CHAPTER

9

Nuclear Magnetic Resonance and Mass Spectrometry

TOOLS FOR STRUCTURE DETERMINATION

Have you known someone who needed an MRI (magnetic resonance imaging) scan for a medical condition, or have you needed one yourself? Have you ever observed someone in an airport security line having their belongings wiped down with a pad that was then placed in some kind of analytical instrument? Have you wondered how scientists determine the structures of compounds found in nature, or have you known a fellow student in a laboratory class who extracted bark, leaves, or fruit to isolate and identify some natural compounds? Or have you wondered how forensic evidence is analyzed in criminal cases, or how pesticides are identified in food samples?

If you have wondered about any of these things, then some of your curiosity will be satisfied by learning about spectroscopic methods such as nuclear magnetic resonance (NMR) spectrometry, which involves the same physical principles as MRI imaging, and MS (mass spectrometry), which is used in some airport screening processes as well as many forensic applications. NMR and MS are workhorse techniques for the study of both biological and nonbiological molecular structure.

IN THIS CHAPTER WE WILL CONSIDER:

- nuclear magnetic resonance (NMR), a form of spectroscopy that is one of the most powerful tools for the identification of functional groups and for the determination of connections between the atoms in molecules
- mass spectroscopy (MS), which allows the determination of exact molecular formulas of molecules both large and small

PHOTO CREDIT: Don Farrall/Photodisc/Getty Images, Inc.

[WHY DO THESE TOPICS MATTER?] At the end of the chapter, we will show just how critical these techniques are for determining the structure of organic molecules. Indeed, before spectroscopy, structure determination could take years or even decades, sometimes providing challenges that stymied future chemistry Nobel laureates!

9.1 INTRODUCTION

- **Spectroscopy** is the study of the interaction of energy with matter.

When energy is applied to matter, it can be absorbed, emitted, cause a chemical change, or be transmitted. In this chapter we shall see how detailed information about molecular structure can be obtained by interpreting results from the interaction of energy with molecules. In our study of nuclear magnetic resonance (NMR) spectroscopy we shall focus our attention on energy absorption by molecules that have been placed in a strong magnetic field. When we study mass spectrometry (MS), we shall learn how molecular structure can be probed by bombarding molecules with a beam of high-energy electrons. These two techniques (NMR and MS) are a powerful combination for elucidating the structures of organic molecules. Together with infrared (IR) spectroscopy (Section 2.15), these methods comprise the typical array of spectroscopic tools used by organic chemists. Later, we shall briefly discuss how gas chromatography (GC) is linked with mass spectrometry in GC/MS instruments to obtain mass spectrometric data from individual components of a mixture.

We begin our study with a discussion of nuclear magnetic resonance spectroscopy.

9.2 NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY

The 1952 Nobel Prize in Physics was awarded to Felix Bloch (Stanford) and Edward M. Purcell (Harvard) for their discoveries relating to nuclear magnetic resonance.

The nuclei of certain elements, including ^{1}H nuclei (protons) and ^{13}C (carbon-13) nuclei, behave as though they were magnets spinning about an axis. When a compound containing protons or carbon-13 nuclei is placed in a very strong magnetic field and simultaneously irradiated with electromagnetic energy of the appropriate frequency, nuclei of the compound absorb energy through a process called magnetic resonance. The absorption of energy is quantized.

- A graph that shows the characteristic energy absorption frequencies and intensities for a sample in a magnetic field is called a **nuclear magnetic resonance (NMR) spectrum**.

As a typical example, the proton (^{1}H) NMR spectrum of bromoethane is shown in Fig. 9.1.

We can use NMR spectra to provide valuable information about the structure of any molecule we might be studying. In the following sections we shall explain how four features of a molecule's proton NMR spectrum can help us arrive at its structure.

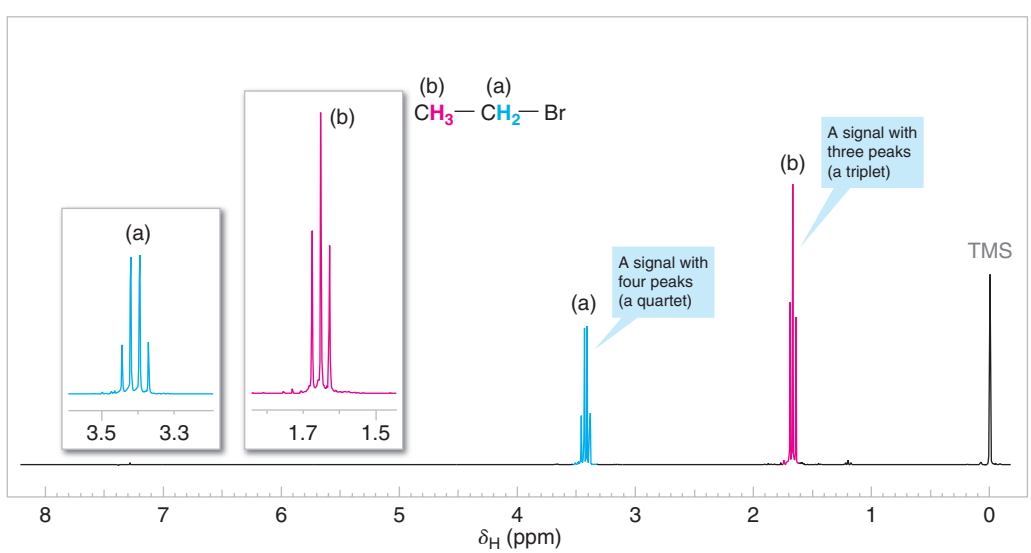


FIGURE 9.1 The 300-MHz ^{1}H NMR spectrum of bromoethane (ethyl bromide). Zoomed-in expansions of the signals are shown in the offset plots.

1. **The number of signals in the spectrum** tells us **how many different sets of protons there are in the molecule**. In the spectrum for bromoethane (Fig. 9.1) there are *two signals arising from two different sets of protons*. One signal (consisting of four peaks) is shown in blue and labeled (a). The other signal (consisting of three peaks) is in red and is labeled (b). These signals are shown twice in the figure, at a smaller scale on the baseline spectrum, and expanded and moved to the left above the base spectrum. [Don't worry now about the signal at the far right of the spectrum (labeled TMS); it comes from a compound (tetramethylsilane) that was added to the bromoethane so as to calibrate the positions of the other signals.]
2. **The position of the signals in the spectrum along the *x*-axis** tells us about the magnetic environment of each set of protons arising largely from the electron density in their environment. We'll learn more about this in Section 9.2A.
3. **The area under the signal** tells us about **how many protons there are in the set being measured**. We'll learn how this is done in Section 9.2B.
4. **The multiplicity (or splitting pattern) of each signal** tells us about **the number of protons on atoms adjacent to the one whose signal is being measured**. In bromoethane, signal (a) is split into a **quartet** of peaks by the three protons of set (b), and signal (b) is split into a *triplet* of peaks by the two protons of set (a). We'll explain splitting patterns in Section 9.2C.

9.2A Chemical Shift

- The position of a signal along the *x*-axis of an NMR spectrum is called its **chemical shift**.
- **The chemical shift of each signal gives information about the structural environment of the nuclei producing that signal.**
- Counting the number of signals in a ^{1}H NMR spectrum indicates, at a first approximation, the number of distinct proton environments in a molecule.

Tables and charts have been developed that allow us to correlate chemical shifts of NMR signals with likely structural environments for the nuclei producing the signals. Table 9.1

TABLE 9.1 APPROXIMATE PROTON CHEMICAL SHIFTS

Type of Proton	Chemical Shift (δ, ppm)	Type of Proton	Chemical Shift (δ, ppm)
1° Alkyl, RCH_3	0.8–1.2	Alkyl bromide, RCH_2Br	3.4–3.6
2° Alkyl, RCH_2R	1.2–1.5	Alkyl chloride, RCH_2Cl	3.6–3.8
3° Alkyl, R_3CH	1.4–1.8	Vinylic, $R_2C{=}CH_2$	4.6–5.0
Allylic, $R_2C{=}\underset{\displaystyle R}{\underset{\vert}{C}}{-}CH_3$	1.6–1.9	Vinylic, $R_2C{=}\underset{\displaystyle R}{\underset{\vert}{C}}H$	5.2–5.7
Ketone, $R\overset{\displaystyle O}{\overset{\Vert}{C}}CH_3$	2.1–2.6	Aromatic, ArH	6.0–8.5
Benzylic, $ArCH_3$	2.2–2.5	Aldehyde, $R\overset{\displaystyle O}{\overset{\Vert}{C}}H$	9.5–10.5
Acetylenic, $RC{\equiv}CH$	2.5–3.1	Alcohol hydroxyl, ROH	0.5–6.0[a]
Alkyl iodide, RCH_2I	3.1–3.3	Amino, $R{-}NH_2$	1.0–5.0[a]
Ether, $ROCH_2R$	3.3–3.9	Phenolic, ArOH	4.5–7.7[a]
Alcohol, $HOCH_2R$	3.3–4.0	Carboxylic, $R\overset{\displaystyle O}{\overset{\Vert}{C}}OH$	10–13[a]

[a]The chemical shifts of these protons vary in different solvents and with temperature and concentration.

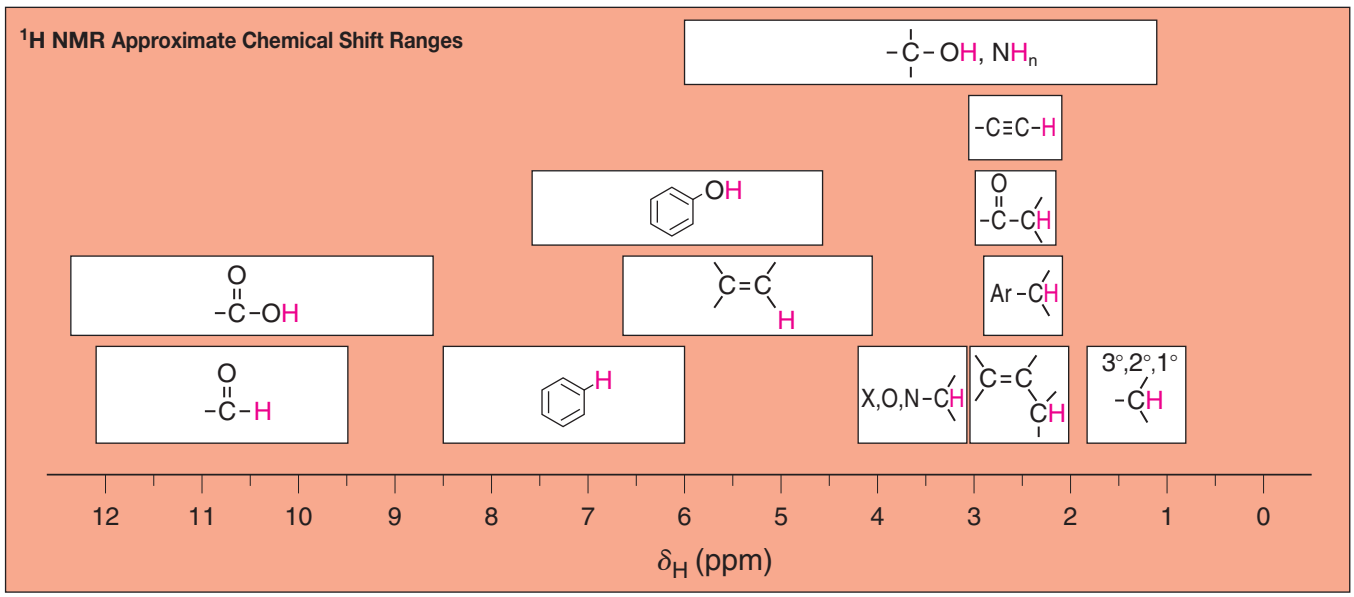


FIGURE 9.2 Approximate proton chemical shifts.

and Fig. 9.2, for example, are useful for this purpose. ^{1}H NMR chemical shifts generally fall in the range of 13–0 ppm (δ).

The chemical shift of a signal in an NMR spectrum depends on the local magnetic environment of the nucleus producing the signal. The local magnetic environment of a nucleus is influenced by electron density and other factors we shall discuss shortly. The physical meaning of chemical shift values relates to the actual frequency of the NMR signals produced by the nuclei. The *practical* importance of chemical shift information is that it gives important clues about molecular structure. Each NMR signal indicates the presence of nuclei in a different magnetic environment.

Chemical shifts are measured along the spectrum axis using a delta (δ) scale, in units of parts per million (ppm). When comparing one signal with another:

- A signal with a chemical shift further to the left in the spectrum than another signal (i.e., at a larger δ or ppm value) has a higher frequency.
- A signal to the right of another signal has a lower frequency.

SOLVED PROBLEM 9.1

Consider the spectrum of bromoethane (Fig. 9.1). What is the chemical shift of the signal in blue for the CH_2 group?

STRATEGY AND ANSWER: The signal for the CH_2 group of bromoethane appears as a symmetrical pattern of four peaks. For a signal with multiple peaks, such as a quartet, the chemical shift is reported as the midpoint of the peaks in the signal. Estimating as well as possible from the zoomed-in offset expansion in Fig. 9.1, the chemical shift of the bromoethane quartet is 3.4 ppm.

The ^{1}H NMR spectrum of 1,4-dimethylbenzene (*p*-xylene), shown in Fig. 9.3, is a simple example that we can use to learn how to interpret chemical shifts. First, note that there is a signal at δ 0. The signal at δ 0 is *not* from 1,4-dimethylbenzene, but from tetramethylsilane (TMS), a compound that is sometimes added to samples as an internal standard to calibrate the chemical shift scale. If the signal from TMS appears at zero ppm, the chemical shift axis is calibrated correctly.

Next we observe that there are only two signals in the ^{1}H NMR spectrum of 1,4-dimethylbenzene other than for TMS, at approximately δ 7.0 and δ 2.3. The existence of just two signals implies that there are only two distinct proton environments in 1,4-dimethylbenzene, a fact we can easily verify for ourselves by examining its structure.

We say, then, that there are "two types" of hydrogen atoms in 1,4-dimethylbenzene, and these are the hydrogen atoms of the methyl groups and the hydrogen atoms of the

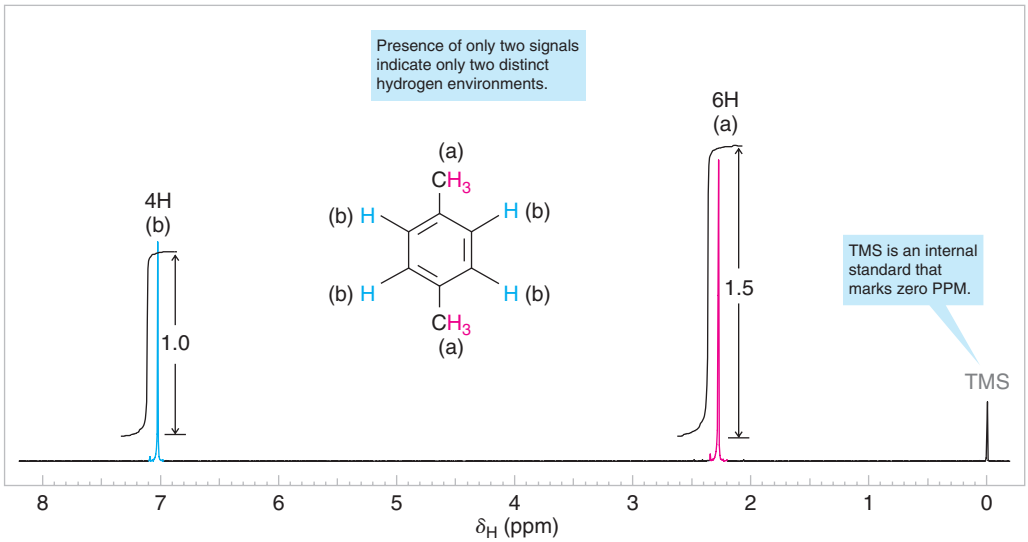


FIGURE 9.3 The 300-MHz ^{1}H NMR spectrum of 1,4-dimethylbenzene.

benzene ring. The two methyl groups produce only one signal because they are equivalent by virtue of the plane of symmetry between them. Furthermore, the three hydrogen atoms of each methyl group are equivalent due to free rotation about the bond between the methyl carbon and the ring. The benzene ring hydrogen atoms also produce only one signal because they are equivalent to each other by symmetry.

Referring to Table 9.1 or Fig. 9.2, we can see that ^{1}H NMR signals for hydrogen atoms bonded to a benzene ring typically occur between δ 6 and 8.5, and that signals for hydrogen atoms on an sp^3 carbon bonded to a benzene ring (benzylic hydrogens) typically occur between δ 2 and 3. Thus, chemical shifts for the signals from 1,4-dimethylbenzene occur where we would expect them to according to NMR spectral correlation charts.

In the case of this example, the structure of the compound under consideration was known from the outset. Had we not known its structure in advance, however, we would have used chemical shift correlation tables to infer likely structural environments for the hydrogen atoms. We would also have considered the relative area of the signals and signal multiplicity, factors we shall discuss in the following sections.

SOLVED PROBLEM 9.2

Based on the information in Table 9.1, in what ppm range would you expect to find the protons of **(a)** acetone (CH_3COCH_3) and **(b)** ethanol?

STRATEGY AND ANSWER: We use a chemical shift correlation table, such as Table 9.1, to find the closest match between the compound of interest and the partial structures shown in the table.

(a) Acetone is a ketone bearing hydrogen atoms on the carbons adjacent to its carbonyl group. Ketones are listed in Table 9.1 as a representative substructure whose protons have a chemical shift range of 2.1–2.6 ppm. Thus, we expect the proton NMR signal from acetone to appear in the 2.1–2.6 ppm range. There will be one signal for all of the hydrogen atoms in acetone because, due to free rotation, they can occupy equivalent magnetic environments at any given instant.

(b) Ethanol is expected to exhibit three proton NMR signals, one for each of its three distinct hydrogen environments. Ethanol contains an alcohol hydroxyl proton, which Table 9.1 lists in the range of 0.5–6.0 ppm; two protons on the carbon bearing the hydroxyl group, which according to Table 9.1 we expect in the 3.3–4.0 ppm range; and a methyl group bonded to no functional groups, which, as a 1° alkyl group, should appear in the 0.8–1.2 ppm range.

PRACTICE PROBLEM 9.1

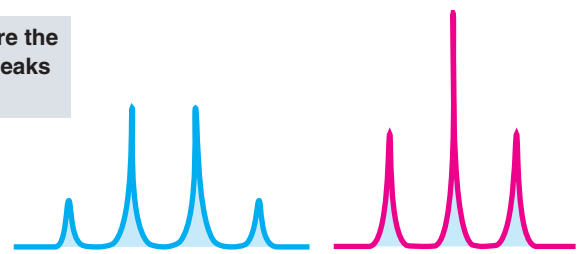
In what chemical shift ranges would you expect to find the proton NMR signals of ethyl acetate ($CH_3CO_2CH_2CH_3$)?

9.2B Integration of Signal Areas

- **The area under each signal in a ^{1}H NMR spectrum is proportional to the number of hydrogen atoms producing that signal.**

In the ^{1}H NMR spectrum of 1,4-dimethylbenzene (Fig. 9.3), you may have noticed curves that resemble steps over each signal. The height of each step (using any unit of measure) is proportional to the area underneath the NMR signal, and also to the number of hydrogen atoms giving rise to that signal. Taking the ratio of the step height associated with one signal to the step height associated with another provides the ratio of the areas for the signals, and therefore represents the number of hydrogen atoms producing one signal as compared to the other. Note that we are discussing the height of the integral steps, not the heights of the signals. It is signal area (**integration**), not signal height, that is important.

Integrals measure the area under the peaks of a signal.



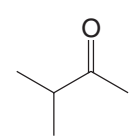
The area under each signal (shown with blue shading above) is measured (integrated) and taken as a ratio against the area of other signals to compare the relative numbers of hydrogen atoms producing each signal in an NMR spectrum.

In Fig. 9.3 we have indicated the relative integral step heights as 1.0 and 1.5 (in dimensionless units). Had these values not been given, we would have measured the step heights with a ruler and taken their ratio. Since the actual number of hydrogen atoms giving rise to the signals is not likely to be 1 and 1.5 (we cannot have a fraction of an atom), we can surmise that the true number of hydrogens producing the signals is probably 2 and 3, or 4 and 6, etc. For 1,4-dimethylbenzene the actual values are, of course, 4 and 6.

Whether NMR data are provided as in Fig. 9.3 with an integral step over each signal, or simply with numbers that represent each signal's relative area, the process of interpreting the data is the same because the area of each signal is proportional to the number of hydrogen atoms producing that signal. It is important to note that in ^{13}C NMR spectroscopy signal area is not relevant in routine analyses.

SOLVED PROBLEM 9.3

What integral values (as whole number ratios) would you expect for signals in the proton NMR spectrum of 3-methyl-2-butanone?



STRATEGY AND ANSWER: There are three distinct proton environments in 3-methyl-2-butanone: the methyl at C1, the methine hydrogen at C3, and the two methyl groups bonded to C3, which are equivalent. The ratio of these signals, in the order just listed, would be 3 : 1 : 6.

9.2C Coupling (Signal Splitting)

Coupling, also referred to as **signal splitting** or signal multiplicity, is a third feature of ^{1}H NMR spectra that provides very useful information about the structure of a compound.

- Coupling is caused by the magnetic effect of nonequivalent hydrogen atoms that are within 2 or 3 bonds of the hydrogens producing the signal.

The effect of the nearby hydrogens is to split (or couple with) the energy levels of the hydrogens whose signal is being observed, and the result is a signal with multiple peaks.

(Notice that we have been careful to differentiate use of the words signal and peak. A group of equivalent hydrogen atoms produces one *signal* that may be split into multiple *peaks*.) We shall explain the physical origin of coupling further in Section 9.9; however, **the importance of coupling is that it is predictable, and it gives us specific information about the constitution of the molecule under study**.

The typical coupling we observe is from nonequivalent, **vicinal** hydrogens, that is, from hydrogens on adjacent carbons, separated by three bonds from the hydrogens producing the signal. Coupling can also occur between nonequivalent **geminal** hydrogens (hydrogens bonded to the same carbon) if the geminal hydrogens are in a chiral or conformationally restricted molecule. (We shall discuss cases of chiral and conformationally restricted molecules in Section 9.8.)

- A simple rule exists for predicting the number of peaks expected from coupling in ^{1}H NMR:

Number of peaks in a ^{1}H NMR signal $= n + 1$

Where n is the number of vicinal and geminal hydrogen atoms that are nonequivalent to the hydrogens producing the signal

This rule is applicable in general to achiral molecules without conformational barriers.

The ^{1}H NMR spectrum of 1,4-dimethylbenzene (Fig. 9.3) is an example where $n = 0$ (in the above equation) regarding the hydrogen atoms producing the signals at δ 7.0 and at δ 2.3. There are no hydrogen atoms on the carbons adjacent to the methyl groups; hence $n = 0$ for the signal at δ 2.3, and the signal is a singlet (signals with only one peak are called **singlets**). And, since all of the hydrogen atoms on the ring are equivalent by symmetry and there are no adjacent nonequivalent hydrogen atoms, $n = 0$ for the hydrogens on the ring producing the signal at δ 7.0, and hence this signal is a singlet as well.

The ^{1}H NMR spectrum of 1,1,2-trichloroethane, shown in Fig. 9.4, provides an example where n is not equal to zero, and coupling is therefore evident. In the spectrum of 1,1,2-trichloroethane we see two signals: one with three peaks and one with two peaks. These signals are called, respectively, a **triplet** and a **doublet**. The signal for the $-CHCl_2$ hydrogen is a triplet because there are two hydrogen atoms on the adjacent carbon ($n = 2$). The signal for the $-CH_2Cl$ hydrogens is a doublet because there is one hydrogen on the adjacent carbon ($n = 1$). We shall consider why this is so in Section 9.9.

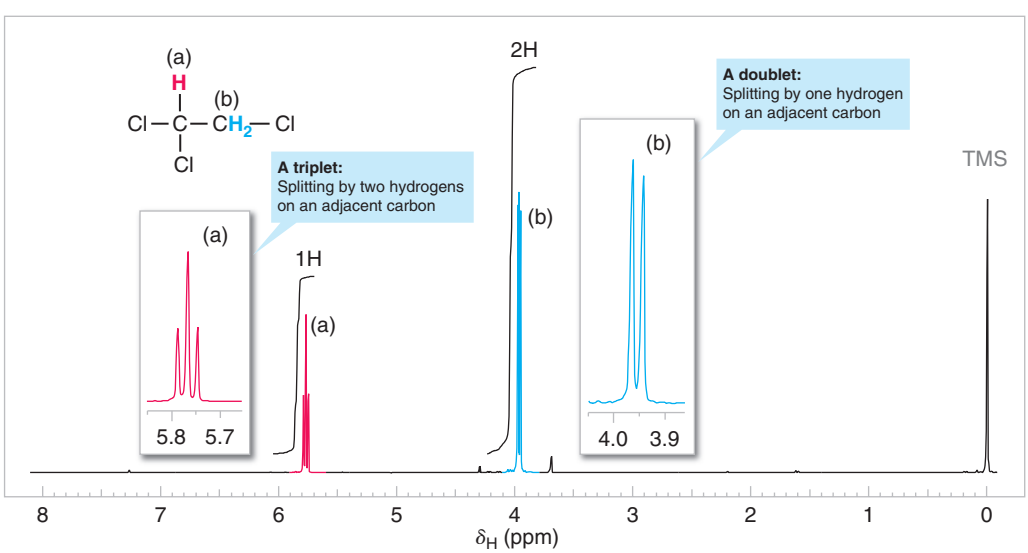


FIGURE 9.4 The 300-MHz ^{1}H NMR spectrum of 1,1,2-trichloroethane. Zoomed-in expansions of the signals are shown in the offset plots.

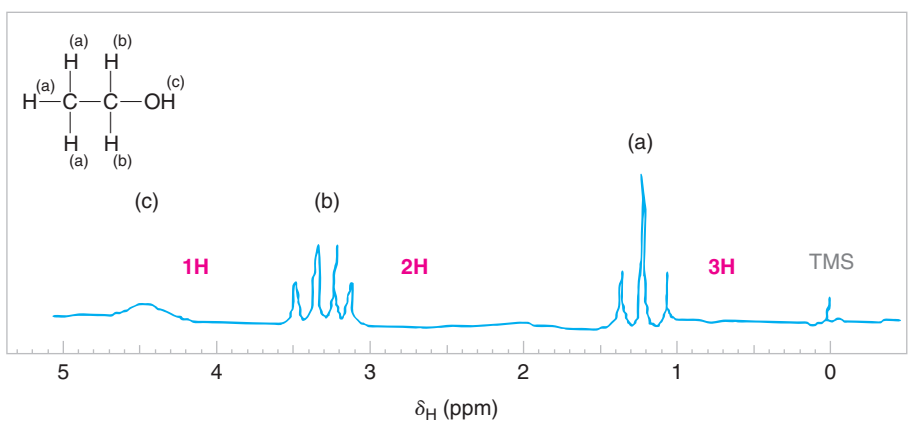
SOLVED PROBLEM 9.4

Sketch a predicted proton NMR spectrum for ethanol, showing signals in the expected chemical shift ranges (based on Table 9.1) and with the appropriate number of peaks in each. (Note one important fact: hydrogen atoms bonded to oxygen and nitrogen do not usually show coupling, but often exhibit a single broad peak instead. We shall explain why later in Section 9.10.)

STRATEGY AND ANSWER: There are four things to pay attention to: (1) the number of signals, (2) the chemical shifts of the signals, (3) the coupling patterns (signal splitting) in the signals, and (4) the relative signal areas. We have already predicted the first two of these in Solved Problem 9.2, part b.

1. In ethanol there are protons in three distinct environments; thus, we expect three signals.
2. The predicted chemical shifts are 3.3–4.0 ppm for the two protons on the alcohol carbon, 0.8–1.2 ppm for the three methyl protons, and 0.5–6.0 ppm for the hydroxyl proton (showing it anywhere in this broad range is acceptable—we shall explain why the range is broad in Section 9.10).
3. Regarding coupling patterns, the alcohol hydrogen does not couple, as we stated earlier. The alcohol —CH_2— group has three vicinal protons (the methyl group); following the $n + 1$ rule these should appear as a quartet. The methyl group has two vicinal protons (the alcohol —CH_2— group), thus it should be a triplet.
4. The relative signal areas are 1 : 2 : 3, according to the number of protons producing each signal, which we indicate as 1H, 2H, and 3H in our sketch.

Last, it is helpful to use letters to assign the protons in a formula to signals associated with them in a spectrum, and we shall do that here.



To verify our sketch we can consult the actual NMR spectrum for ethanol shown in Fig. 9.28. Note that the —OH signal can appear in a wide range, as indicated in Table 9.1.

9.3 HOW TO INTERPRET PROTON NMR SPECTRA

Now that we have had an introduction to key aspects of ^{1}H NMR spectra (chemical shift, peak area, and signal splitting), we can start to apply ^{1}H NMR spectroscopy to elucidating the structure of unknown compounds. The following steps summarize the process:

1. Count the number of signals to determine how many distinct proton environments are in the molecule (neglecting, for the time being, the possibility of overlapping signals).
2. Use chemical shift tables or charts, such as Table 9.1 or Fig. 9.2 (or your own experience over time), to correlate chemical shifts with possible structural environments.
3. Determine the relative area of each signal, as compared with the area of other signals, as an indication of the relative number of protons producing the signal.

4. Interpret the splitting pattern for each signal to determine how many hydrogen atoms are present on carbon atoms adjacent to those producing the signal and sketch possible molecular fragments.
5. Join the fragments to make a molecule in a fashion that is consistent with the data.

As a beginning example, let's interpret the ^{1}H NMR spectrum in Fig. 9.5 for a compound with the molecular formula C_3H_7Br.

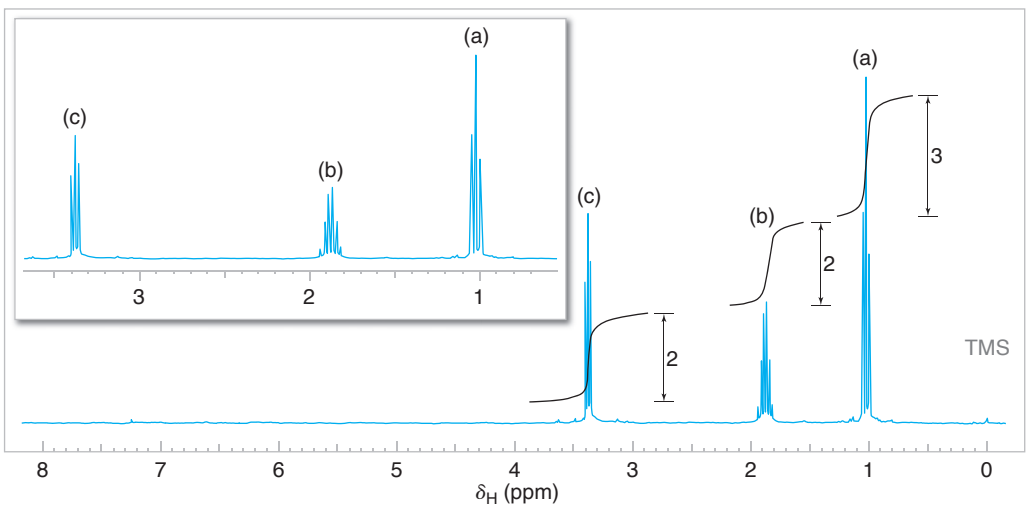
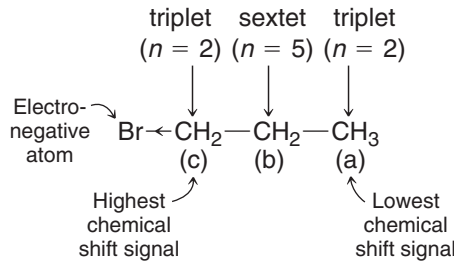


FIGURE 9.5 The 300-MHz ^{1}H NMR spectrum of a compound with the formula C_3H_7Br. Expansions of the signals are shown in the offset plots. (Spectra adapted from Sigma-Aldrich Co. © Sigma-Aldrich Co.)

1. First, we observe that there are three distinct signals, with chemical shifts of approximately δ 3.4, 1.8, and 1.1. One of these signals (δ 3.4) has a noticeably higher frequency chemical shift from the others, indicating hydrogen atoms that are likely to be near an electronegative group. This is not surprising given the presence of bromine in the formula. The presence of three distinct signals suggests that there are only three distinct proton environments in the molecule. For this example, this information alone makes it possible to reach a conclusion about the structure of the compound, since its molecular formula is as simple as C_3H_7Br. (Do you know what the compound is? Even if you do, you should still demonstrate that all of the information in the spectrum is consistent with the structure you propose.)
2. Next, we measure (or estimate) the step heights of the integral curves and reduce them to whole number ratios. Doing so, we find that the ratio is 2 : 2 : 3 (for the signals at δ 3.4, 1.8, and 1.1, respectively). Given a molecular formula that contains seven hydrogen atoms, we infer that these signals likely arise from two CH_2 groups and one CH_3 group, respectively. One of the CH_2 groups must bear the bromine. (Although you almost certainly know the structure of the compound at this point, let's continue with the analysis.) At this point we can begin to sketch molecular fragments, if we wish.
3. Next we evaluate the multiplicity of the signals. The signal at δ 3.4 is a triplet, indicating that there are two hydrogen atoms on the adjacent carbon. Since this signal is **downfield** (vs. **upfied**) and has an integral value that suggests two hydrogens, we conclude that this signal is from the CH_2Br group, and that it is next to a CH_2 group. The signal at δ 1.8 is a sextet, indicating five hydrogen atoms on adjacent carbons. The presence of five neighboring hydrogen atoms ($n = 5$, producing six peaks) is consistent with a CH_2 group on one side and a CH_3 group on the other. Last, the signal at δ 1.1 is a triplet, indicating two adjacent hydrogen atoms. Joining these molecular pieces together on paper or in our mind gives us $BrCH_2CH_2CH_3$ for the structural formula.

1-Bromopropane



We have been careful in the above analysis to evaluate each aspect of the data (chemical shift, integration, and signal splitting). As you gain more skill at interpreting NMR data, you may find that just a portion of the data is sufficient to determine a compound's identity. At other times, however, you will find that more data are necessary than solely a ^{1}H NMR spectrum. Combined analysis of ^{13}C NMR, IR, and other information may be needed, for example. In the above case, knowing the molecular formula, conceiving of the possible isomers, and comparing these with the number of signals (i.e., distinct hydrogen environments) would have been enough by itself to come to the conclusion that the compound is 1-bromopropane. Nevertheless, when working a problem one should still check the final conclusion by verifying the consistency of all data with the proposed structure.

SOLVED PROBLEM 9.5

What compound with molecular formula $C_3H_6Cl_2$ is consistent with the ^{1}H NMR spectrum shown in Fig. 9.6? Interpret the data by assigning each aspect of the spectrum to the structure you propose.

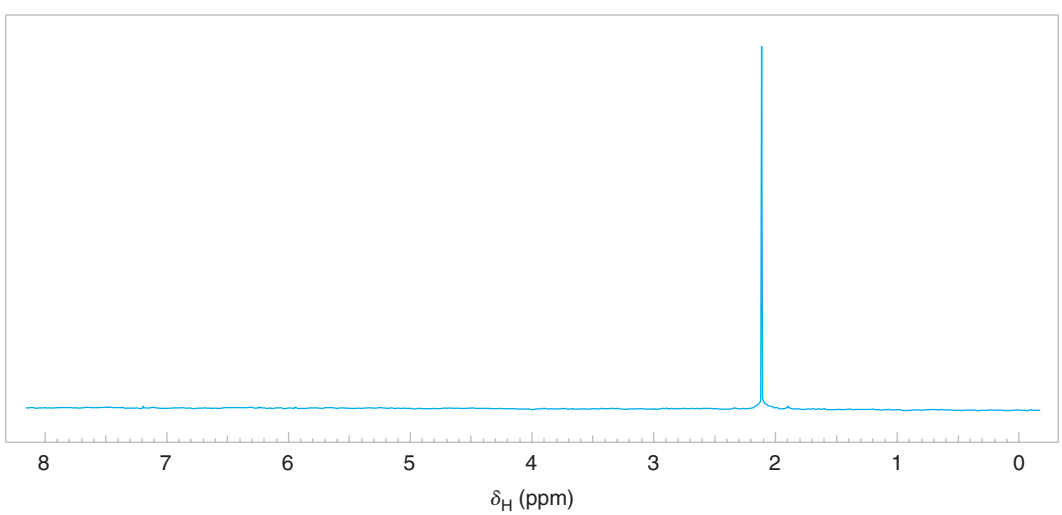


FIGURE 9.6 The 300-MHz ^{1}H NMR spectrum of the compound in Solved Problem 9.5 with molecular formula $C_3H_6Cl_2$. (Spectra adapted from Sigma-Aldrich © Sigma-Aldrich Co.)

STRATEGY AND ANSWER: The spectrum shown in Fig. 9.6 shows only one signal (therefore its integral is irrelevant and not shown). This must mean that the six hydrogen atoms in the formula $C_3H_6Cl_2$ all exist in the same magnetic environment. The presence of two equivalent methyl groups is a likely scenario for six equivalent hydrogen atoms. The only way to have two identical methyl groups with the formula $C_3H_6Cl_2$ is for both chlorine atoms to be bonded at C2 resulting in the structure shown to the right.

PRACTICE PROBLEM 9.2 What compound with molecular formula $C_3H_6Cl_2$ is consistent with the ^{1}H NMR spectrum shown in Fig. 9.7? Interpret the data by assigning each aspect of the spectrum to the structure you propose. (In other words, explain how the chemical shifts, signal areas, and splitting patterns support your conclusion.)

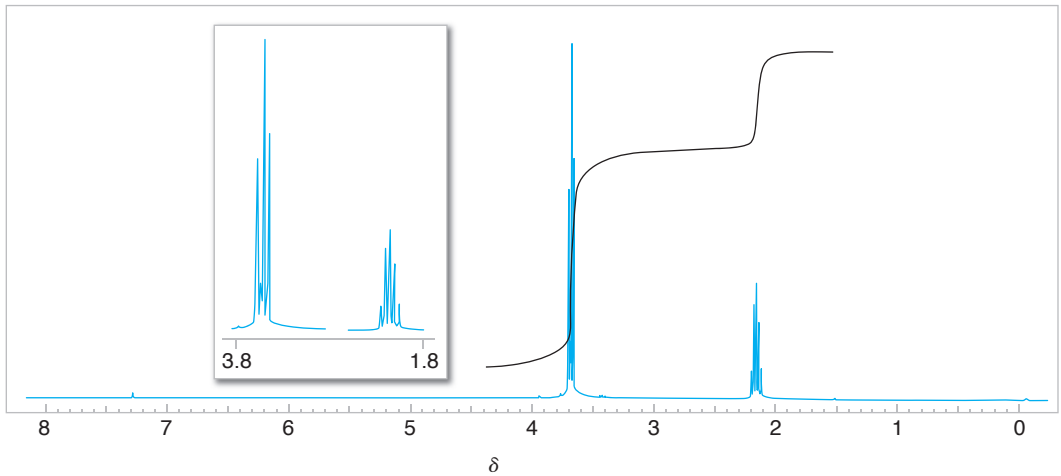


FIGURE 9.7 The 300-MHz ^{1}H NMR spectrum of the compound in Practice Problem 9.2 with formula $C_3H_6Cl_2$. Expansions of the signals are shown in the offset plots. (Spectra adapted from Sigma-Aldrich © Sigma-Aldrich Co.)

Now that we have had an introduction to interpreting NMR spectra, let us briefly explain the physical origin of NMR signals and how NMR spectrometers work, before returning to important information about factors that influence chemical shift and signal splitting.

9.4 NUCLEAR SPIN: THE ORIGIN OF THE SIGNAL

The nuclei of certain isotopes possess the quality of spin, and therefore these nuclei have spin quantum numbers, designated I. The nucleus of ordinary hydrogen, ^{1}H, has a spin quantum number of $\frac{1}{2}$, and it can assume either of two spin states: $+\frac{1}{2}$ or $-\frac{1}{2}$. These correspond to the magnetic moments (m) allowed for $I = \frac{1}{2}$, which are $m = +\frac{1}{2}$ or $m = -\frac{1}{2}$. Other nuclei with spin quantum numbers $I = \frac{1}{2}$ are ^{13}C, ^{19}F, and ^{31}P. Some nuclei, such as ^{12}C, ^{16}O, and ^{32}S, have no spin ($I = 0$), and these nuclei do not give an NMR spectrum. Other nuclei have spin quantum numbers greater than $\frac{1}{2}$. In our treatment here, however, we are concerned primarily with the spectra that arise from ^{1}H and from ^{13}C, both of which have $I = \frac{1}{2}$.

Since the proton is electrically charged, the spinning charge generates a tiny magnetic moment—one that coincides with the axis of spin (Fig. 9.8). This tiny magnetic moment gives the spinning proton properties analogous to those of a tiny bar magnet.

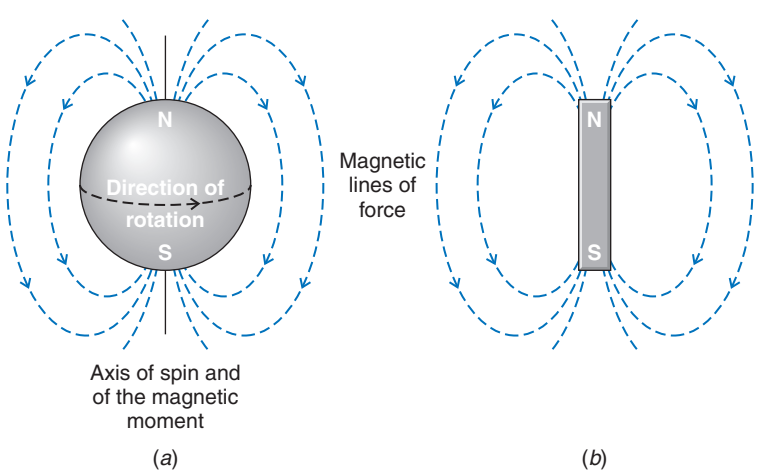


FIGURE 9.8 (*a*) The magnetic field associated with a spinning proton. (*b*) The spinning proton resembles a tiny bar magnet.

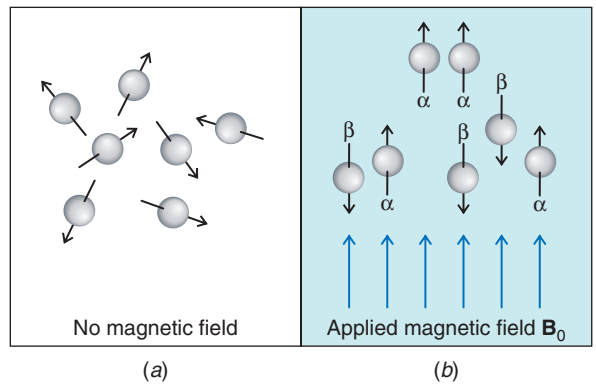


FIGURE 9.9 (*a*) In the absence of a magnetic field the magnetic moments of protons (represented by arrows) are randomly oriented. (*b*) When an external magnetic field ($\mathbf{B}_0$) is applied, the protons orient themselves. Some are aligned with the applied field (α spin state) and some against it (β spin state). The difference in the number of protons aligned with and against the applied field is very small, but is observable with an NMR spectrometer.

In the absence of a magnetic field (Fig. 9.9*a*), the magnetic moments of the protons of a given sample are randomly oriented. When a compound containing hydrogen (and thus protons) is placed in an applied external magnetic field, however, the magnetic moment of the protons may assume one of two possible orientations with respect to the external magnetic field (other orientations are disallowed on the basis of quantum mechanics). The magnetic moment of the proton may be aligned "with" the external field or "against" it (Fig. 9.9*b*). These alignments correspond to the two spin states mentioned earlier.

- The two alignments of the proton's magnetic moment in an external field are not of equal energy. When the proton's magnetic moment is aligned with the magnetic field, its energy is lower than when it is aligned against the magnetic field. The lower energy state is slightly more populated in the ground state.
- Energy is required to "flip" the proton's magnetic moment from its lower energy state (with the field) to its higher energy state (against the field). In an NMR spectrometer this energy is supplied by electromagnetic radiation in the RF (radio frequency) region. When this energy absorption occurs, the nuclei are said to be *in resonance* with the electromagnetic radiation.

The energy required to excite the proton is proportional to the strength of the magnetic field (Fig. 9.10). One can show by relatively simple calculations that, in a magnetic field of approximately 7.04 tesla, for example, electromagnetic radiation of 300×10^6 cycles per second (300 MHz) supplies the correct amount of energy for protons.* The proton NMR spectra shown in this chapter are 300-MHz spectra.

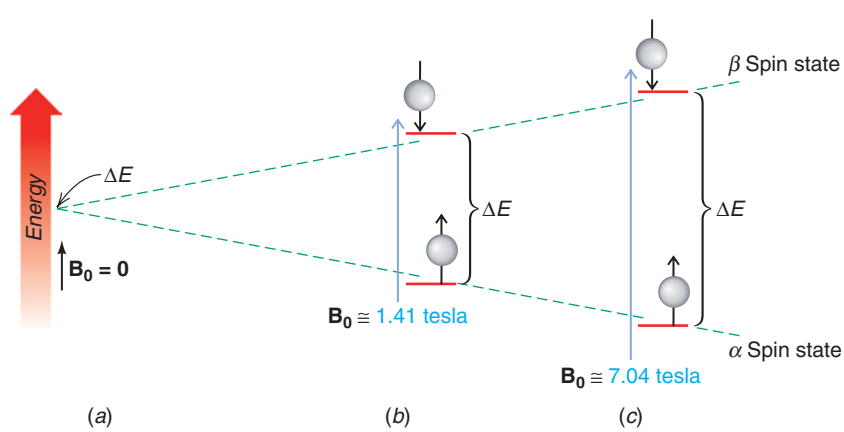


FIGURE 9.10 The energy difference between the two spin states of a proton depends on the strength of the applied external magnetic field, $\mathbf{B}_0$. (*a*) If there is no applied field ($\mathbf{B}_0 = 0$), there is no energy difference between the two states. (*b*) If $\mathbf{B}_0 \cong 1.41$ tesla, the energy difference corresponds to that of electromagnetic radiation of 60×10^6 Hz (60 MHz). (*c*) In a magnetic field of approximately 7.04 tesla, the energy difference corresponds to electromagnetic radiation of 300×10^6 Hz (300 MHz). Instruments are available that operate at these and even higher frequencies (as high as 800 MHz to 1 GHz).

*The relationship between the frequency of the radiation (ν) and the strength of the magnetic field ($\mathbf{B}_0$) is

$$\nu = \frac{\gamma \mathbf{B}_0}{2\pi}$$

where γ is the magnetogyric (or gyromagnetic) ratio. For a proton, $\gamma = 26.753$ rad s^{-1} $tesla^{-1}$.

Let us now consider how the signal from nuclei that are in resonance is detected by NMR spectrometers, and how it is converted to an NMR spectrum.

9.5 DETECTING THE SIGNAL: FOURIER TRANSFORM NMR SPECTROMETERS

Most NMR spectrometers use superconducting magnets that have very high magnetic field strengths. Superconducting magnets operate in a bath of liquid helium at 4.3 degrees above absolute zero, and they have magnetic field strengths more than 100,000 times as strong as Earth's magnetic field.

The stronger the magnet is in a spectrometer, the more sensitive the instrument. Figure 9.11 shows a diagram of a **Fourier transform NMR** spectrometer.

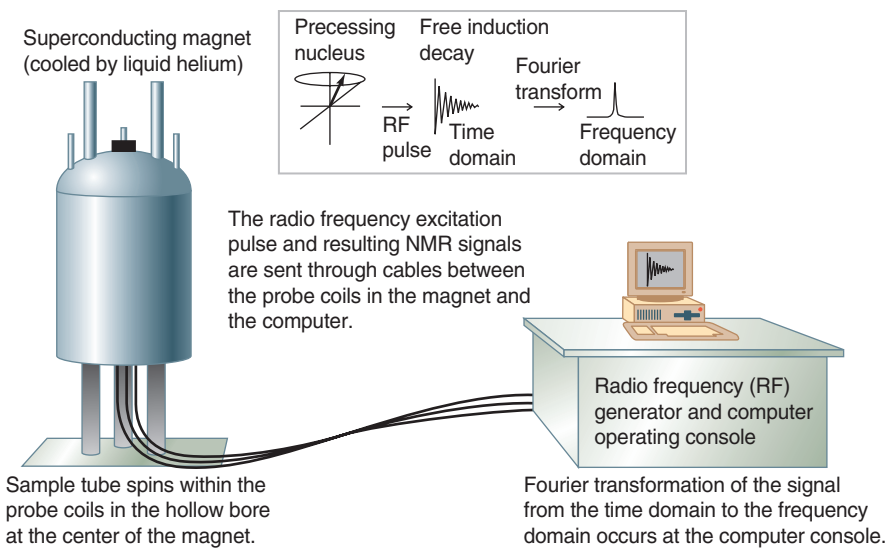


FIGURE 9.11 Diagram of a Fourier transform NMR spectrometer.

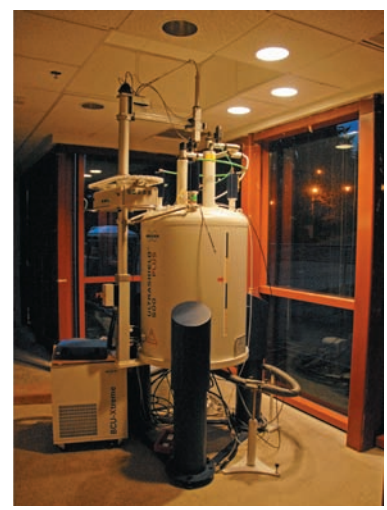


Photo by Craig Fryhle

The superconducting magnet of an FTNMR spectrometer.

As we discussed in the previous section, certain nuclei in the presence of a magnetic field behave as though they were tiny bar magnets that align themselves with or against the applied magnetic field. The nuclei spin (precess) about the spectrometer's magnetic field axis (the "applied" magnetic field), much the same way that a spinning top gyrates around the axis of gravity. The precessional frequency of each nucleus is directly related to its chemical shift. We can illustrate a nuclear magnetic moment precessing about the axis of an applied magnetic field ($\mathbf{B}_0$) using a vector representation, as shown in Fig. 9.12*a*.

Applying a pulse of radio frequency energy that matches the precessional frequency of the nuclear magnetic moment causes the magnetic vector of the nucleus to tip away from the applied magnetic field axis (the *z*-axis) toward the *x*–*y* plane (Fig. 9.12*b*). The nuclear magnetic vector still precesses about the *z*-axis, but it lies in the *x*–*y* plane. From the perspective of a tiny coil of wire (called a receiver coil) situated next to the *x*–*y* plane, rotation of this vector around the *z*-axis but in the *x*–*y* plane presents an oscillating magnetic field to the receiver coil. And just as with large-scale electrical generators, this oscillating magnetic field induces an oscillating electric current in the coil (Fig. 9.12*c*). This current is the signal detected by the NMR spectrometer. Let us briefly explain the properties of this signal further.

Tipping the nuclear magnetic vector away from the axis of the applied magnetic field requires absorption of radio frequency energy by the nucleus. This energy comes from a radio frequency pulse generated by the NMR spectrometer. In a matter of seconds or less, however, the nucleus releases the energy it absorbed back to the sample environment, returning the nucleus to its ground state energy as it moves back toward the *z*-axis. As it does so, the vector component of magnetization in the *x*–*y* axis diminishes, and the observed electrical signal decays (Fig. 9.12*d*). The oscillating electrical signal produced by

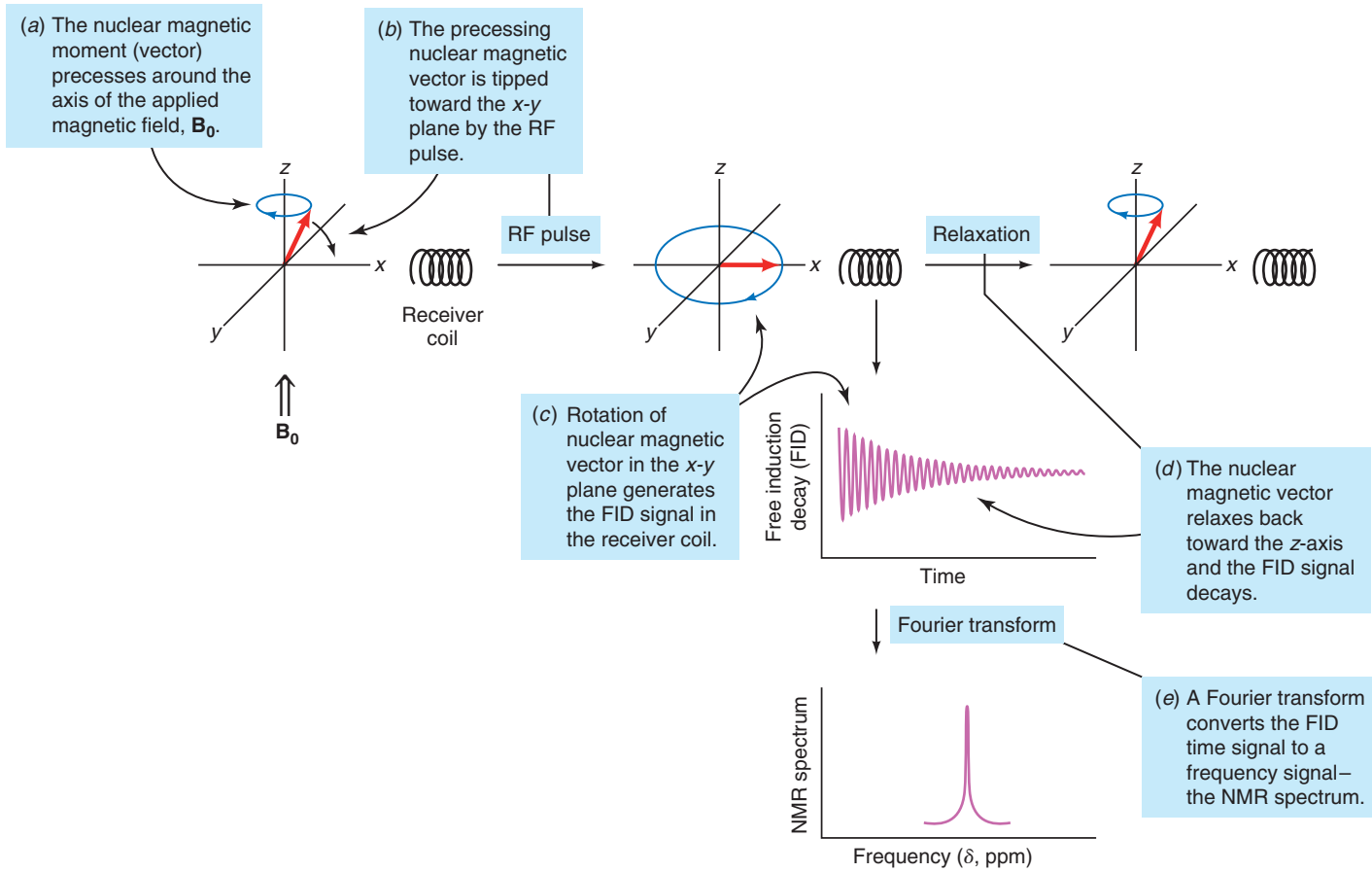


FIGURE 9.12 Origin of the signal in FTNMR spectroscopy.

the excited nucleus is therefore not a signal of steady amplitude, but one that dies away exponentially. This signal is called a free induction decay (FID). The NMR computer applies a mathematical operation called a Fourier transform to convert the signal from a time versus amplitude signal (the FID) to a frequency versus amplitude signal (the NMR spectrum that we interpret, Fig. 9.12*e*).

There is much more that could be said about the origin of NMR signals and how NMR spectrometers work. The interested student is referred to advanced texts on spectroscopy for further information. However, let us conclude with a few final points.

As we mentioned, the chemical shift of an NMR signal is directly related to its precessional frequency. Since most compounds have nuclei in a variety of environments, they have nuclei that precess at a variety of frequencies, and therefore exhibit signals at a variety of chemical shifts. The FID signal detected by the NMR spectrometer is an aggregate of all of these frequencies. A powerful aspect of the Fourier transform (FT), as a mathematical process, is that it extracts these combined frequencies from the FID and converts them to discrete signals that we can interpret in an NMR spectrum.

Another great advantage to Fourier transform spectrometers is that the FT process allows computerized signal averaging of many data scans, which cancels out random electronic noise and enhances the actual NMR signals. This is especially important for samples that produce weak signals. Furthermore, acquisition of the data from each scan is very fast. The radio-frequency pulse used to excite the sample is typically on the order of only 10^{-5} s, and pulses can be repeated within a few seconds or less. Thus, many data scans can be acquired over just a short time, so as to maximize signal averaging and enhance the clarity of the data.

With this introduction to the origin of NMR signals and how spectrometers work, we return to consider further aspects of chemical shift, shielding and deshielding, and signal splitting.

9.6 THE CHEMICAL SHIFT

All protons do not absorb at the same chemical shift (δ) in an external magnetic field. The chemical shift of a given proton is dependent on its chemical environment, as we shall discuss in Section 9.7. The δ value that we report for a proton's chemical shift is actually a measure of its NMR absorption frequency, which is proportional to the external magnetic field strength (Section 9.6A).

- Smaller chemical shift (δ) values correspond with lower absorption frequency.
- Larger chemical shift (δ) values correspond with higher absorption frequency.

Chemical shifts are most often reported in reference to the absorption of the protons of TMS (tetramethylsilane), which is defined as zero on the δ scale. A small amount of TMS is either included as an internal standard in the solvent for a sample, or the NMR spectrometer itself is calibrated electronically to a chemical shift standard.

$Si(CH_3)_4$
Tetramethylsilane (TMS)

- The signal from TMS defines zero ppm on the chemical shift (δ) scale.

Tetramethylsilane was chosen as a reference compound for several reasons. It has 12 equivalent hydrogen atoms, and, therefore, a very small amount of TMS gives a relatively large signal. Because the hydrogen atoms are all equivalent, they give a *single signal*. Since silicon is less electronegative than carbon, the protons of TMS are in regions of high electron density. They are, as a result, highly shielded, and the signal from TMS occurs in a region of the spectrum where few other hydrogen atoms absorb. Thus, their signal seldom interferes with the signals from other hydrogen atoms. Tetramethylsilane, like an alkane, is relatively inert. It is also volatile, having a boiling point of 27 °C. After the spectrum has been determined, the TMS can be removed from the sample easily by evaporation.

9.6A PPM and the δ Scale

The chemical shift of a proton, when expressed in **hertz (Hz)**, is proportional to the strength of the external magnetic field. Since spectrometers with different magnetic field strengths are commonly used, it is desirable to express chemical shifts in a form that is independent of the strength of the external field. This can be done easily by dividing the chemical shift by the frequency of the spectrometer, with both numerator and denominator of the fraction expressed in frequency units (hertz). Since chemical shifts are always very small (typically <5000 Hz) compared with the total field strength (commonly the equivalent of 60, 300, or 600 *million* hertz), it is convenient to express these fractions in units of *parts per million* (ppm). This is the origin of the delta scale for the expression of chemical shifts relative to TMS:

$$\delta = \frac{\text{(observed shift from TMS in hertz)} \times 10^6}{\text{(operating frequency of the instrument in hertz)}}$$

For example, the chemical shift for benzene protons is 2181 Hz when the instrument is operating at 300 MHz. Therefore,

$$\delta = \frac{2181 \text{ Hz} \times 10^6}{300 \times 10^6 \text{ Hz}} = 7.27$$

The chemical shift of benzene protons in a 60-MHz instrument is 436 Hz:

$$\delta = \frac{436 \text{ Hz} \times 10^6}{60 \times 10^6 \text{ Hz}} = 7.27$$

Thus, the chemical shift expressed in ppm is the same whether measured with an instrument operating at 300 or 60 MHz (or any other field strength).

Figure 9.2 (Section 9.2A) gives the *approximate* values of proton chemical shifts for some common hydrogen-containing groups.

9.7 SHIELDING AND DESHIELDING OF PROTONS

- Protons absorb at different NMR frequencies depending on the electron density around them and the effects of local induced magnetic fields.

Protons of Hydrogen Atoms in Alkyl C—H Groups

The external (applied) magnetic field of an NMR spectrometer causes the σ electrons in an alkyl C—H bond to circulate in a way that generates an induced local magnetic field at the proton that is **opposite** to the applied magnetic field (Fig. 9.13). The hydrogen of an alkyl C—H group thus experiences a net smaller magnetic field than the applied field, causing its proton to resonate at a lower frequency (smaller chemical shift). The proton is said to be **shielded** from the applied magnetic field by the circulating σ electrons.

- The chemical shift for hydrogens of unsubstituted alkanes is typically in the range of δ 0.8–1.8.

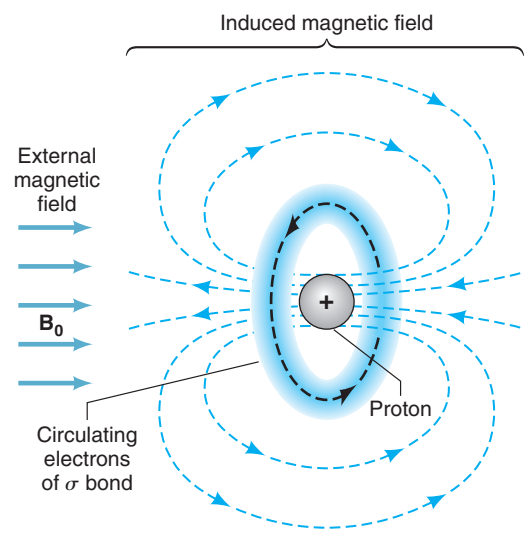


FIGURE 9.13 Circulations of the electrons of a C—H bond under the influence of an external magnetic field. The electron circulations generate a small magnetic field (an induced field) that shields the proton from the external field.

Protons of Hydrogens Near Electronegative Groups

Electronegative groups withdraw electron density from nearby hydrogen atoms, diminishing shielding of their protons by circulating σ electrons. Protons of hydrogen atoms near an electronegative group are said to be **deshielded** from the applied magnetic field, and they resonate at a higher frequency (larger chemical shift) than more shielded protons.

- The chemical shift of hydrogens bonded to a carbon bearing oxygen or a halogen is typically in the range of δ 3.1–4.0.

Protons of Hydrogen Atoms Near π Electrons

The π electrons in alkenes, alkynes, benzene, and others π-bonded groups also circulate so as to generate an induced local magnetic field in the presence of an external magnetic field. Whether shielding or deshielding occurs depends on the location of the protons in the induced magnetic field.

In the case of benzene, where the π-electron system is a closed loop (we shall discuss this in detail in Chapter 14), the external magnetic field induces a local magnetic field with flux lines that add to the external magnetic field in the region of the hydrogens (Fig. 9.14). The result is a deshielding effect on the protons and resonance at a higher frequency (larger chemical shift) than for protons of an alkyl C—H group.

- The hydrogens of benzene absorb at δ 7.27. Hydrogens bonded to substituted benzene rings have chemical shifts in the range of δ 6.0–8.5, depending on the electron-donating or electron-withdrawing effect of the substituents.

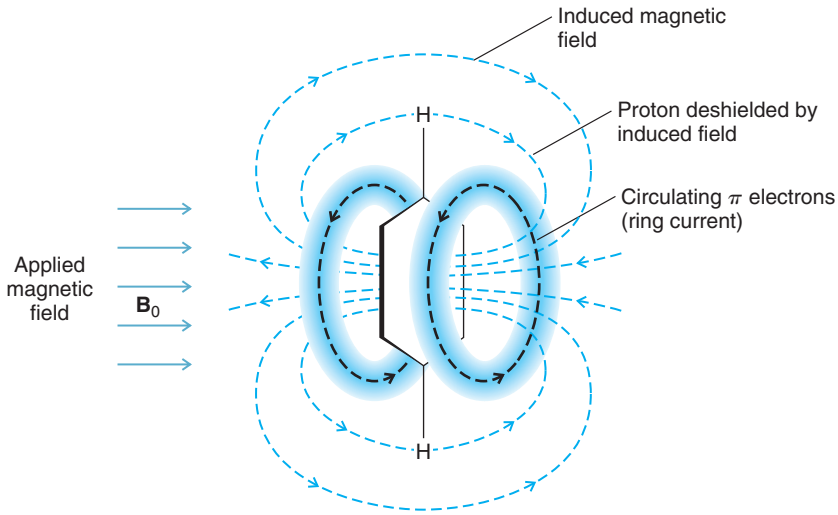


FIGURE 9.14 The induced magnetic field of the π electrons of benzene deshields the benzene protons. Deshielding occurs because at the location of the protons the induced field is in the same direction as the applied field.

The π electrons of an alkene circulate at the π bond itself to also generate an induced local magnetic field that adds to the applied magnetic field in the region of the alkene hydrogens (Fig. 9.15), though not as substantially as in benzene.

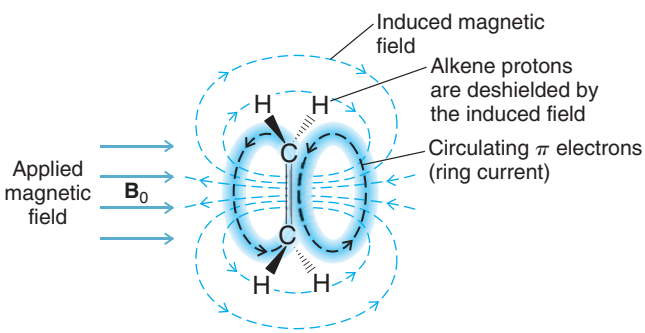


FIGURE 9.15 The induced magnetic field of the π electrons in an alkene deshield the hydrogens of an alkene. Their chemical shift of alkene hydrogens is approximately δ 6.0–4.0.

- The chemical shift of alkene hydrogens is typically in the range of δ 4.0–6.0.

The π electrons of an alkyne also circulate with respect to its π bonds, but in a way that generates an induced magnetic field that is opposite to the applied magnetic field near a terminal alkyne (acetylenic) hydrogen (Fig. 9.16).

- The chemical shift of an alkyne hydrogen is typically in the range of δ 2.5–3.1.

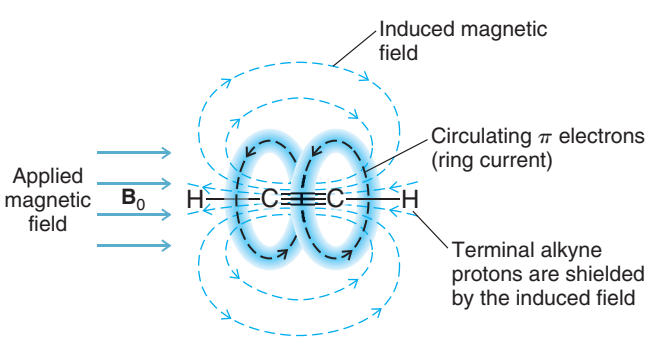


FIGURE 9.16 The induced magnetic field of the π electrons in a triple bond shield terminal alkyne hydrogens. Their chemical shift is approximately δ 3.0–2.1.

9.8 CHEMICAL SHIFT EQUIVALENT AND NONEQUIVALENT PROTONS

Two or more protons that are in identical environments have the same chemical shift and, therefore, give only one ^{1}H NMR signal. How do we know when protons are in the same environment? For most compounds, protons that are in the same environment are also equivalent in chemical reactions. That is, **chemically equivalent** protons are **chemical shift equivalent** in ^{1}H NMR spectra.

9.8A Homotopic and Heterotopic Atoms

How do we decide whether two or more protons in a molecule are in identical environments?

- One way to decide is to replace each hydrogen in turn by some other atom or group (which may be real or imaginary) and then use the result of the replacement to make our decision.

If replacing the hydrogens by a different atom gives the same compound, the hydrogens are said to be **homotopic**.

- Homotopic hydrogens have identical environments and will have the same chemical shift. They are said to be **chemical shift equivalent**.

Consider the hydrogens of ethane as an example. Replacing any one of the six hydrogens of ethane by a different atom, say, by chlorine, gives the same compound: chloroethane.

$$\underset{\textbf{Ethane}}{CH_3CH_3} \xrightarrow[\text{hydrogen by Cl}]{\text{replacement of any}} \underset{\textbf{Chloroethane}}{CH_3CH_2Cl}$$

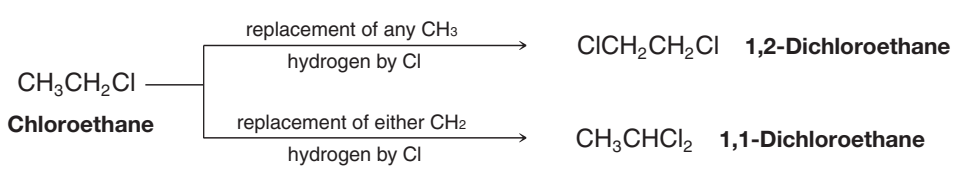
The six hydrogens of ethane are *homotopic* and are, therefore, *chemical shift equivalent*. **Ethane, consequently, gives only one signal in its ^{1}H NMR spectrum**. [Remember, the barrier to rotation of the carbon–carbon bond of ethane is so low (Section 4.8), the various conformations of chloroethane interconvert rapidly.]

- If replacing hydrogens by a different atom gives **different compounds**, the hydrogens are said to be **heterotopic**.
- **Heterotopic atoms have different chemical shifts and are not chemical shift equivalent.**

Consider the set of methyl hydrogens at C2 of chloroethane. Replacing any one of the three hydrogens of the CH_3 group of chloroethane with chlorine yields the same compound, 1,2-dichloroethane. The three protons of the CH_3 group are **homotopic** with respect to each other, and the CH_3 group gives only one ^{1}H NMR signal.

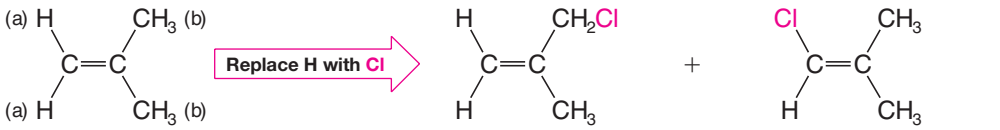
$$\underset{\textbf{Chloroethane}}{CH_3CH_2Cl} \xrightarrow[\text{hydrogen by Cl}]{\text{replacement of } CH_3} \underset{\textbf{1,2-Dichloroethane}}{ClCH_2CH_2Cl}$$

However, if we compare the set of hydrogens of the CH_2 group of chloroethane with those of its CH_3 set we find that the hydrogens of the CH_3 and CH_2 groups are **heterotopic** with respect to each other. Replacing either of the two hydrogens of the CH_2 set by chlorine yields 1,1-dichloroethane, whereas replacing any one of the set of three CH_3 hydrogens yields a different compound, 1,2-dichloroethane.



Chloroethane, therefore, has two sets of hydrogens that are heterotopic with respect to each other, the CH_3 hydrogens and the CH_2 hydrogens. The hydrogens of these two sets are not chemical shift equivalent, and chloroethane gives two ^1H NMR signals.

Consider 2-methylpropene as a further example:



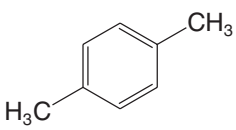
3-Chloro-2-methylpropene **1-Chloro-2-methylpropene**

The six methyl hydrogens (b) are one set of homotopic hydrogens; replacing any one of them with chlorine, for example, leads to the same compound, 3-chloro-2-methylpropene. The two vinyl hydrogens (a) are another set of homotopic hydrogens; replacing either of these leads to 1-chloro-2-methylpropene. 2-Methylpropene, therefore, gives two ^1H NMR signals.

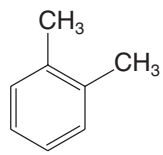
PRACTICE PROBLEM 9.3

Using the method of Section 9.8A, determine the number of expected signals for the following compounds.

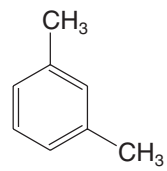
(a)



(b)



(c)



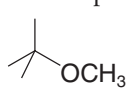
PRACTICE PROBLEM 9.4

How many signals would each compound give in its ^1H NMR spectrum?

(a) CH_3OCH_3

(b)

(c)



(d) 2,3-Dimethyl-2-butene

(e) (*Z*)-2-Butene

(f) (*E*)-2-Butene

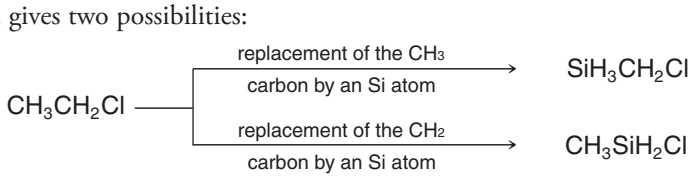
Application to ^{13}C NMR Spectroscopy As a preview of what is to come later in this chapter when we study ^{13}C NMR spectroscopy, let us look briefly at the carbon atoms of ethane to see whether we can use a similar method to decide whether they are homotopic or heterotopic, and whether ethane would give one or two ^{13}C signals. Here we can make our imaginary replacements using a silicon atom.

$$CH_3CH_3 \xrightarrow[\text{an Si atom}]{\text{replacement of either carbon atom by}} SiH_3CH_3$$

Ethane

Only one product is possible; therefore, the carbons of ethane are **homotopic**, and **ethane would give only one signal in its ^{13}C spectrum**.

On the other hand, if we consider chloroethane, replacement of a carbon atom by a silicon atom gives two possibilities:

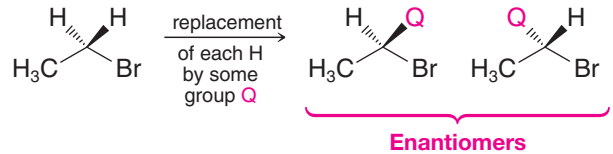


We do not get the same compounds from each replacement. We can conclude, therefore, that the two carbon atoms of chloroethane are **heterotopic**. They are not chemical shift equivalent, and each carbon atom of chloroethane would give a ^{13}C signal at a different chemical shift. **Chloroethane gives two ^{13}C NMR signals.**

9.8B Enantiotopic and Diastereotopic Hydrogen Atoms

If replacement of each of two hydrogen atoms by the same group yields compounds that are enantiomers, the two hydrogen atoms are said to be **enantiotopic hydrogens**.

- Enantiotopic hydrogen atoms have the same chemical shift and give only one ^{1}H NMR signal:*

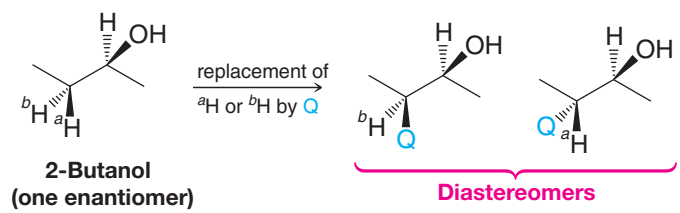


The two hydrogen atoms of the —CH_2Br group of bromoethane are enantiotopic. Bromoethane, then, gives two signals in its ^{1}H NMR spectrum. The three equivalent protons of the —CH_3 group give one signal; the two enantiotopic protons of the —CH_2Br group give the other signal. [The ^{1}H NMR spectrum of bromoethane, as we shall see, actually consists of seven peaks (three in one signal, four in the other). This is a result of signal splitting, which is explained in Section 9.9.]

If replacement of each of two hydrogen atoms by a group, Q, gives compounds that are diastereomers, the two hydrogens are said to be **diastereotopic hydrogens**.

- Except for accidental coincidence, diastereotopic protons do not have the same chemical shift and give rise to different ^{1}H NMR signals.

The two methylene hydrogens labeled ^{a}H and ^{b}H at C3 in 2-butanol are **diastereotopic**. We can illustrate this by imagining replacement of ^{a}H or ^{b}H with some imaginary group Q. The result is a pair of diastereomers. As diastereomers, they have different physical properties, including chemical shifts, especially for those protons near the chirality center.



The diastereotopic nature of ^{a}H and ^{b}H at C3 in 2-butanol can also be appreciated by viewing Newman projections. In the conformations shown below (Fig. 9.17), as is the case for every possible conformation of 2-butanol, ^{a}H and ^{b}H experience different environments because of the asymmetry from the chirality center at C2. That is, the "molecular landscape" of 2-butanol appears different to each of these diastereotopic hydrogens. ^{a}H and ^{b}H

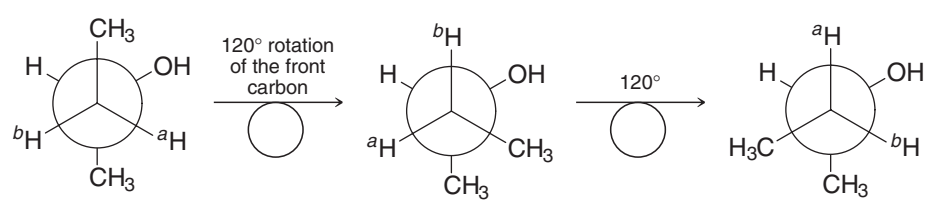
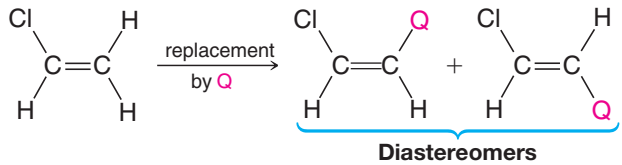


FIGURE 9.17 ^{a}H and ^{b}H (on C3, the front carbon in the Newman projection) experience different environments in these three conformations, *as well as in every other possible conformation of 2-butanol*, because of the chirality center at C2 (the back carbon in the Newman projection). In other words, the molecular landscape as viewed from one diastereotopic hydrogen will always appear different from that viewed by the other. Hence, ^{a}H and ^{b}H experience different magnetic environments and therefore should have different chemical shifts (though the difference may be small). They are not chemical shift equivalent.

*Enantiotopic hydrogen atoms may not have the same chemical shift if the compound is dissolved in a chiral solvent. However, most ^{1}H NMR spectra are determined using achiral solvents, and in this situation enantiotopic protons have the same chemical shift.

experience different magnetic environments, and are therefore not chemical shift equivalent. This is true in general: **diastereotopic hydrogens are not chemical shift equivalent**.

Alkene hydrogens can also be diastereotopic. The two protons of the $=CH_2$ group of chloroethene are diastereotopic:



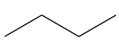
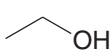
Chloroethene, then, should give signals from each of its three nonequivalent protons: one for the proton of the ClCH= group, and one for each of the diastereotopic protons of the $=CH_2$ group.

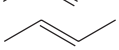
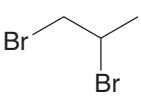
PRACTICE PROBLEM 9.5

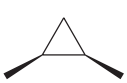
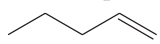
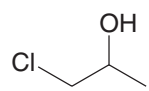
(a) Show that replacing each of the CH_2 protons by some group Q in the (*S*) enantiomer of 2-butanol leads to a pair of diastereomers, as it does for the (*R*) enantiomer.
(b) How many chemically nonequivalent sets of protons are there in 2-butanol?
(c) How many ^1H NMR signals would you expect to find in the spectrum of 2-butanol?

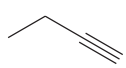
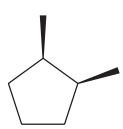
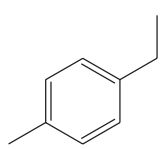
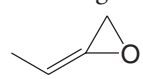
PRACTICE PROBLEM 9.6

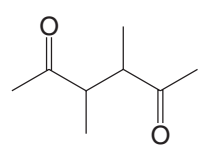
How many ^1H NMR signals would you expect from each of the following compounds?

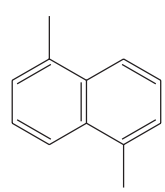
(a) 
(b) 

(c) 
(d) 
(e) 

(f) 
(g) 
(h) 
(i) 
(j) 

(k) 
(l) 
(m) 
(n) 

(o) 

(p) 

9.9 SIGNAL SPLITTING: SPIN–SPIN COUPLING

Signal splitting arises from a phenomenon known as spin–spin coupling. Spin–spin coupling effects are transferred primarily through bonding electrons and lead to **spin–spin splitting**.

- **Vicinal coupling** is coupling between hydrogen atoms on adjacent carbons (vicinal hydrogens), where separation between the hydrogens is by three σ bonds.

The most common occurrence of coupling is vicinal coupling. Hydrogens bonded to the same carbon (geminal hydrogens) can also couple, but only if they are diastereotopic. Long-range coupling can be observed over more than three bond lengths in very rigid molecules such as bicyclic compounds, and in systems where π bonds are involved. We shall limit our discussion to vicinal coupling, however.

9.9A Vicinal Coupling

- Vicinal coupling between heterotopic protons generally follows the $n + 1$ rule (Section 9.2C). Exceptions to the $n + 1$ rule can occur when diastereotopic hydrogens or conformationally restricted systems are involved.

We have already seen an example of vicinal coupling and how the $n + 1$ rule applies in our discussion of the spectrum of 1,1,2-trichloroethane (Fig. 9.4). To review, the signal from the two equivalent protons of the $-CH_2Cl$ group of 1,1,2-trichloroethane is split into a doublet by the proton of the $CHCl_2-$ group. The signal from the proton of the $CHCl_2-$ group is split into a triplet by the two protons of the $-CH_2Cl$ group.

Before we explain the origin of signal splitting, however, let us also consider two examples where signal splitting would *not* be observed. Part of understanding signal splitting is recognizing when you would not observe it. Consider ethane and methoxyacetonitrile. All of the hydrogen atoms in ethane are equivalent, and therefore they have the same chemical shift and do not split each other. The ^1H NMR spectrum of ethane consists of one signal that is a singlet. The spectrum of methoxyacetonitrile is shown in Fig. 9.18. While there are two signals in the spectrum of methoxyacetonitrile, no coupling is observed and therefore both signals are singlets because (1) the hydrogens labeled (a) and (b) are more than three single bonds apart, and (2) the hydrogens labeled (a) are homotopic and those labeled (b) are enantiotopic.

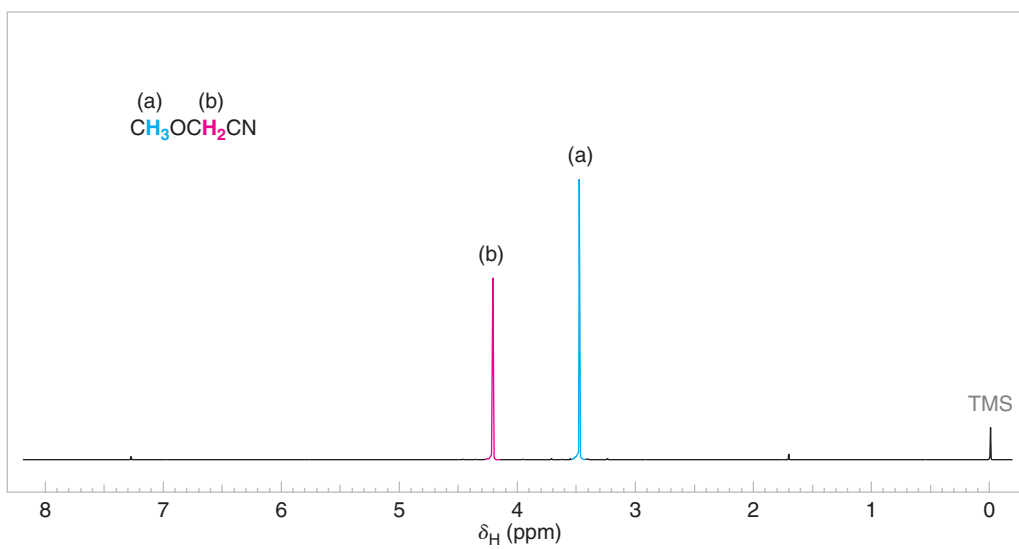


FIGURE 9.18 The 300-MHz ^1H NMR spectrum of methoxyacetonitrile. The signal of the enantiotopic protons (b) is not split.

- **Signal splitting is not observed for protons that are homotopic (chemical shift equivalent) or enantiotopic.**

Let us now explain how signal splitting arises from coupled sets of protons that are not homotopic.

9.9B Splitting Tree Diagrams and the Origin of Signal Splitting

Signal splitting is caused by the magnetic effect of protons that are nearby and nonequivalent to those protons producing a given signal. Nearby protons have magnetic moments that can either add to or subtract from the magnetic field around the proton being observed. This effect splits the energy levels of the protons whose signal is being observed into a signal with multiple peaks.

We can illustrate the origin of signal splitting using **splitting tree diagrams** and by showing the possible combinations of magnetic moment alignments for the adjacent protons (Figs. 9.19, 9.20).

Splitting Analysis for a Doublet Figure 9.19 shows a splitting tree diagram for a doublet. The signal from the observed hydrogen (^{a}H) is split into two peaks of **1 : 1 intensity** by the additive and subtractive effects of the magnetic field from a single adjacent hydrogen (^{b}H) on the applied magnetic field, $\mathbf{B_0}$. The two possible magnetic orientations for the adjacent hydrogen (^{b}H) that align either against or with the applied magnetic field are shown underneath the splitting tree using arrows. J_{ab}, the spacing between the peaks (measured in hertz), is called the coupling constant. (We shall have more to say about coupling constants later.)

Splitting Analysis for a Triplet Figure 9.20 shows a splitting tree diagram for a triplet. The signal from the observed hydrogen (^{a}H) is split into three peaks of **1 : 2 : 1 intensity** by the magnetic effects of two adjacent equivalent hydrogens (^{b}H). The upper level in the diagram represents splitting from one of the adjacent ^{b}H hydrogens, leading initially to two legs that appear like the diagram for a doublet. Each of these legs is split by the second ^{b}H hydrogen, as shown at the next level. The center legs at this level overlap, however, because J_{ab} is the same for coupling of both of the ^{b}H hydrogens with ^{a}H. This overlap of the two center legs reflects the observed 1 : 2 : 1 ratio of intensities in a spectrum, as shown in the simulated triplet in Fig. 9.20. (Note that in any splitting tree diagram, the lowermost level schematically represents the peaks we observe in the actual spectrum.)

The possible magnetic orientations of the two ^{b}H hydrogens that cause the triplet are shown under the splitting diagram with arrows. The arrows indicate that both of the adjacent hydrogens may be aligned with the applied field, or one may be aligned with and the other against (in two equal energy combinations, causing a doubling of intensity), or both may be aligned against the applied field. Diagraming the possible combinations for the nuclear magnetic moments is another way (in addition to the splitting tree diagram) to show the origin of the 1 : 2 : 1 peak intensities that we observe in a triplet.

Splitting Analysis for a Quartet The NMR signal for hydrogens split by three equivalent vicinal hydrogens appears as a quartet with peak intensities in a l : 3 : 3 : 1 ratio. The NMR spectrum of bromoethane (Fig. 9.1), for example, exhibits a quartet for the hydrogens at C1 because they are split by the three equivalent hydrogens of the methyl

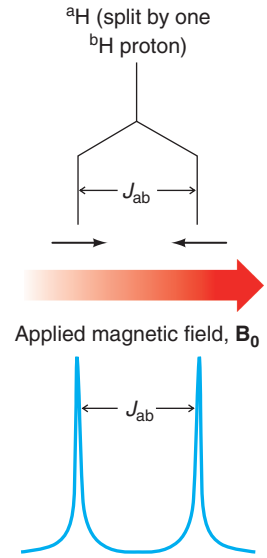
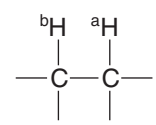


FIGURE 9.19 Splitting tree diagram for a doublet. The signal from the observed hydrogen (^{a}H) is split into two peaks of 1 : 1 intensity by the additive and subtractive effects of the magnetic field from one adjacent hydrogen (^{b}H) on $\mathbf{B_0}$ (the applied field). J_{ab}, the spacing between the peaks (measured in hertz), is called the coupling constant.



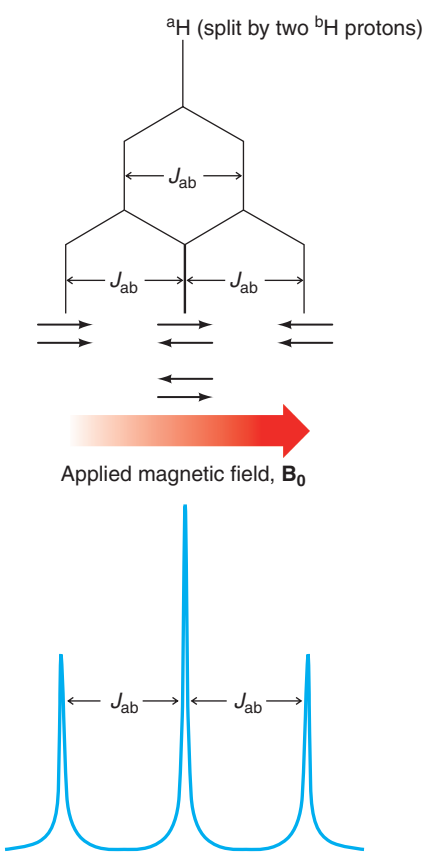
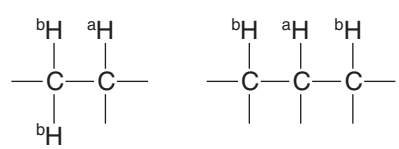


FIGURE 9.20 Splitting tree diagram for a triplet. The signal from the observed hydrogen (^{a}H) is split into three peaks of 1 : 2 : 1 intensity by two adjacent equivalent hydrogens (^{b}H). The upper level of splitting in the diagram represents splitting from one of the adjacent ^{b}H hydrogens, producing a doublet shown as two legs. The second ^{b}H hydrogen splits each of these legs again, as shown at the next level. The center legs at this level overlap however, because J_{ab} is the same* for the coupling of both ^{b}H hydrogens with ^{a}H. This analysis accounts for the observed 1 : 2 : 1 ratio of intensities in a spectrum (simulated in blue). In any splitting tree diagram, the lowermost level most closely represents what we observe in the actual spectrum. The possible magnetic orientations of the two ^{b}H hydrogens are shown under the tree diagram with arrows indicating that both of the adjacent hydrogens may be aligned with the applied field, or one may be aligned with and the other against (in two equal energy combinations, hence twice the intensity), or both may be aligned against the applied field.



*In this example, J_{ab} is the same for both ^{b}H hydrogens because we assume them to be homotopic or enantiotopic (chemical shift equivalent). If they were diastereotopic or otherwise chemical shift nonequivalent, each may have had a different coupling constant with ^{a}H, and the splitting pattern would not have been a pure triplet (or not even a triplet at all). For example, if the two coupling constants had been significantly different, the pattern would have been a doublet of doublets instead of a triplet. Diastereotopic geminal hydrogens that couple with a vicinal hydrogen typically produce a doublet of doublets, because geminal coupling constants are often larger than vicinal coupling constants.

group at C2. A splitting tree analysis for a quartet would be generated following the same path of analysis as for doublets and triplets, but carried to one further level of splitting.

PRACTICE PROBLEM 9.7 Draw a splitting tree diagram for a quartet by adding one more level to the diagram shown in Fig 9.20 for a triplet. Underneath your quartet splitting tree show, using arrows as in Fig. 9.20, the combinations of magnetic orientations that are possible for the three vicinal hydrogens and that lead to the observed 1 : 3 : 3 : 1 ratio of intensities.

Let us conclude this section with two last examples. The spectrum of 1,1,2,3,3-pentachloropropane (Fig. 9.21) is similar to that of 1,1,2-trichloroethane in that it also consists of a 1:2:1 triplet and a 1:1 doublet. The two hydrogen atoms ^{b}H of 1,1,2,3,3-pentachloropropane are equivalent even though they are on separate carbon atoms.

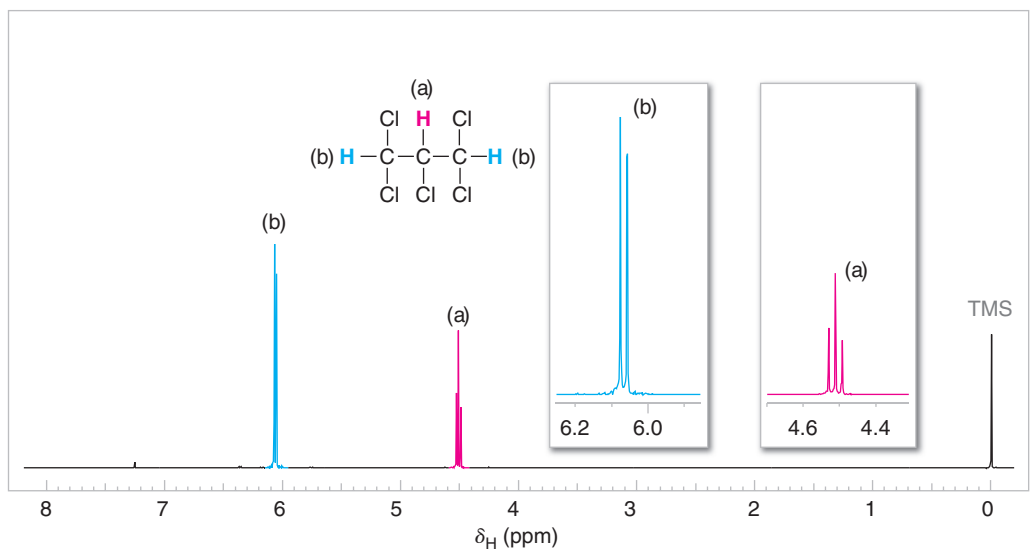
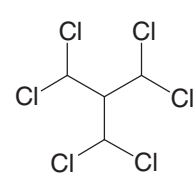


FIGURE 9.21 The 300-MHz ^{1}H NMR spectrum of 1,1,2,3,3-pentachloropropane. Expansions of the signals are shown in the offset plots.

The kind of analysis that we have just given can be extended to compounds with even larger numbers of equivalent protons on adjacent atoms. These analyses also show that ***if there are n equivalent protons on adjacent atoms, these will split a signal into n + 1 peaks***. (We may not always see all of these peaks in actual spectra, however, because some of them may be very small.)

PRACTICE PROBLEM 9.8 The relative chemical shifts of the doublet and triplet of 1,1,2-trichloroethane (Fig. 9.4) and 1,1,2,3,3-pentachloropropane (Fig. 9.21) are reversed. Explain this.

PRACTICE PROBLEM 9.9 Sketch the ^{1}H NMR spectrum you would expect for the following compound, showing the splitting patterns and relative position of each signal.



PRACTICE PROBLEM 9.10 Propose a structure for each of the compounds whose spectra are shown in Fig. 9.22, and account for the splitting pattern of each signal.

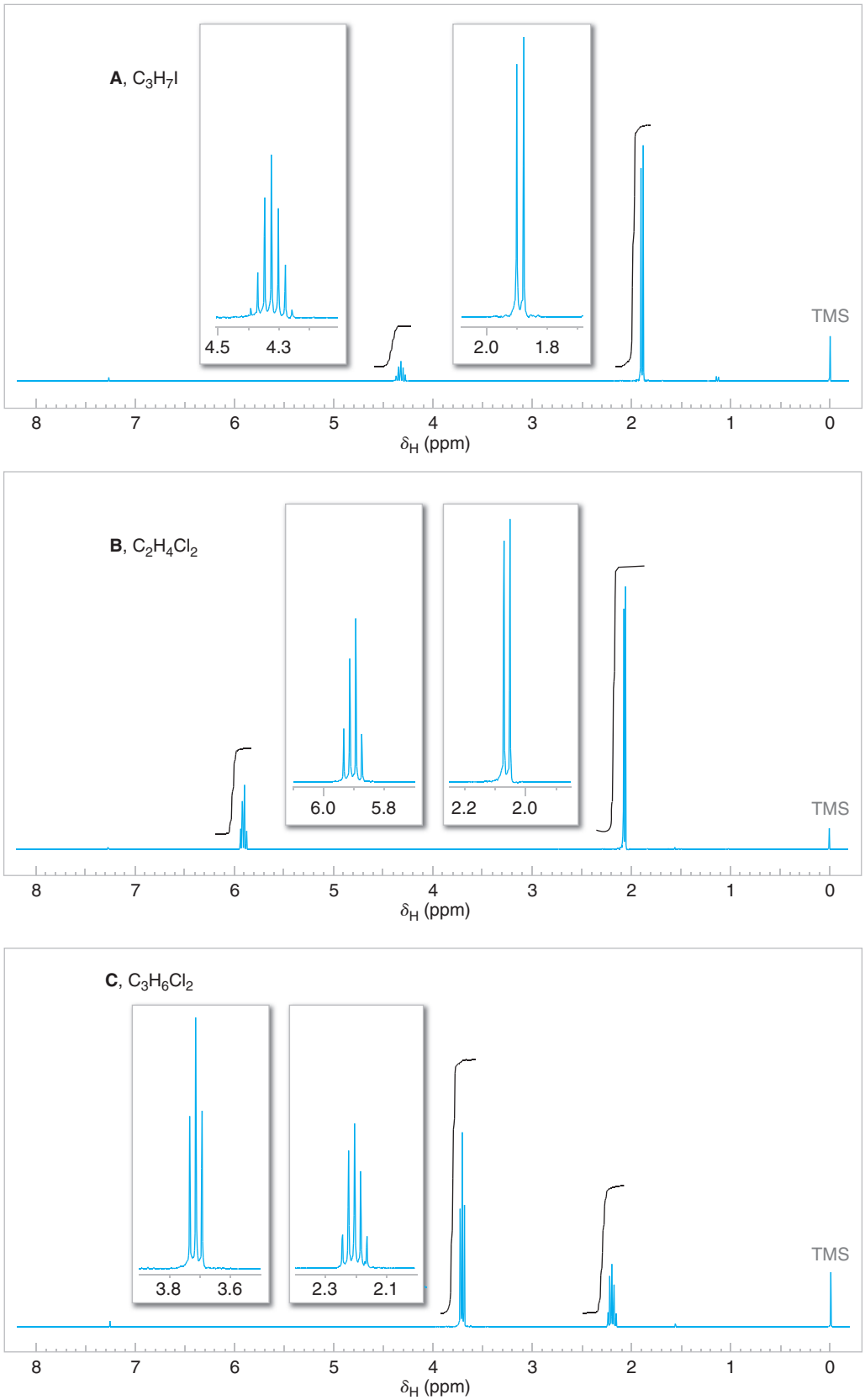


FIGURE 9.22 The 300-MHz ^{1}H NMR spectra for compounds **A**, **B**, and **C** in Practice Problem 9.10. Expansions are shown in the offset plots.

9.9C Coupling Constants—Recognizing Splitting Patterns

Signals from coupled protons share a common coupling constant value. Coupling constants are determined by measuring the separation in **hertz** between each peak of a signal. A typical vicinal coupling constant is 6–8 hertz. We showed how coupling constants are measured in Figs. 9.19 and 9.20, where J_{ab} denotes the **coupling constant** between coupled hydrogens ^{a}H and ^{b}H. Coupling constants are also used when drawing splitting tree diagrams, as shown in Figs. 9.19 and 9.20.

If we were to measure the separation of peaks in both the quartet and the triplet in the NMR spectrum of bromoethane (Fig. 9.1), we would find that they have the same coupling constant. This phenomenon is called **the reciprocity of coupling constants**.

A simulation of the reciprocity of coupling constants for bromoethane is represented in Fig. 9.23. While it is easy to assign the splitting patterns in bromoethane without the analysis of coupling constants, i.e., using solely the $n + 1$ rule (as is also the case for the spectra shown in Fig. 9.22), the reciprocity of coupling constants can be very helpful when assigning sets of coupled protons in the spectra of more complicated molecules.

Helpful Hint

Observing the reciprocity of coupling constants can help assign sets of coupled protons.

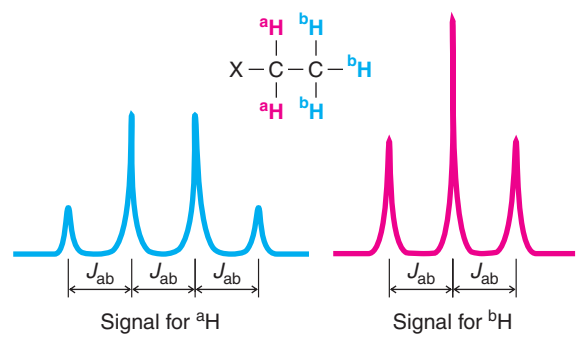


FIGURE 9.23 A theoretical splitting pattern for an ethyl group. For an actual example, see the spectrum of bromoethane (Fig. 9.1).

Other techniques in FTNMR spectroscopy also facilitate the analysis of coupling relationships. One such technique is ^{1}H–^{1}H **co**rrelation **s**pectroscop**y**, also known as ^{1}H–^{1}H COSY (Section 9.12A).

9.9D The Dependence of Coupling Constants on Dihedral Angle

The magnitude of a coupling constant can be indicative of the **dihedral angle (ϕ)** between coupled protons. This fact has been used to explore molecular geometry and perform conformational analysis by NMR spectroscopy. The dependence of the coupling constant on dihedral angles was explored by Martin Karplus (Harvard University), and has become well known as the **Karplus correlation**. A diagram showing the Karplus correlation is given in Fig. 9.24.

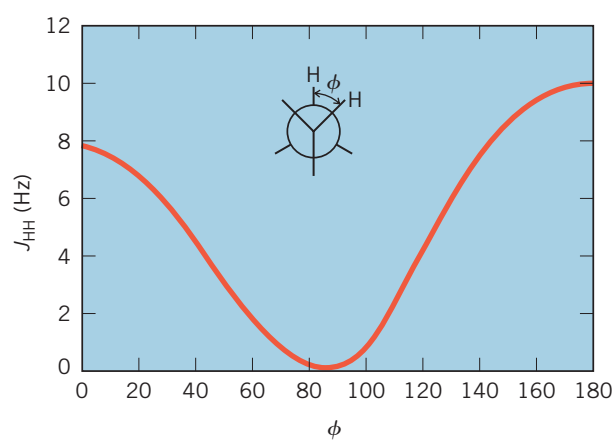
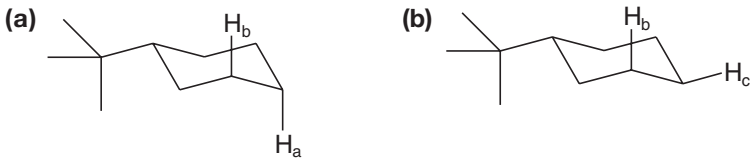


FIGURE 9.24 The Karplus correlation defines a relationship between dihedral angle (ϕ) and coupling constant for vicinal protons. (Reprinted with permission of John Wiley & Sons, Inc. From Silverstein, R., and Webster, F. X., *Spectrometric Identification of Organic Compounds, Sixth Edition*, p. 186. Copyright 1998.)

The influence of dihedral angles on coupling constants is often evident in the ^{1}H NMR spectra of substituted cyclohexanes. The coupling constant between vicinal axial protons ($J_{ax,ax}$) is typically 8–10 Hz, which is larger than the coupling constant between vicinal axial and equatorial protons ($J_{ax,eq}$), which is typically 2–3 Hz. Measuring coupling constants in the NMR spectrum of a substituted cyclohexane can therefore provide information about low energy conformations available to the compound.

PRACTICE PROBLEM 9.11

What is the dihedral angle and expected coupling constant between the labeled protons in each of the following molecules?

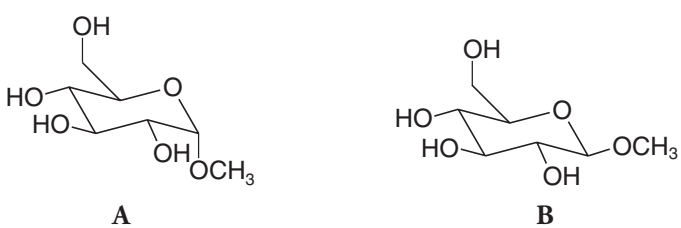


PRACTICE PROBLEM 9.12

Draw the most stable chair conformation of 1-bromo-2-chlorocyclohexane, if the coupling constant between hydrogens on C1 and C2 was found to be 7.8 Hz ($J_{1,2}$ = 7.8 Hz).

PRACTICE PROBLEM 9.13

Explain how you could distinguish between the following two compounds using NMR coupling constants. (These compounds are derived from glucose, by a reaction we shall study in Chapters 16 and 22.)



9.9E Complicating Features

Proton NMR spectra may have features that complicate the analysis when we try to determine the structure of a compound. For example:

1. Signals may overlap. This happens when the chemical shifts of the signals are very nearly the same. In the 60-MHz spectrum of ethyl chloroacetate (Fig. 9.25, top) we see that the singlet of the $-CH_2Cl$ group falls directly on top of one of the outermost peaks of the ethyl quartet. Using NMR spectrometers with higher magnetic field strength (corresponding to ^{1}H resonance frequencies of 300–900 MHz) often allows separation of signals that would overlap at lower magnetic field strengths (Fig. 9.25, bottom).
2. Spin–spin couplings between the protons of nonadjacent atoms may occur. This long-range coupling happens frequently in compounds when π-bonded atoms intervene between the atoms bearing the coupled protons, and in some cyclic molecules that are rigid.

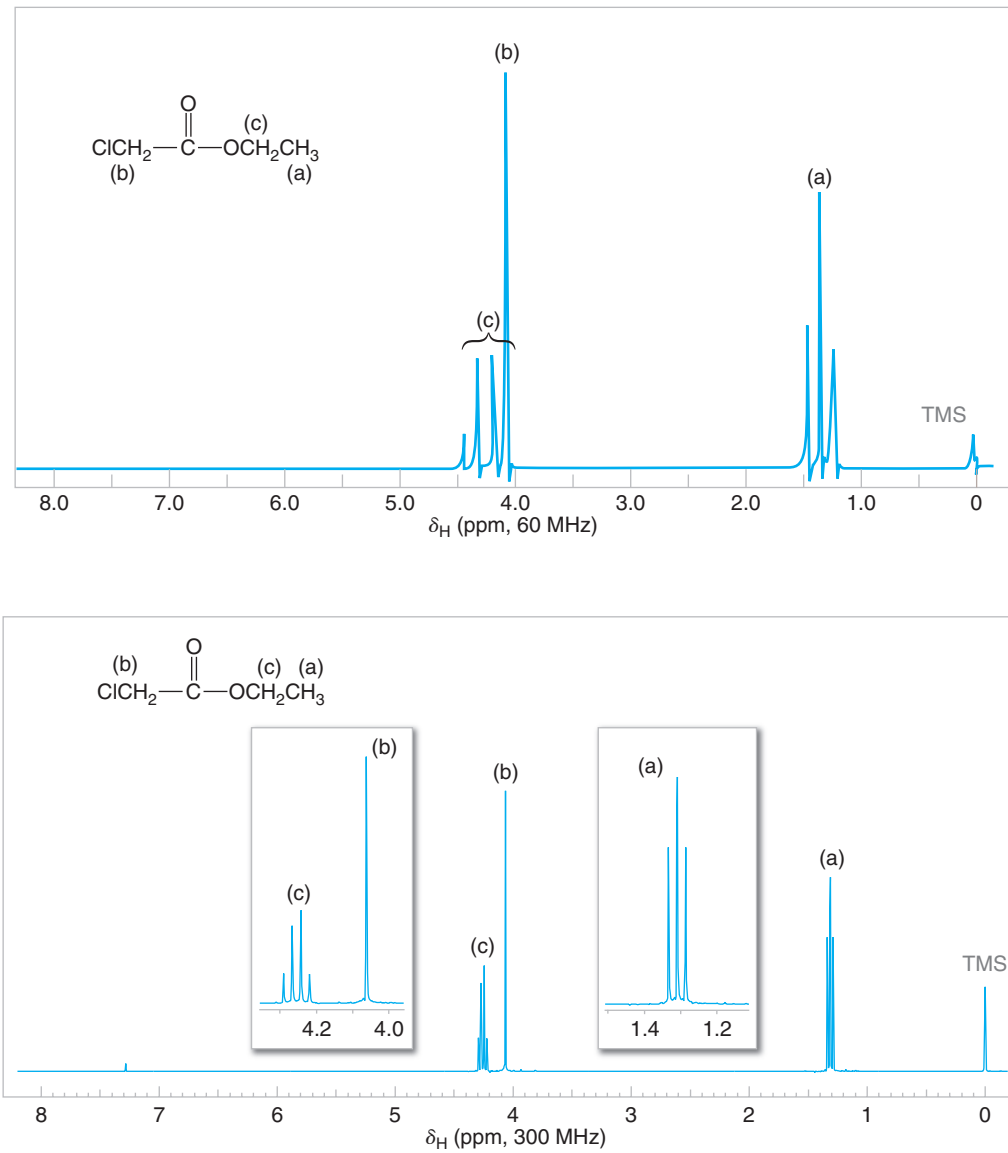
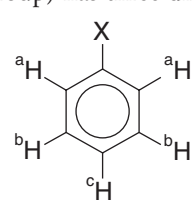


FIGURE 9.25 (*Top*) The 60-MHz ^{1}H NMR spectrum of ethyl chloroacetate. Note the overlapping signals at δ 4. (*Bottom*) The 300-MHz ^{1}H NMR spectrum of ethyl chloroacetate, showing resolution at higher magnetic field strength of the signals that overlapped at 60 MHz. Expansions of the signals are shown in the offset plots.

3. The splitting patterns of aromatic groups can be difficult to analyze. A monosubstituted benzene ring (a phenyl group) has three different kinds of protons:



The chemical shifts of these protons may be so similar that the phenyl group gives a signal that resembles a singlet. Or the chemical shifts may be different and, because of long-range couplings, the phenyl group signal may appear as a very complicated multiplet.

9.9F Analysis of Complex Interactions

In all of the ^{1}H NMR spectra that we have considered so far, we have restricted our attention to signal splittings arising from interactions of only two sets of equivalent protons on adjacent atoms. What kinds of patterns should we expect from compounds in which more than two sets of equivalent protons are interacting? We cannot answer this question

completely because of limitations of space, but we can give an example that illustrates the kind of analysis that is involved. Let us consider a 1-substituted propane:

$$\overset{(a)}{\mathrm{CH_3}}-\overset{(b)}{\mathrm{CH_2}}-\overset{(c)}{\mathrm{CH_2}}-\mathrm{Z}$$

Here, there are three sets of equivalent protons. We have no problem in deciding what kind of signal splitting to expect from the protons of the $\mathrm{CH_3}-$ group or the $-\mathrm{CH_2Z}$ group. The methyl group is spin–spin coupled only to the two protons of the central $-\mathrm{CH_2}-$ group. Therefore, the methyl group should appear as a triplet. The protons of the $-\mathrm{CH_2Z}$ group are similarly coupled only to the two protons of the central $-\mathrm{CH_2}-$ group. Thus, the protons of the $-\mathrm{CH_2Z}$ group should also appear as a triplet.

But what about the protons of the central $-\mathrm{CH_2}-$ group (b)? They are spin–spin coupled with the three protons at (a) and with two protons at (c). The protons at (a) and (c), moreover, are not equivalent. If the coupling constants J_{ab} and J_{bc} have quite different values, then the protons at (b) could be split into a quartet by the three protons at (a) and each line of the quartet could be split into a triplet by the two protons at (c), resulting in 12 peaks (Fig. 9.26).

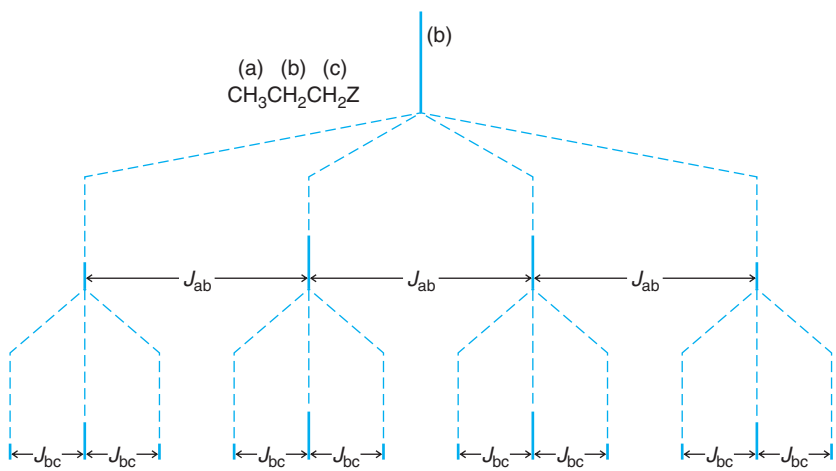


FIGURE 9.26 The splitting pattern that would occur for the (*b*) protons of $\mathrm{CH_3CH_2CH_2Z}$ if J_{ab} were much larger than J_{bc}. Here $J_{ab} = 3J_{bc}$.

It is unlikely, however, that we would observe as many as 12 peaks in an actual spectrum because the coupling constants are such that peaks usually fall on top of peaks. The ^{1}H NMR spectrum of 1-nitropropane (Fig. 9.27) is typical of 1-substituted propane compounds, in that the central $-\mathrm{CH_2}-$ group "sees" five approximately equivalent adjacent protons. Hence, by the $n+1$ rule, we see that the (b) protons are split into six major peaks.

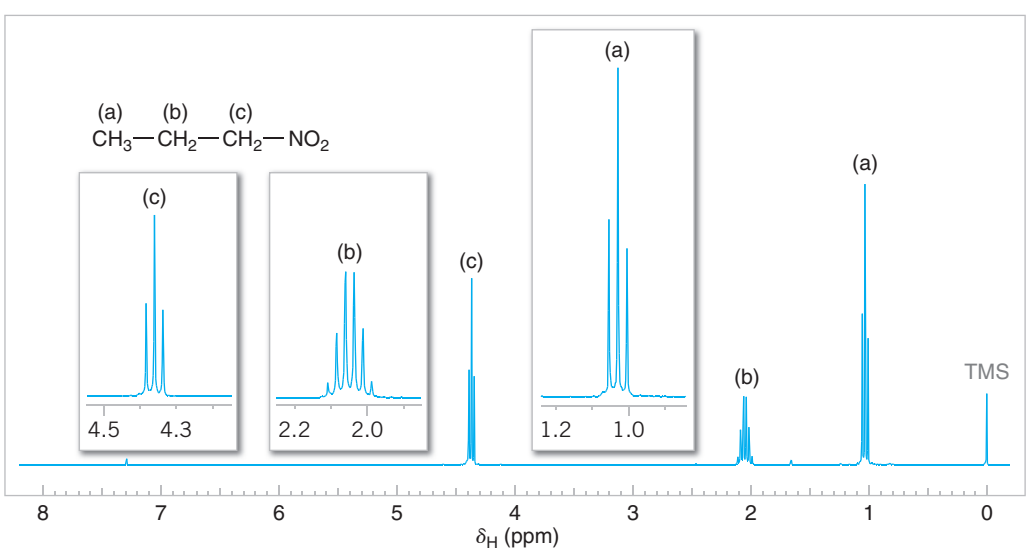


FIGURE 9.27 The 300-MHz ^{1}H NMR spectrum of 1-nitropropane. Expansions of the signals are shown in the offset plots.

PRACTICE PROBLEM 9.14 Carry out an analysis like that shown in Fig. 9.26 and show how many peaks the signal from (b) would be split into if $J_{ab} = 2J_{bc}$ and if $J_{ab} = J_{bc}$. (*Hint*: In both cases peaks will fall on top of peaks so that the total number of peaks in the signal is fewer than 12.)

The presentation we have given here applies only to what are called *first-order spectra*. In first-order spectra, the distance in hertz ($\Delta\nu$) that separates the coupled signals is very much larger than the coupling constant, J. That is, $\Delta\nu >> J$. In *second-order spectra* (which we have not discussed), $\Delta\nu$ approaches J in magnitude and the situation becomes much more complex. The number of peaks increases and the intensities are not those that might be expected from first-order considerations.

9.10 PROTON NMR SPECTRA AND RATE PROCESSES

J. D. Roberts (Emeritus Professor, California Institute of Technology), a pioneer in the application of NMR spectroscopy to problems of organic chemistry, has compared the NMR spectrometer to a camera with a relatively slow shutter speed. Just as a camera with a slow shutter speed blurs photographs of objects that are moving rapidly, the NMR spectrometer blurs its picture of molecular processes that are occurring rapidly.

What are some of the rapid processes that occur in organic molecules? Two processes that we shall mention are chemical exchange of hydrogen atoms bonded to heteroatoms (such as oxygen and nitrogen), and conformational changes.

Chemical Exchange Causes Spin Decoupling An example of a rapidly occurring process can be seen in ^{1}H NMR spectra of ethanol. The ^{1}H NMR spectrum of ordinary ethanol shows the hydroxyl proton as a singlet and the protons of the —CH_2— group as a quartet (Fig. 9.28). In ordinary ethanol we observe *no signal splitting arising from coupling between the hydroxyl proton and the protons of the* —CH_2— *group even though they are on adjacent atoms.*

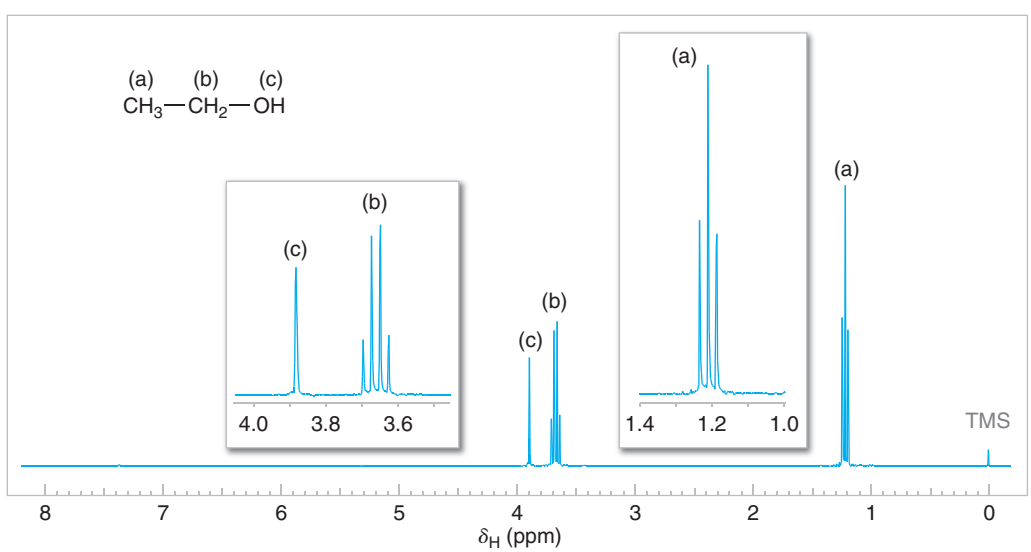


FIGURE 9.28 The 300-MHz ^{1}H NMR spectrum of ordinary ethanol. There is no signal splitting by the hydroxyl proton due to rapid chemical exchange. Expansions of the signals are shown in the offset plots.

If we were to examine a ^1H NMR spectrum of *very pure* ethanol, however, we would find that the signal from the hydroxyl proton was split into a triplet and that the signal from the protons of the $—CH_2—$ group was split into a multiplet of eight peaks. Clearly, in very pure ethanol the spin of the proton of the hydroxyl group is coupled with the spins of the protons of the $—CH_2—$ groups.

Whether coupling occurs between the hydroxyl protons and the methylene protons depends on the length of time the proton spends on a particular ethanol molecule.

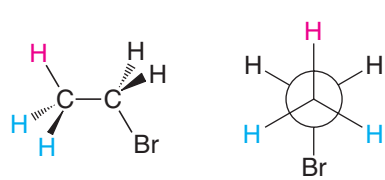
- Protons attached to electronegative atoms with lone pairs such as oxygen (or nitrogen) can undergo rapid **chemical exchange**. That is, they can be transferred rapidly from one molecule to another and are therefore called **exchangeable protons**.

The chemical exchange in very pure ethanol is slow and, as a consequence, we see the signal splitting of and by the hydroxyl proton in the spectrum. In ordinary ethanol, acidic and basic impurities catalyze the chemical exchange; the exchange occurs so rapidly that the hydroxyl proton gives an unsplit signal and that of the methylene protons is split only by coupling with the protons of the methyl group.

- Rapid exchange causes **spin decoupling**.
- Spin decoupling is found in the ^1H NMR spectra of alcohols, amines, and carboxylic acids. The signals of OH and NH protons are normally unsplit and broad.
- Protons that undergo rapid chemical exchange (i.e., those attached to oxygen or nitrogen) can be easily detected by placing the compound in D_2O. The protons are rapidly replaced by deuterons, and the proton signal disappears from the spectrum.

Conformational Changes At temperatures near room temperature, groups connected by carbon–carbon single bonds rotate very rapidly (unless rotation is prevented by some structural constraint, e.g., a rigid ring system). Because of this, when we determine spectra of compounds with single bonds that allow rotation, the spectra that we obtain often reflect the individual hydrogen atoms in their average environment—that is, in an environment that is an average of all the environments that the protons have as a result of conformational changes.

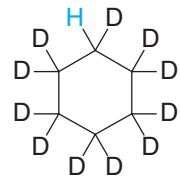
To see an example of this effect, let us consider the spectrum of bromoethane again. The most stable conformation is the one in which the groups are perfectly staggered. In this staggered conformation one hydrogen of the methyl group (in red in the following structure) is in a different environment from that of the other two methyl hydrogen atoms. If the NMR spectrometer were to detect this specific conformation of bromoethane, it would show the protons of the methyl group at *different chemical shifts*. We know, however, that in the spectrum of bromoethane (Fig. 9.1), the three protons of the methyl group give *one signal* (a signal that is split into a triplet by spin–spin coupling with the two protons of the adjacent carbon).



The methyl protons of bromoethane give a single signal because at room temperature the groups connected by the carbon–carbon single bond rotate approximately 1 million times each second. The "shutter speed" of the NMR spectrometer is too slow to "photograph" this rapid rotation; instead, it photographs the methyl hydrogen atoms in their average environments, and in this sense, it gives us a blurred picture of the methyl group.

Rotations about single bonds slow down as the temperature of the compound is lowered. Sometimes, this slowing of rotations allows us to "see" the different conformations of a molecule when we determine the spectrum at a sufficiently low temperature.

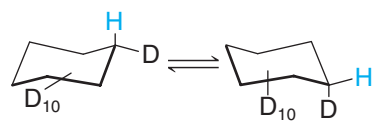
An example of this phenomenon, and one that also shows the usefulness of deuterium labeling, can be seen in the low-temperature ^{1}H NMR spectra of cyclohexane and of undecadeuteriocyclohexane. (These experiments originated with F. A. L. Anet, Emeritus Professor, University of California, Los Angeles, another pioneer in the applications of NMR spectroscopy to organic chemistry, especially to conformational analysis.)



Undecadeuteriocyclohexane

At room temperature, ordinary cyclohexane gives one signal because interconversion of chair forms occurs very rapidly. At low temperatures, however, ordinary cyclohexane gives a very complex ^{1}H NMR spectrum. At low temperatures interconversions are slow; the chemical shifts of the axial and equatorial protons are resolved, and complex spin–spin couplings occur.

At −100 °C, however, undecadeuteriocyclohexane gives only two signals of equal intensity. These signals correspond to the axial and equatorial hydrogen atoms of the following two chair conformations. Interconversions between these conformations occur at this low temperature, but they happen slowly enough for the NMR spectrometer to detect the individual conformations. (The nucleus of a deuterium atom (a deuteron) has a much smaller magnetic moment than a proton, and signals from deuteron absorption do not occur in ^{1}H NMR spectra.)



PRACTICE PROBLEM 9.15 How many signals would you expect to obtain in the ^{1}H NMR spectrum of undecadeuteriocyclohexane at room temperature?

9.11 CARBON-13 NMR SPECTROSCOPY

9.11A Interpretation of ^{13}C NMR Spectra

Helpful Hint

You may also wish to refer to **^{13}C NMR Spectroscopy: A Practical Introduction**, Special Topic A in *WileyPLUS*.

We begin our study of **^{13}C NMR spectroscopy** with a brief examination of some special features of spectra arising from carbon-13 nuclei. Although ^{13}C accounts for only 1.1% of naturally occurring carbon, the fact that ^{13}C can produce an NMR signal has profound importance for the analysis of organic compounds. In some important ways ^{13}C spectra are usually less complex and easier to interpret than ^{1}H **NMR spectra**. The major isotope of carbon, on the other hand, carbon-12 (^{12}C), with a natural abundance of about 99%, has no net magnetic spin and therefore cannot produce NMR signals.

9.11B One Peak for Each Magnetically Distinct Carbon Atom

The interpretation of ^{13}C NMR spectra is greatly simplified by the following facts:

- Each distinct carbon produces one signal in a ^{13}C NMR spectrum.
- Splitting of ^{13}C signals into multiple peaks is not observed in routine ^{13}C NMR spectra.

Recall that in ^{1}H NMR spectra, hydrogen nuclei that are near each other (within a few bonds) couple with each other and cause the signal for each hydrogen to be split into a multiplet of peaks. Coupling is not observed for adjacent carbons because only one out of every 100 carbon atoms is a ^{13}C nucleus (1.1% natural abundance). Therefore, the probability of there being two ^{13}C atoms adjacent to each other in a molecule is only about 1 in 10,000 (1.1% × 1.1%), essentially eliminating the possibility of two neighboring carbon atoms splitting each other's signal into a multiplet of peaks. The low natural abundance of ^{13}C

nuclei and its inherently low sensitivity also have another effect: carbon-13 NMR spectra can be obtained only on pulse FTNMR spectrometers, where signal averaging is possible.

Whereas carbon–carbon signal splitting does not occur in ^{13}C NMR spectra, hydrogen atoms attached to carbon can split ^{13}C NMR signals into multiple peaks. However, it is useful to simplify the appearance of ^{13}C NMR spectra by initially eliminating signal splitting for ^{1}H–^{13}C coupling. This can be done by choosing instrumental parameters that decouple the proton–carbon interactions, and such a spectrum is said to be **broadband (BB) proton decoupled**.

- In a broadband **proton-decoupled** ^{13}C NMR spectrum, each carbon atom in a distinct environment gives a signal consisting of only one peak.

Most ^{13}C NMR spectra are obtained in the simplified broadband decoupled mode first and then in modes that provide information from the ^{1}H–^{13}C couplings (Sections 9.11D and 9.11E).

9.11C ^{13}C Chemical Shifts

As we found with ^{1}H spectra, the **chemical shift** of a given nucleus depends on the relative electron density around that atom.

- Decreased electron density around an atom **deshields** the atom from the magnetic field and causes its signal to occur further to the left in the NMR spectrum at a larger chemical shift (δ) value and higher frequency.
- Relatively higher electron density around an atom **shields** the atom from the magnetic field and causes the signal to occur further to the right in the NMR spectrum at a smaller chemical shift (δ) value and lower frequency.

For example, carbon atoms that are attached only to other carbon and hydrogen atoms are relatively shielded from the magnetic field by the density of electrons around them, and, as a consequence, alkyl carbons produce peaks that are further to the right in ^{13}C NMR spectra. On the other hand, carbon atoms bearing electronegative groups are deshielded from the magnetic field by the electron-withdrawing effects of these groups and, therefore, produce peaks that are further to the left in the NMR spectrum.

- Electronegative groups such as halogens, hydroxyl groups, and other electron-withdrawing functional groups deshield the carbons to which they are attached, causing their ^{13}C NMR peaks to occur at greater chemical shift (δ) values than those of unsubstituted carbon atoms.

Reference tables of approximate chemical shift ranges for carbons bearing different substituents are available. Figure 9.29 and Table 9.2 are examples. [The reference

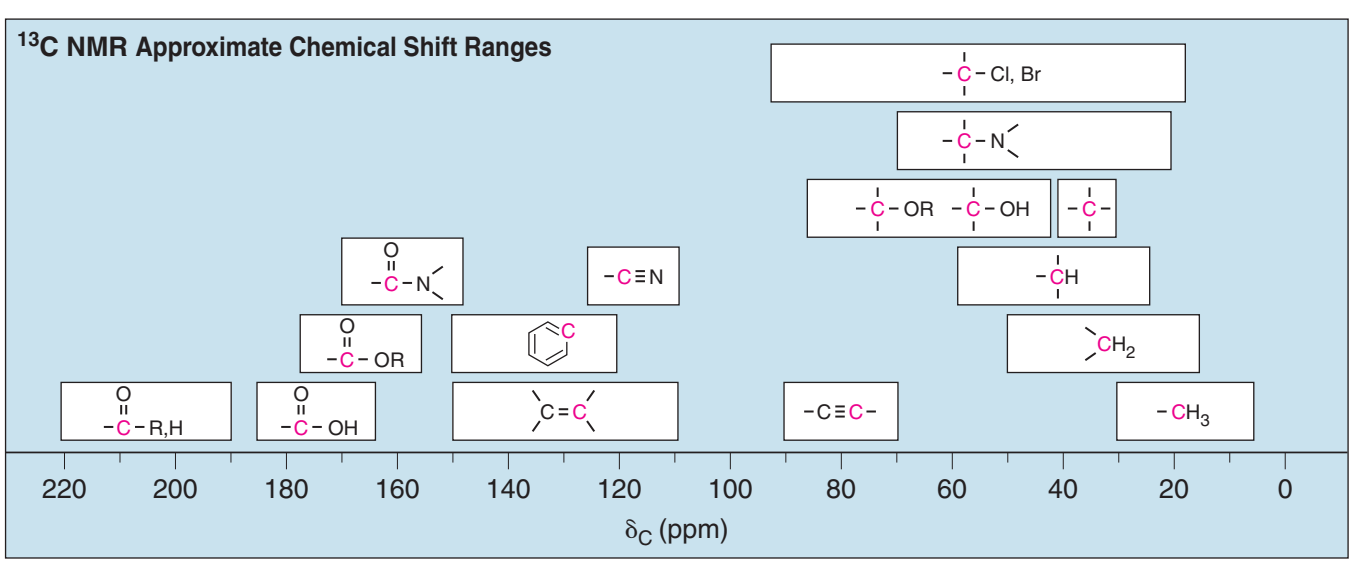
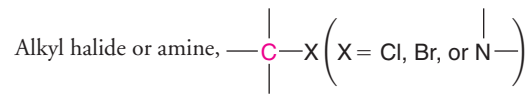
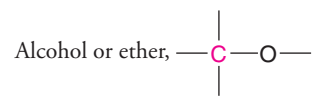
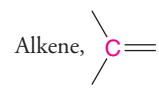
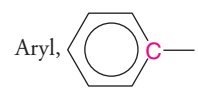
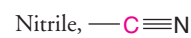
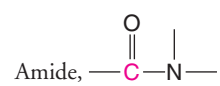
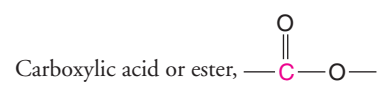
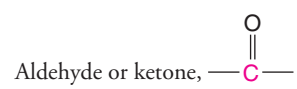


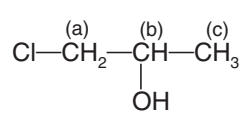
FIGURE 9.29 Approximate ^{13}C chemical shifts.

TABLE 9.2 APPROXIMATE CARBON-13 CHEMICAL SHIFTS

Type of Carbon Atom	Chemical Shift (δ, ppm)
1° Alkyl, RCH_3	0–40
2° Alkyl, RCH_2R	10–50
3° Alkyl, $RCHR_2$	15–50
Alkyl halide or amine, 	10–65
Alcohol or ether, 	50–90
Alkyne,	60–90
Alkene, 	100–170
Aryl, 	100–170
Nitrile, 	120–130
Amide, 	150–180
Carboxylic acid or ester, 	160–185
Aldehyde or ketone, 	182–215

standard assigned as zero ppm in ^{13}C NMR spectra is also tetramethylsilane (TMS), $Si(CH_3)_4$.]

As a first example of the interpretation of ^{13}C NMR spectra, let us consider the ^{13}C spectrum of 1-chloro-2-propanol (Fig. 9.30*a*):



1-Chloro-2-propanol

1-Chloro-2-propanol contains three carbon atoms in distinct environments, and therefore produces three signals in its broadband decoupled ^{13}C NMR spectrum: approximately at δ 20, δ 51, and δ 67. Figure 9.30 also shows a close grouping of three peaks at δ 77. These peaks come from the signal for deuteriochloroform ($CDCl_3$) used as a solvent for the sample. All ^{13}C NMR spectra contain these peaks if $CDCl_3$ was the solvent. Although not of concern to us here, the signal for the single carbon of $CDCl_3$ is split into three peaks by an effect of the attached deuterium.

- The $CDCl_3$ solvent peaks at δ 77 should be disregarded when interpreting ^{13}C spectra.

As we can see, the chemical shifts of the three signals from 1-chloro-2-propanol are well separated from one another. This separation results from differences in shielding by

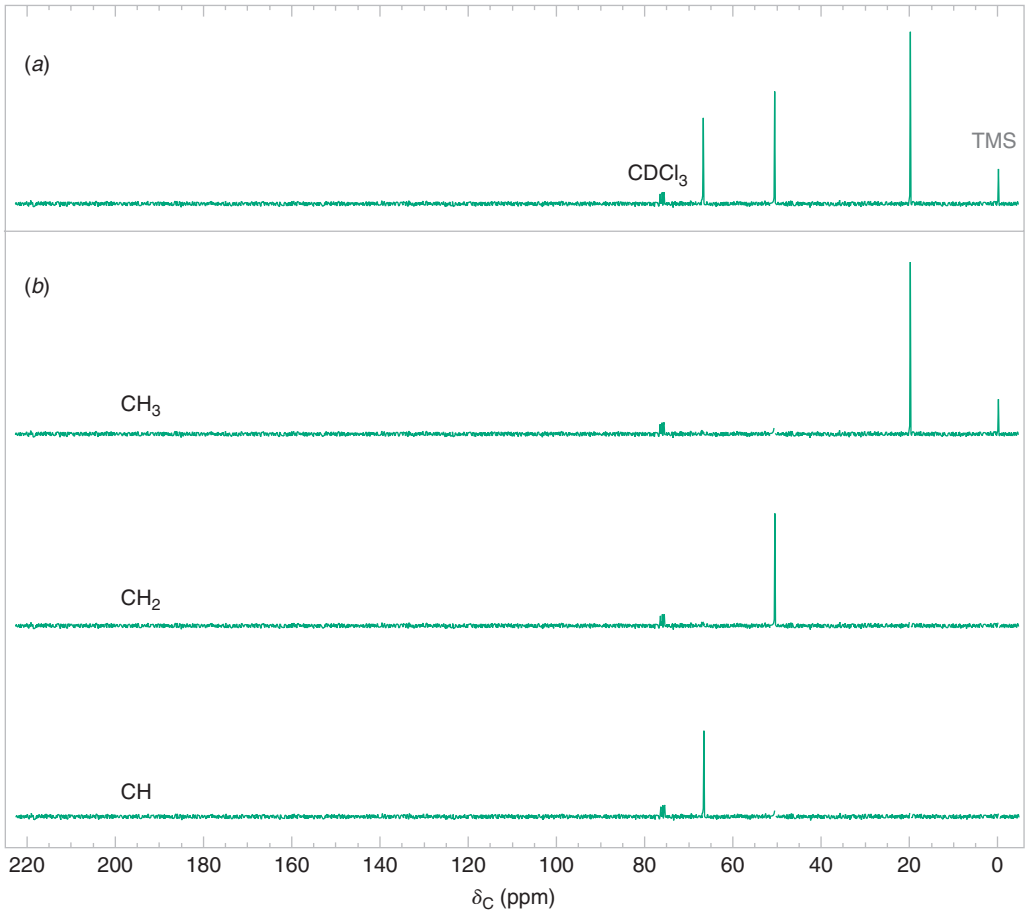


FIGURE 9.30 (*a*) The broadband proton-decoupled ^{13}C NMR spectrum of 1-chloro-2-propanol. (*b*) These three spectra show the DEPT ^{13}C NMR data from 1-chloro-2-propanol (see Section 9.11D). (This will be the only full display of a DEPT spectrum in the text. Other ^{13}C NMR figures will show the full broadband proton-decoupled spectrum but with information from the DEPT ^{13}C NMR spectra indicated near each peak as C, CH, CH_2, or CH_3.)

circulating electrons in the local environment of each carbon. Remember: the lower the electron density in the vicinity of a given carbon, the less that carbon will be shielded, and the further to the left will be the signal for that carbon. The oxygen of the hydroxyl group is the most electronegative atom; it withdraws electrons most effectively. Therefore, the carbon bearing the —OH group is the most *deshielded* carbon, and so this carbon gives the signal at δ 67. Chlorine is less electronegative than oxygen, causing the peak for the carbon to which it is attached to occur at δ 51. The methyl group carbon has no electronegative groups directly attached to it, so it has the smallest chemical shift, appearing at δ 20. Using tables of typical chemical shift values (such as Fig. 9.29 and Table 9.2), one can usually assign ^{13}C NMR signals to each carbon in a molecule, on the basis of the groups attached to each carbon.

9.11D DEPT ^{13}C Spectra

At times, more information than a predicted chemical shift is needed to assign an NMR signal to a specific carbon atom of a molecule. Fortunately, NMR spectrometers can differentiate among carbon atoms on the basis of the number of hydrogen atoms that are attached to each carbon. Several methods to accomplish this are available. One of

the most common is the use of **DEPT (distortionless enhancement by polarization transfer) spectra**. DEPT ^{13}C NMR spectra are very simple to interpret.

- **DEPT ^{13}C NMR spectra** indicate how many hydrogen atoms are bonded to each carbon, while also providing the chemical shift information contained in a broadband proton-decoupled ^{13}C NMR spectrum. The carbon signals in a DEPT spectrum are classified as CH_3, CH_2, CH, or C accordingly.

The hydrogen connectivity information from DEPT NMR data are actually produced using several ^{13}C spectra of the same sample (Fig. 9.30*b*), with the net spectrum result providing the information about the hydrogen substitution at each carbon (Fig. 9.30*a*). In this text we show the ^{13}C peaks labeled according to the information gained from the DEPT spectra for the compound under consideration, rather than reproducing the entire family of spectra that lead to the final result.

As a further example of interpreting ^{13}C NMR spectra, let us look at the spectrum of methyl methacrylate (Fig. 9.31). (This compound is the monomeric starting material for the commercial polymers Lucite and Plexiglas, see Chapter 10.) The five carbons of methyl methacrylate represent carbon types from several chemical shift regions of ^{13}C spectra. Furthermore, because there is no symmetry in the structure of methyl methacrylate, all of its carbon atoms are chemically unique and so produce five distinct carbon NMR signals. Making use of our table of approximate ^{13}C chemical shifts (Fig. 9.29 and Table 9.2), we can readily deduce that the peak at δ 167.3 is due to the ester carbonyl carbon, the peak at δ 51.5 is for the methyl carbon attached to the ester oxygen, the peak at δ 18.3 is for the methyl attached to C2, and the peaks at δ 136.9 and δ 124.7 are for the alkene carbons. Additionally, employing the information from the DEPT ^{13}C spectra, we can unambiguously assign signals to the alkene carbons. The DEPT spectra tell us definitively that the peak at δ 124.7 has two attached hydrogens, and so it is due to C3, the terminal alkene carbon of methyl methacrylate. The alkene carbon with no attached hydrogens is then, of course, C2.

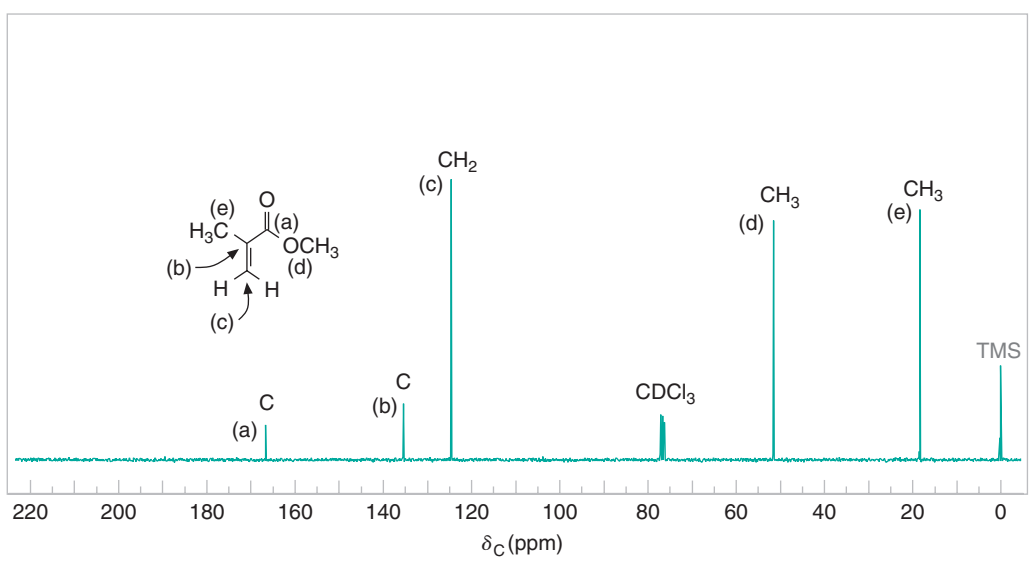


FIGURE 9.31 The broadband proton-decoupled ^{13}C NMR spectrum of methyl methacrylate. Information from the DEPT ^{13}C NMR spectra is given above the peaks.

PRACTICE PROBLEM 9.16 Compounds **A, B**, and **C** are isomers with the formula $C_5H_{11}Br$. Their broadband proton-decoupled ^{13}C NMR spectra are given in Fig. 9.32. Information from the DEPT ^{13}C NMR spectra is given near each peak. Give structures for **A, B**, and **C**.

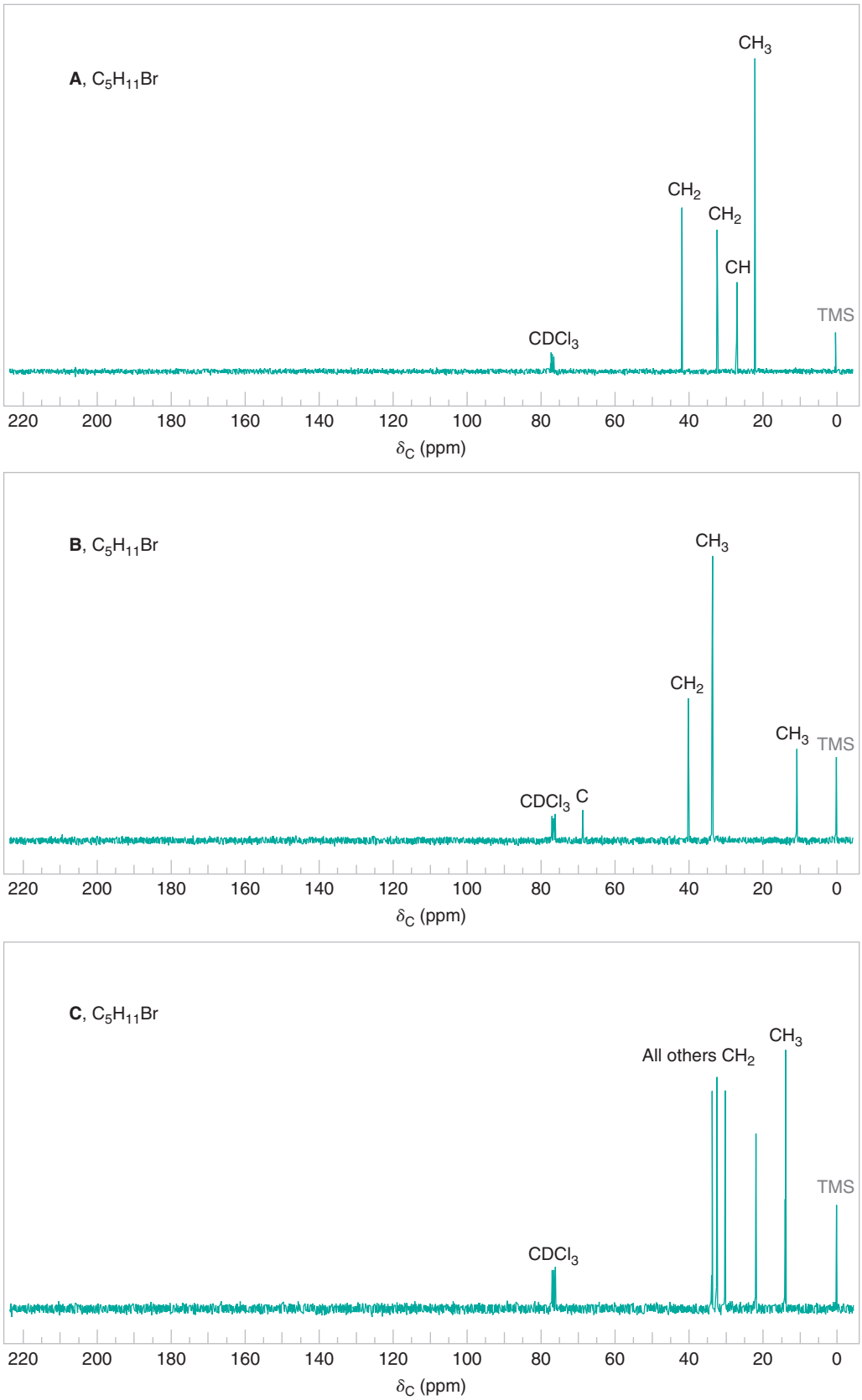


FIGURE 9.32 The broadband proton-decoupled ^{13}C NMR spectra of compounds **A**, **B**, and **C**, Practice Problem 9.16. Information from the DEPT ^{13}C NMR spectra is given above the peaks.

9.12 TWO-DIMENSIONAL (2D) NMR TECHNIQUES

Many NMR techniques are available that greatly simplify the interpretation of NMR spectra. Chemists can readily glean information about spin–spin coupling and the exact *connectivity* of atoms in molecules through techniques called **multidimensional FTNMR spectroscopy**. The most common multidimensional techniques utilize **two-dimensional NMR (2D NMR)** and go by acronyms such as **COSY**, HETCOR or **HSQC**, and a variety of others. [Even three-dimensional techniques (and beyond) are possible, although computational requirements can limit their feasibility.] The two-dimensional sense of 2D NMR spectra does not refer to the way they appear on paper but instead reflects the fact that the data are accumulated using two radio frequency pulses with a varying time delay between them. Sophisticated application of other instrumental parameters is involved as well. Discussion of these parameters and the physics behind multidimensional NMR is beyond the scope of this text. The result, however, is an NMR spectrum with the usual one-dimensional spectrum along the horizontal and vertical axes and a set of correlation peaks that appear in the *x*–*y* field of the graph.

When 2D NMR is applied to ^{1}H NMR it is called **^{1}H–^{1}H correlation spectroscopy** (or **^{1}H–^{1}H COSY** for short). ^{1}H–^{1}H COSY spectra are exceptionally useful for deducing proton–proton coupling relationships. Two-dimensional NMR spectra can also be obtained that indicate coupling between hydrogens and the *carbons* to which they are attached. In this case it is called **heteronuclear correlation spectroscopy** (**HETCOR**). One of the most common types of ^{1}H–^{13}C NMR correlation data is called **HSQC**, for heteronuclear single-quantum correlation spectroscopy. When ambiguities are present in the one-dimensional ^{1}H and ^{13}C NMR spectra, a ^{1}H–^{13}C heteronuclear correlation spectrum can be very useful for assigning precisely which hydrogens and carbons are producing their respective peaks.

9.12A ^{1}H–^{1}H COSY Cross-Peak Correlations

Figure 9.33 shows the ^{1}H–^{1}H COSY spectrum for 1-chloro-2-propanol. In a ^{1}H–^{1}H COSY spectrum the ordinary one-dimensional ^{1}H spectrum is shown along both the horizontal and the vertical axes. Meanwhile, the *x*–*y* field of a ^{1}H–^{1}H COSY spectrum is similar to a topographic map and can be thought of as looking down on the contour lines of a map of a mountain range. Along the diagonal of the ^{1}H–^{1}H COSY spectrum is a view that corresponds to looking down on the ordinary one-dimensional proton spectrum of 1-chloro-2-propanol as though each peak were a mountain. The one-dimensional counterpart of a given peak on the diagonal lies directly below that peak on each axis. The peaks on the diagonal provide no new information relative to that obtained from the one-dimensional spectrum along each axis.

The important and new information from a ^{1}H–^{1}H COSY spectrum (sometimes referred to as simply COSY) comes from the cross-peak correlations, which are the "mountains" that appear off the diagonal.

- Starting at a given off-diagonal cross peak, one imagines two perpendicular lines (parallel to each spectrum axis) leading back to the diagonal. We have drawn these lines in Fig. 9.33 in magenta as an aid. The perpendicular lines are not usually shown in original COSY spectra because their inclusion would unnecessarily complicate the appearance of the data.
- The peaks on the diagonal that are intersected by these perpendicular lines are spin–spin coupled to each other.
- The signals in the one-dimensional spectrum that appear directly below the peaks on the diagonal are spin–spin coupled to each other.

The cross peaks above the diagonal are mirror reflections of those below the diagonal; thus the information is redundant and only cross peaks on one side of the diagonal need to be interpreted.

Let's trace the coupling relationships in 1-chloro-2-propanol made evident in its COSY spectrum (Fig. 9.33). (Even though coupling relationships from the ordinary

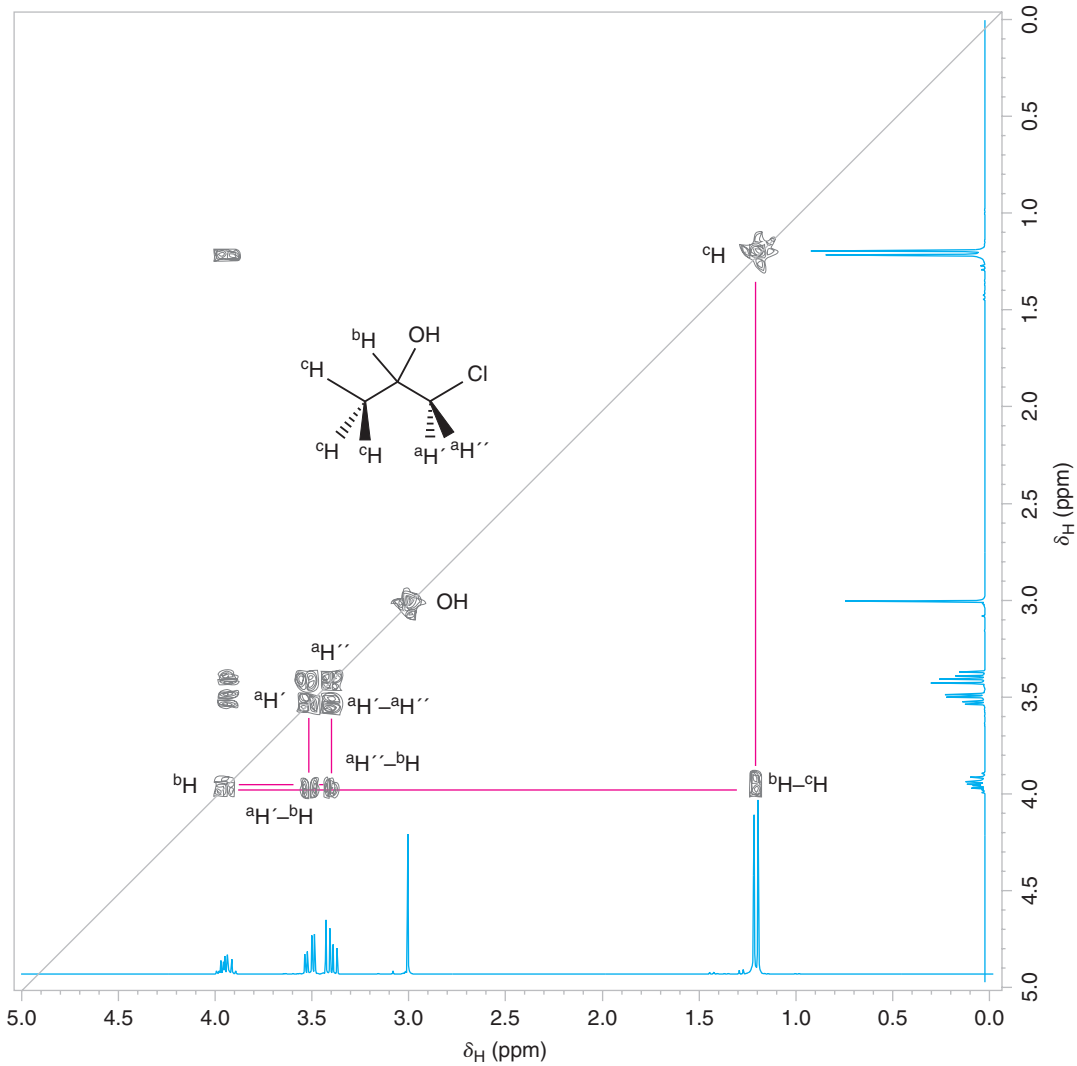


FIGURE 9.33 ^{1}H–^{1}H COSY spectrum of 1-chloro-2-propanol.

one-dimensional spectrum for 1-chloro-2-propanol are fairly readily interpreted, this compound makes a good beginning example for interpretation of COSY spectra.)

1. First we choose a starting point on a one-dimensional axis of the COSY spectrum from which to begin tracing the coupling relationships. It is best to choose a signal whose proton assignment is relatively obvious. For l-chloro-2-propanol, the doublet from the methyl group at δ 1.2 is readily assigned.
2. Next we find the peak on the diagonal that corresponds to the methyl doublet. This peak is on the diagonal directly above the doublet in the one-dimensional spectrum, and we have labeled it ^{c}H in Fig. 9.33.
3. Now we determine which signal is coupled to the methyl doublet by looking for a cross peak that is correlated with it. We draw (or imagine) a line parallel to either axis that starts from the peak for the methyl doublet on the diagonal. Doing so we find that this line leads to a cross peak labeled ^{b}H–^{c}H in Fig. 9.33.
4. Taking a perpendicular line from cross peak ^{b}H–^{c}H back to the diagonal leads to the peak labeled ^{b}H on the diagonal. The signal at δ 3.9 in the one-dimensional spectrum below the ^{b}H diagonal peak is the one that is spin–spin coupled to the methyl doublet, and it is now clear that this signal is from the hydrogen on the alcohol carbon in l-chloro-2-propanol.
5. To continue the sequence of correlations, we can now take a line from diagonal peak ^{b}H back to other cross peaks to which it is correlated. Doing so, we find cross peaks

above the one-dimensional signals at δ 3.5 and 3.4, signifying that ^{b}H at δ 3.9 is spin–spin coupled with the hydrogens producing the signals at both δ 3.5 and 3.4. We have labeled these cross peaks ^{a}H′–^{b}H and ^{a}H″–^{b}H. The signals at δ 3.5 and 3.4 are therefore for the two hydrogens at C1. Because C2 is a chirality center, the hydrogens at C1 are diastereotopic, and therefore they are not chemical shift equivalent. We have labeled them ^{a}H′ and ^{a}H″. We can also see the coupling between ^{a}H′ and ^{a}H″ represented by the cross peak between them labeled ^{a}H′–^{a}H″. This is a geminal coupling rather than a **vicinal coupling**.

9.12B ^{1}H–^{13}C Heteronuclear Correlation Cross-Peak Correlations

In a ^{1}H–^{13}C heteronuclear correlation spectrum a ^{13}C spectrum is presented along one axis and a ^{1}H spectrum is shown along the other. Specifically, the cross peaks in a ^{1}H–^{13}C heteronuclear correlation spectrum indicate which hydrogens are attached to which carbons in a molecule. There is no diagonal spectrum in the *x*–*y* field like that found in the ^{1}H–^{1}H COSY spectrum. If imaginary lines are drawn from a given cross peak to each respective axis in a ^{1}H–^{13}C heteronuclear correlation spectrum, the cross peak indicates that the hydrogen giving rise to the ^{1}H NMR signal on one axis is coupled (and attached) to the carbon that gives rise to the corresponding ^{13}C NMR signal on the other axis. Therefore, it is readily apparent which hydrogens are attached to which carbons.

Let us take a look at the HETCOR spectrum for 1-chloro-2-propanol (Fig. 9.34). Having interpreted the ^{1}H–^{1}H COSY spectrum already, we know precisely which hydrogens of 1-chloro-2-propanol produce each signal in the ^{1}H spectrum.

1. If an imaginary line is taken from the methyl doublet of the proton spectrum at 1.2 ppm (vertical axis) out to the correlation peak in the *x*–*y* field and then dropped down to the ^{13}C spectrum axis (horizontal axis), it is apparent that the ^{13}C peak at 20 ppm is produced by the methyl carbon of 1-chloro-2-propanol (C3).
2. Having assigned the ^{1}H NMR peak at 3.9 ppm to the hydrogen on the alcohol carbon of the molecule (C2), tracing out to the correlation peak and down to the

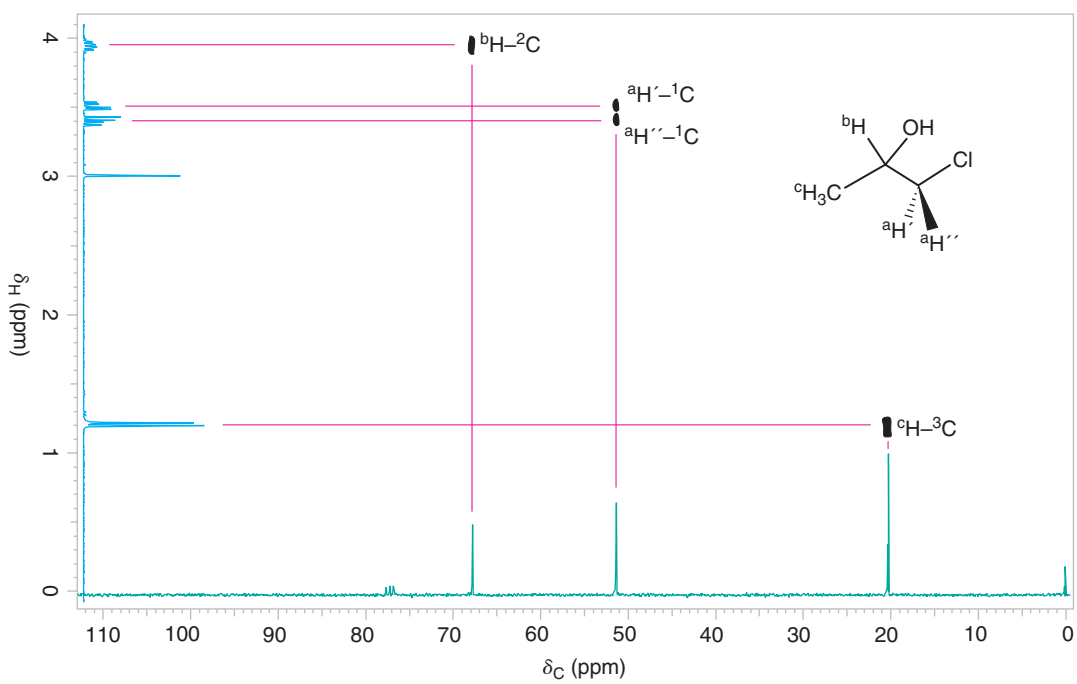
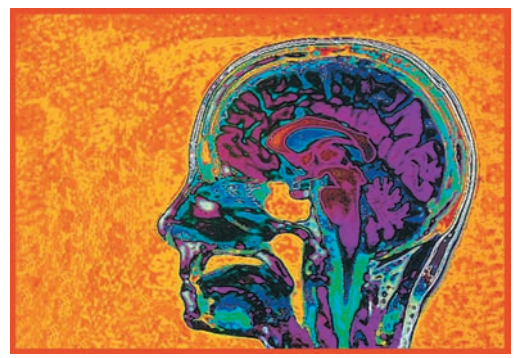


FIGURE 9.34 ^{1}H–^{13}C heteronuclear correlation NMR spectrum of 1-chloro-2-propanol. The ^{1}H NMR spectrum is shown in blue and the ^{13}C NMR spectrum is shown in green. Correlations of the ^{1}H–^{13}C cross peaks with the one-dimensional spectra are indicated by red lines.

THE CHEMISTRY OF... Magnetic Resonance Imaging in Medicine

An important application of ^{1}H NMR spectroscopy in medicine today is a technique called **magnetic resonance imaging**, or **MRI**. One great advantage of MRI is that, unlike X-rays, it does not use dangerous ionizing radiation, and it does not require the injection of potentially harmful chemicals in order to produce contrasts in the image. In MRI, a portion of the patient's body is placed in a powerful magnetic field and irradiated with RF energy.

A typical MRI image is shown at the right. The instruments used in producing images like this one use the pulse method (Section 9.5) to excite the protons in the tissue under observation and use a Fourier transformation to translate the information into an image. The brightness of various regions of the image is related to two things.



Harry Sieplinga/The Image Bank/Getty Images, Inc.

An image obtained by magnetic resonance imaging.

The first factor is the number of protons in the tissue at that particular place. The second factor arises from what are called the **relaxation times** of the protons. When protons are excited to a higher energy state by the pulse of RF energy, they absorb energy. They must lose this energy to return to the lower energy spin state before they can be excited again by a second pulse. The process by which the nuclei lose this energy is called **relaxation**, and the time it takes to occur is the relaxation time.

There are two basic modes of relaxation available to protons. In one, called *spin–lattice relaxation*, the extra energy is transferred to neighboring molecules in the surroundings (or lattice). The time required for this to happen is called T_1 and is characteristic of the time required for the spin system to return to thermal equilibrium with its surroundings. In solids, T_1 can be hours long. For protons in pure liquid water, T_1 is only a few seconds. In the other type of relaxation, called spin–spin relaxation, the extra energy is dissipated by transfer to nuclei of nearby atoms. The time required for this is called T_2. In liquids the magnitude of T_2 is approximately equal to T_1. In solids, however, the T_1 is very much longer.

Various techniques based on the time between pulses of RF radiation have been developed to utilize the differences in relaxation times in order to produce contrasts between different regions in soft tissues. The soft tissue contrast is inherently higher than that produced with X-ray techniques. Magnetic resonance imaging is being used to great effect in locating tumors, lesions, and edemas. Improvements in this technique are occurring rapidly, and the method is not restricted to observation of proton signals.

One important area of medical research is based on the observation of signals from ^{31}P. Compounds that contain phosphorus as phosphate esters (Section 11.10) such as adenosine triphosphate (ATP) and adenosine diphosphate (ADP), are involved in most metabolic processes. Using techniques based on NMR, researchers now have a non-invasive way to follow cellular metabolism.

^{13}C spectrum indicates that the ^{13}C NMR signal at 67 ppm arises from the alcohol carbon (C2).

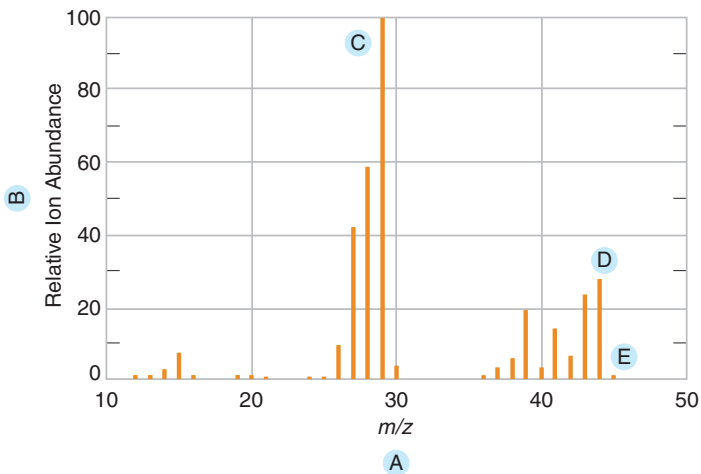
3. Finally, from the ^{1}H NMR peaks at 3.4–3.5 ppm for the two hydrogens on the carbon bearing the chlorine, our interpretation leads us out to the cross peak and down to the ^{13}C peak at 51 ppm (C1).

Thus, by a combination of ^{1}H–^{1}H COSY and ^{1}H–^{13}C heteronuclear correlation spectra, all ^{13}C and ^{1}H peaks can be unambiguously assigned to their respective carbon and hydrogen atoms in 1-chloro-2-propanol. In this simple example using 1-chloro-2-propanol, we could have arrived at complete assignment of these spectra without COSY and heteronuclear correlation data. For many compounds, however, the assignments are quite difficult to make without the aid of these 2D NMR techniques.

9.13 AN INTRODUCTION TO MASS SPECTROMETRY

Mass spectrometry (MS) involves formation of ions in a mass spectrometer followed by separation and detection of the ions according to mass and charge. A mass spectrum is a graph that on the *x*-axis represents the formula weights of the detected ions, and on the *y*-axis represents the abundance of each detected ion. The *x*-axis is labeled *m*/*z*, where m = mass and z = charge. In examples we shall consider, z equals +1, and hence the *x*-axis effectively represents the formula weight of each detected ion. The *y*-axis expresses

relative ion abundance, usually as a percentage of the tallest peak or directly as the number of detected ions. The tallest peak is called the **base peak**. As a typical example, the mass spectrum of propane is shown in Fig. 9.35.



A The *x*-axis, in units of *m/z*, represents the formula weight of the detected ions. ***m/z*** is the mass (*m*) to charge (*z*) ratio. Because *z* is typically +1, *m/z* represents the formula weight of each ion.

B The *y*-axis represents the relative abundance of each detected ion.

C The most abundant ion (tallest peak) is called the **base peak**. The base peak is usually an easily formed fragment of the original compound. In this case it is an ethyl fragment ($C_2H_5^+$, *m/z* 29).

D One of the higher value *m/z* peaks may or may not represent the **molecular ion** (the ion with the formula weight of the original compound). When present, the molecular ion (*m/z* 44 in the case of propane) is usually not the base peak, because ions from the original molecule tend to fragment, resulting in the other *m/z* peaks in the spectrum.

E Small peaks having *m/z* values 1 or 2 higher than the formula weight of the compound are due to ^{13}C and other isotopes (Section 9.17).

FIGURE 9.35 A mass spectrum of propane. (NIST Mass Spec Data Center, S. E. Stein, director, "Mass Spectra" in NIST Chemistry WebBook, NIST Standard Reference Database Number 69, Eds. P. J. Linstrom and W. G. Mallard, June 2005, National Institute of Standards and Technology, Gaithersburg, MD, 20899 http://webbook.nist.gov.)

9.14 FORMATION OF IONS: ELECTRON IMPACT IONIZATION

The ions in mass spectrometry may be formed in a variety of ways. One method for converting molecules to ions (**ionization**) in a mass spectrometer is to place a sample under high vacuum and bombard it with a beam of high-energy electrons (~70 eV, or $\sim 6.7 \times 10^3$ kJ mol^{-1}). This method is called **electron impact (EI)** ionization mass spectrometry. The impact of the electron beam dislodges a valence electron from the gas-phase molecules, leaving them with a +1 charge and an unshared electron. This species is called the **molecular ion** ($M^{+\cdot}$). We can represent this process as follows:

Note the $^{+}_{\cdot}$, representing an unshared electron and the net +1 charge.

$$\underset{\text{Molecule}}{M} + \underset{\text{High-energy electron}}{e^-} \longrightarrow \underset{\text{Molecular ion}}{M^{+\cdot}} + 2\,e^-$$

The molecular ion is a **radical cation** because it contains both an unshared electron and a positive charge. Using propane as an example, we can write the following equation to represent formation of its molecular ion by electron impact ionization:

A radical cation

$$CH_3CH_2CH_3 + e^- \longrightarrow [CH_3CH_2CH_3]^{+\cdot} + 2e^-$$

9.15 DEPICTING THE MOLECULAR ION

Notice that we have written the above formula for the propane radical cation in brackets. This is because we do not know precisely from where the electron was lost in propane. We only know that one valence electron in propane was dislodged by the electron impact process. However, depicting the **molecular ion** with a localized charge and odd electron

is sometimes useful (as we shall discuss in Section 9.16 when considering fragmentation reactions). One possible formula representing the molecular ion from propane with a localized charge and an odd electron is the following:

$$CH_3CH_2^{+}\cdot CH_3$$

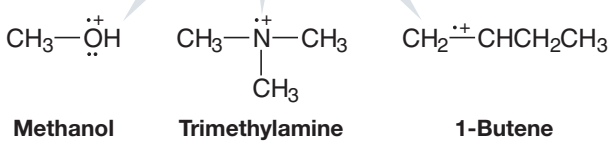
In many cases, the choice of just where to localize the odd electron and charge is arbitrary, however. This is especially true if there are only carbon–carbon and carbon–hydrogen single bonds, as in propane. When possible, though, we write the structure showing the molecular ion that would result from the removal of one of the most loosely held valence electrons of the original molecule. Just which valence electrons are most loosely held can usually be estimated from ionization potentials (Table 9.3). The ionization potential of a molecule is the amount of energy (in electron volts) required to remove a valence electron from the molecule.

As we might expect, ionization potentials indicate that in formation of radical cations the nonbonding electrons of nitrogen, oxygen, and halogen atoms, and the π electrons of alkenes and aromatic molecules, are held more loosely than the electrons of carbon–carbon and carbon–hydrogen σ bonds. Therefore we have the following general rule.

- When a molecule contains oxygen, nitrogen, or a π bond, we place the odd electron and charge at a nitrogen, oxygen, halogen, or π bond. If resonance is possible, the radical cation may be delocalized.

The following are examples of these cases.

Radical cations from ionization of nonbonding or π electrons.



Methanol **Trimethylamine** **1-Butene**

9.16 FRAGMENTATION

Molecular ions formed by EI mass spectrometry are highly energetic species, and in the case of complex molecules, a great many things can happen to them. A molecular ion can break apart in a variety of ways, the fragments that are produced can undergo further **fragmentation**, and so on. We cannot go into all of the processes that are possible, but we can examine a few of the more important ones.

As we begin, let us keep three important principles in mind:

1. The reactions that take place in a mass spectrometer are unimolecular, that is, they do not involve collisions between molecules or ions. This is true because the pressure is kept so low (10^{-6} torr) that reactions involving bimolecular collisions do not occur.
2. We use single-barbed arrows to depict mechanisms involving single electron movements (see Section 3.1A).
3. The relative ion abundances, as indicated by peak intensities, are very important. We shall see that the appearance of certain prominent peaks in the spectrum gives us key information about the structures of the fragments produced and about their original locations in the molecule.

9.16A Fragmentation by Cleavage at a Single Bond

One important type of fragmentation is the simple cleavage of a single bond. With a radical cation this cleavage can take place in at least two ways; each way produces a *cation* and a *radical*. Only the cations are detected in a positive ion mass spectrometer. (The radicals, because they are not charged, are not detected.) With the molecular ion obtained from

TABLE 9.3 IONIZATION POTENTIALS OF SELECTED MOLECULES

Compound	Ionization Potential (eV)
$CH_3(CH_2)_3NH_2$	8.7
C_6H_6 (benzene)	9.2
C_2H_4	10.5
CH_3OH	10.8
C_2H_6	11.5
CH_4	12.7

propane by loss of one carbon–carbon σ bonding electron, for example, two possible modes of cleavage are

$$[CH_3CH_2CH_3]^{+\cdot} \rightarrow CH_3CH_2^+ + \cdot CH_3 \quad \text{or} \quad CH_3CH_2^{\cdot} + {}^+CH_3$$

These two modes of cleavage do not take place at equal rates, however. Although the relative abundance of cations produced by such a cleavage is influenced by the stability of both the carbocation and the radical, the *carbocation's stability is more important.** In the spectrum of propane shown earlier (Fig. 9.35), the peak at *m/z* 29 ($CH_3CH_2^+$) is the most intense peak; the peak at *m/z* 15 (CH_3^+) has a relative abundance of only 5.6%. This reflects the greater stability of $CH_3CH_2^+$ as compared to CH_3^+.

When drawing mechanism arrows to show cleavage reactions it is convenient to choose a localized representation of the radical cation, as we have done above for propane. (When showing only an equation for the cleavage and not a mechanism, however, we would use the convention of brackets around the formula with the odd electron and charge shown outside.) Fragmentation equations for propane would be written in the following way (note the use of single-barbed arrows):

$$CH_3CH_2CH_3 \xrightarrow[-e^-]{} \begin{cases} CH_3CH_2^{+\cdot}CH_3 \longrightarrow CH_3CH_2^+ + \cdot CH_3 \\ \qquad\qquad\qquad\qquad\quad \textbf{m/z 29} \\ \text{or} \\ CH_3CH_2^{+\cdot}CH_3 \longrightarrow CH_3CH_2^{\cdot} + {}^+CH_3 \\ \qquad\qquad\qquad\qquad\quad \textbf{m/z 15} \end{cases}$$

Helpful Hint

Recall that we use single-barbed arrows to show the movement of single electrons, as in the case of these homolytic bond cleavages and other processes involving radicals (see Section 3.1A).

SOLVED PROBLEM 9.6

The mass spectrum of CH_3F is given in Fig. 9.36. **(a)** Draw a likely structure for the molecular ion (*m/z* 34). **(b)** Assign structural formulas to the two other high abundance peaks (*m/z* 33 and *m/z* 15) in the spectrum. **(c)** Propose an explanation for the low abundance of the peak at *m/z* 19.

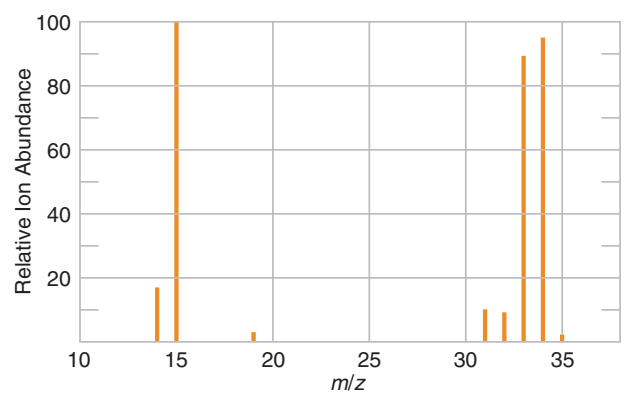


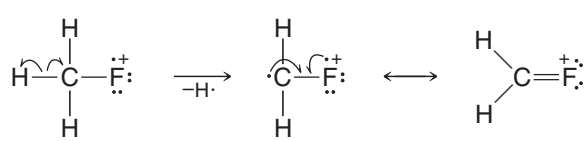
FIGURE 9.36 Mass spectrum for Solved Problem 9.6.

STRATEGY AND ANSWER:

(a) Nonbonding electrons have lower ionization energies than bonding electrons, so we can expect that the molecular ion for CH_3F was formed by loss of an electron from the fluorine atom.

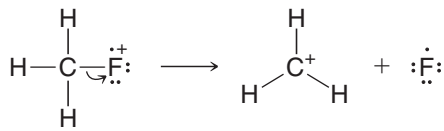
$$e^- + CH_3{-}\ddot{F}: \xrightarrow[\text{(EI)}]{\text{electron impact ionization}} CH_3{-}\ddot{F}:^+ + 2\,e^-$$

(b) The ion with *m/z* 33 differs from the molecular ion by one atomic mass unit, thus a hydrogen atom must have been lost. Cleavage with loss of a hydrogen atom could occur as follows, leaving both the carbon and fluorine with full valence electron shells, but as a cationic species overall.



*This can be demonstrated through thermochemical calculations that we cannot go into here. The interested student is referred to McLafferty, F. W., *Interpretation of Mass Spectra*, 2nd ed.; Benjamin: Reading, MA, 1973; pp. 41, 210–211.

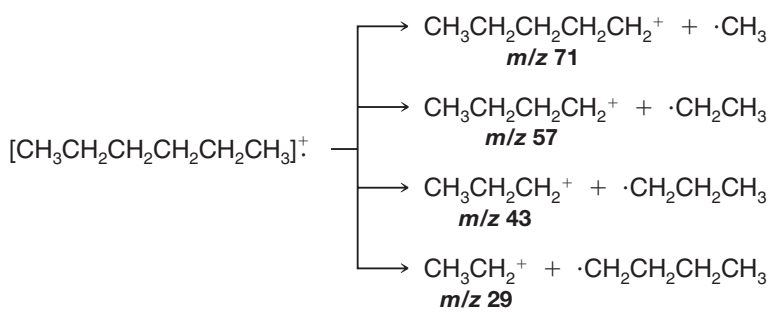
The ion with *m/z* 15 must be a methyl carbocation formed by loss of a fluorine atom, as shown below. The fleeting existence of a methyl carbocation is possible in electron impact ionization (EI) mass spectrometry (MS) because electrons with high kinetic energy bombard the species undergoing analysis, allowing higher energy pathways to be followed than occur with reactions that take place in solution.



(c) The very small *m/z* 19 peak in this spectrum would have to be a fluorine cation. The presence of only 6 valence electrons in an F^+ ion and the strong electronegativity of fluorine would create a very high energy barrier to formation of F^+ and hence, cause it to be formed in very low abundance relative to other ionization and cleavage pathways for CH_3F^+.

9.16B Fragmentation of Longer Chain and Branched Alkanes

The mass spectrum of hexane shown in Fig. 9.37 illustrates the kind of fragmentation that a longer chain alkane can undergo. Here we see a reasonably abundant molecular ion at *m/z* 86 accompanied by a small $M^{+\cdot} + 1$ peak. There is also a smaller peak at *m/z* 71 ($M^{+\cdot} - 15$) corresponding to the loss of $\cdot CH_3$, and the base peak is at *m/z* 57 ($M^{+\cdot} - 29$) corresponding to the loss of $\cdot CH_2CH_3$. The other prominent peaks are at *m/z* 43 ($M^{+\cdot} - 43$) and *m/z* 29 ($M^{+\cdot} - 57$), corresponding to the loss of $\cdot CH_2CH_2CH_3$ and $\cdot CH_2CH_2CH_2CH_3$, respectively. The important fragmentations are just the ones we would expect:



Chain branching increases the likelihood of cleavage at a branch point because a more stable carbocation can result. When we compare the mass spectrum of 2-methylbutane (Fig. 9.38) with the spectrum of hexane, we see a much more intense peak at $M^{+\cdot} - 15$.

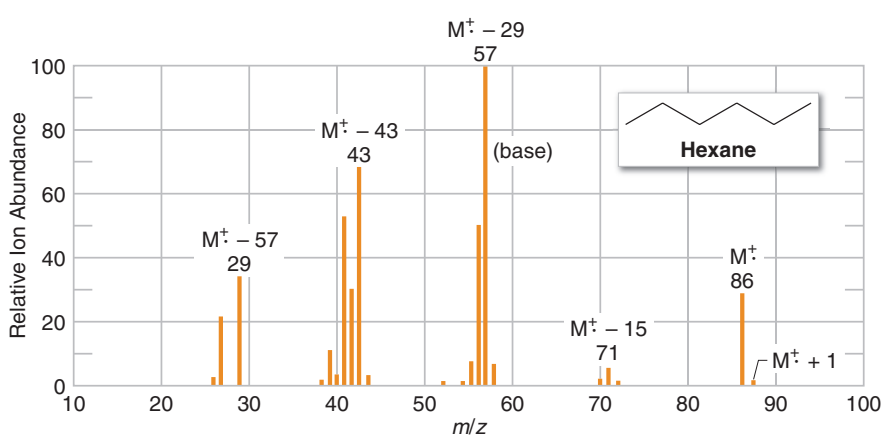


FIGURE 9.37 Mass spectrum of hexane.

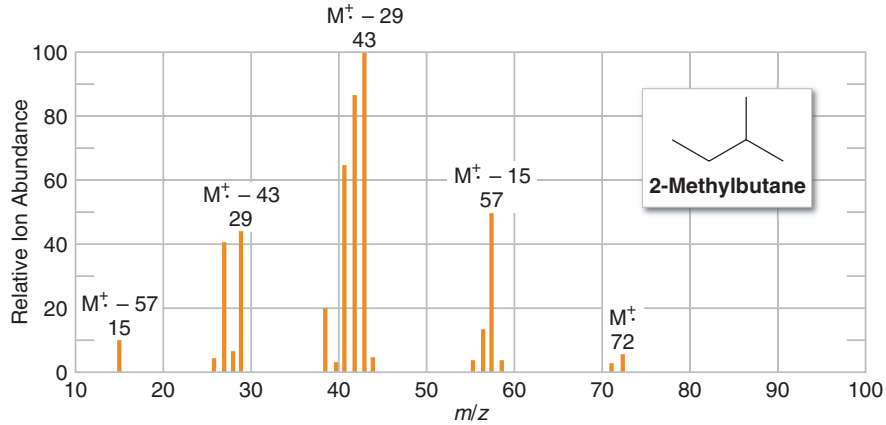
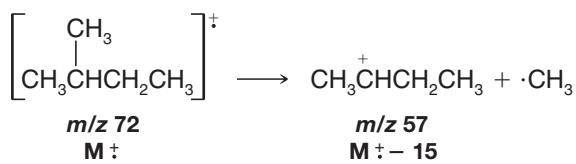


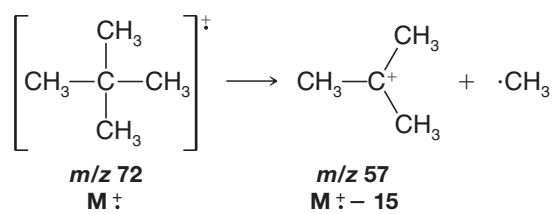
FIGURE 9.38 Mass spectrum of 2-methylbutane.

Loss of a methyl radical from the molecular ion of 2-methylbutane can give a secondary carbocation:



whereas with hexane loss of a methyl radical can yield only a primary carbocation.

With neopentane (Fig. 9.39), this effect is even more dramatic. Loss of a methyl radical by the molecular ion produces a *tertiary* carbocation, and this reaction takes place so readily that virtually none of the molecular ions survive long enough to be detected:



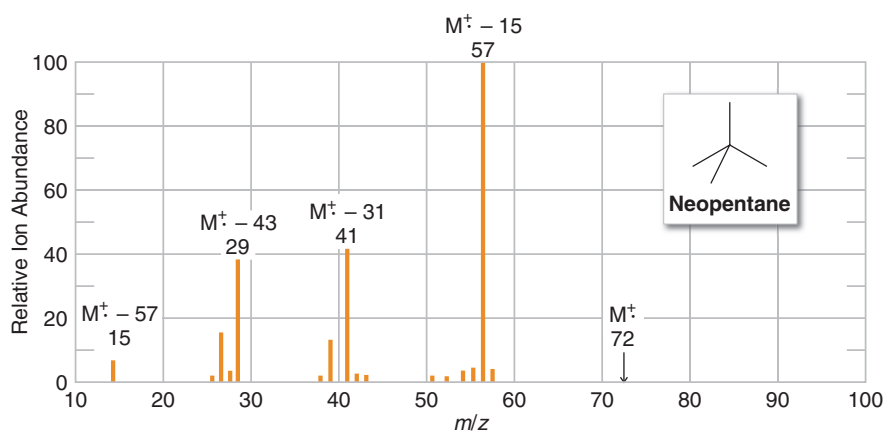


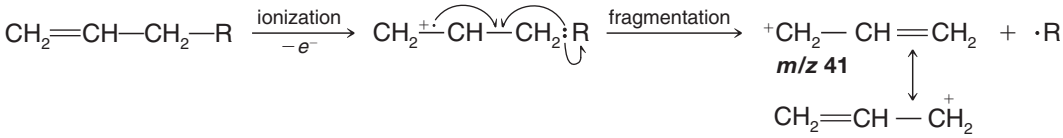
FIGURE 9.39 Mass spectrum of neopentane.

PRACTICE PROBLEM 9.17 In contrast to 2-methylbutane and neopentane, the mass spectrum of 3-methylpentane (not given) has a peak of very low relative abundance at $M^{+\cdot} - 15$. It has a peak of very high relative abundance at $M^{+\cdot} - 29$, however. Explain.

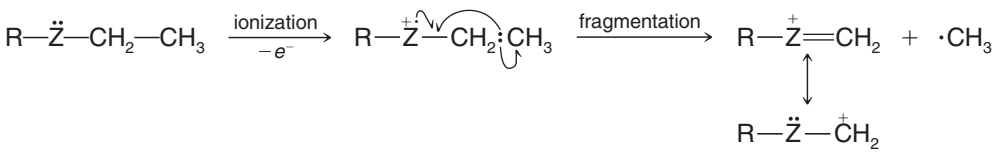
9.16C Fragmentation to Form Resonance-Stabilized Cations

Carbocations stabilized by resonance are usually prominent in mass spectra. Several ways that resonance-stabilized carbocations can be produced are outlined in the following list. These examples begin by illustrating the likely sites for initial ionization (π and nonbonding electrons), as well.

1. Alkenes ionize and frequently undergo fragmentations that yield resonance-stabilized allylic cations:

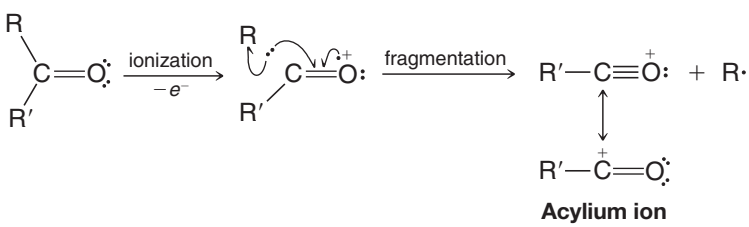


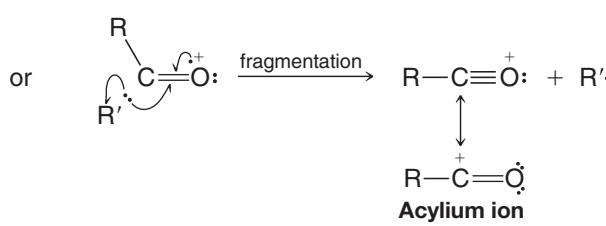
2. Carbon–carbon bonds next to an atom with an unshared electron pair usually break readily because the resulting carbocation is resonance stabilized:



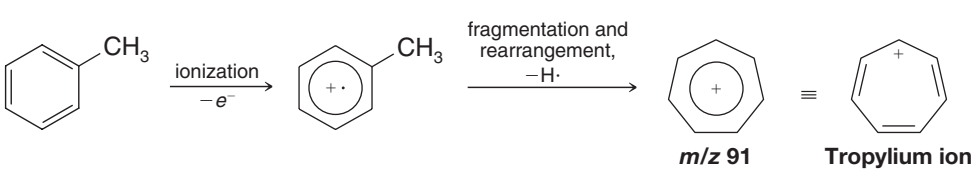
where Z = N, O, or S; R may also be H.

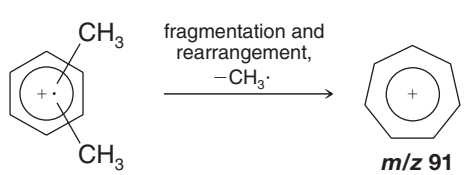
3. Carbon–carbon bonds next to the carbonyl group of an aldehyde or ketone break readily because resonance-stabilized ions called **acylium ions** are produced:





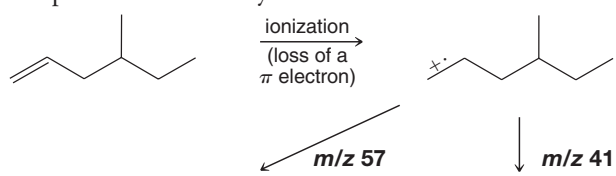
4. Alkyl-substituted benzenes ionize by loss of a π electron and undergo loss of a hydrogen atom or methyl group to yield the relatively stable tropylium ion (see Section 14.7C). This fragmentation gives a prominent peak (sometimes the base peak) at *m*/*z* 91:





5. Monosubstituted benzenes with other than alkyl groups also ionize by loss of a π electron and then lose their substituent to yield a phenyl cation with *m/z* 77:

PRACTICE PROBLEM 9.18 Propose structures and fragmentation mechanisms corresponding to ions with *m/z* 57 and 41 in the mass spectrum of 4-methyl-1-hexene.



SOLVED PROBLEM 9.7

Explain the following observations that can be made about the mass spectra of alcohols:

(a) The molecular ion peak of a primary or secondary alcohol is very small; with a tertiary alcohol it is usually undetectable.

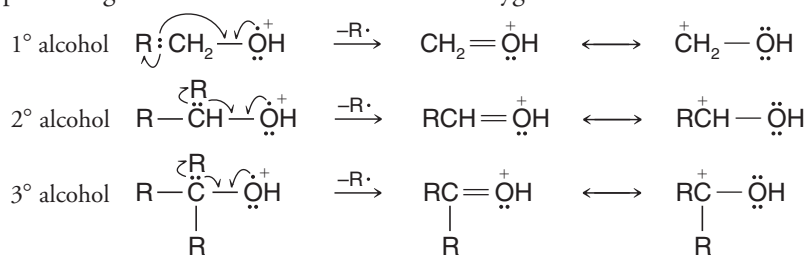
(b) Primary alcohols show a prominent peak at *m/z* 31.

(c) Secondary alcohols usually give prominent peaks at *m/z* 45, 59, 73, and so on.

(d) Tertiary alcohols have prominent peaks at *m/z* 59, 73, 87, and so on.

STRATEGY AND ANSWER:

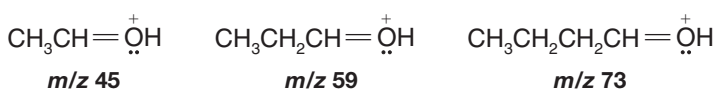
(a) Alcohols undergo rapid cleavage of a carbon–carbon bond next to oxygen because this leads to a resonance-stabilized cation.



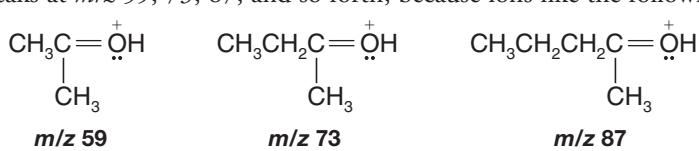
The cation obtained from a tertiary alcohol is the most stable (because of the electron-releasing R groups).

(b) Primary alcohols give a peak at *m/z* 31 due to $CH_2{=}\overset{+}{O}H$.

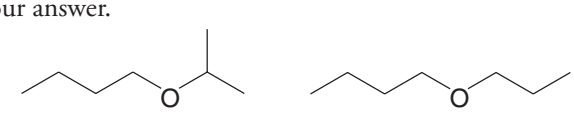
(c) Secondary alcohols give peaks at *m/z* 45, 59, 73, and so forth, because ions like the following are produced.



(d) Tertiary alcohols give peaks at *m/z* 59, 73, 87, and so forth, because ions like the following are produced.



PRACTICE PROBLEM 9.19 Match the mass spectra in Figs. 9.40 and 9.41 to the corresponding compounds shown below. Explain your answer.



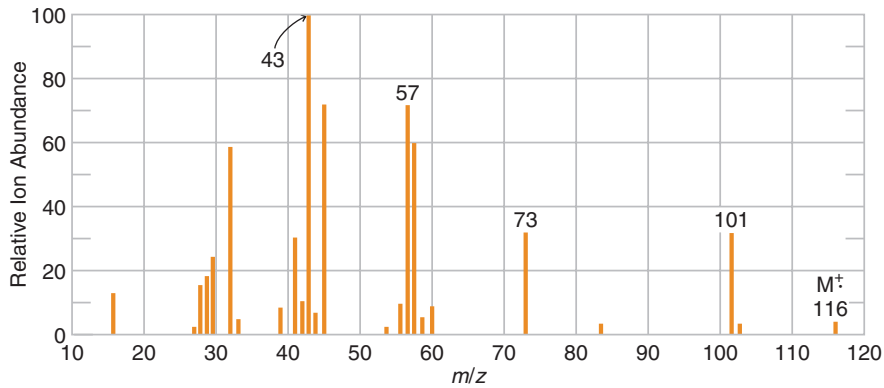


FIGURE 9.40 Mass spectrum for Practice Problem 9.19.

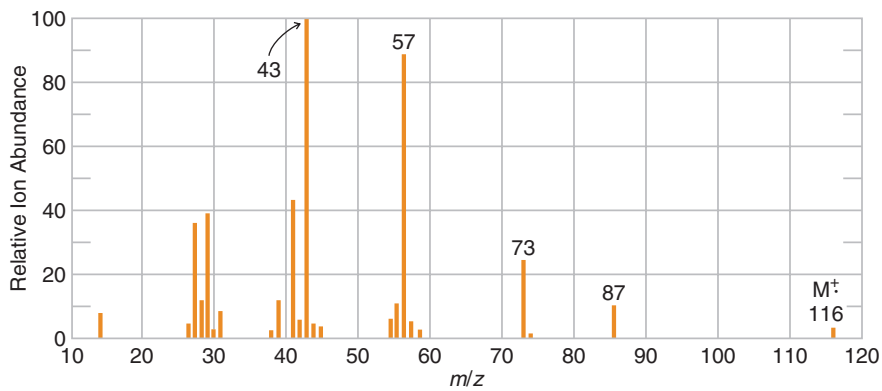
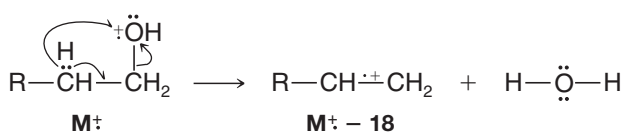


FIGURE 9.41 Mass spectrum for Practice Problem 9.19.

9.16D Fragmentation by Cleavage of Two Bonds

Many peaks in mass spectra can be explained by fragmentation reactions that involve the breaking of two covalent bonds. When a radical cation undergoes this type of fragmentation, the products are *a new radical cation* and *a neutral molecule*. Some important examples, starting from the initial radical cation, are the following:

1. Alcohols frequently show a prominent peak at $M^{+\cdot} - 18$. This corresponds to the loss of a molecule of water (See Solved Problem 9.7):

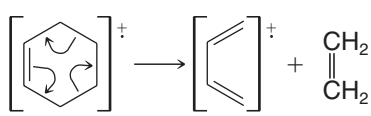


which can also be written as

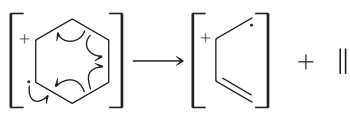
$$[R{-}CH_2{-}CH_2{-}OH]^{+\cdot} \longrightarrow [R{-}CH{=}CH_2]^{+\cdot} + H_2O$$

$M^{+\cdot}$ $\qquad$ $M^{+\cdot} - 18$

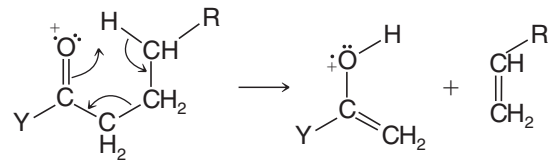
2. Cycloalkenes can undergo a retro-Diels–Alder reaction (Section 13.11) that produces an alkene and an alkadienyl radical cation:



which can also be written as



3. Carbonyl compounds with a hydrogen on their γ carbon undergo a fragmentation called the *McLafferty rearrangement*.



where Y = R, H, OR, OH, and so on.

In addition to these reactions, we frequently find peaks in mass spectra that result from the elimination of other small stable neutral molecules, for example, H_2, NH_3, CO, HCN, H_2S, alcohols, and alkenes.

9.17 ISOTOPES IN MASS SPECTRA

All naturally occurring molecules contain isotopic forms of the atoms that comprise them. The proportion of each isotope is determined by its natural abundance (see Table 9.4 for some common examples). The peaks in a mass spectrum will show the presence of isotopes in a given sample.

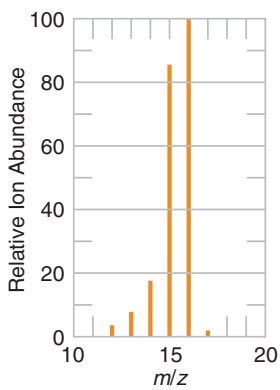


FIGURE 9.42 Mass spectrum for methane.

^{13}C and ^{12}C About 1.1% of all carbon atoms are the ^{13}C isotope. This means that in the mass spectrum of methane, for example, where the formula weight for most methane molecules is 16 atomic mass units, there would also be a small peak at *m/z* 17 next to the peak at *m/z* 16. About 98.9% of the methane molecules in the sample will contain ^{12}C, and the other 1.1% will contain ^{13}C. Figure 9.42 shows the mass spectrum for a sample of methane, in which a small *m/z* 17 peak can be seen for the $M^{+\cdot} + 1$ ion.

For molecules with more than one carbon, the intensity of the $M^{+\cdot} + 1$ peak taken in proportion to the $M^{+\cdot}$ peak can be used as an approximation of the number of carbon atoms in the molecule. This is because there is a 1.1% chance that each carbon in the molecule could be a ^{13}C isotope. However, in large molecules the $(M^{+\cdot} + 1)/M^{+\cdot}$ ratio is altered by the existence of other isotopes with a nominal mass one unit larger than their most abundant form, such as for ^{2}H, ^{17}O, and so on. Therefore, for large molecules the $(M^{+\cdot} + 1)/M^{+\cdot}$ ratio cannot be used reliably as an indication of the number of carbons.

^{35}Cl and ^{37}Cl; ^{79}Br and ^{81}Br Some elements that are common in organic molecules have isotopes that differ by two atomic mass units. These include ^{16}O and ^{18}O, ^{32}S and ^{34}S, ^{35}Cl and

TABLE 9.4 PRINCIPAL STABLE ISOTOPES OF COMMON ELEMENTS[a]

Element	Most Common Isotope	%	Natural Abundance of Other Isotopes	%		%
Carbon	^{12}C	98.93	^{13}C	1.07		
Hydrogen	^{1}H	99.99	^{2}H	0.011		
Nitrogen	^{14}N	99.63	^{15}N	0.368		
Oxygen	^{16}O	99.76	^{17}O	0.038	^{18}O	0.205
Fluorine	^{19}F	100				
Silicon	^{28}Si	92.23	^{29}Si	4.68	^{30}Si	3.09
Phosphorus	^{31}P	100				
Sulfur	^{32}S	94.93	^{33}S	0.76	^{34}S	4.29
Chlorine	^{35}Cl	75.78	^{37}Cl	24.22		
Bromine	^{79}Br	50.69	^{81}Br	49.31		
Iodine	^{127}I	100				

[a]Data based on the 1997 Technical Report of the International Union of Pure and Applied Chemistry (IUPAC), Rosman, K. J. R., Taylor, P. D. P. *Pure and Applied Chemistry*, **1998**, Vol. 70, No. 1, 217–235.

^{37}Cl, and ^{79}Br and ^{81}Br. It is particularly easy to identify the presence of chlorine or bromine using mass spectrometry because the isotopes of chlorine and bromine are relatively abundant.

- The natural abundance of ^{35}Cl is 75.5% and that of ^{37}Cl is 24.5%.
- In the mass spectrum for a sample containing chlorine, we would expect to find peaks separated by two mass units, in an approximately 3 : 1 (75.5% : 24.5%) ratio for the **molecular ion** or any fragments that contain chlorine.

Figure 9.43*a* shows the mass spectrum of chlorobenzene. The peaks at *m/z* 112 and *m/z* 114 in approximately a 3 : 1 intensity ratio are a clear indication that chlorine atoms are present. An *m/z* 77 peak for the phenyl cation fragment is evident, as well.

- The natural abundance of ^{79}Br is 51.5%, and that of ^{81}Br is 49.5%.
- In the mass spectrum for a sample containing bromine we would expect to find peaks separated by two mass units in an approximately 1 : 1 ratio (49.5% : 51.5%).

Figure 9.43*b* shows the mass spectrum of bromomethylbenzene. The peaks at *m/z* 170 and *m/z* 172 in an approximately 1 : 1 intensity ratio are a clear indication that bromine is present. Note that the base peak is *m/z* 91, most likely representing a tropylium cation (Section 9.16C).

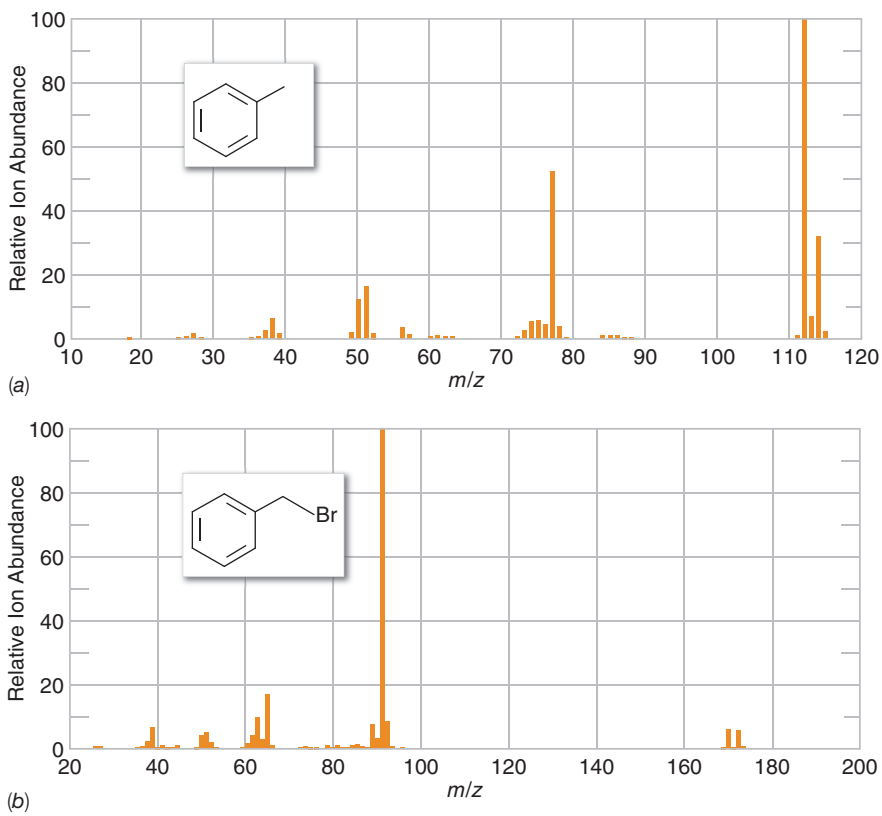


FIGURE 9.43 (*a*) The mass spectrum of chlorobenzene. Note the approximately 3 : 1 intensity ratio of peaks at *m/z* 112 and 114 due to the presence of ^{35}Cl and ^{37}Cl. (*b*) The mass spectrum of bromomethylbenzene. Note the 1 : 1 intensity ratio of peaks at *m/z* 170 and 172 due to the presence of ^{79}Br and ^{81}Br. (a,b: P. J. Linstrom and W. G. Mallard, Eds., NIST Chemistry WebBook, NIST Standard Reference Database Number 69, National Institute of Standards and Technology, Gaithersburg, MD 20899, http://webbook.nist.gov.)

If two bromine or chlorine atoms are present in a molecule, then an $M^{+\cdot} + 4$ peak will appear in addition to the $M^{+\cdot} + 2$ and $M^{+\cdot}$ peaks. In a molecule containing two bromine atoms, for example, the intensity of the $M^{+\cdot} + 4$ peak due to two ^{81}Br atoms present in one molecule is the same as the $M^{+\cdot}$ peak for two ^{79}Br atoms in one molecule. But the probability of having one ^{79}Br and one ^{81}Br is double when two bromines are present (because either bromine atom could be either isotope). Thus, the ratio of intensities for the $M^{+\cdot}$, $M^{+\cdot} + 2$, and $M^{+\cdot} + 4$ peaks will be 1 : 2 : 1 when two bromine atoms are present.

SOLVED PROBLEM 9.8

(a) What approximate intensities would you expect for the $M^{+\cdot}$ and $M^{+\cdot} + 2$ peaks of CH_3Cl?

(b) For the $M^{+\cdot}$ and $M^{+\cdot} + 2$ peaks of CH_3Br?

(c) An organic compound gives an $M^{+\cdot}$ peak at *m/z* 122 and a peak of nearly equal intensity at *m/z* 124. What is a likely molecular formula for the compound?

STRATEGY AND ANSWER:

(a) The $M^{+\cdot}$ + 2 peak due to $CH_3—{}^{37}Cl$ (at *m/z* 52) should be almost one-third as large as the $M^{+\cdot}$ peak at *m/z* 50 because of the relative natural abundances of ^{35}Cl and ^{37}Cl.

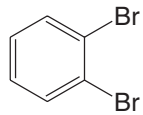
(b) The peaks due to $CH_3—{}^{79}Br$ and $CH_3—{}^{81}Br$ (at *m/z* 94 and *m/z* 96, respectively) should be of nearly equal intensity due to the relative natural abundances of ^{79}Br and ^{81}Br.

(c) That the $M^{+\cdot}$ and $M^{+\cdot}$ + 2 peaks are of nearly equal intensity tells us that the compound contains bromine. C_3H_7Br is therefore a likely molecular formula.

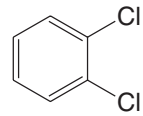
C_3 =	36	C_3 =	36
H_7 =	7	H_7 =	7
^{79}Br =	79	^{81}Br =	81
m/z =	122	*m/z* =	124

PRACTICE PROBLEM 9.20 What are the expected ratios of the $M^{+\cdot}$, $M^{+\cdot}$ + 2, and $M^{+\cdot}$ + 4 peaks for the following compounds?

(a)



(b)



PRACTICE PROBLEM 9.21 Given the mass spectrum in Figure 9.44 and the fact that the ^1H NMR spectrum for this compound consists of only a large doublet and a small septet, what is the structure of the compound? Explain your reasoning.

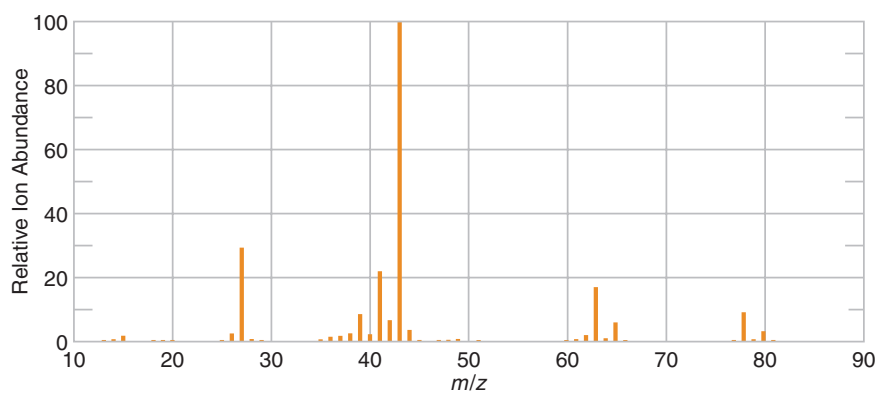


FIGURE 9.44 Mass spectrum for Practice Problem 9.21. P. J. Linstrom and W. G. Mallard, Eds., NIST Chemistry WebBook, NIST Standard Reference Database Number 69, National Institute of Standards and Technology, Gaithersburg, MD 20899, http://webbook.nist.gov.

9.17A High-Resolution Mass Spectrometry

All of the spectra that we have described so far have been determined on what are called "low-resolution" mass spectrometers. These spectrometers, as we noted earlier, measure *m/z* values to the nearest whole-number mass unit. Many laboratories are equipped with this type of mass spectrometer.

Some laboratories, however, are equipped with the more expensive "high-resolution" mass spectrometers. These spectrometers can measure *m/z* values to three or four decimal places and thus provide an extremely accurate method for determining molecular weights. And because molecular weights can be measured so accurately, these spectrometers also allow us to determine molecular formulas.

The determination of a molecular formula by an accurate measurement of a molecular weight is possible because the actual masses of atomic particles (nuclides) are not integers (see Table 9.5). Consider, as examples, the three molecules O_2, N_2H_4, and CH_3OH.

The actual atomic masses of the molecules are all different (though nominally they all have atomic mass of 32):

$$O_2 = 2(15.9949) = 31.9898$$
$$N_2H_4 = 2(14.0031) + 4(1.00783) = 32.0375$$
$$CH_4O = 12.00000 + 4(1.00783) + 15.9949 = 32.0262$$

High-resolution mass spectrometers are capable of measuring mass with an accuracy of 1 part in 40,000 or better. Thus, such a spectrometer can easily distinguish among these three molecules and, in effect, tell us the molecular formula.

The ability of high-resolution instruments to measure exact masses has been put to great use in the analysis of biomolecules such as proteins and nucleic acids. For example, one method that has been used to determine the amino acid sequence in oligopeptides is to measure the exact mass of fragments derived from an original oligopeptide, where the mixture of fragments includes oligopeptides differing in length by one amino acid residue. The exact mass difference between each fragment uniquely indicates the amino acid residue that occupies that position in the intact oligopeptide (see Section 24.5E). Another application of exact mass determinations is the identification of peptides in mixtures by comparison of mass spectral data with a database of exact masses for known peptides. This technique has become increasingly important in the field of proteomics (Section 24.14).

TABLE 9.5 EXACT MASSES OF NUCLIDES

Isotope	Mass
^{1}H	1.00783
^{2}H	2.01410
^{12}C	12.00000 (std)
^{13}C	13.00336
^{14}N	14.0031
^{15}N	15.0001
^{16}O	15.9949
^{17}O	16.9991
^{18}O	17.9992
^{19}F	18.9984
^{32}S	31.9721
^{33}S	32.9715
^{34}S	33.9679
^{35}Cl	34.9689
^{37}Cl	36.9659
^{79}Br	78.9183
^{81}Br	80.9163
^{127}I	126.9045

9.18 GC/MS ANALYSIS

Gas chromatography is often coupled with mass spectrometry in a technique called **GC/MS analysis**. The gas chromatograph separates components of a mixture, while the mass spectrometer then gives structural information about each one (Fig. 9.45). GC/MS can also provide quantitative data when standards of known concentration are used with the unknown.

In GC analysis, a minute amount of a mixture to be analyzed, typically 0.001 mL (1.0 μL) or less of a dilute solution containing the sample, is injected by syringe into a heated port of the gas chromatograph. The sample is vaporized in the injector port and swept by a flow of helium into a capillary column. The capillary column is a thin tube usually 10–30 meters long and 0.1–0.5 mm in diameter. It is contained in a chamber (the "oven") whose temperature can be varied according to the volatility of the samples being analyzed. The inside of the capillary column is typically coated with a "stationary phase" of low polarity (essentially a high-boiling and very viscous liquid that is often a nonpolar silicon-based polymer). As molecules of the mixture are swept through the column by the helium, they travel at different rates according to their boiling points and the degree of affinity for the stationary phase. Materials with higher boiling points or stronger affinity for the stationary phase take longer to pass through the column. Low-boiling and nonpolar materials pass through very quickly. The length of time each component takes to travel through the column is called the retention time. Retention times typically range from 1 to about 30 minutes, depending on the sample and the specific type of column used.

As each component of the mixture exits the GC column it travels into a mass spectrometer. Here, molecules of the sample are bombarded by electrons; ions and fragments of the molecule are formed, and a mass spectrum results similar to those we have studied earlier in this chapter. The important thing, however, is that mass spectra are obtained for *each* component of the original mixture that is separated. This ability of GC/MS to separate mixtures and give information about the structure of each component makes it a virtually indispensable tool in analytical, forensic, and organic synthesis laboratories.

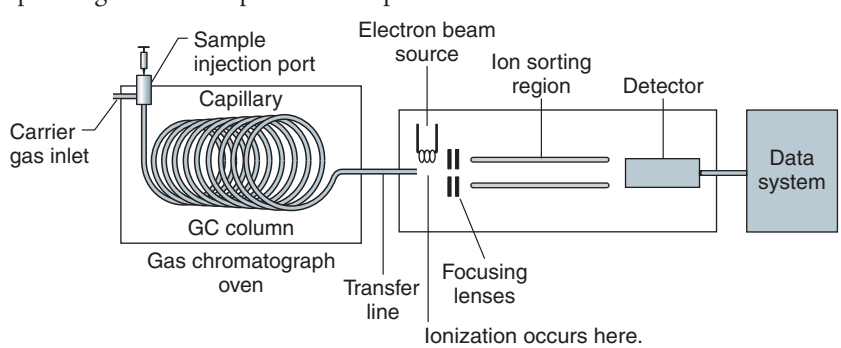


FIGURE 9.45 Schematic of a typical capillary gas chromatograph/mass spectrometer (GC/MS).

9.19 MASS SPECTROMETRY OF BIOMOLECULES

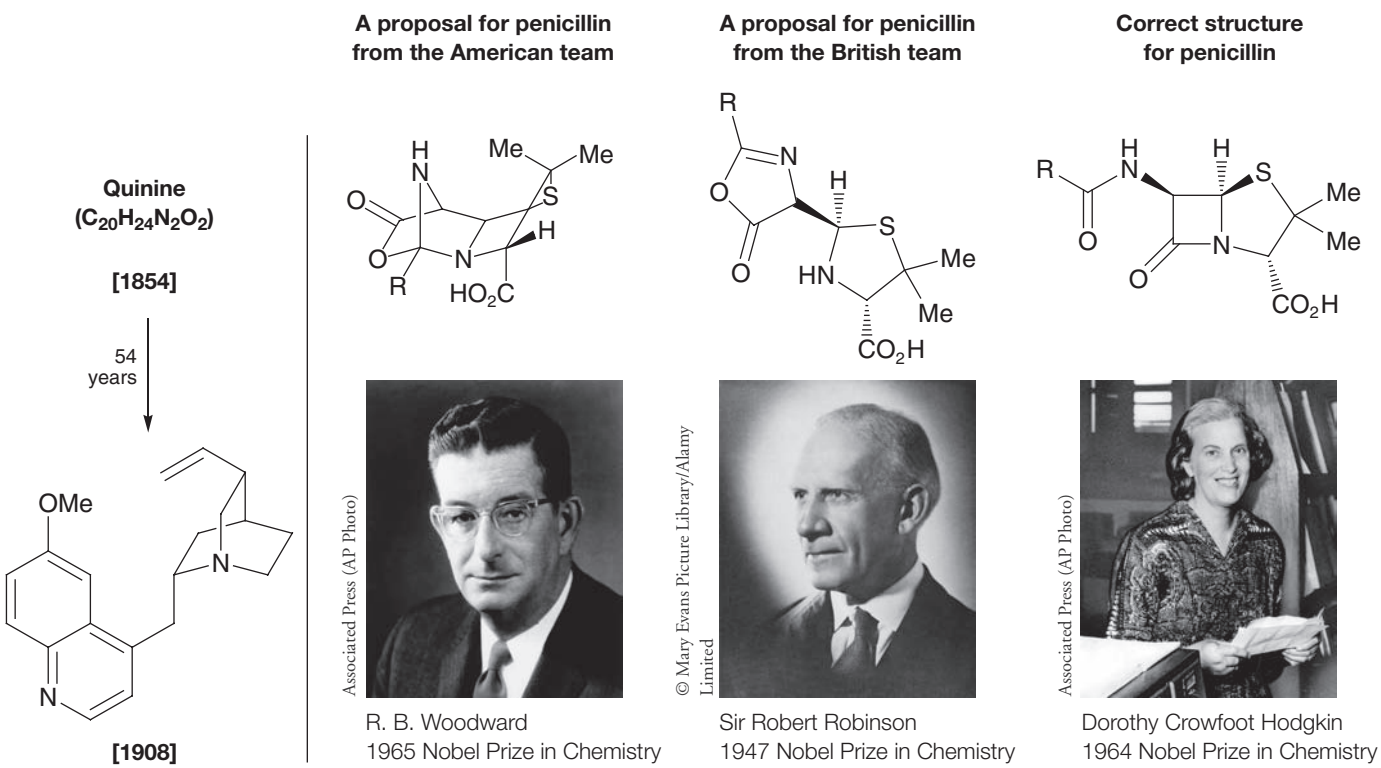
Advances in mass spectrometry have made it a tool of exceptional power for analysis of large biomolecules. **Electrospray ionization**, **MALDI (matrix-assisted laser desorption ionization)**, and other "soft ionization" techniques for nonvolatile compounds and macromolecules make possible analyses of proteins, nucleic acids, and other biologically relevant compounds with molecular weights up to and in excess of 100,000 daltons. Electrospray ionization with quadrupole mass analysis is now routine for biomolecule analysis, as is analysis using MALDI–TOF (time of flight) instruments. Extremely high resolution can be achieved using Fourier transform–ion cyclotron resonance (FT ICR, or FTMS). We shall discuss ESI and MALDI applications of mass spectrometry to protein sequencing and analysis in Sections 24.5E, 24.13B, and 24.14.

WHY Do These Topics Matter?]

STRUCTURE DETERMINATION WITHOUT NMR

With the advent of the techniques you have learned about in this chapter, chemists can determine the complete structures of most organic molecules with only a few milligrams of material and in a relatively short time. However, prior to the introduction of spectroscopy in the late 1950s and 1960s, it was a much different story. In that era, chemists needed grams of a compound and, in some cases, decades of time to determine a compound's structure.

Without spectroscopy, structure determination began with combustion analysis, a method that could be used to determine the molecular formula of the sample by literally burning it and measuring the relative amounts of the combustion products, such as water and carbon dioxide. Then, through painstaking detective work, chemists would perform different chemical reactions to degrade the compound into smaller components. They would then attempt to rebuild those materials into the original compound to determine how those atoms were combined. With unusual or particularly complex compounds, structural determination could be a very slow process; for example, establishing the connectivities of the atoms of quinine, the world's first antimalarial drug, took 54 years.



R. B. Woodward
1965 Nobel Prize in Chemistry

Sir Robert Robinson
1947 Nobel Prize in Chemistry

Dorothy Crowfoot Hodgkin
1964 Nobel Prize in Chemistry

Another example of a structure determination that was particularly difficult, and costly, involved the antibiotic penicillin, first isolated in 1928 by Sir Alexander Fleming. Shortly after it was discovered, scientists knew that this molecule would have tremendous value in combating infections that were previously viewed as untreatable. The challenge was obtaining sufficient supplies to treat everyone who needed it, an issue that became particularly salient during World War II when tens of thousands of soldiers suffered wounds. In response, the American and British governments began an extensive project involving hundreds of scientists on both sides of the Atlantic seeking to make penicillin in the laboratory through organic synthesis. The problem was that the structure of penicillin had not been established, and the American and

British teams, each of which included a future Nobel laureate, generally had different, and incorrect, theories for its connections. As a result, no real quantities of penicillin were synthesized during the war, with fermentation from mold being the main supply for those in need.

Ultimately, it would take a different future Nobel laureate and a different technique to solve the problem—namely, Dorothy Crowfoot Hodgkin and X-ray crystallography. In this method, if a material can be solidified into a regular crystalline form, light can be shone on it, and based on the resultant diffraction pattern due to interactions of the light with the atoms in the crystal, the connections of every non-hydrogen atom can be determined. With X-ray crystallography, penicillin was shown to possess a four-membered ring, a motif not expected to exist because of strain, as we have discussed previously. That ring, in fact, would be a major challenge for its eventual chemical synthesis as we will discuss in Chapter 17, and the problem would take another decade to solve once the structure of penicillin was established.

To learn more about these topics, see:

1. Sheehan, J. C. *The Enchanted Ring: The Untold Story of Penicillin*. MIT Press: Cambridge, **1984**, p. 224.
2. Nicolaou, K. C.; Montagnon, T. *Molecules that Changed the World*. Wiley-VCH: Weinheim, **2008**, p. 366.

SUMMARY AND REVIEW TOOLS

The study aids for this chapter include key terms and concepts (which are hyperlinked to the Glossary from the bold, blue terms in the *WileyPLUS* version of the book at wileyplus.com), a Concept Map, and NMR chemical shift correlation charts.

PROBLEMS

Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

NMR SPECTROSCOPY

The following are some abbreviations used to report spectroscopic data:

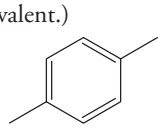
^{1}H NMR: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet

IR absorptions: s = strong, m = moderate, br = broad

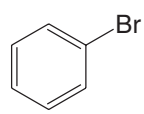
9.22 How many ^{1}H NMR signals (not peaks) would you predict for each of the following compounds? (Consider all protons that would be chemical shift nonequivalent.)

(a)

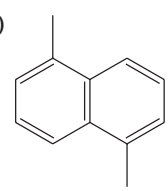
(c)



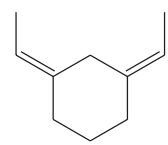
(e)



(g)

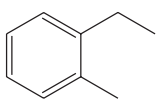


(i)

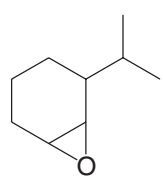


(b)

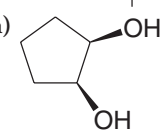
(d)



(f)



(h)



9.23 How many ^{13}C NMR signals would you predict for each of the compounds shown in Problem 9.22?

9.24 Propose a structure for an alcohol with molecular formula $C_5H_{12}O$ that has the ^{1}H NMR spectrum given in Fig. 9.46. Assign the chemical shifts and splitting patterns to specific aspects of the structure you propose.

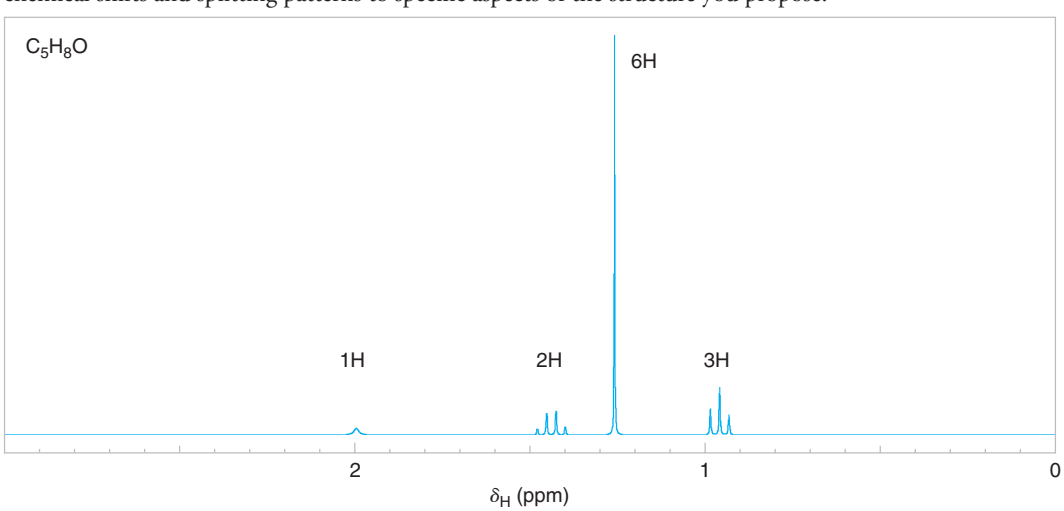


FIGURE 9.46 The ^{1}H NMR spectrum (simulated) of alcohol C_5H_8O, Problem 9.24.

9.25 Propose structures for the compounds **G** and **H** whose ^{1}H NMR spectra are shown in Figs. 9.47 and 9.48.

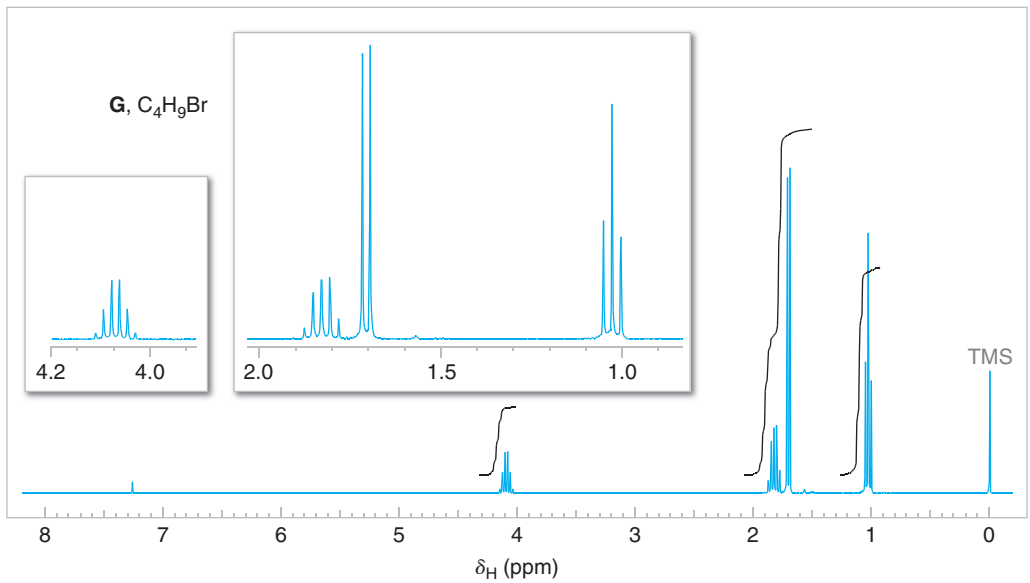


FIGURE 9.47 The 300-MHz ^{1}H NMR spectrum of compound **G**, Problem 9.25. Expansions of the signals are shown in the offset plots.

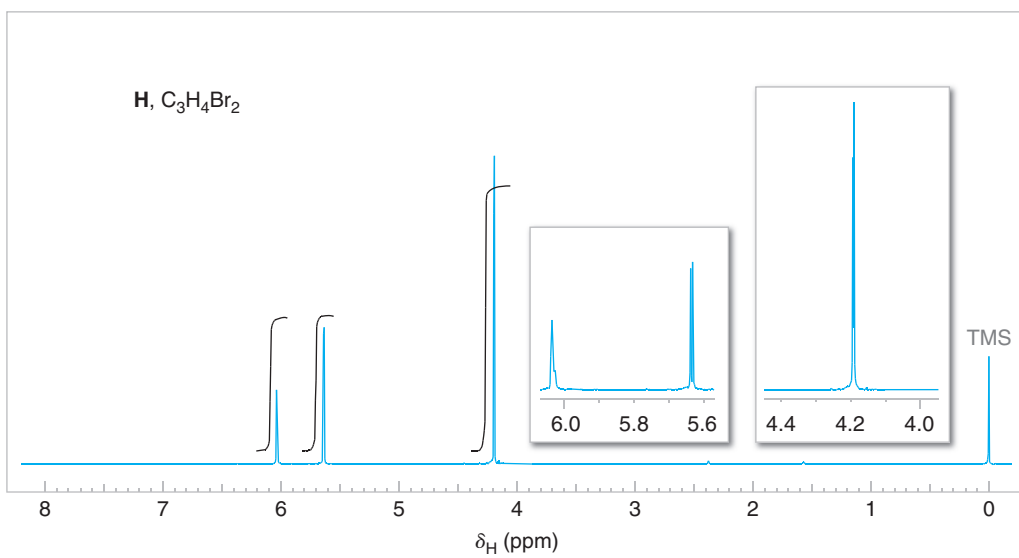


FIGURE 9.48 The 300-MHz ^{1}H NMR spectrum of compound **H**, Problem 9.25. Expansions of the signals are shown in the offset plots.

9.26 Assume that in a certain ^{1}H NMR spectrum you find two peaks of roughly equal intensity. You are not certain whether these two peaks are *singlets* arising from uncoupled protons at different chemical shifts or are two peaks of a *doublet* that arises from protons coupling with a single adjacent proton. What simple experiment would you perform to distinguish between these two possibilities?

9.27 Propose structures for compounds **O** and **P** that are consistent with the following information.

$$\underset{\textbf{O}}{C_6H_8} \xrightarrow[Pt]{H_2\ (2\ equiv.)} \underset{\textbf{P}}{C_6H_{12}}$$

^{13}C NMR for Compound O

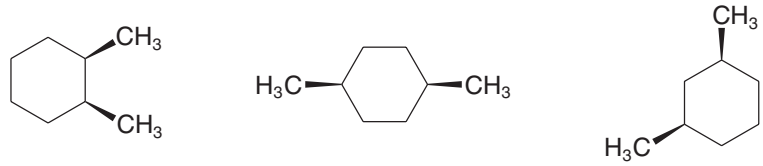
δ (ppm)	DEPT
26.0	CH_2
124.5	CH

9.28 Compound **Q** has the molecular formula C_7H_8. The broad-band proton decoupled ^{13}C spectrum of **Q** has signals at δ 50 (CH), 85 (CH_2), and 144 (CH). On catalytic hydrogenation **Q** is converted to **R** (C_7H_{12}). Propose structures for **Q** and **R**.

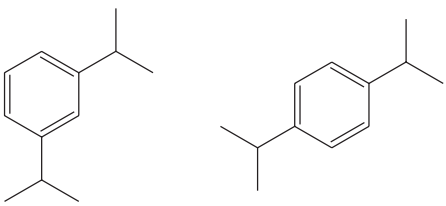
9.29 Explain in detail how you would distinguish between the following sets of compounds using the indicated method of spectroscopy.

(a) ^1H NMR

(c) ^{13}C NMR



(b) ^{13}C and ^1H NMR



9.30 Compound **S** (C_8H_{16}) reacts with one mole of bromine to form a compound with molecular formula $C_8H_{16}Br_2$. The broadband proton-decoupled ^{13}C spectrum of **S** is given in Fig. 9.49. Propose a structure for **S**.

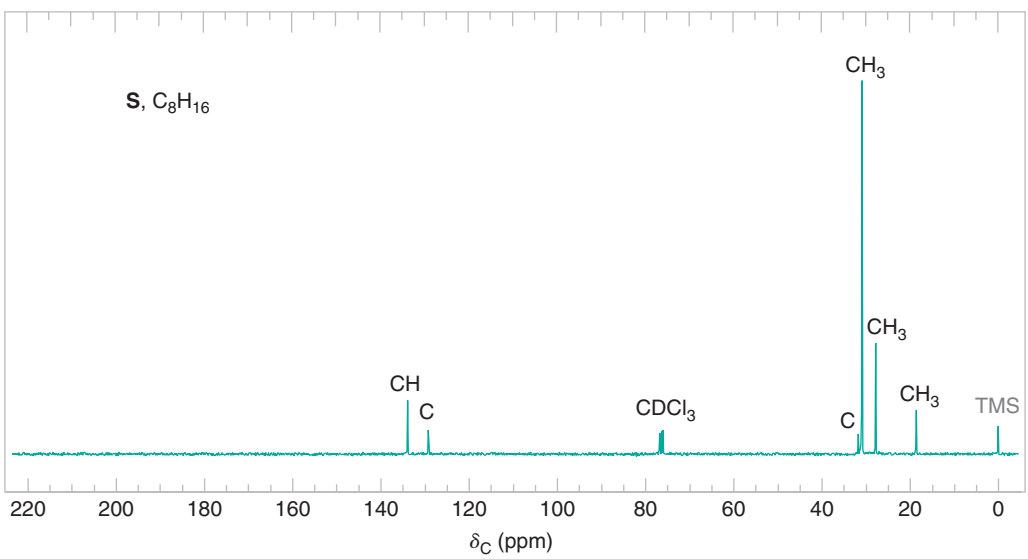


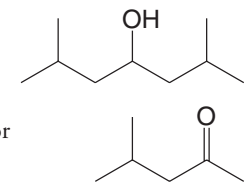
FIGURE 9.49 The broadband proton-decoupled ^{13}C NMR spectrum of compound **S**, Problem 9.30. Information from the DEPT ^{13}C NMR spectra is given above each peak.

MASS SPECTROMETRY

9.31 A compound with molecular formula C_4H_8O has a strong IR absorption at 1730 cm^{-1}. Its mass spectrum includes key peaks at *m/z* 44 (the base peak) and *m/z* 29. Propose a structure for the compound and write fragmentation equations showing how peaks having these *m/z* values arise.

9.32 In the mass spectrum of 2,6-dimethyl-4-heptanol there are prominent peaks at *m/z* 87, 111, and 126. Propose reasonable structures for these fragment ions.

9.33 In the mass spectrum of 4-methyl-2-pentanone a McLafferty rearrangement and two other major fragmentation pathways occur. Propose reasonable structures for these fragment ions and specify the *m/z* value for each.



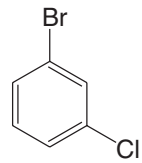
9.34 What are the masses and structures of the ions produced in the following cleavage pathways?

(a) α-cleavage of 2-methyl-3-hexanone (two pathways)

(b) dehydration of cyclopentanol

(c) McLafferty rearrangement of 4-methyl-2-octanone (two pathways)

9.35 Predict the masses and relative intensities of the peaks in the molecular ion region for the following compound.



9.36 Ethyl bromide and methoxybenzene (shown below) have the same nominal molecular weights, displaying a significant peak at *m/z* 108. Regarding their molecular ions, what other features would allow the two compounds to be distinguished on the basis of their mass spectra?

9.37 The homologous series of primary amines, $CH_3(CH_2)_nNH_2$, from CH_3NH_2 to $CH_3(CH_2)_{13}NH_2$ all have their base (largest) peak at *m/z* 30. What ion does this peak represent, and how is it formed?

INTEGRATED STRUCTURE ELUCIDATION

9.38 Propose a structure that is consistent with each set of ^{1}H **NMR** data. **IR** data is provided for some compounds.

(a) $C_4H_{10}O$

δ (ppm)	**Splitting**	**Integration**
1.28	s	9H
1.35	s	1H

(b) C_3H_7Br

δ (ppm)	**Splitting**	**Integration**
1.71	d	6H
4.32	septet	1H

(c) C_4H_8O

δ (ppm)	**Splitting**	**Integration**	**IR**
1.05	t	3H	1720 cm^{-1} (strong)
2.13	s	3H	
2.47	q	2H	

(d) C_7H_8O

δ (ppm)	**Splitting**	**Integration**	**IR**
2.43	s	1H	3200–3550 cm^{-1} (broad)
4.58	s	2H	
7.28	m	5H	

(e) C_4H_9Cl

δ (ppm)	**Splitting**	**Integration**
1.04	d	6H
1.95	m	1H
3.35	d	2H

(f) $C_{15}H_{14}O$

δ (ppm)	**Splitting**	**Integration**	**IR**
2.20	s	3H	1720 cm^{-1} (strong)
5.08	s	1H	
7.25	m	10H	

(g) $C_4H_7BrO_2$

δ (ppm)	**Splitting**	**Integration**	**IR**
1.08	t	3H	2500–3500 cm^{-1} (broad)
2.07	m	2H	1715 cm^{-1} (strong)
4.23	t	1H	
10.97	s	1H	

(h) C_8H_{10}

δ (ppm)	**Splitting**	**Integration**
1.25	t	3H
2.68	q	2H
7.23	m	5H

(i) $C_4H_8O_3$

δ (ppm)	**Splitting**	**Integration**	**IR**
1.27	t	3H	2500–3550 cm^{-1} (broad)
3.66	q	2H	1715 cm^{-1} (strong)
4.13	s	2H	
10.95	s	1H	

(j) $C_3H_7NO_2$

δ (ppm)	Splitting	Integration
1.55	d	6H
4.67	septet	1H

(k) $C_4H_{10}O_2$

δ (ppm)	Splitting	Integration
3.25	s	6H
3.45	s	4H

(l) $C_5H_{10}O$

δ (ppm)	Splitting	Integration	IR
1.10	d	6H	1720 cm^{-1} (strong)
2.10	s	3H	
2.50	septet	1H	

(m) C_8H_9Br

δ (ppm)	Splitting	Integration
2.0	d	3H
5.15	q	1H
7.35	m	5H

9.39 Propose structures for compounds **E** and **F**. Compound **E** (C_8H_6) reacts with 2 molar equivalents of bromine to form **F** ($C_8H_6Br_4$). **E** has the IR spectrum shown in Fig. 9.50. What are the structures of **E** and **F**?

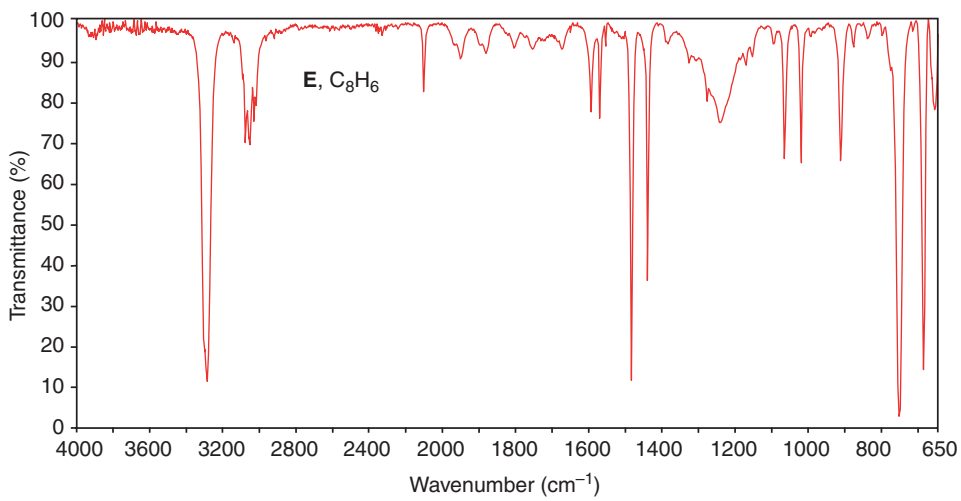


FIGURE 9.50 The IR spectrum of compound **E**, Problem 9.39.

9.40 Regarding compound **J**, $C_2H_xCl_y$, use the ^1H NMR and IR data below to propose a stereochemical formula that is consistent with the data.

	δ (ppm)	Splitting	Integration
^1H NMR	6.3	s	—
IR	3125 cm^{-1}		
	1625 cm^{-1}		
	1280 cm^{-1}		
	820 cm^{-1}		
	695 cm^{-1}		

9.41 When dissolved in $CDCl_3$, a compound (**K**) with the molecular formula $C_4H_8O_2$ gives a ^1H NMR spectrum that consists of a doublet at δ 1.35, a singlet at δ 2.15, a broad singlet at δ 3.75 (1H), and a quartet at δ 4.25 (1H). When dissolved in D_2O, the compound gives a similar ^1H NMR spectrum, with the exception that the signal at δ 3.75 has disappeared. The IR spectrum of the compound shows a strong absorption peak near 1720 cm^{-1}.

(a) Propose a structure for compound **K**.

(b) Explain why the NMR signal at δ 3.75 disappears when D_2O is used as the solvent.

9.42 Compound **T** (C_5H_8O) has a strong IR absorption band at 1745 cm^{-1}. The broad-band proton decoupled ^{13}C spectrum of **T** shows three signals: at δ 220 (C), 23 (CH_2), and 38 (CH_2). Propose a structure for **T**.

9.43 Deduce the structure of the compound that gives the following ^{1}H, ^{13}C, and IR spectra (Figs. 9.51–9.53). Assign all aspects of the ^{1}H, and ^{13}C spectra to the structure you propose. Use letters to correlate protons with signals in the ^{1}H NMR spectrum, and numbers to correlate carbons with signals in the ^{13}C spectrum. The mass spectrum of this compound shows the molecular ion at *m/z* 96.

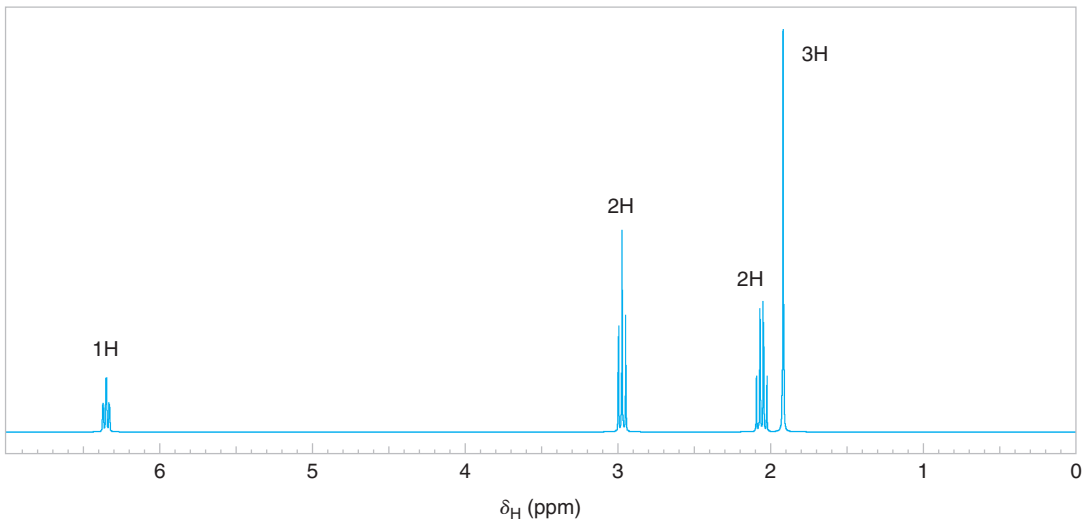


FIGURE 9.51 The ^{1}H NMR spectrum (simulated) for Problem 9.43.

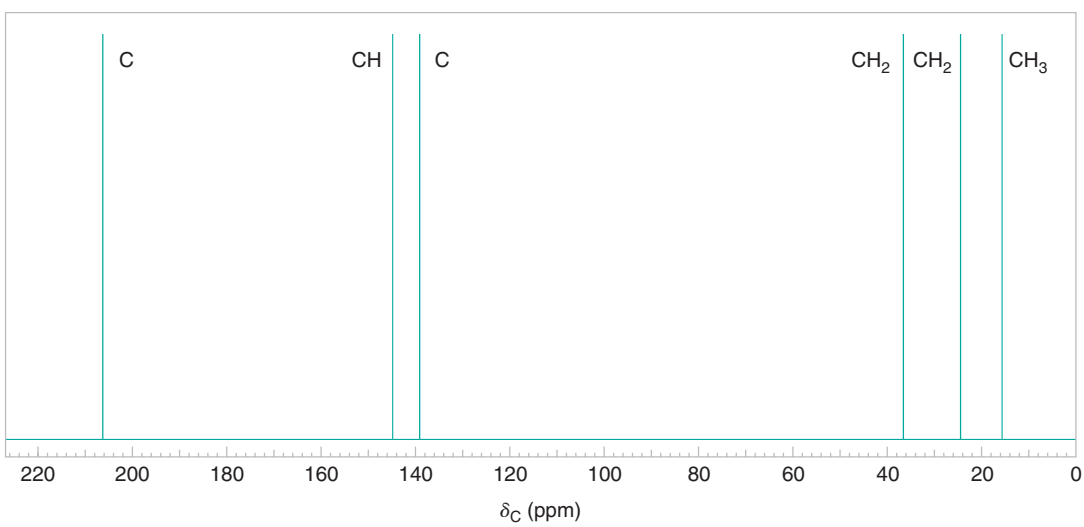


FIGURE 9.52 A simulated broadband proton-decoupled ^{13}C NMR spectrum for Problem 9.43. Information from the DEPT ^{13}C spectra is given above each peak.

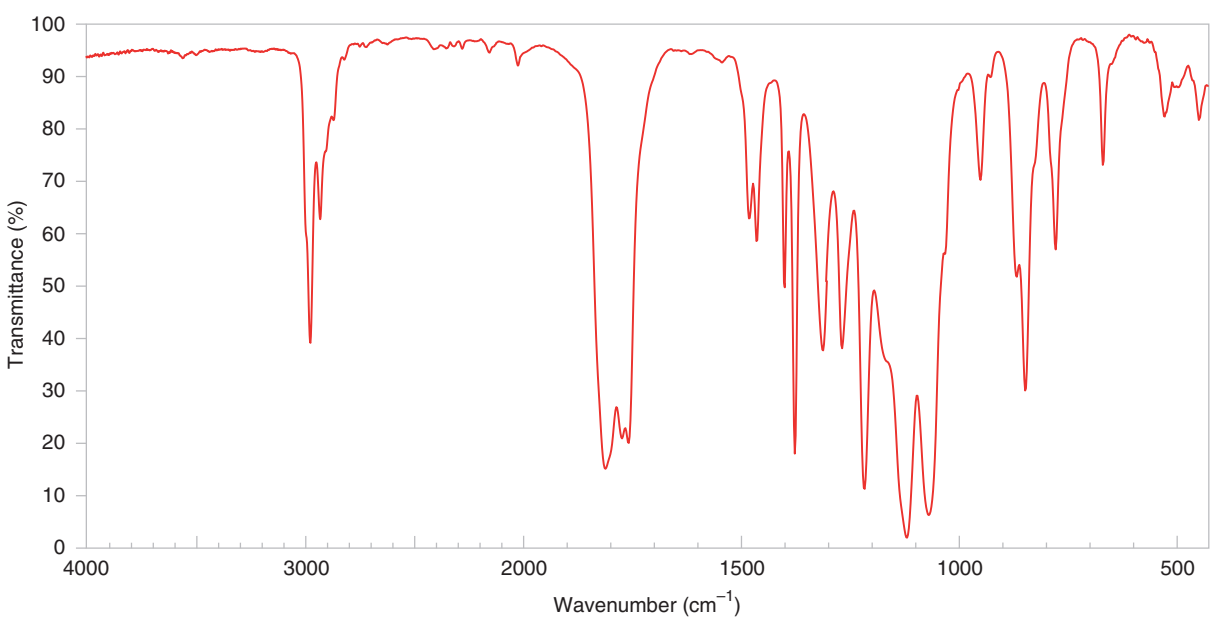


FIGURE 9.53 The IR spectrum for Problem 9.43 (Spectra adapted from Sigma-Aldrich Co. © Sigma-Aldrich Co.)

9.44 Deduce the structure of the compound that gives the following ^{1}H, ^{13}C, and IR spectra (Figs. 9.54–9.56). Assign all aspects of the ^{1}H and ^{13}C spectra to the structure you propose. Use letters to correlate protons with the signals in the ^{1}H NMR spectrum, and numbers to correlate carbons with the signals in the ^{13}C spectrum. The mass spectrum of this compound shows the molecular ion at *m/z* 148.

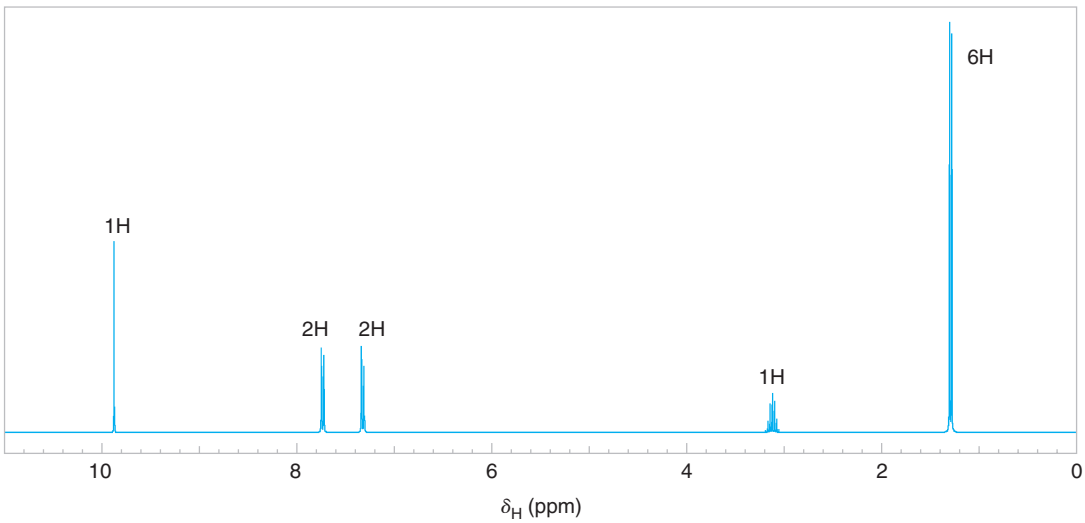


FIGURE 9.54 The 300-MHz ^{1}H NMR spectrum (simulated) for Problem 9.44.

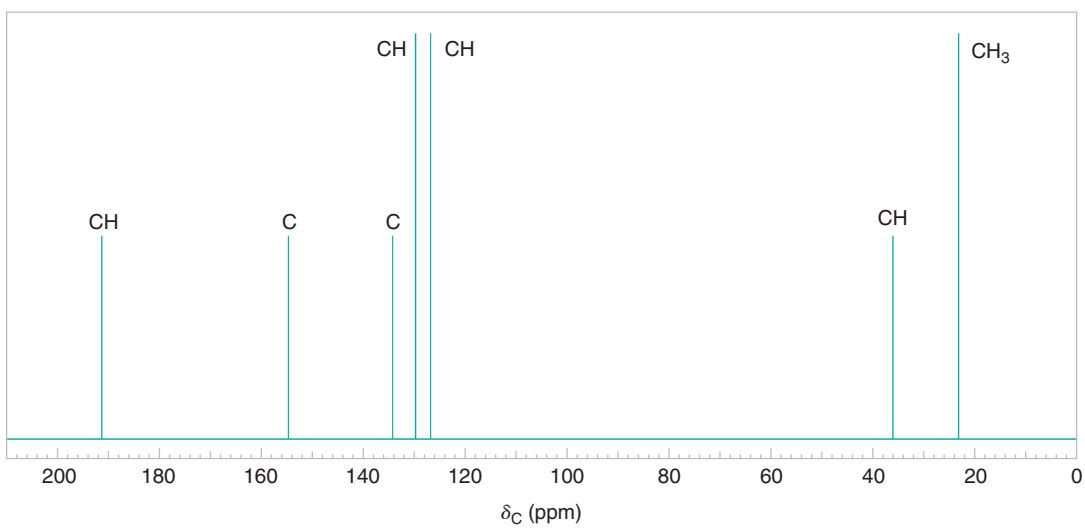


FIGURE 9.55 A simulated broadband proton-decoupled ^{13}C NMR spectrum for Problem 9.44. Information from the DEPT ^{13}C spectra is given above each peak.

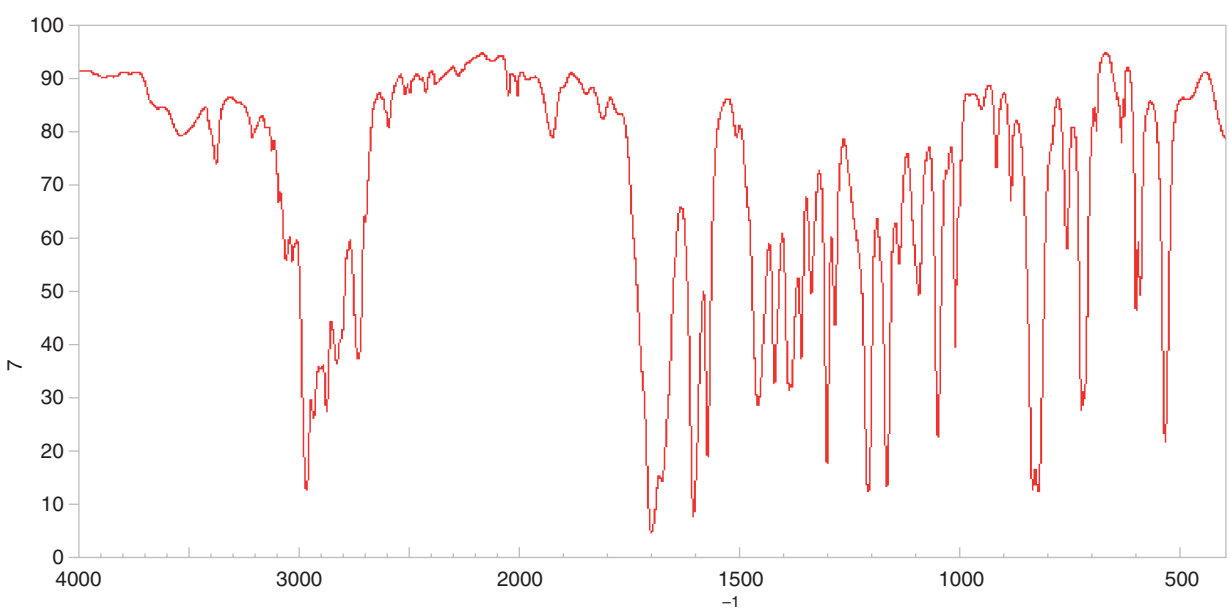


FIGURE 9.56 The IR spectrum for Problem 9.44. (SDBS, National Institute of Advanced Industrial Science and Technology)

9.45 Deduce the structure of the compound that gives the following ^{1}H, ^{13}C, and IR spectra (Figs. 9.57–9.59). Assign all aspects of the ^{1}H and ^{13}C spectra to the structure you propose. Use letters to correlate protons with signals in the ^{1}H NMR spectrum, and numbers to correlate carbons with signals in the ^{13}C spectrum. The mass spectrum of this compound shows the molecular ion at *m/z* 204.

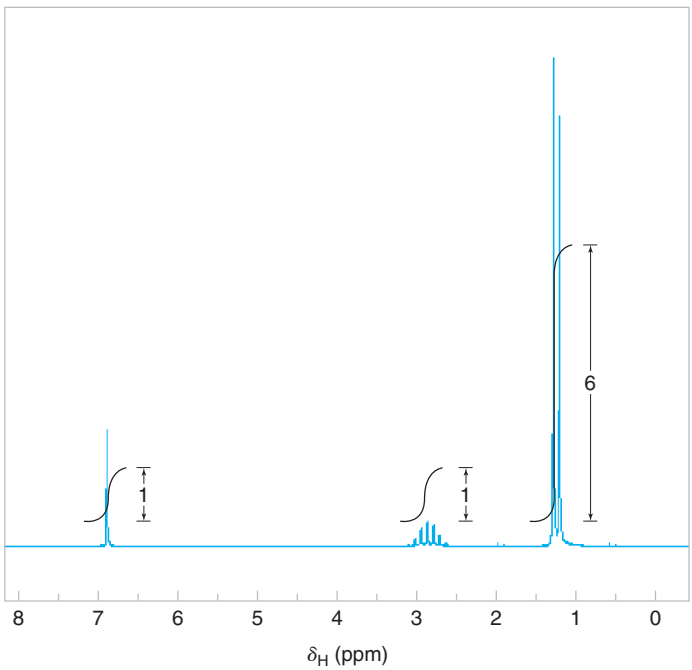


FIGURE 9.57 The 300-MHz ^{1}H NMR spectrum (simulated) for Problem 9.45.

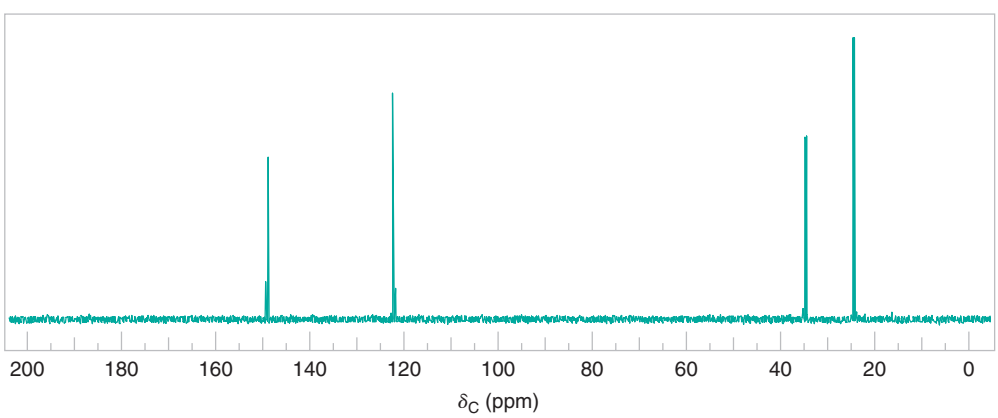


FIGURE 9.58 A simulated broadband proton-decoupled ^{13}C NMR spectrum for Problem 9.45.

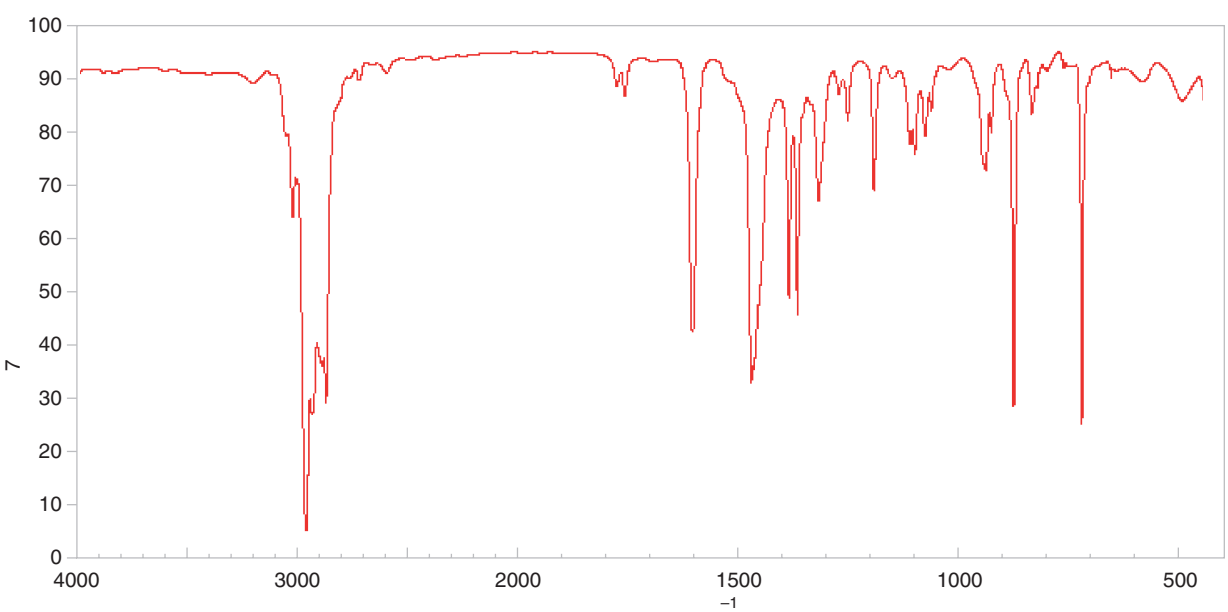


FIGURE 9.59 The IR spectrum for Problem 9.45. (SDBS, National Institute of Advanced Industrial Science and Technology)

9.46 Deduce the structure of the compound ($C_5H_{10}O_3$) that gives the following ^1H, ^{13}C, and IR spectra (Figs. 9.60–9.62), Assign all aspects of the ^1H and ^{13}C spectra to the structure you propose. Use letters to correlate protons with signals in the ^1H NMR spectrum, and numbers to correlate carbons with signals in the ^{13}C spectrum.

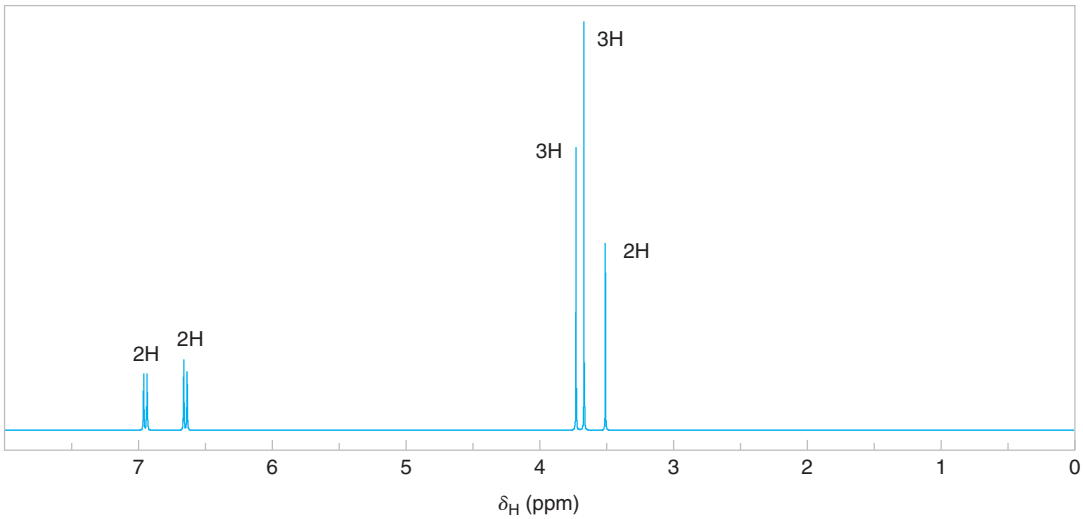


FIGURE 9.60 The 300-MHz ^1H NMR spectrum (simulated) for Problem 9.46.

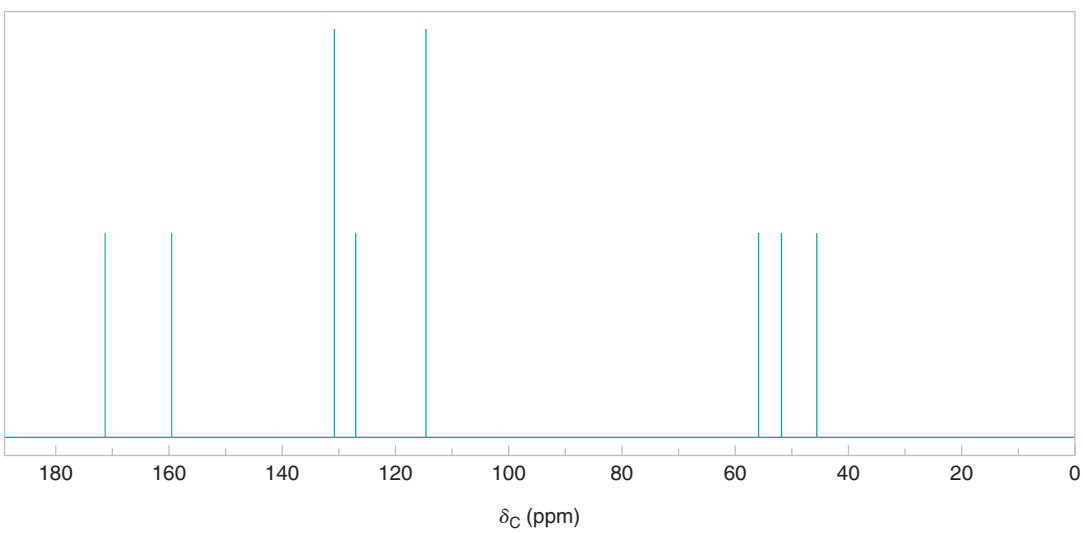


FIGURE 9.61 A simulated broadband proton-decoupled ^{13}C NMR spectrum for Problem 9.46.

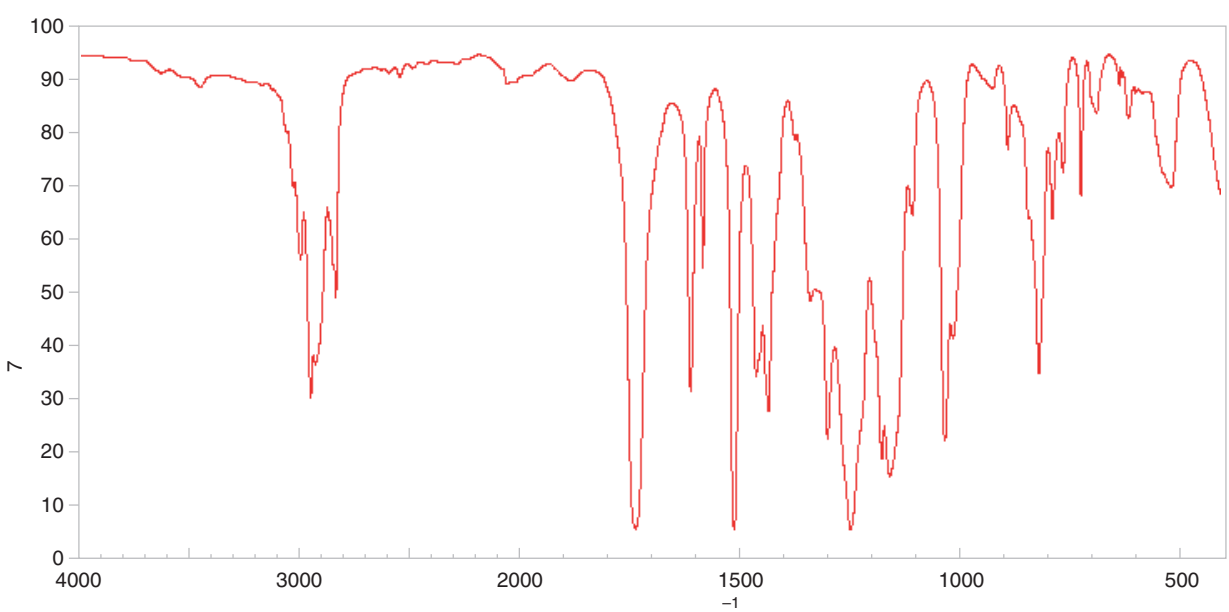


FIGURE 9.62 The IR spectrum for Problem 9.46. (SDBS, National Institute of Advanced Industrial Science and Technology)

CHALLENGE PROBLEMS

9.47 The ^{1}H NMR spectrum of a solution of 1,3-dimethylcyclopentadiene in concentrated sulfuric acid shows three peaks with relative areas of 6 : 4 : 1. What is the explanation for the appearance of the spectrum?

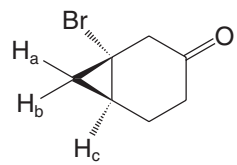
9.48 Acetic acid has a mass spectrum showing a molecular ion peak at *m*/*z* 60. Other unbranched monocarboxylic acids with four or more carbon atoms also have a peak, frequently prominent, at *m*/*z* 60. Show how this can occur.

9.49 The ^{1}H NMR peak for the hydroxyl proton of alcohols can be found anywhere from δ 0.5 to δ 5.4. Explain this variability.

9.50 The ^{1}H NMR study of DMF (*N,N*-dimethylformamide) results in different spectra according to the temperature of the sample. At room temperature, two signals are observed for the protons of the two methyl groups. On the other hand, at elevated temperatures (>130 °C) a singlet is observed that integrates for six hydrogens. Explain these differences.

9.51 The mass spectra of many benzene derivatives show a peak at *m*/*z* 51. What could account for this fragment?

9.52 Consider the following information.



$J_{ab} = 5.3$ Hz

$J_{ac} = 8.2$ Hz

$J_{bc} = 10.7$ Hz

(a) How many total ^{1}H NMR signals would you expect for the above molecule?

(b) H_a appears as a doublet of doublets (dd) at 1.32 ppm in the ^{1}H NMR spectrum. Draw a labeled splitting tree diagram for H_a using the coupling constant values given above.

LEARNING GROUP PROBLEMS

1. Given the following information, elucidate the structures of compounds **A** and **B**. Both compounds are soluble in dilute aqueous HCl, and both have the same molecular formula. The mass spectra of **A** and **B** have $M^{+\cdot}$ 149. Other spectroscopic data for **A** and **B** are given below. Justify the structures you propose by assigning specific aspects of the data to the structures. Make sketches of the NMR spectra.

(a) The IR spectrum for compound **A** shows two bands in the 3300–3500-cm^{-1} region. The broadband proton-decoupled ^{13}C NMR spectrum displayed the following signals (information from the DEPT ^{13}C spectra is given in parentheses with the ^{13}C chemical shifts):

^{13}C NMR: δ 140 (C), 127 (C), 125 (CH), 118 (CH), 24 (CH_2), 13 (CH_3)

(b) The IR spectrum for compound **B** shows no bands in the 3300–3500-cm^{-1} region. The broadband proton-decoupled ^{13}C NMR spectrum displayed the following signals (information from the DEPT ^{13}C spectra is given in parentheses with the ^{13}C chemical shifts):

^{13}C NMR: δ 147 (C), 129 (CH), 115 (CH), 111 (CH), 44 (CH_2), 13 (CH_3)

2. Two compounds with the molecular formula $C_5H_{10}O$ have the following ^{1}H and ^{13}C NMR data. Both compounds have a strong IR absorption band in the 1710–1740-cm^{-1} region. Elucidate the structure of these two compounds and interpret the spectra. Make a sketch of each NMR spectrum.

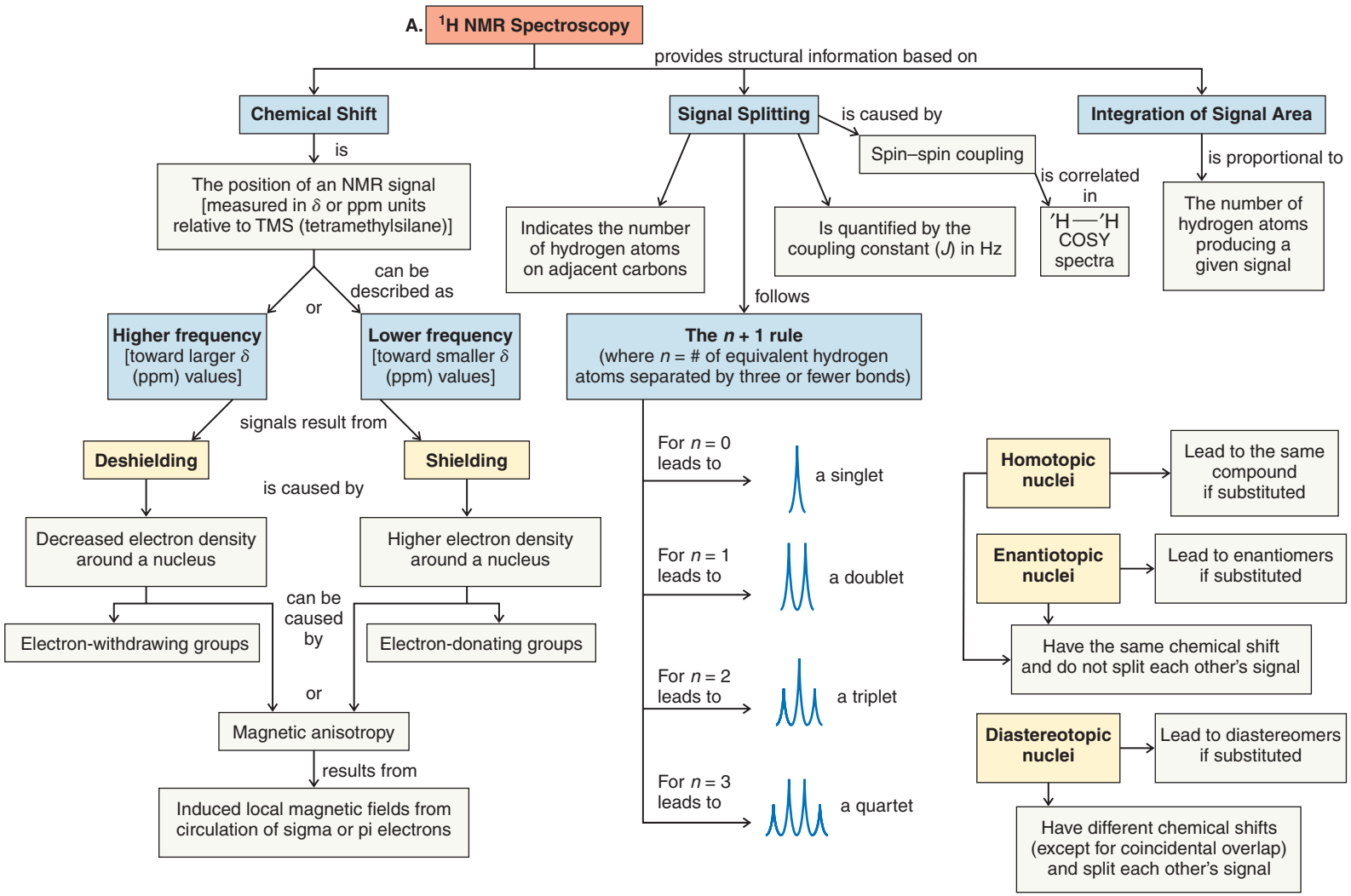
(a) ^{1}H NMR: δ 2.55 (septet, 1H), 2.10 (singlet, 3H), 1.05 (doublet, 6H)

^{13}C NMR: δ 212.6, 41.5, 27.2, 17.8

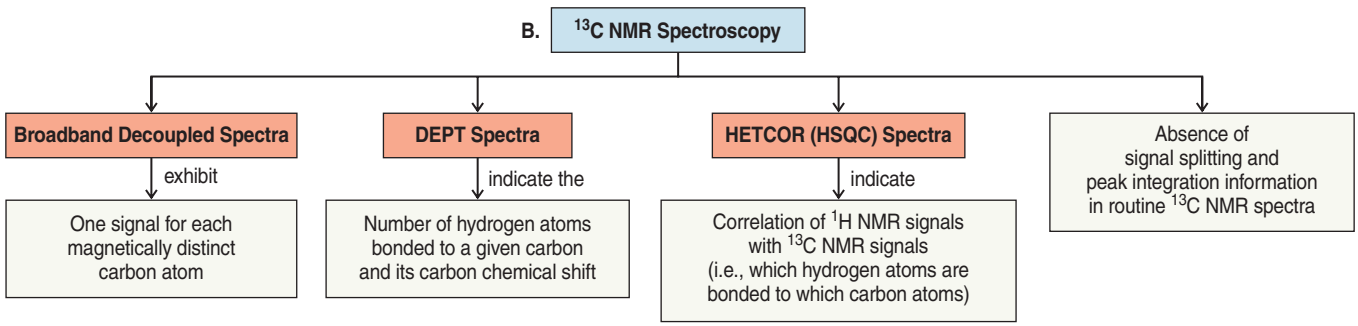
(b) ^{1}H NMR: δ 2.38 (triplet, 2H), 2.10 (singlet, 3H), 1.57 (sextet, 2H), 0.88 (triplet, 3H)

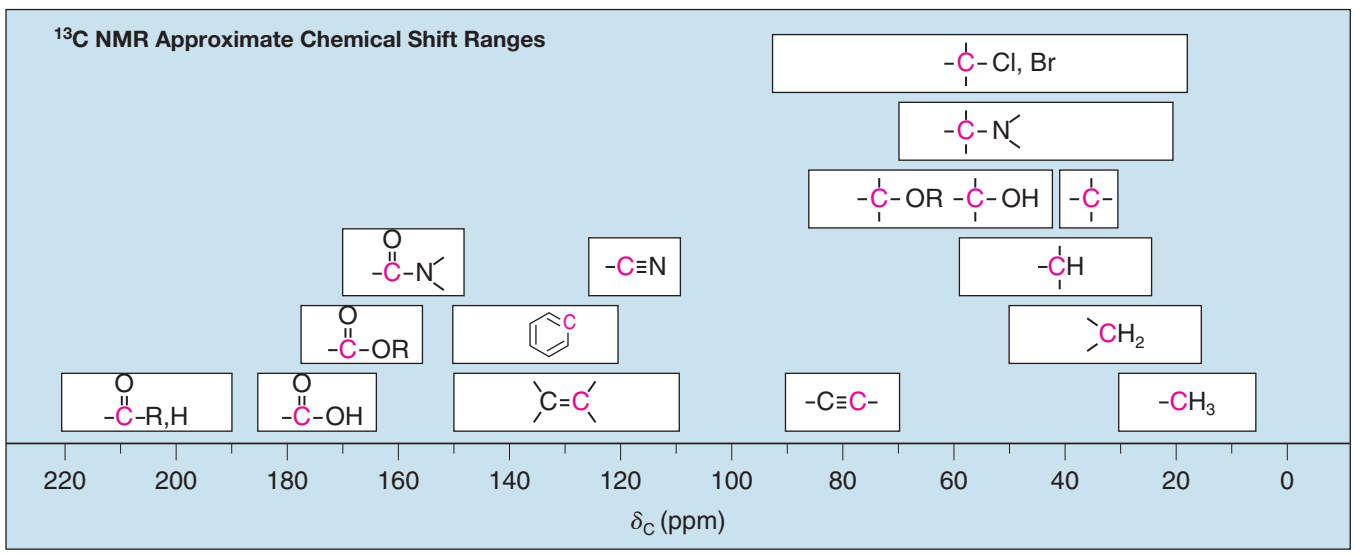
^{13}C NMR: δ 209.0, 45.5, 29.5, 17.0, 13.2

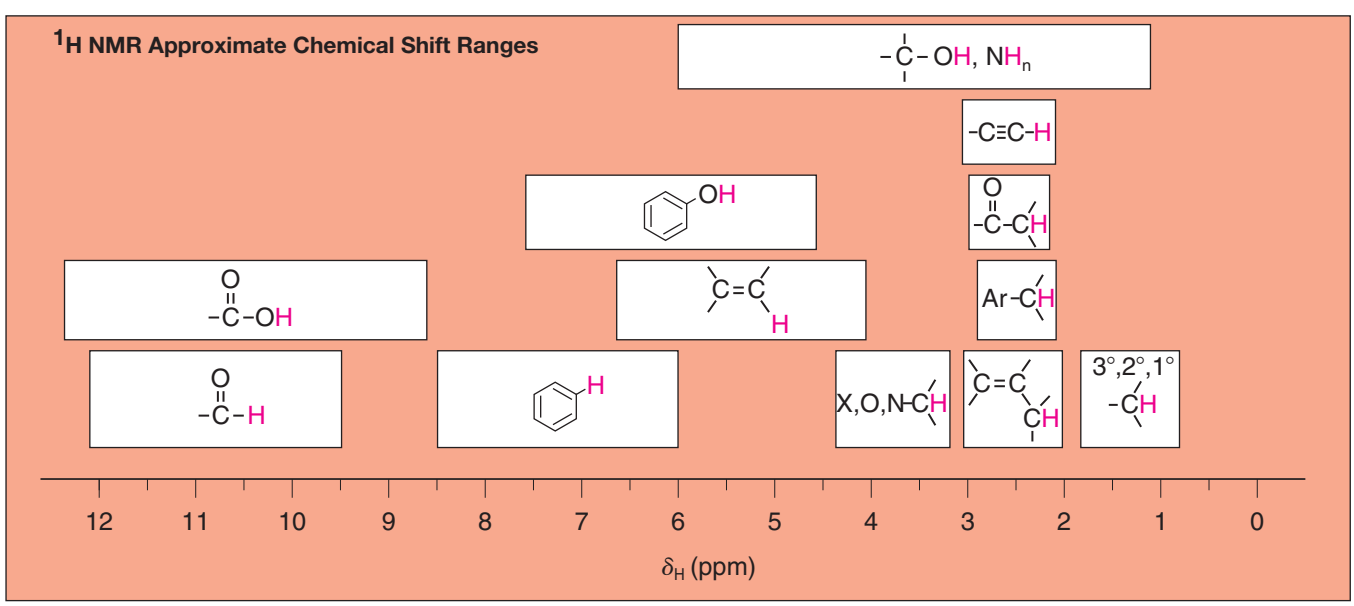
[CONCEPT MAP]


A. ¹H NMR Spectroscopy
provides structural information based on
Chemical Shift
is
The position of an NMR signal [measured in δ or ppm units relative to TMS (tetramethylsilane)]
can be described as
or
Higher frequency [toward larger δ (ppm) values]
Lower frequency [toward smaller δ (ppm) values]
signals result from
Deshielding
Shielding
is caused by
Decreased electron density around a nucleus
Higher electron density around a nucleus
can be caused by
Electron-withdrawing groups
Electron-donating groups
or
Magnetic anisotropy
results from
Induced local magnetic fields from circulation of sigma or pi electrons
Signal Splitting
is caused by
Spin–spin coupling
is correlated in
′H—′H COSY spectra
Indicates the number of hydrogen atoms on adjacent carbons
Is quantified by the coupling constant (J) in Hz
follows
The n + 1 rule
(where n = # of equivalent hydrogen atoms separated by three or fewer bonds)
For n = 0 leads to
a singlet
For n = 1 leads to
a doublet
For n = 2 leads to
a triplet
For n = 3 leads to
a quartet
Integration of Signal Area
is proportional to
The number of hydrogen atoms producing a given signal
Homotopic nuclei
Lead to the same compound if substituted
Enantiotopic nuclei
Lead to enantiomers if substituted
Have the same chemical shift and do not split each other's signal
Diastereotopic nuclei
Lead to diastereomers if substituted
Have different chemical shifts (except for coincidental overlap) and split each other's signal

[CONCEPT MAP]


B. ^{13}C NMR Spectroscopy
Broadband Decoupled Spectra
exhibit
One signal for each magnetically distinct carbon atom
DEPT Spectra
indicate the
Number of hydrogen atoms bonded to a given carbon and its carbon chemical shift
HETCOR (HSQC) Spectra
indicate
Correlation of ^{1}H NMR signals with ^{13}C NMR signals (i.e., which hydrogen atoms are bonded to which carbon atoms)
Absence of signal splitting and peak integration information in routine ^{13}C NMR spectra


^{13}C NMR Approximate Chemical Shift Ranges
-C- Cl, Br
-C- N
-C- OR -C- OH
-C-
-C≡N
-CH
-CH2
-CH3
-C≡C-
-C=C-
-C-R,H
-C-OH
-C-OR
-C-N
220 200 180 160 140 120 100 80 60 40 20 0
δC (ppm)


^{1}H NMR Approximate Chemical Shift Ranges
-C- OH, NHn
-C≡C-H
OH
-C-CH
-C-OH
C=C H
Ar-CH
-C-H
H
X,O,N-CH
C=C CH
3°,2°,1° -CH
12 11 10 9 8 7 6 5 4 3 2 1 0
δH (ppm)