

Oxidation of N-Alkylhydroxylamines. III.¹⁾ Reaction of N-Alkylhydroxylamines with 1,1-Diphenyl-2-picrylhydrazyl

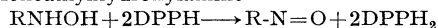
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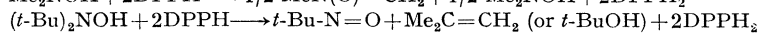
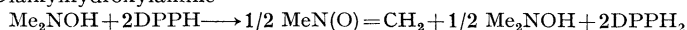
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The title reaction gives products according to the following equations:

a) Monoalkylhydroxylamine



b) Dialkylhydroxylamine



The reaction is first-order with respect to both hydroxylamines and 1,1-diphenyl-2-picrylhydrazyl and the first step in the reaction involves formation of the corresponding nitroxides.

The effects of substituents and solvents on the reaction rate suggest a mechanism in which the nitroxide is formed by one-electron transfer from the nitrogen of the hydroxylamine followed by a proton transfer from the hydroxyl group.

Previously, we showed that oxidation of N-alkylhydroxylamines (hydroxylamines) with a one-electron oxidant produces the corresponding nitroxides, and then the nitroxides are further oxidized to the corresponding nitroso compounds. However, it is unknown whether the nitroxide is produced by the abstraction of a hydrogen atom from the hydroxyl group, or whether one-electron transfer from the lone pair of electrons on the nitrogen atom precedes a proton transfer. While investigating the mechanism of oxidation of hydroxylamines with a one-electron oxidant, a stable free radical, 1,1-diphenyl-2-picrylhydrazyl (DPPH), was found to react readily with hydroxylamines.

Kinetic studies were made on the oxidations of only a few hydroxylamines, because the oxidation products of many hydroxylamines are unstable. Use of the coloured radical, DPPH, with absorption in the visible region, greatly facilitated estimation of the progress of oxidation of hydroxylamines. Moreover, DPPH is a large radical, so kinetic studies provided information on the steric effect of substituents at the α -carbon of hydroxylamines, which could not be observed using smaller radicals.

Result and Discussion

Products and Stoichiometry of the Reaction

The N-alkylhydroxylamines used were monoalkyl-(RNHOH) and dialkyl-(R₁R₂NOH) hydroxylamines with various substituents.

When DPPH was mixed with an excess of the hydroxylamines in ethanol at room temperature, slow disappearance of the characteristic red-colour of DPPH was observed, with development of a yellow colour.

From the ultraviolet spectrum, the yellow colour was attributed to 1,1-diphenyl-2-picrylhydrazine (DPPH₂). The yield of DPPH₂ was found to be nearly quantitative ($\geq 85\%$) with all hydroxylamines tested.

a) Monoalkylhydroxylamines—Monomeric *t*-nitrosobutane was found to be formed (ca. 100%) from *t*-butylhydroxylamine. A *trans*-dimeric nitroso compound was found to be

1) Part II: H. Sayo, S. Ozaki, and M. Masui, *Chem. Pharm. Bull.* (Tokyo), **20**, 1012 (1972).

2) Location: 1, Toneyama-6-chome, Toyonaka.

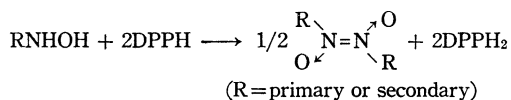
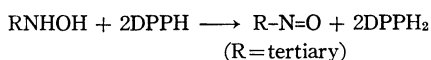
formed from ethylhydroxylamine or cyclohexylhydroxylamine (*ca.* 12% and 5% respectively), and no monomeric nitrosoethane or nitrosocyclohexane was detected. Moreover, no acetaldoxime or cyclohexanoneoxime was detected, although nitrosomethane has been reported to undergo rearrangement, forming formaldoxime, faster than dimerization at room temperature.³⁾ The stoichiometry of the reaction of monoalkylhydroxylamine was estimated from the amount of DPPH remaining after completion of the reaction.

Results on the stoichiometry of the reaction are summarized in Table I, showing that 1 mole of monoalkylhydroxylamine reacts with 2 moles of DPPH.

TABLE I. Reaction of DPPH with *t*-Butylhydroxylamine in Ethanol at Room Temperature

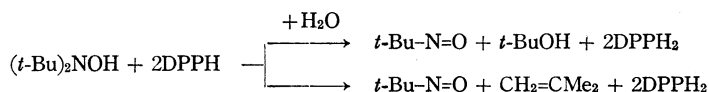
[DPPH] M × 10 ⁵	[Me ₃ CNHOH] M × 10 ⁵	[Consumed DPPH] M × 10 ⁵
4.35	1.80	3.55
12.1	1.87	3.78
12.1	3.74	7.20

Thus the reaction of monoalkylhydroxylamines with DPPH is as follows:



b) Dialkylhydroxylamines—During reaction with excess N,N-di-*t*-butylhydroxylamine, the electron spin resonance (ESR) spectrum of N,N-di-*t*-butylnitroxide was observed (triplet, $A_N=15.9\text{G}$).

Di-*t*-butylnitroxide was found to react further with DPPH to form *t*-nitrosobutane (79%),⁴⁾ *t*-butanol (47%)⁴⁾ and isobutene (6%),⁴⁾ indicating that ejection of the *t*-butyl group may occur. Thus the reaction of N,N-di-*t*-butylhydroxylamine with DPPH is as follows:



On the other hand, the reaction of N,N-dimethylhydroxylamine did not produce nitrosomethane but N-methylmethyleamine N-oxide, MeN(O)=CH₂ (80%), which suggests that intermediate dimethylnitroxide undergoes disproportionation to form MeN(O)=CH₂ and N,N-dimethylhydroxylamine, rather than that it reacts further with DPPH to eject a methyl group.



Thus the over all reaction of N,N-dimethylhydroxylamine is as follows:



The reaction of N,N-di-*t*-butylhydroxylamine or N,N-di-methylhydroxylamine with DPPH suggests that 2 moles of DPPH are required to oxidize 1 mole of N,N-di-*t*-butyl- or N,N-dimethylhydroxylamine. However, 1 mole of N,N-di-*t*-butyl- and N,N-dimethylhydroxylamine were found to consume 2–3 moles of DPPH (Table II) when the reaction occurred in the presence of large excess of DPPH. Thus it seems likely that hydrolysis of the nitrone MeN(O)=CH₂ and hence additional consumption of DPPH by its oxidation of methyl-

3) B.G. Gowenlock and J. Trotman, *J. Chem. Soc.*, 1955, 4190.

4) Mole per cent of starting hydroxylamine.

TABLE II. Reaction of DPPH with Dialkylhydroxylamine in Ethanol at Room Temperature

[DPPH] M × 10 ⁵	[Me ₂ NOH] M × 10 ⁵	[Consumed DPPH] M × 10 ⁵
19.7	3.0	10.8
19.7	6.0	16.4
19.7	9.0	17.1
	[(<i>t</i> -Bu) ₂ NOH]	
11.0	1.49	4.50
11.0	2.98	9.40

hydroxylamine occurs in the solution. *t*-Butanol and isobutene were found to react much slower with DPPH than di-*t*-butylnitroxide.

Kinetic Studies

Reactions were carried out with 4–5 × 10⁻⁵M DPPH and hydroxylamines in large excess, and rates of reactions were followed by observing the decrease in absorption of DPPH at 520 mμ.

The data obtained showed that disappearance of DPPH obeyed first-order law, and the rate constants were directly proportional to the hydroxylamine concentrations. Table III shows that the reaction is first order with respect to each reactant.

TABLE III. Second-order Rate Constants for the Oxidation of Me₂C(COOEt)NHOH in Benzene at 30°

[DPPH] M × 10 ⁵	[Me ₂ C(COOEt)NHOH] M × 10 ⁴	<i>k</i> ₂ × 10 ⁻² , 1M ⁻¹ min ⁻¹
3.78	6.5	6.83
5.67	6.5	6.60
3.78	13.0	6.82

In some kinetic runs in which reaction rates were too fast to be followed under pseudo-first-order conditions, the rate constants for the oxidation of monoalkylhydroxylamines were calculated from equation (1).

$$k_{\text{obs}} \cdot t = 2/(2a-b) \cdot \ln [b(a-X)/a(b-X)] \quad (1)$$

where *a* and *b* are the initial concentration of monoalkylhydroxylamines and DPPH, respectively, and *X* is the concentration of DPPH₂ formed at time *t*. Figure 1 shows a second-order plot of data on the oxidation of ethylhydroxylamine with DPPH at 30° in benzene.

The linearity of the plot indicates that the over-all reaction obeys second-order kinetics and monoalkylhydroxylamines are oxidized to a reactive species, probably the nitroxide, with the observed rate constants, *k*_{obs}, and the intermediates are further oxidized to the corresponding nitroso compounds at a rate faster than that of the first step.

On the other hand the oxidation of dialkylhydroxylamines was found to obey rate equation (2) for over 75% of the reaction (Fig. 2), indicating that these dialkylhydroxylamines react with an equimolar amount of DPPH to form the corresponding nitroxides, which then undergo a second reaction at a much slower rate than preceding one (*k*_{obs}).

$$k_{\text{obs}} \cdot t = 1/(a-b) \cdot \ln [b(a-X)/a(b-X)] \quad (2)$$

Indeed, di-*t*-butylnitroxide was also found to obey rate equation (2) with a rate slower than that of N,N-di-*t*-butylhydroxylamine, *k*_{R₁NOH}/*k*_{R₁NO}=50 (Table IV).

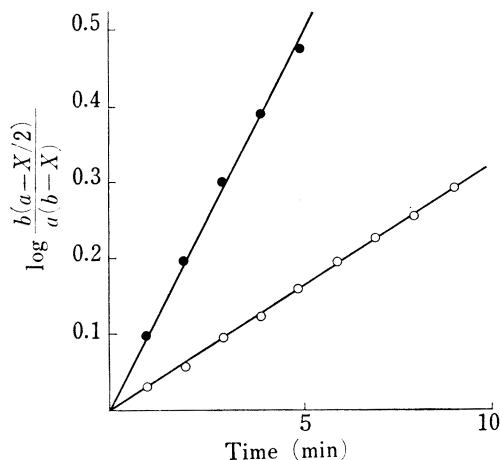


Fig. 1. Second-order Plot for the Reaction of Ethylhydroxylamine with DPPH in Benzene at 30°

○—○ with 2.92×10^{-5} M hydroxylamine and 3.32×10^{-5} M DPPH; ●—● with 5.84×10^{-5} M hydroxylamine and 3.32×10^{-5} M DPPH

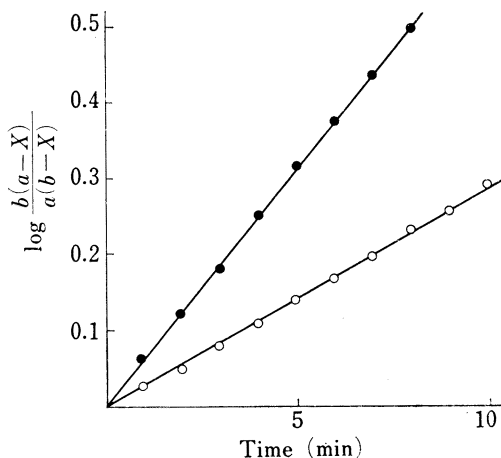


Fig. 2. Second-order Plot for the Reaction of N,N-Dimethylhydroxylamine with DPPH in ethanol at 22°

●—●, with 14.5×10^{-5} M hydroxylamine and 3.12×10^{-5} M DPPH; ○—○, with 7.23×10^{-5} M hydroxylamine and 3.12×10^{-5} M DPPH

TABLE IV. Second-order Rate Constants at 22° in EtOH and Activation Parameters

Compound	k_2 ($M^{-1} \cdot \text{min}^{-1}$)	E_a (kcal.)	ΔS^\ddagger ($\text{cal} \cdot M^{-1} \cdot \text{deg}^{-1}$)
Me_3CNHOH	290	6.8	-33
$\text{Me}_2\text{C}(\text{COOEt})\text{NHOH}$	41.4	8.0	-32
$\text{Me}_2\text{C}(\text{CN})\text{NHOH}$	12.7	9.3	-30
$\text{EtCH}(\text{CN})\text{NHOH}$	25.6	9.6	-28
$\text{C}_6\text{H}_5\text{CH}_2\text{NHOH}$	656	7.3	-29
EtNHOH	403	5.8	-28
Me_2NOH	1560	5.4	-34
$\{\text{Pr}^n\text{CH}(\text{CN})\}_2\text{NOH}$	0.74	9.5	-34
$(\text{Me}_3\text{C})_2\text{NOH}$	1320		
$(\text{Me}_3\text{C})_2\text{NO}$	26	11.6	-21

The activation parameters and the second-order rate constant for the oxidation of mono-, and dialkylhydroxylamines and the nitroxide are summarized in Table IV.

It is seen that the energies of activation are low and the entropies of activation are highly negative and that an electron-withdrawing group retards the rate of the reaction, while the electron-donating group increases it. It is also seen that monoalkylhydroxylamines with a primary or secondary alkyl group (II) are oxidized faster than those with a tertiary alkyl group (I) which results in more steric hindrance: for example $k_{\text{EtCH}(\text{CN})\text{NHOH}}/k_{\text{Me}_2\text{C}(\text{CN})\text{NHOH}} = 2$. Dialkylhydroxylamines (III) react faster than monoalkyl ones ($k_{\text{Me}_2\text{NOH}}/k_{\text{EtNHOH}} = 4$).

The entropies of activation decrease in negativity in the order, (III) < (I) < (II), which seems to show reasonable agreement with the order of crowdedness around the nitrogen atom.

N,N-Di-*t*-butylhydroxylamine is more reactive toward DPPH than the corresponding nitroxide, di-*t*-butylnitroxide. This suggests that the unpaired electrons forming a three electron system delocalized over an NO group are more resistant toward electron abstraction than ordinary unpaired electrons.

The observation that both the polarity of substituents and the crowdedness around the nitrogen atom of hydroxylamines affect the rate of the reaction suggests a transition state involving the nitrogen. The kinetic isotope effect ($k_H/k_D \approx 1.0$) observed in experiments with Me_3CNHOH (k_H) and Me_3CNDOD (k_D) is consistent with the above explanation.

The rate of the reaction was shown to decrease markedly with increase in acidity of the solvent (Table V), suggesting that the proton of a solvent interacts with the nonbonding electron pair at the nitrogen of hydroxylamine resulting in decrease in basicity, *i.e.*, the hydroxylamines are less susceptible to electron abstraction.

TABLE V. Effects of Solvents on the Reaction of N-Alkylhydroxylamines with DPPH at 30°

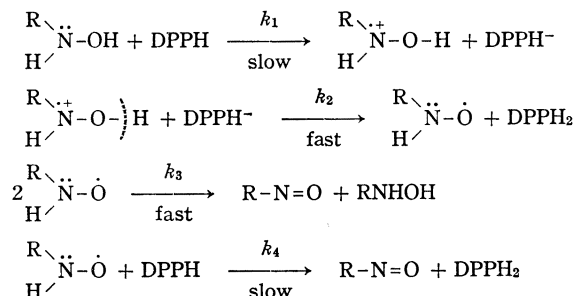
Solvent Compound	Relative rate ^{a)}			
	EtOH	CH ₃ CN	C ₆ H ₆	CCl ₄
Me ₃ CNHOH	1	3.0	24	
Me ₂ C(COOEt)NHOH	1	2.0	11	38
Me ₂ C(CN)NHOH	1	1.2	13	50
EtNHOH	1	3.7	24	

a) In each case the reaction rate in EtOH is taken as unity.

The effect of solvent is considered an additional evidence for a mechanism involving a one-electron transfer from a nonbonding electron pair at the nitrogen atom, not a homolytic hydrogen transfer from the hydroxyl group.

The mechanism of the reaction of hydroxylamines and DPPH can be represented by the following scheme, taking stoichiometric results into account.

Monoalkylhydroxylamine



The following situations may be operative in the above scheme.

1. The first-order dependence on each reactant, the effects of substituents and solvents and the isotope effect on the reaction rates suggest that $k_1 < k_2$.

2. It is concluded that k_3 or $k_4 > k_1$ *i.e.* $k_1 = k_{\text{obs}}$, since the reaction obeys rate eq. (1). Indeed, the rate of disproportionation of N-alkylhydroxylamine has been reported to be 10^6 — $10^7 \text{M}^{-1} \text{sec}^{-1}$, at 25°. ⁵⁾

3. It is also assumed that $k_3 \gg k_4$, since the observed reaction rate of di-*t*-butylnitroxide with DPPH is about one-fiftieth of that of N,N-di-*t*-butylhydroxylamine (Table IV).

The over-all reaction may be presented as follows:

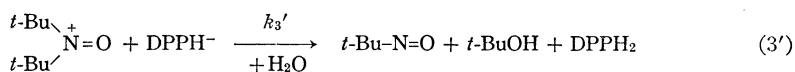
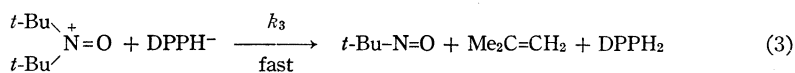
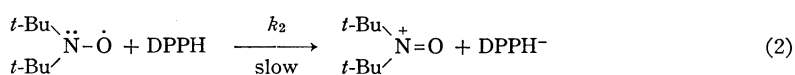
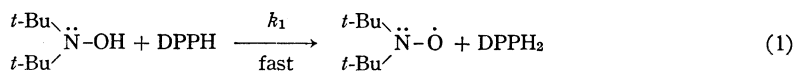
The abstraction by DPPH of one electron from the lone pair of electrons on the nitrogen takes place in a rate-determining step with the rate constant $k_1 = k_{\text{obs}}$. This is followed by rapid removal of a proton of the hydroxyl group to form a nitroxide. Then the nitroxide

5) D.F. Bowman, J.L. Brokenshire, T. Gillan, and K.U. Ingold, *J. Am. Chem. Soc.*, **93**, 6551 (1971).

should undergo almost complete disproportionation forming a hydroxylamine and a nitroso compound.

Dialkylhydroxylamine

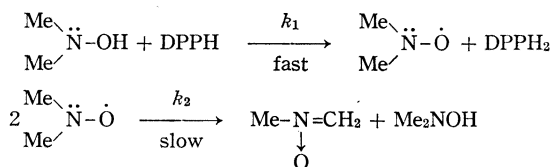
a) N,N-Di-*t*-butylhydroxylamine



The observation that the reaction obeys rate eq. (2) suggests that the observed rate constant k_{obs} represents k_1 , which is consistent with the kinetic data, $k_{\text{obs}}/k_2 \approx 50$.

Di-*t*-butylnitroxide, a radical having no α proton cannot undergo disproportionation and is further oxidized in a way similar to that in step (1), and ejecting a *t*-butyl cation, which is converted to isobutene or reacting with a trace of water in reaction solvent to yield *t*-butanol.

b) N,N-Dimethylhydroxylamine



The reaction obeys rate eq. (2) as in the case of N,N-di-*t*-butylhydroxylamine, so it is considered that $k_1 = k_{\text{obs}}$ and $k_1 > k_2$. Further support that $k_1 > k_2$ is obtained from the following finding. The rate for the bimolecular decay of diethylnitroxide which may be comparable with k_2 has been reported to be $1.9 \pm 0.4 \text{ M}^{-1} \text{ sec}^{-1}$,⁶⁾ while k_1 in ethanol at 25° is $2.6 \times 10^{-1} \text{ M} \text{ sec}^{-1}$.

In the present investigation, N-alkyl and N,N-dialkylhydroxylamines were found to be more reactive with DPPH than alkylamines⁷⁾ ($k_{\text{Me}_2\text{NOH}}/k_{\text{Pr}_2\text{NH}} \approx 1.2 \times 10^5$ at 20° in benzene).

Phenylhydroxylamine has been reported to exhibit greater nucleophilic reactivity than aniline in the reaction with peroxyacetic acid⁸⁾ ($k_{\text{PhNOH}}/k_{\text{PhNH}_2} \approx 6$ at 20° in ethanol).

The above data suggest that the difference between the reactivity of amines and hydroxylamines more marked in a system where one-electron transfer takes place from the nitrogen to an oxidant in a rate-determining step than in the system where nucleophilic attack of the nitrogen occurs.

Experimental

Materials—Benzene was purified as described previously.⁹⁾ Acetonitrile was purified by the method of C.K. Mann.¹⁰⁾ Ethanol was distilled after addition of sodium. Reagent grade carbon tetrachloride was used without further purification.

- 6) K. Adamic, D.F. Bowman, T. Gillan, and K.U. Ingold, *J. Am. Chem. Soc.*, **93**, 902 (1971).
- 7) J.E. Hazell and K.E. Russell, *Can. J. Chem.*, **36**, 1729 (1958).
- 8) K.M. Ibne-Rasa and J.O. Edwards, *J. Am. Chem. Soc.*, **84**, 963 (1962).
- 9) S. Ozaki, H. Sayo, and M. Masui, *Chem. Pharm. Bull.* (Tokyo), **19**, 2389 (1971).
- 10) J.F. O'Donnell, J.T. Ayres, and C.K. Mann, *Anal. Chem.*, **37**, 1161 (1965).

Known methods were used to prepare N,N-dimethylhydroxylamine,¹¹ N,N-di-*t*-butylhydroxylamine,¹² N,N-di-(1-cyanobutyl)hydroxylamine,¹³ cyclohexylhydroxylamine¹⁴ and nitrosocyclohexane.¹⁵ Other monoalkylhydroxylamines and nitrosoalkanes were prepared as described previously⁹. Di-*t*-butylnitroxide was prepared by the method of A.K. Hoffmann.¹²

Reagent grade DPPH and DPPH₂ were used without further purification.

Determination of the Reaction Products—a) DPPH₂: The absorbancy in the visible region ($\lambda=320\text{ m}\mu$, $\epsilon=13200$ in ethanol) was taken as a measure of total DPPH₂ formed in a particular kinetic run with excess hydroxylamine.

b) Monomeric and Dimeric Nitroso Compounds: Monomeric nitroso compounds were estimated by measuring the absorbancy in the visible region, *t*-nitrosobutane and 2-methyl-2-nitroso-1-acetoxyp propane in acetonitrile were measured at $680\text{ m}\mu$, $\epsilon=23$, after vaporizing the compounds by bubbling nitrogen through the reaction mixtures and the condensing them in a dry ice-acetone trap. This operation, however, was unsatisfactory because monomeric nitroso compounds were only partially trapped, because of their high volatility.

t-Nitrosobutane was measured more precisely by gas chromatographic analysis using $10\text{ }\mu\text{l}$ of reaction mixture on a JEOL JGC-750 gas chromatograph. The column was packed with AgNO₃-benzylcyanide on 60–80 mesh NEOPAK 1A. An external standard was used.

Dimeric nitroso compounds were estimated by measuring their ultraviolet absorption, nitrosoethane and nitrosocyclohexane were measured at $275\text{ m}\mu$ ¹⁶ and $283\text{ m}\mu$ respectively, after removal of the solvent and extraction of nitroso compounds with water in which DPPH₂ was almost insoluble. This procedure was found to have the advantage of excluding DPPH₂, which had strong absorption in the ultraviolet region, but dimeric nitroso compounds (10–12%) could only be partially extracted because of their low solubility in water.

c) N-Methylmethyleamine N-Oxide: MeN(O)=CH₂ formed in the oxidation of N,N-dimethylhydroxylamine was hydrolyzed to formaldehyde and methylhydroxylamine.

Formaldehyde was extracted from the reaction mixture (benzene) with 2N HCl and identified as its 2,4-dinitrophenylhydrazone, which was recrystallized from methanol (mp 166–168°).

d) *t*-Butanol and Isobutene: *t*-Butanol and isobutene formed in the reaction of N,N-di-*t*-butylhydroxylamine were estimated by gas chromatographic analysis with the same column used with *t*-nitrosobutane.

Kinetic Studies—Data were obtained by measuring the decrease in absorption of DPPH using a Hitachi 139 spectrophotometer equipped with a cell fitted with a thermostat, and an external recorder.

Reactions were normally carried out in cells of 2 cm path-length by mixing 6 ml of solutions of 10^{-3} – 10^{-4}M hydroxylamine and 1 ml of 10^{-4}M DPPH, separately adjusted to the desired reaction temperature with a thermostat. In experiments with N,N-di-*t*-butylhydroxylamine, which is easily oxidized by air to di-*t*-butylnitroxide, N,N-di-*t*-butylhydroxylammonium perchlorate was used and reactions were started by addition of excess pyridine to deoxygenated reaction mixtures to convert the hydroxylammonium perchlorate to free hydroxylamine. In an experiment without pyridine, oxidation of N,N-di-*t*-butylhydroxylammonium perchlorate with DPPH was negligible.

ESR Measurement—When excess pyridine was added to deoxygenated benzene in a sample tube containing $1.46 \times 10^{-2}\text{M}$ N,N-di-*t*-butylhydroxylammonium perchlorate and $1.12 \times 10^{-2}\text{M}$ DPPH, the ESR spectrum assigned to di-*t*-butylnitroxide ($A_N=15.9\text{ G}$) was observed. The ESR spectrum was recorded on a JEOL P-10 spectrometer.

Acknowledgement This work was supported in part by a Grant from the Ministry of Education, which is gratefully acknowledged.

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- 12) A.K. Hoffmann, A.M. Feldman, E. Gelblum, and W.G. Hodgson, *J. Am. Chem. Soc.*, **86**, 639 (1964).
- 13) M. Masui, Y. Tsuda, and C. Yijima, *J. Chem. Soc.*, **1961**, 4063.
- 14) B.F. Vincent, Jr. and H. Feuer, *J. Am. Chem. Soc.*, **84**, 3772, (1962).
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