

EXPERIMENT 42

NMR Determination of Keto-Enol Equilibrium Constants

In this experiment proton NMR spectroscopy is used in evaluating the equilibrium composition of various keto-enol mixtures. Chemical shifts and spin-spin splitting patterns are employed to assign the spectral features to specific protons, and the integrated intensities are used to yield a quantitative measure of the relative amounts of the keto and enol forms. Solvent effects on the chemical shifts and on the equilibrium constant are investigated for one or more β -diketones and β -ketoesters.

THEORY

Chemical Shifts. In Exp. 32, the Zeeman energy levels of a nucleus in an external applied field were given as

$$E_N = -g_N \mu_N M_I B_{\text{loc}} \quad (1)$$

where $B_{i,\text{loc}}$ is the magnetic induction ("local field") at the nucleus. As a result of the $\Delta M_i = \pm 1$ selection rule, a transition will occur at frequency

$$\nu_i = \left(\frac{g_N \mu_N}{h} \right) B_{i,\text{loc}} = \left(\frac{g_N \mu_N}{h} \right) B(1 - \sigma_i) \quad (2)$$

for a nucleus i ; see Eq. (32-8). The chemical shift in parts per million (ppm) of this nucleus relative to a reference nucleus r is defined by

$$\delta_i = \frac{\nu_i - \nu_r}{\nu_r} \times 10^6 = \frac{\sigma_r - \sigma_i}{1 - \sigma_r} \times 10^6 \approx (\sigma_r - \sigma_i) \times 10^6 \quad (3a)$$

Here the definition is based on the resonant frequencies for a fixed external induction (field) B . A second (nearly equivalent) relation is based on the alternative experimental case, where B is varied to achieve resonance at a fixed instrumental frequency ν . In this case $B_i(1 - \sigma_i) = B_r(1 - \sigma_r)$ and

$$\delta_i = \frac{B_r - B_i}{B_r} \times 10^6 = \frac{\sigma_r - \sigma_i}{1 - \sigma_i} \times 10^6 \approx (\sigma_r - \sigma_i) \times 10^6 \quad (3b)$$

Tetramethylsilane (TMS) is usually used as the proton reference, since it is chemically inert and its 12 equivalent protons give a single transition at a field B_r , higher than the field B_i found in most organic compounds. Thus δ is generally positive and increases when substituents are added that attract electrons and thereby reduce the shielding about the proton. This shielding arises because the electrons near the proton are induced to circulate by the applied field B (see Fig. 1a). This electron current produces a secondary field that *opposes* the external field and thus reduces the local field at the proton. As a result resonance at a fixed frequency such as 60 MHz requires a higher external field for protons with larger shielding. This shielding effect is generally restricted to electrons localized on the nucleus of interest, since random tumbling of the molecules causes the effect of secondary fields due to electrons associated with neighboring nuclei to average to zero. Nuclei such as ^{19}F , ^{13}C , and ^{11}B have more local electrons than hydrogen, hence their chemical shifts are much larger.

Long-range *deshielding* can occur in aromatic and other molecules with delocalized π electrons. For example, when the plane of the benzene molecule is oriented perpendicular to B , circulation of the π electrons produces a ring current (see Fig. 1b). This ring current induces a secondary field at the protons that is *aligned parallel* to B and thus increases

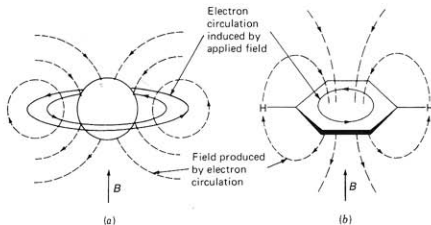


FIGURE 1
Shielding and deshielding of protons: (a) shielding of proton due to induced diamagnetic electron circulation; (b) deshielding of protons in benzene due to aromatic ring currents.

TABLE 1 Typical proton chemical shifts δ

| | | | |
|---|------|---|------|
| CH ₃ protons | | Acetylenic protons | |
| (CH ₃) ₄ Si | 0.0 | HOCH ₂ C≡CH | 2.33 |
| (CH ₃) ₂ C | 0.92 | ClCH ₂ C≡CH | 2.40 |
| CH ₂ CH ₂ OH | 1.17 | CH ₃ COC≡CH | 3.17 |
| CH ₃ COCH ₃ | 2.07 | Olefinic protons | |
| CH ₃ OH | 3.38 | (CH ₂) ₂ C=CH ₂ | 4.6 |
| CH ₃ F | 4.30 | Cyclohexene | 5.57 |
| CH ₂ protons | | CH ₂ CH=CHCHO | 6.05 |
| Cyclopropane | 0.22 | Cl ₂ C=CHCl | 6.45 |
| CH ₂ (CH ₂) ₂ CH ₃ | 1.25 | Aromatic protons | |
| (CH ₂ CH ₂) ₂ CO | 2.39 | Benzene | 7.27 |
| CH ₂ COCH ₂ COOCH ₃ | 3.48 | C ₆ H ₅ CN | 7.54 |
| CH ₂ CH ₂ OH | 3.59 | Naphthalene | 7.73 |
| CH protons | | α -Pyridine | 8.50 |
| Bicyclo[2.2.1]heptane | 2.19 | Aldehydic protons | |
| Chlorocyclopropane | 2.95 | CH ₃ OCHO | 8.03 |
| (CH ₃) ₂ CHOH | 3.95 | CH ₃ CHO | 9.72 |
| (CH ₃) ₂ CHBr | 4.17 | C ₆ H ₅ CHO | 9.96 |

the local field at the protons. This induced field changes with benzene orientation but does not average to zero, since it is not spherically symmetric. Because of this net deshielding effect, the resonance of the benzene protons occurs at a relatively low external field. The proton chemical shift δ for benzene is 7.27, greatly downfield from the value $\delta = 1.43$ that is observed for cyclohexane, in which ring currents do not occur. Similar deshielding occurs for olefinic and aldehydic protons because of the π electron movement. Typical values of δ for different functional groups are shown in Table 1, and additional values are available in Refs. 1 to 3. Although the resonances change somewhat for different compounds, the range for a given functional group is usually small and δ values are widely used for structural characterization in organic chemistry.

Spin-Spin Splitting. High-resolution NMR spectra of most organic compounds reveal more complicated spectra than those predicted by Eq. (2), with transitions often appearing as multiplets. Such *spin-spin splitting patterns* arise because the magnetic moment of one proton (A) can interact with that of a nearby nucleus (B), causing a small energy shift up or down depending on the relative orientations of the two moments. The energy levels of nucleus A then have the form

$$E_A = -g_N \mu_N M_{I_A} (1 - \sigma_A) B + h J_{AB} M_{I_A} M_{I_B} \quad (4)$$

and there is a similar expression for E_B . The spin-spin interaction is characterized by the coupling constant J_{AB} , and the effect is to split the energy levels in the manner illustrated for acetaldehyde in Fig. 2. It is apparent from this diagram that the external field B does not effect the small spin-spin splitting that is characterized by the coupling constant J . The quantity J is a measure of the strength of the pairwise interaction of the proton spin with the spin of another nucleus. Since there are only proton-proton interactions in acetaldehyde, the same splitting occurs for both CH and CH₃ resonances.

The total integrated intensity of the CH and CH₃ multiplets follows the proton ratio of 1:3. However, the intensity distribution within each multiplet is determined by the relative population of the lower level in each transition. Since the level spacing is much less

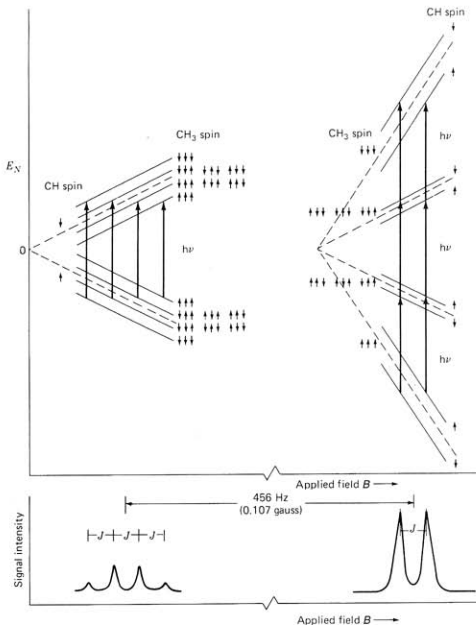
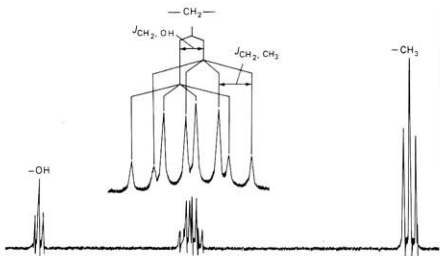


FIGURE 2
Energy levels, transitions, and 60-MHz NMR spectrum for acetaldehyde (CH_3CHO). The coupling $J = J_{\text{CH}_2} = J_{\text{CH}} = 2.2 \text{ Hz}$ ($= 5.2 \times 10^{-4} \text{ gauss} = 5.2 \times 10^{-8} \text{ T}$), constant for CH, the quantum number $M_I = -\frac{1}{2}$ or $+\frac{1}{2}$. For the CH₃ group, $M_I = -\frac{3}{2}, -\frac{1}{2}, +\frac{1}{2}, +\frac{3}{2}$. The dashed lines represent the level spacing that would occur in the absence of the spin-spin interaction. The slopes of the energy levels are greatly exaggerated in the figure. Also, to be correct, all dashed lines should extrapolate to a common $E_N = 0$ at $B = 0$.

than kT , the Boltzmann population factors are essentially identical for these levels. However, there is some degeneracy because rapid rotation of the CH_3 group around the C—C bond makes the three protons magnetically equivalent. The number of spin orientations of the CH_3 protons that produce equivalent fields at the CH proton determine the degeneracy. The eight permutations of the CH_3 spins shown in Fig. 2 thus lead to a predicted intensity ratio of 1:3:3:1 for the CH multiplet. Similarly the CH_3 doublet peaks will be of equal intensity, with a total integrated intensity three times that of the CH peaks. In a more general sense, it can be seen that n equivalent protons interacting with a different proton

FIGURE 3

NMR spectrum of highly purified ethanol obtained at 100 MHz.



will split its resonance into $n + 1$ lines whose relative intensities are given by coefficients of the terms in the binomial expansion of the expression $(\alpha + \beta)^n$. Equivalent protons also interact and produce splitting in the energy levels. However, these splittings are symmetric for upper and lower energy states, so no new NMR resonances are produced.

If a proton is coupled to more than one type of neighboring nucleus, the resultant multiplet pattern can often be understood as a simple stepwise coupling involving different J values. For example, the CH₂ octet that occurs for pure CH₃CH₂OH (Fig. 3) arises from OH doublet splitting ($J = 4.80$ Hz) of the quartet of lines caused by coupling ($J = 7.15$ Hz) with CH₃. It should be mentioned that such regular splitting and intensity patterns are expected for two nuclei A and B only if $|\nu_A - \nu_B| \approx 10J_{AB}$. The spectra for this weakly coupled case are termed *first order*. Since the difference $\nu_A - \nu_B$ (in Hz) increases with the field while J_{AB} does not, NMR spectra obtained with a high-field instrument (400 MHz) are often easier to interpret than those from a low-field spectrometer (60 MHz). However, even if the multiplets are not well separated, it is still possible to deduce accurate chemical shifts and J values using slightly more involved procedures, which are outlined in most texts on NMR spectroscopy.¹⁻⁵ Such an exercise can be done as an optional part of this experiment, although it will not be necessary for the determination of equilibrium constants.

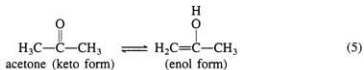
The mechanism of spin-spin coupling is known to be indirect and to involve the electrons in the bonds between interacting nuclei. The spin of the first nucleus A is preferentially coupled antiparallel to the nearest bonding electron via the so-called Fermi contact interaction, which is significant only when the electron density is nonzero at the first nucleus. (Such is the case only for electrons in s orbitals, since p , d , and f orbital wavefunctions have zero values at the nucleus.) This electron-spin alignment information is transmitted by electron-electron interactions to the second nucleus B to produce a field that thus depends on the spin orientation of the first nucleus (Fig. 4). Since the strength of this interaction falls rapidly with separation, only neighboring groups produce significant splitting. A few typical spin-spin coupling constants are given in Table 2 and these, along with the chemical shifts, serve to identify proton functional groups. As mentioned above, the multiplet intensities also give useful information about neighboring groups. Thus NMR spectra can provide detailed structural information about large and complex molecules.



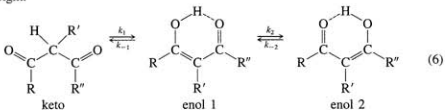
FIGURE 4

Illustration of nuclear spin-spin interaction transmitted via polarization of bonding electrons. The two electrons about each carbon will tend to be parallel, since this arrangement minimizes the electron-electron repulsion (Hund's rule for electrons in degenerate orbitals).

Keto-Enol Tautomerism. It is well known that ketones such as acetone have an isomeric structure, which results from proton movement, called the enol tautomer, an unsaturated alcohol:



For acetone and the majority of cases in which this keto-enol tautomerism is possible, the keto form is far more stable and little if any enol can be detected. However, with β -diketones and β -ketoesters, such factors as intramolecular hydrogen bonding and conjugation increase the stability of the enol form and the equilibrium can be shifted significantly to the right.



The proton chemical environments are quite different for the keto and enol tautomers, and the interconversion rate constants k_1 and k_{-1} between these forms are small enough

TABLE 2 Typical proton spin-spin coupling constants

| Coupling | $J(\text{Hz})$ | Coupling | $J(\text{Hz})$ |
|----------|----------------|----------|----------------|
| | -20 to +5 | | 0 to 3.5 |
| | 2 to 9 | | 6 to 14 |
| | 0 | | |
| | 6 to 9 | | 11 to 19 |
| | 1 to 3 | | |
| | 1 | | |

that distinct NMR spectra are obtained for both forms. In principle, the two enols are also distinguishable when $R' \neq R''$. However, the intramolecular OH proton transfer is quite rapid at normal temperatures, so that a single (average) OH resonance is observed. In general, such averaging occurs when the conversion rates k_2 and k_{-2} (in Hz) exceed the frequency separation $\nu_1 - \nu_2$ (also in Hz) of the OH resonance for the two enol forms.² The magnetic field at the OH proton is thus averaged and resonance occurs at $(\nu_1 + \nu_2)/2$. Similarly, rapid rotation about the C—C bonds of the keto form explains why spectra due to different keto rotational conformers are not observed. Thus distinct spectra are expected only for the two tautomers, and these can be used to determine the equilibrium constant for keto-to-enol conversion:

$$K_c = \frac{(\text{enol})}{(\text{keto})} \quad (7)$$

where parentheses denote concentrations in any convenient units.

The keto arrangement shown in Eq. (6) is the configuration which is electrostatically most favorable, but the steric repulsions between R and R'' groups will be larger for this keto form than for the enol configuration. Indeed, experimental studies have confirmed that the enol concentration is larger when R and R'' are bulky.⁴ This steric effect is less important in the β -ketoesters, in which the $R \cdots R''$ separation is greater. For both β -ketoesters and β -diketones, α substitution of large R' groups results in steric hindrance between R' and R (or R'') groups, particularly for the enol tautomer, whose concentration is thereby reduced. Inductive effects have also been explored; in general, α substitution of electron-withdrawing groups such as —Cl or —CF₃ favor the enol form.⁴

The solvent plays an important role in determining K_c . This can occur through specific solute-solvent interactions such as hydrogen bonding or charge transfer. In addition the solvent can reduce solute-solute interactions by dilution and thereby change the equilibrium if such interactions are different in enol-enol, enol-keto, or keto-keto dimers. Finally the dielectric constant of the solution will depend on the solvent and one can expect the more polar tautomeric form to be favored by polar solvents. Some of these aspects are explored in this experiment.

EXPERIMENTAL

The general features of a CW NMR spectrometer were described briefly in Exp. 32, and details about Fourier-transform NMR instruments are given in Exp. 43. For the spectrometer you are to use, more specific operating instructions will be provided by the instructor. Obtain several milliliters each of acetylacetone ($\text{CH}_3\text{COCH}_2\text{COCH}_3$, $M = 100.13$, density = 0.98 g cm^{-3}) and ethyl acetoacetate ($\text{CH}_3\text{CH}_2\text{OCOCH}_2\text{COCH}_3$, $M = 130.14$, density = 1.03 g cm^{-3}). Prepare small volumes of two solvents and three solutions.

Solvent A: Carbon tetrachloride, spectrochemical grade ($M = 153.83$, density = 1.58 g cm^{-3}) with 5 percent-by-volume tetramethylsilane (TMS) added. Prepare in a 10-mL volumetric flask.

Solvent B: Methanol, spectrochemical grade ($M = 32.04$, density = 0.791 g cm^{-3}) with 5 percent-by-volume TMS added. Prepare in a 5- or 10-mL volumetric flask.

Solution 1: 0.20 mole fraction of acetylacetone in solvent A.

Solution 2: 0.20 mole fraction of acetylacetone in solvent B.

Solution 3: 0.20 mole fraction of ethyl acetoacetate in solvent A.

For FT-NMR instruments that require a deuterated sample for frequency-locking purposes, CDCl_3 and CD_2OD can be used as solvents A and B.

Use a 1-mL pipette graduated in 0.01-mL increments to measure out 0.010 mol of solute, and use a 2-mL graduated pipette to then add the correct amount (0.040 mol) of solvent. You may neglect the presence of the 5 percent TMS when determining the necessary volumes of solvent. **Warning:** All work with TMS should be carried out in a hood. All containers or samples containing TMS should be tightly sealed and stored at low temperatures because of its volatility.

Prepare an NMR tube containing about 1 in. of solvent A and another containing solvent B, and record both NMR spectra, setting the TMS signal at the chart zero. Repeat for solutions 1 to 3, taking care to scan above $\delta = 10$ ppm since the enol OH peak is shifted substantially downfield. Determine which peaks are due to solute and measure chemical shifts for all solute features. Integrate the bands carefully at least three times, expanding the vertical scale by known factors as necessary in order to obtain accurate relative intensity measurements.

CALCULATIONS

Assign all spectral features using Table 1 and other NMR reference sources.^{2,3,5} Tabulate your results and use your integrated intensities to calculate the percentage enol present in solutions 1 to 3. If possible, use the total integral corresponding to the sum of methyl (or ethyl), methylene, methyne, and enol protons. If this proves difficult because of overlap with solvent bands, indicate clearly how you used the intensities to calculate the percentage enol.

For both the enol and the keto forms, compare experimental and theoretical ratios of the integrated intensities for different types of protons (e.g., methyl to methylene protons in the keto form).

Using Eq. (7), calculate K_c and the corresponding standard free-energy difference ΔG° for the change in state keto \rightarrow enol in each solution.

DISCUSSION

Discuss briefly your assignments of chemical shifts and spin-spin splitting patterns of acetylacetone and ethyl acetoacetate. Which compound has a higher concentration of enol form, and what reasons can you offer to explain this result? What changes would you expect in the NMR spectra of these two compounds if the interconversion rate between enol structures were much slower?

Compare the value of K_c for acetylacetone in CCl_4 with that in CH_3OH . What does your result suggest regarding the relative polarity of the enol and keto forms? Which form is favored by hydrogen bonding and why?

Compare your values of ΔG° with those for the gas phase ($\Delta G^\circ = -9.2 \pm 2.1$ kJ mol^{-1} for acetylacetone, $\Delta G^\circ = -0.4 \pm 2.5$ kJ mol^{-1} for ethyl acetoacetate).⁶ What solvent properties might account for any differences you observe?

Additional compounds suitable for studies of steric effects on keto-enol equilibria include α -methylacetylacetone ($\text{CH}_3\text{COCHCH}_3\text{COCH}_3$), diethylmalonate ($\text{CH}_3\text{CH}_2\text{OCOCH}_2\text{COOCH}_2\text{CH}_3$), ethyl benzoylacetate ($\text{C}_6\text{H}_5\text{COCH}_2\text{COOCH}_2\text{CH}_3$), and *t*-butyl acetoacetate ($\text{CH}_3\text{COCH}_2\text{COO}t\text{-Bu}$). Some other possible compounds are listed in Refs. 4 and 5.

Further aspects of this equilibrium that could be studied include the effects of concentration, temperature, and solvent dielectric constants on K_c .⁵

SAFETY ISSUES

Carbon tetrachloride and tetramethylsilane (TMS) are both toxic chemicals; see p. 197 for details about CCl_4 . TMS is volatile and must be kept in a tightly sealed container. Carry out all solution preparations in a fume hood. Use a pipette bulb; do not pipette by mouth. Dispose of waste chemicals as instructed.

APPARATUS

NMR spectrometer with integrating capability; several 5- and 10-mL volumetric flasks; precision 1-mL and 2-mL graduated pipettes; pipetting bulb; NMR tubes; spectrochemical-grade CCl_4 and CH_3OH (or CDCl_3 and CD_3OD); tetramethylsilane, acetylacetone, and ethyl acetoacetate; fume hood.

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