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Studies on Stable Free Radicals. II.*1 Reactivity of Stable Nitroxide Radicals and NMR Spectra of Reaction Products

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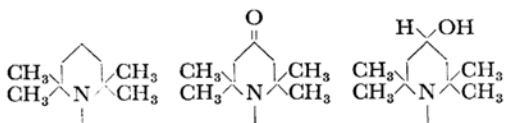
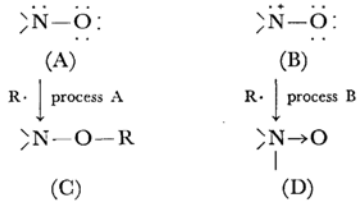
We have isolated coupled products of such stable free radicals as 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl (II), cyclohexane-1-spiro-2'-(4'-oxoimidazolidine-1'-oxyl)-5'-spiro-1''-cyclohexane (IV) and 2,2,6,6-tetramethyl-4-oxopiperidine-1-thiyl derived from bis-[2,2,6,6-tetramethyl-4-oxopiperidyl-(1)]disulfide (VII) with a *C*-radical derived from α,α'-azo-bis(isobutyronitrile). The reactive site in these stable free radicals was studied from the structure of the coupled products. The homolysis of the disulfide (VII) appeared to be accelerated by an attack of the *C*-radical, 1-methyl-1-cyanoethyl. The NMR spectra of the products suggested a slow inversion of the nitrogen atom in piperidine derivatives.

Extremely stable free radicals, such as 2,2,6,6-tetramethylpiperidine-1-oxyl (I), 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl (II) and 2,2,6,6-tetramethyl-4-hydroxypiperidine-1-oxyl (III), have



(I) (II) (III)

recently been prepared[1] by the oxidation of corresponding hindered amines. These radicals, which are considered to exist in an *O*-radical form (A)



*1 Part I: K. Murayama, S. Morimura, O. Amakasu, T. Toda and E. Yamao, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **90**, 296 (1969).

1) M. B. Neiman, Yu. G. Madedova and E. G. Rozantzev, *Azerb. Khim. Zh.*, **1962**, 37.

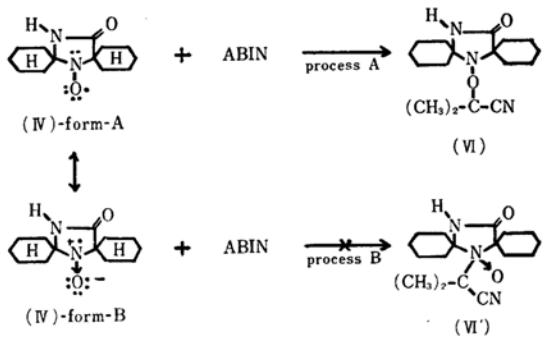
and/or another *N*-radical form (B),[2-4] can be preserved for long periods in air under normal conditions without undergoing any significant changes. It has further been found that these radicals were stable even under ionic reaction conditions.[2]

Reactions of the stable free radicals with *C*-radicals[5,6] have also been found; Neiman *et al.* deduced that the stable free radicals, I, II, and III, reacted only with an active *C*-radical (R·) derived from ethylbenzene,[5] while they did not react with a peroxy radical (ROO·). However, they did not isolate coupled products of the *C*-radical with the stable radicals. Therefore, the reactive site in the stable radicals has not been firmly established as being either an *O*-radical (A) or an *N*-radical (B). Depending upon the radical present either an N-O-R compound (C) (process A) or an *N*-oxide (D) (process B) would be expected when the radicals having Form A and Form B respectively are treated with a reactive radical, R·.

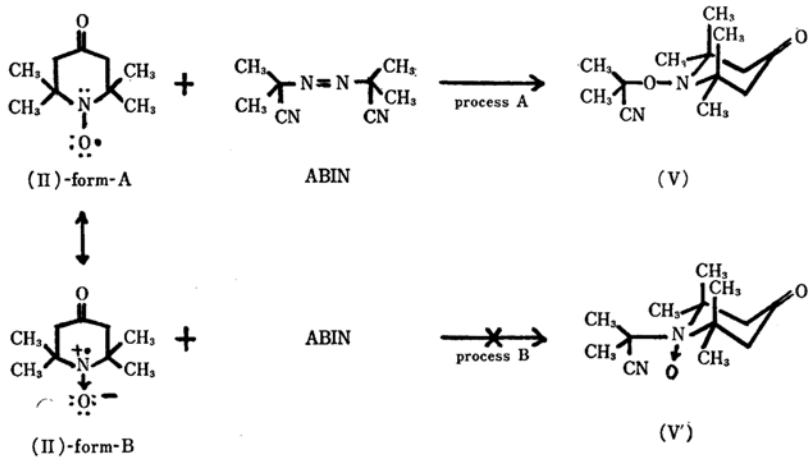
The present authors sought to confirm the reactive site of stable *N*-oxide radicals with another radical by isolating coupled products of the radicals with a typical *C*-radical derived from α,α'-azobisisobutyronitrile (ABIN). From the structure of these coupled products, we have then determined the reactive site in these radicals.

Results and Discussion

The reaction of II or a new stable free radical, cyclohexane-1-spiro-2'-(4'-oxoimidazolidine-1'-oxyl)-5'-spiro-1''-cyclohexane (IV) with ABIN, was carried out in a 2:1 molar ratio in a solution



of anhydrous methanol at 63°C for 30 hr. Subsequently the coupled reaction product, prepared from the 1-methyl-1-cyanoethyl radical (derived from ABIN) and a stable radical, II or IV, was obtained, accompanied by 2,3-dimethyl-2,3-dicyanobutane. As is shown below, the structures of these products were deduced to be 1-(1-methyl-1-cyanoethoxy)-2,2,6,6-tetramethyl-4-oxopiperidine (V) or 1-(1-methyl-1-cyanoethyl)-2,2,6,6-tetramethyl-4-oxopiperidine-1-oxide (V') and cyclohexane-1-spiro-2'-[1'-(1-methyl-1-cyanoethoxy)-4'-oxoimidazolidine]-5'-spiro-1''-cyclohexane (VI) or cyclohexane-1-spiro-2'-[1'-(1-methyl-1-cyanoethyl)-4'-imidazolidine-1'-oxide]-5'-spiro-1''-cyclohexane (VI') respectively, on the basis of the results of elemental analyses, the molecular weight measurements, and the molecular peaks in the mass spectra. The structures V' and VI' were, however, doubtful, since no deoxy products were obtained in the reactions of the above coupled products with triphenylphosphine (or triethylphosphite) in an acetic acid solution at 110°C for 5 hr.[7] Strong support



2) E. G. Rozantzev and M. B. Neiman, *Tetrahedron*, **20**, 131 (1964).

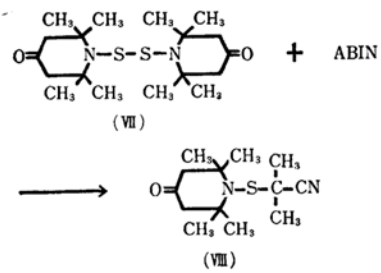
3) H. Lemaire, Y. Marechal, R. Ramasseul and A. Rassat, *Bull. Soc. Chim. France*, **1965**, 372.

4) E. G. Rozantzev and E. G. Gintsberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1966**, 571.

5) a) M. B. Neiman and E. G. Rozatnzev, *ibid.*, **1964**, 1178. b) M. S. Khloplyankina, A. L. Buchachenko, M. B. Neiman and A. G. Vasil, eva, *Kinetikai Kataliz.*, **6**, 394 (1965).

6) E. G. Rozantzev and V. A. Golubev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1966**, 891.

7) L. Horner and H. Hoffmann, *Angew. Chem.*, **68**, 480 (1956).

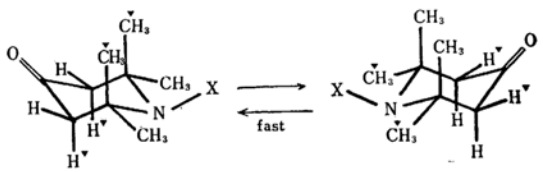


for the two molecular structures V and VI was given by the high-resolution double-focusing mass spectra. The expected molecular ion peaks at *m/e* 238.169 and 305.211, corresponding to $C_{13}H_{22}N_2O_2$ and $C_{17}H_{27}N_3O_2$ respectively, were found by the measurement of the millimass units. Since no fragment ion peak $(M-16)^+$ [8] or $(M-17)^+$ [9] was found, the V′ and VI′ structures were eliminated.

In order to investigate the behavior of stable free radicals other than *N*-oxyl radicals, a reaction of ABIN was carried out with a stable *N*-thiyl radical such as 2,2,6,6-tetramethyl-4-oxopiperidine-1- thiyl, which had been established by Bennett *et al.* using an ESR technique.[10] The precursor, bis-[2,2,6,6-tetramethyl-4-oxopiperidyl-(1)] disulfide (VII),[10] reacted with ABIN in a 1 : 2 molar ratio to give 1-(1-methyl-1-cyanoethylthio)-2,2,6,6-tetramethyl-4-oxopiperidine (VIII) in a benzene solution under gentle reflux for 7 hr. The product VIII could be characterized as the corresponding 2,4-dinitrophenylhydrazone and semicarbazone. The structure of VIII was deduced from the results of elemental analyses and the IR and NMR spectra, especially from the absence of the fragment ion peaks, $(M-32)^+$ and $(M-33)^+$.

This finding that the disulfide VII reacted with ABIN at 80°C to give VIII as the product in a good yield is instructive; over the limited range of 140—200°C, the homolytic fission of the S–S bond into the *N*-thiyl radical has been confirmed by ESR techniques,[10] while we observed no homolytic fission of the S–S bond at 80°C (ESR). Therefore, the homolytic cleavage of the disulfide bond appeared to be accelerated by the action of the 1-methyl-1-cyanoethyl radical at 80°C. Similar cleavages of various disulfides by the 1-methyl-1-cyanoethyl radical have been observed by Schmidt *et al.* when they examined the effect of substituents on the homolysis of the S–S bond.[11]

The NMR spectra of *N*-substituted 2,2,6,6-tetramethyl-4-oxopiperidines (V) and VIII showed interesting features. In the NMR spectra of 2,2,6,6-tetramethyl-4-oxopiperidine (IX),[12] 1,2,2,6,6-pentamethyl-4-oxopiperidine (X)[12] and 1-benzenesulfonyl-2,2,6,6-tetramethyl-4-oxopiperidine (XI),[13] the C-3 and C-5 methylene protons, and the



$[X=-H,(IX),\ -CH_3\ (X),\ -SO_2-C_6H_5\ (XI)]$ [14]

C-2 and C-6 methyl protons have been found to give single sharp lines in a carbon tetrachloride and in a benzene solution. These facts suggest that the nitrogen inversion and/or the ring inversion is rapid at room temperature, as is shown above. It was, however, found that four methyl groups of *N*-substituted piperidines (V) and (VIII) (Fig. 1) gave rise to two sharp lines, indicative of two kinds of methyl protons. A_2B_2 quartets ($J_{gem}=13.5$ cps), indicative of two methylene protons, were further observed as well as in the case of 1-benzenesulfenyl-2,2,6,6-tetramethyl-4-oxopiperidines (XII).[13] Hence, the inversion rates of the nitrogen atom and of the piperi-

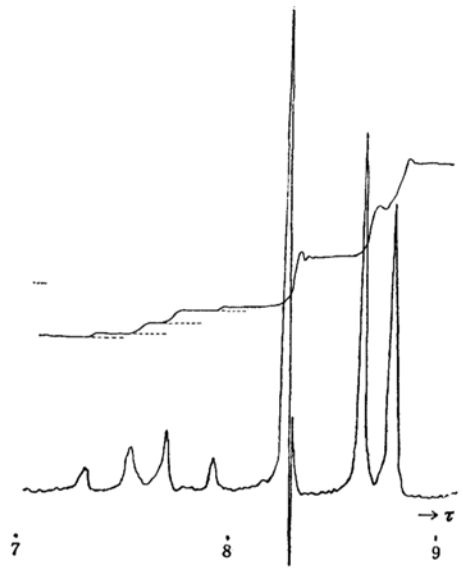


Fig. 1. Methyl and methylene protons (NMR) of 2,2,6,6-tetramethyl-4-oxo-1-(1-methyl-1-cyanoethoxy)piperidine (V) in CCl_4 at 32°, (60 Mc).

8) a) T. A. Bryce and J. R. Maxwell, *Chem. Commun.*, **1965**, 206. b) R. E. Banks, R. N. Haszeldine and M. J. Stevenson, *J. Chem. Soc., C*, **1966**, 901.

9) R. Grigg and B. G. Odell, *ibid., B*, **1966**, 218.

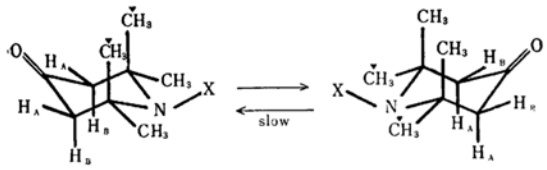
10) J. E. Bennett, H. Sieper and P. Tavs, *Tetrahedron*, **23**, 1697 (1967).

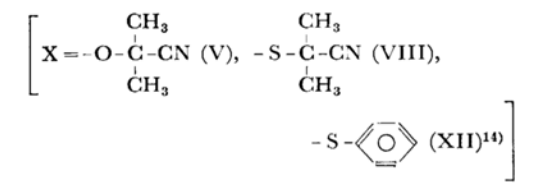
11) U. Schmidt and A. Müller, *Liebigs Ann. Chem.*, **672**, 90 (1964).

12) M. J. Aroney, C.-Y. Chen, R. J. W. Le Fèvre and A. N. Singh, *J. Chem. Soc., B*, **1966**, 98.

13) K. Murayama and T. Yoshioka, *Tetrahedron Letters*, **1968**, 1363.

dine ring may be considered to be slower in V and VIII than in IX, X, and XI.





Thus, we confirmed that the *N*-oxyl and *N*-thiyl radicals could react with the *C*-radical derived from ABIN, and that the reaction apparently proceeded through process A, since no *N*-oxides V′ and VI′ were obtained even by careful separation techniques.

Experimental

All melting points are uncorrected.

The IR spectra were determined by means of Nujol mull and liquid films.

The NMR spectra were obtained using a Varian A-60 NMR spectrometer, using tetramethylsilane as the internal standard at 32°C.

The mass spectra were obtained using a JEOL-JMS-OIS mass spectrometer with an ionizing voltage of 70eV.

2,2,6,6-Tetramethyl-4-oxo-1-(1-methyl-1-cyanoethoxy)-piperidine (V). A mixture of 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl (II) (11.7 g, 0.069 mol) and α,α'-azo-bis(isobutyronitrile)(ABIN) (5.0g, 0.0305 mol) was gently refluxed in a methanol solution for 30hr. After the solvent had then been evaporated under diminished pressure at 30°C, 2,3-dimethyl-2,3-dicyanobutane was excluded by sublimation under diminished pressure (0.060 mmHg) at 90°C. Then the oily residue was chromatographed on 100 g of Brockmann aluminum oxide and eluted with anhydrous petroleum ether to give 7.3 g (50.4 %)[14] of crude V. The crude crystals, V, were recrystallized from petroleum ether to give an analytically pure sample; mp 72.5—73.5°C.

Found: C, 65.48; H, 9.27; N, 11.74%; MW, 226.9 (V. O. P. method in $CHCl_3$). Calcd for $C_{13}H_{22}N_2O_2$: C, 65.55; H, 9.33; N, 11.76%; MW, 238.2.

IR cm^{-1}: $\nu_{C=O}$ 1725; ν_{N-O} 1460 and ν_{C-O} 1145.

NMR (τ)(in CCl_4): 8.78 (6H)(ax CH_3–); 8.63 (6H)(eq CH_3–); 8.28(6H)[$(CH_3)_2$–C(CN)–C≡N]. A_2B_2 quartet (J=13.5 cps); 7.92, 7.70, 7.53 and 7.32(4H).

Mass spectrum: M$^+$, *m/e* 238.169.

Cyclohexane-1-spiro-2′-(4′-oxoimidazolidine-1′-oxyl)-5′-spiro-1″-cyclohexane (IV). To a suspension of cyclohexane-1-spiro-2′-(4′-oxoimidazolidine)-5′-spiro-1″-cyclohexane[15] (corresponding amine) (22.2 g, 0.10 mol) in acetic acid (200 m*l*) were slowly added a solution of EDTA (0.5 g) and sodium tungstate (0.45 g) in water (3 m*l*) and then a 30 % aqueous solution of hydrogen peroxide (25 m*l*) with stirring at room temperature. Stirring was continued for an additional 50 hr at room temperature. After the solvent had been evaporated *in vacuo*, a 50 m*l* portion of water was added to the residue. The suspension of the crude product the (residue) was treated with potassium carbonate, and additional stirring was continued for 3 hr. The separated crystalline substance was filtered and washed with water. By recrystallization from benzene, IV was obtained as faintly reddish crystals, mp 227—228°C, in a good yield of 20.6 g (86.8%).

Found: C, 65.84; H, 8.93; N, 11.87%. Calcd for $C_{13}H_{21}N_2O_2$: C, 65.79; H, 8.92; N, 11.87%.

IR cm^{-1}: $\nu_{C=O}$ 1708; ν_{N-H} 3180 and 3070.

Cyclohexane-1-spiro-2′-[1′-(1-methyl-1-cyanoethoxy)-4′-oxoimidazolidine]-5′-spiro-1″-cyclohexane (VI). A mixture of cyclohexane-1-spiro-2′-(4′-oxoimidazolidine-1′-oxyl)-5′-spiro-1″-cyclohexane (IV) (10.0 g, 0.0422 mol) and ABIN (3.5 g, 0.0214 mol) was refluxed in a methanol solution. After 30hr, 10.3 g (79.8 %) of crude VI were separated out as crystals. These crystals were filtered and washed with ether. The crude material was recrystallized from glacial acetic acid to give an analytically pure sample; 7.8g, mp 190—191°C.

Found: C, 66.64; H, 8.99; N, 13.61%. Calcd for $C_{17}H_{27}N_3O_2$: C, 66.84; H, 8.91; N, 13.76%.

IR cm^{-1}: $\nu_{C=O}$ 1695, ν_{N-O} 1450 and ν_{C-O} 1150.

NMR: only a broad signal of cyclohexane-protons.

Mass spectrum: M$^+$, *m/e* 305.211.

2,2,6,6-Tetramethyl-4-oxo-1-(1-methyl-1-cyanoethylthio)piperidine (VIII). A mixture of bis-[2,2,6,6-tetramethyl-4-oxopiperidyl-(1)] disulfide (VII) (3.7 g, 0.00995 mol) and ABIN (3.2 g, 0.0195 mol) was refluxed in a benzene solution for 7 hr. After the solvent had then been evaporated under diminished pressure, 2,3-dimethyl-2,3-dicyanobutane was removed by sublimation under diminished pressure (0.1 mmHg) at 110—113°C. The oily residue was distilled to give an analytically pure oil, bp 139—141°C/0.05 mmHg, 4.1 g (81.2 %).

Found: C, 61.46; H, 8.65; N, 10.93%. Calcd for $C_{13}H_{22}N_2OS$: C, 61.39; H, 8.72; N, 11.02%.

IR cm^{-1}: $\nu_{C=O}$ 1725 and $\nu_{C\equiv N}$ 2220.

NMR(τ)(in CCl_4): 8.75 (6H)(ax CH_3–); 8.55 (6H)(eq CH_3–); 8.39 (6H)[$(CH_3)_2$–C(CN)–C≡N]; A_2B_2 quartet (J=13.5 cps) 7.79, 7.56, 7.39 and 7.16(4H).

Mass spectrum: M$^+$, *m/e* 254.

2,4-Dinitrophenylhydrazone, mp 155—156°C.

Found: C, 52.46; H, 6.00; N, 19.24%. Calcd for $C_{19}H_{26}N_6O_4S$: C, 52.52; H, 6.03; N, 19.35%.

Semicarbazone, mp 191—192°C.

Found: C, 54.21; H, 7.97; N, 22.32%. Calcd for $C_{14}H_{25}N_5OS$: C, 54.00; H, 8.09; N, 22.49%.

The authors wish to thank Professor Makoto Okawara of the Tokyo Institute of Technology for his valuable comments, Dr. Issei Iwai of these laboratories for his helpful guidance during the course of this work, and Mr. Susumu Higashida for his technical assistance.

14) From the reaction mixture, 2,2,6,6-tetramethyl-1-hydroxy-4-oxopiperidine (XIII) (38.4% yield) was isolated. Detailed mechanism of the formation of XIII will be reported in a forthcoming paper.

15) W. E. Noland, R. J. Sundberg and M. L. Michaelson, *J. Org. Chem.*, **28**, 3576 (1963).