

AUCHE 252 - ORGANIC CHEMISTRY II



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AUCHE 252 - Organic Chemistry II

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CHAPTER OVERVIEW

1: Carbonyl Reactivity

1.1: Structure of the Carbonyl Group

1.2: Reactivity of the Carbonyl Group- Mechanisms of Addition

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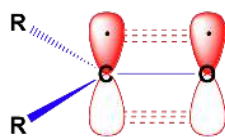
1.1: Structure of the Carbonyl Group

A carbonyl group is a chemically organic functional group composed of a carbon atom double-bonded to an oxygen atom $\rightarrow$ $[C=O]$. 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.

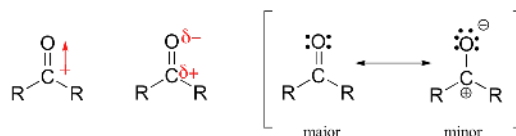
The Carbonyl Group

$C=O$ is prone to additions and nucleophilic attack because of 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.

Before we consider in detail the reactivity of aldehydes and ketones, we need to look back and remind ourselves of what the bonding picture looks like in a carbonyl. Carbonyl carbons are sp^2 hybridized, with the three sp^2 orbitals forming overlaps with orbitals on the oxygen and on the two carbon or hydrogen atoms. These three bonds adopt trigonal planar geometry. The remaining unhybridized $2p$ orbital on the central carbonyl carbon is perpendicular to this plane, and forms a 'side-by-side' π bond with a $2p$ orbital on the oxygen.



The carbon-oxygen double bond is polar: oxygen is more electronegative than carbon, so electron density is higher on the oxygen side of the bond and lower on the carbon side. Recall that bond polarity can be depicted with a dipole arrow, or by showing the oxygen as holding a partial negative charge and the carbonyl carbon a partial positive charge.



A third way to illustrate the carbon-oxygen dipole is to consider the two main resonance contributors of a carbonyl group: the major form, which is what you typically see drawn in Lewis structures, and a minor but very important contributor in which both electrons in the π bond are localized on the oxygen, giving it a full negative charge. The latter depiction shows the carbon with an empty $2p$ orbital and a full positive charge.

Some Carbonyl Compounds

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

Organic Chemistry With a Biological Emphasis by [Tim Soderberg](#) (University of Minnesota, Morris)

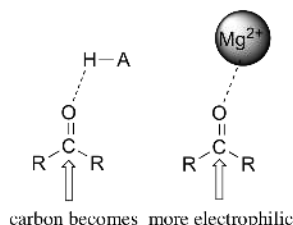
- Prof. Steven Farmer ([Sonoma State University](#))

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1.2: Reactivity of the Carbonyl Group- Mechanisms of Addition

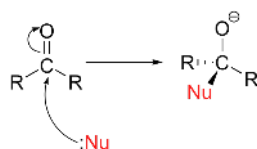
Nucleophilic Addition to Aldehydes and Ketones

The result of carbonyl bond polarization, however it is depicted, is straightforward to predict. The carbon, because it is electron-poor, is an electrophile: it is a great target for attack by an electron-rich nucleophilic group. Because the oxygen end of the carbonyl double bond bears a partial negative charge, anything that can help to stabilize this charge by accepting some of the electron density will increase the bond's polarity and make the carbon more electrophilic. Very often a general acid group serves this purpose, donating a proton to the carbonyl oxygen.

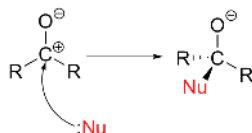


The same effect can also be achieved if a Lewis acid, such as a magnesium ion, is located near the carbonyl oxygen.

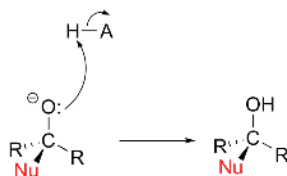
Unlike the situation in a nucleophilic substitution reaction, when a nucleophile attacks an aldehyde or ketone carbon there is no leaving group – the incoming nucleophile simply ‘pushes’ the electrons in the pi bond up to the oxygen.



Alternatively, if you start with the minor resonance contributor, you can picture this as an attack by a nucleophile on a carbocation.



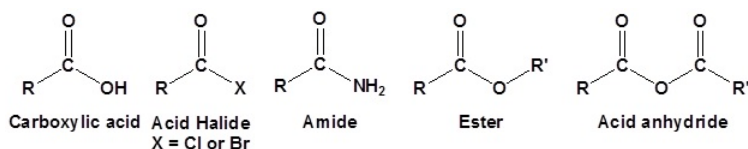
After the carbonyl is attacked by the nucleophile, the negatively charged oxygen has the capacity to act as a nucleophile. However, most commonly the oxygen acts instead as a base, abstracting a proton from a nearby acid group in the solvent or enzyme active site.



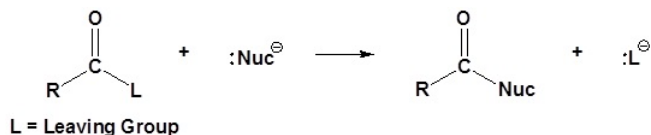
This very common type of reaction is called a **nucleophilic addition**. In many biologically relevant examples of nucleophilic addition to carbonyls, the nucleophile is an alcohol oxygen or an amine nitrogen, or occasionally a thiol sulfur. In one very important reaction type known as an aldol reaction (which we will learn about in section 13.3) the nucleophile attacking the carbonyl is a resonance-stabilized carbanion. In this chapter, we will concentrate on reactions where the nucleophile is an oxygen or nitrogen.

Nucleophilic Substitution of RCOZ (Z = Leaving Group)

Carbonyl compounds with leaving groups have reactions similar to aldehydes and ketones. The main difference is the presence of an electronegative substituent that can act as a leaving group during a nucleophile substitution reaction. Although there are many types of carboxylic acid derivatives known, this article focuses on four: acid halides, acid anhydrides, esters, and amides.

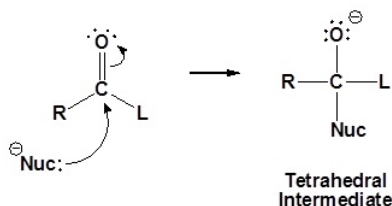


General reaction

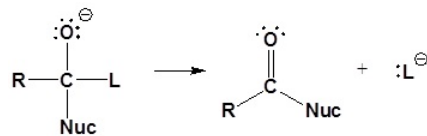


General mechanism

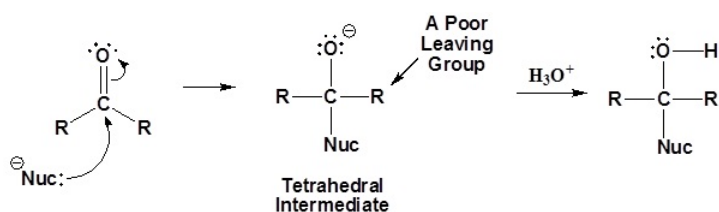
1) Nucleophilic attack on the carbonyl



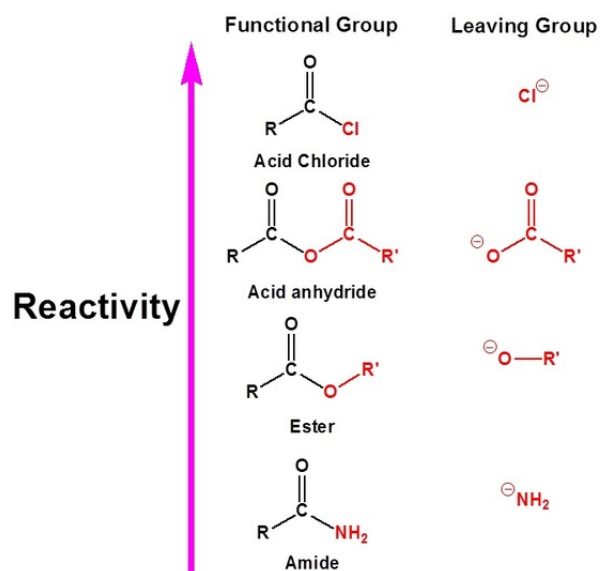
2) Leaving group is removed



Although aldehydes and ketones also contain carbonyls, their chemistry is distinctly different because they do not contain suitable leaving groups. Once a tetrahedral intermediate is formed, aldehydes and ketones cannot reform their carbonyls. Because of this, aldehydes and ketones typically undergo nucleophilic additions and not substitutions.



The relative reactivity of carboxylic acid derivatives toward nucleophile substitutions is related to the electronegative leaving group's ability to activate the carbonyl. The more electronegative leaving groups withdraw electron density from the carbonyl, thereby increasing its electrophilicity.



Contributors

- [Organic Chemistry With a Biological Emphasis](#) by [Tim Soderberg](#) (University of Minnesota, Morris)
- Prof. Steven Farmer ([Sonoma State University](#))

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CHAPTER OVERVIEW

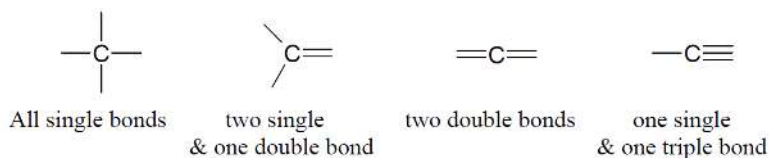
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2.1: Index of Hydrogen Deficiency (IHD)

There is no simple way of predicting how many isomers a given molecular formula will yield, (it can range from one to many). **Structures are different if they cannot be superimposed upon one another.** Keep in mind that there is rotation about all single bonds not involved in a ring, but not about double bonds. Because all of the formulas that you will be dealing with are based on the C atom, it may be useful to review the ways that C can bond to itself and to other atoms. We will limit ourselves, for now, to the C atom with four bonds. Below are the possible combinations of C having a total of four bonds.



In a hydrocarbon where all the C atoms have only single bonds and no rings are involved, the compound would have the maximum number of H atoms. If any of the bonds are replaced with double or triple bonds, or if rings are involved, there would be a “deficiency” of H atoms. By calculating the index of hydrogen deficiency (IHD), we can tell from the molecular formula whether and how many multiple bonds and rings are involved. IHD is also called the [Degree of Unsaturation](#). This will help cut down the possibilities one has to consider in trying to come up with all the isomers of a given formula.

Here is a summary of how the index of hydrogen deficiency (IHD) works.

- A double bond and ring each counts as one IHD.
- A triple bond counts as two IHD.

Hydrocarbons (C_xH_y):

$$IHD = \frac{2x + 2 - y}{2} \quad (2.1.1)$$

(where x and y stand for # of C and H respectively.)

Example 1

IHD for C_2H_4 is

$$\frac{2(2) + 2 - 4}{2} = 1 \quad (2.1.2)$$

This means it can have either one double bond or one ring, but it cannot have a triple bond. Since you cannot form a ring with only two C's, it must have a double bond.

Example 2

IHD for C_4H_6 is

$$\frac{2(4) + 2 - 6}{2} = 2 \quad (2.1.3)$$

This means it can have either one double bond and a ring such as  or two double bonds such as $CH_2=CH-CH=CH_2$ or $CH_2=C=CH-CH_3$ or two rings , or one triple bond, such as $CH_3C\equiv CCH_3$.

Compounds Containing Elements Other than C and H

O and S atoms do not affect the IHD.

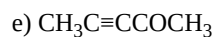
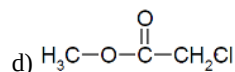
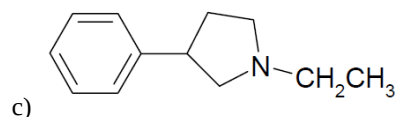
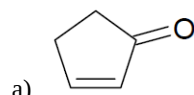
- Halogens (F, Cl, Br, I) are treated like H atoms (CH_2Cl_2 has the same IHD as CH_4).

- For each N, add one to the number of C and one to the number H (CH_5N is treated as C_2H_6 . $\text{CH}_4\text{N}_2\text{O}$ is treated as C_3H_6 by adding 2 to # of C and 2 to # of H).

Do not forget that when double bonds and rings are involved, geometric isomers are possible.

Practice problems

Calculate the IHD for each of the following and see whether it corresponds to the structure shown. (Obviously it should!) Don't peek until you've worked it out yourself, but answers are provided at the bottom.



Answers

- a) IHD = 3
- b) IHD = 2
- c) IHD = 5
- d) IHD = 1
- e) IHD = 3

Contributors

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2.2: Nuclear Magnetic Resonance Spectroscopy

Many kinds of nuclei behave as if they were spinning about an axis, somewhat as the earth spins daily. Because they're positively charged, these spinning nuclei act like tiny magnets and can interact with an external magnetic field, denoted B_0 . Not all nuclei act this way, but fortunately for organic chemists, both the proton (^1H) and the ^{13}C nucleus do have spins. The more common ^{12}C isotope, however, does not have nuclear spin. (In speaking about NMR, the words *proton* and *hydrogen* are often used interchangeably, since a hydrogen nucleus is just a proton.) Let's see what the consequences of nuclear spin are and how we can use the results.

In the absence of an external magnetic field, the spins of magnetic nuclei are oriented randomly. When a sample containing these nuclei is placed between the poles of a strong magnet, however, the nuclei adopt specific orientations, much as a compass needle orients in the earth's magnetic field. A spinning ^1H or ^{13}C nucleus can orient so that its own tiny magnetic field is aligned either with (parallel to) or against (antiparallel to) the external field. The two orientations don't have the same energy, however, and aren't equally likely. The parallel orientation is slightly lower in energy by an amount that depends on the strength of the external field, making this spin state very slightly favored over the antiparallel orientation (Figure 2.2.1).

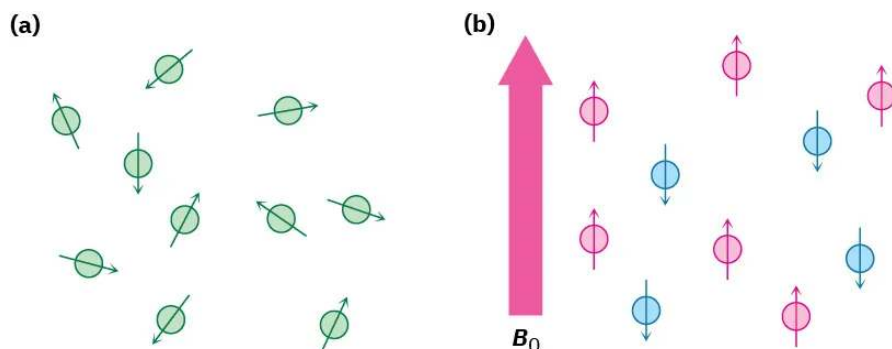


Figure 2.2.1: (a) Nuclear spins are oriented randomly in the absence of an external magnetic field but (b) have a specific orientation in the presence of an external field, B_0 . Some of the spins (red) are aligned parallel to the external field while others (blue) are antiparallel. The parallel spin state is slightly lower in energy and therefore favored.

If the oriented nuclei are irradiated with electromagnetic radiation of the proper frequency, energy absorption occurs and the lower-energy spin state “flips” to the higher-energy state. When this spin-flip occurs, the magnetic nuclei are said to be in resonance with the applied radiation—hence the name *nuclear magnetic resonance*.

The exact frequency necessary for resonance depends both on the strength of the external magnetic field, the identity of the nucleus, and the electronic environment of the nucleus. If a very strong magnetic field is applied, the energy difference between the two spin states is larger and higher-frequency (higher-energy) radiation is required for a spin-flip. If a weaker magnetic field is applied, less energy is required to effect the transition between nuclear spin states (Figure 2.2.2).

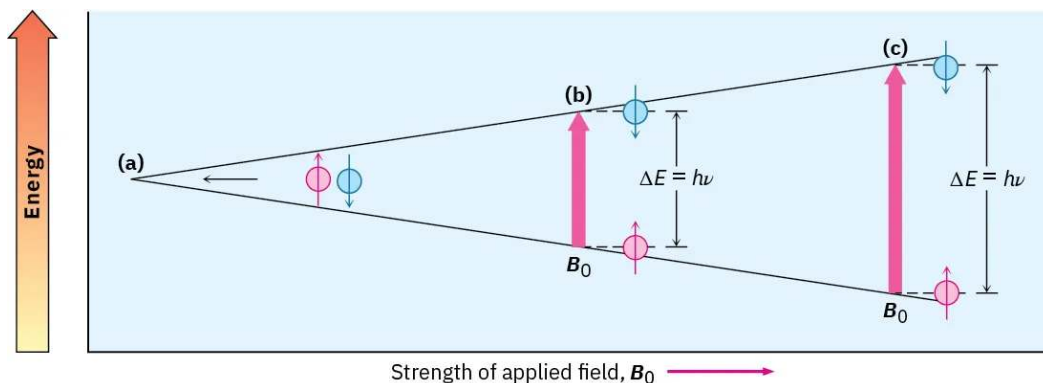


Figure 2.2.2: The energy difference ΔE between nuclear spin states depends on the strength of the applied magnetic field. Absorption of energy with frequency ν converts a nucleus from a lower spin state to a higher spin state. (a) Spin states have equal energies in the absence of an applied magnetic field but (b) have unequal energies in the presence of a magnetic field. At $\nu = 200$ MHz, $\Delta E = 8.0 \times 10^{-5}$ kJ/mol (1.9×10^{-5} kcal/mol). (c) The energy difference between spin states is greater at larger applied fields. At $\nu = 500$ MHz, $\Delta E = 2.0 \times 10^{-4}$ kJ/mol.

In practice, superconducting magnets that produce enormously powerful fields up to 23.5 tesla (T) are sometimes used, but field strengths in the range of 4.7 to 7.0 T are more common. At a magnetic field strength of 4.7 T, so-called radiofrequency (rf) energy in the 200 MHz range ($1 \text{ MHz} = 10^6 \text{ Hz}$) brings a ^1H nucleus into resonance, and rf energy of 50 MHz brings a ^{13}C nucleus into resonance. At the highest field strength currently available in commercial instruments (23.5 T), 1000 MHz energy is required for ^1H spectroscopy. These energies needed for NMR are much smaller than those required for IR spectroscopy; 200 MHz rf energy corresponds to only $8.0 \times 10^{-5} \text{ kJ/mol}$ versus the 4.8 to 48 kJ/mol needed for IR spectroscopy.

^1H and ^{13}C nuclei are not unique in their ability to exhibit the NMR phenomenon. All nuclei with an odd number of protons (^1H , ^2H , ^{14}N , ^{19}F , ^{31}P , for example) and all nuclei with an odd number of neutrons (^{13}C , for example) show magnetic properties. Only nuclei with even numbers of both protons and neutrons (^{12}C , ^{16}O , ^{32}S) do not give rise to magnetic phenomena (Table 2.2.1).

Table 2.2.1: The NMR Behavior of Some Common Nuclei

Magnetic nuclei	Nonmagnetic nuclei
^1H	^{12}C
^{13}C	^{16}O
^2H	^{32}S
^{14}N	
^{19}F	
^{31}P	

? Exercise 2.2.1

The amount of energy required to spin-flip a nucleus depends both on the strength of the external magnetic field and on the nucleus. At a field strength of 4.7 T, rf energy of 200 MHz is required to bring a ^1H nucleus into resonance, but energy of only 187 MHz will bring a ^{19}F nucleus into resonance. Calculate the amount of energy required to spin-flip a ^{19}F nucleus. Is this amount greater or less than that required to spin-flip a ^1H nucleus?

Answer

- $7.5 \times 10^{-5} \text{ kJ/mol}$ for ^{19}F
- $8.0 \times 10^{-5} \text{ kJ/mol}$ for ^1H

? Exercise 2.2.2

Calculate the amount of energy required to spin-flip a proton in a spectrometer operating at 300 MHz. Does increasing the spectrometer frequency from 200 to 300 MHz increase or decrease the amount of energy necessary for resonance?

Answer

$$1.2 \times 10^{-4} \text{ kJ/mol}$$

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2.3: The Nature of NMR Absorptions

From the description thus far, you might expect all ^1H nuclei in a molecule to absorb energy at the same frequency and all ^{13}C nuclei to absorb at the same frequency. If so, we would observe only a single NMR absorption signal in the ^1H or ^{13}C spectrum of a molecule, a situation that would be of little use. In fact, the absorption frequency is not the same for all ^1H or all ^{13}C nuclei. All nuclei in molecules are surrounded by electrons. When an external magnetic field is applied to a molecule, the electrons moving around nuclei set up tiny local magnetic fields of their own. These local magnetic fields act in opposition to the applied field so that the effective field actually felt by the nucleus is a bit weaker than the applied field.

$$B_{\text{effective}} = B_{\text{applied}} - B_{\text{local}}$$

In describing this effect of local fields, we say that nuclei experience **shielding** from the full effect of the applied field by the surrounding electrons. Because each chemically distinct nucleus in a molecule is in a slightly different electronic environment, each nucleus is shielded to a slightly different extent and the effective magnetic field felt by each is slightly different. These tiny differences in the effective magnetic fields experienced by different nuclei can be detected, and we thus see a distinct NMR signal for each chemically distinct ^{13}C or ^1H nucleus in a molecule. As a result, an NMR spectrum effectively maps the carbon–hydrogen framework of an organic molecule. With practice, it's possible to read this map and derive structural information.

Figure 2.3.1 shows both the ^1H and the ^{13}C NMR spectra of methyl acetate, $\text{CH}_3\text{CO}_2\text{CH}_3$. The horizontal axis shows the effective field strength felt by the nuclei, and the vertical axis indicates the intensity of absorption of rf energy. Each peak in the NMR spectrum corresponds to a chemically distinct ^1H or ^{13}C nucleus in the molecule. Note that NMR spectra are formatted with the zero absorption line at the bottom, whereas IR spectra are formatted with the zero absorption line at the top; Section 12.6. Note also that ^1H and ^{13}C spectra can't be observed simultaneously on the same spectrometer because different amounts of energy are required to spin-flip the different kinds of nuclei. The two spectra must be recorded separately.

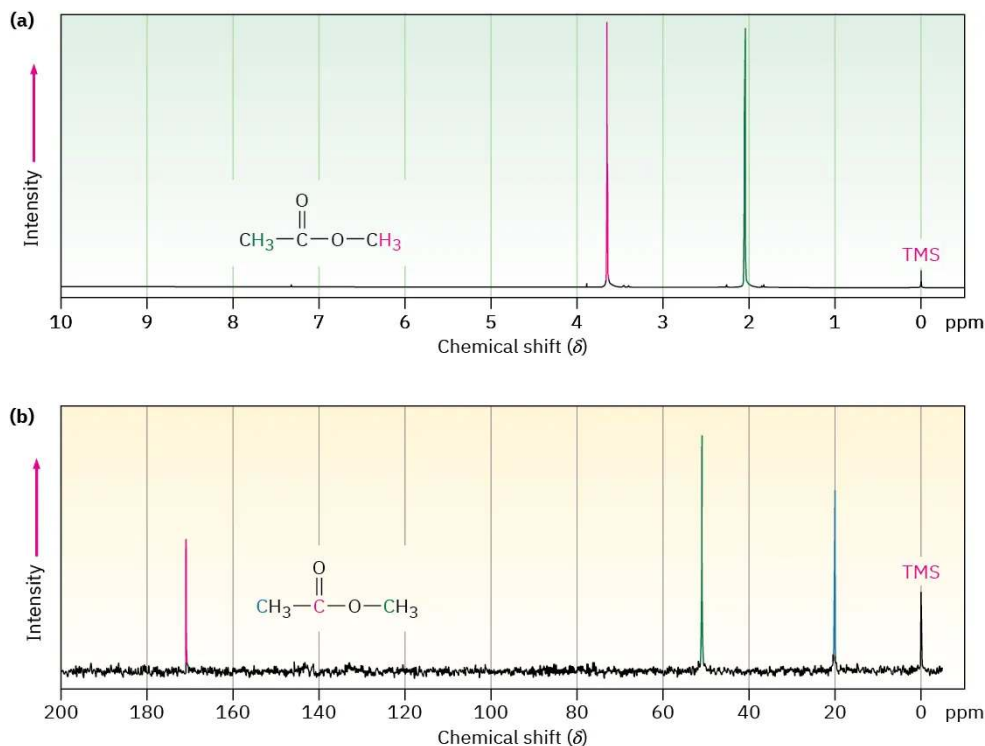


Figure 2.3.1: (a) The ^1H NMR spectrum and (b) the proton-decoupled ^{13}C NMR spectrum of methyl acetate, $\text{CH}_3\text{CO}_2\text{CH}_3$. The small peak labeled "TMS" at the far right of each spectrum is a calibration peak, as explained in the next section.

The ^{13}C NMR spectrum of methyl acetate in Figure 2.3.1b shows three peaks, one for each of the three chemically distinct carbon atoms in the molecule. The ^1H NMR spectrum in Figure 2.3.1a shows only two peaks, however, even though methyl acetate has six hydrogens. One peak is due to the $\text{CH}_3\text{C}=\text{O}$ hydrogens, and the other to the $-\text{OCH}_3$ hydrogens. Because the three hydrogens in each methyl group have the same electronic environment, they are shielded to the same extent and are said to be equivalent.

Chemically equivalent nuclei always show the same absorption. The two methyl groups themselves, however, are not equivalent, so the two sets of hydrogens absorb at different positions.

The operation of a basic NMR spectrometer is illustrated in Figure 2.3.2. An organic sample is dissolved in a suitable solvent (usually deuteriochloroform, CDCl_3 , which has no hydrogens) and placed in a thin glass tube between the poles of a magnet. The strong magnetic field causes the ^1H and ^{13}C nuclei in the molecule to align in one of the two possible orientations, and the sample is irradiated with rf energy. If the frequency of the rf irradiation is held constant and the strength of the applied magnetic field is varied, each nucleus comes into resonance at a slightly different field strength. A sensitive detector monitors the absorption of rf energy, and its electronic signal is then amplified and displayed as a peak.

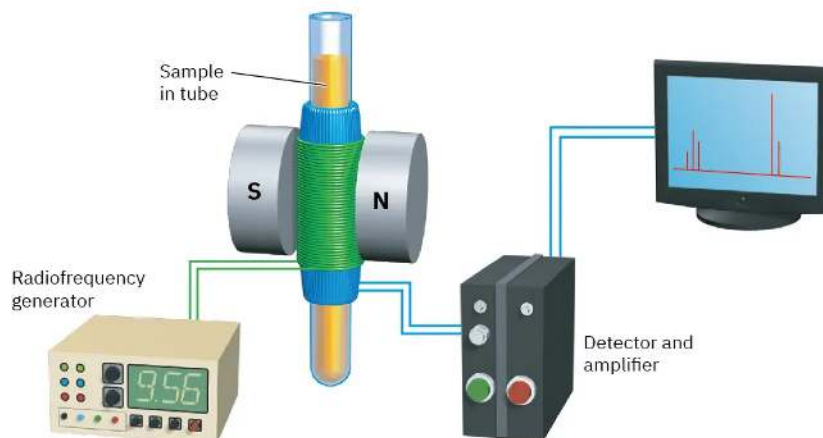
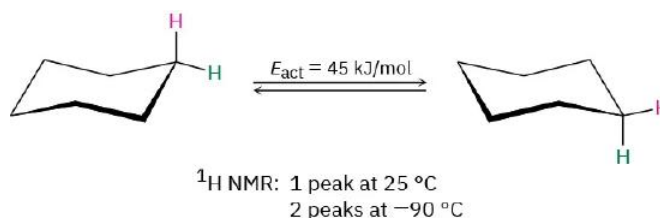


Figure 2.3.2: Schematic operation of a basic NMR spectrometer. A thin glass tube containing the sample solution is placed between the poles of a strong magnet and irradiated with rf energy.

NMR spectroscopy differs from IR spectroscopy (Section 12.6–Section 12.8) in that the timescales of the two techniques are quite different. The absorption of infrared energy by a molecule giving rise to a change in vibrational amplitude is an essentially instantaneous process (about 10^{-13} s), but the NMR process is much slower (about 10^{-3} s). This difference in timescales between IR and NMR spectroscopy is analogous to the difference between cameras operating at very fast and very slow shutter speeds. The fast camera (IR) takes an instantaneous picture and freezes the action. If two rapidly interconverting species are present, IR spectroscopy records the spectrum of both. The slow camera (NMR), however, takes a blurred, time-averaged picture. If two species interconverting faster than 10^3 times per second are present in a sample, NMR records only a single, averaged spectrum, rather than separate spectra of the two discrete species.

Because of this blurring effect, NMR spectroscopy can be used to measure the rates and activation energies of very fast chemical processes. In cyclohexane, for example, a ring-flip (Section 4.6) occurs so rapidly at room temperature that axial and equatorial hydrogens can't be distinguished by NMR; only a single, averaged ^1H NMR absorption is seen for cyclohexane at 25 °C. At –90 °C, however, the ring-flip is slowed down enough that two absorption peaks are visible, one for the six axial hydrogens and one for the six equatorial hydrogens. Knowing the temperature and the rate at which signal blurring begins to occur, it's possible to calculate that the activation energy for the cyclohexane ring-flip is 45 kJ/mol (10.8 kcal/mol).

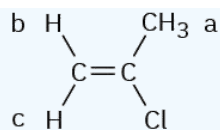


? Exercise 2.3.1

2-Chloropropene shows signals for three kinds of protons in its ^1H NMR spectrum. Explain.

Answer

The vinylic C – H protons are nonequivalent.



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2.4: Chemical Shifts

NMR spectra are displayed on charts that show the applied field strength increasing from left to right (Figure 2.4.1). Thus, the left part of the chart is the low-field, or **downfield**, side, and the right part is the high-field, or **upfield**, side. Nuclei that absorb on the downfield side of the chart require a lower field strength for resonance, implying that they have less shielding. Nuclei that absorb on the upfield side require a higher field strength for resonance, implying that they have more shielding.

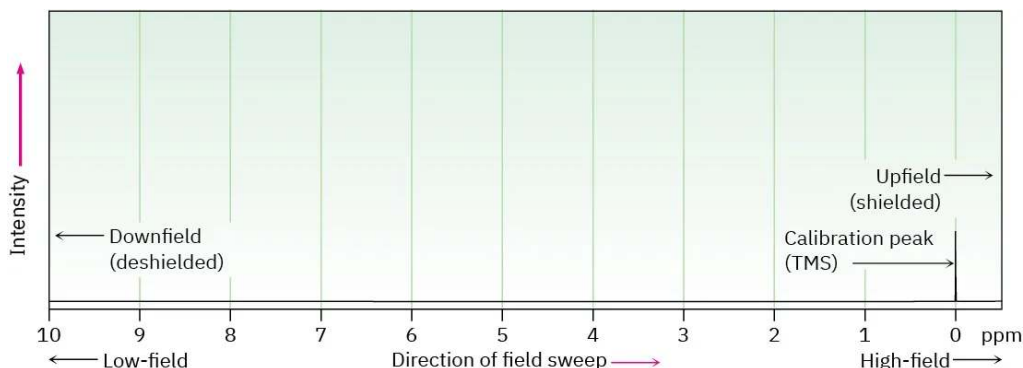


Figure 2.4.1: The NMR chart. The downfield, deshielded side is on the left, and the upfield, shielded side is on the right. The tetramethylsilane (TMS) absorption is used as reference point.

To define the position of an absorption, the NMR chart is calibrated and a reference point is used. In practice, a small amount of tetramethylsilane [TMS; $(\text{CH}_3)_4\text{Si}$] is added to the sample so that a reference absorption peak is produced when the spectrum is run. TMS is used as reference for both ^1H and ^{13}C measurements because in both cases it produces a single peak that occurs upfield of other absorptions normally found in organic compounds. The ^1H and ^{13}C spectra of methyl acetate in Figure 13.4 have the TMS reference peak indicated. The position on the chart at which a nucleus absorbs is called its **chemical shift**. The chemical shift of TMS is set as the zero point, and other absorptions normally occur downfield, to the left on the chart. NMR charts are calibrated using an arbitrary scale called the **delta (δ) scale**, where 1 δ equals 1 part-per-million (1 ppm) of the spectrometer operating frequency. For example, if we were measuring the ^1H NMR spectrum of a sample using an instrument operating at 200 MHz, 1 δ would be 1 part per million of 200,000,000 Hz, or 200 Hz. If we were measuring the spectrum using a 500 MHz instrument, 1 δ = 500 Hz. The following equation can be used for any absorption:

$$\delta = \frac{\text{Observed chemical shift (number of Hz away from TMS)}}{\text{Spectrometer frequency in}} \quad (2.4.1)$$

Although this method of calibrating NMR charts may seem complex, there's a good reason for it. As we saw earlier, the rf frequency required to bring a given nucleus into resonance depends on the spectrometer's magnetic field strength. But because there are many different kinds of spectrometers with many different magnetic field strengths available, chemical shifts given in frequency units (Hz) vary from one instrument to another. Thus, a resonance that occurs at 120 Hz downfield from TMS on one spectrometer might occur at 600 Hz downfield from TMS on another spectrometer with a more powerful magnet.

By using a system of measurement in which NMR absorptions are expressed in relative terms (parts per million relative to spectrometer frequency) rather than absolute terms (Hz), it's possible to compare spectra obtained on different instruments. *The chemical shift of an NMR absorption in δ units is constant, regardless of the operating frequency of the spectrometer.* A ^1H nucleus that absorbs at 2.0 δ on a 200 MHz instrument also absorbs at 2.0 δ on a 500 MHz instrument.

The range in which most NMR absorptions occur is quite narrow. Almost all ^1H NMR absorptions occur from 0 to 10 δ downfield from the proton absorption of TMS, and almost all ^{13}C absorptions occur from 1 to 220 δ downfield from the carbon absorption of TMS. Thus, there is a likelihood that accidental overlap of nonequivalent signals will occur. The advantage of using an instrument with higher field strength (say, 500 MHz) rather than lower field strength (200 MHz) is that different NMR absorptions are more widely separated at the higher field strength. The chances that two signals will accidentally overlap are therefore lessened, and interpretation of spectra becomes easier. For example, two signals that are only 20 Hz apart at 200 MHz (0.1 ppm) are 50 Hz apart at 500 MHz (still 0.1 ppm).

? Exercise 2.4.1

The following ^1H NMR peaks were recorded on a spectrometer operating at 200 MHz. Convert each into δ units.

- a. CHCl_3 ; 1454 Hz
- b. CH_3Cl ; 610 Hz
- c. CH_3OH ; 693 Hz
- d. CH_2Cl_2 ; 1060 Hz

Answer

- a. 7.27 δ
- b. 3.05 δ
- c. 3.46 δ
- d. 5.30 δ

? Exercise 2.4.2

When the ^1H NMR spectrum of acetone, CH_3COCH_3 , is recorded on an instrument operating at 200 MHz, a single sharp resonance at 2.1 δ is seen.

- a. How many hertz downfield from TMS does the acetone resonance correspond to?
- b. If the ^1H NMR spectrum of acetone is recorded at 500 MHz, what would the position of the absorption be in δ units?
- c. How many hertz downfield from TMS does this 500 MHz resonance correspond to?

Answer

- a. 420 Hz
- b. 2.1 δ
- c. 1050 Hz

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2.5: Chemical Shifts in ^1H NMR Spectroscopy

As mentioned previously, differences in chemical shifts are caused by the small local magnetic field of electrons surrounding different nuclei. Nuclei that are more strongly shielded by electrons require a higher applied field to bring them into resonance so they absorb on the right side of the NMR chart. Nuclei that are less strongly shielded need a lower applied field for resonance so they absorb on the left of the NMR chart.

Most ^1H chemical shifts fall within the range 0 to 10 δ , which can be divided into the five regions shown in Figure 2.5.1. By remembering the positions of these regions, it's often possible to tell at a glance what kinds of protons a molecule contains.

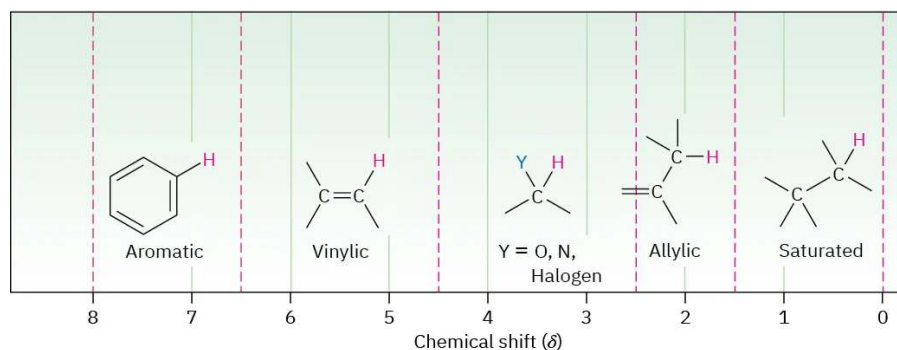
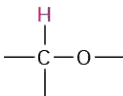
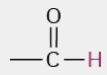
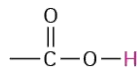


Figure 2.5.1: Regions of the ^1H NMR Spectrum

Figure 2.5.2 shows the correlation of ^1H chemical shift with electronic environment in more detail. In general, protons bonded to saturated, sp^3 -hybridized carbons absorb at higher fields, whereas protons bonded to sp^2 -hybridized carbons absorb at lower fields. Protons on carbons that are bonded to electronegative atoms, such as N, O, or halogen, also absorb at lower fields.

Figure 2.5.2: Correlation of ^1H Chemical Shifts with Environment

Type of hydrogen	Structure	Chemical shift (δ)
Reference	$\text{Si}(\text{CH}_3)_4$	0
Alkyl (primary)	$-\text{CH}_3$	0.7–1.3
Alkyl (secondary)	$-\text{CH}_2-$	1.2–1.6
Alkyl (tertiary)	$-\text{CH}-$	1.4–1.8
Allylic	$\text{C}=\text{C}-\text{CH}_2-$	1.6–2.2
Methyl ketone	$\text{O}=\text{C}-\text{CH}_3$	2.0–2.4
Aromatic methyl	$\text{Ar}-\text{CH}_3$	2.4–2.7
Alkynyl	$-\text{C}\equiv\text{C}-\text{H}$	2.5–3.0
Alkyl halide	$-\text{CH}_2-\text{Hal}$	2.5–4.0
Alcohol	$-\text{CH}_2-\text{OH}$	2.5–5.0

Type of hydrogen	Structure	Chemical shift (δ)
Alcohol, ether		3.3–4.5
Vinylic		4.5–6.5
Aryl	Ar—H	6.5–8.0
Aldehyde		9.7–10.0
Carboxylic acid		11.0–12.0

✓ Worked Example 2.5.1: Predicting Chemical Shifts in ^1H NMR Spectra

Methyl 2,2-dimethylpropanoate $(\text{CH}_3)_2\text{CCO}_2\text{CH}_3$ has two peaks in its ^1H NMR spectrum. What are their approximate chemical shifts?

Strategy

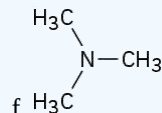
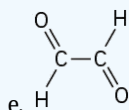
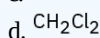
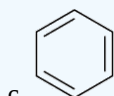
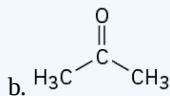
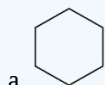
Identify the types of hydrogens in the molecule, and note whether each is alkyl, vinylic, or next to an electronegative atom. Then predict where each absorbs, using Figure 2.5.2 if necessary.

Solution

The $-\text{OCH}_3$ protons absorb around 3.5 to 4.0 δ because they are on carbon bonded to oxygen. The $(\text{CH}_3)_3\text{C}-$ protons absorb near 1.0 δ because they are typical alkane-like protons.

? Exercise 2.5.1

Each of the following compounds has a single ^1H NMR peak. Approximately where would you expect each compound to absorb?



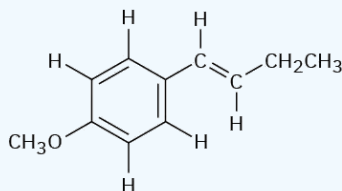
Answer

a. 1.43 δ

- b. 2.17 δ
- c. 7.37 δ
- d. 5.30 δ
- e. 9.70 δ
- f. 2.12 δ

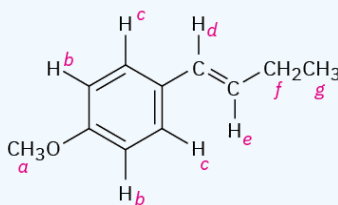
? Exercise 2.5.2

Identify the different types of protons in the following molecule, and tell where you would expect each to absorb:



Answer

There are seven kinds of protons labeled. The types and expected range of absorption of each follow. **a:** ether, 3.5–4.5 δ ; **b:** aryl, 6.5–8.0 δ ; **c:** aryl, 6.5–8.0; **d:** vinylic, 4.5–6.5 δ ; **e:** vinylic, 4.5–6.5 δ ; **f:** alkyl (secondary), 1.2–1.6 δ ; **g:** alkyl (primary), 0.7–1.3 δ .



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2.6: Integration of ^1H NMR Absorptions- Proton Counting

Look at the ^1H NMR spectrum of methyl 2,2-dimethylpropanoate in Figure 2.6.1. There are two peaks, corresponding to the two kinds of protons, but the peaks aren't the same size. The peak at 1.2 δ , due to the $(\text{CH}_3)_3\text{C}-$ protons, is larger than the peak at 3.7 δ , due to the $-\text{OCH}_3$ protons.

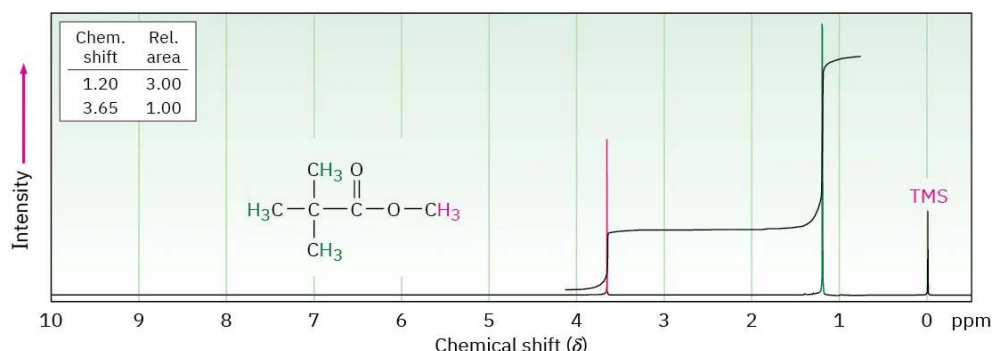


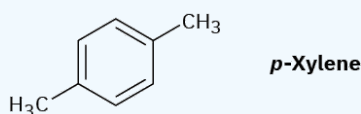
Figure 2.6.1: The ^1H NMR spectrum of methyl 2,2-dimethylpropanoate. Integrating the peaks in a stair-step manner shows that they have a 1 : 3 ratio, corresponding to the ratio of the numbers of protons (3 : 9) responsible for each peak. Modern instruments give a direct digital readout of relative peak areas.

The area under each peak is proportional to the number of protons causing that peak. By electronically measuring, or integrating, the area under each peak, it's possible to measure the relative numbers of the different kinds of protons in a molecule.

Modern NMR instruments provide a digital readout of relative peak areas, but an older, more visual method displays the integrated peak areas as a stair-step line, with the height of each step proportional to the area under the peak, and therefore proportional to the relative number of protons causing the peak. For example, the two steps for the peaks in methyl 2,2-dimethylpropanoate have a 1 : 3 (or 3 : 9) height ratio when integrated—exactly what we expect because the three $-\text{OCH}_3$ protons are equivalent and the nine $(\text{CH}_3)_3\text{C}-$ protons are equivalent.

? Exercise 2.6.1

How many peaks would you expect in the ^1H NMR spectrum of 1,4-dimethylbenzene (*para*-xylene, or *p*-xylene)? What ratio of peak areas would you expect on integration of the spectrum? Refer to Figure 13.4.1 for approximate chemical shifts, and sketch what the spectrum would look like. (Remember from **Section 2.4** that aromatic rings have two resonance forms.)



Answer

Two peaks; 3 : 2 ratio

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2.7: Spin-Spin Splitting in ^1H NMR Spectra

In the ^1H NMR spectra we've seen thus far, each different kind of proton in a molecule has given rise to a single peak. It often happens, though, that the absorption of a proton splits into multiple peaks, called a **multiplet**. For example, in the ^1H NMR spectrum of bromoethane shown in Figure 2.7.1, the $-\text{CH}_2\text{Br}$ protons appear as four peaks (a *quartet*) centered at 3.42δ and the $-\text{CH}_3$ protons appear as three peaks (a *triplet*) centered at 1.68δ .

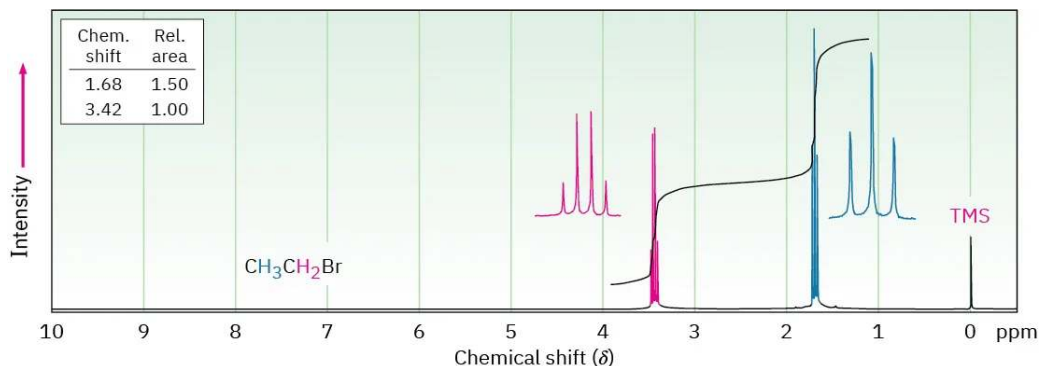


Figure 2.7.1: The ^1H NMR spectrum of bromoethane, $\text{CH}_3\text{CH}_2\text{Br}$. The $-\text{CH}_2\text{Br}$ protons appear as a quartet at 3.42δ , and the $-\text{CH}_3$ protons appear as a triplet at 1.68δ .

Called **spin-spin splitting**, multiple absorptions of a nucleus are caused by the interaction, or **coupling**, of the spins of nearby nuclei. In other words, the tiny magnetic field produced by one nucleus affects the magnetic field felt by a neighboring nucleus. Look at the $-\text{CH}_3$ protons in bromoethane, for example. The three equivalent $-\text{CH}_3$ protons are neighbored by two other magnetic nuclei—the two protons on the adjacent $-\text{CH}_2\text{Br}$ group. Each of the neighboring $-\text{CH}_2\text{Br}$ protons has its own nuclear spin, which can align either with or against the applied field, producing a tiny effect that is felt by the $-\text{CH}_3$ protons.

There are three ways in which the spins of the two $-\text{CH}_2\text{Br}$ protons can align, as shown in Figure 2.7.2. If both proton spins align with the applied field, the total effective field felt by the neighboring $-\text{CH}_3$ protons is slightly larger than it would be otherwise. Consequently, the applied field necessary to cause resonance is slightly reduced. Alternatively, if one of the $-\text{CH}_2\text{Br}$ proton spins aligns with the field and one aligns against the field, there is no effect on the neighboring $-\text{CH}_3$ protons. (This arrangement can occur in two ways, depending on which of the two proton spins aligns which way.) Finally, if both $-\text{CH}_2\text{Br}$ proton spins align against the applied field, the effective field felt by the $-\text{CH}_3$ protons is slightly smaller than it would be otherwise, and the applied field needed for resonance is slightly increased.

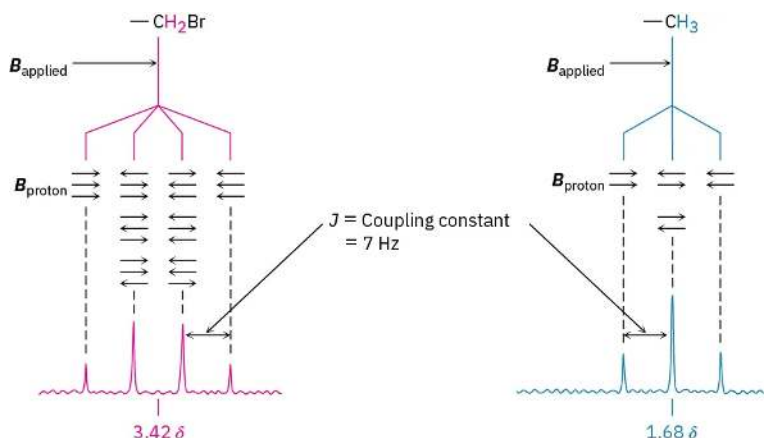


Figure 2.7.2: The origin of spin-spin splitting in bromoethane. The nuclear spins of neighboring protons, indicated by horizontal arrows, align either with or against the applied field, causing the splitting of absorptions into multiplets.

Any given molecule has only one of the three possible alignments of $-\text{CH}_2\text{Br}$ spins, but in a large collection of molecules, all three spin states are represented in a 1 : 2 : 1 statistical ratio. We therefore find that the neighboring $-\text{CH}_3$ protons come into resonance at three slightly different values of the applied field, and we see a 1 : 2 : 1 triplet in the NMR spectrum. One resonance is a little above where it would be without coupling, one is at the same place it would be without coupling, and the third resonance is a little below where it would be without coupling.

In the same way that the -CH_3 absorption of bromoethane is split into a triplet, the $\text{-CH}_2\text{Br}$ absorption is split into a quartet. The three spins of the neighboring -CH_3 protons can align in four possible combinations: all three with the applied field, two with and one against (three ways), one with and two against (three ways), or all three against. Thus, four peaks are produced for the $\text{-CH}_2\text{Br}$ protons in a 1 : 3 : 3 : 1 ratio.

As a general rule, called the $n + 1$ rule, protons that have n equivalent neighboring protons show $n + 1$ peaks in their NMR spectrum. For example, the spectrum of 2-bromopropane in Figure 2.7.3 shows a *doublet* at 1.71 δ and a seven-line multiplet, or *septet*, at 4.28 δ . The septet is caused by splitting of the -CHBr- proton signal by six equivalent neighboring protons on the two methyl groups ($n = 6$ leads to $6 + 1 = 7$ peaks). The doublet is due to signal splitting of the six equivalent methyl protons by the single -CHBr- proton ($n = 1$ leads to 2 peaks). Integration confirms the expected 6 : 1 ratio.

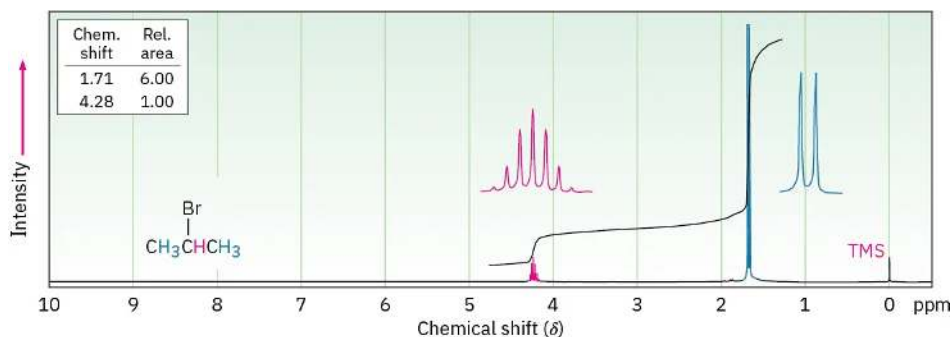


Figure 2.7.3: The ^1H NMR spectrum of 2-bromopropane. The -CH_3 proton signal at 1.71 δ is split into a doublet, and the -CHBr- proton signal at 4.28 δ is split into a septet. Note that the distance between peaks is the same in both multiplets. Note also that the two outer peaks of the septet are small enough to be nearly missed.

The distance between peaks in a multiplet is called the coupling constant and is denoted J . Coupling constants are measured in hertz and generally fall in the range 0 to 18 Hz. The exact value of the coupling constant between two neighboring protons depends on the geometry of the molecule, but a typical value for an open-chain alkane is $J = 6$ to 8 Hz. The same coupling constant is shared by both groups of hydrogens whose spins are coupled and is independent of spectrometer field strength. In bromoethane, for instance, the $\text{-CH}_2\text{Br}$ protons are coupled to the -CH_3 protons and appear as a quartet with $J = 7$ Hz. The -CH_3 protons appear as a triplet with the same $J = 7$ Hz coupling constant.

Because coupling is a reciprocal interaction between two adjacent groups of protons, it's sometimes possible to tell which multiplets in a complex NMR spectrum are related to each other. If two multiplets have the same coupling constant, they are probably related, and the protons causing those multiplets are therefore adjacent in the molecule.

The most commonly observed coupling patterns and the relative intensities of lines in their multiplets are listed in Table Figure 2.7.1. Note that it's not possible for a given proton to have five equivalent neighboring protons. (Why not?) A six-line multiplet, or sextet, is therefore found only when a proton has five nonequivalent neighboring protons that coincidentally happen to be coupled with an identical coupling constant J .

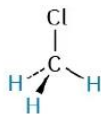
Table 2.7.1: Some Common Spin Multiplicities

Number of equivalent adjacent protons	Multiplet	Ratio of intensities
0	Singlet	1
1	Doublet	1 : 1
2	Triplet	1 : 2 : 1
3	Quartet	1 : 3 : 3 : 1
4	Quintet	1 : 4 : 6 : 4 : 1
6	Septet	1 : 6 : 15 : 20 : 15 : 6 : 1

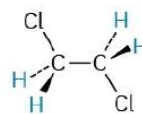
Spin-spin splitting in ^1H NMR can be summarized by three rules.

RULE 1

Chemically equivalent protons don't show spin-spin splitting. Equivalent protons may be on the same carbon or on different carbons, but their signals don't split.



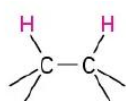
Three C-H protons are chemically equivalent; no splitting occurs.



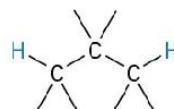
Four C-H protons are chemically equivalent; no splitting occurs.

RULE 2

The signal of a proton with n equivalent neighboring protons is split into a multiplet of $n + 1$ peaks with coupling constant J . Protons that are farther than two carbon atoms apart don't usually couple, although they sometimes show weak coupling when they are separated by a π bond.



Splitting observed



Splitting not usually observed

RULE 3

Two groups of protons coupled to each other have the same coupling constant, J . The spectrum of *para*-methoxypropiphenone in Figure 2.7.4 further illustrates these three rules. The downfield absorptions at 6.91 and 7.93 δ are due to the four aromatic-ring protons. There are two kinds of aromatic protons, each of which gives a signal that is split into a doublet by its neighbor. The $-\text{OCH}_3$ signal is unsplit and appears as a sharp singlet at 3.84 δ . The $-\text{CH}_2-$ protons next to the carbonyl group appear at 2.93 δ in the region expected for protons on carbon next to an unsaturated center, and their signal is split into a quartet by coupling with the protons of the neighboring methyl group. The methyl protons appear as a triplet at 1.20 δ in the usual upfield region.

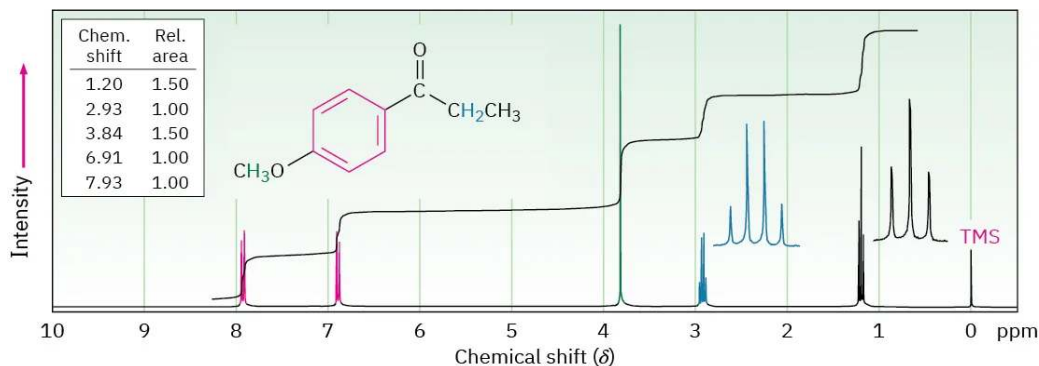


Figure 2.7.4: The ^1H NMR spectrum of *para*-methoxypropiphenone.

✓ Worked Example 2.7.1: Assigning a Chemical Structure from a ^1H NMR Spectrum

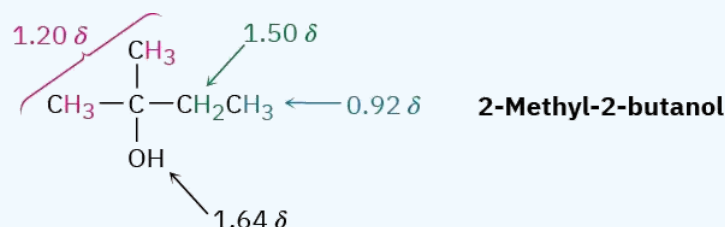
Propose a structure for a compound, $\text{C}_5\text{H}_{12}\text{O}$, that fits the following ^1H NMR data: 0.92 δ (3 H, triplet, $J = 7$ Hz), 1.20 δ (6 H, singlet), 1.50 δ (2 H, quartet, $J = 7$ Hz), 1.64 δ (1 H, broad singlet).

Strategy

It's best to begin solving structural problems by calculating a molecule's degree of unsaturation (we'll see this again in Worked Example 13.4). In the present instance, a formula of $\text{C}_5\text{H}_{12}\text{O}$ corresponds to a saturated, open-chain molecule, either an alcohol or an ether.

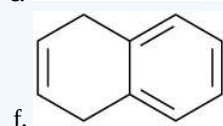
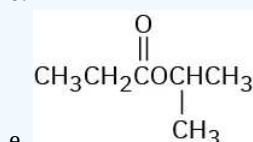
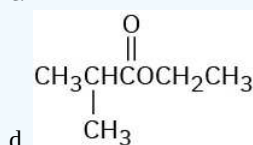
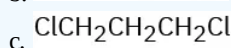
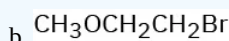
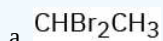
To interpret the NMR information, let's look at each absorption individually. The three-proton absorption at $0.92\ \delta$ is due to a methyl group in an alkane-like environment, and the triplet-splitting pattern implies that the CH_3 is next to a CH_2 . Thus, our molecule contains an ethyl group, CH_3CH_2- . The six-proton singlet at $1.20\ \delta$ is due to two equivalent alkane-like methyl groups attached to a carbon with no hydrogens, $(\text{CH}_3)_2\text{C}$, and the two-proton quartet at $1.50\ \delta$ is due to the CH_2 of the ethyl group. All 5 carbons and 11 of the 12 hydrogens in the molecule are now accounted for. The remaining hydrogen, which appears as a broad one-proton singlet at $1.64\ \delta$, is probably due to an OH group, since there is no other way to account for it. Putting the pieces together gives the structure: 2-methyl-2-butanol.

Solution



? Exercise 2.7.1

Predict the splitting patterns you would expect for each proton in the following molecules:



Answer

- $-\text{CHBr}_2$, quartet; $-\text{CH}_3$, doublet
- $\text{CH}_3\text{O}-$, singlet; $-\text{OCH}_2-$, triplet; $-\text{CH}_2\text{Br}$, triplet
- ClCH_2- , triplet; $-\text{CH}_2-$, quintet
- CH_3- , triplet; $-\text{CH}_2-$, quartet; $-\text{CH}-$, septet; $(\text{CH}_3)_2$, doublet
- CH_3- , triplet; $-\text{CH}_2-$, quartet; $-\text{CH}-$, septet; $(\text{CH}_3)_2$, doublet
- $=\text{CH}$, triplet, $-\text{CH}_2-$, doublet, aromatic C-H, two multiplets

? Exercise 2.7.2

Draw structures for compounds that meet the following descriptions:

- $\text{C}_2\text{H}_6\text{O}$; one singlet
- $\text{C}_3\text{H}_7\text{Cl}$; one doublet and one septet
- $\text{C}_4\text{H}_8\text{Cl}_2\text{O}$; two triplets
- $\text{C}_4\text{H}_8\text{O}_2$; one singlet, one triplet, and one quartet

Answer

- CH_3OCH_3
- $\text{CH}_3\text{CH}(\text{Cl})\text{CH}_3$
- $\text{ClCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{Cl}$
- $\text{CH}_3\text{CH}_2\text{CO}_2\text{CH}_3$ or $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$

? Exercise 2.7.3

The integrated ^1H NMR spectrum of a compound of formula $\text{C}_4\text{H}_{10}\text{O}$ is shown in Figure 2.7.5. Propose a structure.

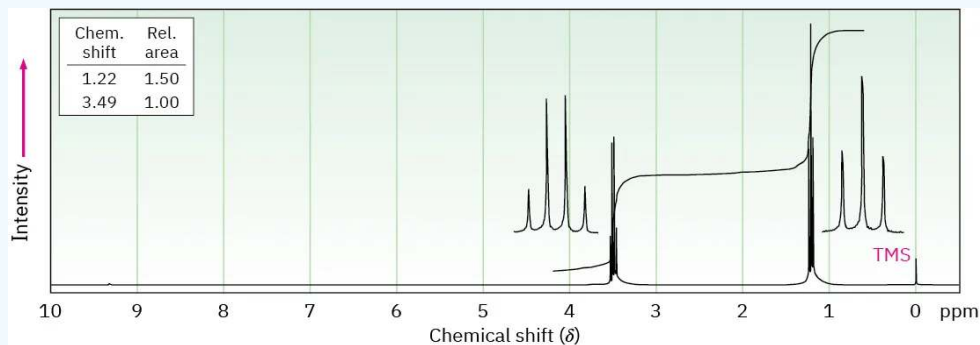
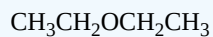


Figure
2.7.5

An integrated ^1H NMR spectrum for Problem 11.

Answer



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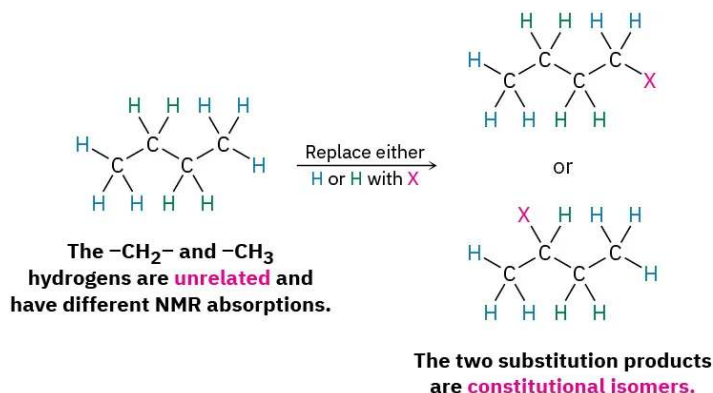
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2.8: ^1H NMR Spectroscopy and Proton Equivalence

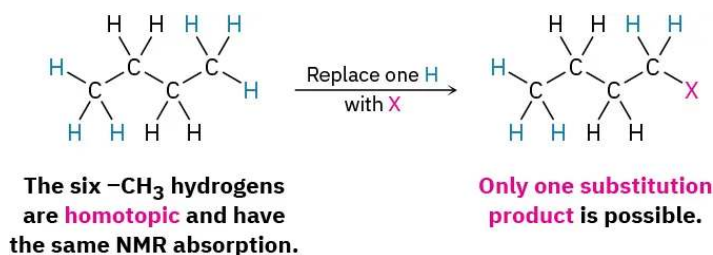
Because each electronically distinct hydrogen in a molecule has its own unique absorption, one use of ^1H NMR is to find out how many kinds of electronically nonequivalent hydrogens are present. In the ^1H NMR spectrum of methyl acetate shown previously, for instance, there are two signals, corresponding to the two kinds of nonequivalent protons present, $\text{CH}_3\text{C}=\text{O}$ protons and $-\text{OCH}_3$ protons.

For relatively small molecules, a quick look at the structure is often enough to decide how many kinds of protons are present and thus how many NMR absorptions might appear. If in doubt, though, the equivalence or nonequivalence of two protons can be determined by comparing the structures that would be formed if each hydrogen were replaced by an X group. There are four possibilities.

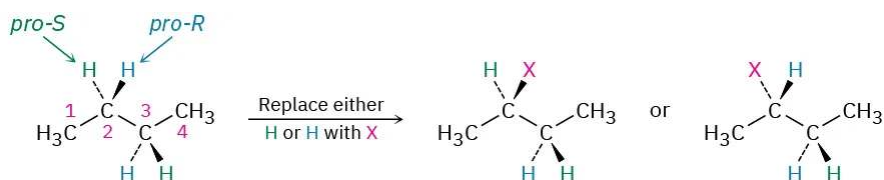
- One possibility is that the protons are chemically unrelated and thus nonequivalent. If so, the products formed on substitution of H by X would be different constitutional isomers. In butane, for instance, the $-\text{CH}_3$ protons are different from the $-\text{CH}_2-$ protons. They therefore give different products on substitution by X than the $-\text{CH}_2-$ protons and would likely show different NMR absorptions.



- A second possibility is that the protons are chemically identical and thus electronically equivalent. If so, the same product would be formed regardless of which H is substituted by X. In butane, for instance, the six $-\text{CH}_3$ hydrogens on C1 and C4 are identical, would give the identical structure on substitution by X, and would show an identical NMR absorption. Such protons are said to be homotopic.



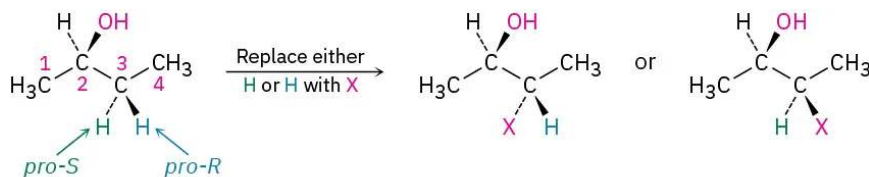
- The third possibility is a bit more subtle. Although they might at first seem homotopic, the two $-\text{CH}_2-$ hydrogens on C2 in butane (and the two $-\text{CH}_2-$ hydrogens on C3) are in fact not identical. Substitution by X of a hydrogen at C2 (or C3) would form a new chirality center, so different enantiomers (Section 5.1) would result, depending on whether the pro-R or pro-S hydrogen had been substituted (Section 5.11). Such hydrogens, whose substitution by X would lead to different enantiomers, are said to be enantiotopic. Enantiotopic hydrogens, even though not identical, are nevertheless electronically equivalent and thus have the same NMR absorption.



The two hydrogens on C2 (and on C3) are **enantiotopic** and have the same NMR absorption.

The two possible substitution products are **enantiomers**.

- The fourth possibility arises in chiral molecules, such as (*R*)-2-butanol. The two $\text{-CH}_2\text{-}$ hydrogens at C3 are neither homotopic nor enantiotopic. Because substitution of a hydrogen at C3 would form a *second* chirality center, different diastereomers (Section 5.6) would result, depending on whether the pro-*R* or pro-*S* hydrogen had been substituted. Such hydrogens, whose substitution by X leads to different diastereomers, are said to be diastereotopic. Diastereotopic hydrogens are neither chemically nor electronically equivalent. They are completely different and would likely show different NMR absorptions.

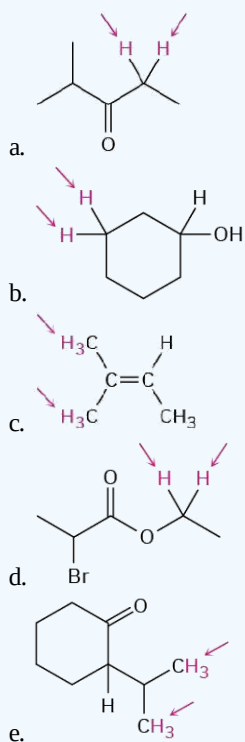


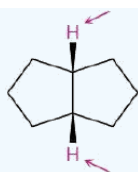
The two hydrogens on C3 are **diastereotopic** and have different NMR absorptions.

The two possible substitution products are **diastereomers**.

? Exercise 2.8.1

Identify the indicated sets of protons as unrelated, homotopic, enantiotopic, or diastereotopic:





f.

Answer

- a. Enantiotopic
- b. Diastereotopic
- c. Diastereotopic
- d. Diastereotopic
- e. Diastereotopic
- f. Homotopic

? Exercise 2.8.2

How many kinds of electronically nonequivalent protons are present in each of the following compounds, and thus how many NMR absorptions might you expect in each?

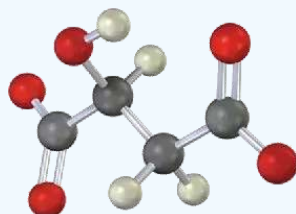
- a. $\text{CH}_3\text{CH}_2\text{Br}$
- b. $\text{CH}_3\text{OCH}_2\text{CH}(\text{CH}_3)_2$
- c. $\text{CH}_3\text{CH}_2\text{CH}_2\text{NO}_2$
- d. Methylbenzene
- e. 2-Methyl-1-butene
- f. *cis*-3-Hexene

Answer

- a. 2
- b. 4
- c. 3
- d. 4
- e. 5
- f. 3

? Exercise 2.8.3

How many absorptions would you expect (S)-malate, an intermediate in carbohydrate metabolism, to have in its ^1H NMR spectrum? Explain.



(S)-Malate

Answer

4

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2.9: More Complex Spin-Spin Splitting Patterns

In the ^1H NMR spectra we've seen so far, the chemical shifts of different protons have been distinct and the spin-spin splitting patterns have been straightforward. It often happens, however, that different kinds of hydrogens in a molecule have accidentally overlapping signals. The spectrum of toluene (methylbenzene) in Figure 2.9.1, for example, shows that the five aromatic ring protons give a complex, overlapping pattern, even though they aren't all equivalent.

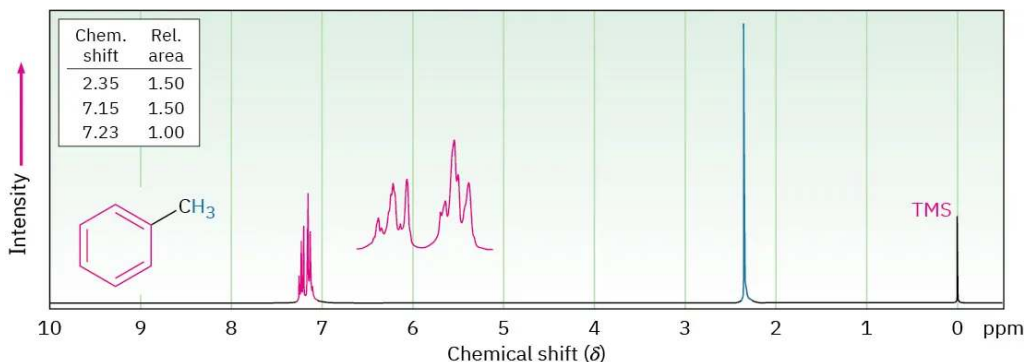


Figure 2.9.1: The ^1H NMR spectrum of toluene, showing the accidental overlap of the five nonequivalent aromatic ring protons.

Yet another complication in ^1H NMR spectroscopy arises when a signal is split by two or more *nonequivalent* kinds of protons, as is the case with *trans*-cinnamaldehyde, isolated from oil of cinnamon (Figure 2.9.2). Although the $n + 1$ rule predicts splitting caused by equivalent protons, splittings caused by nonequivalent protons are more complex.

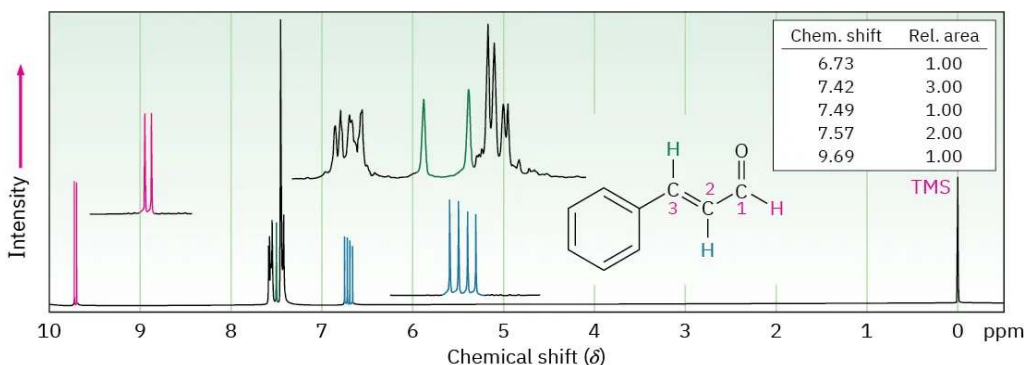


Figure 2.9.2: The ^1H NMR spectrum of *trans*-cinnamaldehyde. The signal of the proton at C2 (blue) is split into four peaks—a doublet of doublets—by the two nonequivalent neighboring protons.

To understand the ^1H NMR spectrum of *trans*-cinnamaldehyde, we have to isolate the different parts and look at the signal of each proton individually.

- The five aromatic proton signals (black in Figure 2.9.2) overlap into a complex pattern with a large peak at 7.42 δ and a broad absorption at 7.57 δ .
- The aldehyde proton signal at C1 (**red**) appears in the normal downfield position at 9.69 δ and is split into a doublet with $J = 6$ Hz by the adjacent proton at C2.
- The vinylic proton at C3 (**green**) is next to the aromatic ring and is therefore shifted downfield from the normal vinylic region. This C3 proton signal appears as a doublet centered at 7.49 δ . Because it has one neighbor proton at C2, its signal is split into a doublet, with $J = 12$ Hz.
- The C2 vinylic proton signal (**blue**) appears at 6.73 δ and shows an interesting, four-line absorption pattern. It is coupled to the two nonequivalent protons at C1 and C3 with two different coupling constants: $J_{1-2} = 6$ Hz and $J_{2-3} = 12$ Hz.

A good way to understand the effect of multiple coupling, such as that occurring for the C2 proton of *trans*-cinnamaldehyde, is to draw a *tree diagram*, like that in Figure 2.9.3. The diagram shows the individual effect of each coupling constant on the overall pattern. Coupling with the C3 proton splits the signal of the C2 proton in *trans*-cinnamaldehyde into a doublet with $J = 12$ Hz. Further coupling with the aldehyde proton then splits each peak of the doublet into new doublets with $J = 6$ Hz, and we therefore observe a four-line spectrum for the C2 proton.

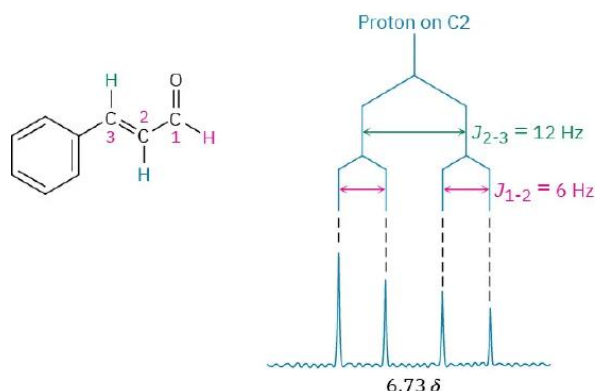


Figure 2.9.3: A tree diagram for the C2 proton of *trans*-cinnamaldehyde shows how it is coupled to the C1 and C3 protons with different coupling constants.

One further trait evident in the cinnamaldehyde spectrum is that the four peaks of the C2 proton signal are not all the same size. The two left-hand peaks are somewhat larger than the two right-hand peaks. Such a size difference occurs whenever coupled nuclei have similar chemical shifts—in this case, 7.49 δ for the C3 proton and 6.73 δ for the C2 proton. The peaks nearer the signal of the coupled partner are always larger, and the peaks farther from the signal of the coupled partner are always smaller. Thus, the left-hand peaks of the C2 proton multiplet at 6.73 δ are closer to the C3 proton absorption at 7.49 δ and are larger than the right-hand peaks. At the same time, the right-hand peak of the C3 proton doublet at 7.49 δ is larger than the left-hand peak because it is closer to the C2 proton multiplet at 6.73 δ . This skewing effect on multiplets can often be useful because it tells where to look in the spectrum to find the coupled partner: look in the direction of the larger peaks.

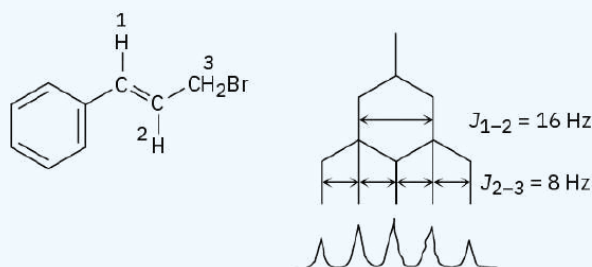
? Exercise 2.9.1

3-Bromo-1-phenyl-1-propene shows a complex NMR spectrum in which the vinylic proton at C2 is coupled with both the C1 vinylic proton ($J = 16$ Hz) and the C3 methylene protons ($J = 8$ Hz). Draw a tree diagram for the C2 proton signal, and account for the fact that a five-line multiplet is observed.



Answer

$$J_{1-2} = 16 \text{ Hz}; J_{2-3} = 8 \text{ Hz}$$



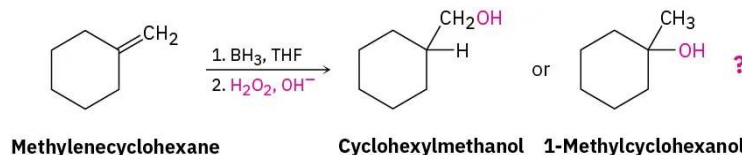
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2.10: Uses of ^1H NMR Spectroscopy

NMR is used to help identify the product of nearly every reaction run in the laboratory. For example, we said in Section 8.5 that hydroboration–oxidation of alkenes occurs with non-Markovnikov regiochemistry to yield the less highly substituted alcohol. With the help of NMR, we can now prove this statement.

Does hydroboration–oxidation of methylenecyclohexane yield cyclohexylmethanol or 1-methylcyclohexanol?



The ^1H NMR spectrum of the reaction product is shown in Figure 2.10.1a. The spectrum shows a two-proton peak at 3.40 δ , indicating that the product has a $-\text{CH}_2-$ group bonded to an electronegative oxygen atom ($-\text{CH}_2\text{OH}$). Furthermore, the spectrum shows no large three-proton singlet absorption near 1 δ , where we would expect the signal of a quaternary $-\text{CH}_3$ group to appear. (Figure 2.10.1b) gives the spectrum of 1-methylcyclohexanol, the alternative product.) Thus, it's clear that cyclohexylmethanol is the reaction product.

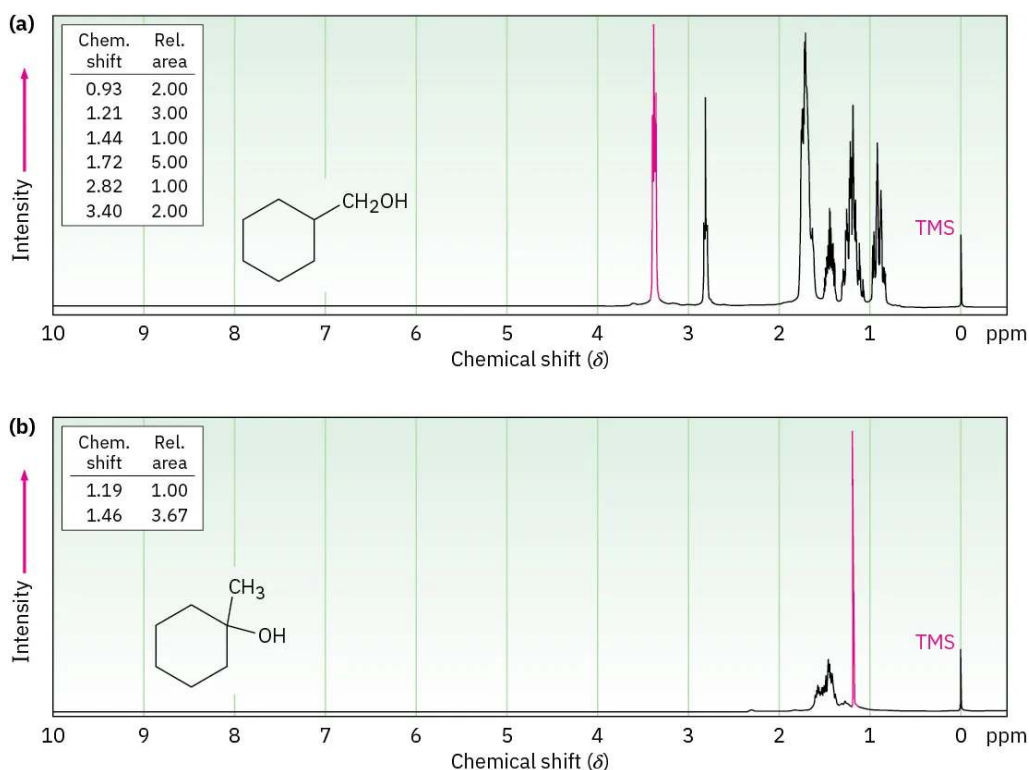


Figure 2.10.1: (a) The ^1H NMR spectrum of cyclohexylmethanol, the product from hydroboration–oxidation of methylenecyclohexane, and (b) the ^1H NMR spectrum of 1-methylcyclohexanol, the possible alternative reaction product.

? Exercise 2.10.1

How could you use ^1H NMR to determine the regiochemistry of electrophilic addition to alkenes? For example, does addition of HCl to 1-methylcyclohexene yield 1-chloro-1-methylcyclohexane or 1-chloro-2-methylcyclohexane?

Answer

1-Chloro-1-methylcyclohexane has a singlet methyl absorption.

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CHAPTER OVERVIEW

3: Alcohols and Ethers

In this chapter, we examine the chemistry of the alcohol family of compounds. Alcohols can undergo a wide variety of reactions, and because of this reactivity and because they can be prepared in a number of different ways, alcohols occupy an important position in organic chemistry.

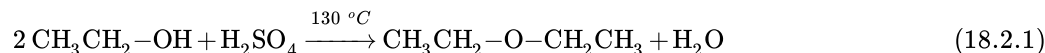
- [3.1: Preparing Ethers](#)
- [3.2: Crown Ethers](#)
- [3.3: Reactions of Ethers- Acidic Cleavage](#)
- [3.4: Cyclic Ethers - Epoxides](#)
- [3.5: Reactions of Epoxides- Ring-opening](#)
- [3.6: Nomenclature of Alcohols](#)
- [3.7: Reactions of Alcohols](#)
- [3.8: Conversion of Alcohols to Alkyl Halides with SOCl₂ and PBr₃](#)
- [3.9: Protecting Groups in Organic Synthesis](#)

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3.1: Preparing Ethers

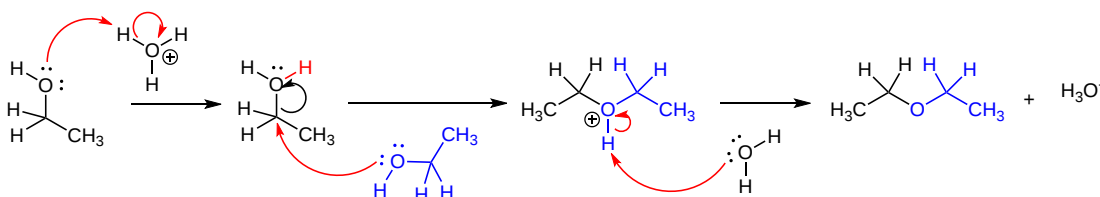
Ether Formation Though Dehydration

Acid-catalyzed dehydration of small 1°-alcohols constitutes a specialized industrial method of preparing symmetrical ethers. This reaction **cannot** be employed to prepare unsymmetrical ethers because a mixture of products is likely to be obtained. Also, 2° and 3° alcohols cannot be used for this reaction because they dehydrate to form alkenes by an E1 mechanism.



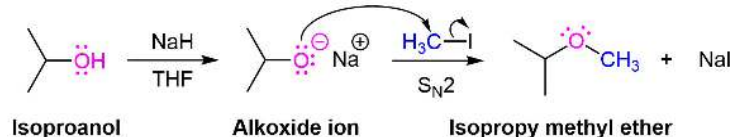
Mechanism

In the first step of the reaction mechanism, one alcohol is protonated to become a good leaving group. In the second step, a second alcohol displaces water from the protonated alcohol during an S_N2 reaction yielding a protonated ether. In the final step, this intermediate is deprotonated to yield the symmetrical ether.



Williamson Ether Synthesis

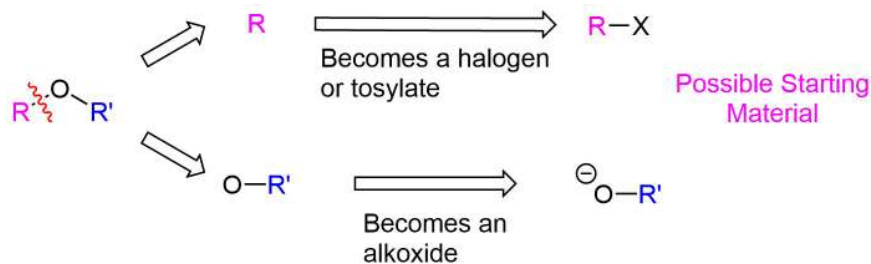
One important procedure, known as the **Williamson Ether Synthesis**, proceeds by an S_N2 reaction of an alkoxide nucleophile with a primary alkyl halide or tosylate. As previously discussed in [Section 17-2](#), alkoxides are commonly created by deprotonating an alcohol with a strong base, such as sodium hydride (NaH). Simple alcohols can be used as 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

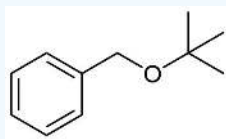
The Williamson ether synthesis has the same limitations as other S_N2 reactions, as discussed in [Section 11-3](#). Since alkoxide anions are strong bases, utilizing 2° or 3° halogen leaving groups could possibly produce an E2 elimination product. When considering the synthesis of an unsymmetrical ether, 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 3.1.1

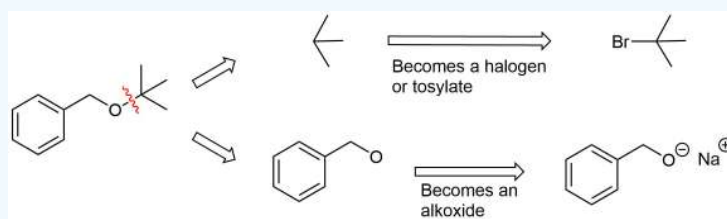
How would you prepare the following molecule using a Williamson Ether Synthesis?



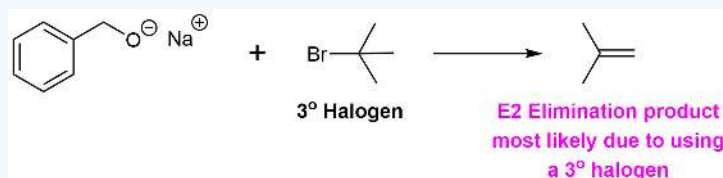
Answer

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.

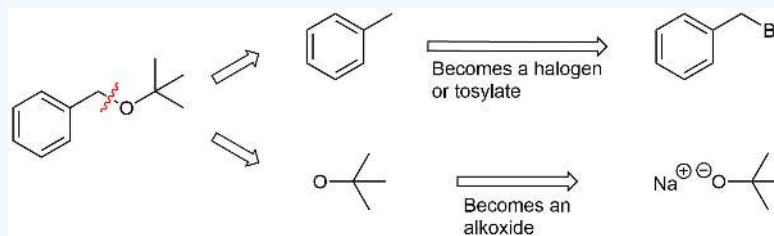
Pathway 1



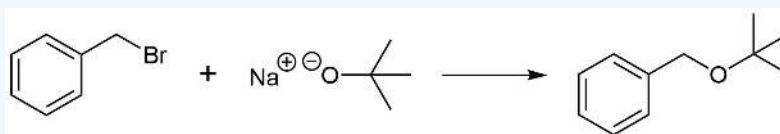
Solution 1



Pathway 2



Solution 2



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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3.2: Crown Ethers

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.

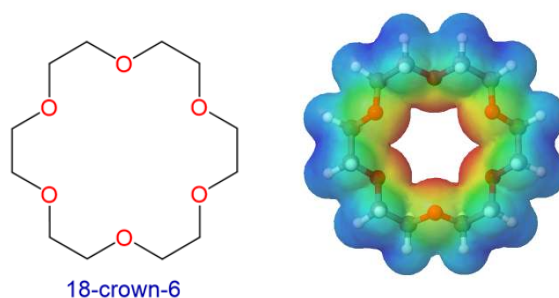
- crown ether

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 $(\text{OCH}_2\text{CH}_2)_n$ or $(\text{OCH}_2\text{CH}_2\text{CH}_2)_n$ 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.



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.

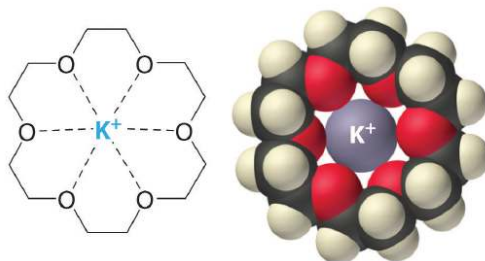
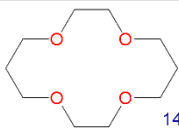
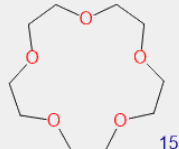
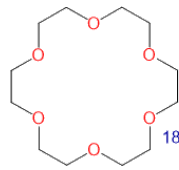
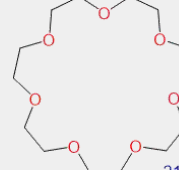


Figure 3.2.1: Potassium complex of the crown ether 18-crown-6. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

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 3.2.1, 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 3.2.1: Crown ethers preferentially bind cations with sizes that match the cavity size of their crown-shaped conformers.

Crown Ether	Cavity Diameter ($\text{\AA}$)	Preferred Cation	Cation Diameter ($\text{\AA}$)
 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.

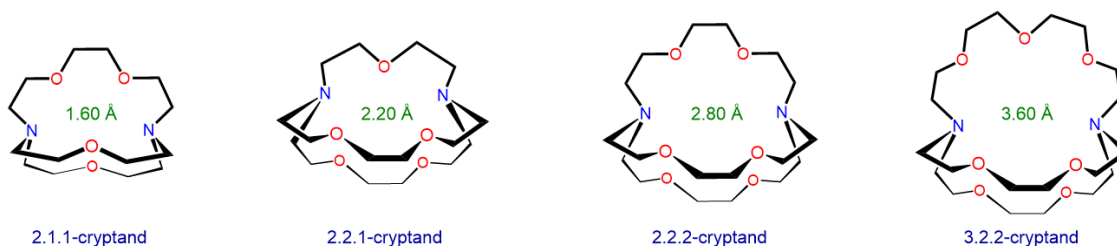


Figure 3.2.2: Structures and approximate binding cavity diameters for several cryptands.

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.

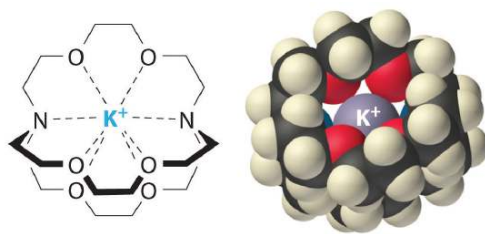


Figure 3.2.3: Potassium complex of 2,2,2-cryptand. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

? Exercise 3.2.1

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 3.2.1 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 binding 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

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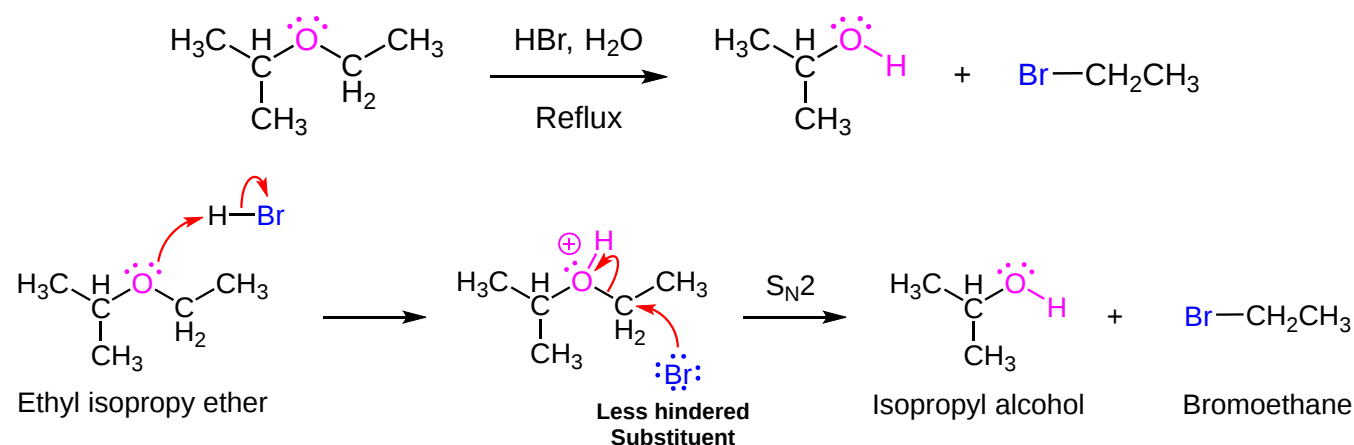
- 18.7: Crown Ethers by Dietmar Kennepohl, Stephen Contakes, Steven Farmer is licensed [CC BY-SA 4.0](#).

3.3: Reactions of Ethers- Acidic Cleavage

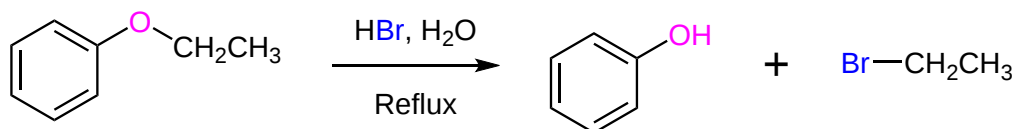
Ethers are known to be unreactive towards most reagents which makes them excellent reaction solvents. The most common reaction of ethers is cleavage of the C–O bond by using strong acids. During acidic cleavage the ether oxygen is protonated to form a good leaving group which can be eliminated as part 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

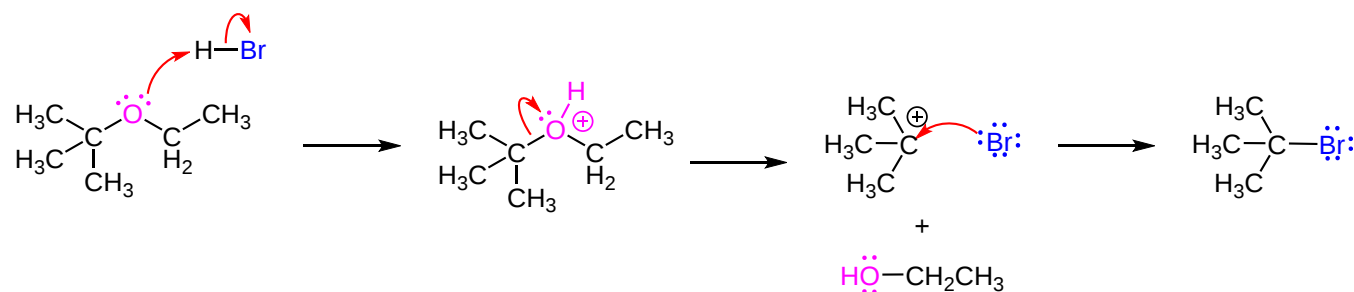
Aqueous solutions of HBr or HI (but not HCl) tend to cleave ethers into alcohol and an alkyl halide product by either an S_N2 or S_N1 mechanism. If the ether is attached to only primary, secondary, or methyl alkyl groups, a selective cleavage will typically take place using an S_N2 mechanism. First, 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°).



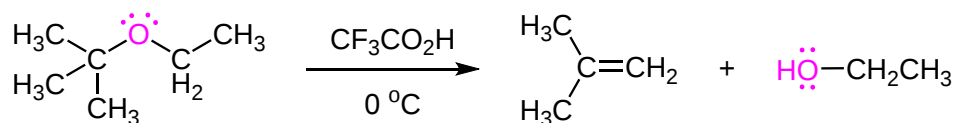
It is important to note that a phenyl substituent on an ether is not capable of participating in the S_N2 reaction of an acidic cleavage. If a phenyl group is present it will become a phenol in the product due to the halide nucleophile preferably attacking the other alkyl substituent.



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 allylic group to preferably become the halogen product of the acidic cleavage. This makes the ether's other alkyl substituent become the alcohol product.

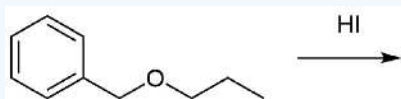


When using a strong acid whose conjugate base is a poor nucleophile, such as trifluoroacetic acid ($\text{CF}_3\text{CO}_2\text{H}$), for the acidic cleavage of an ether with a tertiary alkyl substituent, the mechanism will often be E1 . In this case the tertiary alkyl substituent will lose an adjacent hydrogen to form an alkene product. The ether's other alkyl substituent will form an alcohol product.



? Worked Example 3.3.1

Predict the products of the following reaction:



Answer

Analysis: When considering the acidic cleavage of ethers it is important to realize that $\text{S}_{\text{N}}2$, $\text{S}_{\text{N}}1$, 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 $\text{S}_{\text{N}}2$. However, if one of the substituents is present the reaction will most likely be $\text{S}_{\text{N}}1$ 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 $\text{S}_{\text{N}}1$.

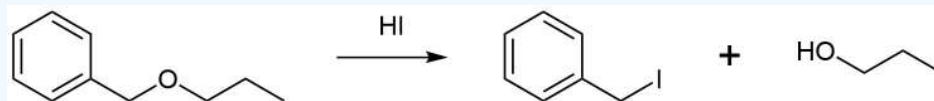
For a $\text{S}_{\text{N}}2$ reaction: The less hindered alkyl substituent of the ether will become a halogen. The other alkyl substituent will become an alcohol.

For a $\text{S}_{\text{N}}1$ 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 substituent will form an alkene and the other alkyl substituent will become an alcohol.

For the reaction proposed above, the reactant contains a benzylic substituent so the reaction will most likely be $\text{S}_{\text{N}}1$. Consequently, the benzylic substituent will become an iodide product and the propyl substituent will become an alcohol.

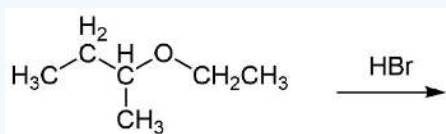
Solution



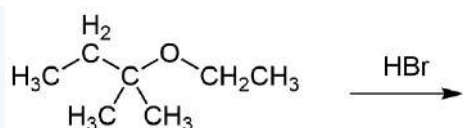
? Exercises 3.3.1

1) Predict the product of the following reactions:

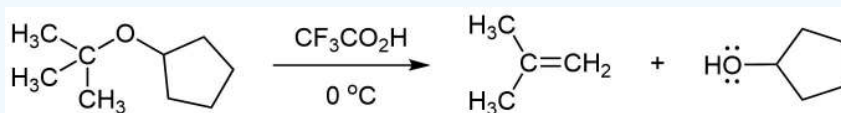
a)



b)



2) Please draw the mechanism for the following reaction:

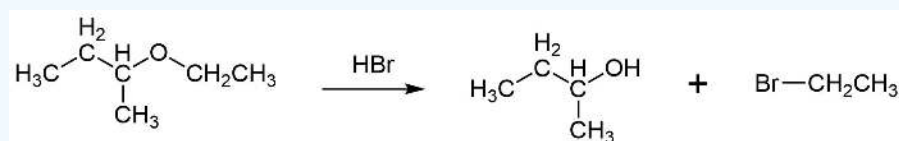


3) Why is HCl less effective at cleaving ethers than HBr or HI?

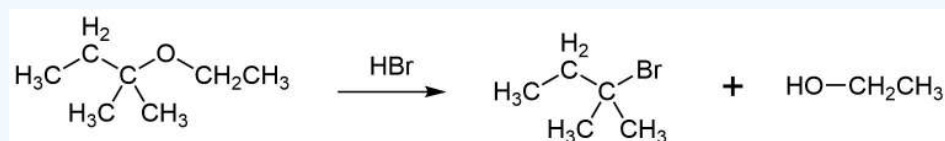
Answer

1)

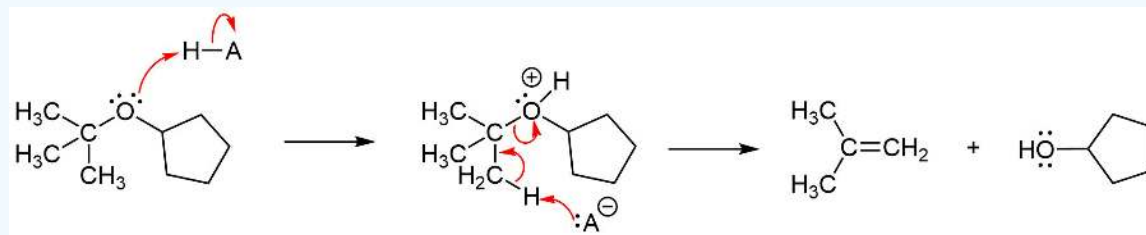
a)



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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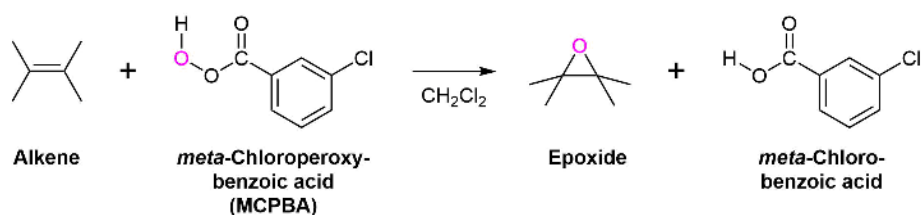
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3.4: Cyclic Ethers - Epoxides

Synthesis of Epoxides

Epoxides are typically prepared by the reaction of an alkene and a peroxycarboxylic acid (RCO_3H), such as *meta*-chloroperoxybenzoic 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 .

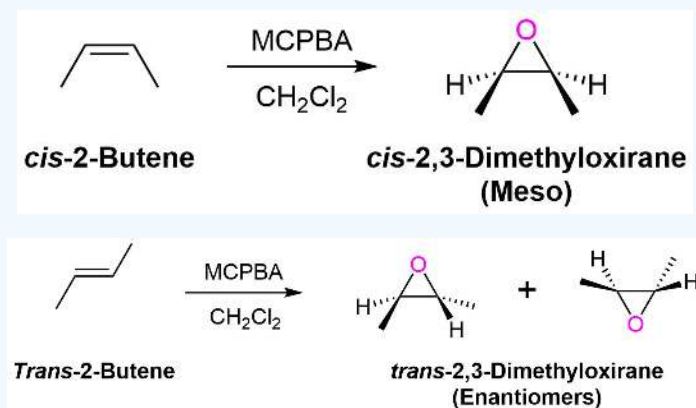
General Reaction



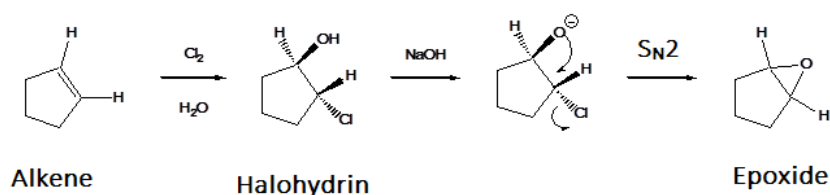
Stereochemical Consideration

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 3.4.2

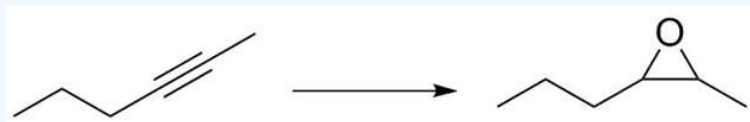


Treatment of an alkene with X_2 & H_2O creates a halohydrin. When a halohydrin is treated with a base the alcohol is deprotonated to form an alkoxide. This causes an intramolecular Williamson ether synthesis to produce an epoxide along with the elimination of HX . Note, that this reaction generally forms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

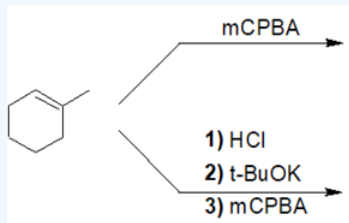


? Exercise 3.4.1

1) What reagents would you use to perform the following transformation?



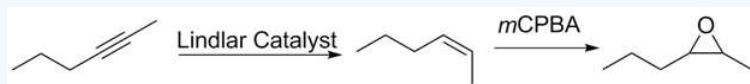
2) Predict the products of the following reactions:



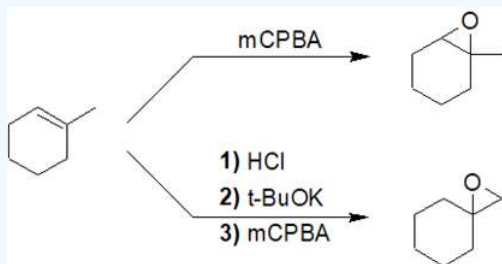
3) Predict the product of the following reaction. Be sure to include proper stereochemistry.

Answer

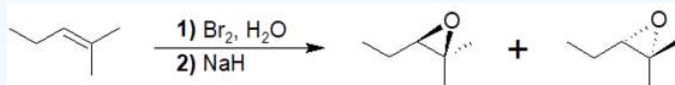
1) Lindlar's catalyst reduces alkynes to cis/Z alkenes. This stereochemistry is retained after epoxidation.



2)



3)



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John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry*, second edition. W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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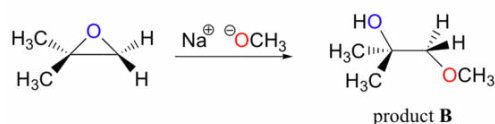
- 18.5: Cyclic Ethers - Epoxides** by Dietmar Kennepohl, Steven Farmer is licensed [CC BY-SA 4.0](#).

3.5: Reactions of Epoxides- Ring-opening

Epoxide Ring-Opening by Alcoholysis

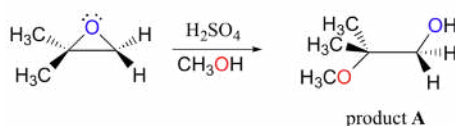
The ring-opening reactions of epoxides provide a nice overview of many of the concepts discussed earlier. Ring-opening reactions can proceed by either S_N2 or S_N1 mechanisms, depending on the nature of the epoxide and on the reaction conditions. If the epoxide is asymmetric, the structure of the product 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:

basic ring-opening:



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.

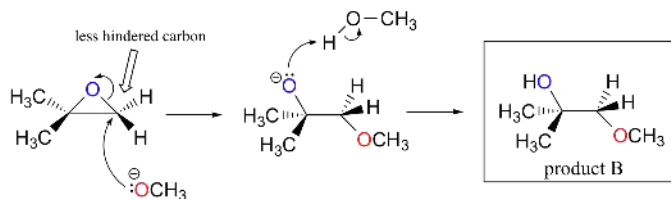
acidic ring-opening:



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.

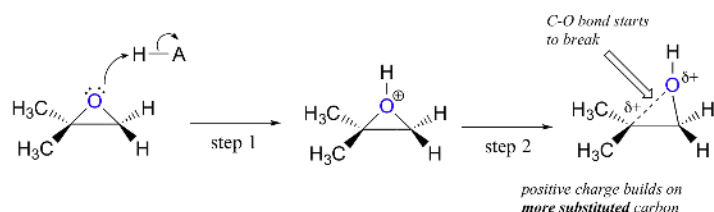


The nucleophile itself is potent: a deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an S_N2 mechanism.

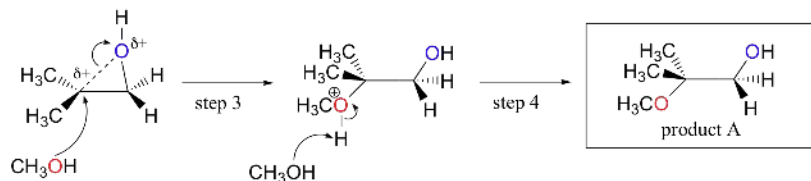
There are two electrophilic carbons in the epoxide, but the best target for the nucleophile in an S_N2 reaction is the carbon that is *least hindered*. This accounts for the observed regiochemical outcome. Like in other S_N2 reactions, nucleophilic attack takes place from the backside, resulting in inversion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

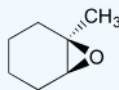


Attack takes place preferentially from the backside (like in an S_N2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks attack from the front side. Notice, however, how the regiochemical outcome is different from the base-catalyzed reaction: in the acid-catalyzed 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

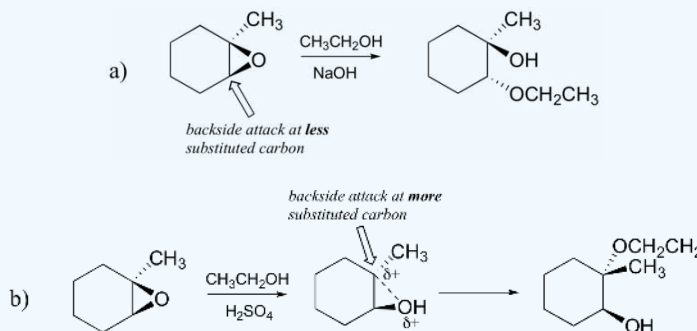
Predict the major product(s) of the ring opening reaction that occurs when the epoxide shown below is treated with:

- ethanol and a small amount of sodium hydroxide
- ethanol and a small amount of sulfuric acid



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

Answer



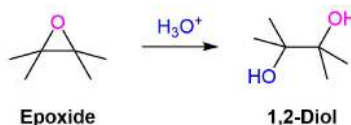
Epoxide Ring-Opening by Hydrolysis

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.

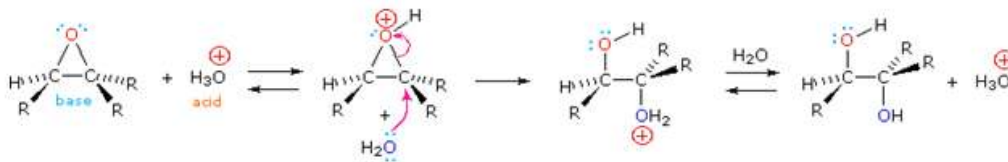
Acid Catalyzed Hydrolysis

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



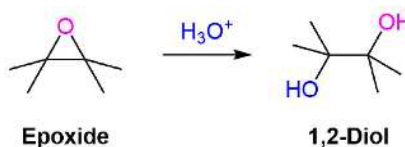
Mechanism



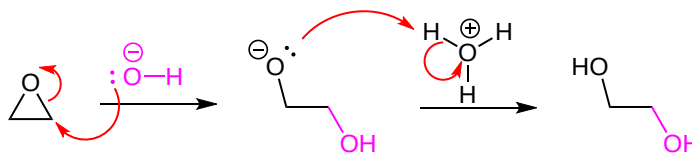
Basic Hydrolysis

Under aqueous basic conditions the epoxide is opened by the attack of hydroxide nucleophile during an $\text{S}_{\text{N}}2$ 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 preferably attack the less substituted epoxide carbon. Because the reaction takes place by an $\text{S}_{\text{N}}2$ mechanism the two -OH groups in the product will be *trans* to each other.

General Reaction



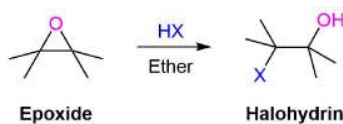
Mechanism



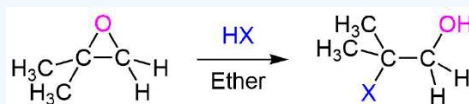
Epoxide Ring-Opening by HX

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 $\text{S}_{\text{N}}2$ like reaction. However, if one of the epoxide carbons is tertiary, the halogen anion will primarily attack the tertiary carbon in an $\text{S}_{\text{N}}1$ like reaction.

General Reaction

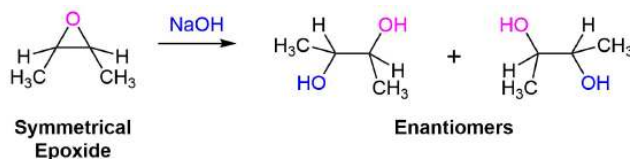


✓ Example 18.6.2



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.



Contributors and Attributions

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

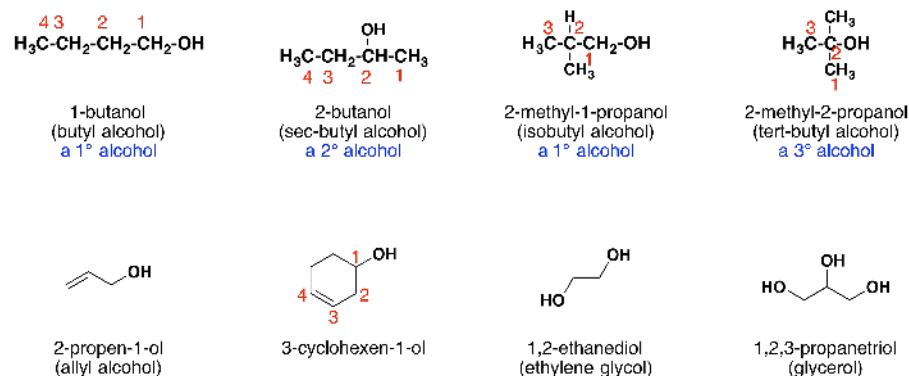
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3.6: Nomenclature of Alcohols

In the IUPAC system of nomenclature, functional groups are normally designated in one of two ways. The presence of the function may be indicated by a characteristic suffix and a location number. This is common for the carbon-carbon double and triple bonds which have the respective suffixes **-ene** and **-yne**. Halogens, on the other hand, do not have a suffix and are named as substituents, for example: $(\text{CH}_3)_2\text{C}=\text{CHCHClCH}_3$ is 4-chloro-2-methyl-2-pentene.

Alcohols are usually named by the first procedure and are designated by an **-ol** suffix, as in ethanol, $\text{CH}_3\text{CH}_2\text{OH}$ (note that a locator number is unnecessary on a two-carbon chain). On longer chains the location of the hydroxyl group determines chain numbering. For example: $(\text{CH}_3)_2\text{C}=\text{CHCH}(\text{OH})\text{CH}_3$ is 4-methyl-3-penten-2-ol. Other examples of IUPAC nomenclature are shown below, together with the common names often used for some of the simpler compounds. For the mono-functional alcohols, this common system consists of naming the **alkyl group** followed by the word **alcohol**. Alcohols may also be classified as primary, **1°**, secondary, **2°**, and tertiary, **3°**, in the same manner as alkyl halides. This terminology refers to alkyl substitution of the carbon atom bearing the hydroxyl group (colored blue in the illustration).



Many functional groups have a characteristic suffix designator, and only one such suffix (other than "-ene" and "-yne") may be used in a name. When the hydroxyl functional group is present together with a function of higher nomenclature priority, it must be cited and located by the prefix **hydroxy** and an appropriate number. For example, lactic acid has the IUPAC name 2-hydroxypropanoic acid.

Contributors

- William Reusch, Professor Emeritus ([Michigan State U.](#)), [Virtual Textbook of Organic Chemistry](#)

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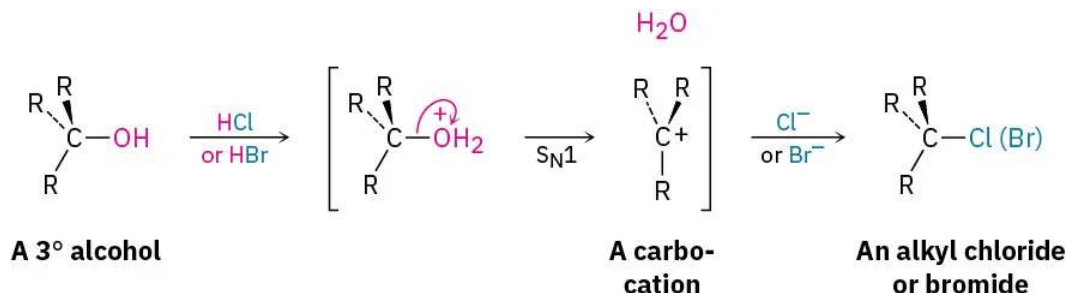
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3.7: Reactions of Alcohols

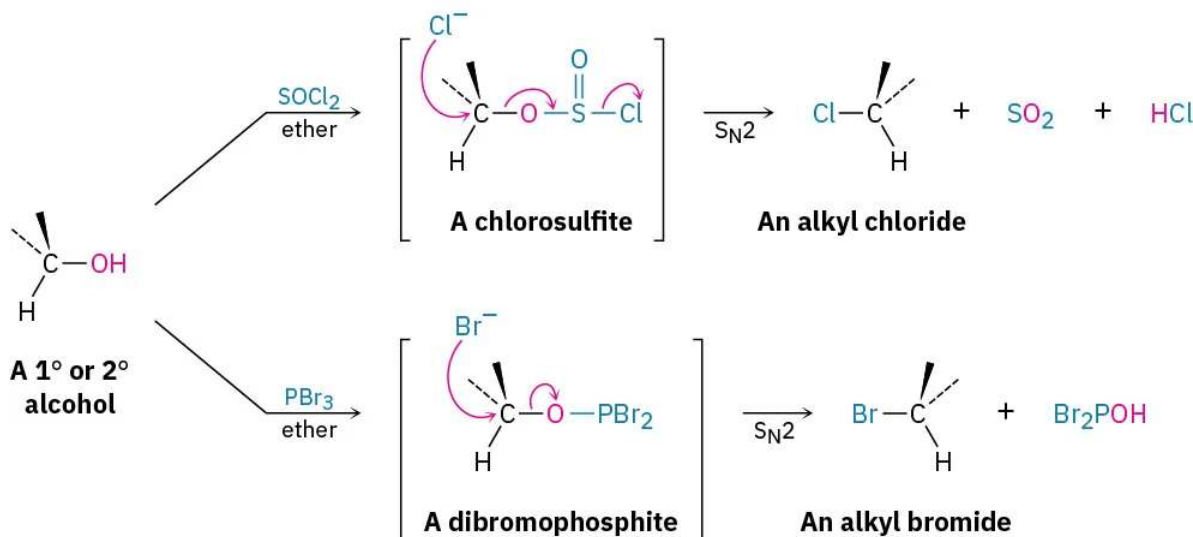
Conversion of Alcohols into Alkyl Halides

Tertiary alcohols react with either HCl or HBr at 0 °C by an S_N1 mechanism through a carbocation intermediate. Primary and secondary alcohols are much more resistant to acid, however, and are best converted into halides by treatment with either SOCl₂ or PBr₃ through an S_N2 mechanism.

The reaction of a tertiary alcohol with HX takes place by an S_N1 mechanism when acid protonates the hydroxyl oxygen atom. Water is expelled to generate a carbocation, and the cation reacts with nucleophilic halide ion to give the alkyl halide product.

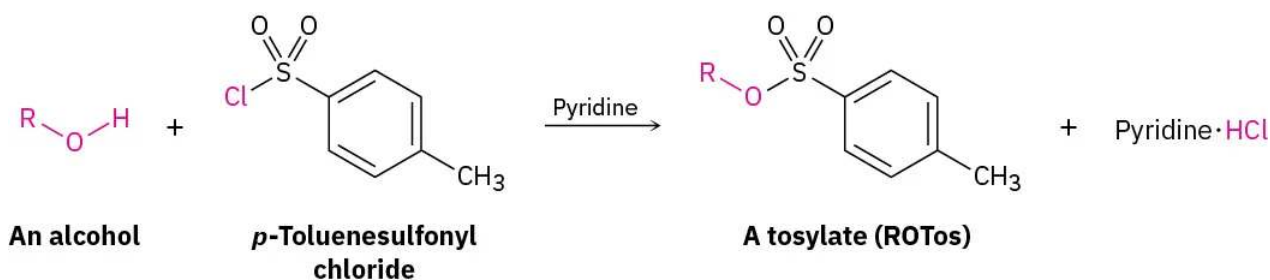


The reactions of primary and secondary alcohols with SOCl₂ and PBr₃ take place by S_N2 mechanisms. Hydroxide ion itself is too poor a leaving group to be displaced by nucleophiles in S_N2 reactions, but reaction of an alcohol with SOCl₂ or PBr₃ converts the –OH into a much better leaving group, either a chlorosulfite (–OSOCl) or a dibromophosphate (–OPBr₂), which is readily expelled by backside nucleophilic substitution.



Conversion of Alcohols into Tosylates

Alcohols react with *p*-toluenesulfonyl chloride (tosyl chloride, *p*-TosCl) in pyridine solution to yield alkyl tosylates, ROTos (Section 11.1). Only the O–H bond of the alcohol is broken in this reaction; the C–O bond remains intact, so no change of configuration occurs if the oxygen is attached to a chirality center. The resultant alkyl tosylates behave much like alkyl halides, undergoing both S_N1 and S_N2 substitution reactions.



One of the most important reasons for using tosylates in $\text{S}_{\text{N}}2$ reactions is stereochemical. The $\text{S}_{\text{N}}2$ reaction of an alcohol with an alkyl halide proceeds with two inversions of configuration—one to make the halide from the alcohol and one to substitute the halide—and yields a product with the same stereochemistry as the starting alcohol. The $\text{S}_{\text{N}}2$ reaction of an alcohol with a tosylate, however, proceeds with only one inversion and yields a product of opposite stereochemistry to the starting alcohol. Figure 17.6 shows a series of reactions on the *R* enantiomer of 2-octanol that illustrates these stereochemical relationships.

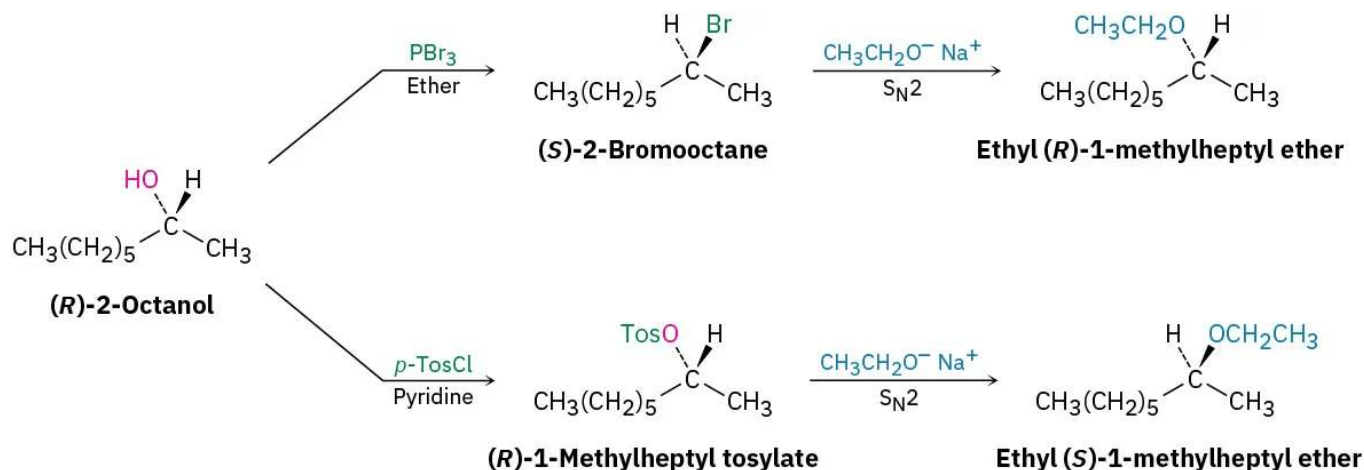
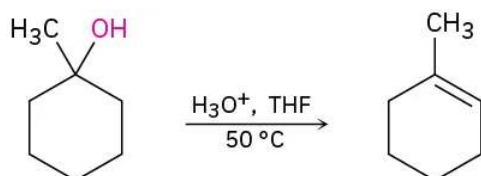


Figure 17.6: Stereochemical consequences of $\text{S}_{\text{N}}2$ reactions on derivatives of (*R*)-2-octanol. Substitution through the halide gives a product with the same stereochemistry as the starting alcohol; substitution through the tosylate gives a product with opposite stereochemistry to the starting alcohol.

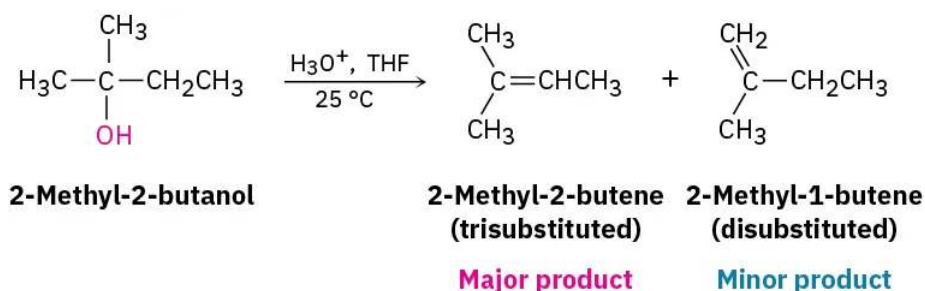
Dehydration of Alcohols to Yield Alkenes

A third important reaction of alcohols, both in the laboratory and in biological pathways, is their dehydration to give alkenes. Because of the usefulness of the reaction, a number of methods have been devised for carrying out dehydrations. One method that works particularly well for tertiary alcohols is the acid-catalyzed reaction discussed in Section 8.1. For example, treatment of 1-methylcyclohexanol with warm, aqueous sulfuric acid in a solvent such as tetrahydrofuran results in loss of water and formation of 1-methylcyclohexene.



1-Methylcyclohexanol **1-Methylcyclohexene (91%)**

Acid-catalyzed dehydrations usually follow Zaitsev's rule and yield the more stable alkene as the major product. Thus, 2-methyl-2-butanol gives primarily 2-methyl-2-butene (trisubstituted double bond) rather than 2-methyl-1-butene (disubstituted double bond).



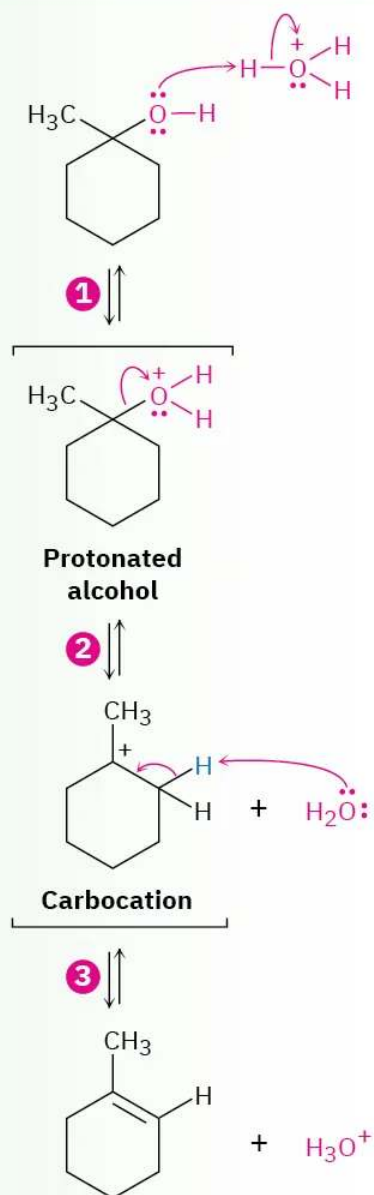
This reaction is an E1 process and occurs by the three-step mechanism shown in Figure 17.7 on the next page. Protonation of the alcohol oxygen is followed by unimolecular loss of water to generate a carbocation intermediate and final loss of a proton from the neighboring carbon atom to complete the process. As with most E1 reactions, tertiary alcohols react fastest because they lead to stabilized, tertiary carbocation intermediates. Secondary alcohols can be made to react, but the conditions are severe (75% H₂SO₄, 100 °C) and sensitive molecules don't survive.

Figure 17.7 MECHANISM Mechanism for the acid-catalyzed dehydration of a tertiary alcohol to yield an alkene. The process is an E1 reaction and involves a carbocation intermediate.

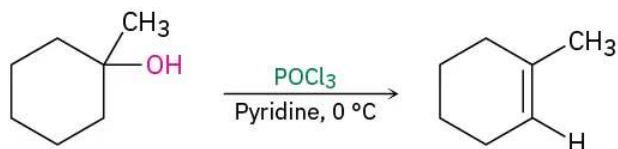
1 Two electrons from the oxygen atom bond to H^+ , yielding a protonated alcohol intermediate.

2 The carbon–oxygen bond breaks, and the two electrons from the bond stay with oxygen, leaving a carbocation intermediate.

3 Two electrons from a neighboring carbon–hydrogen bond form the alkene π bond, and H^+ (a proton) is eliminated.



To circumvent the need for strong acid and allow the dehydration of secondary alcohols in a gentler way, reagents have been developed that are effective under mild, basic conditions. One such reagent, phosphorus oxychloride (POCl_3) in the basic amine solvent pyridine, is often able to effect the dehydration of secondary and tertiary alcohols at 0°C .

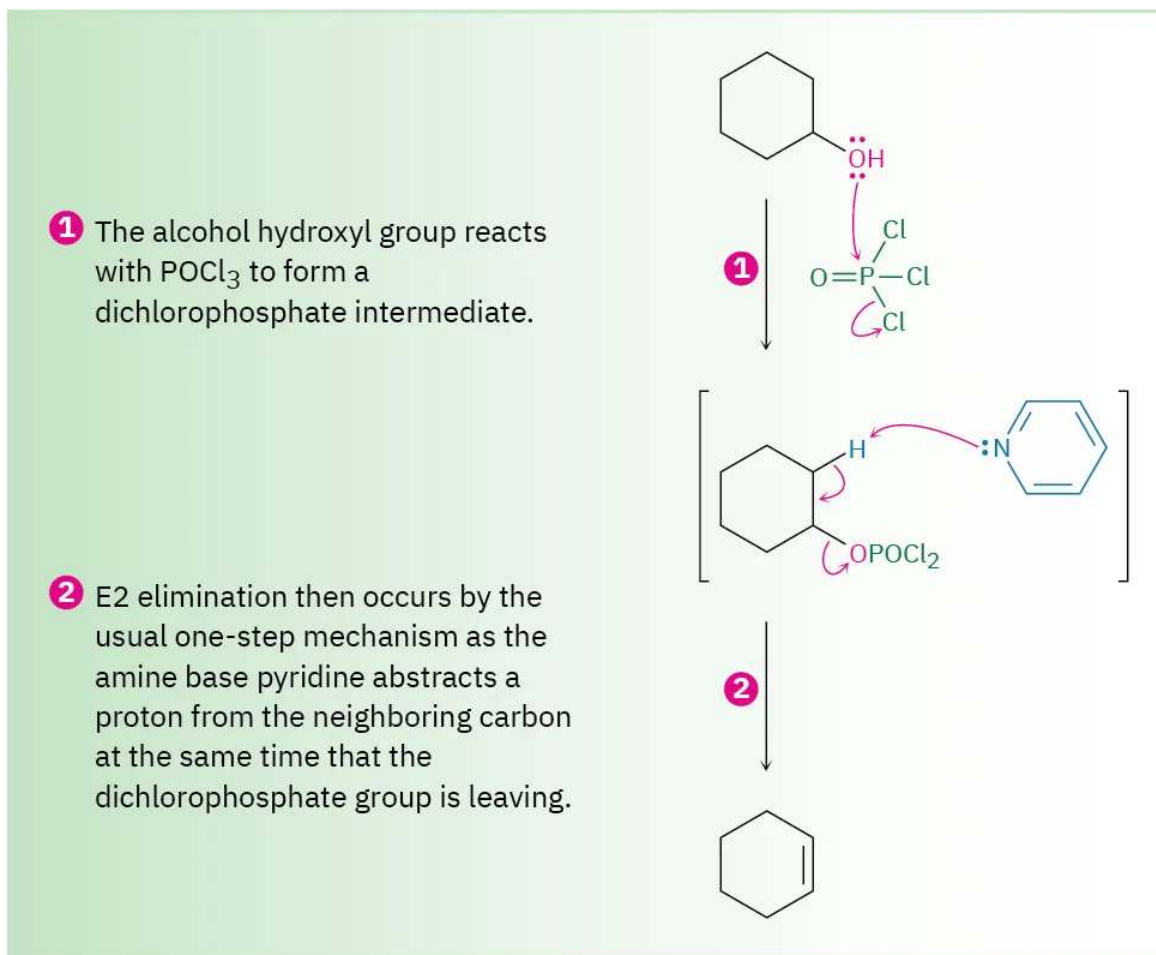


1-Methylcyclohexanol

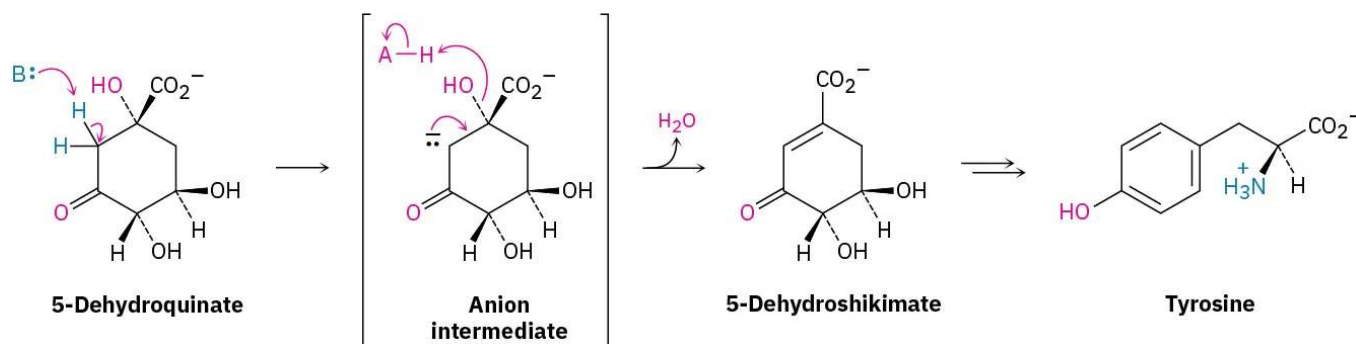
1-Methylcyclohexene (96%)

Alcohol dehydrations carried out with POCl_3 in pyridine take place by an E2 mechanism, as shown in Figure 17.8. Because hydroxide ion is a poor leaving group (Section 11.3), direct E2 elimination of water from an alcohol does not occur. On reaction with POCl_3 , however, the $-\text{OH}$ group is converted into a dichlorophosphate ($-\text{OPOCl}_2$), which is a good leaving group and is readily eliminated. Pyridine is both the reaction solvent and the base that removes a neighboring proton in the E2 elimination step.

Figure 17.8 MECHANISM Mechanism for the dehydration of secondary and tertiary alcohols by reaction with POCl_3 in pyridine. The reaction is an E2 process.



As noted previously, biological dehydrations are also common and usually occur by an E1cB mechanism on a substrate in which the $-\text{OH}$ group is two carbons away from a carbonyl group. One example occurs in the biosynthesis of the aromatic amino acid tyrosine. A base (:B) first abstracts a proton from the carbon adjacent to the carbonyl group, and the anion intermediate then expels the $-\text{OH}$ group with simultaneous protonation by an acid (HA) to form water.

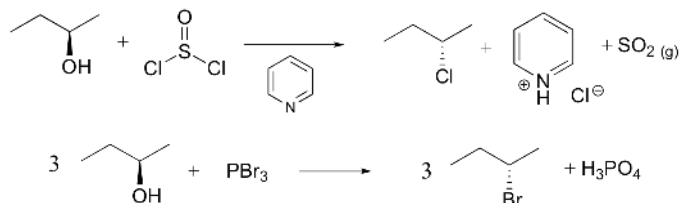


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3.8: Conversion of Alcohols to Alkyl Halides with SOCl₂ and PBr₃

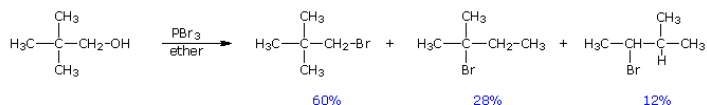
The most common methods for converting 1°- and 2°-alcohols to the corresponding chloro and bromo alkanes (*i.e.* replacement of the hydroxyl group) are treatments with thionyl chloride and phosphorus tribromide, respectively. These reagents are generally preferred over the use of concentrated HX due to the harsh acidity of these hydrohalic acids and the carbocation rearrangements associated with their use.

Synthetic organic chemists, when they want to convert an alcohol into a better leaving group, have several methods to choose from. One common strategy is to convert the alcohol into an alkyl chloride or bromide, using thionyl chloride or phosphorus tribromide:

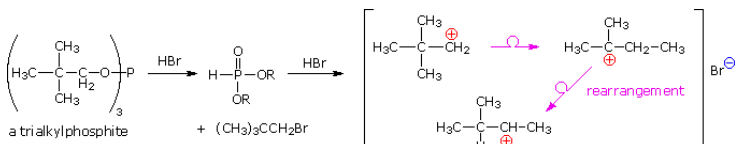


Drawbacks to using PBr₃ and SOCl₂

Despite their general usefulness, phosphorous tribromide and thionyl chloride have shortcomings. Hindered 1°- and 2°-alcohols react sluggishly with the former, and may form rearrangement products, as noted in the following equation.



Below, an abbreviated mechanism for the reaction is displayed. The initially formed trialkylphosphite ester may be isolated if the HBr byproduct is scavenged by base. In the presence of HBr a series of acid-base and S_N2 reactions take place, along with the transient formation of carbocation intermediates. Rearrangement (pink arrows) of the carbocations leads to isomeric products.



Reaction of thionyl chloride with chiral 2°-alcohols has been observed to proceed with either inversion or retention. In the presence of a base such as pyridine, the intermediate chlorosulfite ester reacts to form an "pyridinium" salt, which undergoes a relatively clean S_N2 reaction to the inverted chloride. In ether and similar solvents the chlorosulfite reacts with retention of configuration, presumably by way of a tight or intimate ion pair. This is classified as an S_Ni reaction (nucleophilic substitution internal). The carbocation partner in the ion pair may also rearrange. These reactions are illustrated by the following equations. An alternative explanation for the retention of configuration, involving an initial solvent molecule displacement of the chlorosulfite group (as SO₂ and chloride anion), followed by chloride ion displacement of the solvent moiety, has been suggested. In this case, two inversions lead to retention.

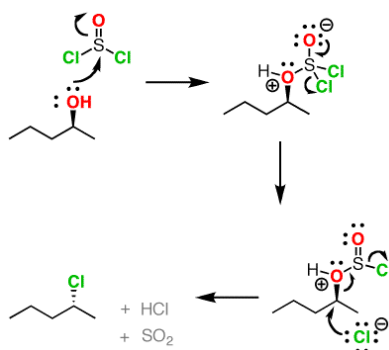
Example 1: Conversion of Alcohols to Alkyl Chlorides



There's one important thing to note here: see the stereochemistry? It's been inverted.*(white lie alert – see below) That's an important difference between SOCl₂ and TsCl, which leaves the stereochemistry alone. We'll get to the root cause of that in a moment, but in the meantime, can you think of a mechanism which results in inversion of configuration at carbon?

Formation of Alkyl Chlorides

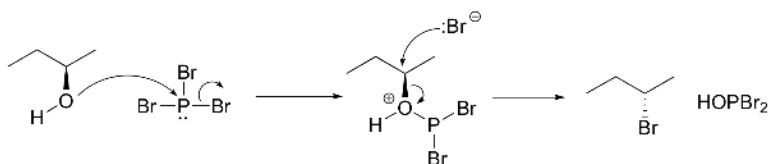
Since the reaction proceeds through a backside attack (S_N2), there is inversion of configuration at the carbon



The mechanism for formation of acid chlorides from carboxylic acids is similar. The conversion of carboxylic acids to acid chlorides is similar, but proceeds through a [1,2]-addition of chloride ion to the carbonyl carbon followed by [1,2]-elimination to give the acid chloride, SO_2 and HCl .

Formation of Alkyl Bromides

The PBr_3 reaction is thought to involve two successive S_N2 -like steps:



Notice that these reactions result in inversion of stereochemistry in the resulting alkyl halide.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

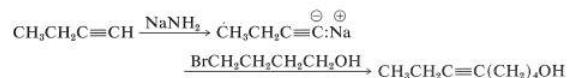
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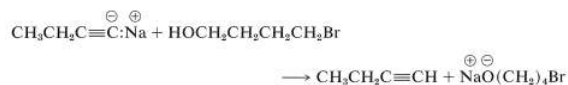
3.9: Protecting Groups in Organic Synthesis

One of the major problems in organic synthesis is the suppression of unwanted side reactions. Frequently the desired reaction is accompanied by reaction at other parts of the molecule, especially when more than one functional group is present. Functional groups usually are the most reactive sites in the molecule, and it may be difficult or even impossible to insulate one functional group from a reaction occurring at another. Therefore any proposed synthesis must be evaluated at each step for possible side reactions that may degrade or otherwise modify the structure in an undesired way. To do this will require an understanding of how variations in structure affect chemical reactivity. Such understanding is acquired through experience and knowledge of reaction mechanism and reaction stereochemistry.

To illustrate the purpose and practice of protecting groups in organic synthesis, let us suppose that the synthesis of *cis*-2-octene, which we outlined in [Section 13-7](#), has to be adapted for the synthesis of 5-octyn-1-ol. We could write the following:

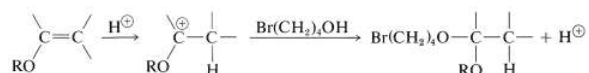


However, the synthesis as written would fail because the alkyne is a weaker acid than the alcohol ([Section 11-8](#)), and the alkynide anion would react much more rapidly with the acidic proton of the alcohol than it would displace bromide ion from carbon:

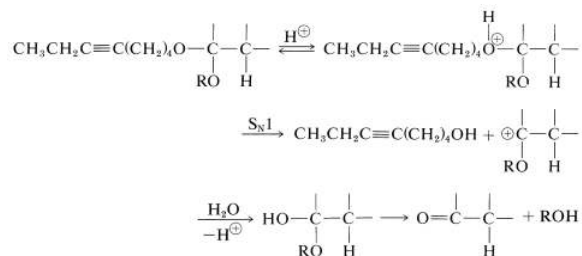


The hydroxyl group of 4-bromo-1-butanol therefore must be protected *before* it is allowed to react with the alkynide salt. There are a number of ways to protect hydroxyl groups, but one method, which is simple and effective, relies on the fact that unsaturated

ethers of the type $\text{RO}-\text{C}=\text{C}-$ are very reactive in electrophilic addition reactions ([Section 10-4](#)). An alcohol readily adds to the double bond of such an ether in the presence of an acid catalyst:



The protected compound is a much weaker acid than the alkyne, and the displacement reaction can be carried out with the alkynide salt without difficulty. To obtain the final product, the protecting group must be removed, and this can be done in dilute aqueous acid solution by an $\text{S}_{\text{N}}1$ type of substitution ([Sections 8-7D](#) and [8-7E](#)):



3.9.1: Contributors and Attributions

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CHAPTER OVERVIEW

4: Redox Reactions

[4.1: Oxidation and Reduction of Organic Compounds - An Overview](#)

[4.2: Nucleophilic Addition of Hydride and Grignard Reagents- Alcohol Formation](#)

[4.3: Oxidation of Alcohols](#)

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4.1: Oxidation and Reduction of Organic Compounds - An Overview

You are undoubtedly already familiar with the general idea of oxidation and reduction: you learned in general chemistry that when a compound or element is oxidized it loses electrons, and when it is reduced it gains electrons. You also know that oxidation and reduction reactions occur in tandem: if one species is oxidized, another must be reduced at the same time - thus the term 'redox reaction'.

Most of the redox reactions you have seen previously in general chemistry probably involved the flow of electrons from one metal to another, such as the reaction between copper ion in solution and metallic zinc:



? Exercise 4.1.1

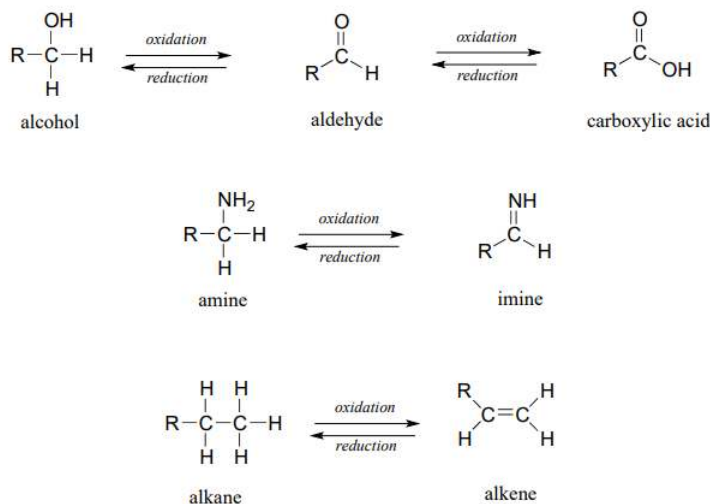
Reading the reaction above from left to right, which chemical species is being oxidized? Which is being reduced?

When we talk about the oxidation and reduction of organic compounds, what we are mainly concerned with is the number of carbon-heteroatom bonds in the compound compared to the number of carbon-hydrogen bonds. (Remember that the term 'heteroatom' in organic chemistry generally refers to oxygen, nitrogen, sulfur, or a halogen).

📌 Note

- Oxidation of an organic compound results an increase in the number of carbon-heteroatom bonds, and/or a decrease in the number of carbon-hydrogen bonds.
- Reduction of an organic compound results in a decrease in the number of carbon-heteroatom bonds, and/or an increase in the number of carbon-hydrogen bonds.

Below are a number of common functional group transformations that are classified as redox.



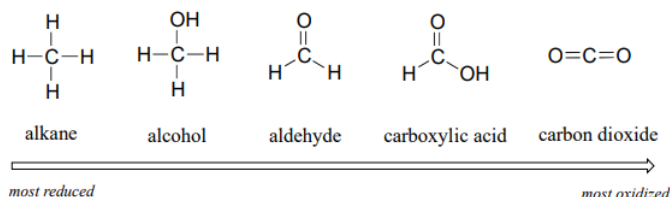
Heteroatoms such as oxygen and nitrogen are more electronegative than carbon, so when a carbon atom gains a bond to a heteroatom, it loses electron density and is thus being oxidized. Conversely, hydrogen is less electronegative than carbon, so when a carbon gains a bond to a hydrogen, it is gaining electron density, and thus being reduced.

? Exercise 4.1.2

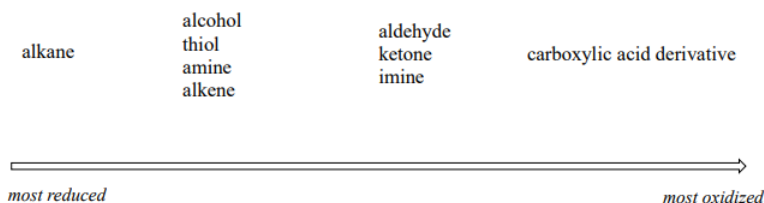
The hydration of an alkene to an alcohol is not classified as a redox reaction. Explain.

For the most part, when talking about redox reactions in organic chemistry we are dealing with a small set of very recognizable functional group transformations. The concept of oxidation state can be useful in this context. When a compound has lots of carbon-hydrogen bonds, it is said to be in a lower oxidation state, or a more reduced state. Conversely, if it contains a lot of carbon-heteroatom bonds, it is said to be in a higher oxidation state.

We'll start with a series of single carbon compounds as an example. Methane, in which the carbon has four bonds to hydrogen, is the most reduced member of the group. The compounds become increasingly oxidized as we move from left to right, with each step gaining a bond to oxygen and losing a bond to hydrogen. Carbon dioxide, in which all four bonds on the carbon are to oxygen, is in the highest oxidation state.

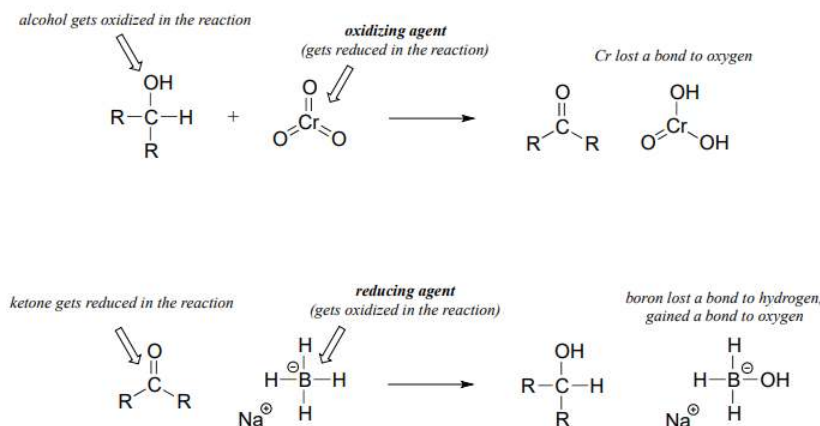


More generally, we can rank the oxidation state of common functional groups:



The alkane oxidation state is the most reduced. Alcohols, thiols, amines, and alkenes are all at the same oxidation state: therefore, a reaction converting one of these groups to another - an alcohol to alkene conversion, for example - is not a redox reaction. Aldehydes, however, are at a higher oxidation state than alcohols, so an alcohol to aldehyde conversion is an oxidation. Likewise, an imine to amine conversion is a reduction, but an imine to ketone conversion is not a redox reaction.

It is important to keep in mind that oxidation and reduction always occurs in tandem: when one compound is oxidized, another compound must be reduced. Often, organic chemists will use the terms oxidizing agent and reducing agent to refer to species that are commonly used, by human chemists or by nature, to achieve the oxidation or reduction of a variety of compounds. For example, chromium trioxide (CrO_3) is a laboratory oxidizing agent used by organic chemists to oxidize a secondary alcohol to a ketone, in the process being reduced to H_2CrO_3 . Sodium borohydride (NaBH_4) is a laboratory reducing agent used to reduce ketones (or aldehydes) to alcohols, in the process being oxidized to NaBH_3OH .



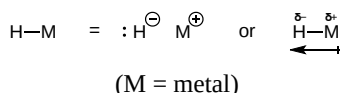
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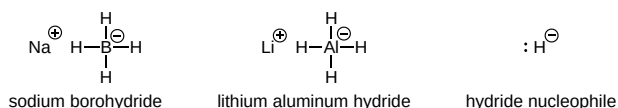
4.2: Nucleophilic Addition of Hydride and Grignard Reagents- Alcohol Formation

Reduction of Carbonyls to Alcohols Using Metal Hydrides

Like carbon, hydrogen can be used as a nucleophile if it is bonded to a metal in such a way that the electron density balance favors the hydrogen side. A hydrogen atom that carries a net negative charge and bears a pair of unshared electrons is called a **hydride ion**. How much negative charge density resides on hydrogen depends on the difference in electronegativity between hydrogen and the metal it's bonded to.

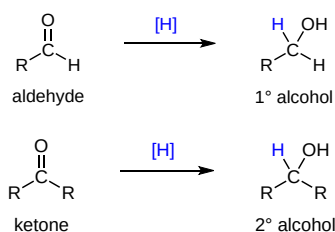


The most common sources of the hydride anion (:H^-) are **lithium aluminum hydride (LiAlH_4)** and **sodium borohydride (NaBH_4)**. Note! The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-hydrogen bond. Also, each are capable of delivering up to 4 hydride equivalents. The reaction equation of hydride reductions are not typically balanced (*i.e.* it does not specify the stoichiometry of the reagent). Because aluminum is less electronegative than boron, the Al-H bond in LiAlH_4 is more polar, thereby, making LiAlH_4 a stronger reducing agent.



General Reaction

Nucleophilic addition of a hydride anion (:H^-) to an aldehyde or a ketone gives a tetrahedral alkoxide anion intermediate, which on protonation yields the corresponding alcohol. Aldehydes produce 1°-alcohols and ketones produce 2°-alcohols. Both LiAlH_4 and NaBH_4 are capable of reducing aldehydes and ketones to the corresponding alcohol.

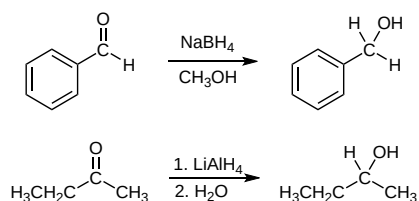


In metal hydrides reductions, the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the sodium borohydride reduction the methanol solvent system achieves this hydrolysis automatically. In the lithium aluminum hydride reduction water is usually added in a second step. The lithium, sodium, boron and aluminum end up as soluble inorganic salts at the end of either reaction.

Predicting the Product of a Hydride Addition to a Carbonyl

During the reduction, the $\text{C}=\text{O}$ double bond in the reactant becomes a $\text{C}-\text{O}$ single bond in the product. The breaking of the $\text{C}=\text{O}$ double bond allows for the formation of two new single bonds in the product. One will be attached to the oxygen ($\text{O}-\text{H}$) and one to the carbon ($\text{C}-\text{H}$).

Example

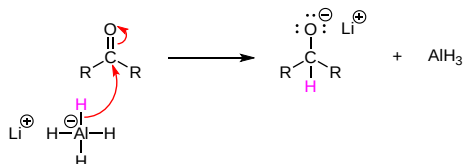


Mechanism for the Reduction of Carbonyls using LiAlH_4

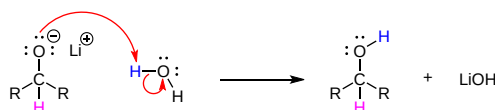
Both NaBH_4 and LiAlH_4 act as if they were a source of hydride. The hydride anion undergoes nucleophilic addition to the carbonyl carbon to form a C-H single bond and forming a tetrahedral alkoxide ion intermediate. The alkoxide ion is subsequently converted to an alcohol by reaction with a proton source (such as water). In the LiAlH_4 reduction, the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the borohydride reduction the hydroxylic solvent system achieves this hydrolysis automatically. The lithium, sodium, boron and aluminum end up as soluble inorganic salts.

Note! The reaction and the corresponding mechanism of hydride reductions of carbonyls is fairly complicated. The following mechanism has been simplified for easier understanding.

1) Nucleophilic attack to form a tetrahedral alkoxide intermediate



2) Protonation to form an alcohol



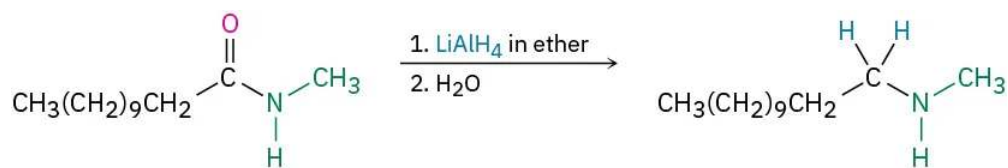
Properties of Hydride Sources

Two practical sources of hydride-like reactivity are the complex metal hydrides lithium aluminum hydride (LiAlH_4) and sodium borohydride (NaBH_4). These are both white (or near white) solids, which are prepared from lithium or sodium hydrides by reaction with aluminum or boron halides and esters. Lithium aluminum hydride is by far the most reactive of the two compounds, reacting violently with water, alcohols and other acidic groups with the evolution of hydrogen gas. The following table summarizes some important characteristics of these useful reagents.

Reagent	Preferred Solvents	Functions Reduced	Reaction Work-up
Sodium Borohydride NaBH_4	ethanol; aqueous ethanol 15% NaOH; diglyme avoid strong acids	aldehydes to 1°-alcohols ketones to 2°-alcohols inert to most other functional groups	1) simple neutralization 2) extraction of product
Lithium Aluminum Hydride LiAlH_4	ether; THF avoid alcohols and amines avoid halogenated compounds avoid strong acids	aldehydes to 1°-alcohols ketones to 2°-alcohols carboxylic acids to 1°-alcohols esters to alcohols epoxides to alcohols nitriles & amides to amines halides & tosylates to alkanes most functional groups react	1) careful addition of water 2) remove aluminum salts 3) extraction of product

Conversion of Amides into Amines: Reduction

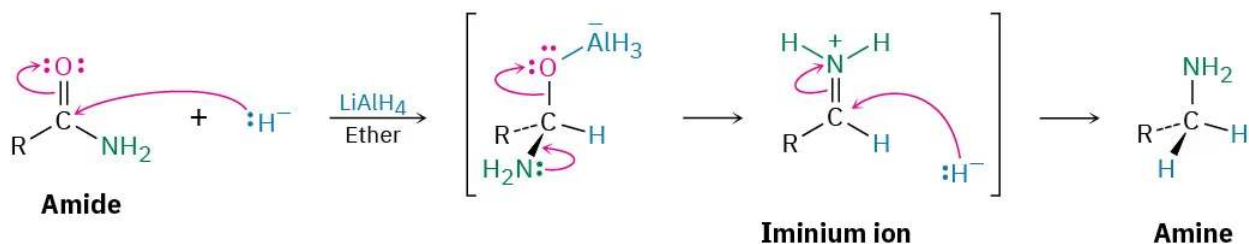
Like other carboxylic acid derivatives, amides can be reduced by LiAlH_4 . The product of the reduction, however, is an amine rather than an alcohol. The net effect of an amide reduction is thus the conversion of the amide carbonyl group into a methylene group (C=). This kind of reaction is specific to amides and does not occur with other carboxylic acid derivatives.



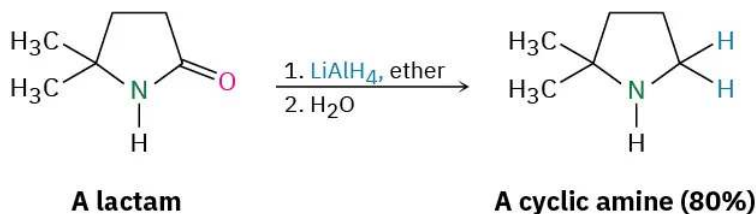
N-Methyldodecanamide

Dodecylmethylamine (95%)

Amide reduction occurs by nucleophilic addition of hydride ion to the amide carbonyl group, followed by expulsion of the oxygen atom as an aluminate anion leaving group to give an iminium ion intermediate. The intermediate iminium ion is further reduced by LiAlH_4 to yield the amine.

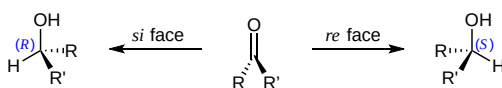


The reaction is effective with both acyclic and cyclic amides, or lactams, and is a good method for preparing cyclic amines.

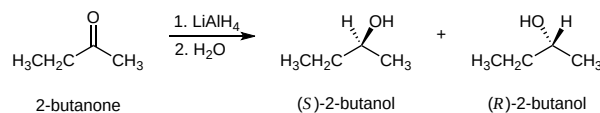


Limitations of Hydride Reductions

A hydride addition to an asymmetric ketone has the possibility of forming a chiral carbon that is not stereospecific. Attack by the hydride can occur from either the *re* or the *si* face of an asymmetrical carbonyl, leading to a mixture of the (*S*) and (*R*) alcohols. These reactions can be made to have stereochemical control by using several different methods including stereospecific reagents, sterics, and by the affect of an enzyme during a biological reduction.



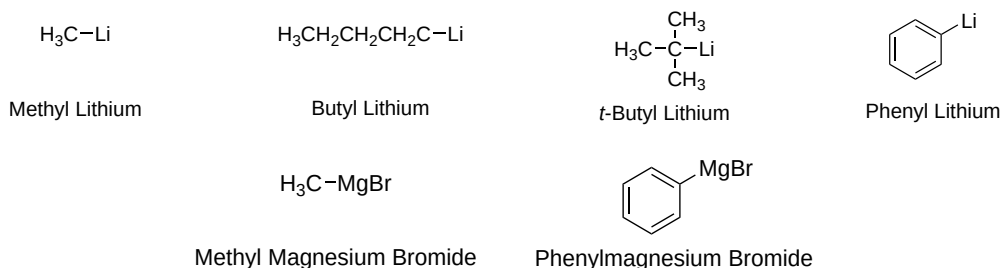
Example



Organometallic Reactions

Common Organometallic Reagents

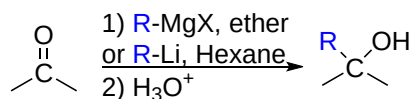
Lithium and magnesium metals reduce the carbon-halogen bonds of alkyl halides to form **organolithium reagents** and **Grignard reagents** respectively. In both cases, the carbon bonds to the metal and has characteristics similar to a **carbanion** (R^-) nucleophile. Some common organometallic reagents are shown below:



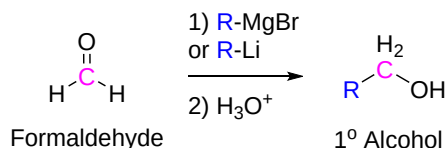
Reaction of Organometallic Reagents with Carbonyls

Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. Aldehydes and ketones will undergo nucleophilic addition with organolithium and Grignard reagent nucleophiles. The nucleophilic carbon in the organometallic reagents forms a C-C single bond with the electrophilic carbonyl carbon. An alkoxide ion intermediate is formed which becomes an alcohol with subsequent protonation with an acid. Both Grignard and organolithium reagents will perform these reactions.

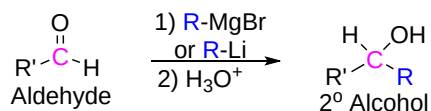
General Reaction



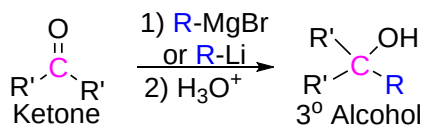
Addition to Formaldehyde gives 1° Alcohols



Addition to Aldehydes gives 2° Alcohols

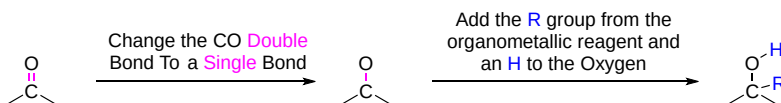


Addition to Ketones gives 3° Alcohols

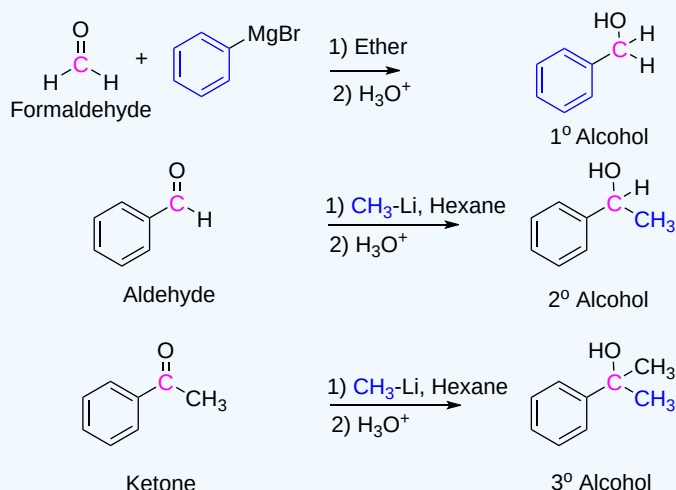


Predicting the Product of Addition of Organometallic Reagents to Aldehydes and Ketones

During the reaction, the C=O double bond in the reactant forms a C-O single bond in the product. The breaking of the C=O double bond allows for the formation of two single bonds in the product. One will be attached to the oxygen and one to the carbon which was originally in the carbonyl. The carbon will gain whatever R group was part of the organometallic reagent and the oxygen will gain a "H".



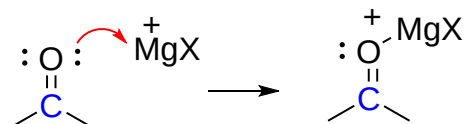
✓ Example 4.2.2



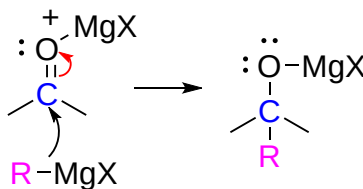
Mechanism for the Addition of Grignard Reagents to Carbonyls

The mechanism starts with the formation of an acid-base complex between ^+MgX and the carbonyl oxygen. The $^+\text{MgBr}$ of the Grignard reagent acts as a Lewis acid and accepts a lone pair of electrons from the carbonyl oxygen. This gives the oxygen a positive charge which correspondingly increases the partial positive charge on the carbonyl carbon increasing its susceptibility to nucleophilic attack. The carbanion nucleophile from the Grignard reagent adds to the electrophilic carbon of the acid-base complex forming a C-C bond. The two electrons of the C=O are pushed toward the carbonyl oxygen atom forming a tetrahedral magnesium alkoxide intermediate. The alkoxide intermediate is converted to an alcohol through addition of an acidic aqueous solution. The ^+MgX ion is also converted to HOMgX .

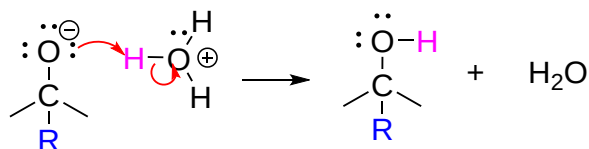
1) Lewis acid-base formation



2) Nucleophilic attack



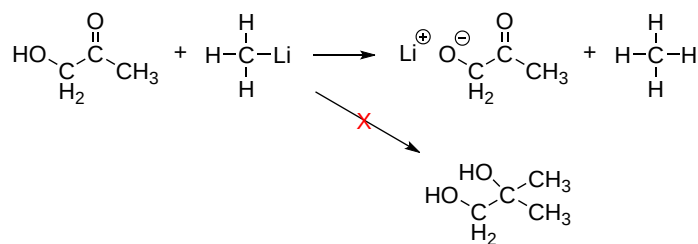
3) Protonation



Limitation of Organometallic Reagents

As discussed above, Grignard and organolithium reagents are powerful bases. Because of this they cannot be used as nucleophiles on compounds which contain acidic hydrogens. If they are used they will act as a base and deprotonate the acidic hydrogen rather

than act as a nucleophile and attack the carbonyl. A partial list of functional groups which cannot be used with organometallic reagents includes: alcohols, amides, 1° amines, 2° amines, carboxylic acids, and terminal alkynes.

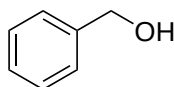


Planning an Alcohol Synthesis Using a Grignard Reaction

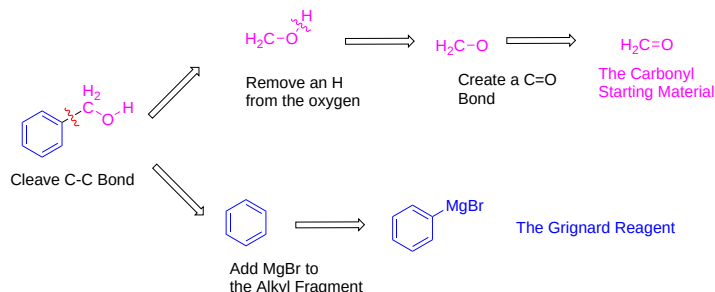
The nucleophilic addition of a Grignard reagent to a carbonyl is a powerful tool in organic synthesis because it forms a C-C bond. Also, there is often more than one way to make a given target molecule. Primary alcohols have one C-C bond which can be retrosynthetically cleaved. Secondary alcohols have two and tertiary alcohols have three.

Example

What reagents are required to make the following molecule using a Grignard Reaction?



Answer



Contributors and Attributions

- Layne A. Morsch (University of Illinois Springfield)
- (1) Chemistry of Amides <https://chem.libretexts.org/@go/page/448785> (accessed Mar 11, 2024)

4.2: Nucleophilic Addition of Hydride and Grignard Reagents- Alcohol Formation is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer & Dietmar Kennepohl.

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4.3: Oxidation of Alcohols

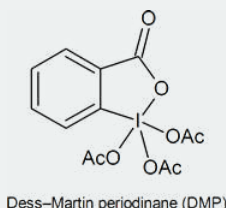
Objectives

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.



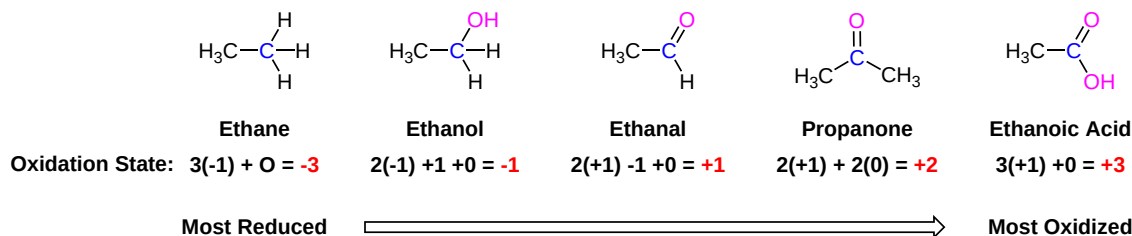
Oxidation States of Carbon

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 do 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:

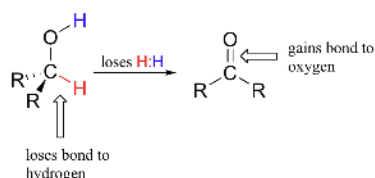
1. A C-C bond does not affect the oxidation state of a carbon. So a carbon attached to 4 carbons has an oxidation state of zero.
2. Every C-H bond will **decrease** the oxidation state of the carbon by 1.
3. Each C-X bond will **increase** the oxidation state of the carbon by 1. Where X is an electronegative, 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.



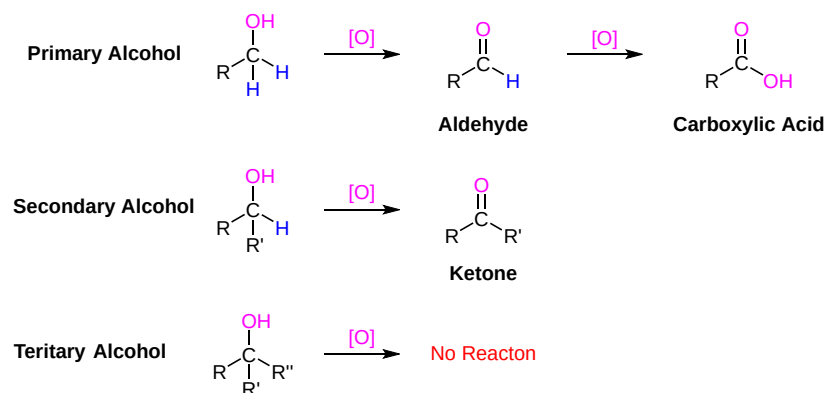
For this section, a simpler way to consider this process is to say that when a carbon atom in an organic compound loses a bond to hydrogen and gains a new bond to a oxygen it has been oxidized. A very commonly example is the oxidation of an alcohol to a ketone or aldehyde. Notice that during this process the carbon atom loses a hydrogen and gains a bond to oxygen.

Dehydrogenation (oxidation) of an alcohol



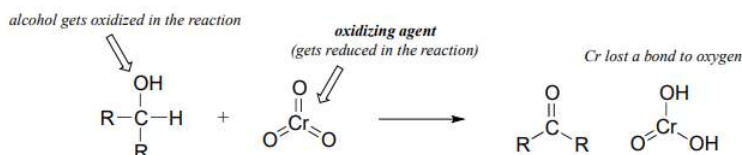
Oxidation of Alcohols

One of the most important reactions of alcohols is their oxidation to carbonyl containing compounds such as aldehydes, ketones, and carboxylic acids. 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.



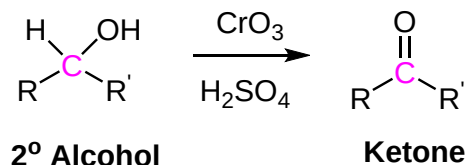
Alcohol Oxidizing Agents

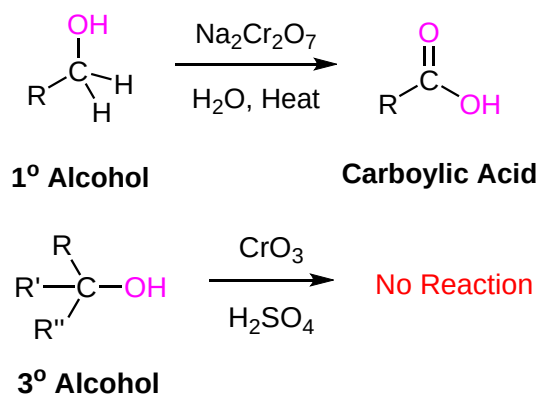
Oxidation and reduction reactions always occur in tandem: when one compound is oxidized, another compound must be reduced. For an alcohol to be oxidized in a reaction there must also be a compound being reduced. This reduced compound is also called the oxidizing agent. For example, chromium trioxide (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.



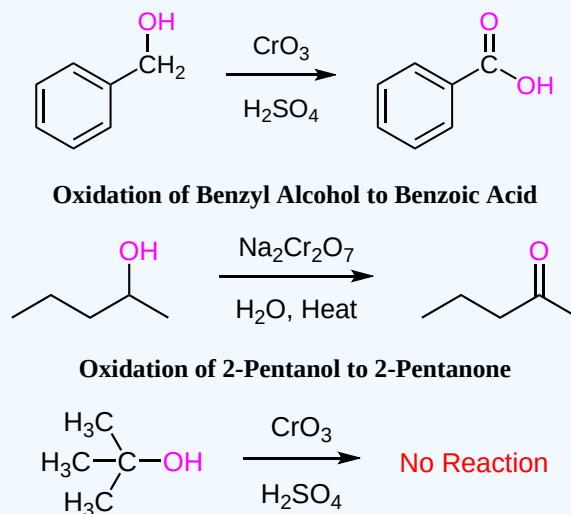
There is a wide selection of oxidizing agents available for use in the organic chemistry laboratory, each with its own particular properties and uses. In addition to CrO_3 , other commonly used oxidizing agents include potassium permanganate (KMnO_4) and sodium dichromate ($\text{Na}_2\text{Cr}_2\text{O}_7$). 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



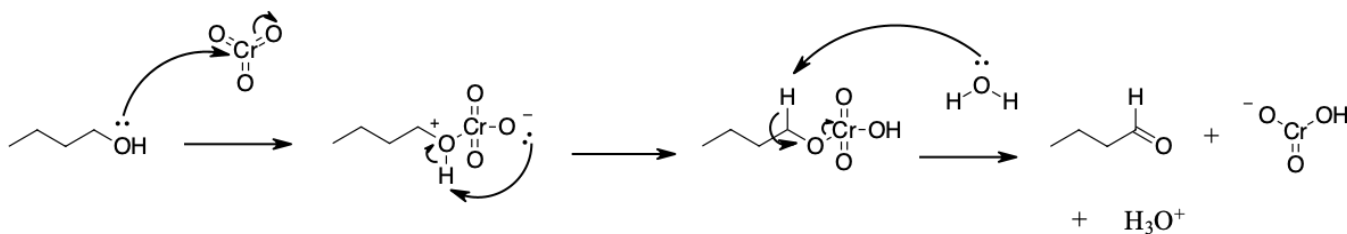


✓ Example 4.3.1



Mechanism

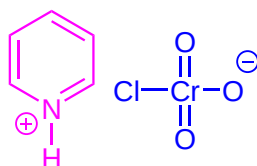
During this reaction mechanism the chromium atom is being reduced from Cr(VI) in the CrO_3 starting material to Cr(IV) in the H_2CrO_3 product. Also, notice the the C=O bond is formed in the third step of the mechanism through an E2 reaction. Although E2 reaction are generally know for forming C=C double 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

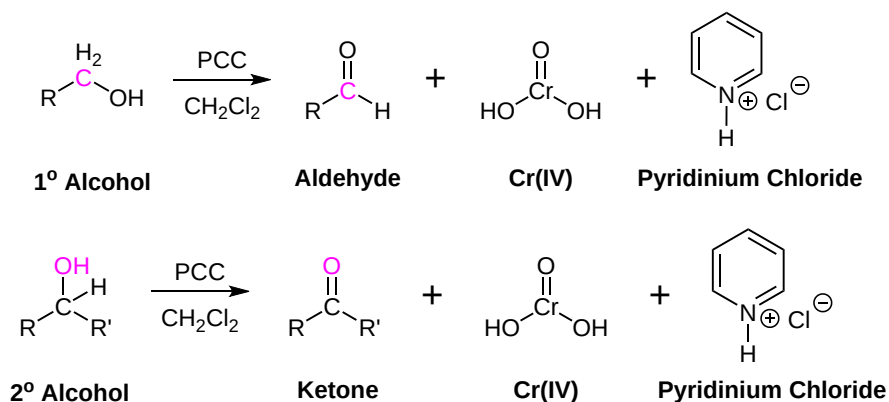
Oxidation of 1° Alcohols with PCC to form Aldehydes

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.

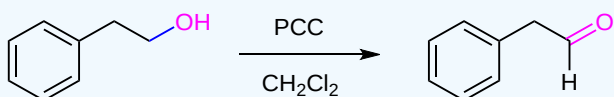


Pyridinium chlorochromate (PCC)

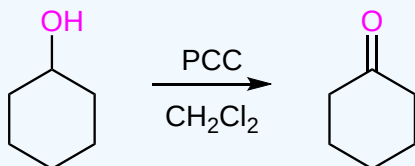
General Reactions



? Example 4.3.2



Oxidation of 2-Phenylethanol to Phenylacetaldehyde



Oxidation of Cyclohexanol to Cyclohexanone

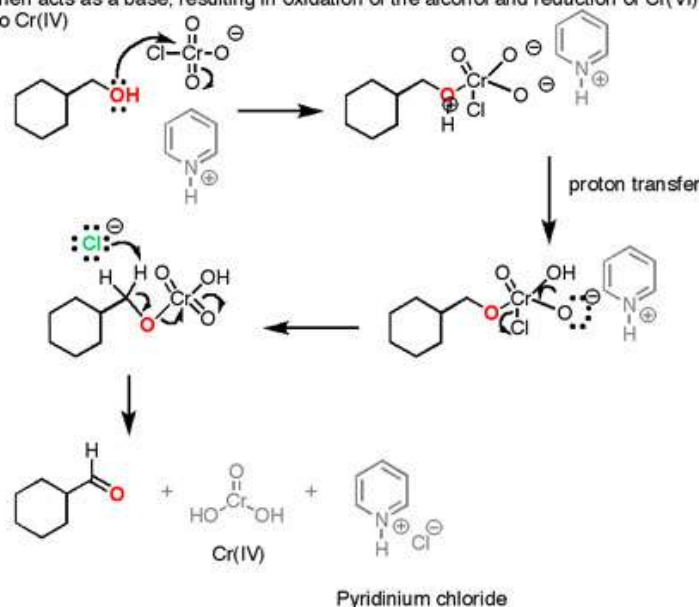
Mechanism

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 $\text{O}=\text{Cr}(\text{OH})_2$).

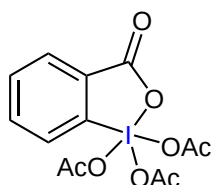
How it works *Oxidation of primary alcohols to aldehydes*

The alcohol coordinates to the chromium(VI) atom, displacing chlorine, which then acts as a base, resulting in oxidation of the alcohol and reduction of Cr(VI) to Cr(IV)



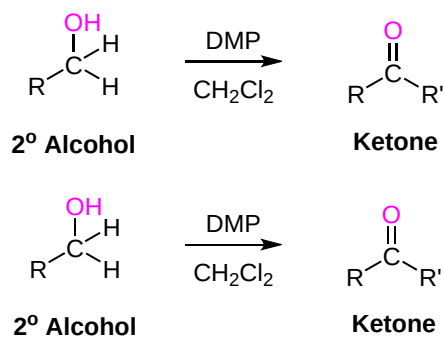
Oxidation of 1° Alcohols with Dess-Martin Periodinane (DMP) to form Aldehydes

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.

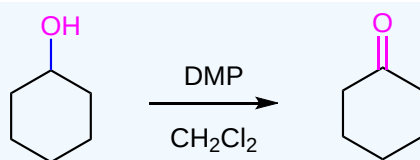


Dess-Martin periodinane (DMP)

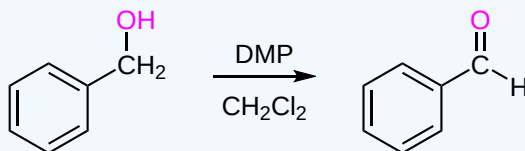
General Reactions



✓ Example 4.3.3



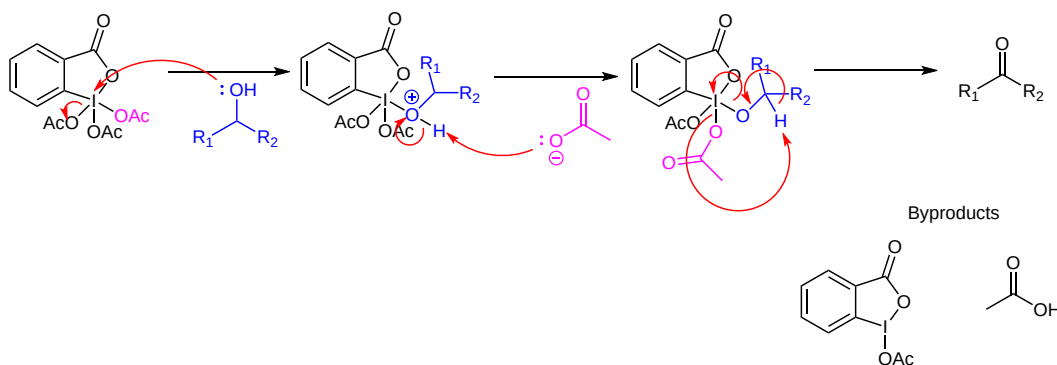
Oxidation of Cyclohexanol to Cyclohexanone



Oxidation of Benzyl Alcohol to Benzaldehyde

Mechanism

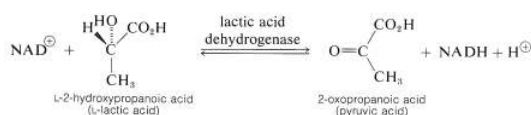
The first step of the mechanism involves the reactant alcohol attacking the Iodine (V) atom and eliminating an acetate (Ac^-) leaving group to form a periodinate intermediate. The next step is a concerted E2-like reaction where a hydrogen is removed from the alcohol, the $\text{C}=\text{O}$ bond is formed, an acetate group is eliminated from the iodine atom, and the iodine (V) atom gains two electrons to be reduced to iodine (III).

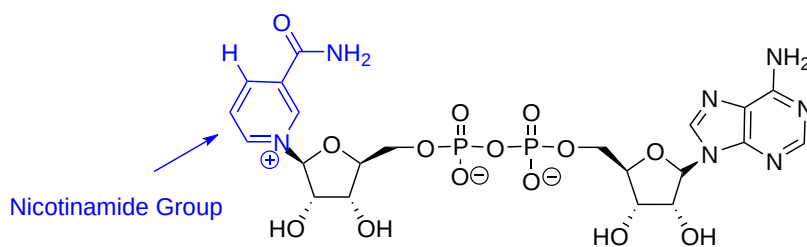


Biological Alcohol Oxidations

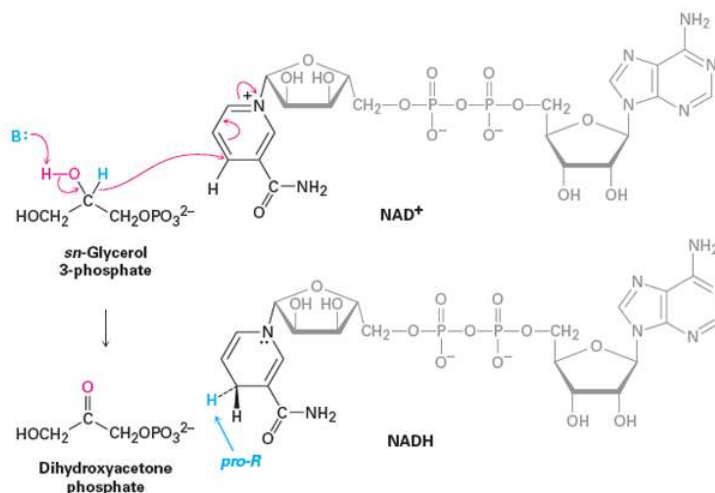
There are many biological oxidations that convert a primary or secondary alcohol to a carbonyl compound. These reactions cannot possibly involve the extreme pH conditions and vigorous inorganic oxidants used in typical laboratory oxidations. Rather, they occur at nearly neutral pH values and they all 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 ($\text{H}^+ + 2\text{e}^-$) 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 $\text{C}=\text{O}$ bond causing a hydride ion to transfer to NAD^+ .



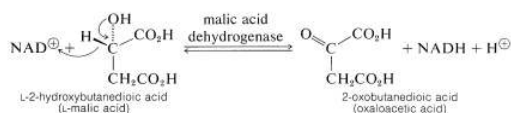


The Structure of NAD⁺



From an outside source. Convert mechanism to use lactic acid.

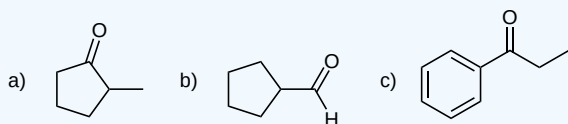
Another example is provided by one of the steps in metabolism by way of the Krebs citric acid cycle, is the oxidation of L-2-hydroxy-butanedioic (L-malic) acid to 2-oxobutanedioic (oxaloacetic) acid. This enzyme functions only with L-malic acid:



Exercises

? Exercise 4.3.1

Draw the alcohol that the following ketones/aldehydes would have resulted from if oxidized. What oxidant could be used?



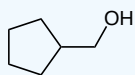
Answer

1)

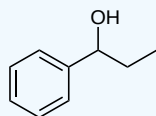
a) Any oxidant capable of oxidizing an alcohol to a ketone would work, such as the Jones reagent (CrO_3 , H_2SO_4 , H_2O), PCC, or Dess-Martin periodinane.



b) Since this is a primary alcohol, there are some precautions necessary to avoid formation of the carboxylic acid. Milder oxidants such as the Dess-Martin periodinane, and also PCC (there is no water to form the carboxylic acid) would work



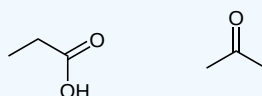
c) Any oxidant capable of oxidizing an alcohol to a ketone would work, such as the Jones reagent (CrO_3 , H_2SO_4 , H_2O), PCC, or Dess-Martin periodinane.



? Exercise 4.3.2

Show the products of the oxidation of 1-propanol and 2-propanol with chromic acid in aqueous solution.

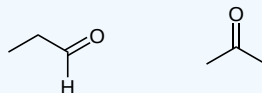
Answer



? Exercise 4.3.3

Show the products of the oxidation of 1-propanol and 2-propanol with Dess-Martin periodinane.

Answer



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CHAPTER OVERVIEW

5: Aldehydes and Ketones

Learning Objectives

When you have completed Chapter 22, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. 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.
3. solve road-map problems that require a knowledge of carbonyl alpha-substitution reactions.
4. define, and use in context, the key terms introduced.

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.

[5.1: Keto-Enol Tautomerism](#)

[5.2: Reactivity of Enols- The Mechanism of Alpha-Substitution Reactions](#)

[5.3: Alpha Halogenation of Aldehydes and Ketones](#)

[5.4: Reactivity of Enolate Ions](#)

[5.5: Alkylation of Enolate Ions](#)

[5.6: Carbonyl Condensations - The Aldol Reaction](#)

[5.7: Carbonyl Condensations versus Alpha Substitutions](#)

[5.8: Dehydration of Aldol Products - Synthesis of Enones](#)

[5.9: Mixed Aldol Reactions](#)

[5.10: Intramolecular Aldol Reactions](#)

[5.11: Nucleophilic Addition of Water- Hydration](#)

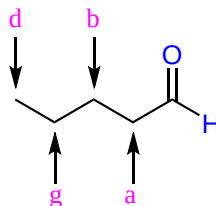
[5.12: Nucleophilic Addition of Alcohols- Acetal Formation](#)

[5.13: Nucleophilic Addition of Amines- Imine and Enamine Formation](#)

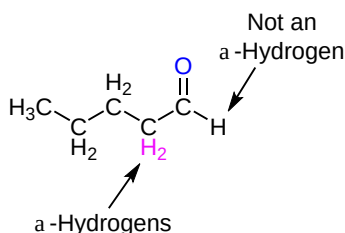
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5.1: Keto-Enol Tautomerism

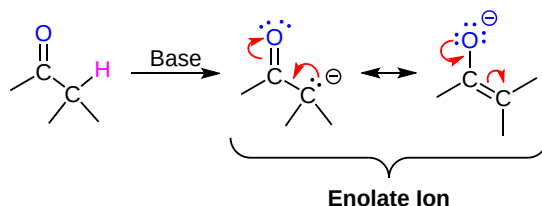
Often, the position of a carbon atom near a carbonyl group is designated using Greek letters. The atom adjacent to the carbonyl is alpha, the next removed is beta and so on. The carbon in the carbonyl group is used as reference point and is not assigned a Greek letter. Likewise, hydrogens bear the same 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, as we shall see shortly. 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.

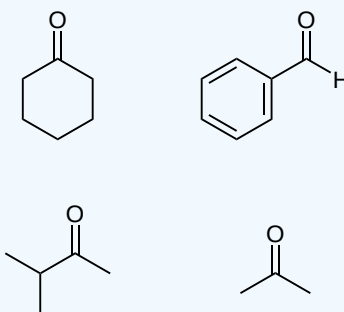


α -hydrogens, which are attached to a carbon directly adjacent to a carbonyl group, display unusual acidity. This is almost exclusively due to the resonance stabilization of the carbanion conjugate base, called an enolate, as illustrated in the diagram below. The effect of the stabilizing C=O is seen 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).

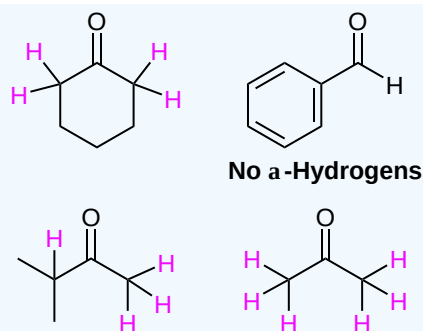


✓ Example 5.1.1

Indicate any α -hydrogens contained in the following molecules:



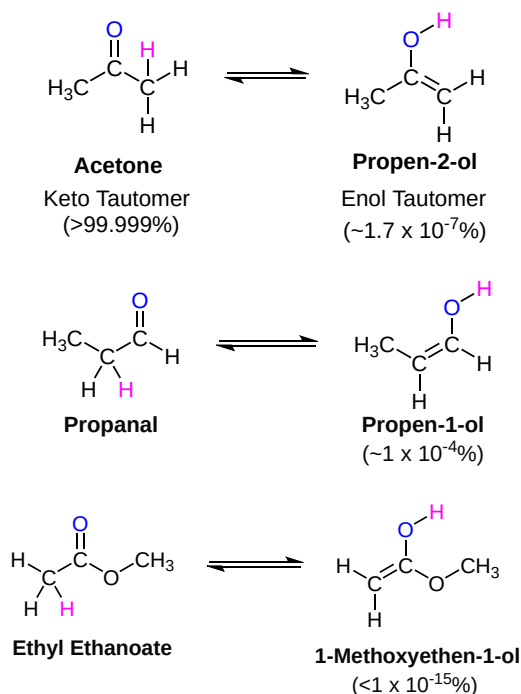
Solution



Keto-enol Tautomerization

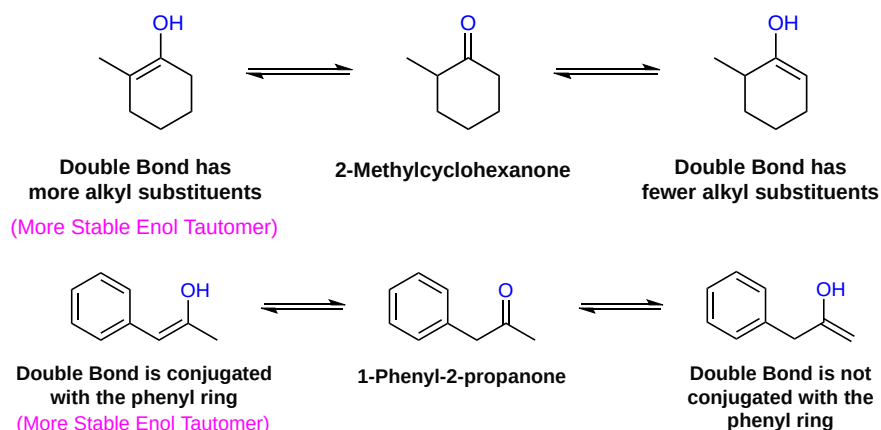
Because of the acidity of α -hydrogens, many carbonyl containing compounds undergo a proton-transfer equilibrium called tautomerism. Tautomers are readily interconverted constitutional isomers, usually distinguished by a different location for an atom or a group. Because tautomers involve the rearrangement 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 alkyl 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.



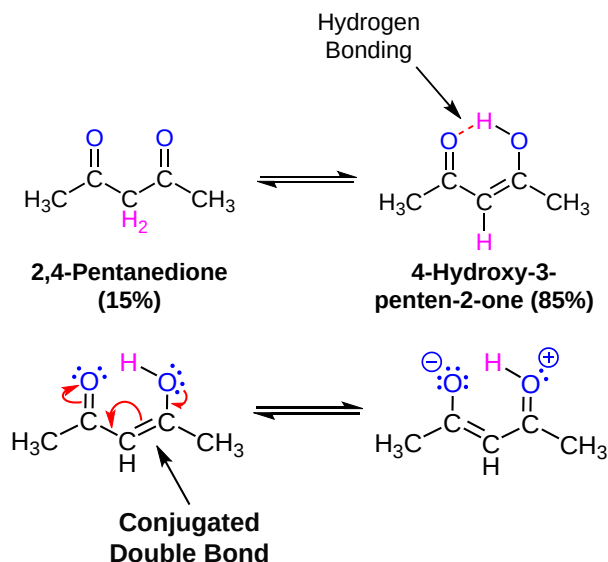
Aldehydes and symmetrical ketones typically only have one possible enol tautomer while asymmetrical ketones can have two or more. The preferred enol tautomer formed can often be predicted by considering effects which can stabilize alkenes, such as conjugation and alkyl group substitution. The asymmetrical 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.



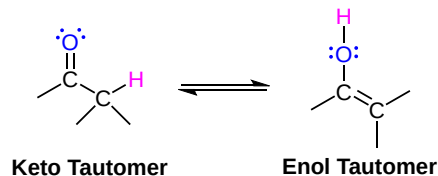
Another effect which can stabilize an enol tautomer is aromaticity. When considering the molecule 2,4-cyclohexadienone, the enol tautomer is the aromatic molecule phenol. The stabilization gained by forming an aromatic ring is sufficient to make phenol the exclusive tautomer present in the equilibrium.



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

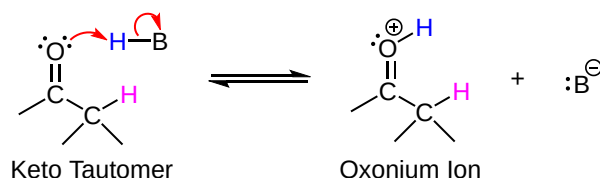


Acidic Conditions

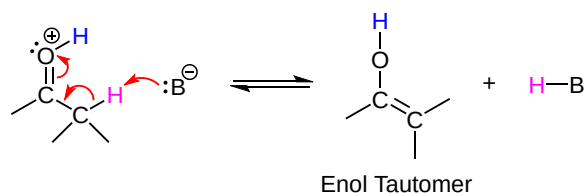
Keto Tautomer → Enol Tautomer

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



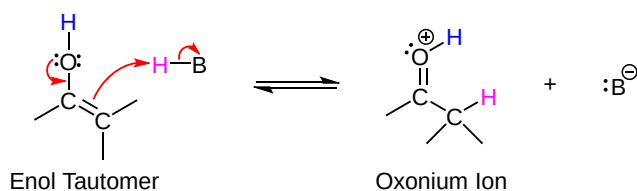
2) Deprotonation of an α -hydrogen to form an enol



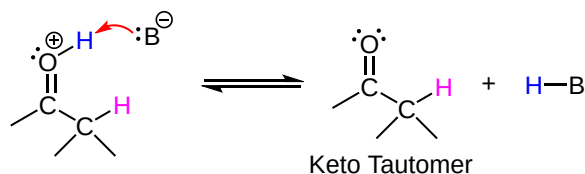
Enol Tautomer → Keto Tautomer

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

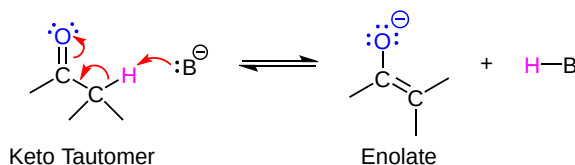


Under Basic Conditions

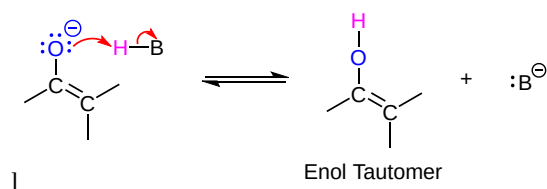
Keto Tautomer → Enol Tautomer

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 pi electrons of the carbonyl bond 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



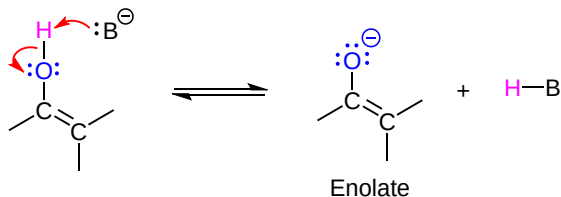
2) Protonation the enolate ion to form an enol



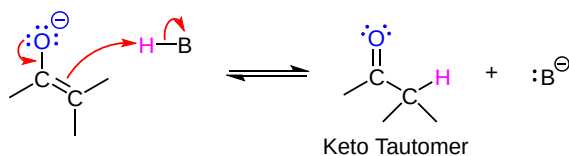
Enol Tautomer → Keto Tautomer

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



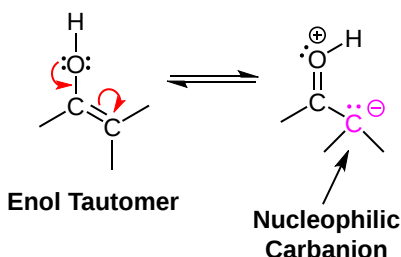
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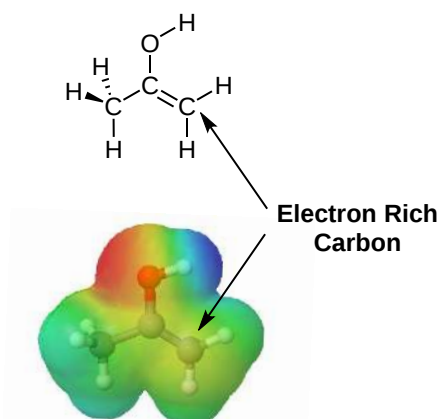
5.2: Reactivity of Enols- The Mechanism of Alpha-Substitution Reactions

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.



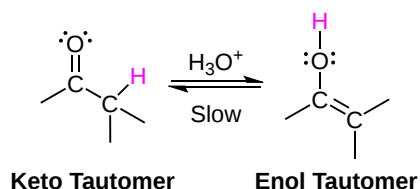
As seen in the electrostatic potential map for propen-2-ol ($\text{CH}_3\text{COH}=\text{CH}_2$), the enol tautomer of acetone, shows an increased electron density on the α -carbon (yellow) especially when compared to the $-\text{CH}_3$ carbon (blue/green). One of the resonance forms of an enol places 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.



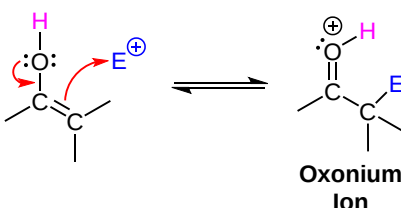
Mechanism of Alpha Substitution Reactions Using an Enol

The mechanism begins with the acid-catalyzed tautomerization to form an enol via the mechanism discussed previously. Lone pair electrons on the enol oxygen move to become a $\text{C}=\text{O}$ pi bond thus creating a positively charged oxonium ion. This also causes electrons from the $\text{C}=\text{C}$ enol pi bond to attack an electrophile forming a $\text{C}-\text{E}$ 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.

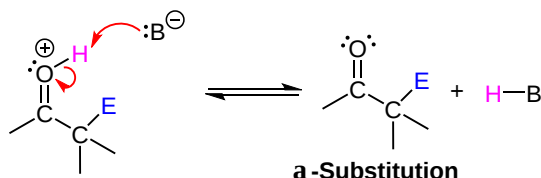
1) Acid catalyzed tautomerization to form an enol



2) The nucleophilic enol attacks the electrophile



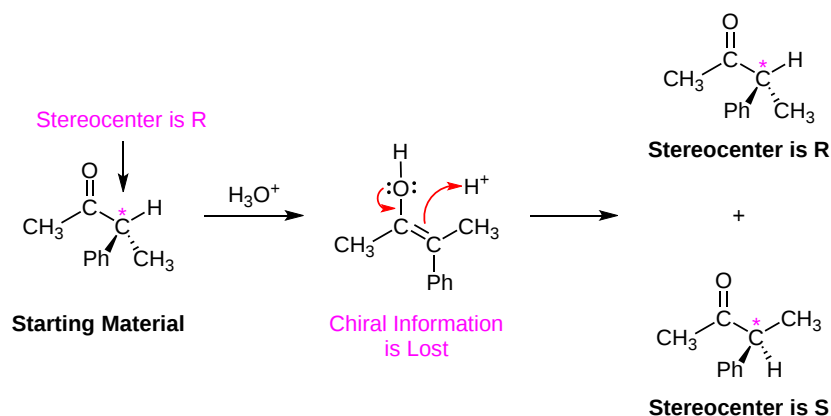
3) Deprotonation of the carbonyl to produce an α -substituted product



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 is formed during the reaction, the product will typically be a racemic mixture of enantiomers at the site of substitution.

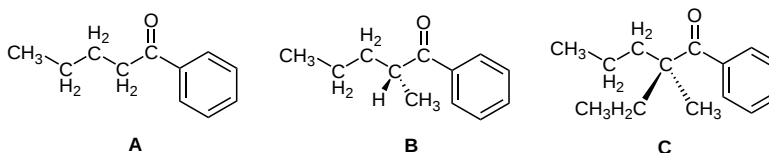
One of the easiest ways of displaying this process is through acid-catalyzed racemization. If a carbonyl compound has an α -carbon with a defined stereochemistry and an α -hydrogen, a racemic mixture can be formed simply through tautomerization. The addition of acid promotes the formation of the enol 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.



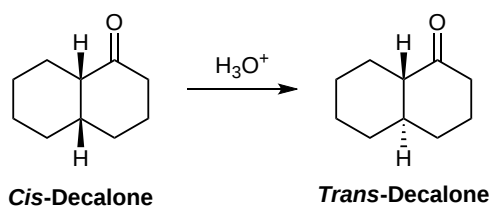
Example of Acid-Catalyzed Racemization

Exercises

1) Which of the following optically active ketones would undergo acid-catalyzed racemization? Explain.



2) When *cis*-Decalone is treated with an acid it becomes *trans*-Decalone almost exclusively becomes *trans*-Decalone. Explain.



Solutions

1) 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.

2) This change involves a process called 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 question 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 to the ketone tautomer, a mixture of both *cis* and *trans* epimers should form. However, as discussed in a previous section, we know that 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.

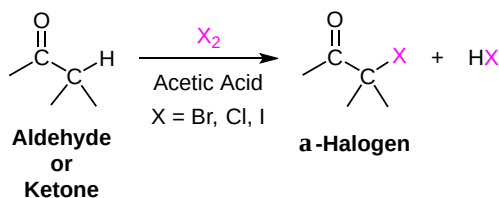
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5.3: Alpha Halogenation of Aldehydes and Ketones

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 (α substitution)



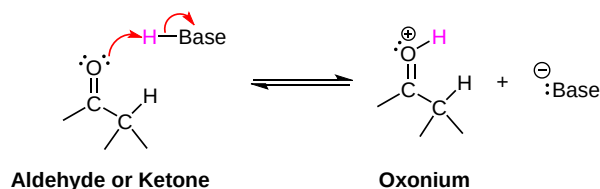
✓ Example 22.3.1



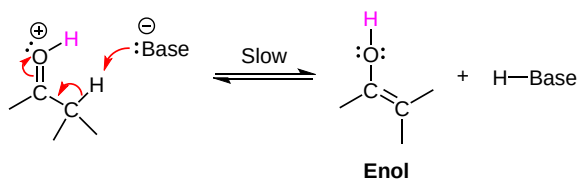
Acid Catalyzed Mechanism

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.

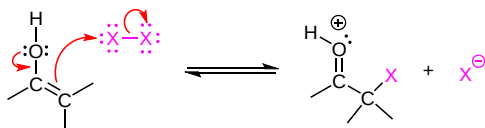
1) Protonation by the acid catalyst



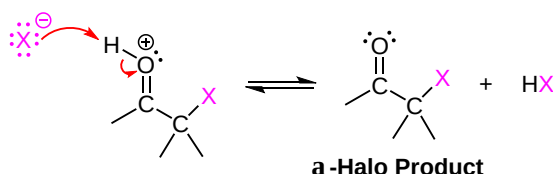
2) Removal of an α -hydrogen to form the enol. This step is slow and represents the rate-determining step.



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:

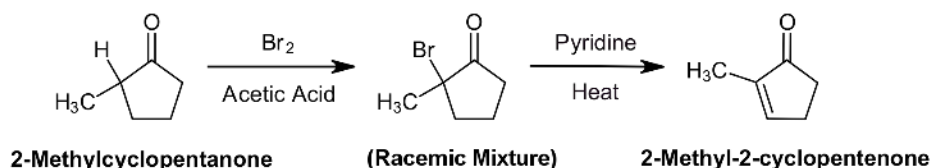
$$\text{rate} = k [\text{ketone}] [\text{H}^+]$$

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.

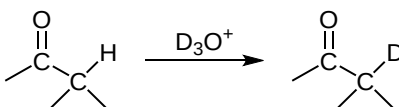
An example of this reaction involves the α -bromination of 2-methylcyclopentanone to form 2-bromo-2-methylcyclopentanone. Because enol tautomers prefer to form on the more substituted α -carbon, α -bromination also occurs on the more substituted α -carbon. Although the enol intermediate causes a racemic 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.



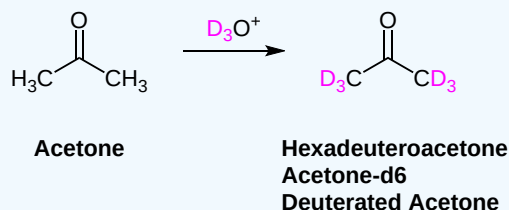
Deuterium Exchange

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)



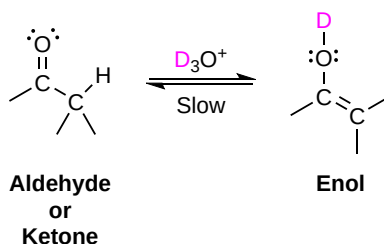
✓ Example 22.3.2



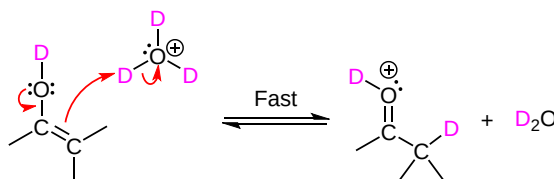
Mechanism in Acidic Conditions

The mechanism for deuterium exchange is virtually the same as keto-enol tautomerism under acidic conditions, as shown in **Section 22.2**. The only difference is that when the keto tautomer is reformed a deuterium is placed in the α -position.

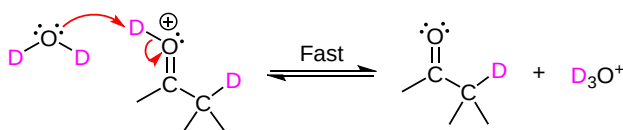
1) Formation of an enol



2) α -Deuteration



3) De-deuteration to form the keto tautomer



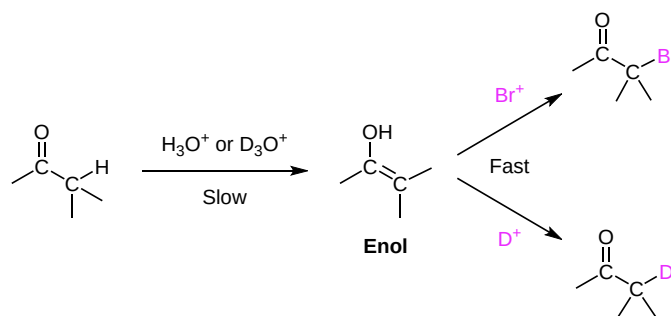
✓ Example 5.3.1

A simple method for determining the number of α -hydrogen in a compound is through reaction of D_3O^+ . The reaction product is then isolated and its molecular weight is determined by mass spectrometry. For example, if cyclopentanone is reacted with D_3O^+ , the isolated product has a molecular weight of 88 g/mol. Please explain how this method works and how many α -hydrogens cyclopentanone is predicted to have.

Solution

During acid catalyzed deuterium exchange each α -hydrogen in the compound is replaced with a deuterium. For each proton (AW = 1) replaced with a deuterium (AW = 2) the molecular weight of the compound is increased by one. Since cyclopentanone has a molecular weight of 84 g/mol and the isolated product has a molecular weight of 88 g/mol it can be predicted that cyclopentanone has four α -hydrogens.

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.



5.3: Alpha Halogenation of Aldehydes and Ketones 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.

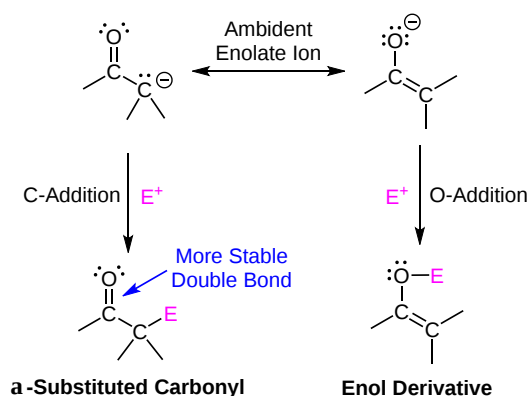
- 22.3: Alpha Halogenation of Aldehydes and Ketones by Dietmar Kennepohl, Layne Morsch, Steven Farmer is licensed [CC BY-SA 4.0](#).

5.4: Reactivity of Enolate Ions

How Enolates React

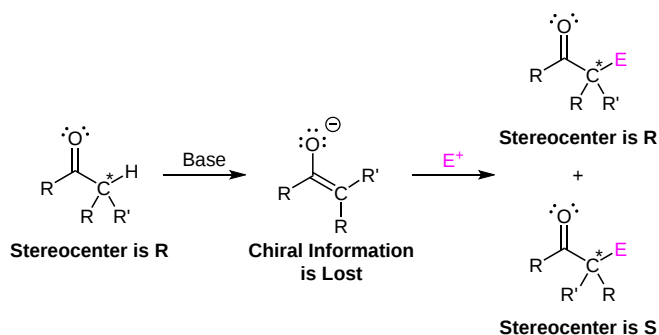
Due to their negative charges, enolates are better and more versatile nucleophiles than enols. The increased reactivity of enolates makes them capable of a wider range of reactions than enols. Also, α -hydrogen containing compounds can be completely converted to an enolate by reaction with a strong base. 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.



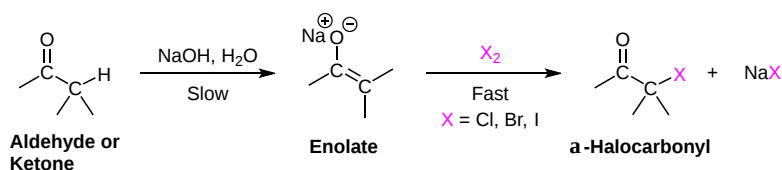
Stereochemical Implication of Enolate Formation

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 enol 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.



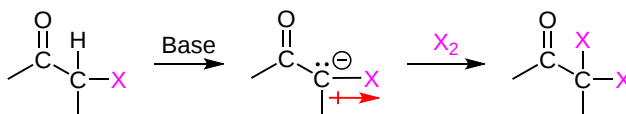
Base Promoted α -Halogenation

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 previously 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.



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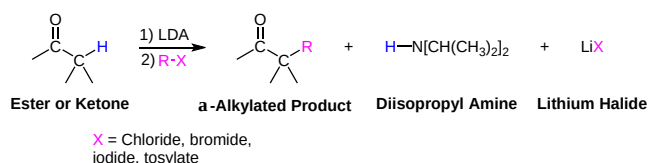
- 22.6: Reactivity of Enolate Ions by Dietmar Kennepohl, Layne Morsch, Steven Farmer is licensed [CC BY-SA 4.0](#).

5.5: Alkylation of Enolate Ions

Alkylation of Enolates

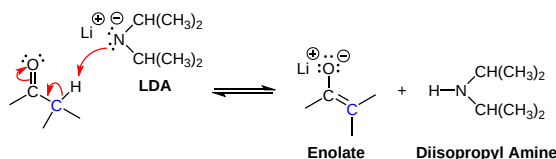
Enolates can be alkylated in the α position through an S_N2 reaction with alkyl halides. During this reaction an α -hydrogen is replaced with an alkyl group and a new C-C bond is formed. The limitations of S_N2 reactions still apply. This includes preferring a good primary or secondary leaving group, 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 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

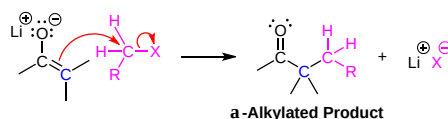


Mechanism

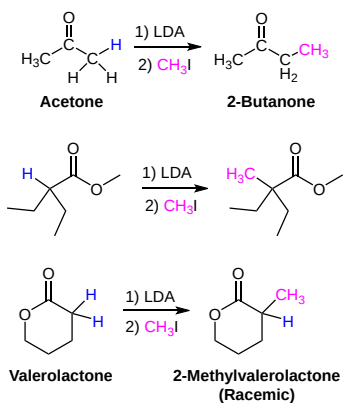
1) Enolate formation



2) S_N2 attack

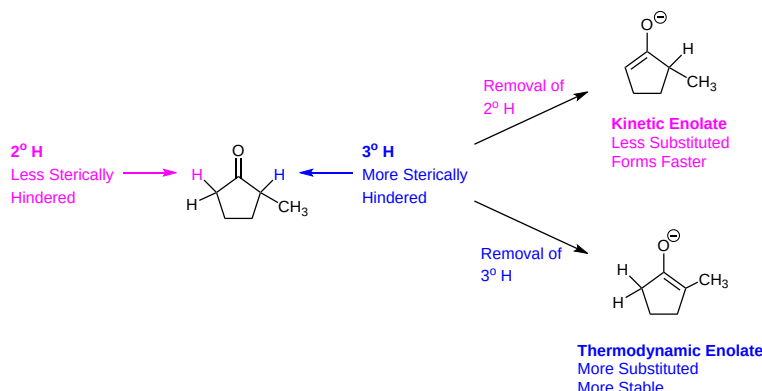


Examples



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

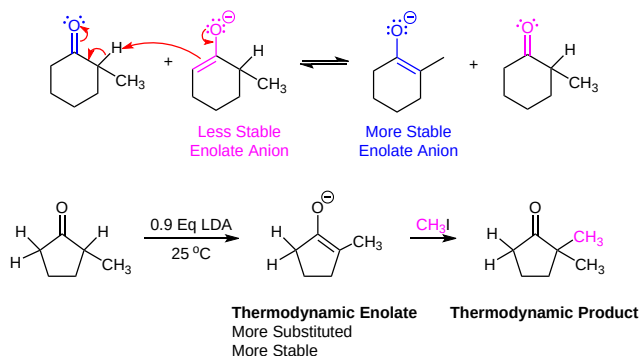
kinetic control (rate) or thermodynamic control (equilibrium). Although a predominant product can be produced, a mixture of products is usually formed causing a reduction in product yield.



Thermodynamic Enolates

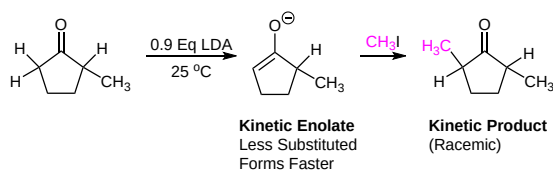
The thermodynamic enolate is formed when the more substituted α -hydrogen is removed. This leads to the more alkyl substituted, therefore the more stable, enolate to be formed. The presence of additional alkyl groups causes the formation of the thermodynamic enolate to be sterically hindered and kinetically 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



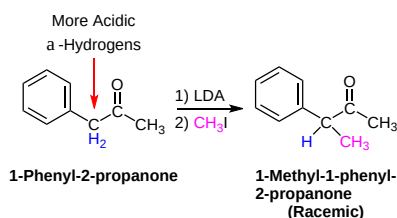
Kinetic Enolates

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°C) prevent enolate equilibration and promote the formation of the kinetic enolate.



When an enolate of an asymmetric ketone is stabilized through additional resonance forms there is no competition between possible enolates despite kinetic or thermodynamic 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



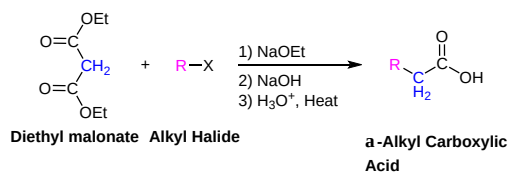
Malonic Ester Synthesis

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 ($\text{pK}_a = 12.6$) 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.

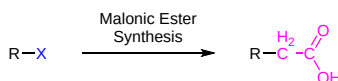


General Reaction



Predicting the Product of a Malonic Ester Synthesis

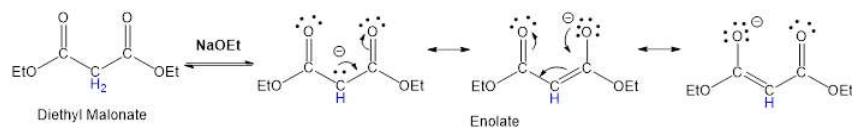
The product of a Malonic Ester Synthesis can be created by simply replacing the halogen on the alkyl halide with a $-\text{CH}_2\text{CO}_2\text{H}$ group.



Malonic ester synthesis takes place in four steps:

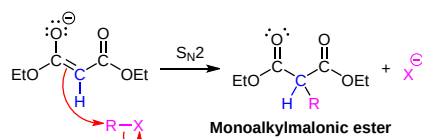
1) Enolate Formation

Reacting diethyl malonate with sodium ethoxide (NaOEt) forms a resonance-stabilized enolate.



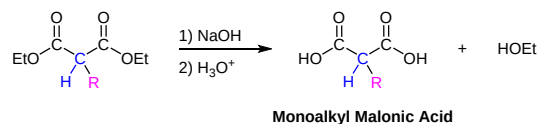
2) Alkylation

The enolate is alkylated via an $\text{S}_{\text{N}}2$ reaction to form an monoalkylmalonic ester.



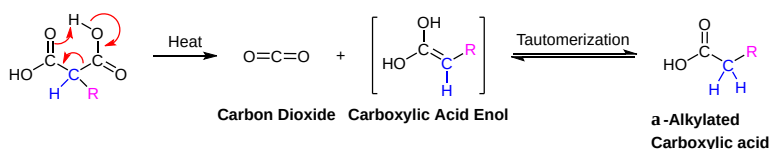
3) Ester hydrolysis and protonation

After alkylation, the diester undergoes hydrolysis with sodium hydroxide to form a dicarboxylate. Subsequent protonation with acid forms a monoalkyl malonic acid.

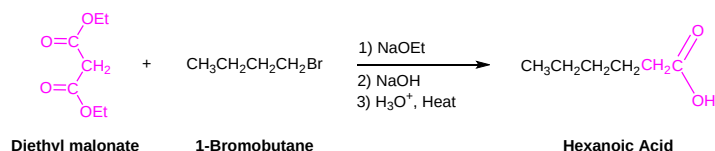


4) Decarboxylation & Tautomerization

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.



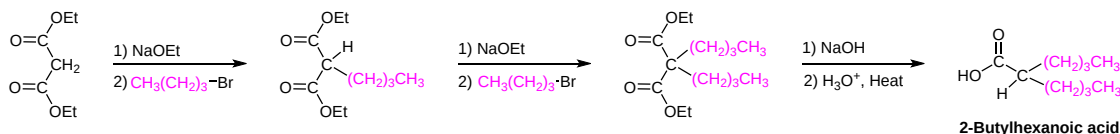
Example



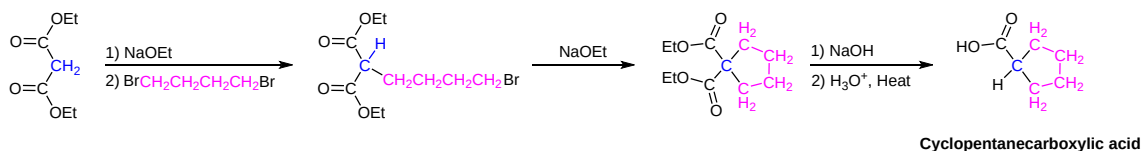
Dialkylation

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



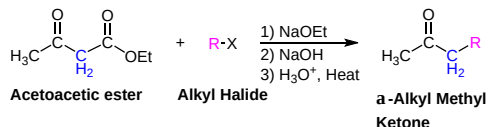
In a variation of the dialkylation reaction - if one molar equivalent of malonic ester is reacted with one molar equivalent of a dihaloalkane and two molar equivalents of sodium ethoxide, a cyclization reaction occurs. By changing the dihaloalkane, three, four, five, and six-membered rings can be created.



The Acetoacetic Ester Synthesis

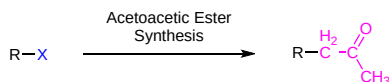
The acetoacetic ester synthesis is a series of reactions which converts alkyl halides into a methyl ketone with three additional carbons. This reaction creates an α -substituted methyl ketone without side-products. The starting reagent for this pathway is ethyl 3-oxobutanoate, also called ethyl acetoacetate, 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

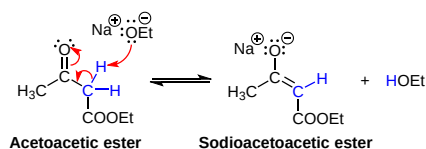
The product of a acetoacetic ester synthesis can be created by replacing halogen on the alkyl halide with a $-\text{CH}_2\text{COCH}_3$ group.



Reaction Steps

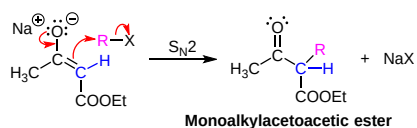
1) Formation of the enolate

As previously described, the α -hydrogens of acetoacetic ester are rather acidic ($\text{pK}_a = 10.7$) allowing the enolate to be easily formed when sodium ethoxide is used as a base.



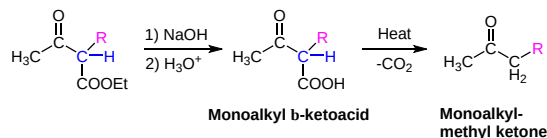
2) Alkylation via an $\text{S}_\text{N}2$ Reaction

Subsequent reaction with an alkyl halide produces a monoalkylacetoacetic ester.

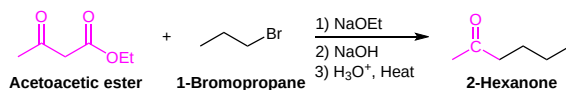


3) Ester hydrolysis and decarboxylation

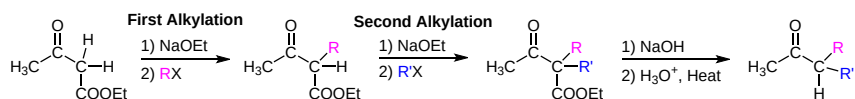
Hydrolysis with NaOH followed by protonation produces an alkylated beta-ketoacid. β -ketoacids are easily decarboxylated to form an α -alkyl substituted methyl ketone and carbon dioxide (CO_2) using a similar mechanism as the malonic ester synthesis.



Examples

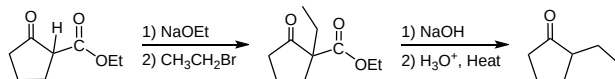


Much like the malonic ester synthesis, a second alkyl group can added before the decarboxylation step.



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 β -keto esters can be alkylated and subsequently decarboxylated to give an α -alkylated cyclic ketone.

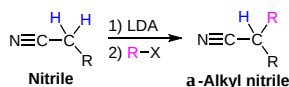
Examples



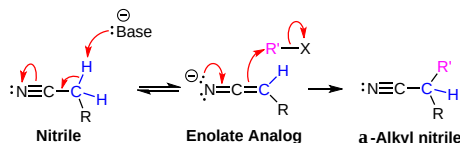
Direct Alkylation of Nitriles

The presence of acidic α -hydrogens in nitriles gives them the ability to form an enolate equivalent which can be also be directly alkylated.

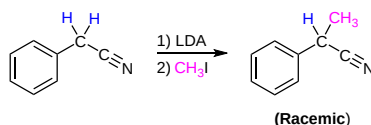
General Reaction



Mechanism



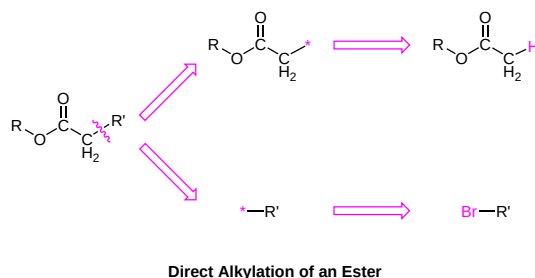
Example

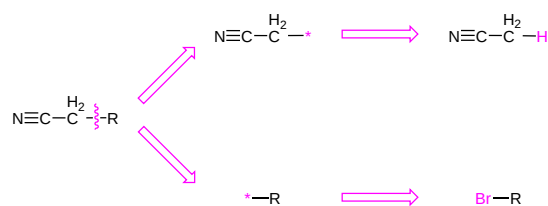


Planning a Synthesis Using Enolate Alkylations

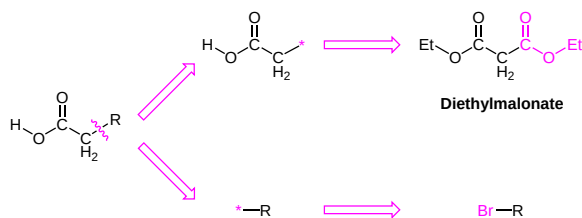
When planning a synthesis that could involve enolates, the key is to recognize the functionality which can form an enolate. During retrosynthetic analysis a C-C bond is broken between the α -carbon and the β -carbon away from this functionality. It is also important to be able to identify specific groups 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.



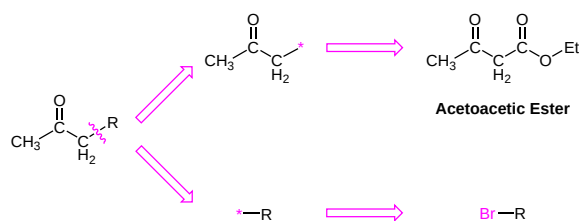


Direct Alkylation of a Nitrile



Diethylmalonate

Malonic Ester Synthesis

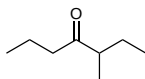


Acetoacetic Ester

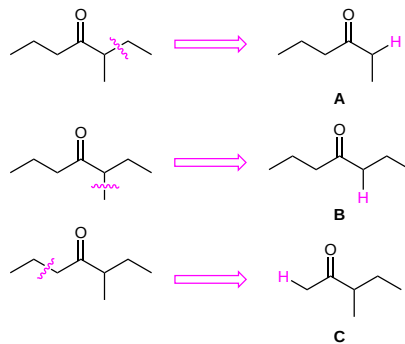
Acetoacetic Ester Synthesis

Worked out example:

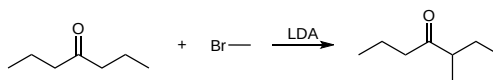
Plan a synthesis of the following molecule using an alkylation of an enolate. Consider multiple pathways and explain which is preferable.



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



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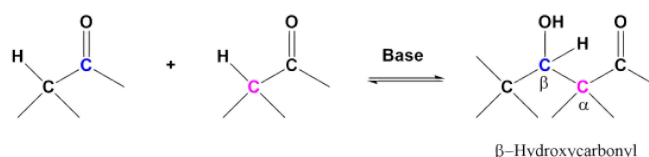
- [22.7: Alkylation of Enolate Ions](#) by Dietmar Kennepohl, Layne Morsch, Steven Farmer, William Reusch is licensed [CC BY-SA 4.0](#).

5.6: Carbonyl Condensations - The Aldol Reaction

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.

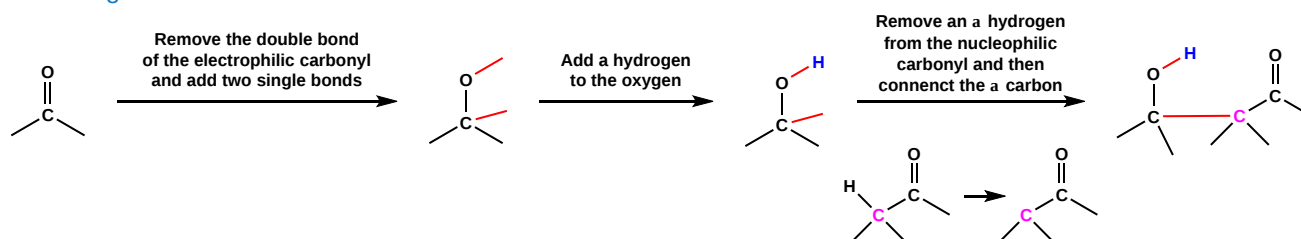
General Aldol reaction



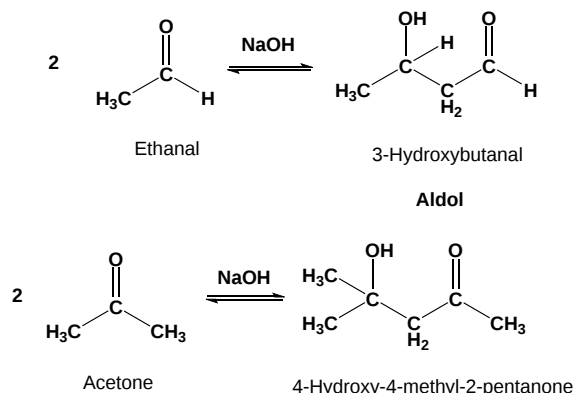
A typical example involves two molecules of acetaldehyde (ethanal) reacting to form beta-hydroxybutanal (3-hydroxybutanal). This product and other beta-hydroxy aldehydes are generically called “aldols” because they contain both an aldehyde and an alcohol functional group.

An aldol reaction, like many carbonyl addition reactions, is an equilibrium reaction and is reversible. The presence of an equilibrium means weaker bases, such as 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



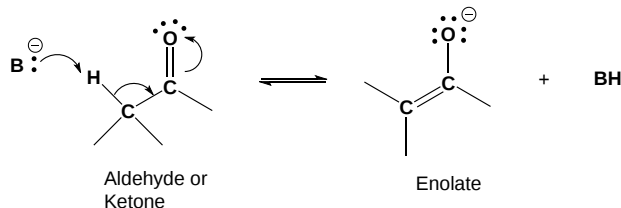
Examples



Mechanism of Aldol Reaction

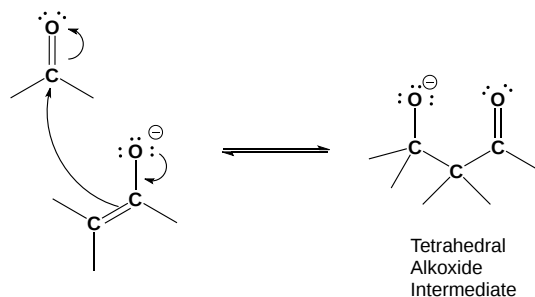
1) Enolate formation

The reaction starts with a base removing an alpha hydrogen to form a nucleophilic enolate.



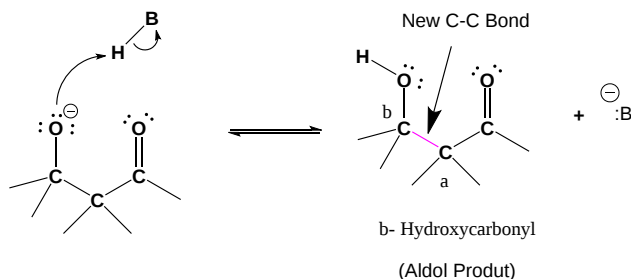
2) Nucleophilic attack by the enolate

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.



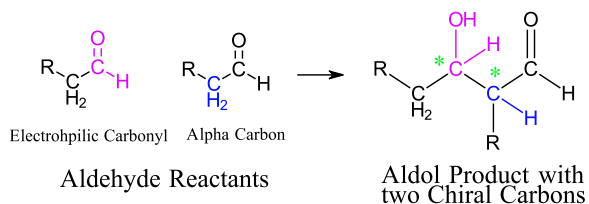
3) Protonation

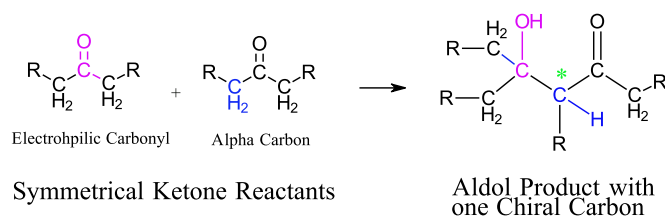
Protonation of the alkoxide forms the neutral aldol product and regenerates the base.



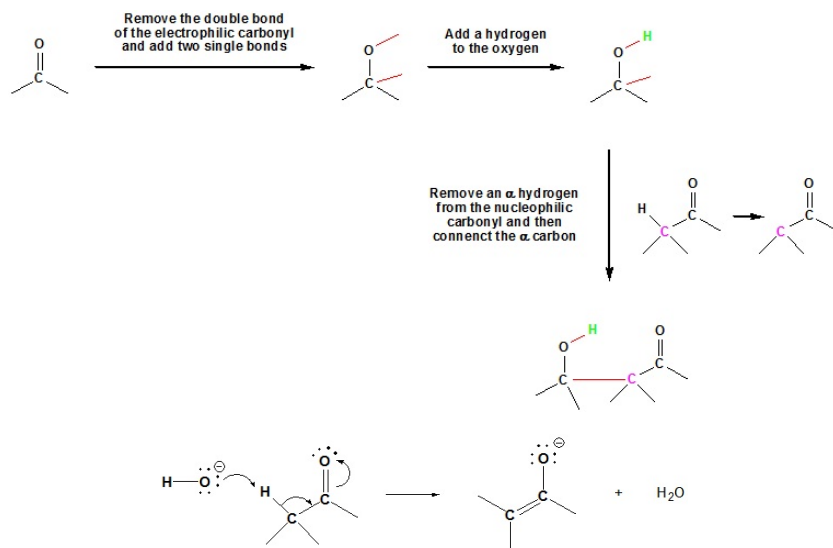
Stereochemical Ramifications of the Aldol Reaction

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.



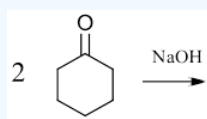


Going from reactants to products simply



? Worked Example

What would be the expected product of the following aldol reaction?



Answer

Analysis:

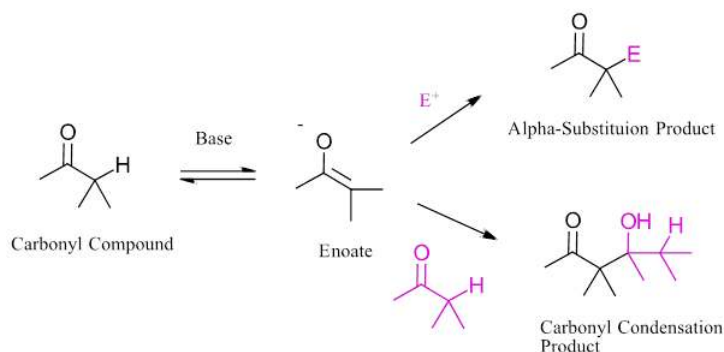
When considering the product of an aldol reaction it is vital to consider each reactant molecule separately. Also, Identify electrophilic carbonyl carbon and any alpha hydrogens present.

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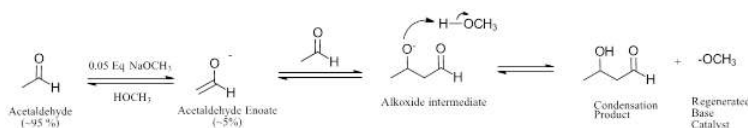
5.7: Carbonyl Condensations versus Alpha Substitutions

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 an 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 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.

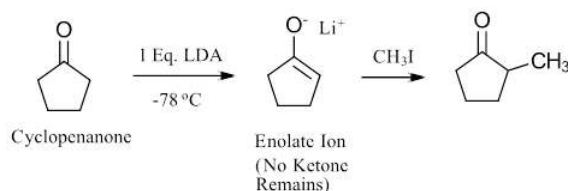
If acetaldehyde was reacted with 0.05 equivalents of sodium methoxide in a methanol solvent only a small amount (~5%) of the enolate would form. The majority of the acetaldehyde would be unchanged and capable of undergoing a condensation reaction with the enolate present. The alkoxide intermediate produced 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 22.7, 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 diisopropylamide (LDA) is added to the reactant at -78°C which completely converts cyclopentanone to the corresponding enolate ion. This leaves none of the ketone carbonyl remaining to undergo a condensation reaction. Methyl iodide is quickly added to react with enolate ion forming the alpha-alkylated product.



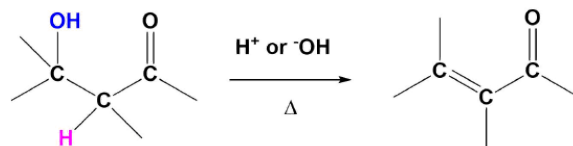
5.7: Carbonyl Condensations versus Alpha Substitutions is shared under a [CC BY-SA 4.0](#) license and was authored, remixed, and/or curated by Steven Farmer, Dietmar Kennepohl, Layne Morsch, & Layne Morsch.

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5.8: Dehydration of Aldol Products - Synthesis of Enones

Aldol Condensation

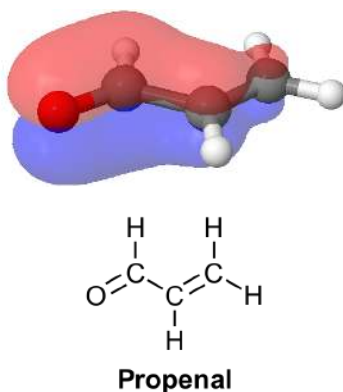
Reactions in which a larger molecule is formed from smaller components, with the elimination of a very small by-product such as water are termed Condensations. Hence the following examples are properly referred to as aldol condensations.



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 11-10) reaction is an α, β -unsaturated aldehyde or ketone (Enones). Although there may be multiple position where the alkene may form, it will always prefer to be in conjugation with the carbonyl.

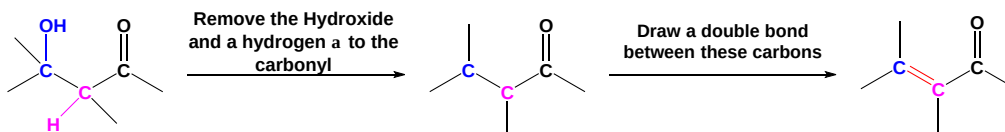
Conjugated enone products are more stable than non-conjugated due to extended P orbital overlap. Conjugation of the p electrons of the alkene and carbonyl bonds provide a molecular-orbital description showing the interaction of p electrons of all four atoms. The additional stability provided by the conjugated carbonyl system of the product makes many aldol reactions thermodynamically factorable.



A representation of pi bonding molecular orbitals of the conjugated enone, propenal, are delocalized through p-orbital overlap

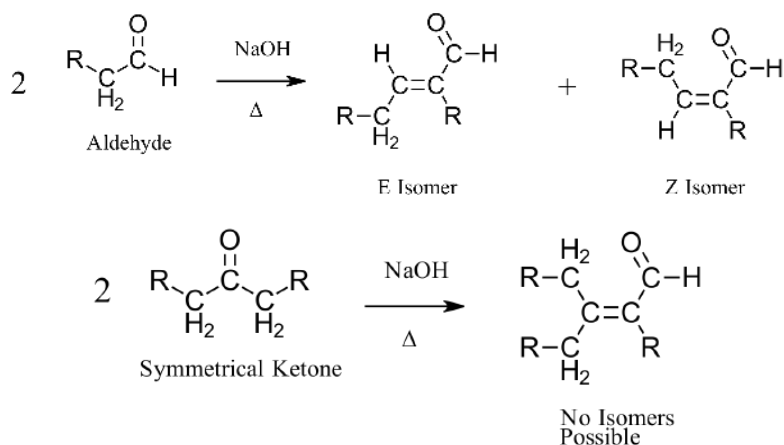
The elimination of water from the reaction mixture can be used to drive the equilibrium towards the products by Le Chatelier's principle. This coupled with the thermodynamic stability of the conjugated product allow for good reaction yields when the formation of the initial aldol intermediate is unfavorable (ketones & sterically hindered aldehydes).

Predicting the Product of an Enone Formation

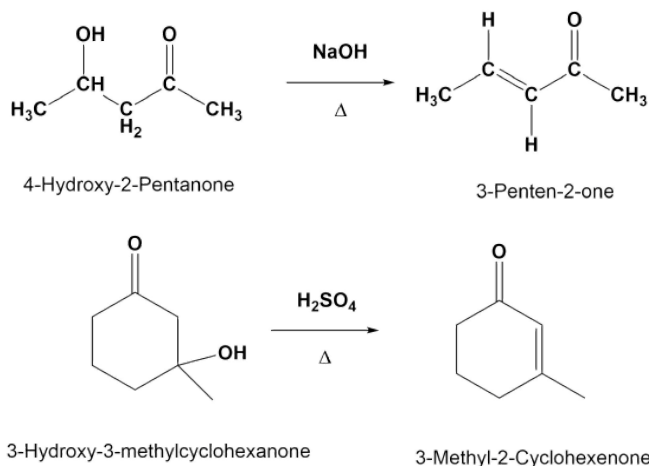


Stereochemical Considerations

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

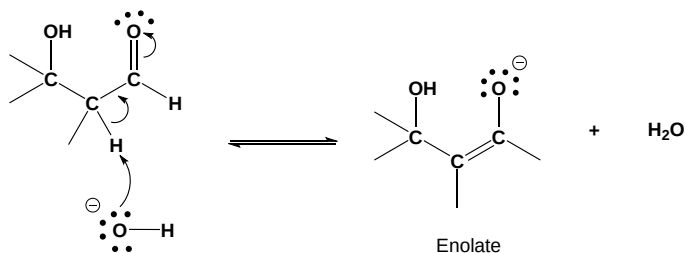


Mechanism

Base Catalyzed Mechanism

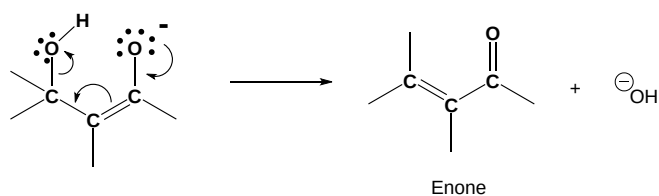
1) Form an enolate

The mechanism starts with the base removing an alpha-hydrogen to form an enolate ion.



2) Form the enone

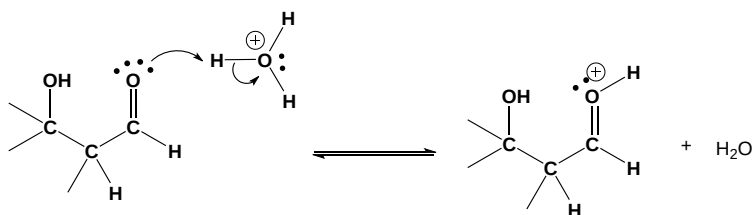
The alkoxide reforming the carbonyl C=O bond promotes the elimination of alcohol OH as a leaving group which reforms the base catalyst. Although the base catalyzed elimination of alcohols is rare, it happens in this case in part due to the stability of the conjugated enone product. This is an example of an E1CB reaction.



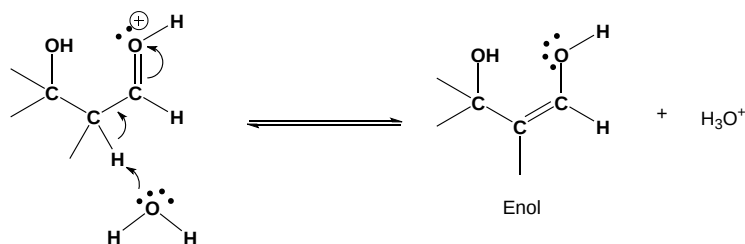
Acidic Conditions Mechanism

1) Protonation

The mechanism starts with the two step tautomerization process to form an enol.

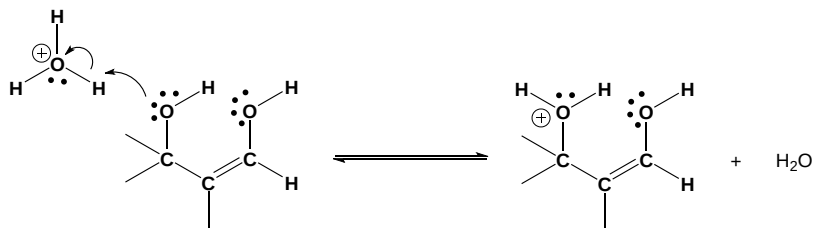


2) Form an enol



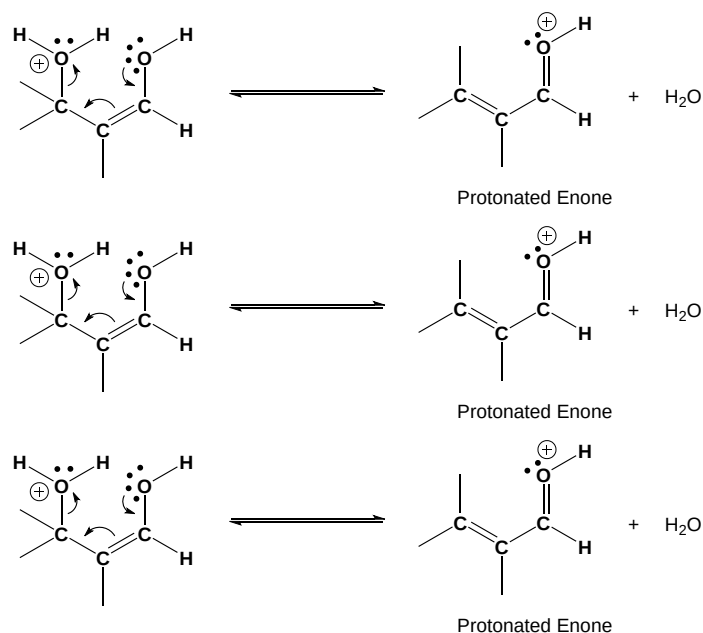
3) Protonation

Protonation of the alcohol OH increases its ability to act as a leaving group.



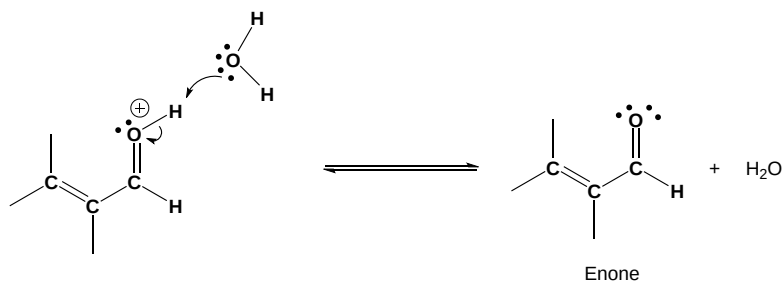
4) Elimination

Lone pair electrons from the enol reform the carbonyl $\text{C}=\text{O}$ bond and promoted the elimination of water as a leaving group.



5) Deprotonation

Deprotonation by water in the final step create the neutral enone product and regenerates the acid catalyst.

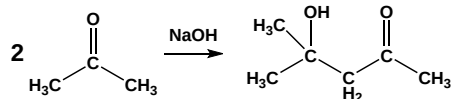


Aldol Condensation

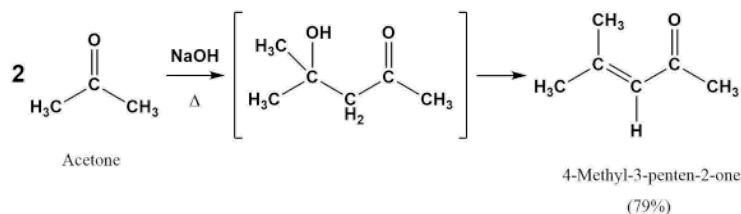
Whether an aldol reaction or an aldol condensation product is formed during a reaction largely depends on the reaction conditions. Typically, a reaction with a base at room temperature provides the aldol reaction product. However, if the reaction mixture is heated the aldol product is quickly converted into the aldol condensation product. If the condensation product is desired the aldol intermediate is usually not isolated.

Examples

Aldol Reaction

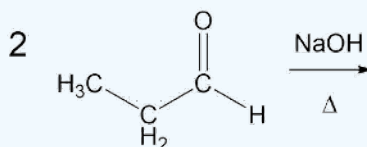


Aldol Condensation



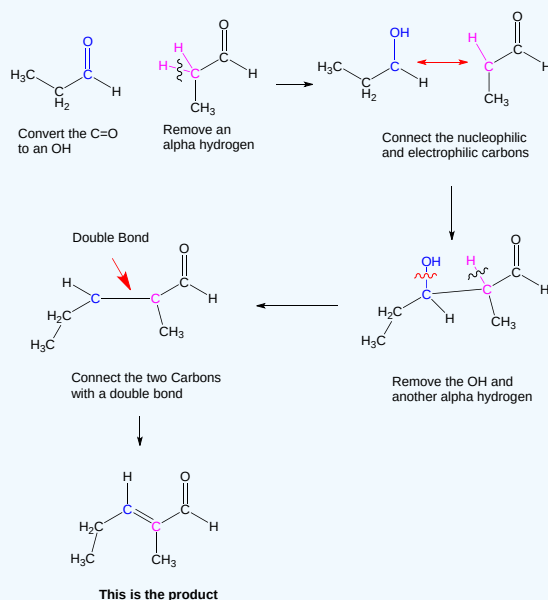
? Worked Example

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 23.3), then convert it to the enone. Note! The double bond always forms in conjugation with the carbonyl.



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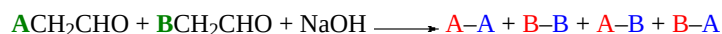
5.9: Mixed Aldol Reactions

Mixed Aldol Reaction and Condensations

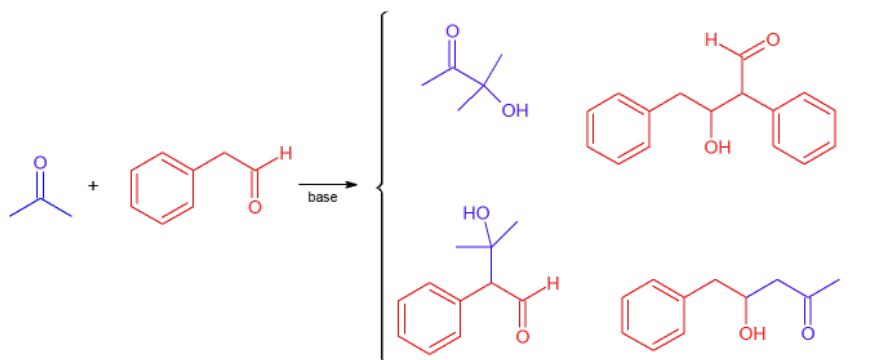
The previous examples of aldol reactions and condensations used a common reactant as both the enolate donor and the electrophilic acceptor. The product in such cases is always a dimer of the reactant carbonyl compound. Aldol condensations between different carbonyl reactants are called crossed or mixed 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 α -H's

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.



Products of a Uncontrolled Mixed Aldol Reaction

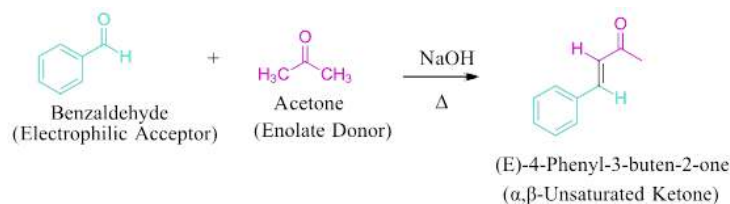


To avoid complex reaction mixtures the reactants should be chosen to favor one particular donor/acceptor reaction. Successful mixed aldol reactions usually use one of two combination of factors.

1) A reaction of an aldehyde with no α -hydrogens with a ketone that has α hydrogens: Aldehydes lacking α -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 enolate 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.

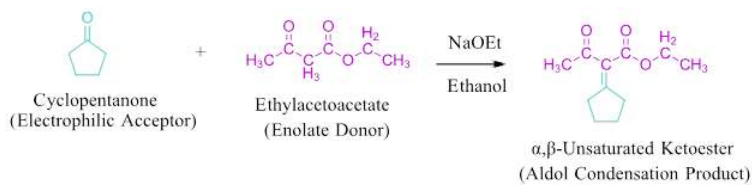
Example: Claisen-Schmidt Condensation



2) One of the reactants has α -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 (**Section 22.5**). 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



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5.10: Intramolecular Aldol Reactions

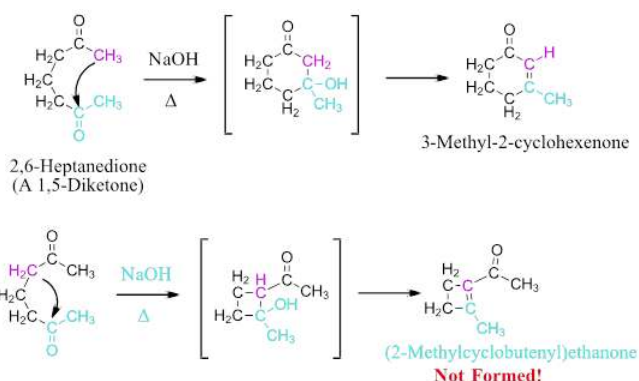
Intramolecular aldol reaction

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 (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.

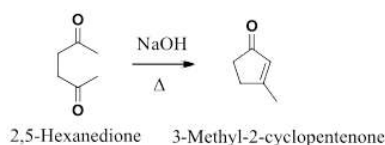
This product selectivity is possible due to all of the steps of the mechanism being reversibly, which tends to produce the most stable product. As with most ring forming reactions, five and six membered rings are preferred due to their relative lack of ring strain compared to other sized rings (See Sections 4.4 & 4.5). Once equilibrium is reached, the relatively strain free and therefore more thermodynamically stable, cyclohexanone product will be preferably formed.

Example



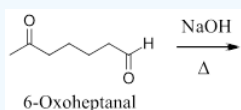
Similar analysis can be used to predict the products of other intramolecular aldol reactions. In a similar reaction, 1,4-diketones, such as 2,5-hexanedione, only form the five-membered ring product, ex. 3-methyl-2-cyclopentenone, without any of the possible cyclopropane product forming.

Example



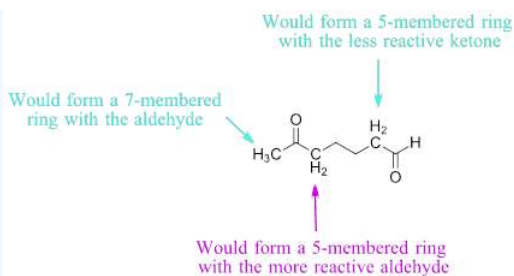
? Worked Example

Please draw the expected product of an intramolecular aldol condensation with the following molecule:

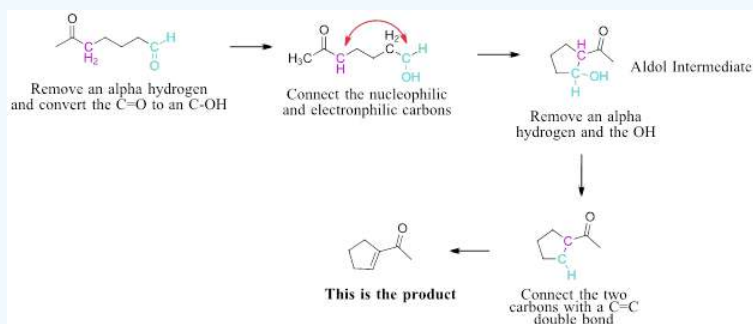


Answer

Analysis: 6-Oxoheptanal has three unique sets of α -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.

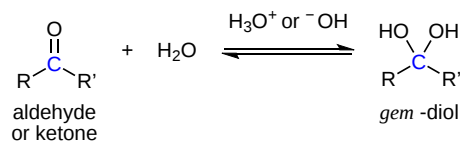


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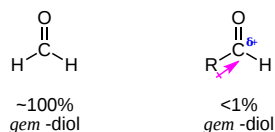
5.11: Nucleophilic Addition of Water- Hydration

It has been demonstrated that water, in the presence of an acid or a base, adds rapidly to the carbonyl group of aldehydes and ketones establishing a reversible equilibrium with a **hydrate** (geminal-diol, *gem*-diol, or 1,1-diol). The term hydrate implies the addition of water. The word geminal or abbreviation *gem* comes from the Latin word for twin, *geminus*.

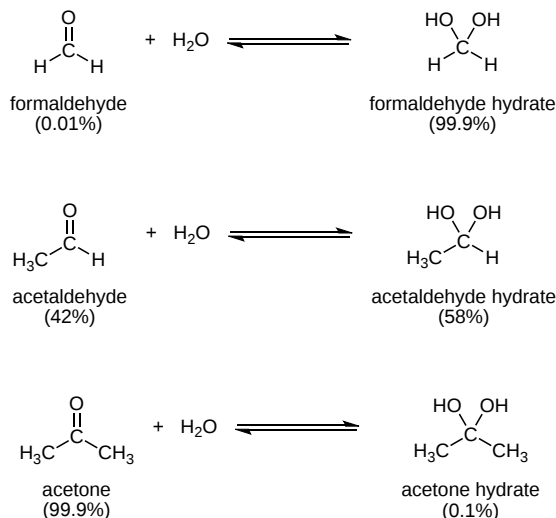


Factors Affecting the Hydrate Equilibrium

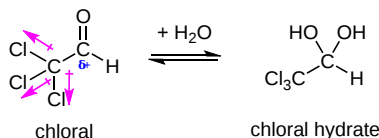
The equilibrium for hydrate formation depends both on steric and electrical factors of the carbonyl as discussed in the previous section. In most cases the resulting *gem*-diol is unstable relative to the reactants and cannot be isolated. Exceptions to this rule exist, one being formaldehyde where the small size of the hydrogen substituents relative to aldehydes and ketones favor hydrate formation. Thus, a solution of formaldehyde in water (formalin) is almost exclusively the hydrate, or polymers of the hydrate. The addition of electron donating alkyl groups stabilized the partial positive charge on the carbonyl carbon and decreases the amount of *gem*-diol product at equilibrium. Because of this ketones tend to form less than 1% of the hydrate at equilibrium.

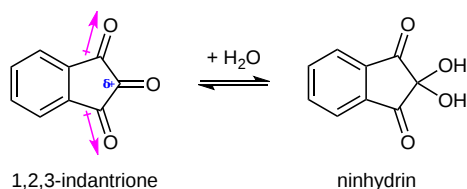


Equilibrium Distribution of Common Aldehydes and Ketones with their Hydrate Forms



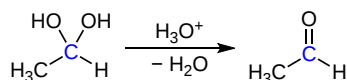
Likewise, the addition of strong electron-withdrawing groups destabilizes the carbonyl and tends to form stable hydrates. Two examples of this are chloral, and 1,2,3-indantrione. It should be noted that chloral hydrate is a sedative and has been added to alcoholic beverages to make a “knock-out” drink also called a Mickey Finn. Also, ninhydrin is commonly used by forensic investigators to reveal fingerprints.





Reversibility of Hydrate Formation

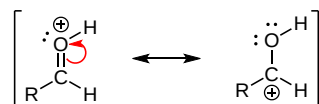
Isolation of hydrates is difficult because the reaction is reversible. Removal of water from the hydrate can cause the conversion of a gem-diol back to the corresponding carbonyl.



Acid or Base Catalyzed Hydrate Formation

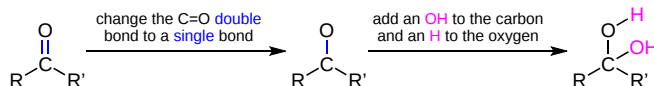
The nucleophilic addition of water to a carbonyl to form a hydrate is usually slow under neutral condition (pH = 7). The rate can be significantly increased through the addition of an acid or base as a catalyst.

The addition of an acid or base changes the mechanism and promote the nucleophilic addition of water to a carbonyl to form a hydrate. Basic conditions speed up the reaction because hydroxide is a better nucleophile than water. Acidic conditions speed up the reaction because the carbonyl becomes protonated. Protonation increases the polarity of the carbonyl bond which increase the partial positive charge on the carbon making it more electrophilic.

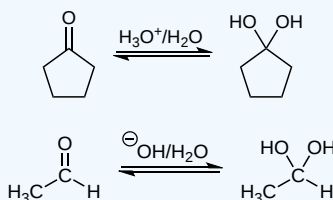


Predicting the Product of a Hydration

Overall, the C=O of the carbonyl in the starting material is removed and replaced by two single bonds both of which are attached to the original carbonyl carbon. Both of these single bonds are attached to OH groups in the product.



✓ Example 5.11.1



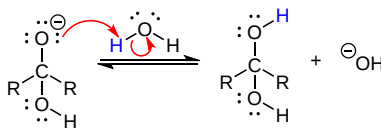
Mechanism of Acid or Base Catalyzed Hydrate Formation

Basic conditions

1) Basic conditions means there is a significant amount of hydroxide present. Hydroxide is a better nucleophile than water which speeds up the reaction. The negatively charged hydroxide forms a single bond with the electrophilic carbonyl carbon. This pushes the two electrons of the pi bond onto the electronegative oxygen forming an alkoxide ion intermediate.

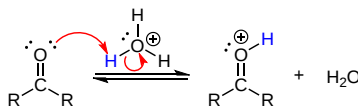


2) Water acts as an acid and protonates the alkoxide ion to form a neutral hydrate while also regenerating hydroxide. The fact that hydroxide is not being used during the reaction is consistent with it acting as a catalyst.

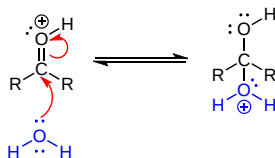


Acidic conditions

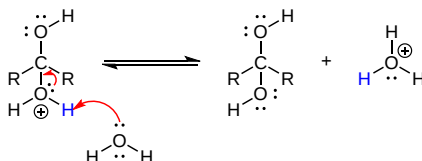
1) Acidic conditions means there is a significant amount of hydronium present. Hydronium protonates the carbonyl oxygen thereby making the carbonyl carbon more electrophilic. After protonation the oxygen becomes positively charged.



2) Under acidic conditions the most nucleophilic species is water. Water forms a single bond with the electrophilic carbon. This pushes the two electrons in the carbonyl pi bond onto the electronegative oxygen. The oxygen from the carbonyl becomes neutral while the oxygen from the water nucleophile becomes positively charged.



3) Water acts as a base and deprotonates the intermediate to produce the neutrally charged hydrate while regenerating hydronium. The fact that hydronium is not being used during the reaction is consistent with it acting as a catalyst.



Contributors and Attributions

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- Layne A. Morsch (University of Illinois Springfield)
- Dr. Krista Cunningham

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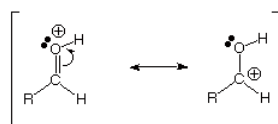
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5.12: Nucleophilic Addition of Alcohols- Acetal Formation

Introduction

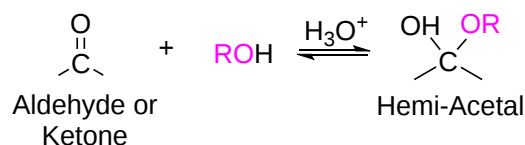
In this organic chemistry topic, we shall see how alcohols (R-OH) add to carbonyl groups. We already saw that water adds rapidly to the carbonyl function of aldehydes and ketones to form geminal-diols. In a similar reaction, one equivalent of an alcohol, in the presence of an acid catalyst, adds reversibly to aldehydes and ketones to form a hydroxy ether called a **hemiacetal** (R₂COHOR') (*hemi*, Greek, half). This reaction can continue by adding another equivalent of an alcohol to form a diether called an **acetal** R₂C(OR')₂. Hemiacetals and acetals are important functional groups because they appear in the structures of many sugars.

An acid catalyst must be used during this reaction because alcohols are weak nucleophiles and would add very slowly under neutral conditions. Under acidic conditions, the oxygen of the carbonyl becomes protonated, increasing the electrophilicity of the carbonyl carbon, speeding up the reaction.

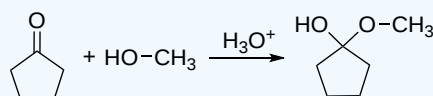


Also, it is common to actively remove the water created with the formation of an acetal by using molecular sieves or a **Dean-Stark trap**. This step is important, since acetal formation is reversible, and the removal of water pushes the equilibrium to the right by Le Chatelier's principle. Indeed, once pure hemiacetals or acetals are obtained, they may be hydrolyzed back to their starting components by treatment with aqueous acid and an excess of water.

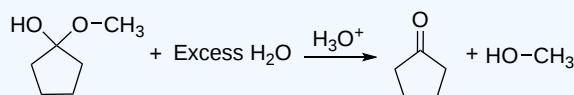
Formation of Hemiacetals



✓ Example 5.12.1: Formation of a Hemiacetal

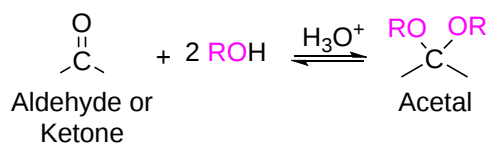


✓ Example 5.12.2: Hemiacetal Hydrolysis Reverting to the Ketone



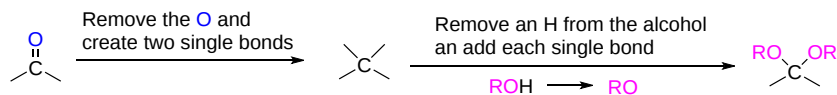
Formation of Acetals

Acetals are geminal-diether derivatives of aldehydes or ketones, formed by reaction with two equivalents (or an excess amount) of an alcohol and elimination of water. Ketone derivatives of this kind were once called ketals, but modern usage has dropped that term. It is important to note that a hemiacetal is formed as an intermediate during the formation of an acetal.

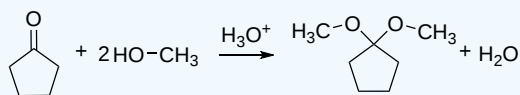


Predicting the Product of a Acetal Formation

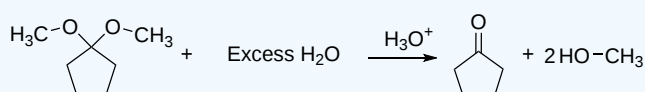
Overall, the carbonyl in the reactant is removed and replaced by two single bonds between oxygen and the original carbonyl carbon. Both of these single bonds are attached O-R groups produced after the reagent alcohol has lost a hydrogen.



✓ Example 5.12.3: Formation of Acetals



✓ Example 5.12.4: Acetal Hydrolysis Reverting to the Ketone

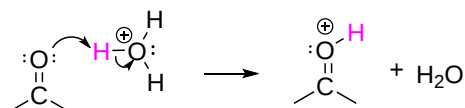


Mechanism for Hemiacetal and Acetal Formation

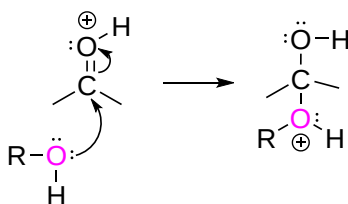
After protonation, an alcohol undergoes nucleophilic addition to the carbonyl group initially forming a hemiacetal upon deprotonation. Further protonation of the OH group in the hemiacetal allows for the elimination of water to form an oxonium ion. A second alcohol nucleophile adds to the oxonium ion to produce a protonated acetal. After deprotonation, the product acetal is formed.

The mechanism shown here applies to both acetal and hemiacetal formation.

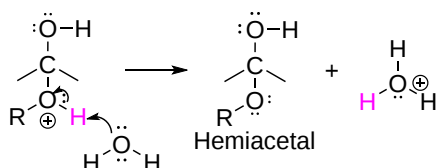
- 1) The acid catalyst protonates the carbonyl oxygen, making the carbonyl carbon more electrophilic.



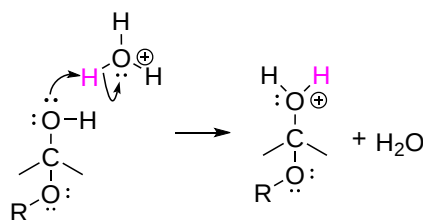
- 2) An alcohol undergoes nucleophilic addition to the carbonyl producing a protonated hemiacetal.



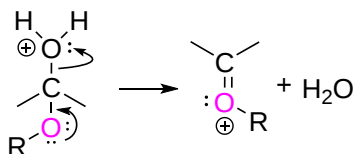
- 3) Water acts as base to cause a deprotonation creating a hemiacetal and hydronium.



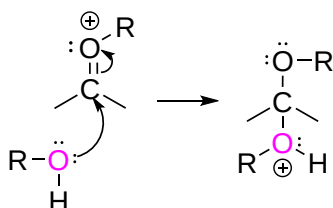
- 4) The OH group of the hemiacetal is protonated making it into a good leaving group.



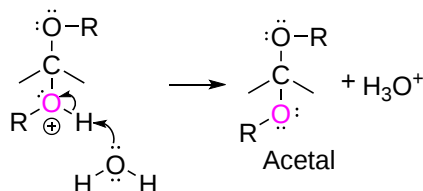
5) Lone pair electrons on the ether oxygen reforms the C=O bond causing the elimination of water and producing an oxonium ion.



6) A second alcohol undergoes nucleophilic addition to oxonium ion producing a protonated acetal.

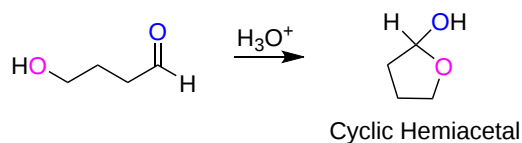


7) Water acts as a base and causes a deprotonation, creating the product acetal and hydronium.

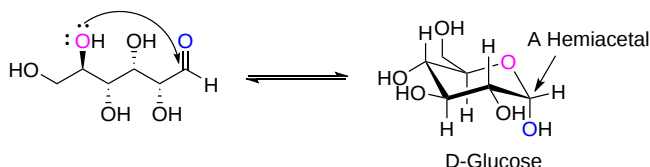


Biological Acetal and Hemiacetal Formation

Molecules which have both an alcohol and a carbonyl can undergo an intramolecular reaction to form a cyclic hemiacetal.



Because sugars often contain alcohol and carbonyl functional groups, intramolecular hemiacetal formation is common in carbohydrate chemistry. For example, the common sugar glucose exists in the cyclic manner more than 99% of the time in a mixture of aqueous solution.

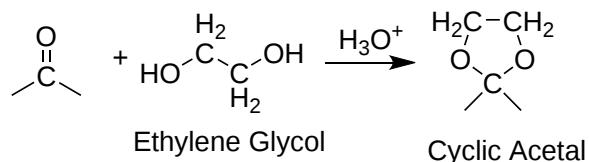


Conversion of D-Glucose to Beta-D-Glucopyranose (Cyclic Hemiacetal)

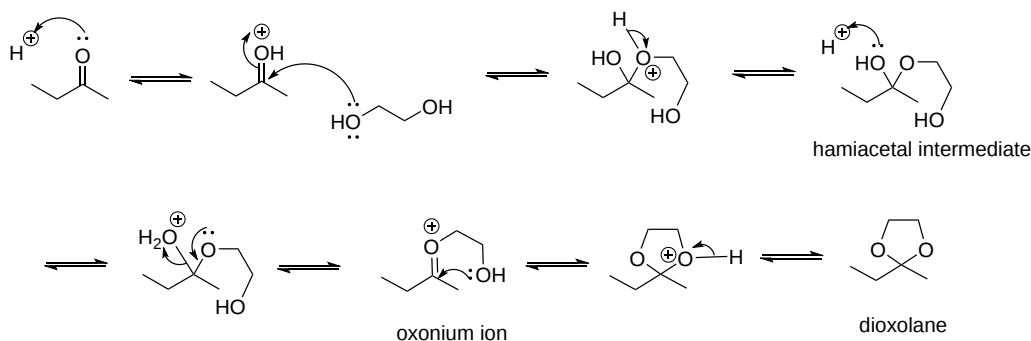
Acetals as Protecting Groups

The importance of acetals as carbonyl derivatives lies chiefly in their stability and lack of reactivity in neutral to strongly basic environments. As long as they are not treated by acids, especially aqueous acid, acetals exhibit all the lack of reactivity associated

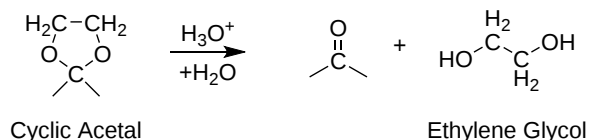
with ethers in general. Among the most useful and characteristic reactions of aldehydes and ketones is their reactivity toward strongly nucleophilic (and basic) metallo-hydride reagents (LiAlH_4 & NaBH_4), and organometallic reagents (RMgX & RLi). If the carbonyl functional group is converted to an acetal these powerful reagents have no effect; thus, acetals are excellent protective groups, when these irreversible addition reactions must be prevented. To accomplish this, it is common to use a diol such as ethylene glycol (rather than two equivalents of a simple alcohol) to form a cyclic acetal ring commonly called a dioxolane.



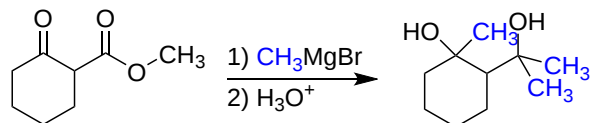
Because both OH groups are part of the same molecule, the second nucleophilic addition in the formation of the acetal is intramolecular and forms a ring. Cyclic acetals are more stable towards hydrolysis than acyclic ones and are also kinetically favored because the intramolecular ring-closing reaction is fast.

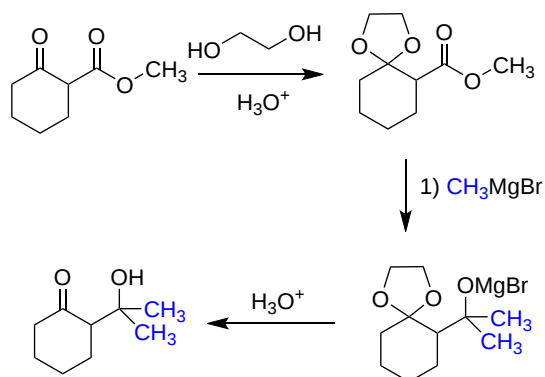


Once the addition reaction is accomplished (or whatever reaction required protecting the carbonyl), the reversibility of acetal formation can be used to reform the original carbonyl.



In the following example we would like a Grignard reagent to react with the ester and not the ketone. This cannot be done without a protecting group because Grignard reagents react with both esters and ketones with the ketone typically more reactive than the ester. This reaction sequence uses ethylene glycol to form the cyclic acetal protecting group for the ketone followed by reaction of the ester with a Grignard reagent. Once this reaction is complete, the acetal is hydrolyzed back to the ketone in the same step that reprotonates the alcohol (while eliminating the MgBr).





Contributors and Attributions

- Layne Morsch (University of Illinois Springfield)

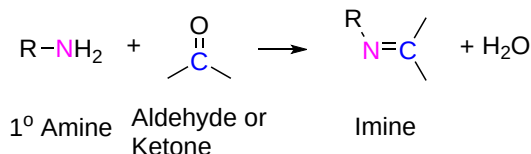
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5.13: Nucleophilic Addition of Amines- Imine and Enamine Formation

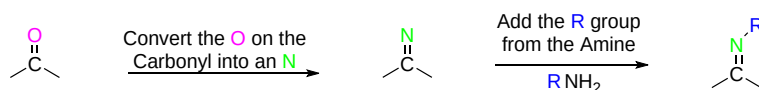
Reaction with Primary Amines to form Imines

The reaction of aldehydes and ketones with ammonia or 1°-amines forms imine derivatives, also known as Schiff bases (compounds having a C=N function). Water is eliminated in the reaction.

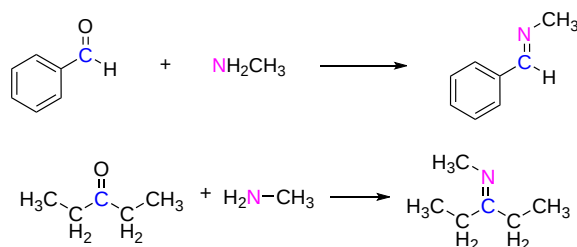


Predicting the Products of an Imine Forming Reaction

During imine formation, the carbonyl oxygen is completely removed. The nitrogen of the 1° amine reactant replaces the carbonyl oxygen to form the imine C=N bond. During the process the nitrogen of the 1° amine loses both of its hydrogens.



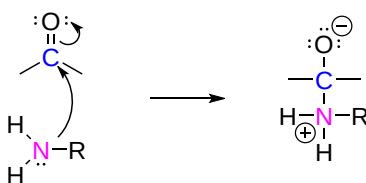
Examples of Imine Forming Reactions



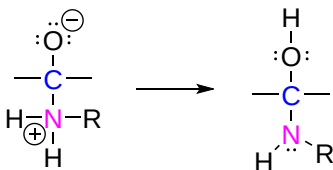
Mechanism of Imine Formation

Imine formation is a reversible process that starts with the nucleophilic addition of a primary amine to the carbonyl group of an aldehyde or ketone. Next, a proton transfer forms a neutral amino alcohol called a carbinolamine. Acid protonation of the carbinolamine oxygen converts it into a better leaving group which is subsequently eliminated as water producing an iminium ion. Deprotonation of nitrogen gives the final imine product.

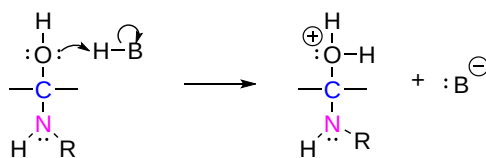
1) Nucleophilic addition



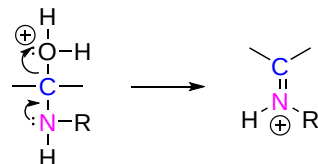
2) Proton transfer



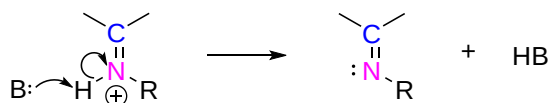
3) Protonation



4) Water is eliminated to form an iminium ion.

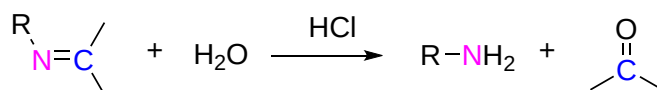


5) Deprotonation



Reversibility of Imine Forming Reactions

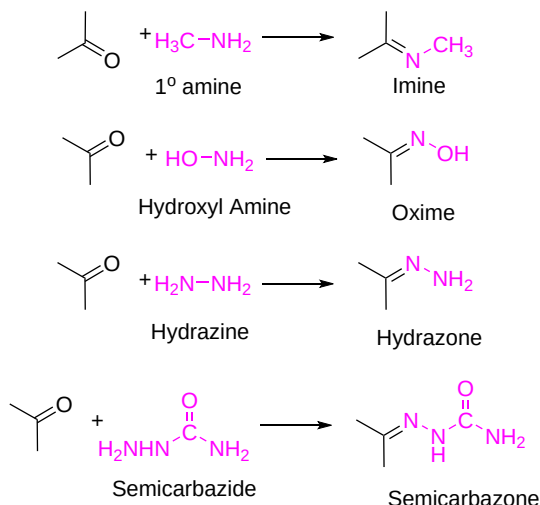
Imines can be hydrolyzed back to the corresponding 1° amine under acidic conditions.



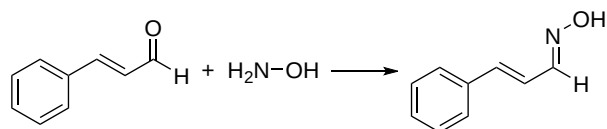
Reactions Involving other Reagents of the type Y-NH₂

A wide variety of substances with -NH₂ groups can react with aldehydes and ketones by an addition-elimination sequence to yield compounds with a carbon-nitrogen double bond. Imines are sometimes difficult to isolate and purify due to their sensitivity to hydrolysis. Consequently, other reagents of the type Y-NH₂ have been studied, and found to give stable products (R₂C=N-Y) useful in characterizing the aldehydes and ketones from which they are prepared. Some of these reagents are listed below, together with the structures and names of their carbonyl reaction products. Hydrazones are used as part of the Wolff-Kishner reduction and will be discussed in more detail in [Section 19.9](#).

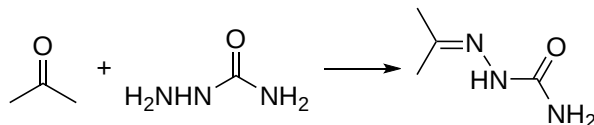
With the exception of unsubstituted hydrazones, these derivatives are easily prepared and are often crystalline solids - even when the parent aldehyde or ketone is a liquid. Since melting points can be determined more quickly and precisely than boiling points, derivatives such as these are useful for comparison and identification of carbonyl compounds. It should be noted that although semicarbazide has three nitrogen groups (-NH₂) only one of them is a reactive amine. The other two are similar to amides and are deactivated by resonance with the adjacent carbonyl group.



Example



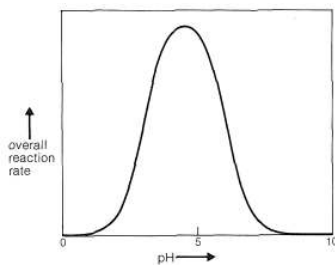
Cinnamaldehyde reacting with hydroxylamine to form cinnamaldehyde oxime



Acetone reacting with semicarbazide to form acetone semicarbazide

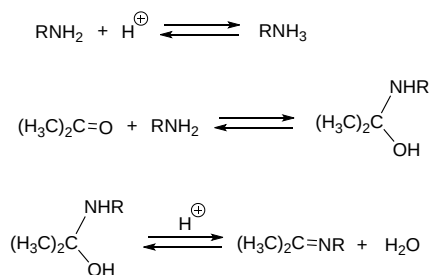
The pH Dependence of Imine Forming Reactions

The pH for reactions which form imine compounds must be carefully controlled. The rate at which these imine compounds are formed is generally greatest near a pH of 5, and drops at higher and lower pH's. At high pH there will not be enough acid to protonate the OH in the intermediate to allow for removal as H₂O. At low pH most of the amine reactant will be tied up as its ammonium conjugate acid and will become non-nucleophilic.



Schematic variation of the rate of condensation of RNH₂ with a carbonyl compound as a function of pH.

Clearly, if the unshared electron pair on the nitrogen of RNH₂ is combined with a proton it cannot attack the carbonyl carbon to give the aminoalkanol produced during the mechanism. So at high acid concentration (low pH) we expect the rate and the equilibrium for the overall reaction to be unfavorable.

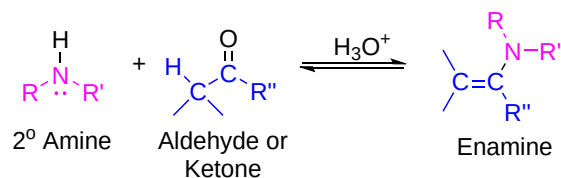


Dehydration of the aminoalkanol is acid catalyzed; this reaction normally is fast at pH values smaller than 3-4. As the pH is increased above 4, the dehydration step in the mechanism decreases in rate because it requires an acid catalyst. At pH 6 dehydration is the slow step of the mechanism, and at higher pH values it finally becomes too slow to give a useful overall rate of reaction.

Reaction with Secondary Amines to form Enamines

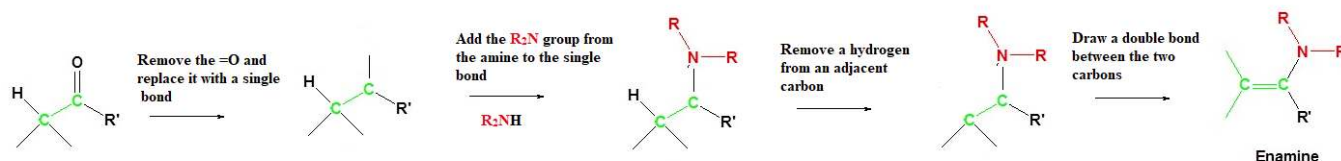
Most aldehydes and ketones react with 2°-amines to give products known as **enamines** (alkene + amine). It should be noted that, like acetal formation, these are acid-catalyzed reversible reactions in which water is lost. Secondary amines form a distinctly

different functional group after nucleophilic addition because they lack the second hydrogen on nitrogen required for imine formation. During this reaction a hydrogen is removed from an adjacent carbon forming a C=C bond.

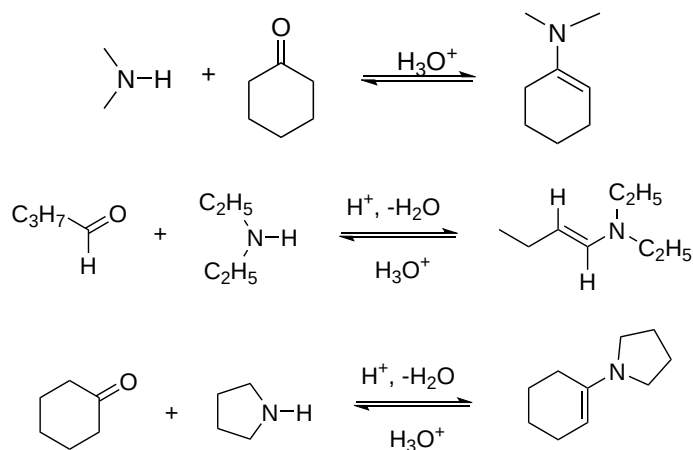


Predicting the Products of an Enamine Forming Reaction

During enamine formation the carbonyl oxygen is completely removed. The nitrogen of the amine reactant replaces the oxygen to form a N-C bond. During the process the amine loses its lone hydrogen. A hydrogen is removed from a carbon adjacent to the original carbonyl carbon forming a C=C between them.

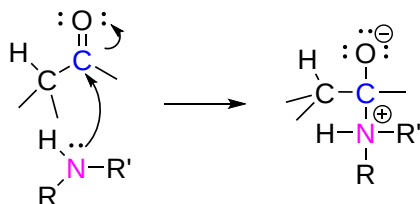


Example

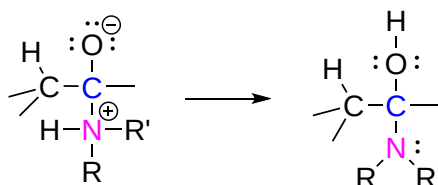


Mechanism

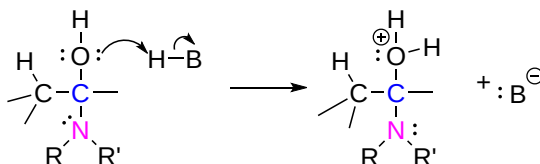
1) The secondary amine undergoes nucleophilic addition to form a neutral tetrahedral intermediate.



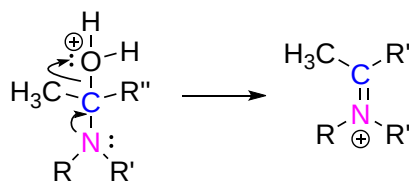
2) A proton is transferred from the ammonium ion moiety of the tetrahedral intermediate to the alkoxide ion moiety. This forms a neutral functional group called a carbinolamine.



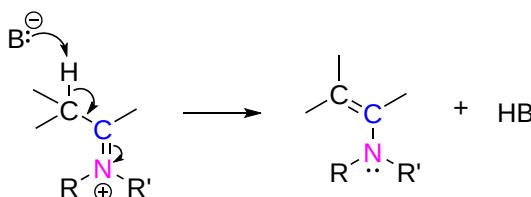
3) The OH group on the carbinolamine is protonated by hydronium turning it into a good leaving group.



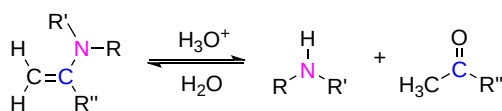
4) The lone pair electrons on the nitrogen form the C=N double bond causing water to be eliminated. This forms an iminium ion



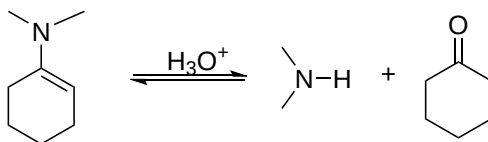
5) Water (or a base) removes a hydrogen from an adjacent carbon to form an alkene bond. This pushes two electrons from the C=N double bond onto the positively charged nitrogen creating the neutral enamine product and hydronium (or BH).



Reversibility of Enamines



Example



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CHAPTER OVERVIEW

6: Carboxylic Acid Derivatives

The compounds discussed in this chapter are all considered to be derived from carboxylic acids, and include acid halides, acid anhydrides, esters and amides (thioesters and acyl phosphates are also briefly mentioned). As you proceed through the chapter, you should be looking for similarities in behaviour among the various classes of compounds. These similarities can be readily understood once you appreciate the fact that, in most of their reactions, carboxylic acid derivatives react via the nucleophilic acyl substitution mechanism.

[6.1: Nucleophilic Acyl Substitution Reactions](#)

[6.2: Nucleophilic Acyl Substitution Reactions of Carboxylic Acids](#)

[6.3: The Claisen Condensation Reaction](#)

[6.4: Mixed Claisen Condensations](#)

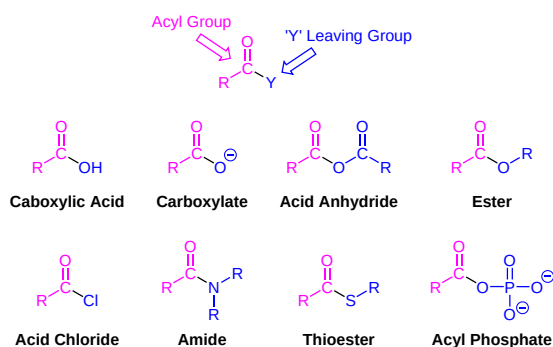
[6.5: Intramolecular Claisen Condensations - The Dieckmann Cyclization](#)

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6.1: Nucleophilic Acyl Substitution Reactions

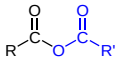
Carboxylic acid derivatives and acyl groups

Carboxylic acid derivatives can be distinguished from aldehydes and ketones by the presence of a group containing an electronegative heteroatom - usually oxygen, nitrogen, sulfur or phosphorus - bonded directly to the carbonyl carbon and represented by the symbol **Y**. The rest of the carboxylic acid derivative is called the **acyl group** which is made up of the carbonyl group and the attached alkyl group (R). Being electronegative, the Y group has the potential of receiving electrons from the alkoxide intermediate created during a nucleophilic acyl substitution and acting as a leaving group. Elimination of a leaving group allows for carbonyl bond reformation and C-Y bond cleavage to complete a substitution reaction.



The stability of a negative charge on a Y group can be gauged by the pK_a of its corresponding conjugate acid (HY). A low conjugate acid pK_a implies that the Y leaving group is a weak base with a stable negative charge and thus would make an efficient leaving group. Likewise, a high conjugate acid pK_a means the Y group would likely make a poor leaving group. As shown in the table below, the conjugate acids of the possible carbide ($R:^-$) and hydride ($H:^-$) leaving groups of aldehydes and ketones have a relatively high pK_a , while those of the Y leaving groups of carboxylic acid derivatives are much lower. In fact, the stability of the leaving groups is an important factor in determining the reactivity of different carboxylic acid derivatives toward nucleophilic acyl substitutions. Based on the pK_a data we can deduce that amides will most likely be the least reactive of the carboxylic acid derivatives.

Carbonyl Compounds and their Leaving Groups

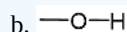
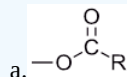
Name	Carbonyl Compound	Leaving Group	Conjugate Acid of the Leaving Group	pK_a
Acid Chloride		Cl^-	H-Cl	-7
Acid Anhydride				3-5
Ester		$^-OR'$	H-OR'	15-16
Carboxylic Acid		^-OH	H-OH	15.7
Amide		$^-NH_2$	H-NH ₂	36
Ketone		$^-R'$	H-R'	50
Aldehyde		^-H	H-H	Very Large

✓ Example 21.2.1

What is the 'Y' group in:

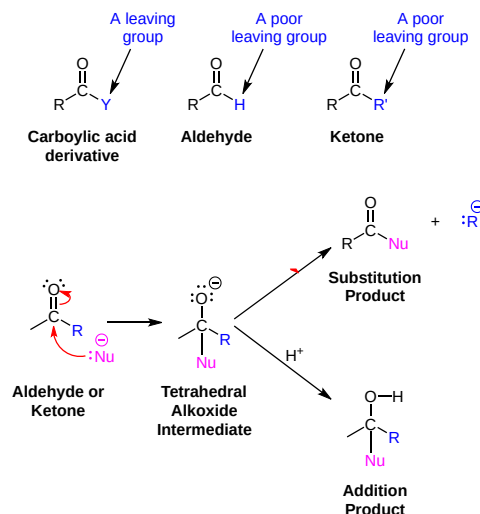
- an acid anhydride?
- a carboxylic acid?

Answers

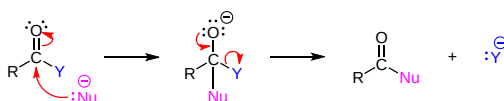


The Mechanism of Nucleophilic Acyl Substitution

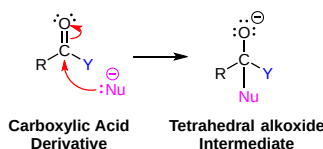
Aldehydes and ketones, along with carboxylic acid derivatives all have the C=O carbonyl bond in common. Thus, the electrophilic character of the carbonyl carbon plays an important part in the reactivity of all of these compounds. Because the carbonyl carbon of aldehydes and ketones do not contain suitable leaving groups, their primary reaction is fundamentally different than carboxylic acid derivatives. Remember that aldehydes and ketones tend to undergo nucleophilic addition to form a tetrahedral alkoxide intermediate. Once formed, the negative charge of the alkoxide intermediate cannot be transferred to other substituents because the potential carbide (R^-) and hydride (H^-) leaving groups are too unstable. Instead the negative charge is held by the alkoxide until protonation converts it into an alcohol.



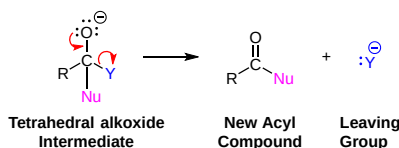
Carboxylic acid derivatives tend to undergo a reaction called nucleophilic acyl substitution. In the same fashion as nucleophilic addition, this mechanism starts with a nucleophilic attack on an electrophilic carbonyl carbon, forming a tetrahedral alkoxide intermediate. The alkoxide negative charge can gain stability by being transferred to the Y leaving group. Elimination of the Y leaving group in the second mechanistic step, allows the C=O carbonyl bond to reform thus creating a new acyl compound. The reaction is considered a substitution due to the Y group of the carboxylic acid derivative being exchanged with an incoming nucleophile.



1) Nucleophilic Addition



2) Leaving Group Removal

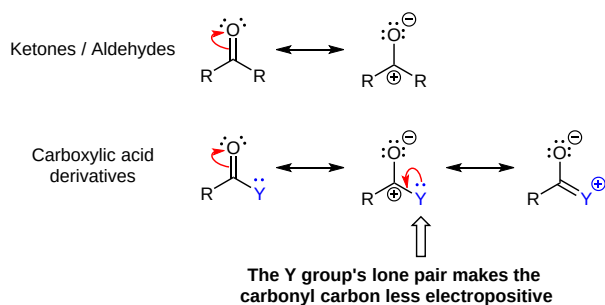


The Relative Reactivity of Carboxylic Acid Derivatives

The relative reactivity of carboxylic acid derivatives is an important concept for entering into a detailed examination of nucleophilic acyl substitutions. There are two main concepts directly relating to the mechanism which when combined lead to an overall explanation of the differences in reactivity: the stability of the carbonyl and the effectiveness of the Y leaving group.

Carbonyl Stability

The rate of the first mechanistic step is mainly affected by the stability of the carbonyl moiety. Stabilization reduces the electrophilic character of the carbonyl carbon by reducing its partial positive charge which in turn reduces the rate of this step of the mechanism. The ability of substituents attached to the carbonyl carbon to donate or withdraw electron density is the primary factor determining carbonyl stabilization. As previously discussed, the presence of two electron donating alkyl substituents reduces the partial positive charge on the carbonyl carbon of ketones making them less reactive to nucleophilic attack than aldehydes. The Y group heteroatom's ability to stabilize a carbonyl by donating electrons through resonance makes most carboxylic acid derivatives even less reactive. Overall, delocalization of the carbonyl carbon's partial positive charge onto the adjacent Y group heteroatom reduces the electrophilic character of the carbonyl. The electronegativity of the Y group heteroatom generally determines extent of this stabilization. The less electronegative the Y group heteroatom the better it is able to stabilize the resonance structure with the delocalized positive charge reducing the carbonyl's electrophilicity.

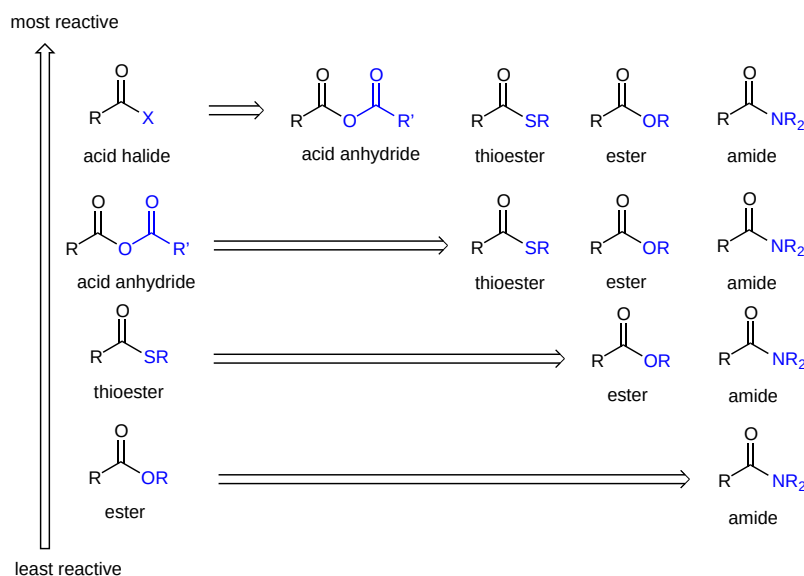


Leaving Group Ability

The leaving group ability of the Y group is the most important factor in determining the rate of the second mechanistic step of nucleophilic acyl substitution. As discussed above, the effectiveness of a leaving group is related to its ability to stabilize a negative charge particularly through having a relatively high electronegativity or having the ability to delocalize the negative charge through resonance. The Y group structural features which allow for the stabilization of a negative charge also allow for the stabilization of the transition state of the second step of the mechanism. Overall, the better the leaving group ability of the Y group, the higher the rate of second step of the mechanism.

These two effects, carbonyl stability and leaving group ability, when combined predict the relative reactivity of carboxylic acid derivatives. Fortunately, the effects tend to work synergistically. Y groups that are effective leaving groups also tend to poorly stabilize carbonyls through resonance making reaction rates of nucleophilic acyl substitution higher. Likewise, poor leaving groups tend to effectively stabilize carbonyls through resonance and reduce reaction rates. In fact, depending on the carbonyl structure, either step one or step two of the mechanism can be the rate determining step. For Y groups with a poor leaving group ability, the second step of the mechanism is rate determining because of the weakly stabilized transition state. The first step of the mechanism is rate determining for Y groups with good leaving group ability because they tend to stabilize the starting material's carbonyl increasing the energy distance to the first transition state.

chapter, highly reactive acid chlorides, when combined with the appropriate nucleophile, can be directly converting into acid anhydrides, thioester, esters, and amides. However, the less reactive amides cannot be directly converted into ester, thioester, anhydrides, or acid chlorides. It is possible to make these conversions with an amide but multiple reaction steps are required.



The nucleophiles required to make the conversion from one carboxylic acid derivative to another are common and have been discussed multiple times in this text. Because the same nucleophile is typically used to convert to a specific carboxylic acid derivative conversion, the reactions are given generic names.

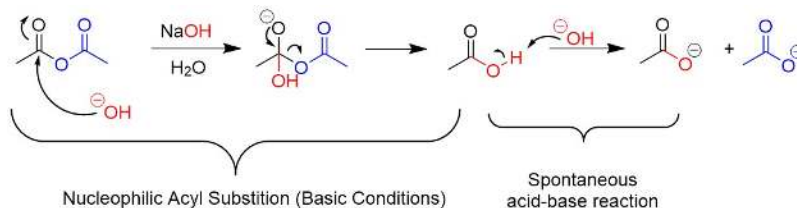
- **Hydrolysis:** A reaction with water as a nucleophile to create a carboxylic acid.
- **Alcoholysis:** A reaction with an alcohol nucleophile to create an ester.
- **Aminolysis:** A reaction with ammonia or an amine nucleophile to create an amide.
- **Reduction:** A reaction with a hydride nucleophile to create an aldehyde or 1° alcohol.
- **Organometallic:** A reaction with a carbanion nucleophile from an organometallic reagent to create a ketone or a 3° alcohol.

Predicting the Product of a Nucleophilic Acyl Substitution Reaction

There are two major pieces of a nucleophilic acyl substitution reaction which need to be identified in order to predict the product: the leaving group of the carboxylic acid derivative (Y) and the nucleophile. It is important to identify if the nucleophile is neutral (i.e. water, alcohols, ammonia, amines) or negatively charged (i.e. hydroxide, alkoxides, hydrides, carbanions). Also, it is important to note that certain hydride and organometallic reagents are capable of a double addition to carboxylic acid derivatives where the first step is a nucleophilic acyl substitution and the second is a nucleophilic addition.

Negatively Charged Nucleophiles

Negatively charged nucleophiles typically perform a Nucleophilic Acyl Substitution reaction under basic conditions. For example, consider the spontaneous hydrolysis reaction for an anhydride electrophile:

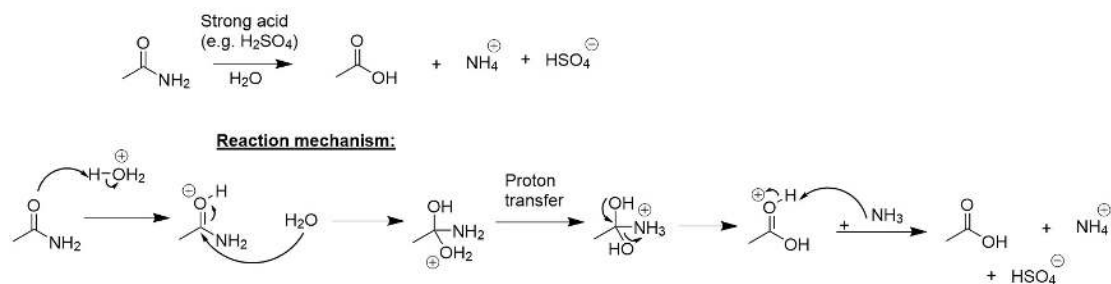


Note that in the reaction drawn above, the product of the Nucleophilic Acyl Substitution reaction (the hydrolysis) also undergoes a spontaneous acid-base reaction with the hydroxide in solution.

Neutral Nucleophiles

Neutral nucleophiles typically perform a Nucleophilic Acyl Substitution reaction under acidic conditions. Under acidic conditions, the H^+ will activate the carbonyl to make it a much better electrophile. For example, consider the spontaneous hydrolysis of an

amide under acidic conditions:



Note that, again, a spontaneous acid-base reaction is the final step (in this case, deprotonation using the amine produced in the NAS reaction). Also note that in the reaction drawn above, the less reactive amide is transformed into a more reactive carboxylic acid. This seemingly non-spontaneous reaction (based on Leaving Group ability) is made spontaneous by the presence of a large excess of water (typically used as the solvent in this reaction). Driving this reaction to completion through use of a large excess of one reagent (water) is an example of Le Chatelier's principle.

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6.2: Nucleophilic Acyl Substitution Reactions of Carboxylic Acids

The poor leaving group ability of -OH makes carboxylic acids relatively unreactive towards nucleophilic acyl substitutions. The addition of a strong acid protonates the carbonyl oxygen making the carbonyl carbon more electrophilic and circumventing this problem. Also, the substitution reaction can be promoted by converting -OH into a better leaving group. Despite the lack of reactivity, under the right conditions carboxylic acids can be successfully converted into acid chlorides, acid anhydrides, esters, and amides through nucleophilic acyl substitution.

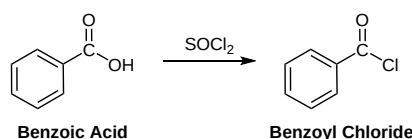
Conversion of Carboxylic acids to Acid Chlorides

Carboxylic acids can be converted to acid chlorides by reaction with thionyl chloride (SOCl_2). During the reaction with thionyl chloride, the hydroxyl group of the carboxylic acid is converted to an acyl chlorosulfite moiety which is a better leaving group. During the reaction a nucleophilic chloride anion is produced which reacts with the acyl chlorosulfite intermediate through nucleophilic acyl substitution to produce an acid halide.

General Reaction



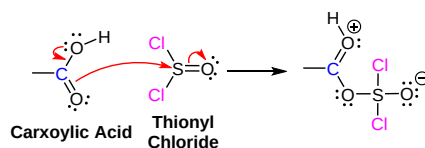
Example



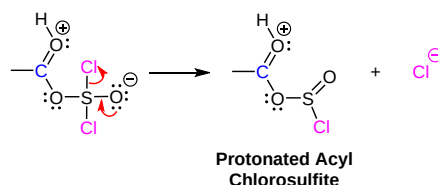
Mechanism

The O=S-Cl bonds of thionyl chloride are analogous to the O=C-Cl bonds of an acid halide in that they can undergo a type of nucleophilic acyl substitution. During the first step of the mechanism, the carboxylic acid reactant acts as a nucleophile and attacks the electrophilic sulfur of thionyl chloride, pushing the pi electrons of the S=O bond onto oxygen. Reforming the S=O bond and eliminating a chloride anion (Cl^-) as a leaving group creates a protonated acyl chlorosulfite. The chlorosulfite group represents an excellent leaving group due to its ability to stabilize a negative charge. The carbonyl of the protonated acyl chlorosulfite intermediate is activated to nucleophilic attack, and promptly reacts with the nucleophilic chloride anion created during the second step of the mechanism to produce a tetrahedral alkoide intermediate. Subsequent reforming of the protonated carbonyl bond eliminates the chlorosulfite group as sulfurdioxide (SO_2) and a chloride anion. Lastly, the chloride anion deprotonates the carbonyl to form the acid chloride product.

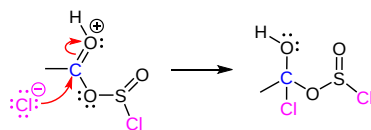
1) Nucleophilic attack on S=O bond



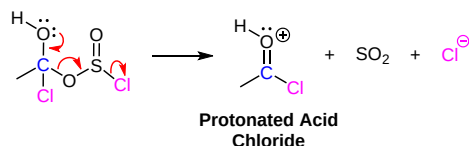
2) Removal of Cl leaving group



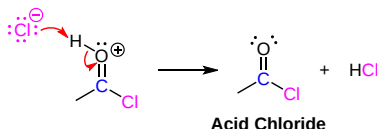
3) Nucleophilic attack on the carbonyl



4) Leaving group removal



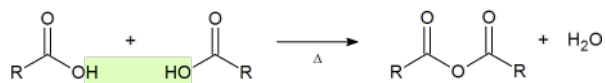
5) Deprotonation



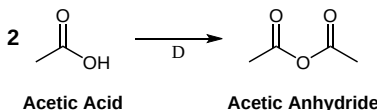
Acid Anhydride Formation

An acid anhydride (or just anhydride) is the product of condensation of two carboxylic acid molecules with the release of a water molecule. The most common anhydride in organic chemistry is acetic anhydride, due to the high temperatures needed to remove water.

General Reaction



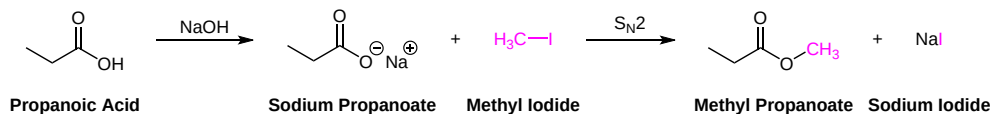
Example



Conversion of Carboxylic Acids into Esters by Alkylation

Carboxylic acids can be easily converted into their conjugate bases through deprotonation with a base, such as sodium hydroxide. The resulting carboxylate can be alkylated using by an S_N2 reaction with either a methyl or primary halide. If a methyl ester is required, methyl iodide (CH_3I) is a commonly used reagent.

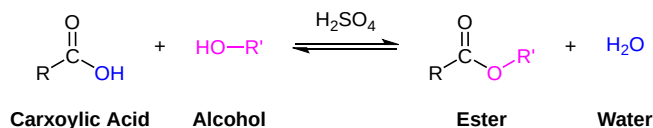
Example



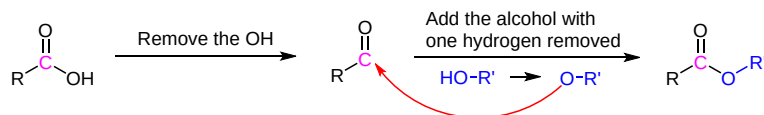
Conversion of Carboxylic Acids to Esters: The Fischer Esterification

Alcohols can be used as nucleophiles to convert carboxylic acids to esters. Due to the poor leaving group ability of $-\text{OH}$ in carboxylic acids, an acid catalyst is required to speed up the reaction. Usually the alcohol starting material is used as the reaction solvent so that it can be present in a large excess. This helps to increase the reaction's yield by pushing reaction equilibrium to the right which can be understood via Le Chatelier's principle.

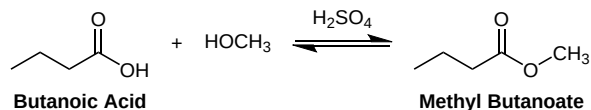
General Reaction



Predicting the Products of a Fischer Esterification



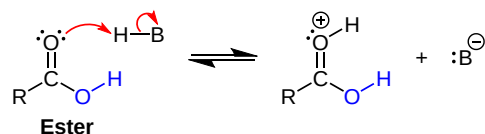
Example



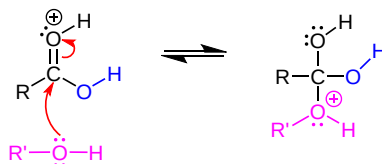
Mechanism

The mechanism begins with protonation of the carbonyl to increase its electrophilic character. A tetrahedral alkoxide intermediate is formed when the alcohol nucleophile adds to the protonated carbonyl, pushing the carbonyl pi electrons onto the oxygen. A different tetrahedral alkoxide intermediate is created when a proton is then transferred to one of the hydroxides (OH), turning it into a good leaving group. Reforming the protonated carbonyl bond then eliminates water as a leaving group. Finally, deprotonation of the carbonyl by water creates the ester product and regenerates the acid catalyst. All the steps of the mechanism are reversible

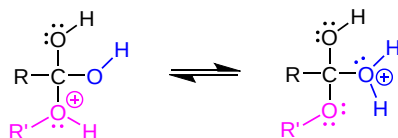
1) Protonation of the carbonyl



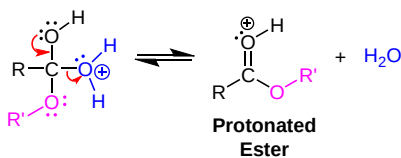
2) Nucleophilic attack on the carbonyl



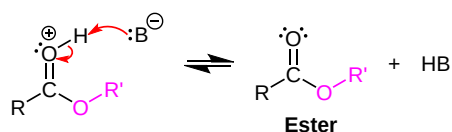
3) Proton transfer



4) Removal of water as a leaving group

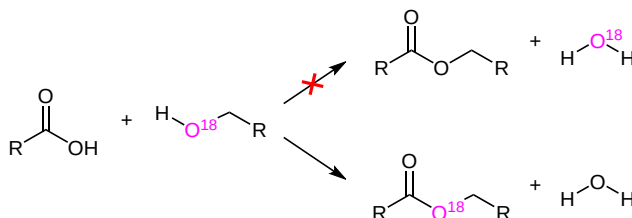


5) Deprotonation



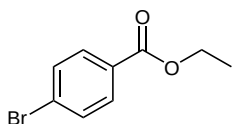
Isotopic Labeling

Evidence to support the Fischer esterification mechanism comes from isotopic labeling experiments with oxygen-18. If the reaction is carried out with an oxygen-18 labeled alcohol, the isotope is found exclusively in the ester and not the water generated. This shows that the C-OH bond of the carboxylic acid and the H-OR bond of the alcohol that is broken during the reaction.

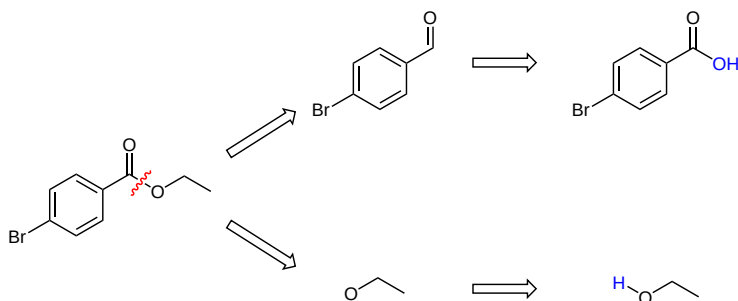


Worked Example: Planning a Synthesis Using a Fischer Esterification

How could the following molecule be made using a Fischer Esterification?

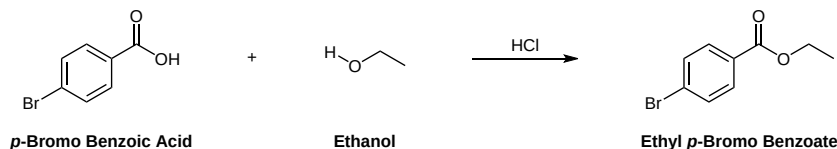


Analysis



The key bond formed during a Fischer Esterification is the C-O sigma bond. The target molecule can be separated into the two required starting materials by breaking this bond. The carbonyl carbon fragment gains an -OH to become a carboxylic acid and the oxygen fragment gains an H to become an alcohol. The carboxylic acid and the alcohol are reacted using a strong acid catalyst.

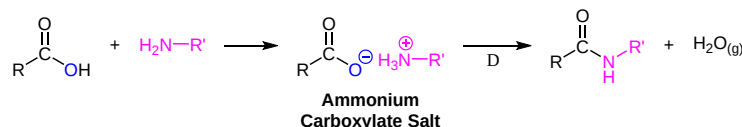
Solution



Direct Conversion of Carboxylic Acids to Amides

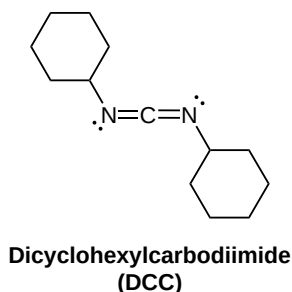
The direct reaction of a carboxylic acid with an amine would be expected to be difficult because the basic amine would deprotonate the carboxylic acid to form a stable carboxylate salt. However when the ammonium carboxylate salt is heated to a temperature above 100 °C, water is driven off and an amide is formed. Due to the extreme conditions, this reaction is rarely used. When converting to an amide it is preferred to convert the carboxylic acid to a more reactive form such as an acid chloride first and then convert this molecule to an amide.

General Reaction



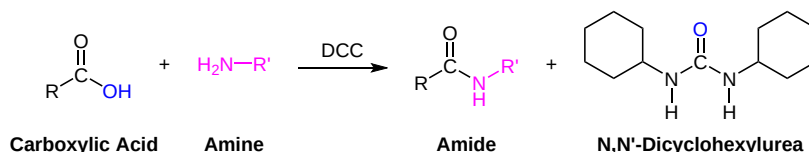
Conversion of Carboxylic Acids to Amides using DCC

The formation of amides from carboxylic acids and amines is a reaction of great importance in biochemistry. Proteins are formed through the creating of amide bonds between amino acid residues, so a great deal of research has been performed to find efficient methods. The direct conversion of a carboxylic acid to amides is difficult because amines are basic and tend to convert carboxylic acids to their highly unreactive carboxylates. One solution to this problem is through the use of dialkylcarbodiimides ($\text{R}-\text{N}=\text{C}=\text{N}-\text{R}$) coupling reagents, such as dicyclohexylcarbodiimide (DCC).

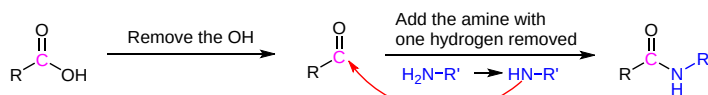


During a DCC amide coupling, the OH of a carboxylic acid is made into a good leaving group which can then be replaced by an amine during nucleophilic acyl substitution. Using DCC as a coupling reagent, 1° and 2° amines can be used to create 2° and 3° amides respectfully.

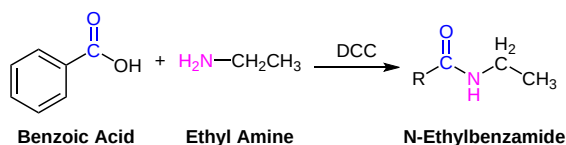
Basic reaction



Predicting the products of DCC Coupling



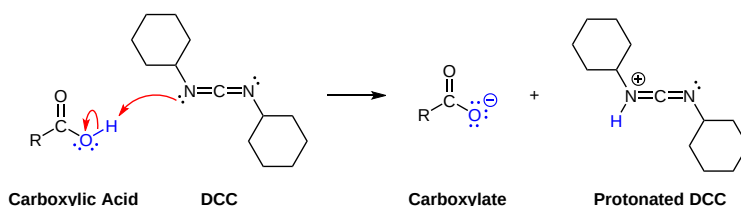
Example



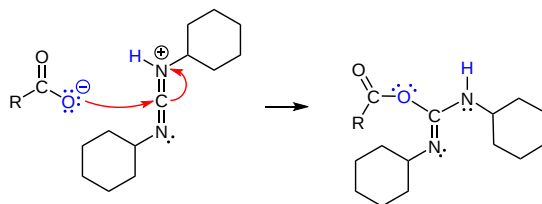
Mechanism

DCC deprotonates the carboxylic acid to form a carboxylate, which is a better nucleophile. The corresponding protonation of DCC increases the electrophilic character of its $\text{C}=\text{N}$ imide bond. The carboxylate nucleophile then adds to the imide bond and pushes the $\text{C}=\text{N}$ pi electrons onto the nitrogen. The amine nucleophile can now add itself to the carbonyl bond as part of a nucleophilic acyl substitution. The DCC coupled oxygen is eliminated as dicyclohexylurea, a good leaving group, to create the amide product.

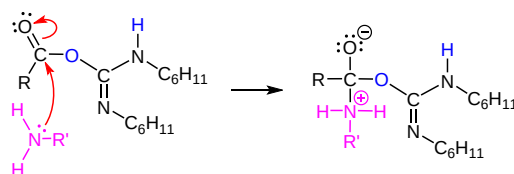
1) Deprotonation



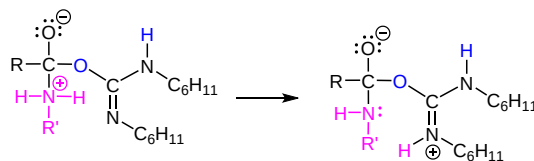
2) Nucleophilic attack by the carboxylate



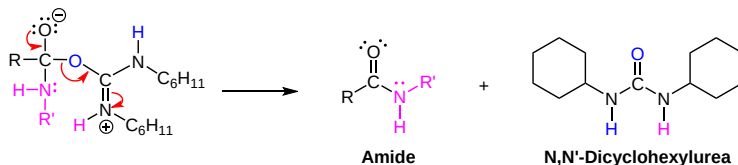
3) Nucleophilic attack by the amine



4) Proton transfer



5) Leaving group removal

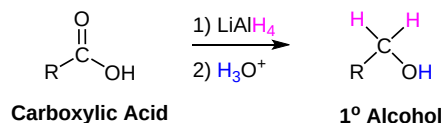


Conversion of Carboxylic acids to 1° alcohols

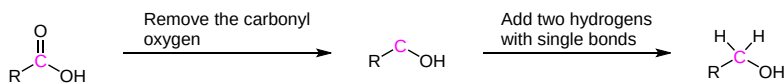
Lithium aluminum hydride (LiAlH₄)

Hydride nucleophiles from lithium aluminum hydride (LiAlH₄) can reduce carboxylic acids to 1° alcohols. Note that NaBH₄ is not a strong enough reducing agent to convert carboxylic acids or esters to alcohols. Because the incoming nucleophile is an "H" the reaction first produces an aldehyde intermediate which is available for further hydride additions. The aldehyde intermediate is difficult to isolate because it is more reactive than the original carboxylic acid. This reaction represents the first example in this chapter where a carboxylic acid derivative can undergo a double nucleophilic addition. In the mechanism of this reaction, a nucleophilic acyl substitution is followed by a nucleophilic addition allowing for two hydride nucleophiles being added to the electrophilic carbonyl carbon of a carboxylic acid.

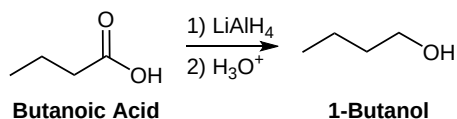
General reaction



Predicting the product of a hydride reduction



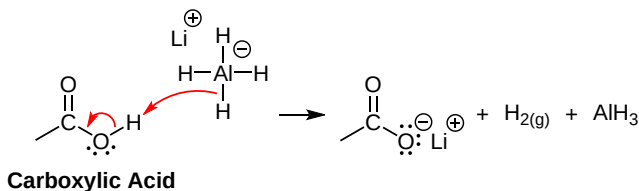
Example



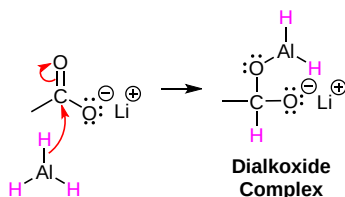
Possible Mechanism

Although the mechanism of this reaction is not precisely known, much of it is understood. Initially, a hydride deprotonates the carboxylic acid to form a lithium carboxylate, hydrogen gas (H_2), and aluminum hydride. Then a hydride nucleophile, from aluminum hydride, adds to the carbonyl carbon as part of a nucleophile acyl substitution. The resulting high-energy dianion intermediate forms a Lewis Acid/Base complex with aluminum, making one of the oxygens a good leaving group (the negative charge on the oxygen complexed to aluminum is not shown in step 2 below). The carbonyl bond is reformed along with the elimination of OAlH_2 as a leaving group to form an aldehyde. A hydride nucleophile from another molecule of LiAlH_4 adds to the re-formed carbonyl carbon as part of a nucleophilic addition. The resulting alkoxide intermediate is protonated during an acidic work-up to form the 1° alcohol product. Due to the formation of a dianion intermediate the reaction requires relatively high temperature and long reaction times.

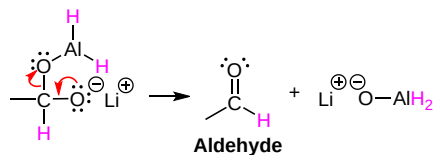
1) Deprotonation



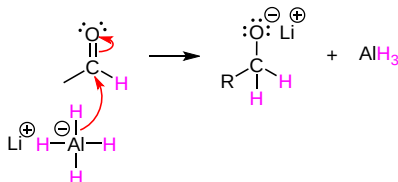
2) Nucleophilic attack by a hydride anion



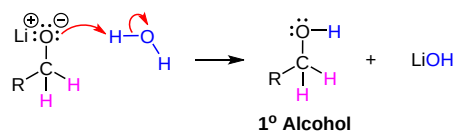
3) Leaving group removal



4) Nucleophilic attack by a hydride anion



5) Alkoxide protonation



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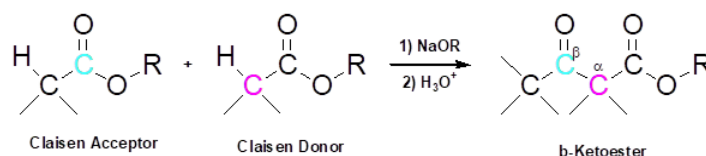
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6.3: The Claisen Condensation Reaction

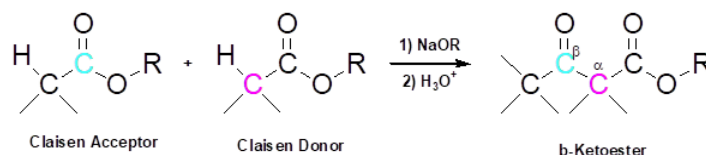
Claisen Condensation

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 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.

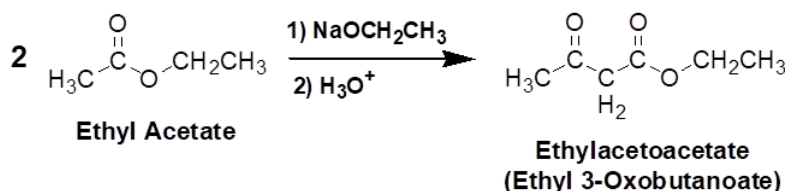
General Reaction



Predicting the Product of a Claisen Condensation



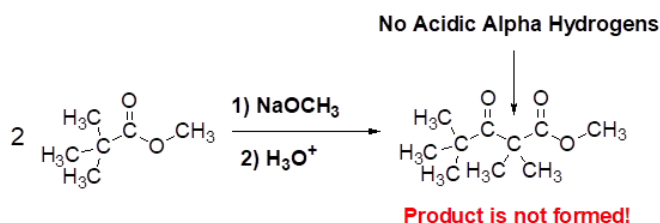
Example



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 form 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.

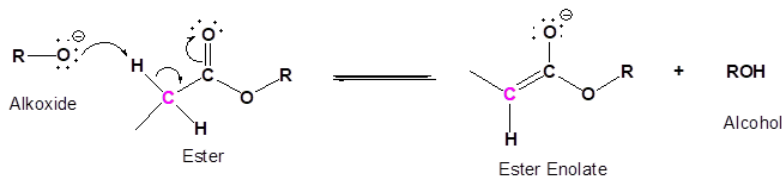


Mechanism

The Claisen condensation mechanism is analogous to the ester saponification reaction seen in [Section 21.6](#).

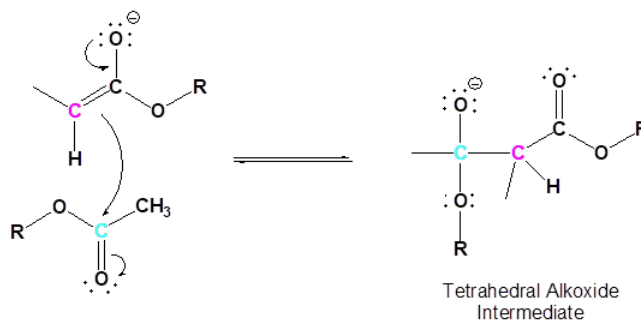
1) Enolate formation

The mechanism starts with the alkoxide base removing an α -hydrogen from the ester to form a nucleophilic ester enolate ion.



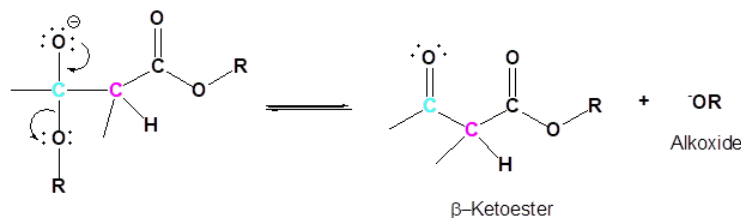
2) Nucleophilic attack

The enolate nucleophile adds to carbonyl carbon of a different ester, forming a tetrahedral alkoxide intermediate.



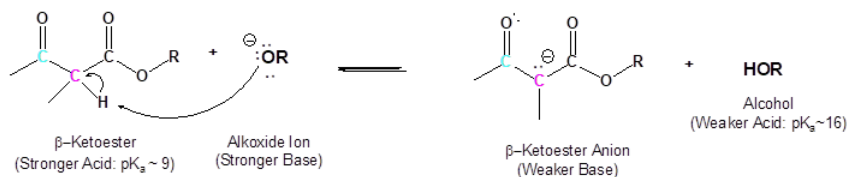
3) Removal of leaving group

The alkoxide then reforms the carbonyl, eliminating the $-OR$ leaving group to form a β -ketoester.



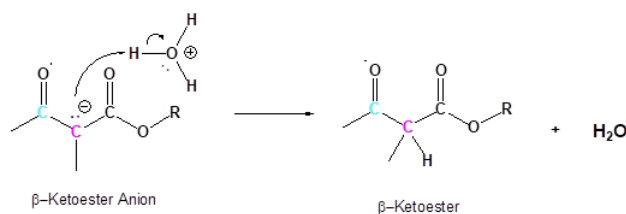
4) Deprotonation

The acidity of β -ketoesters ($pK_a \sim 9$) 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.



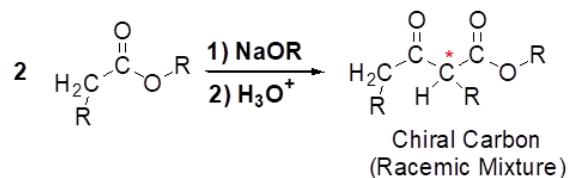
5) Protonation

The enolate is protonated in an acid work-up to form the neutral β -ketoester product.



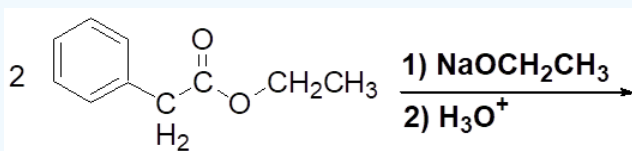
Stereochemical Considerations

The alpha-carbon gains a substituent during the reaction which means it will most likely 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.



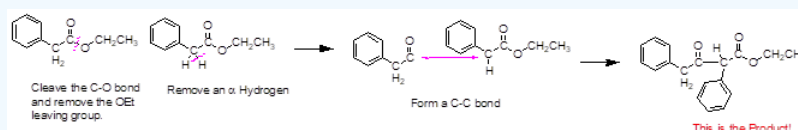
? Worked Example

Draw the products of the following reaction:



Answer

Analysis: Remember to consider each start ester separately.



6.3: The Claisen Condensation Reaction 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.

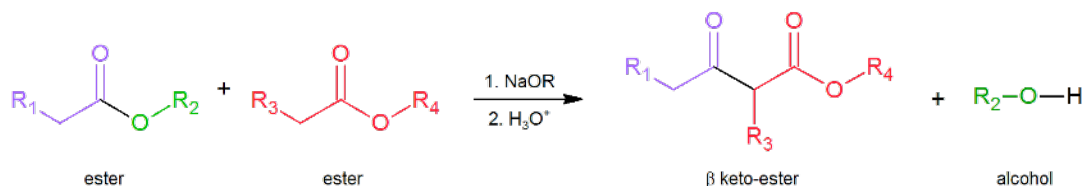
- 23.7: The Claisen Condensation Reaction by Dietmar Kennepohl, Layne Morsch, Steven Farmer is licensed [CC BY-SA 4.0](#).

6.4: Mixed Claisen Condensations

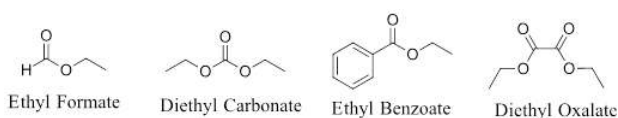
Crossed Claisen Condensation

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

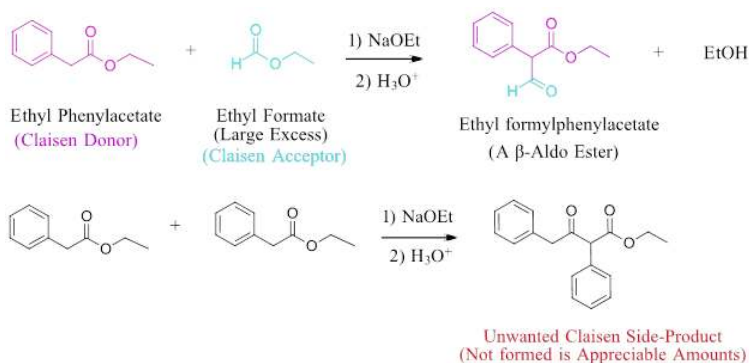


To avoid complex mixtures most Crossed Claisen reactions are usually not successful unless one of the two esters has no α -hydrogens as in the following examples.



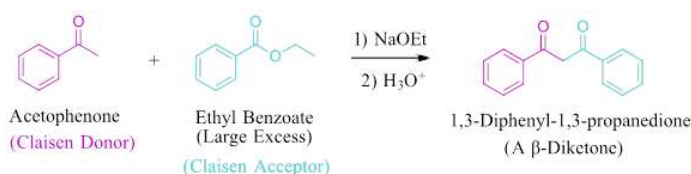
This forces the ester with α -hydrogens to be the Claisen donor (enolate) and the ester without α -hydrogens to be the Claisen acceptor (electrophile). Even with this differentiation, it is possible for the ester with α -hydrogens to undergo a Claisen Condensation with itself to produce an unwanted side-product. This is typically partially prevented by using the ester without α -hydrogens in a large excess.

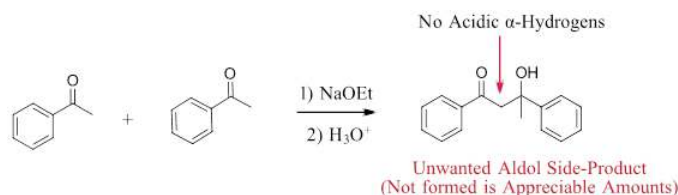
Example - no α hydrogens



Another type of crossed Claisen condensation occurs when a ketone is reacted with an ester. The use of an ester without α -hydrogens is not necessary due to the greater reactivity of the ketone. The α -hydrogens of the ketone are much more acidic ($\text{pK}_a \sim 20$) than those of the ester ($\text{pK}_a \sim 25$). The α 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 α hydrogen. The β -diketone Claisen product can be irreversibly deprotonated due to its more acidic α -hydrogens, making it the reaction's main product.

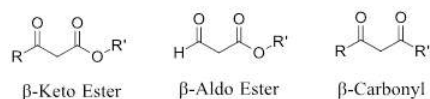
Example - ester with ketone





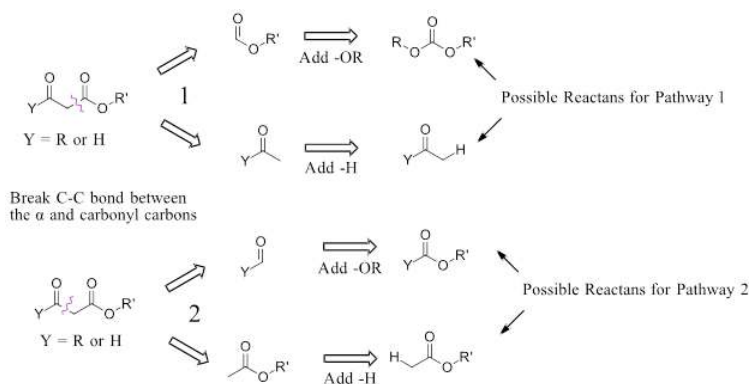
Planning a Synthesis using a Claisen or Crossed Claisen-like Reaction

A Claisen reaction should be considered for a synthesis pathway if the target molecule contains a beta-keto ester, 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 $\text{-OCH}_2\text{CH}_3$ is typically used.

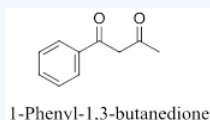
Analysis for Beta-Keto and Aldo Esters



A similar analysis can be performed on a 1,3-diketone and will be presented in the worked example below.

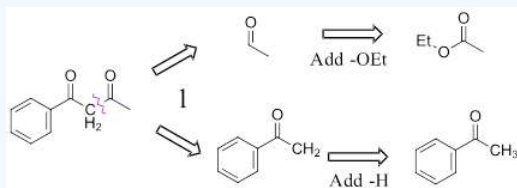
? Worked Example

Show how the following molecule can be made using a Claisen-like condensation.

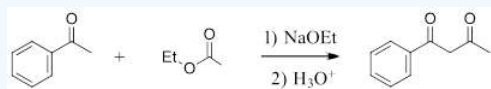


Answer

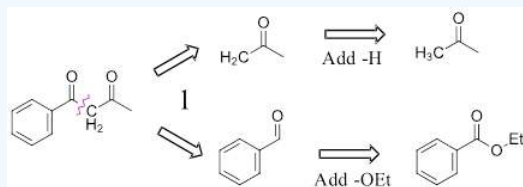
Pathway 1



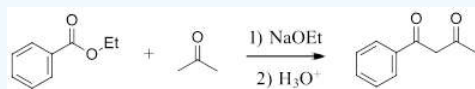
Solution 1



Pathway 2



Solution 2



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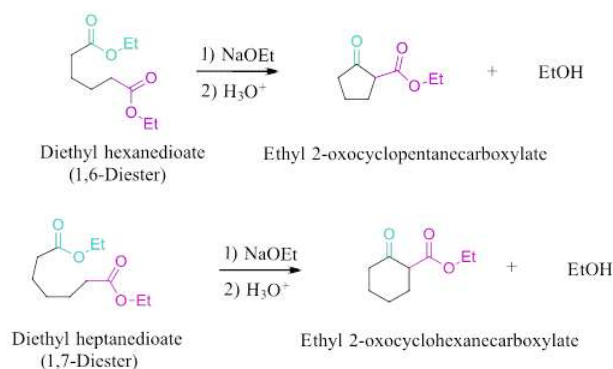
- 23.8: Mixed Claisen Condensations by Dietmar Kennepohl, Layne Morsch, Steven Farmer is licensed [CC BY-SA 4.0](#).

6.5: Intramolecular Claisen Condensations - The Dieckmann Cyclization

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-diester, which produce five-membered rings, and 1,7-diester which produce six membered rings.

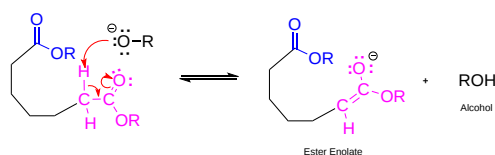
Examples



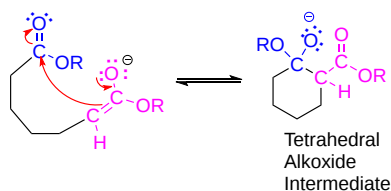
Mechanism

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 reactions 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.

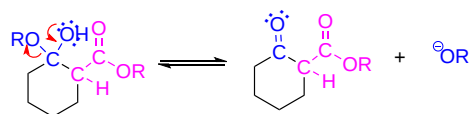
1) Enolate formation



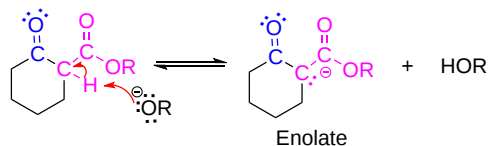
2) Nucleophilic attack



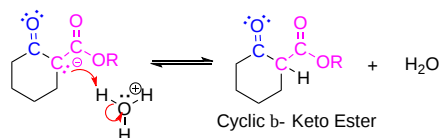
3) Removal of leaving group



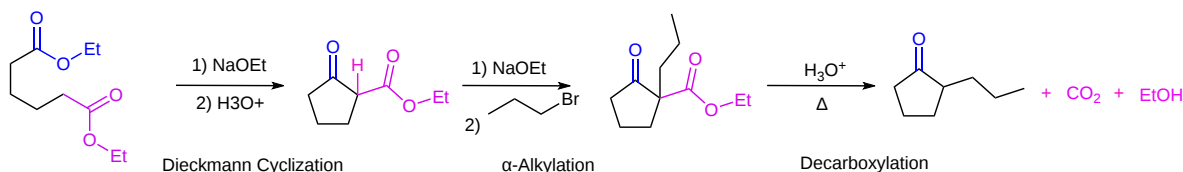
4) Deprotonation



5) Protonation



Further Reactions of the Dieckmann Cyclization Product



The cyclic beta-keto ester product of a Dieckmann cyclization can be modified by reaction similar to those used in the acetoacetic ester synthesis ([Section 22-7](#)). 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.

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CHAPTER OVERVIEW

7: Conjugated Pi Systems

- 7.1: Stability of Conjugated Dienes- Molecular Orbital Theory
- 7.2: Electrophilic Additions to Conjugated Dienes- Allylic Carbocations
- 7.3: Kinetic vs. Thermodynamic Control of Reactions
- 7.4: Naming Aromatic Compounds
- 7.5: Structure and Stability of Benzene
- 7.6: Aromaticity and the Hückel $4n + 2$ Rule
- 7.7: Aromatic Ions
- 7.8: Aromatic Heterocycles - Pyridine and Pyrrole

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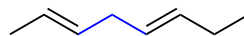
7.1: Stability of Conjugated Dienes- Molecular Orbital Theory

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)



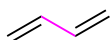
2,5-Octadiene
(Non-Conjugated)



1,3-Cyclohexadiene
(Conjugated)



1,4-Cyclohexadiene
(Non-Conjugated)



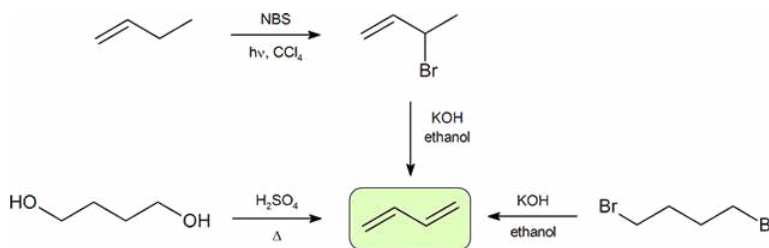
1,3-Butadiene
(Conjugated)



1,4-Pentadiene
(Non-Conjugated)

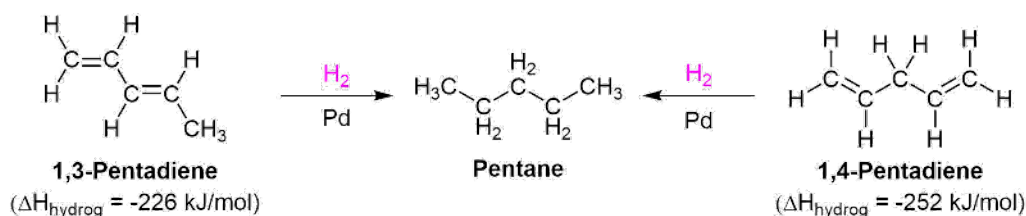
Synthesis of Dienes

Conjugated dienes can be prepared using many of the methods used for the preparation of alkenes previously discussed (**Sections 11-7, 11-8, 11-9, and 11-10**). 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.

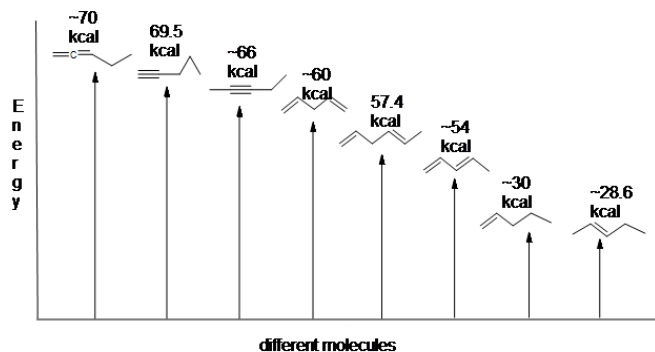


Stability of Conjugated Dienes

Conjugated dienes are known to be more stable than non-conjugated dienes as shown by their experimentally determined heats of hydrogenation. It has been shown that 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.

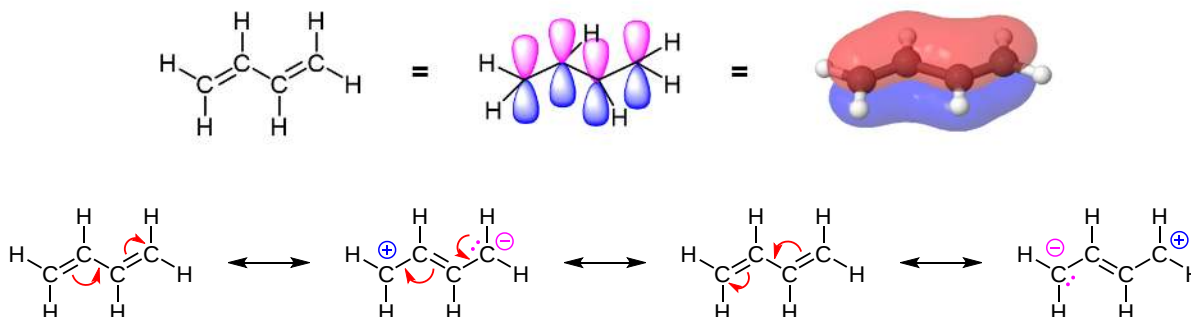


Here is an energy diagram comparing different types of bonds with their heats of hydrogenation to show relative stability of each molecule:

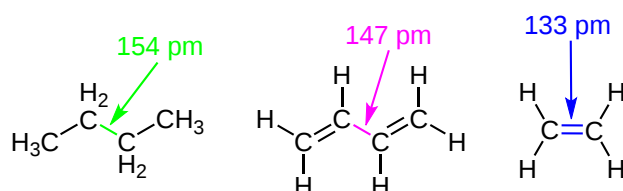


The stabilization of dienes by conjugation is less dramatic than the aromatic stabilization of benzene. Nevertheless, similar resonance and molecular orbital descriptions of conjugation may be written.

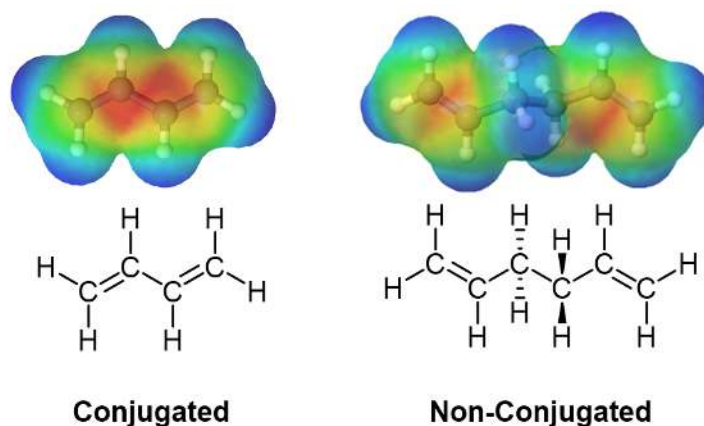
Each alkene carbon in 1,3 dienes are sp^2 hybridized and therefore have one unhybridized p orbital. The four p orbitals in 1,3-butadiene overlap to form a conjugated system which can be represented by the resonance forms shown below. This delocalization of charges stabilizes conjugated diene making them 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.

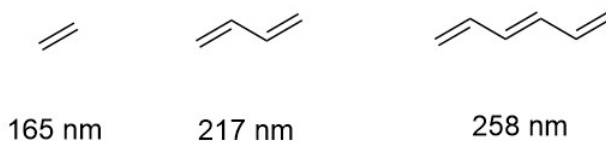


The delocalized electron density of a 1,3 diene can be seen when viewing an electrostatic potential maps. In conjugated dienes, it is observed that the pi electron density overlap (shown in red) is closer together and delocalized in conjugated dienes, while in non-conjugated dienes the pi electron density is located completely on the double bonds.



Experimental Evidence for Conjugation

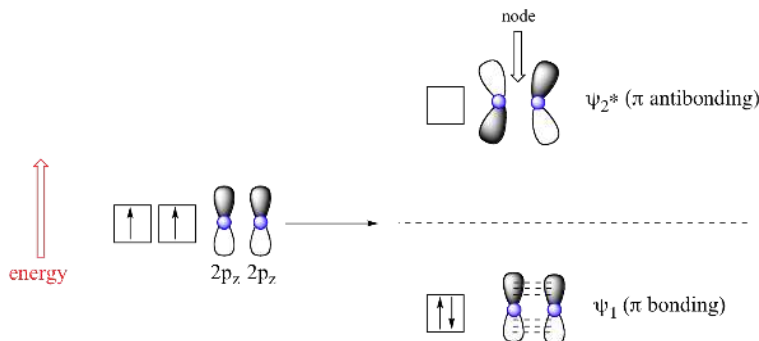
One useful way to test for the presence of conjugation is to expose the pi system to light in the UV to Visible range of the electromagnetic spectrum. Conjugated pi systems absorb photons of lower wavelengths, meaning less energetic photons are absorbed as the length of the conjugated system increases.



This effect is best explained using Molecular Orbital theory, which can be used to show that the increased degree of conjugation produces a smaller gap between the pi and pi* orbitals between which the electrons transition when absorbing light in the UV-Vis spectrum. For now, it is enough to recognize that conjugation can be detected using UV-Vis spectroscopy.

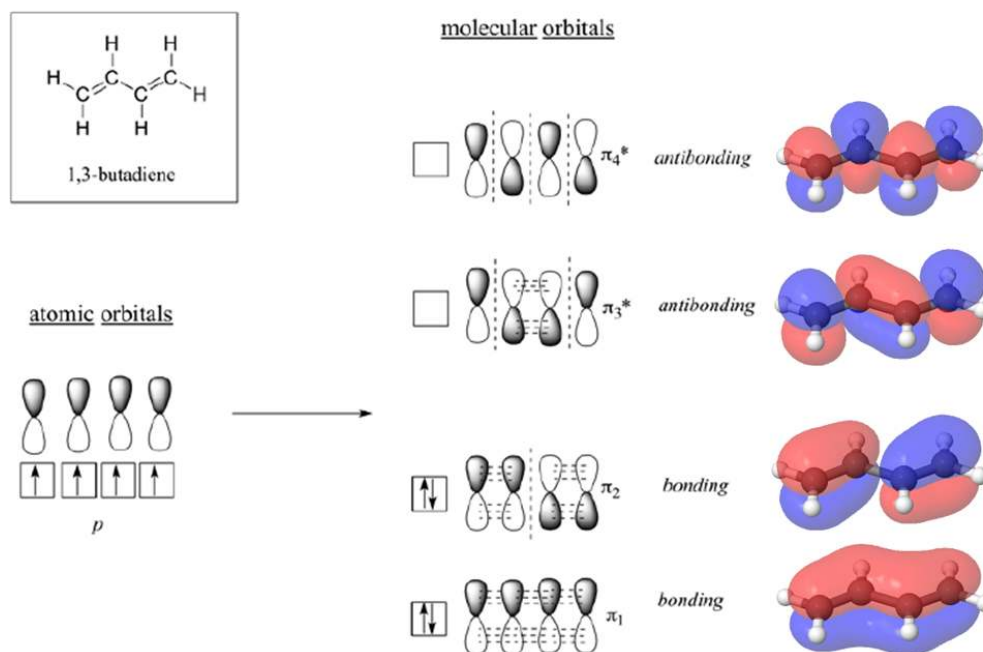
Molecular Orbitals of 1,3 Dienes

According to MO theory discussed in [section 1-11](#), 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 Ψ_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.

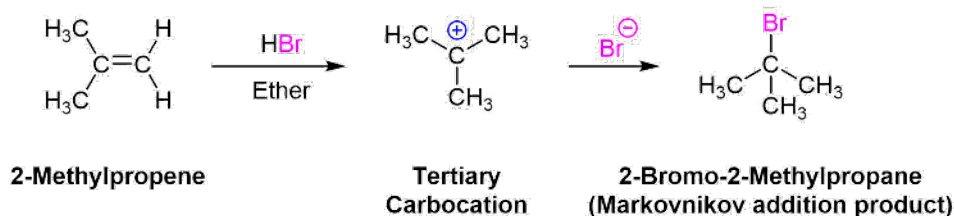


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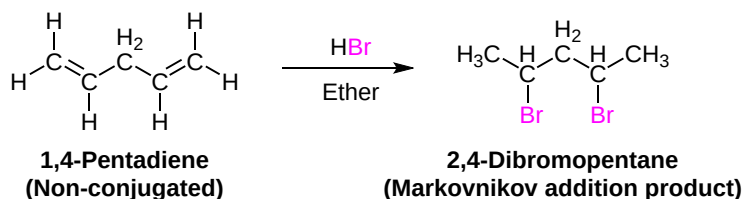
- **14.1: Stability of Conjugated Dienes- Molecular Orbital Theory** by Dietmar Kennepohl, Layne Morsch, Steven Farmer, Tim Soderberg, William Reusch is licensed [CC BY-SA 4.0](#).

7.2: Electrophilic Additions to Conjugated Dienes- Allylic Carbocations

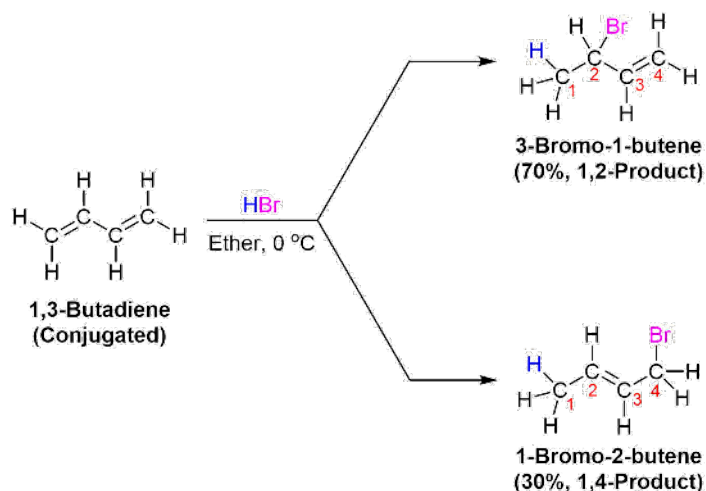
Earlier, we saw that electrophilic addition to a simple alkene would follow Markovnikov's rule. Markovnikov's rule states that for the electrophilic addition of HX, the carbocation intermediate forms on the double bond carbon with the greatest number of alkyl substituents. Because the stability of carbocation intermediates increases as it number of alkyl 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.



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.



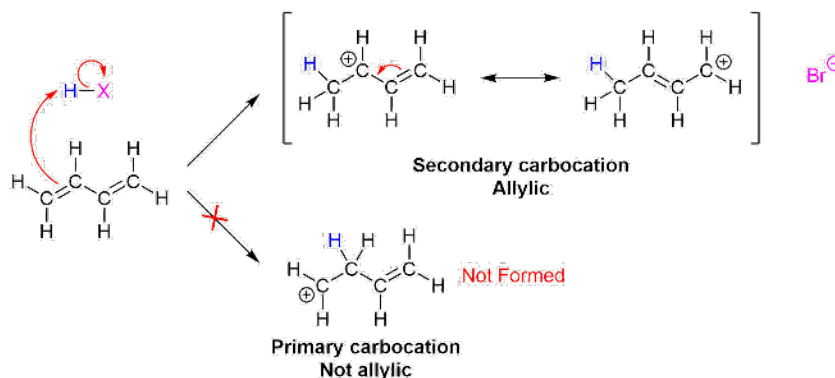
Conjugated dienes undergo the usual reactions of alkenes, such as catalytic hydrogenation, radical additions, and electrophilic additions more readily than most alkenes or dienes that have isolated double bonds. During the electrophilic addition of one equivalent of HX to a conjugated diene, the expected 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

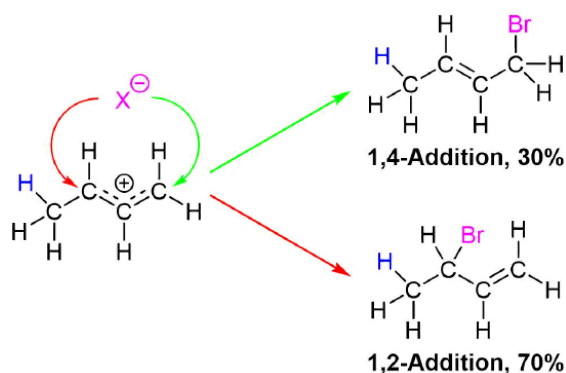
Regardless if the 1,2 or 1,4 addition product is formed, the first step of the mechanism is the protonation of one of the double bonds. In the same manner as the electrophilic addition of HX to an alkene, the protonation occurs regioselectively to give the more stable carbocation. In the case of a conjugated 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)



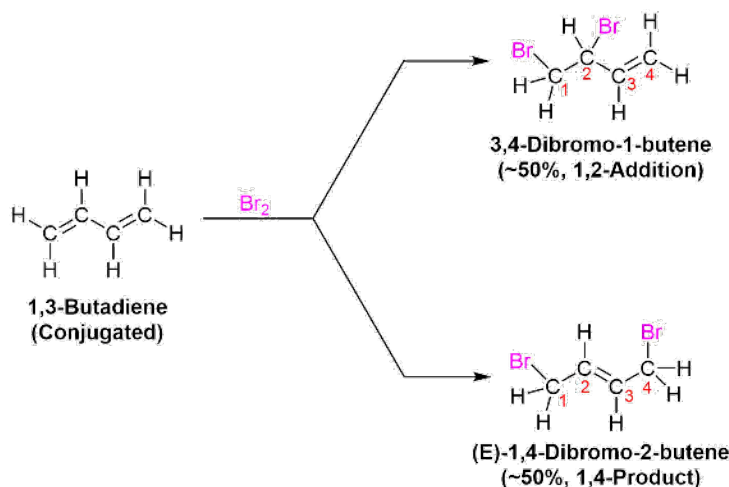
Step 2)

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 1,2-addition product. Attacking the terminal carbon, distant from the site of protonation, leads to the 1,4 addition product.



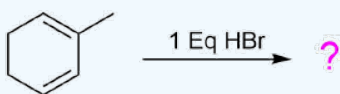
Other Electrophilic Additions

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 7.2.1

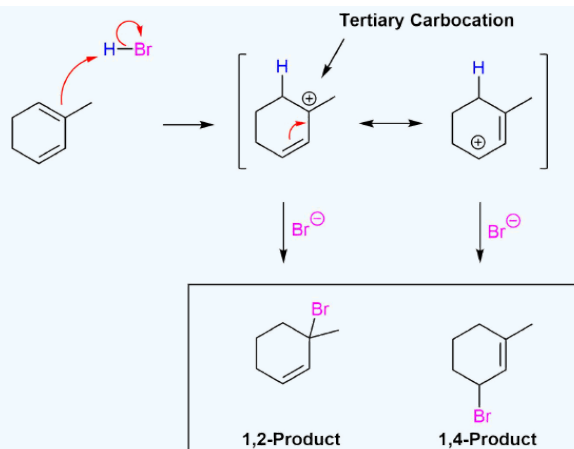
Give the expected products from the following reaction. Show both 1,2 and 1,4 addition products.



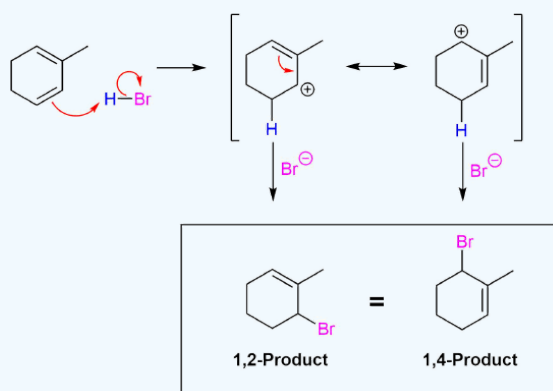
Solution

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.

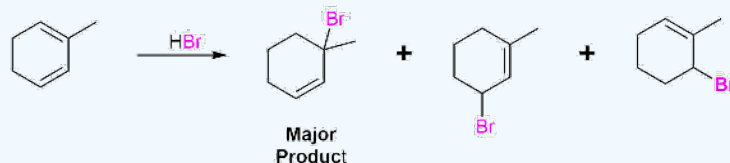
Addition to the first double bond creates a resonance form with a tertiary carbocation intermediate. Due to the stability of the tertiary carbocation this product will most likely go one to be the preferred product of this reaction.



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.



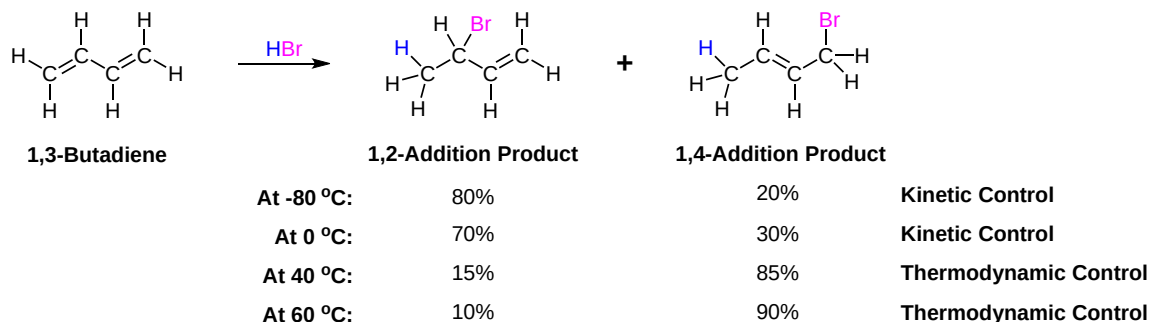
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7.3: Kinetic vs. Thermodynamic Control of Reactions

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 °C or lower, the 1,2 addition product dominates. However, if the same reaction is run at 40 °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.



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**.

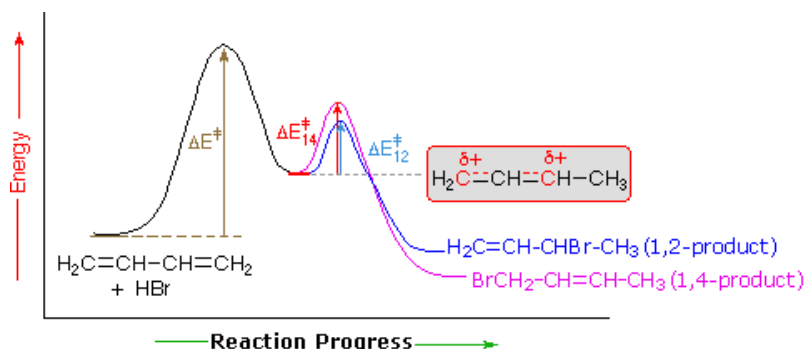
At higher temperatures the reaction to form both products becomes reversible and a reaction equilibrium is reached. When a reaction is reversible the major product is determined by thermodynamic stability. The 1,4 addition product is more stable and becomes the major product under these reaction conditions. 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).

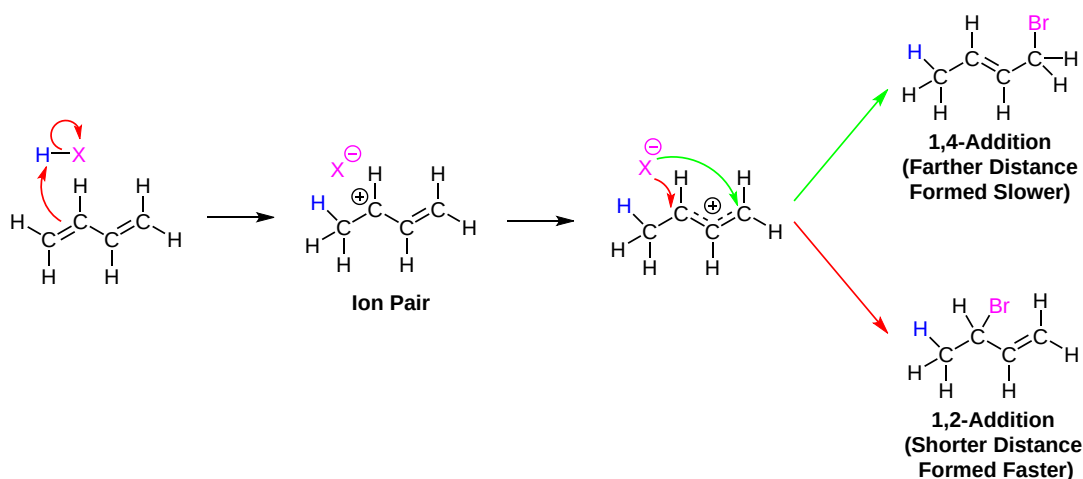
An explanation for the temperature influence is shown in the following energy diagram for the addition of HBr to 1,3-butadiene. The initial step in which a proton bonds to carbon #1 is the **rate determining step**, as indicated by the large activation energy (light gray arrow). The second faster step 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.



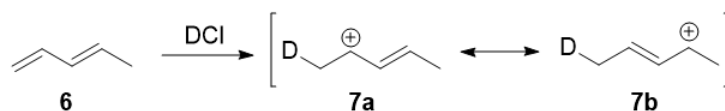
If the reaction temperature is kept sufficiently low, the products will not have enough energy to overcome the reverse activation barrier to regenerate the carbocation intermediate making this step of the mechanism effectively irreversible. This reaction is under kinetic control meaning the product which 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.

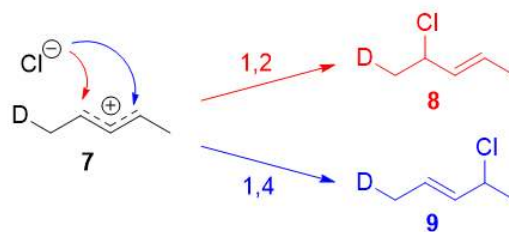


Experimental Evidence for the Ion-Pair Mechanism

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:



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 -78°C 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.

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7.4: Naming Aromatic Compounds

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)

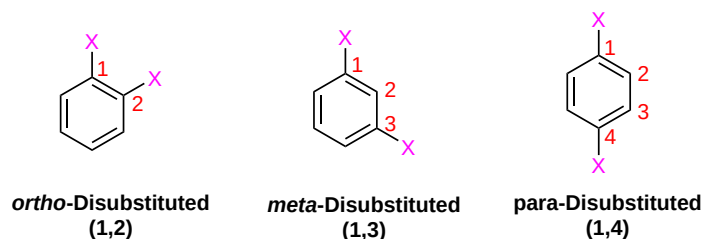


Figure 7.4.2. If any do appear then the compound is not named as a benzene but with a different parent name. These compounds are named as such: *Position prefix-Name of the substituent + Name of parent chain.*

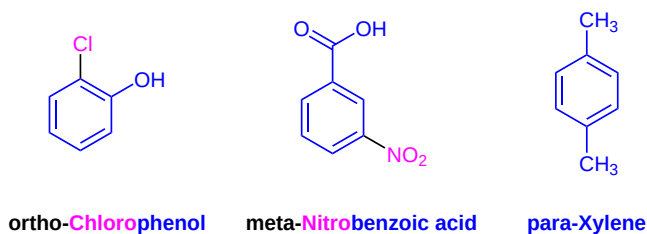
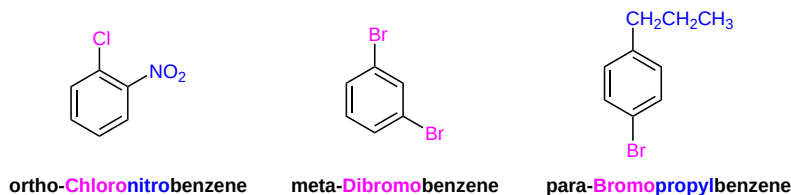
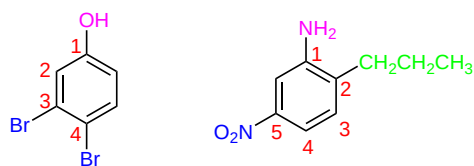


Figure 7.4.2 the compound is named as such: *Position prefix-Names of the substituents in alphabetical order + benzene.* Remember if two of the same substituent appears then the prefix *di-* is used before the substituent's name.



Nomenclature of Benzenes with Three or more Substituents

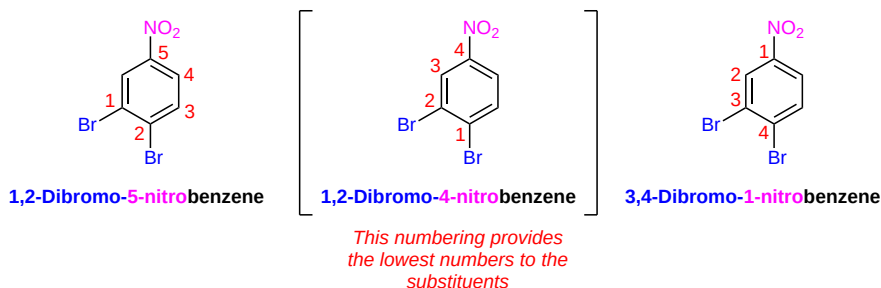
When three or more substituents are present the ortho, meta, para positional prefixes become inadequate and a numbering system for the ring must be applied. Here again it is important to check if any of the substituents are listed in **Figure 7.4.2**. If a substituent from **Figure 7.4.2** is present 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 7.4.2, 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.



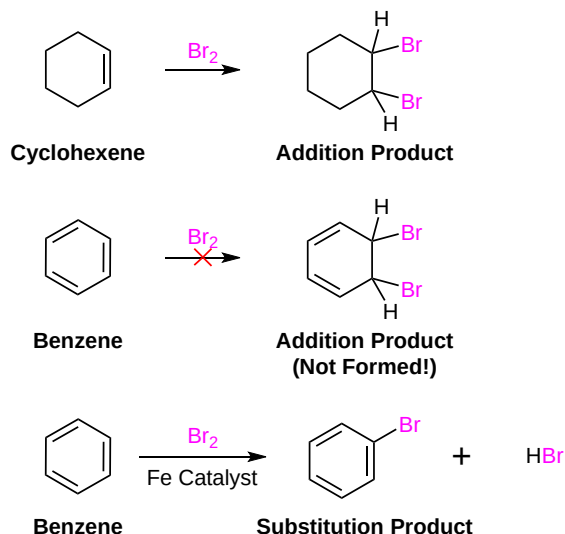
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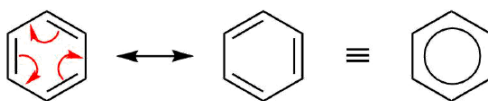
7.5: Structure and Stability of Benzene

Structure of Benzene

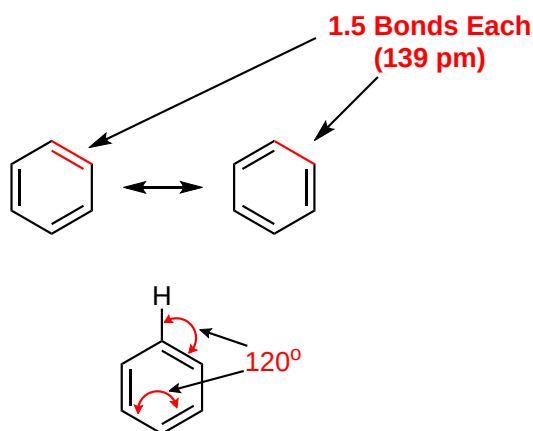
When benzene (C_6H_6) was first discovered its low hydrogen to carbon ratio (1:1) led chemists to believe it contained double or triple bonds. Since double and triple bonds rapidly add bromine (Br_2), this reaction was applied to benzene. Surprisingly, benzene was entirely unreactive toward bromine. 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.

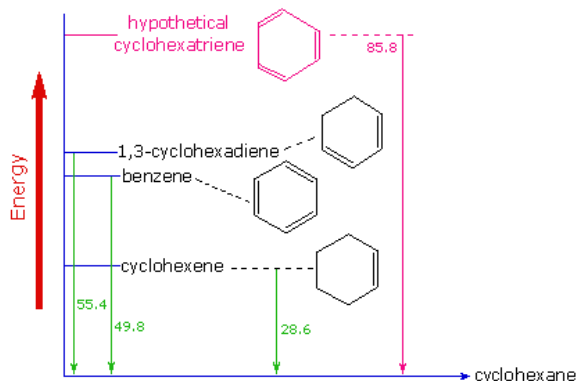


The six-membered ring in benzene is a perfect hexagon with all carbon-carbon bonds having an identical length of 139 pm^1 . The 139 pm bond length is roughly in between those of a $C=C$ double bond (134 pm) and a $C-C$ single (154 pm) which agrees with the benzene ring being a resonance hybrid made up 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 unhybridized 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.

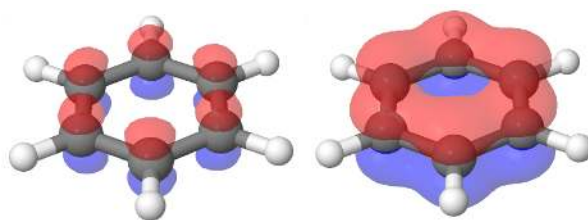


Figure 7.5.1: Each carbon in the benzene ring is sp^2 hybridized with a p orbital perpendicular to the ring plane (Left) Being planar and cyclic allows benzene's p orbitals to undergo cyclic overlap (Right)

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 π electrons are evenly distributed around the ring and that every carbon equivalent.

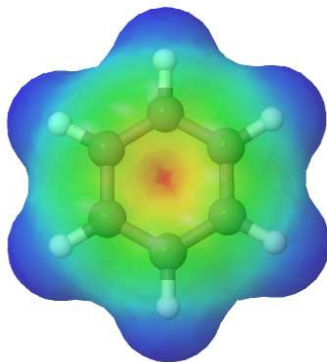
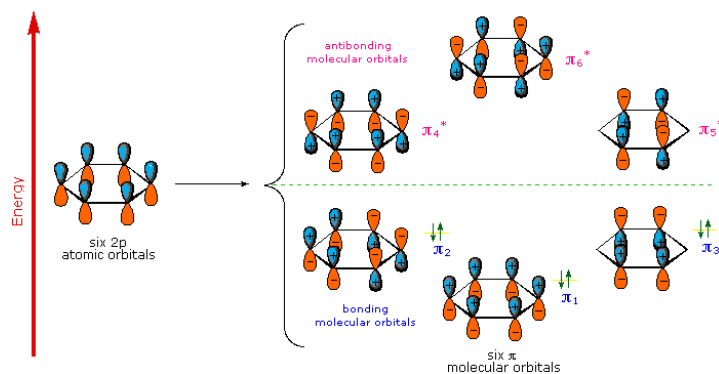


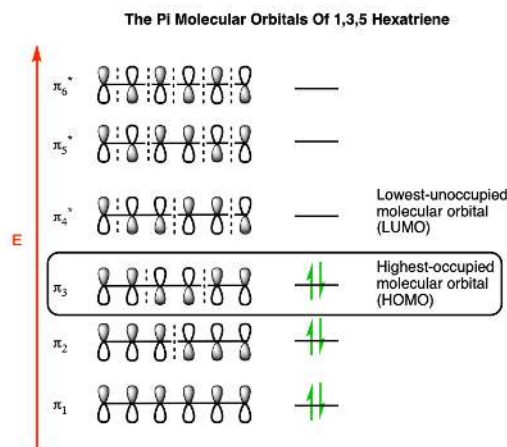
Figure 7.5.2: An electrostatic potential map of benzene

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: π_1 . In π_1 molecular orbital of 1,3,5-hexatriene there are 5 stabilizing bonding interactions where there are 6 stabilizing bonding interactions in the π_1 of benzene. The sixth bonding interaction is made possible by benzene's p orbitals being in a ring. Because benzene's π_1 molecular orbital has more stabilizing bonding interactions it is lower in energy than the π_1 molecular orbital of 1,3,5-hexatriene. This gives benzene the additional aromatic stability not seen in the acyclic 1,3,5-hexatriene.

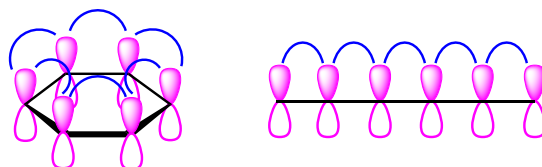


Figure 7.5.3: The π_1 molecular orbital of benzene (Left) has 6 stabilizing bonding interaction where 1,3,5-hexatriene's (Right) only has 5.

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7.6: Aromaticity and the Hückel $4n + 2$ Rule

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 $4n + 2$ π electrons, it is considered **aromatic**. This rule would come to be known as **Hückel's Rule**.

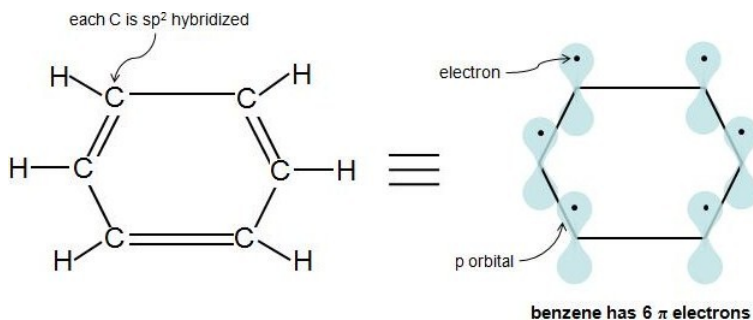
Four Criteria for Aromaticity

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 $4n+2$ π electrons ($n=0$ or any positive integer)

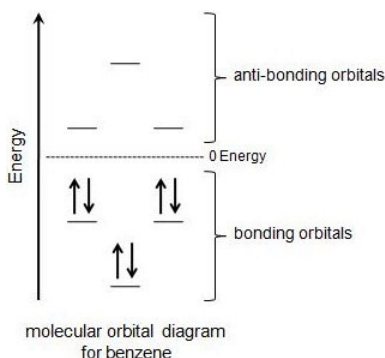
Counting π Electrons?

Perhaps the toughest part of Hückel's Rule is figuring out which electrons in the compound are actually π 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 (π bond) always contributes 2 π electrons. Benzene has 3 double bonds, so it 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 $4n+2$ π electrons. You can see how this works with the molecular orbital diagram for the aromatic compound, benzene, below. Benzene has 6 π electrons. Its first 2 π electrons fill the lowest energy orbital, and it has 4 π 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.



To apply the $4n+2$ rule, first count the number of π 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 π electrons:

$$4n + 2 = 6 \quad (7.6.1)$$

$$4n = 4 \quad (7.6.2)$$

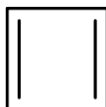
$$n = 1 \quad (7.6.3)$$

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. π 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 are cyclobutadiene, whose shape and alignment of p orbitals suggested it should have substantial electron-delocalization energies.



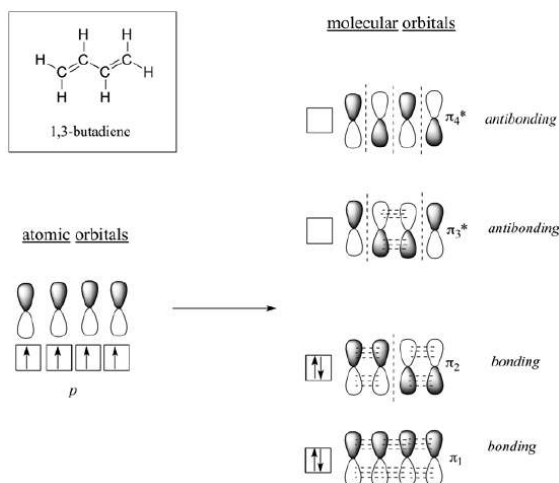
Cyclobutadiene

However, cyclobutadiene was found to be an extremely unstable molecule. 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 an essentially rigid matrix of argon at 8K. On warming to even 35K, it dimerizes through a Diels Alder reaction to yield a tricyclic diene.



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.

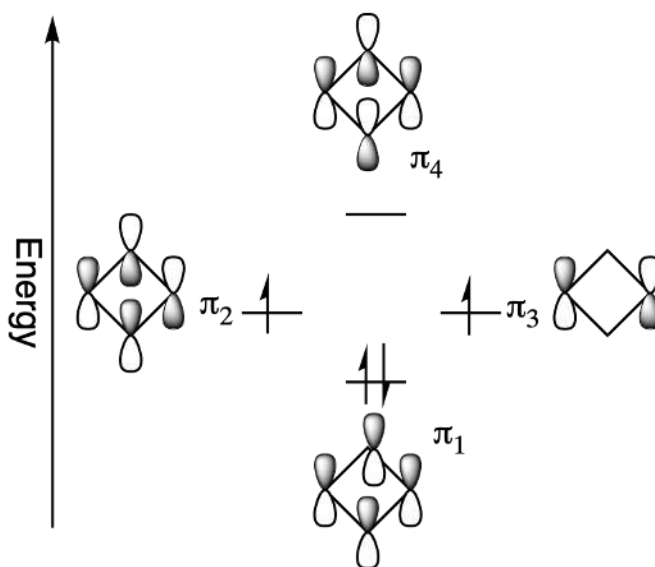
We consider the molecular orbitals diagram of the analogous 1,3-butadiene, the four $2p$ atomic orbitals combine to form four π molecular orbitals of increasing energy. Two bonding π orbitals and two antibonding π^* orbitals. The 4 π electrons of 1,3-butadiene completely fill the bonding molecular orbitals giving it 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 $4n$ π -electron cyclic conjugated compounds is termed **antiaromaticity** and the compounds are called antiaromatic.



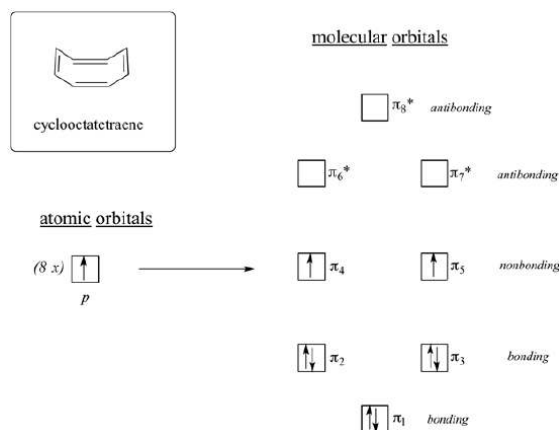
Antiaromaticity gives cyclobutadiene some interesting structural features. Cyclobutadiene's single and double bonds have different bond lengths, 158 pm and 135 pm respectively which give it a rectangular shape. If the double bonds were conjugated, there would only be one average bond length, like benzene, 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. Willstätter (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:



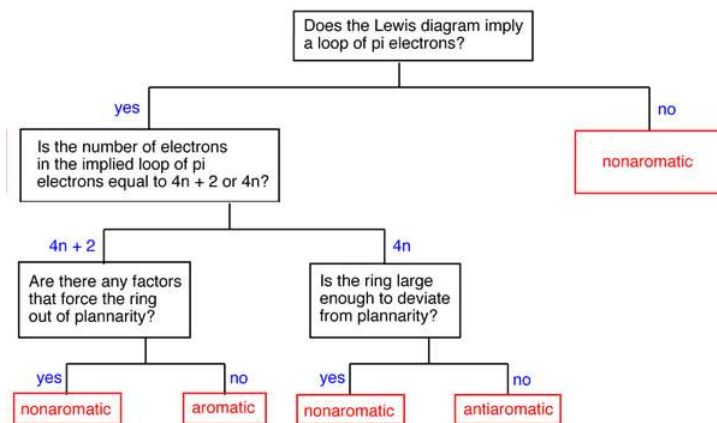
If cyclooctatetraene was flat it would have all the requirements to be antiaromatic. It is cyclic, has a p orbital in every member of the ring, and has 8 pi electrons. When looking at the molecular orbital diagram of cyclooctatetraene we see it shares certain characteristics in common with cyclobutadiene. Two of the molecular orbitals are degenerate non-bonding orbitals. When the molecular orbitals are filled 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.



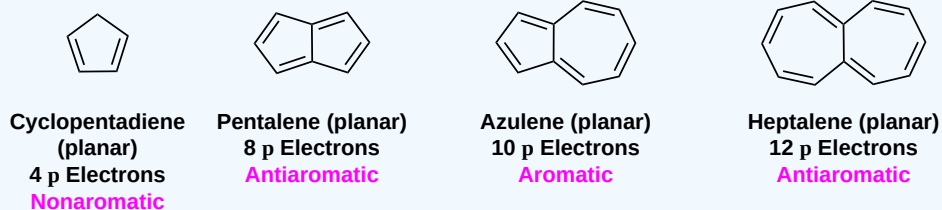
However, cyclooctatetraene is easily prepared and relatively stable. Also, it undergoes addition reactions typical of alkenes. In reality, cyclooctatetraene is not flat but has a tub-like shape. By assuming this shape, the p orbitals between double bond are out of alignment for overlap. Because the double bonds are not conjugated, cyclooctatetraene escapes the destabilizing effects of antiaromaticity. This makes its 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 ask 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 7.6.1



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.

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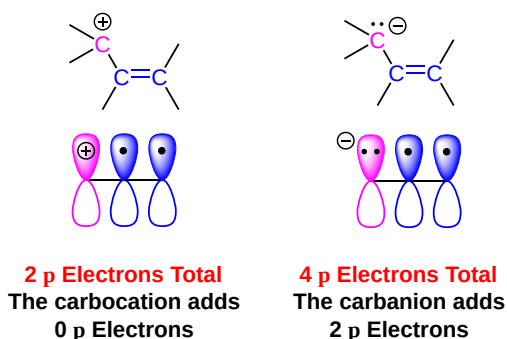
7.7: Aromatic Ions

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.

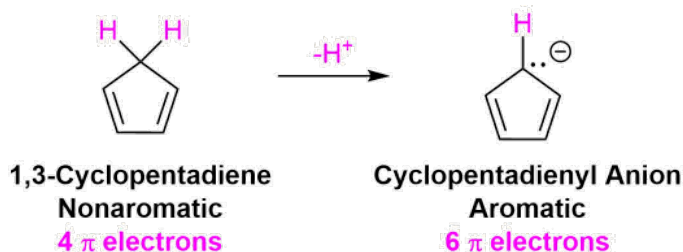
There are two main situations which need to be considered: The conjugation of a carbocation and the conjugation of a carbanion. A carbocation carbon is surrounded by three electron groups giving it sp^2 hybridization. The remaining unhybridized p orbital holds the carbocation's positive charge and is 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 become 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.

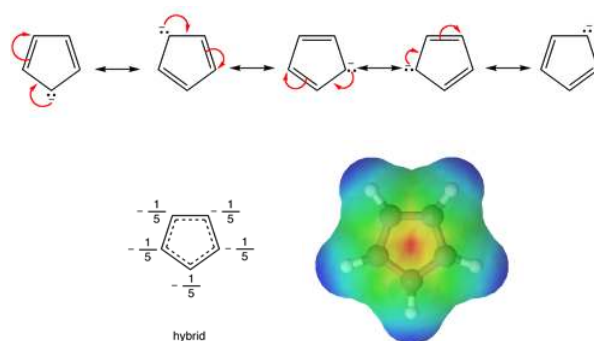


Cyclopentadiene Ion

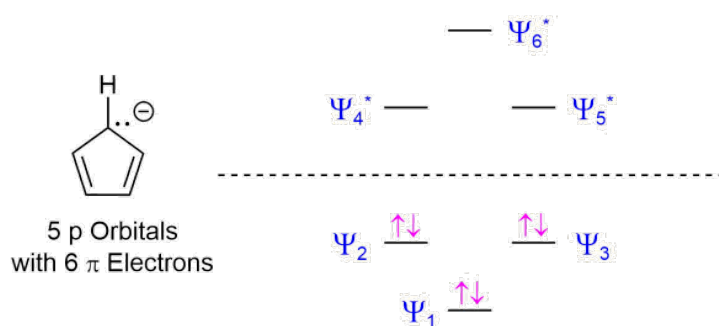
One of the most well known examples of an aromatic ion is the 1,3-cyclopentadienyl anion. 1,3-Cyclopentadiene is nonaromatic due to the presence of an intervening sp^3 hybridized $-CH_2-$ carbon atom which prevents pi electrons from delocalizing about the entire ring. Also, it only has 4 pi electrons which does not follow Hückel's $4n + 2$ rule. However, if a proton is removed from 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.



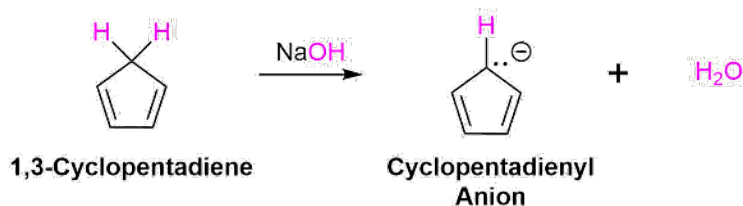
The lone pair electrons and the negative charge are conjugated about the entire ring making each carbon in the cyclopentadienyl anion equivalent with 1/5 the negative charge. The resonance hybrid can be shown by drawing a series of five resonance forms. Also, the electrostatic potential map of the cyclopentadienyl 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 the molecular orbital diagram of the cyclopentadienyl anion. As discussed in **Section 15.3**, 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.



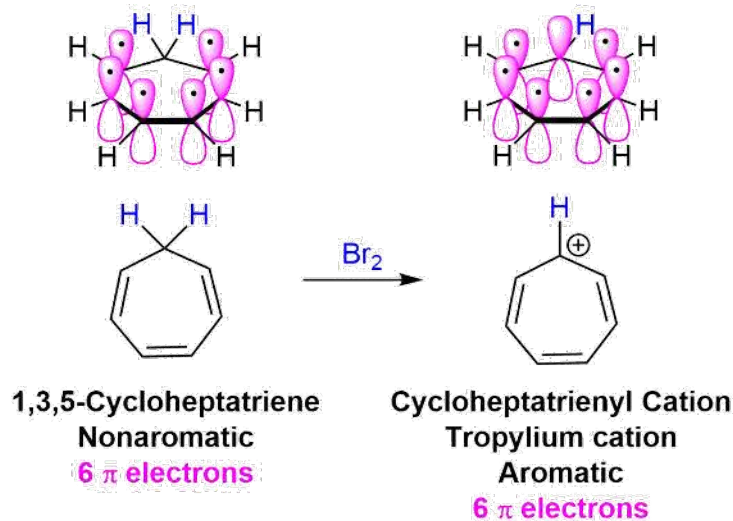
One of the effects of the aromaticity of the cyclopentadienyl anion is that the acidity of 1,3-cyclopentadiene is unusually strong. As previously discussed, stabilizing the conjugate base increases the acidity of the corresponding acid. In this case, the conjugate base of 1,3-cyclopentadiene, the cyclopentadienyl 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.



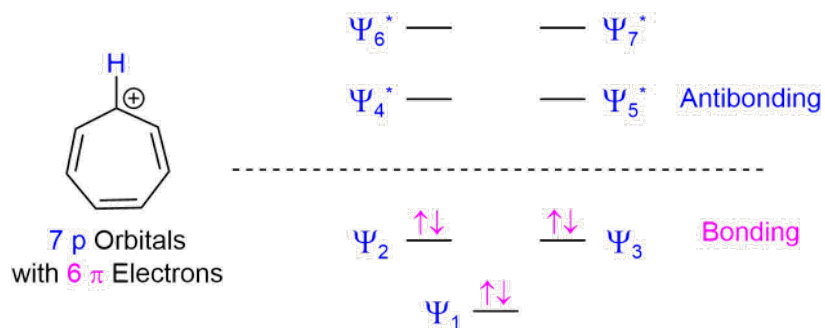
Tropylium ion

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.

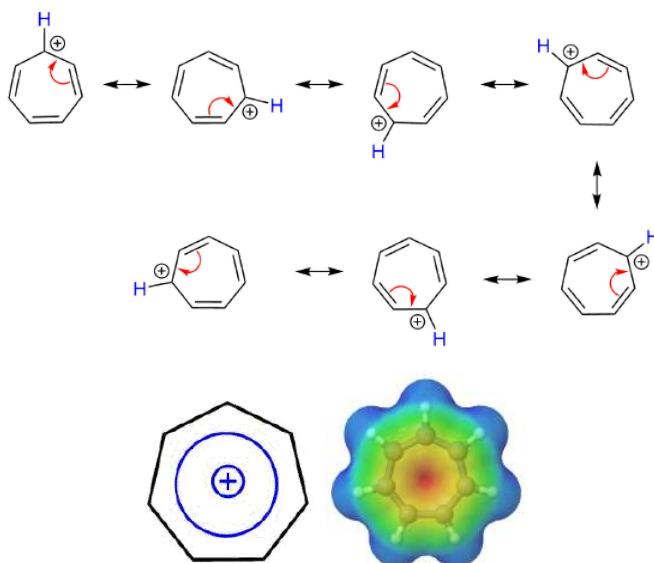
Removal of a hydride from the $-CH_2-$ group in 1,3,5-cycloheptatriene creates an sp^2 hybridized carbocation with a vacant p orbital. The new p orbital allows for cyclic conjugation to occur among the seven p orbitals in the tropylium cation. The vacant p orbital does not change the pi electron count 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 π electrons completely fill the bonding molecular orbitals which is consistent with the tropylium cation being aromatic and therefore unusually stable.

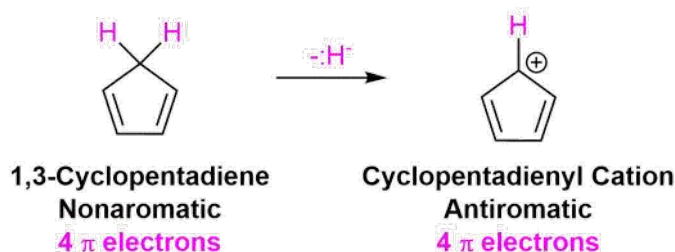


As predicted with aromaticity, the positive charge is completely conjugated about the entire ring giving each carbon $+1/7$ charge. The true resonance hybrid can be depicted by drawing a series of seven resonance form. Also, the electrostatic potential map of the tropylium cation shows the positive charge 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.

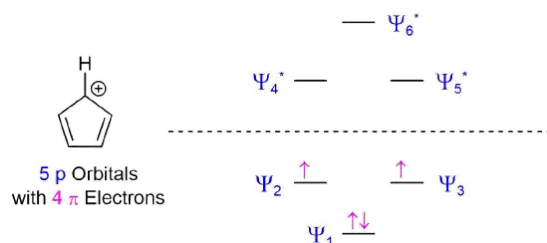


Antiaromatic Ions

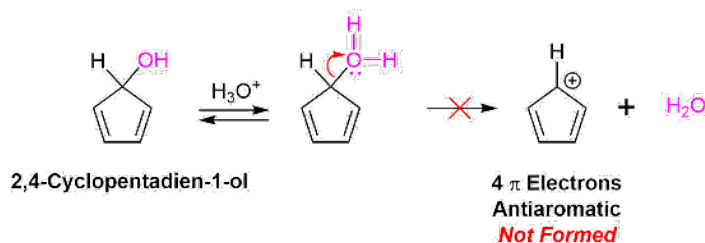
In a similar fashion, cyclically conjugated ions with $4n$ pi electrons can be predicted to be antiaromatic and therefore highly unstable. An excellent example is the cyclopentadienyl cation. Above, the cyclopentadienyl anion was shown to be aromatic, however, the formation of a carbocation produces 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 antiaromatic and very unstable.



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 usually resistant to $\text{S}_{\text{N}}1$ 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.



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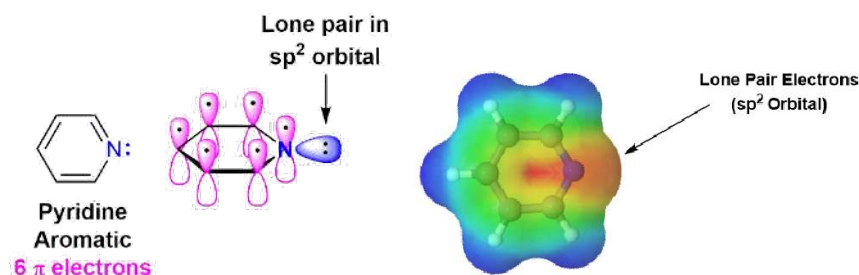
7.8: Aromatic Heterocycles - Pyridine and Pyrrole

Aromatic Heterocycles

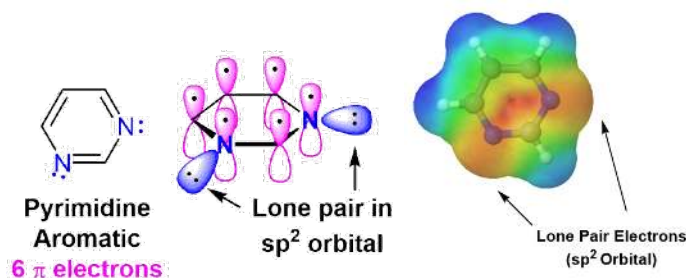
Many cyclic compounds have an element other than carbon present in the ring. Cyclic compounds that include one or more elements other than carbon are called a heterocycle. The most common heterocyclic compounds contain carbon along with nitrogen, oxygen, or sulfur. Because some heterocyclic compounds 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.

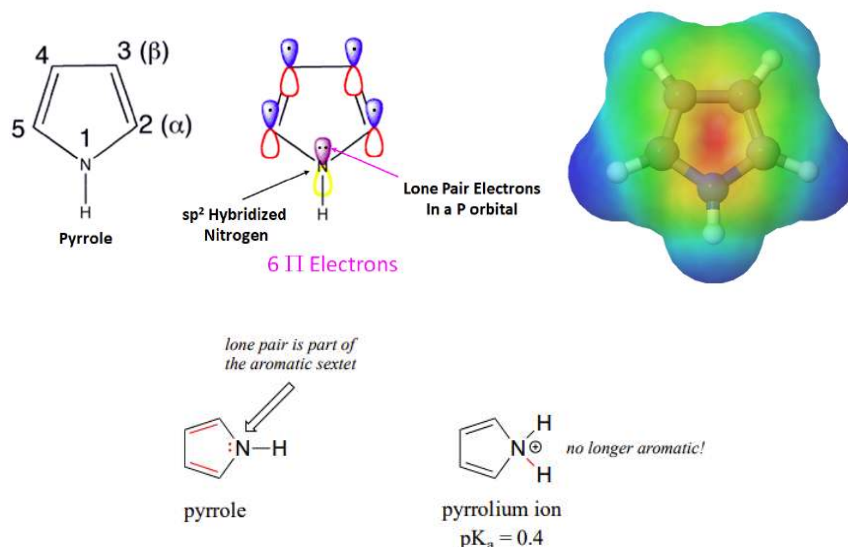


Pyrimidine is another six-membered aromatic heterocycle that is analogous to pyridine. Pyrimidine has four carbon atoms and two nitrogen atoms that are sp^2 hybridized. Each of these atoms contributes a p orbital and a pi electron allowing pyrimidine to be fully conjugated and aromatic. Both of the nitrogens in pyrimidine have lone pair electrons contained in 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.



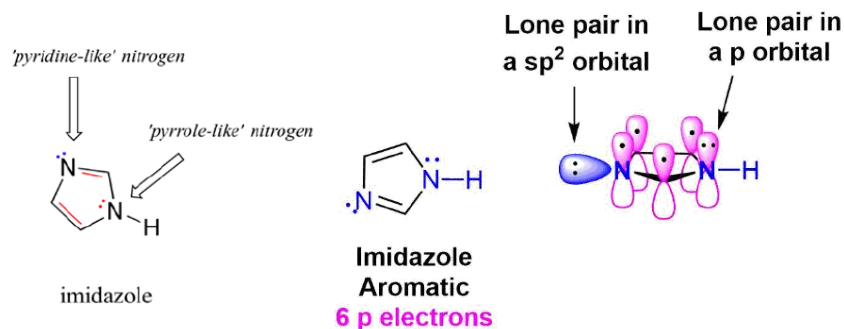
Pyrrole

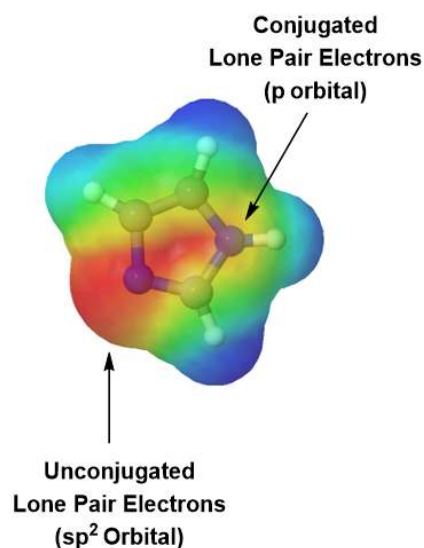
Pyrrole is a five-membered heterocyclic ring which has 5 p orbitals and six pi electrons contributing to its aromaticity. Each carbon in pyrrole contributes one p orbital and pi electron. The nitrogen in pyrrole contributes two pi electrons by becoming sp^2 hybridized and placing its lone pair electrons into a p orbital. The electrostatic potential map of pyrrole shows 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.



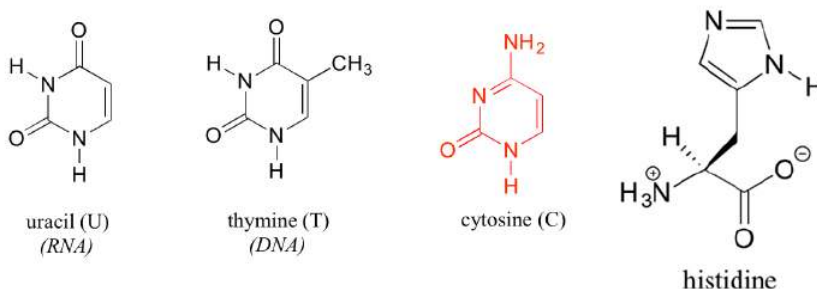
Imidazole

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 its 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.





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 7.8.1

Determine if furan is aromatic. Draw an orbital diagram to support your answer.

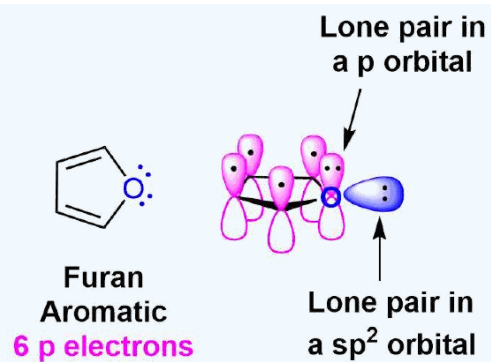


Furan

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 constraints 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.



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CHAPTER OVERVIEW

8: Electrophilic Aromatic Substitutions

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8.2: Electrophilic Aromatic Substitution Reactions - Bromination

8.3: Other Aromatic Substitutions

8.4: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction

8.5: Substituent Effects in Substituted Aromatic Rings

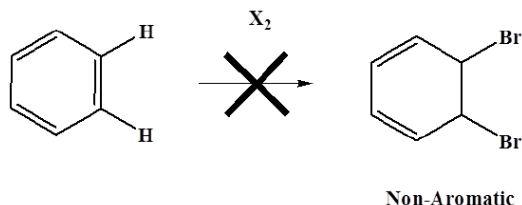
8.6: An Explanation of Substituent Effects

8.7: Clemmensen Reduction

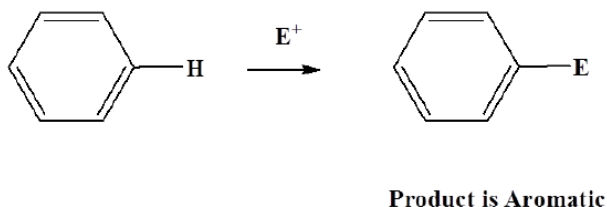
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8.1: Introduction

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.



Benzene can undergo electrophilic aromatic substitution because aromaticity is maintained.



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 ₆ H ₆	+ Cl ₂ & heat FeCl ₃ catalyst	————>	C ₆ H ₅ Cl + HCl Chlorobenzene Cl ⁽⁺⁾ or Br ⁽⁺⁾
Nitration:	C ₆ H ₆	+ HNO ₃ & heat H ₂ SO ₄ catalyst	————>	C ₆ H ₅ NO ₂ + H ₂ O Nitrobenzene NO ₂ ⁽⁺⁾
Sulfonation:	C ₆ H ₆	+ H ₂ SO ₄ + SO ₃ & heat	————>	C ₆ H ₅ SO ₃ H + H ₂ O Benzenesulfonic acid SO ₃ H ⁽⁺⁾
Alkylation: Friedel-Crafts	C ₆ H ₆	+ R-Cl & heat AlCl ₃ catalyst	————>	C ₆ H ₅ -R + HCl An Arene R ⁽⁺⁾
Acylation: Friedel-Crafts	C ₆ H ₆	+ RCOCl & heat AlCl ₃ catalyst	————>	C ₆ H ₅ COR + HCl An Aryl Ketone RCO ⁽⁺⁾

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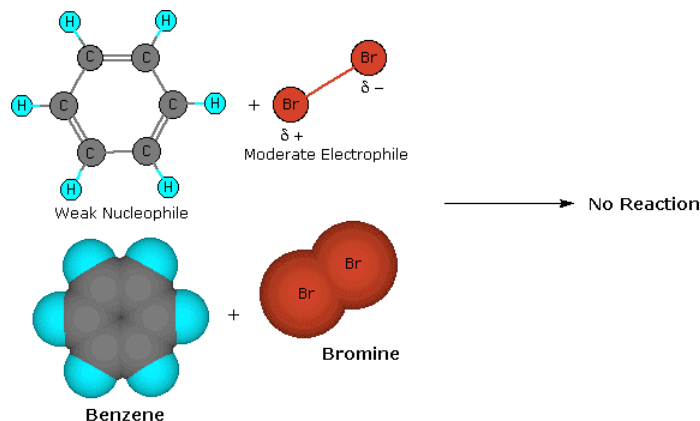
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8.2: Electrophilic Aromatic Substitution Reactions - Bromination

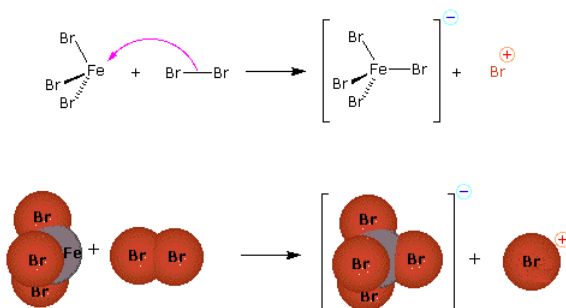
Halogenation is an example of electrophilic aromatic substitution. In electrophilic aromatic substitutions, a benzene is attacked by an electrophile which results in substitution of hydrogens. However, halogens are not electrophilic enough to break the aromaticity of benzenes, which require a catalyst 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.

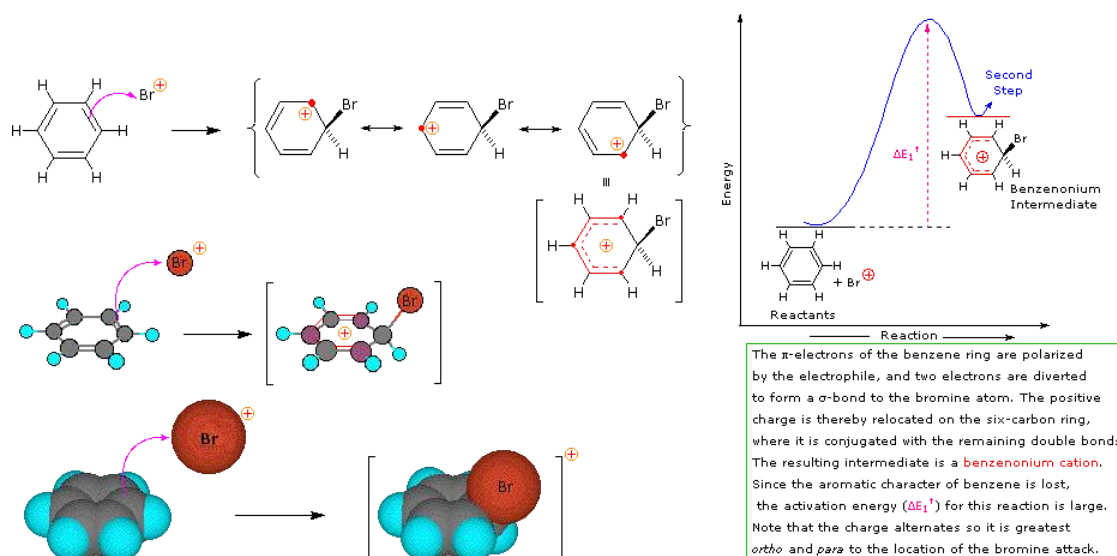


The bromine molecule is polarized so that one end is electrophilic and the other nucleophilic. Although the electrophilic end reacts easily with simple alkenes and dienes, it fails to react with the more stable and weaker nucleophilic π -electron system of benzene.

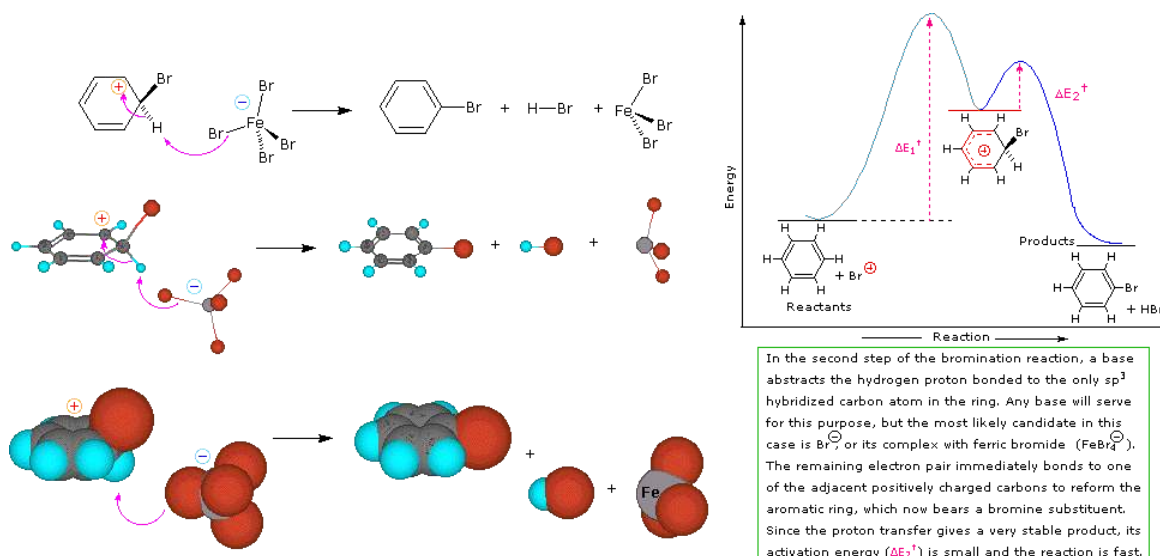


Ferric bromide and other Lewis acids enhance the electrophilic strength of bromine by forming a complex anion, in this case FeBr_4^- . At the same time, this complexation creates the strongly electrophilic bromine cation, which reacts with nucleophiles.

Preliminary step: Formation of the strongly electrophilic bromine cation



Step 1: The electrophile forms a sigma-bond to the benzene ring, generating a positively charged benzenonium intermediate



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).

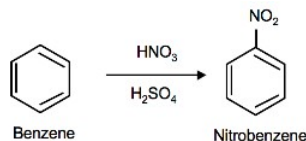
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8.3: Other Aromatic Substitutions

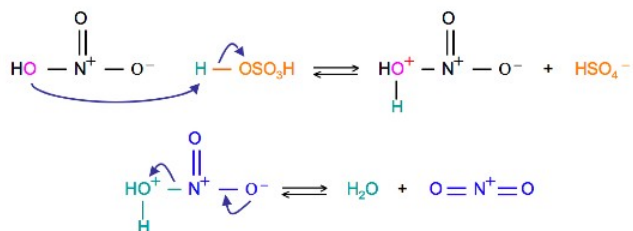
Nitration of Benzene

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.



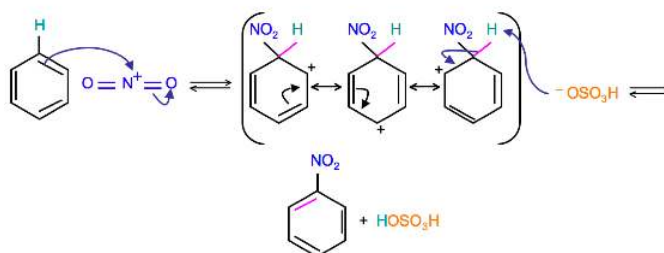
Sulfuric Acid Activation of Nitric Acid

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.

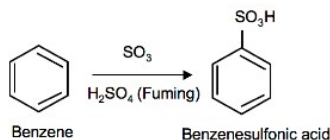
Mechanism



(Resonance forms of the intermediate can be seen in the generalized electrophilic aromatic substitution)

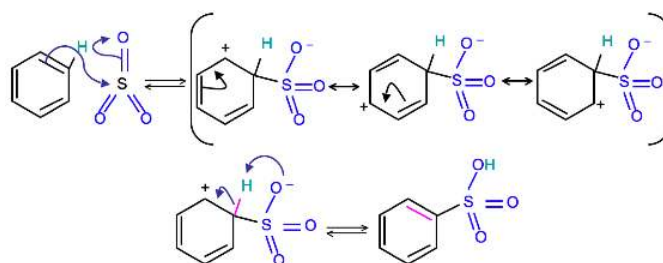
Sulfonation of Benzene

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.



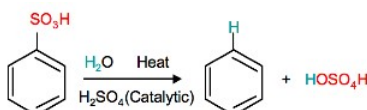
Mechanism

To produce benzenesulfonic acid from benzene, fuming sulfuric acid and sulfur trioxide are added. Fuming sulfuric acid, also referred 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 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. Benzenesulfonyl Chloride is a precursor to sulfonamides, which are used in chemotherapy.

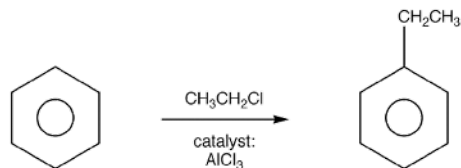
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8.4: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction

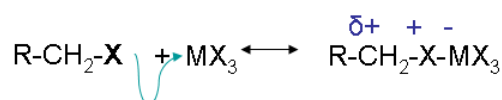
Friedel-Crafts Alkylation

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.



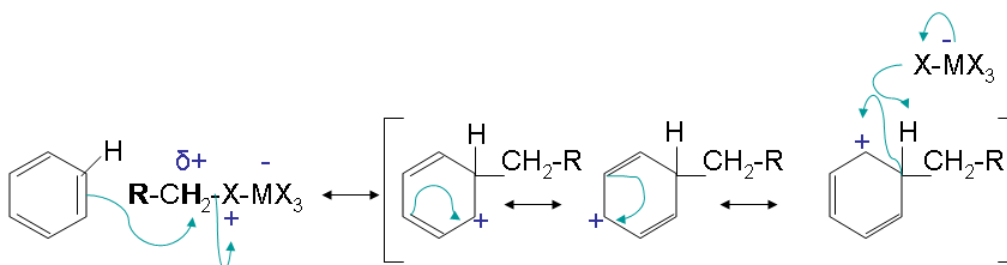
The mechanism takes place as follows:

Step 1:



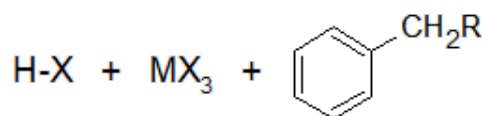
Step one creates a carbocation that acts as the electrophile in the reaction. This step activates the haloalkane. Secondary and tertiary halides only form the free carbocation in this step.

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.

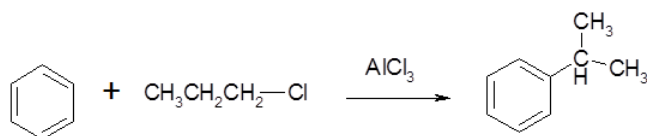
Final Products



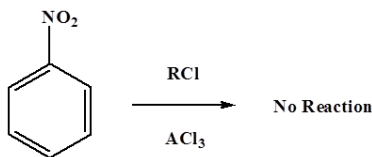
The reactivity of haloalkanes increases as you move up the periodic table and increase polarity. This means that an RF haloalkane is most reactive followed by RCl then RBr and finally RI. This means that the Lewis acids used as catalysts in Friedel-Crafts Alkylation reactions tend have similar halogen combinations such as BF₃, SbCl₅, AlCl₃, SbCl₅, and AlBr₃, all of which are commonly used in these reactions.

Some limitations of Friedel-Crafts Alkylation

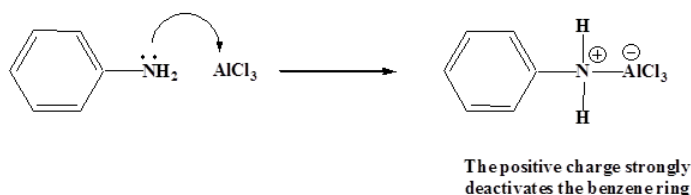
There are possibilities of carbocation rearrangements when you are trying to add a carbon chain greater than two carbons. The rearrangements occur due to hydride shifts and methyl shifts. For example, the product of a Friedel-Crafts Alkylation will show an isomerization when adding a three carbon chain as a substituent. One way to resolve these problems is through Friedel-Crafts Acylation.



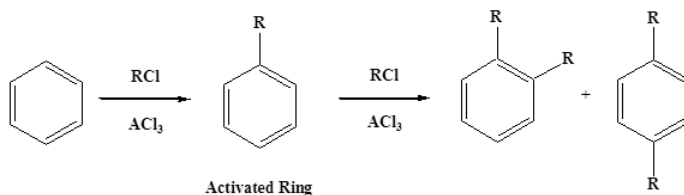
Also, the reaction will only work if the ring you are adding a substituent to is not deactivated. Friedel-Crafts fails when used with compounds such as nitrobenzene and other strong deactivating systems.



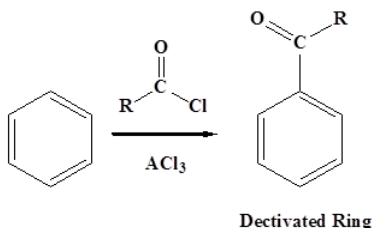
Friedel-Crafts reactions cannot be performed then the aromatic ring contains a NH_2 , NHR , or NR_2 substituent. The lone pair electrons on the amines react with the Lewis acid AlCl_3 . This places a positive charge next to the benzene ring, which is so strongly activating that the Friedel-Crafts reaction cannot occur.



Lastly, Friedel-Crafts alkylation can undergo polyalkylation. The reaction adds an electron donating alkyl group, which activates the benzene ring to further alkylation.

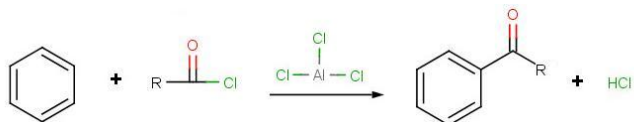


This problem does not occur during Friedel-Crafts Acylation because an acyl group is deactivating, thus prevents further acylations.

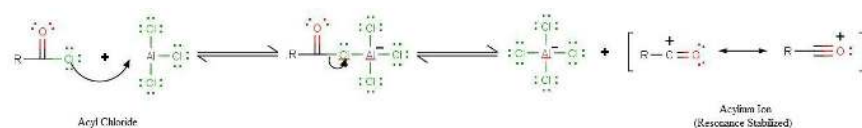


Friedel-Crafts Acylation

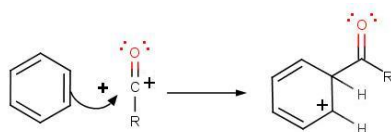
The goal of the reaction is the following:



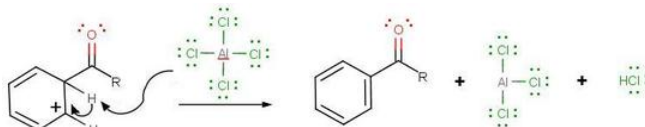
The very first step involves the formation of the acylium ion which will later react with benzene:



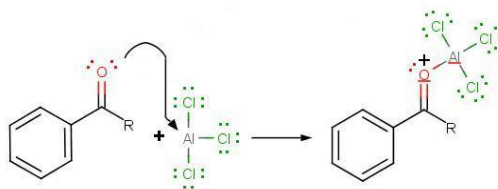
The second step involves the attack of the acylium ion on benzene as a new electrophile to form one complex:



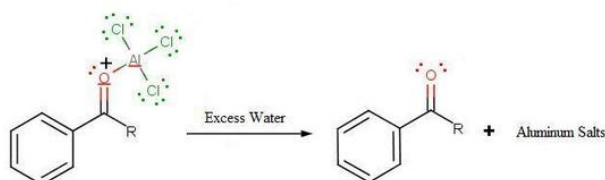
The third step involves the departure of the proton to reform aromaticity:



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 first part of the final product of the reaction, which is a ketone. This 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 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.

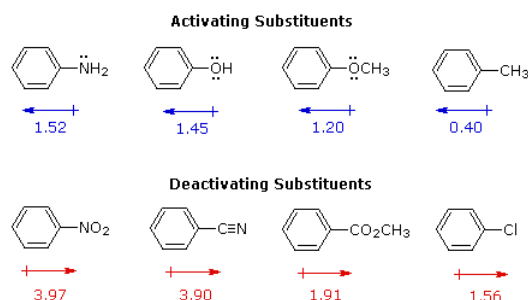
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8.5: Substituent Effects in Substituted Aromatic Rings

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, as illustrated by the case of anisole in the virtual demonstration (above). 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).

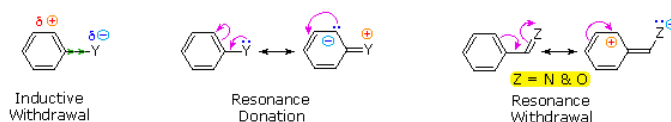


The influence a substituent exerts on the reactivity of a benzene ring may be explained by the interaction of two effects:

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 p- π 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 p- π 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 same diagram) 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.



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8.6: An Explanation of Substituent Effects

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.

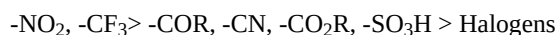
Introduction

Examples of activating groups in the relative order from the most activating group to the least activating:



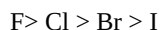
with R as alkyl groups ($\text{C}_n\text{H}_{2n+1}$)

Examples of deactivating groups in the relative order from the most deactivating to the least deactivating:



with R as alkyl groups ($\text{C}_n\text{H}_{2n+1}$)

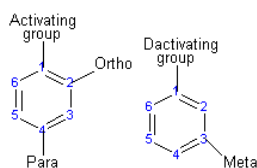
The order of reactivity among Halogens from the more reactive (least deactivating substituent) to the least reactive (most deactivating substituent) halogen is:



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.

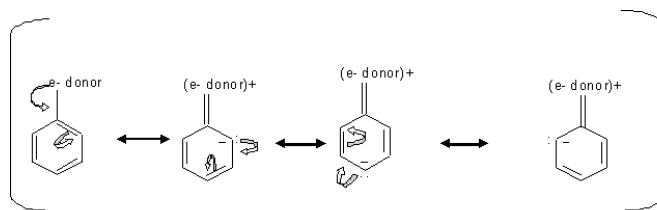


Substituents determine the reaction direction by resonance or inductive effect

Resonance effect is the conjugation between the ring and the substituent, which means the delocalization of the π 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 $-\text{OH}$ 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 substituents is esters or amides, they are less activating because they form resonance structure that pull the electron density away from the ring.

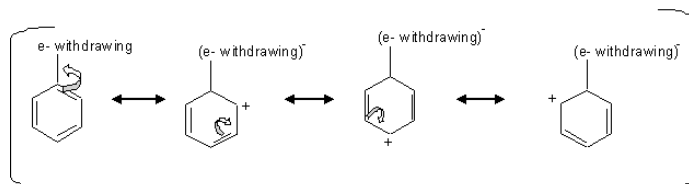


By looking at the mechanism above, we can see how electron donating groups direct electrophilic substitution to the ortho and para positions. Since the extra electron density is localized on the ortho and para carbons, these carbons are more likely to react with the electrophile.

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.

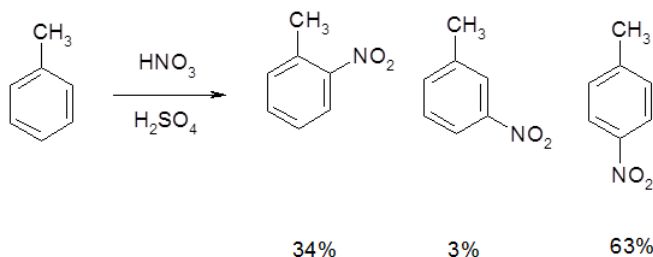
Halogens are an exception of the deactivating group that directs to the ortho or para substitution. The halogens deactivate the ring by inductive effect not by the resonance even though they have an unpaired pair of electrons. The unpaired pair of electrons gets donated to the ring, but the inductive effect pulls away the s electrons from the ring by the electronegativity of the halogens.

Substituents determine the reactivity of rings

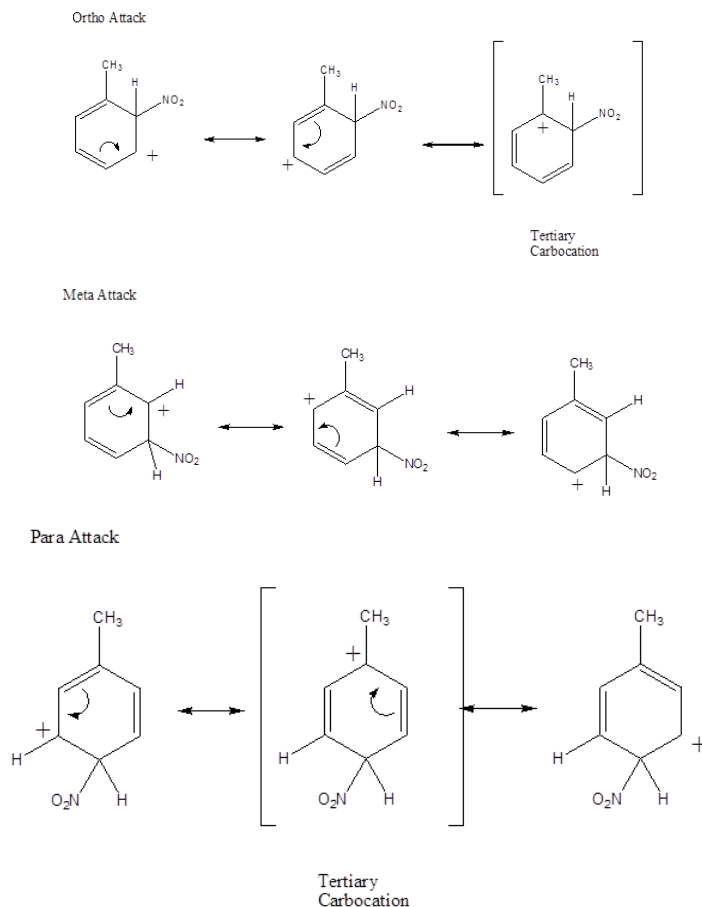
The reaction of a substituted ring with an activating group is faster than the same reaction with benzene. On the other hand, a substituted ring with a deactivated group reacts slower than benzene.

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.

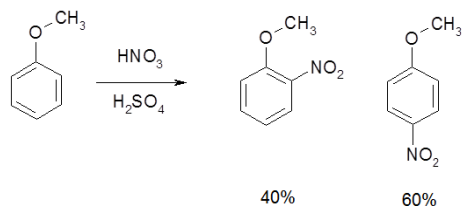
The CH_3 Group is an ortho, para director



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.



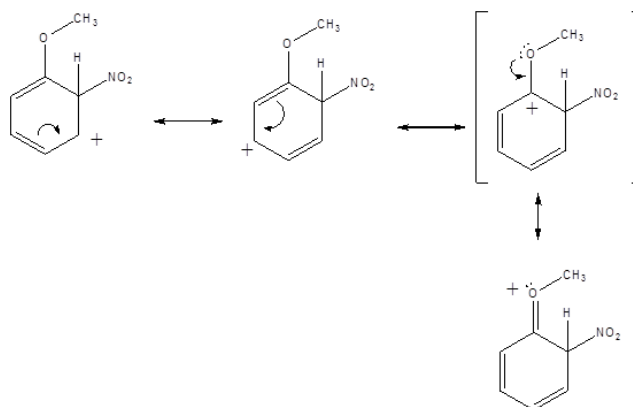
The O-CH₃ Group is an ortho, para director



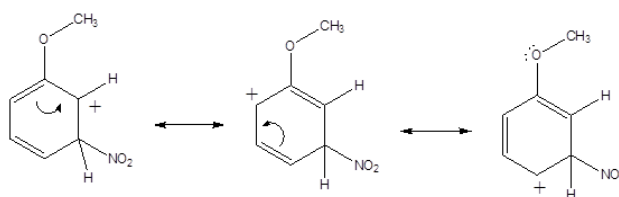
The methoxy group is an example of groups that are ortho, para directors by having an oxygen or nitrogen adjacent to the aromatic ring. This same activation is present with alcohols, amines, esters and amides (with the oxygen or nitrogen attached to the ring, not the carbonyl).

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.

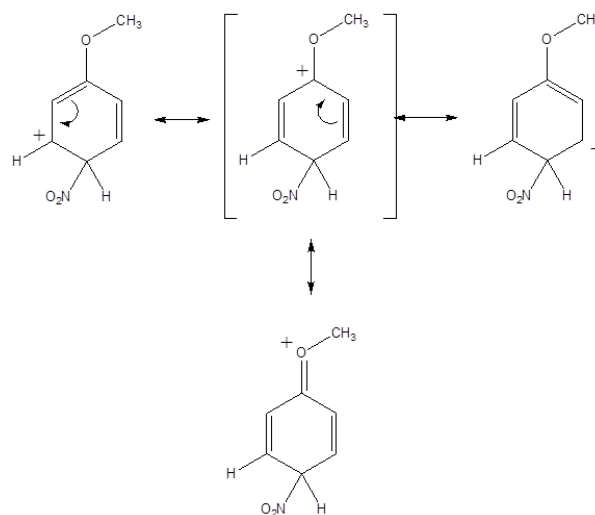
Ortho Attack



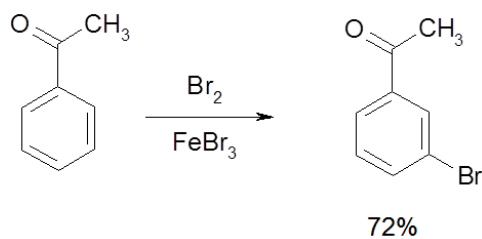
Meta Attack



Para Attack

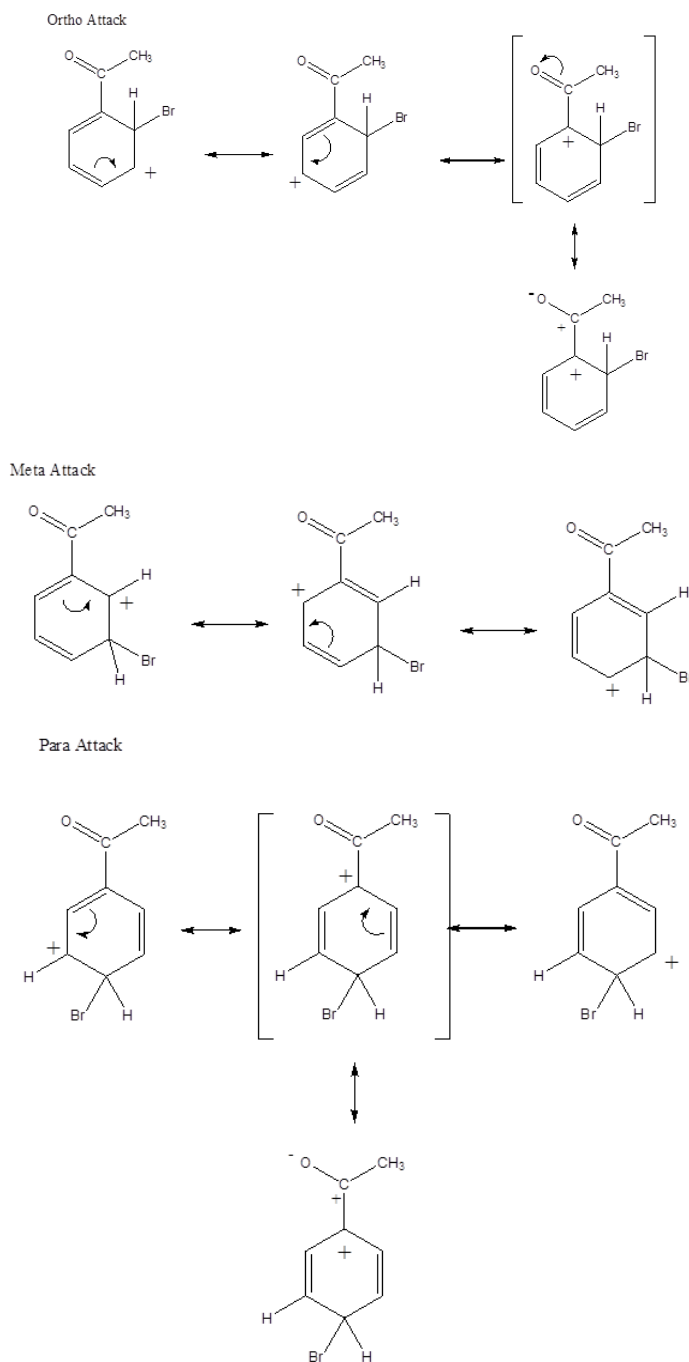


Acyl groups are meta directors



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.



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.

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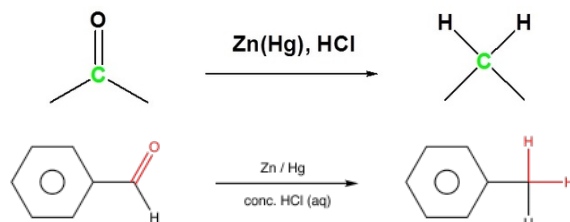
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8.7: Clemmensen Reduction

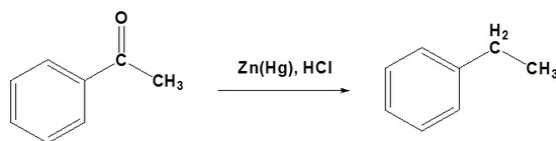
The reaction of aldehydes and ketones with zinc amalgam (Zn/Hg alloy) in concentrated hydrochloric acid, which reduces the aldehyde or ketone to a hydrocarbon, is called Clemmensen reduction.

Introduction

This alternative reduction involves heating a carbonyl compound with finely divided, amalgamated zinc in a hydroxylic solvent (often an aqueous mixture) containing a mineral acid such as HCl. The mercury alloyed with the zinc does not participate in the reaction, it serves only to provide a clean active metal surface.

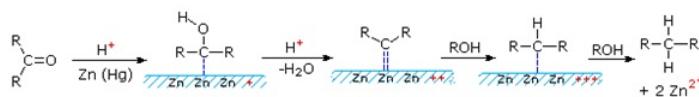


Example



Possible mechanism

The mechanism of Clemmensen reduction is not fully understood; intermediacy of radicals are implicated. Clemmensen reduction is complementary to [Wolff-Kishner reduction](#), which also converts aldehydes and ketones to hydrocarbons, in that the former is carried out in strongly acidic conditions and the latter in strongly basic conditions.



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