Formation of Intramolecular Hydrogen Bond in Hydroxy-substituted Nitroxide Radicals as Evidenced by Electron Spin Resonance

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The nature of the intramolecular hydrogen bond in hydroxysubstituted nitroxide radicals was examined. The hydroxysubstituted radical was produced by the spin trapping reaction of hydroxyalkyl radicals with α-phenyl-*N*-*t*-butylnitrone. The magnitude of the hyperfine splitting caused by β-hydrogen of the radical is strongly dependent on the composition of the solvent, which is attributed to the formation of the intramolecular hydrogen bond. The equilibrium constant of the intramolecular hydrogen bond in an aprotic solvent was determined by observing the magnitude of the hyperfine splitting of β-hydrogen as a function of the amount of added methanol. Based on the temperature dependence of the equilibrium constant, the standard entropy and the standard enthalpy of the formation of the hydrogen-bonded chelate ring was estimated. The same method of analysis was applied to the system of diastereomeric nitroxide and the difference of the internal energy of the chelate ring in the isomers was detected. Moreover, the difference was utilized to separate the ESR spectra of the diastereomers.

Hydrogen bonding in free radicals in solution has been extensively studied by the magnetic resonance technique. In some cases the thermodynamic constants of the formation of the hydrogen bond have been determined, based on the equilibrium study.1—6) Concerning the intramolecular hydrogen bond, hydroxy-substituted semiquinone radicals exhibit an ESR linewidth alternation caused by the formation of the intramolecular hydrogen bond.7,8) The linewidth alternation was also detected in hydroxy-substituted nitroxide radicals due to the formation of the chelate ring.9,10) These studies have confirmed the formation of the intramolecular hydrogen bond, however, experimental difficulties prevent an equilibrium study.

The main difficulty in determining the equilibrium nature of the intramolecular hydrogen bond is to find a sensitive index which establishes the equilibrium state. Also there is characteristic difficulty in studying the hydrogen bond by a magnetic resonance technique: the rate of formation and breakage of the hydrogen bond is very large compared with the time scale of magnetic resonance so that the observed spectrum is that of an equilibrium mean.11)

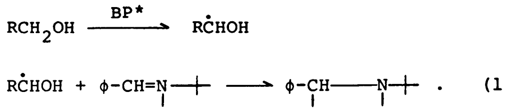
Recently it was pointed out that the hydroxy-substituted nitroxide radicals produced by a spin trapping technique have hyperfine splitting (hfs) of the β-hydrogens which is very sensitive to the solvent.12) Typically, the hfs of β-H decreases forty per cent on changing from an aprotic to a protic solvent. The formation of a chelate ring by the intramolecular hydrogen bond is responsible for the change of the hfs of β-H. The quantitative treatment of the equilibrium is now possible by observing the dependence of the magnitude of the hfs of β-H on the amount of added hydrogen donor such as methanol. Using this technique the standard entropy and the standard enthalpy for the formation of the chelate ring can be estimated by the temperature dependence of the equilibrium constant.

It should be pointed out that IR and NMR studies of the OH···O hydrogen bond were more concerned with the strength of the hydrogen bond than with the structure of the chelate ring.11) In the present system the magnitude of the β-H hfs provides information about the ring conformation while the *g*-values and N-hfs gives details of the OH···O bond.

The strain energy of the chelate ring is expected to be different for different diastereomers. Therefore the difference of the standard enthalpy of the formation of the chelate ring is utilized for the spectroscopic separation of the diastereomeric radical mixture. Hfs of β-H of diastereomers of hydroxy-substituted nitroxide radicals show different temperature dependence in the presence of proton donors. As a result the ESR spectra of diastereomeric systems showed better resolution at low temperature in toluene in the presence of methanol.

Experimental

Hydroxy-substituted nitroxide radicals were produced by the abstraction of a hydrogen atom from alcohols by photo-excited benzophenone (BP) followed by spin trapping with phenyl-*N*-*t*-butyl nitrone (PBN). The reaction scheme for the formation of the radical is as follows:13,14)



$$\mathrm{RCH_2OH} \xrightarrow{\mathrm{BP}^*} \mathrm{R\dot{C}HOH}$$

$$\mathrm{R\dot{C}HOH} + \phi\text{-}\mathrm{CH{=}\underset{\displaystyle O}{\underset{|}{N}}\text{-}}t\text{-Bu} \longrightarrow \phi\text{-}\underset{\displaystyle \mathrm{R\text{-}CH\text{-}OH}}{\underset{|}{\mathrm{CH}}}\text{—}\underset{\displaystyle \mathrm{O}\cdot}{\underset{|}{\mathrm{N}}}\text{-}t\text{-Bu}\ . \qquad (1)$$

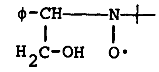
The details of the experimental procedure has been described elsewhere.12) After the formation of nitroxides the parent alcohol was removed completely by vacuum distillation and a known amount of toluene and methanol was introduced under vacuum.

Materials. Benzophenone was recrystallized from petroleum benzine. PBN was purified by sublimation. Toluene was dehydrated by refluxing it with sodium metal and was stored over Na/K alloy under vacuum. Carbon tetrachloride was distilled and stored over calcium chloride. Alcohols were dehydrated by adding calcium hydride and were stored over molecular sieves 4A under vacuum.

The ESR spectrometer employed was operated at the X-band. The temperature of the sample was controlled by a flow of chilled nitrogen. The accuracy of the measurement of the hfs was ±0.005 mT.12)

Results and Discussion

The magnitude of the β-H hfs of the ESR spectra of hydroxymethyl adduct (**1**) is increased considerably by



$$\phi\text{-}\underset{H_2C\text{-}OH}{\underset{|}{CH}}\text{——}\underset{O\cdot}{\underset{|}{N}}\text{—}\!\!+$$

1

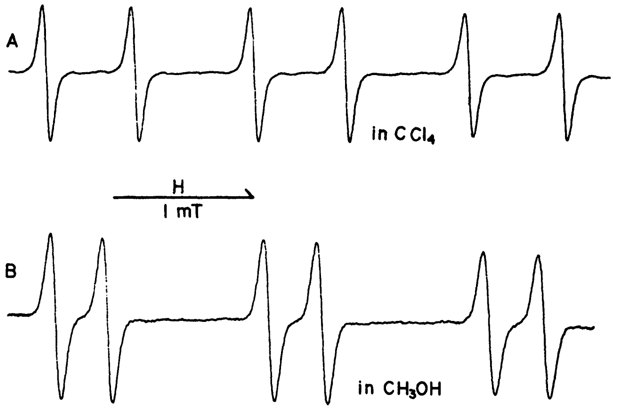


Fig. 1. ESR spectra of hydroxymethyl adduct of PBN(I) in carbon tetrachloride (A) and in methanol (B) at room temperature.

TABLE 1. g-VALUES AND hfs OF NITROXIDE RADICALS

Radical	Solvent	g-Value	A_N/mT	$A_{\beta\text{-}H}$/mT
Hydroxymethyl	toluene	2.0058	1.50	0.66
adduct	methanol	2.0058	1.51	0.36
Di-t-butyl	toluene	2.0061	1.53	—
nitroxide[15]	methanol	2.0058	1.62	—

change from a protic to an aprotic solvent as shown in Fig. 1. The solvent effect on the g-values and N-hfs of nitroxide radicals has been extensively studied by ESR spectroscopy.[3,15] In general, when the solvent changes from protic to aprotic the g-value increases but the N-hfs becomes smaller. The hfs and g-values of radical **1** and di-t-butyl nitroxide in methanol and toluene are listed in Table 1 for comparison. In contrast to the large solvent effect on the magnitude of the hfs of β-H, the effect is small for the hfs of the N^{14} nucleous and the g-value. This fact shows that the solvent did not change the environment of the nitroxide group but changes the steric conformation of the radical. In a protic solvent the hydrogen bond between the solvent and the nitroxide group in the radical is dominant but in an aprotic solvent the hydroxyl group of the radical acts as a hydrogen donor. Thus the intramolecular hydrogen bond in this system effects only the change of steric conformation, *i.e.* the change of the hfs of β-H.

Determination of the Equilibrium Constant for the Formation of Intramolecular Hydrogen Bond. In a pure aprotic solvent observed ESR parameters of radical **1** are the equilibrium mean of the open form radical and intramolecularly hydrogen-bonded radical. Because of the difficulty in deciding the ESR parameters of the independent form, it is impossible to determine the equilibrium constant for the formation and breakage of the intramolecular hydrogen bond.

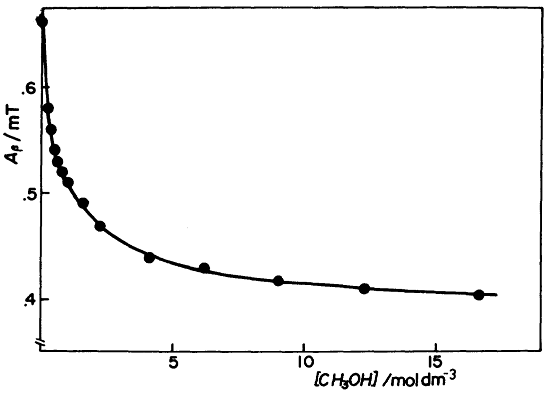
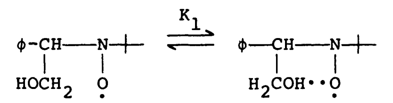


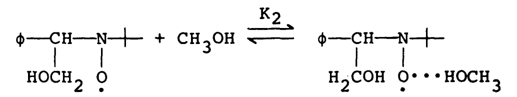
Fig. 2. Variation of β-hydrogen hfs of radical (I) as the function of the amount of methanol in carbon tetrachloride.

When methanol was added to the aprotic solvent solution of radical **1**, the hfs of β-H decreases with the increasing amount of methanol. Figure 2 shows the dependence of the magnitude of the β-H hfs on the amount of methanol in CCl_4. Marked decrease of the hfs was observed on the addition of the small amount of methanol.

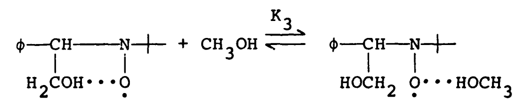
There are three different equilibria in this system in the presence of methanol as follows. When R_O expresses



$$\phi\text{-}\underset{HOCH_2}{\underset{|}{CH}}\text{——}\underset{\dot{O}}{\underset{|}{N}}\text{—}\!\!+ \;\underset{}{\overset{K_1}{\rightleftharpoons}}\; \phi\text{—}\underset{H_2COH\cdots}{\underset{|}{CH}}\text{——}\underset{\dot{O}}{\underset{|}{N}}\text{—}\!\!+ \qquad (2)$$



$$\phi\text{—}\underset{HOCH_2}{\underset{|}{CH}}\text{—}\underset{\dot{O}}{\underset{|}{N}}\text{—}\!\!+ \;+\; CH_3OH \;\overset{K_2}{\rightleftharpoons}\; \phi\text{—}\underset{H_2COH}{\underset{|}{CH}}\text{—}\underset{\dot{O}\cdots HOCH_3}{\underset{|}{N}}\text{—}\!\!+ \qquad (3)$$



$$\phi\text{—}\underset{H_2COH\cdots}{\underset{|}{CH}}\text{——}\underset{\dot{O}}{\underset{|}{N}}\text{—}\!\!+ \;+\; CH_3OH \;\overset{K_3}{\rightleftharpoons}\; \phi\text{—}\underset{HOCH_2}{\underset{|}{CH}}\text{—}\underset{\dot{O}\cdots HOCH_3}{\underset{|}{N}}\text{—}\!\!+ \qquad (4)$$

the open form radical and R_I and R_H denotes the radicals with an intramolecular hydrogen bond and with an intermolecular hydrogen bond, respectively, then

$$K_1 = [R_I]/[R_O] \qquad (5)$$

$$K_2 = [R_H]/[R_O][CH_3OH] \qquad (6)$$

$$K_3 = [R_H]/[R_I][CH_3OH], \qquad (7)$$

K_1, K_2, and K_3 are not independent and have the relation $K_1=K_2/K_3$. Observed hfs of β-H is expressed as

$$\bar{A} = P(R_O)A(R_O) + P(R_I)A(R_I) + P(R_H)A(R_H), \qquad (8)$$

where P denotes the fraction of each radical and A denotes the hfs of each radical. By a simple calculation

$$\bar{A} = \{1+K_1+[R_H]K_1/[R_I]\}^{-1}\{A(R_O) + K_1A(R_I) + [R_H]K_1/[R_I]\}. \qquad (9)$$

Based on the experimental fact that N-hfs and g-value of radical **1** in a pure aprotic solvent coincide with those in methanol as shown in Table 1, K_1 can be assumed to be very large. Equation 9 then becomes[16–18]

$$\bar{A} = \{1+[R_H]/[R_I]\}^{-1}\{A(R_I) + [R_H]/[R_I]\}. \qquad (10)$$

Rewriting Eq. 10 one obtains[18]

$$1/(A(R_I) - \bar{A}) = (1/K_3)[CH_3OH]^{-1}(A(R_I) - A(R_H)) + 1/(A(R_I) - A(R_H)). \qquad (11)$$

If the initial concentration of methanol is sufficiently higher than the radical concentration, the plot of $1/(A(R_I)-\bar{A})$ against the reciprocal concentration of methanol gives K_3 and $A(R_H)$. In this plot one can employ the hfs of the β-H in pure aprotic solvent as $A(R_I)=0.66\pm0.01$ mT.

The dotted line in Fig. 3 shows the plot based on Eq. 11 of the hfs shown in Fig. 2. At high concentrations of methanol the points deviate from the linear dependence. This is attributed to the formation of a hydrogen-bonded complex where two or more methanol molecules are present. The resulting equilibrium constant K_3 from Fig. 3 is 2.0 mol^{-1} dm^3 and $A(R_H)$ is 0.43 mT.

Standard Enthalpy and Standard Entropy of the Formation of Hydrogen-bonded Chelate Ring. The temperature dependence of the equilibrium constant K_3 can give the standard enthalpy difference ΔH° and standard entropy difference ΔS° for Eq. 4. Carbon tetrachloride solutions freeze at a comparatively higher temperature so that toluene was chosen as the solvent for the study of temperature dependence. Before applying Eq. 11 at various temperatures it is confirmed that $A(R_I)$ in pure toluene did not show temperature dependence. The solid lines in Fig. 3 show the plot based on Eq. 11 at various temperatures in toluene. The plot shows that K_3 increases with the lowering of the temperature. K_3's derived from Fig. 3 are listed in Table 2. The slope and the intercept of Van't-Hoff plot (Fig. 4) gives $\Delta H^\circ = -7.4\pm0.5$ kJ mol^{-1} and $\Delta S^\circ = -19\pm2$ J mol^{-1} K^{-1}.

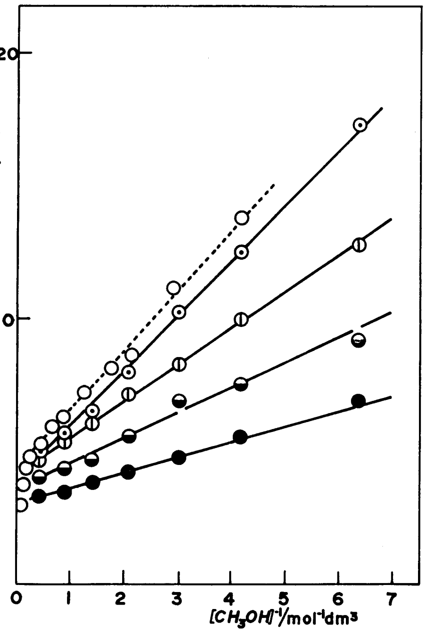


Fig. 3. The plot based on Eq. 11 for hydroxymethyl adduct.
○: In CCl$_4$ at 290 K, ⊙: in toluene at 298 K, ⦶: in toluene at 273 K, ◒: in toluene at 246 K, ●: in toluene at 217 K.

Table 2. Equilibrium constants K_3 and limiting hfs $A(R_H)$ at various temperatures

T/K	K_3/mol^{-1} dm^3 a)	$A(R_H)$/mT b)
217	6.1	0.41
246	3.7	0.41
273	2.9	0.38
298	1.9	0.34

a) Average error is ± 0.8. b) Average error is ± 0.09.

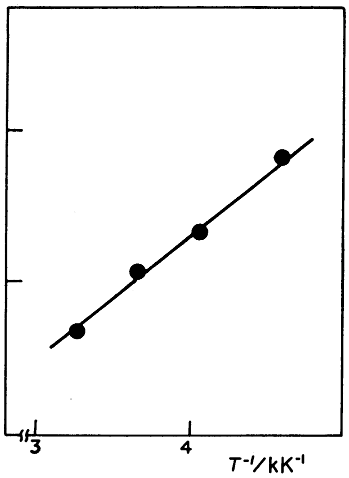


Fig. 4. Van't-Hoff plots for equilibrium contants K_3 derived from Fig. 3.

If one assumes that the standard ethalpies for the formation of hydrogen bonds on both sides of Eq. 4 are equal, ΔH° given above is that for the formation of the chelate ring. This assumption is justified by the fact that the g-value and N-hfs did not change on the addition of methanol. Since the g-value and N-hfs reflect the electronic structure around nitroxide function, the strength of the hydrogen bond of the radicals in Eq. 4 are the same.

The absolute value of ΔH° is interpreted to be the increment of the energy of interaction among substituents and that of energy of strain caused by the formation of the ring structure.

Intramolecular Hydrogen Bonds in Diastereomeric Nitroxides. When ethanol is used instead of methanol in the reaction (1) a nitroxide radical bearing two asymmetric carbons is produced. The formation of an intramolecular hydrogen bond in the diastereomer gives the cis-trans isomer as shown in Fig. 5.[12] The ESR spectra of the 1-hydroxyethyl adduct in toluene is shown in Fig. 6A. The regular distortion of each line indicates the presence of the diastereomer. The hfs constants of each isomer have been determined by spectrum simulation.

From the discussion in the former section it was concluded that the ΔH° of Eq. 4 is the enthalpy of the chelate ring formation. The isomers shown in Fig. 5 have different ΔH° because of the difference of the repulsion of the substituents mainly between the phenyl and methyl groups. It causes a difference of the temperature dependence of K_3. Figures 6B—6D show the temperature dependence of the ESR spectra of the

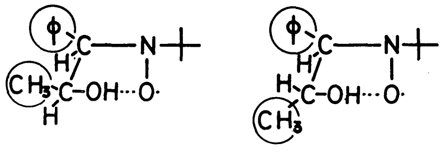


Fig. 5. Cis-trans isomer of 1-hydroxyethyl adduct produced by chelate ring formation.

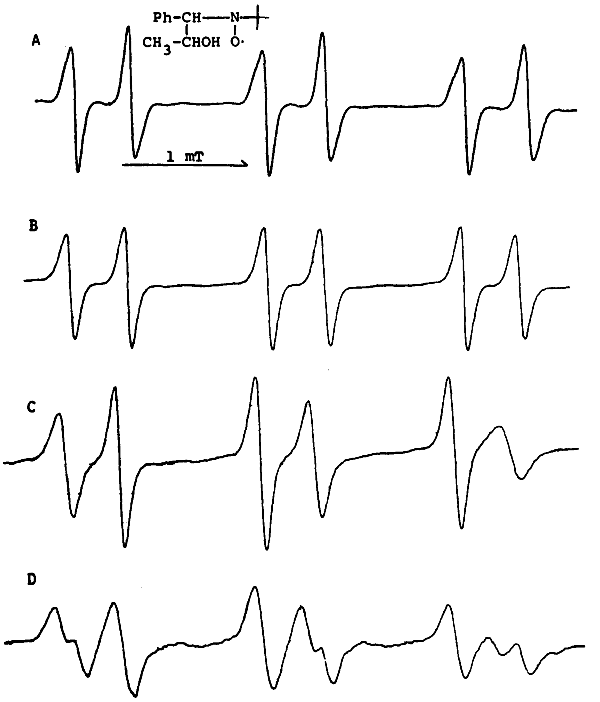


Fig. 6. ESR spectra of 1-hydroxyethyl adduct in toluene at room temperature (A), in toluene with 5 mol dm^{-3} methanol at 297 K(B), at 257 K(C), and at 208 K(D).

hydroxyethyl adduct in toluene containing 5 mol dm^{-3} methanol. At room temperature the resolution of the isomer is even poorer on the addition of methanol than in pure toluene, however, at 308 K the isomer clearly shows the difference in the hfs of the β-H. This experimental fact is explained by the difference of ΔH° for each isomer resulting in the difference of the temperature dependence of K_3 and also that of the hfs. The assignment of the ESR spectra to each isomer is now possible. The radical with the larger temperature dependence is the cis isomer and that with the smaller temperature dependence is the trans isomer. This assignment is in good accord with the assignment based on the small g-value difference of the isomer.[12]

A quantitative treatment of the difference of ΔH° for the isomers is possible for the 1-hydroxybutyl adduct of PBN. In this case the resolution is the best in pure toluene solution and the magnitude of the β-H hfs for each isomer is determined by spectrum simulation.[12] By the addition of methanol the resolution is diminished. The hfs constants of each isomer at various temperature were determined by spectrum simulation for each toluene solution of the radical containing a known amount of methanol. The same treatment as for the hydroxymethyl adduct using Eq. 11 gives the Van't-Hoff plot for each isomer. The resulting ΔH° is -10.2 ± 3.8 kJ mol^{-1} for the radical with smaller β-H hfs (cis isomer) and the radical with larger β-H hfs (trans isomer) has -6.2 ± 2.2 kJ mol^{-1} as ΔH°. The difference of ΔH° for the isomer is comparable in magnitude with the difference of the heat of formation of the cis-trans isomer in substituted cycloalkanes.[19]

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