CHAPTER 6

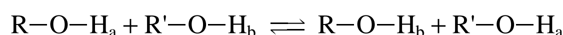
NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

Part Four: Other Topics in One-Dimensional NMR

In this chapter, we shall consider some additional topics in one-dimensional nuclear magnetic resonance (NMR) spectroscopy. Among the topics that will be covered will be the variability in chemical shifts of protons attached to electronegative elements such as oxygen and nitrogen, the special characteristics of protons attached to nitrogen, the effects of solvent on chemical shift, lanthanide shift reagents, and spin decoupling experiments.

6.1 PROTONS ON OXYGEN: ALCOHOLS

For most alcohols, no coupling is observed between the hydroxyl hydrogen and vicinal hydrogens on the carbon atom to which the hydroxyl group is attached (^3J for R—CH—OH) under typical conditions of determining the ^1H NMR spectrum. Coupling does, in fact, exist between these hydrogens, but the spin–spin splitting is often not observed due to other factors. Whether or not spin–spin splitting involving the hydroxyl hydrogen is observed for a given alcohol depends on several factors, including temperature, purity of the sample, and the solvent used. These variables are all related to the rate at which hydroxyl protons exchange with one another (or the solvent) in solution. Under normal conditions, the rate of exchange of protons between alcohol molecules is faster than the rate at which the NMR spectrometer can respond.



$$R{-}O{-}H_a + R'{-}O{-}H_b \rightleftharpoons R{-}O{-}H_b + R'{-}O{-}H_a$$

About 10^{-2} to 10^{-3} sec is required for an NMR transitional event to occur and be recorded. At room temperature, a typical pure liquid alcohol sample undergoes intermolecular proton exchange at a rate of about 10^5 protons/sec. This means that the average residence time of a single proton on the oxygen atom of a given alcohol is only about 10^{-5} sec. This is a much shorter time than is required for the nuclear spin transition that the NMR spectrometer measures. Because the NMR spectrometer cannot respond rapidly to these situations, the spectrometer "sees" the proton as unattached more frequently than it is attached to oxygen, and the spin interaction between the hydroxyl proton and any other proton in the molecule is effectively decoupled. *Rapid chemical exchange decouples spin interactions,* and the NMR spectrometer records only the *time-averaged environment* it detected for the exchanging proton. The hydroxyl proton, for instance, often exchanges between alcohol molecules so rapidly that that proton "sees" all the possible spin orientations of hydrogens attached to the carbon as a single time-averaged spin configuration. Similarly, the α hydrogens see so many different protons on the hydroxyl oxygen (some with spin $+\frac{1}{2}$ and some with spin $-\frac{1}{2}$) that the spin configuration they sense is an average or intermediate value between $+\frac{1}{2}$ and $-\frac{1}{2}$, that is, zero. In effect, the NMR spectrometer is like a camera with a slow shutter speed that is used to

photograph a fast event. Events that are faster than the click of the shutter mechanism are blurred or averaged.

If the rate of exchange in an alcohol can be slowed to the point at which it approaches the "time-scale of the NMR" (i.e., $<10^2$ to 10^3 exchanges per second), then coupling between the hydroxyl proton and vicinal protons on the hydroxyl-bearing carbon can be observed. For instance, the NMR spectrum of methanol at 25°C (ca. 300 K) consists of only two peaks, both singlets, integrating for one proton and three protons, respectively. However, at temperatures below −33°C (<240 K), the spectrum changes dramatically. The one-proton O—H resonance becomes a quartet (^3J = 5 Hz), and the three-proton methyl resonance becomes a doublet (^3J = 5 Hz). Clearly, at or below −33°C (<240 K) chemical exchange has slowed to the point at which it is within time-scale of the NMR spectrometer, and coupling to the hydroxyl proton is observed. At temperatures between 25°C and −33°C (300 K to 240 K), transitional spectra are seen. Figure 6.1 is a stacked plot of NMR spectra of methanol determined at a range of temperatures from 290 K to 200 K.

The room temperature spectrum of an ordinary sample of ethanol (Fig. 6.2) shows no coupling of the hydroxyl proton to the methylene protons. Thus, the hydroxyl proton is seen as a broad singlet, and the methylene protons (split by the methyl group) are seen as a simple quartet. The rate of hydroxyl proton exchange in such a sample is faster than the NMR time-scale, and coupling between the hydroxyl and methylene protons is effectively removed. However, if a sample of ethanol is purified to eliminate all traces of impurity (especially of acids and water, further slowing the O—H proton exchange rate), the hydroxyl–methylene coupling can be observed in the form of increased complexity

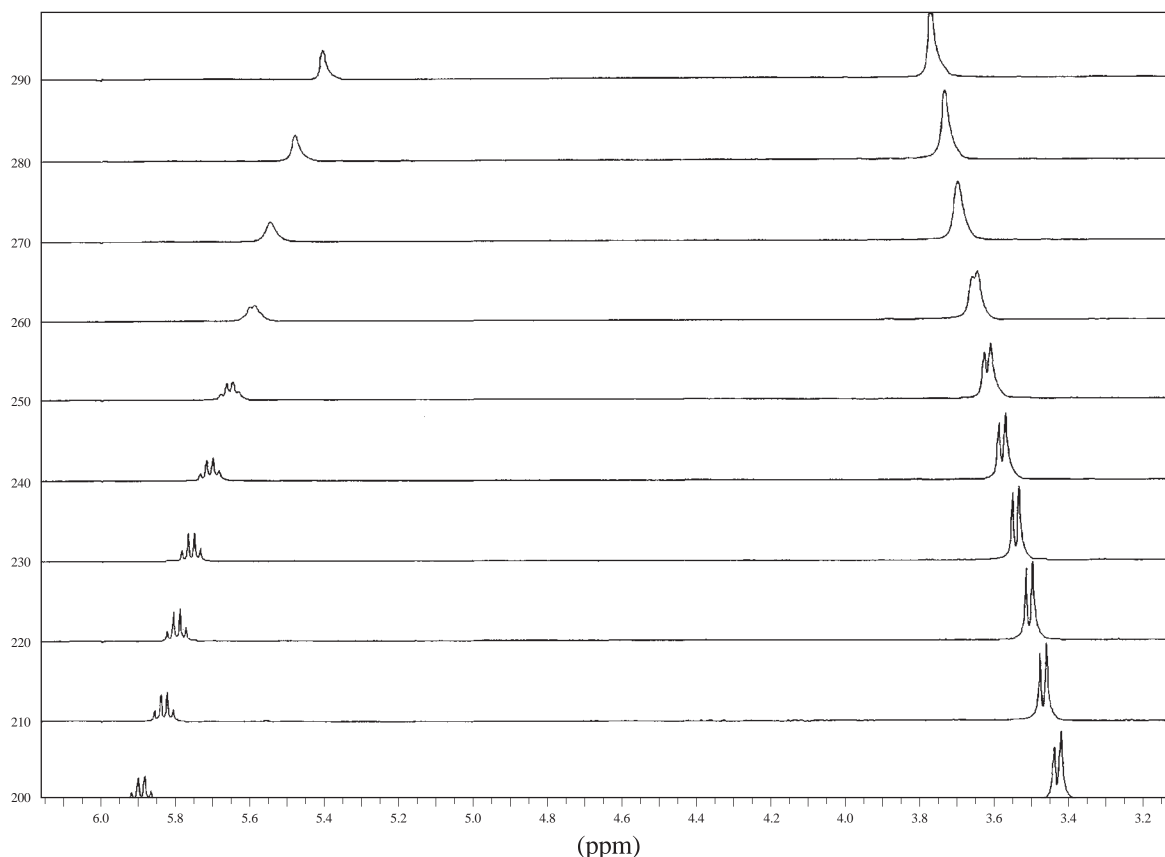


FIGURE 6.1 Stacked plot of NMR spectra of methanol determined at a range of temperatures from 290 K to 200 K.

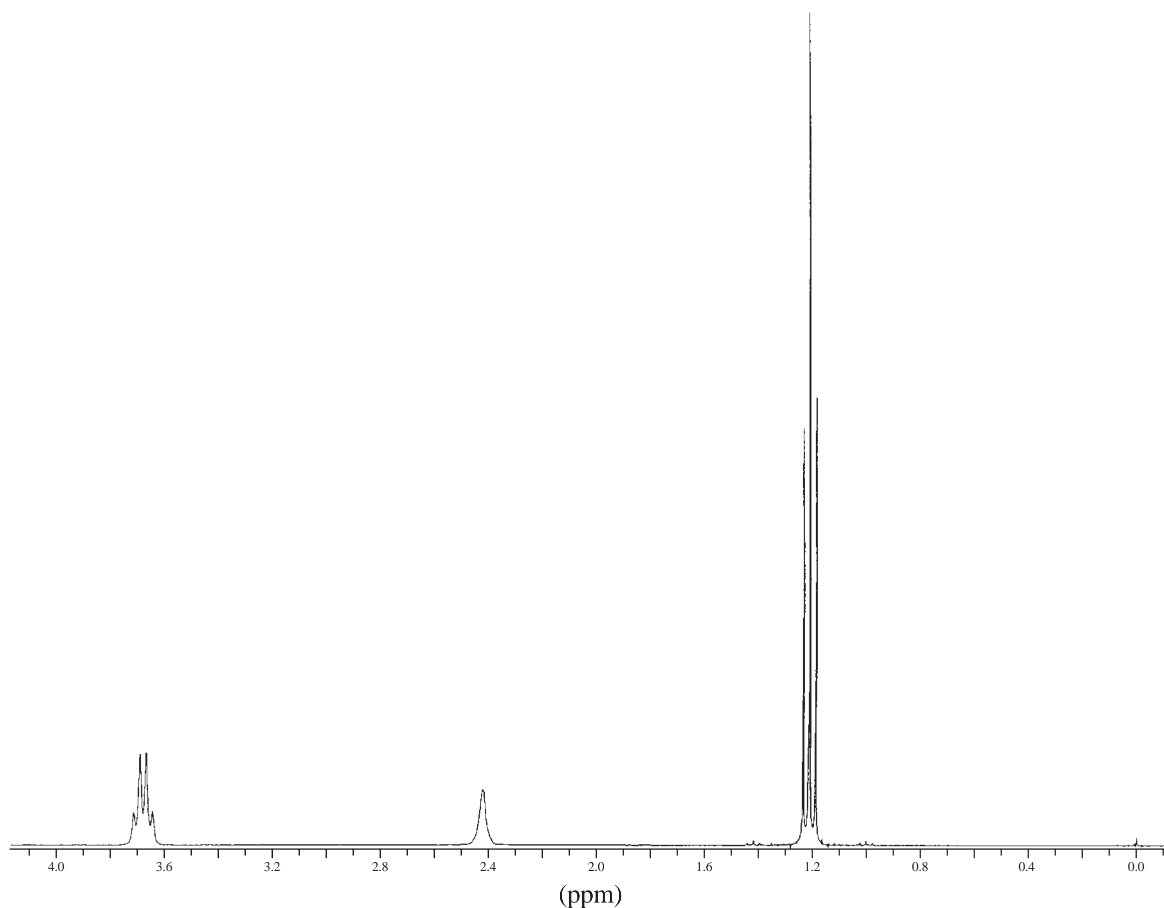
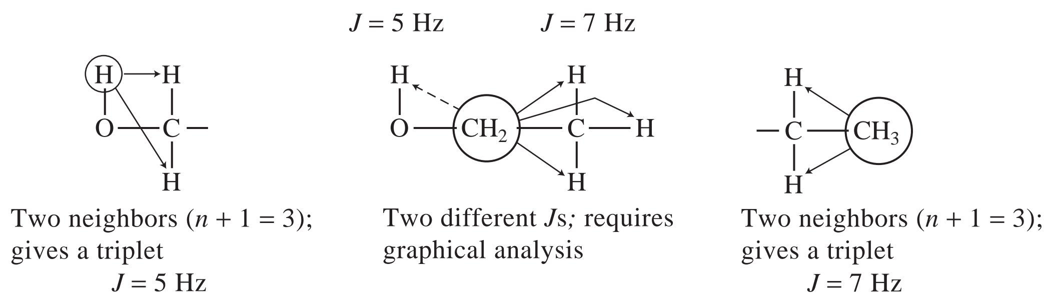


FIGURE 6.2 The NMR spectrum of an ordinary ethanol sample.

of the spin–spin splitting patterns. The hydroxyl absorption becomes a triplet, and the methylene absorptions are seen as an overlapping pair of quartets. The hydroxyl resonance is split (just as the methyl group is, but with a different J value) into a triplet by its two neighbors on the methylene carbon.



The coupling constant for the methylene–hydroxyl interaction is found to be ^3J (CH_2, OH) = ~5 Hz. The methyl triplet is found to have a different coupling constant, ^3J (CH_3, CH_2) = ~7 Hz, for the methylene–methyl coupling. The methylene protons are **not** split into a quintet by their four neighbors as the coupling constants for hydroxyl–methylene and methyl–methylene are different. As discussed in Chapter 5, the $n + 1$ Rule does not apply in such an instance; each coupling interaction is independent of the other, and a graphical analysis is required to approximate the correct pattern.

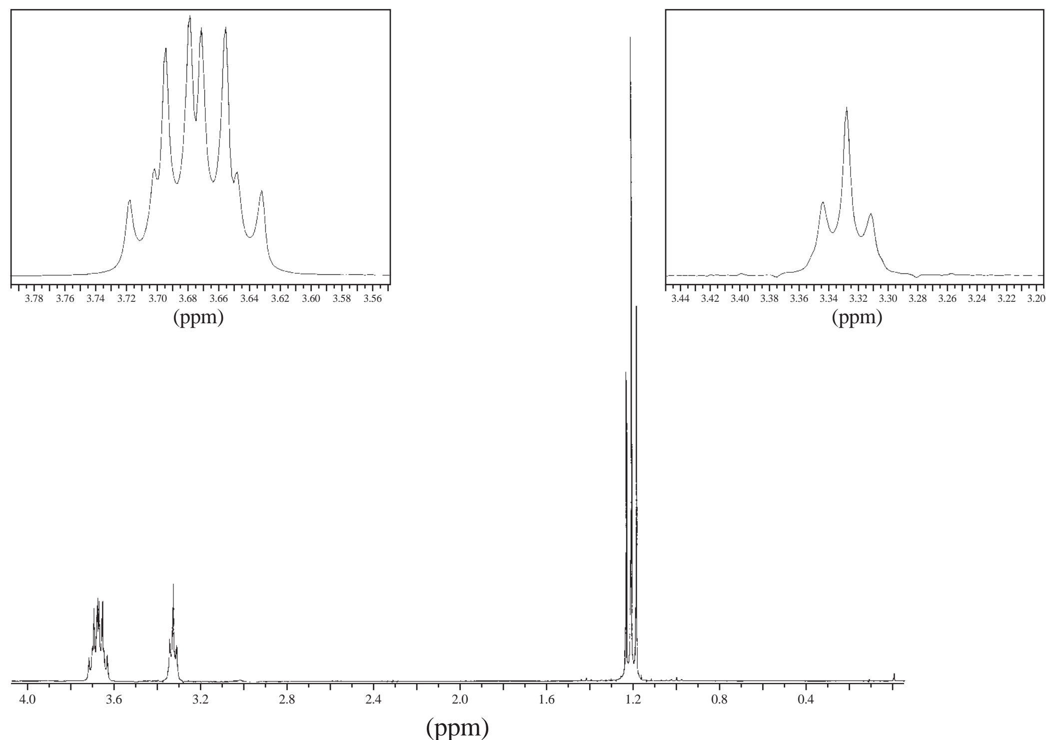


FIGURE 6.3 The NMR spectrum of an ultrapure sample of ethanol. Expansions of the splitting patterns are included.

Figure 6.3 shows the spectrum of ultrapure ethanol. Notice in the expanded splitting patterns that the methylene protons are split into two overlapping quartets (a doublet of quartets).[1,2] If even a drop of acid (including water) is added to the ultrapure ethanol sample, proton exchange becomes so fast that the methylene and hydroxyl protons are decoupled, and the simpler spectrum (Fig. 6.2) is obtained.

6.2 EXCHANGE IN WATER AND D_2O

A. Acid/Water and Alcohol/Water Mixtures

When two compounds, each of which contains an O—H group, are mixed, one often observes only a single NMR resonance due to O—H. For instance, consider the spectra of (1) pure acetic acid, (2) pure water, and (3) a 1:1 mixture of acetic acid and water. Figure 6.4 indicates their general appearances. Mixtures of acetic acid and water might be expected to show three peaks since there are two distinct types of hydroxyl groups in the solutions—one on acetic acid and one on water. In addition, the methyl group on acetic acid should give an absorption peak. In actuality, however, mixtures of these two reagents produce only two peaks. The methyl peak occurs at its normal position in the mixture, but there is only a single hydroxyl peak *between* the hydroxyl positions of the pure substances. Apparently, exchange of the type shown on p. 333 occurs so rapidly that the NMR again "sees" the hydroxyl protons only in an averaged environment intermediate between the two

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1 By convention, this pattern would best be referred to as a "quartet of doublets" since the quartet coupling (7 Hz) is larger than the doublet coupling (5 Hz).

2 Try drawing the splitting tree diagram for these resonances. See Problem 1 at the end of this chapter.

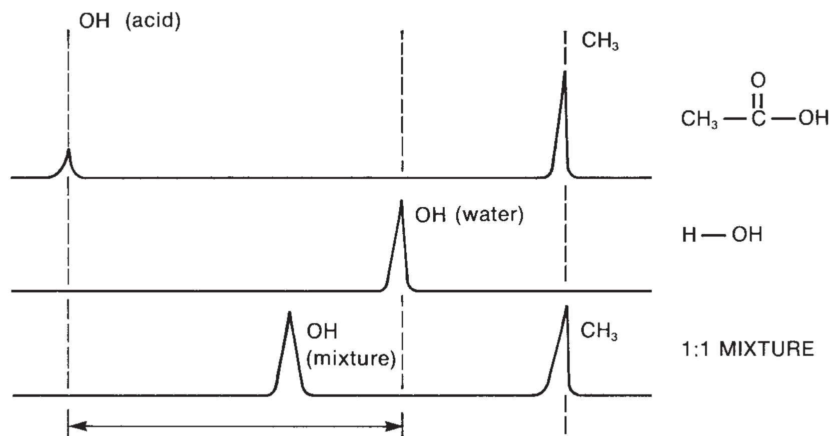
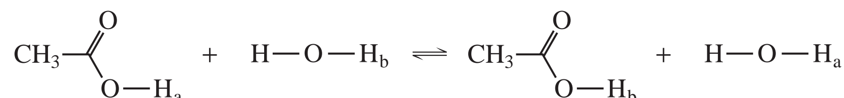


FIGURE 6.4 A comparison of the spectra of acetic acid, water, and a 1:1 mixture of the two.

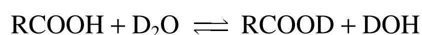
extremes of the pure substances. The exact position of the O—H resonance depends on the relative amounts of acid and water. In general, if there is more acid than water, the resonance appears closer to the pure acid hydroxyl resonance. With the addition of more water, the resonance moves closer to that of pure water. Samples of ethanol and water show a similar type of behavior, except that at low concentration of water in ethanol (1%) both peaks are still often observed. As the amount of water is increased, however, the rate of exchange increases, and the peaks coalesce into the single averaged peak.



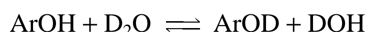
B. Deuterium Exchange

When compounds with acidic hydrogen atoms are placed in D_2O, the acidic hydrogens exchange with deuterium. Sometimes, a drop of acid or base catalyst is required, but frequently the exchange occurs spontaneously. The catalyst, however, allows a faster approach to equilibrium, a process that can require anywhere from several minutes to an hour or more. Acids, phenols, alcohols, and amines are the functional groups that exchange most readily. Basic catalysis works best for acids and phenols, while acidic catalysis is most effective for alcohols and amines.

Basic catalyst

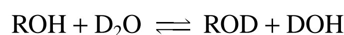


$$RCOOH + D_2O \rightleftharpoons RCOOD + DOH$$

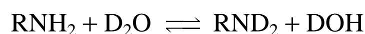


$$ArOH + D_2O \rightleftharpoons ArOD + DOH$$

Acidic catalyst



$$ROH + D_2O \rightleftharpoons ROD + DOH$$



$$RNH_2 + D_2O \rightleftharpoons RND_2 + DOH$$

The result of each deuterium exchange is that the peaks due to the exchanged hydrogens "disappear" from the ^{1}H NMR spectrum. Since all of the hydrogens end up in HOD molecules, the "lost" hydrogens generate a new peak, that of the hydrogen in HOD. If the NMR spectrum of a particular substance is complicated by the presence of an OH or NH proton, it is possible to simplify the spectrum by removing the peak arising from the exchangeable protons: simply add a few drops of deuterium oxide to the NMR tube containing the solution of the compound being studied. After recapping and shaking the tube vigorously for a few seconds, return the sample tube to the probe and acquire a new spectrum. The added deuterium oxide is immiscible with the NMR solvent and forms a layer on top of the solution. The presence of this layer, however, does not usually interfere in the determination of the spectrum. The resonance from the exchangeable proton will either disappear or greatly diminish in intensity, and a new peak, owing to the presence of H—O—D, will likely be observed, generally between 4.5 and 5.0 ppm. An interesting spectral simplification resulting from D_2O exchange is observed in the case of 2-chloroethanol (Fig. 6.5). The bottom ^{1}H NMR spectrum of 2-chloroethanol clearly shows the OH proton as a broad unsymmetric resonance centered at 2.22 ppm. Note also the complicated appearance of the resonances for the methylene protons at 3.68 and 3.87 ppm resulting from vicinal coupling of the hydroxyl group to the adjacent methylene (**H**O—C**H**$_2$—CH$_2$—Cl), which also creates second-order effects in the methylene adjacent to the chlorine group. After addition of D_2O to the sample and thorough mixing, the ^{1}H NMR spectrum was acquired again (Fig. 6.5, top spectrum). Note the nearly complete disappearance of

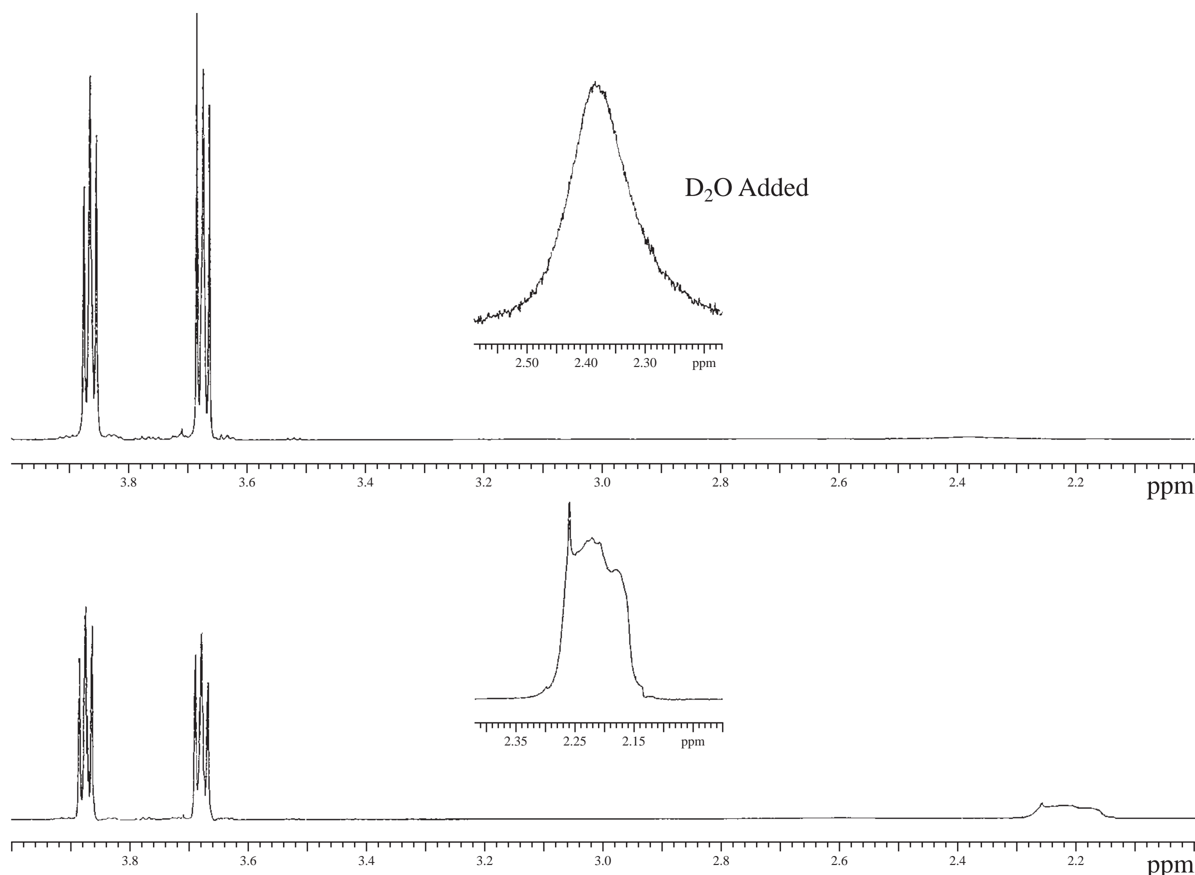
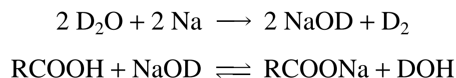


FIGURE 6.5 The 500-MHz ^{1}H NMR spectrum of 2-chloroethanol before (bottom) and after treatment with D_2O (top).

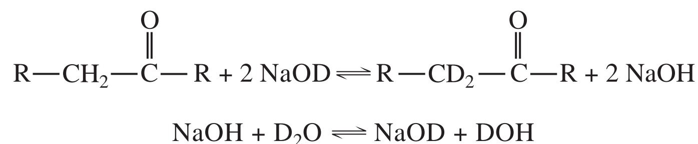
the OH resonance, which is reduced to a very weak, broad signal at 2.38 ppm. Furthermore, the coupling of the hydroxyl proton to the adjacent methylene is removed, and the two methylene groups appear as nearly first-order multiplets.

D_2O can be used as a solvent for NMR, and it is useful for highly polar compounds that do not dissolve well in the standard organic NMR solvents. For instance, some carboxylic acids are difficult to dissolve in $CDCl_3$. A basic solution of NaOD in D_2O is easily produced by adding a small chip of sodium metal to D_2O. This solution readily dissolves carboxylic acids since it converts them to water-soluble (D_2O-soluble) sodium carboxylate salts. The peak due to the hydrogen of the carboxyl group is lost, and a new HOD peak appears.



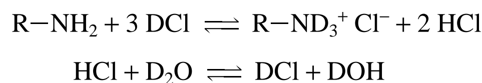
$$2\,D_2O + 2\,Na \longrightarrow 2\,NaOD + D_2$$
$$RCOOH + NaOD \rightleftharpoons RCOONa + DOH$$

This D_2O/NaOD solvent mixture can also be used to exchange the α hydrogens in some ketones, aldehydes, and esters.



$$NaOH + D_2O \rightleftharpoons NaOD + DOH$$

Amines dissolve in solutions of D_2O to which the acid DCl has been added. The amino protons end up in the HOD peak.



$$R{-}NH_2 + 3\,DCl \rightleftharpoons R{-}ND_3^+\,Cl^- + 2\,HCl$$
$$HCl + D_2O \rightleftharpoons DCl + DOH$$

Figure 6.6 shows a slightly different application of deuterium exchange in NMR spectroscopy. In this case, the bicyclic ketone shown was obtained from a highly diastereoselective cyclization reaction. Unfortunately, the stereoisomer formed (**C4 *anti***) had the opposite relative configuration at C4 from what was desired for the project. Since the C4 stereocenter is adjacent to a ketone, the researcher thought it would be possible to epimerize that position using base to form a planar enolate that could be reprotonated from the opposite face. The extent of epimerization was determined by ^1H NMR as follows: First, the pure **C4 *anti*** diastereomer was dissolved in methanol-d_4 (CD_3OD), and the ^1H NMR spectrum was acquired (Fig. 6.6, bottom). Note the cyclopropyl protons H_{7n} and H_{7x} (n stands for *endo* and x stands for *exo*) at 0.51 and 0.45 ppm. A small chip of sodium metal was then placed in the solution, which reacted with the CD_3OD to form D_2 gas and the base $NaOCD_3$. The solution was mixed thoroughly, and the ^1H NMR spectrum was acquired again (Fig. 6.6, top). Several changes in the spectra were noted. Most obvious was the appearance of a second set of cyclopropyl protons at 0.70 and 0.18 ppm, indicating that a second diastereomer was formed, **C4 *syn-d₃***, in which the cyclopropane protons experience a very different shielding environment relative to that in **C4 *anti-d₃***. Integration of the two sets of cyclopropyl protons indicates the equilibrium ratio of the two diastereomers is 57:43, favoring **C4 *anti-d₃***. The other noticeable change is in the region between 2.6 and 1.8 ppm. Two types of α hydrogens are found here—those on carbons 2 and 4, adjacent to the ketone carbonyl and those adjacent to the alkene on the pendant allyl group. One of the cyclohexane ring protons (C5) also appears in this region of the spectrum. Before the deuterium exchange, these hydrogens are observed as several overlapping signals in the 2.6- to 1.8-ppm region. After the treatment with $NaOCD_3/CD_3OD$, all of the hydrogens on C2 and C4 for both diastereomers disappear from the ^1H spectrum. This leaves one of the C5 hydrogens and the allylic hydrogens (three hydrogens for each diastereomer, six total) visible in the 2.6 to 1.8 ppm region.

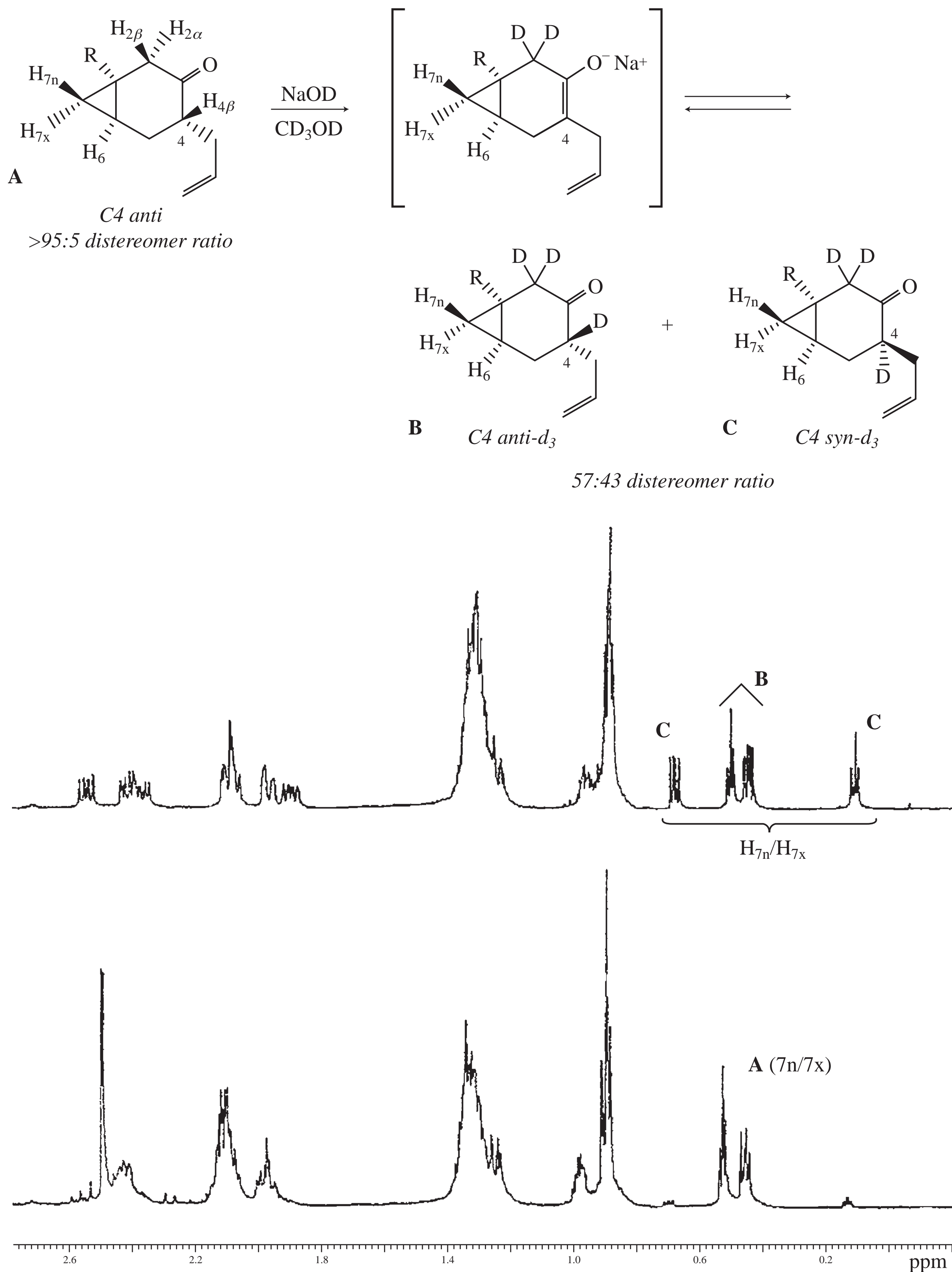
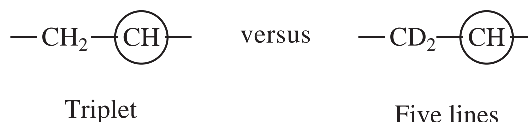


FIGURE 6.6 Upfield portion of 500 MHz ^{1}H NMR spectrum of bicyclic ketone **C4 *anti*** (A) in CD_3OD before (bottom) and after (top) treatment with $NaOCD_3$. This base treatment promotes epimerization of the C4 stereocenter and deuterium exchange to from a mixture of **C4 *anti-d₃*** (B) and **C4 *syn-d₃*** (C).

It is important to note that the presence of deuterium in a compound can actually complicate a proton spectrum in some cases. Since deuterium has $I = 1$, multiplets can end up with more peaks than they originally had. Consider the methine hydrogen in the following case. This hydrogen would be a triplet in the all-hydrogen compound, but it would be a five-line pattern in the deuterated compound. The proton-coupled ^{13}C spectrum would also show an increased complexity due to deuterium (see Section 4.13, p. 199).



C. Peak Broadening Due to Exchange

Rapid intermolecular proton exchange often (but not always!) leads to *peak broadening*. Rather than having a sharp and narrow line shape, the peak sometimes increases in width at the base and loses height as a result of rapid exchange. Note the hydroxyl peak in Figure 6.2. An O—H peak can often be distinguished from all other singlets on the basis of this shape difference. Peak broadening is caused by factors that are rather complicated, and we will leave their explanation to more advanced texts. We note only that the phenomenon is *time dependent,* and that the intermediate transitional stages of peak coalescence are sometimes seen in NMR spectra when the rate of exchange is neither slower nor faster than the NMR time-scale but instead is on approximately the same order of magnitude. Figure 6.7 illustrates these situations.

Also, do not forget that when the spectrum of a pure acid or alcohol is determined in an inert solvent (e.g., $CDCl_3$ or CCl_4), the NMR absorption position is concentration dependent. You will recall that this is due to hydrogen-bonding differences. If you have not, now is a good time to reread Sections 3.11C and 3.19F.

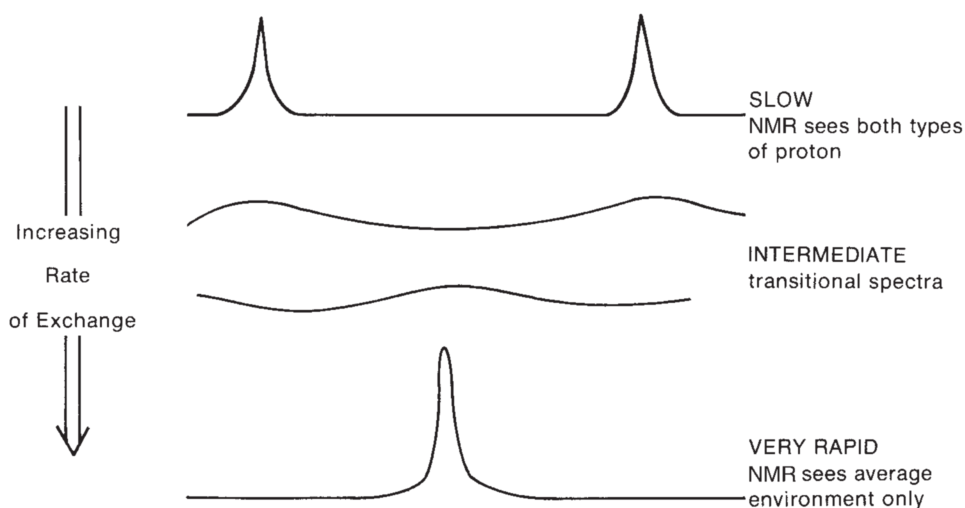
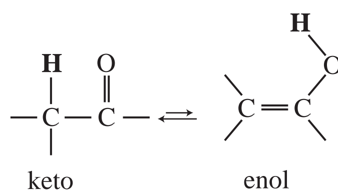


FIGURE 6.7 The effect of the rate of exchange on the NMR spectrum of a hydroxylic compound dissolved in water.

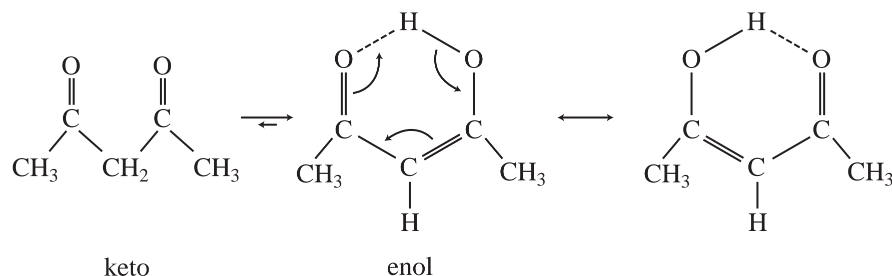
6.3 OTHER TYPES OF EXCHANGE: TAUTOMERISM

The exchange phenomena that have been presented thus far in this chapter have been essentially *intermolecular* in nature. They are examples of **dynamic NMR**, in which the NMR spectrometer is used to study processes that involve the rapid interconversion of molecular species. The rates of these interconversions as a function of temperature can be studied, and they can be compared with the NMR time-scale.

Molecules with structures that differ markedly in the arrangement of atoms but that exist in equilibrium with one another are called **tautomers**. The most common type of tautomerism is **keto–enol tautomerism**, in which the species differ mainly by the position of a hydrogen atom.



In general, the keto form is much more stable than the enol form, and the equilibrium lies strongly in favor of the keto form. Keto–enol tautomerism is generally considered an *intermolecular* process. 1,3-Dicarbonyl compounds are capable of exhibiting keto–enol tautomerism; this is illustrated for the case of **acetylacetone**. For most 1,3-dicarbonyl compounds, the equilibrium lies substantially to the right, favoring the *enol*. The enol form is stabilized through the formation of a strong *intramolecular* hydrogen bond. Note that both methyl groups are equivalent in the enol due to resonance (see arrows).



The proton NMR spectrum of acetylacetone is shown in Figure 6.8. The O—H proton of the enol form (not shown) appears very far downfield, at $\delta = 15.5$ ppm. The vinyl C—H proton is at $\delta = 5.5$ ppm. Note also the strong CH_3 peak from the enol form (2.0 ppm) and compare it with the much weaker CH_3 peak from the keto form (2.2 ppm). Also note that the CH_2 peak at 3.6 ppm is weak. Clearly, the enol form predominates in this equilibrium. The fact that we can see the spectra of both tautomeric forms, superimposed on each other, suggests that the rate of conversion of keto form to enol form, and vice versa, must be slow on the NMR time-scale.

By comparing the integrals of the two different methyl peaks, one can easily calculate the equilibrium distribution of the two tautomers.

Another type of tautomerism, *intra*molecular in nature, is called **valence tautomerism** (or **valence isomerization**). Valence tautomers rapidly interconvert with one another, but the tautomeric forms differ principally by the positions of *covalent bonds* rather than by the positions of protons. There are many examples of valence tautomerism in the literature. An interesting example is the isomerization of **bullvalene**, an interesting compound with threefold symmetry. At low temperatures (below −85°C), the proton NMR spectrum of bullvalene consists of four complex multiplets (each

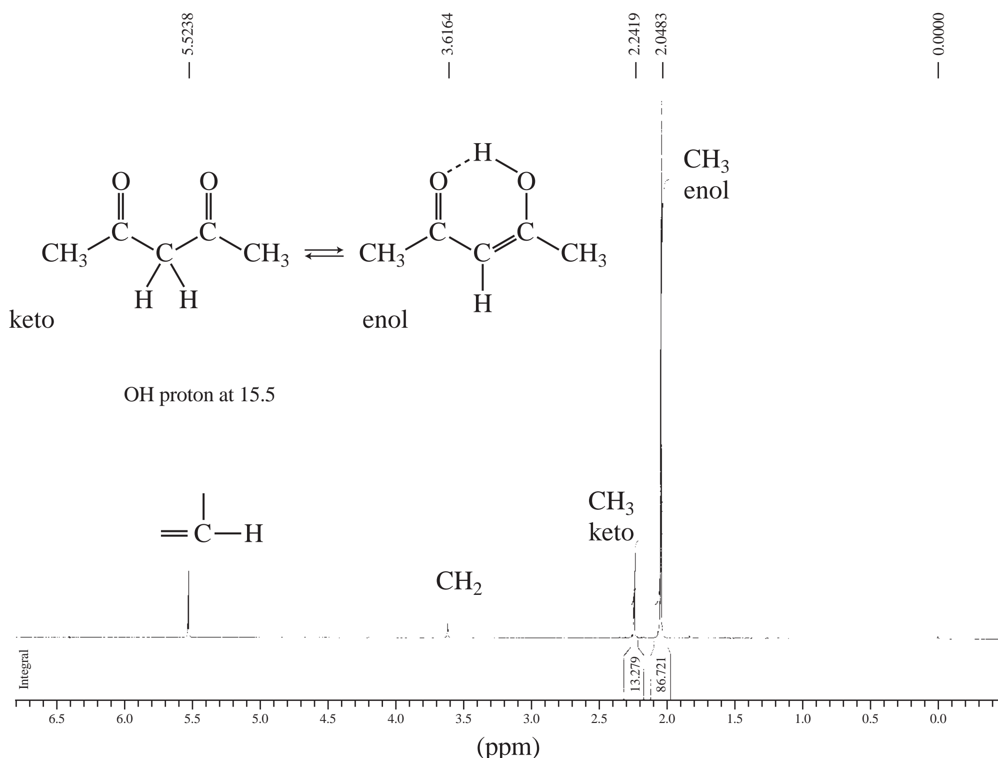
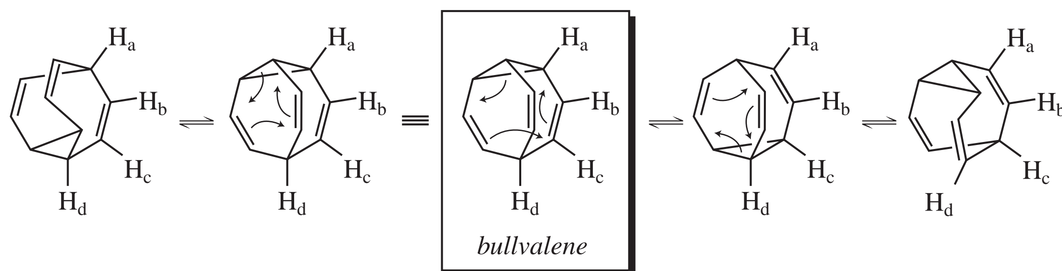


FIGURE 6.8 ^{1}H NMR spectrum of acetylacetone. The O—H proton of the enol tautomer is not shown.

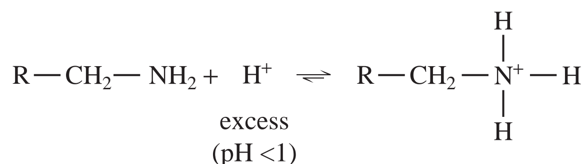
of the hydrogens labeled H_a—H_d on the structure below are in unique environments; there are three equivalent H_a positions, three equivalent hydrogens for each of H_b and H_c, and a single hydrogen in environment H_d). As the temperature is raised, however, the multiplets broaden and move closer together. Eventually, at +120°C, the entire spectrum consists of *one* sharp singlet—all of the hydrogens are equivalent on the NMR time-scale at that temperature.

To explain the temperature-dependent behavior of the spectrum of bullvalene, chemists have determined that bullvalene rearranges through a series of isomerizations known as **Cope rearrangements**. Notice that repeated Cope rearrangements involve all positions, and as a result all 10 hydrogens in bullvalene become equivalent if the rate of Cope rearrangement is faster than the NMR time-scale. An examination of the temperature at which the different multiplets coalesce into one very broad singlet (+15°C) allows the energy of activation, and thus the rate constant, for the isomerization to be determined. This process would be virtually impossible to study by any other technique except NMR spectroscopy.



6.4 PROTONS ON NITROGEN: AMINES

In simple amines, as in alcohols, intermolecular proton exchange is usually fast enough to decouple spin–spin interactions between protons on nitrogen and those on the α carbon atom. Under such conditions, the amino hydrogens usually appear as a broad singlet (unsplit), and in turn the hydrogens on the α carbon are also unsplit by amino hydrogens. The rate of exchange can be made slower by making the solution strongly acidic (pH < 1) and forcing the protonation equilibrium to favor the quaternary ammonium cation rather than the free amine.



Under these conditions, the predominant species in solution is the protonated amine, and intermolecular proton exchange is slowed, often allowing us to observe spin–spin coupling interactions that are decoupled and masked by exchange in the free amine. In amides, which are less basic than amines, proton exchange is slow, and coupling is often observed between the protons on nitrogen and those on the

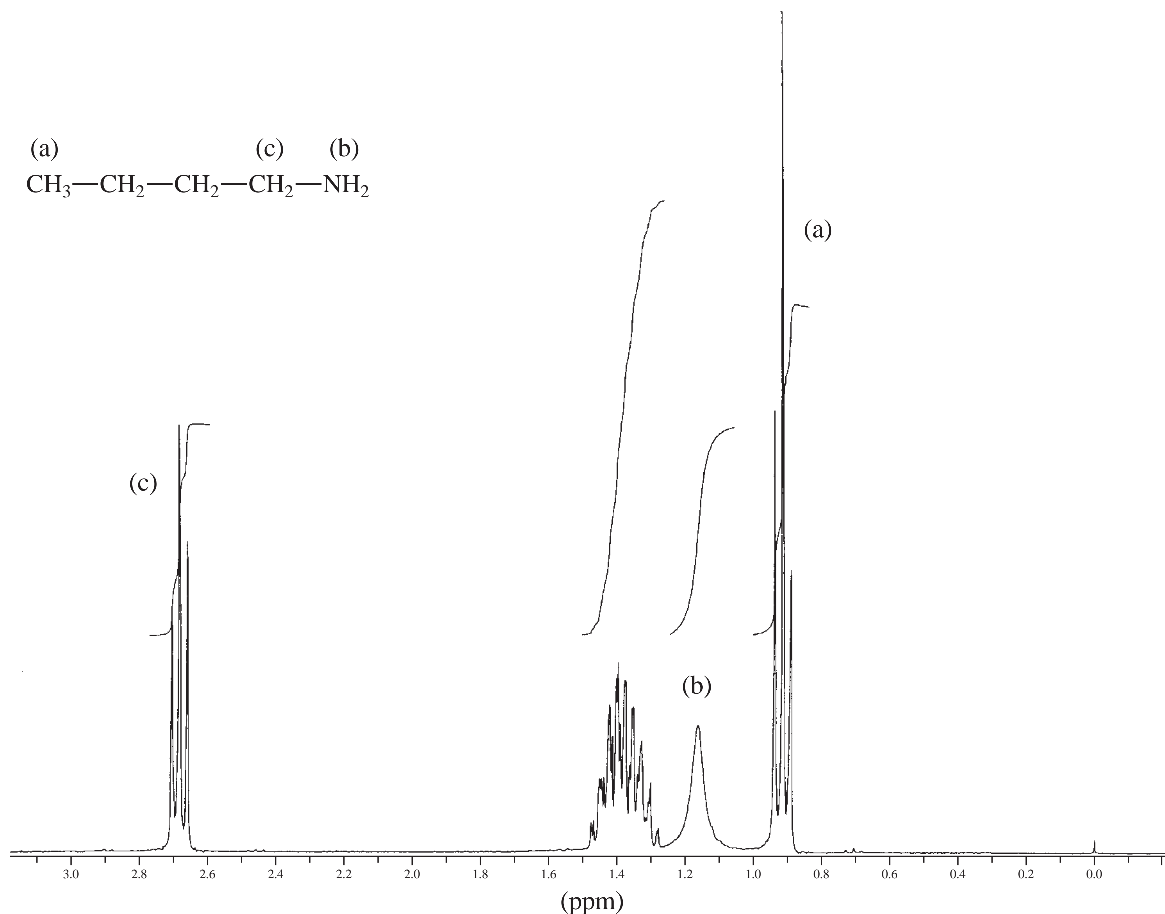


FIGURE 6.9 The NMR spectrum of *n*-butylamine.

α carbon of an alkyl substituent that is substituted on the same nitrogen. The spectra of *n*-butylamine (Fig. 6.9) and 1-phenylethylamine (Fig. 6.10) are examples of uncomplicated spectra (no ^3J HN—CH splitting).

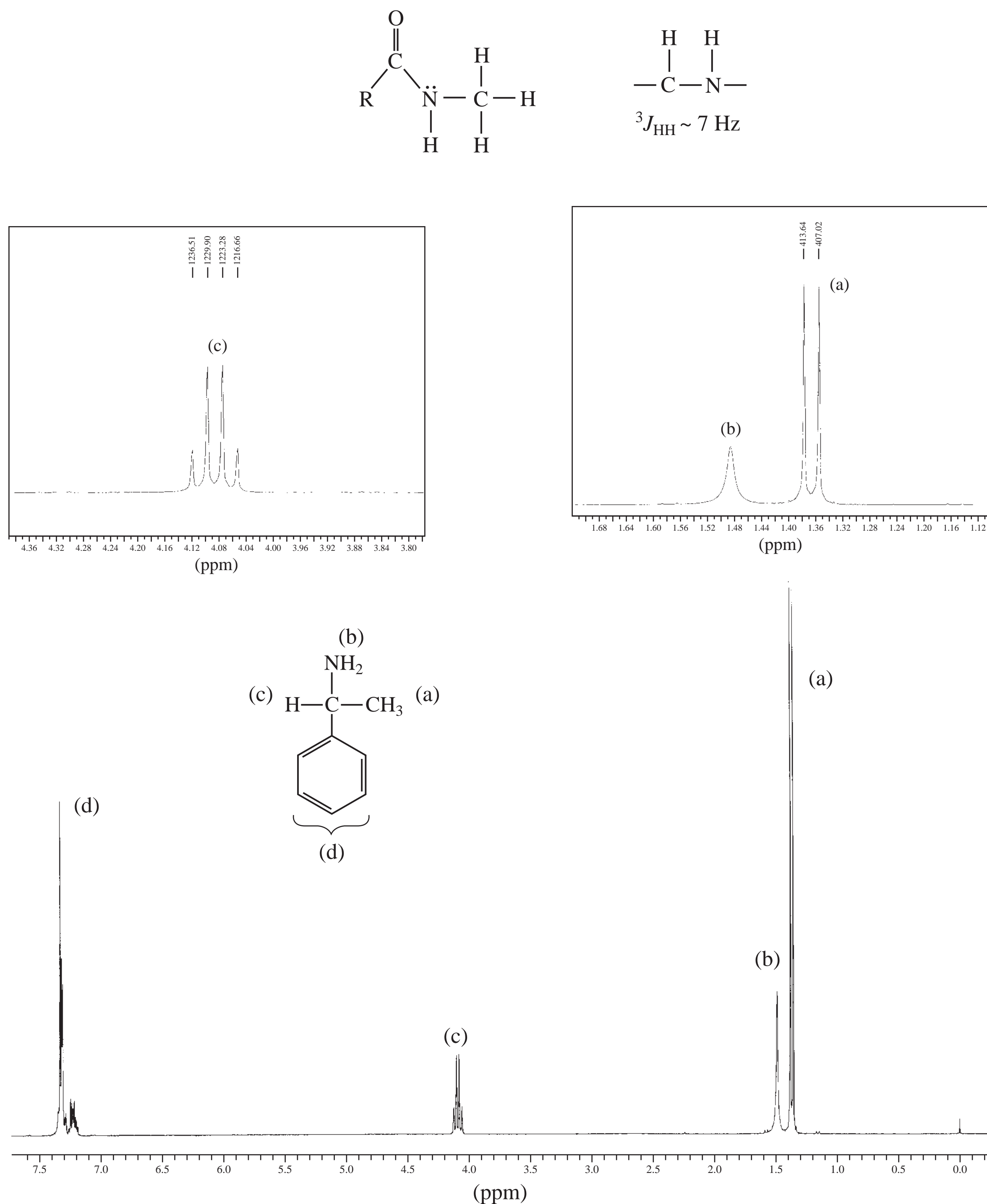
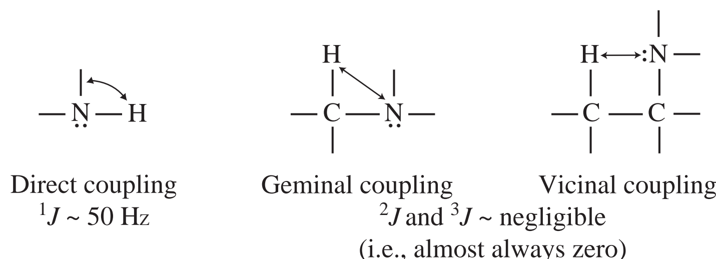


FIGURE 6.10 The NMR spectrum of 1-phenylethylamine.

Unfortunately, the spectra of amines are not always this simple. Another factor can complicate the splitting patterns of both amines and amides: Nitrogen itself has a nuclear spin, which is unity ($I = 1$). Nitrogen can therefore adopt three spin states: +1, 0, and −1. On the basis of what we know so far of spin–spin coupling, we can predict the following possible types of interaction between H and N:



Of these types of coupling, the geminal and vicinal types are very rarely seen, and we can dismiss them. Observation of direct coupling is infrequent but not unknown. Direct coupling is not observed if the hydrogen on the nitrogen is undergoing rapid exchange. The same conditions that decouple NH—CH or HO—CH proton–proton interactions also decouple N—H nitrogen–proton interactions. When direct coupling is observed, the coupling constant is found to be quite large: $^1J \sim 50$ Hz.

One of the cases in which both N—H and CH—NH proton–proton coupling can be observed is the NMR spectrum of methylamine in aqueous hydrochloric acid solution (pH < 1). The species actually being observed in this medium is methylammonium chloride, that is, the hydrochloride salt of methylamine. Figure 6.11 simulates this spectrum. The peak at about 2.2 ppm is due to water (of which there is plenty in aqueous hydrochloric acid solution!). Figures 6.12 and 6.13 analyze the remainder of the spectrum.

6.5 PROTONS ON NITROGEN: QUADRUPOLE BROADENING AND DECOUPLING

Elements that have $I = \frac{1}{2}$ have approximately spherical distributions of charge within their nuclei. Those that have $I > \frac{1}{2}$ have ellipsoidal distributions of charge within their nuclei and as a result have a **quadrupole moment.** Thus, a major factor determining the magnitude of a quadrupole moment is the symmetry about the nucleus. Unsymmetrical nuclei with a large quadrupole moment are very sensitive both to interaction with the magnetic field of the NMR spectrometer and to magnetic and electric perturbations of their valence electrons or their environment. Nuclei with large quadrupole moments undergo nuclear spin transitions at faster rates than nuclei with small moments and easily reach *saturation*—the condition in which nuclear spin transitions (both absorption and emission) occur at a rapid rate. Rapid nuclear transitions lead to an effective decoupling of the nucleus with a quadrupole moment from the adjacent NMR-active nuclei. These adjacent nuclei see a single averaged spin ($I_{effective} = 0$) for the nucleus with the quadrupole moment, and no splitting occurs. Chlorine, bromine, and iodine have large quadrupole moments and are effectively decoupled from interaction with adjacent protons. Note, however, that fluorine ($I = \frac{1}{2}$) has no quadrupole moment, and it does couple with protons.

Nitrogen has a moderate-size quadrupole moment, and its spin transitions do not occur as rapidly as those in the heavier halogens. Furthermore, the transitional rates and lifetimes of its excited spin states (i.e., its quadrupole moments) vary slightly from one molecule to another. Solvent

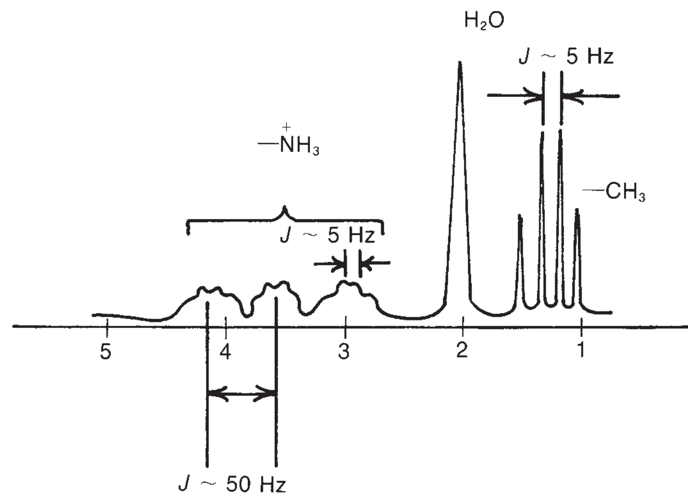


FIGURE 6.11 ^{1}H NMR spectrum of $CH_3NH_3^+$ in H_2O (pH < 1).

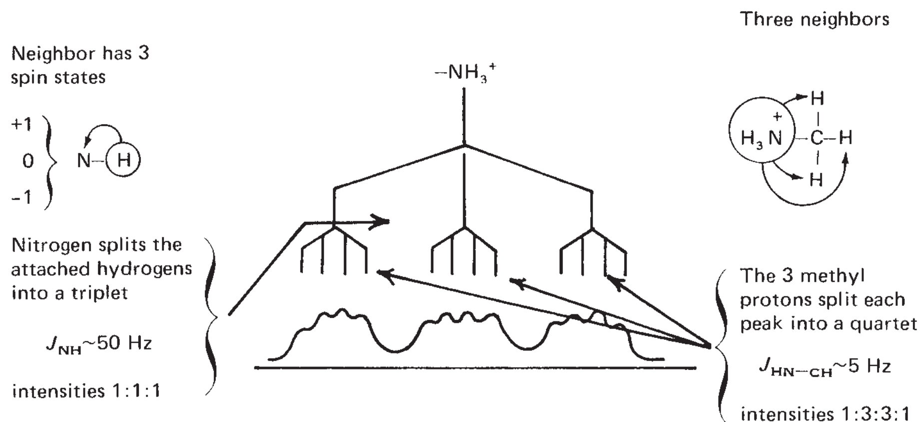


FIGURE 6.12 An analysis of the ^{1}H NMR spectrum of methylammonium chloride: protons on nitrogen.

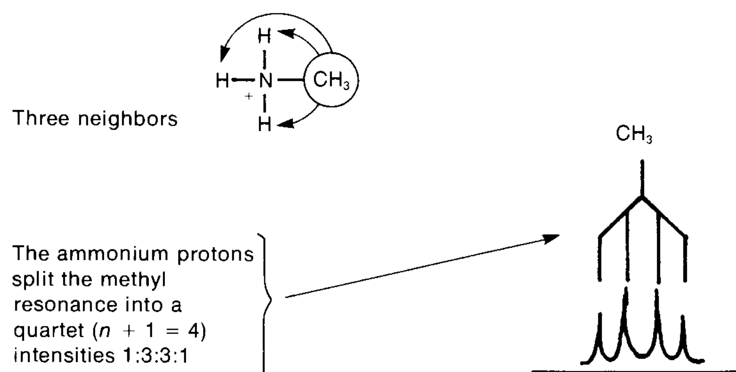


FIGURE 6.13 An analysis of the ^{1}H NMR spectrum of methylammonium chloride: methyl protons.

environment and temperature also seem to affect the quadrupole moment. As a result, three distinct situations are possible with a nitrogen atom:

1. **Small quadrupole moment for nitrogen.** In this case, coupling is seen. An attached hydrogen (as in N—H) is split into three absorption peaks because of the three possible spin states of nitrogen (+1, 0, −1). This first situation is seen in the spectrum of methylammonium chloride (Figs. 6.11 to 6.13). Ammonium, methylammonium, and tetraalkylammonium salts place the nitrogen nucleus in a very symmetrical environment, and $^{1}H—^{15}N$ coupling is observed. A similar circumstance occurs in borohydride ion, where $^{1}H—^{11}B$ and $^{1}H—^{10}B$ couplings are readily observed.
2. **Large quadrupole moment for nitrogen.** In this case, no coupling is seen. Due to rapid transitions among the three spin states of nitrogen, an attached proton (as in N—H) "sees" an averaged (zero) spin state for nitrogen. A singlet is observed for the hydrogen. This second situation is seen frequently in primary aromatic amines, such as substituted anilines.
3. **Moderate quadrupole moment for nitrogen.** This intermediate case leads to peak broadening, called **quadrupole broadening,** rather than splitting. The attached proton (as in N—H) is "not sure of what it sees." Figure 6.14, the NMR spectrum of pyrrole, shows an extreme example of quadrupole broadening in which the NH absorption extends from 7.5 to 8.5 ppm.

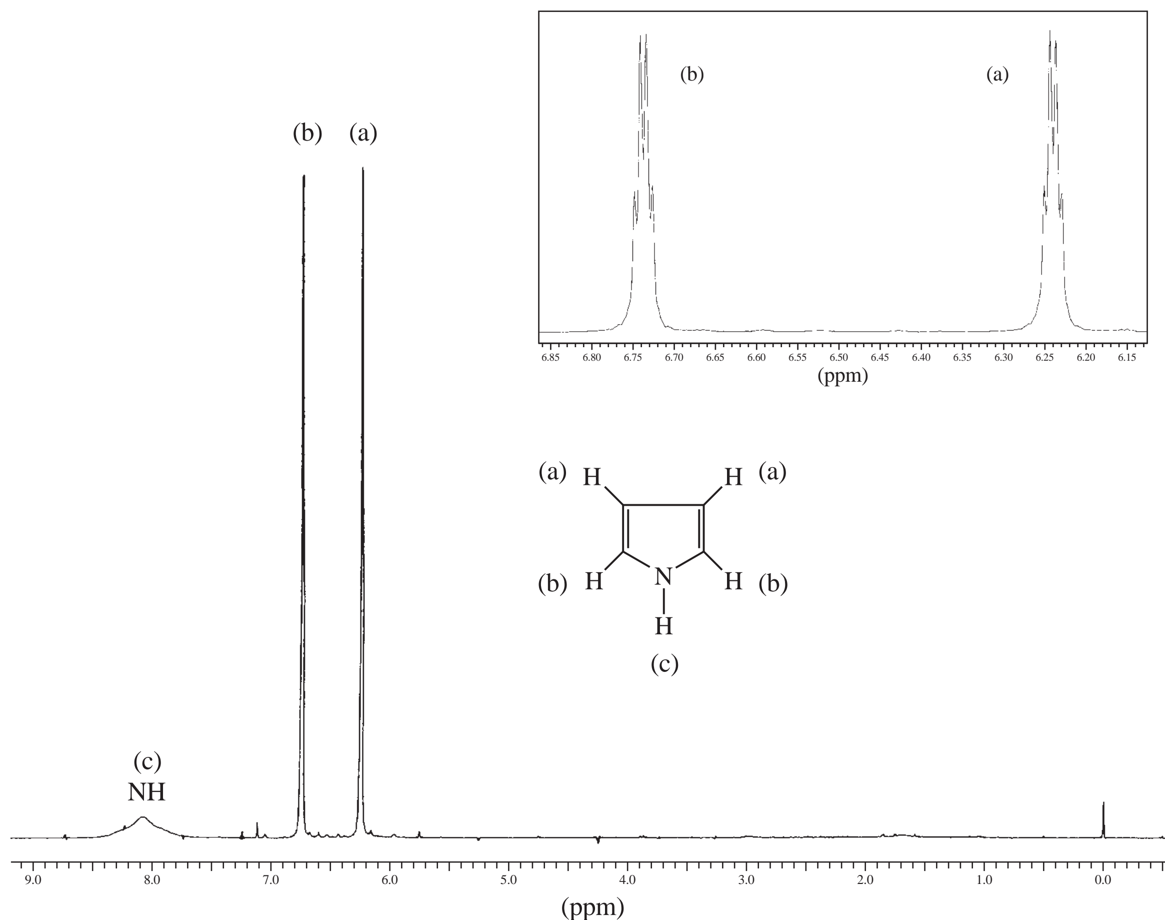


FIGURE 6.14 ^{1}H NMR spectrum of pyrrole. The inset shows expansions of the resonances of the ring C—H protons.

6.6 AMIDES

Quadrupole broadening usually affects only the proton (or protons) attached directly to nitrogen. In the proton NMR spectrum of an amide, we usually expect to see the NH proton appear as a broadened singlet. In some cases, the broadening is due to proton exchange, but recall that the lower acidity of the amide proton slows chemical exchange (Section 6.4). In many instances, one will observe the protons on a carbon atom adjacent to the nitrogen split by the NH proton (^3J H—C—N—H). Nevertheless, the NH peak will still appear as a broad singlet; nuclear quadrupole broadening obscures any coupling to the NH. This is illustrated in the ^{1}H NMR spectrum of *N*-ethylnicotinamide (Fig. 6.15). Note the methylene protons at 3.5 ppm are split by the vicinal methyl protons and the N—H proton and should be a doublet of quartets. In this case, the resonance is an apparent pentet (apparent quintet) because the two types of vicinal couplings are approximately equal in magnitude. The amide N—H is a broadened singlet at 6.95 ppm.

While considering the NMR spectra of amides, note that groups attached to an amide nitrogen often exhibit different chemical shifts. For instance, the NMR spectrum of *N*,*N*-dimethylformamide shows two distinct methyl peaks (Fig. 6.16). Normally, one might expect the two identical groups attached to nitrogen to be chemically equivalent because of free rotation around the C—N bond to the carbonyl group. However, the rate of rotation around this

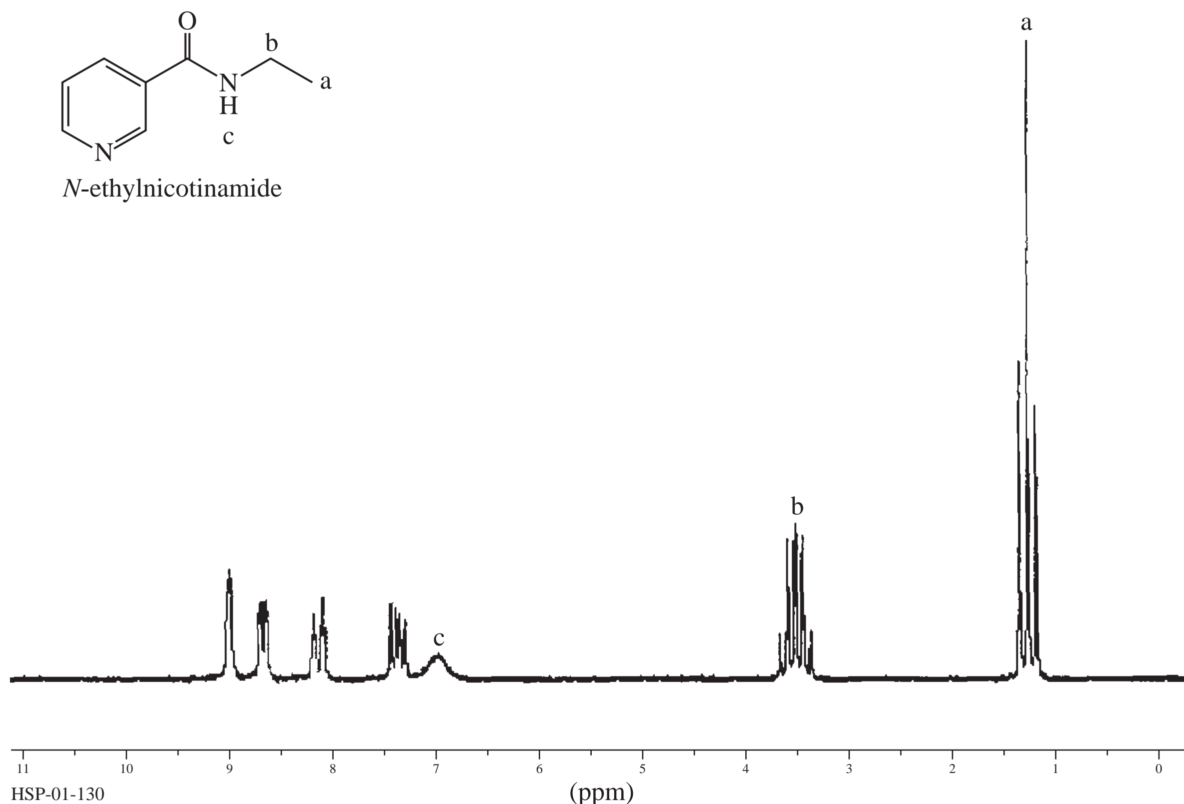


FIGURE 6.15 ^{1}H NMR spectrum of *N*-ethylnicotinamide.

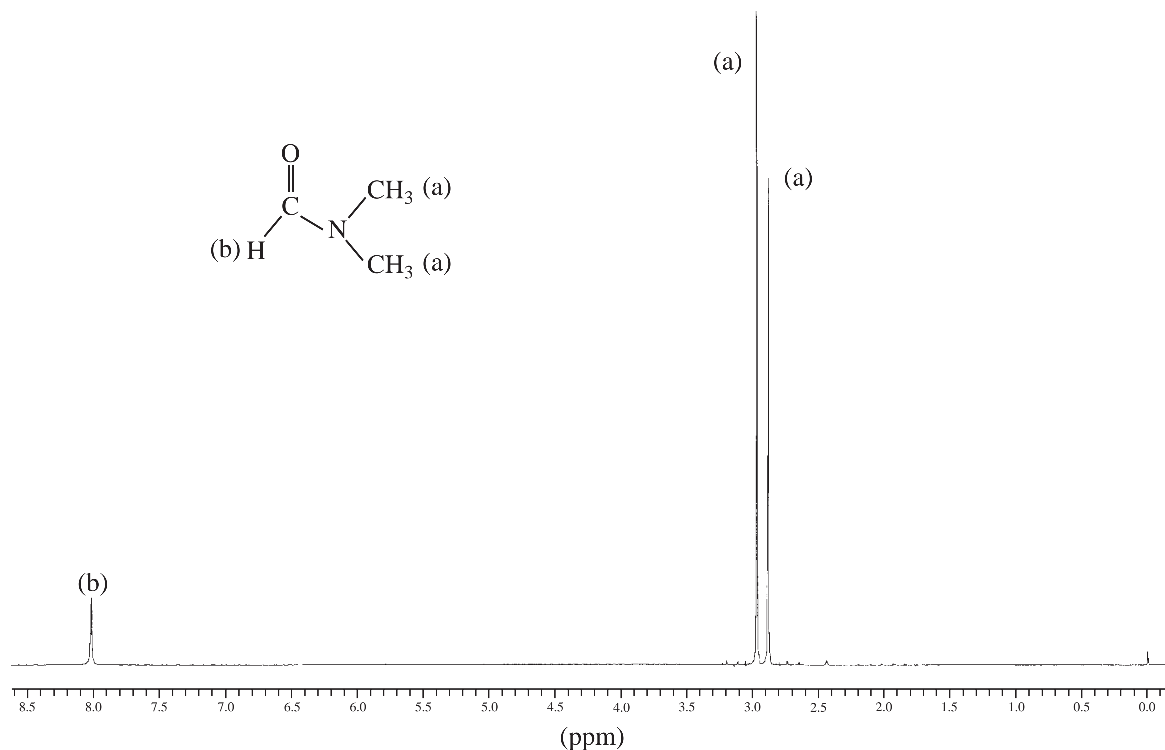
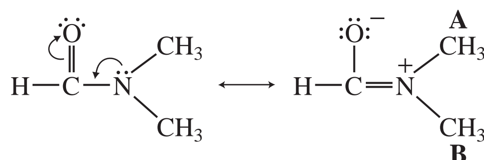
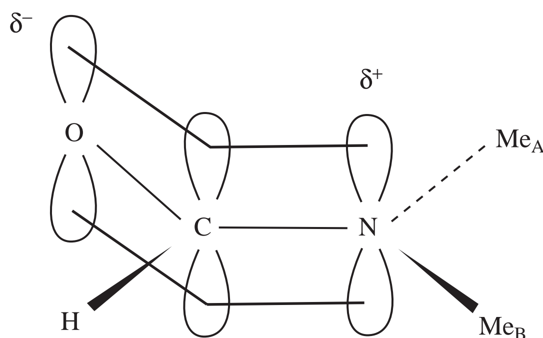


FIGURE 6.16 The ^{1}H NMR spectrum of *N,N*-diethylformamide.

bond is slowed by resonance interaction between the unshared pair of electrons on nitrogen and the carbonyl group.



The resonance delocalization requires that the molecule adopt a planar geometry, and it thus interferes with free rotation. If the free rotation is slowed to the point that it takes longer than an NMR transition, the NMR spectrometer sees two different methyl groups, one on the same side of the C=N bond as the carbonyl group and the other on the opposite side. Thus, the groups are in magnetically different environments and have slightly different chemical shifts.



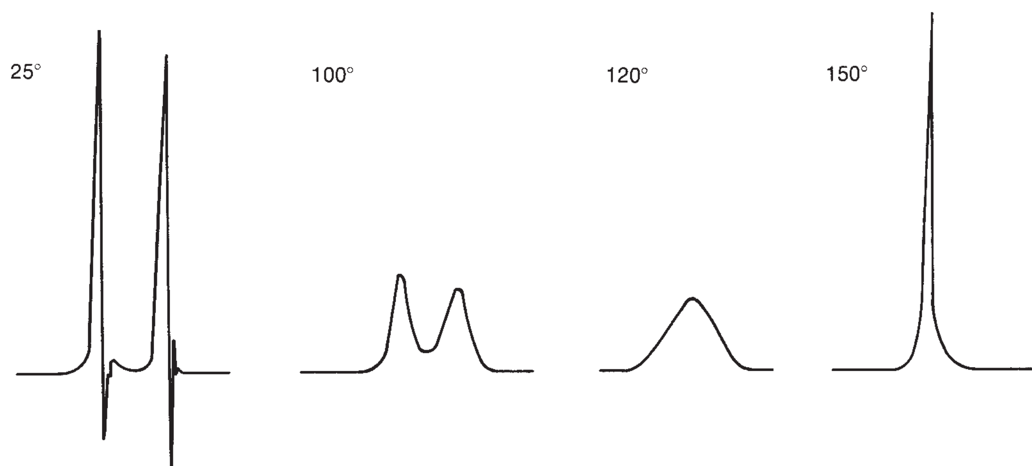


FIGURE 6.17 The appearance of the methyl resonances of *N,N*-dimethylformamide with increasing temperature.

If one successively raises the temperature of the dimethylformamide sample and redetermines the spectrum, the two peaks first broaden (80–100°C), then merge to a single broad peak (~120°C), and finally give a sharp singlet (150°C). The increase of temperature apparently speeds up the rate of rotation to the point at which the NMR spectrometer records an "average" methyl group. That is, the methyl groups exchange environments so rapidly that during the period of time required for the NMR excitation of one of the methyl protons, that proton is simultaneously experiencing all of its possible conformational positions. Figure 6.17 illustrates changes in the appearance of the methyl resonances of *N*,*N*-dimethylformamide with temperature.

In Figure 6.18, the spectrum of chloroacetamide appears to show quadrupole broadening of the $-NH_2$ resonance. Also, notice that there are *two* N—H peaks. In amides, restricted rotation often occurs about the C—N bond, leading to nonequivalence of the two hydrogens on the nitrogen as was observed for the methyl groups of *N*,*N*'-dimethylformamide. Even in a substituted amide (RCONHR'), the single hydrogen could have two different chemical shifts.

Depending on the rate of rotation, an averaging of the two NH absorptions could lead to peak broadening (see Sections 6.1, 6.2C, and 6.4). Thus, in amides, three different peak-broadening factors must always be considered:

1. Quadrupole broadening
2. An intermediate rate of hydrogen exchange on nitrogen
3. Nonequivalence of the NH hydrogen(s) due to restricted rotation

The last two effects should disappear at higher temperatures, which increase either the rate of rotation or the rate of proton exchange.

6.7 THE EFFECT OF SOLVENT ON CHEMICAL SHIFT

Chemists generally obtain the NMR spectrum of a substance by following a typical routine. The substance must be dissolved in a solvent, and the solvent that is selected should have certain desirable properties. It should be inexpensive, it should dissolve a wide range of substances, and it should contain deuterium for locking and shimming purposes on Fourier transform (FT)

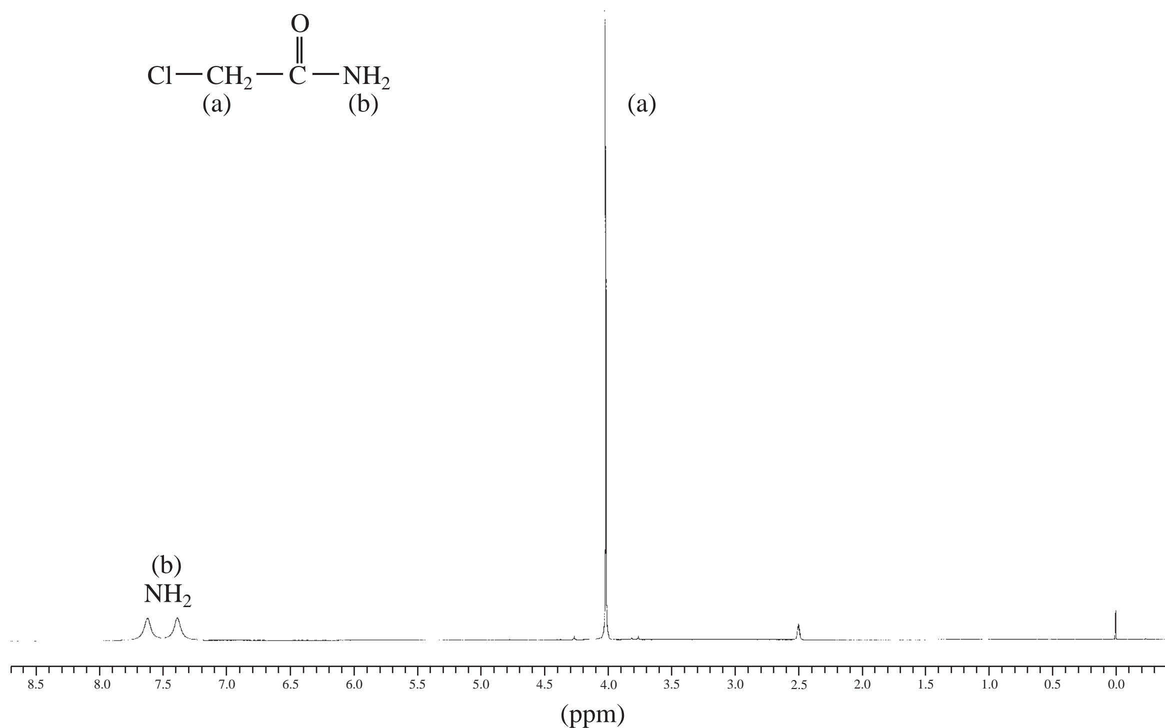


FIGURE 6.18 The ^{1}H NMR spectrum of chloroacetamide.

NMR instruments. Deuteriochloroform (chloroform-*d*, $CDCl_3$) fulfills these requirements. This solvent works well in most applications, and chemists frequently do not consider the role of the solvent in determining the spectrum beyond this point.

The observed chemical shifts, however, depend not only on the structure of the molecule being studied, but also on the interactions between the sample molecule and the surrounding solvent molecules. If the solvent consists of nonpolar molecules, such as hydrocarbons, there is only weak interaction between solute and solvent (van der Waals interactions or London forces), and the solvent has only a minimal effect on the observed chemical shift.

If the solvent that is selected is polar (e.g., acetone, acetonitrile, chloroform, dimethylsulfoxide, and methanol), there are stronger dipole interactions between solvent and solute, especially if the solute molecule also contains polar bonds. The interactions between the polar solvent and a polar solute are likely to be stronger than the interactions between the solvent and tetramethylsilane (TMS, which is nonpolar), and the result is that the observed chemical shift of the molecule of interest will be shifted with respect to the observed chemical shift in a nonpolar solvent. The magnitude of this **solvent-induced shift** can be on the order of several tenths of a parts per million in a proton spectrum. Furthermore, simply changing the concentration of the solute can result in chemical shift changes, especially for environments near a hydrogen bond donor/acceptor or an exchangeable site.

One can get a sense of how common solvent-induced shifts are by looking at a series of spectra in a reference work such as *The Aldrich Library of ^{13}C and ^{1}H FT-NMR Spectra.* All of the spectra in this library were carefully referenced to TMS = 0.00 ppm. Looking through the spectra of nonaromatic esters and lactones in the *Aldrich Library,* for example, one sees the resonance from the residual chloroform peak (the small amount of $CHCl_3$ remaining in the $CDCl_3$) varies from 7.25 to 7.39 ppm. This chemical shift variability is from the small changes in the local shielding environment of the $CHCl_3$ induced by the solute (and vice versa) via intermolecular interactions. Great care must be taken when comparing one's own experimental data with tabulated

spectral data from the literature for chemical shift matches. Many researchers use NMR solvents that do not contain TMS and thus reference their chemical shift to the residual solvent signal, which we have just seen can vary. One should be sure to reference spectra in the same way as the literature data. When making such comparisons, it is not at all uncommon to have consistent chemical shift mismatches across a spectrum, with all of the resonances 0.06 ppm higher (or lower) than the literature data, for example.

If the solvent has a strong diamagnetic anisotropy (e.g., benzene, pyridine, or nitromethane), the interaction between the solute and the anisotropic field of the solvent will give rise to significant chemical shift changes. Again, the solvent will interact more strongly with the solute than it does with TMS. The result is a significant chemical shift change for the solute molecules with respect to the chemical shift of TMS. Solvents such as benzene and pyridine will cause the observed resonance of a given proton to be shifted to a higher field (smaller δ), while other solvents, such as acetonitrile, cause a shift in the opposite direction. This difference appears to be dependent on the shape of the solvent molecules. Aromatic solvents, such as benzene and pyridine, are flat, of course, while acetonitrile has a rod-like shape. The shape of the solvent molecule affects the nature of the solute–solvent complexes that are formed in solution.

Figure 6.19 shows the ^{1}H NMR spectrum of 2-phenyl-4-penten-2-ol acquired in various solvents. Note the chemical shift variability in the vinyl hydrogens between 5 and 6 ppm. The other

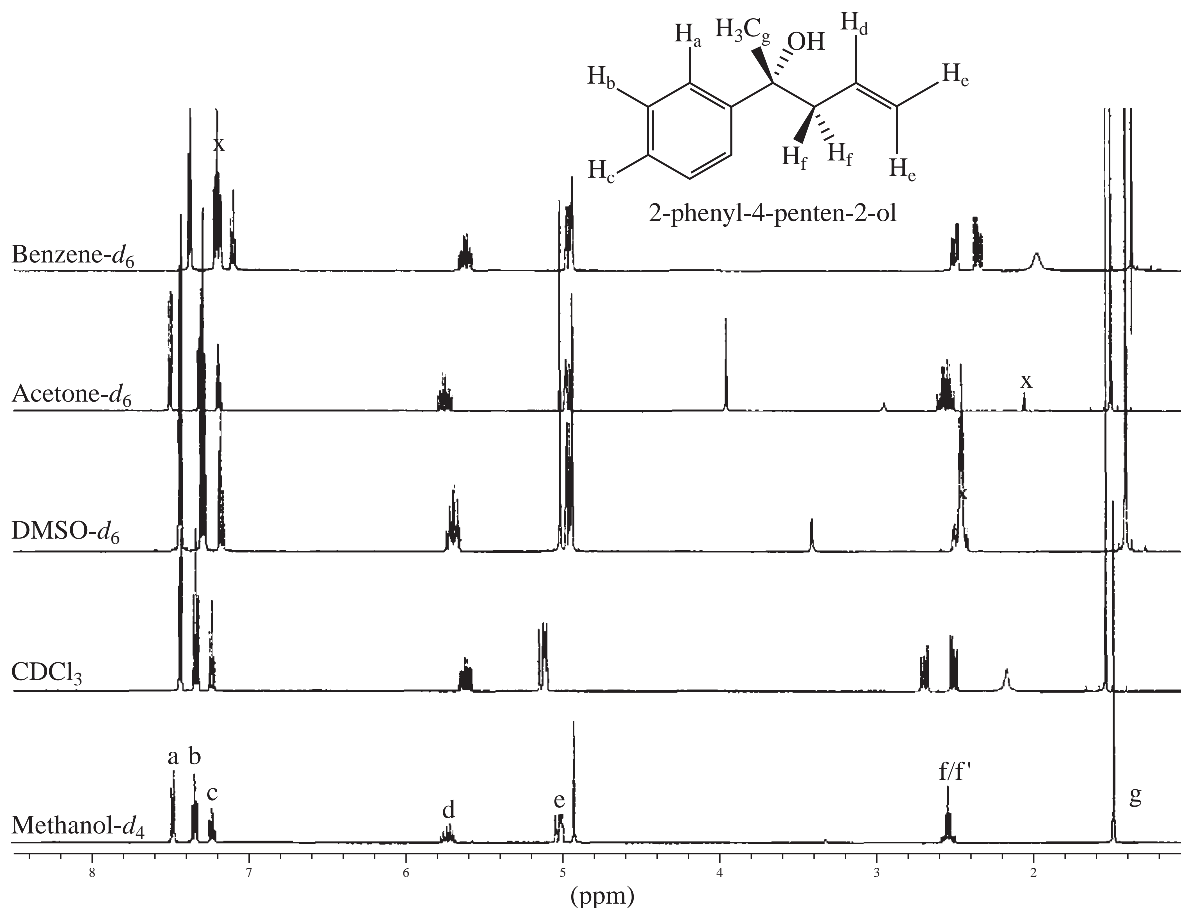


FIGURE 6.19 The ^{1}H NMR spectrum of 2-phenyl-4-penten-2-ol in various solvents. Signals marked with an x are from solvent or water.

significant differences are seen in the signals from the diastereotopic allylic methylene protons appearing between 2.1 and 2.4 ppm. In methanol-d_4, DMSO-d_6, and acetone-d_6, the signals for these protons are significantly overlapped second-order resonances. In DMSO-d_6, there is the added complication that the methylene protons overlap with the residual signal from DMSO-d_5 at 2.5 ppm. In chloroform and benzene, however, the allylic methylene signals are well separated, and the coupling constants can be readily measured.

Figure 6.20 shows the ^{1}H NMR spectrum of ethyl 2-methyl-4-pentenoate acquired in various solvents. As in the previous example, the vinyl hydrogen chemical shifts vary with solvent, most notably in acetone-d_6 and benzene-d_6, the solvents with the greatest diamagnetic anisotropy in this group. Note also that in acetone-d_6 it is possible to readily distinguish the *E* and Z alkene protons, H_b and H_c, whereas these signals are partially overlapped in the spectra acquired in the other solvents. The hydrogen α to the ester carbonyl and allylic hydrogen signals between 2 and 3 ppm also have chemical shifts that vary with solvent. These three resonances are well separated in methanol-d_4 and $CDCl_3$. In DMSO-d_6 and acetone-d_6, one of the signals is partially obscured by solvent or water signals. In benzene-d_6, the resonances of one of the allylic hydrogens and the α hydrogen are overlapped. Note also that in benzene-d_6, the resonance at 3.8 ppm from the ethoxy methylene group displays the diastereotopic nature of those protons. In the other solvents, the ethoxy group has the expected quartet/triplet splitting pattern in the spectrum.

FIGURE 6.20 The ^{1}H NMR spectrum of ethyl 2-methyl-4-pentenoate in various solvents. Signals marked with an x are from solvent or water.

The chemist can use these solvent-induced chemical shift changes to clarify complex spectra that feature overlapping multiplets. Often, by adding just a small amount (5–20%) of a benzene-d_6 or pyridine-d_5 to the $CDCl_3$ solution of an unknown, a dramatic effect on the appearance of the spectrum can often be observed. The chemical shifts of peaks in the proton spectrum can be shifted by as much as 1 ppm, with the result that overlapping multiplets may be separated from one another sufficiently to allow them to be analyzed. The use of this "benzene trick" is an easy way to simplify a crowded spectrum.

Solvents also play a role in NMR spectroscopy as common impurities in samples, especially in synthetic work, for which trace amounts of solvents that could not be removed completely by rotary evaporation often remain in samples. Other common trace impurities in spectra include water (either from the deuterated solvent or from the surface of the glass) and stopcock grease. Occasionally, one will see resonances in an NMR spectrum from plasticizer that has leached from laboratory tubing. Being able to spot these trace impurities for what they are and "mentally edit" the spectrum to avoid distraction by the extraneous resonances is a valuable skill. Just as chemical shifts of sample resonances can change in different solvents, the chemical shifts of these trace impurities also appear at different places in the spectrum in different solvents. Tables listing the properties of common NMR solvents will often include an entry for the chemical shift of residual water as well. Trace water, for example, appears at 1.56 ppm in $CDCl_3$, but at 0.40 ppm in benzene-d_6 (C_6D_6) and at 2.13 ppm and 4.78 ppm in acetonitrile-d_3 (CD_3CN) and methanol-d_4 (CD_3OD), respectively. Some years ago, Gotleib and coworkers published extensive tabulations of the ^{1}H and ^{13}C chemical shifts of common laboratory solvents in $CDCl_3$, acetone-d_6, DMSO-d_6, benzene-d_6, (C_6D_6), acetonitrile-d_3, methanol-d_4, and D_2O in the *Journal of Organic Chemistry* (see references).

6.8 CHEMICAL SHIFT REAGENTS

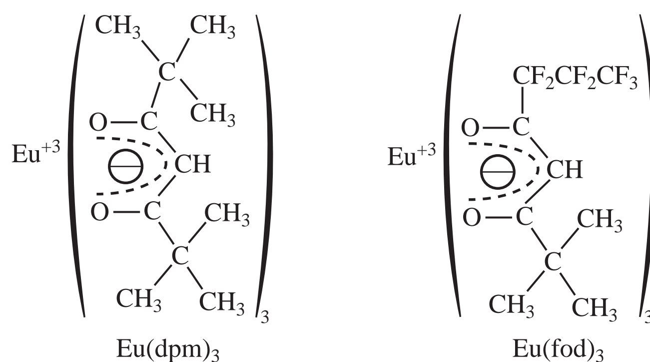
Often, the low-field (60- or 90-MHz) spectrum of an organic compound, or a portion of it, is almost undecipherable because the chemical shifts of several groups of protons are all very similar. In such a case, all of the proton resonances occur in the same area of the spectrum, and often peaks overlap so extensively that individual peaks and splittings cannot be extracted. One of the ways in which such a situation can be simplified is by the use of a spectrometer that operates at a frequency higher. Although coupling constants do not depend on the operation frequency or the field strength of the NMR spectrometer, chemical shifts in Hertz *are* dependent on these parameters (as Section 3.17 discussed). This circumstance can often be used to simplify an otherwise-undecipherable spectrum.

Suppose, for instance, that a compound contains three multiplets: a quartet and two triplets derived from groups of protons with very similar chemical shifts. At 60 MHz, these peaks may overlap and simply give an unresolved envelope of absorptions. In redetermining the spectrum at higher field strengths, the coupling constants do not change, but the chemical shifts in Hertz (not parts per million) of the proton groups (H_A, H_B, H_C) responsible for the multiplets do increase. At 300 MHz, the individual multiplets are cleanly separated and resolved (see, for example, Fig. 3.35). Also remember that second-order effects disappear at higher fields, and that many second-order spectra become first order at or above 300 MHz (Sections 5.7A and 5.7F).

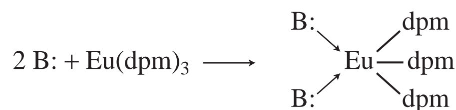
Researchers have known for some time that interactions between molecules and solvents, such as those due to hydrogen bonding, can cause large changes in the resonance positions of certain types of protons (e.g., hydroxyl and amino). They have also known that changing from the usual NMR solvents such as $CDCl_3$ to solvents such as benzene, which impose local anisotropic effects

on surrounding molecules, can greatly affect the resonance positions of some groups of protons (just discussed in Section 6.7). In many cases, it is possible to resolve partially overlapping multiplets by such a solvent change. However, the use of **chemical shift reagents**, an innovation dating from the late 1960s, allows a rapid and relatively inexpensive means of resolving overlapping multiplets in some spectra. Most of these chemical shift reagents are organic complexes of paramagnetic rare-earth metals from the lanthanide series. When such metal complexes are added to the compound for which the spectrum is being determined, profound shifts in the resonance positions of the various groups of protons are observed. The direction of the shift (upfield or downfield) depends primarily on which metal is used. Complexes of europium, erbium, thulium, and ytterbium shift resonances to lower field (larger δ), while complexes of cerium, praseodymium, neodymium, samarium, terbium, and holmium generally shift resonances to higher field. The advantage of using such reagents is that shifts similar to those observed at higher field can be induced without the purchase of a high-field NMR instrument.

Of the lanthanides, europium is probably the most commonly used metal for shift reagents. Two of its widely used complexes are *tris*-(dipivalomethanato) europium and *tris*-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium, frequently abbreviated $Eu(dpm)_3$ and $Eu(fod)_3$, respectively.



These lanthanide complexes produce spectral simplifications in the NMR spectrum of any compound with a relatively basic pair of electrons (an unshared pair) which can coordinate with Eu^{3+}. Typically, aldehydes, ketones, alcohols, thiols, ethers, and amines all interact:



The amount of shift a given group of protons experiences depends on (1) the distance separating the metal (Eu^{3+}) and that group of protons and (2) the concentration of the shift reagent in the solution. Because of the latter dependence, it is necessary to include the number of mole equivalents of shift reagent used or its molar concentration when reporting a lanthanide-shifted spectrum.

The spectra of 1-hexanol (Figs. 6.21 and 6.22) beautifully illustrate the distance factor. In the absence of shift reagent, the spectrum shown in Figure 6.21 is obtained. Only the triplet of the terminal methyl group and the triplet of the methylene group next to the hydroxyl are resolved in the spectrum. The other protons (aside from O—H) are found together in a broad, unresolved group.

With the shift reagent added (Fig. 6.22), each of the methylene groups is clearly separated and is resolved into the proper multiplet structure. The spectrum is in every sense *first order* and thus simplified; all of the splittings are explained by the $n + 1$ Rule.

Note one final consequence of the use of a shift reagent. Figure 6.22 shows that the multiplets are not as nicely resolved into sharp peaks as one usually expects. The europium cation of the shift reagent causes a small amount of line broadening by decreasing the relaxation time of the protons in the sample. At high shift-reagent concentrations this problem becomes serious, but at most useful concentrations the amount of broadening is tolerable.

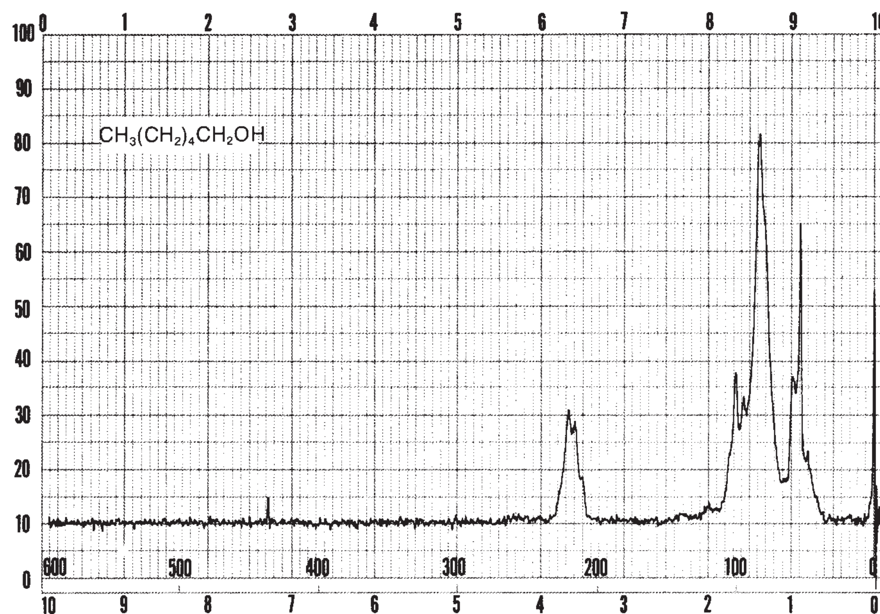


FIGURE 6.21 The normal 60-MHz ^{1}H NMR spectrum of 1-hexanol.

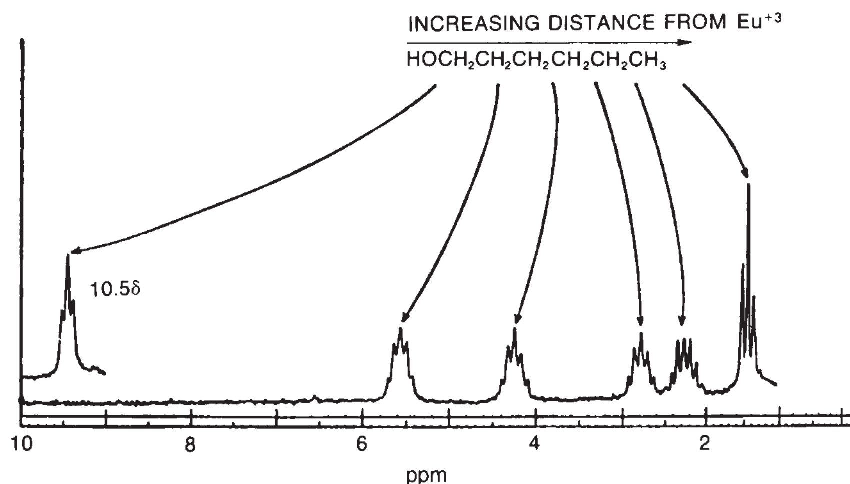
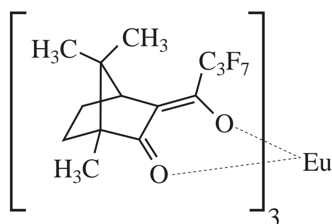


FIGURE 6.22 The 100-MHz NMR spectrum of 1-hexanol with 0.29-mole equivalent of $Eu(dpm)_3$ added. (From Sanders, J. K. M., and D. H. Williams, *Chemical Communications* (1970): 442. Reprinted by permission.)

Today, most laboratories have access to high-field NMR spectrometers (operating at a ^1H frequency of 300 MHz or greater), and simple chemical shift reagents as discussed above are infrequently used. Lanthanide complexes in which the organic ligand on the metal is optically active, however, create a **chiral shift reagent**. One such reagent commonly used for this purpose is tris [3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium(III) [$Eu(hfc)_3$]. When $Eu(hfc)_3$ complexes to a chiral molecule, diastereomeric complexes are formed, which gives rise to different chemical shifts for protons that were previously identical.

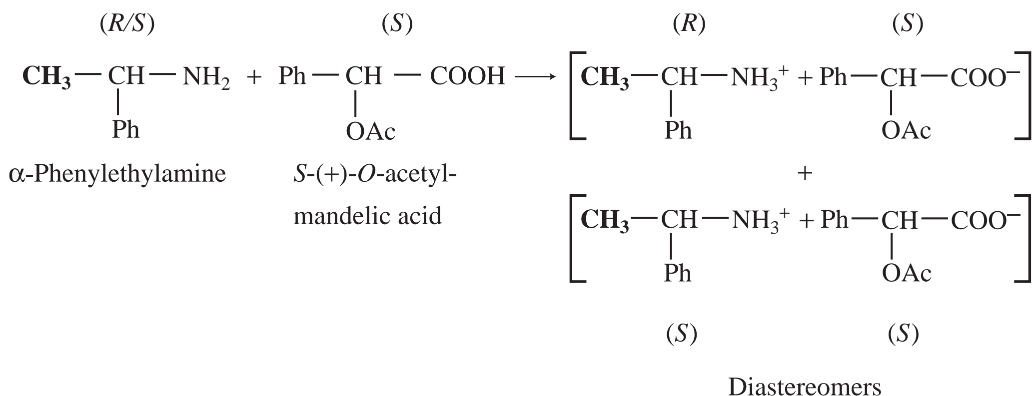


Tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium(III) [$Eu(hfc)_3$]

6.9 CHIRAL RESOLVING AGENTS

A group attached to a stereocenter normally has the same chemical shift whether the stereogenic center has *R* or *S* configuration. However, the group can be made diastereotopic in the NMR (have different chemical shifts) when the racemic parent compound is treated with an optically pure **chiral resolving agent** to produce diastereomers. In this case, the group is no longer present in two enantiomers but in two different *diastereomers*, and its chemical shift is different in each environment.

For instance, if a mixture containing both the *R* and *S* enantiomers of α-phenylethylamine is mixed with an equimolar amount of optically pure (*S*)-(+)-*O*-acetylmandelic acid in an NMR tube containing $CDCl_3$, two diastereomeric salts form:



The methyl groups in the amine portion of the salts are attached to a stereocenter, *S* in one case and *R* in the other. As a result, the methyl groups themselves are now diastereotopic, and they have different chemical shifts. In this case, the *R* isomer is downfield, and the *S* isomer is upfield. Since the methyl groups are adjacent to a methine (CH) group, they appear as doublets at approximately 1.1 and 1.2 ppm, respectively, in the NMR spectrum of the mixture (the exact chemical shifts vary slightly with concentration) (Fig. 6.23).

These doublets may be integrated to determine the exact percentages of the *R* and *S* amines in the mixture. In the example shown, the NMR spectrum was determined with a mixture made by dissolving

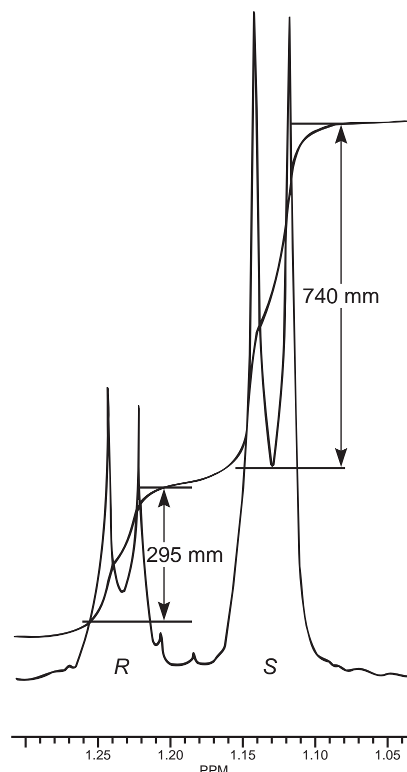


FIGURE 6.23 The 300-MHz ^{1}H spectrum of a 50–50 mixture of (*S*)-α-phenylethylamine from a resolution and unresolved (racemic) α-phenylethylamine in $CDCl_3$ with the chiral resolving agent (*S*)-(+)-*O*-acetylmandelic acid added.

equal quantities of unresolved (±)-α-phenylethylamine and a student's resolved product, which contained predominantly (*S*)-(−)-α-phenylethylamine.

Similarly, an optically pure amine can be used as a chiral resolving agent to analyze the optical purity of a chiral carboxylic acid. For example, addition of optically pure (*S*)-(−)-α-phenylethylamine to a $CDCl_3$ solution of *O*-acetylmandelic acid will form diastereomeric salts as illustrated above. In this case, one would look for the two doublets (one for each enantiomer) from the Ph–C**H**–OAc methine between 5 and 6 ppm in the ^{1}H NMR spectrum.

When one needs to determine the optical purity of a compound that is not amenable to salt formation (i.e., not a carboxylic acid or amine), analysis by NMR becomes slightly more difficult. It is frequently necessary to determine the enantiomeric excesses of chiral secondary alcohols, for example. In these cases, derivatization of the alcohol through covalent attachment of an optically pure auxiliary provides the mixture of diastereomers for analysis. This requires reacting a (usually small, a few milligrams) sample of sample alcohol with the optically pure derivatizing agent. Sometimes, purification of the products is necessary. In the example shown below, a chiral secondary alcohol is reacted with (*S*)-2-methoxyphenylacetic acid [(*S*)-MPA] using dicyclohexylcarbodiimide (DCC) to form diastereomeric esters. After workup, the ^{1}H NMR spectrum of product mixture is acquired, and the resonances from oxygenated methine (***H***CR_1R_2–O–Aux, there will be one signal for each diastereomer) are integrated to determine the optical purity (enantiomeric excess) of the original alcohol sample. Because the products are diastereomers, other methods of analysis (for example, gas chromatography) could also be used for this purpose.

This process is illustrated in Figure 6.24 for 2-pentanol and α-methoxyphenylacetic acid (MPA). To simplify the discussion, ^{1}H NMR spectra from two separate samples are shown. The ester formed from (*R*)-2-pentanol and (*R*)-MPA produced the top spectrum in Figure 6.24, and the ester formed from (*R*)-2-pentanol and (*S*)-MPA produced the bottom spectrum. Most diagnostic are the chemical

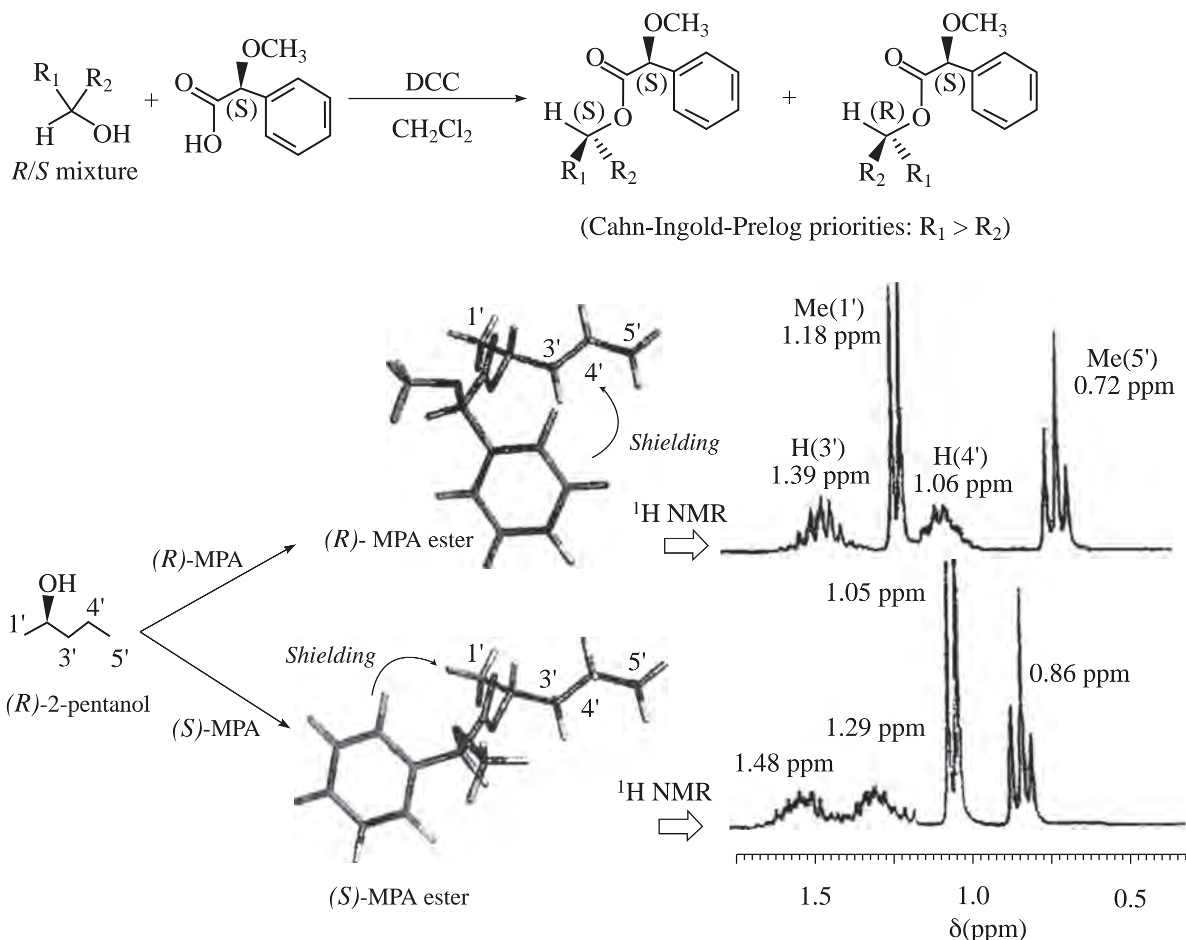


FIGURE 6.24 Use of 2-methoxyphenylacetic acid (MPA) as a chiral derivatizing reagent. (From Seco, J. M., E. Quinoa, and R. Riguera, *Chemical Reviews 104* (2004): 17–117.) Reprinted by permission.

shifts of the methyl doublets. The lowest energy conformation of the (*R*, *R*) ester places position 3' in the shielding region of the phenyl ring, and the methyl group (position 1') is not significantly perturbed, and its doublet appears at 1.18 ppm. In the lowest energy conformation of the (*R*, *S*) ester, however, the methyl group is shielded by the phenyl ring, and its doublet appears upfield at 1.05 ppm. One can imagine an analogous set of spectra would be produced by esters formed by reaction of just one enantiomer of MPA with a mixture of 2-pentanol enantiomers. Integration of the two different methyl doublets would give the enantiomeric ratio of the alcohol sample.

6.10 DETERMINING ABSOLUTE AND RELATIVE CONFIGURATION VIA NMR

A. Determining Absolute Configuration

The methods described in Section 6.9 are very useful for determining optical purities (enantiomeric excesses), but it is usually not possible to determine with certainty the *absolute* configuration of the major enantiomer present unless one has access to authentic samples of each pure enantiomer. This is rarely the case in natural product isolation or synthesis research. In 1973, Mosher described a method

to determine the absolute configuration of secondary alcohols by NMR analysis, and since that time his method has been expanded and refined. In Mosher's method, the alcohol is reacted separately with each enantiomer of methoxytrifluoromethylphenylacetic acid (MTPA) or the corresponding acid chloride (MTPA-Cl) (Fig. 6.25). Note that the carboxylic acid and the acid chloride have the same three-dimensional arrangement of substituents on the stereogenic center but have opposite *R*/*S* configurations as a result of a Cahn–Ingold–Prelog priority change in converting the –OH of the acid to the –Cl of the acid chloride. This unfortunate circumstance has resulted in many instances of confusion and incorrect stereochemical assignments.

After the two MTPA esters are prepared, the NMR spectrum (^{19}F, ^{1}H, and/or ^{13}C) of each derivative is acquired, and the chemical shifts of each resonance are compared. The chemical shift of the resonances for the groups directly attached to the stereocenter in the spectrum of the (*R*) ester is subtracted from the corresponding chemical shifts for those resonances in the spectrum of the (*S*) ester [$\delta(S) - \delta(R) = \Delta\delta^{SR}$]. The absolute configuration of the substrate is then deduced by interpreting the signs of the $\Delta\delta$ values using certain empirical models for the most stable conformation of the esters (Fig. 6.26). Based on his experiments, Mosher concluded that the CF_3 group, Cα, the carboxyl group of the ester, and the oxygenated methine (Cl') are all coplanar. This conformation results in differential shielding of L_1 and L_2 by the phenyl group of the MTPA ester (see Section 3.12 for a discussion of shielding effects of aromatic rings). In the (*R*)-MTPA ester, L_2 is shielded by the phenyl group (Fig. 6.26a). The opposite is true in the (*S*)-MTPA ester—L_1 is shielded by the phenyl group (Fig. 6.26b). As a result, all the protons (or carbons) that are relatively shielded in the (*R*)-MTPA ester will have a positive $\Delta\delta^{SR}$ value (L_2 in Fig. 6.26c), and those not shielded by the phenyl will have a negative $\Delta\delta^{SR}$ value (L_1 in Fig. 6.26c). If the alcohol has the opposite configuration, the shielding environments are reversed (Fig. 6.26d). Once the $\Delta\delta^{SR}$ values are determined for the groups flanking the MTPA ester, one can use the structural models in Figure 6.26c and 6.26d to assign L_1 and L_2 and thereby determine the absolute configuration of the original alcohol. In common practice, most researchers use the *modified Mosher method*, which involves examination of the $\Delta\delta^{SR}$ values not just for the groups directly attached to the stereocenter in question, but to *all* the protons (or carbons) in the compound. In this way, a representative sign of $\Delta\delta^{SR}$ for the substituents L_1 and L_2 can be determined, thus helping to prevent confusion that could arise from an anomalous chemical shift.

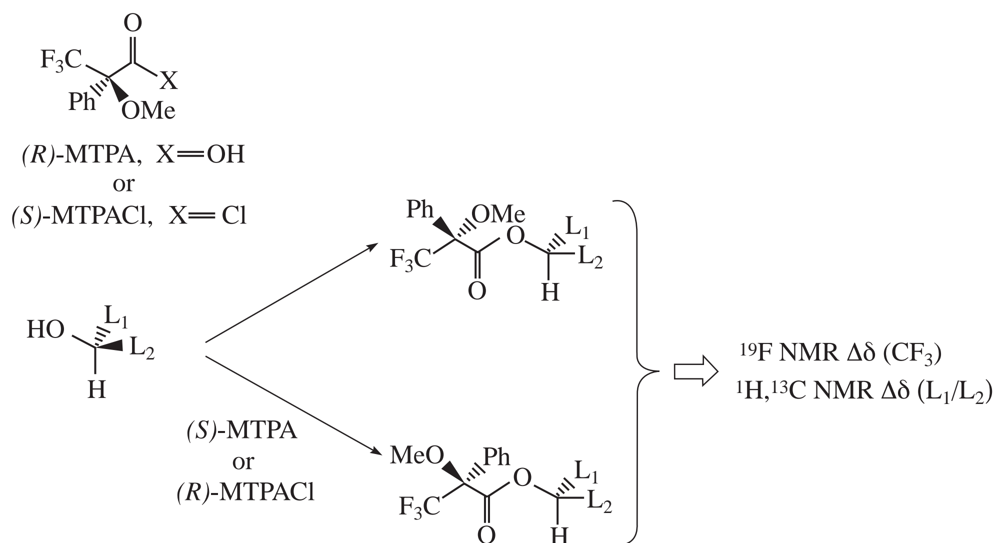


FIGURE 6.25 Formation of Mosher ester derivatives (From Seco, J. M., E. Quinoa, and R. Riguera, *Chemical Reviews 104* (2004): 17–117.) Reprinted by permission.

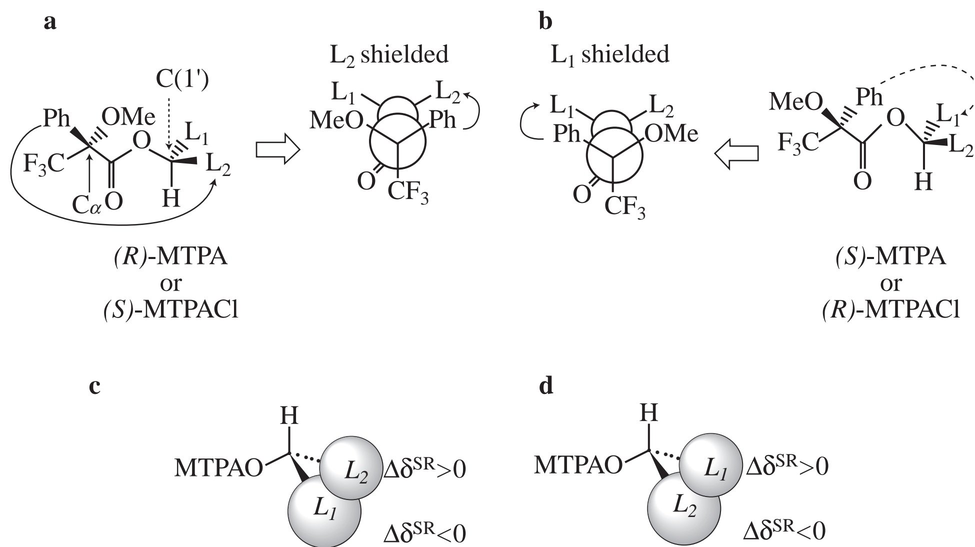


FIGURE 6.26 Analysis of Mosher ester derivatives to determine. (From Seco, J. M., E. Quinoa, and R. Riguera, *Chemical Reviews* 104 (2004): 17–117.)

The Mosher method can also be applied to β-chiral primary alcohols and α-chiral tertiary alcohols. Mosher amides can be prepared from chiral amines and analyzed in a similar fashion. A number of other chiral derivatizing reagents for the determination of absolute configuration of alcohols, amines, carboxylic acids, and sulfoxides have been developed over the years. In general, these chiral auxiliaries all have three features in common: (1) a functional group that allows efficient covalent attachment of the auxiliary to the substrate; (2) a polar or bulky group to fix the compound of interest in a particular conformation; and (3) a group that is able to produce a significant anisotropic effect in the dominant conformation that results in differential shielding in the two species (diastereomers) used in the determination.

Mosher originally used ^{19}F spectroscopy to determine absolute configuration of MTPA derivatives, but today most researchers use ^{1}H NMR for this purpose. ^{19}F has the advantage of an uncrowded spectrum since the only fluorine signals are likely from the MTPA auxiliary itself. ^{1}H NMR is useful in most circumstances, but overlap of resonances can still be a problem, even with a high-field spectrometer, if $\Delta\delta^{SR}$ is small. ^{13}C NMR spectroscopy has the advantage of a wider chemical shift range and therefore less likelihood of resonance overlap. Furthermore, ^{13}C NMR provides useful information even when one or more of the substituents on the stereocenter have no protons. The low sensitivity of ^{13}C, however, presents a limitation if only minute quantities of the substrates are available.

B. Determining Relative Configuration

In Chapter 5, we saw many instances when ^{1}H–^{1}H coupling constants could be used to assign relative configuration, especially when the conformation of the compound can be inferred. We will not expand on that discussion here. For some classes of compounds, simple ^{13}C NMR spectroscopy can be used very reliably to assign relative stereochemical configuration. One of the most reliable examples is the [^{13}C]acetonide method for determining relative configuration of acyclic 1,3-diols. The conformational preferences for 2,2-dimethyl-l,3-dioxolanes (acetone ketals, acetonides) were already well known by 1990, when Rychnovsky correlated the ^{13}C chemical shifts of acetonide methyl groups to stereochemical configuration. Acetonides of *syn*-1,3-diols adopted a chair conformation in which one methyl group of the acetonide is in an axial position and the other methyl group is in an equatorial position. The methyl group in the more shielded axial position has a chemical shift of ~19 ppm in the ^{13}C NMR spectrum and the less-shielded methyl group in the equatorial position appears at ~30 ppm (Fig. 6.27). Conversely,

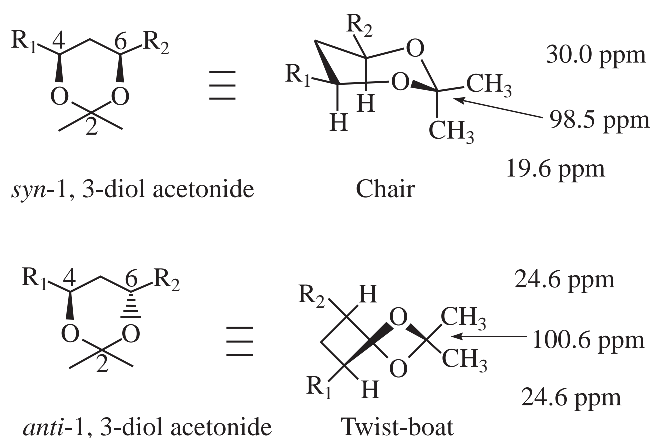


FIGURE 6.27 ^{13}C NMR chemical shift correlations for 1,3-diol acetonides. (From Rychnovsky, S. D., B. N. Rogers, and T. I. Richardson, *Accounts of Chemical Research 31* (1998): 9–17.)

the acetonide derivatives of *anti*-1,3-diols exist in a twist boat conformation to alleviate steric repulsions in the chair conformations. In the *anti*-1,3-diol acetonides, the two methyl groups both appear at ~25 ppm in the ^{13}C NMR spectrum. The chemical shift of the acetal carbon also correlates well to stereochemical configuration, with the acetal carbon of *syn*-1,3-diol acetonides appearing at 98.5 ppm and that of the *anti*-1,3-diol acetonide appearing at 100.6 ppm in the ^{13}C NMR spectrum.

Analysis of literature ^{13}C NMR data for hundreds of 1,3-diol acetonides have proven this method reliable. Only a few types of substituents (R_1 and/or R_2) are problematic. The chemical shift correlations shown in Figure 6.27 only become unreliable when the substituents in the 4 and/or 6 position of the dioxolane ring are an *sp*-hybridized carbon (alkyne or nitrile). Use of the acetal carbon chemical shift correlation is not quite as reliable, but of the hundreds of acetonides examined, fewer than 10% of *syn*-l,3-diol acetonides and 5% of *anti*-1,3-diol acetonides would be misassigned based on the chemical shift of the acetal carbon alone—and practially none will be misassigned if the acetal chemical shift is considered in conjunction with the acetonide methyl chemical shifts. The only drawbacks to this method is that the acetonide derivatives must be prepared from the diol substrates, but this is easily accomplished with a mixture of acetone, 2,2-dimethoxypropane, and pyridinium/*p*-toluenesulfonate (PPTS). When only a small amount of sample is available, ^{13}C-enriched acetone can be used to prepare the acetonides. The [^{13}C]acetonide method is also readily applied to complex natural products containing several different 1,3-diols.

6.11 NUCLEAR OVERHAUSER EFFECT DIFFERENCE SPECTRA

In many cases of interpretation of NMR spectra, it would be helpful to be able to distinguish protons by their *spatial* location within a molecule. For example, for alkenes it would be useful to determine whether two groups are *cis* to each other or whether they represent a *trans* isomer. In bicyclic molecules, the chemist may wish to know whether a substituent is in an *exo* or in an *endo* position. Many of these types of problems cannot be solved by an analysis of chemical shift or by examination of spin–spin splitting effects.

A handy method for solving these types of problems is nuclear Overhauser effect **(NOE) difference spectroscopy**. This technique is based on the same phenomenon that gives rise to the nuclear Overhauser effect (Section 4.5), except that it uses *homonuclear*, rather than a heteronuclear, decoupling. In the discussion of the nuclear Overhauser effect, attention was focused on the case in which a hydrogen atom was directly bonded to a ^{13}C atom, and the hydrogen nucleus was saturated by a broadband signal. In fact, however, for two nuclei to interact via the nuclear Overhauser effect,

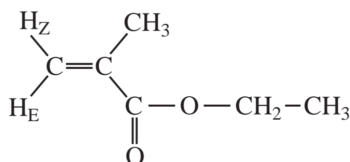
the two nuclei do not need to be directly bonded; it is sufficient that they be *near* each other (generally within about 4 Å). Nuclei that are in close spatial proximity are capable of relaxing one another by a **dipolar** mechanism. If the magnetic moment of one nucleus, as it precesses in the presence of an applied magnetic field, happens to generate an oscillating field that has the same frequency as the resonance frequency of a nearby nucleus, the two affected nuclei will undergo a mutual exchange of energy, and they will relax one another. The two groups of nuclei that interact by this dipolar process must be very near each other; the magnitude of the effect decreases as r^{-6}, where r is the distance between the nuclei.

We can take advantage of this dipolar interaction with an appropriately timed application of a low-power decoupling pulse. If we irradiate one group of protons, any nearby protons that interact with it by a dipolar mechanism will experience an enhancement in signal *intensity*.

The typical NOE difference experiment consists of *two* separate spectra. In the first experiment, the decoupler frequency is tuned to match exactly the group of protons that we wish to irradiate. The second experiment is conducted under conditions identical to the first experiment, except that the frequency of the decoupler is adjusted to a value far away in the spectrum from any peaks. The two spectra are subtracted from each other (this is done by treating digitized data within the computer), and the *difference* spectrum is plotted.

The NOE difference spectrum thus obtained would be expected to show a *negative* signal for the group of protons that had been irradiated. *Positive* signals should be observed *only* for those nuclei that interact with the irradiated protons by means of a dipolar mechanism. In other words, only those nuclei that are located within about 3 to 4 Å of the irradiated protons will give rise to a positive signal. All other nuclei that are not affected by the irradiation will appear as very weak or absent signals.

The spectra presented in Figure 6.28 illustrate an NOE difference analysis of **ethyl methacrylate**.



The upper spectrum shows the normal proton NMR spectrum of this compound. We see peaks arising from the two vinyl hydrogens at 5.5 to 6.1 ppm. It might be assumed that H_E should be shifted further downfield than H_Z owing to the through-space deshielding effect of the carbonyl group. It is necessary, however, to confirm this prediction through experiment to determine unambiguously which of these peaks corresponds to H_Z and which corresponds to H_E.

The second spectrum was determined with the simultaneous irradiation of the methyl resonance at 1.9 ppm. We immediately see that the 1.9-ppm peak appears as a strongly negative peak. The only peak in the spectrum that appears as a positive peak is the vinyl proton peak at 5.5 ppm. The other vinyl peak at 6.1 ppm has nearly disappeared, as have most of the other peaks in the spectrum. The presence of a positive peak at 5.5 ppm confirms that this peak must come from proton H_Z; proton H_E is too far away from the methyl group to experience any dipolar relaxation effects.

The above result could have been obtained by conducting the experiment in the opposite direction. Irradiation of the vinyl proton at 5.5 ppm would have caused the methyl peak at 1.9 ppm to be positive. The results, however, would not be very dramatic; it is always more effective to irradiate the group with the larger number of equivalent hydrogens and observe the enhancement of the group with the smaller number of hydrogens rather than vice versa.

Finally, the third spectrum was determined with the simultaneous irradiation of the H_E peak at 6.1 ppm. The only peak that appears as a positive peak is the H_Z peak at 5.5 ppm, as expected. The methyl peak at 1.9 ppm does not show any enhancement, confirming that the methyl group is distant from the proton responsible for the peak at 6.1 ppm.

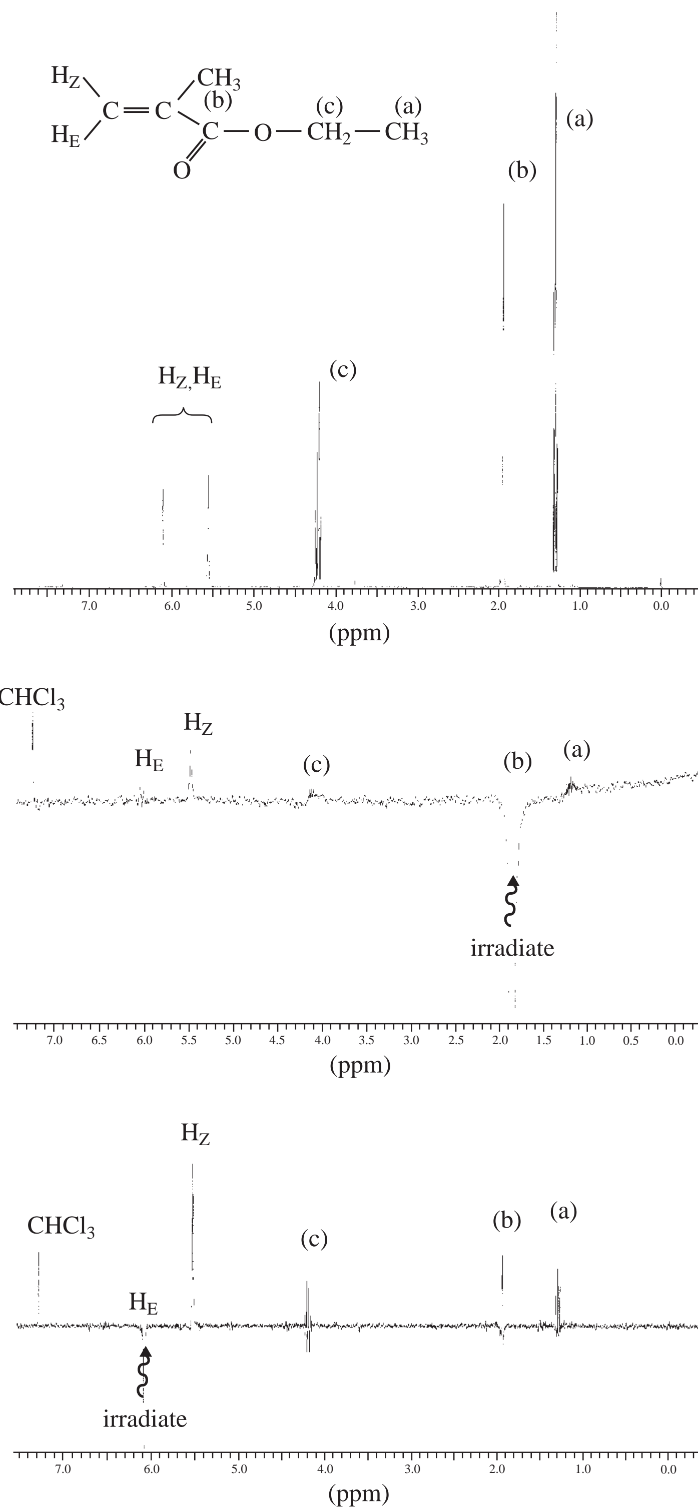


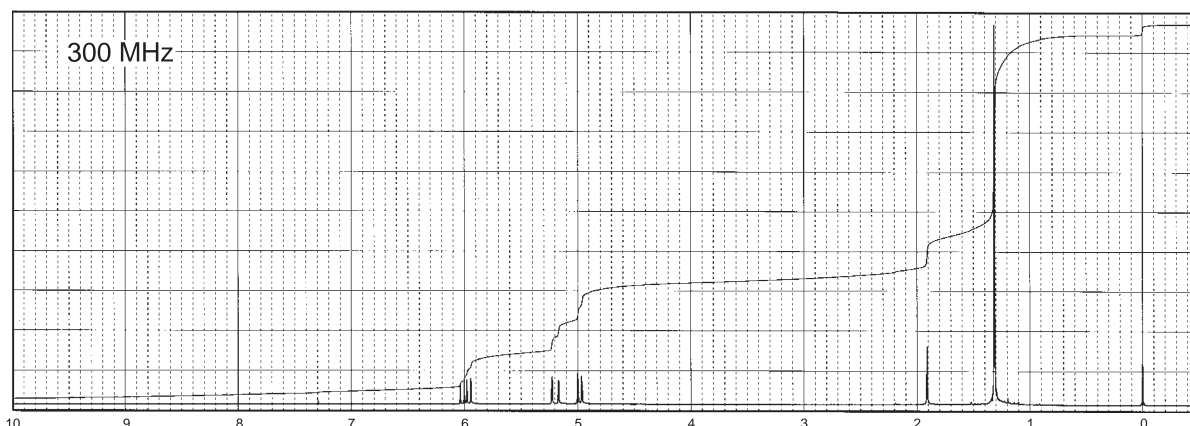
FIGURE 6.28 NOE difference spectrum of ethyl methacrylate. Top spectrum: proton NMR spectrum of ethyl methacrylate without decoupling. Middle spectrum: NOE difference spectrum with irradiation at 1.9 ppm. Bottom spectrum: NOE difference spectrum with irradiation at 6.1 ppm.

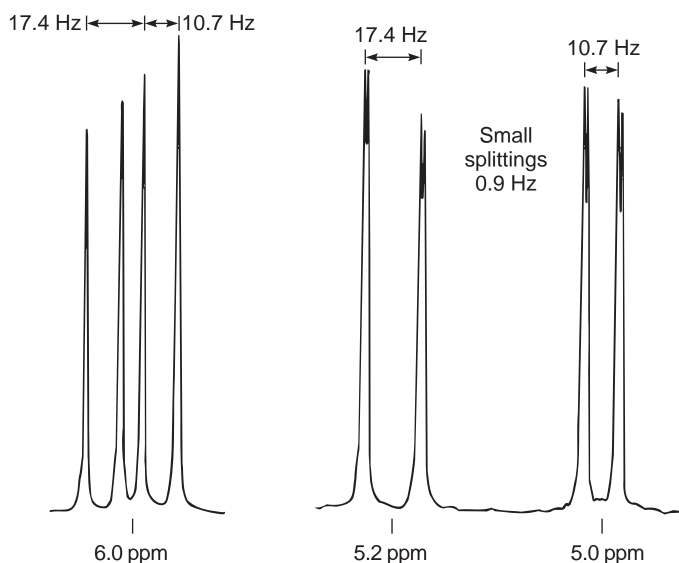
This example is intended to illustrate how NOE difference spectroscopy can be used to solve complex structural problems. This technique is particularly well suited to the solution of problems involving the location of substituents around an aromatic ring and stereochemical differences in alkenes or in bicyclic compounds.

PROBLEMS

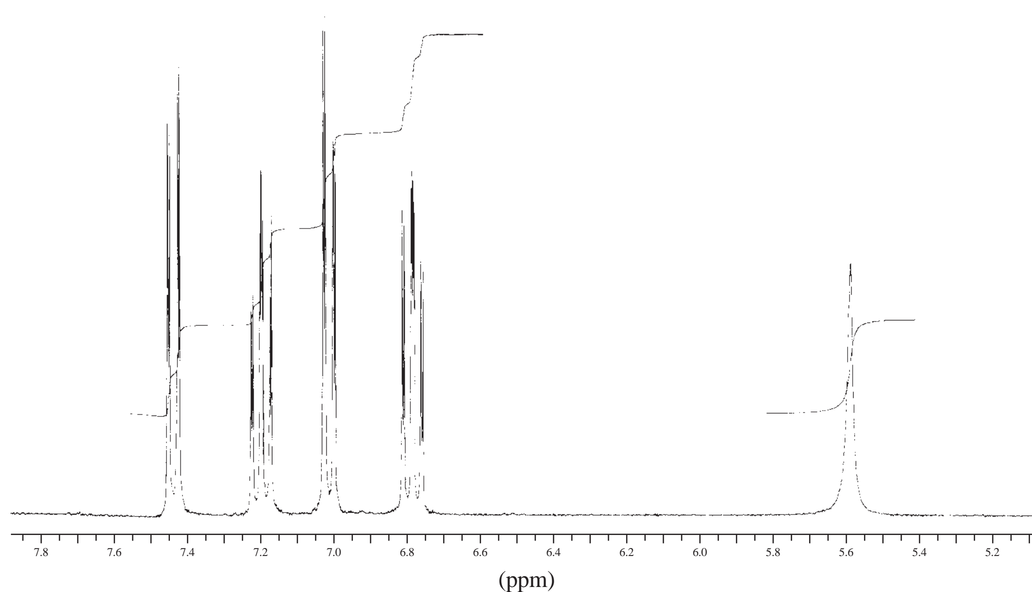
***1.** The spectrum of an ultrapure sample of ethanol is shown in Figure 6.3. Draw a tree diagram for the methylene groups in ethanol that takes into account the coupling to both the hydroxyl and methyl groups.

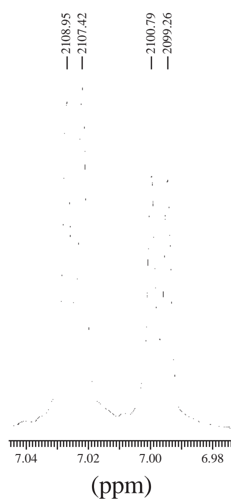
***2.** The following spectrum is for a compound with the formula $C_5H_{10}O$. The peak at about 1.9 ppm is solvent and concentration dependent. Expansions are included, along with an indication of the spacing of the peaks in Hertz. The pairs of peaks at about 5.0 and 5.2 ppm have fine structure. How do you explain this small coupling? Draw the structure of the compound, assign the peaks, and include tree diagrams for the expanded peaks in the spectrum.

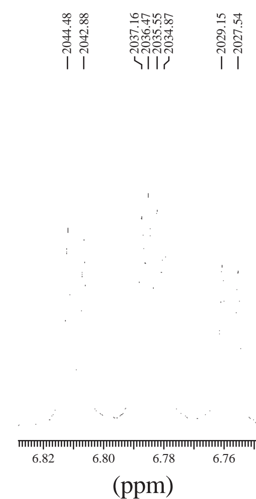




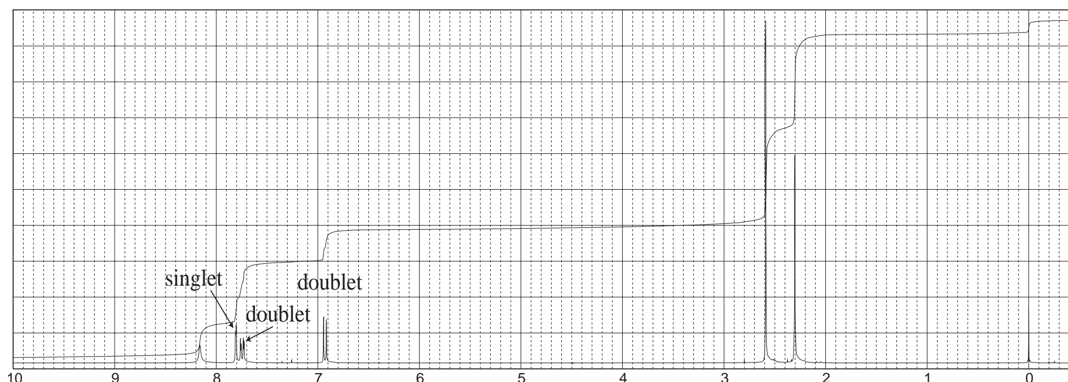
***3.** Determine the structure of the aromatic compound with formula C_6H_5BrO. The peak at about 5.6 ppm is solvent dependent and shifts readily when the sample is diluted. The expansions that are provided show ^4J couplings of about 1.6 Hz.



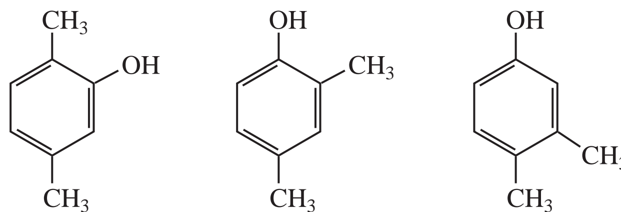


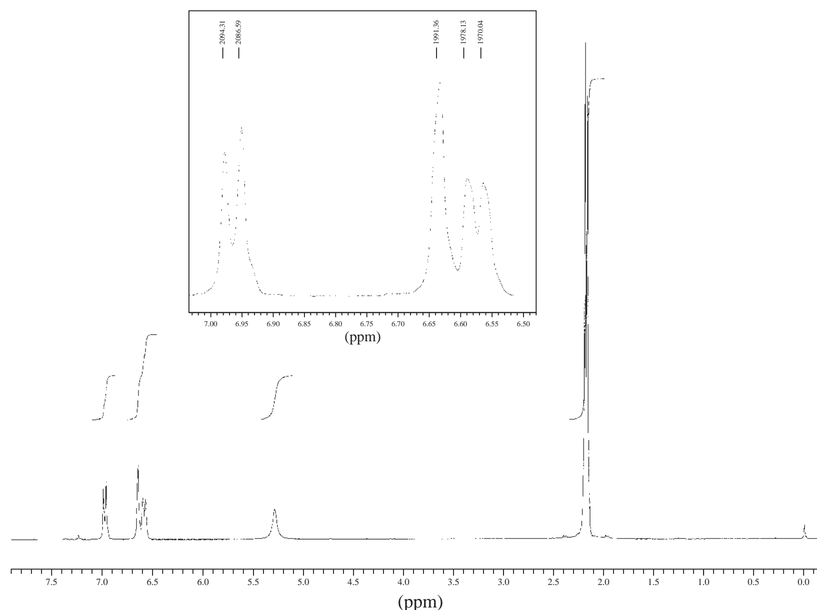


***4.** The compound with the spectrum shown is derived from 2-methylphenol. The formula of the product obtained is $C_9H_{10}O_2$. The infrared spectrum shows prominent peaks at 3136 and 1648 cm^{-1}. The broad peak at 8.16 ppm is solvent dependent. Determine the structure of this compound using the spectrum provided and calculations of the chemical shifts (see Appendix 6). The calculated values will be only approximate but should allow you to determine the correct structure.



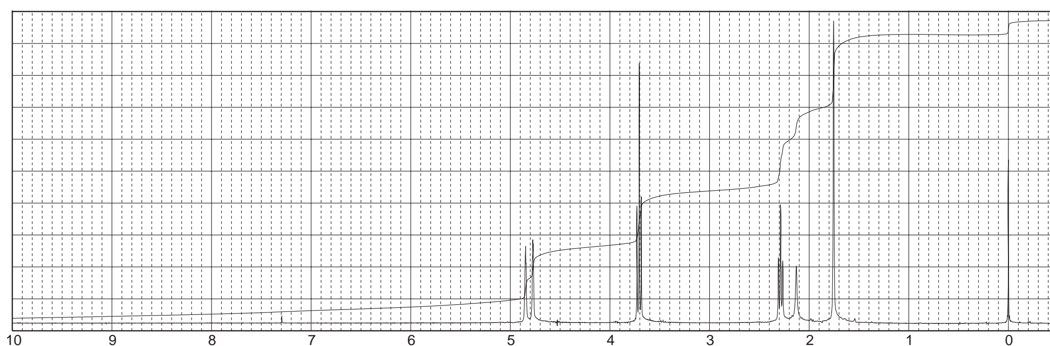
***5.** The spectrum and expansions provided in this problem are for one of the compounds shown below. The broad peak at 5.25 ppm is solvent dependent. Using calculations of the *approximate* chemical shifts and the appearance and position of the peaks (singlet and doublets), determine the correct structure. The chemical shifts may be calculated from the information provided in Appendix 6. The calculated values will be only approximate but should allow you to determine the correct structure.

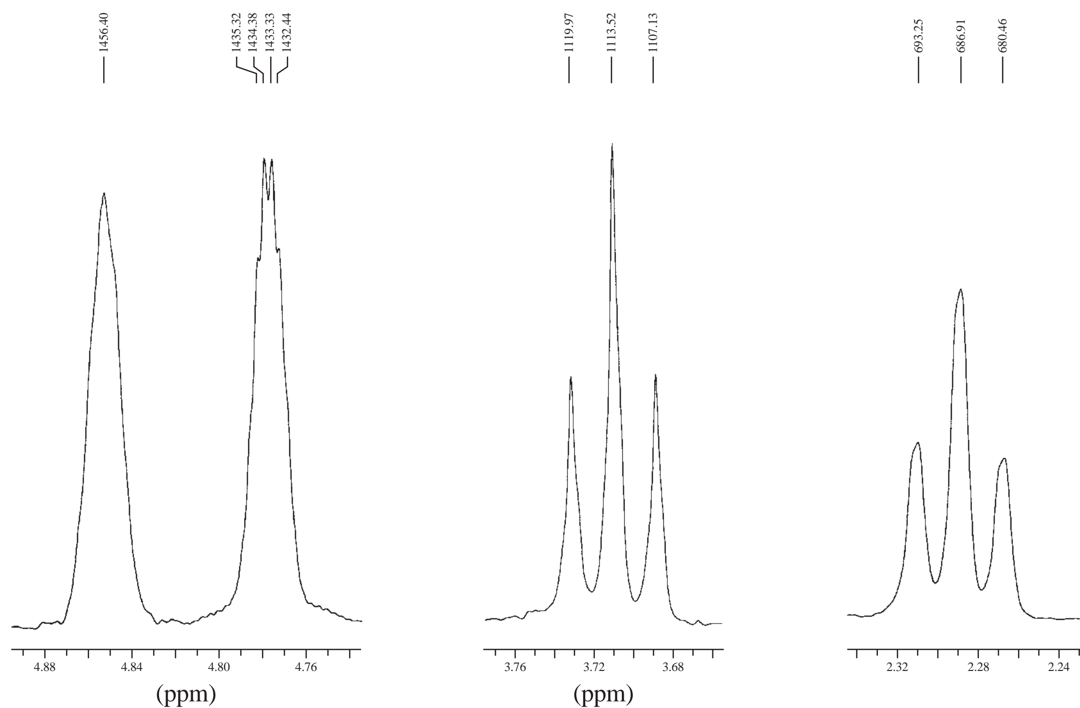




***6.** The proton NMR spectrum for a compound with formula $C_5H_{10}O$ is shown. Determine the structure of this compound. The peak at 2.1 ppm is solvent dependent. Expansions are provided for some of the protons. Comment on the fine structure on the peak at 4.78 ppm. The normal carbon-13, DEPT-135, and DEPT-90 spectra data are tabulated.

Normal Carbon	DEPT-135	DEPT-90
22 ppm	Positive	No peak
41	Negative	No peak
60	Negative	No peak
112	Negative	No peak
142	No peak	No peak

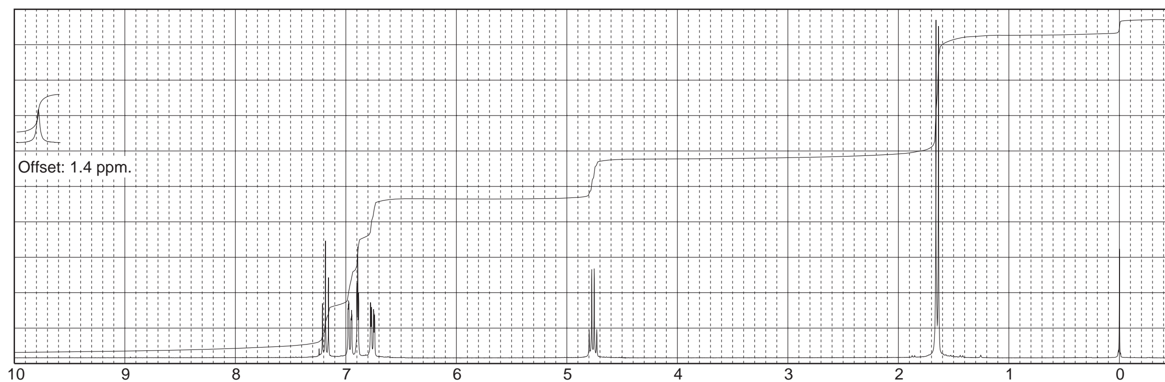


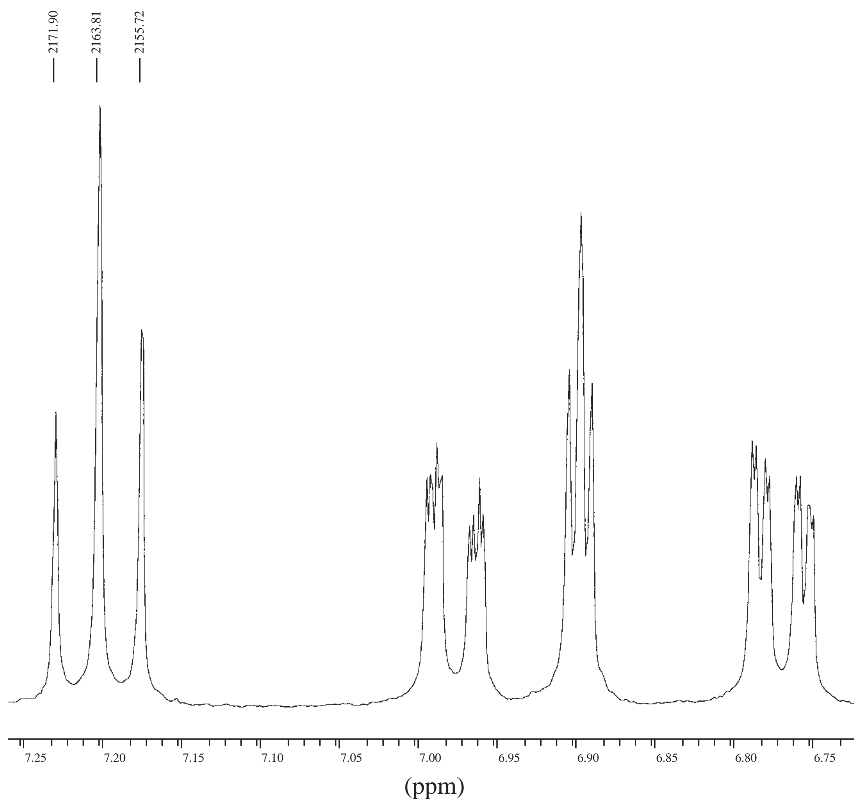


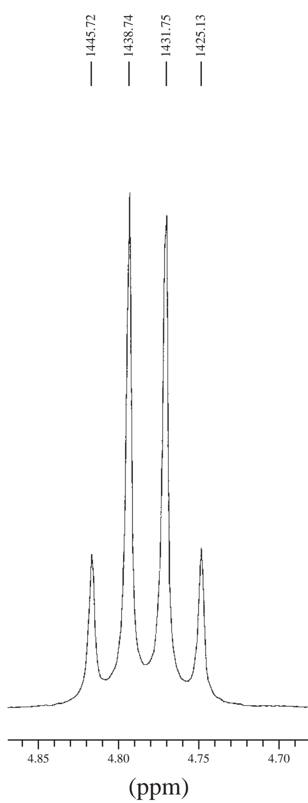
7. The proton NMR spectrum of a compound with formula $C_5H_{10}O$ is shown. The peak at 2.1 ppm is solvent dependent. The infrared spectrum shows a broad and strong peak at 3332 cm^{-1}. The normal carbon-13, DEPT-135, and DEPT-90 spectra data are tabulated.

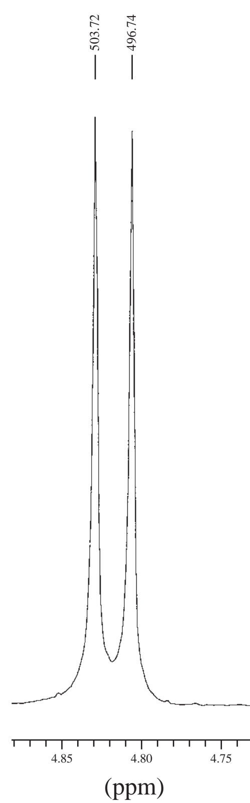
Normal Carbon	DEPT-135	DEPT-90
11 ppm	Negative	No peak
18	No peak	No peak
21	Positive	No peak
71	Negative	No peak

8. Determine the structure of the aromatic compound with formula $C_9H_9ClO_3$. The infrared spectrum shows a very broad band from 3300 to 2400 cm^{-1} and a strong band at 1714 cm^{-1}. The full proton NMR spectrum and expansions are provided. The compound is prepared by a nucleophilic substitution reaction of the sodium salt of 3-chlorophenol on a halogen-bearing substrate.

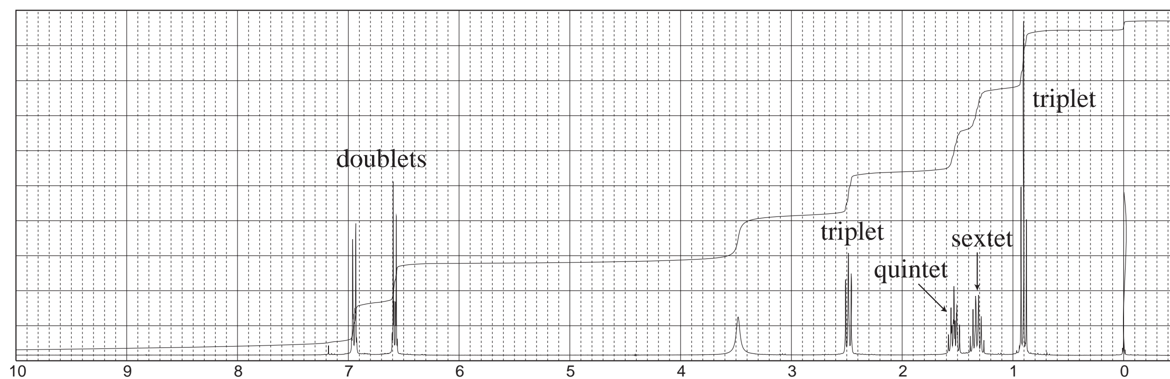



2171.90
2163.81
2155.72
7.25
7.20
7.15
7.10
7.05
7.00
6.95
6.90
6.85
6.80
6.75
(ppm)


1445.72
1438.74
1431.75
1425.13
4.85
4.80
4.75
4.70
(ppm)

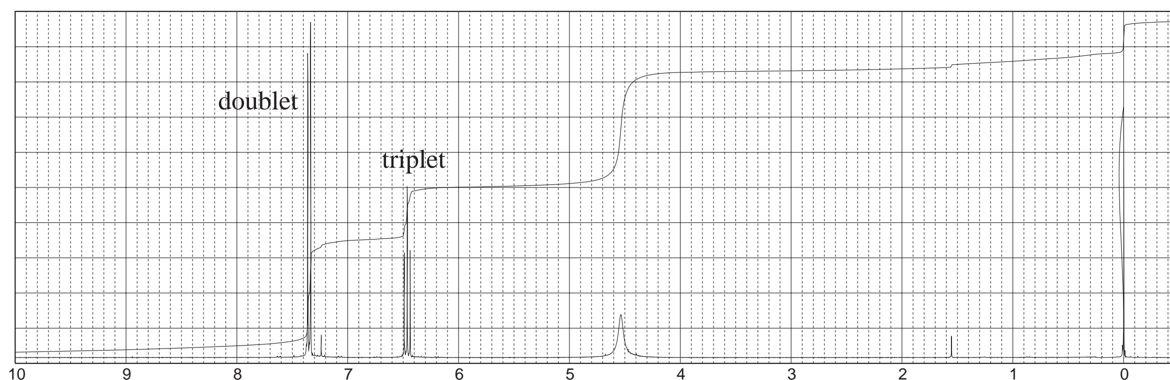

503.72
496.74
4.85
4.80
4.75
(ppm)

***9.** Determine the structure of a compound with formula $C_{10}H_{15}N$. The proton NMR spectrum is shown. The infrared spectrum has medium bands at 3420 and 3349 cm^{-1} and a strong band at 1624 cm^{-1}. The broad peak at 3.5 ppm in the NMR shifts when DCl is added, while the other peaks stay in the same positions.

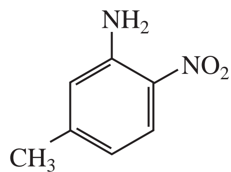


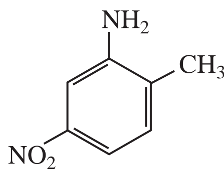
***10.** Determine the structure of a compound with formula $C_6H_5Br_2N$. The proton NMR spectrum is shown. The infrared spectrum has medium bands at 3420 and 3315 cm^{-1} and a strong band at 1612 cm^{-1}. The normal carbon, DEPT-135, and DEPT-90 spectra data are tabulated.

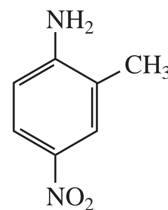
Normal Carbon	DEPT-135	DEPT-90
109 ppm	No peak	No peak
119	Positive	Positive
132	Positive	Positive
142	No peak	No peak

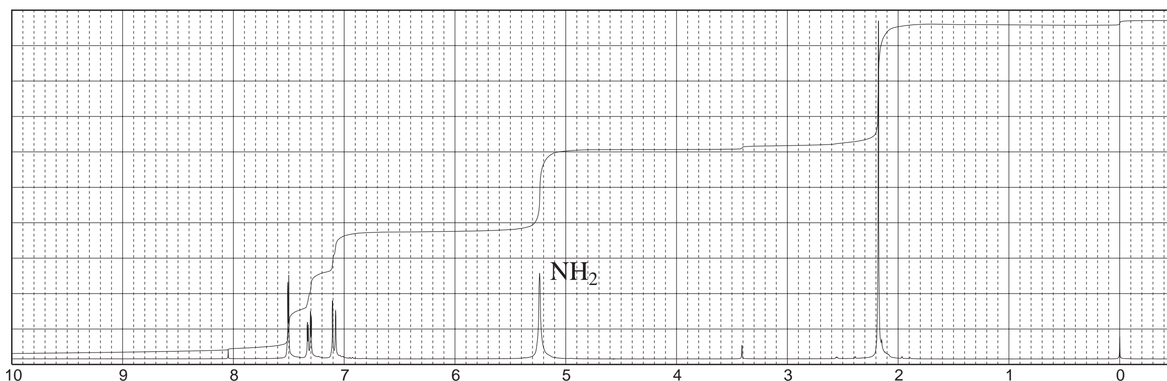


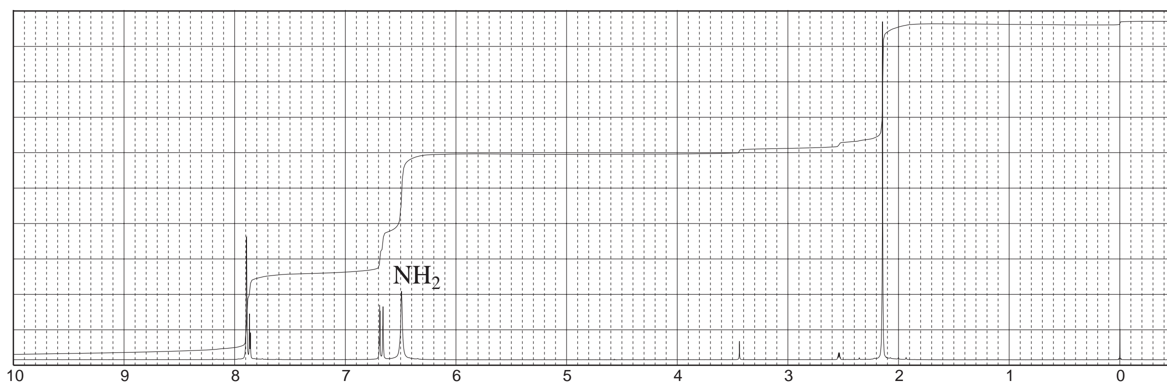
11. There are three spectra shown in this problem along with three structures of aromatic primary amines. Assign each spectrum to the appropriate structure. You should calculate the *approximate* chemical shifts (Appendix 6) and use these values along with the appearance and position of the peaks (singlet and doublets) to assign the correct structure.

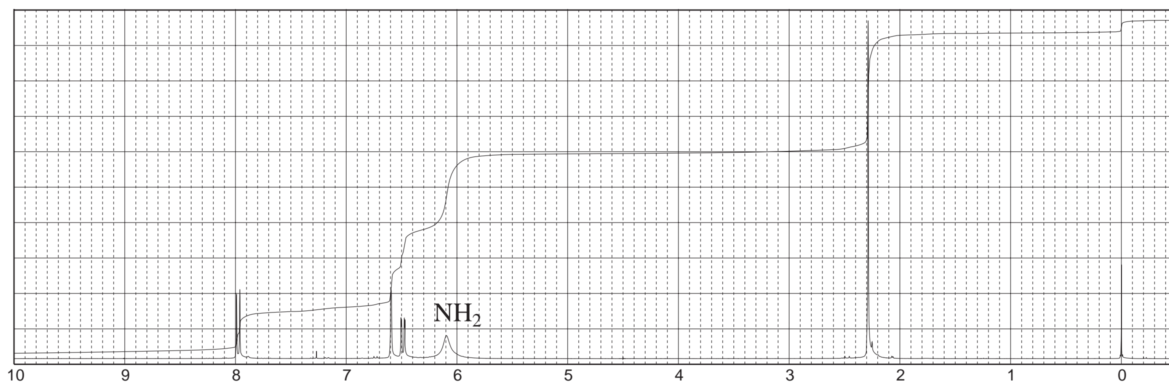




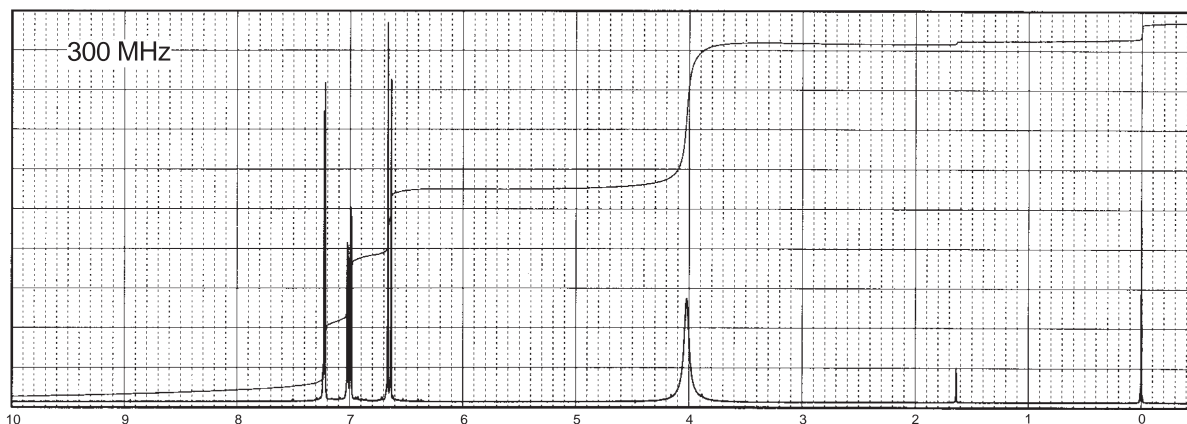


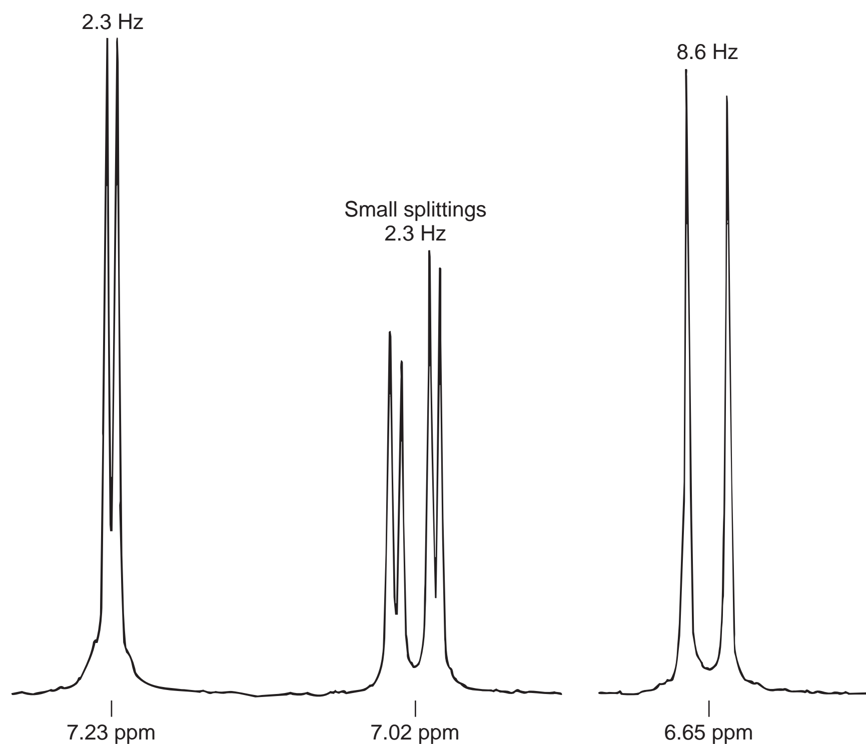




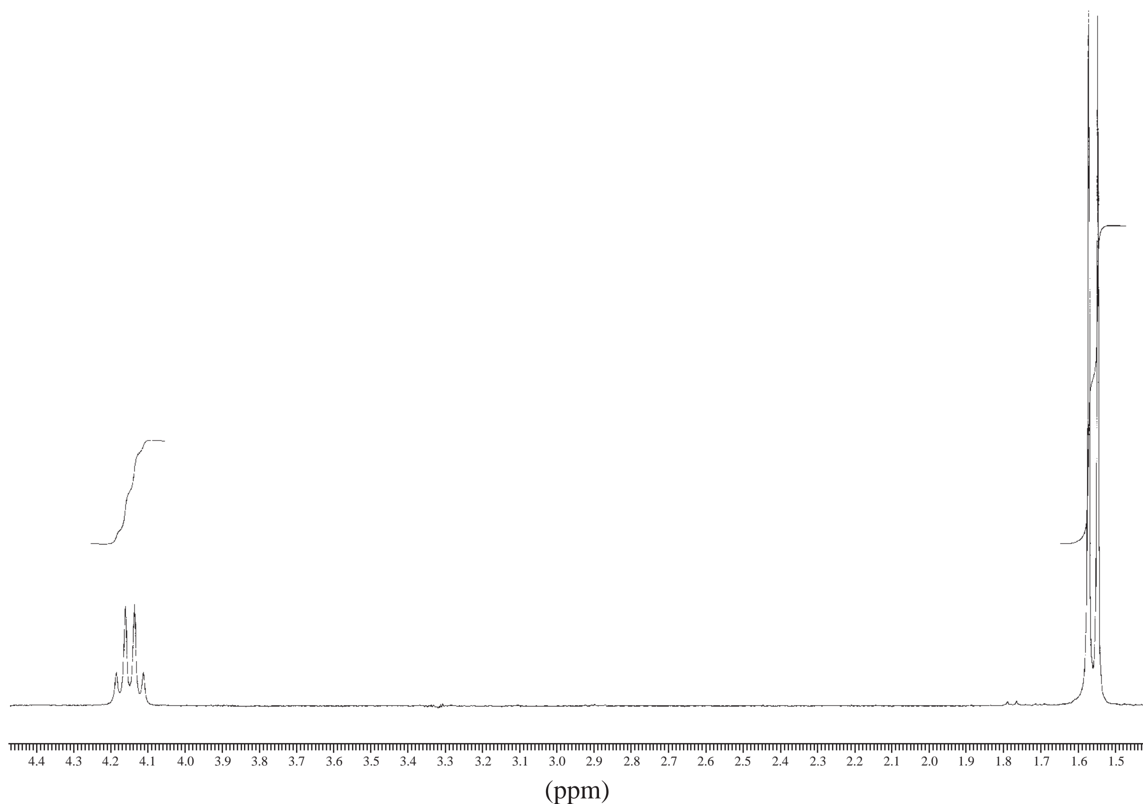


***12.** When aniline is chlorinated, a product with the formula $C_6H_5NCl_2$ is obtained. The spectrum of this compound is shown. The expansions are labeled to indicate couplings, in Hertz. Determine the structure and substitution pattern of the compound and assign each set of peaks. Explain the splitting patterns.

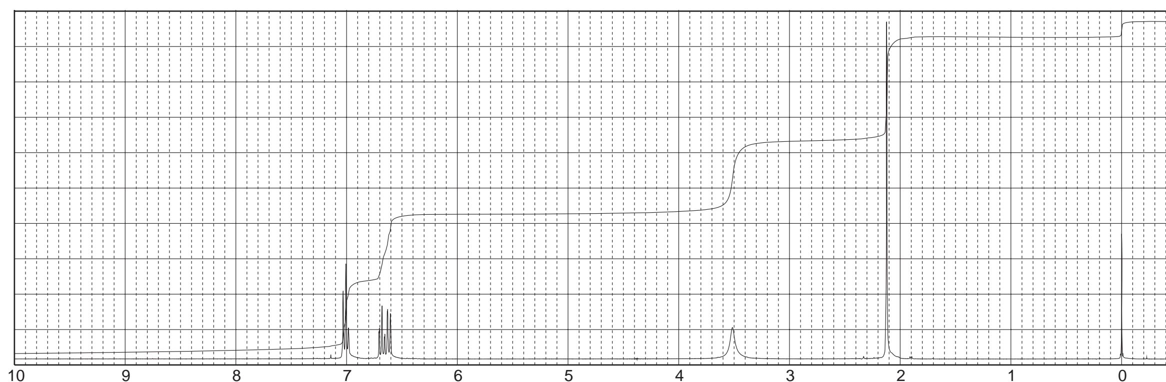


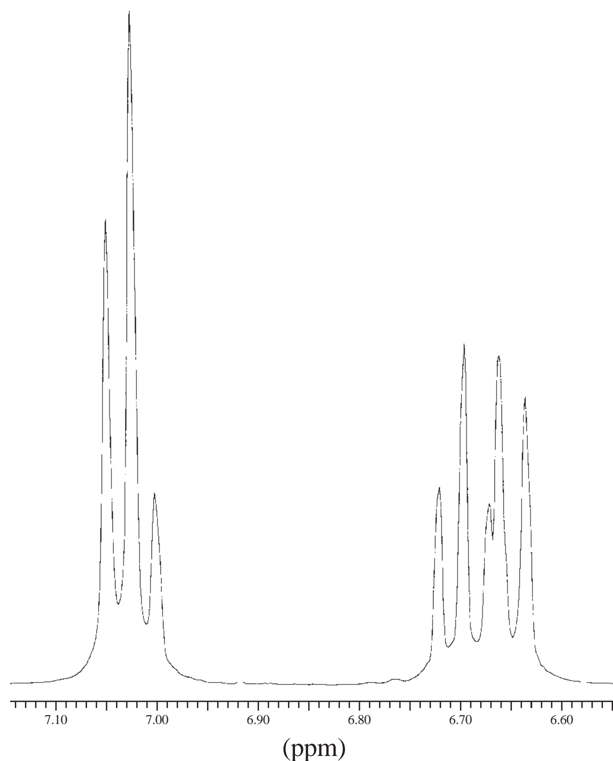


***13.** A naturally occurring amino acid with the formula $C_3H_7NO_2$ gives the following proton NMR spectrum when determined in deuterium oxide solvent. The amino and carboxyl protons merge into a single peak at 4.9 ppm in the D_2O solvent (not shown); the peaks of each multiplet are separated by 7 Hz. Determine the structure of this amino acid.

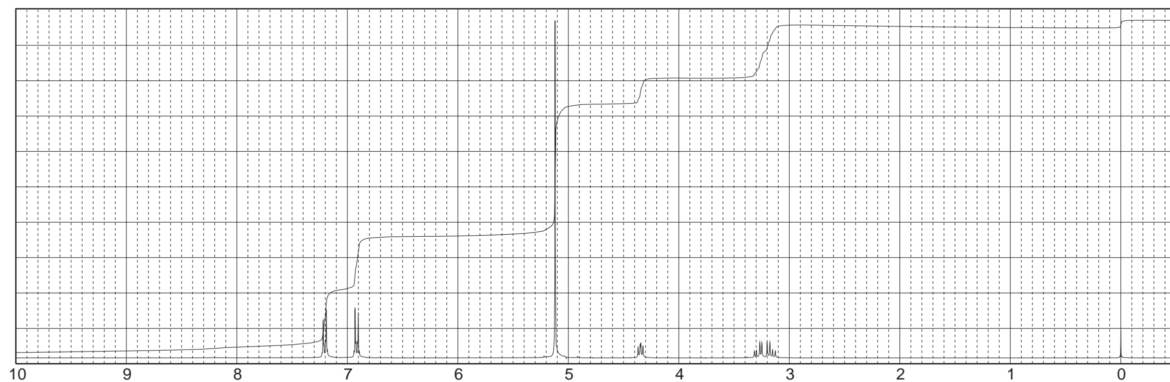


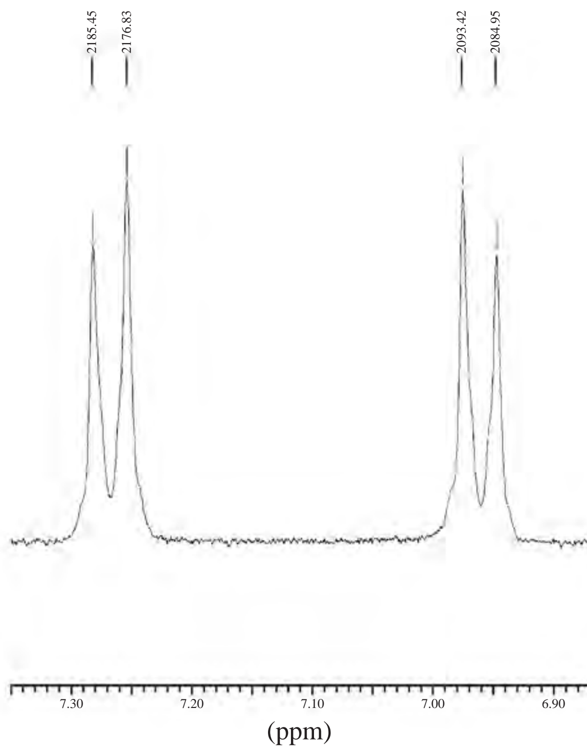
14. Determine the structure of a compound with formula C_7H_9N. The proton NMR spectrum is shown, along with expansions of the region from 7.10 to 6.60 ppm. The three-peak pattern for the two protons at about 7 ppm involves overlapping peaks. The broad peak at 3.5 ppm shifts when DCl is added, while the other peaks stay in the same positions. The infrared spectrum shows a pair of peaks near 3400 cm^{-1} and an out-of-plane bending band at 751 cm^{-1}.

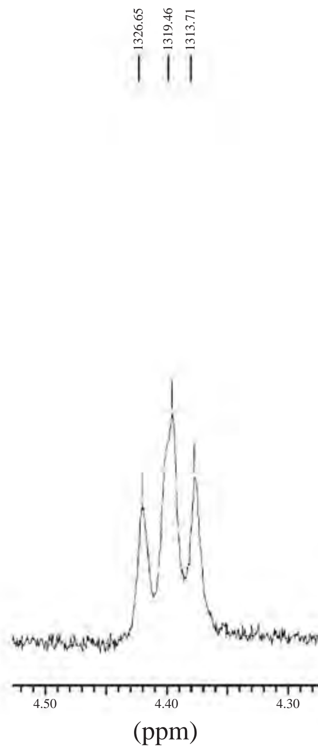


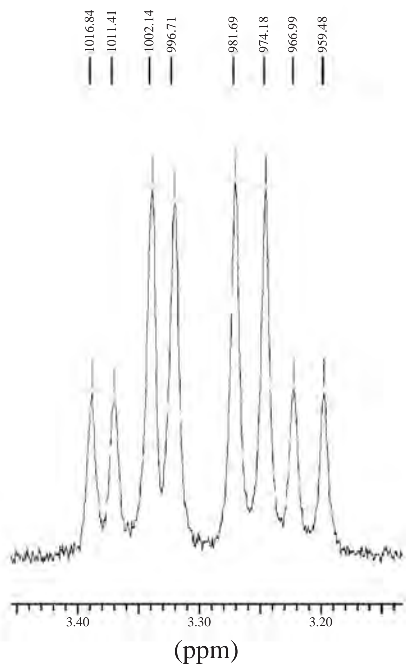


15. A naturally occurring amino acid with the formula $C_9H_{11}NO_3$ gives the following proton NMR spectrum when determined in deuterium oxide solvent with DCl added. The amino, carboxyl, and hydroxyl protons merge into a single peak at 5.1 ppm (4 H) in D_2O. Determine the structure of this amino acid and explain the pattern that appears in the range 3.17 to 3.40 ppm, including coupling constants.



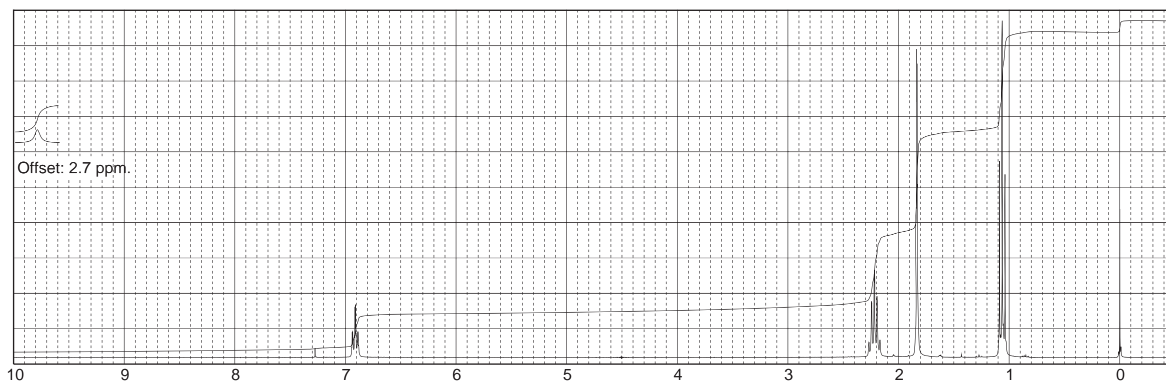

2185.45
2176.83
2093.42
2084.95
7.30
7.20
7.10
7.00
6.90
(ppm)

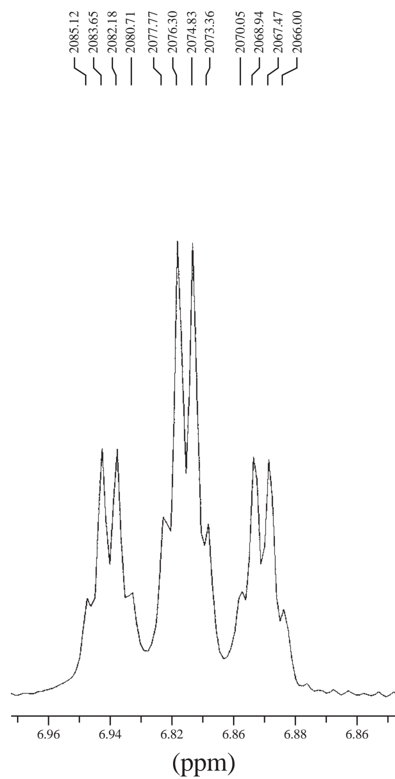

1326.65
1319.46
1313.71
4.50
4.40
4.30
(ppm)

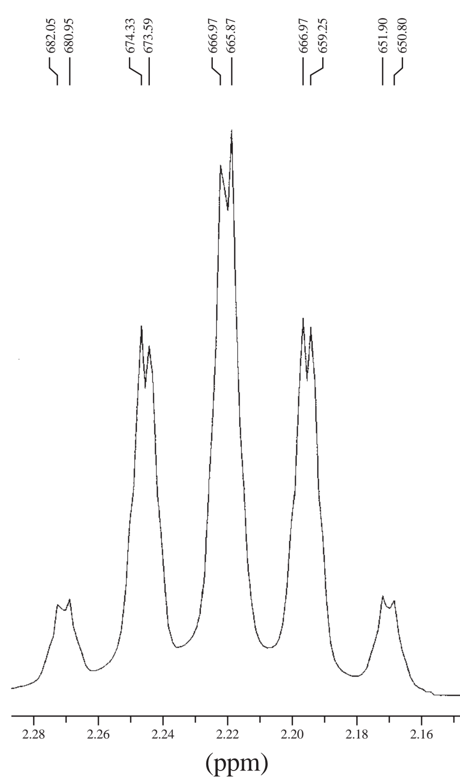

1016.84
1011.41
1002.14
996.71
981.69
974.18
966.99
959.48
3.40
3.30
3.20
(ppm)

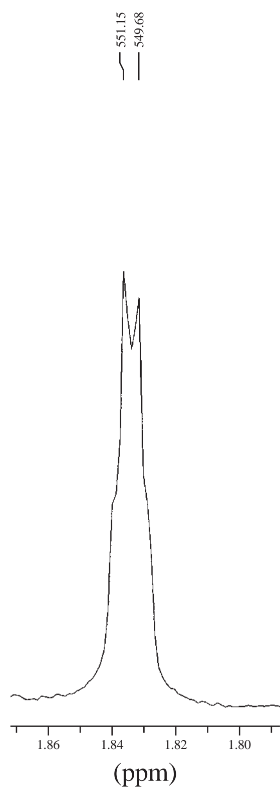
16. Determine the structure of a compound with formula $C_6H_{10}O_2$. The proton NMR spectrum with expansions is provided. Comment regarding why the proton appearing at 6.91 ppm is a triplet of quartets, with spacing of 1.47 Hz. Also comment on the "singlet" at 1.83 that shows fine structure. The normal carbon, DEPT-135, and DEPT-90 spectral results are tabulated.

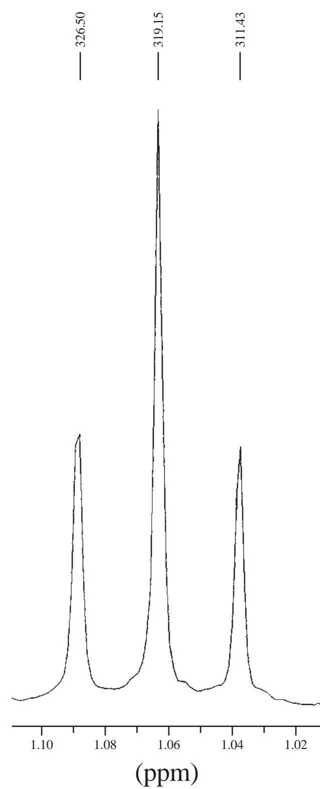
Normal Carbon	DEPT-135	DEPT-90
12 ppm	Positive	No peak
13	Positive	No peak
22	Negative	No peak
127	No peak	No peak
147	Positive	Positive
174	No peak	No peak



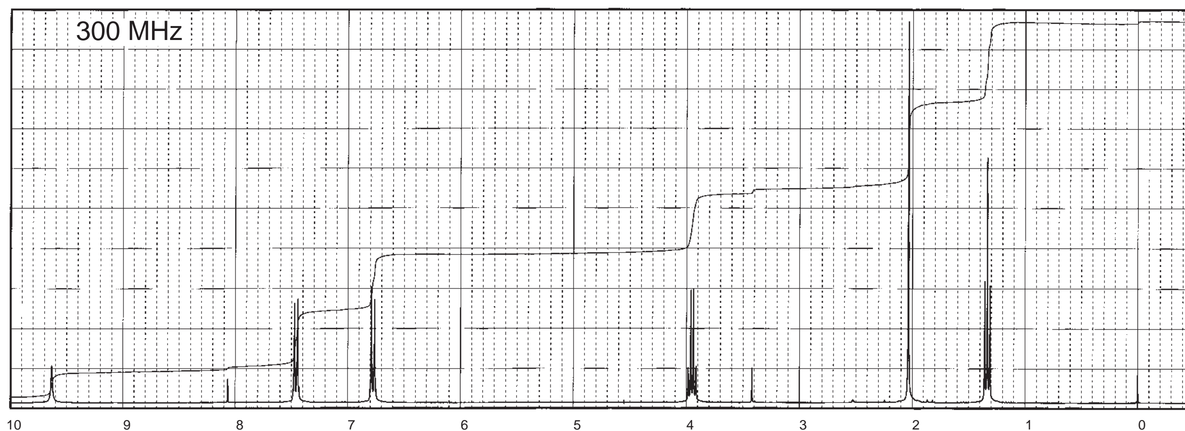

2085.12
2083.65
2082.18
2080.71
2077.77
2076.30
2074.83
2073.36
2070.05
2068.94
2067.47
2066.00
6.96
6.94
6.82
6.86
6.88
6.86
(ppm)

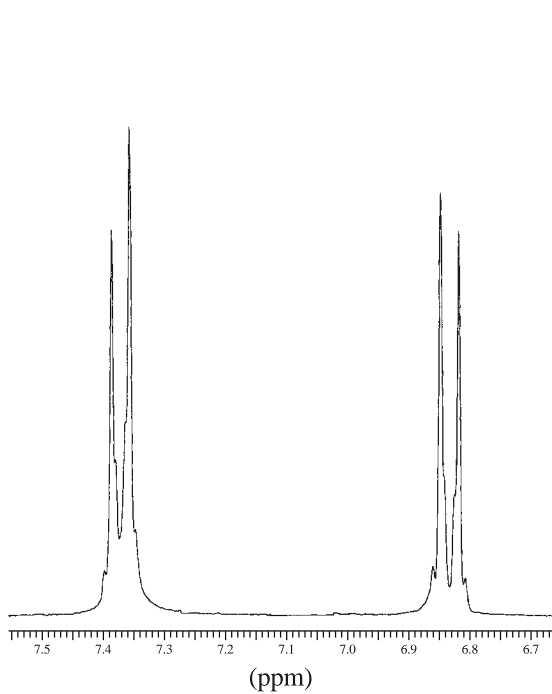

682.05
680.95
674.33
673.59
666.97
665.87
666.97
659.25
651.90
650.80
2.28
2.26
2.24
2.22
2.20
2.18
2.16
(ppm)

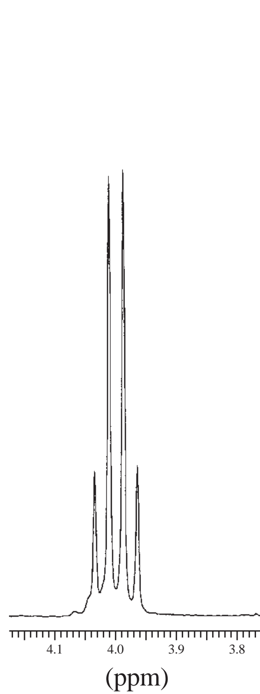

551.15
549.68
1.86
1.84
1.82
1.80
(ppm)

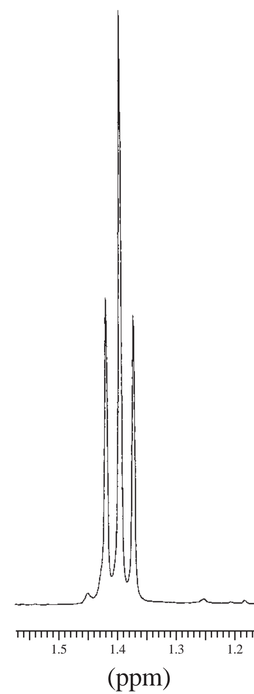

326.50
319.15
311.43
1.10
1.08
1.06
1.04
1.02
(ppm)

17. The following proton NMR spectrum is of a discontinued analgesic drug, phenacetin ($C_{10}H_{13}NO_2$). Phenacetin is structurally related to the very popular and current analgesic drug acetaminophen. Phenacetin contains an amide functional group. Two tiny impurity peaks appear near 3.4 and 8.1 ppm. Give the structure of this compound and interpret the spectrum.

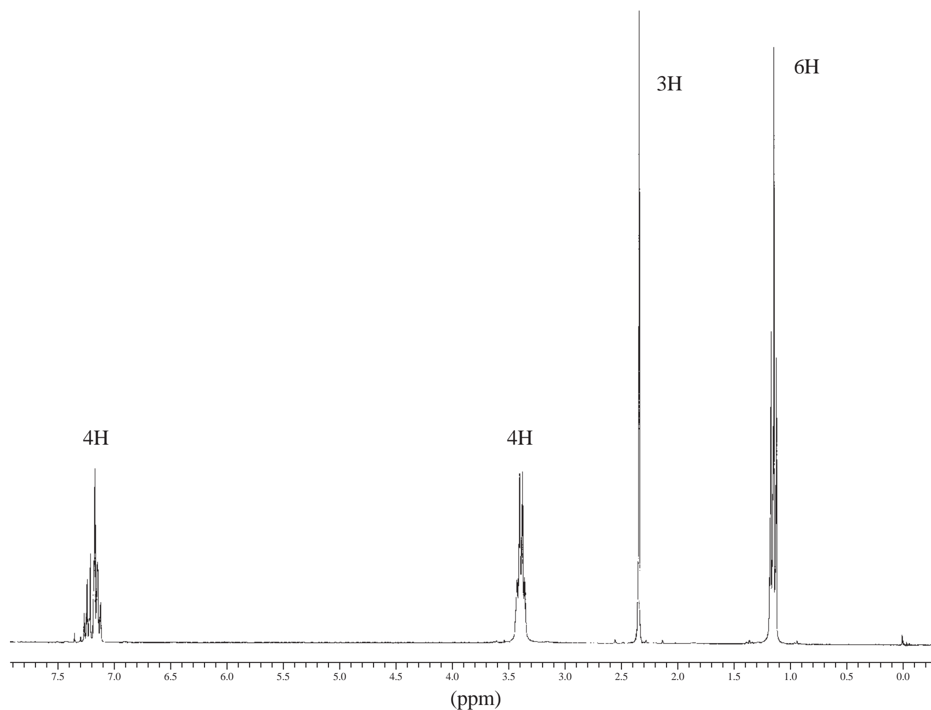


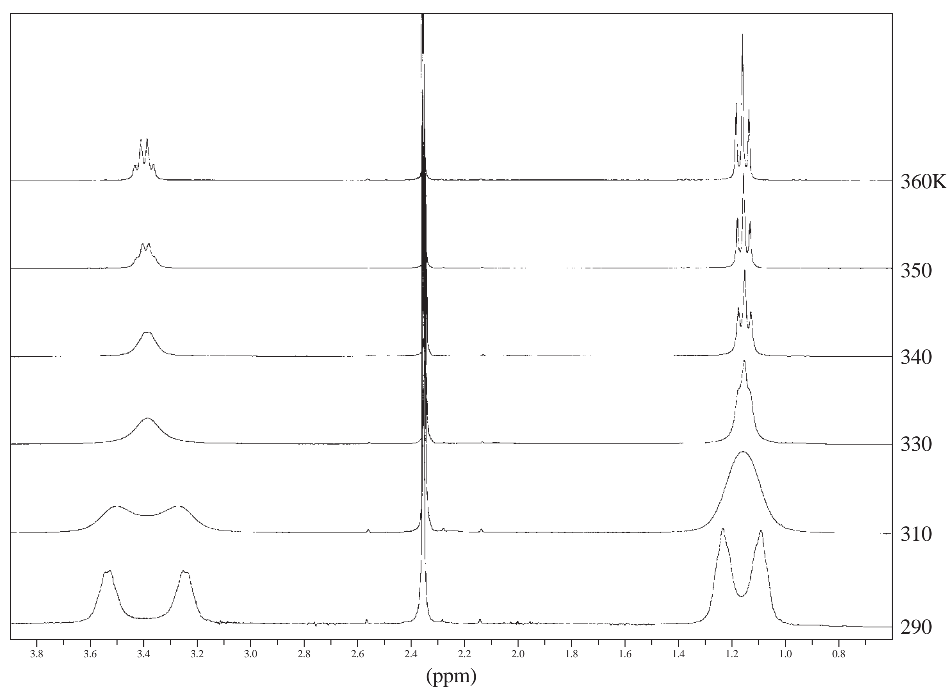




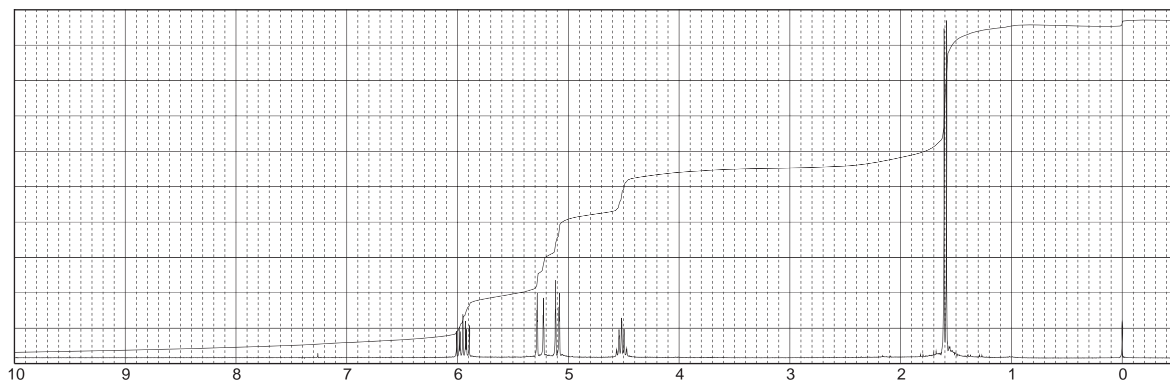


18. The proton NMR spectrum shown in this problem is for a common insect repellent, *N*,*N*-diethyl-*m*-toluamide, determined at 360 K. This problem also shows a stacked plot of this compound determined in the temperature range of 290 to 360 K (27–87°C). Explain why the spectrum changes from two pairs of broadened peaks near 1.2 and 3.4 ppm at low temperature to a triplet and quartet at the higher temperatures.

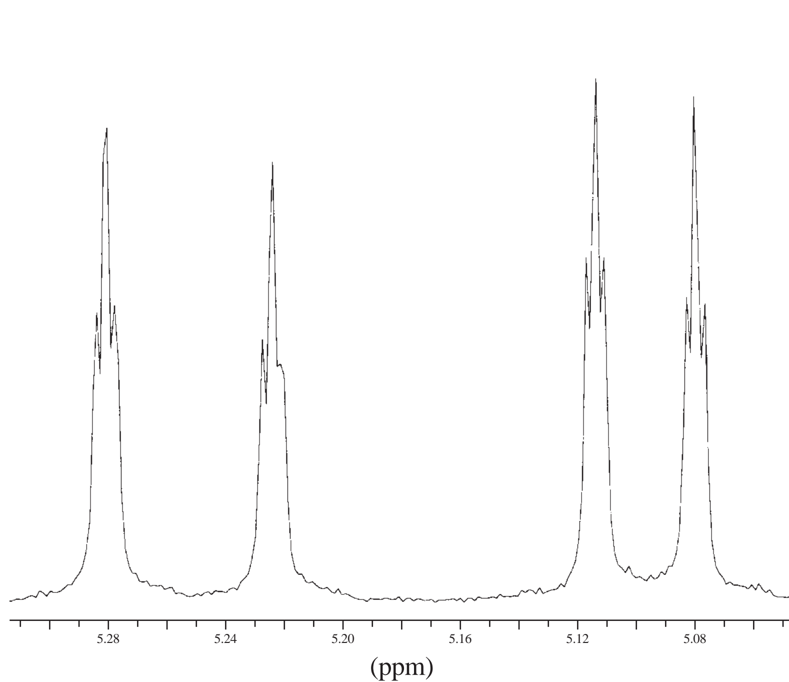


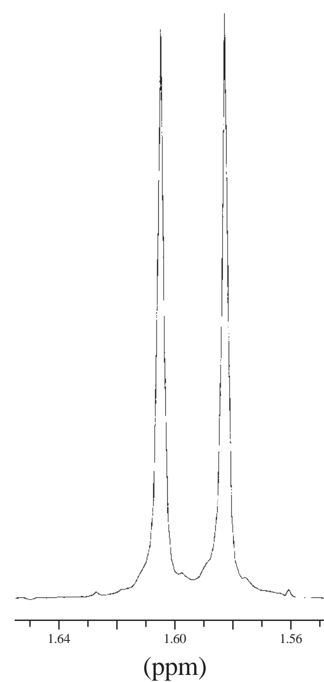


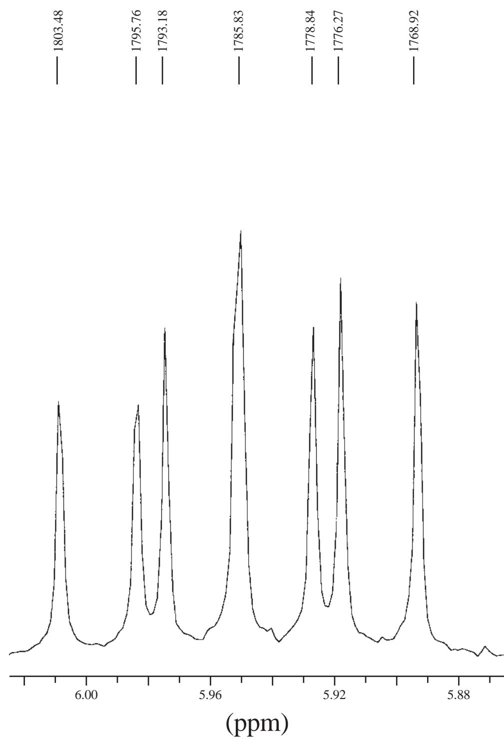
19. The proton NMR spectral information shown in this problem is for a compound with formula C_4H_7Cl. Expansions are shown for each of the unique protons. The original “quintet” pattern centering on 4.52 ppm is simplified to a doublet by irradiating (decoupling) the protons at 1.59 ppm (see Section 6.10). In another experiment, decoupling the proton at 4.52 ppm simplifies the original pattern centering on 5.95 ppm to the four-peak pattern shown. The doublet at 1.59 ppm becomes a singlet when the proton at 4.52 ppm is irradiated (decoupled). Determine the coupling constants and draw the structure of this compound. Notice that there are ^2J, ^3J, and ^4J couplings present in this compound. Draw a tree diagram for the proton at 5.95 ppm (nondecoupled) and explain why irradiation of the proton at 4.52 ppm simplified the pattern. Assign each of the peaks in the spectrum.

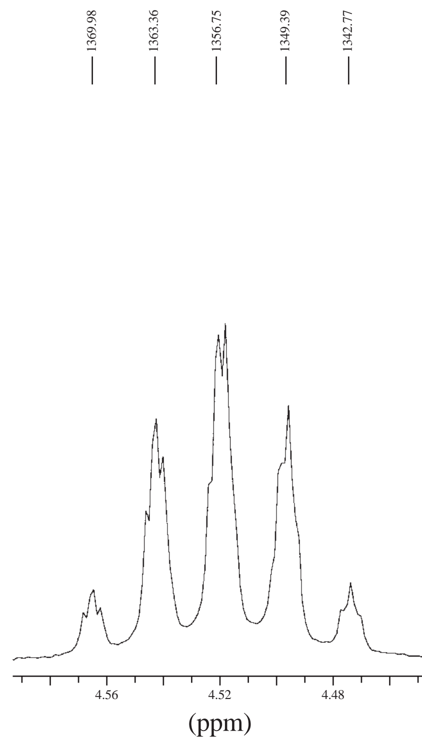


1585.81 1584.71 1583.97 1568.90 1567.79 1567.06 1535.81 1534.70 1533.97 1525.51 1524.78 1523.67 481.66 475.04



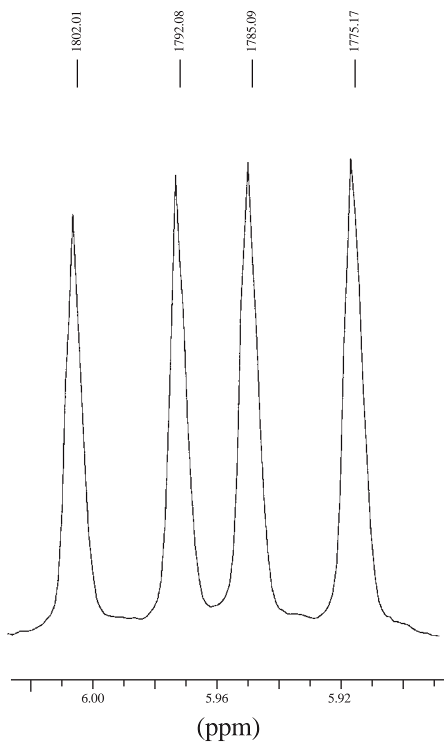


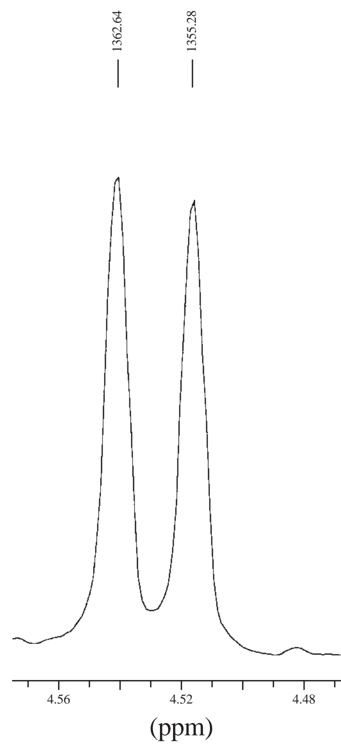




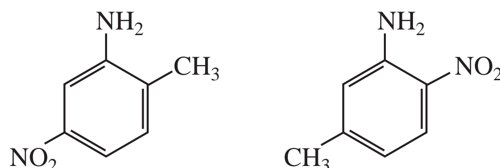
irradiation of proton at 4.52 ppm

irradiation of proton at 1.59 ppm





20. In Problem 11, calculations proved to be a good way of assigning structures to the spectra of some aromatic amines. Describe an experimental way of differentiating between the following amines:



***21.** At room temperature, the NMR spectrum of cyclohexane shows only a single resonance peak. As the temperature of the sample is lowered, the sharp single peak broadens until at −66.7°C it begins to split into two peaks, both broad. As the temperature is lowered further to −100°C, each of the two broad bands begins to give a splitting pattern of its own. Explain the origin of these two families of bands.

***22.** In *cis*-1-bromo-4-*tert*-butylcyclohexane, the proton on carbon-4 is found to give resonance at 4.33 ppm. In the *trans* isomer, the resonance of the C4 hydrogen is at 3.63 ppm. Explain why these compounds should have different chemical shift values for the C4 hydrogen. Can you explain the fact that this difference is not seen in the 4-bromomethylcyclohexanes except at very low temperature?

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In addition to these references, also consult textbook references, compilations of spectra, computer programs, and NMR-related Internet addresses cited at the end of Chapter 5.