394 © 1981 The Chemical Society of Japan *Bull. Chem. Soc. Jpn.*, **54**, 394—398 (1981) [Vol. 54, No. 2

Electron Spin Resonance Study on the Difference of Structure in Diastereomeric Nitroxyl Radicals

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(Received July 5, 1980)

Electron spin resonance spectra of nitroxyl radicals bearing two asymmetric carbons were observed. The radicals were produced by the abstraction of a hydrogen atom from ethers and amines by photoexcited benzophenone, followed by spin trapping with phenyl-*N*-*t*-butylnitrone. The spectra showed the presence of two radical species assignable to diastereomers in most cases. The presence of isomers was seen more clearly in ESR spectra of radicals produced from ethers than those from amines. The origin of the different ESR parameters of the isomer was discussed in detail and it was concluded that the functional group on β-carbon acts as a group of proximity to nitroxyl function. The difference of the electronegativity of the atom in each functional group causes the difference of the extent of the separation of isomers. The effects of proximity groups on observed ESR parameters are concluded to be the same as the solvent effect.

Diastereomers have chemically different properties. Different spectroscopic properties are also found, which are caused by the difference in the interaction of substituents.

As for free radicals having two chiral centers, it is possible to identify each diastereomer by ESR spectroscopy. Jonkman *et al.* detected the difference of hyperfine structure (hfs) in nitroxyl radicals having two asymmetric carbons on both sides of the nitroxyl function.[1)] Also, Laroff *et al.* observed the difference of hfs in anion radicals from both ascorbic and araboascorbic acid.[2)] However, the difference has not been discussed in relation to the structure of the radical because of the difficulty in systematic production of radicals.

Recently, it was pointed out that the spin trapping reaction using phenyl-*N*-*t*-butylnitrone (PBN, *N*-benzylidene-*t*-butylamine *N*-oxide) is an effective way of producing nitroxyl radicals having two asymmetric carbons on one side of the nitroxyl function.[3)] In the case of spin adducts produced from alcohol, a clear separation of hfs of the isomer was detected in an aprotic solvent; this was attributed to the formation of an intramolecular hydrogen bond. In the present study the difference of ESR parameters was also observed in open chain diastereomeric nitroxyls.

The condition which should be fulfilled for the detection of the difference in ESR parameters in an open chain diastereomeric nitroxyl radical is that the substituents attached to the asymmetric carbons should be bulky. The nitroxyl radicals produced by the addition of the radical formed by the abstraction of a hydrogen atom from an etherial compound have an alkoxyl group on β-carbon. Also, those from amines have amino or alkylamino group on β-carbon. In these radicals most of the substituents on β-carbon are bulky. In addition, there is no functional group to form tight hydrogen bonding.

The notable experimental result shown in this report is that the separations of isomers in spin adducts from ethers were much larger than those from amines. Moreover, the reproduction of the spectrum by the spectrum simulation showed that the difference of the g-value and hfs of $^{14}N(A_N)$ play a dominant role in giving the characteristic overlapped spectrum pattern. The hfs of β-H ($A_{\beta H}$) depends on the magnitude of the dihedral angle, which is directly derived from the steric conformation. The g-value and A_N depend on the electronic and steric structure of nitroxyl group. Thus, the result was interpreted by the difference of the dipole moment of CO bond and CN bond when they act as a group of proximity to the nitroxyl group. This leads to the conclusion that the difference of g- and A_N-value in stereoisomer of spin adducts from ether is based on the difference in the distance between oxygen atom and nitroxyl group. The effect of a proximity group is shown to be the same as the solvent effect on nitroxyl radicals.

Experimental

Approximately 10^{-4} mol PBN and 10^{-4} mol benzophenone was dissolved in 1 cm^3 ether and amine. The solution was packed into a pyrex ampoule having an ESR sample tube as a side arm and was degassed by the freeze-pump-thaw method. Radicals are produced by the irradiation of UV light from an 1 kW mercury arc.[3,4)] The period of irradiation was 5 to 10 min, depending on the yield of radicals.

The PBN used was purified by the sublimation technique. Benzophenone was recrystallized twice from a petroleum ether solution. Guaranteed grade ethers were treated with potassium hydroxide to remove peroxy derivatives and were dried over Na–K alloy. Amines were distilled and stored over potassium hydroxide. The ampoule were charged with ether or amine by vacuum distillation.

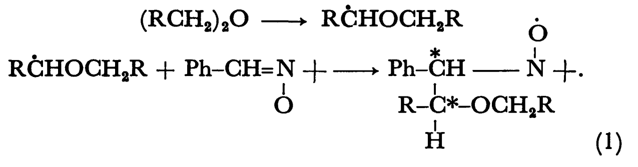
The solvent effect on the spectral pattern was examined in some cases with the use of same technique as described elsewhere.[3)]

The hfs and g-value were determined by use of aqueous solution of potassium peroxylamine disulfonate buffered with 0.2 M K_2CO_3 solution. The solution was packed in a capillary tube and attached on the sample tube, ESR spectra being recorded simultaneously. The g-value and ^{14}N hfs have been reported to be 2.005560 ± 0.000004[5)] and 13.091 ± 0.004,[6)] respectively. Computer spectrum simulation was applied to analyze the overlapped spectra.

Results and Discussion

Ether. It is well known that photoexcited benzophenone abstracts hydrogen on the carbon adjacent to the etherial oxygen.[4–10)] When one applies the spin trapping reaction with PBN, the assignment of the resulting radical is sometimes ambiguous because of the absence of the hfs from the trapped group. However there have been some examples in which the hfs from the trapped group appears.[11] Also, the ENDOR study of spin adducts has clearly shown the presence of the hfs from trapped groups.[12] In the present experiment, the spin adducts from anisole showed the hfs of methylene proton in phenoxymethyl group. Therefore, it is reasonable to assign the nitroxyl radicals as spin adducts of a radical hydrogen abstracted from the carbon adjacent to the etherial oxygen.

The ethers chosen as radical sources are symmetric to avoid a system which would produce two different radicals to be trapped. The reaction scheme for the production of the nitroxyl radical is as follows:



$$(RCH_2)_2O \longrightarrow R\dot{C}HOCH_2R$$

$$R\dot{C}HOCH_2R + \text{Ph–CH=}\underset{\displaystyle O}{\underset{|}{N}}\text{–}\!\!+ \longrightarrow \text{Ph–}\underset{\displaystyle \underset{\displaystyle \underset{\displaystyle H}{|}}{\text{R–C*–OCH}_2\text{R}}}{\underset{|}{\overset{*}{C}H}} \text{——} \overset{\displaystyle \dot{O}}{\overset{|}{N}} \!\!+. \qquad (1)$$

The formed radical should have an open chain structure because there is no donative hydrogen which is capable of forming an appreciable intramolecular hydrogen bond. The fact that the hfs of β-hydrogen was very insensitive to the change of solvent from aprotic to protic shows the absence of intramolecular hydrogen bonds.

Figure 1A shows a typical ESR spectra observed in the etherial system. In tetrahydrofuran, the spectrum shows an asymmetric pattern due to the presence of two radical species. These are reproducible by means of spectrum simulation by overlapping two ESR spectra which have four different parameters, namely $A_{\beta H}$, A_N, g-value, and linewidth. The stick spectrum in Fig. 1A shows the position of the ESR lines from each radical. Almost all ethers tried in this experiment gave ESR spectra which showed the presence of two radical species which have different hfs and g-value. The result of the analysis for several etherial spin adducts are listed in Table 1.

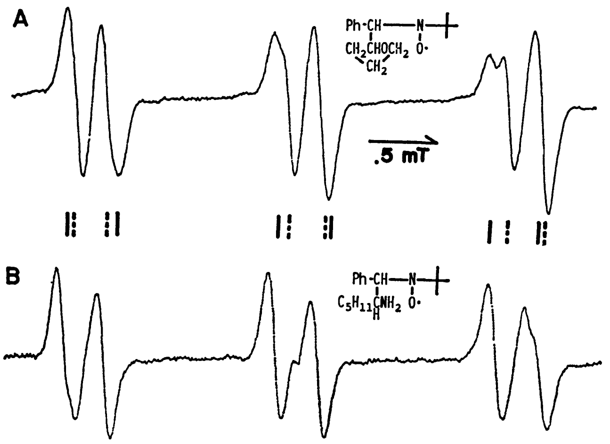


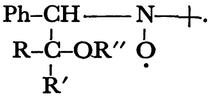
Fig. 1. ESR spectra of nitroxyl radicals produced by spin trapping with PBN.
A: From tetrahydrofuran, B: from *n*-hexylamine. Stick spectrum shows the line position of spectrum A.

In order to confirm that the overlapped spectrum is due to two asymmetric carbons, some radical sources which cannot produce the spin adducts with two asymmetric carbons by reaction (1) were examined. Diisopropylether, anisole (Fig. 2A), and 1,3,5-trioxane were chosen for this purpose. All of the resulting spin adducts showed a symmetric line shape and can be assignable to single radical species.

Table 1 shows that the radical with larger $A_{\beta H}$ has smaller A_N and larger g-value. Therefore the resolution

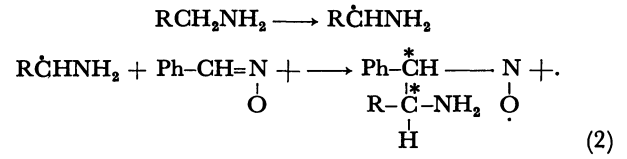
TABLE 1. HYPERFINE SPLITTING CONSTANTS OF NITROXYLS PRODUCED FROM ETHERS

Parent ether	R[a]	R′ [b]	R″ [c]	$A_{\beta H}$ / 10^{-4} T	A_N / 10^{-4} T	Δg[d] / 10^{-4} T	ΔH_{msl}[e] / 10^{-4} T
Ethyl ether	H	CH_3	C_2H_5	2.5 1.7	14.6 15.0	0.2	1.1 1.0
Propyl ether	H	C_2H_5	C_3H_7	2.4 1.7	14.2 14.6	0.2	1.3 1.0
Butyl ether	H	C_3H_7	C_4H_9	2.6 1.8	14.5 15.0	0.2	1.0 0.8
Tetrahydrofuran	H	CH_2–	CH_2–	2.5 1.7	14.3 14.7	0.2	1.0 0.8
Tetrahydopyran	H	CH_2–	CH_2–	2.5 1.7	14.3 14.8	0.2	1.3 1.0
Dioxane	H	CH_2–	CH_2O–	2.4 1.6	14.6 15.0	0.2	1.3 1.0
Phenylethyl ether	H	CH_3	Ph	2.4 1.5	14.2 14.5	0.2	1.3 1.0
Isopropyl ether	CH_3	CH_3	$CH(CH_3)_2$	2.3	14.5		
Trioxane	H	CH_2O	CH_2O	2.1	14.7		
Anisole	H	H	Ph	2.5[f]	14.7		

a), b), c) Substituents in the structure shown as  $\text{Ph–}\underset{\displaystyle \underset{\displaystyle R'}{|}}{\underset{|}{\text{R–C–OR}''}}\text{——}\underset{\displaystyle \dot{O}}{\underset{|}{N}}\text{—}\!\!+$. d) First set minus second set. 10^{-4} T corresponds to the g difference of 0.0007 at the observed external field. e) Maximum slope line width of Gaussian line shape used for spectrum simulation. f) $A_{\gamma H}=0.4\times 10^{-4}$ T (2H).

of lines from each radical is the best for the high field doublet, as is noticed in the spectra of Fig. 1A. It is also noted that the ESR parameters do not largely depend on the difference of R′ and R″.

Amine. Photoexcited benzophenone also abstracts hydrogen on the carbon adjacent to each amino group.[13–15] To avoid the formation of spin adducts of different substituents from a single amine source, chosen secondary and tertiary amines have a symmetric structure in which alkyl groups are the same. The reaction scheme of the formation of the radical in a primary amine is as follows:



$$RCH_2NH_2 \longrightarrow R\dot{C}HNH_2$$

$$R\dot{C}HNH_2 + \underset{\displaystyle O}{Ph\text{–}CH\text{=}\overset{|}{N}} + \longrightarrow \begin{array}{l} Ph\text{–}\overset{*}{\dot{C}}H \text{——} N + . \\ \quad R\text{–}\overset{*}{C}\text{–}NH_2 \;\; \dot{O} \\ \qquad\; H \end{array} \qquad (2)$$

Figure 1B shows the typical recorder trace for the adduct from hexylamine. The difference in the ESR spectral pattern in diastereomer is small compared to the radical from ether. The results of the analysis using spectrum simulation are listed in Table 2. The difference of the ESR parameters of isomers is mainly characterized by the magnitude of $A_{\beta H}$. However, the difference within an isomer is very small when R and R′ are small substituents. Isopropylamine was chosen as a source of radical which cannot produce diastereomers. The ESR spectrum shows the presence of a single radical (Fig. 2B).

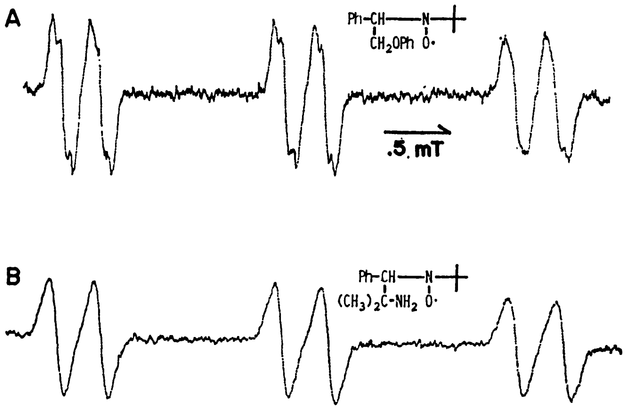


Fig. 2. ESR spectra of nitroxyl radicals produced by spin trapping with PBN.
A: From anisole, B: from isopropylamine.

The solvent effect on the spectral pattern was also very poor in both protic and aprotic solvents, which showed that the structure of the alkylamino adduct is open chain.

Interpretation of the Difference of ESR Parameters in Isomer. By the inspection of the ESR parameters summarized in Tables 1 and 2, one can find some

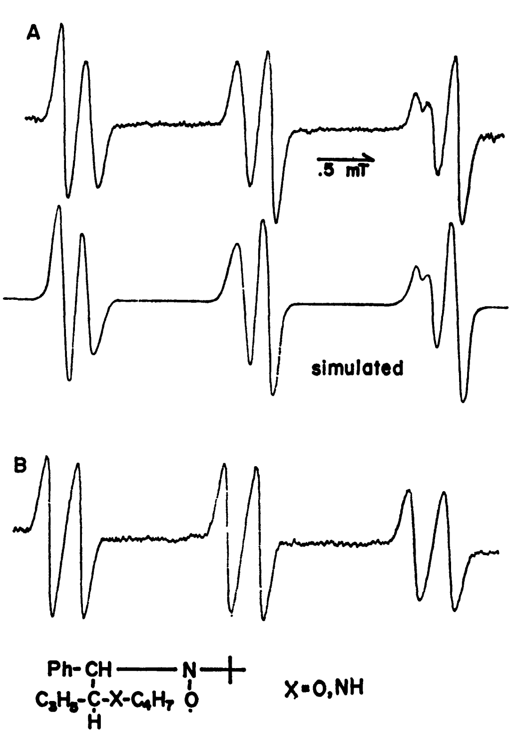
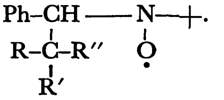


Fig. 3. ESR spectra of nitroxyl radicals produced by spin trapping with PBN.
A: From butyl ether, B: from dibutylamine.

TABLE 2. HYPERFINE SPLITTING CONSTANTS OF NITROXYLS PRODUCED FROM AMINES

Parent amine	R[a)]	R′[b)]	R″[c)]	$\frac{A_{\beta H}}{10^{-4}\,T}$	$\frac{A_N}{10^{-4}\,T}$	$\frac{\Delta g^{d)}}{10^{-4}\,T}$
Propylamine	H	C_2H_5	NH_2	2.8	15.1	
Butylamine	H	C_3H_7	NH_2	2.7	14.7	
Hexylamine	H	C_5H_{11}	NH_2	2.7 3.0	14.8 15.0	0
Diethylamine	H	CH_3	NHC_2H_5	2.9	14.8	
Dibutylamine	H	C_3H_7	NHC_4H_9	2.6	14.8	
Triethylamine	H	CH_3	$N(C_2H_5)_2$	1.9 2.3	15.1 15.3	0.1
Phenethylamine	CH_3	Ph	NH_2	2.5 2.9	14.6 14.8	0
Isopropylamine	CH_3	CH_3	NH_2	2.8	14.7	

a), b), c) Substituents in the structure shown as



$$\begin{array}{l} Ph\text{–}CH \text{——} N\text{—}+. \\ \;\; R\text{–}\overset{|}{C}\text{–}R'' \;\; \overset{|}{\dot{O}} \\ \qquad R' \end{array}$$

d) First set minus second set. 10^{-4} T corresponds to the g difference of 0.0007 at the observed external field.

contrast due to the difference of radical sources. The difference within each diastereomer is larger for the spin adducts from ether than those from amines. This is illustrated in Fig. 3 as the comparison of the ESR spectra of the adducts produced from dibutyl ether and dibutylamine. In spite of the similarity of the structure of the radical, the extent of the separation of the isomer in ESR spectra is very different. In particular, the difference of A_N and g-value can be noted from Table 1. It is also noted that the dependence of ESR parameters on the bulkiness of R, R′, and R″ is poor. The origin of the difference is discussed in connection with the steric structure of radicals.

Conformation of Radical: Though the radical has an open chain structure, the most probable conformation of the molecule can be specified because of the bulkiness of the substituents. Based on the fact that the magnitude of the $A_{\beta H}$ is 0.2 to 0.3 mT, the dihedral angle between C–H$_\beta$ and the unpaired electron orbital is estimated to be around 70° to 80° by McConnell's $\cos^2\theta$ rule.[16,17]

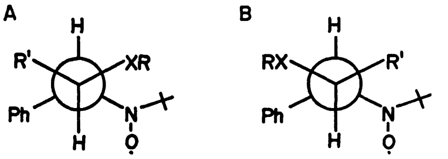


Fig. 4. Steric conformation of diastereomeric nitroxyls. Note the distance between X and N.

The most probable conformation around C$_\alpha$ and C$_\beta$ is *trans* with respect to two hydrogens considering the smallest possible interaction between substituents.[18] Then the difference of the configuration in diastereomer produces the difference of the conformational structure, as illustrated in Fig. 4. It is noted that in one stereoisomer (Fig. 4A) the distance between XR and NO is closer than in the other. In the structure shown in Fig. 4, the dominant steric interactions between substituents are (R′-Ph) and (XR-NO) for Fig. 4A and (R′-NO) and (XR-Ph) for Fig. 4B. The repulsive interactions among (XR-Ph) and (R′-Ph) are effective for the determination of the equilibrium conformations which cause the characteristic $A_{\beta H}$ for each radical. In contrast, the interactions shows (XR-NO) and (R′-NO) should be effective not only in determining the conformation but in changing the electronic structure of the nitroxyl group. The change of the electronic state of nitroxyl group reflected on the g-value and A_N.

By taking into account the fact that the bond angles of C–O–C and C–N–C are around 110°, the total structures of the spin adducts from dialkyl ether and dialkylamine are very similar. In spite of such similarities of the structure, the extents of the separation of the ESR parameters are very different.

It is now almost clear that the difference is caused by the presence of oxygen and nitrogen atoms in the side chain of each radical. The difference of the magnitude of the perturbation from oxygen and nitrogen decides the difference of the spectral pattern.

Proximity Effect on Nitroxyl Group: As has been discussed by many investigators, the solvent effects on the ESR parameters of nitroxyl radicals can be explained qualitatively by the amount of contribution from each resonance structure shown below:

$$\underset{\text{I}}{\text{N–O}\cdot} \rightleftarrows \underset{\text{II}}{\dot{\text{N}}^{+}\text{–O}^{-}}.$$

The effect of increasing the dipole moment of the solvent results in the increase of the contribution from structure II. This also explains the result of the present experiment: If one replaces the dipole moment of the solvent by the bond moment[19] of the proximity group, the larger bond moment of C–O bond explains that the separation of the isomer in the spin adducts from ether is larger than in those from amines which are perturbed by the bond moment of C–N.

The present experimental result of the solvent effect on A_N and g-value also supports the interpretation. The shifts of A_N and g-value are almost the same for the isomer in various solvents. Also, $A_{\beta H}$ did not change appreciably by the solvent. As a result the manner of the overlap of the two spectra of isomer did not change. This shows that the interaction which determines the spectral pattern is an intramolecular one which acts in a way additive to the solvent effect.

The solvent effect on the ESR parameters of the nitroxyl radicals has been analyzed on a molecular orbital basis. Kawamura *et al.* thoroughly described the solvent effect on g-value and A_N of di-*t*-butyl nitroxyl radical on the basis of a molecular orbital treatment.[20] As regards the A_N of the present system the effect of the neighboring group on each nitroxyl function can be explained by a simple MO scheme. The inspection of Dreiding model tells us that the hetero atom (X) in Fig. 4B is very close to the p orbital of nitrogen atom. The simplest MO feature of nitroxyl group is that the three electrons are in orbitals derived from linear combinations of the nitrogen and oxygen 2p orbitals. The bonding orbital is occupied by two electrons and the antibonding orbital is occupied by the unpaired electron. The effect of the nearby electronegative group on the 2p atomic orbital of the nitrogen atom is identical to the decrease of the absolute value of the Coulomb integral of the nitrogen. Consequently, the nitrogen character of π^* orbital increased, resulting in the increase of the A_N. The extent of the increase depends on the electronegativity of the hetero atom in the neighboring group. Therefore, the larger separations of the isomer in the adducts from ether than in those from amines can be explained.

Moreover the discussion above makes the assignment of the isomer possible. The isomer which has larger A_N value is assignable to the structure shown in Fig. 4B.

In alkylamino adduct the presence of diastereomer was detected clearly when the higher alkylamine was chosen as the radical source. The inspection of Table 2 tells us that the difference of g-value was small and the spectrum pattern was characterized mainly by the difference of β-hydrogen hfs. It is concluded that steric hindrance is the main cause of the separation in alkylamino adduct.

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