Fundamentals of Spectroscopy and Applications to Structure Determination
F12FSA

Lecture 1

Dr. Paul A. Clarke

Room C24

Office Hours: Tuesday 9:30-10:30am

Overview

- Using lectures, workshops and problem seminars this course will enable you to use NMR and Mass Spec techniques for structure elucidation of organic molecules of reasonable complexity. Particular emphasis will be given to problem solving.
- In order, we will look at the structural information which may be gained from analysis of 13C NMR, 1H NMR and Mass Spectrometry.
- This component of the course will be assessed by two group exercises in structural elucidation and by an exam question.

Resources

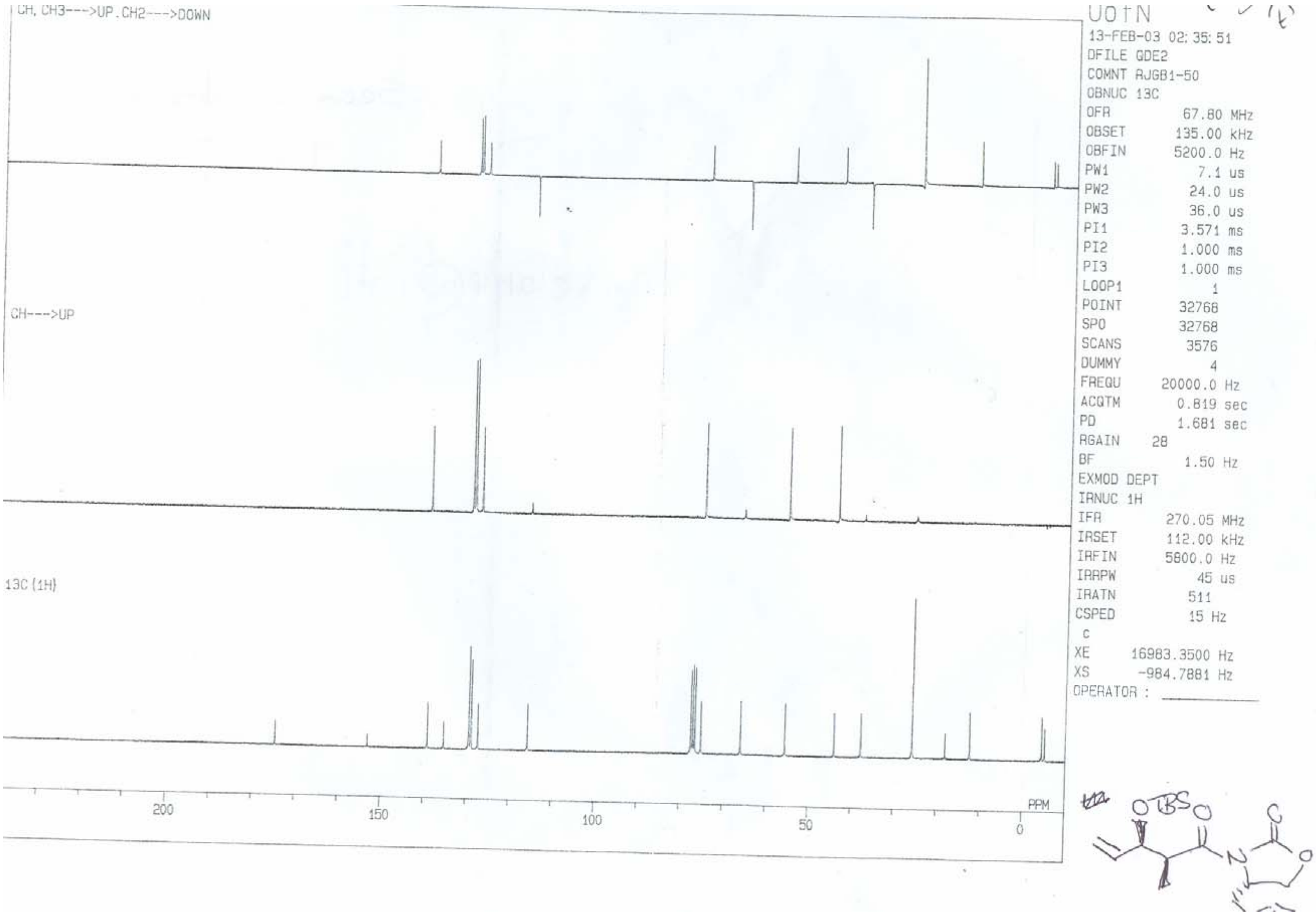
- Web Pages:
- www.nottingham.ac.uk/~pczpac1/NMRweb/outline.htm
- Books:
- Clayden, Greeves, Warren & Wothers:
- ‘*Organic Chemistry*’
- Harwood & Claridge:
- *‘Introduction to Organic Spectroscopy’*
- Williams & Flemming:
- *‘Spectroscopic Methods in Organic Chemistry’*

13C NMR

- 13C NMR provides information on the carbon skeleton of an organic molecule. It gives information on the number of carbons present and their chemical environments.

- We will look at a typical 13C NMR and work through its features and find out what these features tell us about the structure of the molecule.

Typical 13C NMR Spectrum



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COMNT RJGB1-50
OBNUC 13C
OFR          67.80 MHz
OBSET       135.00 kHz
OBFIN       5200.0 Hz
PW1            7.1 us
PW2           24.0 us
PW3           36.0 us
PI1          3.571 ms
PI2          1.000 ms
PI3          1.000 ms
LOOP1            1
POINT        32768
SPO          32768
SCANS         3576
DUMMY            4
FREQU      20000.0 Hz
ACQTM        0.819 sec
PD           1.681 sec
RGAIN    28
BF            1.50 Hz
EXMOD DEPT
IRNUC 1H
IFR         270.05 MHz
IRSET       112.00 kHz
IRFIN       5800.0 Hz
IRRPW           45 us
IRATN          511
CSPED           15 Hz
 c
XE      16983.3500 Hz
XS       -984.7881 Hz
OPERATOR : ____________
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Chemical Shift

- What is chemical shift?
- Chemical shift is the position (in ppm) a resonance comes along the horizontal axis.

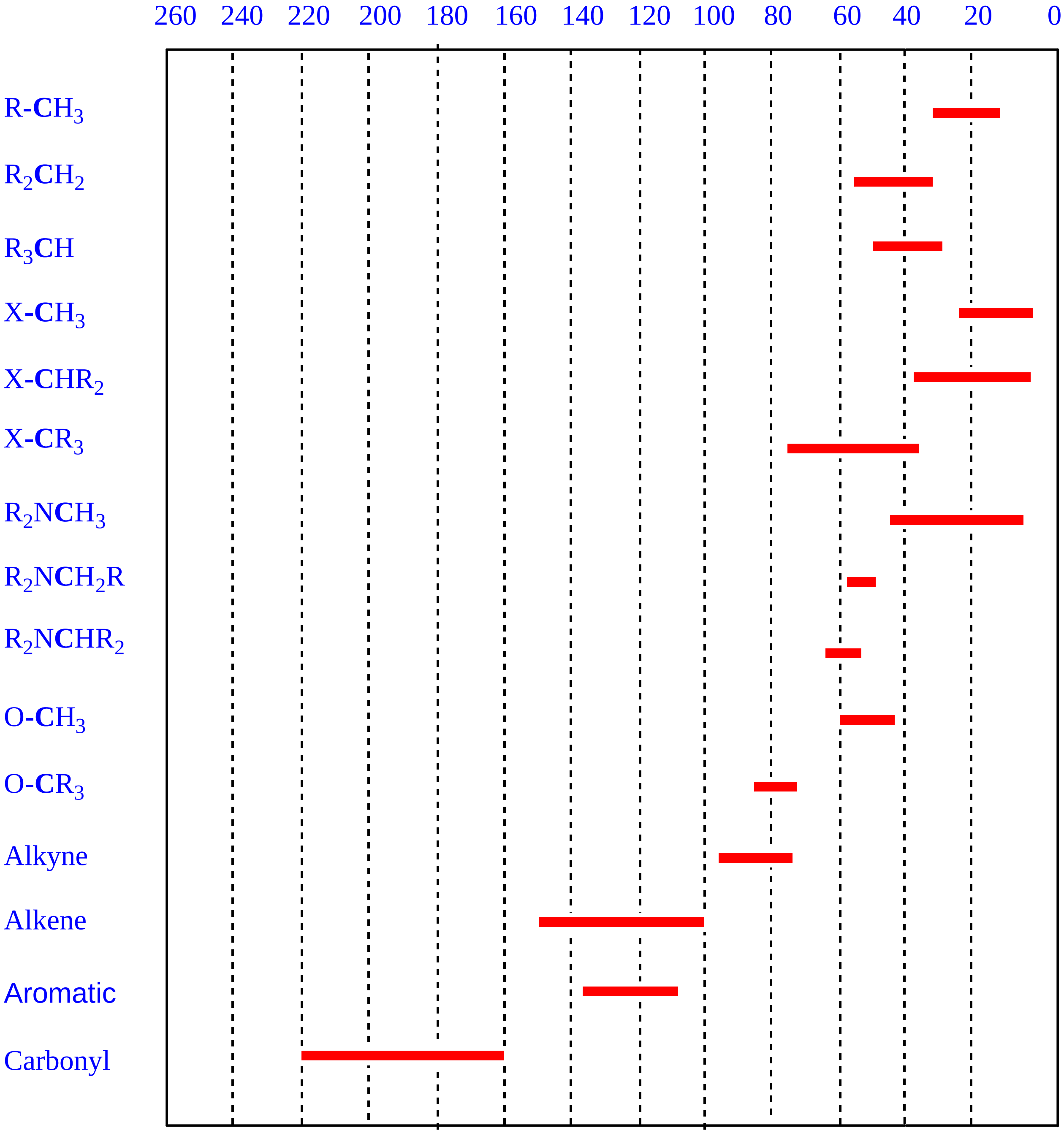
- How does chemical shift relate to structure?
- Chemical shift tells us about the chemical and structural environment of a particular nucleus.

- 1) Inductive effects:
- Electron withdrawing groups ‘deshield’ the nucleus. The resonates at a higher frequency (ppm value).
- The opposite is also true.
- Other effects will be dealt with later in 1H NMR section.

Example of Inductive Effects

$^{13}CH_3$-R	$\delta(^{13}CH_3)$ ppm
– Li	-14
– H	-2
– $SiMe_3$	0
– CH_3	8
– NH_2	27
– COR	30
– OH	50
– F	70

Typical 13C NMR Chemical Shifts



13C DEPT Experiments

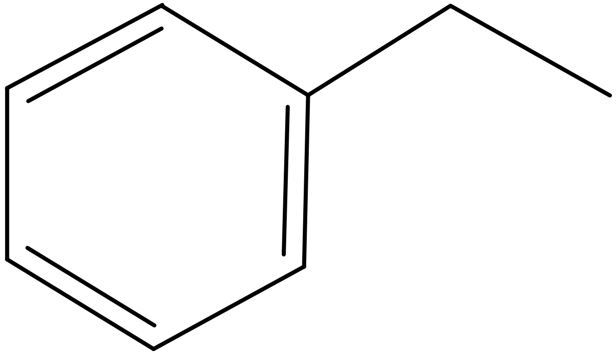
- Large molecules can generate very complicated 13C NMR spectra, due to the 13C coupling to the adjacent 1Hs. This can lead to many carbon multiplets overlapping with each other. To simplify the spectra yet retain the information we have developed DEPT.
- All signals are singlets, but they appear in different phases dependant upon their multiplicities.

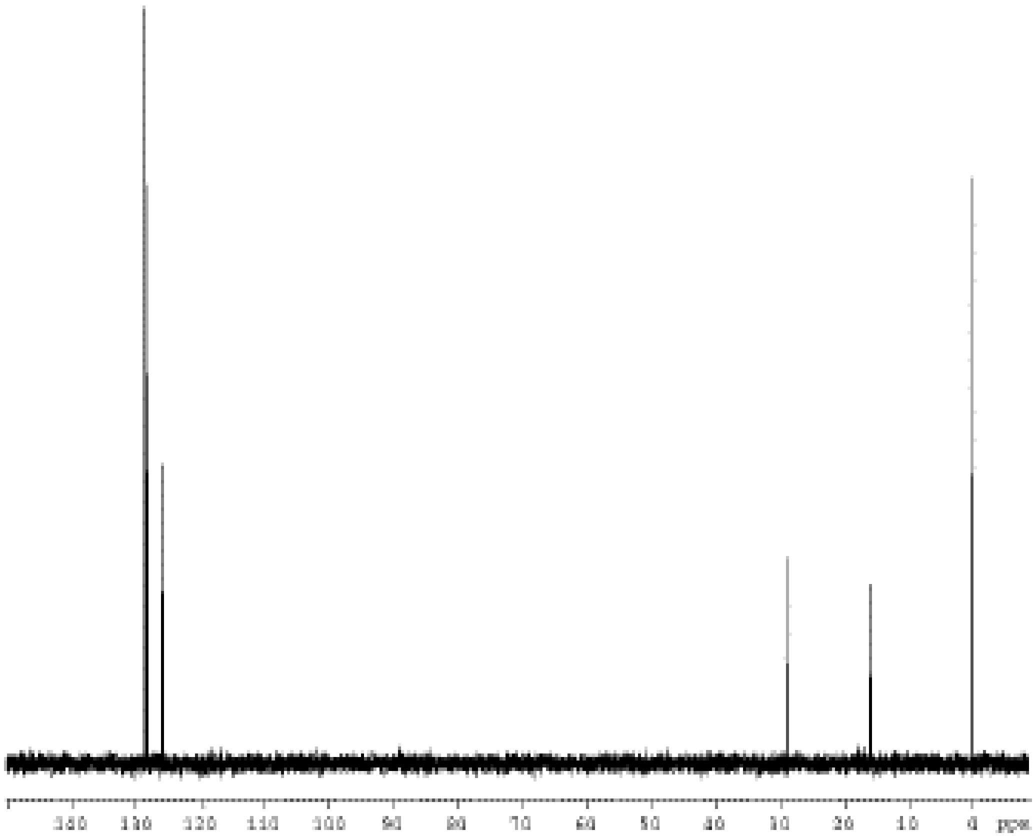
	C	CH	CH_2	CH_3
DEPT 45		+	+	+
DEPT 90	0	+	0	0
DEPT 135	0	+	-	+

Example of DEPT Experiment

- Ethyl benzene

- DEPT 45: all signals are positive.

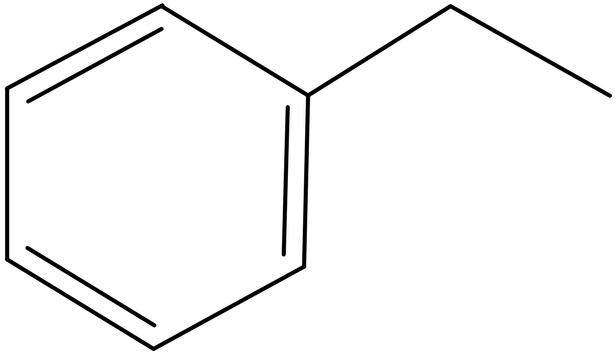


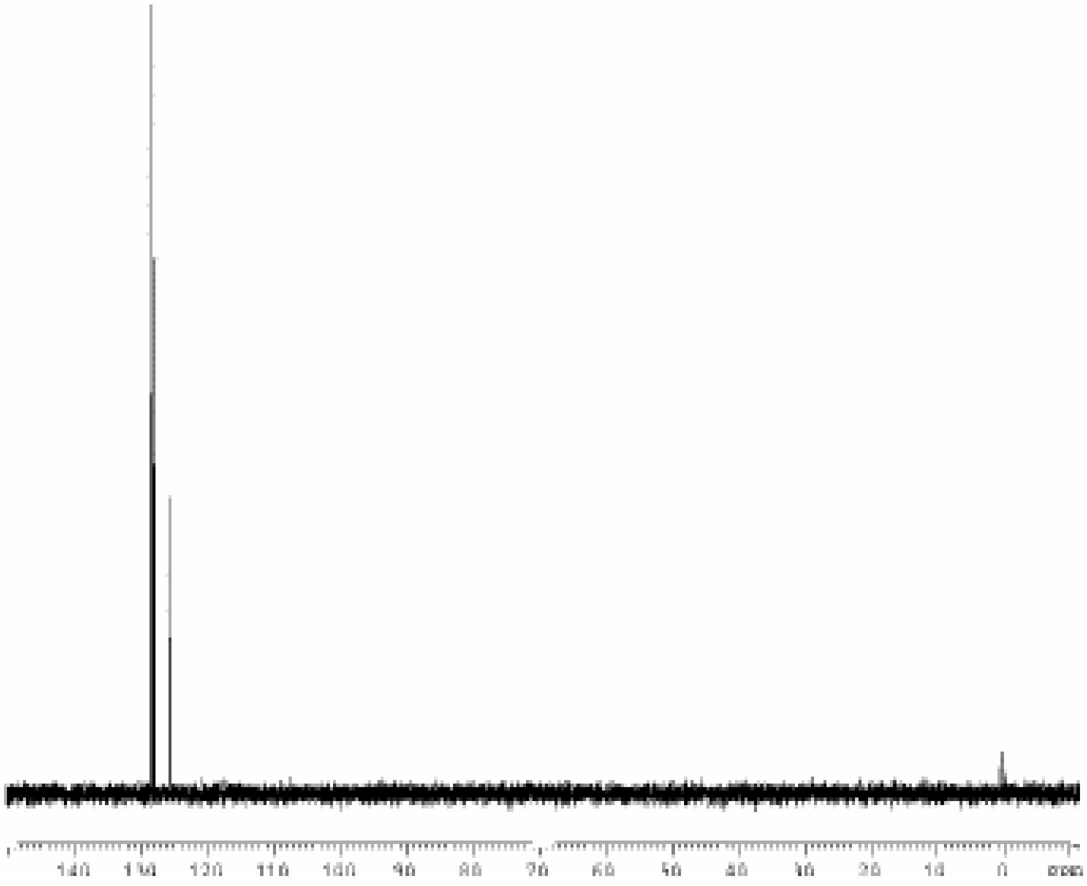


Example of DEPT Experiment

- Ethyl benzene

- DEPT 90: only shows CH signals.

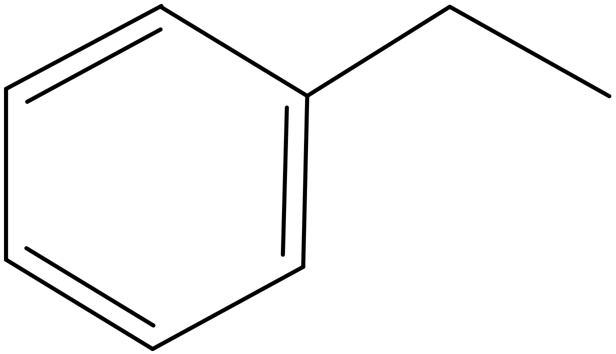


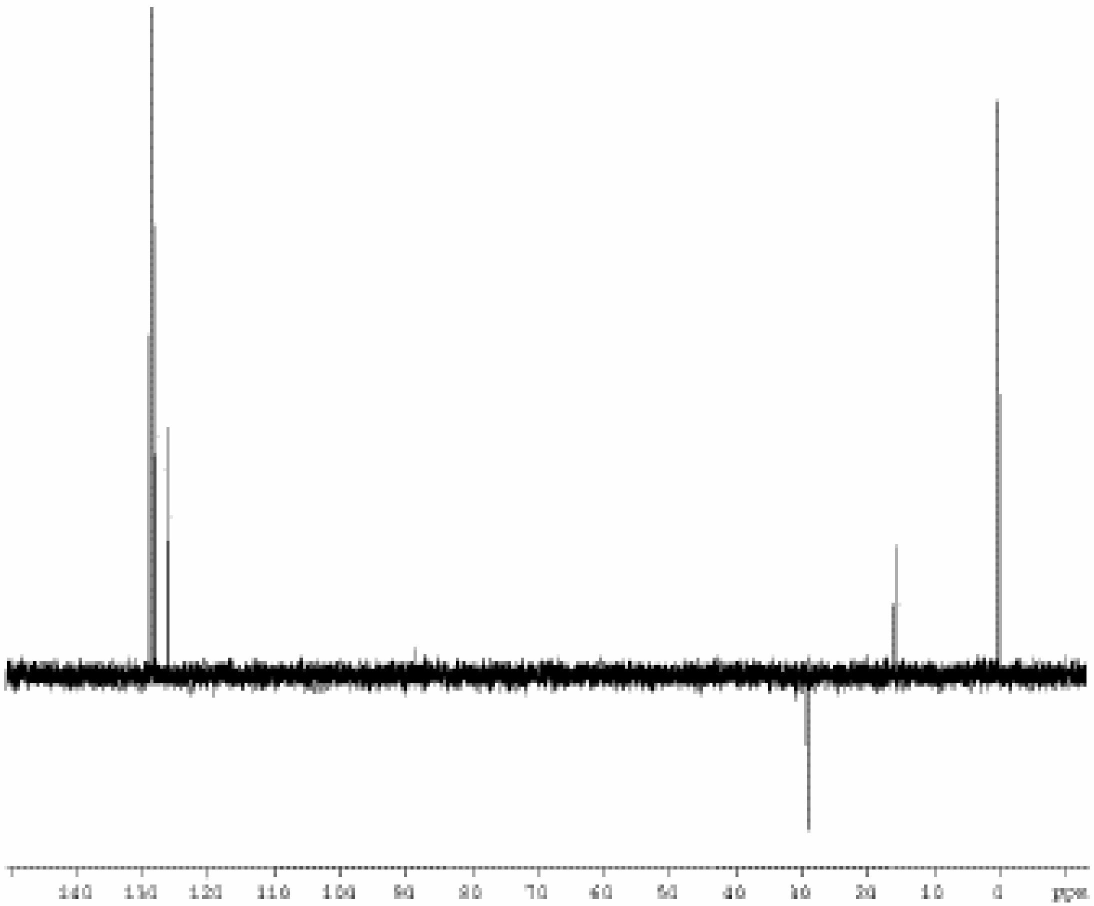


Example of DEPT Experiment

- Ethyl benzene

- DEPT 135: CH and CH_3 signals are positive. CH_2 signals are negative.





Summary

- ^{13}C NMR can tell us how many C are in the molecule.
- ^{13}C NMR can tell us how many ^{1}H are attached to each C.
- ^{13}C NMR can tell us whether the C is bonded to an electron donating or withdrawing functional group.
- An idea of molecular structure can be obtained.
- You should now be in a position to answer the 13C NMR questions in the handout.

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Lecture 2

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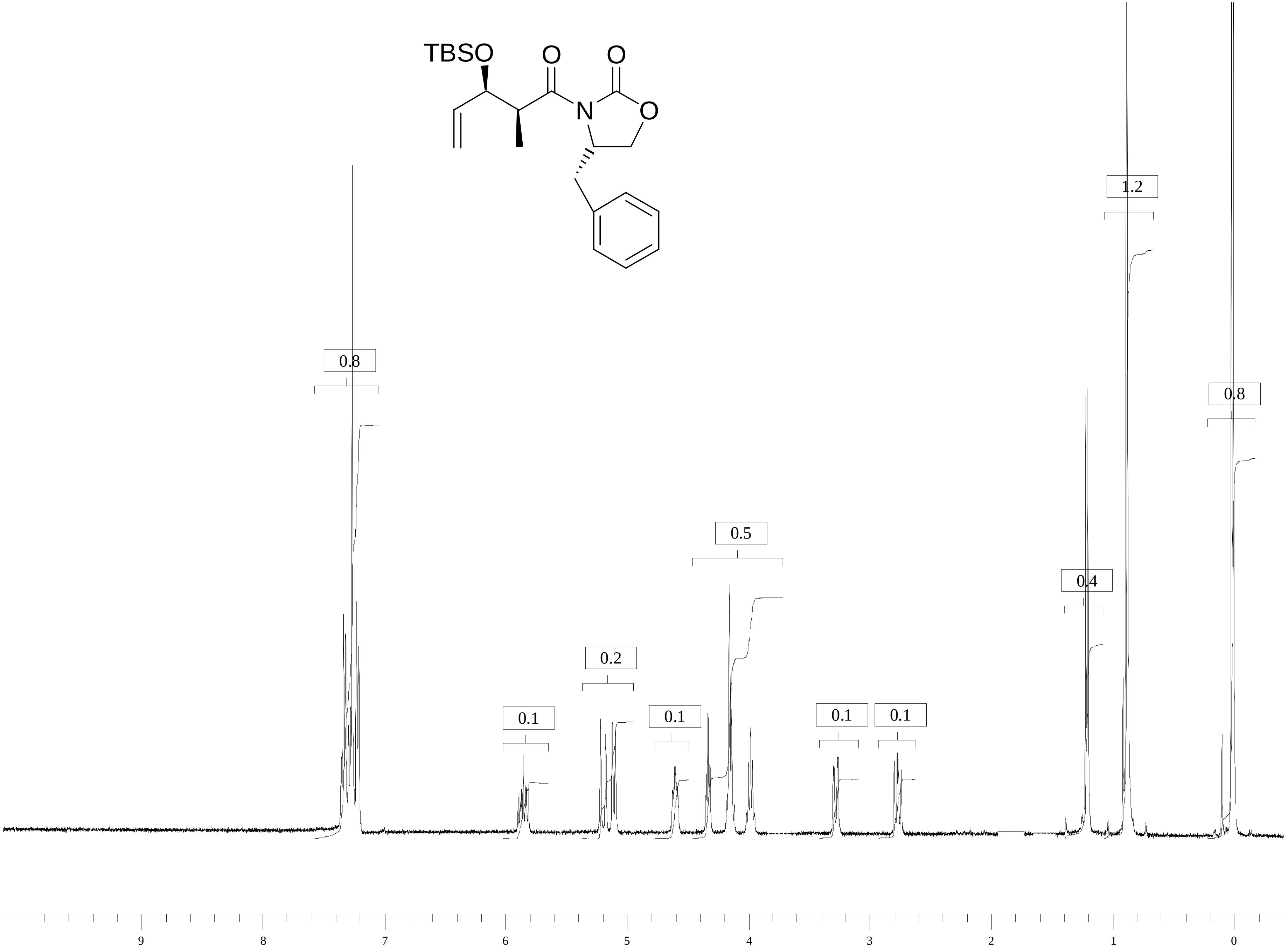
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O
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0.2
0.1
0.5
0.1
0.1
0.4
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9
8
7
6
5
4
3
2
1
0

Features of a 1H NMR Spectrum

- From the previous slide you will have noticed several features:
- Smaller range of chemical shift (δ) than 13C.
- Different peaks have different intensities, which relate to the number of ^{1}Hs giving rise to the signal.
- Complex coupling and fine structure details the interactions with neighbouring 1H - extent of which is characterised by *J*- value (Hz).

- Look at each of these in turn.

1H NMR: Inductive Effects

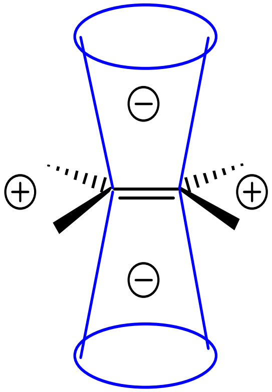
Range ~0-12 ppm as only s-electrons. Effects fall of rapidly. Not usually seen after 3 bonds.

X-CH_2^A-CH_2^B-CH_3^C in ppm

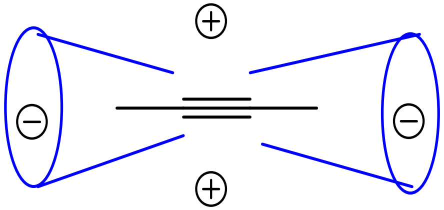
X	CH_2^A	CH_2^B	CH_3^C
Et	1.3	1.3	0.9
CO_2H	2.3	1.7	1.0
OH	3.6	1.6	0.9
NO_2	4.4	2.1	1.0

Anisotropic Effect

- Often the distribution of electrons in a chemical bond is unsymmetrical, and the shift of any nucleus near this bond is dependant to its position relative to it.
- Most pronounced in unsaturated systems with π-electrons.
- This gives rise to highly spatially dependant shielding effects.



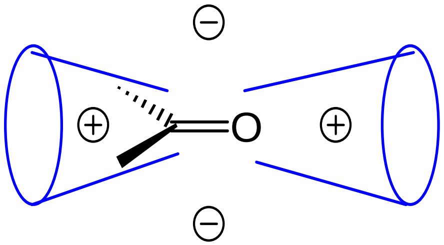
Alkene



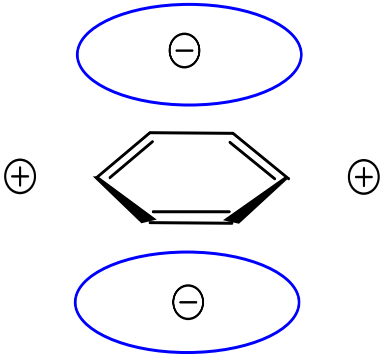
Alkyne

⊕ DESHIELDED

⊖ SHIELDED

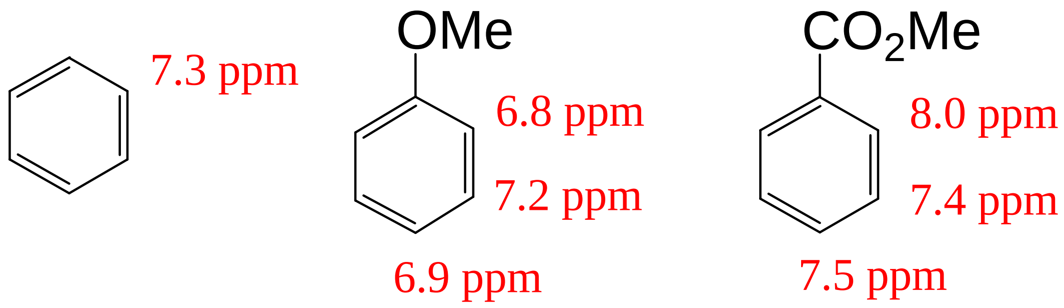


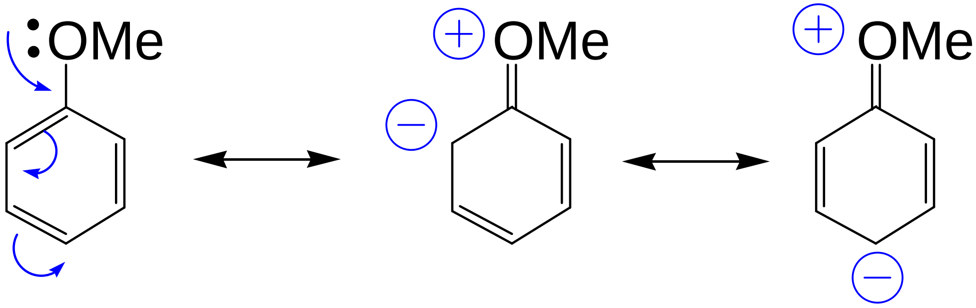
Carbonyl



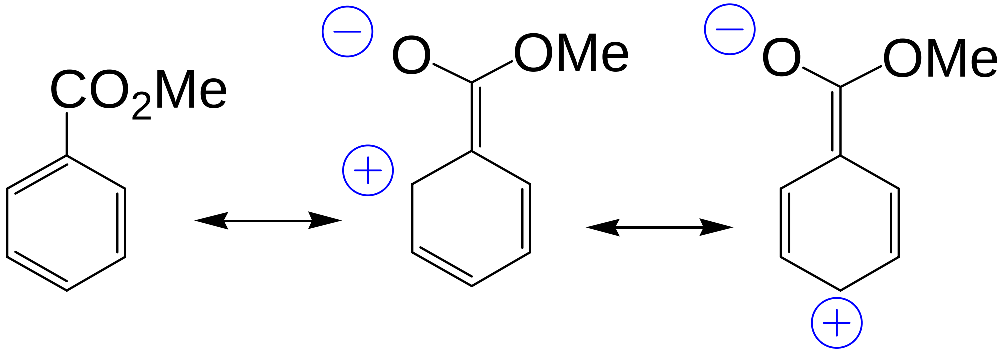
Aromatic

Mesomeric Effects





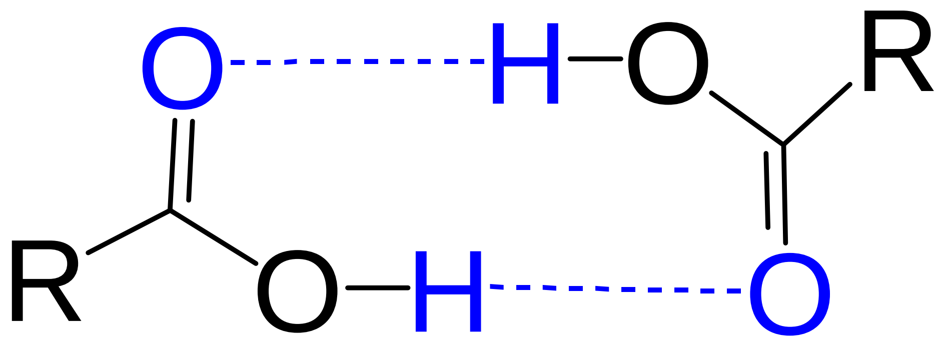
⊖ Increase in electron density: Shielded



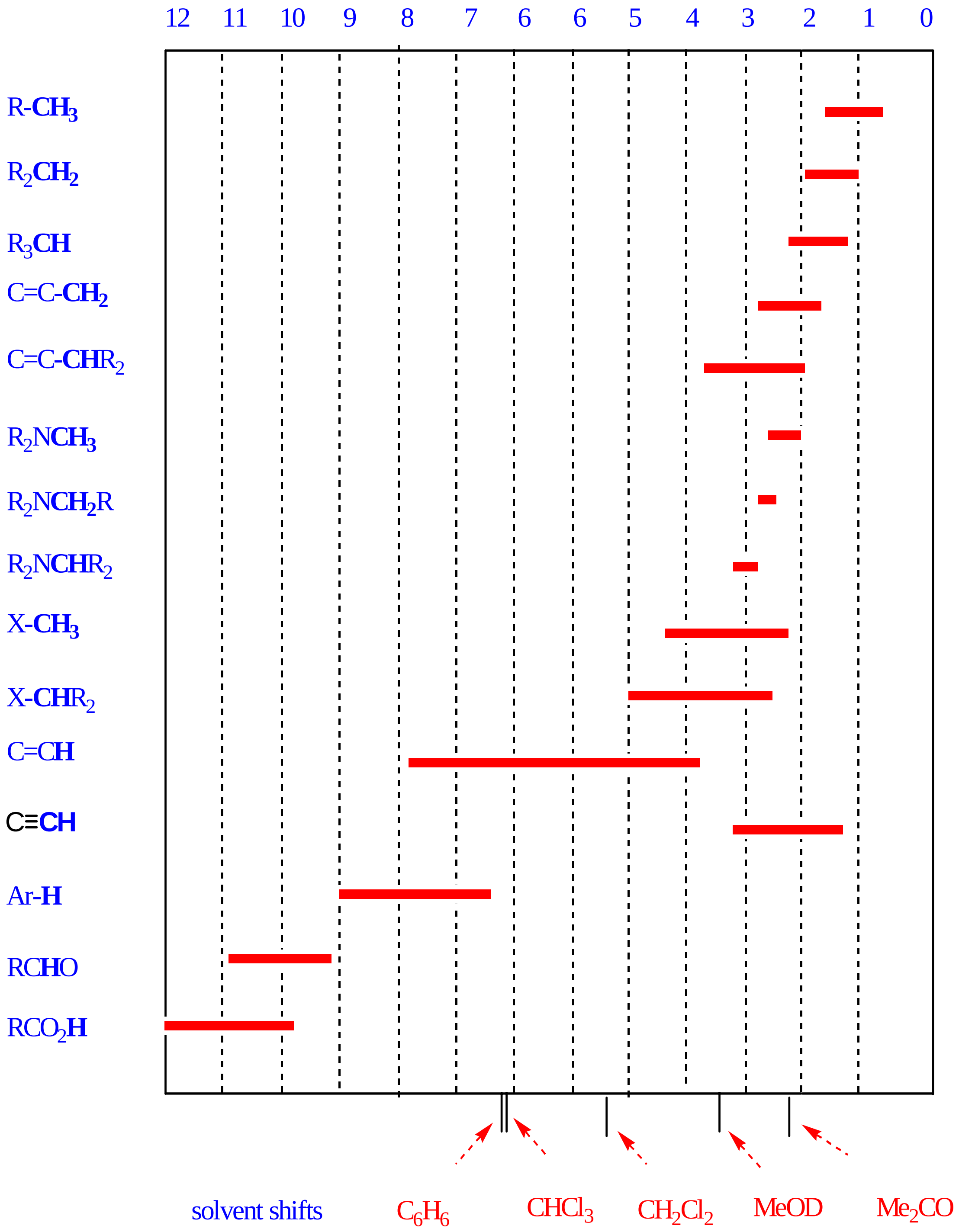
⊕ Decrease in electron density: Deshielded

Hydrogen Bonding

- Hydrogen bonding has an electron withdrawing effect on 1Hs involved.
- 1Hs resonate at a higher frequency.
- Example: RCO_2H, where H at 10-12 ppm.



^{1}H NMR Shifts



Intensities and Integration

- Intensity of a signal is directly proportional to the number of 1H resonances producing it

- On a 1H NMR spectrum this is represented by the height of the integral trace over the peak.

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Lecture 3

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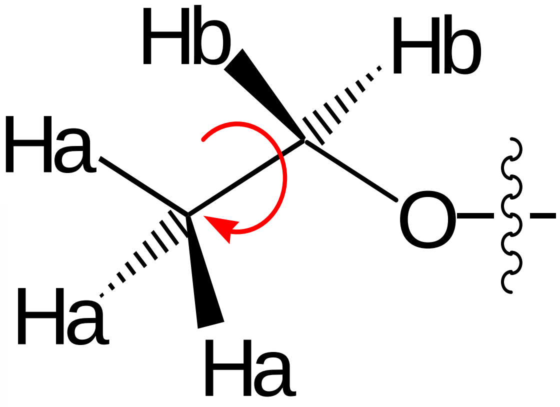
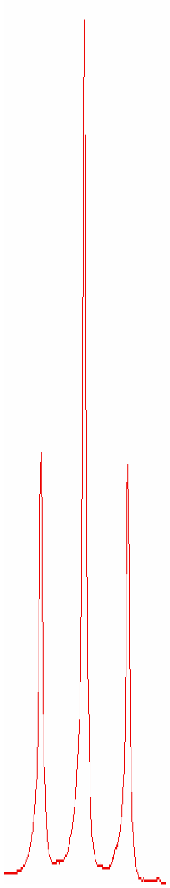
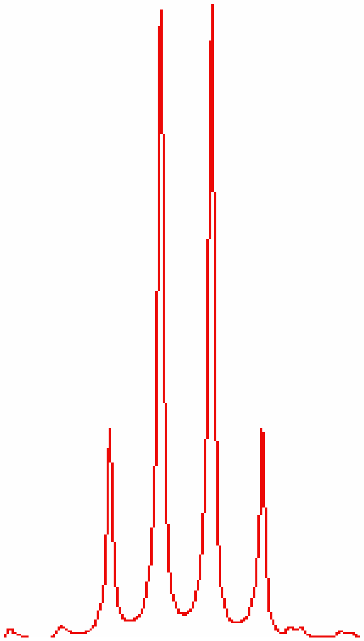
Spin-Spin Coupling: Ethyl Group

- Look at protons. As rotation about the Ca-Cb bond is fast all the CH_3 groups 1H exchange environments rapidly and are exactly equivalent.
- As they are equivalent they do not couple to each other.
- Similarly the CH_2 group 1Hs do not couple to each other.
- 1H couple to other 1H on ADJACENT carbons.





CH_3-CH_2



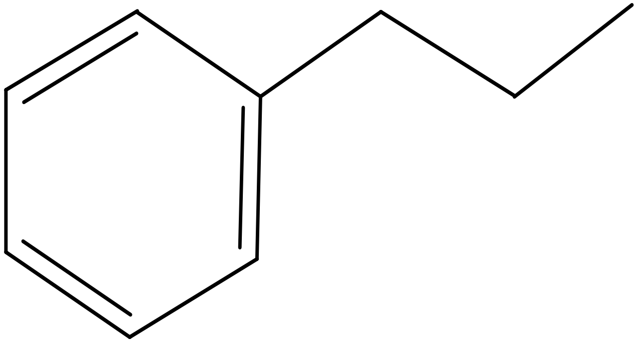
Spin-Spin Coupling

- Helpful tool: signal is split into 2nI+1 peaks. Where n=number of adjacent nuclei and I= spin quantum number.
- For CH_3 coupled to CH_2: 2x2x1/2+1=3 (triplet).
- For CH_2 coupled only to CH_3: 2x3x1/2+1=4 (quartet).
- For 1H NMR this tool reduces to n+1 peaks for simple systems.
- The gaps between the lines are the coupling constants (*J*) in Hz.
- If two signals are coupled this value will be identical for each signal.
- If Ha coupled to Hb with *J* = 7 Hz then Hb MUST couple to Ha with *J* = 7 Hz

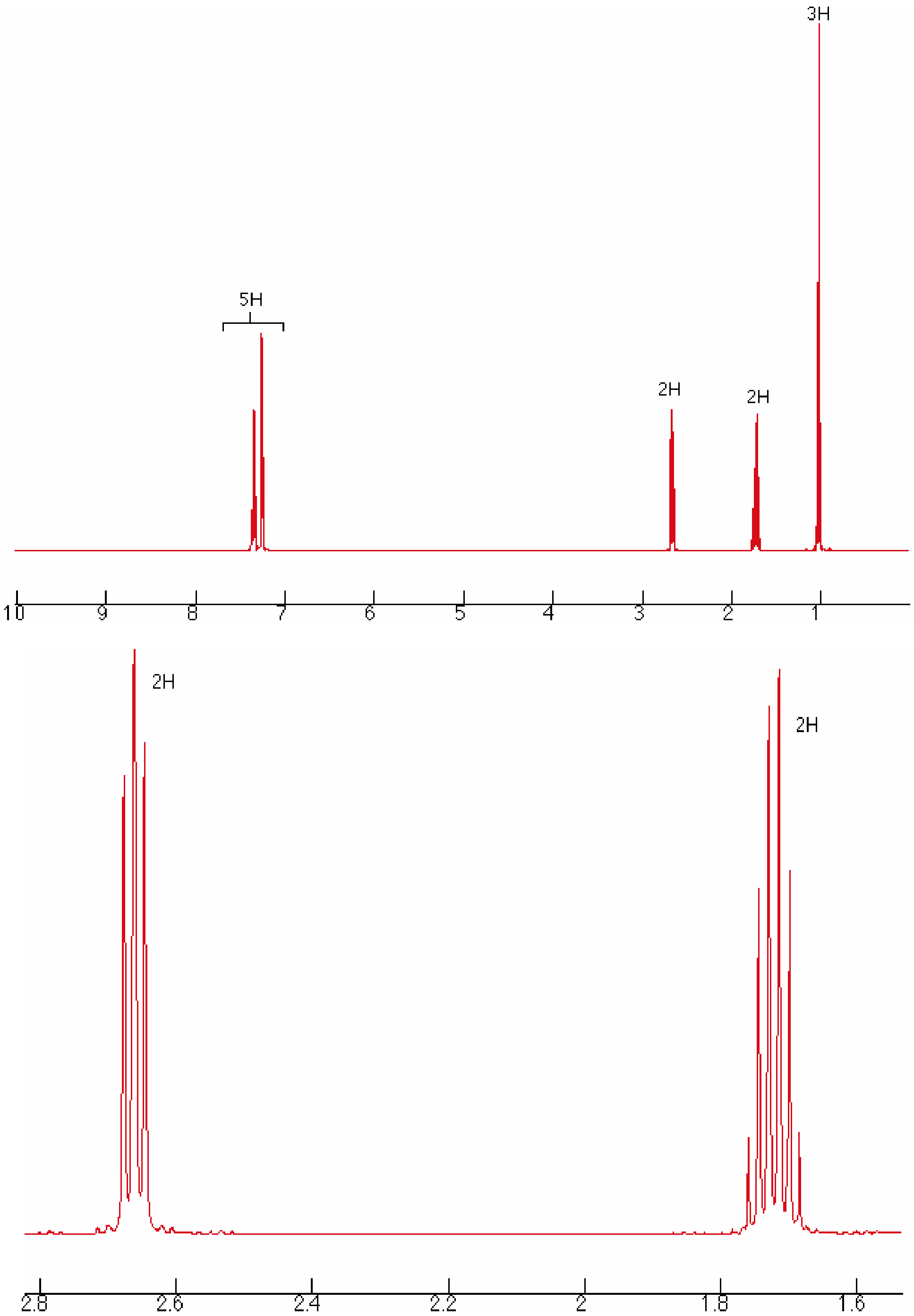
Spin-spin Coupling:

Example 2

- Example of propyl benzene ===>



- 1Hs couple to other non-equivalent 1Hs. Usually on adjacent carbons.



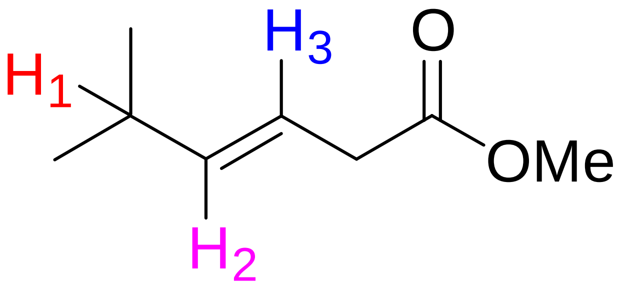
Summary

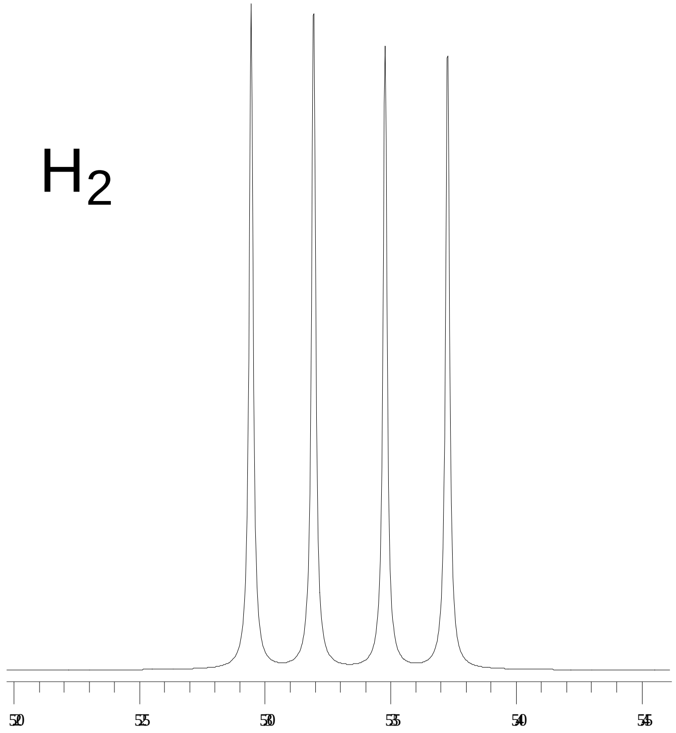
- 1H NMR tells us the number of 1H in a molecule.
- 1H NMR tells us the number of 1H which make up each signal.
- 1H NMR tells us about the chemical environment (i.e. functional group) associated with the 1H.
- A further idea of molecular structure can be obtained.

- You should now be in a position to attempt the first few 1H NMR questions in the handouts and on the website.

More Complicated Spin Systems

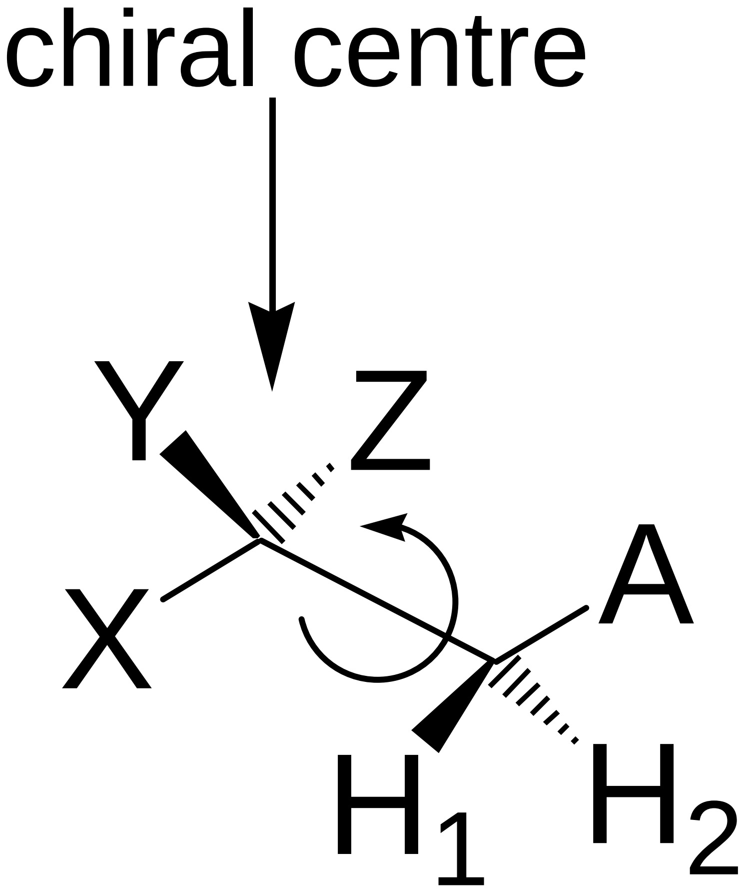
- n+1 only applicable if all the coupled nuclei are equivalent.
- If a 1H is coupled to 2 non-equivalent 1H then you get a doublet from each coupling.
- These two doublets are called a double doublet (dd).
- This can occur when the 1H being coupled to are clearly different. Compare the environments of H_1 and H_3 w.r.t. H_2. They are different.



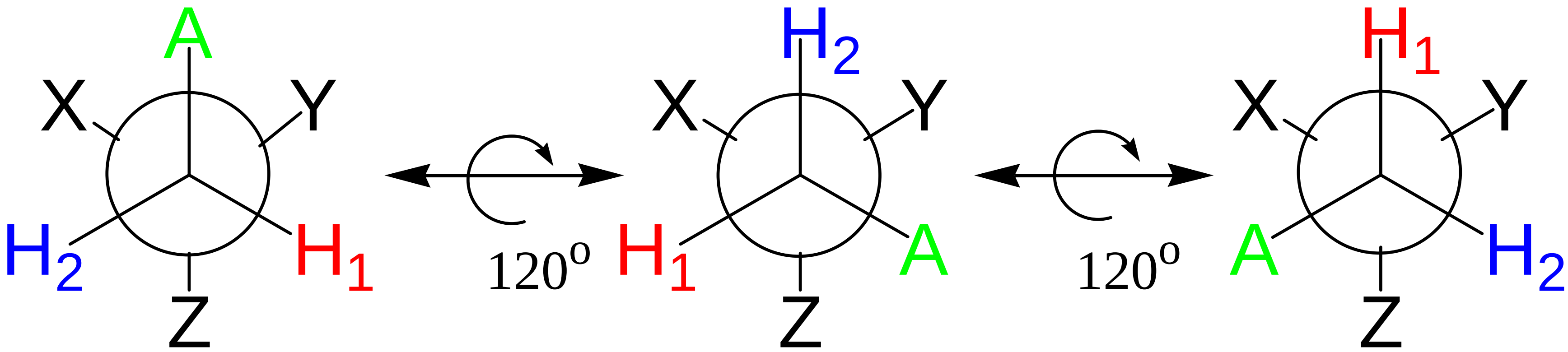


Effect of Diastereotopicity

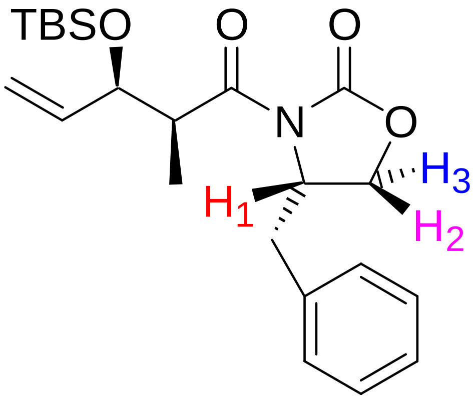
- It is not uncommon for 1H of a CH_2 group resonate at different frequencies and couple differently to other nuclei. They can also couple to each other!
- They are inequivalent. *i.e*. diastereotopic.
- Often occurs when there is a chiral centre in the molecule.

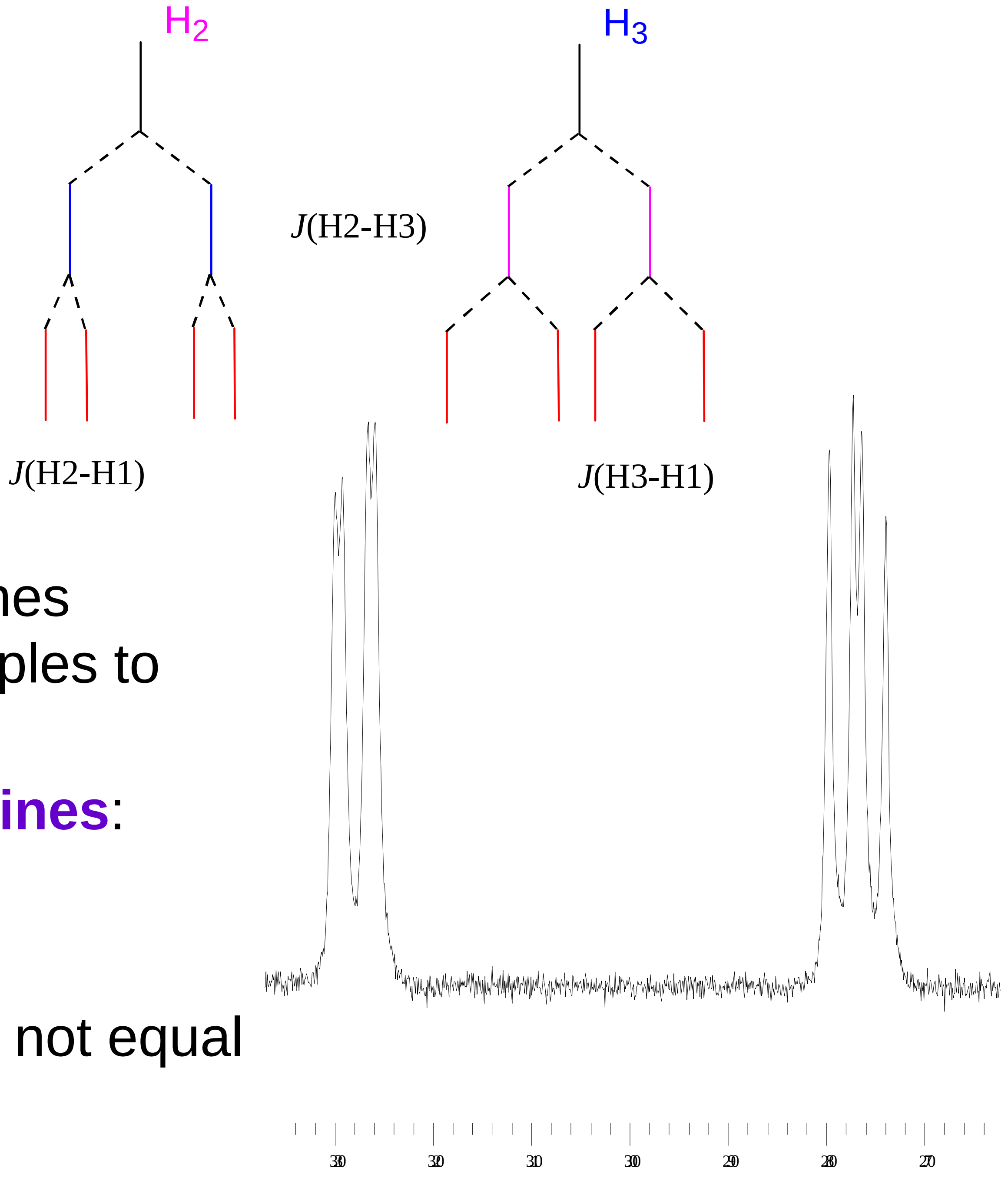


- H_1 and H_2 are diastereotopic.
- No matter what rotomeric form, the 2 protons are NEVER mutually interchangeable.
- Due to this H_1 and H_2 can have large Geminal (J^2) coupling to each other.



- For example:





- For H2:
- H2 couples to H3: 2 lines (doublet). H2 also couples to H1: 2 lines (doublet).
- Therefore a total of **4 lines**: double doublet.
- Similarly for H3.
- NOTE: J(H2-H1) does not equal J(H3-H1).

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Lecture 4

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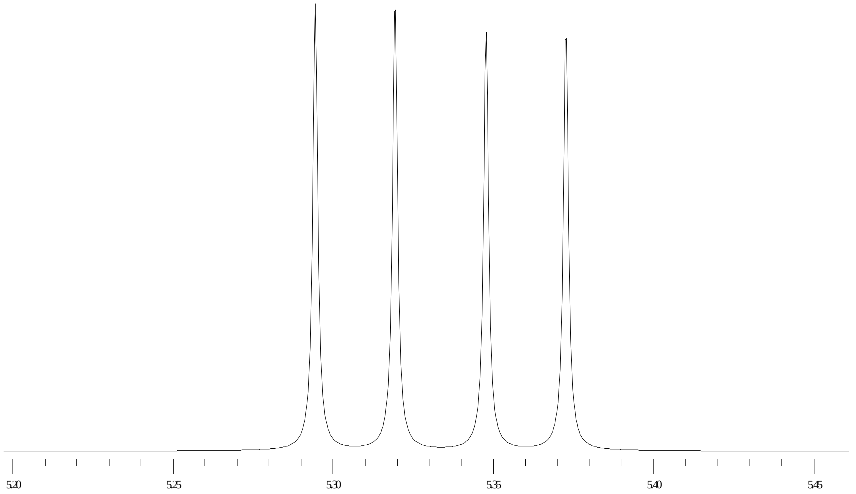
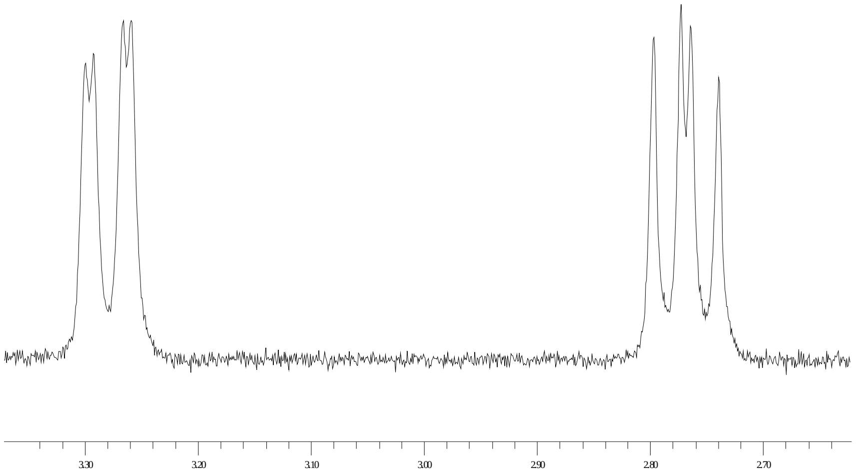
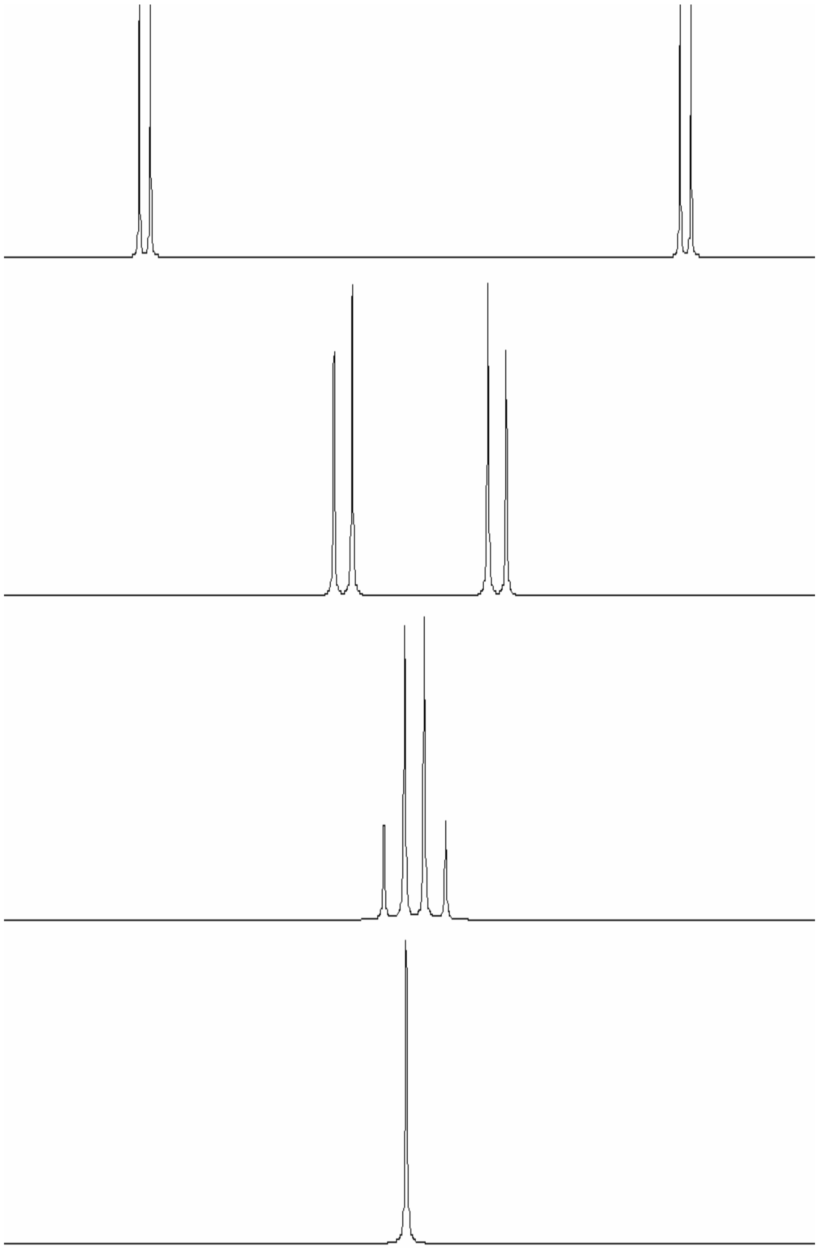
Failure of 1st Order Approx.





- In the first example the peak heights of the dd were equal. In the second example they were not.
- This happens when the chemical shift differences between two coupled protons is reduced and is of a similar magnitude to their mutual coupling. For a J^3 system usually when $\Delta\upsilon < 10J$.
- This can be a useful tool in determining coupled 1H.



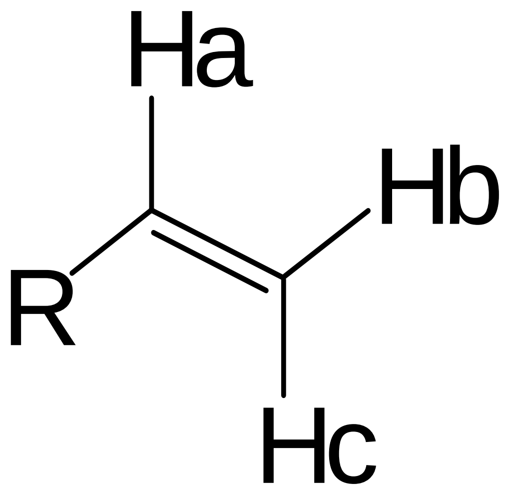
- For a 2 spin system:
- AX system: $\Delta\upsilon/J=10$ (Ideal)
- AM system: $\Delta\upsilon/J=5$, note roofing effect.
- AB system: $\Delta\upsilon/J=1.5$, looks like quartet, but not.
- A2 system: $\Delta\upsilon/J=0$, equivalent.
- Roofing points to coupled partner.

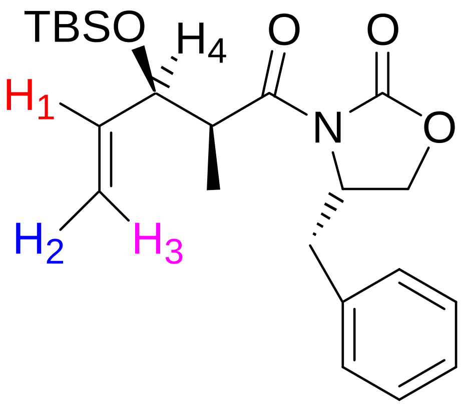
- For a 3 spin system:
- Classic non first order 3 spin systems are the AMX and ABX systems. Note the roofing effect as the chemical shift difference between 2 of the 3 coupled nuclei gets smaller.
- In these systems each signal is a double doublet (dd) 4 lines. The diastereotopic system earlier was an example of this.

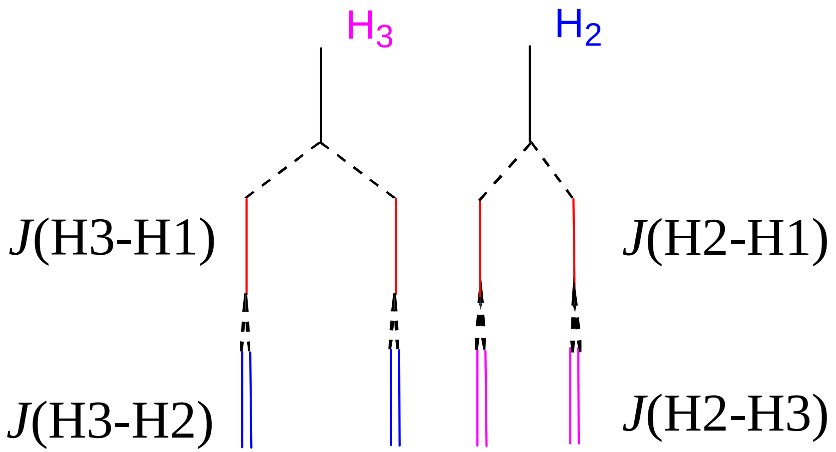
How *J* Values are Influenced by Structure?

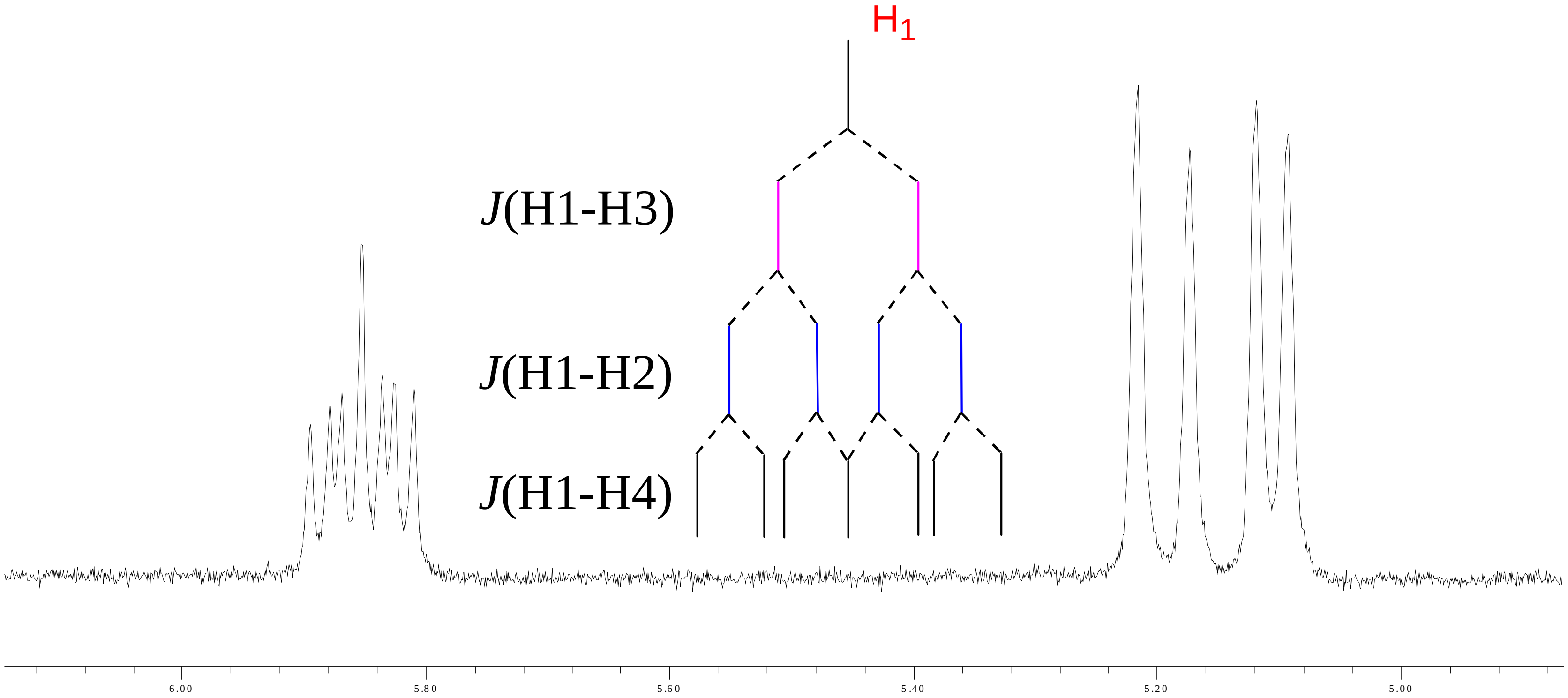
- The magnitude of *J* depends on several factors.
- **1) Distance:** The closer the 1H the larger the coupling.
- Aromatic rings: ortho (~8Hz)> meta (~3Hz)> para (~1Hz).
- Aliphatic: J^2 (10-15 Hz) > J^3 (~7 Hz) > J^4(~1 Hz).

- 2) Orbital Alignment
- Allylic systems.
- *J*(a-c) ~ 14-16 Hz
- *J*(a-b) ~ 8-10 Hz
- *J*(b-c) ~ 1 Hz

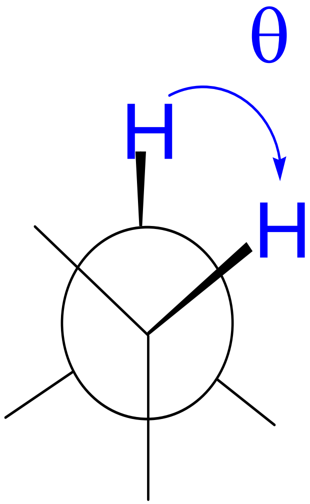


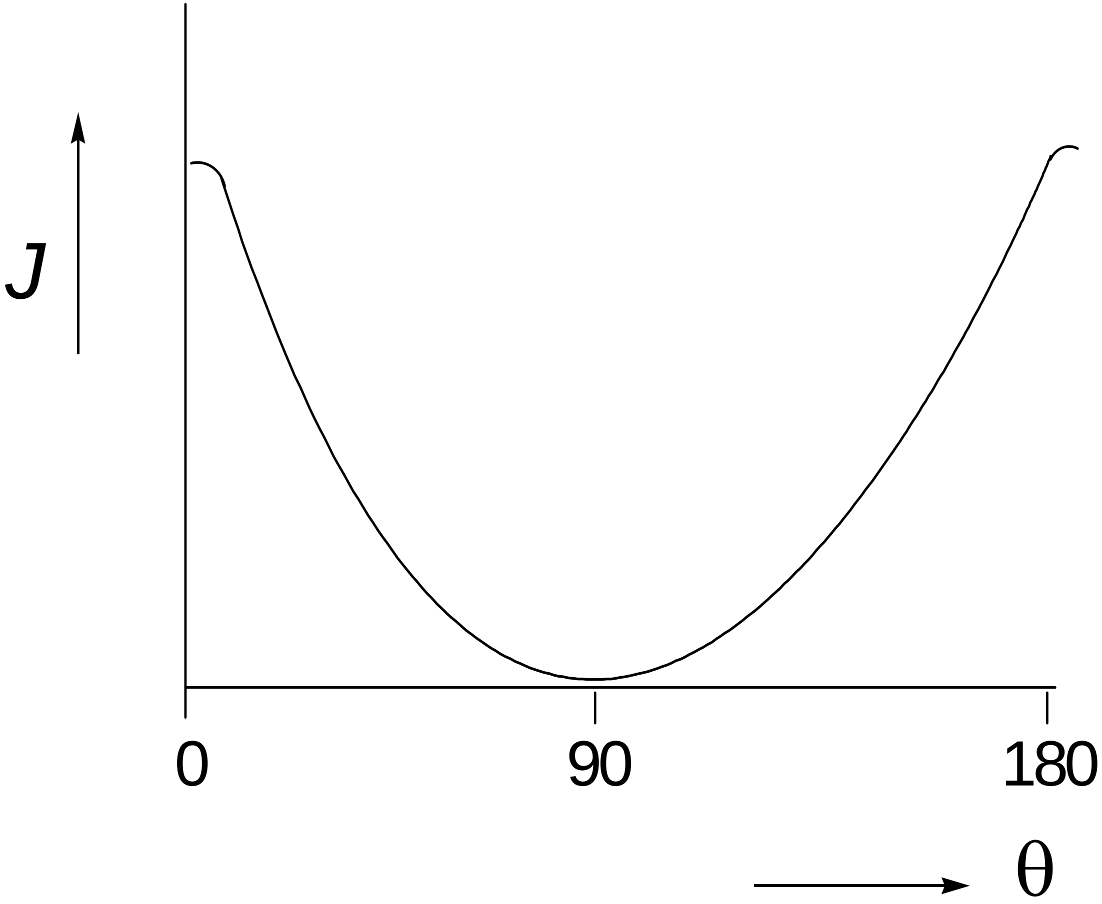

TBSO
H4
O
O
H1
N
O
H2
H3


H3
H2
J(H3-H1)
J(H2-H1)
J(H3-H2)
J(H2-H3)

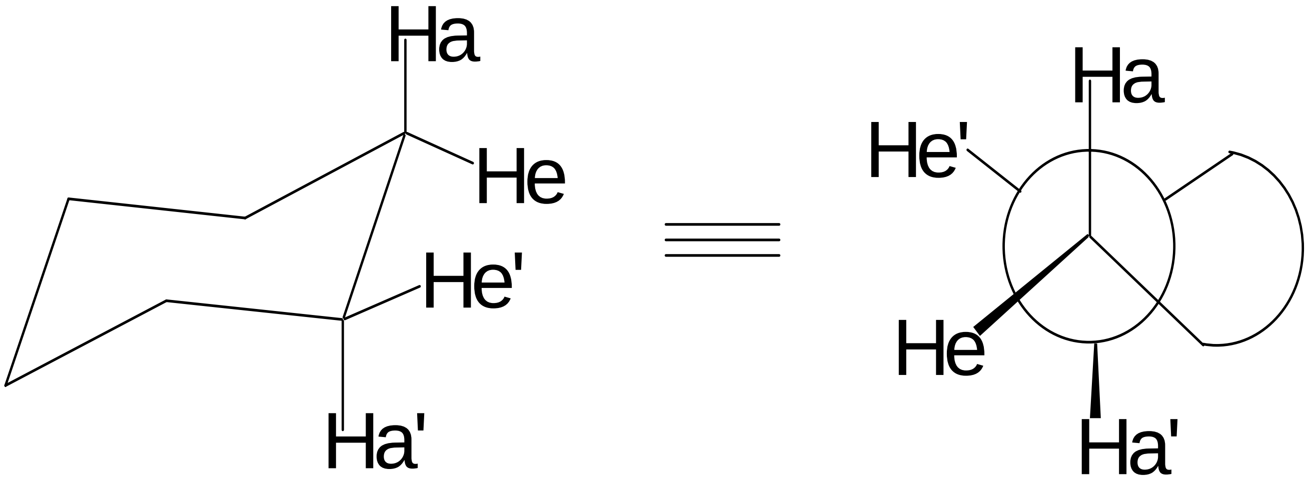

H1
J(H1-H3)
J(H1-H2)
J(H1-H4)
6.00
5.80
5.60
5.40
5.20
5.00

Dihedral angle (J^3 coupling). Karplus curve





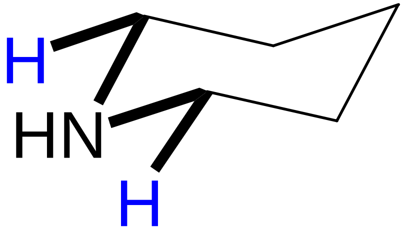
No coupling when θ = 90 degrees



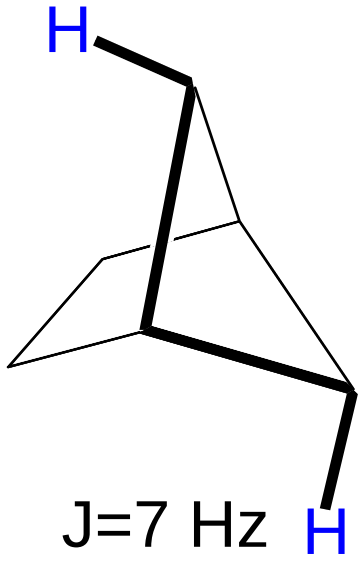
Expected	***J*aa'**	**>**	***J*ae'**	**≈**	***J*ee'**
Angle	180°		60°		60°
Actual *J*	10-13		2-5		2-5

- 3) Long Range Coupling.

- Long range coupling can occur if the chains adopt a zig-zag conformation.
- So-called W-coupling.
- *J* values vary depending on the actual molecule.



J= 1.5 Hz



J=7 Hz

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Lecture 5

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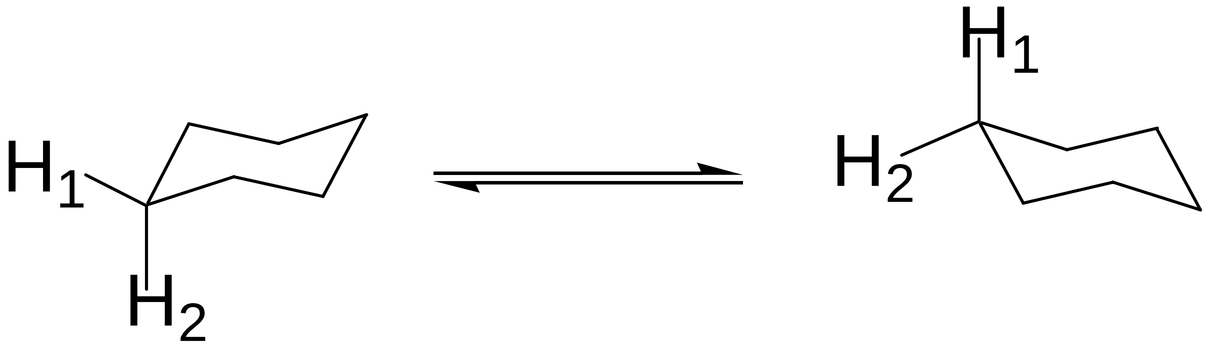
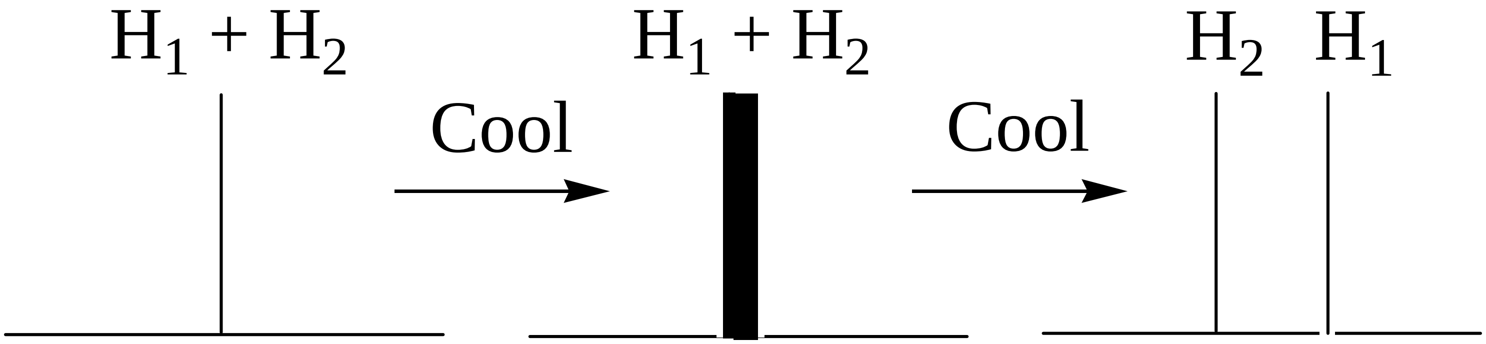
Dynamic Effects in NMR

- A solution spectrum usually represents an average of all possible conformations or orientations. This is because motions are fast compared to the NMR time scale.
- But often find that hindered rotation about bonds or change between conformations is slow on the NMR time scale. In this case we often see two sets of peaks - one for each conformer or rotomer.

Example: Axial *vs* Equatorial ^{1}Hs in Cyclohexanes





Room temp.
Ring flipping is fast

Flipping slow.
Signal broadens.

Flipping slow.
Distinct signals.

Deuterium Exchange

- Relatively acidic protons (1H) can be exchanged with deuterium (2H) by the addition of D_2O. This means that they will not show up in a ^1H NMR spectrum. Adding D_2O to a NMR sample is a useful method for determining the presence of CO_2H, OH, SH and NH_2 groups - as the addition of D_2O can cause these peaks to vanish.

$$RCO_2H + D_2O \rightleftharpoons RCO_2^- + HD_2O^+ \rightleftharpoons RCO_2D + HOD$$

D = ^2H where I = 1

$J^3(HD) < 1$ Hz so unless very high resolution it just looks like coupling has vanished as well.

Correlation (2D-) Spectroscopy

- Homonuclear (H-H Cosy)
- Cross peaks show which 1H are coupled to which.

- Heteronuclear (C-H Cosy)
- Shows which 1H are directly bonded to which carbons.

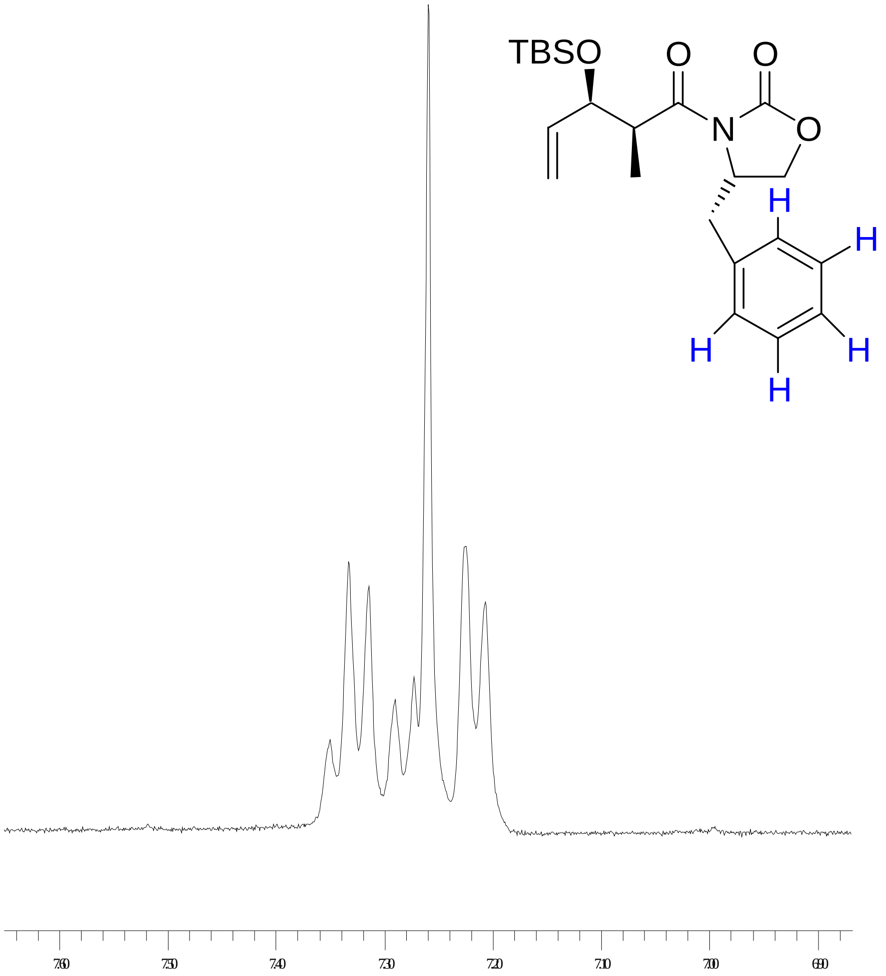
Spotter’s Guide to NMR

- Does it contain:
- Aromatics
- Aliphatics
- Vinylic (double bond 1H)
- 1H next to O or N
- Me groups (3H, s, d or t)
- 1H on heteroatoms (OH or NH)
- Integrals. How many ^{1}H of each type.
- Coupled 1H (start with easy Me groups).
- **NB: coupled 1Hs have same *J* values.**

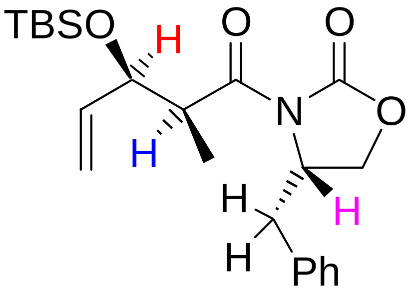
Completing the Interpretation

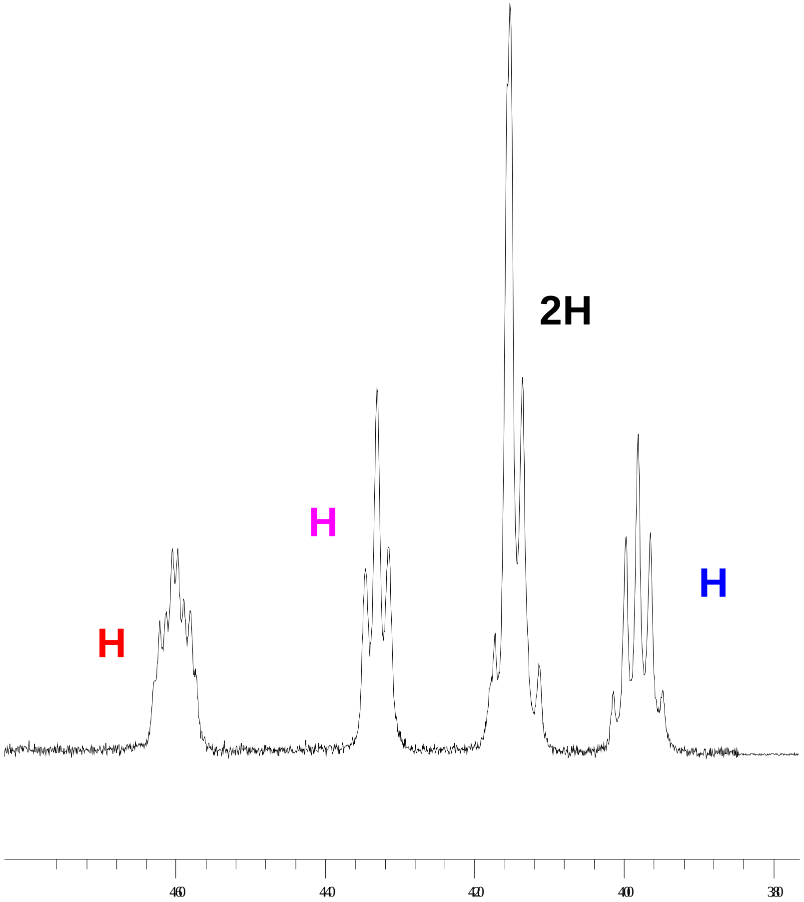
- Using what we have learnt we can complete the interpretation of our sample spectrum.

- Complex multiplet with an integral of 5 at between 7-8ppm is diagnostic of a phenyl (Ph) group.

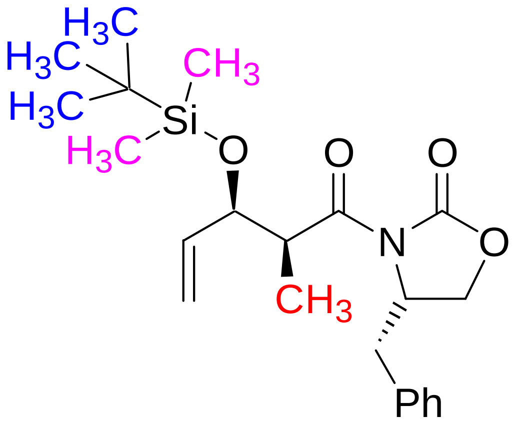


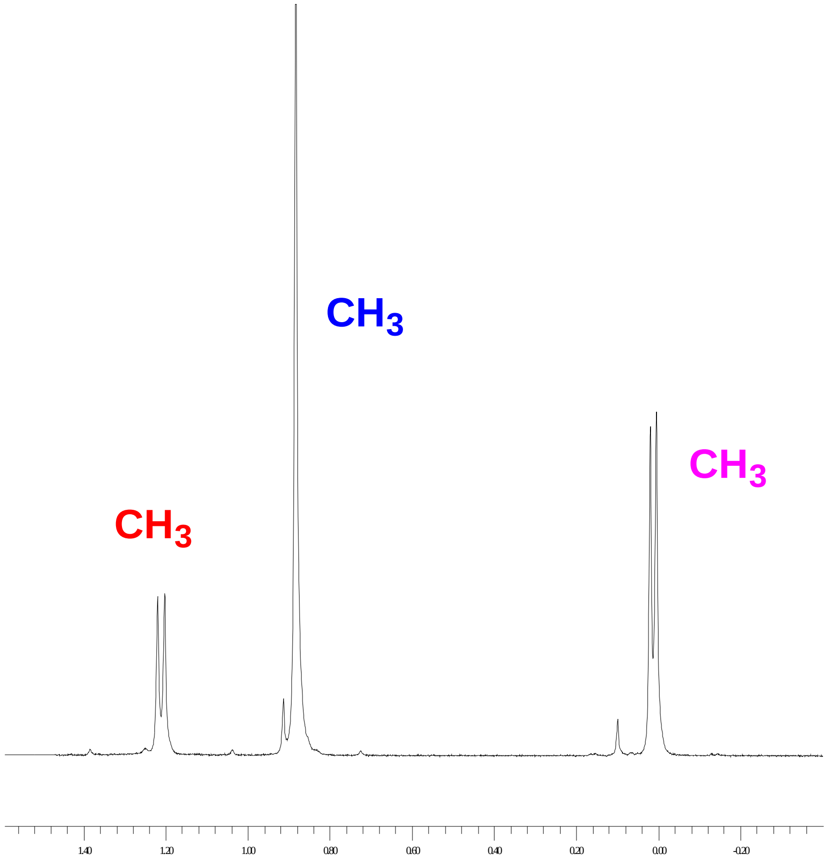
- H is a multiplet as it has large J^3 couplings but also smaller, unresolved, allylic couplings.
- H is a dq but overlapping peaks give the appearance of 5 lines.
- H multiplet couples to both sets of diastereotopic CH_2. similar J values give the appearance of a broad t.
- **2H** is a multiplet for the diastereotopic benzylic CH_2 group. This has both J^2 and J^3 couplings.





- CH_3 doublet coupled to adjacent 1H.
- $(CH_3)_3$ is a singlet as all CH3 groups are equivalent.
- $2CH_3$ are diastereotopic and this shows up in the 1H NMR as two 3H singlets. NOTE: these are two singlets NOT a 6H doublet.
- We have now assigned the complete 1H NMR spectrum of our compound.
- You should now be able to attempt all the problems on the website and in workshops.





Fundamentals of Spectroscopy and Applications to Structure Determination
F12FSA

Lecture 6

Dr. Paul A. Clarke

Room C24

Office Hours: Tuesday 9:30-10:30am

Mass Spectrometry

- Involves the separation and measurement of ions according to their mass-to-charge ratio (m/z).
- Can be used to determine molecular weight and molecular formulae.
- Further, the production of fragment ions leads to useful information about molecular structure.

- How do we carry out the required ionization?

Ionization

- Electron ionization (EI): The sample, which is under vacuum, is bombarded with a stream of electrons from an anode held at a voltage difference of 70eV. At this voltage many fragments are produced which leads to lots of structural information.
- Removal of 1 electron from the molecule results in a $M^{+\bullet}$, called the molecular ion. Thus the m/z value of the molecular ion gives the molecular weight of the sample.

- Chemical ionization (CI): The sample id mixed with a reactant gas (e.g. NH_3, CH_4) which is at a higher pressure. The gas molecule is ionized first. This collides with the sample which is then ionized. Ionization of the sample is due to protonation so $m/z = (M+1)^+$ is observed.

- CI is a softer ionization method so less fragmentation observed.

- Fast Atom Bombardment (FAB): Xe accelerated by ion gun. These Xe collide with sample causing ionization of the sample. Soft ionziation technique which is useful for large and/or fragile molecules. In general there is little fragmentation and $m/z = (M+1)^+$ is observed.

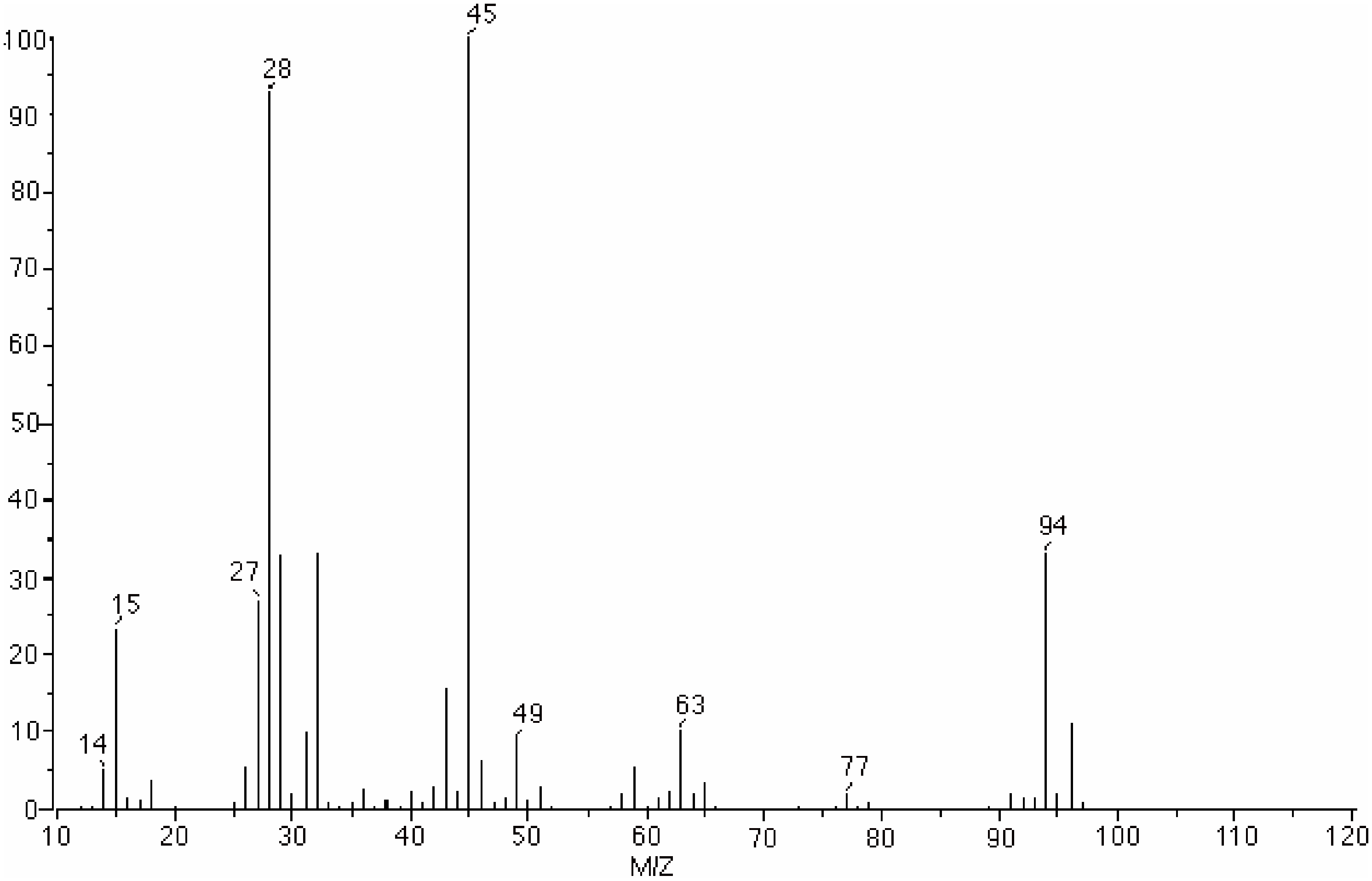
Information available from MS

- From $M^{+\bullet}$: RMM. At high resolution can get molecular formulae as well. Can distinguish been CH_2 and N (both 14).

- Isotope abundances: Few elements are monoisotopic and this helpful in structure determination. E.g. Cl consists of 2 isotopes ^{35}Cl and ^{37}Cl in a ratio 3:1. Hence compounds with 1 Cl will produce 2 m/z peaks in a 3:1 ratio, with the smaller peak 2 mass units higher.

- Similarly Br consists of 2 isotopes ^{79}Br and ^{81}Br in a ratio of 1:1. If a sample contained 2 Br atoms then 3 m/z peaks would be present, each separated by 2 mass units and in a ratio of 1:2:1.

C_3H_7OCl



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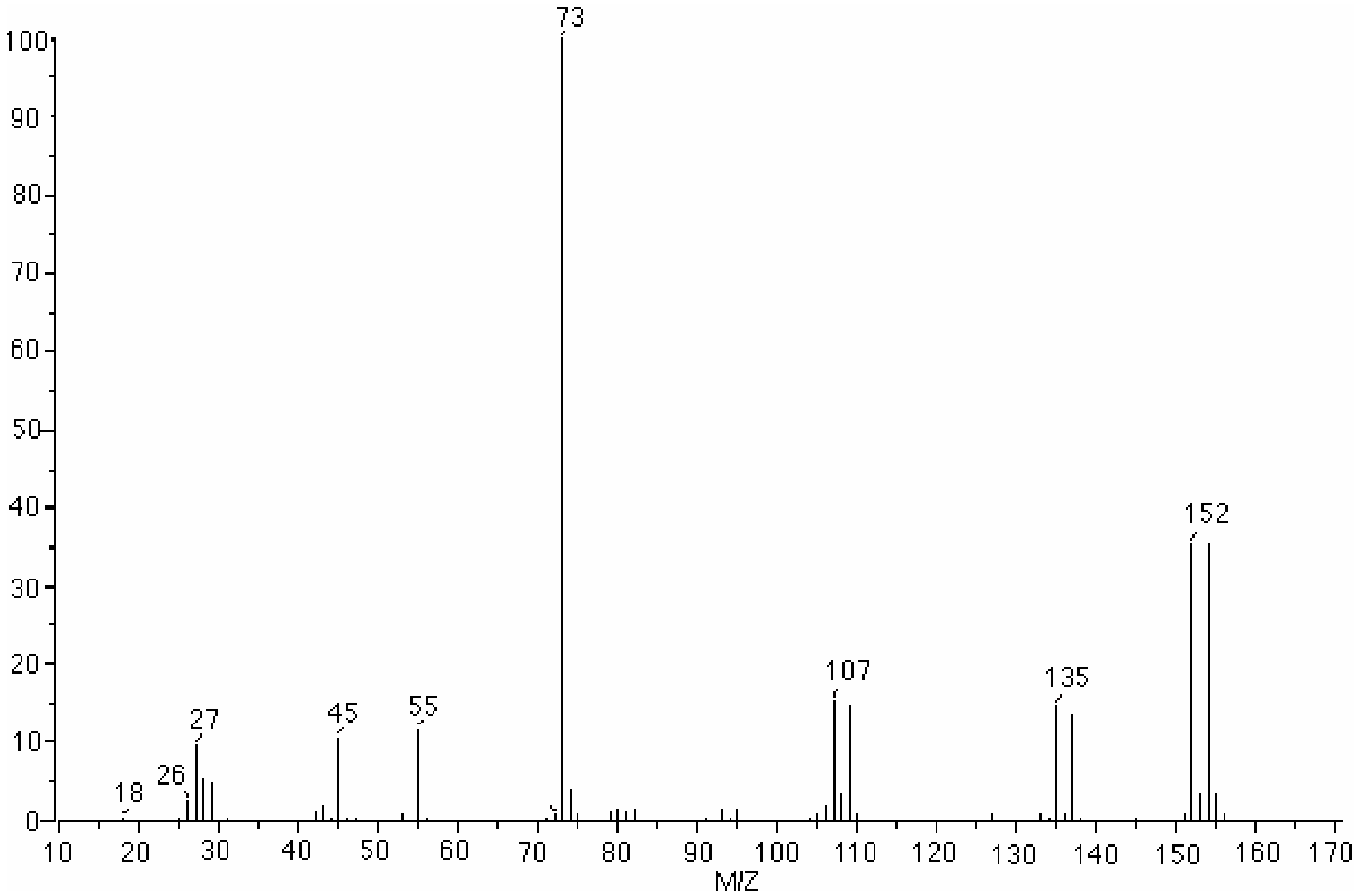
110
120
M/Z

$C_3H_5BrO_2$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130
140
150
160
170
M/Z

Isotope Table

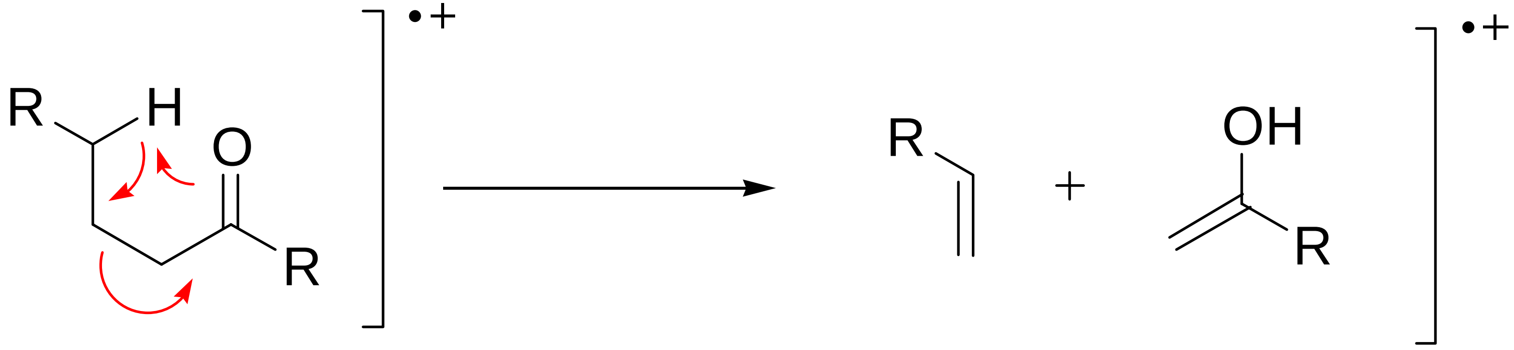
Element	Most common isotope	M+1	M+2
carbon	^{12}C	^{13}C (1.11)	
hydrogen	^{1}H	^{2}H (0.016)	
oxygen	^{16}O	^{17}O (0.04)	^{18}O (0.2)
chlorine	^{35}Cl		^{37}Cl (32.5)
bromine	^{79}Br		^{81}Br (98.0)

- Most important isotope for organic chemists is 13C. ^{12}C:^{13}C ~100:1.1. Therefore size of ($M^{+\bullet}$+1) peak in relation to $M^{+\bullet}$ gives an indication of the number of C atoms present.

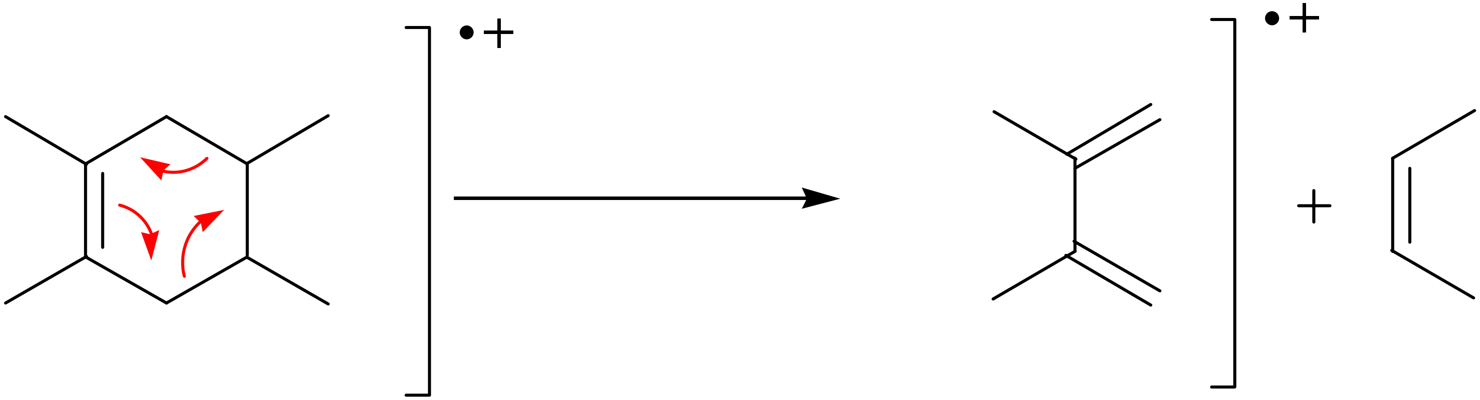
- Nitrogen Rule: As N is valency 3 and has an even atomic mass all organic compounds containing an odd number of N (I, 3, *etc.*) will show and odd molecular weight.

- Common Fragmentations and Rearrangements: Include loss of methyl (15), ethyl (29), water (18), phenyl (77), halogen, CO_2 (44), *etc.*

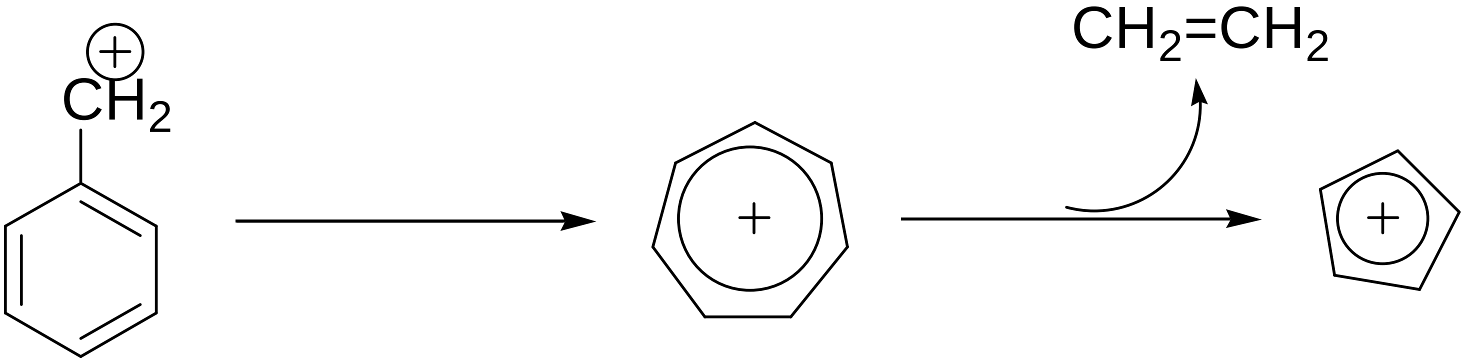
- **McLafferty rearrangement:** Carbonyl compounds with γ-hydrogens.



Retro Diels-Alder:



- Tropylium:



- Ethylene extrusion: