Chapter 14.

Physical Basis of NMR Spectroscopy.

Today the most widely used method for determining the structure of organic compounds is nuclear magnetic resonance (NMR) spectroscopy. NMR spectroscopy involves putting a compound into a magnetic field and measuring the absorption of radio waves by the $^1\text{H}$, $^{13}\text{C}$, $^{19}\text{F}$, $^{31}\text{P}$, or other nuclei. Each nucleus in a different environment absorbs radio waves of a different energy. For example, if one looks at the $^1\text{H}$ NMR spectrum for a compound like $(\text{CH}_3)_3\text{C}$-$\text{CH}_2$-$\text{OH}$, one sees one absorption for the OH $^1\text{H}$, one for the CH$_2$ $^1\text{H}$'s, and one for the C$(\text{CH}_3)_3$ $^1\text{H}$'s. The $^{13}\text{C}$ NMR spectrum shows one absorption for each C atom in the compound. The NMR spectra thus give direct information about the nature of the chemical environment of each magnetically active nucleus in the molecule.

The physical basis of NMR spectroscopy is as follows.

• Like the electron, the nucleus has spin. The $^1\text{H}$ has a spin of 1/2, as do $^{13}\text{C}$, $^{19}\text{F}$, and $^{31}\text{P}$, while $^{14}\text{N}$ and $^2\text{H}$ have spins of 1. Only nuclei that contain odd mass numbers (such as $^1\text{H}$, $^{13}\text{C}$, $^{19}\text{F}$, and $^{31}\text{P}$) or odd atomic numbers (such as $^{14}\text{N}$ and $^2\text{H}$) give rise to NMR signals because only nuclei with nuclear spin >0 can be detected by NMR spectroscopy.

• Since the nucleus has a charge and because of its "spin", nuclei act like tiny magnets. If one applies an external magnetic field $B_0$ to the nuclei, the tiny magnets of the nuclei align themselves with the field, some parallel and some anti-parallel. The parallel arrangement has a slightly lower energy than the anti-parallel arrangement.

• The difference in energy between the two alignments is directly proportional to the strength of the applied field. Because the two alignments are different in energy, there is a slightly higher population of nuclei in the lower energy state than in the higher energy state. When an external energy source (radio waves) that matches the energy difference between the two states is applied, energy is absorbed, causing the nucleus to spin flip from one orientation to the other. Note that radio waves are very low energy radiation! There’s not much difference in energy between the spin states (<0.1 cal), even with a very strong magnetic field.

• A nucleus is in resonance when it absorbs radiofrequency radiation and spin flips to a higher energy state.

Thus two variables characterize NMR: 1. An applied magnetic field, $B_0$; and 2, the frequency of the radiation used for resonance (in MHz). The
frequency needed for resonance and the applied magnetic field strength are directly proportional. The stronger the applied magnetic field, the larger the energy difference between the two nuclear spin states, and the higher the frequency needed for resonance.

**Why should different \(^1\)H nuclei in a compound absorb radio waves of different energies?** Don’t they experience the same external magnetic field? They do and they don’t (*see p.500 and fig. 14.4.*). The external magnetic field is indeed identical for all the nuclei. However, each nucleus is surrounded by electrons, which are charged, so when they experience a magnetic field, they circulate in such a way as to create an opposing magnetic field. This is called shielding. A \(^1\)H nucleus surrounded by a large number of electrons (attached to electropositive elements) will experience a much smaller magnetic field than a \(^1\)H nucleus surrounded by a small number of electrons (attached to electronegative elements). The \(^1\)H attached to an electronegative element is said to be deshielded. The same is true of other nuclei.

**If we keep a magnetic field constant and vary the radio wave frequency, different nuclei will resonate at different frequencies.** We can measure this resonance and plot it as a function of radio wave frequency. In practice, it’s easier to keep the radio wave frequency constant and to vary the magnetic field. The most commonly used \(^1\)H NMR spectrometers use radio waves with frequencies of 60 MHz to 500 Mhz, while the frequencies are one-fourth of this for \(^{13}\)C NMR experiments.

We do the NMR experiment by dissolving the compound to be analyzed in a solvent that lacks any \(^1\)H nuclei (CCl\(_4\) or a deuterated solvent like CDCl\(_3\) or D\(_2\)O). The solution is placed in a tube, which is placed in a magnet. The sample is irradiated with radio waves of constant frequency as the magnetic field is slowly varied. At different magnetic field strengths, different absorbances are measured.

**When we vary the magnetic field, we only need to change its strength by a few millionths to observe all the different resonances of all the different atoms in the compound.** This is why we measure the resonance of nuclei in ppm. Most \(^1\)H nuclei resonate within a range of 10 ppm of each other. Most \(^{13}\)C nuclei, on the other hand, resonate in a range of about 220 ppm of each other. The radio wave frequencies used for \(^{13}\)C NMR spectroscopy are one fourth of those used for \(^1\)H NMR spectroscopy.

**We use tetramethylsilane, or TMS, which has twelve identical \(^1\)H nuclei, as a standard for \(^1\)H and \(^{13}\)C resonance.** We arbitrarily define the magnetic field strength required for TMS to resonate with a given radio wave energy as 0 ppm. The resonances of other kinds of \(^1\)H’s are then
measured in ppm with respect to TMS (see p.495)). The resonance of a particular kind of $^1$H is called its chemical shift, and it is often written as $\delta$ (delta). In the case of neopentyl alcohol (2,2- dimethyl-1-propanol), three resonances are observed at about $\delta$ 3.3 1.7, and ~1.0 ppm downfield (more deshielded) of TMS. As I said, the $^1$H’s in most organic compounds resonate in the region 0-10 ppm, although there are exceptions to this rule.

$^{13}$C nuclei usually resonate in the range 0-220 ppm. (TMS was chosen as a standard because most $^1$H and $^{13}$C nuclei resonate downfield of the same nuclei in TMS.) When an NMR spectrum is plotted, 0 ppm is placed on the right, with increased deshielding as we move to the left. The right of the spectrum is called upfield, while the left of the spectrum is called downfield. The chemical shift values of the nuclei in a particular compound are independent of the radio wave frequency used to measure them.

Chemical shift = observed chemical shift in MHz/ frequency of spectrometer (MHz)

We can use a 60 MHz or 400 MHz instrument to measure the chemical shifts of the $^1$H’s in ethanol, but the values are identical. The magnetic field strengths required for resonance are of course different, but the ppm change in magnetic field strength from TMS is not.

Interpreting NMR Spectra: Symmetry.
The first thing to predict is how many resonances a compound will exhibit. Just because a compound has x number of $^1$H’s doesn’t mean that x number of resonances will be observed. Symmetry will often reduce the number of resonances. Let’s look at neopentyl alcohol again, (CH$_3$)$_3$C–CH$_2$–OH. We have three C atoms, each of which is a different kind — the methyl C’s, the C attached to two C’s (quaternary C), and the methylene C attached to one C and the OH— so we expect to see three different $^{13}$C resonances. We have a total of 12 H atoms, but some of these have identical environments. The 9 H’s in the three methyl groups attached to the quaternary C have the same connections and exchange their environments constantly by rapid rotation about C–C $\sigma$ bonds, so they experience the same deshielding, so they resonate at the same frequency. They are said to be chemically equivalent. Likewise for the 2 H’s in the methylene group. In the end we expect to see three $^1$H resonances for this compound.
Atoms with different connectivities are in principle expected to have different resonances.
Atoms with identical connectivities may or may not be chemically equivalent.
For example, in cyclopentanol, the two H atoms on C2 are not equivalent. One is cis to the OH, and the other is trans to the OH. Atoms that have the same connectivity but don’t have identical resonances are said to be chemically inequivalent, or diastereotopic.
In this class, we will label chemically equivalent atoms with identical letters, and chemically inequivalent atoms with different letters. So all 9 H’s of the t-butyl group of neo-pentyl alcohol will be labelled Hₐ, the two methylene H’s will be labelled Hₖ, and the alcohol H is labeled Hₐ.

• Here’s a method for determining whether or not two atoms with the same connectivities are chemically equivalent. Draw the compound twice. In one of the structures, replace one of the atoms in question with a different test atom. In the other, replace the other atom in question with the test atom. If the two structures are identical or enantiomers, then the atoms in the original structure are chemically equivalent; if the two structures are diastereomers, then the atoms in the original structure are chemically inequivalent.
• In any compound containing a stereocenter that has a group XCH₂Y, where X and Y are different (e.g. CH₃-CHCl-CH₂-CH₃), the H atoms in the CH₂ group are always chemically inequivalent (see page 499). This is because replacing one H atom in XCH₂Y with a test atom generates a new stereocenter, so replacing one or the other H atom always generates different diastereomers of the compound, our positive test for chemically inequivalent atoms.
• A compound doesn’t have to have a stereocenter to give a positive test for chemically inequivalent atoms, though; see cyclopentanol.
• Cyclohexane has axial and equatorial H’s, so we might predict it would show two resonances. This would be somewhat incorrect. The amount of time required to record a NMR spectrum for a compound that interacts with radio waves of say 100 MHz frequency (about 10 ns) is much longer than the amount of time required for cyclohexane to flip back and forth many times. As a result, every H spends time in both the axial and equatorial positions during the time scale of the experiment, and the axial and equatorial H’s can’t be distinguished. At room temperature, cyclohexane shows just one resonance for all the ¹H’s. However, at very low temperatures (-90 °C), where ring flipping is greatly slowed, two
resonances are seen. In practice, for spectra at or around room
temperature, we can look at the flat structure to determine which atoms
are inequivalent. In the case of cyclohexane, all H atoms are labelled \( \text{H}_a \)
and all C atoms are \( \text{C}_a \).

Problems for class: Pentane, 1,1-dimethylcyclohexane, cyclopentanol.

Interpreting \(^1\text{H} \) NMR Spectra.
The \(^1\text{H} \) NMR spectrum gives us information about the number of
chemically different H atoms, the chemical environment of each atom, the
number of H atoms giving rise to each resonance, and the number of
nearby magnetic nuclei (usually other H atoms).
Chemically inequivalent H’s resonate at different field strengths, while
chemically equivalent H’s resonate at the same field strength. We have
talked in detail about how you can tell whether H atoms are chemically
identical or different. For example, in 1,1-dimethylcyclohexane, we expect
to see four sets of resonances: one from the Me H’s, one from C2 and C6,
one from C3 and C5, and one from C4. The resonances of \(^1\text{H} \)’s tend to fall
into the range 0.5-11 ppm downfield of
TMS. The range can be divided into six regions. \(^1\text{H} \) nuclei in certain kinds
of chemical environments resonate in certain regions, while others
resonate in other regions:
Saturated alkyl groups resonate from 0.5 to 1.5 ppm.
H atoms on C’s adjacent to C=O or C=C groups and RC≡CH between 1.5
and 2.5 ppm.
H atoms attached to C atoms bearing one heteroatom (H–C–X; X= O, N, S,
halogen) resonate between 2.5 and 4.5 ppm.
Alkenyl H atoms (R\(_2\)C=CHR) and H atoms attached to C atoms bearing
two heteroatoms (HCX\(_2\)R) resonate between 5 and 6.5 ppm.
Aryl H atoms resonate between 6.5 and 8.0 ppm.
Finally, H atoms in XCHO groups (X= C, N, O) resonate between 7.8 and 10.5 ppm. (These ranges are approximate; H atoms in compounds with unusual structures can resonate at unusual frequencies.) Carboxylic acid H’s resonate way downfield, while alcohol and amine H’s may resonate anywhere (depends on the degree of H-bonding).

A H atom near two deshielding groups falls further downfield than if either one of the deshielding groups were present alone. For example, MeOCH₂Me has δ ~3.4 ppm, PhCH₂Me has δ ~ 2.3 ppm, but MeOCH₂Ph has δ ~ 5.5. Within each region, methyl H’s resonate slightly more upfield (smaller δ) than methylene or methine H’s, and electronegative atoms or groups that are one C removed tend to shift the resonance a little more downfield (larger δ). The chemical shifts of H atoms attached to heteroatoms are not constant, even for a given compound, and vary tremendously depending on concentration, solvent, and temperature.

Integration
If one measures the areas under the resonances in a ¹H NMR spectrum, one can determine the number of H atoms contributing to each resonance. This process is called integration. It used to be done by cutting the peaks out of the paper and weighing them, but today we do it by computer. Let’s look at the ¹H NMR spectrum of methyl formate, HCO₂CH₃. We expect to see two resonances: one at about δ 4.0 ppm for the methyl group and one at about δ 8.0 ppm for the carbonyl H. If we integrate these two peaks, the ratio of the δ 8.0 peak to the 4.0 peak will be approximately 1:3, since one H atom contributed to the downfield peak while three contributed to the upfield peak.

Note that we obtain only the ratio of H atoms contributing to the different resonances, not necessarily the total number of H atoms in that compound.

For example, if we integrate the spectrum of methyl pivalate Me₃CCO₂Me, which has two resonances at δ 3.7 and 1.2 ppm, we find a 1:3 ratio of peaks, the same as in methyl formate. We can’t tell beforehand whether we have four, eight, twelve, or sixteen H atoms in the compound, just that we have two kinds of H atoms in a 3:1 ratio.

Spin-Spin Coupling: The coupling constant, $J$. (section 14.6)
The most complex aspect of ¹H NMR spectra is spin-spin coupling. Consider CHBr₂CHCl₂. Hₐ will experience a magnetic field of a particular strength, and we expect to see one resonance from it. However, there is
a non-equivalent magnetic atom next door on C2, Hb. Hb has about a 50% probability of aligning with the external magnetic field, and about a 50% probability of aligning against it. When Hb aligns with the field, Ha experiences a slightly stronger magnetic field, and when Hb aligns against the field, Ha experiences a slightly weaker magnetic field. We therefore expect that the resonance due to Ha would be split into two resonances of equal height centered around the "true" resonance frequency. This expectation is true. The Ha resonance is observed to be a doublet. Likewise, the Hb resonance is also a doublet, due to the effect of Ha on the magnetic field experienced by Hb.

\(^1\text{H}–\ ^1\text{H}\) coupling is often observed between chemically inequivalent \(^1\text{H}\)’s separated by two or three bonds. This is called two-bond and three-bond coupling. Three-bond coupling, i.e. coupling between \(^1\text{H}\) atoms on adjacent C atoms, H–C–C–H, is observed most frequently. Two-bond coupling is observed between diastereotopic H atoms. Four- and five-bond coupling is observed only occasionally in compounds with rigid geometries. Coupling between equivalent \(^1\text{H}\)’s is not observed.

We have seen that in CHBr\(_2\)CHCl\(_2\), Ha splits the resonance of Hb into two signals. The extent of splitting is called the coupling constant and is commonly abbreviated J. We have also seen that Hb splits the resonance of Ha. Hb and Ha split each other with the same coupling constant. Coupling constants are usually measured in Hz, not in ppm, because they are independent of spectrometer frequency when expressed in Hz. Three-bond coupling constants usually range between 0 and 12 Hz, while two-bond coupling constants may range up to 20 Hz. The H–C–C–H three-bond coupling constant is usually about 7.0 Hz when there is free rotation about the C–C bond. When there is not free rotation, as in cyclic compounds or in double bonds, the coupling constants may be very large or very small.

In cyclohexanes that are conformationally locked into a chair, the coupling between adjacent axial H’s is usually large, between equatorial and an adjacent axial is medium, and between adjacent equatorial H’s is usually very small. The coupling between H’s that are \textit{trans} on a double bond is usually quite large (11-18 Hz), for \textit{cis} it is medium sized (ca. 5-10 Hz), and for terminal =CH\(_2\) groups the coupling between the two H’s is usually very small (ca. 0-3 Hz).

\textbf{Coupling constants}: One can calculate coupling constants in Hz by measuring the chemical shifts of the two peaks that are split and using the formula:
Coupling constant (Hz) = \( \Delta \delta \) (ppm) \* spectrometer frequency (MHz) where \( \Delta \delta \) is the difference in the chemical shift of the two peaks.

Now consider CHBr2CH2Cl. There are one Ha and two Hb. Consider the environment of Ha. It experiences a magnetic field strength that is affected by the spins of its two neighbors, Hb. Before, when there was one Hb, we saw that Ha could experience two different magnetic fields, depending on whether the spin of Hb was up or down. Now, Ha might experience three different magnetic field strengths, depending on whether the Hb’s are up-up, up-down, down-up, or down-down. (Down-up is experienced the same way as updown, since the sum of the effect on the magnetic field is 0.) The resonance for Ha will be split into three resonances, a triplet, with a 1:2:1 ratio.

What about Hb in CHBr2CH2Cl? It has one inequivalent neighbor, Ha. Its resonance is a doublet. The distance between two lines of the triplet for Ha, the coupling constant, is the same as the distance between the two lines of the doublet for Hb. Also, the integration of the triplet due to Ha and the doublet due to Hb will give a 1:2 ratio for the two peaks. In other words, the splitting doesn’t change the total area under the resonances.

Now look at CHBr2CH3. Ha has three neighbors Hb. These might be up-up-up, up-up-down, up-down-up, down-up-up, down-down-up, down-up-down, up-down-down, or down-down-down. As a result Ha might experience four different magnetic field strengths with a probability of 1:3:3:1. The signal for Ha is a quartet in the ratio 1:3:3:1. The signal for Hb remains a doublet.

The number of peaks into which a resonance is split is called its multiplicity. The multiplicity of a \(^1\)H with \( n \) equivalent neighbors is \( n+1 \), with the relative intensities of the resonances given by the polynomial expansion (below).
We call the multiplicities singlets, doublets, triplets, quartets, quintets, sextets, etc. Other magnetically active nuclei, such as $^{31}$P, $^2$H, and $^{19}$F, can also split the resonance of a $^1$H.

$^{13}$C NMR: the number of signals in a $^{13}$C NMR spectrum gives the number of different types of C atoms in the molecule. Peak intensity is not proportional to the number of absorbing carbons. Hence integration is not informative under the usual conditions. $^{13}$C NMR peaks are not split due to low abundance of $^{13}$C nuclei (1.1% abundance) hence the chance of two $^{13}$C nuclei being bonded to each other is very small.

To summarize: The $^1$H NMR spectrum detects a single resonance for every non-equivalent $^1$H in the compound. The chemical shift of the resonance, which is independent of spectrometer frequency when it is expressed in ppm, gives information about the chemical environment of the $^1$H's. The resonances can be integrated to obtain the number of H atoms contributing to each resonance. The multiplicity of a resonance tells us how many neighbors the $^1$H’s contributing to that resonance have. The coupling constant J is independent of spectrometer frequency when expressed in Hz. The value of the coupling constant gives us information on the nature of the spatial relationship between the atoms that are coupled (two-bond or three-bond, fixed or varying orientation, etc.).