[Chem. Pharm. Bull. 31(10)3385—3390(1983)]

Electron Spin Resonance Spectra of *N*-Nitrosodialkylamine Radical Cations Electrochemically Generated in Solution

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(Received March 11, 1983)

The paramagnetic species formed by *in situ* electrochemical oxidation of *N*-nitroso-2,2,6,6-tetramethylpiperidine (**1**), *N*-nitrosodicyclohexylamine (**2**), and *N*-nitrosodiisopropylamine (**3**) in acetonitrile or propionitrile at −30—−90 °C have been identified as the radical cations, $>N^+=N-\dot{O}$, derived from the parent nitrosamines by one-electron transfer. The radical cations are σ-radicals isoelectronic with the corresponding iminoxy radicals and show long-range couplings to hydrogen atoms, but the value of hyperfine splitting constant of the nitroso-nitrogen (*ca.* 45 G) is the largest known for a nitrogen atom in an organic molecule. The order to stability of the radical cations is as follows: that derived from **1** > that from **2** > that from **3**.

Keywords——electron spin resonance spectra; *N*-nitrosodialkylamine radical cation; σ-radical; hyperfine splitting constant; electrochemical oxidation; cyclic voltammetry

In the electrochemical oxidation of dialkylnitrosamines such as *N*-nitrosodibutylamine and *N*-nitrosodicyclohexylamine in acetonitrile, *N*-nitramines and β-ketonitrosamines have been found as the major products.[1] While the corresponding *N*-nitrosamine radical cations have been assumed to be generated by initial one-electron transfer from the substrates, the subsequent reaction processes of the radical cations to give the final products are still uncertain. Information on the nature of the radical cations will be of great help in elucidating the mechanism of the electrochemical oxidation.

Mishra and Symons have irradiated *N*-nitrosodimethylamine using ^{60}Co γ-rays at *ca.* −200 °C and have detected the simultaneous formation of two paramagnetic centers; one of them, with a large nitrogen isotropic coupling (*ca.* 40 G), has been assigned as the *N*-nitrosodimethylamine radical cation.[2] However, there is no precedent for an electron spin resonance (ESR) spectrum of an *N*-nitrosamine radical cation in fluid solution with well-defined hyperfine splittings (*hfs*'s).[3] This paper reports the ESR spectra of radical cations derived from *N*-nitroso-2,2,6,6-tetramethylpiperidine (**1**), *N*-nitrosodicyclohexylamine (**2**) and *N*-nitrosodiisopropylamine (**3**).

Results and Discussion

N-Nitrosodialkylamine radical cations are too labile to detect at ambient temperature. Thus, cyclic voltammetry of the parent nitrosamines in acetonitrile usually shows two or three anodic peaks without any cathodic counterpart.[1] At lower temperatures (−30—−40 °C), however, reversible or quasireversible behavior was observed in the first anodic waves of three compounds, **1**, **2**, and **3**, out of fifteen *N*-nitrosodialkylamines examined (Fig. 1), indicating that the radical cations of the three nitrosamines are relatively stable under the conditions used.

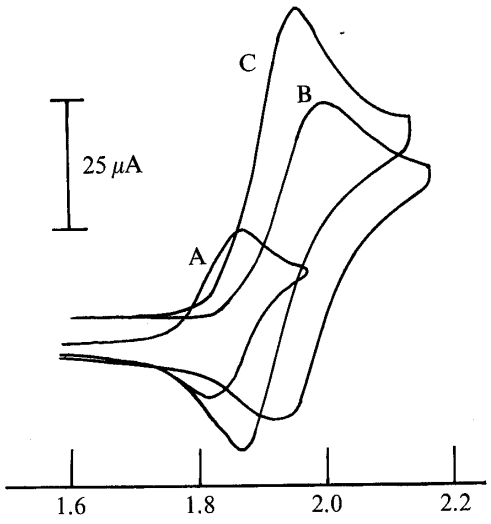

Fig. 1. Cyclic Voltammograms of the Nitrosamines **1** (1.96 mM; voltage sweep rate, 50 mV s^{-1}) (A), **2** (1.95 mM; 200 mV s^{-1}) (B), and **3** (2.03 mM; 200 mV s^{-1}) (C)

In acetonitrile containing 0.1 M Et_4NClO_4 at −40 °C; glassy carbon anode (area, 0.072 cm^2).

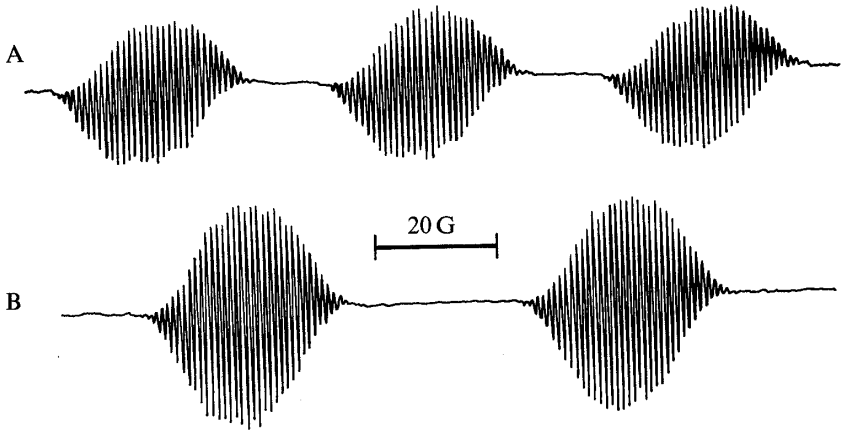

Fig. 2. ESR Spectra of *in Situ* Electrolyzed Solutions of the Nitrosamine **1** (10 mM) (A) and Its ^{15}N-Labeled Derivative (See the Text) (10 mM) (B) in Acetonitrile (0.1 M Et_4NClO_4) at −30 °C

N-Nitroso-2,2,6,6,-tetramethylpiperidine Radical Cation

In situ electrolysis of **1** in acetonitrile at −30 °C gave an ESR spectrum with the following parameters:[4] $g=2.0026$,[5] $A_1=45.0$ (1N), $A_2=6.58$ (1N), $A_3=2.82$ (8H), and $A_4=0.94$ G (6H). The *g*-factor and nitrogen *hfs*'s are similar to those reported for the *N*-nitrosodimethylamine radical cation, *viz.* 2.0023, 40.3 and *ca.* 4.7 G, respectively.[2] The value for A_1, which is, as far as we are aware, the largest isotropic *hfs* constant found for a nitrogen atom in an organic molecule, gives $a_s^2=0.0818$ as the spin density on the 2*s* orbital of the nitrogen atom. Since the ESR spectrum was measured in fluid solution and gave no anisotropic parameters, the spin density on the 2*p* orbital of the nitrogen, the *p*/*s* ratio, and the bond angle at the nitrogen atom could not be calculated.

In order to gain a better understanding of the spectrum, the nitrosamine **1** containing ^{15}N in the nitroso group was also electrolyzed *in situ*. The ESR spectrum of the labeled compound showed distinct two-fold symmetry (Fig. 2), which confirms that the nitrogen in the nitroso group has the largest *hfs* constant. The following parameters were obtained: $g=2.0025$, $A_1=62.0$ ($1^{15}N$), $A_2=6.58$ ($1^{14}N$), $A_3=2.82$ (8H), and $A_4=0.94$ G (6H). The ratio of $A_1(^{15}N)/A_1(^{14}N)$, 1.378, is close to the value calculated from atomic *hfs* data of ^{14}N and ^{15}N, 1.402.[6]

The above results indicate that the radical species observed here is the *N*-nitroso-2,2,6,6-tetramethylpiperidine radical cation (**4**) derived from **1** as a result of a one-electron transfer, and that it is a σ-radical isoelectronic with the well-known iminoxy radicals,[7] as suggested for the *N*-nitrosodimethylamine radical cation.[2] By analogy with the ESR data for cyclohexanone iminoxy radicals,[7c] the assignments shown in structure **4** are reasonable. Under the experimental conditions used, the radical cation **4** must undergo rapid ring inversion but the configuration about the N–N bond must be maintained, as in the parent nitrosamine.[8]

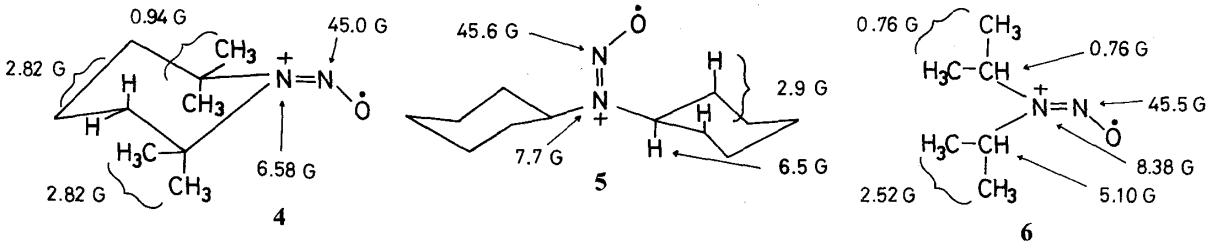

Chart 1

N-Nitrosodicyclohexylamine Radical Cation

Cyclic voltammetry of the nitrosamine **2** in acetonitrile at $-40\,^{\circ}C$ showed an anodic peak with its cathodic counterpart when the voltage sweep rate was increased to $200\,mV\,s^{-1}$ (see Fig. 1). On electrolysis of **2** under these conditions, however, only an ill-defined ESR Spectrum was obtained, though a large *hfs* constant (45.6 G) was recognized. The radical cation from **2** must be less stable than that from **1**. When the electrolysis was carried out in propionitrile at $-60\,^{\circ}C$, a fairly well-defined spectrum was obtained (Fig. 3), which gave the following parameters: $g=2.0028$, $A_1=45.6$ (1N), $A_2=7.7$ (1N), $A_3=6.5$ (1H), and $A_4=2.9$ G (2H). Comparison of the data with those reported for substituted bicyclic ketone iminoxy radicals[9] suggests the assignments in structure **5**, which is based on the general conclusion of Gilbert and Norman[7b] that most effective coupling occurs *via* a planar σ-framework, *cis* to the iminoxy oxygen. Under the experimental conditions, the radical cation **5** seems not to undergo rapid ring inversion (*cf.* the radical cation **4**) probably

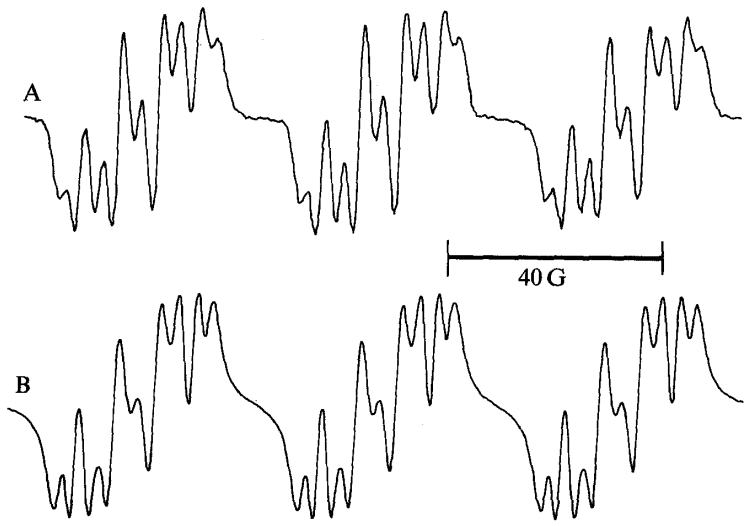

Fig. 3. ESR Spectrum of an *in Situ* Electrolyzed Solution of the Nitrosamine **2** (10 mM) in Propionitrile (0.1 M $NaClO_4$) at $-60\,^{\circ}C$ (A) and Its Computer Simulation (B)

Computer simulation was performed by using the coupling constants given in the text and a line width of 0.5 G (Lorentzian line shape).

because of the lower temperature.

N-Nitrosodiisopropylamine Radical Cation

In situ electrolysis of the nitrosamine **3** in propionitrile at −70 °C gave the spectrum shown in Fig. 4: $g=2.0026$. Although the value of *hfs* for the nitroso nitrogen was immediately apparent [$A_1=45.5$ G (1N)], unambiguous interpretation of the other *hfs*'s was difficult owing to the poor resolution of the spectrum. The center part of the spectrum obtained with a smaller modulation amplitude (0.25 G) is compared in Fig. 5 with its computer simulation calculated with the following set of *hfs* constants: $A_2=8.38$ (1N), $A_3=5.10$ (1H), $A_4=2.52$ (6H), and $A_5=0.76$ G (7H). The assignments shown in structure **6** seem plausible, but the difference between the calculated and experimental spectra suggests that the protons assigned to A_4 and/or A_5 are not entirely equivalent and have slightly different *hfs* constants. Attempts to improve the resolution of the spectrum were not successful at the experimental temperature. Electrolysis of the nitrosamine **3** was also carried out at −90 °C, where the radical cation **6** would be more stable and hence a smaller modulation and a slower scan rate could be used for the ESR measurement to attain a better resolution. At this temperature, however, the rate of molecular tumbling of the radical cation was not fast enough to average out the anisotropies effectively, and hence only a poorly-resolved spectrum

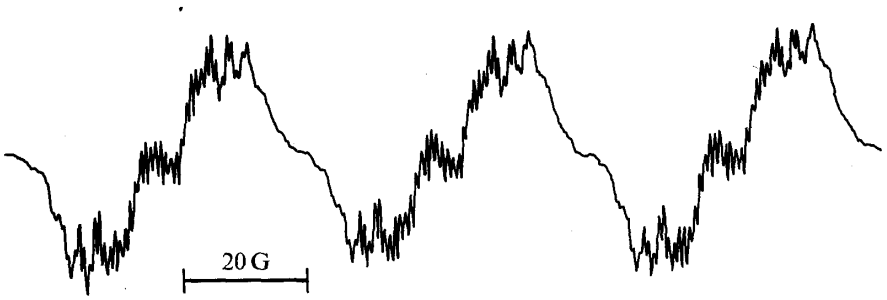

Fig. 4. ESR Spectrum of an *in Situ* Electrolyzed Solution of the Nitrosamine **3** (10 mM) in Propionitrile (0.1 M $NaClO_4$) at −70 °C

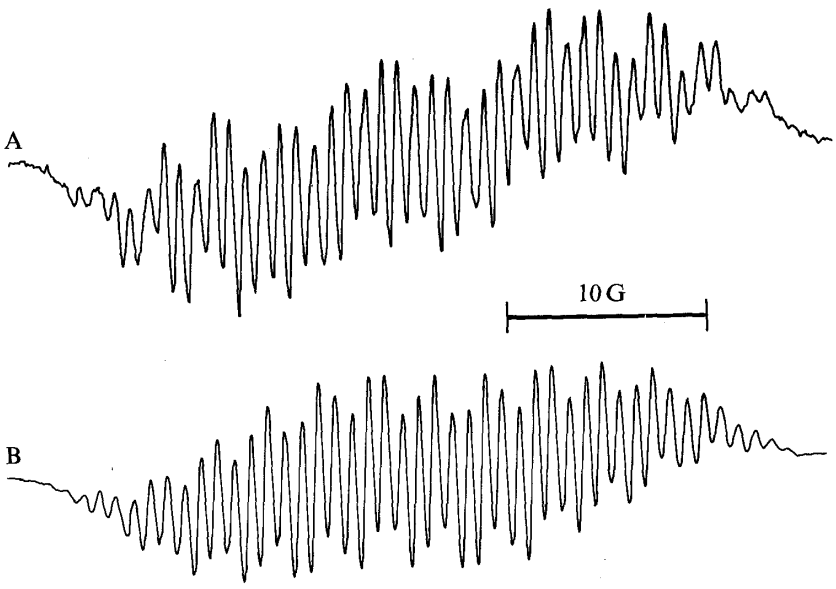

Fig. 5. ESR Spectrum (Central One-Third) of an *in Situ* Electrolyzed Solution of the Nitrosamine **3** (10 mM) in Propionitrile (0.1 M $NaClO_4$) at −70 °C (A) and Its Computer Simulation (B)

was obtained. A similar phenomenon was observed on electrolysis of the nitrosamine **1** in propionitrile at −90 °C.

It is interesting to note that the nitrosamines **1** and **2** are noncarcinogens and **3** is a weak carcinogen.[10] The radical cations derived from them showed the following order of stability in the present study: **4**>**5**>**6**. On the other hand, dialkylnitrosamines with unbranched carbon skeletons such as *N*-nitrosodimethylamine, *N*-nitrosodiethylamine, *etc.* are powerful carcinogens, and their radical cations were too labile to detect under the present experimental conditions. These observations might suggest a radical stability-carcinogenic activity relationship, but a larger number of dialkylnitrosamines should be examined before a definite conclusion can be reached.

Although the final products of electrolysis of the nitrosamine **1** have not been identified yet, the nitrosamine **2** has been found to give the corresponding nitramine and β-keto-nitrosamine[1] and formation of *N*-nitrodiisopropylamine has been confirmed in the electrolysis of **3**.[11] Thus, the present results support the conclusion that *N*-nitrosamine radical cations are the primary intermediates in the electrochemical oxidation of their parent nitrosamines.

Experimental

Materials——*N*-Nitrosodialkylamines were prepared from the reaction of dialkylamines and sodium nitrite in aqueous hydrochloric acid. The nitrosamines **2** (mp, 105 °C) and **3** (mp, 48 °C) were recrystallized from hexane and petroleum ether, respectively. Other nitrosamines including **1** were purified by distillation. All procedures were conducted under an extractor hood. The nitrosamine **1** labeled with ^{15}N was prepared from $Na^{15}NO_2$ (CEA, >99%) and gave the expected analytical values.

Methods——Cyclic voltammetry was carried out essentially as described previously.[12] ESR spectra were recorded on a JEOL JES-FE 1X spectrometer equipped with 100 kHz field modulation and a ES-UCT-2AX variable temperature accessory. The electrolysis cell used for internal generation of the radical cations was a Pyrex capillary (i.d., 1 mm; length, 100 mm) with a Pyrex reservoir (i.d., 10 mm; length, 70 mm) at the top. The cell was attached to the ESR spectrometer so that the central region of the capillary was located in the center of the ESR cavity. A platinum wire anode, which was covered by polyethylene tubing except at both ends, was inserted into the capillary and a platinum wire cathode was placed in the reservoir. A solution of a nitrosamine (*ca.* 10 mM) in acetonitrile containing 0.1 M tetraethylammonium perchlorate or in propionitrile containing 0.1 M sodium perchlorate was deoxygenated in the reservoir by flushing with dry N_2 gas, and then introduced into the capillary. The solution was subjected to constant current electrolysis (0.01—0.03 mA), which was performed with a Hokuto-Denko HA-111 potentiostat-galvanostat, and the ESR spectrum was monitored. During the electrolysis, N_2 gas was passed over the solution. The *g*-value was determined by comparing the spectrum with that of aqueous peroxylamine disulfonate ($g=2.0055$). Computer simulation of the spectrum was carried out using a JEOL EC-100 computer system.

Acknowledgement This work was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health and Welfare and from the Ministry of Education.

References and Notes

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