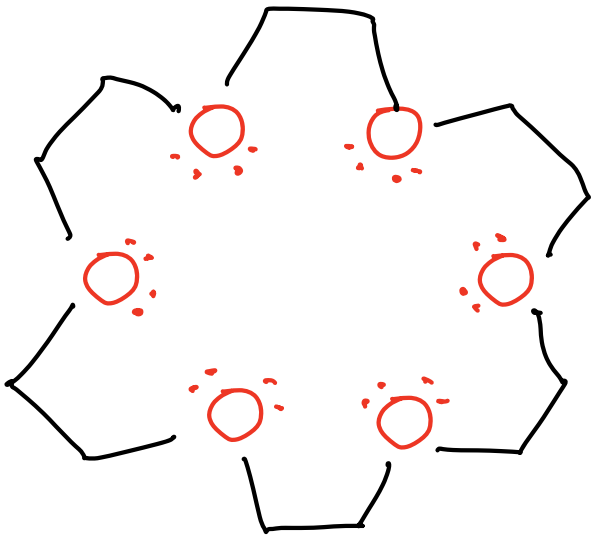
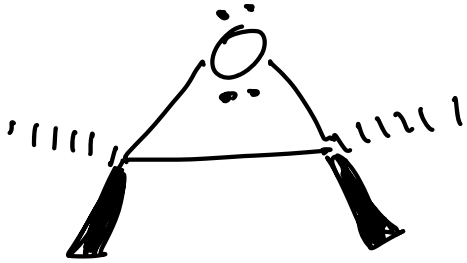
Crown Ethers → bind cations based on



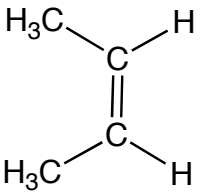


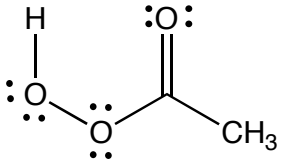
Epoxide

Important because they can be formed from alkenes or halohydrins AND

Epoxides are also involved in a number of biological processes including oxidative damage

Epoxide Formation





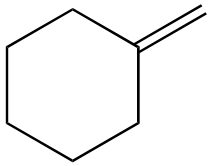
Products

Summary: Alkenes react with peracids in a single concerted step

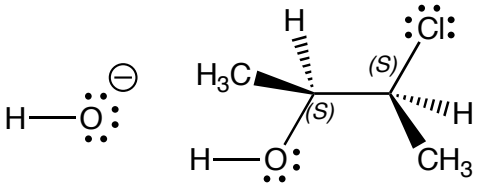
Regiochemistry: N/A

Stereochemistry: Mixed when new chiral centers are created

Example:



CH_3CO_3H



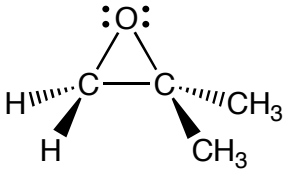
Products

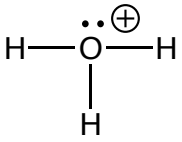
Summary: Halohydrins react in base to give the alkoxide that reacts antiperiplanar to give the epoxide.

Regiochemistry: N/A

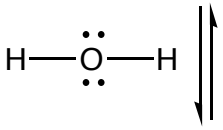
Stereochemistry: Antiperiplanar transition state

Acid-Catalyzed Epoxide Opening

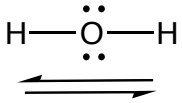








Products



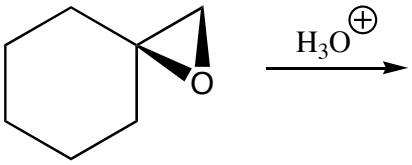


Summary: In acid, epoxides are protonated to give a highly reactive cation intermediate that reacts with nucleophiles at the more highly substituted carbon atom

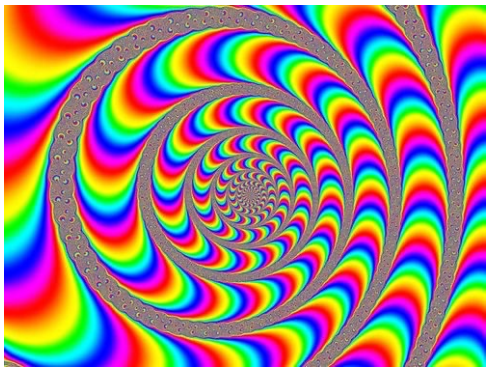
Regiochemistry: "Markovnikov" Attack at more highly substituted C atom

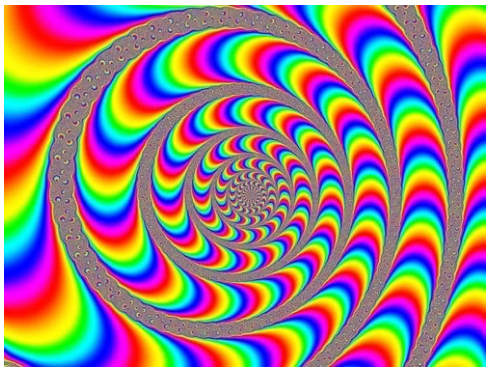
Stereochemistry: Anti

Example:

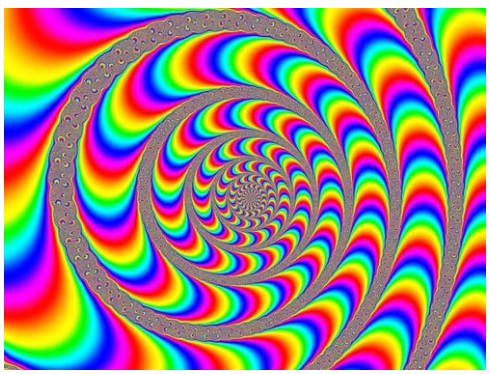


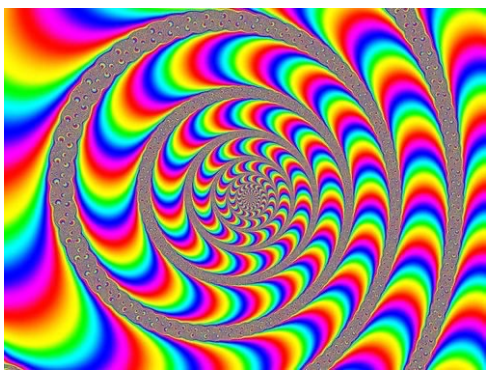
Flashback!!





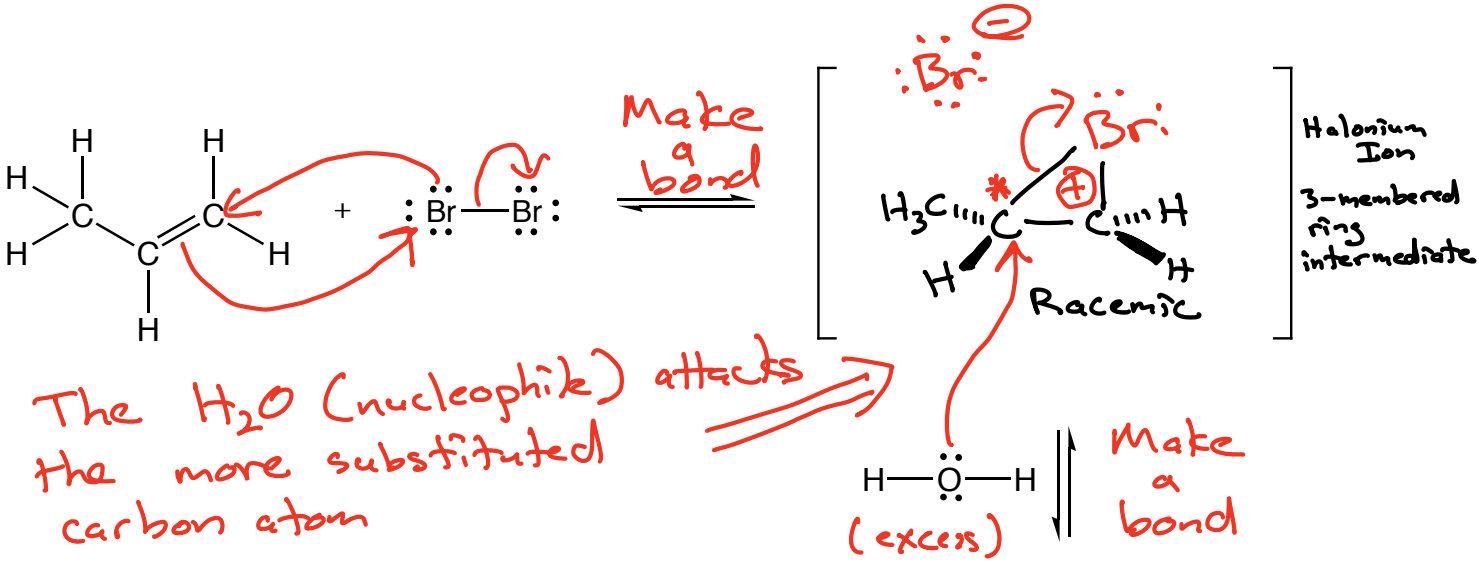


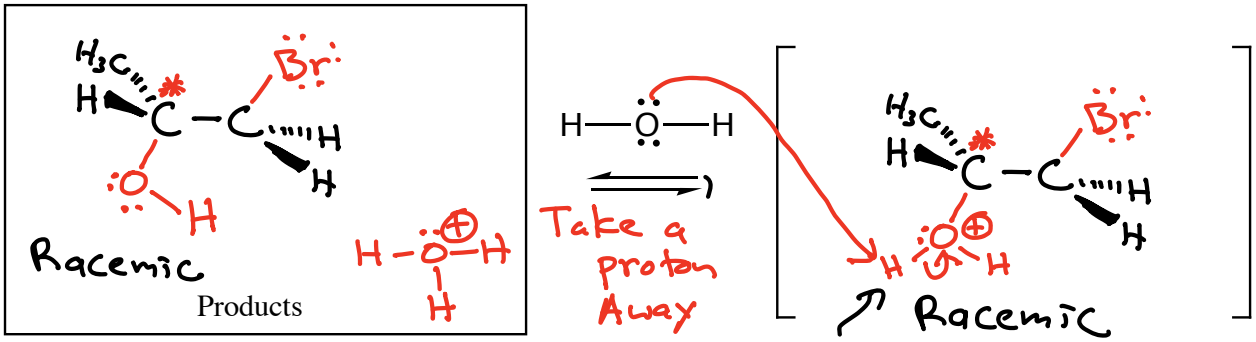




Flashback!!

Alkene Hydrohalogenation





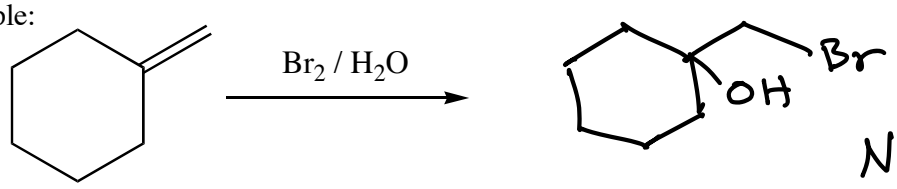
pH drops during the reaction!

Summary: Alkene reacts with X_2 to give a 3-membered ring intermediate (halonium ion) → H_2O attacks the more substituted C atom and we take a proton away to give the halohydrin product.

Regiochemistry: Markovnikov (OH on more substituted C atom)

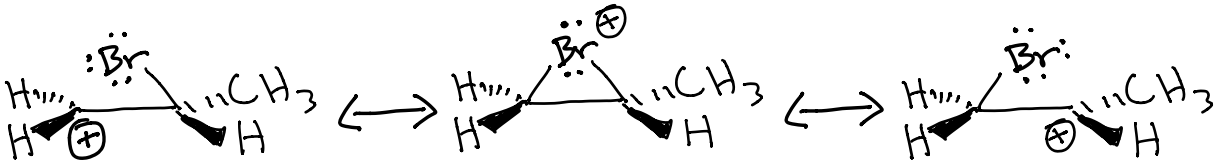
Stereochemistry: Anti

Example:



Not Chiral

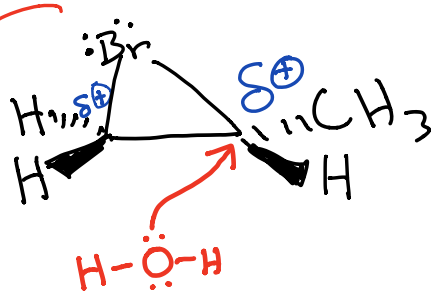
Flashback → Halohydrin Mechanism



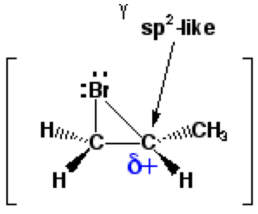
Minor Contributor

Major Contributor

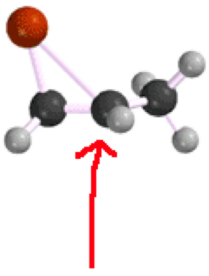
Resonance Hybrid

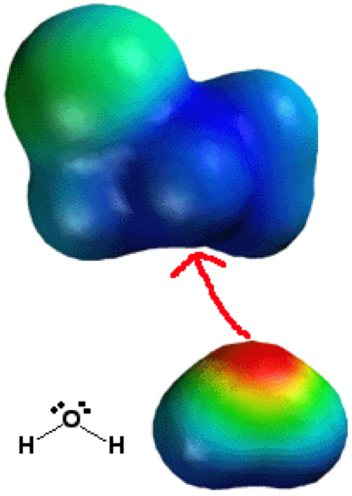


Water attacks the more substituted carbon atom because there is more partial ⊕ charge



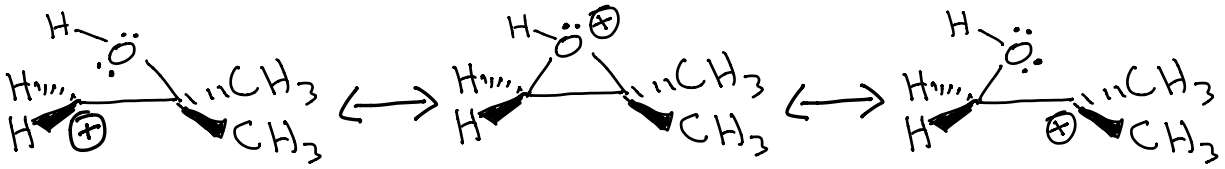
Resonance hybrid

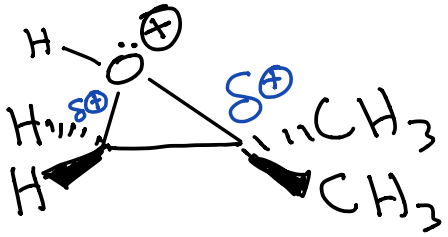




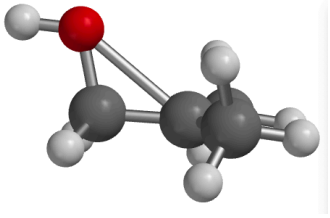
Nucleophiles Attack the More Positively-Charged Carbon Atom From This Face Leading to Markovnikov Regiochemistry and Trans Stereochemistry of Addition

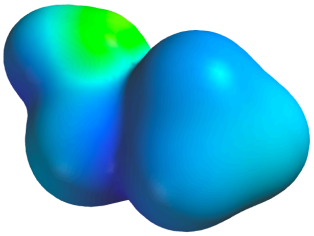
Epoxide in acid

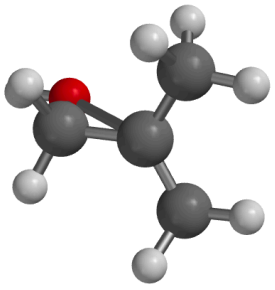


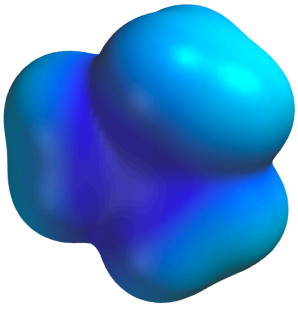




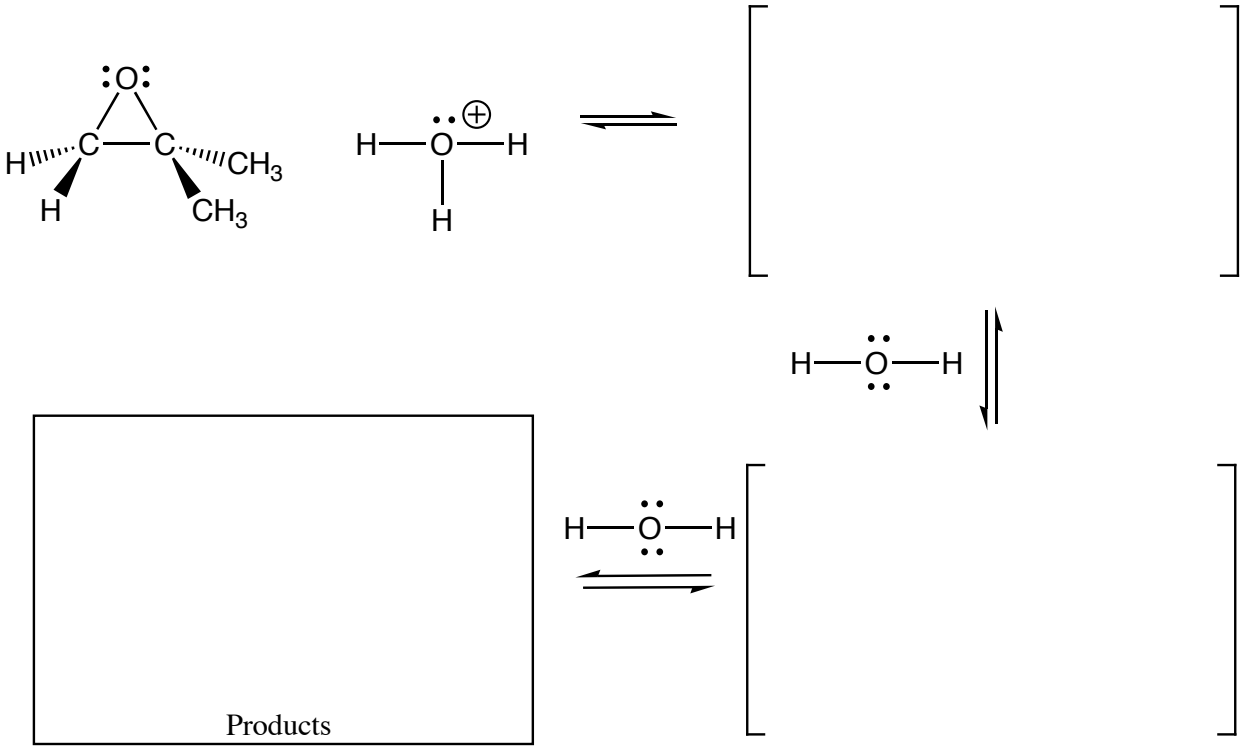






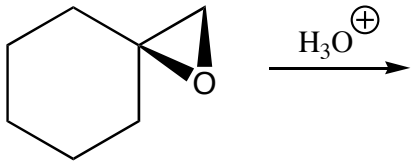


Acid-Catalyzed Epoxide Opening

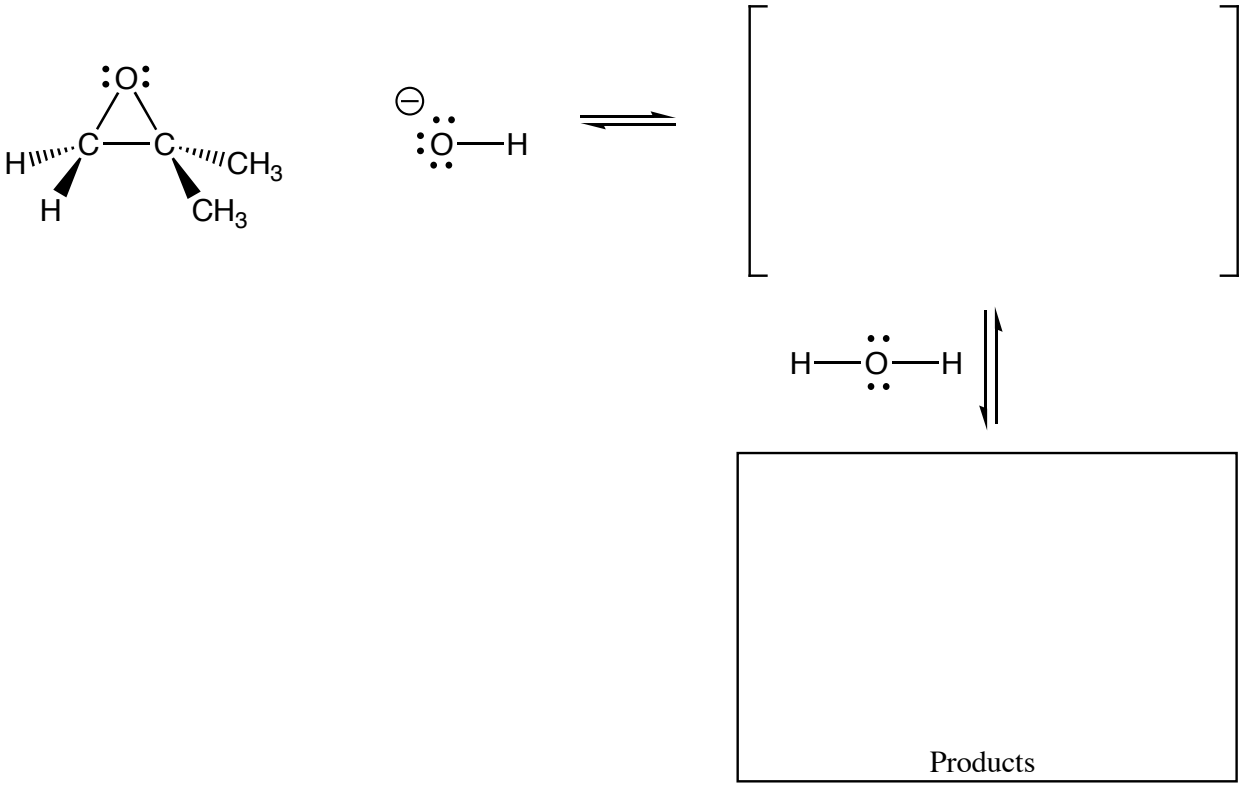


Summary:	In acid, epoxides are protonated to give a highly reactive cation intermediate that reacts with nucleophiles at the more highly substituted carbon atom
Regiochemistry:	"Markovnikov" Attack at more highly substituted C atom
Stereochemistry:	Anti

Example:

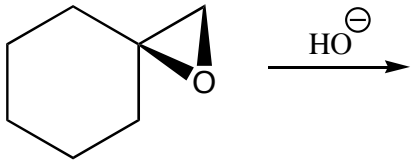


Nucleophilic ~~Base Promoted~~ Epoxide Opening

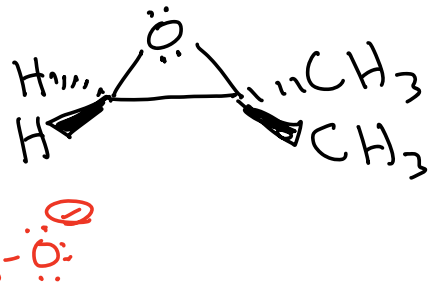


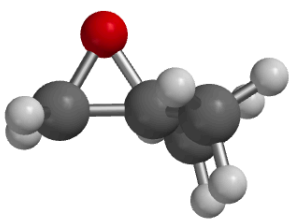
Summary:	Epoxides add strong nucleophiles at the less hindered carbon atom
Regiochemistry:	Less hindered (non-Markovnikov)
Stereochemistry:	Anti addition

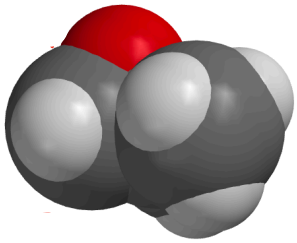
Example:



Epoxide reacting with nucleophile



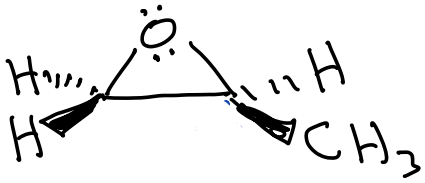




H-O⊖

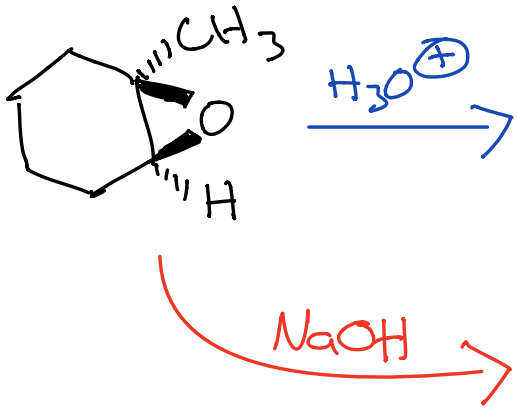


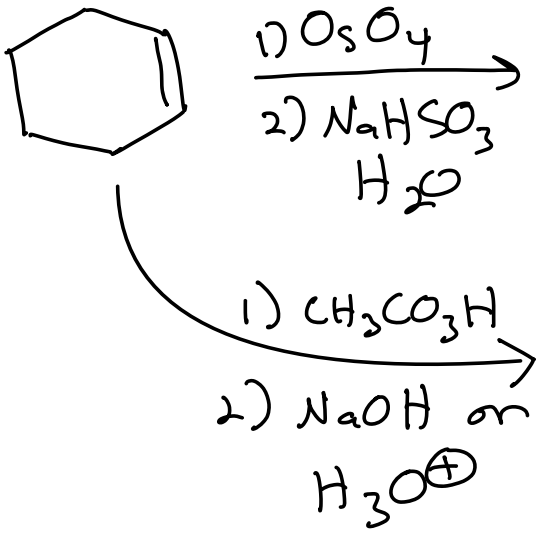
Watch out for the stereochemistry!



$H_3O^{\oplus}$ →

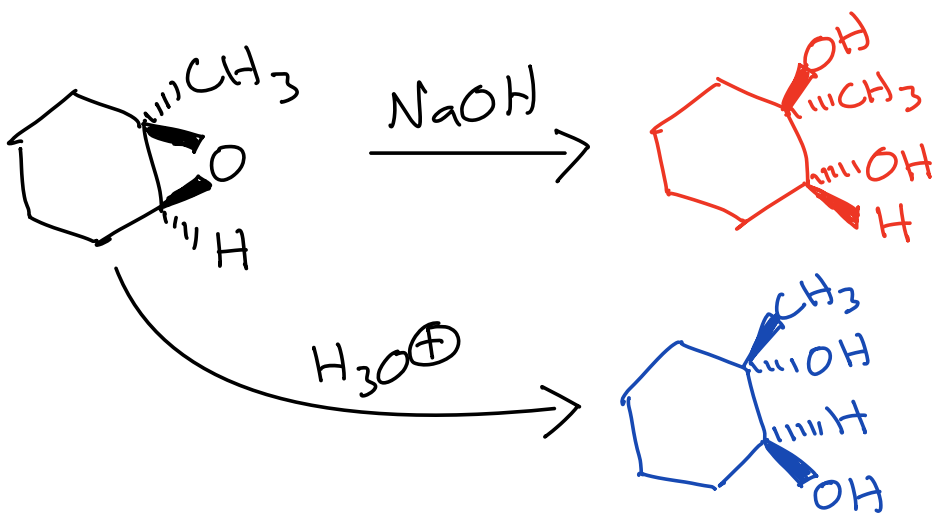
NaOH →


CH3
O
H
H3O⊕
NaOH

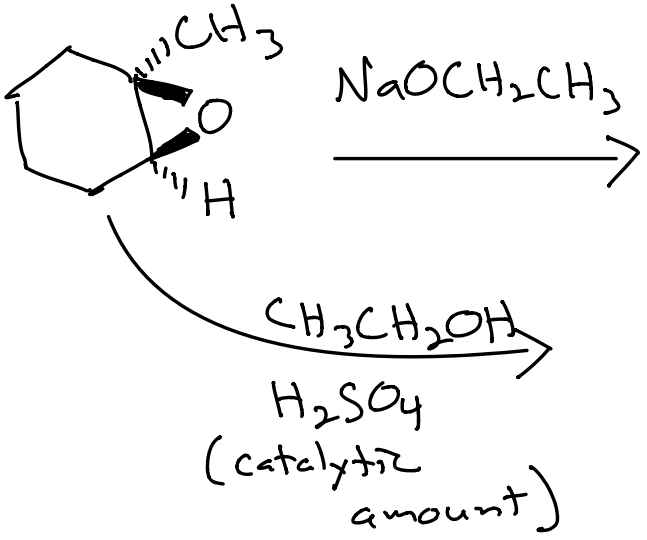




Watch out for the stereochemistry!

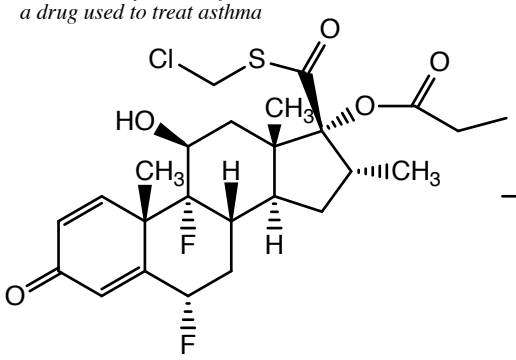


Works with alkoxides and alcohols as well



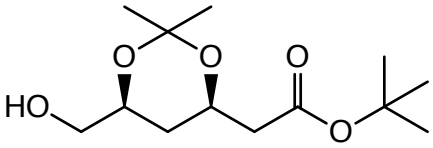
Reactions in the Context of Complex Molecules

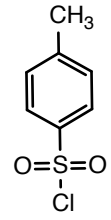
Used in the synthesis of Fluticasone (Flonase), a drug used to treat asthma



NaI

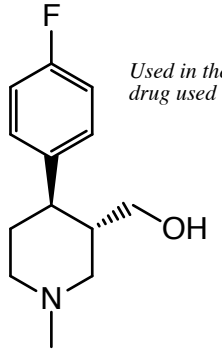
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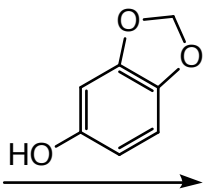
Used in the synthesis of Lipitor

NaCN



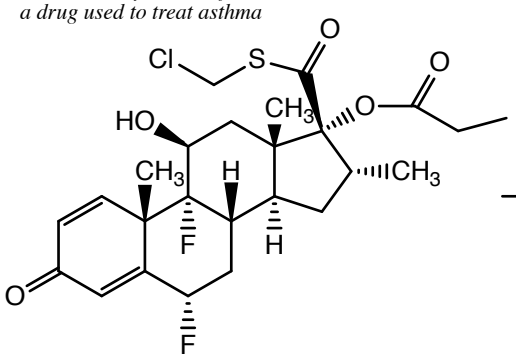
Used in the synthesis of Paxil, a drug used to treat depression

$SOCl_2$



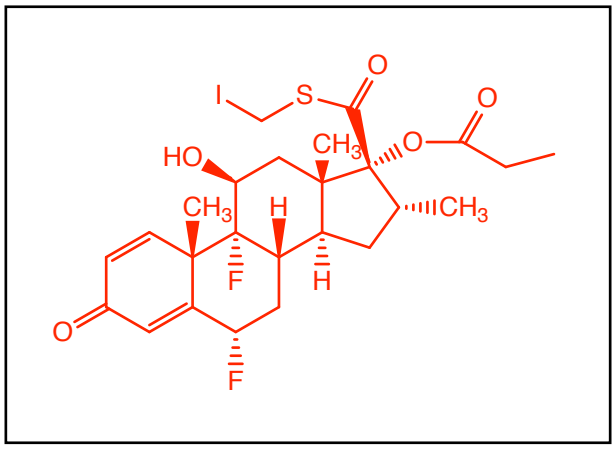
Reactions in the Context of Complex Molecules

Used in the synthesis of Fluticasone (Flonase), a drug used to treat asthma

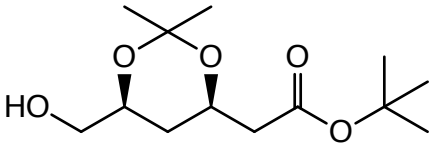


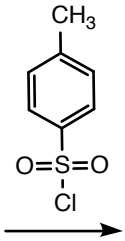
NaI

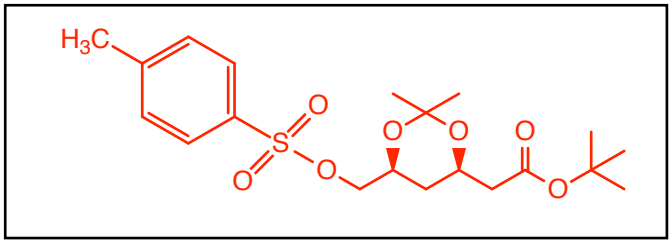
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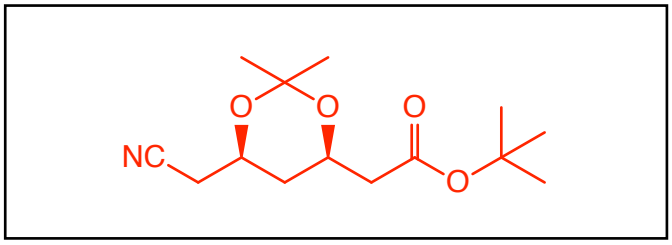
Used in the synthesis of Lipitor



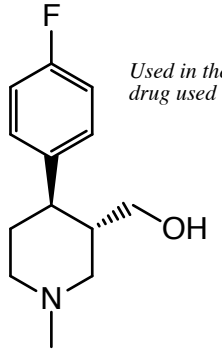




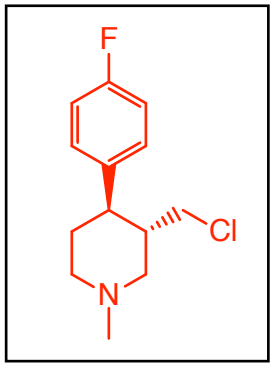
NaCN

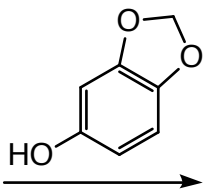


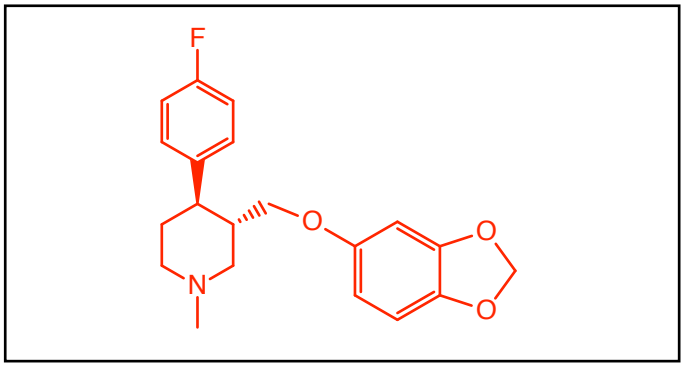
Used in the synthesis of Paxil, a drug used to treat depression



$SOCl_2$

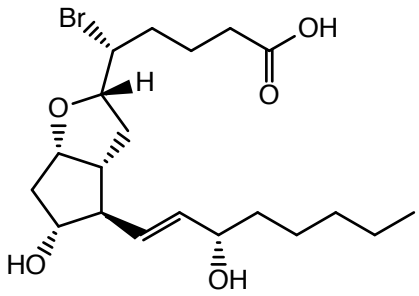






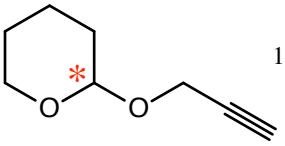
Reactions in the Context of Complex Molecules

Used in the synthesis of several protaglandins

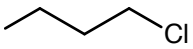


excess KO*t*Bu
*t*BuOH

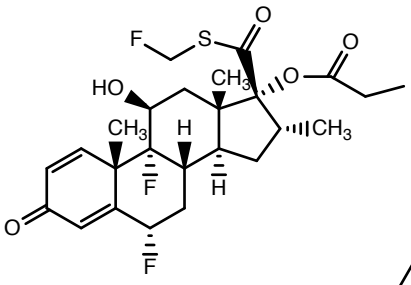
Used in the synthesis of protaglandin C_2



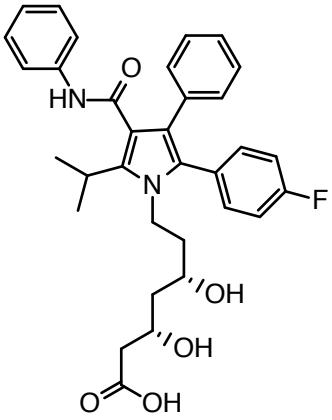
(racemic)

1. 1 eq. $NaNH_2$ THF (ether solvent)
2. 

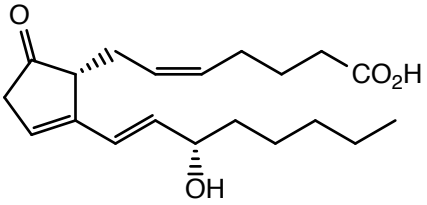
DMSO (polar aprotic solvent) NaCN



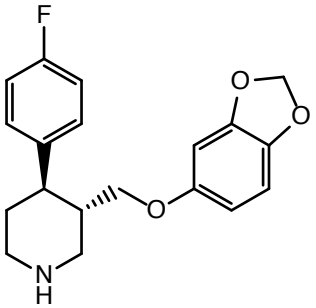
Fluticasone (Flonase)



Atorvastatin (Lipitor)



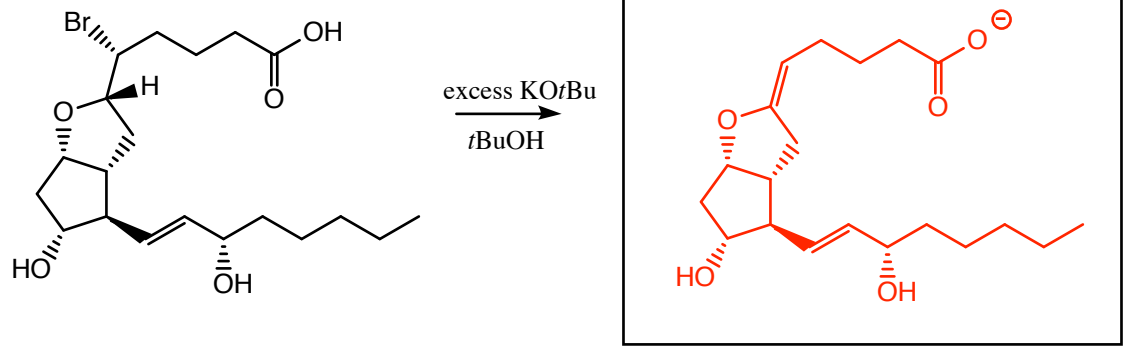
Prostaglandin C_2



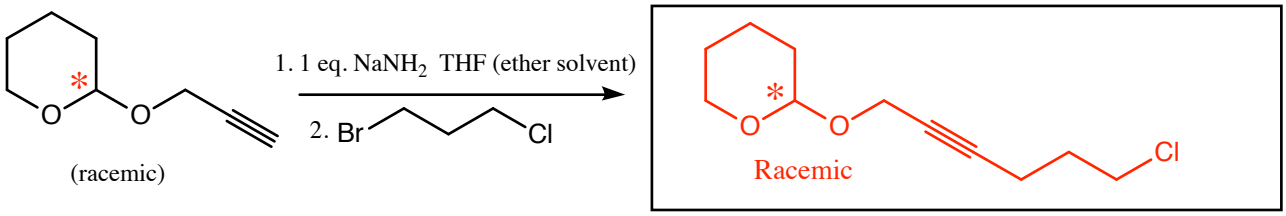
Paroxetine (Paxil)

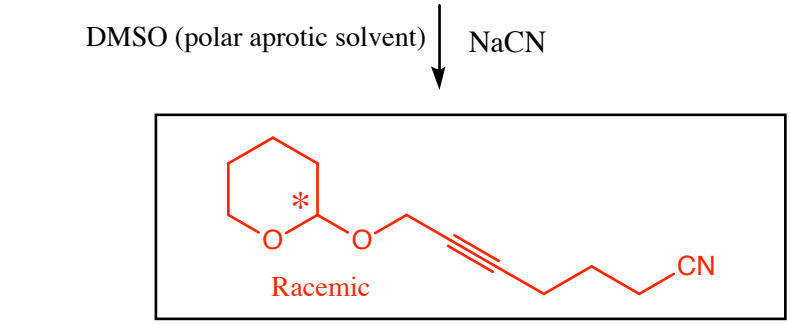
Reactions in the Context of Complex Molecules

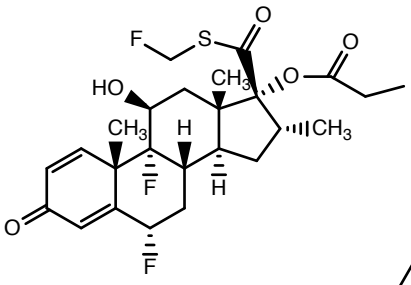
Used in the synthesis of several protaglandins



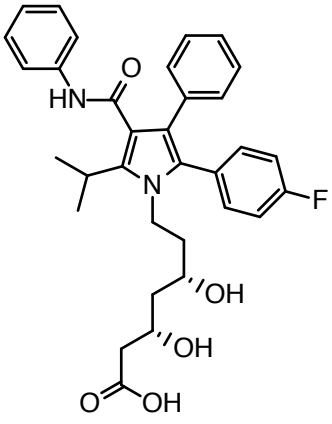
Used in the synthesis of protaglandin C_2



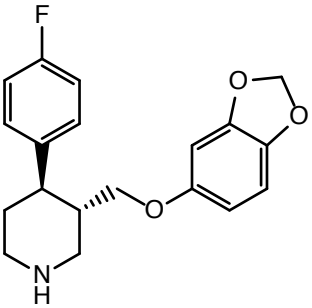




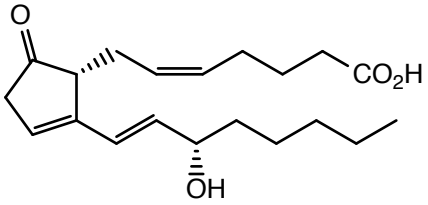
Fluticasone (Flonase)



Atorvastatin (Lipitor)



Paroxetine (Paxil)



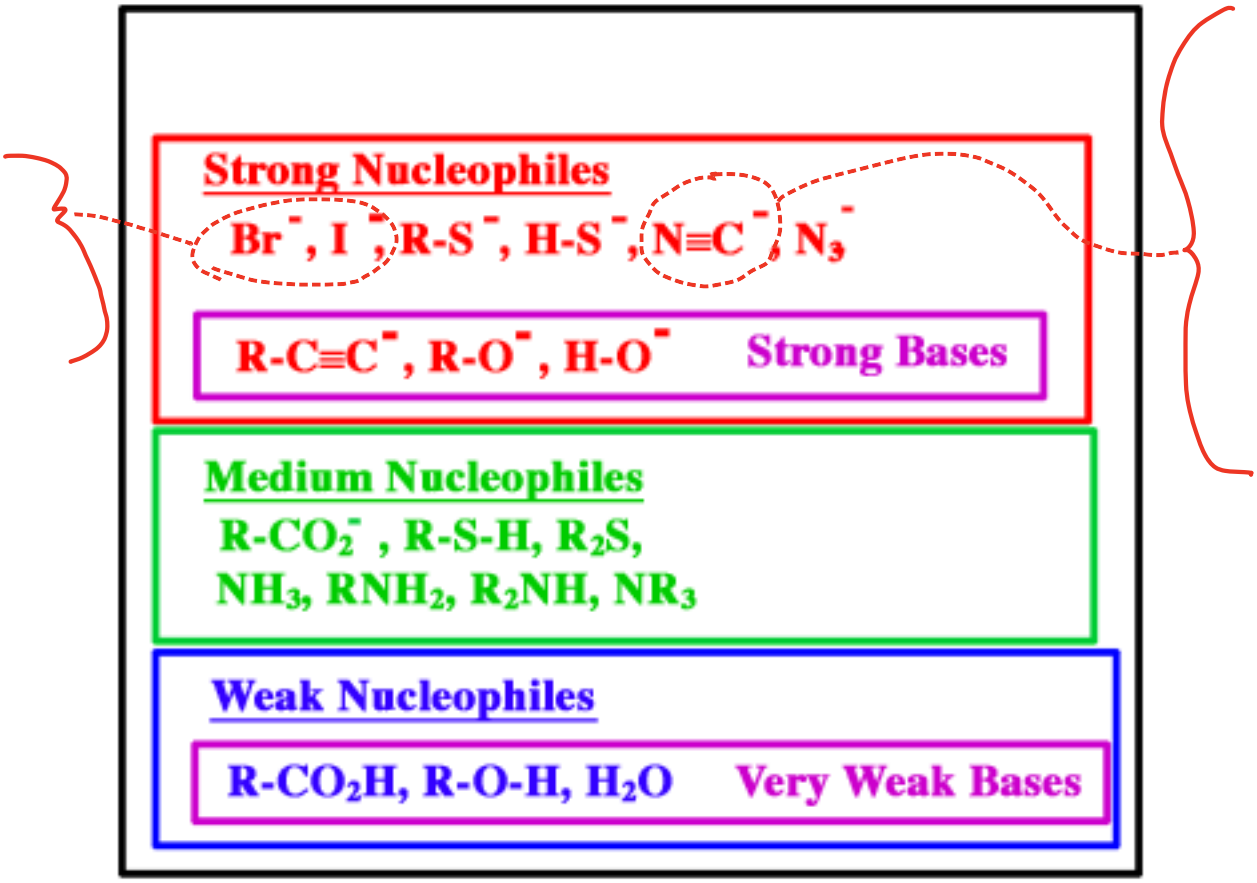
Prostaglandin C_2

Here are some things I wish I had said when we were talking about substitution and elimination reactions:

Good leaving group →

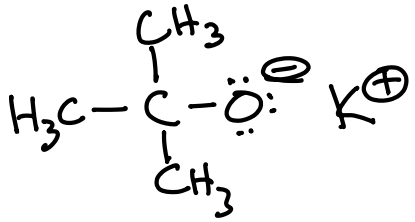
Nucleophiles → not simple to explain what makes a good nucleophile → the Table for reference

Table of Nucleophiles



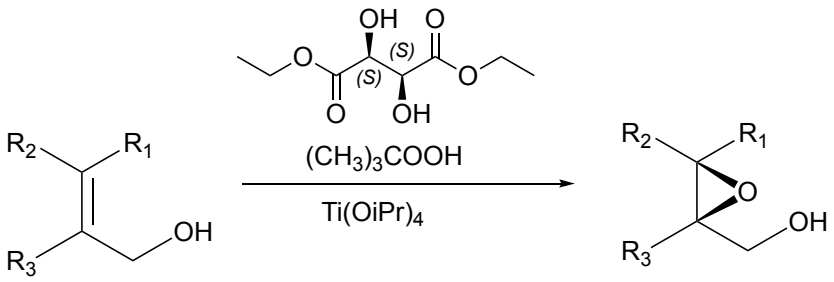
Special Case

***Tert*-Butoxide ($tBuO^-$) is a strong base, but is not a nucleophile due to steric hindrance.**

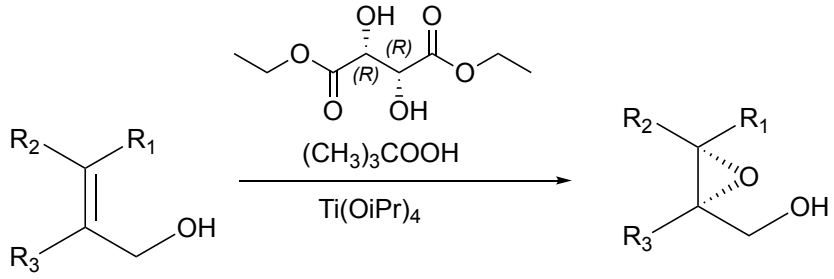


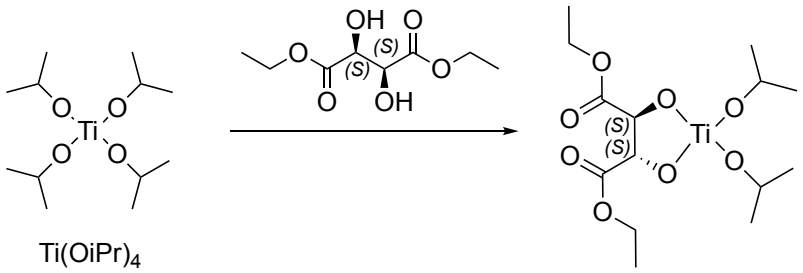
"KOtBu" or "$tBuO^-$"

The Sharpless Epoxidation 2001 Nobel prize for making single enantiomer products!



R_1, R_2, R_3 can be any alkyl group or H





$Ti(OiPr)_4$

The true situation is more complicated than this

The First Practical Method for Asymmetric Epoxidation

Tsutomu Katsuki, K. Barry Sharpless*[18]

Department of Chemistry, Stanford University
Stanford, California 94305

Received May 5, 1980

Sir:

As revealed in Scheme I, we have discovered a new metal-catalyzed asymmetric epoxidation process which is far more selective than any of the previously described methods[1] for this type of asymmetric transformation. The simplicity of this new method is one of its more attractive aspects; the necessary components [(+) or (−)-diethyl tartrate,[2] titanium tetraisopropoxide, and *tert*-butyl hydroperoxide] are all[3] commercially available at low to moderate cost.[4]

Scheme I

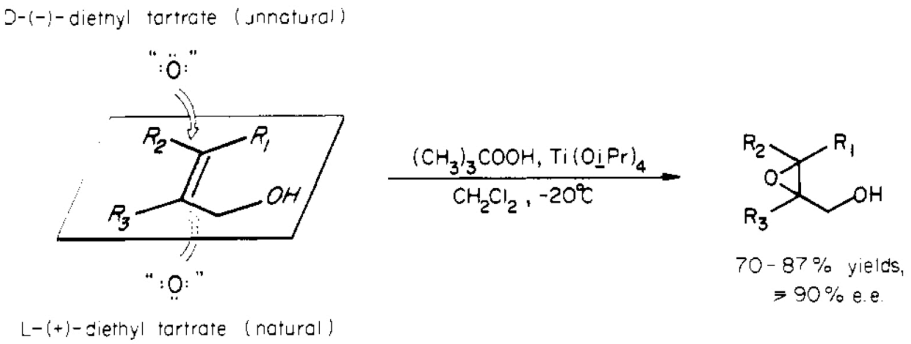
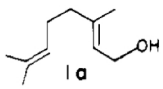
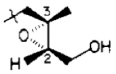
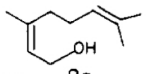
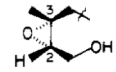
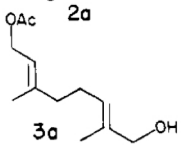
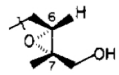
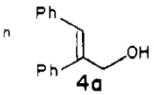
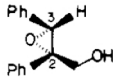
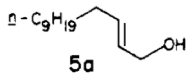
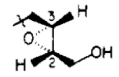
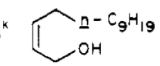
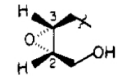
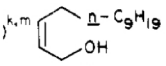
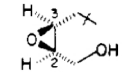
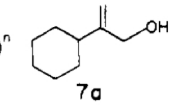
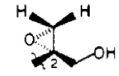


Table I. Asymmetric Epoxidation of Allylic Alcohols[a]

	Allylic Alcohol	Epoxyalcohol	% yield[b]	% e.e.[c]	Configuration[d]
(1)	 1a	1b 	77	95 (Eu, M)	2(S), 3(S)[e]
(2)	 2a	2b 	79	94 (Eu, M)	2(S), 3(R)[f]
(3)	 3a	3b 	70[g]	>95 (Eu)	6(S), 7(S)[g]
(4)[h]	 4a	4b 	87	>95 (Eu)	2(S), 3(S)[i]
(5)	 5a	5b 	79	>95 (M)	2(S), 3(S)[j]
(6)[k]	 6a	6b 	82	90 (M)	2(S), 3(R)[l]
(7)[k,m]	 6a	6c 	80	90 (M)	2(R), 3(S)[m]
(8)[n]	 7a	7b 	81	>95 (M)	2(S)[o]

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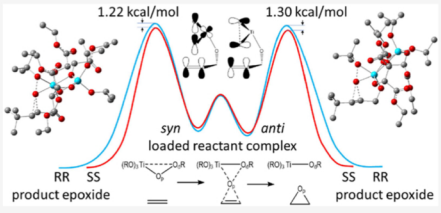
Mechanism of the Sharpless Epoxidation Reaction: A DFT Study

Robert D. Bach* and H. Bernhard Schlegel

Cite This: *J. Phys. Chem. A* 2024, 128, 2072−2091 Read Online

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ABSTRACT: The Sharpless reaction is an enantioselective epoxidation of prochiral allylic alcohols that employs a Ti(IV) catalyst formed from titanium tetra(isopropoxide), Ti(O-*i*-Pr)$_4$, diethyl tartrate (DET), and the oxidizing agent *tert*-butyl hydroperoxide. The M06-2X DFT functional with the 6-311+G-(d,p) basis set has been employed to model the structures and energetics of the Sharpless epoxidation reaction. The monomeric tetracoordinate titanium(IV) diethyltartrate is thermodynamically strongly favored to dimerize, producing a pentacoordinate catalyst, [Ti(DET)(O-i-Pr)$_2$]$_2$, that is a more reactive chiral epoxidation catalyst. The rapid ligand exchange reactions needed to generate the "loaded" catalyst and to repeat the overall catalytic cycle have been examined and are found to have activation energies that are much lower than the epoxidation barriers. The transition structures and activation energies for the enantioselective epoxidation of allyl alcohol, *trans*-methyl-allyl alcohol and *trans-tert*-butyl-allyl alcohol with the "loaded" Sharpless catalyst, [Ti$_2$(DET)$_2$(O-*i*-Pr)$_2$-(OAllyl)-(OO*t*-Bu)], are presented. The effect of the C═O···Ti interactions on the activation energies and the significance of the O−C−C═C dihedral angle on the enantioselectivity of the epoxidation reaction are discussed.



To understand NMR you need to know the following:

A. Physics: Moving charge generates a magnetic field, and a moving magnetic field causes charges to move in a conductor.

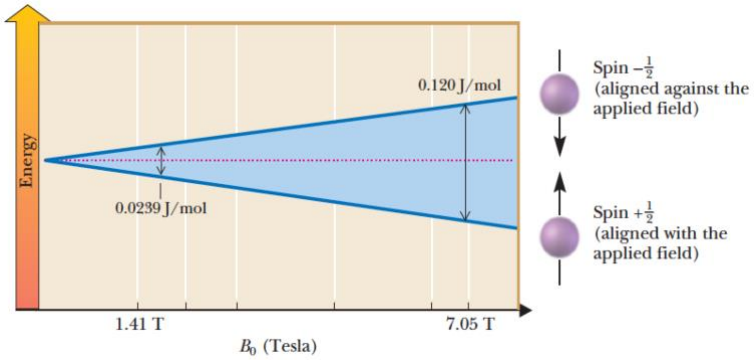
B. Atomic nuclei, like electrons, have a quantum mechanical property of "spin". Spin can be thought of as a small magnetic field around the nucleus created as if the positive charge of the nucleus were circulating.

C. NMR, nuclear magnetic resonance, is used to assign structures of organic molecules.

D. We care about the nuclei ^{1}H and ^{13}C since these are commonly found in organic molecules and they have spin quantum numbers of 1/2.

E. Nuclei with spin quantum number 1/2 are quantized in one of two orientations, "+1/2" (lower energy) or "-1/2"(higher energy) in the presence of an external magnetic field, that is, with and against the external field, respectively.

F. **The difference in energy between the +1/2 and -1/2 nuclear spin states is proportional to the strength of the magnetic field felt by the nucleus.**



G. Electron density is induced to circulate in a strong external magnetic field, which in turn produces a magnetic field that opposes the external magnetic field. This **shields** nuclei from the external magnetic field. The greater the electron density around a nucleus, the more shielded it is, and the lower the energy (frequency) of electromagnetic radiation required to flip its nuclear spin.

H. In the classic ^{1}H-NMR experiment, the molecule of interest is placed in solvent (the solvent has deuterium atoms in place of H atoms so the solvent molecules will not show up in the spectra, see R.) then is put in a spinning tube in a very strong magnetic field. The sample is exposed to radiofrequency irradiation and if it is of exactly the right frequency energy is absorbed and spins flip from +1/2 to -1/2 (come into resonance). The absorbed energy is plotted in the spectra.

I. All ^{1}H-NMR spectra are recorded as **chemical shift (∂, delta)** in the units of **ppm** (parts per million). Shielding magnetic field effects are around 1 millionth as large as the external magnetic field in which the sample is placed. Tetramethylsilane (TMS, $(CH_3)_4Si$)) is placed in the sample as a standard and assigned the value of 0.0 ppm. ***Warning the NMR scale is plotted "backwards", with higher values to the left!!***

Certain nuclei such as ^1H nuclei have a quantum mechanical property called that comes with an associated

.

^1H nuclei can exist in two different , $+1/2$ and $-1/2$.

In a , the nuclei with spin line up with $(+1/2)$ and against $(-1/2)$ the magnetic field.

Nuclei in the are of lower energy and nuclei in the are of higher energy in a magnetic field.

The between the $+1/2$ and $-1/2$ spin states

experienced by the nuclei

of exactly the right energy (i.e. frequency) is by $+1/2$ spin state nuclei causing them to to the $-1/2$ spin state.

NMR experiment →

 $-\frac{1}{2}$

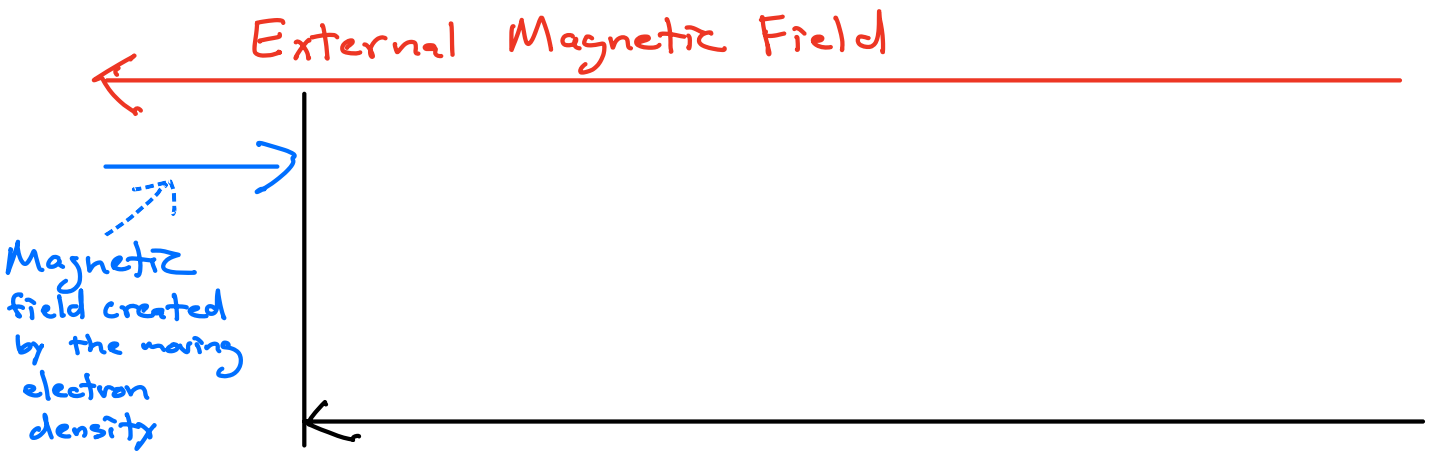
 $+\frac{1}{2}$

The ^1H nucleus of spin state $+\frac{1}{2}$ absorbs a quanta of energy of precisely the correct frequency and the nucleus is "excited" to the $-\frac{1}{2}$ spin state

Key Point →

We monitor the energy that is absorbed by the nuclear spins as they flip

Shielding →



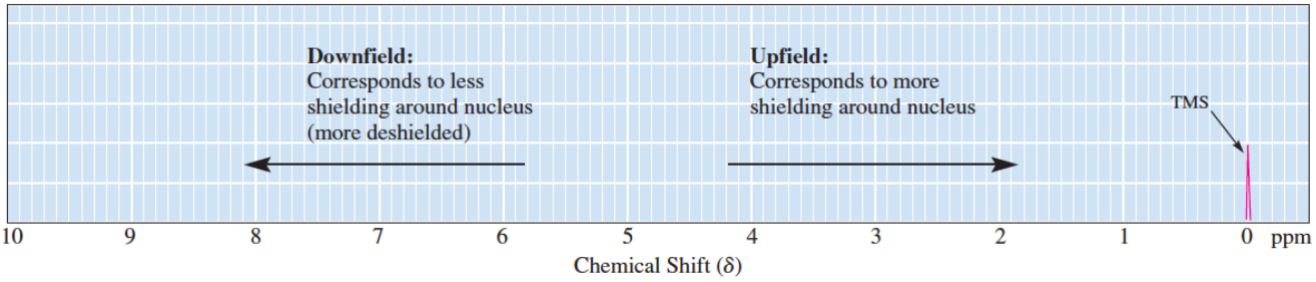
The magnitude of the magnetic field experienced by a nucleus under the electron density.

Shielding Bottom Line ⟶

⇒ More electron density generates a

so a nucleus under more electron density experiences a

⇒ More electron density around a nucleus provides of the external magnetic field



J. The hybridization state of carbon atoms attached to an H atom influences shielding in predictable ways by removing differing amounts of electron density around adjacent nuclei.

K. Electron density in pi bonds also has a large effect on H atom shielding because pi electrons are more free to circulate in an a magnetic field compared to electron density in sigma bonds. Geometry of the pi bond is important.

Table 13.3 The Effect of Hybridization on Chemical Shift

Type of Hydrogen (R = alkyl)	Name of Hydrogen	Chemical Shift δ
RCH_3, R_2CH_2, R_3CH	Alkyl	0.8–1.7
$R_2C{=}C(R)CHR_2$	Allylic	1.6–2.6
$RC{\equiv}CH$	Acetylenic	2.0–3.0
$R_2C{=}CHR$, $R_2C{=}CH_2$	Vinylic	4.6–5.7
RCHO	Aldehydic	9.5–10.1

Type of Hydrogen (R = alkyl, Ar = aryl)	Chemical Shift (δ)*	Type of Hydrogen (R = alkyl, Ar = aryl)	Chemical Shift (δ)*
		RCH_2OH	3.4-4.0
R_2NH	0.5-5.0	RCH_2Br	3.4-3.6
ROH	0.5-6.0	RCH_2Cl	3.6-3.8
RCH_3	0.8-1.0	$RCOCH_3$	3.7-3.9
RCH_2R	1.2-1.4	$RCOCH_2R$	4.1-4.7
R_3CH	1.4-1.7	RCH_2F	4.4-4.5
$R_2C{=}CRCHR_2$	1.6-2.6	$ArOH$	4.5-4.7
$RC{\equiv}CH$	2.0-3.0	$R_2C{=}CH_2$	4.6-5.0
$RCCH_3$	2.1-2.3	$R_2C{=}CHR$	5.0-5.7
$RCCH_2R$	2.2-2.6	$H_2C(O)CH_2$	3.3-4.0
$ArCH_3$	2.2-2.5	RCH	9.5-10.1
RCH_2NR_2	2.3-2.8	$RCOH$	10-13
RCH_2I	3.1-3.3		
RCH_2OR	3.3-4.0		

* Values are relative to tetramethylsilane. Other atoms within the molecule may cause the signal to appear outside these ranges.

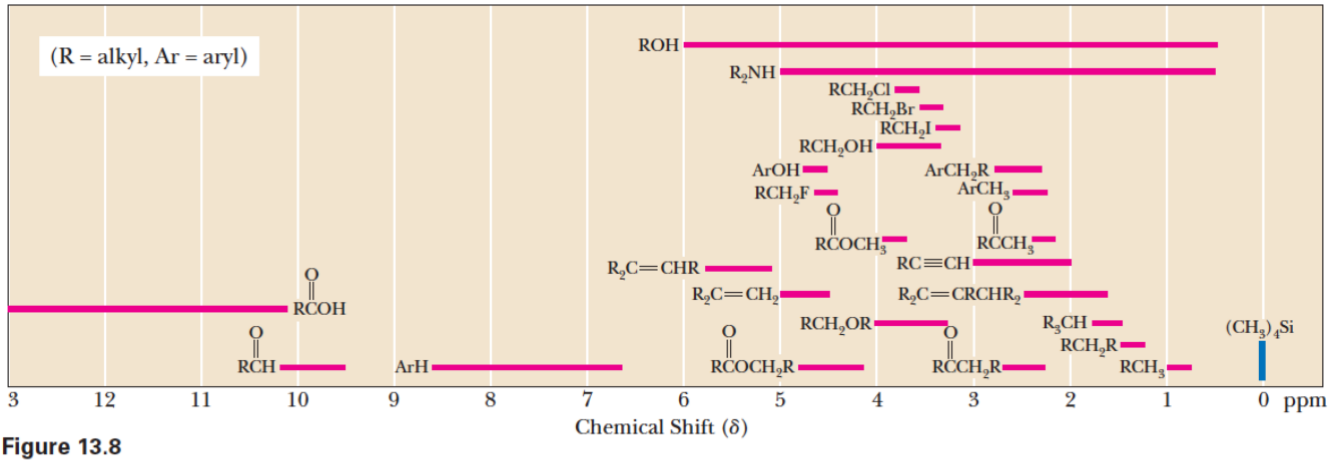


Figure 13.8
Average values of chemical shifts of representative types of hydrogens. These values are approximate. Other atoms or groups in the molecules may cause signals to appear outside of these ranges.

L. Chemically **equivalent** H atoms give rise to the same ^{1}H-NMR signal. **Equivalent** H atoms have the same chemical environment because they are bonded to the same freely rotating sp^3 C atom (molecular motion, nanosecond, is fast compared the time it takes for a spin to flip, microsecond) OR they are equivalent due to symmetry in the molecule.

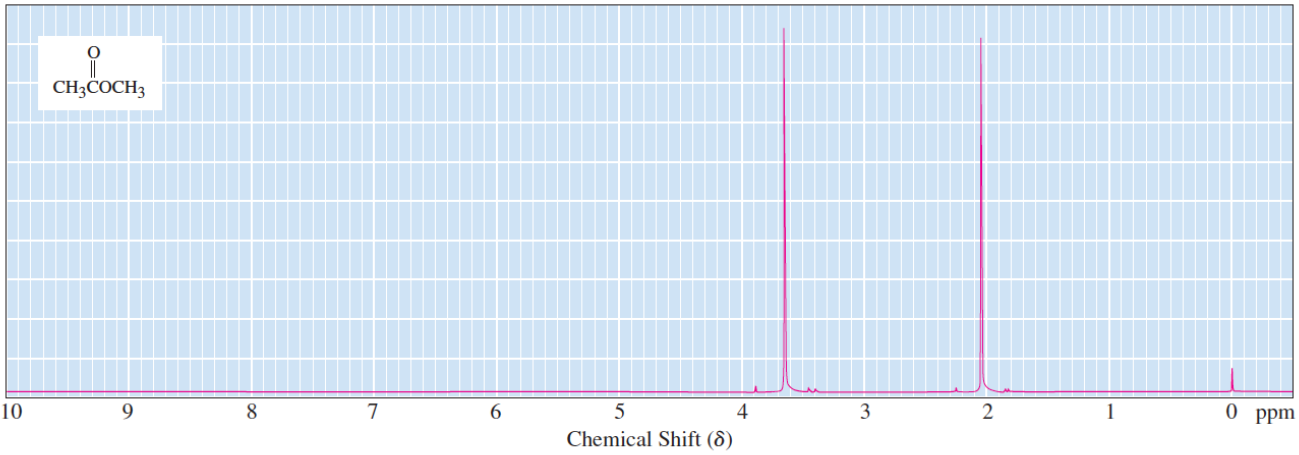


Figure 13.5
^{1}H-NMR spectrum of methyl acetate

M. The area of a ^{1}H-NMR signal is proportional to the number of equivalent H atoms that give rise to that signal.

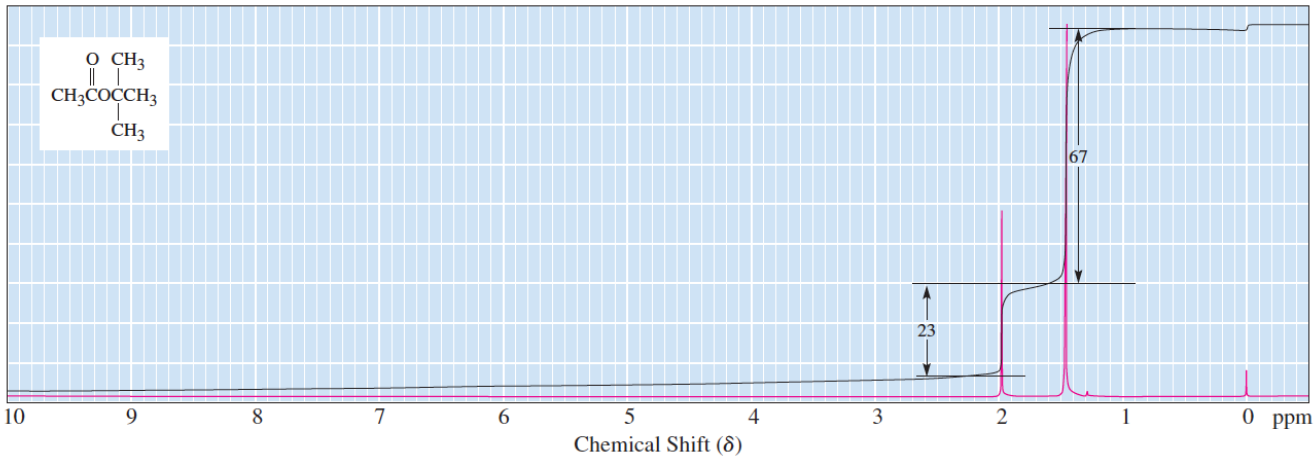
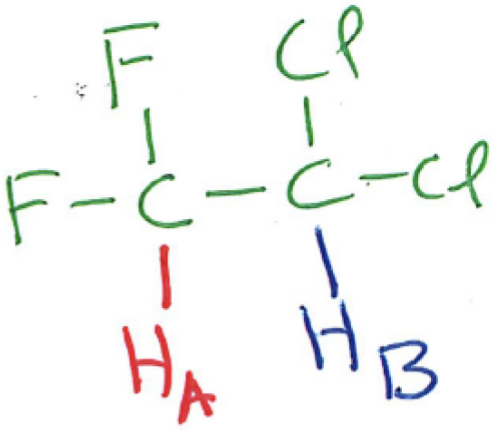


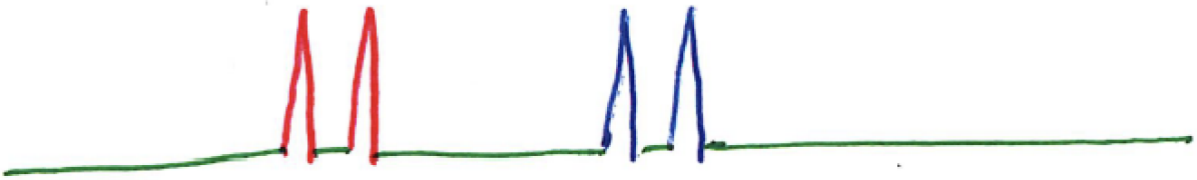
Figure 13.7
^{1}H-NMR spectrum of *tert*-butyl acetate showing the integration. The total vertical rise of 90 chart divisions corresponds to 12 hydrogens, 9 in one set and 3 in the other.

Surprising Fact → The absolute energy difference between ^1H nuclei in a $+1/2$ and $-1/2$ spin state is so small → according to the Boltzmann distribution, at any one time there is only a small excess of ^1H nuclear spins in the $+1/2$ spin state

Definition →

N. Adjacent nuclei have magnetic fields associated with their spins. The spins of equivalent adjacent nuclei can be either +1/2 or -1/2, and at room temperature they are found in about a 50:50 mixture at any given nucleus (very slight excess of lower energy +1/2). These can add to give n+1 different spin **combinations** in the proportions predicted by Pascal's triangle. Each different spin combination produces a different magnetic field, which leads to n+1 splittings in the peaks of the NMR spectra of the adjacent (no more than three bonds away) nuclei.





General case → For "n" equivalent adjacent H atoms a signal is split into "n+1" peaks

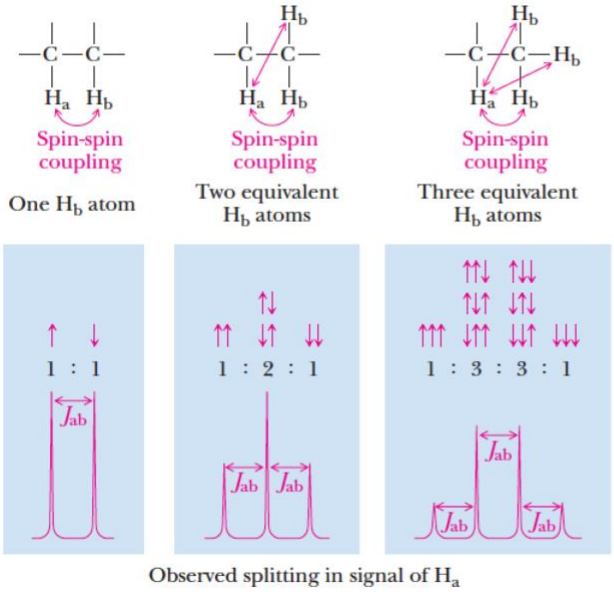


Figure 13.15
The origins of signal splitting patterns. Each arrow represents an H_b nuclear spin orientation.

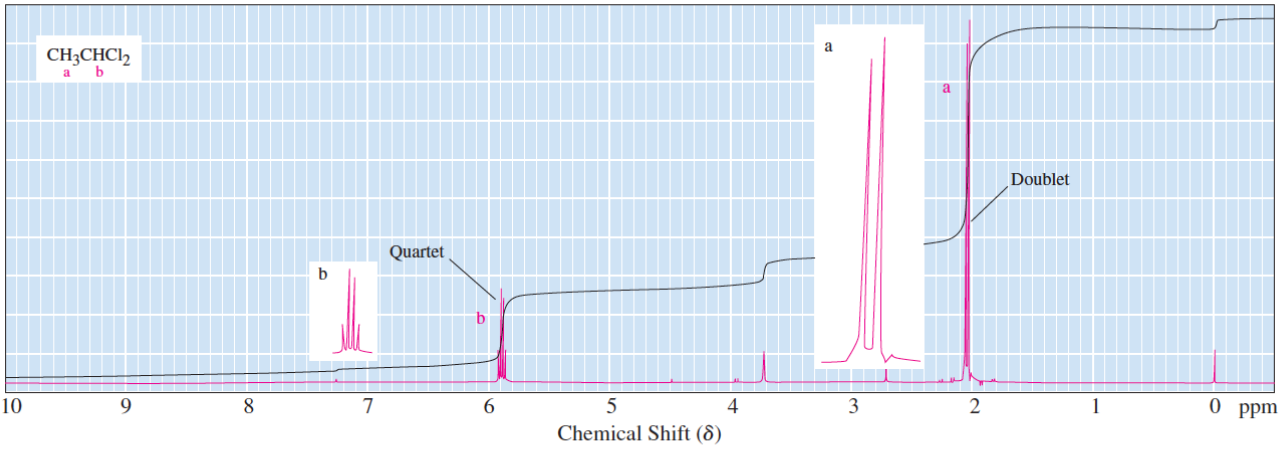
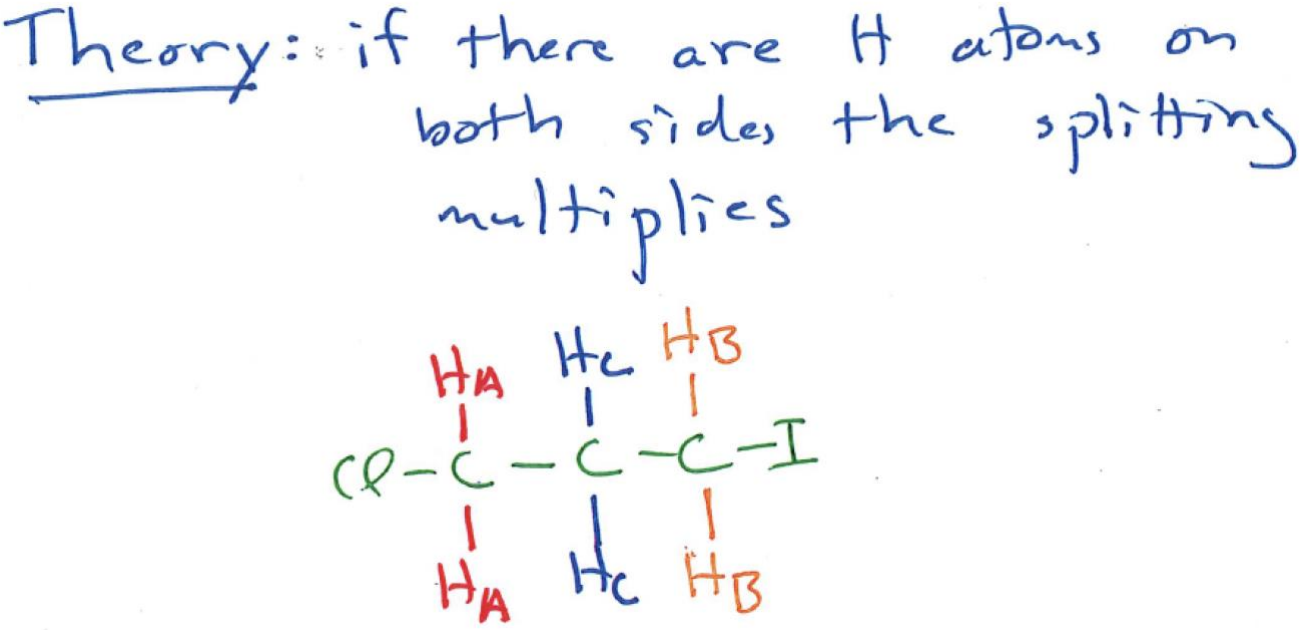
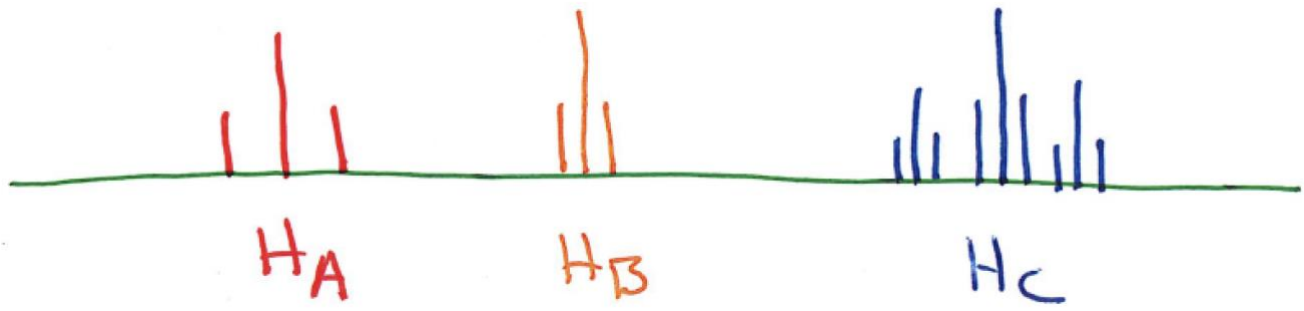


Figure 13.12
^{1}H-NMR spectrum of 1,1-dichloroethane.

O. THEORY: When there are two sets of adjacent H atoms, the number of peaks multiply. For example, a CH_2 group with a CH_2 group and a CH_3group on either side should show 3 x 4 = 12 splittings! You can say this group is a "triplet of quartets" (or a "quartet of triplets").

P. WHAT YOU WILL SEE IN REALITY : For alkyl groups complex splittings simplify because coupling constants ("J") are all about the same. In practice, if there are n adjacent H atoms, equivalent or not, you will see n+1 peaks. This is an approximation, but almost always true on spectra taken with all but the most sophisticated NMR spectrometers.

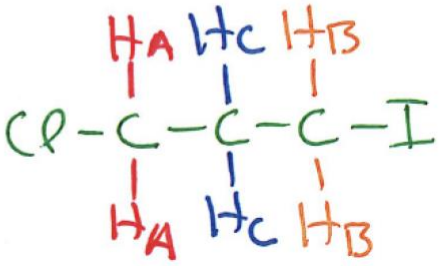


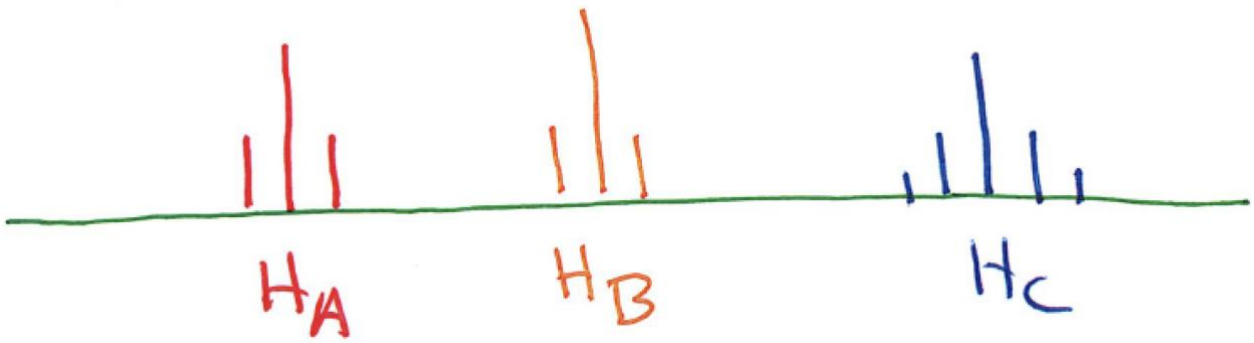


Reality: The splitting does multiply, but $J_{AC} = J_{BC}$ causing overlap of peaks

$\Rightarrow$ we observe $n+1$ peaks

(n = total # of adjacent H atoms)





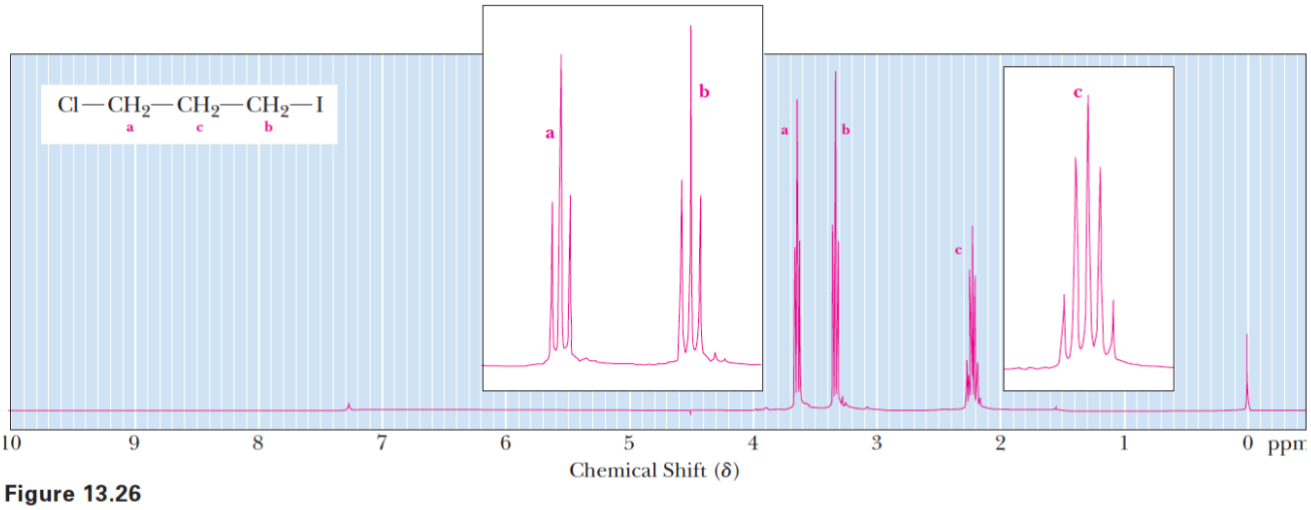


Figure 13.26
300 MHz ^{1}H-NMR spectrum of 1-chloro-3-iodopropane

Recap:

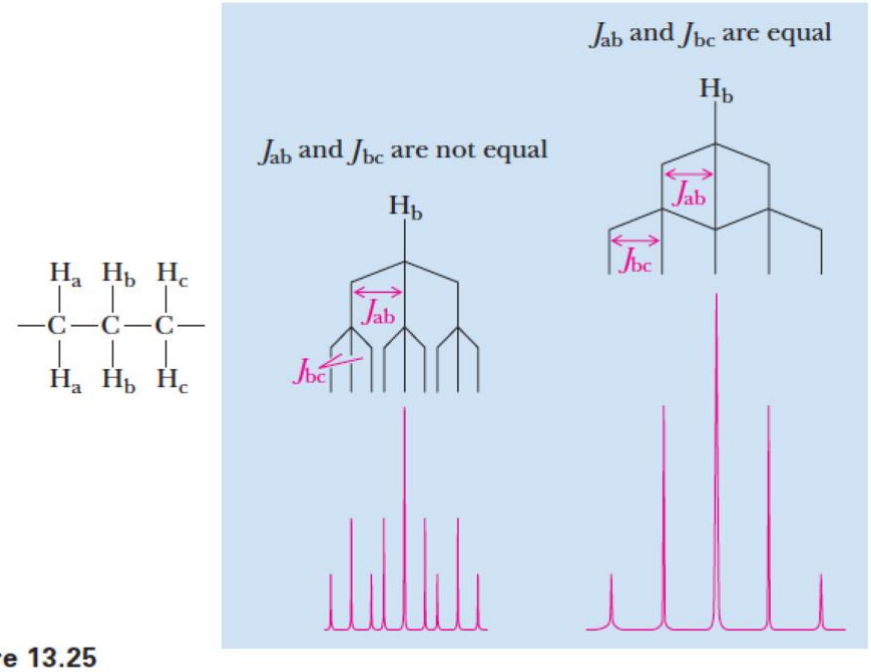


Figure 13.25
Simplification of signal splitting that occurs when coupling constants are the same.

Q. Non-equivalent H atoms on the same C atom can split each other (called geminal coupling), for example on alkenes or small rings. This coupling usually has very small coupling constants, so is difficult to see on some spectra.

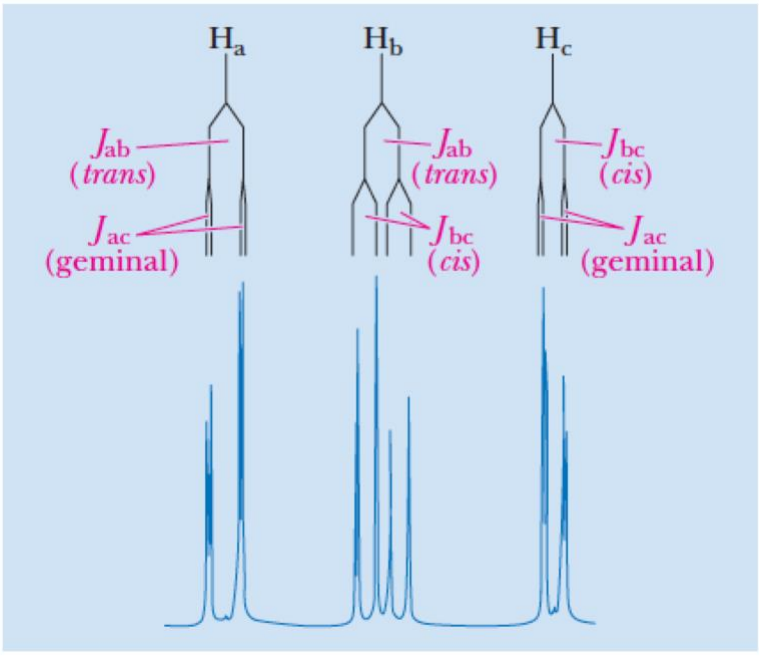


Figure 13.22
Tree diagrams for the complex coupling seen for the alkenyl H atoms in the ^{1}H-NMR spectrum of ethyl propenoate.

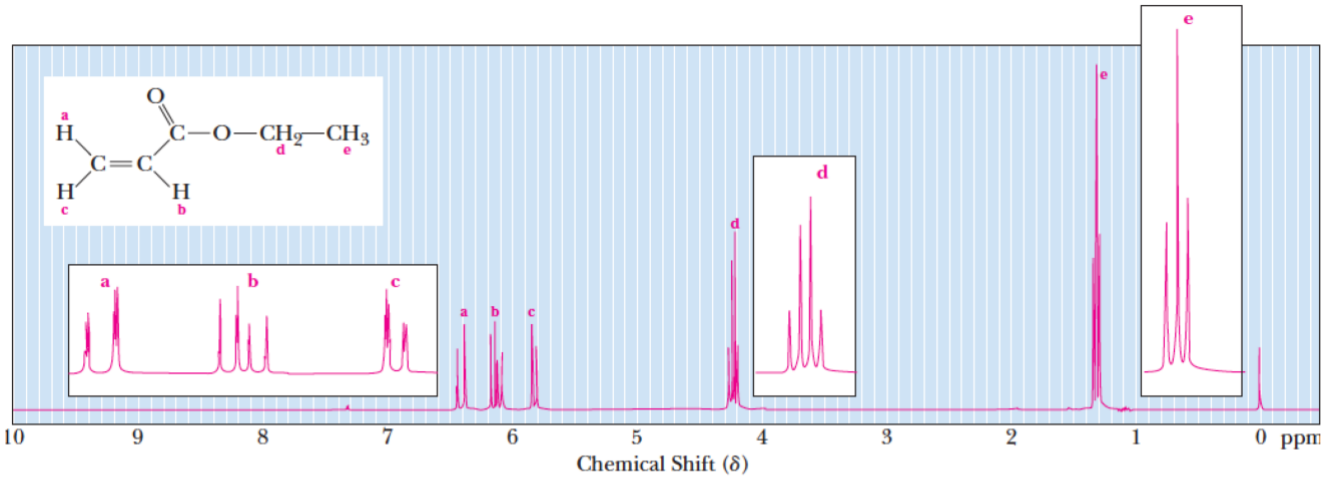
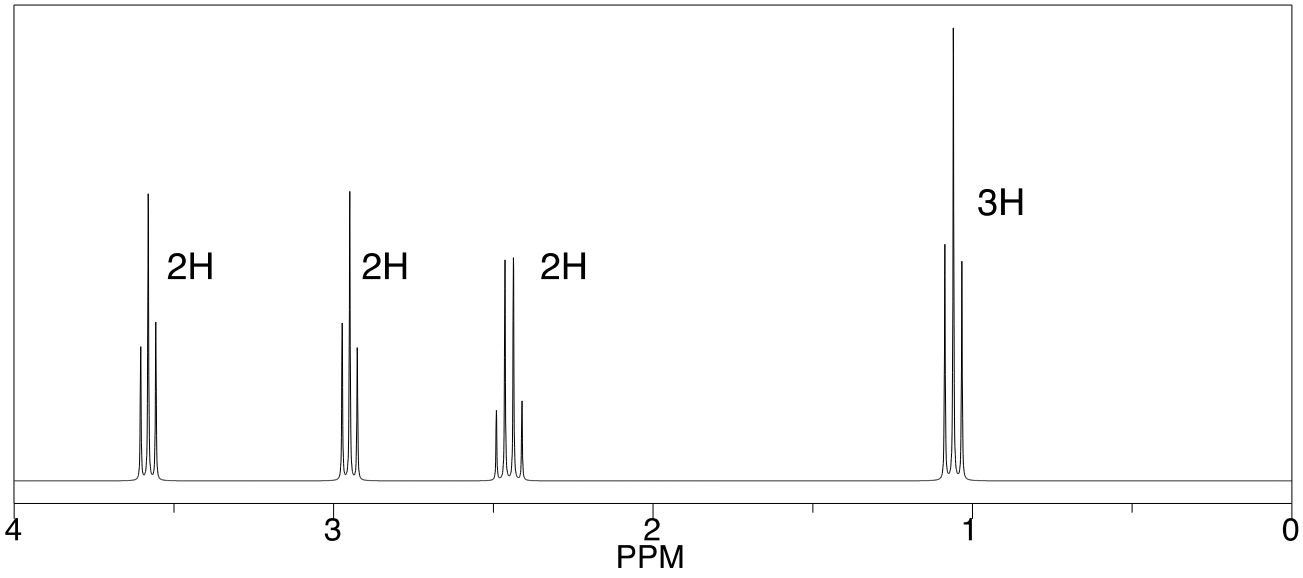
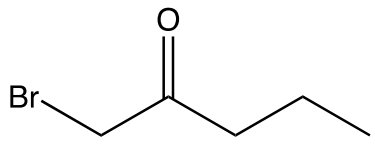


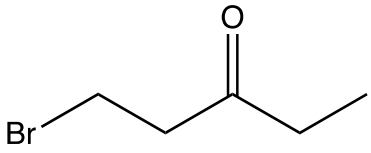
Figure 13.21
300 MHz ^{1}H-NMR spectrum of ethyl propenoate.

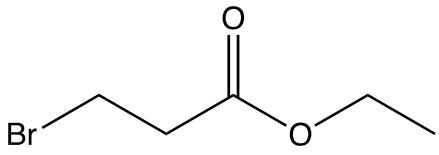
V. When solving NMR spectra problems:

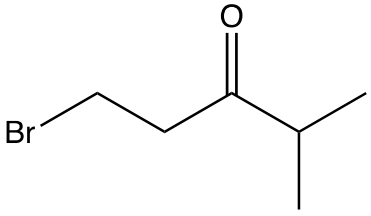
1) **Determine number and relative integrations of signals predicted for a given structure**
2) **Make sure the splitting pattern matches with the spectrum for each signal and**
3) **If the number and relative integrations as well as splitting patterns match with the spectra, compare expected chemical shifts with those of the signals in the spectra.**

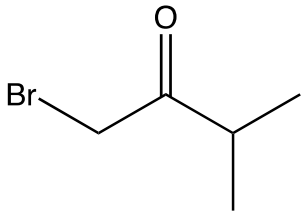


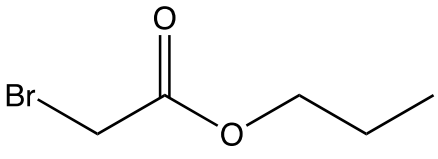






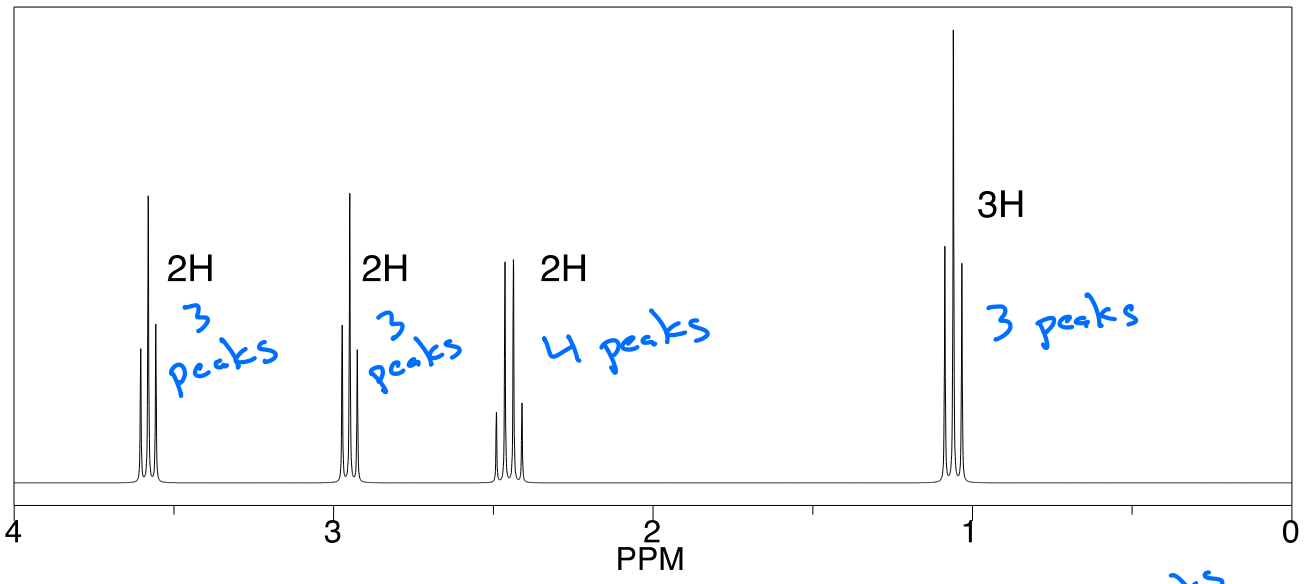


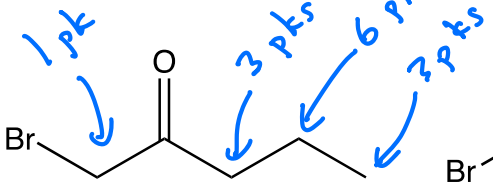




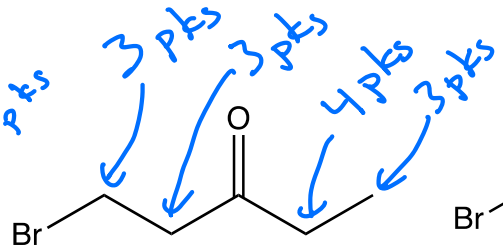
V. When solving NMR spectra problems:

1) **Determine number and relative integrations of signals predicted for a given structure**
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3) **If the number and relative integrations as well as splitting patterns match with the spectra, compare expected chemical shifts with those of the signals in the spectra.**

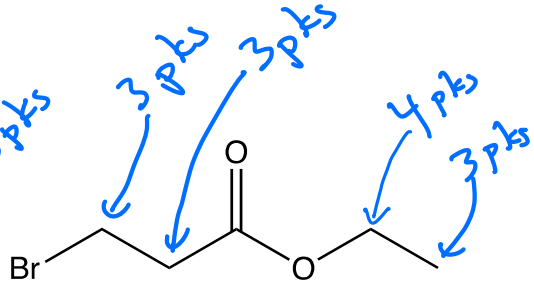




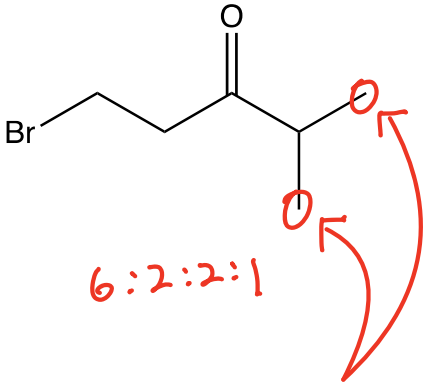
3 : 2 : 2 : 2



3 : 2 : 2 : 2

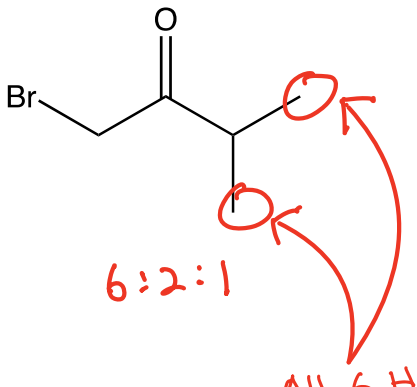


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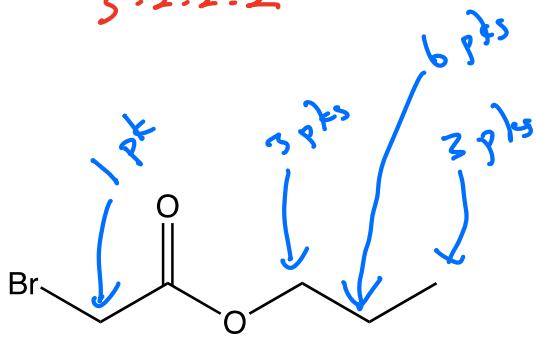
6 : 2 : 2 : 1

All 6 H atoms on the 2 methyl groups are equivalent due to symmetry



6 : 2 : 1

All 6 H atoms on the 2 methyl groups are equivalent due to symmetry



3 : 2 : 2 : 2

Type of Hydrogen (R = alkyl, Ar = aryl)	Chemical Shift (δ)*	Type of Hydrogen (R = alkyl, Ar = aryl)	Chemical Shift (δ)*
		RCH_2OH	3.4-4.0
R_2NH	0.5-5.0	RCH_2Br	3.4-3.6
ROH	0.5-6.0	RCH_2Cl	3.6-3.8
RCH_3	0.8-1.0	$RCOCH_3$	3.7-3.9
RCH_2R	1.2-1.4	$RCOCH_2R$	4.1-4.7
R_3CH	1.4-1.7	RCH_2F	4.4-4.5
$R_2C{=}CRCHR_2$	1.6-2.6	$ArOH$	4.5-4.7
$RC{\equiv}CH$	2.0-3.0	$R_2C{=}CH_2$	4.6-5.0
$RCCH_3$	2.1-2.3	$R_2C{=}CHR$	5.0-5.7
$RCCH_2R$	2.2-2.6	$H_2C{-}CH_2$	3.3-4.0
$ArCH_3$	2.2-2.5	RCH	9.5-10.1
RCH_2NR_2	2.3-2.8	$RCOH$	10-13
RCH_2I	3.1-3.3		
RCH_2OR	3.3-4.0		

* Values are relative to tetramethylsilane. Other atoms within the molecule may cause the signal to appear outside these ranges.

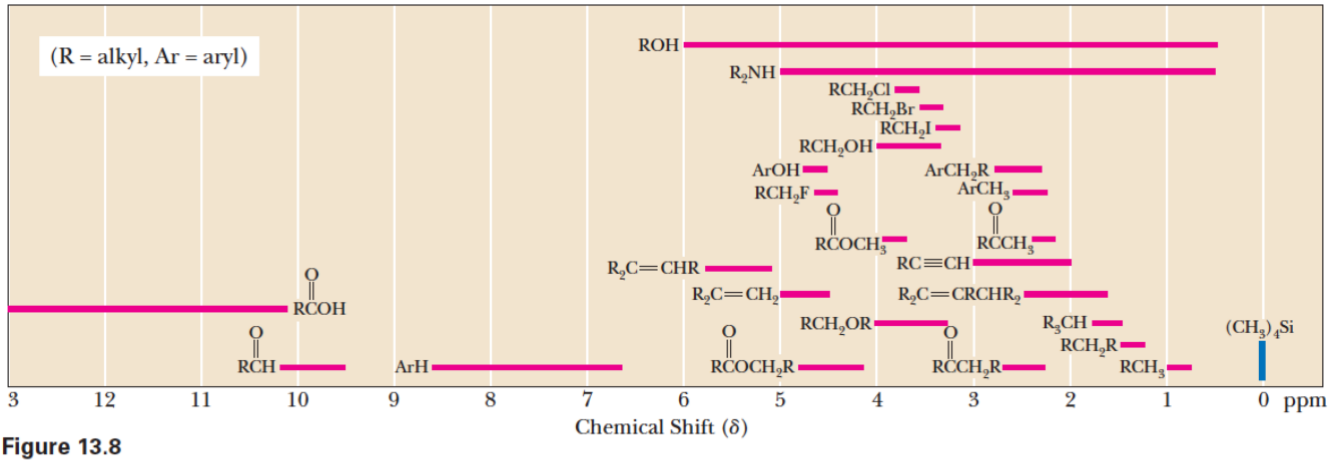


Figure 13.8
Average values of chemical shifts of representative types of hydrogens. These values are approximate. Other atoms or groups in the molecules may cause signals to appear outside of these ranges.