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ESR Spectra of piperidinyl-1-oxy radicals

Kunihisa SOGABE*, Kazuo HARA*, and Taido TAKAHASHI**

Abstruct : Piperidinyl-1-oxy and three dicarboximidyl-1-oxy radicals were produced by UV photolysis or oxidation of a corresponding N-hydroxyl amine and N-hydroxyl dicarboximides. Each spectrum gave an evidence for a long range interaction of an unpaired electron with some protons at γ- or δ-position, in spite of different radical types or radical structures. Especially, piperidinyl-1-oxy radical showed a remarkable spectral changes with an interconversion between two chair conformations at $-130\sim+110$°C. All dicarboximidyl-1-oxy radicals exhibited no spectral change because of a weak long range interaction, a diacyl planar structure, and no occurrence of ring cleavage under a prolonged UV irradiation.

INTRODUCTION

An interesting behavior of a cyclo or cyclo acyl nitroxide generally differs from that of a corresponding alkyl or acyl nitroxide radical. A nitroxide formed in cyclo amines is a σ-radical, in which an unpaired electron resides in an orbital with significant s character, and one produced in cyclo acyl amides or cyclo diacyl amides is a π-radical, in which the unpaired electron is involved in a nitrogen $2p$ orbital.[1] Tempo and proxy radicals, widely used as a spin label, have been the subject of the considerable controversy because of thier sharp hyperfine coupling of *ca.* 1.3 mT and stability of radicals. Piperidinyl-1-oxy is well compared with cyclo hexyl radical about two chair conformations arised from a steric interaction between two axial and two equatorial protons at δ-positions and about similar long range interaction.[2]

The π-radical is subdivided into two groups, in which one is the nitroxide such as 2 pyrrolidone-1-oxy, or 2 piperidone-1-oxy with a cyclo carboximide structure and a nitrogen hyperfine coupling of *ca.* 0.6-0.7mT, and the other is such the nitroxide as succimidyl-1-oxy or phthalimidy-1-oxy with a cyclo dicarboximide structure and a hyperfine coupling of *ca.* 0.3-0.4mT for a nitrogen nucleus. Such a difference in the nitrogen hyperfine coupling is postulated to result from an increase in a planarity around the NO moiety by introducing the acyl group.

Despite N-hydroxy piperidine, N-hydroxy succimide, or N-hydroxy phthalimide is a re-

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* Fac. of Educ., Shimane Univ., 1060 Nishikawatsu Matsue 690

** Present address : 36-6 Nagahisaguchi, Nagahisa, Ohda. 694

agent for peptide synthesis, few informations on the reactivity or the long range interaction for these reagents have been obtained. To discuss the reactivity or behavior of these two different type of nitroxide radicals and to detect the long range interaction in the dicarboximides, N-hydroxy piperidine, N-hydroxy succimide, N-hydroxy phthalimide, or 5 norbornene 2,3 dicarboximide was photolysed or oxidized and the spectral change was measured under various temperature.

EXPERIMENTAL

N-hydroxy piperidine, N-nitroso piperidine, and 2,6 dimethyl piperidine were purchased from Aldrich Chemical Co., and three dicarboximides from Tokyo Kasei Co.. All samples were dissolved in dioxane by a concentration of *ca.* 10^{-2}mol/*l*. At low temperature, methylene chloride was used in stead of dioxane. Dioxane and methylene chloride were distilled before use. ESR Spectra were recorded at various temperature using JEOL FE-1X and a variable temperature apparatus. 500W Xe lamp was used as a UV source and UV light was directly irradiated on sample in the ESR cavity.

RESULTS AND DISCUSSION

UV Photolysis of N-hydroxy succimide, N-hydroxy phthalimide, or N-hydroxy 5 norbornene 2,3 dicarboximide produces a corresponding π-nitroxide which is identified as succimidyl-1-oxy, phthalimidyl-1-oxy, or 5 norbornene 2,3 dicarboximidyl-1-oxy radical

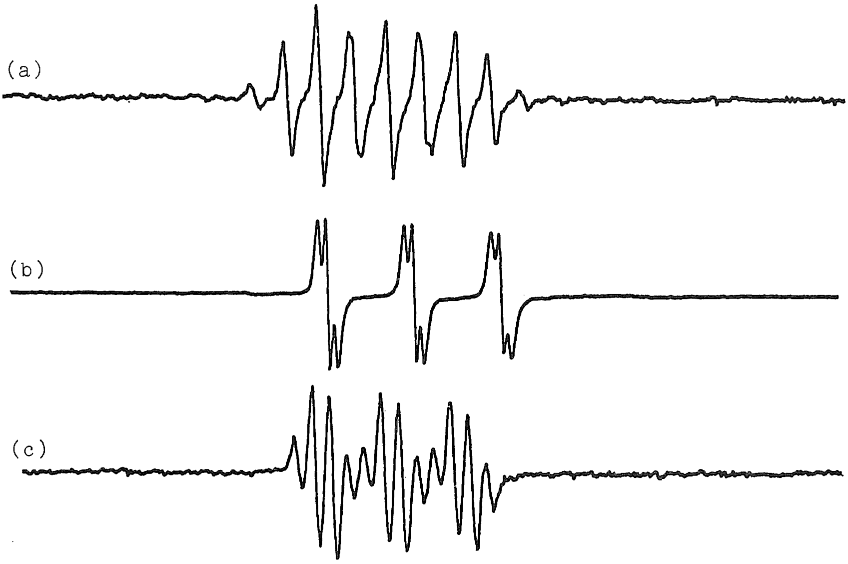

Fig. 1 ESR Spectra of dicarboximidyl-1-oxy radicals. (a) succimidyl-1-oxy, (b) phthalimidyl-1-oxy, and (c) 5 norbornene 2,3 dicarboximidyl-1-oxy.

respectively. The spectra are shown in Fig. 1 (a) - (c) and their ESR parameters are summearized in Table 1. The significant smaller A_N values are characteristic to dicarboximidyl-1-oxy radicals, exhibiting an extensive localization of an unpaired electron on two carbonyl groups.[1] The g and A_N values of both succimidy-1-oxy and 5 norbornene 2,3 dicarboximidyl-1-oxy radicals are very close but slightly deviate from those of phthalimidyl-1-oxy. An introduction of a phenyl ring into the dicarboximidyl-1-oxy radical may lead to a decrease in the localization of the unpaired electron on two carbonyl groups and so result in an increase of A_N value.

Table 1

radical	g-value	hyperfine constant (mT)			
		A_N	A_H		
Succimidyl-l-oxy	2.0078	0.37	0.18	(4H, δ)	
Phthalimidyl-l-oxy	2.0072	0.46	0.04	(2H, ε)	
5 Norbornene 2, 3 dicarboximidyl-l-oxy	2.0077	0.38	0.09	(3H, ε)	
2, 6 Dimethyl piperidinyl-l-oxy	2.0061	1.68	1.28	(2H, γ)	
Piperidinyl-l-oxy	2.0062	1.63	1.18	(4H, γ)	at+110℃
	2.0061	1.67	2.01	(axial)	at−110℃
			0.36	(equa.)	
			0.06	(3H, δ)	

Each spectrum shows a triplet, a quartet, or a quintet with very small hyperfine coupling, which is interpreted as a result of a long range interaction of an unpaired with two equivalent protons in phthalimidyl-1-oxy, three in 5 norbornene 2,3 dicarboximidyl-1-oxy, or four in succimidyl-1-oxy radical respectively. Such a long range interaction is too weak to detect in acyl nitroxides except both carbamoyl and ethoxy carbonyl nitroxide radicals, much less in diacyl nitroxides.[3] The striking fact that the long range interaction over the carbonyl group is found in these cyclo diacyl nitroxide radicals is particularly noteworthy. These radicals are very stable and result in no spectral change under a prolonged UV irradiation.

UV Irradiation of N-hydroxy piperidine or N-nitroso piperidine in dioxane gives the same spectrum shown in Fig. 2 (a). The spectrum comprised of a triplet quintet is identified to result from piperidinyl-1-oxy radical and ESR parameters are summarized in Table 1. As well as cyclohexane, piperidine ring prefers two chair conformations, in which a rapid exchange of two axial protons with two equatorial ones brings four equivalent protons. The interaction of the unpaired electron on NO moiety with four equivalent protons constitutes the quintet with a relative intensity ratio of 1 : 4 : 6 : 4 : 1. Also as can be found in Fig. 2 (c) a spectrum produced in 2,6 dimethyl piperidine shows a triplet triplet, in which hyperfine couplings for a nitrogen and two axial protons are almost same as those of piperidinyl-1-oxy radical. Because a steric hinderance of dimethyl group at σ-position, no long range interaction is found in this radical as well as tempo or proxy spin label.

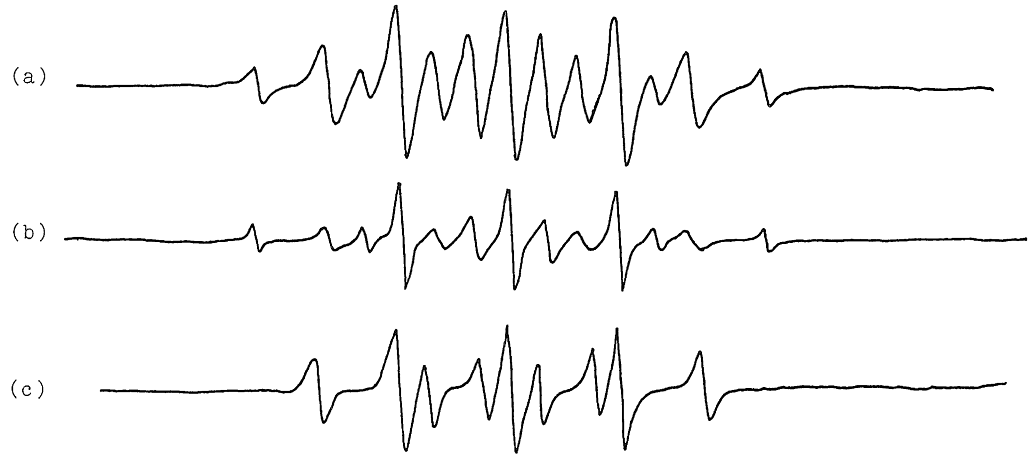

Fig. 2 ESR Spectra of piperidinyl-1-oxy radicals produced by (a) UV irradiation, and (b) lead peroxide oxidation of piperidine, and (c) UV irradiation of 2,6 dimethyl piperidine.

When N-hydroxy piperidine is oxidized by lead peroxide, a spectrum with a triplet quintet as shown in Fig. 2 (b), in which the quintet shows an abnormal intensity ratio because of a mutual arrangement of a sharp and abroad line, is observed in cyclohexyl radical with similar structure as piperidinyl-1-oxy.4) Such an abnormal pattern may be interpreted as a result of an intermediate conversion of a piperidine chair ring, whereas a normal quintet shown in Fig. 2 (a) may be arised from a fast conversion with increasing temperature under UV irradiation.

To study an effect of a slow interconversion of a chair ring on hyperfine couplings of both axial and equatorial protons, a spectral change of the piperidinyl-1-oxy radical in methylene chloride is recorded at various temperature of $-130\sim+110$°C. An anomalous temperature variation of this spectrum is shown in Fig. 3 (a)-(e) respectively. As can be found from Fig. 3 (a), the spectrum shows a triple triplet, in which the first triplet with a relative intensity ratio of 1 : 1 : 1 and a coupling constant of 1.67mT, the second triplet with a intensity of 1 : 2 : 1 and a coupling of 2.01mT, and the third with 1 : 2 : 1 ratio and the smaller coupling of 0.36mT are included and are subdivided into a quartet with an intensity ratio of 1 : 3 : 3 : 1. The quartet is consisted of three equivalent protons at δ- and ε-positions. At this temperature, no conversion of the chair conformation occurs and a gauche type is developed for piperidinyl-1-oxy radical.

In the gauche conformation of the piperidinyl-1-oxy, an usual dihedral angle relation descrived below can apply to an estimation for a hyperfine coupling of both axial and equatorial protons at γ-positions.

Fig. 3 ESR spectra of piperidinyl-1-oxy radical recorded at (a) −130°C, (b) −90°C, (c) −50°C, (d) 0°C, and (e) +110°C.

$$A_{H\gamma} = B^{H}\sigma_{N} \cos^{2}\theta$$

where the θ is defined as an angle between ONC and NCH plane and the hyperconjugation term $B^{H}\sigma^{N}$ is known to be 2.5~3.0 mT for nitroxides.[5)] Supposing the ideal chair conformation for the piperidinyl-1-oxy radical under a slow conversion, the dihedral angles are calculated as $\theta = 30^{\circ}$ and $\theta = 90^{\circ}$ for the axial and equatorial proton respectively, yielding the spectrum shown in Fig. 2 (a).

The coupling for the axial protons decreases with increasing temperature, whereas the nitrogen hyperfine coupling remains constant. As can be seen in Fig. 3 (b), the interaction of

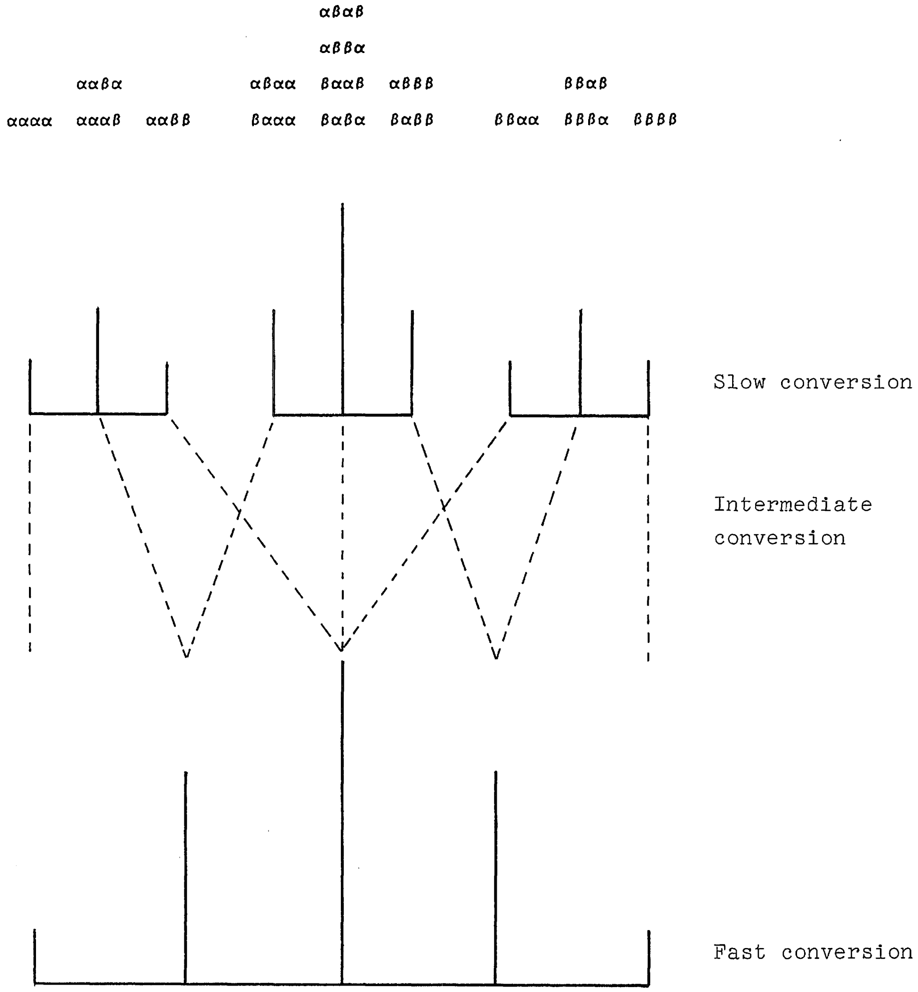

Fig. 4 Theoretical analysis of anomalous spectrum of piperidinyl-1-oxy radical.

the unpaired electron with three equivalent protons at δ-and ε-positions becomes weak at -100°C and hence the quartet disappears at -90°C, while the triplet due to the two equivalent, equatorial protons changes its intensity ratio at -90°C. In Fig. 3 (c), the outer and the central sharp lines remain thier intensity but the middle one is too broad to detect. This is considered to be arised from a linewidth alternation of γ-proton multiplets. When difference in frequency between the inner and the central lines is very large, such the exchange of the linewidth often occurs.[4)]

The fast conversion of the piperidine ring average out the dihedral angles, θ_{axial} and $\theta_{\mathrm{euatorial}}$, producing the quintet arised from γ-four equvalent protons as shown in Fig. 3 (e) or Fig. 2 (a). The hyperfine coupling of the γ-proton calculated by the $\cos^2\theta$ rule is $A_{\mathrm{H}}=1.18\mathrm{mT}$ at $\theta=60°$, and these results give excellent agreement with the observed value.

The spectral change in Fig. 3 (a)-(e) can be analysed by theoretical pattern drawn below, in which the only simplified triplet triplet is displayed (Fig. 4). From this theoretical analysis, the anomalous pattern shown in Fig. 2 (b) or Fig. 3 (c) is found to be caused by the interconversion of the chair conformation.[2)]

In the case of succimidyl-1-oxy, phthalimidyl-1-oxy, or 5 norbornene 2,3 dicarboximidyl-1-oxy radical, no spectral change is observed at various temperature. The result shows that the long range interaction observed in the dicarboximidyl-1-oxy radical is very weak because of having diacyl groups. Also resistibility of these dicarboximides against UV irradation is considered to be based on this structure, and hence a reaction pathway for peptide synthesis should proceed a different route.

Present authors have found the existence of the long range interaction in succimidyl-1-oxy, phthalimidyl-1-oxy, or 5 norbornene 2,3 dicarboximidyl-1-oxy as well as piperidinyl-1-oxy radical, but no evidence for a ring breaking in piperidine or cyclo diacyl link under UV irradiation. Further study needs for seeking out a reaction route of peptide synthesis under another conditions.

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