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Oxidation of N-Alkylhydroxylamines. I. Nitroxides formed on Oxidation of N-Alkylhydroxylamines with Lead Tetraacetate[1]

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N-Alkylhydroxylamines are shown to be easily oxidized to corresponding nitroso compounds with lead tetraacetate in benzene. The N-alkylhydroxylamines are found to react with equimolar lead tetraacetate and corresponding alkylnitroxides are detected during the oxidation.

These results propose a mechanism in which lead tetraacetate acts as a hydrogen abstracting oxidant and the N-alkylhydroxylamines are oxidized to nitroso compounds *via* corresponding alkylnitroxides.

While many studies have been carried out on the oxidation of amines, there are comparatively few investigations on that of hydroxylamine derivatives.

Previous works on the oxidation of hydroxylamine derivatives are usually confined to a few hydroxylamine derivatives such as phenylhydroxylamine,[3] cyclohexylhydroxylamine[4] and hydroxylamine,[5] because most hydroxyalmine derivatives are unstable and easily oxidized under atmosphere.

In an oxidation system where the nitrogen atom of phenylhedroxylamine performs a nucleophilic attack on the oxygen of oxidant, phenylhydroxylamine has been reported to exhibit greater reactivity toward peroxyacetic acid than aniline,[3] although phenylhydroxylamine is weaker base than aniline and has normal polarizability.

For example, the rate of oxidation of phenylhydroxylamine with peroxyacetic acid in ethanol is faster than that of aniline[3] by six times.

The abnormal nucleophilic reactivity of phenylhydroxylamine towards peroxyacetic acid was suggested to be due to an additional factor so-called Alpha-Effect[6] besides basicity and polarizability.

However, in oxidation where radical mechanism may operate, for example, in oxidation with hydrogen abstracting oxidant or with electrochemical process, some differences in reactivity between hydroxylamines and amines or among hydroxylamines should be interpreted in terms of other factor than those described above.

As a part of study on the oxidation of aliphatic hydroxylamines, we have first investigated oxidation of N-alkylhydroxylamines of the type RMe_2CNHOH, where R is Me, Et, CH_2OH, CH_2OAc, COOEt or CN, and found that those hydroxyalmines were easily oxidized to the corrsponding nitroso compounds via alkylnitroxides.

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[1] A part of this paper was presented at the 89th Annual Meeting of Pharmaceutical Society of Japan, Nagoya, Apr. 1969.

[2] Location: 5, *Toneyama-6-chome, Toyonaka.*

[3] K.M. Ibne-Rasa and J.O. Edwards, *J. Am. Chem. Soc.*, **84**, 963 (1962).

[4] N.B. Shitova, K.I. Matveev, and M.M. Danilova, *Kinet. Katal.*, **7**, 995 (1966).

[5] *a*) V.I. Jindal, M.C. Agrawal, and S.P. Mushran, *J. Chem. Soc.* (*A*), **1970**, 2060; *b*) W.A. Waters, and I.R. Wilson, *ibid.*, **1966**, 534; *c*) M.N. Hughes and G. Stedman, *J. Chem. Soc.*, **1963**, 2824; *d*) T.B. Morgan, G. Stedman, and (in part) M.N. Hughes, *J. Chem. Soc.* (*B*), **1968**, 344; *e*) M.A. Hussain and G. Stedman, *ibid.*, **1968**, 597.

[6] J.O. Edwards and R.G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).

There are many papers reporting the detection and the nature of the free readicals,[7] however, few have considered the reaction mechanism by estimating the reaction product.

In the present study, we investigated the oxidation product of N-alkylhydroxylamines, nitroso compounds, and proposed a mechanism for the oxidation of N-alkylhydroxylamines in which free radicals may operate.

Result and Disussion

When N-Alkylhydroxylamines of the type RMe_2CNHOH ($3—8\times10^{-3}$M) were added to benzene solution of lead tetraacetate ($6—8\times10$M^{-3}) at 25°, the solution rapidly turned blue and gave white precipitate of lead diacetate. The blue colour gradually faded under light, and was assumed to be due to a nitroso compound.

Thus the nitroso compounds corresponding to N-alkylhydroxylamines were prepared by another method to estimate their absorpfon maxima and extinction coefficinets in the visible region (Table I).

Table I. Absorption Maximum and Extinction Conflicient of Nitroso Compounds[a)]
RMe_2CNHOH (in Benzene at 25°)

R	Me	Et	CH_2OH	CH_2OAc	COOEt	CN
λ_{max} mμ	680	680	680	680	675	652
(ε)	(22.5)	(22.5)	b)	(22.5)	(1.9)	b)

a) The absorption is due to the monomeric form of nitroso compouund. Hence the extinction coefficient of nitroso compound varies with the degree of dimerisation which depends on both solvent and temmperature. A detailed discussion on the general properties of nitroso compounds have been reported by B. G. Gowenlock (B.G. Gowenlock, *Quarterly Revs.*, **12**, 321 (1958).

b) When R was CH_2OH or CN nitroso compound was not obtained as stable crystal.

After the reaction of the N-alkylhydroxylamines with excess amount of lead tetraacetate has been completed, aliquot portion of the reaction solution was examined spectrophotometrically for the nitroso compound according to the method described in experimental section. The results showed that the blue colour was due to corresponding nitroso composed and in the case of *tert*-butylhydroxylamine the yield of *tert*-nitrosobutane was 91—94%.

The amount of lead tetraacetate remaining in the reaction solution was determined. As shown in Table II, lead tetraacetate was found to react with equimolar *tert*-butylhydoxylamine.

Table II. Oxidation of *tert*-Butylhydroxylamine with Lead Tetraacetate

Initial concentration		Pb(OAc)$_4$ recovered from the final solution mM
$Pb(OAc)_4$ mM	Me_3CNHOH mM	
9.28	3.30	5.80
9.80	8.08	1.88
8.05	7.20	0.90
8.50	7.65	0.85
8.02	7.73	0.34

On the basis of this result the stoichiometry for the reaction of N-alkylhydroxylamine with lead tetraacetate was shown to be as follows.

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[7] a) C.J.W. Gutch and W.A. Waters, *J. Chem. Soc.* (*B*), **1965**, 751; b) J.Q. Adams, S.W. Nicksic, and J.R. Thomas, *J. Chem. Phys.*, **45**, 654 (1966).

$$RMe_2CNHOH + Pb(OAc)_4 \longrightarrow RMe_2CN{=}O + Pb(OAc)_2 + 2HOAc$$

In the above reaction at 25°, the rate of the formation of the nitroso compound was too fast to obtain information about the reacfon mechanism by ordinary kinetic method under the conditions which favoured to measure the appearance of nitroso compound spectrophotometrically, *i.e.*, reaction with N-alkylhydroxylamines ($>5\times10^{-3}$ M) and excess amont of lead tetraacetate. The absorption due to the nitroso compound reached to its maximum in a few minutes in the reaction with any N-alkylhydroxyalmine examined.

No effect on the rate of the formation of nitroso compound was observed by lowering the reaction temperature below 10°.

It is likely that some free radicals would participate as intermediates in a reacfon, when oxidation is carried out with such a hydrogen abstracting oxidant as lead tetracetate.

Therefore an attempt to detect free radicals, probably, nitroxide was undertaken for the purpose of getting some informations about the present reactions.

As shown in Table III, electron spin resonance (ESR) singles due to two free radicals were observed when the reaction was carried out as follows.

TABLE III. Alkylnitroxides $RMe_2CNHO\cdot$ and Dialkylnitroxides $(RMe_2C)_2NO\cdot$ formed during the Oxidation of N-Alkylhydroxylamines

R	*hfs* Constants (in gauss)		
	$RMe_2CNHO\cdot$		$(RMe_2C)_2NO\cdot$
	A_{N}	A_{NH} (A_{ND})	A_{N}
Me	13.3	11.6 (2.1)	15.5
Et	13.4	12.0	15.5
CH_2OH	12.3	12.3	15.4
CH_2OAc	*a*)		14.9
COOEt	*b*)		14.6
CN	*b*)		14.3

a) In 1,1-dimethyl-2-acetoxyethylhydroxylamine, additional signals due to radicals besides alkylnitroxide and dialkylnitroxide made the assignment quite difficult.

b) When R is COOEt or CN signal due to alkylnitroxide was not observed.

Excess amount of solid lead tetraacetate was added to benzene solution of N-alkylhydroxylamines (0.1—0.5 M) in a sample tube, where free radicals were generated continuously over half an hour as solid lead tetraacetate dissolved into benzene.

One of the signals, triplet with dublet splitting which appeared earlier than another one and attained to maximum in about twenty minutes was assinged as alkylnitroxide, $RMe_2CNHO\cdot$ with known nitrogen (A_{N} 11—13 gauss) and hydrogen (A_{NH} 11—12 gauss)[8] *hfs* contants.

The assignment of *hfs* due to proton of the alkylnitroxide was supported by comparison of ESR spectrum from *tert*-butylhydroxylamine with that from *tert*-butylhydroxylamine labeled with deuterium in the position of the proton attaching to the nitrogen, Me_3CNDOD. The signals due to *tert*-butylhydroxylamine gave a triplet with doublet splitting from one proton (A_{NH} 11.6 gauss), on the other hand deuterated *tert*-butylhydroylamine gave a triplet with triplet splitting from one deuteron (A_{ND} 2.1 gauss) (Fig. 1, Fig. 2).).

Another signal of 1 : 1 : 1 triplet, which appeared later and increased in intensity with time and more stable than the former was found not to appear when the reaction was examined in dark.

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8) Th. A.J. Wajer, A. Mackor, and Th. J. de Boer, *Tetrahedron*, **25**, 175 (1969).

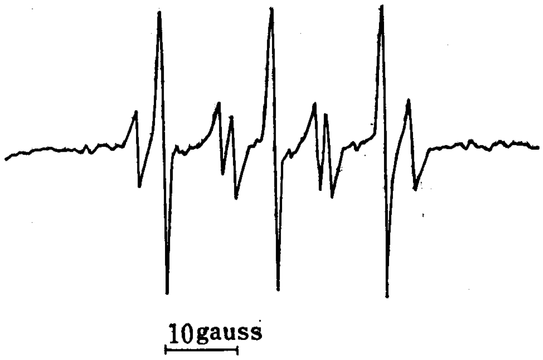

Fig. 1. ESR Spectrum of $Me_3CNHO\cdot$ and $(Me_3C)_2NO\cdot$

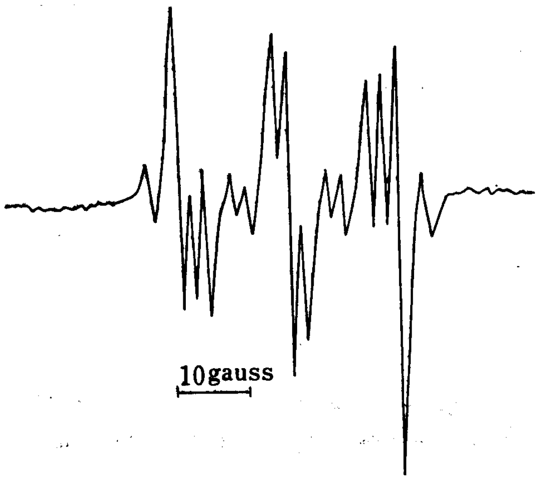

Fig. 2. ESR Spectrum of $Me_3CNDO\cdot$, $Me_3CNHO\cdot$ and $(Me_3C)_2NO\cdot$

It was also observed that benzene solution of the nitroso compounds which had been exposed to visible light showed the same signal of 1:1:1 triplet as that appearing in the oxidation of corresponding N-alkylhydroxylamine.

These observations suggested that this signal was due to the free radical generated by photolysis of the oxidation product, nitroso compound, and not generated in the process of the oxidation of N-alkylhydroxylamine to corresponding nitroso compound.

On the basis of these results and their coupling constants the signals of 1:1:1 triplet were assigned to be due to di-alkylnitroxides.

It has been reported that the reaction of *tert*-alkylnitroso compound with cyclohexylhydroxylamine at room temperature shows the ESR signal due to alkylnitroxide,[8] however, the benzene solution of *tert*-butylhydroxylamihe and *tert*-nitrosobutane was found not to show the signal of *tert*-butylnitroxide.

tert-Nitrosobutane was assured not to react with *tert*-butylhydroxylamine even at 50° in dark, by measuring the absorption due to *tert*-nitrosobutane, which did not show any decrease in intensity over two hours.

Acetoxy radical seems not to be so stable as to maintain sufficient concentration to react with unstable species such as acetoxy radical itself or alkylnitroxide, since acetoxy radical was not detected in the present system.

Therefore, acetoxy radical should react mainly with N-alkylhydroxylamine which is present in large concentration.

On the other hand the disproportionation of two alkylnitroxides was likely to take place,[9] because these alkylnitroxides were relatively stable as to be detected in the present system.

From these results we considered that the alkylnitroxides, dialkylnitroxides and the nitroso compounds should be formed in the following sequence of the reactions.

$$RMe_2CNHOH + Pb(OAc)_4 \longrightarrow RMe_2CNHO\cdot + Pb(OAc)_2 + [AcO\cdot] + AcOH$$

$$RMe_2CNHO\cdot + Pb(OAc)_4 \longrightarrow RMe_2CN{=}O + Pb(OAc)_2 + [AcO\cdot] + AcOH$$

$$RMe_2CNHOH + [AcO\cdot] \longrightarrow RMe_2CNHO\cdot + AcOH$$

$$2RMe_2CNHO\cdot \longrightarrow RMe_2CN{=}O + RMe_2CNHOH^{9)}$$

$$RMe_2CN{=}O \xrightarrow{h\nu} [RMe_2C\cdot] + [NO\cdot]$$

$$RMe_2CN{=}O + [RMe_2C\cdot] \longrightarrow (RMe_2C)_2NO\cdot$$

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[9] K. Adamic, D.F. Bowman, T. Gillan, and U. Ingold, *J. Am. Chem. Soc.*, **93**, 902 (1971).

As previously described, the above reactions were too fast to get detailed information about the reaction mechanism.

At the present, an attempt to present proper interpretation for the differences of reactivity among N-alkylhydroxylamines was unsuccessful. Further study on the oxidation of N-alkylhydorxylamines with other oxidants is now in progress.

Experimental

Materials——N-Alkylhydroxylamines were prepared by reduction of corresponding nitroalkanes with zinc dust. Nitroso compounds were prepared according to the literature.[10)]

1,1-Dimethyl-2-hydroxyethylhydroxylamine (I) and 1,1-dimethyl-2-acetoxyethylhydroxylamine hydrochloride (II) are new N-alkylhydroxylamines. These N-alkylhydroxylamines are not stable and purified materials are hardly obtainable.

(I) mp 50—52° *Anal.* Calcd. for $C_4H_{11}O_2N$: C, 45.71; H, 10.48, N, 13.33. Found: C, 44.86; H, 10.72; N, 12.84.

(II) mp 108—110° *Anal.* Calcd. for $C_6H_{14}O_3NCl$: C, 39.24; H, 7.63; N, 7.63. Found: C, 37.95; H, 7.79; N, 7.49.

Commercial lead tetraacetate was recrystallized from acetic acid and analysed according to the standard method,[11)] after being hydrolysed to lead dioxide.

Purified benzene was dried over sodium wire.

Determination of the Nitroso Compounds and Lead Tetraacetate Remaining in the Reaction Mixture When oxidation of N-alkylhydroxylamines with lead tetraacetate had been completed, the reaction mixture contained nitroso compound, lead tetraacetate, lead diacetate and lead dioxide which had been produced by hydrolysis of lead tetraacetate with trace of water in benzene.

After lead diacetate and lead dioxide interferring the spectrophotometric measurements of nitroso compounds had been removed by shaking 10 ml of the reaction mixture with 20 ml of water containing 25% sodium acetate, 5% acetic acid and 2% sodium thiosulfate, optical density of the benzene solution was measured.

These procedures were undertaken in dark to avoid decomposition of the nitroso compounds.

The concentration of lead tetraacetate remaining in the reaction mixture was determined by the same method as that used for the analysis of lead tetraacetate after the precipitate of lead diacetate had been filtered off.

Generation of the Free Radicals——The ESR spectra were recorded on JEOL P-10 and coupling constants were measured relative to manganese chloride.

Clearly resolved splittings were obtained when a slight excess of solid lead tetraacetate was added to dried and deoxygenated benzene solution containing 0.1—0.5M N-alkylhydroxylamines in a sample tube (7 mm OD).

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10) *a)* W.D. Emmons, *J. Am. Chem. Soc.*, **79**, 6522 (1957); *b)* O. Piloty and Grafschwerin, *Ber.*, **34**, 1863 (1901).

11) S. Takagi, "Quantitative Analysis Experiment and Calculations," Kyoritsu, Tokyo, 1949, P. 371.