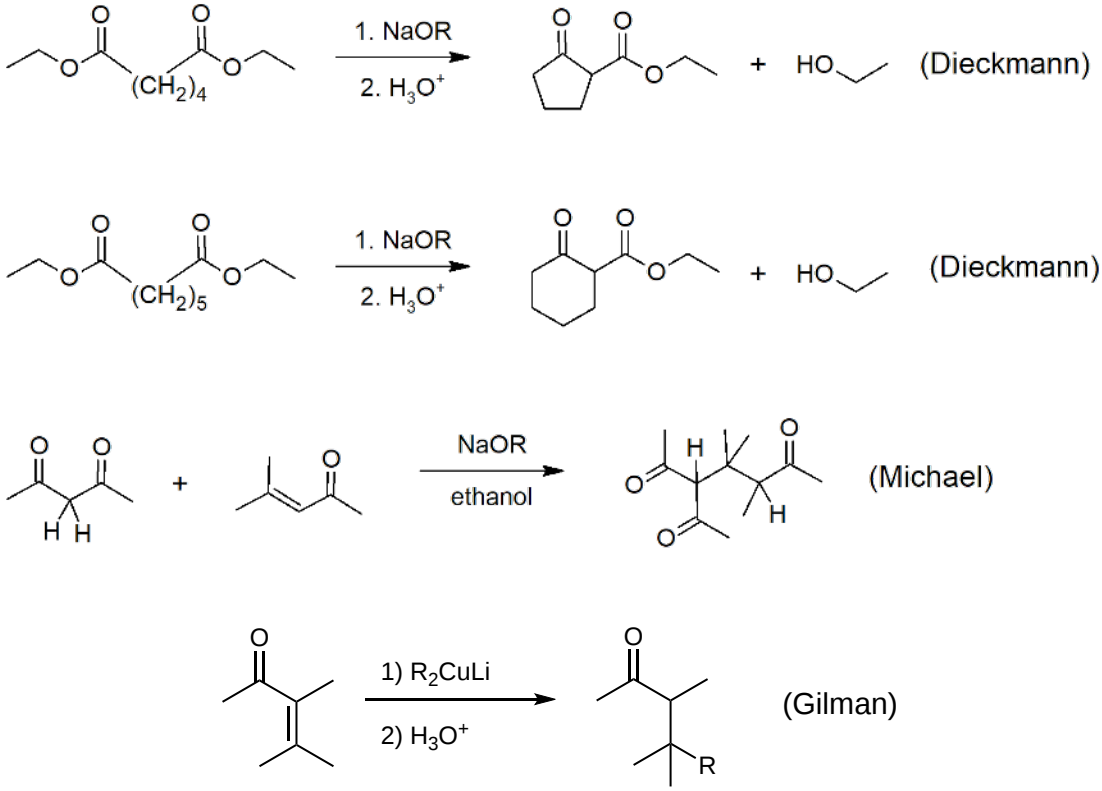

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CHAPTER OVERVIEW

8: Conjugated Compounds

Learning Objectives

After you have completed Chapter 8, you should be able to

1. full fill all of the detailed objectives listed under each individual section.
2. use the reactions discussed, along with those from previous chapters, when designing multi-step syntheses.
3. use the reactions and concepts discussed to solve road-map problems.
4. define, and use in context, the key terms introduced.

Chapter Videos

This video focuses on stereochemistry in the Diels-Alder reaction

This video explains the use of the Diels-Alder Drawing Tool to predict the structure of reaction products.

You have already studied the chemistry of compounds that contain one carbon-carbon double bond. In this chapter, you will focus your attention on compounds that contain two or more such bonds. In particular you will study the properties of those compounds that contain two carbon-carbon double bonds which are separated by one carbon-carbon single bond. These compounds are called “conjugated dienes.”

To understand the properties exhibited by conjugated dienes, you must first examine their bonding in terms of the molecular orbital theory introduced in CHM 222. Then, you must learn how the products of a reaction are dependent on both thermodynamic and kinetic considerations. Which of these two factors is the most important can sometimes determine which of two possible products will predominate when a reaction is carried out under specific conditions.

8.1: Introduction
8.2: Stability of Conjugated Dienes- Molecular Orbital Theory
8.3: Electrophilic Additions to Conjugated Dienes- Allylic Carbocations
8.4: Kinetic vs. Thermodynamic Control of Reactions
8.5: The Diels-Alder Cycloaddition Reaction
8.6: Characteristics of the Diels-Alder Reaction
8.7: Diene Polymers- Natural and Synthetic Rubbers (reference only)
8.8: Structure Determination in Conjugated Systems - Ultraviolet Spectroscopy (reference only)
8.9: Interpreting Ultraviolet Spectra- The Effect of Conjugation (reference only)
8.10: Conjugation, Color, and the Chemistry of Vision (reference only)
8.S: Conjugated Compounds and Ultraviolet Spectroscopy (Summary)

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8.1: Introduction

Objective

After completing this section, you should be able to determine whether or not a molecule contains a conjugated system, given its Kekulé, condensed or shorthand formula.

Key Terms

Make certain that you can define, and use in context, the key terms below.

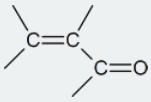
- conjugated diene
- conjugated double bonds
- diene
- enone
- polyene

Study Notes

Conjugated double bonds are double bonds which are separated by one carbon-carbon single bond. Thus the double bonds in butadiene, CH_2=CH-CH=CH_2, are conjugated, and this compound is an example of a *conjugated diene*.

Just as the term *diene* indicates the presence of two carbon-carbon double bonds in a compound, so the term *polyene* is used to describe compounds containing many carbon-carbon double bonds.

An *enone* is a compound containing a carbon-carbon double bond (ene) and a carbonyl group (one). A conjugated enone contains the structural unit:



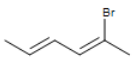
Conjugated Dienes

A diene is a hydrocarbon chain that has two double bonds that may or may not be adjacent to each other. This section focuses on the delocalization of pi systems by comparing two neighboring double bonds. The arrangements of these double bonds can have varying affects on the compounds reactivity and stability.

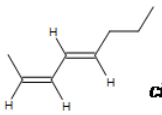
Naming Dienes

First identify the longest chain containing both carbons with double bonds in the compound. Then give the lowest possible number for the location of the carbons with double bonds and any other functional groups present (remember when naming alkenes that some groups take priority such as alcohols). Do not forget stereochemistry or any other orientation of the double bond such as (E/Z,cis or trans).

Examples:

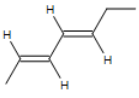


2-Bromo-2,4-hexadiene



cis-2-*trans*-4-octadiene

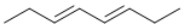
1,3-cyclopentadiene



trans-2,4-heptadiene

Conjugated vs. Nonconjugated vs. Cumulated Dienes

Conjugated dienes are two double bonds separated by a single bond

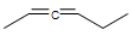


3,5-octadiene

Nonconjugated (Isolated) dienes are two double bonds are separated by more than one single bond.

2,5-heptadiene

Cumulated dienes (allenes) are two double bond connected to a carbon atom.



2,3-hexadiene

The reactivity of these molecules is substantially different from that of alkenes which have isolated C=C. These molecules are thus considered a different class of organic molecule. Conjugated dienes, especially butadiene, are very important materials in the production of rubber, and thus for the tires of our cars.

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8.2: Stability of Conjugated Dienes- Molecular Orbital Theory

Objectives

After completing this section, you should be able to

1. write a reaction sequence to show a convenient method for preparing a given conjugated diene from an alkene, allyl halide, alkyl dihalide or alcohol (diol).
2. identify the reagents needed to prepare a given diene from one of the starting materials listed in Objective 1, above.
3. compare the stabilities of conjugated and non-conjugated dienes, using evidence obtained from hydrogenation experiments.
4. discuss the bonding in a conjugated diene, such as 1,3-butadiene, in terms of the hybridization of the carbon atoms involved.
5. discuss the bonding in 1,3-butadiene in terms of the molecular orbital theory, and draw a molecular orbital for this and similar compounds.

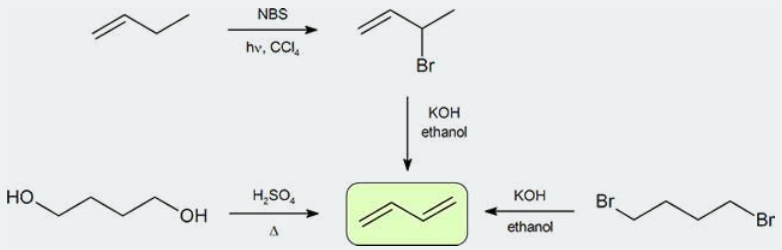
Key Terms

Make certain that you can define, and use in context, the key terms below.

- delocalized electrons
- node

Study Notes

The two most frequent ways to synthesize conjugated dienes are dehydration of alcohols and dehydrohalogenation of organohalides, which were introduced in the preparation of alkenes. The following scheme illustrates some of the routes to preparing a conjugated diene.

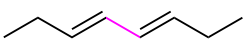


The formation of synthetic polymers from dienes such as 1,3-butadiene and isoprene is discussed later in this chapter. Synthetic polymers are large molecules made up of smaller repeating units. You are probably somewhat familiar with a number of these polymers; for example, polyethylene, polypropylene, polystyrene and poly(vinyl chloride).

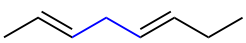
As the hydrogenation of 1,3-butadiene releases less than the predicted amount of energy, the energy content of 1,3-butadiene must be lower than we might have expected. In other words, 1,3-butadiene is more stable than its formula suggests.

Conjugated vs. Non-conjugated Dienes

Dienes are compounds which contain two double bonds. These dienes can be non-conjugated (the two double bonds are separated by at least one sp^3 hybridized atom. Conjugated dienes have the two double bonds separated by a single bond. Conjugated dienes have properties and reactivity which are distinctly different than non-conjugated dienes. Determining if double bonds are conjugated represents an important skill in organic chemistry.



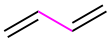
3,5-Octadiene
(Conjugated)



2,5-Octadiene
(Non-Conjugated)

1,3-Cyclohexadiene
(Conjugated)

1,4-Cyclohexadiene
(Non-Conjugated)

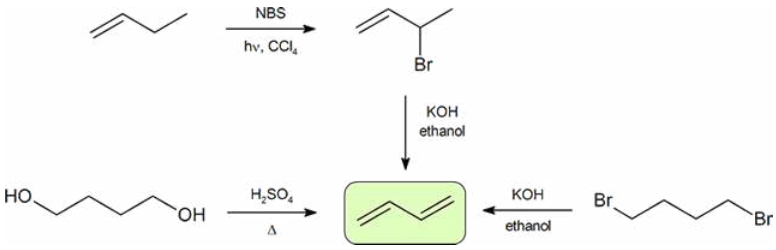


1,3-Butadiene
(Conjugated)

1,4-Pentadiene
(Non-Conjugated)

Synthesis of Dienes

Conjugated dienes can be prepared using many of the methods used for the preparation of alkenes previously discussed in the elimination sections of Chapter 2. A convenient method starts with the free radical halogenation of the allylic carbon of an alkene using NBS. The resulting halide can then be reacted with a strong base to result in E2 elimination and create a diene product. The compound, 1,3-butadiene, is the simplest conjugated diene and has an important use in the synthesis of polymers. Many simple dienes, such as 1,3-butadiene and isoprene, can be prepared industrially by the double dehydration of alcohols and the double dehydrohalogenation of organohalides.



Stability of Conjugated Dienes

Conjugated dienes are known to be more stable than non-conjugated dienes as shown by their experimentally determined heats of hydrogenation. As alkenes become more stable, they contain less energy, and therefore release less heat during hydrogenation. Experiments have shown that conjugated dienes have a lower heat of hydrogenation (-226 kJ/mol) than non-conjugated dienes (-251 kJ/mol). Using the differences in heats of hydrogenation the stabilization energy in conjugated dienes can be estimate to be roughly 25 kJ/mol.

1,3-Pentadiene
(ΔH_{hydrog} = -226 kJ/mol)

Pentane

1,4-Pentadiene
(ΔH_{hydrog} = -252 kJ/mol)

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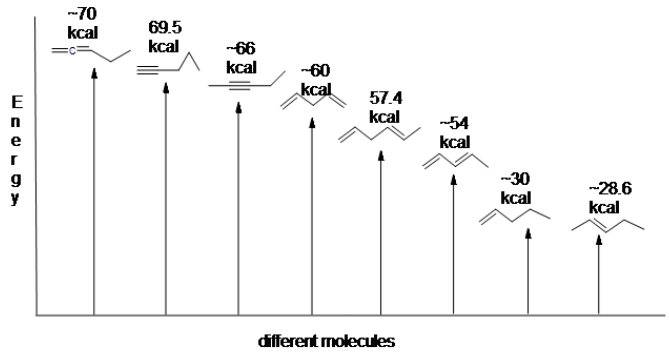
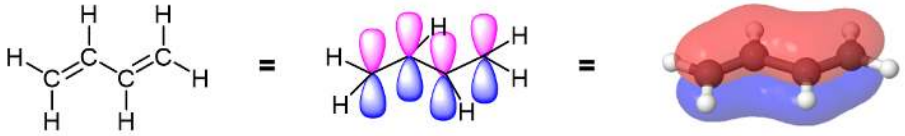
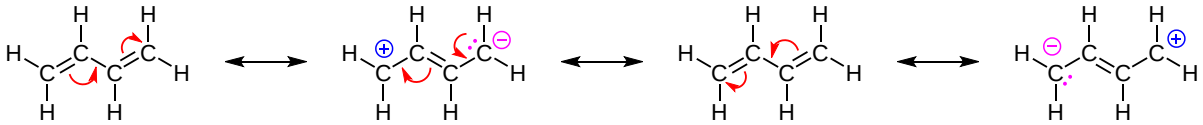
Here is an energy diagram comparing different types of bonds with their heats of hydrogenation to show relative stability of each molecule:



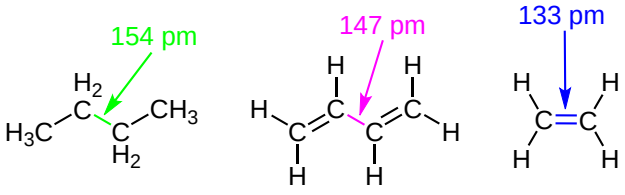
The stabilization of dienes by conjugation is less dramatic than the aromatic stabilization of benzene. Nevertheless, similar resonance and molecular orbital descriptions of conjugation may be written.

Each alkene carbon in 1,3-dienes is sp^2 hybridized and therefore has one unhybridized *p* orbital. The four *p* orbitals in 1,3-butadiene overlap to form a conjugated system which can be represented by the resonance forms shown below. This delocalization of charges stabilizes conjugated dienes making them more stable than non-conjugated dienes.

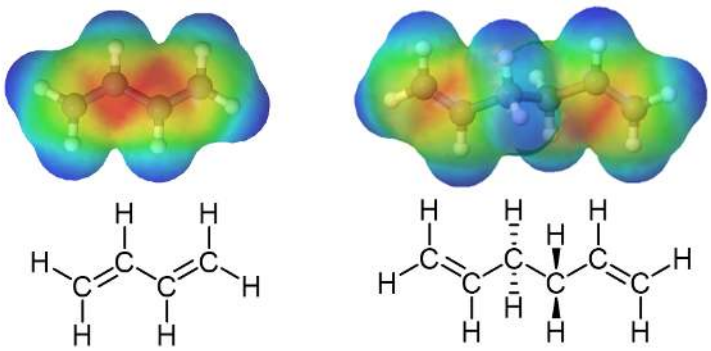




Evidence of conjugation in 1,3 dienes is seen in the single bond being stronger and shorter (147 pm) than an ordinary alkane C-C bond (154 pm). The resonance hybrid of a 1,3-butadiene shows this bond to contain significant double bond character with its bond length being roughly the average of a single and double bond.



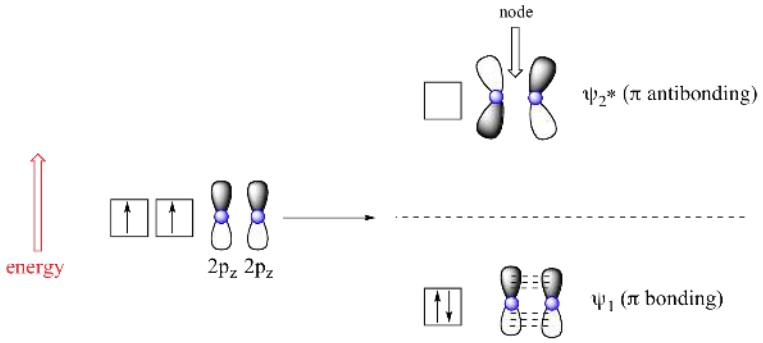
The delocalized electron density of a 1,3 diene can be seen when viewing an electrostatic potential maps. In conjugated dienes, it is observed that the pi electron density overlap (shown in red) is closer together and delocalized in conjugated dienes, while in non-conjugated dienes the pi electron density is located completely on the double bonds.



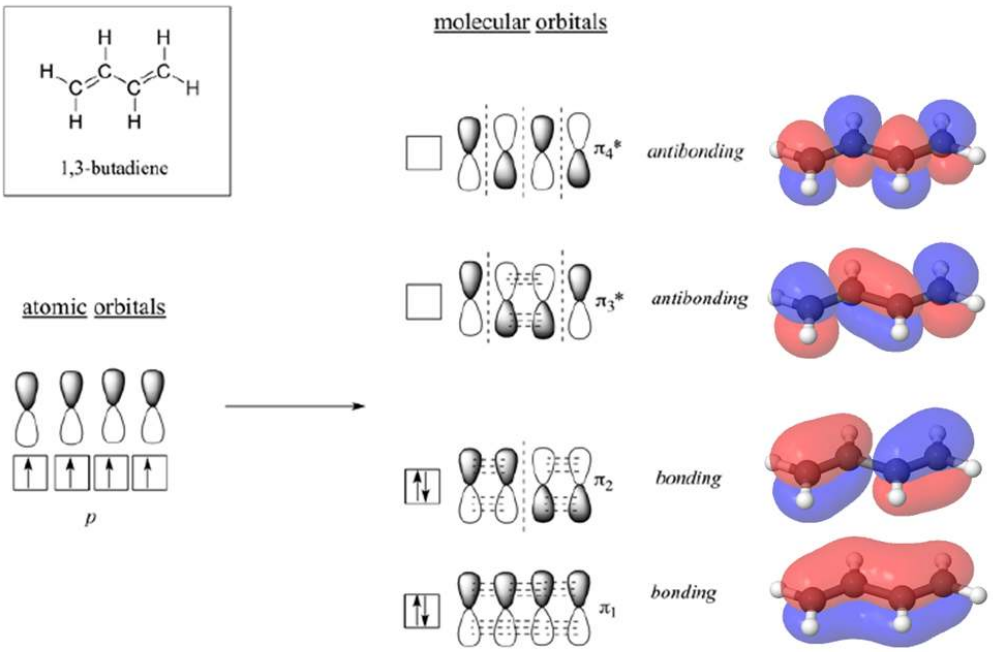
Conjugated Non-Conjugated

Molecular Orbitals of 1,3 Dienes

According to MO theory, when a double bond is non-conjugated, the two atomic $2p_z$ orbitals combine to form two **pi (π) molecular orbitals**, one a low-energy π bonding orbital and one a high-energy **π-star (π*) anti-bonding molecular orbital**. These are sometimes denoted, in MO diagrams like the one below, with the Greek letter psi (Ψ) instead of π. In the bonding Ψ_1 orbital, the two (+) lobes of the $2p_z$ orbitals interact constructively with each other, as do the two (-) lobes. Therefore, there is increased electron density between the nuclei in the molecular orbital – this is why it is a bonding orbital. In the higher-energy anti-bonding Ψ_2* orbital, the (+) lobes of one $2p_z$ orbital interacts destructively with the (-) lobe of the second $2p_z$ orbital, leading to a node between the two nuclei and overall repulsion. By the *aufbau* principle, the two electrons from the two atomic orbitals will be paired in the lower-energy $\Psi_1$orbital when the molecule is in the ground state.



With a conjugated diene, such as 1,3-butadiene, the four *2p* atomic orbitals combine to form four pi molecular orbitals of increasing energy. Two bonding pi orbitals and two anti-bonding pi* orbitals. The combination of four pi molecular orbitals allow for the formation of a bonding molecular orbital that is lower in energy than those created by an unconjugated alkene. The 4 pi electrons of 1,3-butadiene completely fill the bonding molecular orbitals giving is the additional stability associated with conjugated double bonds.



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8.3: Electrophilic Additions to Conjugated Dienes- Allylic Carbocations

Objectives

After completing this section, you should be able to

1. write an equation for the addition of one or two mole equivalents of a halogen or a hydrogen halide to a nonconjugated diene.
2. write an equation for the addition of one or two mole equivalents of a halogen or a hydrogen halide to a conjugated diene.
3. write the mechanism for the addition of one mole equivalent of hydrogen halide to a conjugated diene, and hence account for the formation of 1,2- and 1,4-addition products.
4. explain the stability of allylic carbocations in terms of resonance.
5. draw the resonance contributors for a given allylic carbocation.
6. predict the products formed from the reaction of a given conjugated diene with one mole equivalent of halogen or hydrogen halide.
7. predict which of the possible 1,2- and 1,4-addition products is likely to predominate when one mole equivalent of a hydrogen halide is reacted with a given conjugated diene.
8. use the concept of carbocation stability to explain the ratio of the products obtained when a given conjugated diene is reacted with one mole equivalent of hydrogen halide.

Key Terms

Make certain that you can define, and use in context, the key terms below.

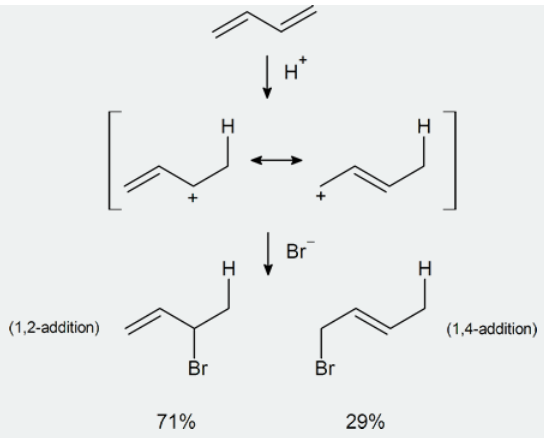
- 1,2-addition
- 1,4-addition

Study Notes

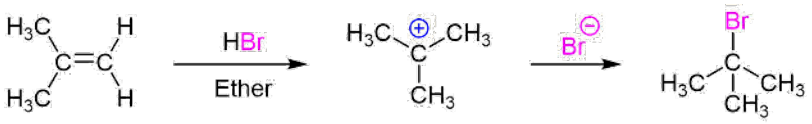
Notice that the numbers used in the expressions 1,2-addition and 1,4-addition do *not* refer to the positions of the carbon atoms in the diene molecule. Here, 1,2 indicates two neighboring carbon atoms, while 1,4 indicates two carbon atoms which are separated in the carbon chain by two additional carbon atoms. Thus in 1,2- and 1,4-additions to 2,4-hexadiene, the additions actually occur at carbons 2 and 3, and 2 and 5, respectively.

The term “monoadduct” should be interpreted as meaning the product or products formed when one mole of reagent adds to one mole of substrate. In the objectives above, this process is referred to as the addition of one mole equivalent (or one mol equiv).

In CHM 222 we saw that electrophilic addition to a simple alkene would follow Markovnikov’s rule, where the stability of the carbocation intermediate would increase: primary < secondary < tertiary. With conjugated dienes the allylic carbocation intermediately generated has different resonance forms. The following scheme represents the mechanism for the addition of HBr to 1,3-butadiene (at 0°C). Note the resonance contributors for the allylic carbocation intermediate and that the product resulting from the secondary cation is generated in higher yield than from the primary cation as you might expect from our discussions until now. However, in the next section you will see that the resulting product ratio can be drastically affected by a number of reaction conditions, including temperature.

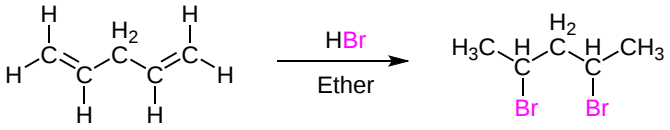


In the Alkene Chapter we saw that electrophilic addition to a simple alkene would follow Markovnikov's rule. Markovnikov's rule states that for the electrophilic addition of HX, the carbocation intermediate forms on the double bond carbon with the greatest number of alkyl substitutents. Because the stability of carbocation intermediates increases as it number of alky groups increases (primary < secondary < tertiary), this regioselectivity is provided by preferably forming a more stable carbocation intermediate during the reaction. During the electrophilic addition of HBr to 2-methylpropene, the more stable tertiary carbocation intermediate is preferably formed which yields the Markovnikov addition product 2-bromo-2-methylpropane. Formation of 1-bromo-2-methylpropane does not occur because it would require the formation of a less stable primary carbocation intermediate.



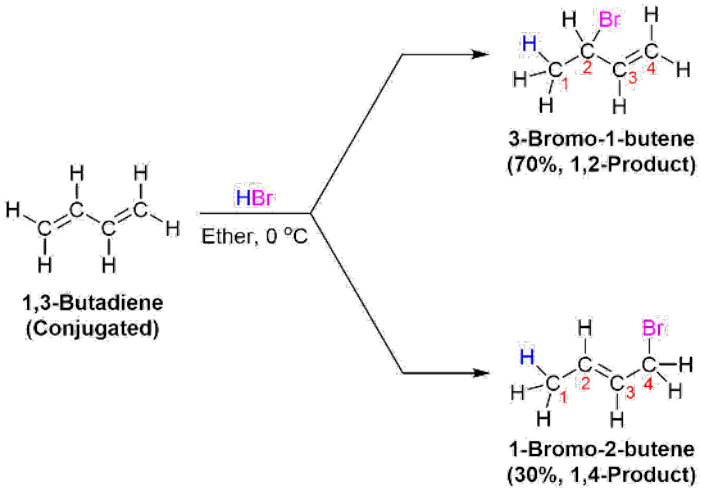
2-Methylpropene | **Tertiary Carbocation** | **2-Bromo-2-Methylpropane (Markovnikov addition product)**

When an electrophilic addition is performed on a non-conjugated diene, the double bonds react in much the same manner as individual alkenes. During the addition of two equivalents of HBr to 1,4-pentadiene, a non-conjugated diene, Markovnikov's rule is still followed producing 2,4-dibromopentane as the product.



1,4-Pentadiene (Non-conjugated) | **2,4-Dibromopentane (Markovnikov addition product)**

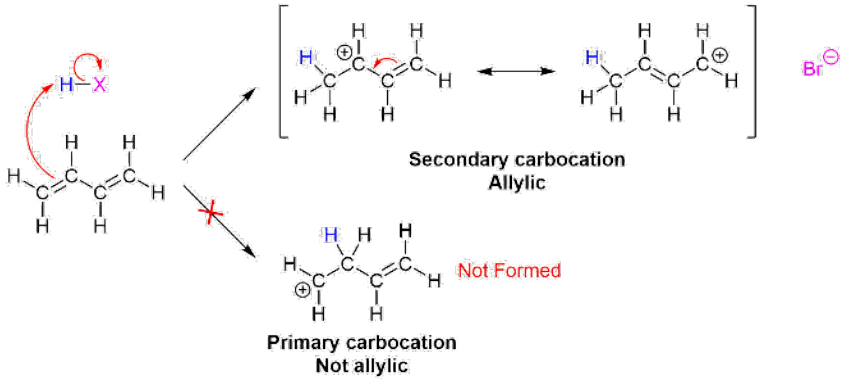
Conjugated dienes undergo the usual reactions of alkenes, such as catalytic hydrogenation, radical additions, and electrophilic additions more readily than most alkenes or dienes that have isolated double bonds. During the electrophilic addition of one equivalent of HX to a conjugated diene, the expected Markovnikov addition product is formed during a process called **1,2-addition**. In addition, an unexpected product is formed from **1,4-addition**, i.e. the halogen bonds at the terminal carbon atoms of a conjugated diene and the remaining double bond shifts to the 2,3-location. Note, the numbers (1 and 4) refer to which of the four carbons making up the conjugated diene the H and Br are bonded to in the products and are not used for the compounds IUPAC nomenclature. Although there are various methods for effecting the relative ratio of 1,2 and 1,4 addition products during the electrophilic addition to a conjugated diene, a mixture of these products is almost always produced. When one equivalent HBr undergoes electrophilic addition to 1,3-butadiene, 1,2 addition provides the expected Markovnikov product 3-bromo-1-butene in a 70% yield. This process is called a 1,2 addition because the hydrogen from HBr (labeled blue) bonds to the first carbon of the diene and the bromine from HBr bonds to the second carbon of the diene. The compound 1-bromo-2-butene is also produced in a 30% yield during the reaction as product of 1,4 addition. Here the hydrogen of HBr bonds to the first carbon of the diene and the Br bonds to the fourth carbon of the diene.



The Mechanism for Electrophilic Addition of HBr to a Conjugated Diene

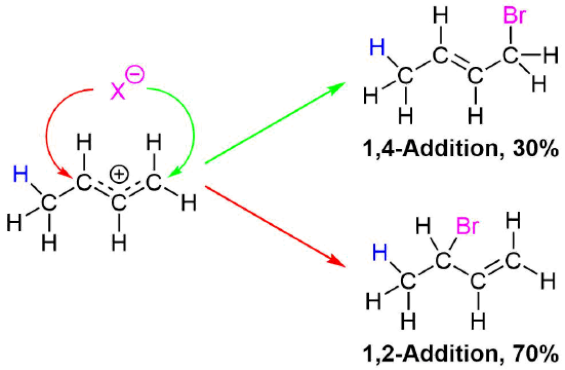
Regardless if the 1,2 or 1,4 addition product is formed, the first step of the mechanism is the protonation of one of the double bonds. In the same manner as the electrophilic addition of HX to an alkene, the protonation occurs regioselectively to give the more stable carbocation. In the case of a conjugated diene, the more stable cation is not only secondary, but also *allylic*, and therefore enjoys the stabilization created from the positive charge being distributed over two carbons by resonance. The resonance hybrid of the allylic carbocation intermediate can be depicted by two resonance forms (shown below) both of which have a full positive charge.

Step 1)



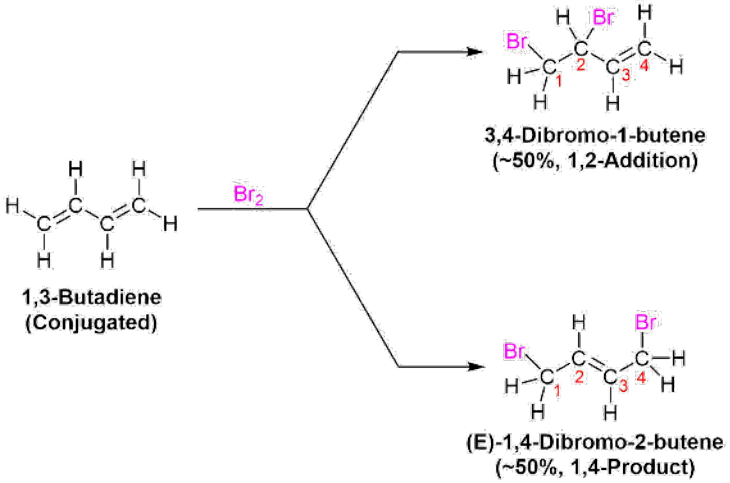
Step 2)

This allylic carbocation, more properly denoted as the resonance hybrid shown below, has two carbons which have significant positive charge. The halide ion can attack either carbon. Attacking the central carbon, adjacent to the site of protonation, leads to the the 1,2-addition product. Attacking the terminal carbon, distant from the site of protonation, leads to the 1,4 addition product.



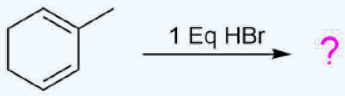
Other Electrophilic Additions

Formation of both 1,2- and 1,4-addition products occurs not only with hydrogen halides, but also with other electrophiles such as the halogens (X_2). The electrophilic addition of bromine to 1,3-butadiene is an example. As shown below, a roughly 50:50 mixture of 3,4-dibromo-1-butene (the expected 1,2 addition product) and 1,4-dibromo-2-butene (the 1,4 addition product) is obtained. The double bond of the 1,4 addition product is primarily formed as the (E) isomer.



Worked Example 8.3.1

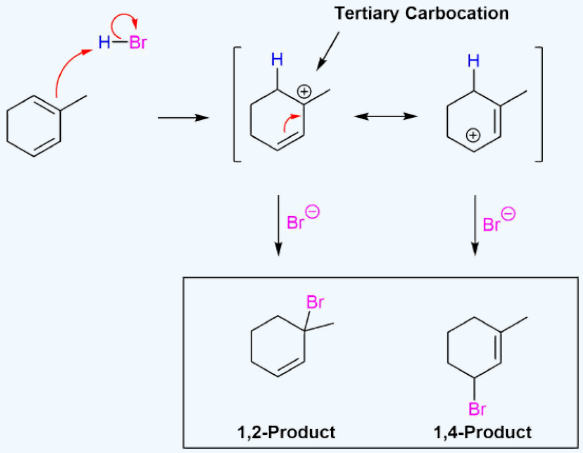
Give the expected products from the following reaction. Show both 1,2 and 1,4 addition products.



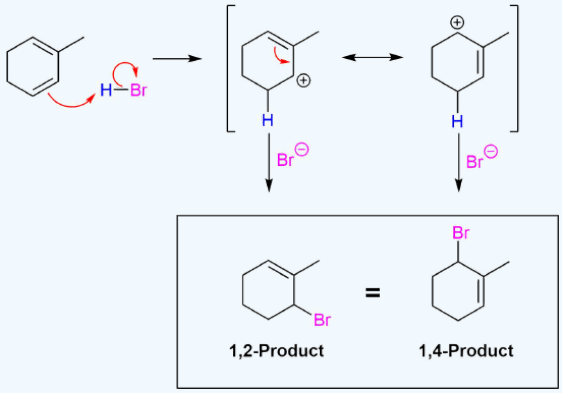
Solution

For this example the two double bonds in the diene are not equivalent and must be considered separately. Each double bond of the reactant has the possibility of forming a 1,2 and a 1,4 addition product so the reaction has the possibility of forming four product. Protonate each double bond separately and draw out the resonance forms of the allylic carbocation intermediate created. Then react each resonance form with Br- to create the two possible products. Repeat this process with the second double bond to create the four possible product. Lastly, look for symmetry in the products to see if any are same molecule. Also, consider the stability of each carbocation created during this process. The most stable carbocation will generally product the favored product of the reaction.

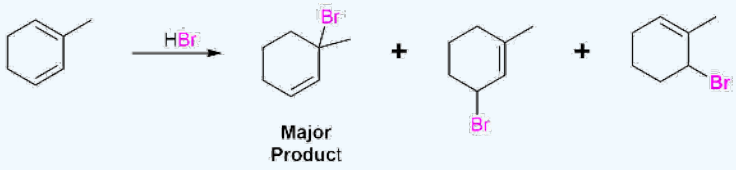
Addition to the first double bond creates a resonance form with a tertiary carbocation intermediate. Due to the stability of the tertiary carbocation this product will most likely go one to be the preferred product of this reaction.



Addition to the second double bond creates a symmetrical compound so only one product is formed.



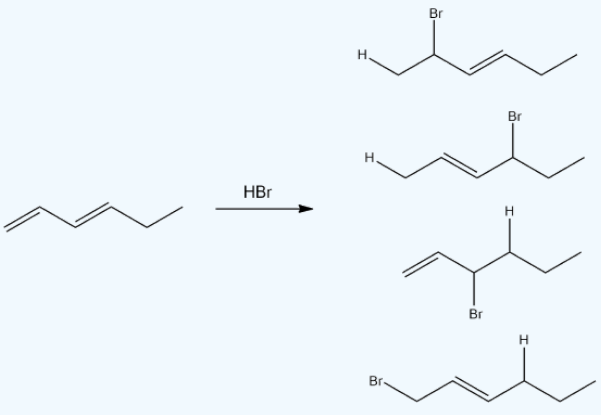
Over the reaction proposed would be expected to form three products.



? Exercise 8.3.1

Give the 1,2 and the 1,4 products of the addition of one equivalent of HBr to 1,3-hexa-diene.

Answer



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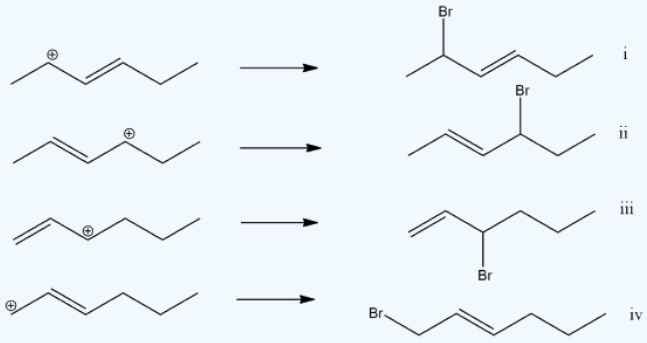
Exercise 8.3.2

Look at the previous addition reaction of HBr with a diene (Exercise 1). Predict which of them would be the major products and which will be the minor.

Answer

The products i-iii all show a secondary cation intermediate which is more stable than primary. Therefore those would be major products and the iv product would be the minor product.



Exercise 8.3.3

Write out the products of 1,2 addition and 1,4- addition of HBr to 1,3-cyclohexadiene.

Answer

The same product will result from 1,2 and 1,4 addition.

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8.4: Kinetic vs. Thermodynamic Control of Reactions

Objectives

After completing this section, you should be able to

1. explain the difference between thermodynamic and kinetic control of a chemical reaction; for example, the reaction of a conjugated diene with one equivalent of hydrogen halide.
2. draw a reaction energy diagram for a reaction which can result in both a thermodynamically controlled product and a kinetically controlled product.
3. explain how reaction conditions can determine the product ratio in a reaction in which there is competition between thermodynamic and kinetic control.

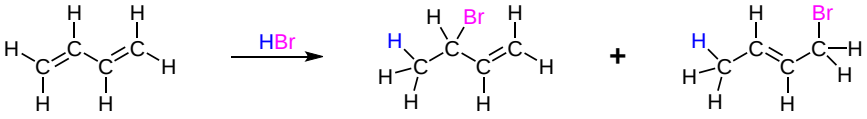
Key Terms

Make certain that you can define, and use in context, the key terms below.

- kinetic control
- thermodynamic control

Like non-conjugated dienes, conjugated dienes are subject to attack by electrophiles. In fact, conjugated dienes experience relatively greater kinetic reactivity when reacted with electrophiles than non-conjugated dienes do. The reaction mechanism is similar to other electrophilic addition reactions to alkenes. During the electrophilic addition of HBr to a 1,3-butadiene, however, there are two possible outcomes once the carbocation intermediate is formed. The allyl carbocation is stabilized by resonance structures that vary in the position of the carbocation. This allows the bromide ion to add to either of these carbons resulting in the formation 1,2 and 1,4 addition products. When this reaction is run at a temperature of 0 ^{o}C or lower, the 1,2 addition product dominates. However, if the same reaction is run at 40 ^{o}C the 1,4 addition product dominates.

The reaction of one equivalent of hydrogen bromide with 1,3-butadiene yields different product ratios under different reaction conditions and is a classic example of the concept of **thermodynamic** versus **kinetic** control of a reaction.



1,3-Butadiene | **1,2-Addition Product** | **1,4-Addition Product**

At -80 ^{o}C:	80%	20%	**Kinetic Control**
At 0 ^{o}C:	70%	30%	**Kinetic Control**
At 40 ^{o}C:	15%	85%	**Thermodynamic Control**
At 60 ^{o}C:	10%	90%	**Thermodynamic Control**

At lower temperatures the formation of the 1,2 and 1,4 addition products are irreversible and thus do not reach equilibrium. When a reaction is irreversible the major product is determined by the relative reaction rates and not by thermodynamic stability. Of the two products, the formation of the 1,2 addition product has a higher rate of reaction and forms faster making it the major product. The reaction product which forms with a higher rate of reaction is called the **Kinetic Product** and when the kinetic product dominates, the reaction is said to be under **Kinetic Control**.

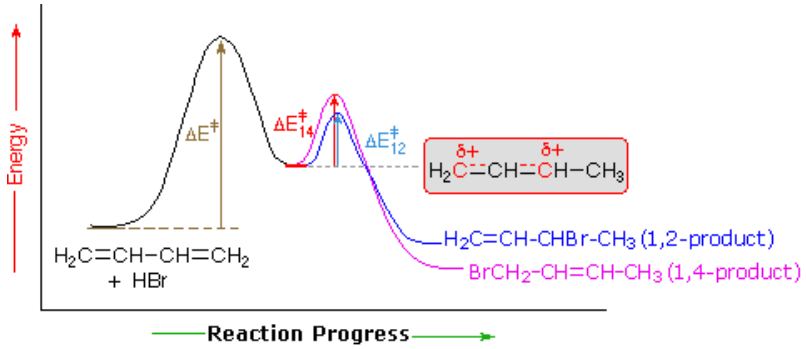
At higher temperatures the reaction to form both products becomes reversible and a reaction equilibrium is reached. When a reaction is reversible the major product is determined by thermodynamic stability. The 1,4 addition product is more stable and becomes the major product under these reaction conditions. The more stable product is called the **Thermodynamic Product** and when the thermodynamic product dominates, the reaction is said to be under **Thermodynamic Control**.

The 1,4 addition product is more stable because it has an internal, disubstituted double bond, and we know that as a general rule that the thermodynamic stability of an alkene increases with increasing substitution. So, when compared to the terminal, monosubstituted alkene of the 1,2 addition product, the 1,4 addition product is expected to be more stable.

> *A simple definition is that the kinetic product is the product that is formed faster, and the thermodynamic product is the product that is more stable. This is precisely what is happening here. The kinetic product is 3-bromobut-1-ene, and the thermodynamic product is 1-bromobut-2-ene (specifically, the trans isomer).*

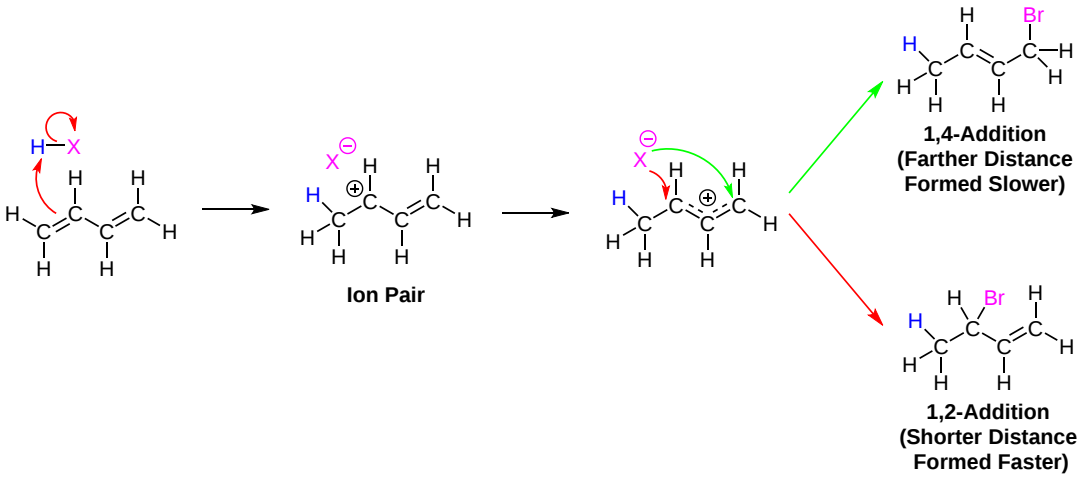
An explanation for the temperature influence is shown in the following energy diagram for the addition of HBr to 1,3-butadiene. The initial step in which a proton bonds to carbon #1 is the **rate determining step**, as indicated by the large activation energy (light gray arrow). The second faster step is the **product determining step**, and there are two reaction paths (colored blue for 1,2-addition and magenta for 1,4-addition).

At elevated temperatures, the products are more likely to have enough energy to overcome the reverse activation barrier for the second step allowing regeneration of the carbocation intermediate. Under these conditions, this step of the mechanism will be reversible and an equilibrium will be established. Since the system is no longer limited by temperature, the system will minimize its Gibbs free energy, which is the thermodynamic criterion for chemical equilibrium. This places the reaction under *thermodynamic control* and the most thermodynamically stable molecule, the 1,4 addition product, will be predominantly formed.



If the reaction temperature is kept sufficiently *low*, the products will not have enough energy to overcome the reverse activation barrier to regenerate the carbocation intermediate making this step of the mechanism effectively irreversible. This reaction is under kinetic control meaning the product which forms faster, the kinetic product, will predominate.

Of the two reaction pathways, the 1,2-addition has a smaller activation energy and would be expected to have a higher reaction rate than the 1,4-addition. The high reaction rate for 1,2-addition can be attributed to the formation of an ion pair during the reaction mechanism. This means that, after a double bond is protonated, the halide counterion remains in close proximity to the carbocation generated. Immediately following dissociation of HX, the chloride ion is going to be much closer to C−2 than it is to C−4, and therefore attack at C−2 is much faster. This ion pair mechanism is a pre-exponential constant effects that is attributed to the proximity and frequency of collision rather than a activation barrier effect.



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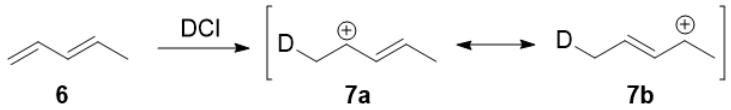
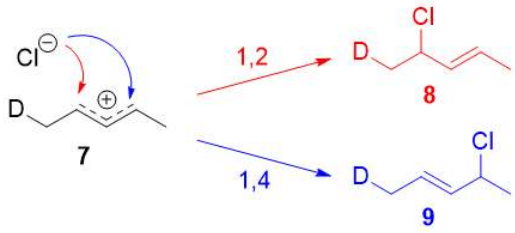
Experimental Evidence for the Ion-Pair Mechanism

In 1979, Nordlander *et al.* carried out a similar investigation on the addition of DCl (deuterated hydrochloric acid) to a different substrate, 1,3-pentadiene. This experiment was ingenious, because it was designed to proceed via an almost symmetrical intermediate:



6 **7a** **7b**

Resonance forms **7a** and **7b** are both allylic and secondary. There is a very minor difference in their stabilities arising from the different hyperconjugative ability of C-D *vs* C-H bonds, but in any case, it is not very large. Therefore, if we adopt the explanation in the previous section, one would expect there not to be any major *kinetic* pathway, and both 1,2- and 1,4-addition products (**8** and **9**) would theoretically be formed roughly equally.



Instead, it was found that the 1,2-addition product was favored over the 1,4-addition product. For example, at -78ºC in the absence of solvent, there was a roughly (75:25) ratio of 1,2- to 1,4-addition products. Clearly, there is a factor that favors 1,2-addition that does not depend on the electrophilicity of the carbon being attacked! The authors attributed this effect to an *ion pair* mechanism. This means that, after the double bond is protonated (deuterated in this case), the chloride counterion remains in close proximity to the carbocation generated. Immediately following dissociation of DCl, the chloride ion is going to be much closer to *C-2* than it is to *C-4*, and therefore attack at *C-2* is much faster. In fact, normal electrophilic addition of HX to conjugated alkenes in polar solvents can also proceed via similar ion pair mechanisms. This is reflected by the greater proportion of *syn* addition products to such substrates.

? Exercise 8.4.1

Why is the 1,4-addition product the thermodynamically more stable product?

Answer

The 1,4- product is more thermodynamically stable because there are two alkyl groups on each side of the double bond and more substituted alkenes are more stable.

? Exercise 8.4.2

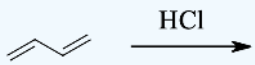
Addition of 1 equivalent of bromine to 2,4-hexadiene at 0 degrees C gives 4,5-dibromo-2-hexene plus an isomer. What is the structure of that isomer?

Answer

2,5-Dibromo-3-hexene

? Exercise 8.4.3

Draw the kinetic product of the following reaction.

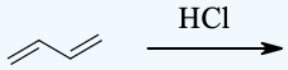


Answer

3-Chloro-1-butene

Exercise 8.4.4

Draw the thermodynamic product of the following reaction.



Answer

1-Chloro-2-butene

Exercise 8.4.5

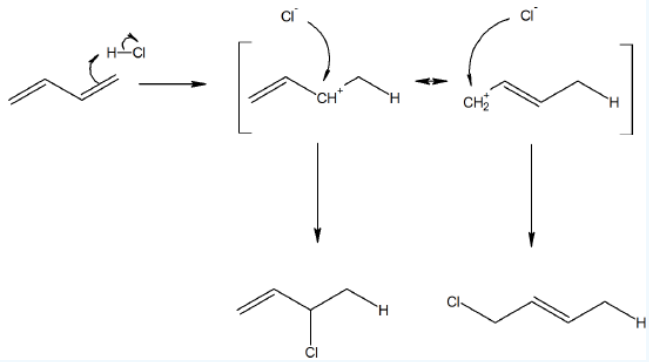
What would be the major product of the addition of HBr to 2,3-dimethyl-1,3-cyclohexadiene under thermodynamic conditions?

Answer

Exercise 8.4.6

Consider the reaction of 1,3-butadiene with HCl. Propose a mechanism for the reaction. Also, Predict why the 1,4 adduct is the major product in this reaction compared to the 1,2.

Answer



Even though the cation would prefer to be in a secondary position in the transition state, the final product is less stable with a terminal alkene. Therefore the major product will be the 1,4 adduct.

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8.5: The Diels-Alder Cycloaddition Reaction

Objectives

After completing this section, you should be able to

1. write an equation to represent a typical Diels-Alder reaction.
2. draw the structure of the product formed when a given conjugated diene reacts with a given dienophile in a Diels-Alder reaction.
3. identify the diene and dienophile that must be used to prepare a given compound by a Diels-Alder reaction.
4. explain the general mechanism of the Diels-Alder reaction, without necessarily being able to describe it in detail.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Diels-Alder cycloaddition
- pericyclic reaction

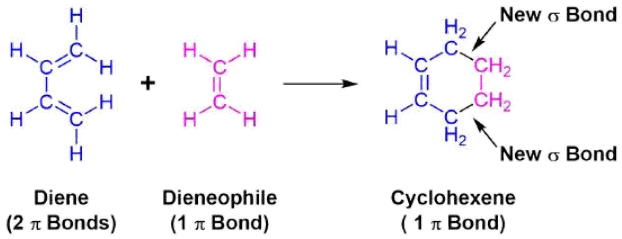
Study Notes

The Diels-Alder reaction is an example of an organic chemical reaction which does not proceed by either a polar or a free radical pathway, but rather a pericyclic reaction.

Although we do not expect you to be able to provide a detailed account of the mechanism of this reaction, you should learn enough about the Diels-Alder reaction to fulfill the objectives stated above. You will find it useful to contrast the mechanism of the Diels-Alder reaction with the polar and radical mechanisms studied earlier.

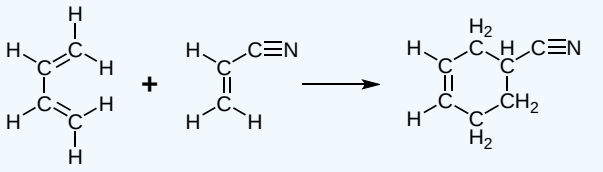
The unique character of conjugated dienes manifests itself dramatically in the **Diels-Alder Cycloaddition Reaction**. The Diels-Alder reaction is an important and widely used synthetic method for making six-membered rings. In the Diels-Alder reaction, a conjugated diene, simply referred to as the **diene**, reacts with a double or triple bond co-reactant called the **dienophile**, because it combines with (has an affinity for) the diene. During the reaction, two pi-bonds are converted to two sigma-bonds. The Diels-Alder cycloaddition is classified as a pericyclic process. Pericyclic reactions involve the redistribution of bonding electrons in a single step mechanism and will be discussed in greater detail in **Chapter 9**. In particular, the Diels-alder reaction is called a [4+2] process because the diene has four pi-electrons that shift position in the reaction and the dienophile has two.

General Reaction



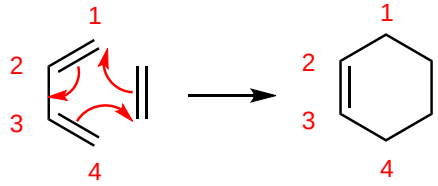
An example of the Diels-Alder reaction is the cycloaddition of 1,3-butadiene to cyanoethene (acrylonitrile) to form 4-cyanocyclohexene.

Example 8.5.1

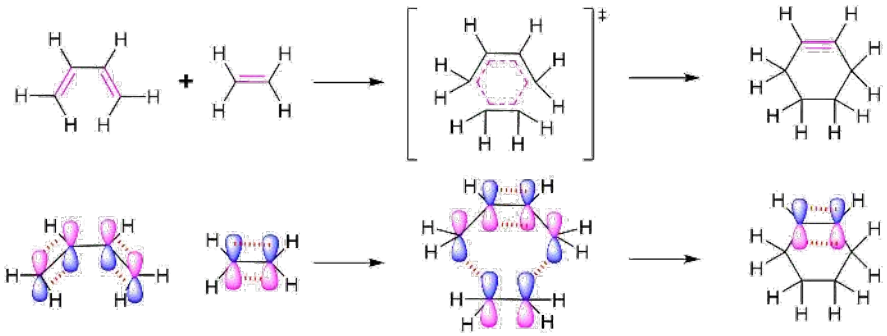


Mechanism

All of the electron rearrangements of the Diels-Alder reaction take place once in a single mechanistic step. During this step carbons 1 and 4 of the diene and both alkene carbons of the dienophile, rehybridize from sp^2 to sp^3 and electrons rearrange to create two new sigma bonds in the cyclic product. Carbons 2 and 3 of the diene remain sp^2 hybridized and form a new pi bond in the product.



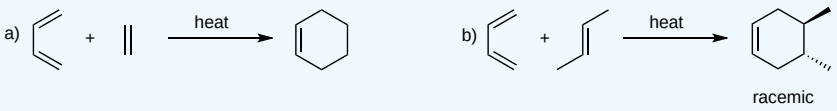
The mechanism occurs through a cyclic transition state in which there is head-on overlap of two p orbitals on carbons 1 and 4 of the diene with the two p orbitals from the alkene of the dienophile to form two new sigma bonds in the cyclohexene product. The remaining two p orbitals from the diene overlap to form the new pi bond.



Exercise 8.5.1

Predict the product of the following Diels-Alder reactions.

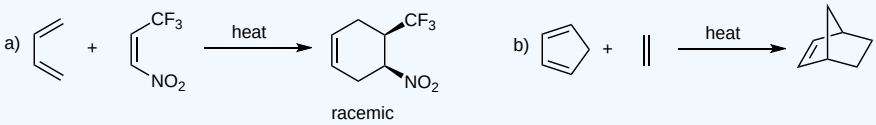
Answer



Exercise 8.5.2

Predict the product of the following Diels-Alder reactions.

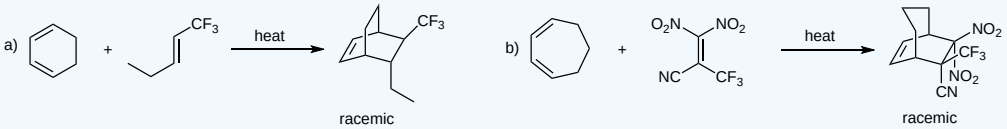
Answer



Exercise 8.5.3

Predict the product of the following Diels-Alder reactions.

Answer



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8.6: Characteristics of the Diels-Alder Reaction

Objectives

After completing this section, you should be able to

1. determine whether or not a given compound would behave as a reactive dienophile in a Diels-Alder reaction.
2. predict the stereochemistry of the product obtained from the reaction of a given diene with a given dienophile.
3. recognize that in order to undergo a Diels-Alder reaction, a diene must be able to assume ans-cis geometry, and determine whether or not a given diene can assume this geometry.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- dienophile
- dimerization

Study Notes

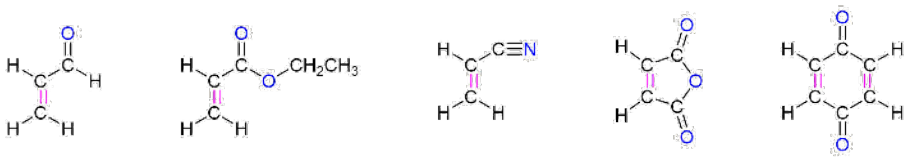
Make sure that you understand that the *s*-cis and *s*-trans forms of a diene such as 1,3-butadiene are conformers, not isomers.

In fulfilling Objective 2, above, you must recognize that the Diels-Alder reaction is stereospecific.

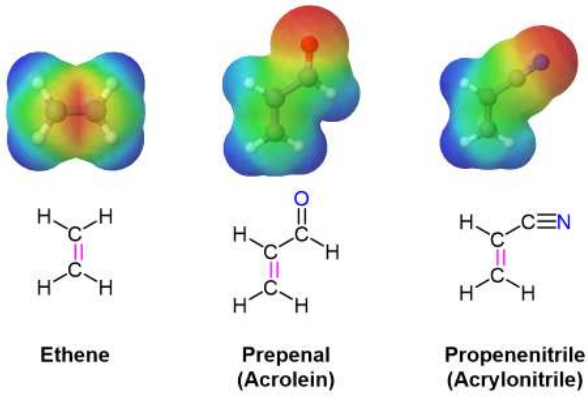
Finally, note a reaction in the reading shows 1,3-cyclopentadiene reacting with another molecule of 1,3-cyclopentadiene. When the same compound acts as both diene and dienophile in a Diels-Alder reaction, it is a dimerization.

The Dienophile

In general, Diels-Alder reactions proceed fastest with electron-withdrawing groups on the dienophile (diene lover). Ethylene reacts slowly while **acrolein (propenal), ethyl acrylate (ethyl propenoate), and the other molecules shown below** are highly reactive in a Diels-Alder reaction.

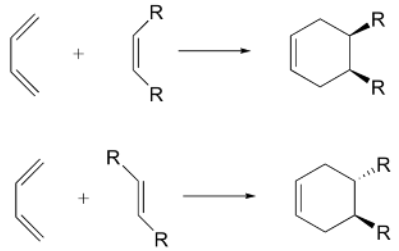


These compounds typically have a double or triple bond to an electronegative element in conjugation with the double bond in the dienophile. A resonance form can be drawn which places a positive charge on the dienophile double bond. This results in the double bond being less electron rich (greater electron density shown in Red/Orange) than ethylene. Electrostatic potential maps show that the electron-withdrawing groups pull electron density away from the double bond.

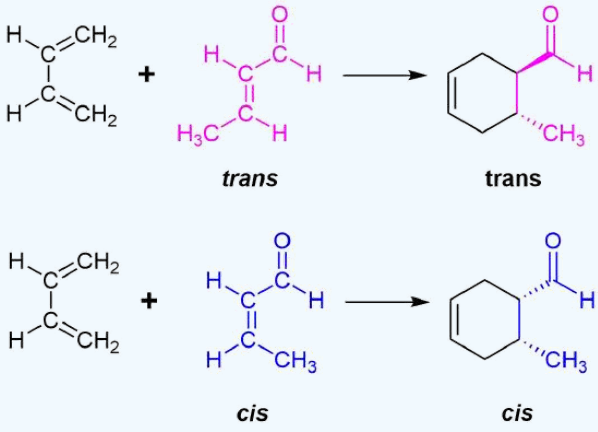


Stereochemistry of Diels-Alder (dienophile)

The Diels-Alder reaction is enormously useful for synthetic organic chemists, not only because ring-forming reactions are useful in general but also because in many cases multiple new stereocenters are formed, and the reaction is inherently stereospecific. During a Diels-Alder reaction the stereochemistry of the dienophile is retained in the product. A *cis* dienophile will generate a cyclohexene ring with *cis (syn)* substitution on the two carbons from the dienophile. Likewise a *trans* dienophile will generate a cyclohexene ring with *trans (anti)* substitution on these two carbon.



Example 8.6.1



The retention of stereochemistry is due to the planar nature of both reactants and that the forming process is **suprafacial** (i.e. to or from the same face of each plane). This stereospecificity also confirms the concerted nature of the Diels-Alder mechanism. The drawing below illustrates this fact for the reaction of 1,3-butadiene with (E)-dicyanoethene. The trans relationship of the cyano groups in the dienophile is preserved in the six-membered ring of the adduct.

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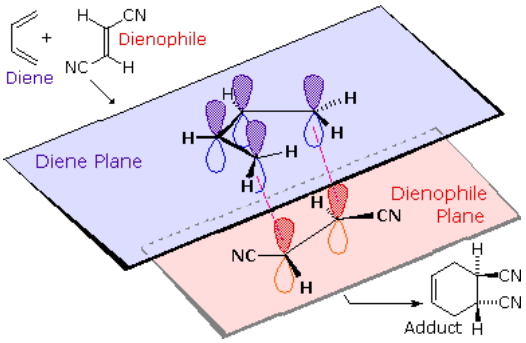
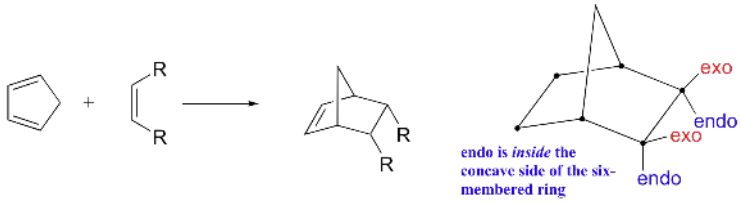
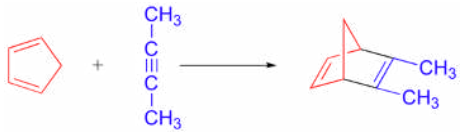


Another facet of the stereochemical retention of the dienophile is that only the endo product, rather than the alternative exo product, is formed. The words *endo* and *exo* are used to indicate relative stereochemistry when referring to bicyclic structures like substituted norbornanes. The endo position on a bicyclic structure refers to the position that is *inside* the concave shape of the larger (six-membered) ring. As you might predict, the **exo position** refers to the *outside* position. Diels-Alder reactions with cyclic dienes favor the formation of bicyclic structures in which substituents are in the **endo position**. Preference of the endo position is also a facet of the suprafacial nature of the Diels-Alder reaction. The orbital overlap required for the reaction is greater when the dienophile lies directly underneath the diene.

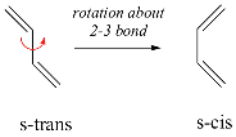


Alkynes can also serve as dienophiles in Diels-Alder reactions:

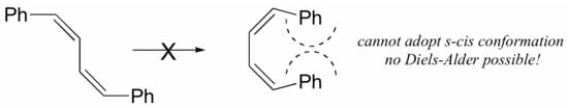


The Diene

In general, Diels-Alder reactions proceed fastest with electron-donating groups on the diene (eg. alkyl groups). The Diels-Alder reaction is a single step process, so the diene component must adopt an s-cis conformation in order for the end carbon atoms (#1 & #4) to bond simultaneously to the dienophile. For many acyclic dienes the s-trans conformer is more stable than the s-cis conformer (due to steric crowding of the end groups), but the two are generally in rapid equilibrium, permitting the use of all but the most hindered dienes as reactants in Diels-Alder reactions.



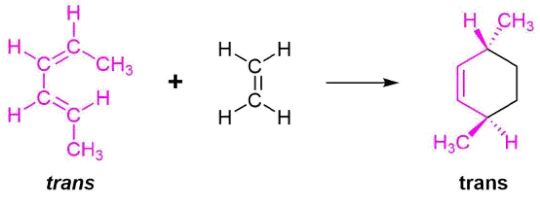
For some dienes, extreme steric hindrance causes the s-cis conformation to be highly strained, and for this reason such dienes do not readily undergo Diels-Alder reactions.



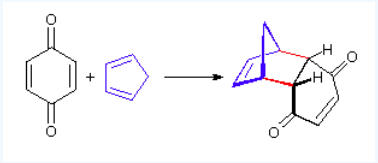
Cyclic dienes, on the other hand, are ‘locked’ in the s-cis conformation, and are especially reactive. The result of a Diels-Alder reaction involving a cyclic diene is a **bicyclic** structure:

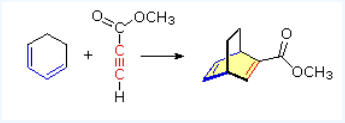
Stereochemistry of Diels-Alder (diene)

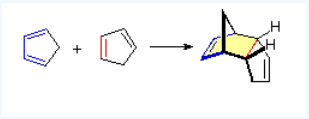
The 1 and 4 Carbons in the diene have the possibility of forming two new stereocenters in the cyclohexene product. Similarly to the effects of dienophile stereochemistry, the positioning of substituents on the 1 and 4 carbons in the diene determine the stereochemistry in the product. The diene substituents can be thought of as being either cis (both facing in or both facing out) or trans and the stereochemistry is retained to form a cis or trans cyclohexene product.

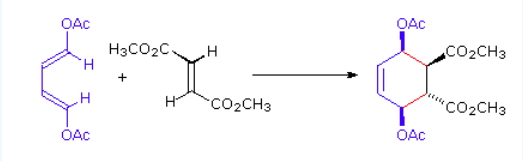


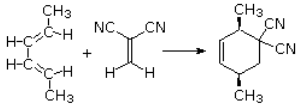
Examples 8.6.1

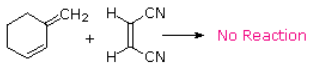








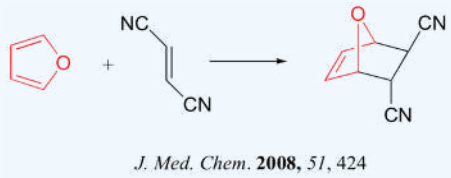




The Essential Characteristics of the Diels-Alder Cycloaddition Reaction:

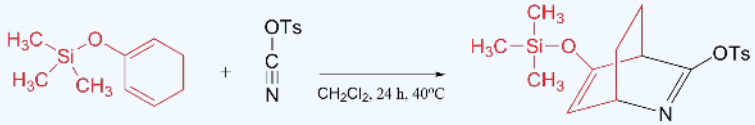
i. The reaction always creates a new six-membered ring.
ii. The diene component must be able to assume an s-cis conformation.
iii. Electron withdrawing groups on the dienophile facilitate reaction.
iv. Electron donating groups on the diene facilitate reaction.
v. Steric hindrance at the bonding sites may inhibit or prevent reaction.
vi. The reaction is stereospecific with respect to substituent configuration in both the dienophile and the diene.

Examples 8.6.2



J. Med. Chem. **2008,** *51*, 424

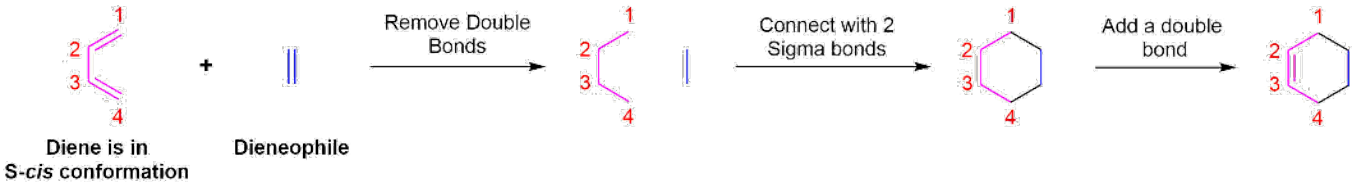
Org. Lett. **2001,** *3*, 1559



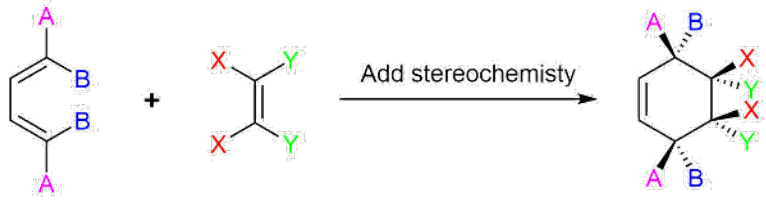
J. Org. Chem. **2003,** *68*, 8256

Predicting the Product of a Diels-Alder Reaction

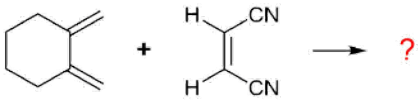
Start by rotating the diene until it is in the s-cis conformation then point it towards the double bond of the dienophile. Remove the double bonds present in the diene and dieneophile. Connect carbons 1 and 4 of the the diene to a carbon in the dienophile double bond using a sigma bond to create a six-membered ring. Create a double bond between carbons 2 and 3 of diene.



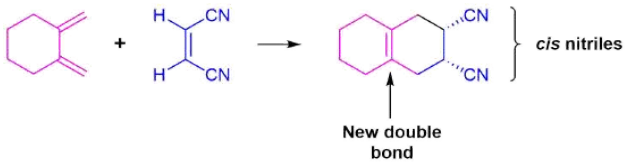
Determine if any substituents attached to either the double bond of the dieneophile or carbons 1 and 4 of the diene have a *cis*/*trans* conformation. If so make sure the substituents have the same configuration in the cycloalkene product.



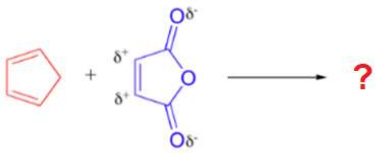
Predict the product of the following reaction:



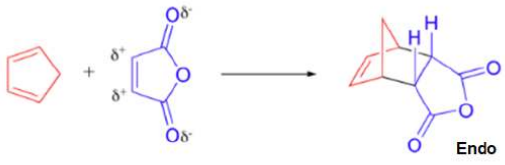
The diene is locked into an s-cis configuration which will promote the reaction. The ring portion of the diene will act as electron donating groups which will also promote the reaction. Because the diene already contained a ring the product will be bicyclic. The dienophile has two nitriles attached to it both of which are electron withdrawing. Since the two nitriles in the dieneophile are *cis* to each other the the two nitriles will be cis to each other in the product.



Predict the product of the following reaction:

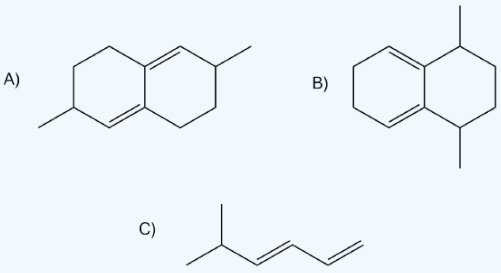


A particularly rapid Diels-Alder reaction takes place between cyclopentadiene and maleic anhydride. Cyclopentadiene is held in the required s-cis configuration so it will make a good diene for a Diels-Alder reaction. Maleic anhydride is also a very good dienophile, because the electron-withdrawing effect of the carbonyl groups causes the two alkene carbons to be electron-poor, and thus a good target for attack by the pi electrons in the diene. Since it is part of a ring, the double bond of maleic anhydride is in a cis configuration so the cyclohexene ring will also have a cis configuration. Lastly, the product will prefer the endo position.



Exercise 8.6.1

Of the following dienes, which are S-trans and which are s-cis? Of those that are s-trans, are they able to rotate to become s-cis?



Answer

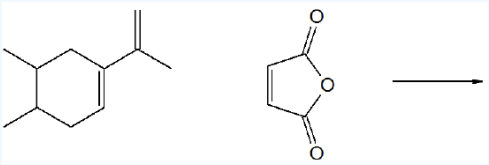
A) s-trans, unable to rotate to become s-cis

B) s-cis

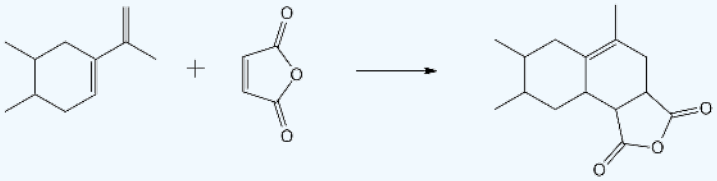
C) s-trans, can rotate to become s-cis.

Exercise 8.6.2

Predict the product of the following reaction.



Answer



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8.7: Diene Polymers- Natural and Synthetic Rubbers (reference only)

Objectives

After completing this section, you should be able to

1. show that the polymerization of a diene, such as 1,3-butadiene or isoprene (2-methyl-1,3-butadiene), can result in the formation of either a cis or trans polymer.
2. draw the structure of natural rubber.
3. explain, briefly, the process of vulcanization.

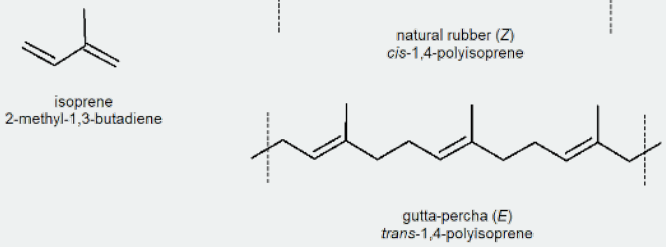
Key Terms

Make certain that you can define, and use in context, the key terms below.

- cross-link
- vulcanization

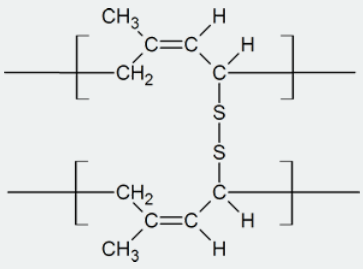
Study Notes

Natural rubber is formed from the isoprene monomer and has *Z* stereochemistry. The *E* polymer gutta-percha also occurs naturally, but is more brittle than rubber. Uses of this thermoplastic include dentistry, electrical insulators and the covering on golf balls.



Before 1839, the uses of natural rubber were somewhat limited. It became sticky in summer, hardened and cracked in winter, and was susceptible to attack by a variety of solvents. Charles Goodyear became interested in rubber in 1831, and bought the Eagle India Rubber Company of Woburn, Massachusetts, in 1838. In January of 1839, Goodyear accidentally placed a sample of rubber that had been mixed with sulfur and lead(II) oxide on a hot stove; the result was a product similar to charred leather, which did not melt below 138°C. Goodyear was granted a U.S. patent for his process (called vulcanization) in June of 1844. The story of vulcanization is an example of how major scientific and technological advances are often brought about as a result of an accidental discovery.

Notice that in the vulcanization process, the sulfur bridges are attached to allylic carbon atoms which connect the long *Z* polymer chains of rubber.



Vulcanized rubber

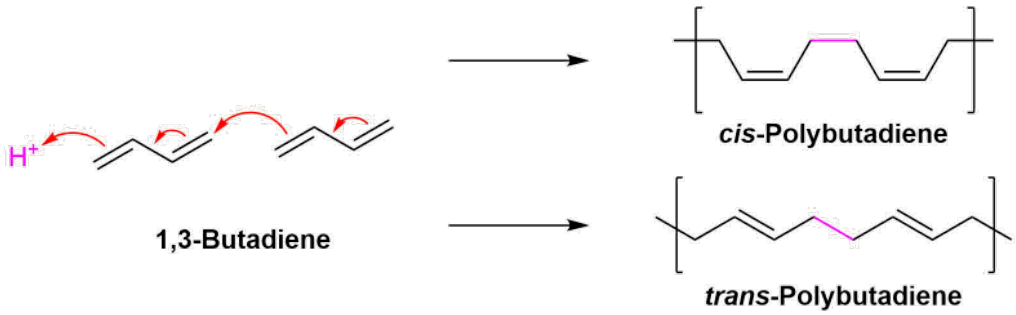
The amount of sulfur used in the vulcanization process will depend on the rigidity required in the product. For example, about 5% sulfur is used when producing rubber for rubber bands; about 30% sulfur is used when making rubber for use in battery casings. There are several characteristics of dienes and rubbers that you should recognize. First, be aware of the similarity between the polymerization of a diene and the 1,4-addition reactions of dienes. Second, recognize the similarity between a vulcanized rubber and a peptide containing cysteine cross-links. Third, be aware that as natural rubber contains double bonds, it will display some of the properties of simple alkenes.

The 1,4 polymerization of 1,3-butadiene shown in the reading produces the *trans* form of polybutadiene. However, it should be noted that the *cis* form shown here can also be formed.

cis- polbutadiene

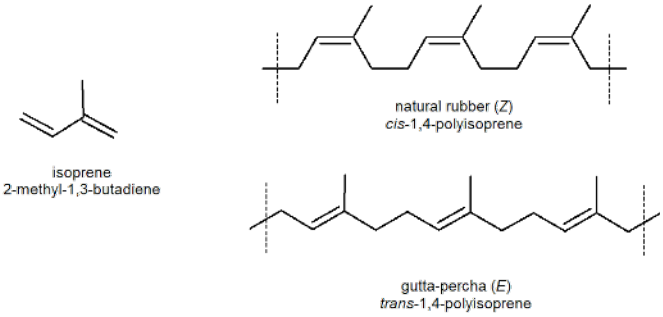
Polymerization of 1,3-Butadiene

Conjugated dienes can be polymerized much like alkenes **(**Section 8-10**)** to form important compounds like rubber. Diene polymers are more structurally complex and have the possibility of forming different isomers. The polymerization of conjugated dienes are commonly initiated by ether a radical or an acid. Interactions between double bonds on multiple chains leads to cross-linkage which creates elasticity within the compound. The polymerization takes place by a type of 1,4 addition to 1,3-butadiene which leads to the possibility of forming cis (*Z*) or trans (*E*) double bonds in the polymer product.

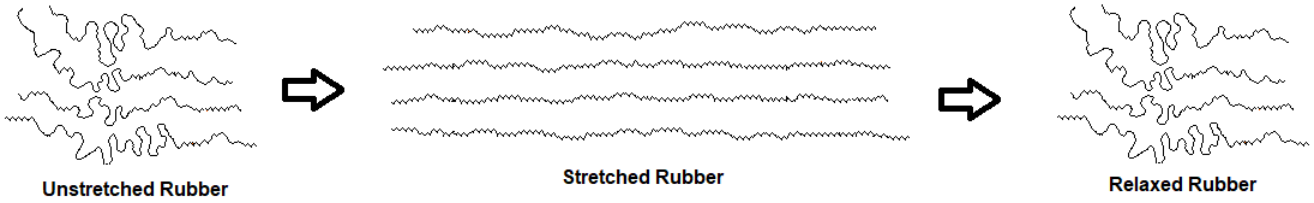


Natural Rubber

Rubber is undoubtedly the best known and most widely used compound of this kind. Natural rubber is an addition polymer that is obtained as a milky white colloidal suspension known as latex with the major source being a tropical rubber tree (*Hevea brasiliensis*). Natural rubber is from the monomer isoprene (2-methyl-1,3-butadiene), which is a conjugated diene hydrocarbon as mentioned above. The double bonds in rubber all have a Z-configuration, which causes this macromolecule to adopt a kinked or coiled conformation. This is reflected in the physical properties of rubber. Despite its high molecular weight (about one million), crude latex rubber is a soft, sticky, elastic substance. Chemical modification of this material is normal for commercial applications. Gutta-percha (structure below) is a naturally occurring E-isomer of rubber. Here the hydrocarbon chains adopt a uniform zig-zag or rod like conformation, which produces a more rigid and tough substance. Uses of gutta-percha include electrical insulation and the covering of golf balls.

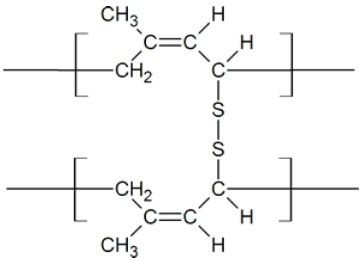


Due to rubber being an amorphous polymer, its coiled polymer chains can be straightened by stretching. The more highly-ordered chains in the stretched conformation are entropically unstable and return to their original coiled state when allowed to relax.

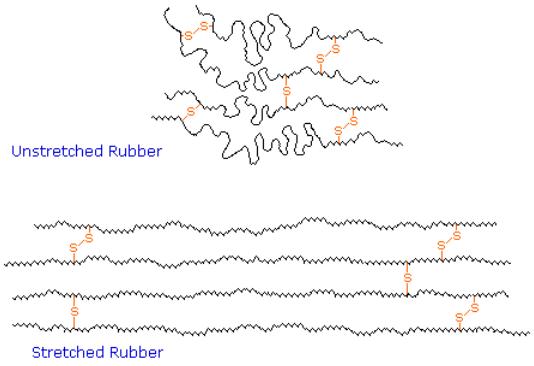


Vulcanization

Charles Goodyear accidentally discovered that by mixing sulfur and rubber, the properties of the rubber improved in being tougher, resistant to heat and cold, and increased in elasticity. This process was later called vulcanization after the Roman god of fire. Sulfur vulcanization is a chemical process for converting natural rubber or related polymers into more durable materials by heating them with sulfur or other equivalent curatives. Sulfur forms cross-links (bridges) between sections of polymer chains which results in increased rigidity and durability, as well as other changes in the mechanical and electronic properties of the material. A vast array of products are made with vulcanized rubber, including tires, shoe soles, hoses, and conveyor belts.

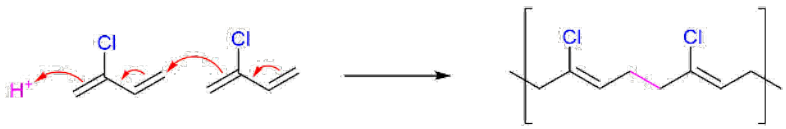


At 2 to 3% crosslinking a useful soft rubber, that no longer suffers stickiness and brittleness problems on heating and cooling, is obtained. At 25 to 35% crosslinking a rigid hard rubber product is formed. The following illustration shows a section of amorphous rubber cross-linked with sulfur by the vulcanization process.



Synthetic Rubber

Neoprene (also **polychloroprene** or **pc-rubber**) is a family of synthetic rubbers that are produced by polymerization of 2-chloro-1,3-butadiene (chloroprene). Neoprene exhibits good chemical stability and maintains flexibility over a wide temperature range. Neoprene is sold either as solid rubber or in latex form and is used in a wide variety of applications, such as laptop sleeves, orthopaedic braces (wrist, knee, etc.), electrical insulation, liquid and sheet applied elastomeric membranes or flashings, and automotive fan belts.



Chloroprene
(2-Chloro-1,3-butadiene)

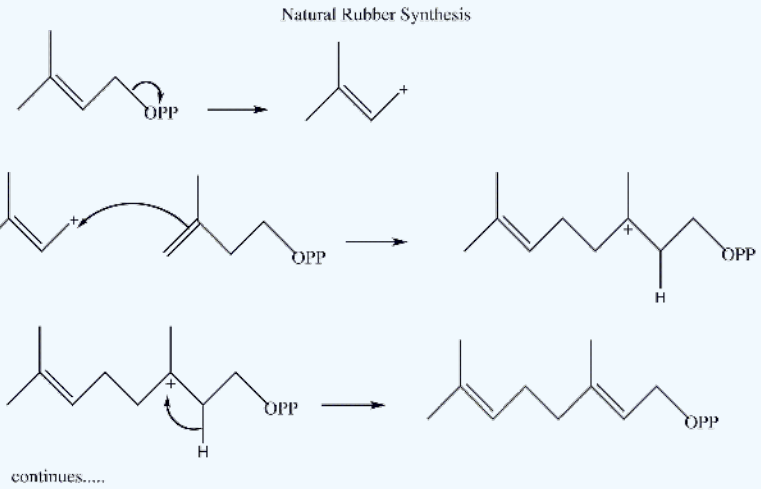
(Z) Neoprene

Exercise 8.7.1

a. Draw out the mechanism for the natural synthesis of rubber from 3-methyl-3-butenyl pyrophosphate and 2-methyl-1,3-butadiene. Show the movement of electrons with arrows
b. Draw a segment for the polymer that may be made from 2-*tert*-butyl-1,3-butadiene.
c. Propose the mechanism for the acid catalyzed polymerization of 2-methyl-1,3-butadiene.

Answer

1)



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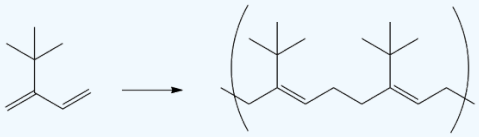
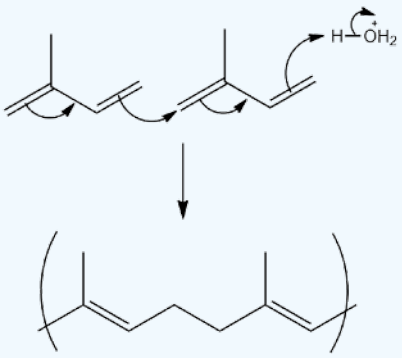


3)



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8.8: Structure Determination in Conjugated Systems - Ultraviolet Spectroscopy (reference only)

Objectives

After completing this section, you should be able to

1. identify the ultraviolet region of the electromagnetic spectrum which is of most use to organic chemists.
2. interpret the ultraviolet spectrum of 1,3-butadiene in terms of the molecular orbitals involved.
3. describe in general terms how the ultraviolet spectrum of a compound differs from its infrared and NMR spectra.

Key Terms

Make certain that you can define, and use in context, the key term below.

- ultraviolet (UV) spectroscopy
- Molar absorptivity

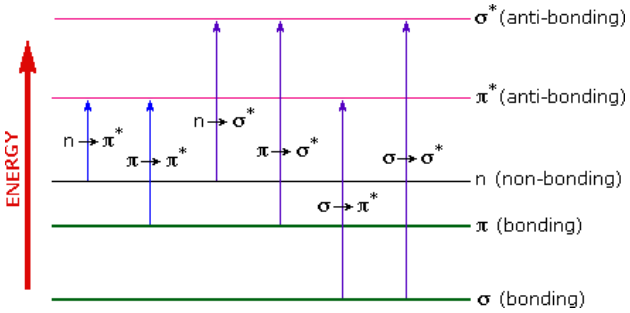
Study Notes

Ultraviolet spectroscopy provides much less information about the structure of molecules than do the spectroscopic techniques studied earlier (infrared spectroscopy, mass spectroscopy, and NMR spectroscopy). Thus, your study of this technique will be restricted to a brief overview. You should, however, note that for an organic chemist, the most useful ultraviolet region of the electromagnetic spectrum is that in which the radiation has a wavelength of between 200 and 400 nm.

UV-Visible Absorption Spectra

To understand why some compounds are colored and others are not, and to determine the relationship of conjugation to color, we must make accurate measurements of light absorption at different wavelengths in and near the visible part of the spectrum. Commercial optical spectrometers enable such experiments to be conducted with ease, and usually survey both the near ultraviolet and visible portions of the spectrum. Ultraviolet-visible absorption spectroscopy provides much less information about the structure of molecules than do the spectroscopic techniques studied earlier (infrared spectroscopy, mass spectroscopy, and NMR spectroscopy) and mainly provides information about conjugated pi systems. For an organic chemist the most useful ultraviolet region of the electromagnetic spectrum involves radiation with a wavelength between 200 and 400 nm. UV/Vis absorption spectra also involve radiation from the visible region of the electromagnetic spectrum with wavelengths between 400 and 800 nm.

A diagram highlighting the various kinds of electronic excitation that may occur in organic molecules is shown below. Of the six transitions outlined, only the two lowest energy ones, n to pi* and pi to pi* (colored blue) are achieved by the energies available in the 200 to 800 nm range of a UV/VIs spectrum. These energies are sufficient to promote or excite a molecular electron to a higher energy orbital in many conjugated compounds.



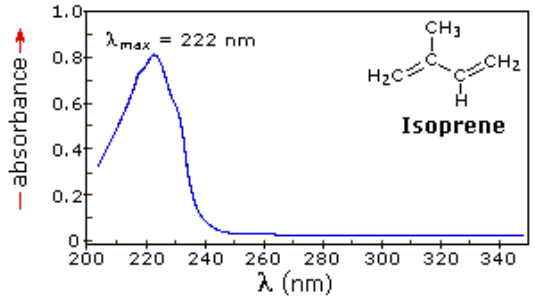
When sample molecules are exposed to light having an energy that matches a possible electronic transition within the molecule, some of the light energy will be absorbed as the electron is promoted to a higher energy orbital. A UV/Vis spectrometer records the wavelengths at which absorption occurs, together with the degree of absorption at each wavelength. A**bsorbance**, abbreviated 'A', is a unitless number which contains the same information as the 'percent transmittance' number used in IR spectroscopy. To

calculate absorbance at a given wavelength, the computer in the spectrophotometer simply takes the intensity of light at that wavelength *before* it passes through the sample (I_0), divides this value by the intensity of the same wavelength *after* it passes through the sample (I), then takes the $\log_{10}$ of that number:

$$A = \log\left(\frac{I_0}{I}\right)$$

The resulting spectrum is presented as a graph of absorbance (A) versus wavelength, as in the isoprene spectrum shown below. Since isoprene is colorless, it does not absorb in the visible part of the spectrum and this region is not displayed on the graph. Notice that the convention in UV-vis spectroscopy is to show the baseline at the bottom of the graph with the peaks pointing up. Wavelength values on the x-axis are generally measured in nanometers (nm) rather than in cm^{-1} as is the convention in IR spectroscopy.

Typically, there are two things that are noted and recorded from a UV-Vis spectrum. The first is **λ_{max}**, which is the wavelength at maximal light absorbance. As you can see, isoprene has **$\lambda_{max,}$** = 222 nm. The second valuable piece of data is the absorbance at the **λ_{max}**. In the isoprene spectrum the absorbance at the value **λ_{max}** of 222 nm is about 0.8.



Molar absorptivity

Molar absorptivity (*epsilon*) is a physical constant, characteristic of the particular substance being observed and thus characteristic of the particular electron system in the molecule. Molar absorptivities may be very large for strongly absorbing chromophores (>100,000) and very small if absorption is weak (10 to 100). The magnitude of *epsilon* reflects both the size of the chromophore and the probability that light of a given wavelength will be absorbed when it strikes the chromophore. Molar absorptivity (ϵ) is defined via Beer's law as:

$$\epsilon = \frac{A}{c\,l}$$

where

- A is the sample absorbance
- c is the sample concentration in moles/liter
- l is the length of light path through the sample in cm

If the isoprene spectrum show above was obtained from a dilute hexane solution (c = 4 * 10^{-5} moles per liter) in a 1 cm sample cuvette, a simple calculation using the above formula indicates a molar absorptivity of 20,000 at the maximum absorption wavelength, symbolized as λ_{max}.

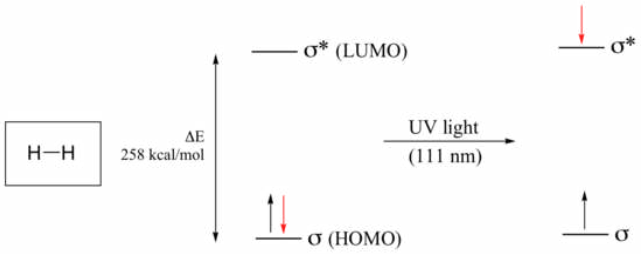
The only molecular moieties likely to absorb light in the 200 to 800 nm region are functional groups that contain pi-electrons and hetero atoms having non-bonding valence-shell electron pairs. Such light absorbing groups are referred to as **chromophores**. A list of some simple chromophores and their light absorption characteristics are provided below. The oxygen non-bonding electrons in alcohols and ethers do not give rise to absorption above 160 nm. Consequently, pure alcohol and ether solvents may be used for spectroscopic studies.

Chromophore	Example	Excitation	λmax, nm	ε @ λmax	Solvent
C=C	Ethene	π → π*	171	15,000	hexane
C≡C	1-Hexyne	π → π*	180	10,000	hexane

Chromophore	Example	Excitation	λmax, nm	ε @ λmax	Solvent
C=O	Ethanal	n → π* π → π*	290 180	15 10,000	hexane hexane
N=O	Nitromethane	n → π* π → π*	275 200	17 5,000	ethanol ethanol
C-X X=Br X=I	Methyl bromide Methyl Iodide	n → σ* n → σ*	205 255	200 360	hexane hexane

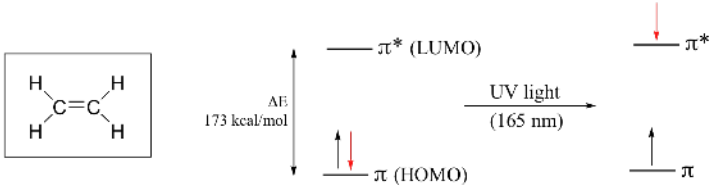
Electronic Transitions (cause of UV-Visible absorption)

As previously noted, electronic transitions in organic molecules lead to UV and visible absorption. As a rule, energetically favored electron promotion will be from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO), and the resulting species is called an **excited state.** The molecular orbital picture for the hydrogen molecule (H_2) consists of one bonding σ MO, and a higher energy antibonding σ* MO. When the molecule is in the ground state, both electrons are paired in the lower-energy bonding orbital – this is the Highest Occupied Molecular Orbital (HOMO). The antibonding σ* orbital, in turn, is the Lowest Unoccupied Molecular Orbital (LUMO).

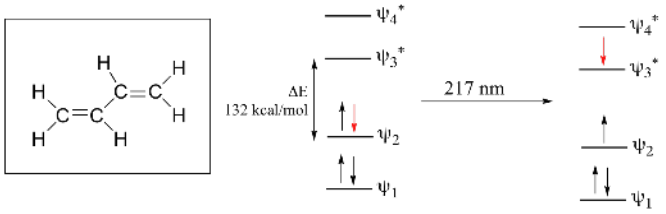


If the molecule is exposed to light of a wavelength with energy equal to ΔE, the HOMO-LUMO energy gap, this wavelength will be absorbed and the energy used to bump one of the electrons from the HOMO to the LUMO – in other words, from the σ to the σ* orbital. This is referred to as a **σ - σ* transition**. ΔE for this electronic transition is 258 kcal/mol, corresponding to light with a wavelength of 111 nm.

When a double-bonded molecule such as ethene (common name ethylene) absorbs light, it undergoes a **π - π* transition**. Because π- π* energy gaps are narrower than σ - σ* gaps, ethene absorbs light at 165 nm - a longer wavelength than molecular hydrogen.

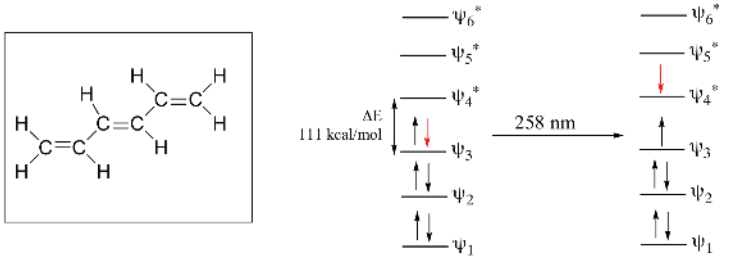


The electronic transitions of both molecular hydrogen and ethene are too energetic to be accurately recorded. Where electronic transition becomes useful to most organic and biological chemists is in the study of molecules with conjugated pi systems. In these groups, the energy gap for π -π* transitions is smaller than for isolated double bonds, and thus the wavelength absorbed is longer. The MO diagram for 1,3-butadiene, the simplest conjugated system. Recall that we can draw a diagram showing the four pi MO's that result from combining the four $2p_z$ atomic orbitals. The lower two orbitals are pi bonding, while the upper two are pi antibonding.

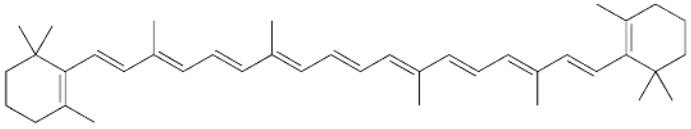


Comparing this MO picture to that of ethene, our isolated pi-bond example, we see that the HOMO-LUMO energy gap is indeed smaller for the conjugated system. 1,3-butadiene absorbs UV light with a wavelength of 217 nm.

As conjugated pi systems become larger, the energy gap for a π - π* transition becomes increasingly narrow, and the wavelength of light absorbed correspondingly becomes longer. The absorbance due to the π - π* transition in 1,3,5-hexatriene, for example, occurs at 258 nm, corresponding to a **Δ**E of 111 kcal/mol.

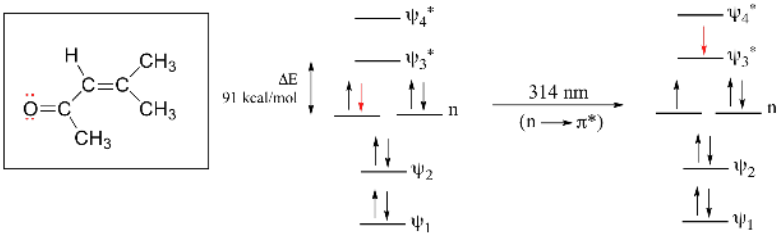


In molecules with extended pi systems, the HOMO-LUMO energy gap becomes so small that absorption occurs in the visible rather then the UV region of the electromagnetic spectrum. Beta-carotene, with its system of 11 conjugated double bonds, absorbs light with wavelengths in the blue region of the visible spectrum while allowing other visible wavelengths – mainly those in the red-yellow region - to be transmitted. This is why carrots are orange.



β-carotene

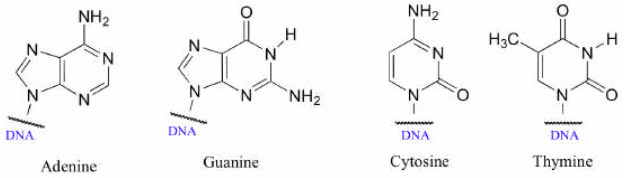
The conjugated pi system in 4-methyl-3-penten-2-one gives rise to a strong UV absorbance at 236 nm due to a π - π* transition. However, this molecule also absorbs at 314 nm. This second absorbance is due to the transition of a non-bonding (lone pair) electron on the oxygen up to a π* antibonding MO:



This is referred to as an $n-\pi^*$ transition. The nonbonding (n) MO's are higher in energy than the highest bonding p orbitals, so the energy gap for an $n-\pi^*$ transition is smaller that that of a $\pi-\pi^*$ transition – and thus the $n-\pi^*$ peak is at a longer wavelength. In general, $n-\pi^*$ transitions are weaker (less light absorbed) than those due to $\pi-\pi^*$ transitions.

Use of UV/Vis Spectroscopy in Biological Systems

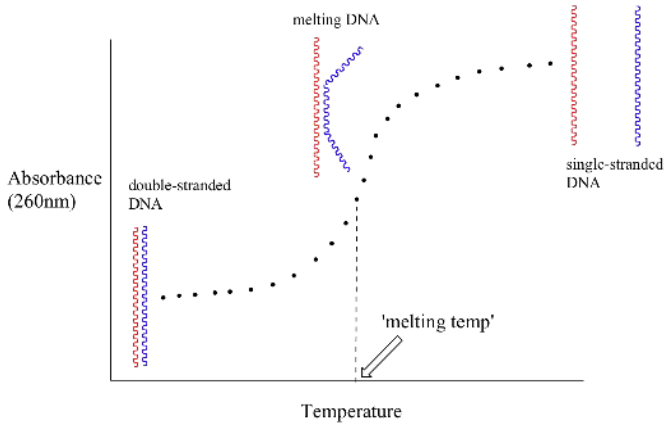
The bases of DNA and RNA are good chromophores:



Adenine Guanine Cytosine Thymine

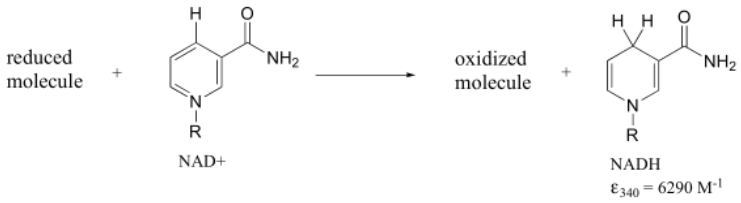
Biochemists and molecular biologists often determine the concentration of a DNA sample by assuming an average value of ε = 0.020 ng^{-1}×mL for double-stranded DNA at its λ_{max} of 260 nm (notice that concentration in this application is expressed in mass/volume rather than molarity: ng/mL is often a convenient unit for DNA concentration when doing molecular biology).

Because the extinction coefficient of double stranded DNA is slightly lower than that of single stranded DNA, we can use UV spectroscopy to monitor a process known as DNA melting. If a short stretch of double stranded DNA is gradually heated up, it will begin to 'melt', or break apart, as the temperature increases (recall that two strands of DNA are held together by a specific pattern of hydrogen bonds formed by 'base-pairing').

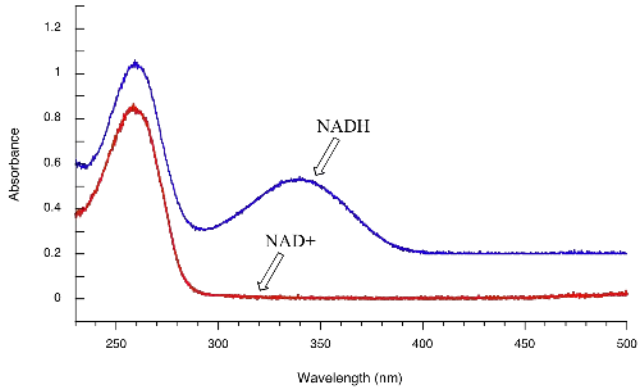


As melting proceeds, the absorbance value for the sample increases, eventually reaching a high plateau as all of the double-stranded DNA breaks apart, or 'melts'. The mid-point of this process, called the 'melting temperature', provides a good indication of how tightly the two strands of DNA are able to bind to each other.

Later we will see how the Beer - Lambert Law and UV spectroscopy provides us with a convenient way to follow the progress of many different enzymatic redox (oxidation-reduction) reactions. In biochemistry, oxidation of an organic molecule often occurs concurrently with reduction of nicotinamide adenine dinucleotide (NAD^+, the compound whose spectrum we saw earlier in this section) to NADH:

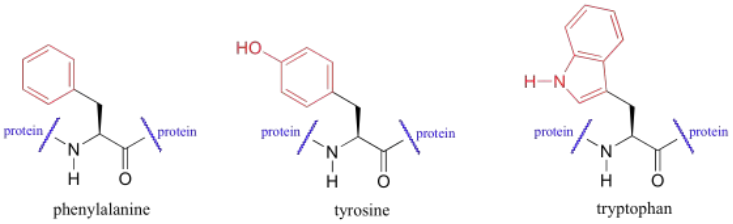


Both NAD^+ and NADH absorb at 260 nm. However NADH, unlike NAD^+, has a second absorbance band with λ_{max} = 340 nm and ε = 6290 $L{*}mol^{-1}{*}cm^{-1}$. The figure below shows the spectra of both compounds superimposed, with the NADH spectrum offset slightly on the y-axis:



By monitoring the absorbance of a reaction mixture at 340 nm, we can 'watch' NADH being formed as the reaction proceeds, and calculate the rate of the reaction.

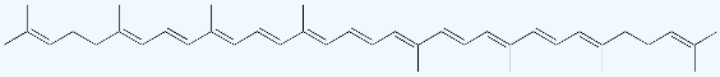
UV spectroscopy is also very useful in the study of proteins. Proteins absorb light in the UV range due to the presence of the aromatic amino acids tryptophan, phenylalanine, and tyrosine, all of which are chromophores.



Biochemists frequently use UV spectroscopy to study conformational changes in proteins - how they change shape in response to different conditions. When a protein undergoes a conformational shift (partial unfolding, for example), the resulting change in the environment around an aromatic amino acid chromophore can cause its UV spectrum to be altered.

Exercise 8.8.1

1. 50 microliters of an aqueous sample of double stranded DNA is dissolved in 950 microliters of water. This diluted solution has a maximal absorbance of 0.326 at 260 nm. What is the concentration of the original (more concentrated) DNA sample, expressed in micrograms per microliter?
2. What is the energy range for 300 nm to 500 nm in the ultraviolet spectrum? How does this compare to energy values from NMR and IR spectroscopy?
3. Identify all isolated and conjugated pi bonds in lycopene, the red-colored compound in tomatoes. How many pi electrons are contained in the conjugated pi system?



lycopene

Answer

1) Using ε = A/c, we plug in our values for ε and A and find that c = 3.27 x 10^{-5}M, or 32.7 mM.

2)

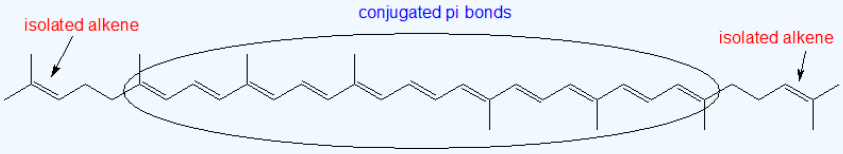
$E = hc/\lambda$

$E = (6.62 \times 10^{-34}\ \text{Js})(3.00 \times 10^{8}\ \text{m/s})/(3.00 \times 10^{-7}\ \text{m})$

$E = 6.62 \times 10^{-19}\ \text{J}$

The range of 3.972×10^{-19} to 6.62×10^{-19} joules. This energy range is greater in energy than the in NMR and IR.

3)



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8.9: Interpreting Ultraviolet Spectra- The Effect of Conjugation (reference only)

Objective

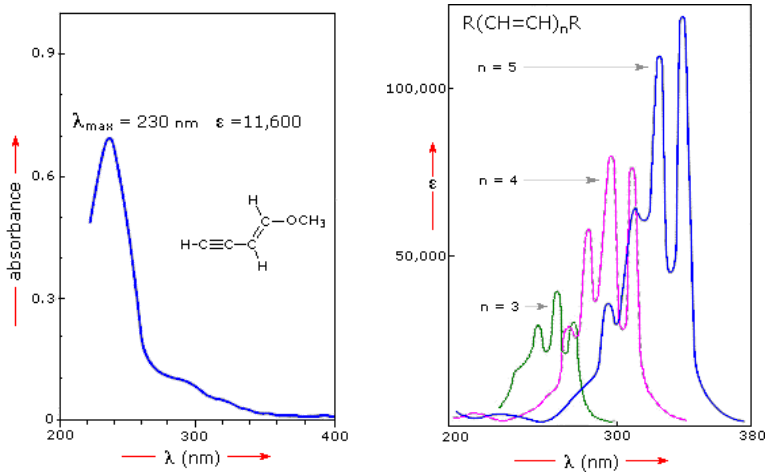
After completing this section, you should be able to use data from ultraviolet spectra to assist in the elucidation of unknown molecular structures.

Study Notes

It is important that you recognize that the ultraviolet absorption maximum of a conjugated molecule is dependent upon the extent of conjugation in the molecule.

The Importance of Conjugation

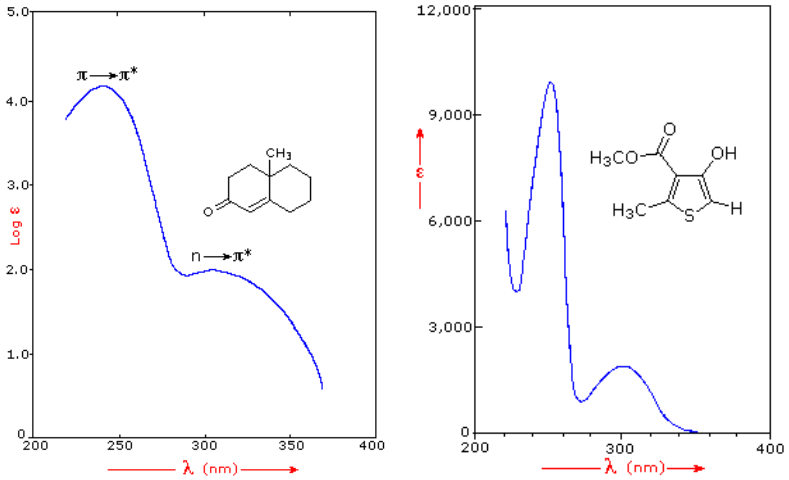
A comparison of the UV/Vis absorption spectrum of 1-butene, λ_{max} = 176 nm, with that of 1,3-butadiene, λ_{max} = 292 nm, clearly demonstrates that the effect of increasing conjugation is to shift toward longer wavelength (lower frequency, lower energy) absorptions. Further evidence of this effect is shown below. The spectrum on the left illustrates that conjugation of double and triple bonds also shifts the absorption maximum to longer wavelengths. From the polyene spectra displayed in the right it is clear that each additional double bond in the conjugated pi-electron system increases the absorption maximum about 30 nm. Also, the molar absorptivity (ε) roughly doubles with each new conjugated double bond. Spectroscopists use the terms defined in the table below when describing shifts in absorption. Thus, extending conjugation generally results in bathochromic and hyperchromic shifts in absorption.



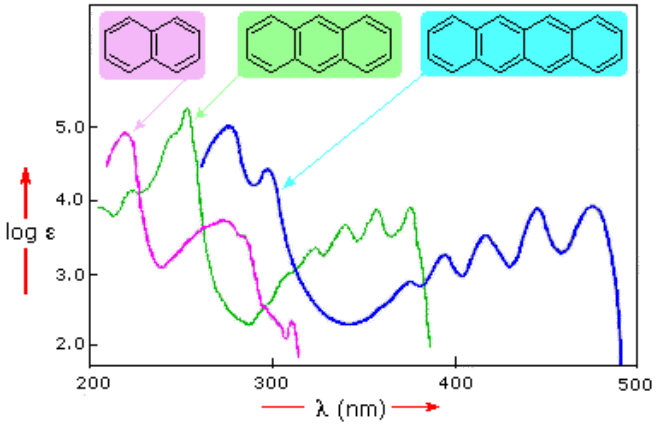
Terminology for Absorption Shifts

Nature of Shift	Descriptive Term
To Longer Wavelength	Bathochromic
To Shorter Wavelength	Hypsochromic
To Greater Absorbance	Hyperchromic
To Lower Absorbance	Hypochromic

Many other kinds of conjugated pi-electron systems act as chromophores and absorb light in the 200 to 800 nm region. These include unsaturated aldehydes and ketones and aromatic ring compounds. A few examples are displayed below. The spectrum of the unsaturated ketone (on the left) illustrates the advantage of a logarithmic display of molar absorptivity. The $\pi \rightarrow \pi^*$ absorption located at 242 nm is very strong, with an ε = 18,000. The weak $n \rightarrow \pi^*$ absorption near 300 nm has an ε = 100.

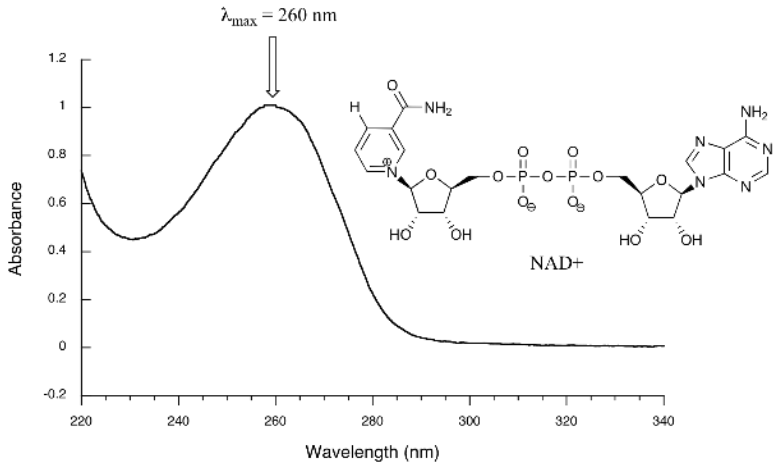


Benzene exhibits very strong light absorption near 180 nm (ε > 65,000) , weaker absorption at 200 nm (ε = 8,000) and a group of much weaker bands at 254 nm (ε = 240). Only the last group of absorptions are completely displayed because of the 200 nm cut-off characteristic of most spectrophotometers. The added conjugation in naphthalene, anthracene and tetracene causes bathochromic shifts of these absorption bands, as displayed in the chart below. All the absorptions do not shift by the same amount, so for anthracene (green shaded box) and tetracene (blue shaded box) the weak absorption is obscured by stronger bands that have experienced a greater red shift. As might be expected from their spectra, naphthalene and anthracene are colorless (with their absorptions in the UV range), but tetracene is orange (since its absorptions move into the visible range).

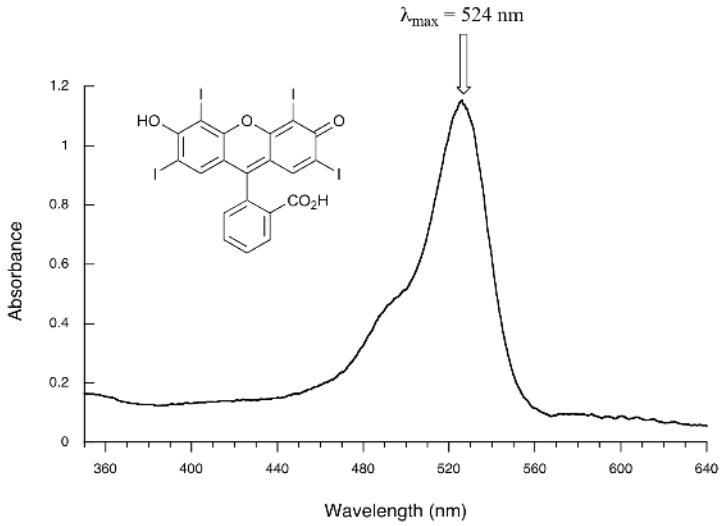


Looking at UV-Vis Spectra

Below is the absorbance spectrum of an important biological molecule called nicotinamide adenine dinucleotide, abbreviated NAD^+. This compound absorbs light in the UV range due to the presence of conjugated pi-bonding systems.



Below is the absorbance spectrum of the common food coloring Red #3. The extended system of conjugated pi bonds causes the molecule to absorb light in the visible range. Because the λ_{max} of 524 nm falls within the green region of the spectrum, the compound appears red to our eyes (recalling the color wheel from Section 14.7).



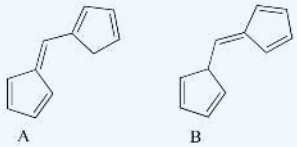
Example 14.8.2

How large is the π - π* transition in 4-methyl-3-penten-2-one?

Solution

Example 14.8.3

Which of the following molecules would you expect absorb at a longer wavelength in the UV region of the electromagnetic spectrum? Explain your answer.



Solution

Exercise 8.9.1

Which of the following would show UV absorptions in the 200-300 nm range?

Answer

B and D would be in that range.

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8.10: Conjugation, Color, and the Chemistry of Vision (reference only)

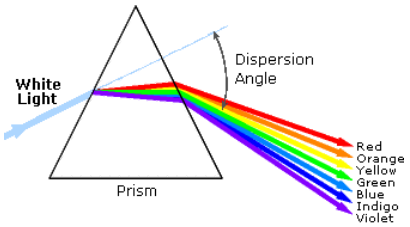
Objectives

After completing this section, you should be able to

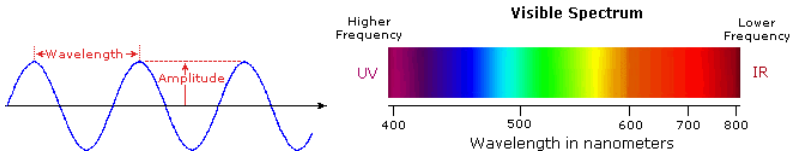
1. explain why some organic compounds have different colors based on compound structure and our perception of light.
2. state the relationship between frequency of light absorbed and the extent of conjugation in an extended pi electron system.

Introduction

An obvious difference between certain compounds is their color. Thus, quinone is yellow; chlorophyll is green; and aspirin is colorless. In this respect the human eye is functioning as a spectrometer analyzing the light reflected from the surface of a solid or passing through a liquid. Although we see sunlight (or white light) as uniform or homogeneous in color, it is actually composed of a broad range of radiation wavelengths in the ultraviolet (UV), visible and infrared (IR) portions of the spectrum. As shown on the image below, the component colors of the visible portion can be separated by passing sunlight through a prism, which acts to bend the light in differing degrees according to wavelength.

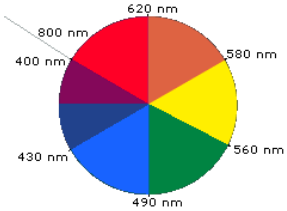


Visible wavelengths cover a range from approximately 400 to 800 nm. The longest visible wavelength is red and the shortest is violet. The wavelengths of what we perceive as particular colors in the visible portion of the spectrum are displayed and listed below.



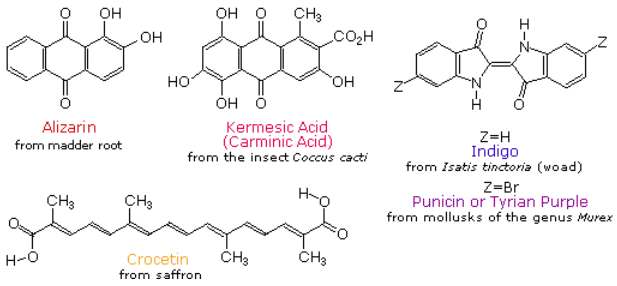
- **Violet:** 400 - 420 nm
- **Indigo:** 420 - 440 nm
- **Blue:** 440 - 490 nm
- **Green:** 490 - 570 nm
- **Yellow:** 570 - 585 nm
- **Orange:** 585 - 620 nm
- **Red:** 620 - 780 nm

When white light passes through or is reflected by a colored substance, a characteristic portion of the mixed wavelengths is absorbed. The remaining light will then assume the complementary color to the wavelength(s) absorbed. This relationship is demonstrated by the color wheel shown below. Here, complementary colors are diametrically opposite each other. Thus, absorption of violet (400-440 nm) light renders a substance yellow, and absorption of 490-560 nm (green) light makes it red. Green is unique in that it can be created by absorption close to 400 nm as well as absorption near 800 nm.

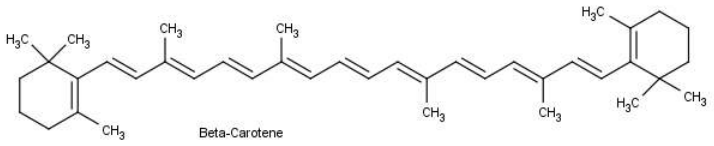


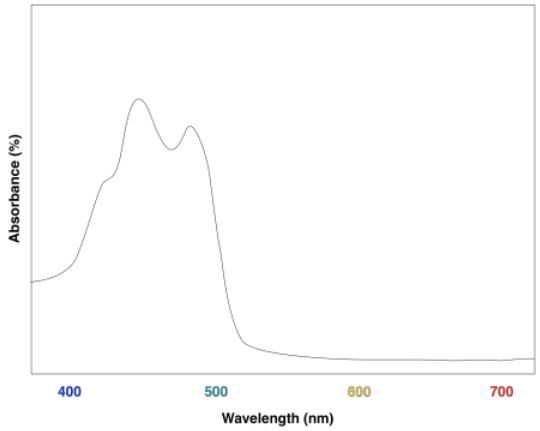
Early humans valued colored pigments, and used them for decorative purposes. Many of these were inorganic minerals, but several important organic dyes were also known. These included the crimson pigment, kermesic acid, the blue dye, indigo, and the yellow saffron pigment, crocetin. A rare dibromo-indigo derivative, punicin, was used to color the robes of the royal and wealthy. A common feature of all these colored compounds, displayed below, is a system of **extensively conjugated π-electrons**.

Some Natural Organic Pigments

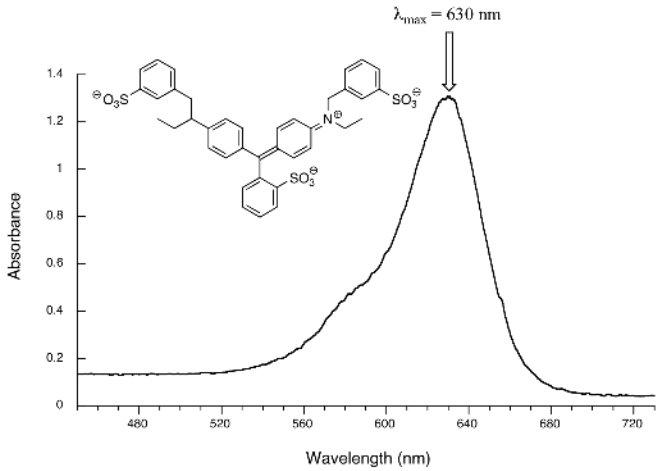


By understanding visible light, complementary colors, and adsorption the color of organic compounds can be understood. Beta-carotene, a compound found in carrots, is a deep orange color. Beta-carotene has 11 conjugated double bonds which places its λ_{max} at 455 nm which is within the blue region of the visible spectrum. The Beta-carotene compound absorbs blue from white light so it appears orange which is the the complementary color of blue.





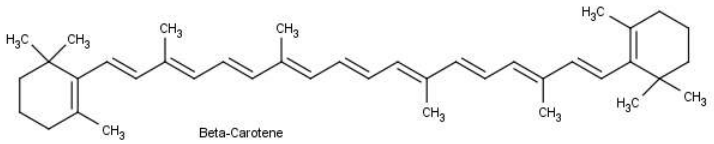
Another example is seen in the absorption spectrum of another food coloring, Blue #1:

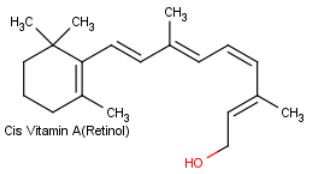


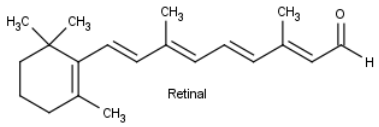
Blue #1 absorbs at a λ_{max} at 630 nm which is the color red in the visible spectrum. Blue is the complementary color of red.

Mechanism of Vision

Conjugation is also important in light sensitive compounds used for vision. Beta carotene, found in carrots and other natural products is cleaved into the liver and converted into Vitamin A, also known as retinol. Vitamin A is critical for vision because it is needed by the retina of eye. Retinol can be oxidized to an aldehyde called retinal which is also important for vision.



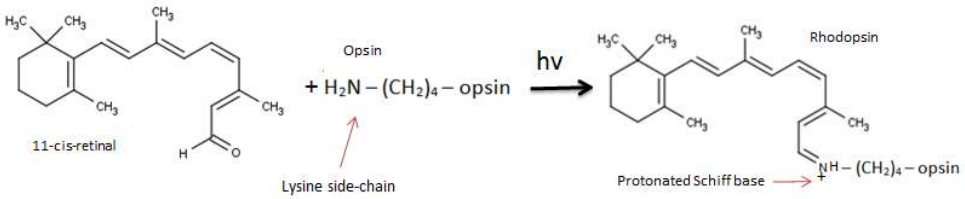




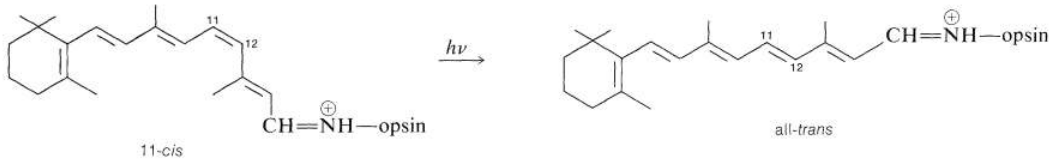
The eye is an extraordinarily sensitive instrument. Although its wavelength response is restricted to 400-800 nm, but its degree of sensitivity is such that a fully dark-adapted eye can clearly detect objects in light so dim as to correspond to a light input over the retina of only about 10,000 quanta 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 (λ_{max} = 500nm) 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.

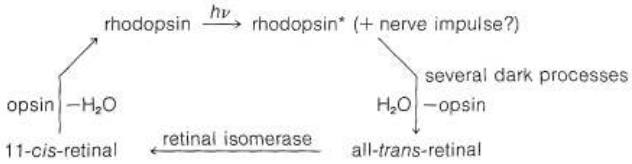
Rhodopsin, is made up of a protein (opsin) and retinal. Opsin does not absorb visible light, but when it is bonded with 11-cis-retinal to from rhodopsin, the new molecule has a very broad absorption band in the visible region of the spectrum. Rhodopsin is formed by an an imine (Schiff base) functional group 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 nm. The combination of opsin with 11-cis-retinal produces a remarkable shift of λ_{max} to longer wavelengths (430 nm to 620 nm, depending on the species). 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 moiety fo rhodopsin from *cis* to *trans* to form a compound called metarhodopsin II. The new form of trans-retinal does not fit as well into the opsin protein, and so a series of geometry changes in the protein begins. As the protein changes its geometry, it initiates a cascade of biochemical reactions that result in changes in charge so that a large potential difference builds up across the neuron membranes. This potential difference is passed along to an adjoining nerve cell as an electrical impulse. The nerve cell carries this impulse to the brain, where the visual information is interpreted.

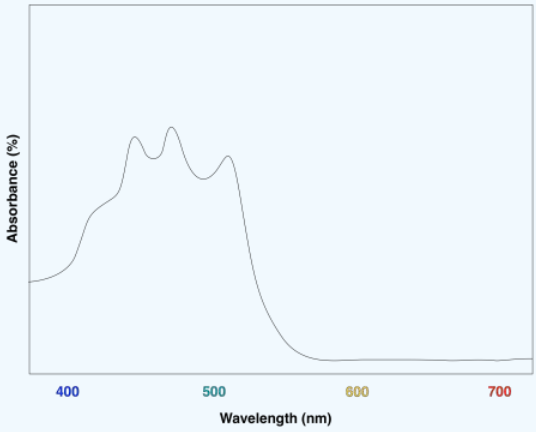


Metarhodopsin II can then be recycled back to rhodopsin by first cleaving to form all-*trans*-retinal and the isomerization back to 11-*cis*-retinal by the enzyme retinal isomerase. Finally, 11-*cis*-retinal is once again coupled with opsin to form rhodopsin.



? Exercise 8.10.1

Lycopene is conjugated compound found in tomatoes. What colors correspond to the UV-Vis absorption maxima of lycopene? What color do we see when we look at lycopene?



Answer

The absorption maxima of lycopene are regions of blue and green in the visible spectrum. Lycopene would be expected to appears orange and red.

Exercise 8.10.2

Asprin has a λ_{max} of 220 nm. Briefly explain why Asprin appears white.

Answer

Asprin absorbs in the ultraviolet portion of the electromagnetic spectrum. Asprin cannot remove any colors from white light by absorption so the compound itself appears white. Many compounds with a relatively small amount of conjugation appear white because they only absorb in the ultraviolet and not the visible region.

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8.S: Conjugated Compounds and Ultraviolet Spectroscopy (Summary)

Concepts & Vocabulary

14.0 Introduction

- Dienes that consist of two double bonds separated by a single bond are conjugated.
- Dienes that have the double bonds separated by more than one single bond are isolated (non-conjugated)

14.1 Stability of Conjugated Dienes - Molecular Orbital Theory

- Conjugated dienes are more stable than non-conjugated dienes.
- Electrons in conjugated dienes are delocalized due to overlap of all 4 p-orbitals.
- Molecular orbitals show stability of dienes and allylic carbocations.

14.2 Electrophilic Additions to Conjugated Dienes - Allylic Carbocations

- Addition to conjugated dienes occur at multiple positions due to resonance of the allyl carbocation intermediate called 1,2 and 1,4 addition.

14.3 Kinetic vs. Thermodynamic Control of Reactions

- Lower transition states lead to kinetic products.
- More stable products lead to thermodynamic products.
- Kinetic reaction conditions favor 1,2 addition to conjugated dienes.
- Thermodynamic reaction conditions favor 1,4 addition to conjugated dienes.
- For some reactions, the kinetic and thermodynamic products are the same molecule.

14.4 The Diels-Alder Cycloaddition Reaction

- Cycloaddition reactions involve concerted bonding of two independent pi-electron systems for form a new ring.
- The Diels-Alder reaction is a widely used [4+2] cycloaddition that froms two new sigma bonds.

14.5 Characteristics of the Diels-Alder Reaction

- The Diels-Alder reaction is stereospecific with cis dienophiles yielding *cis* substitution and *trans* dienophiles generate trans substitution.
- The diene in a Diels-Alder reaction must be able to adopt an s-cis conformation.
- Diels-Alder reactions with cyclic dienes favor endo substituents.

14.6 Diene Polymers - Natural and Synthetic Rubbers (reference only)

- Dienes can form polymers including natural examples such as rubber which is formed from isoprene monomers.

14.7 Ultraviolet Spectroscopy (reference only)

- When UV and visible light is absorbed, electrons are excited from a bonding or non-bonding orbital to a nearby anti-bonding orbital.
- Colored organic molecules all include extensive conjugated pi electron systems.
- UV absorbance is higher energy than visible light, allowing for excitation of electrons without the low energy pi-bonding to pi anti-bonding transitions available in highly conjugated molecules.
- Chromophores are molecules or structural features that absorb light in the UV-Visible range.

14.8 Interpreting Ultraviolet Spectra: The Effect of Conjugation (reference only)

- Conjugated pi systems lowers the energy gap for π -π* transitions causing the molecule to absorb light of a longer wavelength.
- Many molecules absorb in the UV spectrum. As the energy gap becomes smaller, these absorbances move into the visible spectrum, starting with violet light which makes the resulting molecules appear yellow.

14.9 Conjugation, Color, and the Chemistry of Vision (reference only)

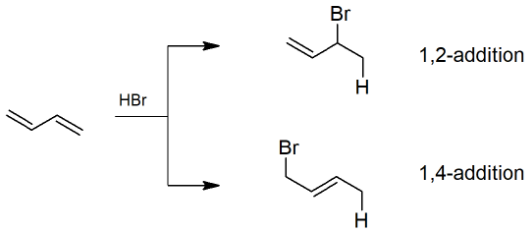
- Absorption of light causes chemical changes in the rods and cones in eyes leading to visual sensations.

Skills to Master

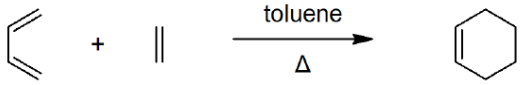
- Skill 14.1 Differentiate between conjugated and isolated dienes.
- Skill 14.2 Explain stability of conjugated dienes using Molecular Orbital Theory.
- Skill 14.3 Draw mechanisms for 1,2 and 1,4 addition to conjugated dienes.
- Skill 14.4 Predict kinetic and thermodynamic products of addition reactions to conjugated dienes.
- Skill 14.5 Explain kinetic and thermodynamic control of reactions.
- Skill 14.6 Identify dienes and dienophiles for Diels-Alder Cycloaddition reactions.
- Skill 14.7 Determine products of Diels-Alder Cycloaddition, including stereochemistry and endo/exo.
- Skill 14.8 Draw mechanisms for Diels-Alder Cycloaddition.

Summary of Reactions

Electrophilic Addition



Diels−Alder Cycloaddition



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CHAPTER OVERVIEW

9: Orbitals and Organic Chemistry - Pericyclic Reactions

Chapter Videos

This video introduces the Woodward-Hoffmann Rules and orbital symmetry to explain pericyclic reactions.

This video introduces the strategy for understanding electrocyclic reactions.

9.1: Molecular Orbitals of Conjugated Pi Systems
9.2: Electrocyclic Reactions
9.3: Stereochemistry of Thermal Electrocyclic Reactions

9.4: Photochemical Electrocyclic Reactions
9.5: Cycloaddition Reactions
9.6: Stereochemistry of Cycloadditions
9.7: Sigmatropic Rearrangements (reference only)
9.8: Some Examples of Sigmatropic Rearrangements (reference only)
9.9: A Summary of Rules for Pericyclic Reactions

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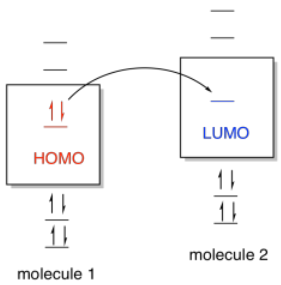
9.1: Molecular Orbitals of Conjugated Pi Systems

Frontier Molecular Orbital Theory

Prior to 1965, pericyclic reactions were known as "no mechanism reactions" since no one could adequately explain why reaction outcomes changed depending on whether reactants were exposed to heat or light. In 1965 Robert Burns Woodward and Roald Hoffmann used **Frontier Molecular Orbital Theory**, initially proposed by Kenichi Fukui, to develop their **Theory of Conservation of Orbital Symmetry** where outcomes of pericyclic reactions are explained by examining the **Highest Occupied Molecular Orbital (HOMO)** or **Lowest Unoccupied Molecular Orbital (LUMO)** of the reacting system. Their analysis of cycloadditions, electrocyclic reactions, and sigmatropic rearrangements is commonly referred to as the Woodward-Hoffmann Rules. A detailed analysis of three reaction types is provided in the subsequent sections of this chapter.

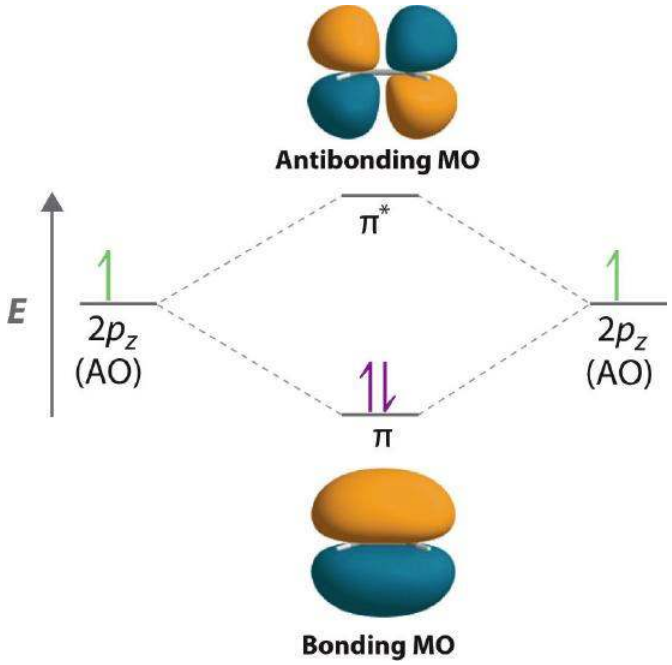
HOMO and LUMO are often referred to as **frontier orbitals** and their energy difference is termed the **HOMO–LUMO gap**. One common way of thinking about reactions in this way is through the concept of frontier orbitals. This idea says that if one species is going to donate electrons to another in order to form a new bond, then the donated electrons are most likely going to come from the highest occupied energy level. In this level, called the highest occupied molecular orbital (HOMO), the electrons are further from the nucleus and therefore less tightly held by the protons in the nucleus. The electrons would be donated, in turn, to the lowest empty energy level on the other species, called the lowest unoccupied molecular orbital (LUMO).



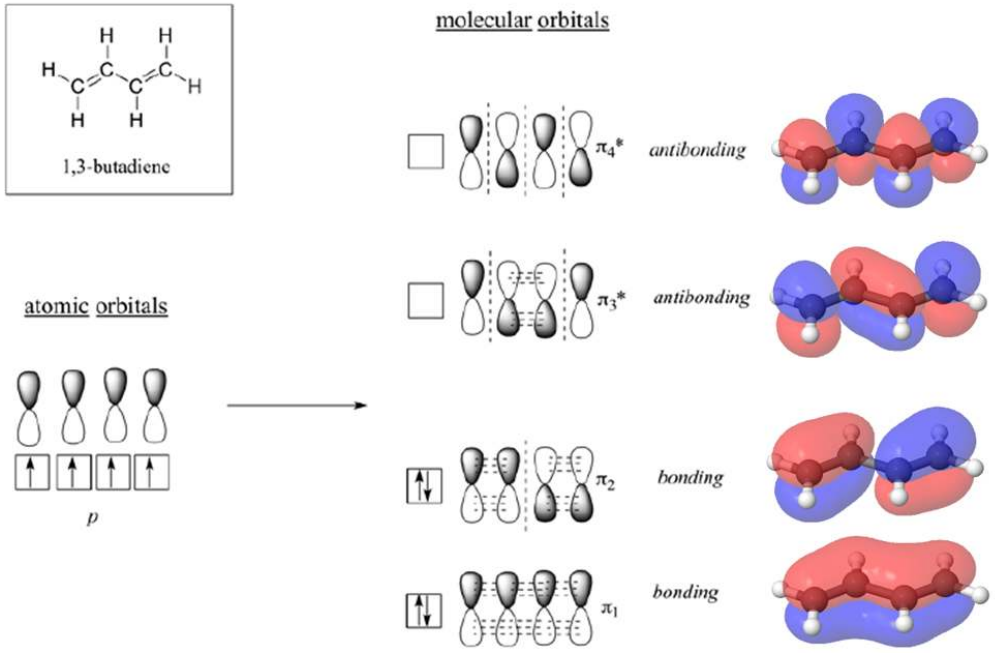
Molecular orbital interaction between frontier orbitals.

Molecular Orbitals

According to MO theory, when a double bond is non-conjugated, the two atomic $2p_z$ orbitals combine to form two **pi (π) molecular orbitals**, one a low-energy pi bonding orbital and one a high-energy **pi-star (π*) anti-bonding molecular orbital**. These are sometimes denoted, in MO diagrams like the one below, with the Greek letter psi (Ψ) instead of pi. In the bonding Ψ_1 orbital, the two (+) lobes of the $2p_z$ orbitals interact constructively with each other, as do the two (-) lobes. Therefore, there is increased electron density between the nuclei in the molecular orbital – this is why it is a bonding orbital. In the higher-energy anti-bonding Ψ_2* orbital, the (+) lobes of one $2p_z$ orbital interacts destructively with the (-) lobe of the second $2p_z$ orbital, leading to a node between the two nuclei and overall repulsion. By the *aufbau* principle, the two electrons from the two atomic orbitals will be paired in the lower-energy $\Psi_1$orbital when the molecule is in the ground state.

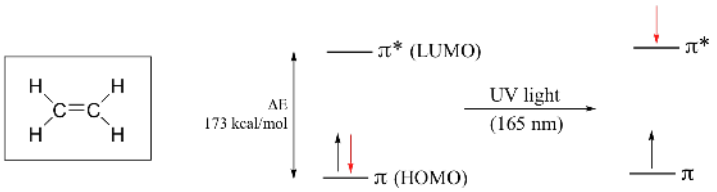


With a conjugated diene, such as 1,3-butadiene, the four *2p* atomic orbitals combine to form four pi molecular orbitals of increasing energy. Two bonding pi orbitals and two antibonding pi* orbitals. The combination of four pi molecular orbitals allow for the formation of a bonding molecular orbital that is lower in energy than those created by an unconjugated alkene. The 4 pi electrons of 1,3-butadiene completely fill the bonding molecular orbitals giving is the additional stability associated with conjugated double bonds.

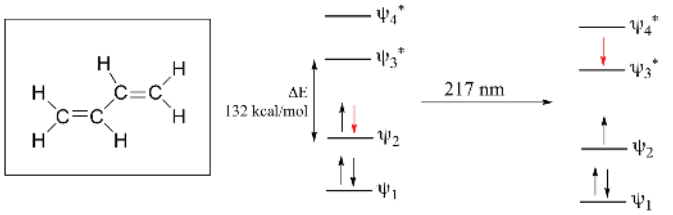


Electronic Transitions

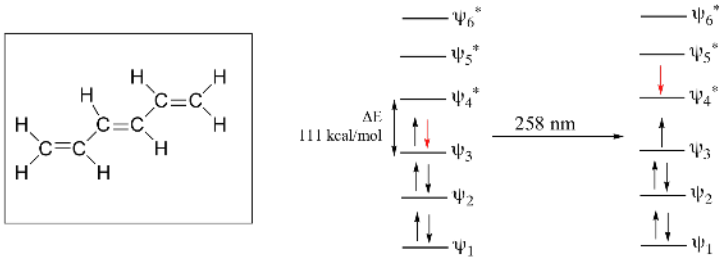
When a double-bonded molecule such as ethene (common name ethylene) absorbs 165 nm light, it undergoes a **pi - pi* transition**. An electron is moved from the HOMO of ethene to the LUMO placing the molecule in an **excited state**.



Where electronic transition becomes useful to most organic and biological chemists is in the study of molecules with conjugated pi systems. In these groups, the HOMO–LUMO gap energy gap for pi - pi* transitions is smaller than for isolated double bonds, and thus the wavelength absorbed is longer. The MO diagram for 1,3-butadiene, the simplest conjugated system. Recall that we can draw a diagram showing the four pi MO's that result from combining the four $2p_z$ atomic orbitals. The lower two orbitals are pi bonding, while the upper two are pi antibonding. Comparing this MO picture to that of ethene, our isolated pi-bond example the HOMO would be psi 2 and the LUMO would be psi 3. The HOMO-LUMO energy gap is smaller for the conjugated 1,3-butadiene system which absorbs UV light with a wavelength of 217 nm.



As conjugated pi systems become larger, the HOMO–LUMO gap energy gap for a pi - pi* transition becomes increasingly narrow, and the wavelength of light absorbed correspondingly becomes longer. The absorbance due to the pi - pi* transition in 1,3,5-hexatriene, for example, occurs at 258 nm.



Woodward-Hoffmann Rules

Much of what we have said about the electronic factors controlling pericyclic reactions was formulated in the mid 1960s by the American chemists R. B. Woodward and R. Hoffmann, in terms of what came to be called the **orbital symmetry** principles, or the **Woodward-Hoffmann rules**. This approach says that many details of pericyclic reactions can explained by "conservation of orbital symmetry." This requires the symmetries of the molecular orbitals of reactants to be the same as the molecular orbitals of the products for a reaction to proceed.

The original approach of Woodward and Hoffmann involved construction of an "orbital correlation diagram" to see if the lobes of the reactant molecular orbitals match phases and allow for overlap required for bonding to occur. The symmetries of the appropriate reactant and product orbitals were matched to determine whether the transformation could proceed without a symmetry imposed conversion of bonding reactant orbitals to antibonding product orbitals. If the correlation diagram indicated that the reaction could occur without encountering such a **symmetry-imposed barrier**, it was termed **symmetry allowed**. If a symmetry barrier was present, the reaction was designated **symmetry-forbidden**.

? Exercise 9.1.1

Using the molecular orbital diagram for 1,3,5-hexatriene determine the HOMO and LUMO for both the ground and excited state.

Answer

For the ground state the HOMO is psi 3 and LUMO is psi 4.

For the excited state the HOMO is psi 4 and LUMO is psi 5.

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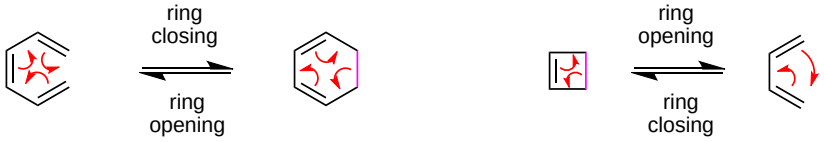
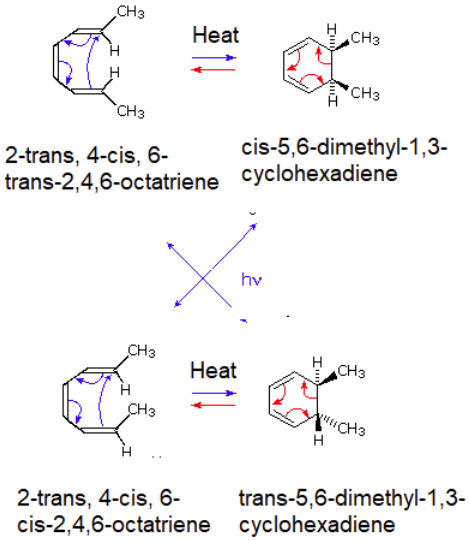
9.2: Electrocyclic Reactions

An electrocyclic reaction is the concerted cyclization of a conjugated pi-electron system by converting one pi-bond to a ring forming a σ-bond. The key sigma bond must be formed at the terminus of a pi system. These reactions are classified by the number of pi electrons involved. Thus, 4 pi reactions form 4 membered rings, as in a conjugated diene can being converted into a cyclobutene. Also, 6 pi reactions form 6 membered rings as in a conjugated triene can be converted into a cyclohexadiene. These reactions are often reversible with the reverse reaction called an *electrocyclic ring opening*. Although more pi electrons can be used, the 4 pi and 6 pi variants are by far the most common and are illustrated below with the key sigma bond highlighted in magenta.

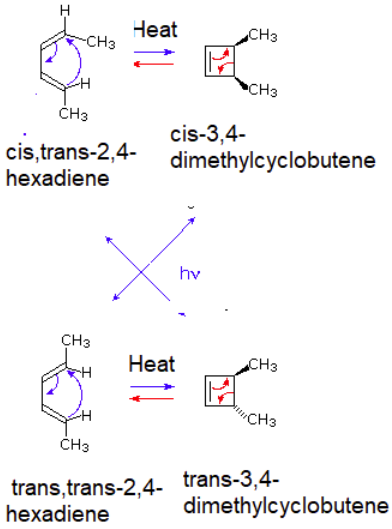


6 pi Electrocyclic Reaction 4 pi Electrocyclic Reaction

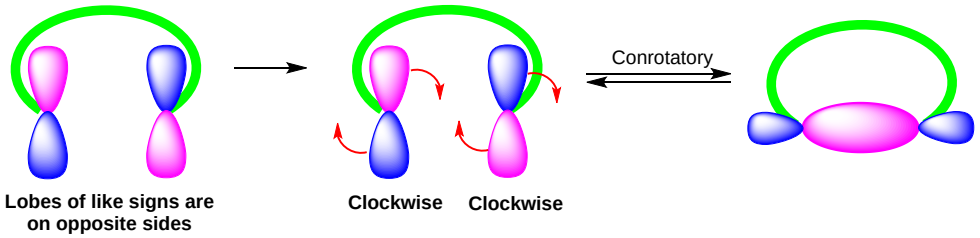
A striking feature of electrocyclic reactions that proceed by concerted mechanisms is their high degree of stereospecificity. For example, 2-*trans*, *4-cis*, *6-trans*-2,4,6-octatriene undergoes ring closure to *cis*-5,6-dimethyl-1,3-cyclohexadiene under thermal conditions i.e. when heated. Similarly the isomeric 2-*trans*, *4-cis*, *6-cis*-2,4,6-octatriene *produces trans*-5,6-dimethyl-1,3-cyclohexadiene, as noted below. However these results are completely reversed if the reaction is run under photochemical conditions (Irradiation with ultraviolet light). For example if 2-*trans*, *4-cis*, *6-cis*-2,4,6-octatriene is irradiated with UV light *cis*-5,6-dimethyl-1,3-cyclohexadiene would be produced.



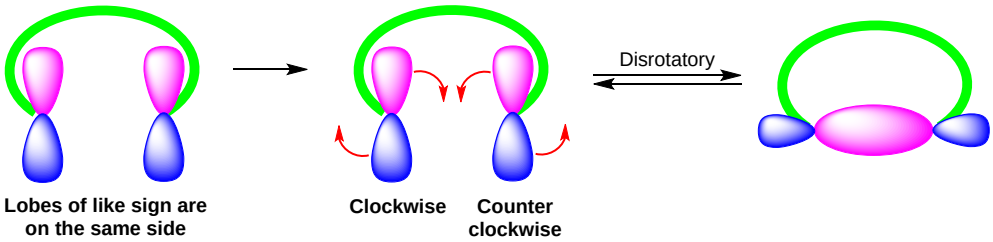
Similar results are seen with the 4 pi electrocyclic reaction of *cis*,*trans*-2,4-hexadiene being heated to exclusively form *cis*-3,4-dimethylcyclobutene and being irradiated with UV light to exclusively form *trans*-3,4-dimethylcyclobutene. Likewise, *trans*,*trans*-2,4-hexadiene forms *trans*-3,4-dimethylcyclobutene when heated and *cis*-3,4-dimethylcyclobutene when being irradiated with UV light.



The stereospecificity of electrocyclic reaction can be explained by considering the terminal lobes of the molecular orbital for the conjugated pi-electron system. For electrocyclic reactions to occur, molecular orbital lobes with the same sign from the HOMO of the molecule must rotate to form/break the key ring sigma bond. If the orbital lobes involved both rotate in the same direction (both counterclockwise or both clockwise), the process is called conrotatory. This typically occurs when orbital lobes of the same sign are on opposite sides of the molecule.



If the orbitals involved rotate in opposite directions (one clockwise and one counterclockwise), the process is called disrotatory. These differences in rotation are critically important when stereocenters are formed or broken. This typically occurs when orbital lobes of the same sign are on the same side of the molecule.

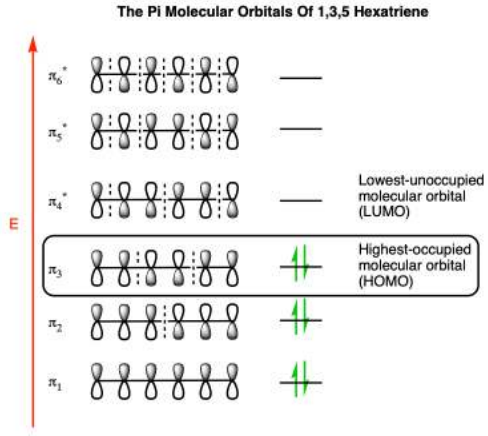


9.2: Electrocyclic Reactions is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer, Dietmar Kennepohl, William Reusch, Kevin M. Shea, & Kevin M. Shea.

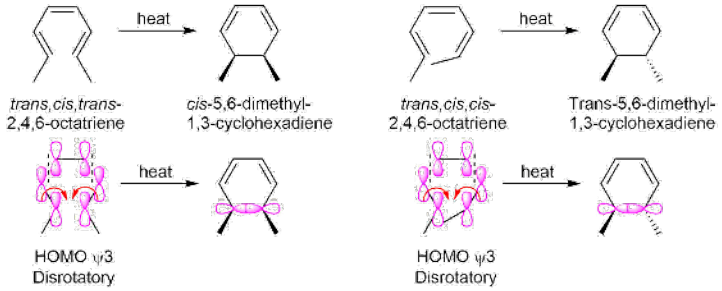
9.3: Stereochemistry of Thermal Electrocyclic Reactions

Frontier orbital theory can be used to predict the stereochemistry of electrocyclic reactions. Electrons in the HOMO are the highest energy and therefore the most easily moved during a reaction. A molecular orbital diagram can be used to determine the orbital symmetry of a conjugated polyene's HOMO. Thermal reactions utilize the HOMO from the ground-state electron configuration of the molecular orbital diagram while photochemical reactions utilize the HOMO in the excited-state electron configuration.

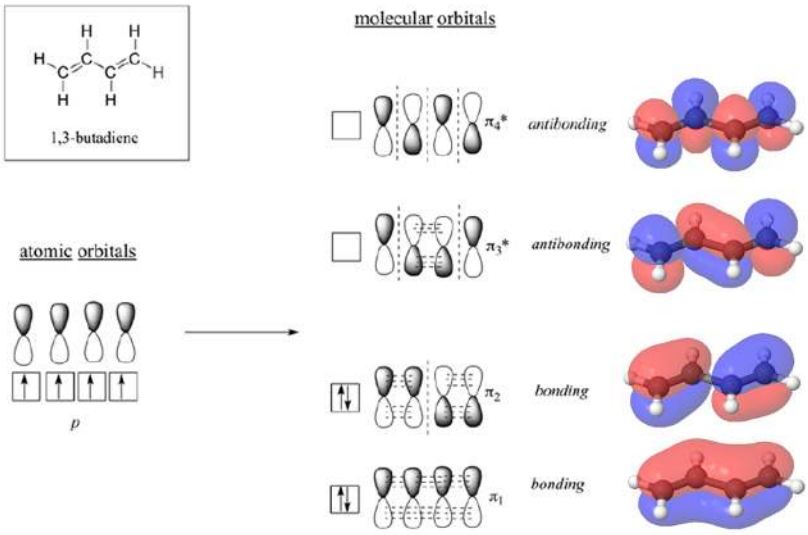
The molecular orbital of 1,3,5-hexatriene in its ground state electron configuration has psi three as its HOMO. The terminal molecular orbital lobes of the HOMO with the same sign are on the same side which predicts disrotatory ring closure under thermal conditions.



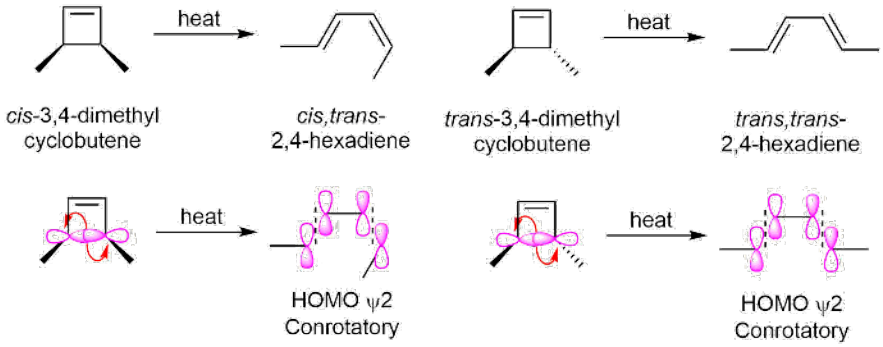
Disrotatory cyclization is observed during the electrocyclic reaction of 2,4,6-octatriene. The *trans,cis,cis*-2,4,6-octatriene isomer produces *cis*-5,6-dimethyl-1,3-cyclohexadiene as the product of thermal cyclization while the *trans,cis,cis*-2,4,6-octatriene isomer produces *trans*-5,6-dimethyl-1,3-cyclohexadiene.



The molecular orbital of a conjugated diene, such as 1,3-butadiene has psi two as the HOMO in its ground state electron configuration. The terminal molecular orbital lobes of the HOMO with the same sign are on opposite sides which predicts conrotatory ring closure under thermal conditions. However, the equilibrium of the electrocyclic reaction only allows for the ring opening to be observed.



Thus heating *cis*-3,4-dimethylcyclobutene causes the conrotatory ring opening to form *cis*,*trans*-2,4-hexadiene. Likewise, *trans*-3,4-dimethylcyclobutene forms *trans*,*trans*-2,4-hexadiene when heated.



A pattern begins to form revealing a relationship between the number of double bonds in the conjugated polyene and the rotation during electrocyclic reactions. For thermal electrocyclic reactions, polyenes with an odd number of double bonds undergo disrotation and those with an even number of double bond undergo conrotation.

? Exercise 9.3.1

The thermal electrocyclic ring opening of *trans*-3,4-dimethylcyclobutene could form *trans*,*trans*-2,4-hexadiene or *cis*,*cis*-2,4-hexadiene. However, the *trans*,*trans*-2,4-hexadiene is the isomer obtained from the reaction. Explain how it is possible to get both products and why the *trans*,*trans*-2,4-hexadiene is preferred.

Answer

Dienes undergo conrotation during thermal electrocyclic ring opening. Conrotation means the orbital nodes both rotate in the same direction either both clock with or both counter clockwise. If the nodes both rotate counter clockwise the *trans*,*trans*-2,4-hexadiene isomers forms. If they both rotate clockwise the *cis*,*cis*-2,4-hexadiene isomer is formed. Trans double bonds are more stable than cis due to steric strain. The *trans*,*trans*-2,4-hexadiene is perferably formed because it is more stable.

? Exercise 9.3.2

If a conjugated tetraene were to undergo a thermal electrocylic reaction would the orbital nodes undergo con or disrotation?

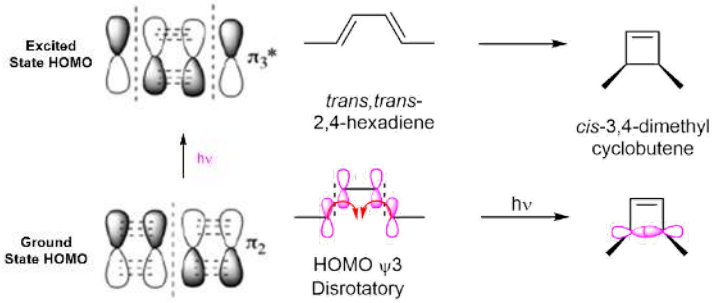
Answer

A tetraene has an even number of double bonds so it would be expected to undergo conrotation.

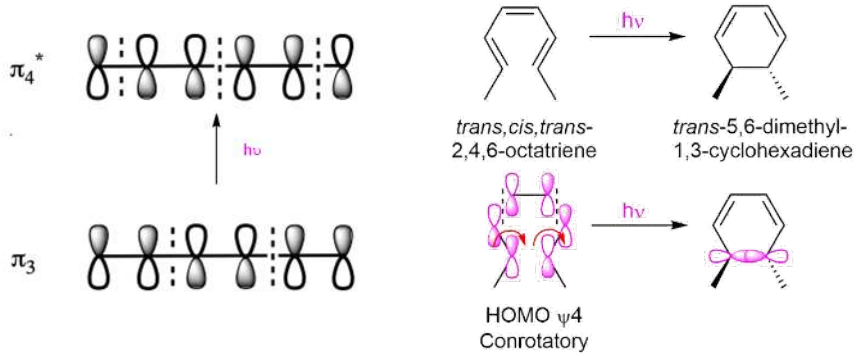
9.3: Stereochemistry of Thermal Electrocyclic Reactions is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer & Kevin M. Shea.

9.4: Photochemical Electrocyclic Reactions

Irradiation of a conjugated polyene with ultraviolet light causes an electron from the groud-state HOMO to be excited to the ground state LUMO. This creates a new higher energy HOMO in an electron configuration called the excited state. Electron excitation changes the symmetry of the new HOMO which has a corresponding effect on the reaction stereochemistry. Under photochemical reaction conditions conjugated dienes undergo disrotatory cyclization whereas under thermal conditions they underwent conrotatory cyclization. Likewise, conjugated triene undergo conrotatory photochemical cyclization while undergoing disrotatory thermal cyclization. For example, trans,trans-2,4-hexadiene undergoes conrotatory photochemical cyclization to form *cis*-3,4-dimethylcyclobutene.



The conjugated tirene, *trans*,*cis*,*trans*-2,4,6-octatriene undergoes conrotation to form *trans*-5,6-dimethyl-1,3-cyclohexadiene during photochemical cyclization.



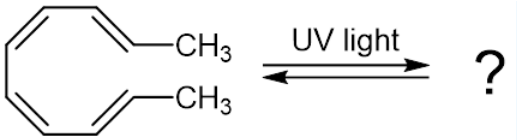
Generalized Statement of Woodward-Hoffmann Rules for Electrocyclic Reactions

Thermal and photochemical electrocyclic reactions always produce the opposite stereochemistry products due to the difference in symmetries in their HOMO frontier orbitals. This idea can be combined with the trend of even and odd polyenes to provide simple rules to predict the stereochemistry of electrocyclic reactions.

Number of Double Bonds	Thermal	Photochemical
Odd	Disrotatory	Conrotatory
Even	Conrotatory	Disrotatory

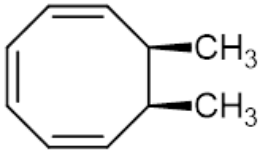
? Exercise 9.4.1

Would the following electrocyclic reaction be con or disrotatory? Please draw the expected product.



Answer

An even number of double bonds in photochemical conditions predicts a disrotatory reaction.



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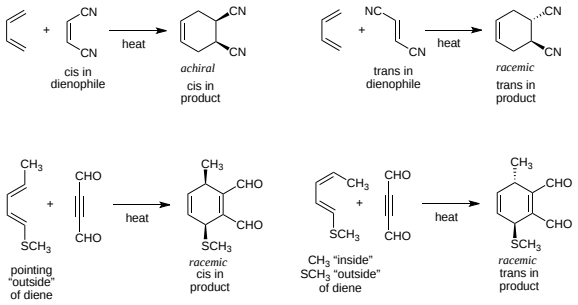
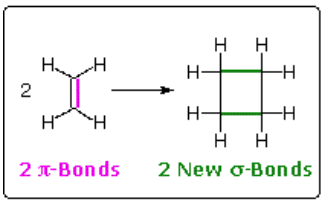
9.5: Cycloaddition Reactions

A concerted combination of two pi-electron systems to form a ring of atoms having two new σ bonds and two fewer pi bonds is called a **cycloaddition reaction**. The number of participating pi-electrons in each component is given in brackets preceding the name of the reaction. The Diels-Alder reaction is the most useful cycloaddition reaction due to the ubiquity of 6-membered rings and its ability to reliably control stereochemistry in the product. In the Diels-Alder cycloaddition reaction, a conjugated diene, simply referred to as the **diene**, reacts with a double or triple bond coreactant called the **dienophile**, because it combines with (has an affinity for) the diene. The Diels-Alder reaction is a [4+2] cycloaddition (4 pi electrons from the diene and 2 pi electrons from the dienophile) that yields a functionalized 6-membered ring product. During the Diels-Alder reaction, two pi-bonds are converted to two sigma-bonds.

Due to the concerted mechanism for cycloaddition reactions, the geometry of atoms on the dienophile or the diene maintain their orientation in the product. This is a critical point for the 4 atoms (both dienophile atoms and the terminal atoms of the diene) that become sp^3 hybridized and thus are potential stereocenters in the product. (As a reminder, when chiral products are formed, we obtain a racemic mixture of enantiomers.) As highlighted below, cis dienophiles yield cis substituents in the product, while trans dienophiles yield trans product substituents. Substituents on the terminal atoms of the diene also can become stereocenters and this analysis is a little less straightforward than for dienophile substituents. The way to think about the diene substituents is whether the are pointing "outside" or "inside" the diene. These orientations are illustrated below. When groups are both pointing "outside" or "inside", we can consider them to be cis and they will end up cis in the product. When one group is pointing "outside" and one "inside", we can consider them as trans and they will be trans in the product.



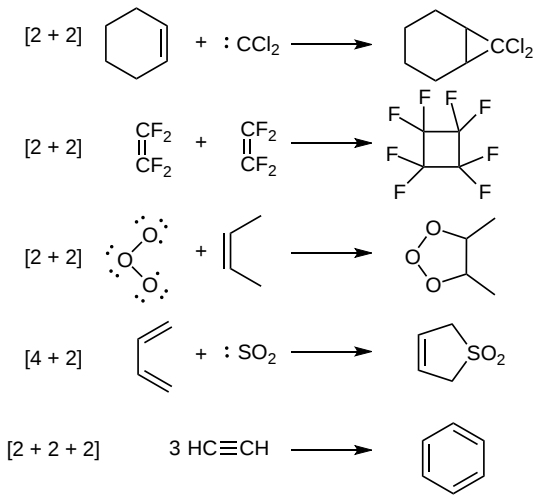
Another important reaction is the [2+2] cycloaddition of two alkene containing molecules to form a 4-membered cyclobutane ring. The [2 + 2] cycloaddition of two alkenes does not occur by simply heating but can only be achieved by *irradiation* with ultraviolet light.



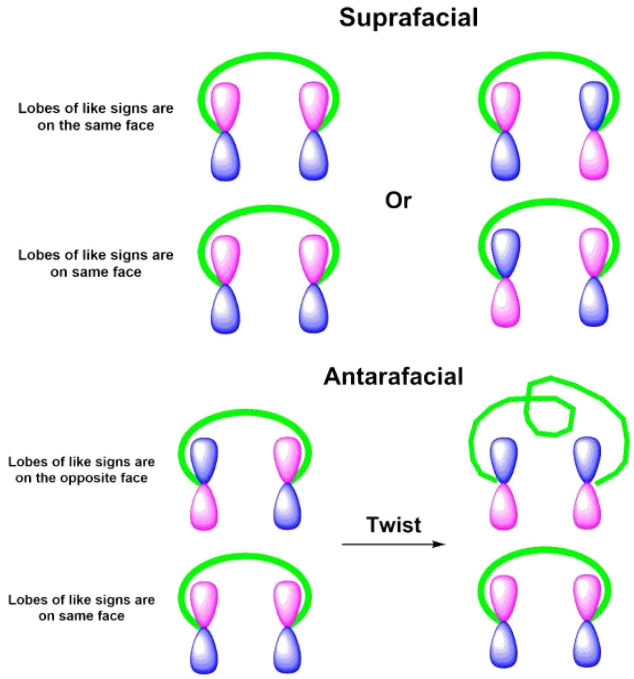
A [2+2] Cycloaddition

Photo [2+2] Cycloaddition

Many other cycloadditions are known, such as [2 + 2 + 2], and other types of [2 + 2], which give different size of rings. Some specific examples are shown below:



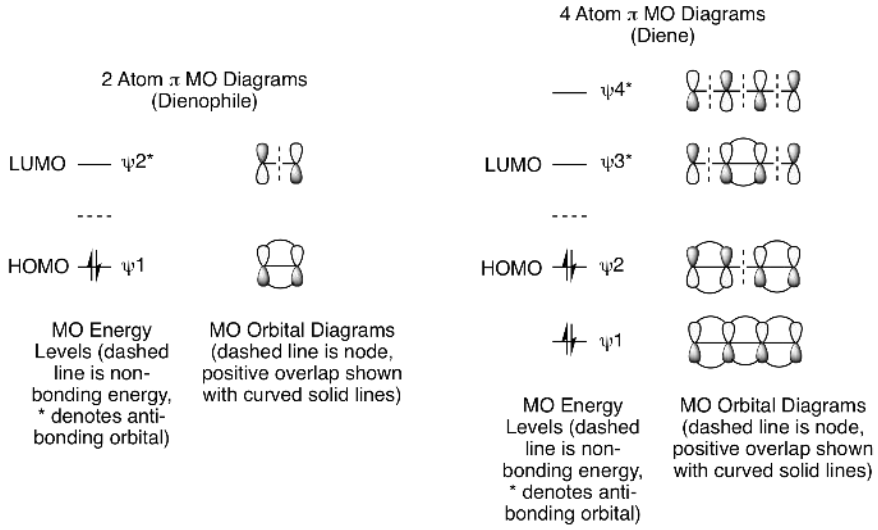
Like other pericyclic reactions, cycloadditions are determined by the orbital symmetry of the frontier orbitals of the reactants. For bonding to occur in a cycloaddition, the terminal lobes of the frontier orbitals of the two pi systems must have the correct symmetry. Correct symmetry can be obtained in two different ways. If the signs on the orbital lobes are the same on the faces of both reactants then the reaction undergoes a **suprafacial cycloaddition**. If the signs of the orbital lobes are the same on the face of one reactant but opposite on the other reactant then the reaction undergoes an **antarafacial cycloaddition**. Although both types are symmetry allowed, the fact that antarafacial cycloadditions require the twisting of a pi orbital system makes them more difficult to achieve.



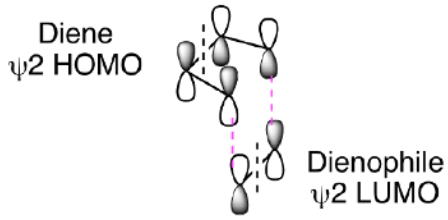
9.5: Cycloaddition Reactions is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer, Marjorie C. Caserio, Kevin M. Shea, & Kevin M. Shea.

9.6: Stereochemistry of Cycloadditions

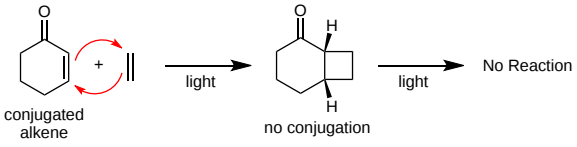
Frontier orbital theory can be used to predict if a given cycloaddition will occur with suprafacial or with antarafacial geometry. In a standard Diels-Alder reaction, bonding interactions are created when the electron containing HOMO of the diene donates electrons to the electron vacant LUMO of the other the dienophile. The dienophile has one pi bond, so it will use the pi MOs for a 2 atom system. The dienophile has 2 pi electrons which makes psi 2* its LUMO. The diene has two pi bonds, so it will use the pi MOs for a 4 atom system. The diene has has 4 pi electrons makes psi 2 its HOMO.



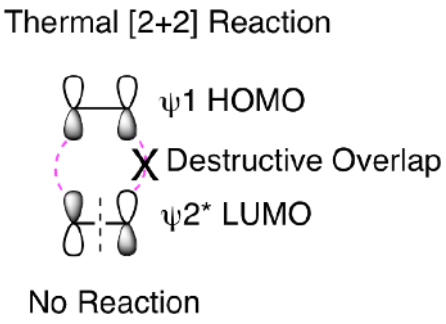
These MO diagrams show that the ground-state frontier orbitals of both reactants have terminal lobes with matching signs. The symmetry of these orbitals are such that bond formation will easily occur under thermal conditions with suprafacial geometry as shown below. (Note: The dashed black lines in the figure below represent nodes in the pi molecular orbitals of the diene and dienophile.) The two new sigma bonds, shown as dashed magenta lines below, are formed from constructive overlap of the terminal dienophile orbitals with the terminal orbitals of the diene.



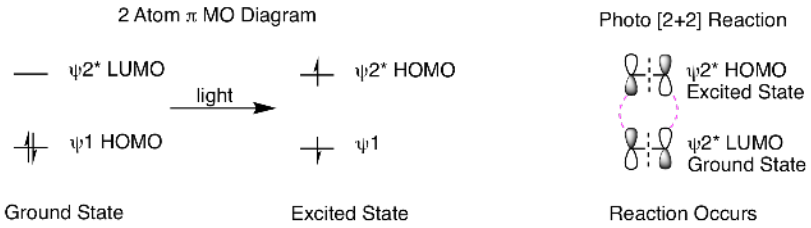
Photochemical [2+2] cycloadditions are excellent reactions for the synthesis of strained products containing 4-membered rings. One of the reaction partners must be conjugated so that it can absorb light and become an excited state molecule. These reactions produce strained 4-membered rings but are not reversible because the products lack conjugation and, thus, can't absorb light to facilitate a cycloreversion.



So, why won't this reaction happen thermally? How does our molecular orbital analysis help us understand the importance of this being a photochemical reaction? First, let's look at the orbital analysis if we tried to do a thermal [2+2] reaction. As shown below, we cannot get suprafacial overlap for both of the 2 pi reactants when trying to combine psi 1 HOMO with psi 2* LUMO. This means that it is not favorable to convert the two reactant pi bonds into two new product pi bonds.



What happens when we shine light on the reaction? Light creates an excited state molecule by promoting an electron in the HOMO to the LUMO, as shown below. This means the excited state HOMO is the ground state LUMO. We need to understand a few key points about photoreactions before doing our molecular orbital analysis. Excited state molecules are very short lived, relaxing back to the ground state very quickly. Therefore, it is practically impossible for two excited state molecules to find each other in a reaction. Instead, reactions occur between one excited state molecule and one ground state molecule. When only one molecule is conjugated, that is the molecule that will form the excited state. If both reactants are conjugated, either can form the excited state. The orbital analysis is shown below. First, we see the orbital picture when a ground state molecule absorbs light to form an excited state. Second, when we analyze the reaction, it is now psi 2* HOMO of the excited state molecule reacting with psi 2* LUMO of the ground state molecule. This gives suprafacial constructive overlap for both orbitals and the 2 reactant pi bonds can be converted into two product sigma bonds.



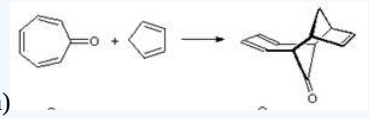
Cycloaddition reactions can be categorized based on the total number electrons involved in the rearrangement. The [4+2] Diels-Alder reaction involves 6 electrons and takes place using a suprafacial pathway under thermal conditions. The thermal [2+2] cycloaddtion of two alkenes involves 4 electrons and must take place by antarafacial pathway. However, the pathway is reversed for photochemical [2+2] cycloaddtions which take place by a supraficial pathway. These ideas can be generalized using the rules for cycloadditions below.

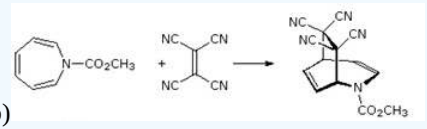
Generalized Statement of Woodward-Hoffmann Rules for Cycloadditions

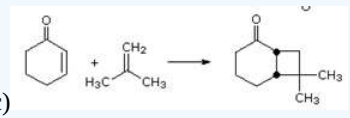
Number of Electrons	Thermal	Photochemical
4n + 2	Suprafacial (Allowed)	Antarafacial (Forbidden)
4n	Antarafacial (Forbidden)	Suprafacial (Allowed)

Exercise 9.6.1

1) For the following reactions determine what type of cycloaddition is occurring, is the reaction supra or antarafacial, and would the reaction require thermal or photochemical conditions.

a) 

b) 

c) 

Answer

a) [6+4], suprafacial, thermal.

b) [4+2], suprafacial, thermal.

c) [2+2], antarafacial, photochemical.

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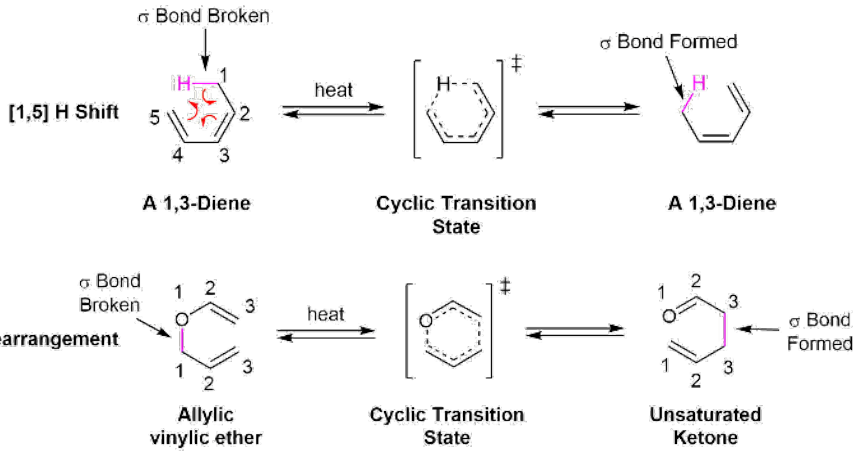
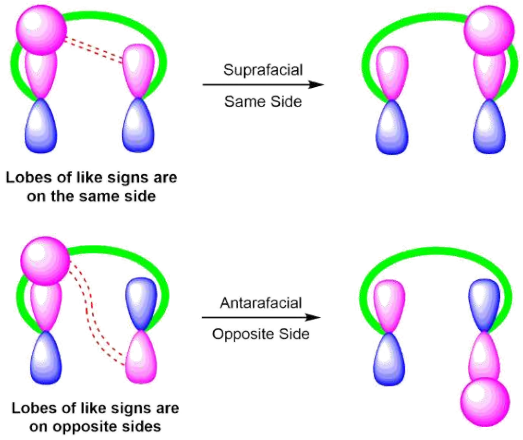
9.7: Sigmatropic Rearrangements (reference only)

Molecular rearrangements in which a σ-bonded atom or group, flanked by one or more π-electron systems, shifts to a new location with a corresponding reorganization of the π-bonds are called **sigmatropic reactions**. The reactant and product have the same number and type of bonds, just different bond locations. These rearrangements are described by two numbers set in brackets, which refer to the position of the sigma bond in the reactant that is broken compared to the position of the sigma bond in the product that is formed. The most common examples include hydrogen shifts across a diene system (called a [1,5] H shift) and rearrangements of double allyl-type systems (called [3,3] rearrangements).

As shown in the examples below, the atoms on the sigma bond in the reactant that is broken (magenta bond) are both labeled "1", and the numbering of atoms on each side of that sigma bond continue until the atoms connected by the new sigma bond in the product (magenta) are reached. Thus, the H shift is [1,5] because the key sigma bond in both the reactant and product is to the H while the H moves from C-1 to C-5. For the [3,3] rearrangement, the broken sigma bond migrates across two allyl-type systems and forms between atoms "3" and "3" in the product. This particular example is a Claisen rearrangement since an allyl vinyl ether is transformed into a 1,4-carbonyl alkene.



The migration of a group during a sigmatropic rearrangement is controlled by the orbital symmetries of the alkenes involved. Sigmatropic rearrangements can occur on one face of the molecule (think top or bottom, like a syn addition to an alkene) which is called a suprafacial reaction or from one face to the other (think from top to bottom or vice versa, like an anti addition to an alkene) which is called antarafacial. We will explore this idea further in the next section.



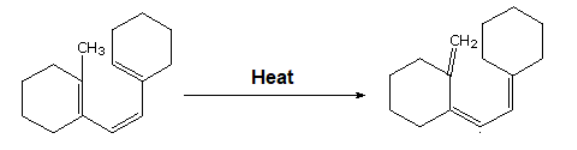
Generalized Statement of Woodward-Hoffmann Rules for Sigmatropic Rearrangements

Suprafacial and antarafacial sigmatropic rearrangements are considered symmetry-allowed by the Woodward-Hoffmann rules. However, suprafacial reactions are much more common. Note! These rules for sigmatropic rearrangements are the same as those given for cycloaddition reactions in **Section 30-3**.

Number of Double Bonds	Thermal	Photochemical
Odd	Suprafacial	Antarafacial
Even	Antarafacial	Suprafacial

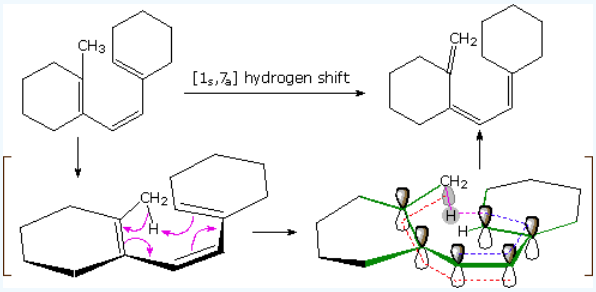
Exercise 9.7.1

For the following sigmatropic hydrogen shift please use braked number to discribe the reaction. Predict if the hydrogen shift will be suprafacial and antarafacial. Lastly, draw in arrows to discribe the mechanism for this reaction.



Answer

An example of an [1,7] hydrogen shift is shown in the following diagram. The conjugated alkene has three double bonds, which is an odd number, and the reaction is occuing under thermal conditions. This means the reaction is predicted to be suprafacial. The conjugated triene assumes a nearly planar coiled conformation in which a methyl hydrogen is oriented just above the end carbon atom of the last double bond. A [1_s,7_a] sigmatropic hydrogen shift may then take place, as described by the four curved arrows. With reference to the approximate plane of this π-electron system (defined by the green bonds), the hydrogen atom departs from the bottom face and bonds to the top face, so the transfer is antarafacial.



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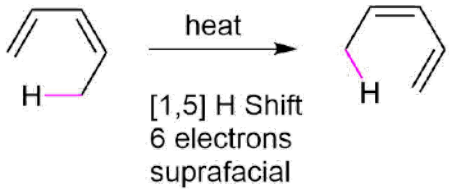
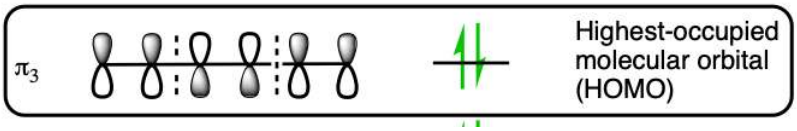
9.8: Some Examples of Sigmatropic Rearrangements (reference only)

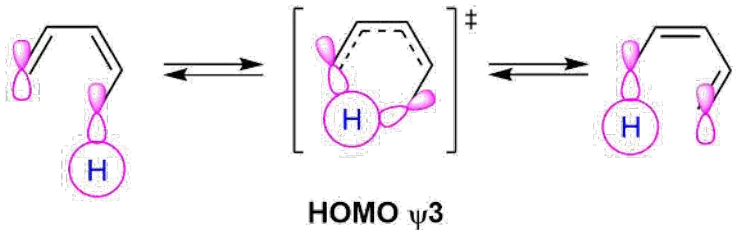
A sigmatropic rearrangement which involves a [1,5] hydrogen shift, like the one shown below illustrates, a hydrogen atom (s orbital) moving across a 5 atom system containing two conjugated double bonds. Since there are three curved arrows in the mechanism, this is a 6 pi reaction. The rules for sigmatropic rearrangements discussed in the last section predict the hydrogen atom will undergo a suprafacial shift. The C-H bond breaking and the C-H bond forming, magenta dashed lines, are both on the bottom face of the molecule's pi system.



The suprafacial nature of this reaction comes from the orbital symmetry of the HOMO from a 6 pi electron molecular orbital. The orbital lobes on the terminal ends have the same sign on the same side.

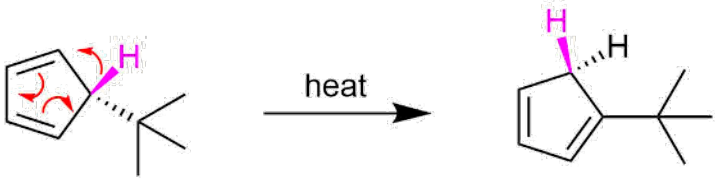


During the reaction mechanism the hydrogen atom, an s orbital, is passes from one molecular to another of the same sign on the same side of the molecule or suprafacial.



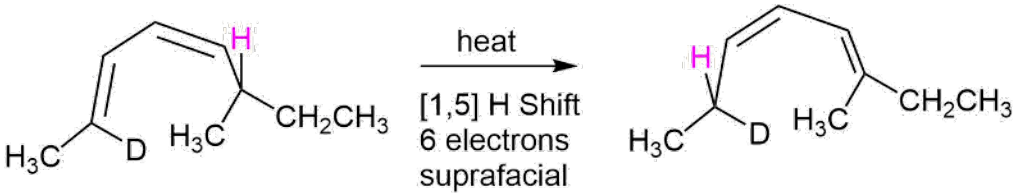
HOMO ψ3

For example, 5-*t*-butyl-1,3-cyclopentadiene easily undergoes a [1,5] suprafacial shift of a hydrogen atom under thermal conditions to yield 1-*t*-butyl-1,3-cyclopentadiene as a rearranged product.



[1,5] H Shift
Suprafacial

As another example, heating S-2-deuterio-6-methyl-(2E,4Z)-2,4-octadiene undergoes a thermal [1,5] suprafacial shift of a hydrogen to produce the product, R-2-deuterio-6-methyl-(2Z,4E)-3,5-octadiene with stereochemical control.



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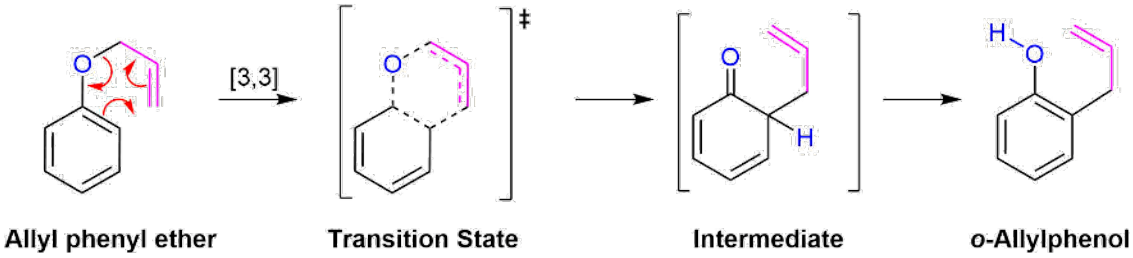
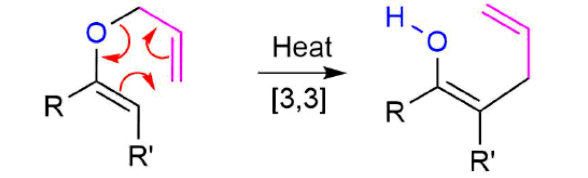
Claisen Rearrangement

A very important example of a [3,3] sigmatropic reaction is the **Claisen rearrangement** of an allyl aryl ether or an allyl vinyl ether (**Section 18-4**). Heating an allyl aryl ether to 250 °C causes an sigmatropic rearrangement to produce an *o*-allylphenol. This rearrangement initially produces the non-aromatic 6-allyl-2,4-cyclohexadienone intermediate which quickly undergoes a proton shift to reform the aromatic ring in the *o*-allylphenol product. Claisen rearrangement occurs in a six-membered, cyclic transition state involving the movement of six bonding electron.



Allyl phenyl ether **Transition State** **Intermediate** ***o*-Allylphenol**

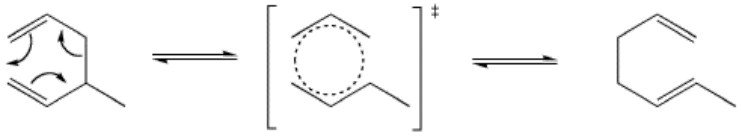
Allyl vinyl ethers can also undergo a Claisen rearrangement when heated to form gamma, delta -unsaturated ketones or aldehydes.



An allyl vinyl ether **An unsaturated Ketone**

Cope Rearrangement

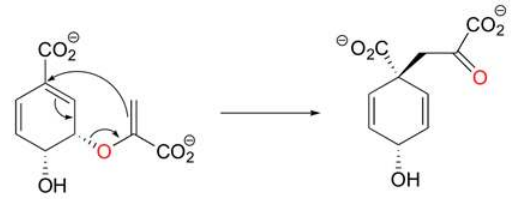
Another important example of a [3,3] sigmatropic reaction is the **cope rearrangement**. This reaction converts between isomers of a 1,5-hexadiene through a cyclic transition state.



Both Cope and Claisen rearrangements involve the movement of six electrons which means they both react by suprafacial pathways under thermal conditions. These reactions can be considered to occur due to changes in overlap between orbitals around the cyclic transition state. Two orbitals which form the sigma bond being broken tilt away from each other while two orbitals that are pi bonding tilt toward each other to from a new sigma bond. After the change there are now two p orbitals parallel to each other on the left which then form new pi bonds.

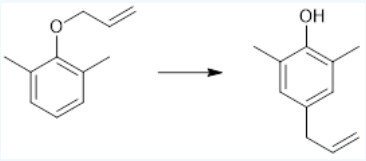
Orbital rearrangement in a Cope rearrangement

Sigmatropic rearrangements are rare in biological chemistry. One example is the chorismate mutase catalyzed Claisen rearrangement of chorismate (a allylic vinyl ether) to form prephenate. Prephenate is a precursor in the biosynthetic pathway of aromatic amino acids phenylalanine and tyrosine.



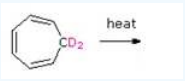
Exercise 9.8.1

1) A Claisen rearrangement performed in the presence of ortho-substituents exclusively leads to para-substituted rearrangement products. This occurs via a Claisen rearrangement followed by a Cope rearrangement. Draw out the intermediates formed during this transformation and the mechanims for both rearrangments.

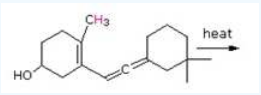


2) Please draw the expected products of the following [1,5] suprafacial shifts.

a)

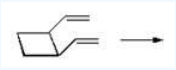


b)



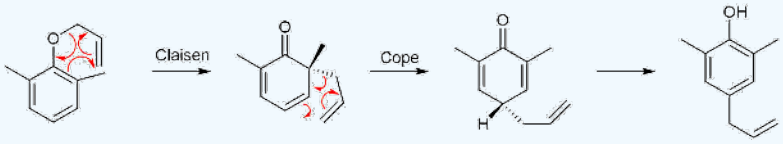
3) Please draw the product of the following [3,3] suprafacial shifts.

a)



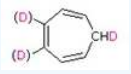
Answer

1)

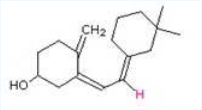


2)

a)



b)



3)

a)

9.8: Some Examples of Sigmatropic Rearrangements (reference only) is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer & Kevin M. Shea.

9.9: A Summary of Rules for Pericyclic Reactions

Before pericyclic reactions can be put to use in a predictable and controlled manner, a broad mechanistic understanding of the factors that influence these concerted transformations must be formulated. The simplest, albeit least rigorous, method for predicting the configurational path favored by a proposed pericyclic reaction is based upon a transition state electron count. In most of the earlier examples, pericyclic reactions were described by a cycle of curved arrows, each representing a pair of bonding electrons. The total number of electrons undergoing reorganization is always even, and is either a **4n+2** or **4n** number (where n is an integer). Once this electron count is made, the following table may be used for predictions. It is important to remember that going from thermal to photochemical conditions or going from 4n to 4n+2 reaction electrons changes the outcome of the reaction.

	Electron Count	**Stereochemistry**
Thermal Reactions (Ground State)	**4n + 2**	Suprafacial or Disrotatory
	4n	Antarafacial or Conrotatory
	Electron Count	**Stereochemistry**
Photochemical Reactions (Excited State)	**4n + 2**	Antarafacial or Conrotatory
	4n	Suprafacial or Disrotatory

? Exercise 9.9.1

Predict the stereochemistry of the following reactions:

a. The photochemical cyclization of a conjugated tetraene.
b. The thermal cyclization of a conjugated tetraene
c. A thermal [4+4] cycloaddition
d. A photochemical [2+5] cycloaddition
e. A thermal [3,5] sigmatropic rearrangement

Answer

a) Disrotatory

b) Conrotatory

c) Antarafacial

d) Suprafacial

e) Antarafacial

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CHAPTER OVERVIEW

10: Benzene and Aromaticity

Learning Objectives

After you have completed Chapter 10, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. use the information presented in this chapter, along with material from earlier chapters, to solve problems, particularly road-map problems and those requiring an understanding of spectroscopy.
3. explain the concept of aromaticity and the stability of aromatic compounds.
4. define, and use in context, the key terms introduced.

Chapter Videos

This video provides an introduction to the concept of aromaticity.

In CHM 222, we identified an aromatic compound as being a compound which contains a benzene ring (or phenyl group). It is now time to define aromaticity in a more sophisticated manner. In this chapter, we discuss the stability of benzene and other aromatic compounds, explaining it in terms of resonance and molecular orbital theory. You will study the nomenclature of aromatic compounds and the Hückel ($4n + 2$) rule for predicting aromaticity. The chapter concludes with a brief summary of the spectroscopic properties of arenes.

10.1: Introduction
10.2: Naming Aromatic Compounds
10.3: Structure and Stability of Benzene
10.4: Aromaticity and the Hückel 4n + 2 Rule
10.5: Aromatic Ions
10.6: Aromatic Heterocycles - Pyridine and Pyrrole
10.7: Polycyclic Aromatic Compounds
10.8: Spectroscopy of Aromatic Compounds (CHM 222 topic)
10.S: Benzene and Aromaticity (Summary)

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10.1: Introduction

Objectives

After completing this section, you should be able to

1. explain what is meant by the term “aromatic compound.”
2. identify the aromatic portions present in naturally occurring compounds, given the necessary structures.

Key Terms

Make certain that you can define, and use in context, the key term below.

- aromatic

Study Notes

At this point in the course, we shall use the term *aromatic* to describe those compounds which contain a benzene ring. A broader definition of aromaticity will be given later in this chapter.

The 100 Year Mystery of Benzene

It took humans over 100 years to determine and confirm the structure of benzene. Why did it take so long? Why was there such a curiosity? The 1:1 ratio of carbon to hydrogen in the empirical formula and low chemical reactivity of benzene were a paradox to chemists in the early 1800s. In 1825, Michael Faraday isolated an oily residue of gas lamps. Faraday called this liquid "bicarburet of hydrogen" and measured the boiling point to be 80 °C. Additionally, Faraday determined the empirical formula to be CH. About nine years later, Eilhard Mitscherlich synthesized the same compound from benzoic acid and lime (CaO).

During the mid to late 1800's, several possible structures (shown below) were proposed for benzene.

It was not until the 1930's that Kekule's structure was confirmed by X-ray and electron diffraction. During the end of Kekule's career he revealed that the structure came to him in a vision after enjoying a glass or two of wine by the fire in his favorite chair. His inspiration for the structure of benzene was derived from an ouroboros (a snake eating its own tail) in the flames.

Benzene, C_6H_6, is the simplest member of a large family of hydrocarbons, called aromatic hydrocarbons. These compounds contain ring structures and exhibit bonding that must be described using the resonance hybrid concept of valence bond theory or the delocalization concept of molecular orbital theory. (To review these concepts, refer to the earlier chapters on chemical bonding). The resonance structures for benzene, C_6H_6, are:

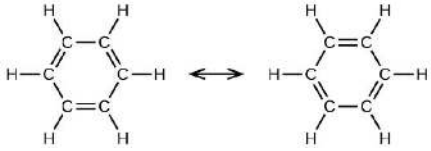


Figure 10.1.1.

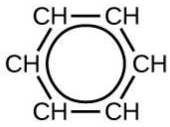
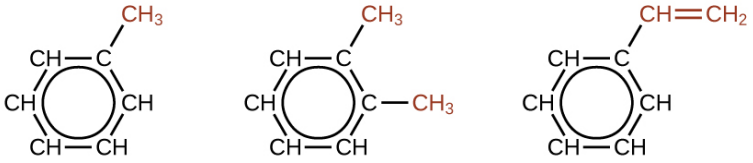


Figure 10.1.2: This condensed formula shows the unique bonding structure of benzene.

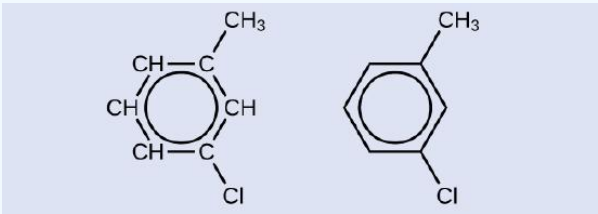
There are many derivatives of benzene. The hydrogen atoms can be replaced by many different substituents. Aromatic compounds more readily undergo substitution reactions than addition reactions; replacement of one of the hydrogen atoms with another substituent will leave the delocalized double bonds intact. The following are typical examples of substituted benzene derivatives:



Toluene and xylene are important solvents and raw materials in the chemical industry. Styrene is used to produce the polymer polystyrene.

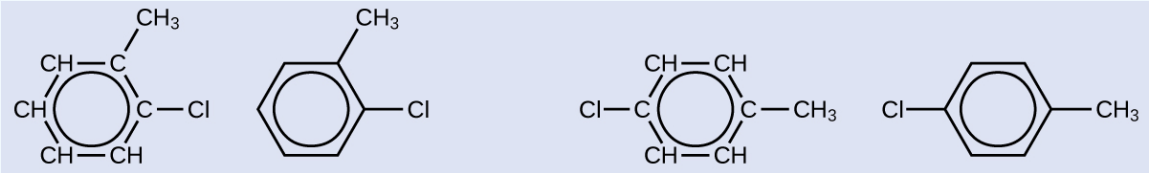
Structure of Aromatic Hydrocarbons

One possible isomer created by a substitution reaction that replaces a hydrogen atom attached to the aromatic ring of toluene with a chlorine atom is shown here. Draw two other possible isomers in which the chlorine atom replaces a different hydrogen atom attached to the aromatic ring:



Solution

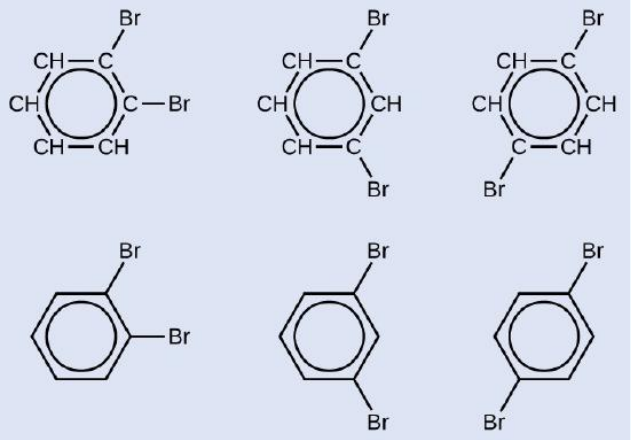
Since the six-carbon ring with alternating double bonds is necessary for the molecule to be classified as aromatic, appropriate isomers can be produced only by changing the positions of the chloro-substituent relative to the methyl-substituent:



Exercise 10.1.1

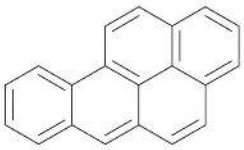
Draw three isomers of a six-membered aromatic ring compound substituted with two bromines.

Answer



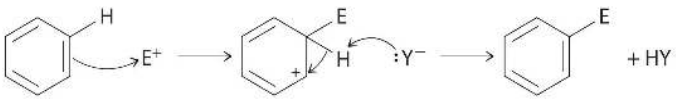
Most arenes that contain a single six-membered ring are volatile liquids, such as benzene and the xylenes, although some arenes with substituents on the ring are solids at room temperature. In the gas phase, the dipole moment of benzene is zero, but the presence of electronegative or electropositive substituents can result in a net dipole moment that increases intermolecular attractive forces and raises the melting and boiling points. For example, 1,4-dichlorobenzene, a compound used as an alternative to naphthalene in the production of mothballs, has a melting point of 52.7 °C, which is considerably greater than the melting point of benzene (5.5 °C).

Certain aromatic hydrocarbons, such as benzene and benz[a]pyrene, are potent liver toxins and carcinogens. In 1775, a British physician, Percival Pott, described the high incidence of cancer of the scrotum among small boys used as chimney sweeps and attributed it to their exposure to soot. His conclusions were correct: benz[a]pyrene, a component of chimney soot, charcoal-grilled meats, and cigarette smoke, was the first chemical carcinogen to be identified.



Benz[a]pyrene

Although arenes are usually drawn with three C=C bonds, benzene is about 150 kJ/mol more stable than would be expected if it contained three double bonds. This increased stability is due to the delocalization of the pi electron density over all the atoms of the ring. Compared with alkenes, arenes are poor nucleophiles. Consequently, they do not undergo addition reactions like alkenes; instead, they undergo a variety of electrophilic aromatic substitution reactions that involve the replacement of –H on the arene by a group –E, such as $–NO_2$, $–SO_3H$, a halogen, or an alkyl group, in a two-step process. The first step involves addition of the electrophile (E) to the pi system of benzene, forming a carbocation. In the second step, a proton is lost from the adjacent carbon on the ring:



The carbocation formed in the first step is stabilized by resonance.

> *Arenes undergo substitution reactions rather than elimination because of increased stability arising from delocalization of their π electron density.*

Many substituted arenes have potent biological activity. Some examples include common drugs and antibiotics such as aspirin and ibuprofen, illicit drugs such as amphetamines and peyote, the amino acid phenylalanine, and hormones such as adrenaline.

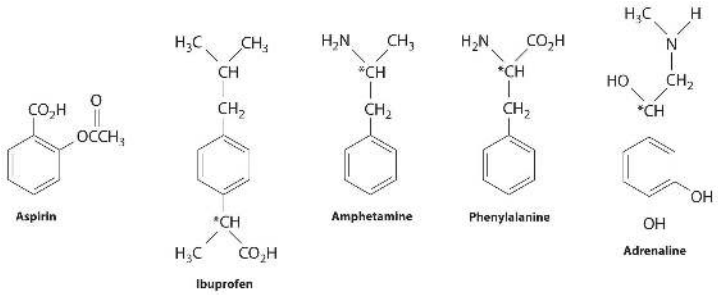


Figure 10.1.3*: Biologically Active Substituted Arenes*

Aspirin (antifever activity), ibuprofen (antifever and anti-inflammatory activity), and amphetamine (stimulant) have pharmacological effects. Phenylalanine is an amino acid. Adrenaline is a hormone that elicits the "fight or flight" response to stress. Chiral centers are indicated with an asterisk.

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10.2: Naming Aromatic Compounds

Objectives

After completing this section, you should be able to

1. draw the structure of each of the common aromatic compounds in Figure 1 (Common benzene derived compounds with various substituents), given their IUPAC-accepted trivial names.
2. write the IUPAC-accepted trivial name for each of the compounds in Figure 1, given the appropriate Kekulé, condensed or shorthand structure.
3. identify the ortho, meta and para positions in a monosubstituted benzene ring.
4. use the ortho/meta/para system to name simple disubstituted aromatic compounds.
5. draw the structure of a simple disubstituted aromatic compound, given its name according to the ortho/meta/para system.
6. provide the IUPAC name of a given aromatic compound containing any number of the following substituents: alkyl, alkenyl or alkynyl groups; halogens; nitro groups; carboxyl groups; amino groups; hydroxyl groups.
7. draw the structure of an aromatic compound containing any number of the substituents listed in Objective 6, above, given the IUPAC name.
8. provide the IUPAC name of a given aromatic compound in which the phenyl group is regarded as a substituent.
9. draw the Kekulé, condensed or shorthand structure of an aromatic compound in which the phenyl group is regarded as a substituent, given its IUPAC name.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- arene
- benzyl group
- phenyl group

Study Notes

You should already know the names and structures of several of the hydrocarbons shown in Figure 1. A compound containing a benzene ring which has one or more alkyl substituents is called an arene.

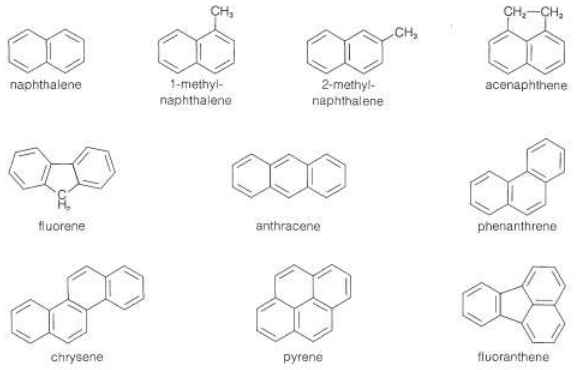
A phenyl group consists of a benzene ring with one of its hydrogens removed.

You should memorize the structures and formulas shown in Figure 1. You will meet these compounds frequently throughout the remainder of this course.

Note that the ortho/meta/para system cannot be used when more than two substituents are present in the benzene ring. The “numbering system” can be used instead of the ortho/meta/para system in most cases when only two substituents are present.

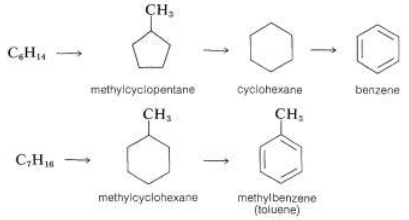
Sources of Aromatic Compounds

Initially aromatic compounds were isolated from coal tar. Coal tar, which is a distillate obtained when heating coal at 1000 ^{o}C in the absence of air, is a source of an amazing number of aromatic compounds. Many simple aromatic compounds, some of which include nitrogen, oxygen, and sulfur, as well as hydrocarbons are obtained.



Some of the Aromatic Compounds Obtained from Coal Tar

Prior to World War II, coal tar was the only important source of aromatic hydrocarbons, but during the war the demand for benzene and toluene, a precursor to the explosive TNT, rose so sharply that other sources had to be found. Today, most of the benzene and almost all of the toluene produced in the United States are derived from petroleum. Although petroleum does contain some aromatic compound, it is primarily made up of alkanes of various chain lengths. Aromatic compounds are synthesized from petroleum the by a process referred to in the petroleum industry as catalytic re-forming or hydroforming. This involves heating a C6-C10 alkane fraction of petroleum with hydrogen in the presence of a catalyst to modify the molecular structure of its components. Some amazing transformations take place, and the C6-C7 alkanes can be converted to cycloalkanes, which, in turn, are converted to arenes. Benzene, and methylbenzene (toluene) are produced primarily in this way.



Nomenclature of Mono-Substituted Benzenes

Unlike aliphatic organics, nomenclature of benzene-derived compounds can be confusing because a single aromatic compound can have multiple possible names (such as common and systematic names) be associated with its structure. Common names are often used in the nomenclature of aromatic compounds. IUPAC still allows for some of the more widely used common name to be used. A partial list of these common name is shown in Figure 1 and there are numerous others. These common names take the place of the benzene base name. Methylbenzene is commonly known with the base name toluene, hydroxyphenol is known as phenol etc. It is very important to be able to identify these structures as they will be utilized in the nomenclature of more complex compounds.

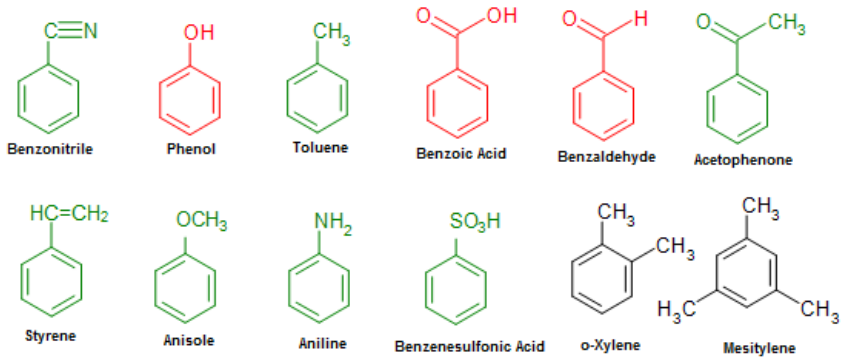
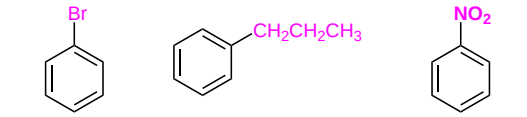


Figure 10.2.1: Common Names for Mono-Substituted and Poly-Substituted Benzenes

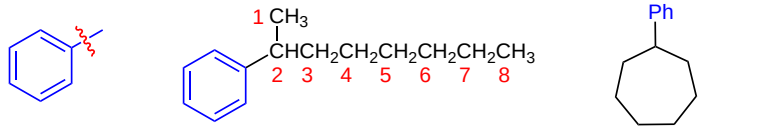
Mono-substituted benzene rings, with a substituent not on the list above, are named with benzene being the parent name. These compounds are named as such: *Name of the substituent + Benzene.*



Bromobenzene **Propyl**benzene **Nitro**benzene

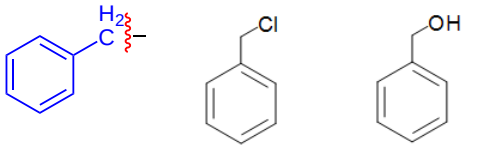
The use of Phenyl and Benzyl in Nomenclature

If the alkyl group attached to the benzene contains seven or more carbons the compounds is named as a phenyl substituted alkane. The name phenyl (C_6H_5-)is often abbreviated (Ph) and comes from the Greek word **pheno** which means "I bear light". This name commemorates the fact that benzene was first isolated by Michael Faraday in 1825 from the residue left in London street lamps which burned coal gas. If the alkyl substituent is smaller than the benzene ring (six or fewer carbons), the compound is named as an alkyl-substituted benzene following the rules listed above.



Phenyl group **2-Phenyl**octane **Phenyl**cycloheptane

The benzyl group (abbv. Bn), similar to the phenyl group and can be written as $C_6H_5CH_2$-R, $PhCH_2$-R, or Bn-R. Nomenclature of benzyl group based compounds are very similar to the phenyl group compounds. For example, a chlorine attached to a benzyl group would simply be called benzyl chloride, whereas an OH group attached to a benzyl group would simply be called benzyl alcohol.

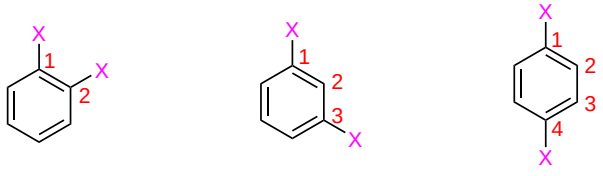


Benzyl group **Benzyl Chloride** **Benzyl Alcohol**

Nomenclature of Disubstituted Benzenes

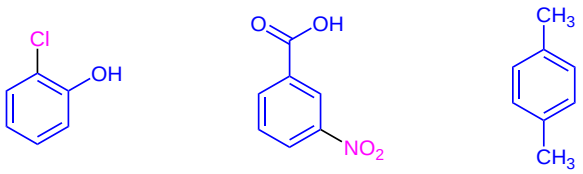
With disubstituted benzenes there are three distinct positional isomers which can occur and must be identified in the compounds name. Although numbering can be used to indicate the position of the two substituents it is much more common for the compounds to be named using prefixes. These prefixes are italicized and are often abbreviated with a single letter. They are defined as the following:

- ***ortho- (o-):*** 1,2- (next to each other in a benzene ring)
- ***meta- (m):*** 1,3- (separated by one carbon in a benzene ring)
- ***para- (p):*** 1,4- (across from each other in a benzene ring)



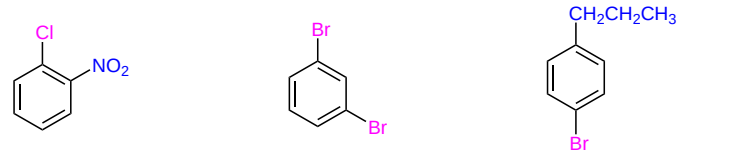
***ortho*-Disubstituted (1,2)** ***meta*-Disubstituted (1,3)** **para-Disubstituted (1,4)**

Figure 10.2.2. If any do appear then the compound is not named as a benzene but with a different parent name. These compounds are named as such: *Position prefix-Name of the substituent + Name of parent chain.*



ortho-Chlorophenol **meta-Nitrobenzoic acid** **para-Xylene**

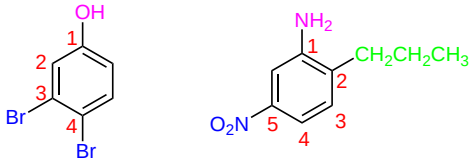
Figure 10.2.3 the compound is named as such: *Position prefix-Names of the substituents in alphabetical order + benzene.* Remember if two of the same substituent appears then the prefix *di-* is used before the substituent's name.



ortho-Chloronitrobenzene **meta-Dibromobenzene** **para-Bromopropylbenzene**

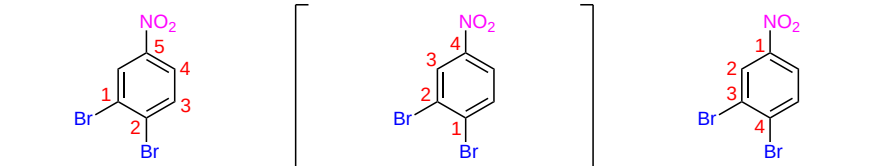
Nomenclature of Benzenes with Three or more Substituents

When three or more substituents are present the ortho, meta, para positional prefixes become inadequate and a numbering system for the ring must be applied. Here again it is important to check if any of the substituents are listed in **Figure 1.** If a substituent from **Figure 1** is present it is given the parent name in the nomenclature. Also, this substituent is given position one in the numbering system. The other substituents are numbered such that they get the lowest possible sum. In the compound's name the substituents are given their position number and listed alphabetically. Remember that di-, tri, tetra- prefixes are still used to indicate multiple of the same substituent being present but are ignored for alphabetical listing.



3,4-Dibromophenol **5-Nitro-2-propylaniline**

Figure 10.2.4, the benzene ring is named in the same fashion as cycloalkanes. The lowest possible number is given to the substituents present. This is best done by arbitrarily giving a substituent position one and then numbering the rest of the substituents. Then this process is repeated with the other substituents. Which ever iteration provides the lowest overall sum of numbers will be used in the compound's name. The substituents are assigned a location number, listed alphabetically and the suffix *-benzene* is added.



1,2-Dibromo-5-nitrobenzene **1,2-Dibromo-4-nitrobenzene** **3,4-Dibromo-1-nitrobenzene**

This numbering provides the lowest numbers to the substituents

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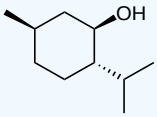
Exercises

Exercise 10.2.1

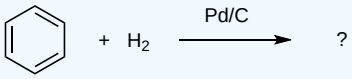


(True/False) The compound above contains a benzene ring and thus is aromatic.

Answer

False, this compound does not contain a benzene ring in its structure.

Exercise 10.2.2

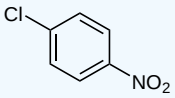


Answer

No reaction, benzene requires a special catalyst to be hydrogenated due to its unusual stability given by its three conjugated pi bonds.

Exercise 10.2.3

Name the following compound using OMP nomenclature:



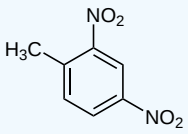
Answer

p-chloronitrobenzene

Exercise 10.2.4

Draw the structure of 2,4-dinitrotoluene.

Answer



Exercise 10.2.5

(True/False) Benzyl chloride can be abbreviated Bz-Cl.

Answer

False, the correct abbreviation for the benzyl group is Bn, not Bz. The correct abbreviation for Benzyl chloride is Bn-Cl.

Exercise 10.2.6

Benzoic Acid has what R group attached to its phenyl functional group?

Answer

COOH

Exercise 10.2.7

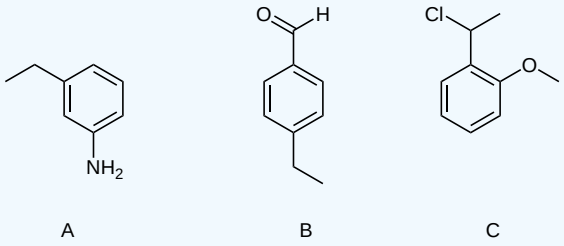
List the corresponding positions for the OMP system (o-, m-, p-).

Answer

Ortho - 1,2 ; Meta - 1,3 ; Para - 1,4

Exercise 10.2.8

State wither the following is para, meta, or ortho substituted.



A B C

Answer

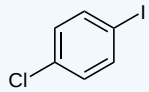
A – meta; B – para; C – ortho

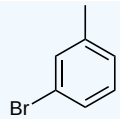
Exercise 10.2.9

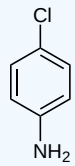
Draw the following structures

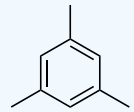
a. p-chloroiodobenzene
b. m-bromotoluene
c. p-chloroaniline
d. 1,3,5-trimethylbenzene

Answer

A) 

C) 

B) 

D) 

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10.3: Structure and Stability of Benzene

Objectives

After completing this section, you should be able to

1. compare the reactivity of a typical alkene with that of benzene.
2. Use the heat of hydrogenation data to show that benzene is more stable than might be expected for “cyclohexatriene.”
3. state the length of the carbon-carbon bonds in benzene, and compare this length with those of bonds found in other hydrocarbons.
4. describe the geometry of the benzene molecule.
5. describe the structure of benzene in terms of resonance.
6. describe the structure of benzene in terms of molecular orbital theory.
7. draw a molecular orbital diagram for benzene.

Key Terms

Make certain that you can define, and use in context, the key term below.

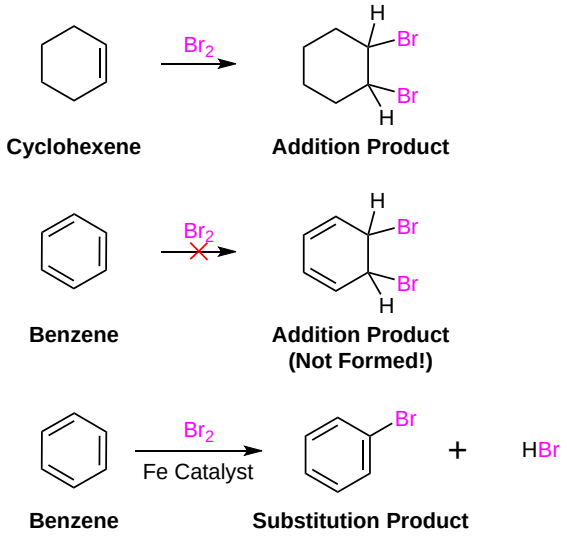
- degenerate

Study Notes

Note that the figure showing the molecular orbitals of benzene has two bonding (π_2 and π_3) and two anti-bonding (π^* and π_5^*) orbital pairs at the same energy levels. Orbitals with the same energy are described as degenerate orbitals.

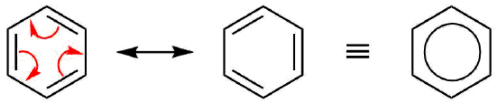
Structure of Benzene

When benzene (C_6H_6) was first discovered its low hydrogen to carbon ratio (1:1) led chemists to believe it contained double or triple bonds. Since double and triple bonds rapidly add bromine (Br_2), this reaction was applied to benzene. Surprisingly, benzene was entirely unreactive toward bromine. In addition, if benzene is forced to react with bromine through the addition of a catalyst, it undergoes **substitution reactions** rather than the addition reactions that are typical of alkenes. These experiments suggested that the six-carbon benzene core is unusually stable to chemical modification.

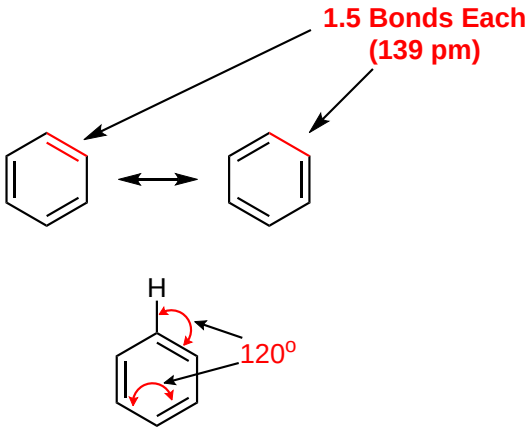


The conceptual contradiction presented by a high degree of unsaturation (low H:C ratio) and high chemical stability for benzene and related compounds remained an unsolved puzzle for many years. Eventually, the presently accepted structure of benzene as a hexagonal, planar ring of carbons with alternating single and double bonds was adopted, and the exceptional chemical stability of this system was attributed to special resonance stabilization of the conjugated cyclic triene. No single structure provides an accurate

representation of benzene as it is a combination of two structurally and energetically equivalent resonance forms representing the continuous cyclic conjugation of the double bonds. In the past, the benzene resonance hybrid was represented by a hexagon with a circle in the center to represent the benzene's pi-electron delocalization. This method has largely been abandoned because it does not show the pi electrons contained in benzene. Currently, the structure of benzene is usually represented by drawing one resonance form with the understanding that it does not completely represent the true structure of benzene.

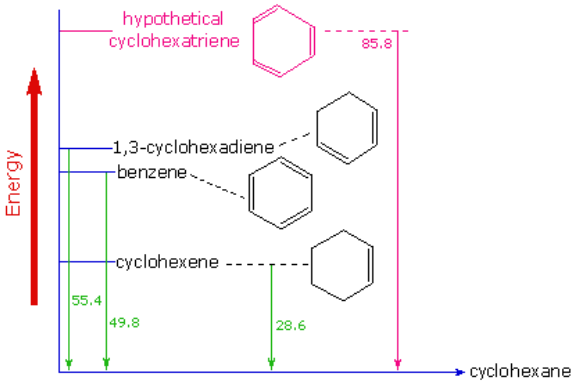


The six-membered ring in benzene is a perfect hexagon with all carbon-carbon bonds having an identical length of 139 pm[1]. The 139 pm bond length is roughly in between those of a C=C double bond (134 pm) and a C-C single (154 pm) which agrees with the benzene ring being a resonance hybrid made up of 1.5 C-C bonds. Each carbon in the benzene ring is sp^2 hybridized which makes all the C-C-C and H-C-C bond angles in benzene 120° and makes the overall molecule planar.



The High Stability of Benzene

In previous polyalkene, examples the electron delocalization described by resonance enhanced the stability of the molecule. However, benzene's stability goes beyond this. Evidence for the enhanced thermodynamic stability of benzene was obtained from measurements of the heat released when double bonds in a six-carbon ring are hydrogenated (hydrogen is added catalytically) to give cyclohexane as a common product. In the following diagram cyclohexane represents a low-energy reference point. Addition of hydrogen to cyclohexene produces cyclohexane and releases heat amounting to 28.6 kcal per mole. If we take this value to represent the energy cost of introducing one double bond into a six-carbon ring, we would expect a cyclohexadiene to release 57.2 kcal per mole on complete hydrogenation, and 1,3,5-cyclohexatriene to release 85.8 kcal per mole.



These **heats of hydrogenation** would reflect the relative thermodynamic stability of the compounds. In practice, 1,3-cyclohexadiene is slightly more stable than expected, by about 2 kcal, presumably due to conjugation of the double bonds. **Benzene, however, is an extraordinary 36 kcal/mole more stable than expected**. This sort of stability enhancement is called

aromaticity and molecules with aromaticity are called aromatic compounds. Benzene is the most common aromatic compound but there are many others. Aromatic stabilization explains benzene's lack of reactivity compared to typical alkenes.

Atomic Orbitals of Benzene

Also, each of benzene's six carbon atoms are sp^2 hybridized and have an unhybrized p orbital perpendicular to plane of the ring. Because each of the six carbon atoms and their corresponding p orbitals are equivalent, it is impossible for them to only overlap with one adjacent p orbital to create three defined double bonds. Instead each p orbital overlaps equally with both adjacent orbitals creating a cyclic overlap involving all six p orbitals. This allows the p orbitals to be delocalized in molecular orbitals that extend all the way around the ring allowing for more overlap than would be obtained from the linear 1,3,5-hexatriene equivalent.

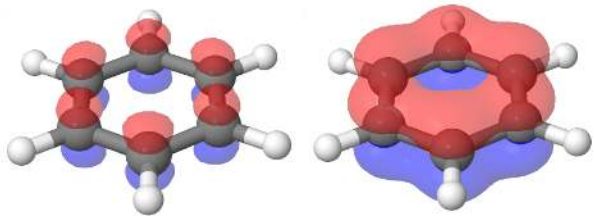


Figure 10.3.1: Each carbon in the benzene ring is sp2 hybrized with a p orbital perpendicular to the ring plane (Left) Being planar and cyclic allows benzene's p orbitals to undergo cyclic overlap (Right)

For this to happen, of course, the ring must be planar – otherwise the *p* orbitals couldn't overlap properly and benzene is known to be a flat molecule. An electrostatic potential map of benzene, shown below, shows that the pi electrons are evenly distributed around the ring and that every carbon equivalent.

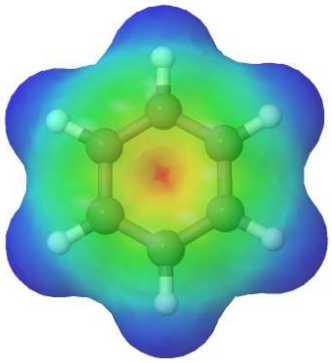
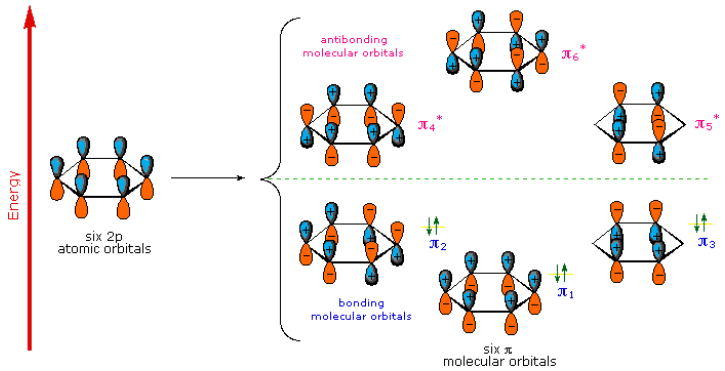


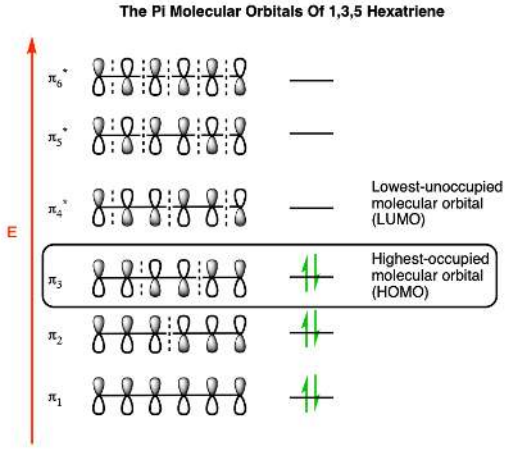
Figure 10.3.2: An electrostatic potential map of benzene

The Molecular Orbitals of Benzene

A molecular orbital description of benzene provides a more satisfying and more general treatment of "aromaticity". We know that benzene has a planar hexagonal structure in which all the carbon atoms are sp^2 hybridized, and all the carbon-carbon bonds are equal in length. As shown below, the remaining cyclic array of six p-orbitals (one on each carbon) overlap to generate six molecular orbitals, three bonding and three antibonding. The plus and minus signs shown in the diagram do not represent electrostatic charge, but refer to phase signs in the equations that describe these orbitals (in the diagram the phases are also color coded). When the phases correspond, the orbitals overlap to generate a common region of like phase, with those orbitals having the greatest overlap (e.g. π_1) being lowest in energy. The remaining carbon valence electrons then occupy these molecular orbitals in pairs, resulting in a fully occupied (6 electrons) set of bonding molecular orbitals. It is this completely filled set of bonding orbitals, or **closed shell**, that gives the benzene ring its thermodynamic and chemical stability, just as a filled valence shell octet confers stability on the inert gases.



To better see source of the stabilizing aromaticity effect created by the cyclic p orbitals of benzene, the molecular orbitals of 1,3,5-hexatriene must be investigated. The molecule 1,3,5-hexatriene contains six p orbitals which all overlap but in a linear fashion. As with benzene, this overlap creates 3 stabilized bonding molecular which are completely filled with six p electron. As expected, the conjugation creates a marked increase of stability in 1,3,5-hexatriene but not as much as in benzene.



The main difference in stability can be seen when comparing the lowest energy molecular orbital of 1,3,5-hexatriene and benzene: pi_1. In pi_1 molecular orbital of 1,3,5-hexatriene there are 5 stabilizing bonding interactions where there are 6 stabilizing bonding interactions in the pi_1 of benzene. The sixth bonding interaction is made possible by benzene's p orbitals being in a ring. Because benzene's pi_1 molecular orbital has more stabilizing bonding interactions it is lower in energy than the pi_1 molecular orbital of 1,3,5-hexatriene. This gives benzene the additional aromatic stability not seen in the acyclic 1,3,5-hexatriene.

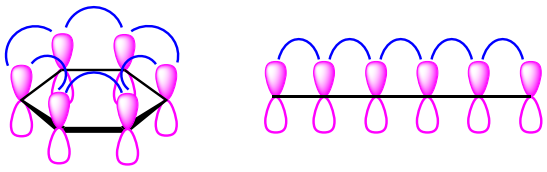


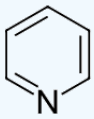
Figure 10.3.3: The pi_1 molecular orbital of benzene (Left) has 6 stabilizing bonding interaction where 1,3,5-hexatriene's (Right) only has 5.

Exercises

https://chem.libretexts.org/@go/page/443829

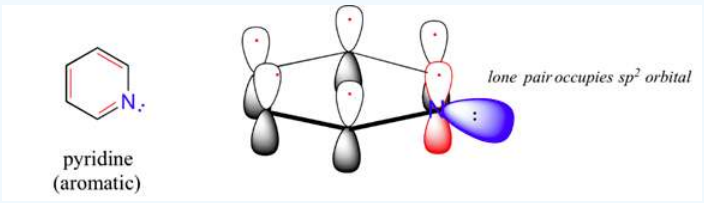
Exercise 10.3.1

The molecule, pyridine, is planar with bond angles of 120º. Pyridine has many other characteristics similar to benzene. Draw a diagram showing the p orbitals in pyridine and use it to explain its similarity to benzene.



Answer

The nitrogen and each carbon in the pyridine ring is sp^2 hybridized. In the bonding picture for pyridine, the nitrogen is sp^2-hybridized, with two of the three sp^2 orbitals forming sigma overlaps with the sp^2 orbitals of neighboring carbon atoms, and the third nitrogen sp^2 orbital containing the lone pair electrons. The unhybridized p orbital contains a single electron, which is part of the 6 pi-electron system delocalized around the ring. Pyridine is most likely aromatic which gives it its planar shape and 120º bond angles.



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10.4: Aromaticity and the Hückel 4n + 2 Rule

Objectives

After completing this section, you should be able to

1. define aromaticity in terms of the Hückel 4*n* + 2 rule.
2. use the Hückel 4*n* + 2 rule to determine whether or not a given polyunsaturated cyclic hydrocarbon should exhibit aromatic properties.
3. describe the difference in properties between an aromatic hydrocarbon, such as benzene, a non-aromatic polyunsaturated cyclic hydrocarbon, such as cyclooctatetraene, and an anti-aromatic polyunsaturated hydrocarbon, such as cyclobutadiene.
4. draw molecular orbital diagrams for aromatic species, such as benzene, the cyclopentadienyl anion and pyridine, and compare these diagrams with those obtained for anti-aromatic species, such as cyclobutadiene and the cyclopentadienyl cation.

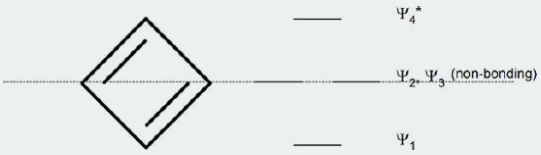
Study Notes

The following mnemonic device (Frost's Circle) will help you establish the approximate energy levels for the molecular orbitals of various organic ring systems.

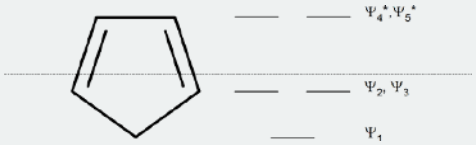
Whatever the size of the ring, place one point of the ring down to the bottom. The corners of the ring, where the carbons are located, will roughly approximate the location and pattern of the molecular orbital energy levels. Cut the ring exactly in half. The energy levels in the top half will be anti-bonding (Ψ^*) orbitals and those in the bottom will be bonding (Ψ) orbitals. If the carbons fall directly in the centre of the ring (e.g., four-membered rings) the energy levels there are non-bonding.

cyclopropenyl ring (three-membered ring)

cyclobutadienyl ring (four-membered ring)



cyclopentadienyl ring (five-membered ring)



In 1931, German chemist and physicist Erich Hückel proposed a theory to help determine if a planar ring molecule would have aromatic properties. His rule states that if a cyclic, planar molecule has 4n+2 pi electrons, it is considered aromatic. This rule would come to be known as **Hückel's Rule**.

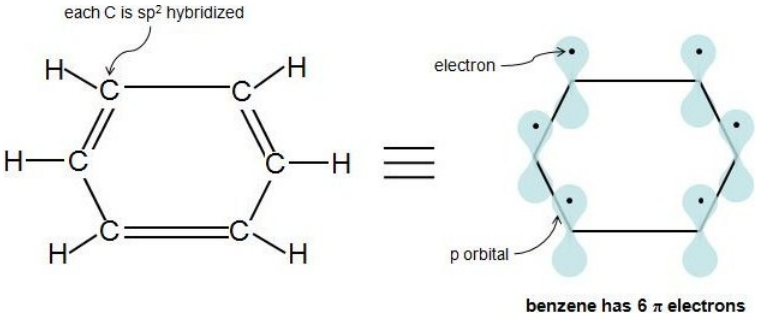
Four Criteria for Aromaticity

When deciding if a compound is aromatic, go through the following checklist. If the compound does not meet all the following criteria, it is likely not aromatic.

1. The molecule is cyclic (a ring of atoms)
2. The molecule is planar (all atoms in the molecule lie in the same plane)
3. The molecule is fully conjugated (p orbitals at every atom in the ring)
4. The molecule has 4n+2 pi electrons (n=0 or any positive integer)

Counting pi Electrons?

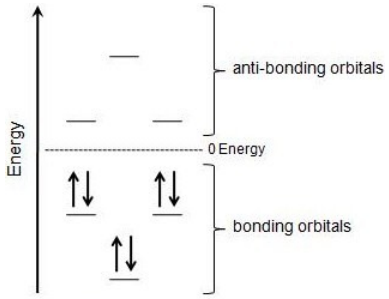
Perhaps the toughest part of Hückel's Rule is figuring out which electrons in the compound are actually pi electrons. Once this is figured out, the rule is quite straightforward. Pi electrons lie in the p orbitals and sp^2 hybridized atoms have 1 of these p orbitals each. When looking at a C=C double bond we know that there is one sigma bond and one pi bond. The pi bond is formed by the overlap of 1 p orbital from each carbon in the double bond. Each p orbital contains one electron so when the two p orbitals overlap the two electrons become a pi bond and are thus called pi electrons. Because aromaticity deals directly with double bonds and conjugation it is simpler to just count the number pi electrons in a compound. Each double bond (pi bond) always contributes 2 π electrons. Benzene has 3 double bonds, so it has 6 pi electrons.



benzene has 6 π electrons

Why 4n+2 π Electrons?

According to Hückel's Molecular Orbital Theory, a compound is particularly stable if all of its bonding molecular orbitals are filled with paired electrons. This is true of aromatic compounds, meaning they are quite stable. With aromatic compounds, 2 electrons fill the lowest energy molecular orbital, and 4 electrons fill each subsequent energy level (the number of subsequent energy levels is denoted by n), leaving all bonding orbitals filled and no anti-bonding orbitals occupied. This gives a total of 4n+2 pi electrons. You can see how this works with the molecular orbital diagram for the aromatic compound, benzene, below. Benzene has 6 pi electrons. Its first 2 pi electrons fill the lowest energy orbital, and it has 4 pi electrons remaining. These 4 fill in the orbitals of the succeeding energy level. Notice how all of its bonding orbitals are filled, but none of the anti-bonding orbitals have any electrons.



molecular orbital diagram
for benzene

To apply the 4n+2 rule, first count the number of pi electrons in the molecule. Then, set this number equal to 4n+2 and solve for n. If n is 0 or any positive integer (1, 2, 3,...), the rule has been met. For example, benzene has six pi electrons:

$$4n+2 = 6 \tag{10.4.1}$$
$$4n = 4 \tag{10.4.2}$$
$$n = 1 \tag{10.4.3}$$

For benzene, we find that n=1, which is a positive integer, so the rule is met.

With Hückel's theory we can assume that if a molecule meets the other criteria for aromaticity and also has 2, 6, 10, 14, 18 etc. pi electrons it will most likely be aromatic.

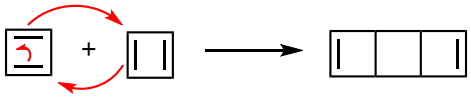
Antiaromaticity

More than 100 years ago, chemists 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 is cyclobutadiene, whose shape and

alignment of p orbitals suggested it should have substantial electron-delocalization energies.

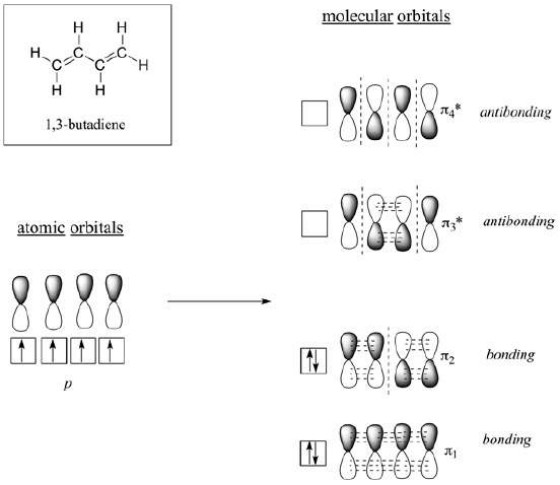
Cyclobutadiene

However, cyclobutadiene was found to be an extremely unstable molecules. In fact, cyclobutadiene is even more reactive than most alkenes. The synthesis of cyclobutadiene eluded chemists 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, cyclobutadiene was captured in a rigid matrix of argon at 8 K. On warming to even 35 K , it dimerizes through a Diels Alder reaction to yield a tricyclicdiene.



Due to the square ring, cyclobutadiene was expected to have some degree of destabilization associated with ring strain. However, estimations of the strain energies, though substantial, did not account for cyclobutadiene's high degree of instability. Also, why was it not being stabilized through cyclic conjugation in the same way as benzene. The answer can be seen in the molecular orbitals.

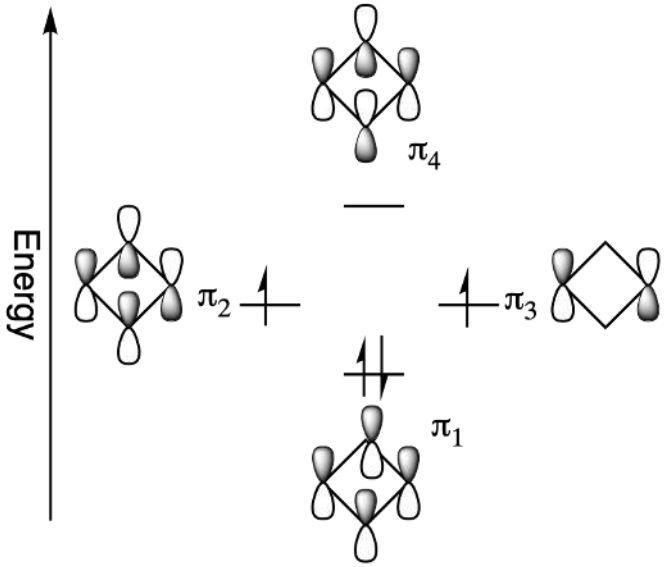
When considering the molecular orbital diagram of the analogous 1,3-butadiene, the four *2p* atomic orbitals combine to form four pi molecular orbitals of increasing energy. Two bonding pi orbitals and two antibonding pi* orbitals. The 4 pi electrons of 1,3-butadiene completely fill the bonding molecular orbitals giving is the additional stability associated with conjugated double bonds.



However, when placed into a ring the molecular orbitals undergo a significant change. The four p orbitals of cyclobutadiene combine to form the following 4 molecular orbitals:

- a bonding molecular orbital which is lower in energy than the atomic orbitals
- two degenerate non-bonding molecular orbitals which are of equivalent energy to the atomic orbitals
- one antibonding molecular orbital which is higher in energy

The non-bonding orbitals represent that there is no direct interaction between adjacent atoms. When adding cyclobutadiene's 4 pi electrons to the molecular orbital diagram, the bonding orbital is filled and both non-bonding orbitals are singly occupied. If cyclobutadiene's double bonds were delocalized, all the pi electrons would be in low energy bonding orbitals. However, only two of the pi electrons are in bonding orbitals; the other two are non-bonding. In addition, the molecular orbital diagram shows that two of the electrons are unpaired, a situation called a triplet state, which usually makes organic molecules very reactive. For cyclobutadiene cyclic conjugation has made the molecule less stable. This unexpected instability in 4n pi-electron cyclic conjugated compounds is termed **antiaromaticity** and the compounds are called antiaromatic.

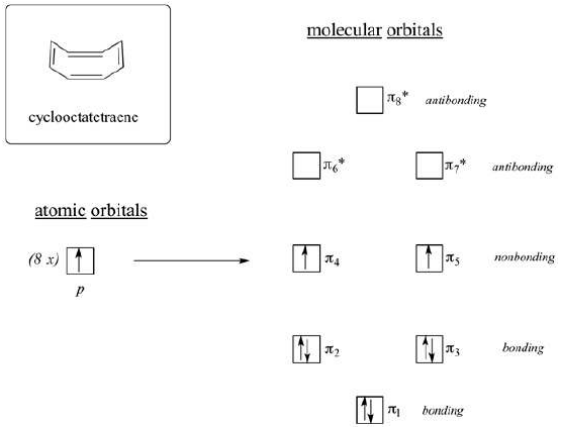


Antiaromaticity gives cyclobutadiene some interesting structural features. Cyclobutadiene's single and double bonds have different bond lengths, 158 pm and 135 pm respectively which give it a rectangular shape. If the double bonds were conjugated, there would only be one average bond length, like benzene, and shape would be square. In fact, cyclobutadiene's double bonds are not conjugated but locked into position.

Just like 4n + 2 rule with aromaticity, compounds which are flat, cyclic, have a p orbital at every member of the ring, and 4n pi electrons should be antiaromatic. Another potentially antiaromatic molecule is 1,3,5,7-cyclooctatetraene.

Cyclooctatetraene was first synthesized in 1911 by a German chemist, R. Willstatter (Nobel Prize 1915), who reported an extraordinary thirteen-step synthesis of cyclooctatetraene from a rare alkaloid called pseudopelletierine isolated from the bark of pomegranate trees. 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:

If cyclooctatetraene was flat it would have all the requirements to be antiaromatic. It is cyclic, has a p orbital in every member of the ring, and has 8 pi electrons. When looking at the molecular orbital diagram of cyclooctatetraene we see it shares certain characteristics in common with cyclobutadiene. Two of the molecular orbitals are degenerate non-bonding orbitals. When the molecular orbitals are fill with cyclooctatetraene's 8 pi electrons the last two electrons are unpaired in the two nonbonding orbitals creating a triplet state. Based off the molecular orbital diagram cyclooctatetraene should be antiaromatic.

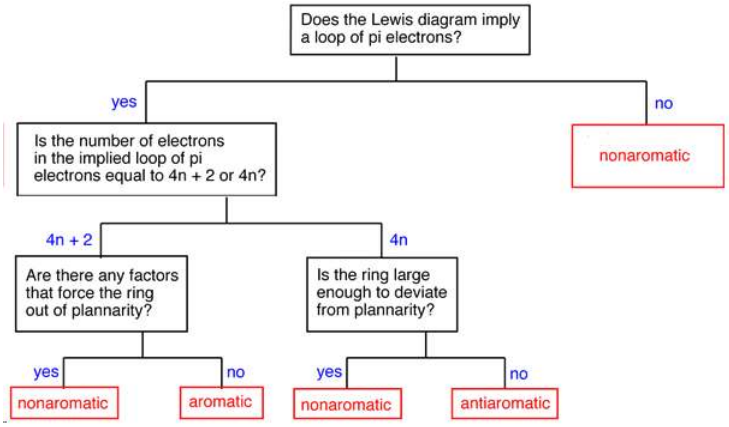


However, cyclooctatetraene is easily prepared and relatively stable. Also, it undergoes addition reactions typical of alkenes. In reality, cyclooctatetraene is not flat but has a tub-like shape. By assuming this shape, the p orbtials between double bond are out of

alignment for overlap. Because the double bonds are not conjugated, cyclooctatetraene escapes the destabilizing effects of antiaromaticity. This makes its its pi bonds react like 'normal' alkenes. Because cyclooctatetraene is not flat nor conjugated it is properly defined as non-aromatic. In general, if an antiaromatic compound has the ability to form a non-planar shape it will do so to avoid destabilization by becoming non-aromatic.

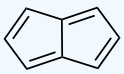
Determining if a Compound is Aromatic, Antiaromatic, or Nonaromatic

To make this determination it is important to first determine if the compound has the possibility of cyclic conjugation. This requires that the compound be cyclic and have a p orbital at every atom in the ring. If the compound does not have both of these criteria it cannot be aromatic or antiaromatic and must therefore be nonaromatic. Next the number of pi electrons in the ring is determined to see if it follows the count of aromaticity (4n + 2) or antiaromaticity (4n). Before making the final determination, it is vital to know the actual geometry of the molecule. Despite the number of pi electrons, a compound cannot be aromatic or antiaromatic if its geometry is not planar to allow for p orbital overlap.

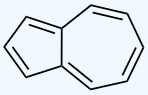


Example 10.4.1

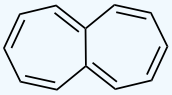
Cyclopentadiene (planar)
4 p Electrons
Nonaromatic



Pentalene (planar)
8 p Electrons
Antiaromatic



Azulene (planar)
10 p Electrons
Aromatic



Heptalene (planar)
12 p Electrons
Antiaromatic

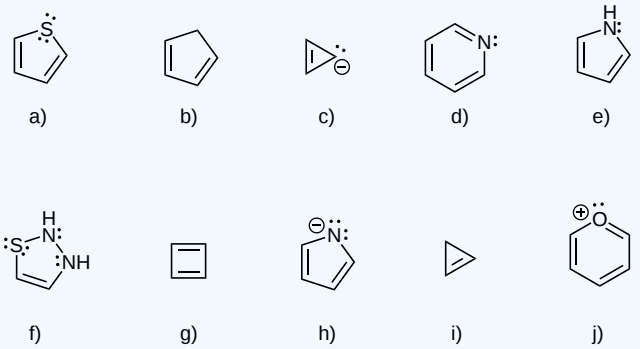
A Common Misconception

A very common misconception is that hybridization can be used to predict the geometry, or that hybridization somehow involves an energy cost associated with 'promoting' electrons into the hybrid orbitals. **This is entirely wrong.** Hybridization is always determined by geometry. You can only assign hybridization states to an atom if you already know its geometry, based on some experimental or theoretical evidence. The geometry of the oxygen in furan is trigonal planar and therefore the hybridization must be sp^2.

The *specific* rule is that if you have an sp^2 conjugated system, the lone pair will be involved ***if it makes the system more stable.*** In this case, conferring Hückel 4n+2 aromaticity. For furan with *two* lone pairs on the oxygen atom, if we count electrons from the carbon atoms, we have 4 (one per carbon). So adding two electrons from one of the lone pairs will give 6 = 4(1)+2, so Hückel rule is applicable and furan is aromatic.

Exercise 10.4.1

Using the criteria for aromaticity, determine if the following molecules are aromatic:



Answer

a) Aromatic - only 1 of S's lone pairs counts as pi electrons, so there are 6 pi electrons, n=1

b) Not aromatic - not fully conjugated, top C is sp^3 hybridized

c) Not aromatic - C with lone pair is sp^3 hybridized to avoid being antiaromatic if the lone pair was in a p orbital

d) Aromatic - N is using its 1 p orbital for the electrons in the double bond, so its lone pair of electrons are not pi electrons, there are 6 pi electrons, n=1

e) Aromatic - there are 6 pi electrons (4 from 2 pi bonds and 2 from the N lone pair in a p orbital), n=1

f) Not aromatic - not all atoms are sp^2 hybridized, the N in between the N and S is sp^3 hybridized, if all atoms were sp^2 hybridized there would be 8 pi electrons and the molecule would be antiaromatic

g) Antiaromatic - there are 4 pi electrons and the molecule is planar

h) Aromatic - only 1 of N's lone pairs counts as pi electrons, so there are 6 π electrons, n=1

i) Not aromatic - not fully conjugated, top C is sp^3 hybridized

j) Aromatic - O is using its 1 p orbital for the elections in the double bond, so its lone pair of electrons are not pi electrons, there are 6 pi electrons, n=1

Exercise 10.4.2

To be aromatic, a molecule must be planar, conjugated, and obey the 4n+2 rule. Is the following molecule aromatic?

Answer

No, it is not. It is not planar. If it was planar, it would be antiaromatic with 8 pi electrons (4n = 8 with n=2).

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1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th ed. New York: W. H. Freeman & Company, 2007.
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4. Lewis, David and David Peters. Facts and Theories of Aromaticity. London, England: Macmillan Press, 1975.

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10.5: Aromatic Ions

Objectives

After completing this section, you should be able to

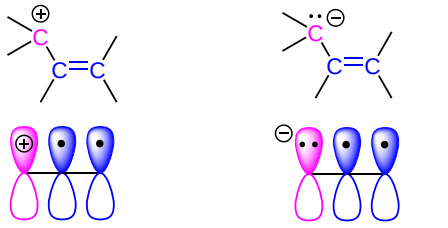
1. use the Hückel 4*n* + 2 rule to explain the stability of the cyclopentadienyl anion, the cycloheptatrienyl cation and similar species.
2. use the Hückel 4*n* + 2 rule to determine whether or not a given unsaturated cyclic hydrocarbon anion or cation is aromatic.
3. draw the resonance contributors for the cyclopentadienyl anion, cation and radical, and similar species.

Aromatic Ions

As previously, noted a ring must be fully conjugated to have the potential to be aromatic. This means that every atom in the ring must have a *p* orbital which can overlap with adjacent *p* orbitals. Until now the atoms providing the *p* orbitals have been neutral sp^2 hybridized carbons, however it is also possible for sp^2 hybridized carbons to have a charge. There are several examples of cationic and anionic compounds with unexpected stabilities that suggest that they are aromatic. It is important to understand how charged carbons in these compounds will affect the determination of aromaticity.

There are two main situations which need to be considered: The conjugation of a carbocation and the conjugation of a carbanion. A carbocation carbon is surrounded by three electron groups giving it sp^2 hybridization. The remaining unhybridized *p* orbital holds the carbocation's positive charge and is vacant of pi electrons. Although a carbocation is capable of extending conjugation it does not add to the compound's pi electron count.

A carbanion carbon is surrounded by four electron groups and would normally be sp^3 hybridized. However, to obtain the stabilizing effects of conjugation, carbanion carbons can becomes sp^2 hybridized putting the set of lone pair electrons into the unhybridized *p* orbital. Because the carbanion's *p* orbital contains two electrons in the form of a set of lone pair electrons, it increases a compound's pi electron count by 2.

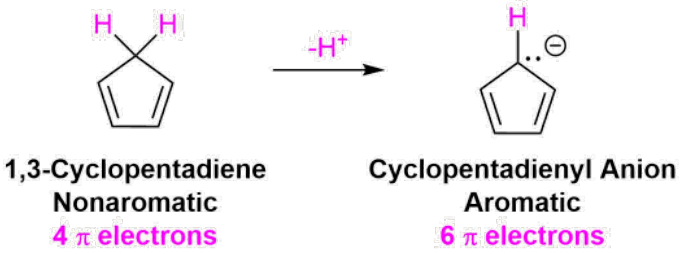


2 p Electrons Total
The carbocation adds
0 p Electrons

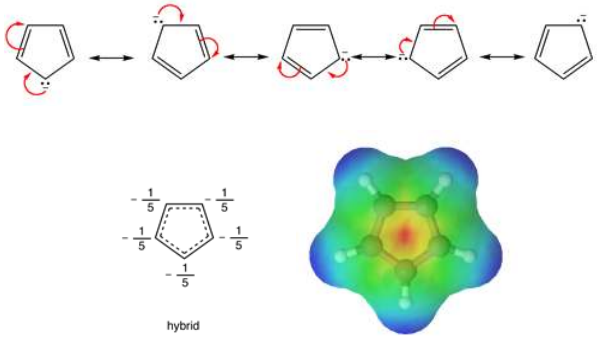
4 p Electrons Total
The carbanion adds
2 p Electrons

Cyclopentadiene Ion

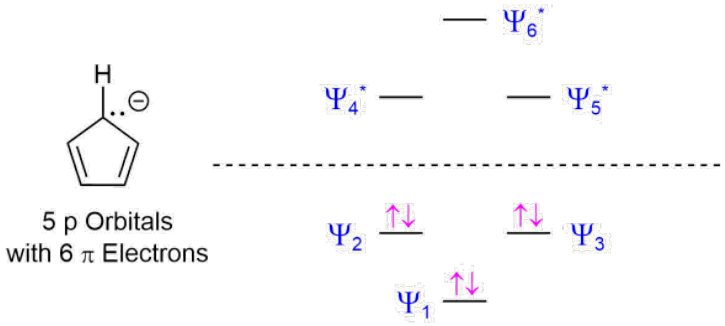
One of the most well know examples of an aromatic ion is the 1,3-cyclopentadiene ion. 1,3-Cyclopentadiene is nonaromatic due to the presence of an intervening sp^3 hybridized -CH_2- carbon atom which prevents pi electrons from delocalizing about the entire ring. Also, it only has 4 pi electrons which does not follow Hückel's 4n + 2 rule. However, if a proton is removed form the CH_2 group to form the cyclopentadienyl anion, the carbon atom becomes sp^2 hybridized and the two electrons of the resulting lone pair occupy the newly produced *p* orbital. This increases the number of pi electrons in the cyclopentadienyl anion to 6 which follows the 4n +2 rule. Moreover, this new *p* orbital overlaps with the *p* orbitals already present allowing for cyclic delocalization of pi electrons about the entire ring.



The lone pair electrons and the negative charge are conjugated about the entire ring making each carbon in the cyclopentadienyl anion equivalent with 1/5 the negative charge. The resonance hybrid can be shown by drawing a series of five resonance form. Also, the electrostatic potential map of the cyclopentadienyl anion shows the negative charge, seen in red/yellow is distributed over the entire ring. The fact that the red/yellow color is held in the center of the ring indicates that the extra electrons of the ion are involved in the aromatic p-electron system.

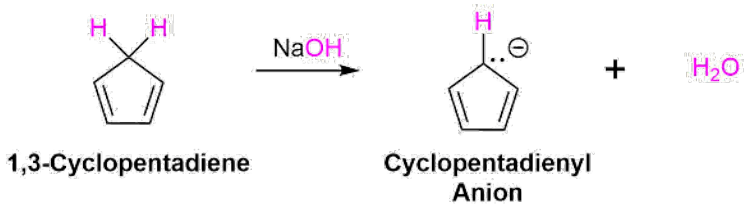


The reason why the 4n +2 rule still works for a 5 p orbital ring system can be seen by looking at the molecular orbital diagram of the cyclopentadienyl anion. The molecular orbital diagram of a 5 p orbital system is made up of 3 bonding MO's and 2 antibonding MO's. The 6 pi electrons gained by forming an anion is enough to completely fill the bonding MO's in the diagram giving the cyclopentadienyl anion aromaticity.



Note: There should only be 5 molecular orbitals in the diagram above. Psi 6 is not part of the correct diagram.

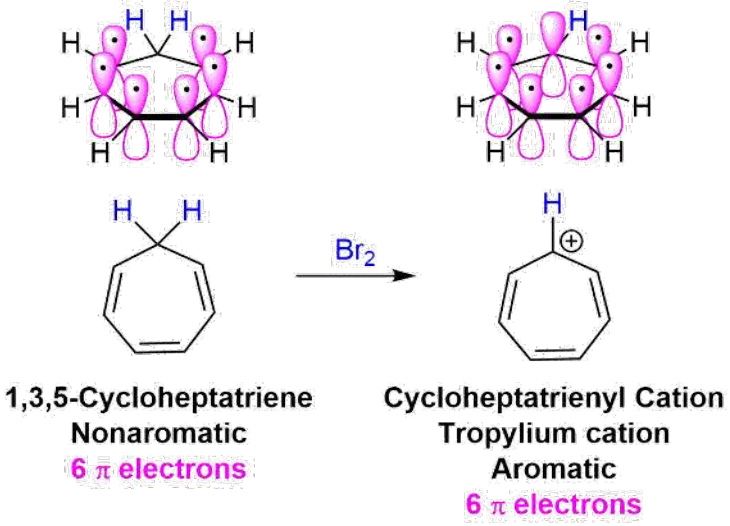
One of the effects of the aromaticity of the cyclopentadienyl anion is that the acidity of 1,3-cyclopentadiene is unusually strong. As previously discussed, stabilizing the conjugate base increases the acidity of the corresponding acid. In this case, the conjugate base of 1,3-cyclopentadiene, the cyclopentadienyl anion, is stabilized through aromaticity. This makes 1,3-cyclopentadiene one of the most acidic hydrocarbons known with a pK_a of 16. This is almost 10^{30} times more acidic than cyclopentane. Because of its acidity, cyclopentadiene can be deprotonated by moderately strong bases such as NaOH.



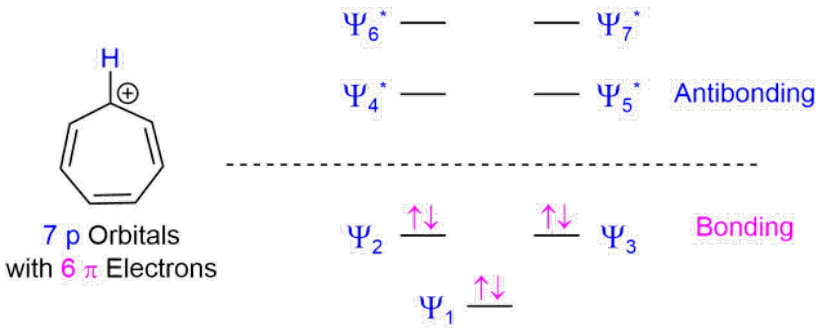
Tropylium ion

The molecule 1,3,5-cycloheptatriene has six pi electrons but is nonaromatic due the presence of an sp^3 hybridized -CH_2- group which prevents cyclic delocalization. When 1,3,5-cycloheptatriene is reacted with a reagent that can remove a hydride ion ($H:^-$), the 1,3,5-cycloheptatrienyl cation, which is commonly known as the tropylium cation, is formed with unexpected ease. Despite the presence of an electron deficient carbocation, the tropylium cation is unusually stable and can be isolated as a salt.

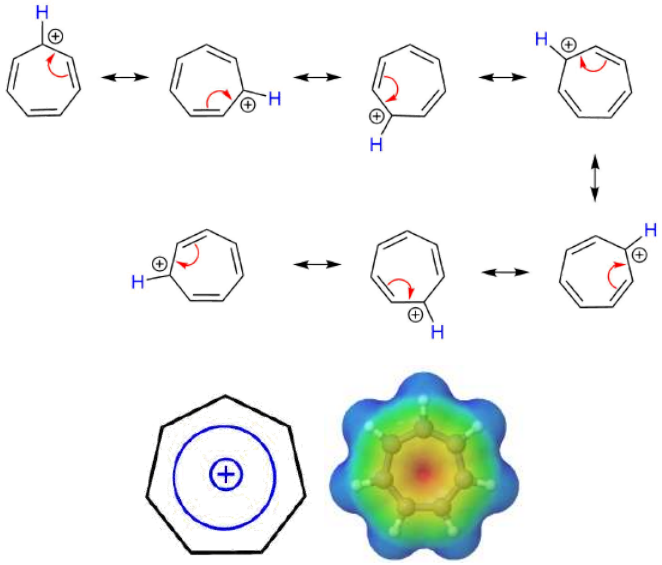
Removal of a hydride from the -CH_2- group in 1,3,5-cycloheptatriene creates an sp^2 hybridized carbocation with a vacant *p* orbital. The new *p* orbital allows for cyclic conjugation to occur among the seven *p* orbitals in the tropylium cation. The vacant *p* orbital does not change the pi electron count so the tropylium cation has 6 pi electrons which obeys the 4n + 2 rule for aromaticity.



The molecular orbital diagram for the 7 *p* orbitals in the tropylium cation has three bonding MO's and 4 antibonding MO's. The tropylium cation's 6 pi electrons completely fill the bonding molecular orbitals which is consistent with the tropylium cation being aromatic and therefore unusually stable.

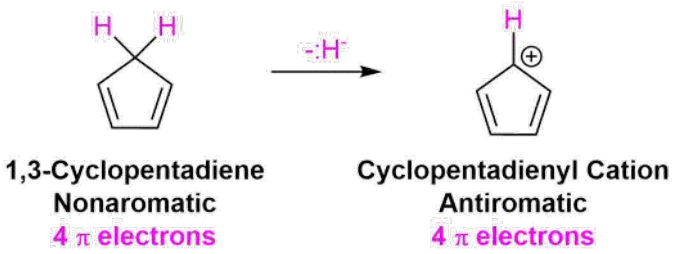


As predicted with aromaticity, the positive charge is completely conjugated about the entire ring giving each carbon +1/7 charge. The true resonance hybrid can be depicted by drawing a series of seven resonance form. Also, the electrostatic potential map of the tropylium cation shows the positive charge is evenly distributed over the entire ring. The equivalency of the carbons in the seven membered ring is experimentally supported by an ^1H NMR spectrum of the tropylium cation which contains one peak showing that all seven protons are equivalent.

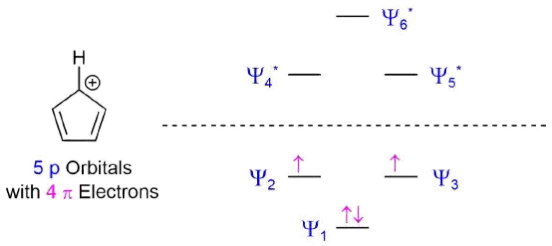


Antiaromatic Ions

In a similar fashion, cyclically conjugated ions with 4n pi electrons can be predicted to be antiaromatic and therefore highly unstable. An excellent example is the cyclopentadienyl cation. Above, the cyclopentadienyl anion was shown to be aromatic; however, the formation of a carbocation produces a different result. Although the vacant *p* orbital provided by the carbocation allows for cyclic conjugation to occur, the compound only has 4 pi electrons.

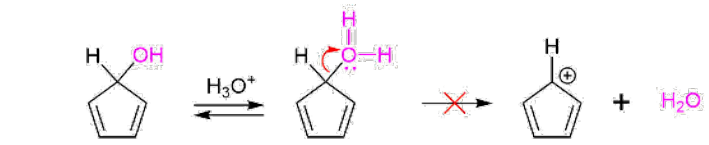


After placing these 4 pi electrons into the molecular orbital for a cyclic 5 *p* orbital species the bonding molecular orbitals remain unfilled. Two of the pi electrons are unpaired in degenerate molecular orbitals creating the highly unstable triplet state. As predicted by Hückel's Rule, the cyclopentadienyl cation has 4n pi electrons and should be anitaromatic and very unstable.



Note: There should only be 5 molecular orbitals in the diagram above. Psi 6 is not part of the correct diagram.

Although there is some discussion as to whether the cyclopentadienyl cation is truly antiaromatic, there is experimental evidence which shows it is usually unstable. In particular, the compound 2,4-cyclopentadien-1-ol is unusually resistant to S_N1 reactions with acid halides. The carbocation intermediate created during the mechanism of this reaction would be expected to easily form due to the resonance stabilization provided by the two double bonds. Because the carbocation intermediate is antiaromatic it does not form so the reaction does not occur.



2,4-Cyclopentadien-1-ol

4 π Electrons
Antiaromatic
Not Formed

Exercise 10.5.1

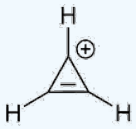
Are all bonds equivalent cyclopentadienyl anion? How many lines (signals) would you expect to see in a ^{1}H and ^{13}C NMR spectrum?

Answer

Due to the cyclopentadienyl anion being fully conjugated and aromatic all protons and carbons are equivalent. Both the ^{1}H and ^{13}C NMR spectrum would only have one signal.

Exercise 10.5.2

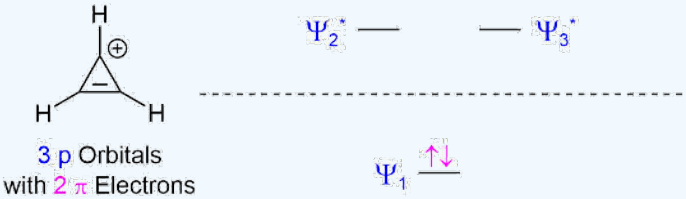
Is the cyclopropenium ion aromatic? Use the 4n + 2 rule and the MO diagram for a 3 p orbital ring system to explain your answer.



Cyclopropenium Ion

Answer

The cyclopropenium ion has 2 pi electrons which follows the 4n + 2 rule when n = 0. When considering the molecular orbital diagram for a 3 p orbital ring system the is one bonding MO and two antibonding MO's. The two pi electrons completely fill the bonding MO allowing for aromaticity.



3 p Orbitals
with 2 π Electrons

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10.6: Aromatic Heterocycles - Pyridine and Pyrrole

Objectives

After completing this section, you should be able to

1. draw the structure of the common aromatic heterocycles pyridine and pyrrole.
2. use the Hückel $4n + 2$ rule to explain the aromaticity of each of pyridine and pyrrole.
3. draw a diagram to show the orbitals involved in forming the conjugated six pi electron systems present in aromatic heterocycles such as pyridine, pyrrole, etc.

Key Terms

Make certain that you can define, and use in context, the key terms below.

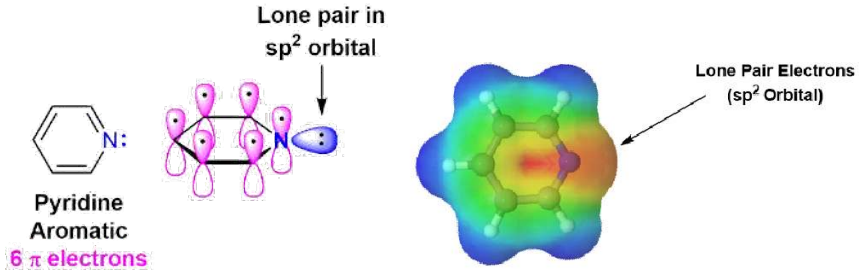
- carbocycles
- heterocycles

Aromatic Heterocycles

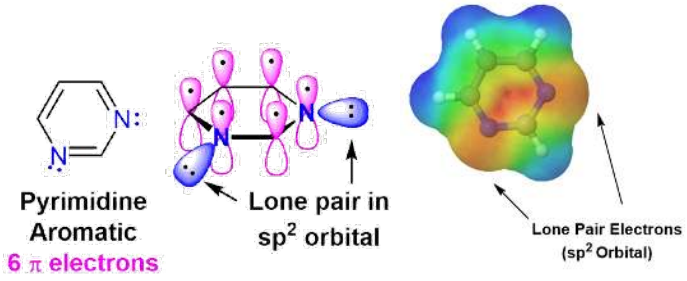
Many cyclic compounds have an element other than carbon present in the ring. Cyclic compounds that include one or more elements other than carbon are called heterocycles. The most common heterocyclic compounds contain carbon along with nitrogen, oxygen, or sulfur. Because some heterocyclic compounds are aromatic, it is important to discuss how the inclusion of non-carbon atoms affects the determination of aromaticity.

Pyridine & Pyrimidine

Pyridine is an example of a six-membered aromatic heterocycle and has an electronic structure similar to benzene. In the bonding picture of pyridine the five carbons and single nitrogen are all sp^2 hybridized. All six of these atoms have a p orbital perpendicular to the plane of the ring and each contains one pi electron which allows the ring to be fully conjugated. This makes the pi electron count for pyridine 6 pi electrons. In much the same fashion as benzene, the 6 pi electrons follow the 4n + 2 rule and completely fill the bonding molecular orbitals which fulfills the electronic requirement for aromaticity. The lone pair electrons on pyridine's nitrogen are contained in a sp^2 orbital that lies in the same plane as the ring and does not overlap with the p orbitals of the ring. The lone pair electrons are not part of the aromatic system and do not affect the p electron count. Pyridine's electrostatic potential map shows that the lone pair electrons, shown in a yellow/red color, are locked onto the nitrogen and not distributed around the ring.

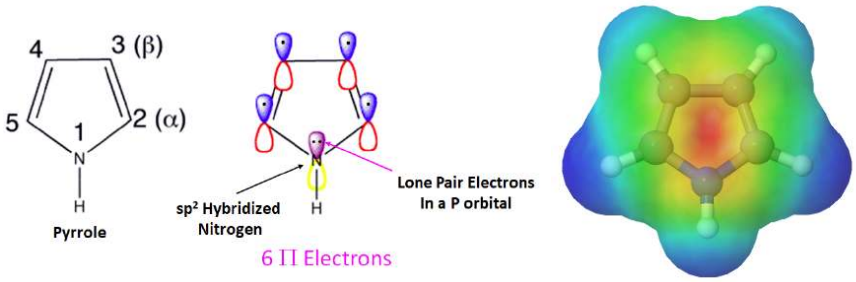


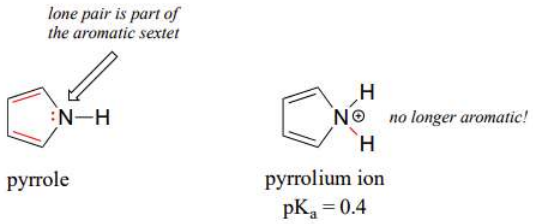
Pyrimidine is an another six-membered aromatic heterocycle that is analogous to pyridine. Pyrimidine has four carbons atoms and two nitrogen atoms that are sp^2 hybridized. Each of these atoms contributes a p orbital and a pi election allowing pyrimidine to be fully conjugated and aromatic. Both of the nitrogens in pyrimidine have lone pair electrons contained in a sp^2 orbitals and are not involved in the aromatic system. An electrostatic potential map of pyrimidine shows that neither set of lone pair electrons is distributed around the ring.



Pyrrole

Pyrrole is a five-membered heterocyclic ring which has 5 p orbitals and six pi electrons contributing to its aromaticity. Each carbon in pyrrole contributes one p orbital and pi electron. The nitrogen in pyrrole contributes two pi electrons by becoming sp^2 hybridized and placing its lone pair electrons into a p orbital. The electrostatic potential map of pyrrole show the nitrogen's lone pair electrons are distributed in the ring. Because the nitrogen lone pair *is* part of the aromatic sextet the electrons are very stable and are much less available for bonding to a proton (and if they *do* pick up a proton, the molecule loses aromaticity). Pyrrole is a very weak base: the conjugate acid, the pyrrolium ion, is a strong acid with a pK_a of 0.4.





Imidazole

Imidazole is another five-membered heterocyclic ring which has 6 pi electrons and is aromatic. Both of the nitrogen atoms are sp^2 hybridized. One nitrogen is pyridine-like because it is part of a double bond and adds one pi electron to the aromatic pi ring. The other nitrogen is not part of a double bond making it pyrrole-like allowing it to contribute 2 pi electrons from it lone pair electrons. When looking at the electrostatic potential map of imidazole, the lone pair electrons on the pyrrole-like nitrogen are distributed around the ring while the lone pair electrons on the pyridine-like nitrogen are non-conjugated and locked into place.

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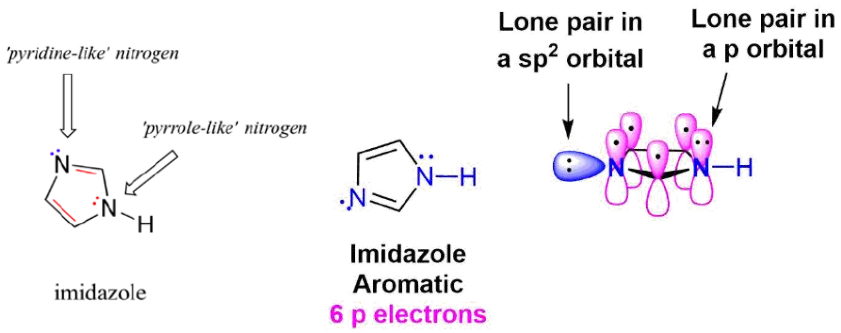
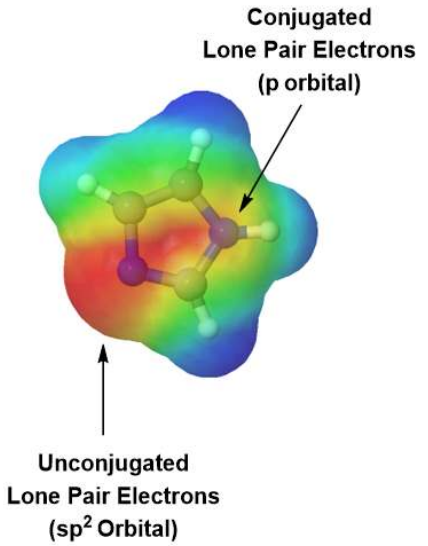
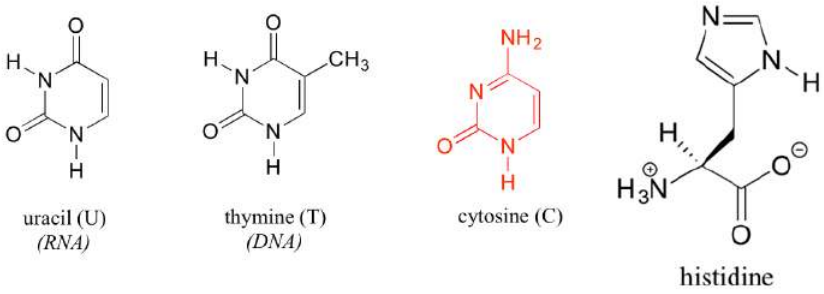




Pyrimidine and imidazole rings are particularly important in biological chemistry. Pyrimidine, for instance, is the parent ring system in cytosine, thymine, and uracil, three of the five heterocyclic amine bases found in nucleic acids. An aromatic imidazole ring is present in histidine, one of the amino acids found in proteins.



? Worked Example 10.6.1

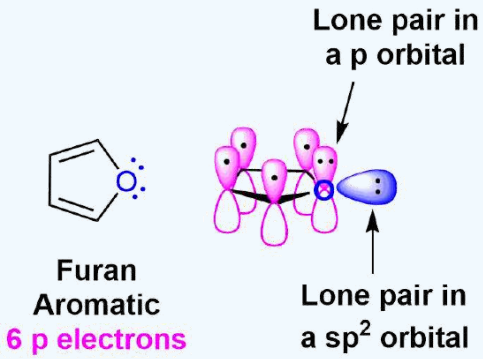
Determine if furan is aromatic. Draw an orbital diagram to support your answer.

Furan

Answer

For a molecule to be aromatic it must: Be cyclic, be planar, be fully conjugated, and have 4n+2 π electrons.

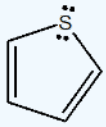
Furan is obviously cyclic and can be assumed to be planar due to the constrains of having a five membered ring with two double bonds. To be fully conjugated each atom in the ring must have a p orbital. Although the oxygen has 4 electron groups and appears to be sp^3 hybridized, it will become sp^2 hybridized to gain the stability of conjugation. Becoming sp^2 hybridized allows the oxygen atom to put a set of lone pair electrons into a p orbital allowing it to be part of the cyclic conjugation. These two pi electrons along with the 4 pi electrons provided by the two double bonds gives furan 6 pi electrons total. This follows the 4n + 2 rule making furan aromatic.



Exercises

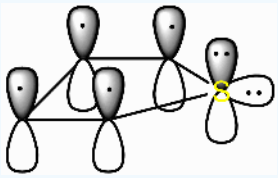
Exercise 10.6.1

Draw the orbitals of thiophene to show that it is aromatic.



Answer

This drawing shows thiophene has 6 electrons in the pi-orbital.



Exercise 10.6.2

The thiazolium ring is a five-membered sulfur containing aromatic ring system which is found in biological systems, such as thiamine diphosphate (ThDP). Describe how thiazolium ring is aromatic.

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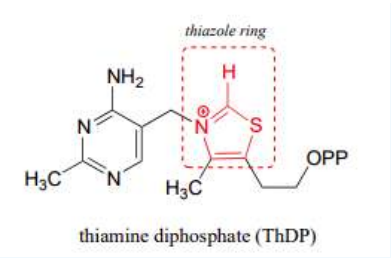
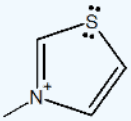
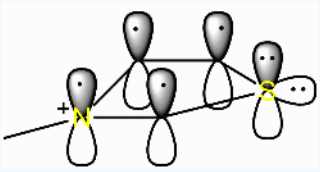




Answer

Similar to the previous question, the drawing shows that there are only 6 electrons in the pi-system.



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10.7: Polycyclic Aromatic Compounds

Objectives

After completing this section, you should be able to draw the resonance contributors for polycyclic aromatic compounds, such as naphthalene, anthracene, etc.

Key Terms

Make certain that you can define, and use in context, the key term below.

- polycyclic aromatic compounds

Study Notes

As their name indicates, *polycyclic aromatic hydrocarbons* are aromatic hydrocarbons which contain more than one benzenoid (i.e., benzene-like) ring. This section deals only with those compounds in which the benzenoid rings are fused together; in other words, compounds in which at least one carbon-carbon bond is common to two aromatic rings. Another type of polycyclic aromatic hydrocarbon contains two or more benzenoid rings joined by a carbon-carbon single bond. The simplest compound of this type is biphenyl, the compound from which PCBs (polychlorinated biphenyls) are derived.

Polycyclic Aromatic Compounds

Hückel's 4n +2 rule for aromaticity does not only apply to mono-cyclic compounds. Benzene rings may be joined together (fused) to give larger polycyclic aromatic compounds. A few examples are drawn below, together with the approved numbering scheme for substituted derivatives. The peripheral carbon atoms (numbered in all but the last three examples) are all bonded to hydrogen atoms. Unlike benzene, all the C-C bond lengths in these fused ring aromatics are not the same, and there is some localization of the pi-electrons. The six benzene rings in coronene are fused in a planar ring; whereas the six rings in hexahelicene are not joined in a larger ring, but assume a helical turn, due to the crowding together of the terminal ring atoms (in the structure below, note that the top right and center right rings are not attached to one another). This helical configuration renders the hexahelicene molecule chiral, and it has been resolved into stable enantiomers.

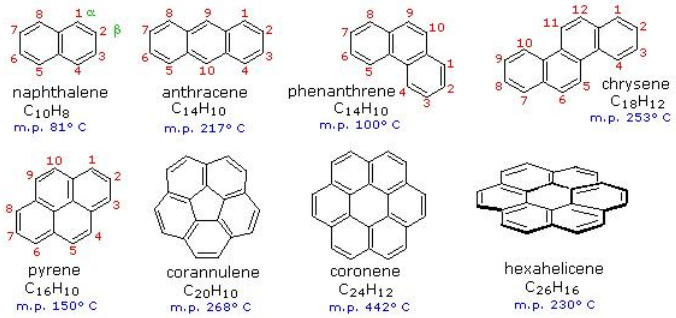
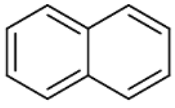
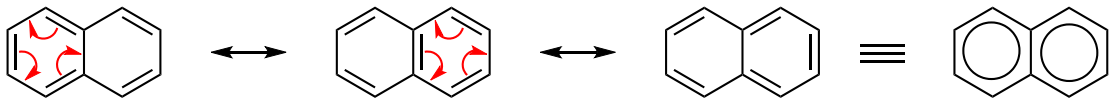


***Figure 2**: Examples of Polycyclic Aromatic Hydrocarbons (PAHs).*

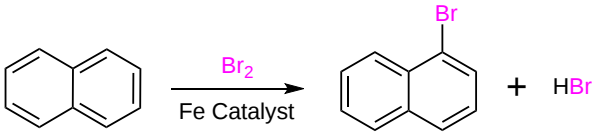
Probably the most well know polycyclic aromatic compound which only contains carbon is naphthalene ($C_{10}H_8$). Naphthalene shares many of the same characteristic as benzene. Naphthalene is cyclic and known to be flat. Each carbon in naphthalene is sp^2 hybridized so it is completely conjugated. The true structure of naphthalene is a combination of three resonance hybrids.



Naphthalene

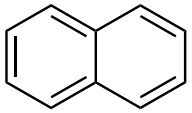


Heat of hydrogenation experiments with naphthalene shows an unusual "aromatic" stabilization energy. Also, naphthalene prefers to react with electrophiles to give substitution products rather than the typical double bond addition products.

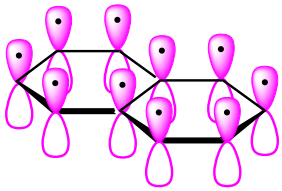


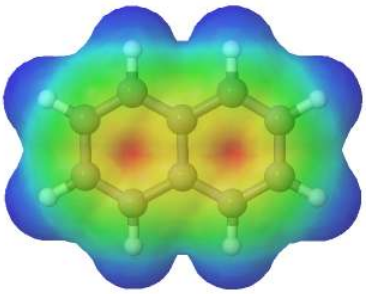
Naphthalene **1-Bromonaphthalene Substitution Product**

Every carbon in naphthalene is sp^2 hybridized so there is conjugated p orbital overlap over the entire ring system. The electrostatic potential map shows that pi electrons in naphthalene are evenly distributed making each carbon equivalent.

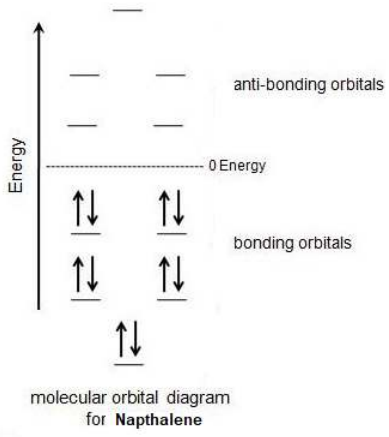


Naphthalene
Aromatic
10 p electrons





Lastly, naphthalene has 10 pi electrons which fulfills Hückel's rule. The importance of the 4n + 2 rule can be seen when considering the molecular orbital diagram of naphthalene. Naphthalene has 10 p orbitals which is 4 more than benzene. In the molecular orbital diagram of naphthalene, the 4 additional p orbitals become 2 bonding orbitals and two anti-bonding orbitals. The two additional bonding orbitals require 4 additional pi electrons to be filled so naphthalene needs 10 pi electrons in total to fill all of the bonding molecular orbitals.



Polycyclic Aromatic Heterocycles

There is a wide variety of polycyclic aromatic heterocycles, many of which contain nitrogen, oxygen, or sulfur. Some of the biologically important structures, are the nitrogen containing polycyclic aromatic heterocycles indole, quinoline, isoquinoline, and purine which are all polycyclic aromatic heterocycles commonly found in nature. Notice that these compound all have 10 pi electrons.

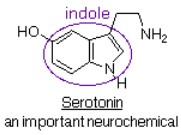
Indole

Quinoline

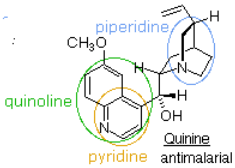
Isoquinoline

Purine

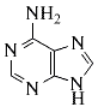
Indole, quinoline, and isoquinoline all contain a hetrocyclic ring fused to benzene. Purine is made up to two heterocyclic rings, imidazole and pyrimidine, fused together. Quinoline is found in the antimalarial drug quinine. Indole is found in the neurotransmitter serotonin. The purine ring structure is found in adenine and guanine, two important parts of DNA and in the stimulant caffeine.



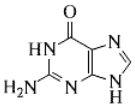
Serotonin
an important neurochemical



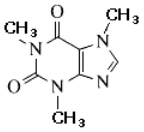
pyridine Quinine antimalarial



adenine



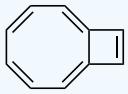
guanine



caffeine

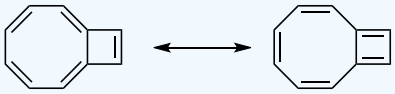
Exercise 10.7.1

This is an isomer of naphthalene. Is it aromatic? Draw a resonance structure for it.



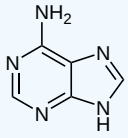
Answer

Yes, it is aromatic. 4n+2 pi-electrons.



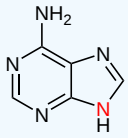
Exercise 10.7.2

The following molecule is adenine. It has a purine core. For the nitrogen atoms in the core, how many electrons are donated into the pi system?



Answer

There is only one nitrogen of the core that contributes to the pi-system (in red). With this one lone pair the core is aromatic with 10 electrons in the pi-system.



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10.8: Spectroscopy of Aromatic Compounds (CHM 222 topic)

Objectives

After completing this section, you should be able to

1. determine whether an unknown compound contains an aromatic ring by inspection of its infrared spectrum, given a table of characteristic infrared absorptions.
2. state the approximate chemical shift of aryl protons in a proton NMR spectrum.
3. explain why signals resulting from the presence of aryl protons are found downfield from those caused by vinylic protons in a proton NMR spectrum.
4. propose possible structures for an unknown aromatic compound, given its proton NMR spectrum, other spectroscopic data (such as a ^{13}C NMR or infrared spectrum), or both.

Key Terms

Make certain that you can define, and use in context, the key term below.

- ring current

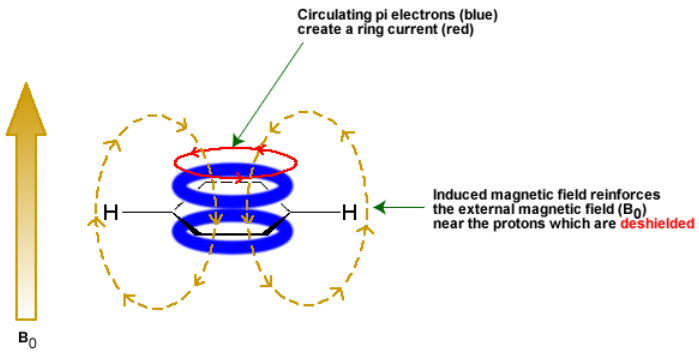
Study Notes

It is not necessary that you memorize detailed spectroscopic data. In the laboratory, on assignments and when writing examinations, you will be provided with a table of characteristic infrared absorptions to assist you in interpreting infrared spectra.

The important points to note about the proton NMR of aromatic compounds are the approximate chemical shifts of such protons and the complex splitting pattern that is sometimes observed. You are advised not to spend too long trying to understand why the signal for an aryl proton is found downfield from the signal for a vinylic proton. In general, we want you to be able to interpret NMR spectra, and leave the underlying theory for subsequent chemistry courses.

The chemical shifts of aromatic protons

Some protons resonate much further downfield than can be accounted for simply by the deshielding effect of nearby electronegative atoms. Vinylic protons (those directly bonded to an alkene carbon) and aromatic (benzylic) protons are dramatic examples.



We'll consider the aromatic proton first. Recall that in benzene and many other aromatic structures, a sextet of p electrons is delocalized around the ring. When the molecule is exposed to B_0, these p electrons begin to circulate in a **ring current**, generating

their own induced magnetic field that opposes B_0. In this case, however, the induced field of the p electrons does not shield the benzylic protons from B_0 as you might expect– rather, it causes the protons to experience a *stronger* magnetic field in the direction of B_0 – in other words, it *adds* to B_0 rather than subtracting from it.

To understand how this happens, we need to understand the concept of **diamagnetic anisotropy** (anisotropy means `non-uniformity`). So far, we have been picturing magnetic fields as being oriented in a uniform direction. This is only true over a small area. If we step back and take a wider view, however, we see that the lines of force in a magnetic field are actually anisotropic. They start in the 'north' direction, then loop around like a snake biting its own tail.

If we are outside the ring in the figure above, we feel a magnetic field pointing in a northerly direction. If we are inside the ring, however, we feel a field pointing to the south.

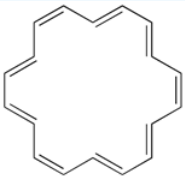
In the induced field generated by the aromatic ring current, the benzylic protons are outside the ring – this means that the induced current in this region of space is oriented in the *same* direction as B_0.

In total, the benzylic protons are subjected to three magnetic fields: the applied field (B_0) and the induced field from the electrons pointing in one direction, and the induced field of the non-aromatic electrons pointing in the opposite (shielding) direction. The end result is that benzylic protons, due to the anisotropy of the induced field generated by the ring current, appear to be highly de-shielded. Their chemical shift is far downfield, in the 6.5-8 ppm region.

The presence of anisotropy effects is often used to indicate aromaticity in a molecule. An example is the nonaromatic 8 pi electron cyclooctatetraene. In order to avoid anti-aromatic destabilization, the molecule takes a non-planar conformation which prevents conjugation and ring currents. Consequently, the molecule's protons absorbed at 5.8 ppm which is within the alkene region of ^{1}H NMR.

? Exercise 10.8.1

The ^{1}H-NMR spectrum of [18] annulene has two peaks, at 8.9 ppm and -1.8 ppm (upfield of TMS!) with an integration ratio of 2:1. Explain the unusual chemical shift of the latter peak.



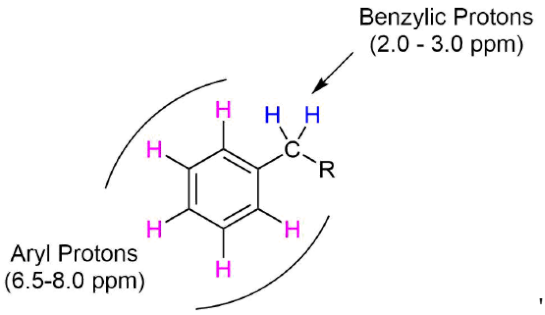
[18] annulene

Answer

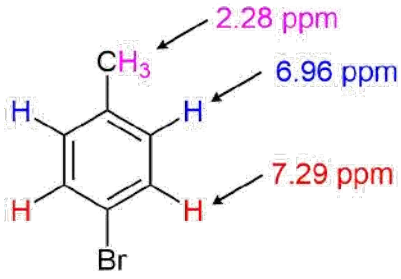
The molecule contains two groups of equivalent protons: the twelve pointing to the outside of the ring, and the six pointing into the center of the ring. The molecule is aromatic, as evidenced by the chemical shift of the ‘outside’ protons’ (and the fact that there are 18 pelectrons, a Hückel number). The inside protons are *shielded* by the induced field of the aromatic ring current, because *inside the ring this field points in the opposite direction of B_0*. This is the source of the unusually low (negative relative to TMS) chemical shift for these protons.

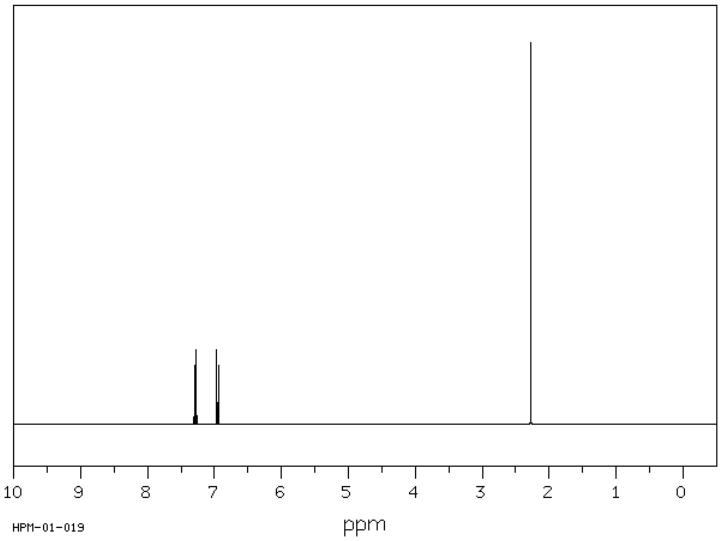
Characteristic ^{1}H NMR Absorptions of Aromatic Compounds

Protons directly attached to an aromatic ring, commonly called aryl protons, show up about 6.5-8.0 PPM. This range is typically called the aromatic region of an ^{1}H NMR spectrum. Protons on carbons directly bonded to an aromatic ring, called benzylic protons, show up about 2.0-3.0 PPM.



For the ^{1}H NMR spectrum of p-bromotoluene, the absorption for the benzylic protons appears as a strong singlet at 2.28 ppm. Due to the molecule's symmetry, the aryl protons appear as two doublets at 6.96 & 7.29 ppm.





Characteristic ^{13}C NMR Absorptions of Aromatic Compounds

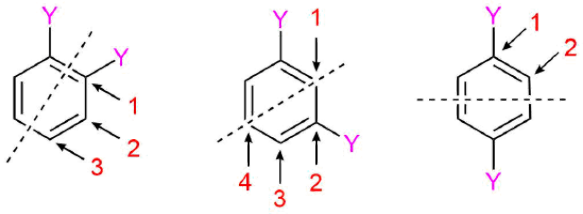
Carbons in an aromatic ring absorb in the range of 120-150 ppm in a ^{13}C NMR spectrum. This is virtually the same range as nonaromatic alkenes (110-150 ppm) so peaks in this region are not definitive proof of a molecule's aromaticity.

Due to the decoupling in ^{13}C NMR, the number of absorptions due to aromatic carbons can easily be observed. This can be used to determine the relative positions (*ortho*, *meta*, or *para*) for di-substituted benzenes. Peak assignments can be simplified by noting that ^{13}C peaks tend to be larger if two carbons contribute to the absorption.

Symmetrical Di-substituted Benzenes

Benzenes substituted with two identical groups have a relatively high amount of symmetry. In all three configurations, there is a plane of symmetry which reduces the number of distinct aryl carbon absorptions to less than six. The *ortho* configuration has a plane of symmetry which mirrors each carbon in the benzene ring causing only three ^{13}C aryl absorptions to occur. The *meta* configuration's plane of symmetry mirrors two carbons of the benzene ring allowing for four aryl absorptions to occur. The *para*

configuration actually has two planes of symmetry (one vertical and one horizontal on the structure below) through the benzene ring, which only allows two distinct aryl absorptions to occur.



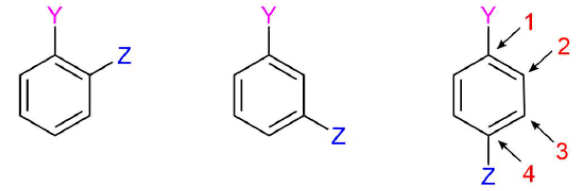
Ortho
Three ^{13}C Arene Peaks

Meta
Four ^{13}C Arene Peaks

Para
Two ^{13}C Arene Peaks

Asymmetrical Di-substituted Benzenes

The lack of a plane of symmetry in asymmetrical di-substituted benzenes makes each carbon in the *ortho* and *meta* configuration unique. Consequently, their ^{13}C NMR spectra show six arene absorptions. However, the *para* configuration has a plane of symmetry drawn through the two substituents which mirrors two carbons of the benzene ring causing only 4 arene absorptions to appear.

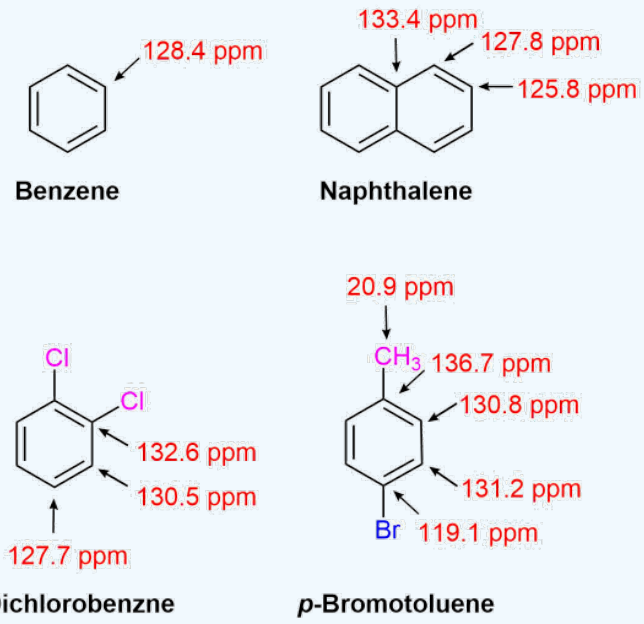


Ortho
No Symmetry
Six ^{13}C Arene Peaks

Meta
No Symmetry
Six ^{13}C Arene Peaks

Para
Four ^{13}C Arene Peaks

Example 10.8.1



Benzene

Naphthalene

***o*-Dichlorobenzne**

***p*-Bromotoluene**

Charateristic IR Absorption of Benzene Derivatives

Arenes have absorption bands in the 650-900 cm^{-1} region due to bending of the C–H bond out of the plane of the ring. The exact placement of these absorptions can indicate the pattern of substitution on a benzene ring. However, this is beyond the scope of introductory organic chemistry. Arenes also possess a characteristic absorption at about 3030-3100 cm^{-1} as a result of the aromatic C–H stretch. It is somewhat higher than the alkyl C–H stretch (2850–2960 cm^{-1}), but falls in the same region as olefinic compounds. Two bands (1500 and 1660 cm^{-1}) caused by C=C in plane vibrations are the most useful for characterization as they are intense and are likely observed.

In aromatic compounds, each band in the spectrum can be assigned:

- C–H stretch from 3100-3000 cm^{-1}
- overtones, weak, from 2000-1665 cm^{-1}
- C–C stretch (in-ring) from 1600-1585 cm^{-1}
- C–C stretch (in-ring) from 1500-1400 cm^{-1}
- C–H "oop" from 900-675 cm^{-1}

Note that this is at slightly higher frequency than is the –C–H stretch in alkanes. This is a very useful tool for interpreting IR spectra. Only alkenes and aromatics show a C–H stretch slightly higher than 3000 cm^{-1}.

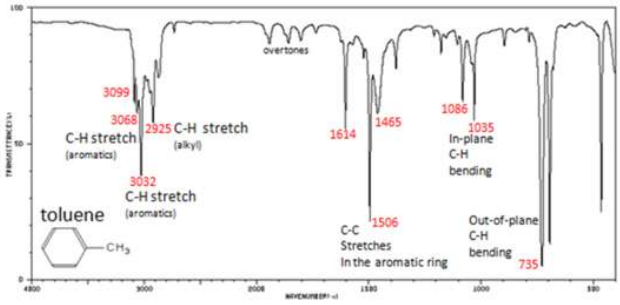
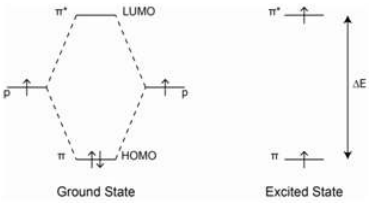


Figure 6. Infrared Spectrum of Toluene

Ultraviolet Spectroscopy

The presence of conjugated π bonds makes aromatic rings detectable in a UV/Vis spectrum. Benzene primarily absorbs through a be a π-π* transition over the range from 160-208 nm with a λ_{max} value of about 178 nm.



Benzene shows a less intense absorption in 230-276 nm range. These absorptions are due to vibrational fine structure often displayed by rigid molecules such as benzene and other aromatic compounds.

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10.S: Benzene and Aromaticity (Summary)

Concepts & Vocabulary

15.0 Introduction

- Aromatic compounds contain ring structures with a special type of resonance delocalization.
- Aromatic compounds can be drawn with alternating single and double bonds, each atom in the ring must have a p-orbital available.

15.1 Naming Aromatic Compounds

- Disubstituted benzene derivatives are often named using ortho (1,2), meta (1,3) and para (1,4).
- There are common benzene derivative names that are used by IUPAC such as toluene, phenol, benzoic acid and benzaldehyde.
- A benzene group that is named as a substituent is called phenyl.
- A benzene with a CH_2 as a substituent group is called benzyl.

15.2 Structure and Stability of Benzene

- Benzene does not undergo the same reactions that alkenes do, due to its aromatic stability.
- Aromatic molecules must have all ring atoms in the same plane to allow delocalization of the pi electrons.
- Heats of hydrogenation can be used to show the special stability of benzene compared to what would be expected for a theoretical cyclohexatriene molecule.

15.3 Aromaticity and the Hückel 4n + 2 Rule

- The four criteria for aromaticity are that the molecule must:
  - be cyclic
  - be planar
  - be fully conjugated
  - have 4n+2 π Electrons
- Ionic molecules and heterocyclic molecules can also be aromatic if they meet the four criteria.

15.4 Aromatic Ions

- Carbanions and carbocations that meet the rules for aromaticity are also aromatic.

15.5 Aromatic Heterocycles: Pyridine and Pyrrole

- Heterocycles that meet the rules for aromaticty are also aromatic.
- If a lone pair of electrons on a ring atom can result in 4n+2 π Electrons, they will be in a p-orbital. If not, they will remain in hybrid orbitals.

15.6 Polycyclic Aromatic Compounds

- Benzene rings can be fused together to give larger aromatic compounds with mutliple rings called polycyclic aromatic compounds (or polycyclic aromatic hydrocarbons).

15.7 Spectroscopy of Aromatic Compounds

- Aromatic compounds can be identified by common infrared absorptions in the 3000-3100 cm^{-1} and 1500-1600 cm^{-1}.
- In ^1H NMR, aromatic hydrogens appear in the 6.5-8 ppm region.

Skills to Master

- Skill 15.1 Name substituted benzene molecules.
- Skill 15.2 Use the criteria for aromaticity to determine if a molecule is aromatic or not.
- Skill 15.3 Determine whether lone pairs of electrons for ions and heterocycles will be in p orbitals or hybrid orbitals.

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CHAPTER OVERVIEW

11: Chemistry of Benzene - Electrophilic Aromatic Substitution

Learning Objectives

When you have completed Chapter 11, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. solve road-map problems that require an understanding of the chemistry discussed in this chapter and those that preceded it.
3. design multistep syntheses using the reactions discussed in this and the preceding chapters. In particular you should be prepared to show how an aromatic compound containing two or more substituents could be synthesized, taking care to introduce the substituents into the ring in the correct order.
4. define, and use in context, the key terms introduced.

Chapter Video

This video provides an introduction to electophilic aromatic substitution reactions.

In the preceding chapter, you studied the concept of aromaticity and spent considerable time on the theoretical aspects of the chemistry of aromatic compounds. In this chapter, you will begin to study the chemical reactions of aromatic compounds, focusing in particular on electrophilic aromatic substitution, and to a lesser extent on nucleophilic aromatic substitution. We will discuss, in detail, the mechanism of electrophilic substitution, paying particular attention to the factors that determine both the rate and position of substitution in those aromatic compounds which already have one or more substituents present in the aromatic ring. When we discuss nucleophilic aromatic substitution, you will see that it can be achieved by two different mechanisms, one of which involves the formation of an unusual looking intermediate, benzyne.

You will also see how alkyl and acyl groups can be introduced on to an aromatic ring; how, once introduced, alkyl groups can be converted to carboxyl groups; and how bromine can be introduced to the alkyl side chain of alkylbenzene. The latter reaction is particularly useful because the benzylic bromide so produced undergoes the reactions of a typical alkyl bromide, thus providing us with a synthetic route to a large variety of compounds.

11.1: Introduction

11.2: Electrophilic Aromatic Substitution Reactions - Bromination

11.3: Other Aromatic Substitutions

11.4: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction
11.5: Substituent Effects in Substituted Aromatic Rings
11.6: An Explanation of Substituent Effects
11.7: Trisubstituted Benzenes - Additivity of Effects
11.8: Nucleophilic Aromatic Substitution (reference only)
11.9: Benzyne (reference only)
11.10: Benzylic Bromination of Aromatic Compounds
11.11: Reduction of Aromatic Compounds (reference only)
11.12: Synthesis of Polysubstituted Benzenes
11.S: Chemistry of Benzene - Electrophilic Aromatic Substitution (Summary)

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11.1: Introduction

Objective

After completing this section, you should be able to identify electrophilic substitution as the single most important reaction of aromatic compounds.

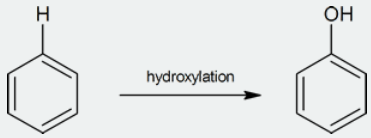
Key Terms

Make certain that you can define, and use in context, the key terms below.

- acylation
- alkylation
- electrophilic substitution
- halogenation
- hydroxylation
- nitration
- sulfonation

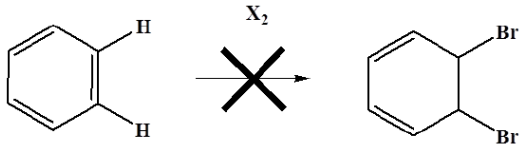
Study Notes

In this chapter, you will study all of the reactions shown in the Reaction Type table. In addition to these five reaction types, we also add a sixth common electrophilic substitution known as hydroxylation.



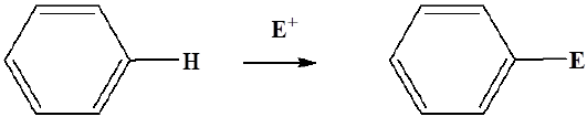
It is important that you recognize the similarities between these reactions to minimize the amount you must memorize.

The six pi electrons obey Huckel's rule so benzene is especially stable. This means that the aromatic ring wants to be retained during reactions. Because of this benzene does not undergo addition like other unsaturated hydrocarbons.



Non-Aromatic

Benzene can undergo electrophilic aromatic substitution because aromaticity is maintained.



Product is Aromatic

Other Examples of Electrophilic Aromatic Substitution

Many other substitution reactions of benzene have been observed, the five most useful are listed below (chlorination and bromination are the most common halogenation reactions). Since the reagents and conditions employed in these reactions are electrophilic, these reactions are commonly referred to as **Electrophilic Aromatic Substitution**. The catalysts and co-reagents

serve to generate the strong electrophilic species needed to effect the initial step of the substitution. The specific electrophile believed to function in each type of reaction is listed in the right hand column.

Reaction Type	Typical Equation				Electrophile $E^{(+)}$
Halogenation:	C_6H_6	+ Cl_2 & heat $FeCl_3$ catalyst	——>	C_6H_5Cl + HCl Chlorobenzene	$Cl^{(+)}$ or $Br^{(+)}$
Nitration:	C_6H_6	+ HNO_3 & heat H_2SO_4 catalyst	——>	$C_6H_5NO_2$ + H_2O Nitrobenzene	$NO_2^{(+)}$
Sulfonation:	C_6H_6	+ H_2SO_4 + SO_3 & heat	——>	$C_6H_5SO_3H$ + H_2O Benzenesulfonic acid	$SO_3H^{(+)}$
Alkylation: Friedel-Crafts	C_6H_6	+ R-Cl & heat $AlCl_3$ catalyst	——>	C_6H_5-R + HCl An Arene	$R^{(+)}$
Acylation: Friedel-Crafts	C_6H_6	+ RCOCl & heat $AlCl_3$ catalyst	——>	C_6H_5COR + HCl An Aryl Ketone	$RCO^{(+)}$

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11.2: Electrophilic Aromatic Substitution Reactions - Bromination

Objectives

After completing this section, you should be able to

1. write the detailed mechanism for the reaction of bromine with benzene in the presence of a suitable catalyst.
2. draw the resonance contributors for the carbocation which is formed during the reaction of bromine with benzene.
3. compare the reaction which takes place between bromine and benzene and the reaction which takes place between bromine and an alkene.
4. draw an energy diagram for the reaction of bromine with benzene.
5. identify the reagents required to bring about aromatic bromination.
6. write an equation to represent aromatic bromination.

Study Notes

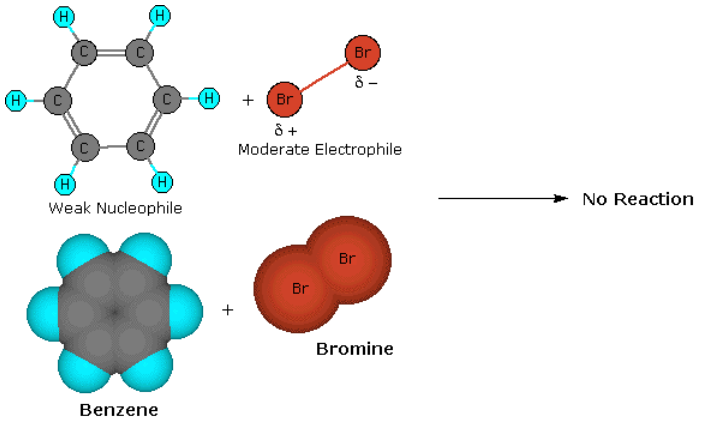
The Mechanism for Electrophilic Substitution Reactions of Benzene is the key to understanding electrophilic aromatic substitution. You will see similar equations written for nitration, sulphonation, acylation, etc., with the major difference being the identity of the electrophile in each case.

Note that the carbocation intermediate formed has a number of resonance forms.

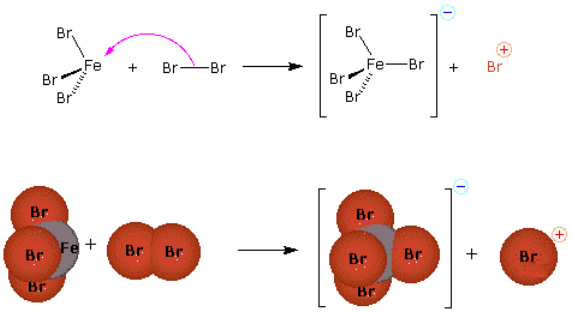
Halogenation is an example of electrophilic aromatic substitution. In electrophilic aromatic substitutions, a benzene is attacked by an electrophile which results in substitution of hydrogens. However, halogens are not electrophilic enough to break the aromaticity of benzenes, which require a catalyst to activate.

A Mechanism for Electrophilic Substitution Reactions of Benzene

A two-step mechanism has been proposed for these electrophilic substitution reactions. In the first, slow or rate-determining, step the electrophile forms a sigma-bond to the benzene ring, generating a positively charged **arenium intermediate**. In the second, fast step, a proton is removed from this intermediate, yielding a substituted benzene ring. The following four-part illustration shows this mechanism for the bromination reaction. Also, an animated diagram may be viewed.

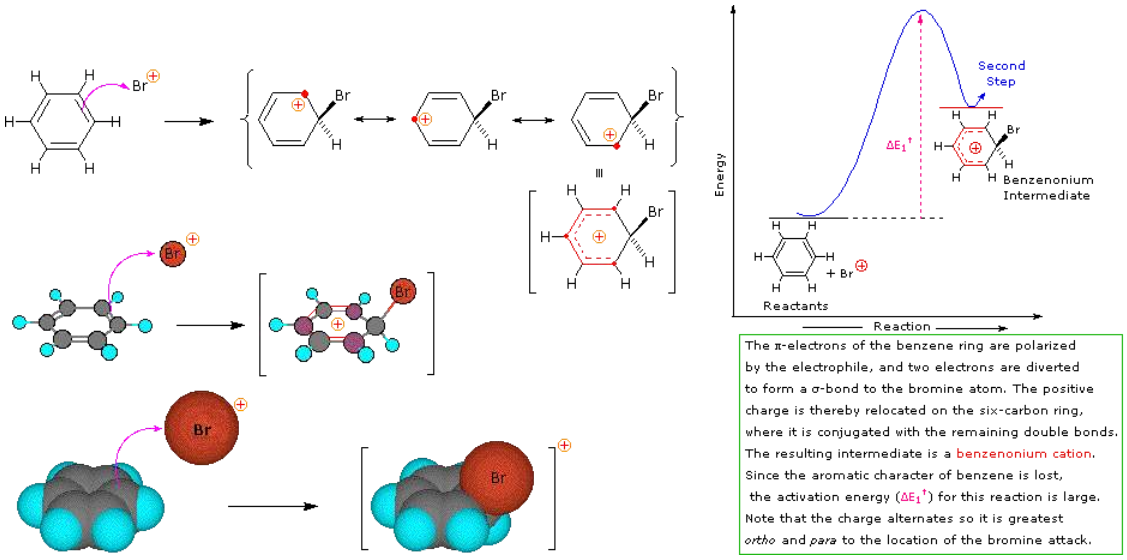


The bromine molecule is polarized so that one end is electrophilic and the other nucleophilic. Although the electrophilic end reacts easily with simple alkenes and dienes, it fails to react with the more stable and weaker nucleophilic π-electron system of benzene.



Ferric bromide and other Lewis acids enhance the electrophilic strength of bromine by forming a complex anion, in this case $FeBr_4^{\ominus}$. At the same time, this complexation creates the strongly electrophilic bromine cation, which reacts with nucleophiles.

Preliminary step: Formation of the strongly electrophilic bromine cation



The π-electrons of the benzene ring are polarized by the electrophile, and two electrons are diverted to form a σ-bond to the bromine atom. The positive charge is thereby relocated on the six-carbon ring, where it is conjugated with the remaining double bonds. The resulting intermediate is a benzenonium cation. Since the aromatic character of benzene is lost, the activation energy ($\Delta E_1^{\dagger}$) for this reaction is large. Note that the charge alternates so it is greatest *ortho* and *para* to the location of the bromine attack.

Step 1: The electrophile forms a sigma-bond to the benzene ring, generating a positively charged benzenonium intermediate

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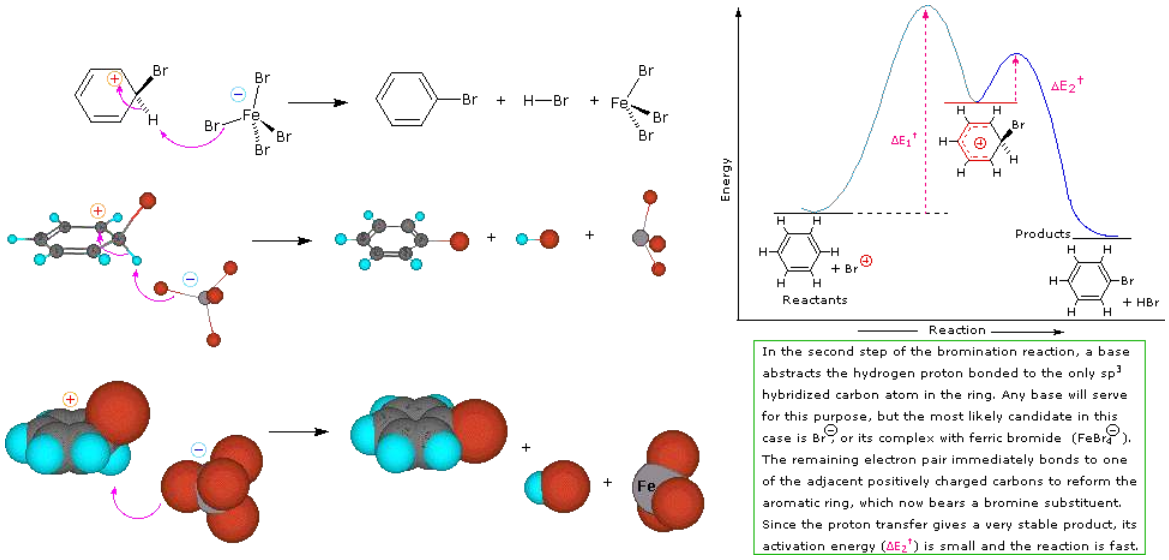


Step 2: A proton is removed from this intermediate, yielding a substituted benzene ring

This mechanism for electrophilic aromatic substitution should be considered in context with other mechanisms involving carbocation intermediates. These include S_N1 and E1 reactions of alkyl halides, and Brønsted acid addition reactions of alkenes.

To summarize, when carbocation intermediates are formed one can expect them to react further by one or more of the following modes:

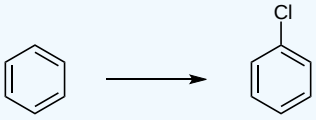
1. The cation may bond to a nucleophile to give a substitution or addition product.
2. The cation may transfer a proton to a base, giving a double bond product.
3. The cation may rearrange to a more stable carbocation, and then react by mode #1 or #2.

S_N1 and E1 reactions are respective examples of the first two modes of reaction. The second step of alkene addition reactions proceeds by the first mode, and any of these three reactions may exhibit molecular rearrangement if an initial unstable carbocation is formed. The carbocation intermediate in electrophilic aromatic substitution (the arenium ion) is stabilized by charge delocalization (resonance) so it is not subject to rearrangement. In principle it could react by either mode 1 or 2, but the energetic advantage of reforming an aromatic ring leads to exclusive reaction by mode 2 (*ie.* proton loss).

Exercises

? Exercise 11.2.1

What reagents would you need to get the given product?

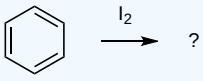


Answer

Cl_2 and $AlCl_3$ or Cl_2 and $FeCl_3$

? Exercise 11.2.2

What product would result from the given reagents?

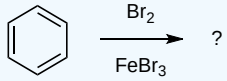


Answer

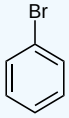
No Reaction

Exercise 11.2.3

What is the major product given the reagents below?



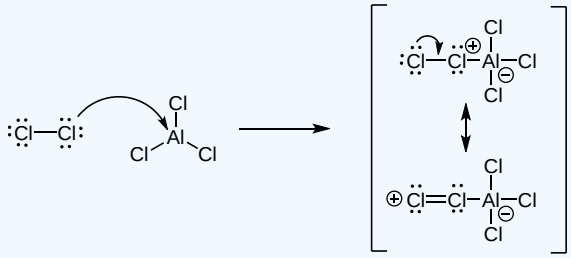
Answer



Exercise 11.2.4

Draw the formation of Cl^+ from $AlCl_3$ and Cl_2.

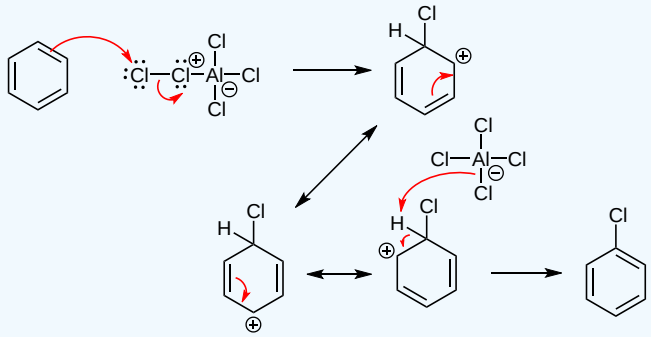
Answer



Exercise 11.2.5

Draw the mechanism of the reaction between Cl^+ and a benzene.

Answer



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11.3: Other Aromatic Substitutions

Objectives

After completing this section, you should be able to

1. write a balanced equation for the halogenation (Cl, Br) of benzene in the presence of a suitable catalyst or promoter.
2. draw the resonance contributors for the carbocation which is formed during the reaction of chlorine or bromine with benzene.
3. write the equation for the nitration and sulfonation of benzene.
4. write the detailed mechanism for the nitration and sulfonation of benzene.
5. write the equation for the reduction of an aromatic nitro compound to an amine.
6. identify aromatic sulfonation as being a reversible process, and describe the conditions under which the forward and reverse reactions are favored.
7. write the equation for the desulfonation of an aromatic sulfonic acid.
8. identify aromatic sulfonic acids as being key intermediates in the manufacture of sulfa drugs.

Key Terms

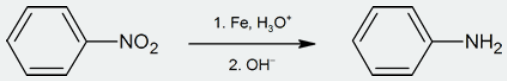
Make certain that you can define, and use in context, the key term below.

- nitronium ion, (NO^{+2})

Study Notes

You should be careful to remember that iodine and fluorine cannot be introduced into an aromatic ring by the method used for bromine and chlorine.

The nitration of an aromatic ring is an important synthetic pathway to generating arylamines. The reaction below shows one common method of reducing the nitro group.

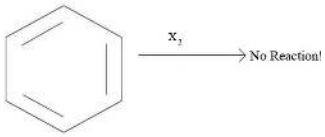


Halogenation of Benzene

Halogenation is an example of electrophilic aromatic substitution. In electrophilic aromatic substitutions, a benzene is attacked by an electrophile which results in substitution of hydrogens. However, halogens are not electrophilic enough to break the aromaticity of benzenes, which require a catalyst to activate.

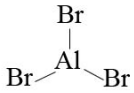
Activation of Halogen

(where X= Br or Cl, we will discuss further in detail later why other members of the halogen family Flourine and Iodine are not used in halogenation of benzenes)

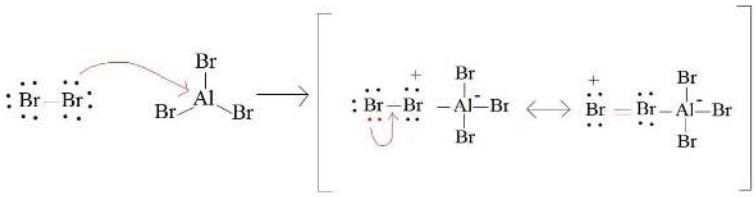


Hence, halogen needs the help and aid of Lewis Acidic Catalysts to activate it to become a very strong electrophile. Examples of these activated halogens are Ferric Halides (FeX_3) Aluminum Halides (AlX_3) where X= Br or Cl. In the following examples, the halogen we will look at is Bromine.

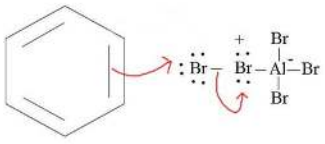
In the example of bromine, in order to make bromine electrophilic enough to react with benzene, we use the aid of an aluminum halide such as aluminum bromide.

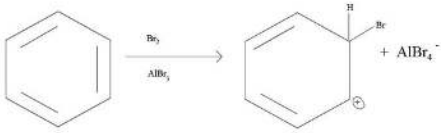


With aluminum bromide as a Lewis acid, we can mix Br_2 with $AlBr_3$ to give us Br^+. The presence of Br^+ is a much better electrophile than Br_2 alone. Bromination is achieved with the help of $AlBr_3$ (Lewis acid catalysts) as it polarizes the Br-Br bond. The polarization causes the bromine atoms within the Br-Br bond to become more electrophilic. The presence of Br^+ compared to Br_2 alone is a much better electrophile that can then react with benzene.

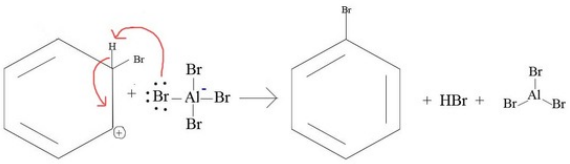


As the bromine has now become more electrophilic after activation of a catalyst, an electrophilic attack by the benzene occurs at the terminal bromine of Br-Br-$AlBr_3$. This allows the other bromine atom to leave with the $AlBr_3$ as a good leaving group, $AlBr_4$-.





After the electrophilic attack of bromide to the benzene, the hydrogen on the same carbon as bromine can be easily eliminated to reform the aromatic benzene ring. Hence, the overal reaction is an electrophilic aromatic SUBSTITUTION. Since the by-product aluminum tetrabromide can act as a base, it removes the Hydrogen on the same carbon as bromine.



In the end, $AlBr_3$ is not consumed by the reaction and is regenerated. It serves as our catalyst in the halogenation of benzenes.

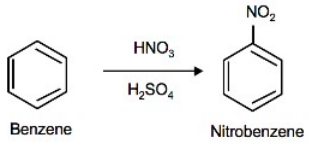
Dissociation Energies of Halogens and its Effect on Halogenation of Benzenes

The electrophilic bromination of benzenes is an exothermic reaction. The exothermic rates of aromatic halogenation decrease down the periodic table in the halogen family. Flourination is the most exothermic and Iodination would be the least. Being so exothermic, a reaction of flourine with benzene is explosive! For iodine, electrophilic iodination is generally endothermic, hence a reaction is often not possible. Similar to bromide, chlorination would require the aid of an activating presence such as Alumnium Chloride or Ferric Chloride. The mechanism of this reaction is the same as with Bromination of benzene.

Nitration and sulfonation of benzene are two examples of electrophilic aromatic substitution. The nitronium ion (NO_2^+) and sulfur trioxide (SO_3) are the electrophiles and individually react with benzene to give nitrobenzene and benzenesulfonic acid respectively.

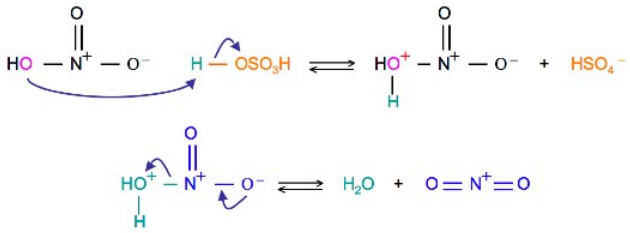
Nitration of Benzene

The source of the nitronium ion is through the protonation of nitric acid by sulfuric acid, which causes the loss of a water molecule and formation of a nitronium ion.



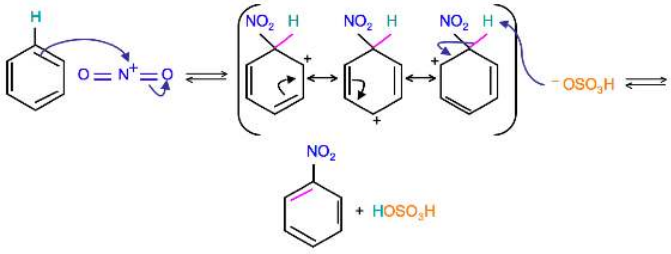
Sulfuric Acid Activation of Nitric Acid

The first step in the nitration of benzene is to activate HNO_3 with sulfuric acid to produce a stronger electrophile, the nitronium ion.



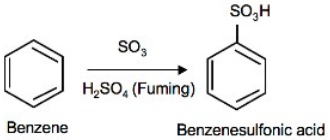
Because the nitronium ion is a good electrophile, it is attacked by benzene to produce Nitrobenzene.

Mechanism



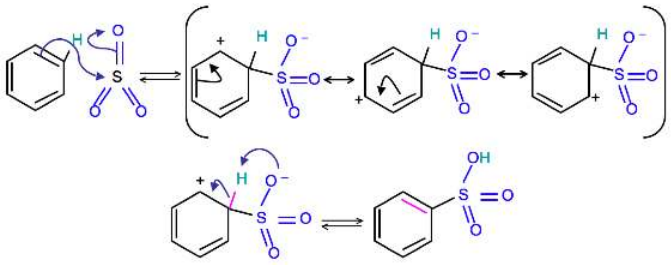
Sulfonation of Benzene

Sulfonation is a reversible reaction that produces benzenesulfonic acid by adding sulfur trioxide and fuming sulfuric acid. The reaction is reversed by adding hot aqueous acid to benzenesulfonic acid to produce benzene.



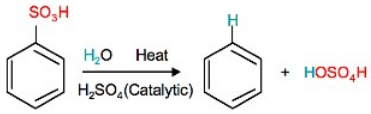
Mechanism

To produce benzenesulfonic acid from benzene, fuming sulfuric acid and sulfur trioxide are added. Fuming sulfuric acid, also refered to as *oleum*, is a concentrated solution of dissolved sulfur trioxide in sulfuric acid. The sulfur in sulfur trioxide is electrophilic because the oxygens pull electrons away from it because oxygen is very electronegative. The benzene attacks the sulfur (and subsequent proton transfers occur) to produce benzenesulfonic acid.



Reverse Sulfonation

Sulfonation of benzene is a reversible reaction. Sulfur trioxide readily reacts with water to produce sulfuric acid and heat. Therefore, by adding heat to benzenesulfonic acid in diluted aqueous sulfuric acid the reaction is reversed.



Further Applications of Nitration and Sulfonation

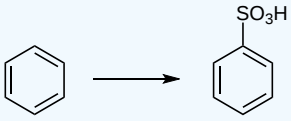
Nitration is used to add nitrogen to a benzene ring, which can be used further in substitution reactions. The nitro group acts as a ring deactivator. Having nitrogen present in a ring is very useful because it can be used as a directing group as well as a masked amino group. The products of aromatic nitrations are very important intermediates in industrial chemistry.

Because sulfonation is a reversible reaction, it can also be used in further substitution reactions in the form of a directing or blocking group because it can be easily removed. The sulfonic group blocks the carbon from being attacked by other substituents and after the reaction is completed it can be removed by reverse sulfonation. Benzenesulfonic acids are also used in the synthesis of detergents, dyes, and sulfa drugs. Bezenesulfonyl Chloride is a precursor to sulfonamides, which are used in chemotherapy.

Exercises

? Exercise 11.3.1

1. What is/are the required reagent(s)for the following reaction:

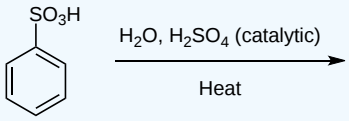


Answer

SO_3 and H_2SO_4 (fuming)

? Exercise 11.3.2

What is the product of the following reaction:



Answer

Exercise 11.3.3

Why is it important that the nitration of benzene by nitric acid occurs in sulfuric acid?

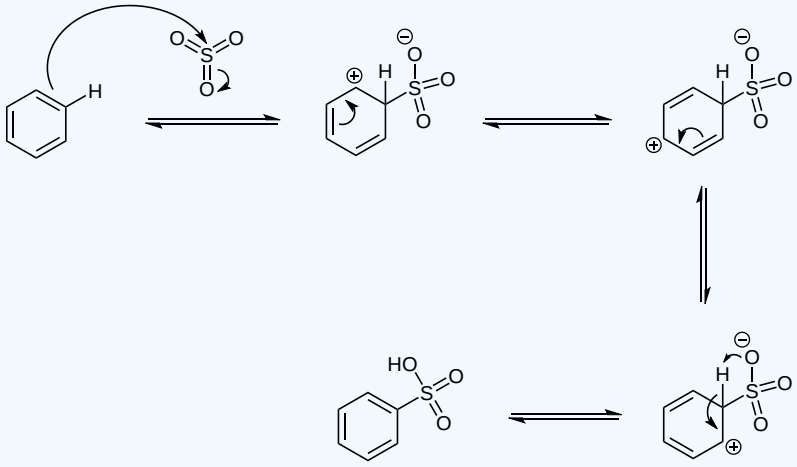
Answer

Sulfuric acid is needed in order for a good electrophile to form. Sulfuric acid protonates nitric acid to form the nitronium ion (water molecule is lost). The nitronium ion is a very good electrophile and is open to attack by benzene. Without sulfuric acid the reaction would not occur.

Exercise 11.3.4

Write a detailed mechanism for the sulfonation of benzene, including all resonance forms.

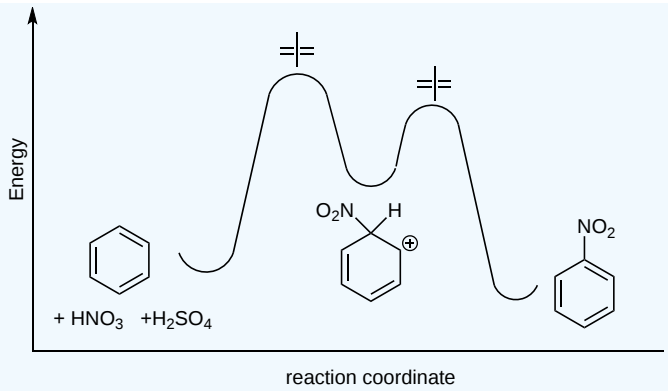
Answer



Exercise 11.3.5

Draw an energy diagram for the nitration of benzene. Draw the intermediates, starting materials, and products. Label the transition states.

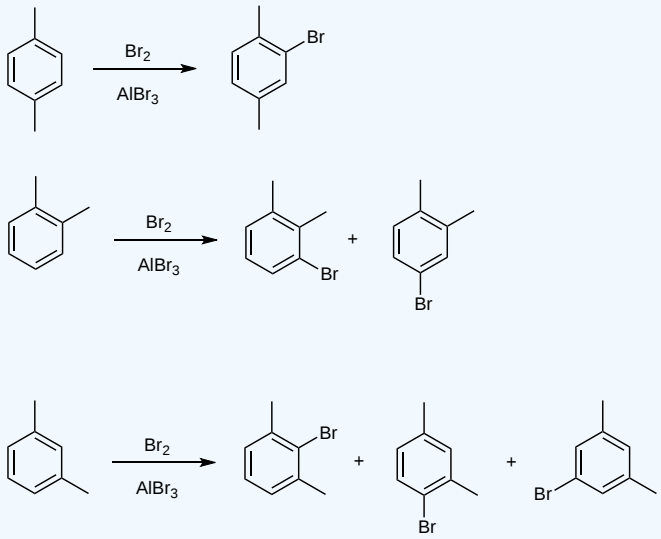
Answer



Exercise 11.3.6

In each case, how many products would be possible for the bromination of *p*-xylene, *o*-xylene, and *m*-xylene?

Answer

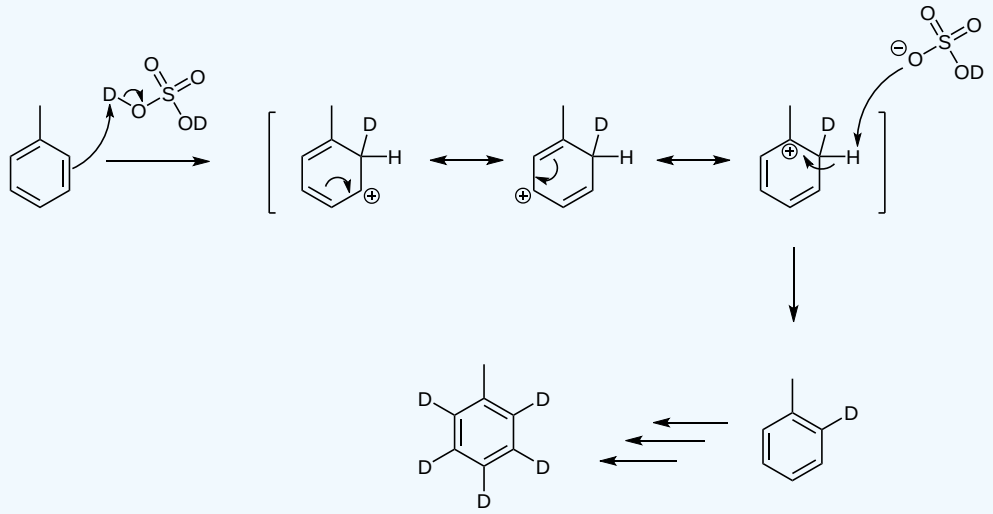


Exercise 11.3.7

If toluene is treated with D_2SO_4 all the hydrogen's are replaced with deuterium. Explain.

Answer

The deuterium is added to the ring. When the ring "re-aromatizes" the base removes the hydrogen before the deuterium (remember, the C-D bond is stronger than the C-H bond) and therefore D is left on the ring. This continues for the rest of the hydrogens on the ring.



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2. Malhotra, Ripudaman, Subhash C. Narang, and George A. Olah. Nitration: Methods and Mechanisms. New York: VCH Publishers, Inc., 1989.
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4. Vollhardt, Peter. Organic Chemistry : Structure and Function. 5th ed. Boston: W. H. Freeman & Company, 2007.

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11.4: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction

Objectives

After completing this section, you should be able to

- write the equation for the preparation of an alkylbenzene by a Friedel-Crafts alkylation reaction.
- identify the product formed from the Friedel-Crafts alkylation of a given aromatic compound.
- identify the aromatic compound needed to prepare a given arene by a Friedel-Crafts alkylation.
- identify the alkyl halide and catalyst needed to form a specified arene from a given aromatic compound.
- write the detailed mechanism for the Friedel-Crafts alkylation reaction, and identify the similarities between this reaction and those electrophilic aromatic substitution reactions you studied previously in Chapter 11.
- show how alkyl halides and acylhalides can be used as alkylating agents in Friedel-Crafts alkylation reactions.
- discuss the limitations of the Friedel-Crafts alkylation reaction, paying particular attention to the structure of the alkyl halide, the structure of the aromatic substrate and the problem of polyalkylation.
- write an equation for a typical Friedel-Crafts acylation.
- write the detailed mechanism of the Friedel-Crafts acylation reaction.
- identify the product formed by the Friedel-Crafts acylation of a given aromatic compound.
- identify the aromatic compound, and the reagent and catalyst needed to prepare a given ketone through a Friedel-Crafts acylation reaction.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- acyl group
- Friedel-Crafts acylation reaction
- Friedel-Crafts alkylation reaction
- polyalkylation

Study Notes

A Friedel-Crafts alkylation reaction is an electrophilic aromatic substitution reaction in which a carbocation is attacked by a pi bond from an aromatic ring with the net result that one of the aromatic protons is replaced by an alkyl group. If you prefer, you may regard these reactions as involving an attack by an aromatic ring on a carbocation. The latter approach is the one used in the textbook, but the former approach is probably more common.

When more than one alkyl group is introduced into an aromatic ring during the course of a Friedel-Crafts alkylation reaction, polyalkylation is said to have occurred.

The four limitations on the use of Friedel-Crafts alkylations are as follows:

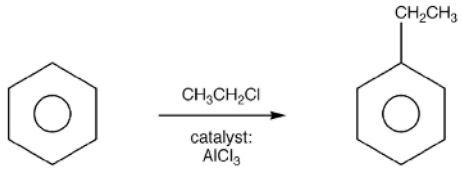
1. vinyl and aryl halides cannot be used to form carbocations.
2. the aromatic substrate must not contain a strongly deactivating group, or groups, such as NH_2, NHR or NR_2, which form complexes with the Lewis acid catalyst and in so doing become strongly deactivating.
3. polyalkylation, which can be overcome by using a large excess of the aromatic substrate.
4. carbocation rearrangements may occur in any reaction that involves a carbocation.

The reaction of an aromatic substrate with an acid chloride (or acid anhydride) in the presence of an aluminum chloride catalyst is used to introduce an acyl group (C=O) into the aromatic ring through an electrophilic aromatic substitution mechanism. Such reactions are Friedel-Crafts acylation reactions.

Friedel-Crafts Alkylation

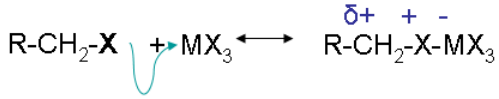
Friedel-Crafts Alkylation was first discovered by French scientist Charles Friedel and his partner, American scientist James Crafts, in 1877. This reaction allowed for the formation of alkyl benzenes from alkyl halides, but was plagued with unwanted

supplemental activity that reduced its effectiveness.



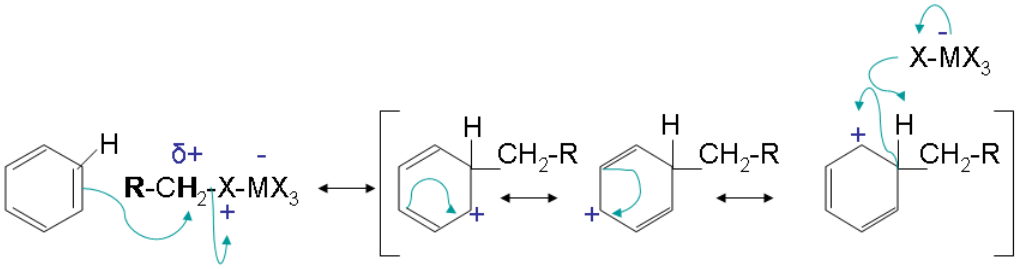
The mechanism takes place as follows:

Step 1:



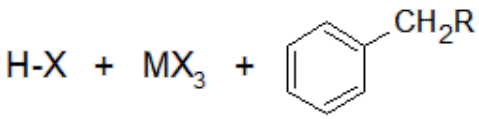
Step one creates a carbocation that acts as the electrophile in the reaction. This steps activates the haloalkane. Secondary and tertiary halides only form the free carbocation in this step.

Steps 2 and 3:



Step 2 has an electron pair from the aromatic ring attack the carbocation forming a new C-C bond. The arenium ion intermediate results with stabilization from multiple resonance forms. The loss of a proton then gives the neutral alkylated substitution product.

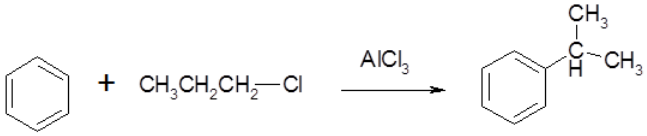
Final Products



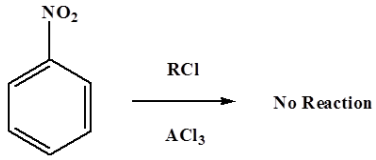
The reactivity of haloalkanes increases as you move up the periodic table and increase polarity. This means that an RF haloalkane is most reactive followed by RCl then RBr and finally RI. This means that the Lewis acids used as catalysts in Friedel-Crafts Alkylation reactions tend have similar halogen combinations such as BF_3, $SbCl_5$, $AlCl_3$, $SbCl_5$, and $AlBr_3$, all of which are commonly used in these reactions.

Some limitations of Friedel-Crafts Alkylation

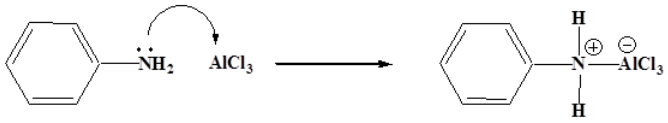
There are possibilities of carbocation rearrangements when you are trying to add a carbon chain greater than two carbons. The rearrangements occur due to hydride shifts and methyl shifts. For example, the product of a Friedel-Crafts Alkylation will show an iso rearrangement when adding a three carbon chain as a substituent. One way to resolve these problems is through Friedel-Crafts Acylation.



Also, the reaction will only work if the ring you are adding a substituent to is not deactivated. Friedel-Crafts reactions fail when used with compounds such as nitrobenzene and other strong deactivating systems.

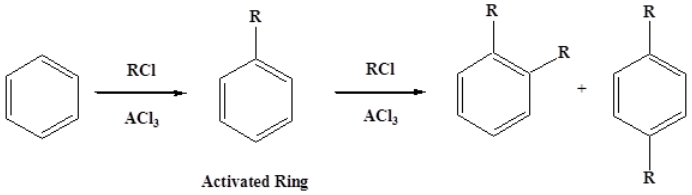


Friedel-Crafts reactions cannot be preformed then the aromatic ring contains a NH_2, NHR, or NR_2 substituent. The lone pair electrons on the amines react with the Lewis acid $AlCl_3$. This places a positive charge next to the benzene ring, which is so strongly activating that the Friedel-Crafts reaction cannot occur.



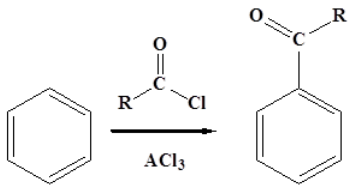
The positive charge strongly deactivates the benzene ring

Lastly, Friedel-Crafts alkylation can undergo polyalkylation. The reaction adds an electron donating alkyl group, which activates the benzene ring to further alkylation.



Activated Ring

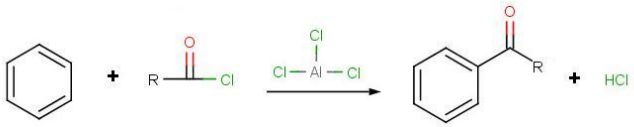
This problem does not occur during Friedel-Crafts Acylation because an acyl group is deactivating, thus prevents further acylations.



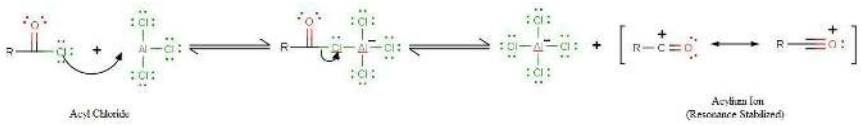
Dectivated Ring

Friedel-Crafts Acylation

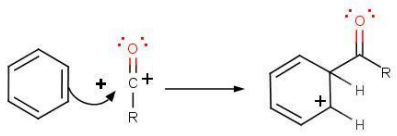
The goal of the reaction is the following:



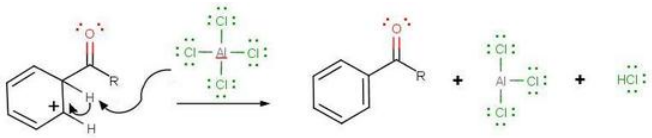
The very first step involves the formation of the acylium ion which will later react with benzene:



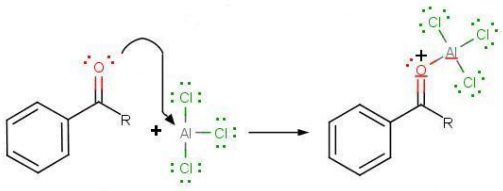
The second step involves the attack of the acylium ion on benzene as a new electrophile to form one complex:



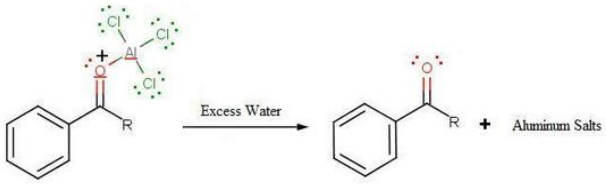
The third step involves the departure of the proton to reform aromaticity:



During the third step, $AlCl_4$ returns to remove a proton from the benzene ring, which enables the ring to return to aromaticity. In doing so, the original $AlCl_3$ is regenerated for use again, along with HCl. Most importantly, we have the final product of the reaction, which is a ketone. The first part of the product is the complex with aluminum chloride as shown:



The final step involves the addition of water to liberate the final product as the acylbenzene:

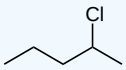
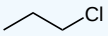


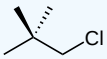
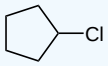
Because the acylium ion (as was shown in step one) is stabilized by resonance, no rearrangement occurs (unlike in Friedel-Crafts Alkylation reactions - see Limitation 1 above). Also, because of of the deactivation of the product, it is no longer susceptible to electrophilic attack and hence, no longer goes into further reactions (Limitation 3 above from Friedel-Crafts Alkylation reactions). However, as not all is perfect, Limitation 2 still prevails where Friedel-Crafts Acylation fails with strong deactivating rings.

Exercises

? Exercise 11.4.1

Which of the following will NOT undergo a rearrangement in a Friedel-Crafts reaction?

A) CH_3Cl B)  C) 

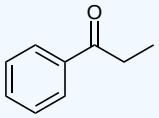
D)  E) 

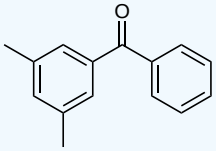
Answer

A, B, and E will not undergo a rearrangement.

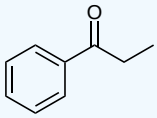
Exercise 11.4.2

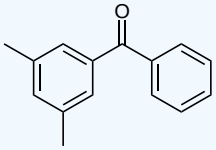
Suggest an acyl chloride that was used to make the following compounds:

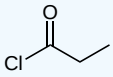
A) 

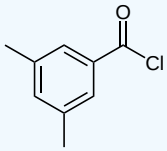
B) 

Answer

A) 

B) 





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11.5: Substituent Effects in Substituted Aromatic Rings

Objectives

After completing this section, you should be able to

1. describe the two ways in which a substituent influences the electrophilic substitution of a monosubstituted aromatic compound.
2. classify each of the following substituents as being either activating or deactivating with respect to electrophilic aromatic substitution: $-NH_2$, $-OH$, $-NHR$, $-NR_2$, $-OR$, $-NHCOR$, alkyl (R), phenyl, R_3N^+, $-NO_2$, $-CN$, $-COR$, $-CO_2H$, $-CO_2R$, $-CHO$, halogens.
3. list a given series of substituents (selected from those given in Objective 2) in order of increasing or decreasing ability to activate or deactivate an aromatic ring with respect to electrophilic substitution.
4. explain, in general terms, the factors that determine whether a given substituent will activate or deactivate an aromatic ring with respect to electrophilic substitution.
5. list a given series of aromatic compounds in order of increasing or decreasing reactivity with respect to electrophilic substitution.
6. explain the inductive effects displayed by substituents such as nitro, carboxyl, alkyl and the halogens during electrophilic aromatic substitution reactions.
7. explain the resonance effects displayed by substituents such as nitro, carbonyl-containing, hydroxy, alkoxy and amino groups during electrophilic aromatic substitution reactions.

Key Terms

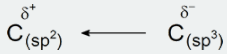
Make certain that you can define, and use in context, the key terms below.

- inductive effect
- resonance effect

Study Notes

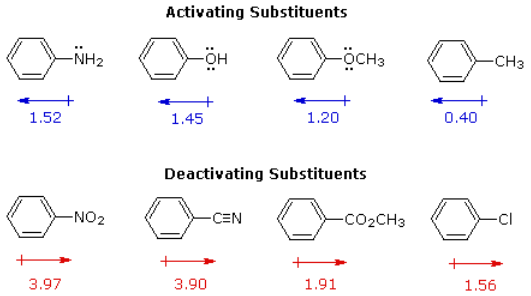
On reading Objective 2 students may exclaim “How am I ever going to memorize all of this!”—or words to that effect. The answer is that if you are trying to memorize such things, you are taking the wrong approach to organic chemistry. What you should be doing is trying to understand the factors that determine whether a given substituent will activate or deactivate a benzene ring with respect to electrophilic substitution.

Note that one argument sometimes used to explain the ability of alkyl groups to donate electrons inductively to an aromatic ring is that sp^2-hybridized carbon atoms are more electronegative than sp^3-hybridized carbon atoms. Thus, a sigma bond between sp^2- and sp^3-carbon is slightly polarized, as follows:



When substituted benzene compounds undergo electrophilic substitution reactions of the kind discussed above, **two related features must be considered:**

I. The first is the relative reactivity of the compound compared with benzene itself. Experiments have shown that substituents on a benzene ring can influence reactivity in a profound manner. For example, a hydroxy or methoxy substituent increases the rate of electrophilic substitution about ten thousand fold. In contrast, a nitro substituent decreases the ring's reactivity by roughly a million. This **activation** or **deactivation** of the benzene ring toward electrophilic substitution may be correlated with the electron donating or electron withdrawing influence of the substituents, as measured by molecular dipole moments. In the following diagram we see that electron donating substituents (blue dipoles) activate the benzene ring toward electrophilic attack, and electron withdrawing substituents (red dipoles) deactivate the ring (make it less reactive to electrophilic attack).

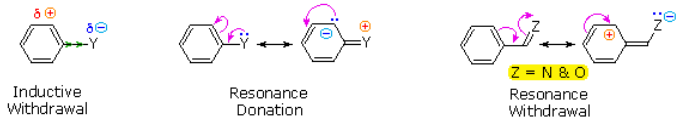


The influence a substituent exerts on the reactivity of a benzene ring may be explained by the interaction of two effects:

The first is the **inductive effect** of the substituent. Most elements other than metals and carbon have a significantly greater electronegativity than hydrogen. Consequently, substituents in which nitrogen, oxygen and halogen atoms form sigma-bonds to the aromatic ring exert an inductive electron withdrawal, which deactivates the ring (left-hand diagram below).

The second effect is the result of **conjugation** of a substituent function with the aromatic ring. This conjugative interaction facilitates electron pair donation or withdrawal, to or from the benzene ring, in a manner different from the inductive shift. If the atom bonded to the ring has one or more non-bonding valence shell electron pairs, as do nitrogen, oxygen and the halogens, electrons may flow into the aromatic ring by pi-pi conjugation (resonance), as in the middle diagram. Finally, polar double and triple bonds conjugated with the benzene ring may withdraw electrons, as in the right-hand diagram. Note that in the resonance examples all the contributors are not shown. In both cases the charge distribution in the benzene ring is greatest at sites ortho and para to the substituent.

In the case of the nitrogen and oxygen activating groups displayed in the top row of the previous diagram, electron donation by resonance dominates the inductive effect and these compounds show exceptional reactivity in electrophilic substitution reactions. Although halogen atoms have non-bonding valence electron pairs that participate in pi-pi conjugation, their strong inductive effect predominates, and compounds such as chlorobenzene are less reactive than benzene. The three examples on the left of the bottom row (in the diagram above) are examples of electron withdrawal by conjugation to polar double or triple bonds, and in these cases the inductive effect further enhances the deactivation of the benzene ring. Alkyl substituents such as methyl increase the nucleophilicity of aromatic rings in the same fashion as they act on double bonds.

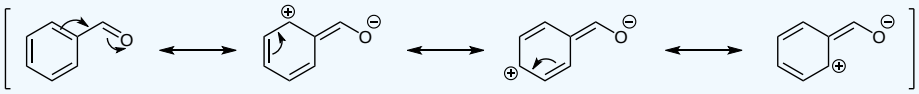


Exercises

? Exercise 11.5.1

Draw the resonance structures for benzaldehyde to show the electron-withdrawing group.

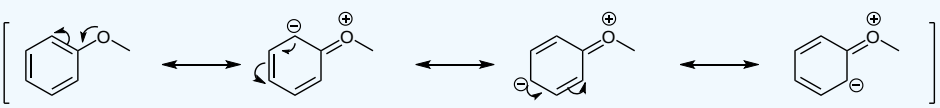
Answer



? Exercise 11.5.2

Draw the resonance structures for methoxybenzene to show the electron-donating group.

Answer



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11.6: An Explanation of Substituent Effects

Objectives

After completing this section, you should be able to

1. draw the resonance contributors for the carbocation intermediate formed during the reaction of a given monosubstituted benzene derivative with any of the electrophiles discussed in this chapter.
2. classify each of the substituents listed in Objective 2 of Section 11.5 as being either meta or ortho/para directing.
3. classify each of the substituents listed in Objective 2 of Section 11.5 as being ortho/para directing activators, ortho/para directing deactivators, or meta directing deactivators.
4. predict the product or products formed from the reaction of a given monosubstituted benzene derivative with each of the electrophiles discussed in this chapter.
5. explain, by drawing the resonance contributors for the intermediate carbocation, why the electrophilic substitution of an alkyl benzene results in a mixture of mainly ortho- and para- substituted products.
6. explain why the electrophilic substitution of phenols, amines and their derivatives proceeds more rapidly than the electrophilic substitution of benzene itself.
7. explain, by drawing the resonance contributors for the intermediate carbocation, why meta substitution predominates in electrophilic aromatic substitution reactions carried out on benzene derivatives containing one of the substituents R_3N^+, NO_2, CO_2H, CN, CO_2R, COR or CHO.
8. explain why electrophilic aromatic substitution of benzene derivatives containing one of the substituents listed in Objective 7, above, proceeds more slowly than the electrophilic substitution of benzene itself.
9. explain, by drawing the resonance contributors for the intermediate carbocation, why the electrophilic aromatic substitution of halobenzenes produces a mixture of mainly ortho- and para-substituted products.
10. explain why the electrophilic aromatic substitution of halobenzenes proceeds more slowly than does the electrophilic substitution of benzene itself.
11. use the principles developed in this chapter to predict in which of the three categories listed in Objective 3, above, a previously unencountered substituent should be placed.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- steric effect
- steric hindrance

Study Notes

As you saw in Section 11.5, a substituent on a benzene ring can be an activator or a deactivator. At the same time, a substituent can also be a meta director or an ortho/para director. Of the four possible combinations, only three are known—there are no meta directing activators.

If you look at the data for the nitration of toluene, you will see that the yield of *o*-nitrotoluene is 63% and that of *p*-nitrotoluene is 34%. Statistically, we should expect to obtain twice as much ortho product as para product, because the former is produced by attack at either of two carbon atoms whereas the latter is produced by attack at only one carbon atom.

In this instance, the observed ortho/para ratio is almost 2:1, as we might expect. However, if we study the ortho/para ratio found in the nitration of a number of other arenes, we see that this is not always the case. Note that the data for the nitration of toluene given in the table below differ from those presented elsewhere. The variation may result from a difference in temperature, reaction conditions or reagent, and emphasizes the point that it is the trends which are important, not the numbers themselves.

Substrate	% ortho	% para	ortho/para ratio
toluene	58	37	1.57:1

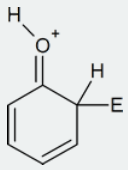
ethylbenzene	45	49	0.92:1
isopropylbenzene	30	62	0.48:1
tert-butylbenzene	16	73	0.22:1

[**Source:** These data were taken from the audiocassette *Some Organic Reaction Pathways*, by Peter Sykes. London: Educational Techniques Subject Group, The Chemical Society, 1975.]

Table 11.6.1**:** Nitration of arenes

The table above shows us that as the size of the alkyl substituent already present in the ring increases, attack at the ortho position becomes more difficult, and the percentage of ortho isomers in the mixture of products decreases. This is an example of a *steric effect*—an effect caused by the size of the substituent—and we would say that as the size of the alkyl group increases, attack at the ortho position becomes less favorable as a result of *steric hindrance*. Note that the size of the electrophile can also be a factor in determining the ortho/para ratio: the larger the electrophile, the less able it is to attack at the ortho position, particularly if the substituent already present in the ring is itself quite bulky.

When drawing the resonance contributors to the carbocation formed during an electrophilic aromatic substitution, bear in mind that those of the type



are particularly important, because in such structures each atom possesses a complete octet of electrons.

Note that, as do the hydroxyl and amino groups, the halogens have an inductive electron-withdrawing effect and a resonance electron-releasing effect on a benzene ring. The difference in behavior during electrophilic substitutions arises because, with the hydroxyl and amino groups, the resonance effect is much greater than the inductive effect, whereas with the halogens, there is a much finer balance. In the case of the latter, the inductive effect reduces the overall reactivity, but the resonance effect means that this reduction is felt less at the ortho and para positions than at the meta position.

Substituted rings are divided into two groups based on the type of the substituent that the ring carries:

- **Activated rings**: the substituents on the ring are groups that donate electrons.
- **Deactivated rings**: the substituents on the ring are groups that withdraw electrons.

Introduction

Examples of activating groups in the relative order from the most activating group to the least activating:

$$-NH_2, -NR_2 > -OH, -OR > -NHCOR > -CH_3 \text{ and other alkyl groups}$$

with R as alkyl groups (C_nH_{2n+1})

Examples of deactivating groups in the relative order from the most deactivating to the least deactivating:

$$-NO_2, -CF_3 > -COR, -CN, -CO_2R, -SO_3H > \text{Halogens}$$

with R as alkyl groups (C_nH_{2n+1})

The order of reactivity among Halogens from the more reactive (least deactivating substituent) to the least reactive (most deactivating substituent) halogen is:

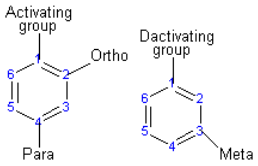
$$F > Cl > Br > I$$

The order of reactivity of the benzene rings toward the electrophilic substitution when it is substituted with a halogen groups, follows the order of electronegativity. The ring that is substituted with the most electronegative halogen is the most reactive ring (less deactivating substituent) and the ring that is substituted with the least electronegative halogen is the least reactive ring (more

deactivating substituent), when we compare rings with halogen substituents. Also the size of the halogen effects the reactivity of the benzene ring that the halogen is attached to. As the size of the halogen increase, the reactivity of the ring decreases.

The direction of the reaction

The activating group directs the reaction to the ortho or para position, which means the electrophile substitutes for the hydrogen that is on carbon 2 or carbon 4. The deactivating group directs the reaction to the meta position, which means the electrophile substitutes for the hydrogen that is on carbon 3 with the exception of the halogens which are deactivating groups but direct the ortho or para substitution.

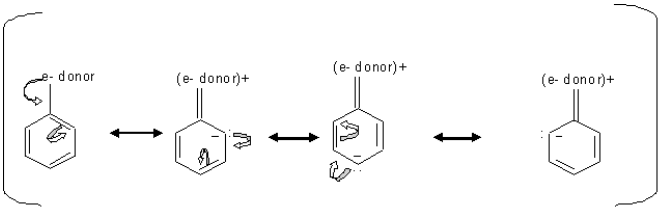


Substituents determine the reaction direction by resonance or inductive effect

Resonance effect is the conjugation between the ring and the substituent, which means the delocalizing of the pi electrons between the ring and the substituent. Inductive effect is the withdraw of the sigma (the single bond) electrons away from the ring toward the substituent, due to the higher electronegativity of the substituent compared to the carbon of the ring.

Activating groups (ortho or para directors)

When substituents such as -OH have an unshared pair of electrons, the resonance effect is stronger than the inductive effect which make these substituents stronger activators, since this resonance effect direct the electron toward the ring. In cases where the subtituents are esters or amides, they are less activating because they form resonance structures that pull the electron density away from the ring.

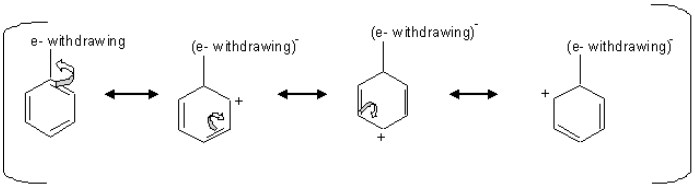


By looking at the mechanism above, we can see how electron donating groups direct electrophilic substitution to the ortho and para positions. Since the extra electron density is localized on the ortho and para carbons, these carbons are more likely to react with the electrophile.

Inductive effects of alkyl groups activate the direction of the ortho or para substitution, which is when s electrons gets pushed toward the ring.

Deactivating group (meta directors)

The deactivating groups deactivate the ring by the inductive effect in the presence of an electronegative atom that withdraws electron density away from the ring.



The mechanism above shows that when electron density is withdrawn from the ring, that leaves the carbons at the ortho, para positions with a partial positive charge which is unfavorable for the electrophile, so the electrophile attacks the carbon at the meta positions.

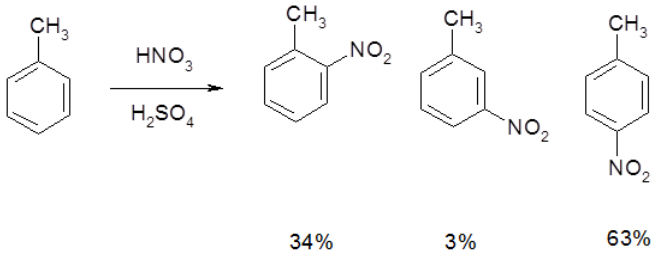
Halogens are an exception of the deactivating group that directs to the ortho or para substitution. The halogens deactivate the ring by inductive effect not by the resonance even though they have an unpaired pair of electrons. The unpaired pair of electrons gets donated to the ring, but the inductive effect pulls away the s electrons from the ring by the electronegativity of the halogens.

Substituents determine the reactivity of rings

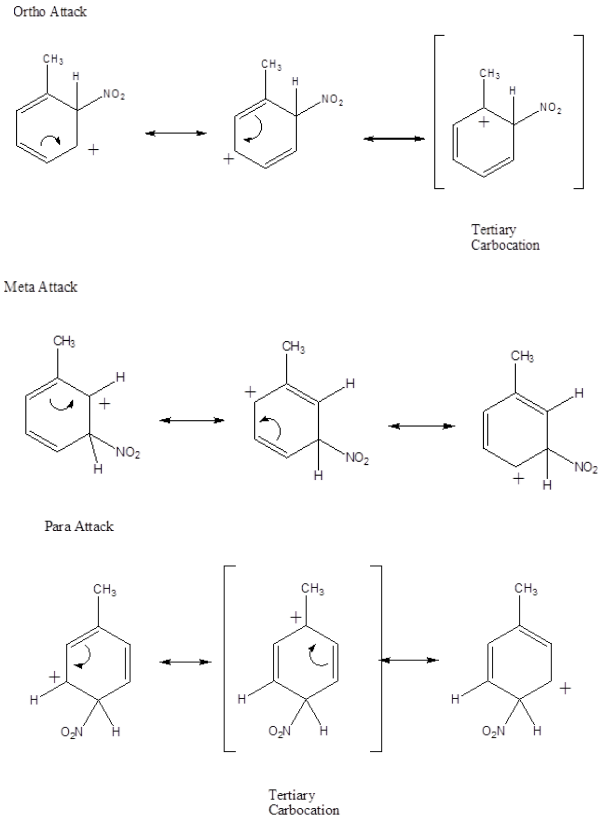
The reaction of a substituted ring with an activating group is faster than the same reaction with benzene. On the other hand, a substituted ring with a deactivated group reacts slower than benzene.

Activating groups speed up reaction with electrophiles due to increased electron density on the ring. This stabilizes the intermediate carbocation, which decreases the activation energy for the reaction. On the other hand, deactivating groups withdraw electron density away from the carbocation formed in the intermediate step, increasing the activation energy, which slows down the reaction.

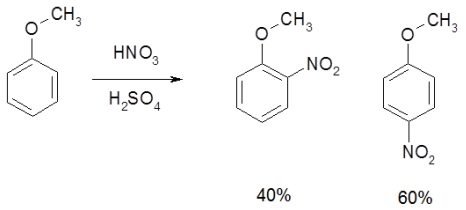
The CH_3 Group is an ortho, para director



Alkyl groups are inductively donating, therefore are activators. This results in o/p attack to form a tertiary arenium carbocation which speeds up the reaction.



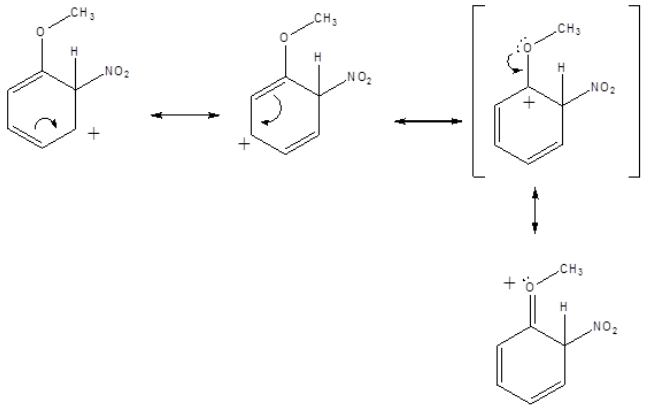
The O-CH_3 Group is an ortho, para director



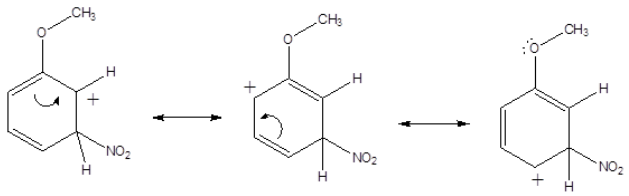
The methoxy group is an example of groups that are ortho, para directors by having an oxygen or nitrogen adjacent to the aromatic ring. This same activation is present with alcohols, amines, esters and amides (with the oxygen or nitrogen attached to the ring, not the carbonyl).

Groups with an oxygen or nitrogen attached to the aromatic ring are ortho and para directors since the O or N can push electrons into the ring, making the ortho and para positions more reactive and stabilizing the arenium ion that forms. This causes the ortho and para products to form faster than meta. Generally, the para product is preferred because of steric effects.

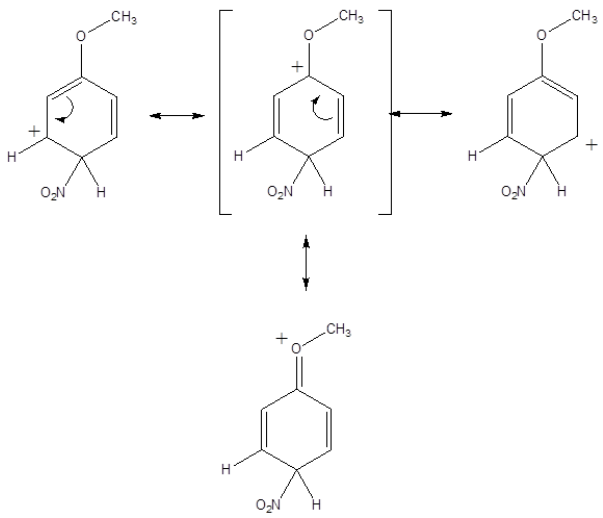
Ortho Attack



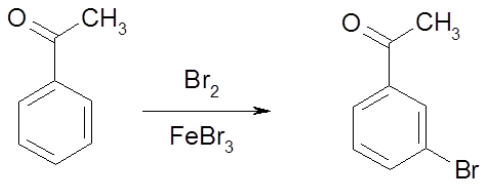
Meta Attack



Para Attack



Acyl groups are meta directors

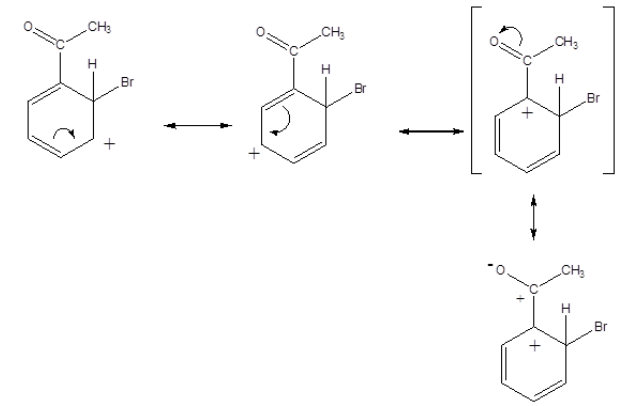


72%

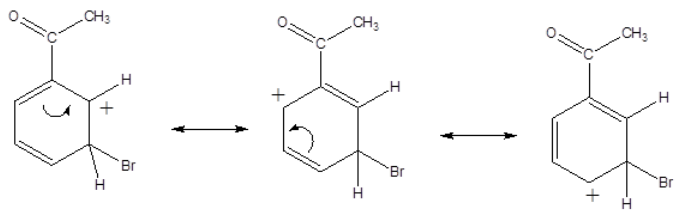
Ketones are an example of groups that deactivate an aromatic ring through resonance. Similar deactivation also occurs with ammonium ions, nitro groups, aldehydes, nitriles, sulfonic acids, and groups with a carbonyl attached to the ring (amides, esters, carboxylic acids, and anhydrides).

Acyl groups are resonance deactivators. Ortho and para attack produces a resonance structure which places the arenium cation next to an additional cation. This destabilizes the arenium cation and slows down ortho and para reaction. By default the meta product forms faster because it lacks this destabilizing resonance structure.

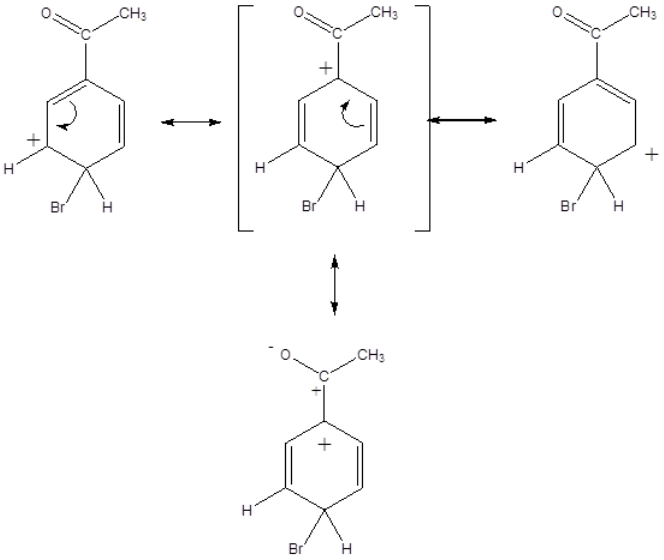
Ortho Attack



Meta Attack



Para Attack



Halogens

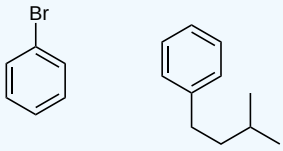
Halogens are an interesting hybrid case. They are ortho, para directors, but deactivators. Overall, they remove electron density from the ring, making it less reactive. However, due to their resonance donation to the ring, if it does react, it reacts primarily at ortho and para positions.

References

1. Schore, N.E. and P.C. Vollhardt. 2007. *Organic Chemistry, structure and function*, 5th ed. New York,NY: W.H. Freeman and Company.
2. Fryhle, C.B. and G. Solomons. 2008. *Organic Chemistry*, 9th ed.Danvers,MA: Wiley.

? Exercise 11.6.1

Predict the pattern of the electrophilic substitution on these rings:



Answer

The first substitution is going to be ortho and/or para substitution since we have a halogen substituent. The second substitution is going to be ortho and/or para substitution also since we have an alkyl substituent.

Exercise 11.6.2

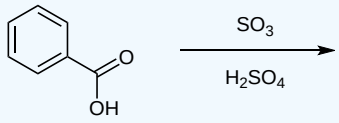
Which nitration product is going to form faster: nitration of aniline or nitration of nitrobenzene?

Answer

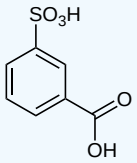
The nitration of aniline is going to be faster than the nitration of nitrobenzene, since the aniline is a ring with NH_2 substituent and nitrobenzene is a ring with NO_2 substituent. As described above NH_2 is an activating group which speeds up the reaction and NO_2 is a deactivating group that slows down the reaction.

Exercise 11.6.3

Predict the product of the following sulfonation reaction:



Answer



Exercise 11.6.4

Classify these two groups as activating or deactivating groups:

A. alcohol

B. ester

Answer

A. alcohol is an activating group.

B. Esters can be either. If the oxygen atom is next to the ring, esters are activating. However if the carbonyl is next to the ring, the ester is a deactivating group.

Exercise 11.6.5

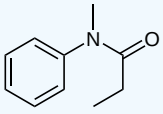
Does a chloride substituent activate or deactivate an aromatic ring?

Answer

Chloride deactivate an aromatic ring due to the inductive effect.

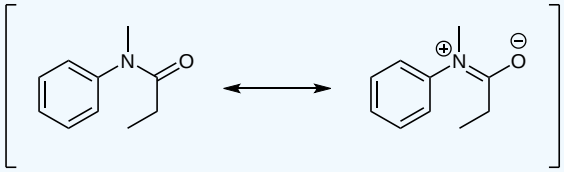
Exercise 11.6.6

The following compound is less reactive towards electrophilic substitution than aniline? Explain.



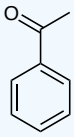
Answer

As seen in resonance the electron density is also localized off of the ring, thereby deactivating it compared to aniline.

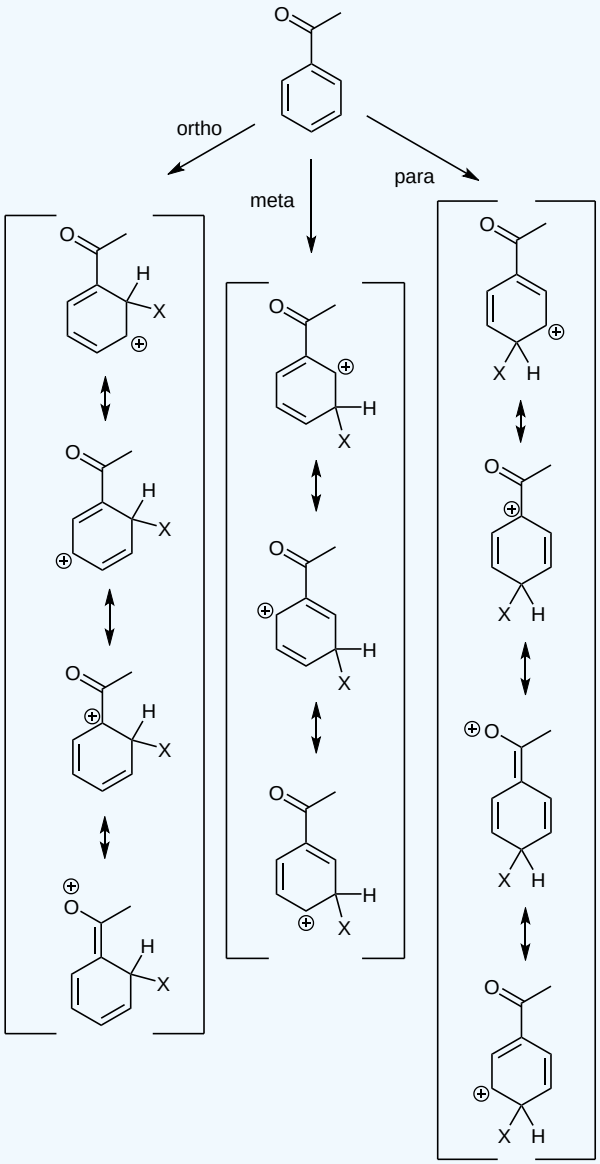


? Exercise 11.6.7

Consider the intermediates of the following molecule during an electrophilic substitution. Draw resonance structures for ortho, meta, and para attacks.



Answer



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11.7: Trisubstituted Benzenes - Additivity of Effects

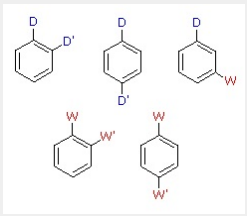
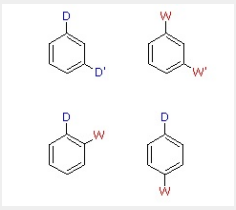
Objectives

After completing this section, you should be able to

1. predict the position or positions at which electrophilic substitution will occur when a third substituent is introduced into a disubstituted benzene ring.
2. explain the observed substitution pattern when a third substituent is introduced into a disubstituted benzene ring.

Orientational Interaction of Substituents

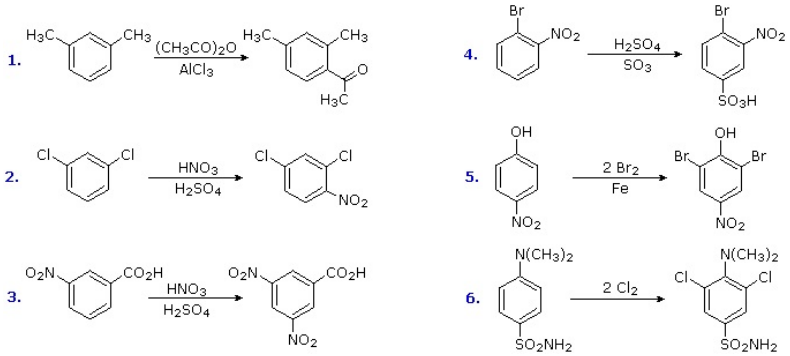
When a benzene ring has two substituent groups, each exerts an influence on subsequent substitution reactions. The activation or deactivation of the ring can be predicted more or less by the sum of the individual effects of these substituents. The site at which a new substituent is introduced depends on the orientation of the existing groups and their individual directing effects. We can identify two general behavior categories, as shown in the following table. Thus, the groups may be oriented in such a manner that their directing influences act in concert, reinforcing the outcome; or are opposed (antagonistic) to each other. Note that the orientations in each category change depending on whether the groups have similar or opposite individual directing effects.

Antagonistic or Non-Cooperative	**Reinforcing or Cooperative**
	

D = Electron Donating Group (ortho/para-directing)
W = Electron Withdrawing Group (meta-directing)

Reinforcing or Cooperative Substitutions

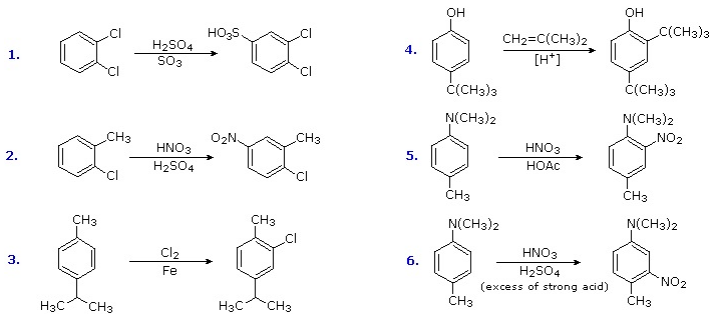
The products from substitution reactions of compounds having a reinforcing orientation of substituents are easier to predict than those having antagonistic substituents. For example, the six equations shown below are all examples of reinforcing or cooperative directing effects operating in the expected manner. Symmetry, as in the first two cases, makes it easy to predict the site at which substitution is likely to occur. Note that if two different sites are favored, substitution will usually occur at the one that is least hindered by ortho groups.



The first three examples have two similar directing groups in a meta-relationship to each other. In examples 4 through 6, oppositely directing groups have an ortho or para-relationship. The major products of electrophilic substitution, as shown, are the sum of the individual group effects. The strongly activating hydroxyl (–OH) and amino ($–NH_2$) substituents favor dihalogenation in examples 5 and 6.

Antagonistic or Non-Cooperative Substitutions

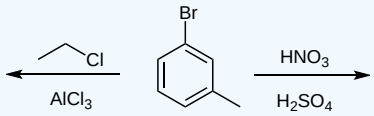
Substitution reactions of compounds having an antagonistic orientation of substituents require a more careful analysis. If the substituents are identical, as in example 1 below, the symmetry of the molecule will again simplify the decision. When one substituent has a pair of non-bonding electrons available for adjacent charge stabilization, it will normally exert the product determining influence, examples 2, 4 & 5, even though it may be overall deactivating (case 2). Case 3 reflects a combination of steric hindrance and the superior innate stabilizing ability of methyl groups relative to other alkyl substituents. Example 6 is interesting in that it demonstrates the conversion of an activating ortho/para-directing group into a deactivating meta-directing "onium" cation [$–NH(CH_3)_2^{(+)}$] in a strong acid environment.

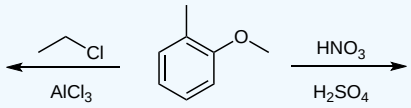


Exercises

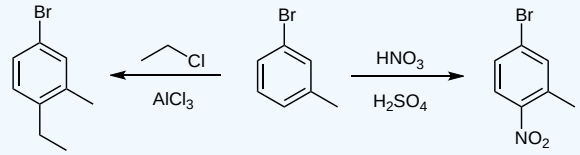
? Exercise 11.7.1

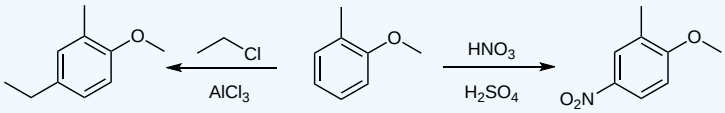
Predict the products of the following reactions:





Answer





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11.8: Nucleophilic Aromatic Substitution (reference only)

Objectives

After completing this section, you should be able to

1. identify the conditions necessary for an aryl halide to undergo nucleophilic aromatic substitution, and give an example of such a reaction.
2. write the detailed mechanism for a nucleophilic aromatic substitution reaction.
3. compare the mechanism of a nucleophilic aromatic substitution reaction and the S_N1 and S_N2 mechanisms discussed earlier.
4. identify the product formed when a given nucleophile reacts with a given aryl halide in a nucleophilic aromatic substitution reaction.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Meisenheimer complex
- nucleophilic aromatic substitution

Study Notes

A *nucleophilic aromatic substitution reaction* is a reaction in which one of the substituents in an aromatic ring is replaced by a nucleophile.

A *Meisenheimer complex* is a negatively charged intermediate formed by the attack of a nucleophile upon one of the aromatic-ring carbons during the course of a nucleophilic aromatic substitution reaction. A typical Meisenheimer complex is shown in the reaction scheme below. Notice how this particular complex can be formed from two different starting materials by using a different nucleophile in each case.

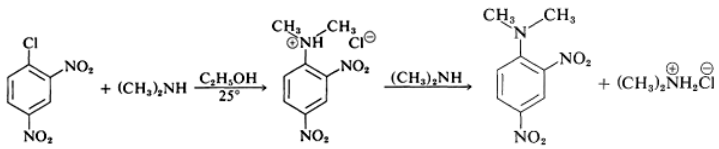
A Nucleophilic Aromatic Displacement Reactions of Aryl Halides

The carbon-halogen bonds of aryl halides are like those of alkenyl halides in being much stronger than those of alkyl halides. The simple aryl halides generally are resistant to attack by nucleophiles in either S_N1 or S_N2 reactions. 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.

Addition-Elimination Mechanism of Nucleophilic Substitution of Aryl Halides

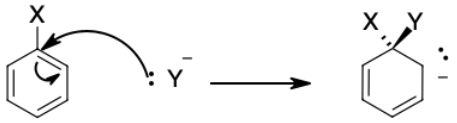
Although the simple aryl halides are inert to the usual nucleophilic reagents, considerable activation is produced by strongly electron-attracting substituents provided these are located in either the ortho or para positions, or both. For example, the displacement of chloride ion from 1-chloro-2,4-dinitrobenzene 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 108:



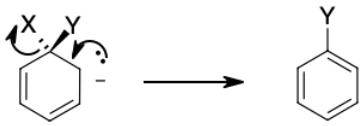
A related reaction is that of 2,4-dinitrofluorobenzene with the amino groups of peptides and proteins, and this reaction provides a means for analysis of the N-terminal amino acids in polypeptide chains.

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.

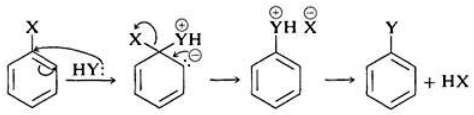
The generally accepted mechanism of nucleophilic aromatic substitution of aryl halides carrying activating groups involves two steps. The first step involves attack of the nucleophile $Y:^{\ominus}$ at the carbon bearing the halogen substituent to form an intermediate carbanion. The aromatic system is destroyed on forming the anion, and the carbon at the reaction site changes from planar (sp^2 bonds) to tetrahedral (sp^3 bonds).



In the second step, loss of an anion, $X^{\ominus}$ or $Y^{\ominus}$, regenerates an aromatic system, and, if $X^{\ominus}$ is lost, the overall reaction is nucleophilic displacement of X by Y.

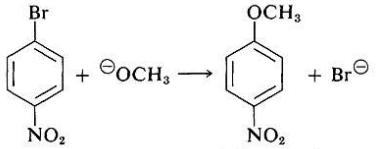


In the case of a neutral nucleophilic reagent, Y or HY, the reaction sequence would be the same except for the necessary adjustments in the charge of the intermediate:



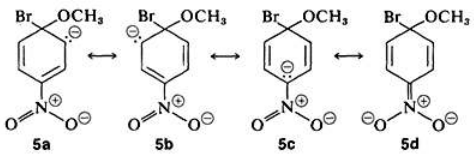
Why is this reaction pathway generally unfavorable for the simple aryl halides? The answer is that the intermediate is too high in energy to be formed at any practical rate. Not only has it lost the aromatic stabilization of the benzene ring, but its formation results in transfer of a negative charge to the ring carbons, which themselves are not very electronegative.

However, when strongly 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 methoxid (OCH_3) in the reaction of 4-bromonitrobenzene and methoxide ion:

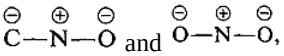


4-nitromethoxybenzene

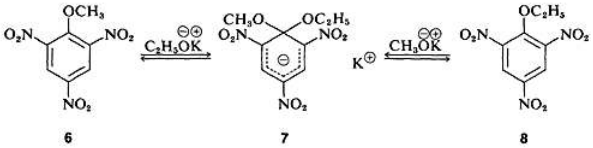
The anionic intermediate formed by addition of methoxide ion to the aryl halide can be described by the valence-bond structures 5a-5d. Of these structures 5d is especially important because in it the charge is transferred from the ring carbons to the oxygen of the nitro substituent:



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 5c and 5d in which the negative charges are both on atoms next

to positive nitrogen,  and ,

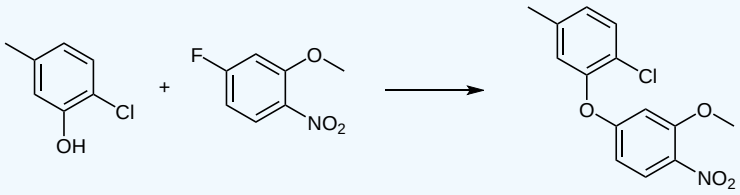
In a few instances, stable compounds resembling the postulated reaction intermediate have been isolated. One classic example is the complex 7 (isolated by J. Meisenheimer), which is the product of the reaction of either the methyl aryl ether 6 with potassium ethoxide, or the ethyl aryl ether 8 and potassium methoxide:



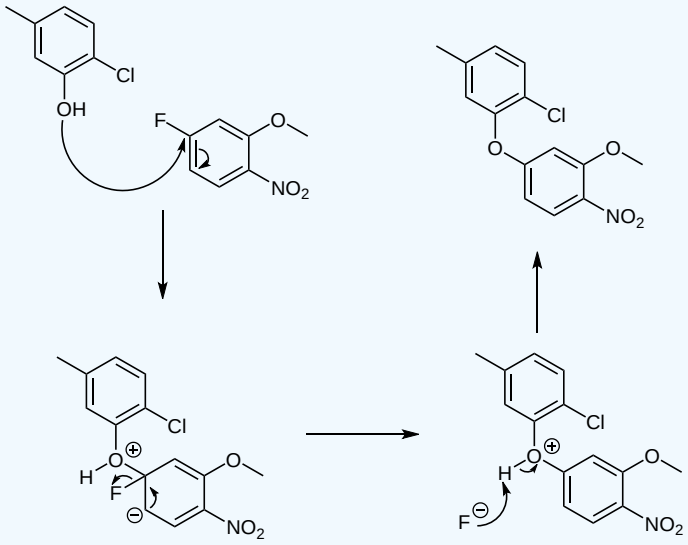
Exercises

? Exercise 11.8.1

Propose a mechanism for the following reaction:



Answer



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11.9: Benzyne (reference only)

Objectives

After completing this section, you should be able to

1. identify the reagents and conditions required to produce phenol from chlorobenzene on an industrial scale.
2. write the mechanism for the conversion of an alkyl halide to a phenol through a benzyne intermediate.
3. discuss the experimental evidence which supports the existence of benzyne intermediates.
4. discuss the bonding in benzyne, and hence account for its high reactivity.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- benzyne
- elimination-addition mechanism

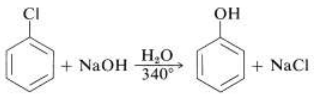
Study Notes

An elimination-addition mechanism involves the elimination of the elements of a small molecule from a substrate to produce a highly reactive intermediate, which then undergoes an addition reaction.

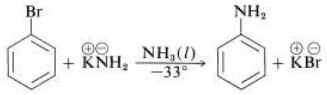
The elimination-addition mechanism of nucleophilic aromatic substitution involves the remarkable intermediate called benzyne or arynes.

Elimination-Addition Mechanism of Nucleophilic Aromatic Substitution. Arynes

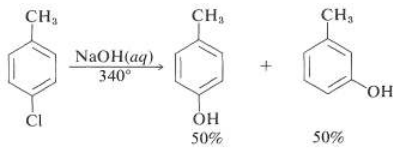
The reactivities of aryl halides, such as the halobenzenes, are exceedingly low toward nucleophilic reagents that normally effect substitution with alkyl halides and activated aryl halides. Substitutions do occur under forcing conditions of either high temperatures or very strong bases. For example, 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):



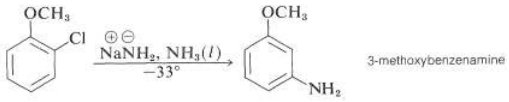
In addition, aryl chlorides, bromides, and iodides can be converted to areneamines $\mathrm{ArNH_2}$ by the conjugate bases of amines. In fact, the reaction of potassium amide with bromobenzene is extremely rapid, even at temperatures as low as -33° with liquid ammonia as solvent:



However, substitution reactions of this type differ from the previously discussed substitutions 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:

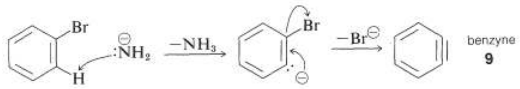


Even more striking is the exclusive formation of 3-methoxybenzenamine in the amination of 2-chloromethoxybenzene. Notice that this result is a violation of the principle of least structural change:



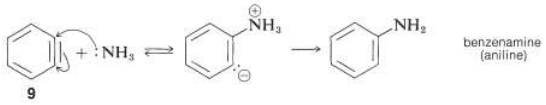
The mechanism of this type of reaction has been studied extensively, and much evidence has accumulated in support of a stepwise process, which proceeds first by base-catalyzed *elimination* of hydrogen halide (HX) from the aryl halide - as illustrated below for the amination of bromobenzene:

Elimination

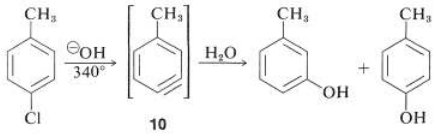


The product of the elimination reaction is a highly reactive intermediate 9 called **benzyne**, or **dehydrobenzene**, which differs from benzene in having two fewer hydrogens and an extra bond between two ortho carbons. Benzyne reacts rapidly with any available nucleophile, in this case the solvent, ammonia, to give an addition product:

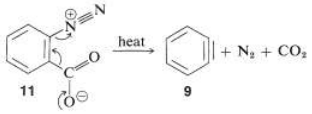
Addition



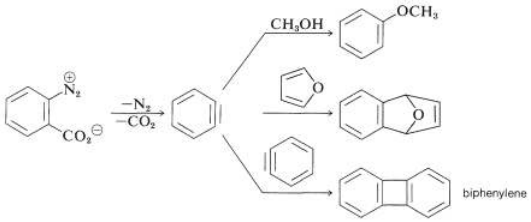
The rearrangements in these reactions result from the attack of the nucleophile at one or the other of the carbons of the extra bond in the intermediate. With benzyne the symmetry is such that no rearrangement would be detected. With substituted benzynes isomeric products may result. Thus 4-methylbenzyne, 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 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:



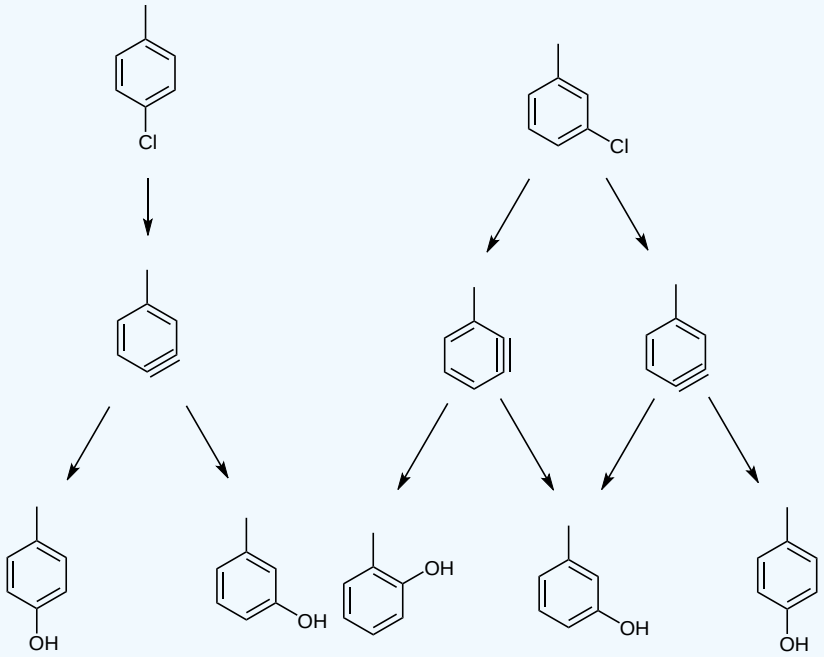
Exercises

Exercise 11.9.1

When *p*-chlorotoluene is reacted with NaOH, two products are seen. While when *m*-chlorotoluene is reacted with NaOH, three products are seen. Explain this.

Answer

You need to look at the benzyne intermediates. The para substituted only allows for two products, while the para produces two different alkynes which give three different products.



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11.10: Benzylic Bromination of Aromatic Compounds

Objectives

After completing this section, you should be able to

1. write an equation to describe the oxidation of an alkylbenzene to a carboxylic acid. (reference only)
2. identify the reagents required to oxidize a given alkylbenzene to a carboxylic acid. (reference only)
3. identify the product formed from the side-chain oxidation of a given alkylbenzene. (reference only)
4. identify the aromatic compound needed to produce a given carboxylic acid through side-chain oxidation. (reference only)
5. write the equation for the bromination of an alkylbenzene side chain.
6. identify the reagents and conditions necessary to bring about bromination in the side chain of an alkylbenzene.
7. identify the product formed when a given alkylbenzene undergoes side-chain bromination.
8. identify the alkylbenzene needed to prepare a given benzylic bromide by radical substitution.
9. write the mechanism for the radical substitution at the benzylic position of an alkylbenzene.
10. explain the stability of benzylic radicals in terms of resonance, and draw the resonance contributors of a given benzyl radical.
11. explain, and illustrate with appropriate examples, the importance of benzylic bromides as intermediates in organic syntheses.
12. arrange a given series of radicals (including benzylic type radicals) in order of increasing or decreasing stability.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- benzylic oxidation (reference only)
- benzylic position
- side-chain oxidation

Study Notes

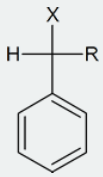
In alkylbenzenes, the carbon atom which is attached to the aromatic ring is particularly reactive. Reactions taking place at this carbon atom are said to occur at the *benzylic position*.

You may wish to review Section 5.3 to remind yourself about allylic bromination using N-bromosuccinimide.

Benzylic halides undergo the typical reactions of alkyl halides; thus, you can expect to see such compounds used frequently in multistep syntheses.

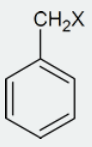
Note that we have adopted the terminology given below.

Any compound of the type



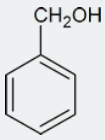
(where X = halogen) will be referred to as a “benzylic halide.”

Compounds of the type



are actually called benzyl chloride, benzyl bromide, etc.

The compound



is called benzyl alcohol.

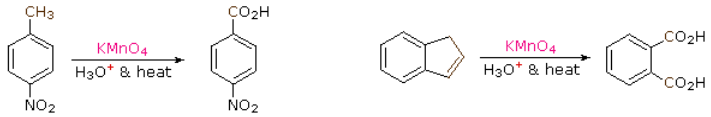
Oxidation of Alkyl Side-Chains (reference only)

The benzylic hydrogens of alkyl substituents on a benzene ring are activated toward free radical attack, as noted earlier. Furthermore, S_N1 S_N2 and E1 reactions of benzylic halides, show enhanced reactivity, due to the adjacent aromatic ring. The possibility that these observations reflect a general benzylic activation is supported by the susceptibility of alkyl side-chains to oxidative degradation, as shown in the following examples (the oxidized side chain is colored). Such oxidations are normally effected by hot acidic permanganate solutions, but for large scale industrial operations catalyzed air-oxidations are preferred. Interestingly, if the benzylic position is completely substituted this oxidative degradation does not occur (second equation, the substituted benzylic carbon is colored blue).

$$C_6H_5-CH_2CH_2CH_2CH_3 + KMnO_4 + H_3O^+ + heat \longrightarrow C_6H_5-CO_2H + CO_2$$

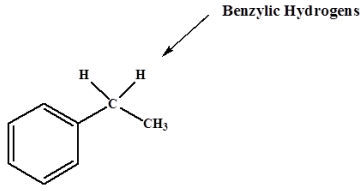
$$p-(CH_3)_3C-C_6H_4-CH_3 + KMnO_4 + H_3O_6+ + heat \longrightarrow p-(CH_3)_3C-C_6H_4-CO_2H$$

These equations are not balanced. The permanganate oxidant is reduced, usually to Mn(IV) or Mn(II). Two other examples of this reaction are given below, and illustrate its usefulness in preparing substituted benzoic acids.

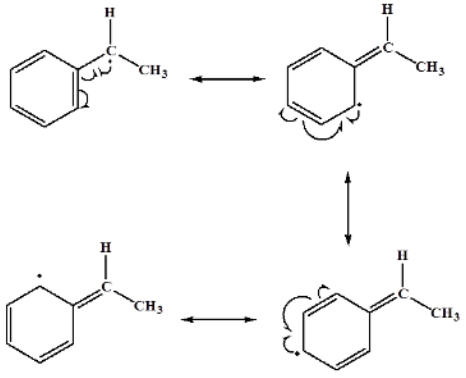


Bromination of the Benzylic Carbon

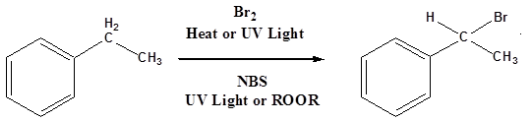
The benzylic C-H bonds weaker than most sp^3 hybridized C-H. This is because the radical formed from homolysis is resonance stabilized.



Resonance stabilization of the benzylic radical

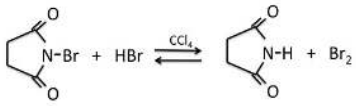


Because of the weak C-H bonds, benzylic hydrogens can form benzylic halides under radical conditions.



NBS as a Bromine Source

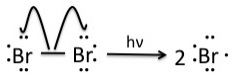
NBS (N-bromosuccinimide) is the most commonly used reagent to produce low concentrations of bromine. When suspended in tetrachloride (CCl_4), NBS reacts with trace amounts of HBr to produce a low enough concentration of bromine to facilitate the allylic bromination reaction.



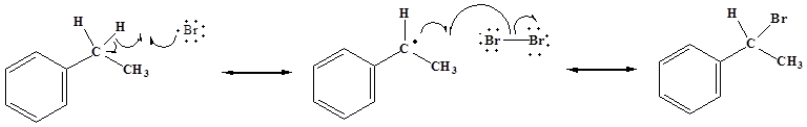
Allylic Bromination Mechanism

Step 1: Initiation

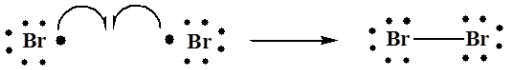
Once the pre-initiation step involving NBS produces small quantities of Br_2, the bromine molecules are homolytically cleaved by light to produce bromine radicals.



Step 2 and 3: Propagation (steps that form the desired product and regenerate the chain propagating radical)



Step 4: Termination (not useful for desired product formation)



Exercises

? Exercise 11.10.1

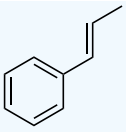
Consider a benzyl radical. Would it be more stable than an alkyl radical? Explain.

Answer

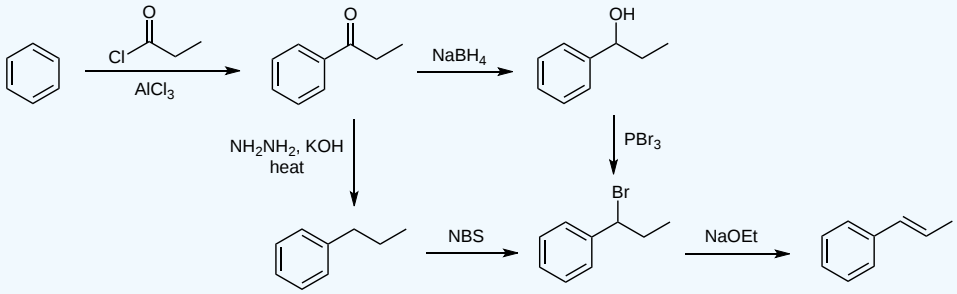
Yes it would be more stable than an alkyl radical. The benzyl radical is stabilized through several resonance structures where the radical is moved through the ring via the pi system there.

? Exercise 11.10.2

How would you make the following molecule starting with benzene?



Answer



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11.11: Reduction of Aromatic Compounds (reference only)

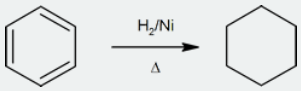
Objectives

After completing this section, you should be able to

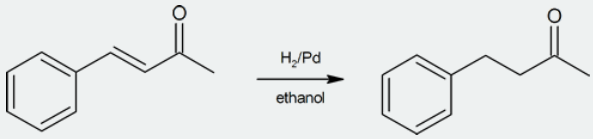
1. write an equation to represent the reduction of a substituted benzene to a substituted cyclohexane.
2. identify the catalyst and reagents used to reduce aromatic rings.
3. compare the ease of reduction of alkenes with the difficulty in reducing benzene rings, and show how this difference in reactivity can be used in organic synthesis.
4. write an equation to illustrate the reduction of an aromatic ketone to an arene.
5. explain why Friedel-Crafts acylation, followed by reduction, provides a better route to primary alkylbenzenes than does direct alkylation.
6. show how a specified alkylbenzene may be prepared by a Friedel-Crafts acylation, followed by reduction. Specify all reagents, the structure of the intermediate ketone, and the necessary starting material.

Study Notes

Catalytic hydrogenation of aromatic rings requires forcing conditions (high heat and hydrogen pressure).

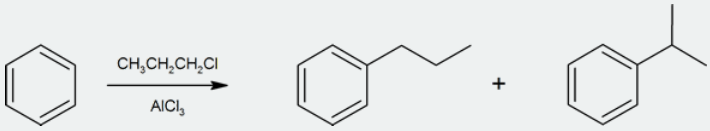


Under milder conditions it is possible to reduce the double-bond of an alkene without reducing the aromatic ring.

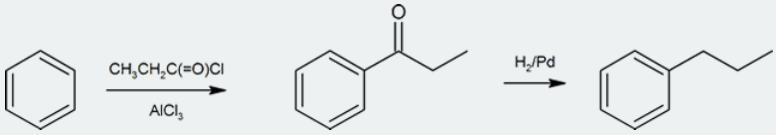


Notice in the above equation that H_2/Pd does not reduce the keto-carbonyl group. Remember, however, that H_2/Pd will reduce a keto-carbonyl group when it is directly attached to an aromatic ring (see equations 4 and 5 under Carbonyl Reductions).

This reduction of the (C=O) group next to an aromatic ring is an important synthetic tool. Recall the Friedel-Crafts alkylation from Section 16.3. When attaching larger alkyl groups to arenes there is a possibility of rearrangement of the alkyl group structure.

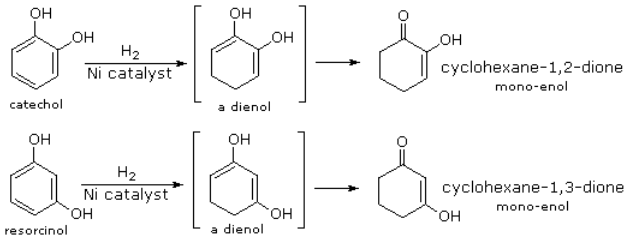


To generate the target compound (in this case *n*-propylbenzene) in a more controlled fashion, one can simply use the equivalent Friedel-Crafts acylation and then reduce the keto-carbonyl group next to the ring as a final step.

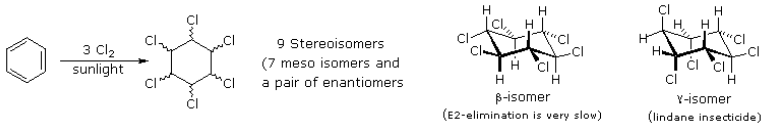


Aromatic Reduction Reactions

Although it does so less readily than simple alkenes or dienes, benzene adds hydrogen at high pressure in the presence of Pt, Pd or Ni catalysts. The product is cyclohexane and the heat of reaction provides evidence of benzene's thermodynamic stability. Substituted benzene rings may also be reduced in this fashion, and hydroxy-substituted compounds, such as phenol, catechol and resorcinol, give carbonyl products resulting from the fast ketonization of intermediate enols. Nickel catalysts are often used for this purpose, as noted in the following equations.

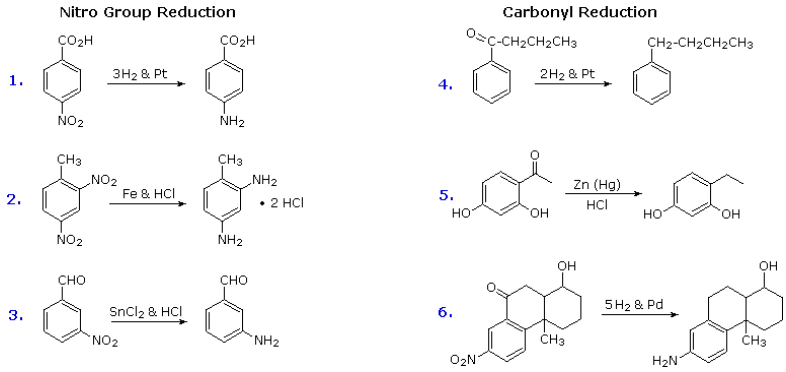


Benzene is more susceptible to radical addition reactions than to electrophilic addition. We have already noted that benzene does not react with chlorine or bromine in the absence of a catalyst and heat. In strong sunlight or with radical initiators benzene adds these halogens to give hexahalocyclohexanes. It is worth noting that these same conditions effect radical substitution of cyclohexane, the key factors in this change of behavior are the pi-bonds array in benzene, which permit addition, and the weaker C-H bonds in cyclohexane. The addition of chlorine is shown below on the left; two of the seven meso-stereoisomers are displayed to the right.



Reduction of Nitro Groups and Aryl Ketones

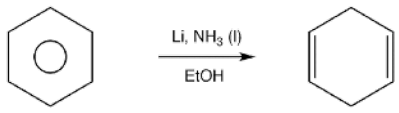
Electrophilic nitration and Friedel-Crafts acylation reactions introduce deactivating, meta-directing substituents on an aromatic ring. The attached atoms are in a high oxidation state, and their reduction converts these electron withdrawing functions into electron donating amino and alkyl groups. Reduction is easily achieved either by catalytic hydrogenation (H_2 + catalyst), or with reducing metals in acid. Examples of these reductions are shown here, equation 6 demonstrating the simultaneous reduction of both functions. Note that the butylbenzene product in equation 4 cannot be generated by direct Friedel-Crafts alkylation due to carbocation rearrangement. The zinc used in ketone reductions, such as 5, is usually activated by alloying with mercury (a process known as amalgamation).



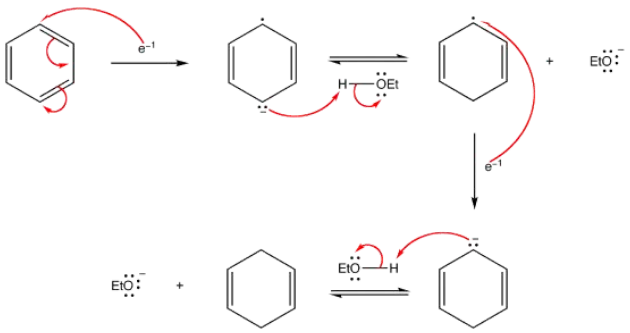
Several alternative methods for reducing nitro groups to amines are known. These include zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution. The procedures described above are sufficient for most cases.

The Birch Reduction

Another way of adding hydrogen to the benzene ring is by treatment with the electron rich solution of alkali metals, usually lithium or sodium, in liquid ammonia. See examples of this reaction, which is called the **Birch Reduction.** The Birch reduction is the dissolving-metal reduction of aromatic rings in the presence of an alcohol.



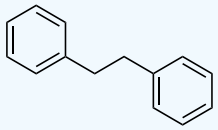
Mechanism:



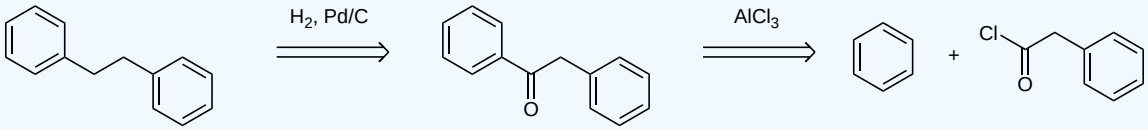
Exercises

Exercise 11.11.1

How would you make the following from benzene and an acid chloride?



Answer



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11.12: Synthesis of Polysubstituted Benzenes

Objectives

After completing this section, you should be able to

1. design a multistep synthesis which may involve reactions in the alkyl side chain of an alkylbenzene and the electrophilic substitution reactions discussed in this chapter. You should pay particular attention to
   a. carrying out the reactions in the correct order.
   b. using the most appropriate reagents and conditions.
   c. the limitations of certain types of reactions.
2. analyze a proposed multistep synthesis involving aromatic substitution to determine its feasibility, point out any errors in the proposal and identify possible problem areas.

Study Notes

As you can see, designing a multistep synthesis requires an analytical mind and an ability to think logically, as well as a knowledge of organic reactions. The best way to become an expert in designing such syntheses is to get lots of practice by doing plenty of problems.

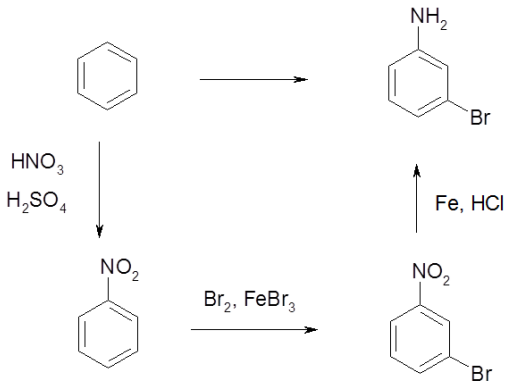
The ability to plan a successful multi step synthesis of complex molecules is one of the goals of organic chemists. It requires a working knowledge of the uses and limitations of many organic reactions - not only which reactions to use, but when. A few examples follow:

From benzene make *m*-bromoaniline

In this reaction three reactions are required.

1. A nitration
2. A conversion from the nitro group to an amine
3. A bromination

Because the end product is meta, a meta directing group must be utilized. Of the nitro, bromine, and amine group, only the nitro group is meta direction. This means that the first step need to be the nitration and not the bromination. Also, the conversion of the nitro group to an amine must occur last because the amine group is ortho/para direction.

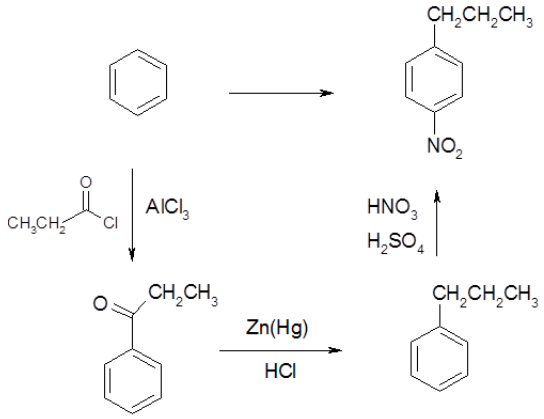


From benzene make *p*-nitropropylbenzene :

In this reaction three reactions are required.

1. A Friedel Crafts acylation
2. A conversion from the acyl group to an alkane
3. A nitration

Because the propyl group has more than two carbons, it must be added in two steps. A Friedel Crafts acylation followed by a Clemmensen Reduction. (Note: We would use a Wolff-Kishner reduction here (hydrazine, KOH, heat).) Remember that Friedel Crafts reactions don't happen if the benzene ring is strongly deactivated. This means that the acyl group must go on first. Because the end product is para, a para directing group must be utilized. Of the nitro, acyl, and alkane group, only the alkane group is para directing. This means that the acyl group must be converted to an alkane prior to the nitration step.



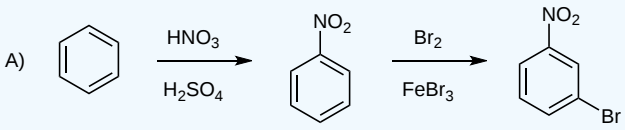
Exercises

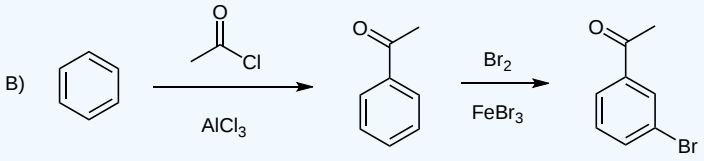
Exercise 11.12.1

How would make the following compounds from benzene?

a. *m*-bromonitrobenzene
b. *m*-bromoethylbenzene

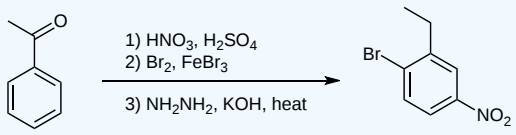
Answer





Exercise 11.12.2

There is something wrong with the following reaction, what is it?



Answer

> The bromine should be in the meta position. Right now it is in the ortho position, from perhaps reversing the order of steps 2 and 3. BUT the ethyl group is last to form, and the ketone and nitro groups would both encourage a meta substitution.

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11.S: Chemistry of Benzene - Electrophilic Aromatic Substitution (Summary)

Concepts & Vocabulary

16.0 Introduction

- Aromatic compounds don't typically undergo addition reactions.
- Aromatic compounds typically undergo substitution reactions.

16.1 Electrophilic Aromatic Substitution Reactions: Bromination

- Aromatic molecules only react with strong electrophiles.
- The first step in many electrophilic aromatic substitution mechanisms is activation or formation of the electrophile.
- The electrophilic aromatic substitution mechanism occurs in two steps. The first is addition of the electrophile to the ring and the second is elimination of a hydrogen from the ring to re-form the pi bond and restore aromaticity.
- In bromination of an aromatic ring, molecular bromine (Br_2) is reacted with iron tribromide ($FeBr_3$) to form the strongly electrophilic bromine cation and $FeBr_4$. Following this, the aromatic ring is reacted with the bromine cation and adds to the ring to form a benzenonium cation. This molecule then reacts with one of the bromine atoms from $FeBr_4$ to lose a hydrogen forming the product and HBr as well as reforming the iron tribromide.

16.2 Other Aromatic Substitutions

- Aluminum bromide ($AlBr_3$) can be used in place of $FeBr_3$ to create the bromine cation. Also the chlorides of aluminum and iron can also be used to create a chlorine cation which will also undergo electrophilic aromatic substitution.
- Reacting nitric acid and sulfuric acid forms nitronium (NO_2^+), which will react with aromatics for form nitro compounds.
- Sulfonation of aromatics can be accomplished by reacting with sulfur trioxide and sulfuric acid to yield sulfonic acids.

16.3 Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction

- Friedel-Crafts reactions incorporate activation of alkyl and acyl halides by reacting them with a Lewis Acid catalyst, $AlCl_3$.
- Friedel-Crafts alkylations allow for adding alkyl chains to aromatic rings.
- After activation with aluminum chloride, alkyl carbocations can undergo rearrangement if it leads to a more stable intermediate.
- Friedel-Crafts acylations add alkyl ketones to aromatic rings.

16.4 Substituent Effects in Substituted Aromatic Rings

- Aromatic inductive effects are caused by differences in electronegativity between atoms bonded to the ring and the ring carbons.
- Most common heteroatoms (N, O, halogens) donate electron density toward the ring by resonance.
- Aromatic resonance effects are caused by conjugation of substituents with the pi bonds of the ring.
- Substituents that increase the electron density of the ring activate the ring (make more reactive) toward electrophilic substitution.
- Substituents that decrease the electron density of the ring deactivate the ring (make less reactive) toward electrophilic substitution.

16.4b An Explanation of Substituent Effects

- Steric effects can increase para substitution as ortho/para directors become larger.
- Activating groups are ortho/para (o, p) directors.
- Deactivating groups are meta directors.
- Alkyl groups inductively donate electron density to the ring making them o, p directors.
- Groups with an O or N attached to the aromatic ring are activators and o, p directors due to resonance.
- Groups attached to the aromatic ring with a pi bond to an electronegative atom (C=O or C=N) are deactivators and m directors due to resonance.
- Halogens are o, p directors, but are deactivators.

16.5 Trisubstituted Benzenes: Additivity of Effects

- When there is more than one group attached to an aromatic ring, these groups may reinforce directing effects (cooperative) or have opposing directing effects (non-cooperative).

16.6 Nucleophilic Aromatic Substitution (reference only)

- Highly activated aromatic rings can react with strong nucleophiles through a substitution mechanism.
- The mechanism typically begins with addition of a nucleophile followed by elimination of a leaving group.

16.7 Benzyne (reference only)

- Under highly reactive conditions, a mechanism that begins with elimination for form a benzyne molecule intermediate followed by addition of a nucleophile resulting in nucleophilic aromatic substitution.

16.8 Benzylic Bromination of Aromatic Compounds

- Radical halogenation will occur at the benzylic carbon, due to stabilization of radical intermediates.

16.9 Reduction of Aromatic Compounds

- Nitro groups can be selectively reduced to amines with $SnCl_2$ and HCl or with Fe and HCl.

16.10 Synthesis of Polysubstituted Benzenes

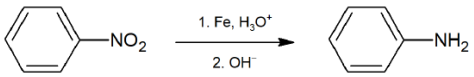
- Multistep synthesis requires a combination of forward (from the starting material) and backward (from the target compound) thinking.

Skills to Master

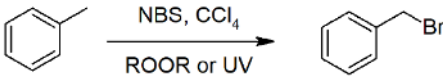
- Skill 16.1 Write detailed electrophilic aromatic substitution mechanisms (halogentation, nitration, sulfonation, Friedel-Crafts alkyation and acylation).
- Skill 16.2 Write detailed mechanisms for formation of reactive electrophiles.
- Skill 16.3 Predict and explain rearrangements that can occur during Friedel-Crafts alkylation.
- Skill 16.4 Explain activation and deactivation of aromatic rings toward electrophilic aromatic substitution.
- Skill 16.5 Explain ortho, para vs. meta directing during electrophilic aromatic substitution reactions.
- Skill 16.6 Combine activation and deactivation and directing effects to predict products of reactions of substituted aromatic molecules.
- Skill 16.7 Solve multistep synthesis problems incorporating directing effects and side-chain reactions.

Summary of Reactions

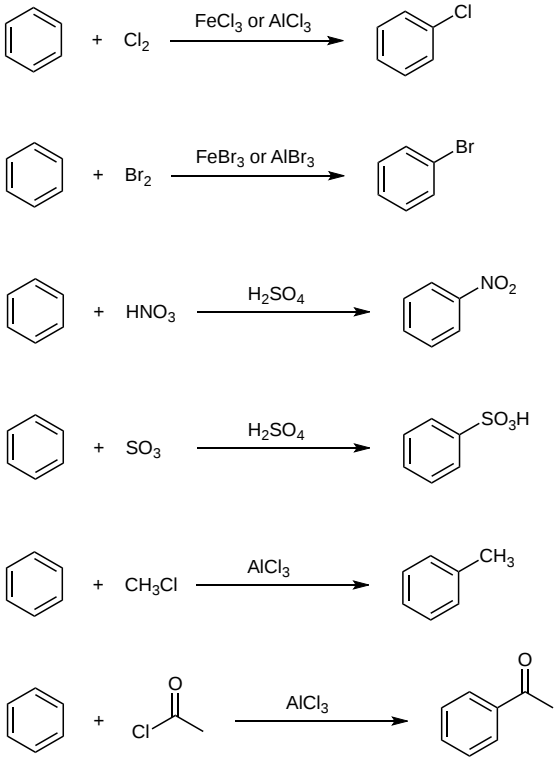
Reduction of Nitro Group



Benzylic Bromination of Alkylbenzene



Electrophilic Aromatic Substitution



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CHAPTER OVERVIEW

12: Transition Metal Catalyzed Carbon-Carbon Bond Forming Reactions

12.1: Introduction to Transition Metals and Mechanistic Steps

12.2: Pd-Catalyzed Cross Coupling Reactions

12.3: Olefin Metathesis

Chapter Videos

This video provides an introduction to palladium catalyzed reactions.

This video provides an introduction to olefin metathesis.

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12.1: Introduction to Transition Metals and Mechanistic Steps

Objectives

After completing this section, you should be able to:

1. Understand bonding, electron counting, and oxidation states for transition metal complexes
2. Draw and understand common transition metal mechanistic steps

Key Terms

Make certain that you can define, and use in context, the key terms below.

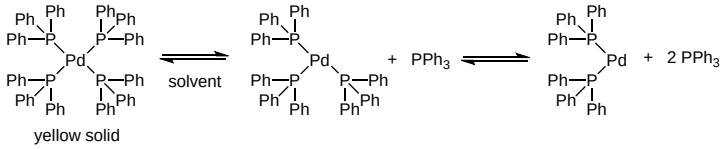
- Transition metal complex
- Ligands
- 18-electron rule
- Metal oxidation state
- Oxidative addition
- Transmetallation
- Reductive elimination
- Migratory insertion
- Beta hydrogen elimination

Study Notes

Transition metal catalyzed carbon-carbon bond forming reactions provide powerful methods to form key bonds in ways that are often impossible with traditional main group organometallic compounds (e.g., Grignard and organolithium reagents). This chapter provides an introduction to transition metal complexes including their bonding and common reactions. The following chapters will explore the most common transition metal catalyzed reactions including Pd catalyzed cross coupling reactions and olefin metathesis.

Content

Before learning about reactions catalyzed by transition metal complexes, we first need to understand a little about their structure and behavior. To begin, we need to update our vocabulary. You've already seen that we refer to molecules containing transition metals as **complexes**. Transition metal complexes contain the metal and other molecules bonded to the metal. These molecules bound to the metal are called **ligands**. Bonds between transition metals and their ligands are weaker than the covalent bonds you are used to from standard organic molecules. This is one reason why transition metals make such excellent catalysts, they are able to make and break bonds to ligands frequently throughout the course of a reaction. For example, tetrakis triphenylphosphine palladium is a yellow solid in which Pd has 4 triphenylphosphine ligands. As shown below, when dissolved in a solvent, this complex exists in equilibrium with complexes containing three and two triphenylphosphine ligands.



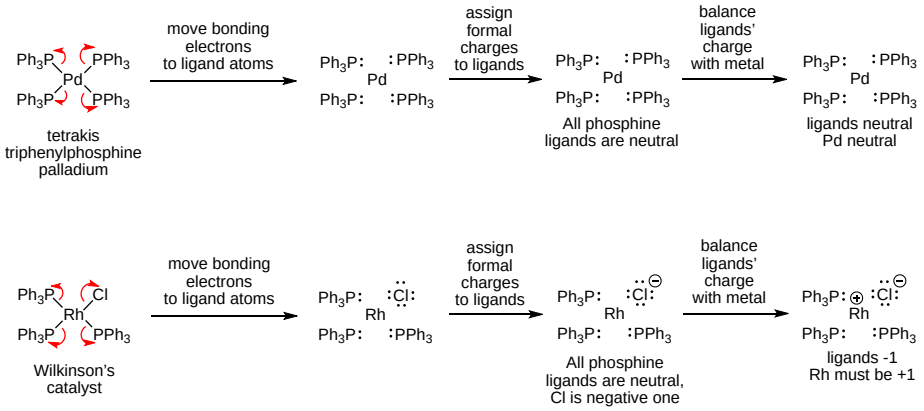
Electron Counting

Much time in introductory organic chemistry is spent discussing the octet rule (based on filling s and p orbitals). Transition metals have ready access to d-orbitals, so the octet rule does not apply. Instead, we add 10 electrons (because of the 5 d orbitals) and come up with the **18-electron rule**. Transition metal complexes containing 18 electrons are generally stable and unreactive. For active catalysts, we must have metals that are surrounded by fewer than 18 electrons. Also, we need to learn how to determine the formal charge on the metal. This is called the metal's **oxidation state**. Metals with high oxidation states are electron poor and are much more reactive than low oxidation state or neutral metal complexes.

We will start by analyzing metal complexes where the ligands are bound to the metal via sigma bonds, like in tetrakis triphenylphosphine palladium above. First, we must determine the oxidation state (formal charge) of the metal. To do this, we will 1) Consider the sigma bond electrons between the metal and the ligand as belonging to the ligand. 2) Assign a formal charge to the ligand atoms bound to the metal using standard organic chemistry formal charge rules. 3) Add up the charges on all of the ligands.

4) The metal oxidation state balances the ligands' summed formal charges so that the overall complex is neutral (or negative if it's an anionic complex/positive if it's a cationic complex).

Let's practice this by looking at a Pd complex ($Pd(PPh_3)_4$) and a Rh complex ($(Ph_3P)_3RhCl$). Phosphine ligands are common in transition metal complexes, and their charge is always neutral. (Just like N, which is in the same column in the periodic table, P is neutral with 3 bonds and a lone pair.) Halogens with eight electrons and no bonds have a negative one formal charge. So, in the Pd complex, the ligands have no formal charge, and Pd has a zero oxidation state: Pd(0). In the Rh complex, the net charge on the ligands is negative one. The metal must balance that charge so that the overall complex is neutral. This means Rh has a +1 oxidation state: Rh(I).



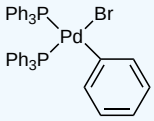
The next step is to detemine the total electron count around the metal to see if it satisfies the 18-electron rule. To do this, we must determine 1) The total electrons donated to the metal from the ligands. 2) The valence electrons from the transition metal based on its oxidation state. 3) Add the ligand electrons plus the metal electrons.

Ligand electron counting is as simple as counting the bonds from the ligands to the metal and multiplying by 2. In both of the complexes above, there are four sigma bonds from the ligands to the metals, so there are 8 electrons from the ligands. To determine the metal's valence electrons, we must look at the periodic table and factor in its oxidation state. In the Pd complex above, we determined it is Pd(0) which means Pd has all of its valence electrons. It is in group 10 in the periodic table, so it has 10 valence electrons. In Wilkinson's catalyst above, we determined it is Rh(I) which means Rh has lost one valence electron. Rh is in group 9, so it has 8 valence electrons as a +1 metal.

Thus, we can complete our analysis of the example complexes above. Tetrakis triphenylphosphine palladium has 8 ligand electrons plus 10 metal electrons for a total of 18 electrons. It satisfies the 18 electron rule and is unreactive until it loses one or two ligands in solution. Wilkinson's catalyst has 8 ligand electrons plus 8 metal electrons for a total of 16 electrons. Thus, it can form one more bond and is reactive.

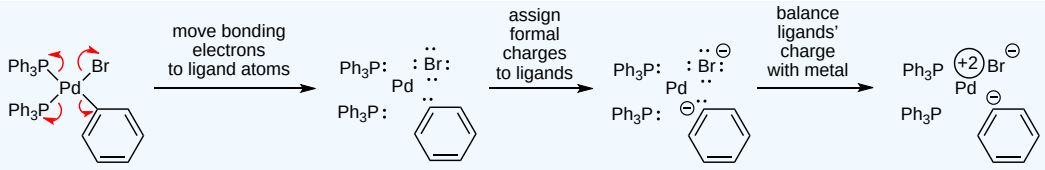
Exercise 12.1.1

The following Pd complex is commonly formed in Pd catalyzed cross coupling reactions. Perform an electron counting analysis on the complex to determine the oxidation state of Pd and the total Pd electron count.



Answer

Following our strategy from above, we can determine that we have two negative one ligands, the Br and the Ph. This means that Pd must balance the net -2 charge by being in its +2 oxidation state: Pd(II). For the total electron count, we again have 8 ligand electrons. Metal ligands are 8 for a +2 Pd (two fewer than the 10 electrons for the neutral Pd). The means our total electron count is 16.



Common Mechanistic Steps

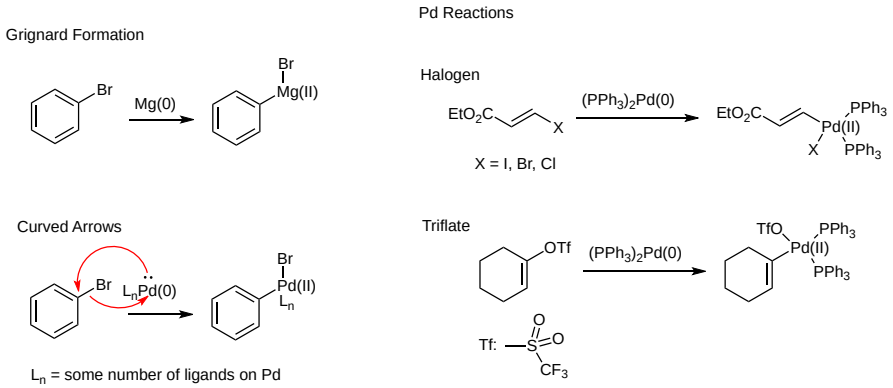
Many transition metal catalyzed reactions share common mechanistic steps that include oxidative addition, reductive elimination, transmetallation, migratory insertion, and beta hydrogen elimination. We will explore each of these individually and then see in the next chapter how that are combined in specific Pd catalyzed cross coupling reactions.

One note about organometallic mechanisms is that chemists often don't use curved arrows to show electron flow. Why? It is often because electron flow isn't always clear. For example, some of these mechanisms might actually be radical reactions. In this chapter, we will shown how electrons could flow if they were polar reactions since this often helps students understand what is happening. However, in keeping with the conventions of transition metal mechanisms, we won't always do this.

Oxidative Addition

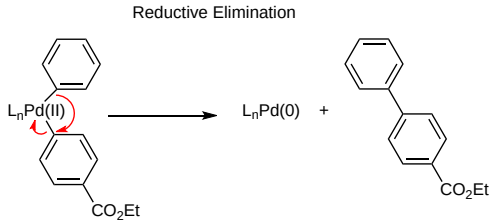
Many transition metal catalyzed reactions begin with a step called oxidative addition where the metal adds to a carbon-halogen bond. You have already seen this reaction type though it may not have been called an oxidative addition. Forming a Grignard reagent from Mg and an organohalogen compound is an oxidative addition. This step is oxidative with respect to the metal because it formally loses electrons when adding carbon and halogen ligands. In the examples below, a neutral metal adds two -1 ligands, meaning the metal becomes +2. We will see many examples of oxidative addition of Pd(0). Two are shown below highlighting the reactivity of halogens and triflates (OTf). (If you haven't met a triflate before, it is a more reactive version of a tosylate that can easily be made from an alcohol or a carbonyl. We will see examples of this in later sections.) A third Pd(0) example is shown to illustrate how you can think about electron flow and curved arrows for oxidative addition. As mentioned above, we generally won't draw curved arrows for this step, and the arrows likely don't depict what is actually happening in the mechanism. The most common and synthetically useful oxidative additions occur between Csp-X/OTf or Csp^2-X/OTf and metals like Pd. So, we will encountered oxidative additions with vinyl, phenyl/aryl, and alkynyl substrates.

Oxidative Addition Examples



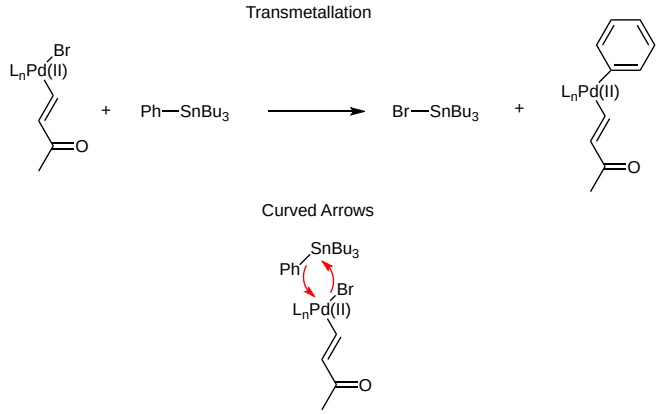
Reductive Elimination

The opposite mechanistic step to oxidative addition is reductive elimination. In this step, two groups bound to the metal, often two carbon ligands, form a new bond while formally giving electrons back to the metal. Thus, this step reduces the metal. It is often the last step in the cycle, regenerating the transition metal catalyst and forming the key carbon-carbon bond in the product. Curved arrows are show below, but this is another step where we will normally resist drawing curved arrows.



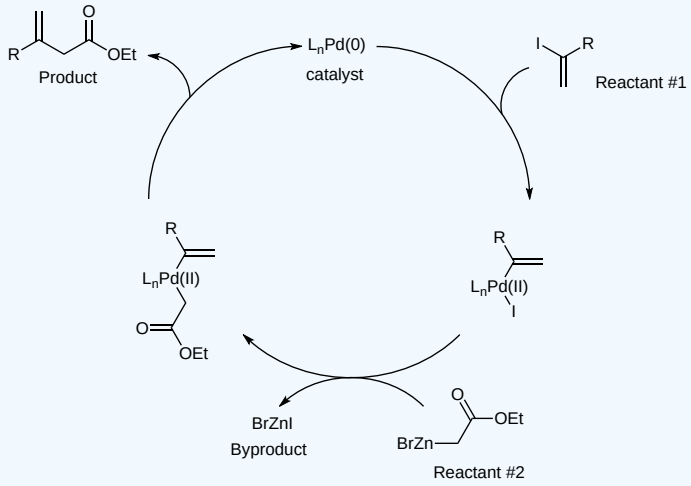
Transmetallation

A common strategy to form a new carbon bond to the transition metal catalyst is to start with a carbon group on a different metal. The stoichiometric metal reagent then transfers the carbon group to the catalytic metal during the catalytic cycle. We will see in the next section that Pd participates in transmetallation with metals like B, Sn, Cu, and Ni. As shown below, the net result is that the halogen group on the catalytic metal (Pd) switches places with the carbon group on the stoichiometric metal (Sn). Also, note that the oxidation state of Pd doesn't change, so this is neither an oxidation nor a reduction.



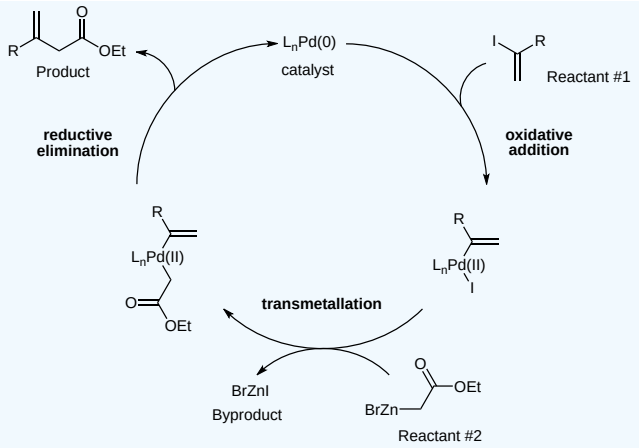
Exercise 12.1.2

Shown below is the catalytic cycle for a Negishi reaction. Label each mechanistic step as oxidative addition, reductive elimination, or transmetallation.



Answer

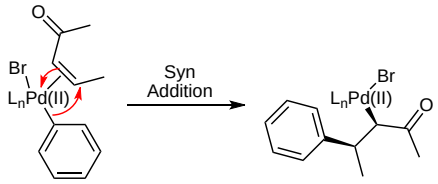
As with many Pd catalyzed reactions, the steps proceed in this order: oxidative addition (making one Pd-C bond), transmetallation (making a second Pd-C bond), and reductive elimination (making the key C-C bond).



Migratory Insertion

Some transition metal catalyzed reactions involve addition of a metal-carbon bond across a pi bond, like an alkene or alkyne, that is also bound to the metal. This is a powerful way to build up complexity in a molecule, especially when it is an intramolecular reaction, and we will see numerous examples of this step when we explore the Heck reaction in the next section. As shown below, an alkene (or alkyne) that is complexed to the metal via its pi bond can insert into an adjacent metal-carbon sigma bond. This is a syn addition to the alkene and is similar to the alkene hydrogenation mechanism that you learned previously. The new carbon-carbon bond generally forms at the least hindered/most electron poor carbon of the alkene.

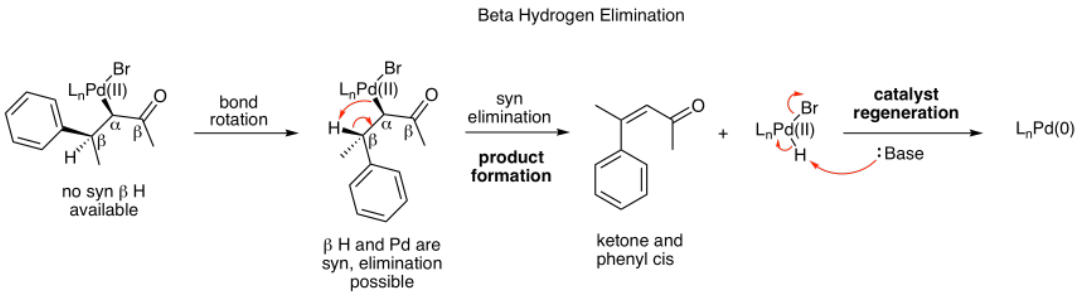
Migratory Insertion



Beta Hydrogen Elimination

For many transition metal complexes bound to an sp^3 hybridized carbon, beta hydrogen elimination is a common mechanistic step. This is a product yielding step and demonstrates the ability of transition metal reactions to form alkene products. Unlike E2 reactions that proceed via an anti elimination, beta hydrogen eliminations are syn eliminations. This has important implications for product alkene geometry and must be carefully considered when proposing this type of mechanistic step. In some complicated substrates, a syn arrangement of the metal and beta hydrogen are not possible. In these cases, the base included in the reaction mixture that usually regenerates the active catalyst instead does a traditional anti E2 reaction to yield an alkene product. We will see examples of this in the following section.

Beta hydrogen elimination reactions occur most often after migratory insertion steps. We can explore this mechanism beginning with the product of our migratory insertion step shown above. The migratory insertion product has two beta carbons; however, only the beta carbon on the left has a hydrogen. In the initial conformation, this beta hydrogen is anti to the Pd, so intramolecular elimination is not possible. Thus, our next step is a bond rotation to orient the Pd and beta H syn. Our syn beta hydrogen elimination is now possible, and the reaction occurs. This generates our alkene product with the ketone and phenyl positioned cis, due to their orientation in the reactive conformation. Note that this reaction does not regenerate our Pd(0) catalyst. Instead, we form a Pd(II) complex containing a Pd-H bond. Standard reaction conditions include a base so that deprotonation and loss of bromide regenerates the active catalyst.



Contributors

- Prof. Kevin Shea (Smith College)

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12.2: Pd-Catalyzed Cross Coupling Reactions

Learning Objectives

After completing this section, you should be able to:

1. Identify common Pd-catalyzed carbon-carbon bond forming reactions
2. Draw and understand reaction mechanisms
3. Use reactions in synthesis problems

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Stille reaction
- Suzuki reaction
- Sonogashira reaction
- Heck reaction

Study Notes

Palladium catalyzed reactions are the most common transition metal catalyzed cross coupling reactions. Their importance was recognized with the 2010 Nobel Prize for Richard Heck, Ei-ichi Negishi, and Akira Suzuki. These reactions provide straightforward methods for the construction of Csp^2-Csp^2 and Csp^2-Csp bonds. We will see many examples of these types of bond formations throughout this chapter. While learning this material, don't forget to contrast Pd catalyzed reactions with popular intro orgo carbon-carbon bond forming reactions like Grignard or organolithium reactions with carbonyls and epoxides. At least one component of these reactions was sp^3 hybridized, so it was impossible to generate the types of bonds that are formed most commonly by Pd catalyzed reactions. Adding Pd catalyzed reactions to your organic chemistry toolbox will greatly expand the types of molecules that you are able to synthesize.

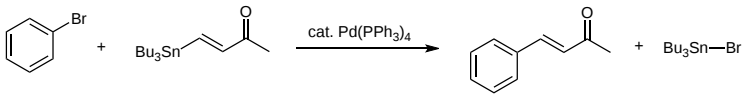
Content

This chapter will focus on learning and applying common Pd catalyzed reactions for the formation of Carbon-Carbon bonds: Stille, Suzuki, Sonogashira, and Heck. If you haven't already, please refer to the previous section for a discussion of transition metal structure and bonding along with common mechanistic steps in transition metal catalyzed reactions.

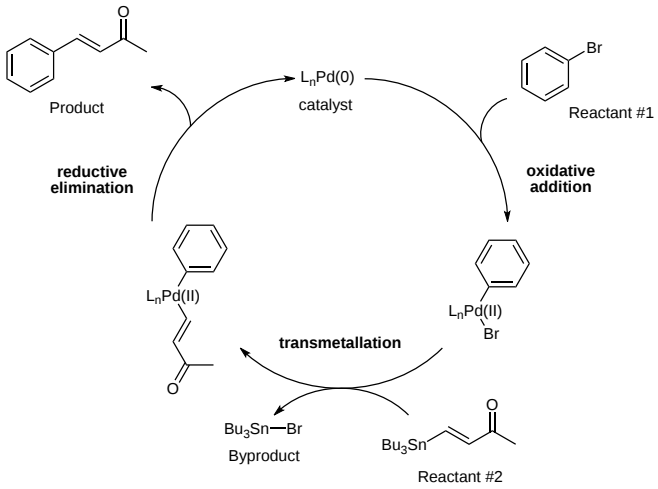
For all of the reactions in this chapter, we will depict the palladium catalyst as $L_nPd(0)$ to acknowledge that some number of ligands are bound to Pd but their actual number and structure are unimportant to the mechanism. Two things happen when a Pd complex dissolves in the reaction solvent. First, bonds to phosphine ligands break to establish an equilibrium with complexes having fewer ligands and open coordination sites for reactions to occur. Second, some reactions will begin with Pd(II) reagents. For example, most Sonogashira reactions are run with $PdCl_2(PPh_3)_2$. These Pd reagents are reduced under the reaction conditions by several possible mechanisms that we won't concern ourselves with here. The net result is that Pd(0) is produced in the flask, and this complex can then catalyze the desired reactions. Even though we will generally ignore the phosphine ligands, the structure of these molecules is critically important to the success of Pd catalyzed reactions. Many of the recent advances in this field were made possible by the development of novel phosphine ligands.

Stille Reaction

The Stille reaction is the simplest Pd catalyzed cross coupling reaction where an organohalide combines with an organotin in the presence of a Pd(0) catalyst to form a new C-C bond. To avoid side reactions and production of mixtures, both components generally have Csp^2 or Csp atoms bonded to the halogen and the tin. An example reaction and mechanism are shown below. Oxidative addition of bromobenzene with the Pd catalyst yields the first Pd(II) intermediate. Transmetallation transfers the alkene from Sn to Pd, generating the tributyltin bromide byproduct and the desired Pd(II) intermediate with two C-Pd bonds. Finally, reductive elimination generates the desired product and regenerates the Pd(0) catalyst.

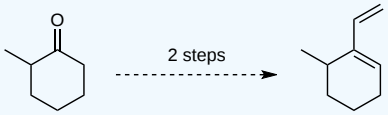


Mechanism



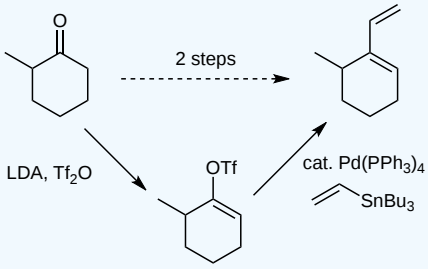
Exercise 12.2.1

Complete the following synthesis in 2 steps, one of which is a Stille reaction.



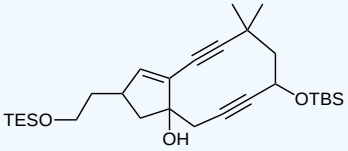
Answer

Thinking retrosynthetically, we must be forming the single bond between the alkenes using a Stille reaction. That means we need to convert the ketone into a vinyl halide or halide equivalent in the first step. This is easily done by forming an enolate and adding triflic anhydride to make a vinyl triflate. As explained in the previous chapter, vinyl triflates participate readily in transition metal catalyzed reactions. So, our two step synthesis is 1) Deprotonation with LDA (to ensure we form the least substituted kinetic enolate) followed by addition of triflic anhydride to yield the vinyl triflate. 2) Stille reaction with vinyl tributyltin to generate the target.



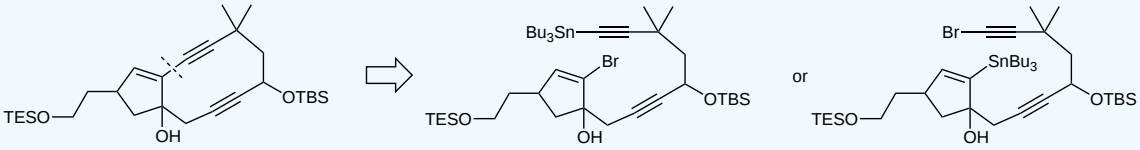
Exercise 12.2.2

Using retrosynthetic analysis, how would you make this target in one step using a Stille reaction?



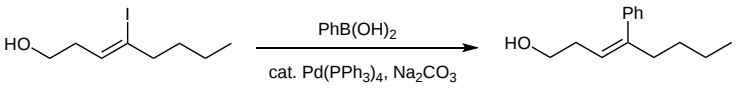
Answer

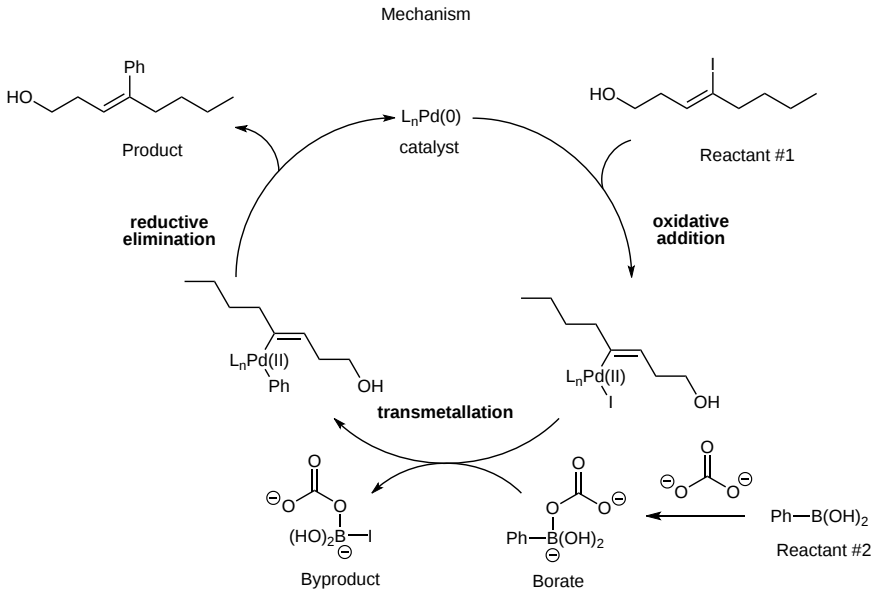
The key bond is the one between the alkene and the alkyne. This is the bond we will make in the forward direction using the Stille reaction.



Suzuki Reaction

The Suzuki reaction is similar to the Stille reaction but with boron used instead of tin for the transmetallation step. It also differs from the Stille reaction because Suzuki reactions require the presence of a base to activate the boron reagent prior to transmetallation. As shown below, the mechanistic steps are the same for these two popular transformations with the addition of the base promoted boron activation step that forms the reactive borate (negatively charged boron) compound. This borate reagent can be formed by a variety of oxygen bases in addition to carbonate like hydroxide and alkoxides (e.g., ethoxide, t-butoxide).

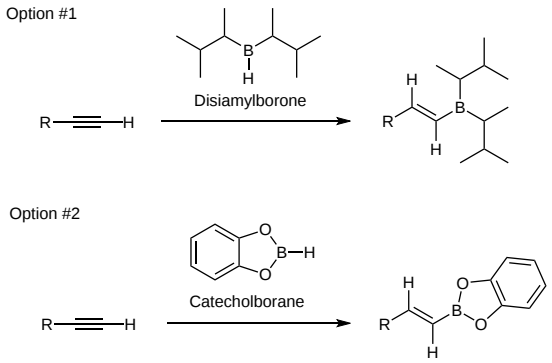




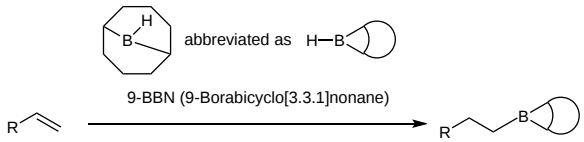
There are several advantages of the Suzuki reaction. First, we are already familiar with forming C-B bonds from intro orgo using a hydroboration reaction. Previously, we always followed this step with an oxidation reaction to form an alcohol. Now we can form the organoboron compound and use it in a Suzuki reaction. We can react alkenes or alkynes in hydroboration reactions to yield organoboron reagents for transmetallation. Several examples are shown below. Hydroboration of terminal alkynes is synthetically useful (internal alkynes yield product mixtures) when using hindered boranes like disiamylborane or catecholborane. Like all hydroborations, the reactions are syn additions with the larger boron adding to the less hindered side of the alkyne resulting in trans alkene products. To generate alkylboron reagents for use in Suzuki reactions, the most common reagent is 9-BBN (pictured

below). A second advantage is the Suzuki reaction provides a way to use Pd catalysis to easily make Csp^2-Csp^3 or Csp-Csp^3 bonds which can be challenging to make with other Pd catalyzed reactions. Hydroboration of an alkene provides the requisite B-Csp^3 reagent (the 9-BBN derivative shown below) that participates in transmetallation then reductive elimination to yield the desired bond. We will see an example of this in one of the problems below.

Hydroboration of alkynes: Synthesis of vinylboron reagents

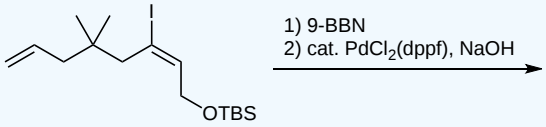


Hydroboration of alkenes: Sythesis of alkylboron reagents



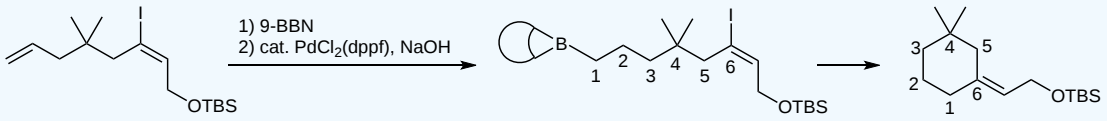
Exercise 12.2.3

What is the product of the follow reaction sequence?



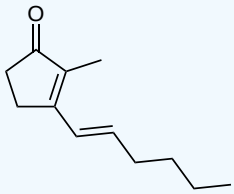
Answer

The first step is a hydroboration reaction with 9-BBN which is selective for the much less hindered terminal alkene. This sets up an example of a very synthetically useful intramolecular Suzuki reaction to form a 6-membered ring.



Exercise 12.2.4

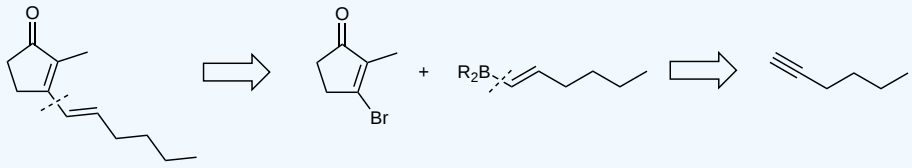
Propose a synthesis of the following target starting with compounds containing 6 carbons or fewer. One of your starting materials must be an alkyne.



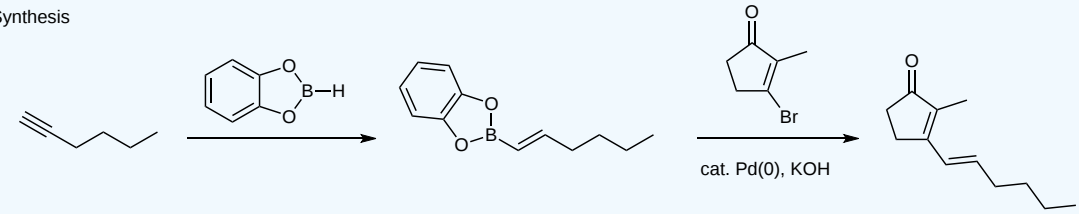
Answer

Thinking retrosynthetically, we can split the molecule between the two alkenes into two 6-carbon fragments that can be combined using a Suzuki reaction. The boron-containing component can then be simplified to the requisite alkyne starting material. In the forward direction, we start with 1-hexyne and hydroborate it with catecholborane (a 6-carbon reagent) to yield the vinylborane that participates in a Suzuki reaction with our 5-membered ring vinyl bromide to yield the target.

Retrosynthetic Analysis

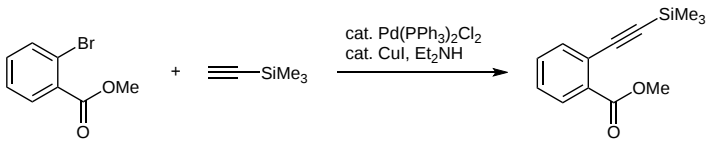


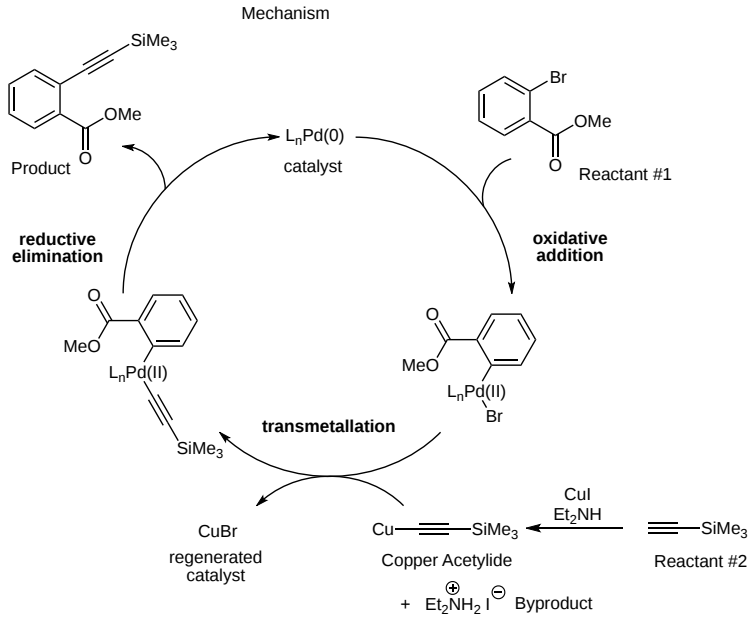
Synthesis



Sonogashira Reaction

The Sonogashira reaction enables the combination of an unsaturated carbon-containing halide or triflate with a terminal alkyne to yield a new Csp-Csp or Csp-Csp^2 bond. One interesting aspect of this reaction is that it is catalyzed by a combination of Pd (to form the C-C bond) and Cu (to activate the terminal alkyne for transmetallation). Another key reagent is an amine base that promotes formation of the copper acetylide that participates in the transmetallation step. An example Sonogashira reaction and the mechanism is shown below. This is a very useful reaction and an important addition to our synthesis toolbox.

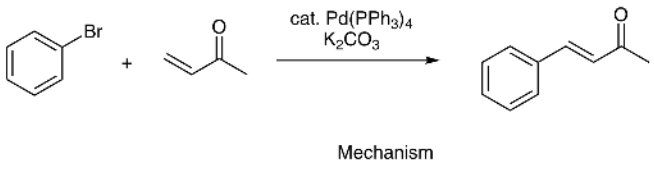




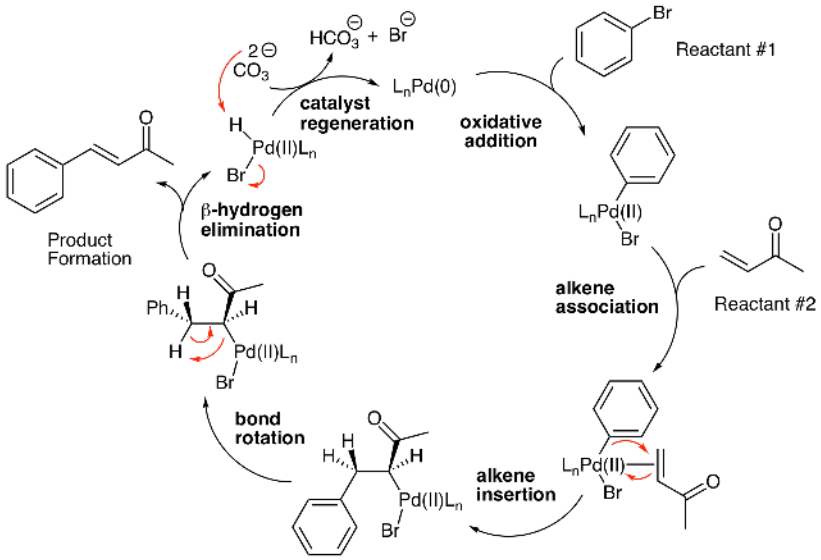
The previous three reactions, Stille, Suzuki, and Sonogashira, share a similar mechanism that includes oxidative addition, transmetallation, and reductive elimination steps. Other reactions with different metals have a similar catalytic cycle with palladium. Although we won't discuss them here, you are well equipped to understand these reactions when you see them in the literature. Two of the most common examples are the Negishi reaction (transmetallation with zinc) and the Kumada reaction (transmetallation with magnesium).

Heck Reaction

The Heck reaction proceeds via a different mechanistic pathway than the Stille, Suzuki, or Sonogashira reactions because it does not contain transmetallation or reductive elimination steps. Instead, the Heck reaction relies on an alkene insertion step for carbon-carbon bond formation and beta hydrogen elimination to generate the product. (As a reminder, these steps were described in detail in the previous section.) An example of the reaction and its mechanism are shown below. A few key points about the mechanism are worth highlighting. The alkene insertion step usually places the Pd at the more substituted position and the carbon at the least substituted position. This step is a syn addition to the alkene which necessitates a bond rotation in the next step to place a beta hydrogen syn to the Pd. There are two possible Hs that can end up syn but the conformation that places the phenyl and the ketone anti is preferred. (Note that for this mechanism, only one beta carbon has Hs. The other beta carbon is the ketone. In many reactions, there are several alkenes that can form. Heck reactions generally produce the most stable possible alkene product.) This conformation yields the more stable trans alkene product in the beta hydrogen elimination step. The Pd(0) catalyst is regenerated in the final deprotonation step that explains the need for base in the mechanism.



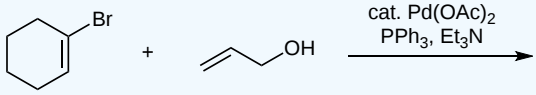
Mechanism



Heck reactions are commonly run intermolecularly, between two different reactants. However, the true power of the Heck reaction for synthesis becomes apparent when studying intramolecular Heck reactions. This is a very useful technique for quickly building molecular complexity. We will see an example of this in one of the problems below.

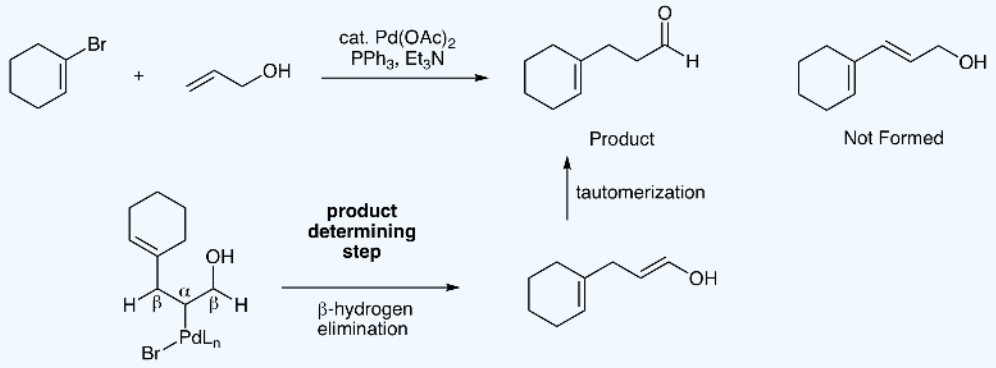
Exercise 12.2.6

Predict the product of the following intermolecular Heck reaction.



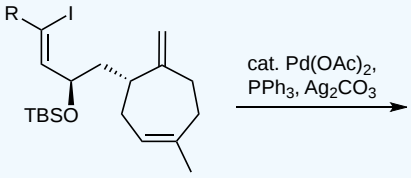
Answer

This is a tricky problem. Most students quickly predict the conjugated diene shown below that doesn't form. This is a good illustration of the importance of evaluating potential products formed from the beta hydrogen elimination step. In this reaction, there are two beta carbons with Hs that can be eliminated with Pd. One option, the beta H on the left, yields the conjugated diene. The other option, the beta H on the right, yields an enol product that tautomerizes to the observed aldehyde product. Carbonyls are more stable than alkenes, so this thermodynamic difference drives the reaction to the aldehyde.



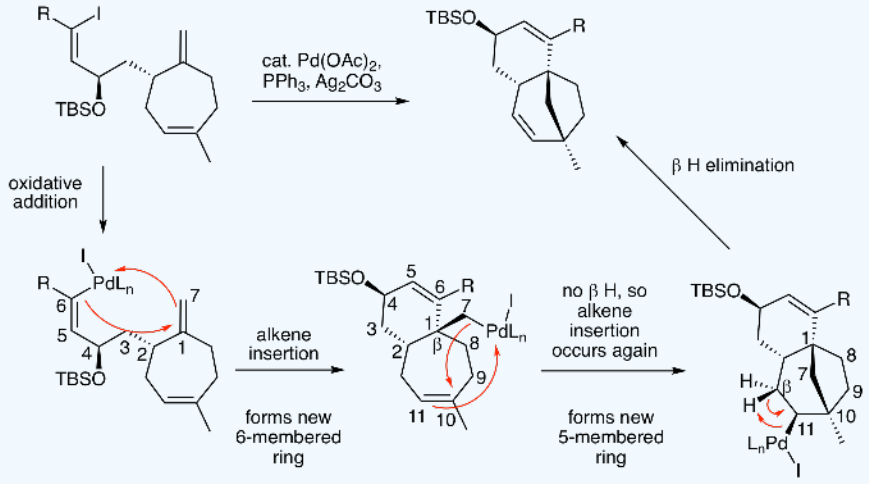
Exercise 12.2.7

Predict the product of the following intramolecular Heck reaction.



Answer

This is an excellent example of what is known as a Heck zipper reaction where multiple alkene insertions occur to form more than one ring. Working through the mechanism, we can see what is happening. After the initial oxidative addition step, the first alkene insertion occurs to form the new 6-membered ring. Normally, we would next perform a beta hydrogen elimination reaction to generate the product. However, this molecule has a quaternary carbon at the beta position, so beta hydrogen elimination is impossible. When that happens, the molecule undergoes another alkene insertion to form a second new ring. In this case, a new five membered ring. We again look to find a cis beta hydrogen. That is now possible when the Pd is on carbon #11 and the final product is formed.



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12.3: Olefin Metathesis

Objectives

After completing this section, you should be able to:

1. Identify ring closing and cross metathesis reactions
2. Draw and understand reaction mechanisms
3. Use reactions in synthesis problems

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Schrock catalyst
- Grubbs 1st generation catalyst
- Grubbs 2nd generation catalyst
- Ring closing metathesis
- Olefin (alkene) metathesis
- Alkyne metathesis
- Cross metathesis

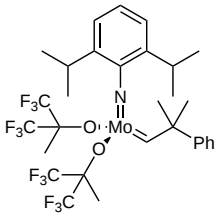
Study Notes

Olefin metathesis reactions enable formation of new carbon-carbon bonds between two starting alkenes while generating ethylene as a byproduct. (This results in the loss of two carbons from the starting material(s) to form ethylene.) Alkyne metathesis, generating acetylene as a byproduct, is also possible but is much less common. The most powerful metathesis reaction is the intramolecular version known as Ring Closing Metathesis (RCM). The intermolecular variation is also useful and is known as Cross Metathesis (CM). Thanks mainly to the work of Robert Grubbs (Caltech) and Richard Schrock (MIT) in the 1990s, these reactions have become popular tools for synthetic organic chemists. For their key research on these reactions, Grubbs and Schrock, along with Yves Chauvin, were awarded the 2005 Nobel Prize in Chemistry. RCM provides you with another highly useful method for the synthesis of rings. This reaction is especially valuable as a method for the synthesis of large rings which are often challenging to synthesize. For the purposes of retrosynthetic analysis using RCM, we look for ring sizes of 5 or larger containing an alkene. So, the cyclohexene Diels-Alder retron is also a ring closing metathesis retron.

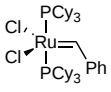
Content

This chapter will focus on learning and applying olefin metathesis reactions for the synthesis of rings. We will meet the most common reaction catalysts, learn the reaction mechanism, and see several examples. We will also see brief examples of alkyne metathesis and cross metathesis.

Olefin metathesis catalysts (shown below) are examples of metal-carbene complexes where the reactive metal (either Ru or Mo) contains a double bond to the carbon ligand that participates in the reaction. Furthermore, these highly reactive catalysts are actually examples of what chemists call precatalysts. The compound introduced into the reaction undergoes one round of the catalytic cycle before forming the molecule that catalyzes all further reactions. The precatalysts are less reactive than the actual catalysts, enabling chemists to handle them more easily outside of the reaction flask. Most of the original research in the Grubbs and Schrock labs was conducted in glove boxes under inert atmosphere conditions since early catalysts were highly sensitive to air and moisture. The popularity of the Grubbs catalysts is their combination of stability outside the glove box, reactivity, and functional group compatibility (only reacting with alkenes and not other functional groups).

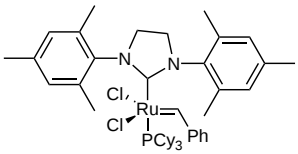


Schrock catalyst



Cy = cyclohexyl

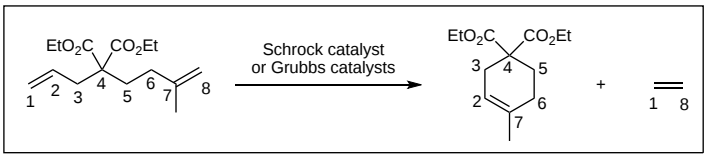
Grubbs 1st generation catalyst



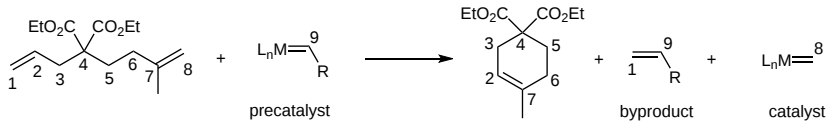
Cy = cyclohexyl

Grubbs 2nd generation catalyst

An example ring closing metathesis (RCM) reaction is shown below along with the mechanism. In this case, we are forming a six membered ring. As mentioned above, RCM reactions generate ethylene as a byproduct, meaning that the starting diene has two more carbons than the cyclic product. Don't forget this key point when planning syntheses using RCM. The initial steps of the reaction convert the precatalyst (the molecules shown above) into the actual catalyst for the reaction. Active metathesis catalysts have CH_2 attached to the metal with the structure $L_nM{=}CH_2$. So, initially the alkene byproduct containing the R group present in the precatalyst is formed along with the active catalyst and the desired product. We can now draw out the reaction mechanism with the correct catalyst. (For all future problems, we will ignore the precatalyst reaction and draw mechanisms beginning with what we know is the active catalyst, $L_nM{=}$.) The RCM mechanism is a series of [2+2] and retro [2+2] cycloaddition reactions. Transition metals can react using d orbitals making thermal [2+2] reactions allowed mechanistic steps (unlike what we learned in the cycloadditions chapter about main group [2+2] reactions). A critical point about the first step is the regiochemistry of how the catalyst reacts with the substrate. For the reaction to be productive and lead to ring formation, the metal must react at the more hindered position. This helps explain why there is a strong preference for the catalyst to react with the least hindered alkene first, in this case the monosubstituted C1-C2 alkene. This first step yields a metallocyclobutane that breaks apart by a retro [2+2] cycloaddition to generate the ethylene byproduct and a new metal carbene with the catalyst covalently bonded to our substrate. Ring formation occurs in the next step, our second [2+2] cycloaddition. The final cycloreversion regenerates the catalyst and installs the alkene in our six-membered ring product.



Formation of Active Catalyst - Precatalyst Reaction



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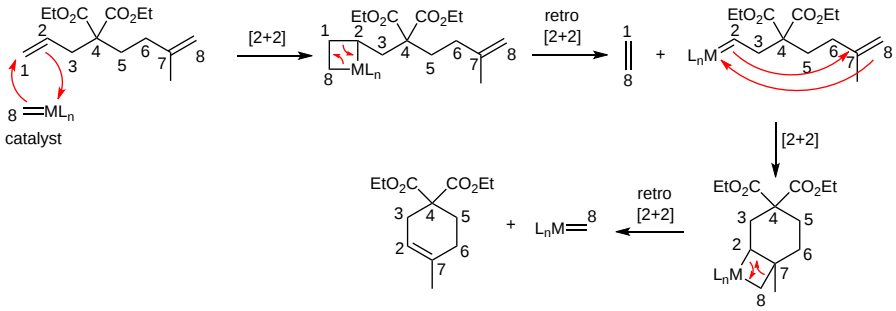
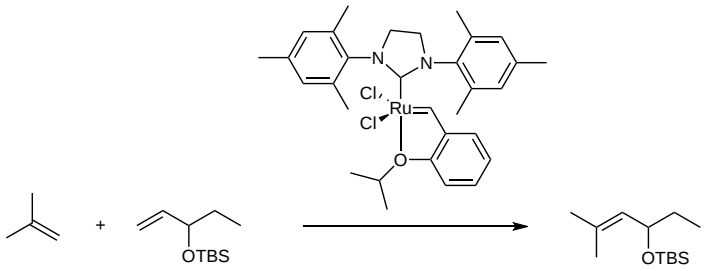
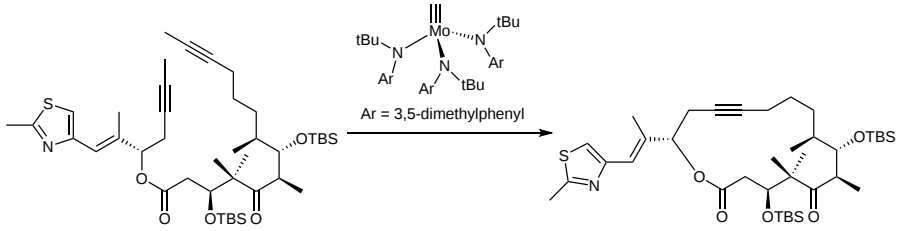


Cross metathesis reactions enable formation of a substituted alkene in an intermolecular reaction with a second alkene. There are significant selectivity challenges to avoid producing large product mixtures, including E/Z product isomers. One example of a relatively straightforward application of cross metathesis is shown below. Producing a new alkene with symmetrical substitution on one side obviates the potential alkene isomer problem. So, starting with isobutylene and a monosubstituted alkene leads to generation of a trisubstituted alkene product. (As we saw previously with RCM, ethylene is generated as a reaction byproduct.) Note that we have a slightly different catalyst that was developed to promote cross metathesis. This modification of the Grubbs second generation catalyst is know as the Hoveyda-Grubbs catalyst.

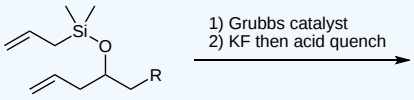


Alkyne metathesis is a useful variant of standard olefin metathesis. Tungsten and molybdenum catalysts have been developed that enable efficient ring closing alkyne metathesis. Not surprisingly, this strategy is only useful for the synthesis of large rings which are able to handle the significant ring strain introduced by a cyclic alkyne. A leader in this field is Alois Fürstner who published the following transformation as part of a total synthesis of epothilone C.



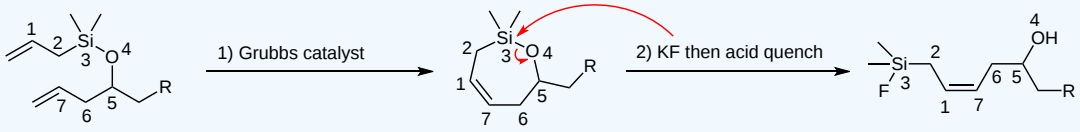
Exercise 12.3.1

Propose a product for the following reaction sequence.



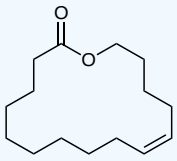
Answer

The first step is a standard ring closing metathesis reaction to form a seven-membered ring. This step highlights that heterocyclic rings can be easily made using olefin metathesis. The second step is less straightforward but should make you think about silyl ether deprotection with fluoride to yield alcohols. In this case, since the silyl group is part of the ring, it opens the ring to yield an acyclic allyl silane. This highlights the possibility of using RCM to selectively synthesize acyclic cis alkenes. You should also note that the allyl silane in the product can be oxidized to an allylic alcohol by treatment with hydrogen peroxide.



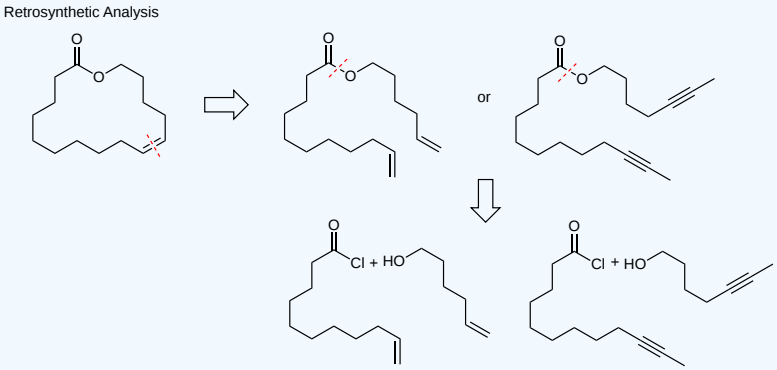
Exercise 12.3.2

Starting with compounds containing 12 carbons or fewer, propose two different syntheses of the target compound. Your answers should both incorporate ring closing metathesis, but you should use two different versions of RCM.



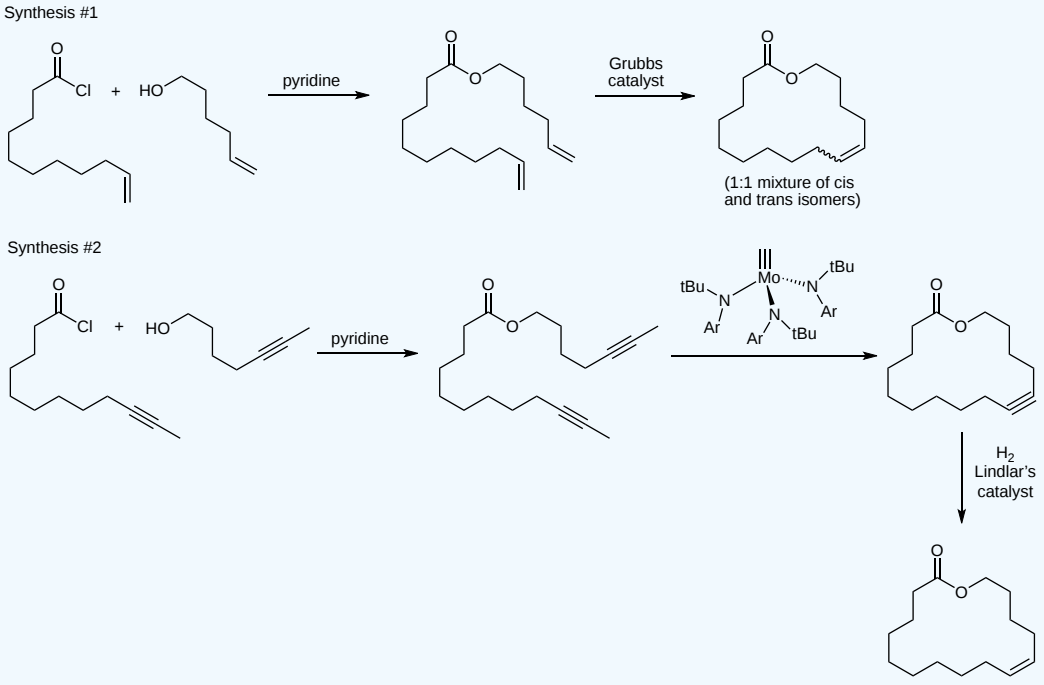
Answer

This problem provides an opportunity to use both alkene and alkyne metathesis. Thinking retrosynthetically, the first disconnection is to break open the ring. Don't forget to add the extra carbons necessary for the alkene and alkyne metathesis reactions. Next, you should break the ester bond to yield an acid chloride and an alcohol that fit the 12 carbons or fewer limitation.



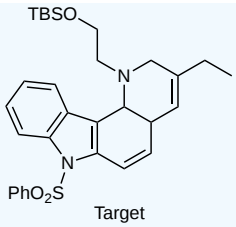
Synthesis #1 is likely the most obvious choice. Form the ester in the first step then use the Grubbs catalyst to form the 16-membered ring. One issue with this synthesis is the unfortunate limitation of alkene RCM for large rings that often generates cis/trans product mixtures. In fact, this reaction yields a 1:1 mixture of the cis and trans isomers.

Synthesis #2 enables you to address this problem while adding an extra step to your synthesis. (This is often preferred over making difficult to separate alkene isomers.) The first step generates the diyne ester that is cyclized using alkyne RCM in the second step. This cyclic alkyne (stable in such a large ring) can be hydrogenated using Lindlar's catalyst to yield exclusively the desired cis alkene.

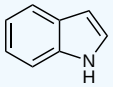


Exercise 12.3.3

The following target is a key synthetic intermediate in a published synthesis of pseudotabersonine. Propose a one-step synthesis of this tetracycle beginning with a substituted indole as your bicyclic starting material.



Target

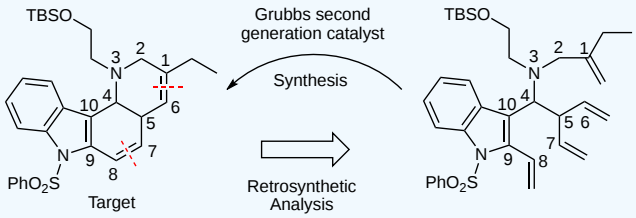


Indole

Answer

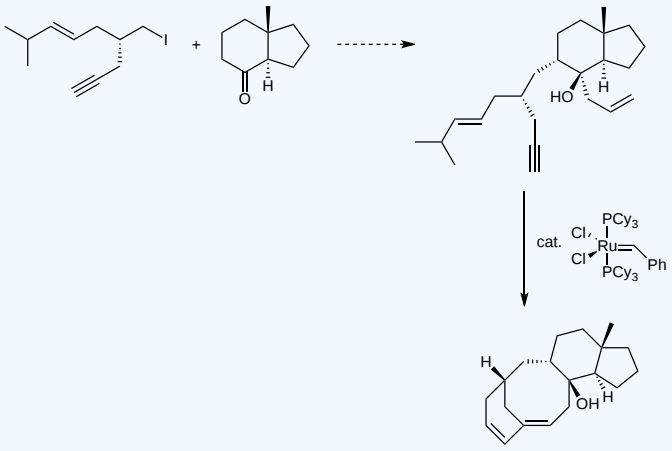
Reference: Organic Letters 2010

Since we are beginning with the two rings in the indole moiety, we must disconnect the other two rings in our retrosynthetic analysis. Both have an alkene making them retrons for alkene ring closing metathesis. As always when using RCM, be sure to add the carbons that will be lost in the forward direction. The resulting tetraene is the starting material that the Martin group reacted with the Grubbs catalyst in their 2010 *Organic Letters* paper.



? Exercise 12.3.4

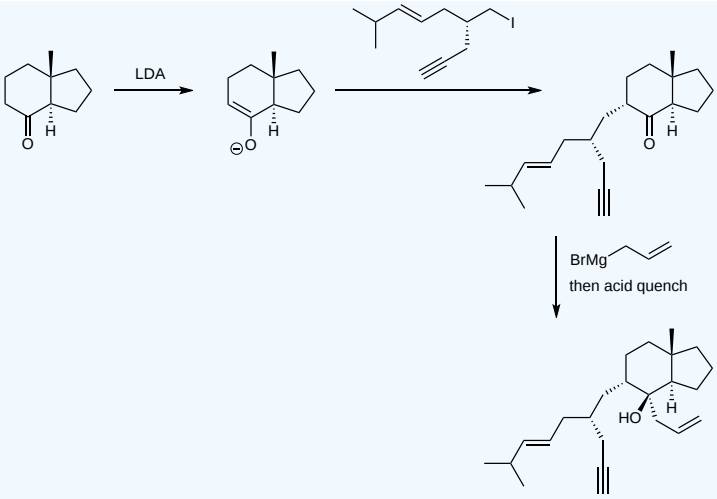
The following synthetic sequence outlines a strategy that can be applied to the synthesis of taxol-like molecules. First, propose a synthesis of the key ring-closing metathesis precursor. Second, propose a mechanism for the ring-closing metathesis reaction.



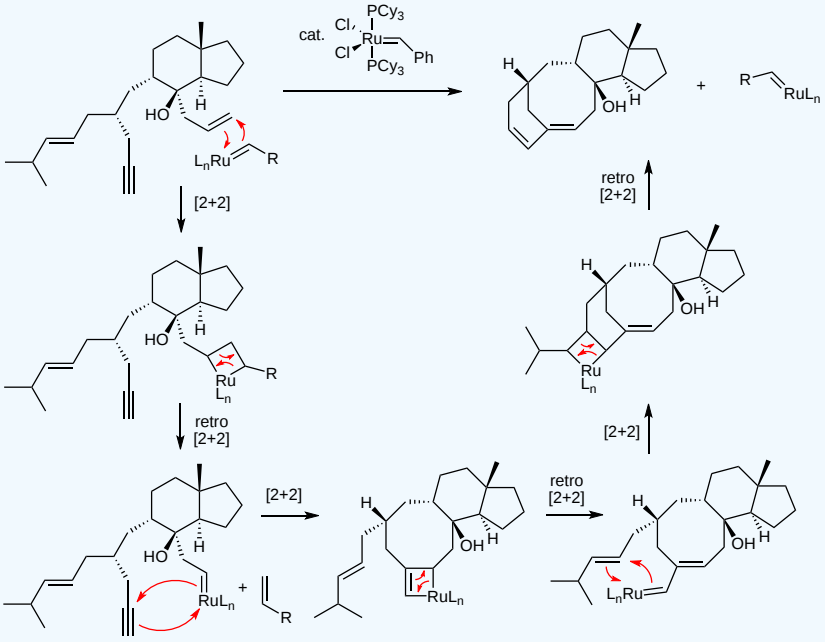
Answer

Reference: Organic Letters 2004

The synthesis part of the question involves reactions from intro orgo. The first step is an enolate alkylation between the two starting materials. The final step is a Grignard addition to the ketone.



This is an interesting substrate for olefin metathesis. It contains two alkenes and an alkyne which all have to react to form the target molecule. The most reactive functional group is the terminal alkene which is where the mechanism begins. We do our standard [2+2] and retro [2+2] reactions to generate the ruthenium intermediate that can react with the alkyne to form the 8-membered ring. This [2+2] reaction yields a metallocyclobutene (not butane) that opens to yield the desired cyclooctene with the ruthenium still in the molecule. This molecule can complete the mechanism with another round of [2+2] and retro [2+2] reactions. Please note this is an example of a RCM reaction that does not use L_nRu= as the catalyst. Because of the structure of alkene in the final [2+2] reaction, the catalyst contains an isopropyl group. This was the result of reaction optimization when synthesizing the target molecule in the Granja lab.



Contributors

- Prof. Kevin Shea (Smith College)

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