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Electrochemical Oxidation of *N*-Nitrosodialkylamines: Mechanism of *N*-Nitramine and β-Ketonitrosamine Formation[1)]

MASAICHIRO MASUI,* KOICHI NOSE, SATOMI TERAUCHI, EIKO YAMAKAWA, JISOOK JEONG, CHIHIRO UEDA, and HIDENOBU OHMORI

Faculty of Pharmaceutical Sciences, Osaka University, 1–6 Yamadaoka, Suita, Osaka 565, Japan

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Electrochemical oxidation of *N*-nitrosamines (**1**) derived from symmetrical dialkylamines was investigated in acetonitrile in the presence of dissolved oxygen. On cyclic voltammetry at ambient temperature, **1** showed two or three irreversible anodic peaks, depending upon the structure. Macroscale electrolysis, either controlled potential or constant current, of **1** which showed three voltammetric peaks gave the corresponding nitramine (**2**) and *N*-alkyl-*N*-(2-oxoalkyl)nitrosamine (**3**) as the main products. In the case of **1** which showed two voltammetric peaks, however, the side-chain oxidized nitrosamine **3** was not obtained. It is suggested that the oxygen atom incorporated in the products **2** and **3** originated from dioxygen dissolved in the medium, and that the numbers of electrons required for the formation of **2** and **3** are one and two, respectively. A possible reaction sequence, which involves the reactions of the radical cation (**4**) derived from **1** and a radical formed by intramolecular rearrangement of **4** with dioxygen, is proposed.

Keywords——*N*-nitrosodialkylamine; *N*-nitramine; *N*-alkyl-*N*-(2-oxoalkyl)nitrosamine; electrochemical oxidation; cyclic voltammetry; controlled potential electrolysis; constant current electrolysis

Electrochemical oxidation of *N*-nitrosodialkylamines (**1**) such as *N*-nitrosodibutylamine and *N*-nitrosodicyclohexylamine in acetonitrile with dissolved oxygen has been found to give the corresponding nitramines (**2**) and β-ketonitrosamines (**3**).[2)] Although the formation of *N*-nitrosodialkylamine radical cations by the initial one-electron transfer from the substrates has been confirmed by electron spin resonance spectroscopy,[3)] the following processes leading to the final products are not yet clear. Since oxidative degradation of *N*-nitrosamines by enzymatic processes to give reactive alkylating agents is suggested to be responsible for mutagenic induction in living organisms[4)] and a β-oxygenated nitrosamine can be one of the intermediates in such processes,[5)] the mechanism of electrochemical oxidation of **1** seems worthy of further investigation.

This paper reports the results of cyclic voltammetry, controlled potential electrolysis, and constant current electrolysis of **1** derived from various symmetrical dialkylamines in acetonitrile in the presence of dissolved oxygen. The mechanisms of the oxidation are discussed.

R_2N–NO (**1**)
a, R=Me; **b**, R=Et; **c**, R=Pr; **d**, R=iso-Pr; **e**, R=Bu;
f, R=Amyl; **g**, R=Hexyl; **h**, R=Heptyl; **i**, $R_2=-(CH_2)_5-$;
j, $R_2=-(CH_2)_4-$; **k**, $R_2=-(CH_2)_2-O-(CH_2)_2-$; **m**, R=Cyclohexyl
R_2N–NO_2 (**2**) R′–CO–CH_2–N(NO)–R (**3**)

Chart 1

Results

Cyclic Voltammetry

At ambient temperature, the nitrosamines **1** generally showed two or three irreversible anodic peaks in acetonitrile containing 0.1 M tetraethylammonium perchlorate (TEAP) in the presence of dissolved oxygen.[2,6] All potentials were measured against an aqueous saturated calomel electrode (S.C.E.) except where otherwise noted. The values of the peak currents and the peak potentials are summarized in Table I.[7] The second and the third anodic peaks are ascribed to the oxidation of the corresponding β-ketonitrosamine (**3**) and nitramine (**2**), respectively, formed at the first wave. Typical examples of the voltammograms are illustrated in Fig. 1.[8]

TABLE I. Results of Cyclic Voltammetry of **1**[a]

Compound	E_{p1}[b,c]	i_p/C[d]	E_{p2}[b,e]	E_{p3}[b,f]
1a	2.04	38.8	—	2.4
1b	1.92	31.3	—	2.3
1c	1.85	25.5	2.05	2.3
1d	1.80	26.7	—	2.35
1e	1.84	25.1	2.05	2.3
1f	1.84	24.1	2.05	2.3
1g	1.83	22.1	2.00	2.3
1h	1.84	20.8	2.05	2.3
1i	2.01	47.1[g]	—	2.23
1j	1.85	40.5[g]	—	2.25
1k	2.00	43.8[g]	—	2.17
1m	1.72	21.9	2.00	2.27

a) In acetonitrile containing 0.1 M TEAP and saturated with O_2 at 25 °C; glassy carbon anode (area = 0.071 cm^2); voltage sweep rate, 50 mVs^{-1}; concentration of **1**, *ca.* 2 mM. *b*) V *vs.* S.C.E. *c*) The peak potential of the first anodic peak. *d*) Peak current of the first anodic peak; μA/mM. *e*) The second anodic peak. *f*) The third anodic peak. *g*) The peak current was sensitive to small amounts of water contaminating the medium.

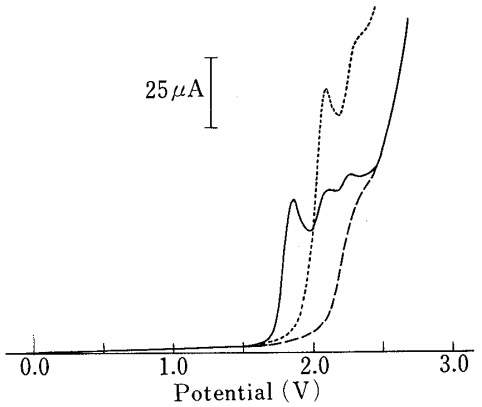


Fig. 1. Typical Cyclic Voltammograms of **1c** (2.15 mM, Solid Line), **2c** (2.07 mM, Broken Line), and **3c** (2.19 mM, Dashed Line)

In acetonitrile containing 0.1 M TEAP and saturated with oxygen: glassy carbon anode (area = 0.071 cm^2); voltage sweep rate, 50 mVs^{-1}; at −30 °C (see footnote 8). Potentials were measured against an Ag wire. Curves for the reverse scan are omitted for simplicity.

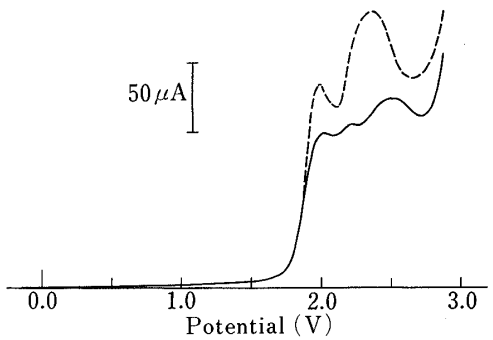


Fig. 2. Typical Cyclic Voltammograms of **1i** (2.05 mM)

In acetonitrile containing 0.1 M TEAP and saturated with oxygen at 25 °C. Solid line, without added water; the peak around 2.5 V is due to the background. Broken line, in the presence of 1% H_2O. Glassy carbon anode (area = 0.071 cm^2); voltage sweep rate, 50 mVs^{-1}. Curves for the reverse scan are omitted for simplicity.

TABLE II. Effects of Oxygen and Water on the i_p/C Value of the First Anodic Peak of **1**[a]

Compound	i_p/C (μA/mM)			
	$+O_2$[b]	$+O_2$,[b] $+H_2O$[c]	$-O_2$[d]	$-O_2$,[d] $+H_2O$[c]
1e	22.8	24.0	36.2	41.7
1m	19.0	20.0	30.0	34.0
1i	40.8[e]	51.5	53.6	63.4
1j	25.8[e]	47.1	36.8	58.3
1i-D	17.2	17.7	21.0	23.2

a) In acetonitrile containing 0.1 M TEAP at 25 °C; voltage sweep rate, 30 mVs^{-1}; concentration of **1**, *ca.* 2 mM. *b*) Saturated with oxygen. *c*) In the presence of 1% water. *d*) Deoxygenated with Ar. *e*) The peak current was sensitive to small amounts of water contaminating the medium.

Effects of added water and dissolved oxygen on the voltammetry of **1** were examined. Typical results on the first anodic peak are shown in Table II. In the case of **1** derived from acyclic secondary amines (except for dimethyl- and diethylamines), the voltammetric peaks (including the second and the third peaks) were little affected by a small amount of water (<1%) provided that the medium was saturated with oxygen (*cf.* the results for **1e** and **m** in Table II). On the other hand, the first anodic peak of **1** derived from cyclic amines and dimethyl- and diethylamines increased with the water content and a new peak appeared at the expense of the third anodic peak (Fig. 2), indicating that the enhanced i_p/C values (Table I) for these nitrosamines can be ascribed to the effect of trace amounts of water unavoidably contaminating the medium. Although the new peak appeared at the potential region of the third anodic peak, the origin of the two peaks cannot be the same, because on electrolysis of these nitrosamines in the presence of added water the corresponding nitramines **2** were not obtained. When the oxygen in the medium was removed by bubbling argon gas, the first anodic peak of **1** increased without exception and the second and third peaks became obscure; under these conditions, addition of water enhanced the first anodic peak further. However, the effects of water and oxygen seem to be diminished by substituting the α-hydrogens of **1** with heavier isotopes, as exemplified by the results for the α-deuterated derivative (**1i-D**) of nitrosopiperidine (see Table II).

Macroscale Electrolysis

Table III shows typical results of exhaustive controlled potential electrolysis of some selected nitrosamines at ambient temperature. These results agree well with the voltammetric behavior of **1** described above. (i) Both the nitramines **2** and the β-ketonitrosamines **3** were isolated in the electrolysis of **1** which gave three anodic peaks on cyclic voltammetry in the presence of oxygen (runs 1 and 4), while in the case of **1** without the second anodic peak, the corresponding β-ketonitrosamine was not obtained (runs 8 and 9). (ii) On electrolysis of **1i** in the presence of water (run 11 and *cf.* Table I), nitropiperidine **2i** was not formed and the coulometric *n*-value increased. However, the effects of added water on the electrolysis of other nitrosamines examined, including **1i-D**, were relatively small. (iii) When the electrolysis was carried out in deoxygenated acetonitrile, neither the nitramine **2** nor the β-ketonitrosamine **3** was obtained and the *n*-value increased.[9] The nature of the products in these electrolyses is still uncertain, though small amounts of *N*-alkylacetamides were detected in some cases (see runs 3 and 7).

The effects of alkyl chain length of **1** on the product distribution were examined. For this purpose, it is more practical to carry out the electrolysis at a constant current and to interrupt it at an early stage of the procedure. Constant current electrolysis was found to give essentially

TABLE III. Results of Controlled Potential Electrolysis of **1**[a]

No.	Compound (Amount/mmol)	Conditions[b]	E_{an}[c]	*n*-Value (F per mol)	Products identified (Yield, %)[d]
1	**1e** (0.7)	$+O_2$	1.80	1.4	**2e** (52), **3e** (6), A-1[e] (trace)
2	**1e** (0.7)	$+O_2$, $+H_2O$	1.80	1.7	**2e** (41), **3e**[f]
3	**1e** (0.7)	$-O_2$	1.80	>3	**2e** and **3e** (none), A-2[g] (7)[h]
4	**1m** (0.5)	$+O_2$	1.65	1.2	**2m** (54), **3m** (18), A-3[i] (7)
5	**1m** (0.5)	Air	1.65	1.3	**2m** (55), **3m** (13), A-3[i] (8)
6	**1m** (0.5)	$+O_2$, $+H_2O$	1.65	1.5	**2m** (50), **3m** (14), A-3[i] (7)
7	**1m** (0.5)	$-O_2$	1.65	2.9	**2m** and **3m** (none), A-3[i] (15)
8	**1d** (1.0)	$+O_2$	1.88	2.5	**2d** (36)
9	**1i** (0.6)	$+O_2$	1.90	2.0	**2i** (42)
10	**1i** (0.6)	Air	1.90	2.0	**2i** (54)
11	**1i** (0.6)	$+O_2$, $+H_2O$	1.90	>4	**2i** (none)
12	**1i** (0.6)	$-O_2$	1.90	>4	**2i** (none)
13	**1i**-D (0.6)	Air	1.90	1.6	**2i**-D (64)
14	**1i**-D (0.6)	$+O_2$, $+H_2O$	1.90	1.8	**2i**-D (50)

a) In acetonitrile containing 0.1 M TEAP at ambient temperature. *b*) $+O_2$, saturated with oxygen; $-O_2$, deoxygenated with Ar; Air, under a normal atomosphere; $+H_2O$, in the presence of 1% water. *c*) Anode potential, V *vs.* S.C.E. *d*) Determined by GLC. The low yield of **3e** (runs No. 1, *cf.* Table IV) can be partly ascribed to its decomposition under the GLC conditions. *e*) *N*-Butylacetamide. *f*) Not determined. *g*) *N*-Butyl-*N*-(2-acetylaminobutyl)nitrosamine (see Experimental). *h*) Isolated yield. *i*) *N*-Cyclohexylacetamide.

TABLE IV. Results of Constant Current Electrolysis of **1**[a]

Compound	Yield (%)[b] of		Yield (%) of **1** recovered	*n*-Value[b]	No. of H^+ liberated[c]
	2	**3**			
1b	29	—	87	3.0	3.0
1d	32	—	83	2.0	1.8
1c	55	29	72	1.2	1.6
1e	55	35	71	1.2	1.3
1f	52	30	72	1.4	1.5
1g	52	34	70	1.2	1.1

a) In acetonitrile containing 0.1 M TEAP and saturated with oxygen at 0 °C; amount of **1**, *ca.* 1 mmol; current density, 0.5 mA/cm^2; geometric electrode area, 9.4 cm^2; 0.35 F per mol of **1** was allowed to consume; the results are averages of 3 runs. *b*) Based on the amount of **1** consumed. *c*) Per molecule of **1** consumed.

the same results as those obtained in controlled potential electrolysis. Since β-ketonitrosamines **3** are rather unstable and their oxidation potentials are close to those of the parent nitrosamines, prolonged electrolysis and losses during isolation are liable to reduce the apparent yields. As seen in the typical examples (Table IV), where the yields of the products were determined by high-performance liquid chromatography (HPLC), a straight alkyl chain larger than *n*-propyl does not seem to change the reaction process significantly. For these nitrosamines the yields of **3** increased as compared to the results in Table III. However, the [**2**]/[**3**] product ratio tended to vary with small changes in the electrolysis conditions such as temperature, amount of water contaminating the medium, the flow rate of oxygen passing over the anolyte (see Experimental), current density, *etc.* As expected from the results of cyclic voltammetry, β-oxygenated products were not detected in the electrolysis of **1b** and **d**. In all cases, the number of protons liberated roughly coincides with the *n*-value based on the consumed substrate (apparent *n*-value) (Table IV, columns 5 and 6).

Although the apparent *n*-values for **1c** and **e**—**g** (Table IV) suggest that the numbers of

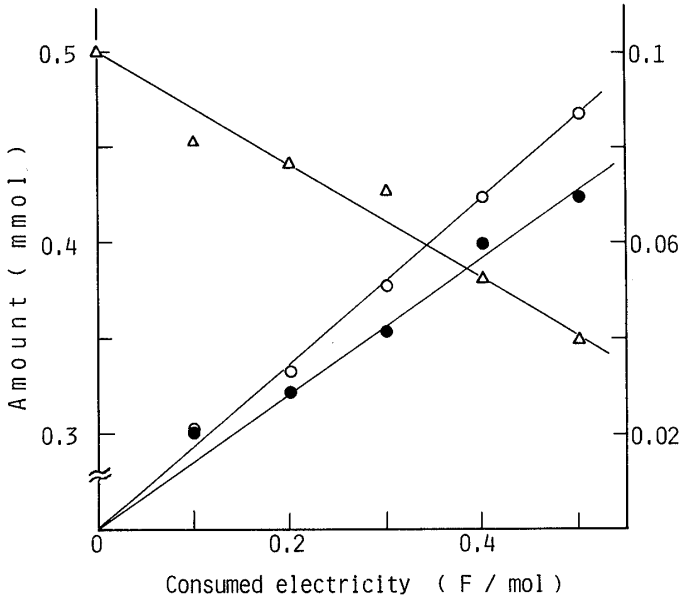


Fig. 3. Change in the Amounts of **1e**, **2e**, and **3e** During the Constant Current Electrolysis of **1e**

Triangles, **1e** (left ordinate). Open circles and solid circles, **2e** and **3e**, respectively (right ordinate). In acetonitrile (25 ml) containing 0.1 M TEAP and saturated with oxygen at 0 °C; initial amount of **1e**, 0.50 mmol; current density, 0.5 mA/cm^2. Each point represents the average of 3 runs.

electrons required for the formation of **2** and **3** (true *n*-values) are both less than two, the exact value for each compound is not clear from the results described above because the combined yield of **2** and **3** is not quantitative. However, when the electrolysis of **1e** was carried out with an amount of the substrate smaller than that in Table IV, the sum of the yields of **2e** and **3e** was found to be almost quantitative at the early stage of the electrolysis (consumed electricity <0.6 F per mol of **1e**). The results are illustrated in Fig. 3, where the concentrations of the substrate and the products are linearly correlated with the electricity allowed to consume. The apparent *n*-value under these conditions was calculated to be 1.5 (based on the amount of products) or 1.6 (based on the consumed substrate) and the average yields of **2e** and **3e** are 54 and 46%, respectively, indicating that the true *n*-values are $n=1$ for **2** and $n=2$ for **3** or *vice versa*.[10] Since the oxidation numbers required to convert **1** to **2** and to **3** are two and four, respectively, it seems reasonable to conclude that the *n*-value for **2** is unity and that for **3** is two.

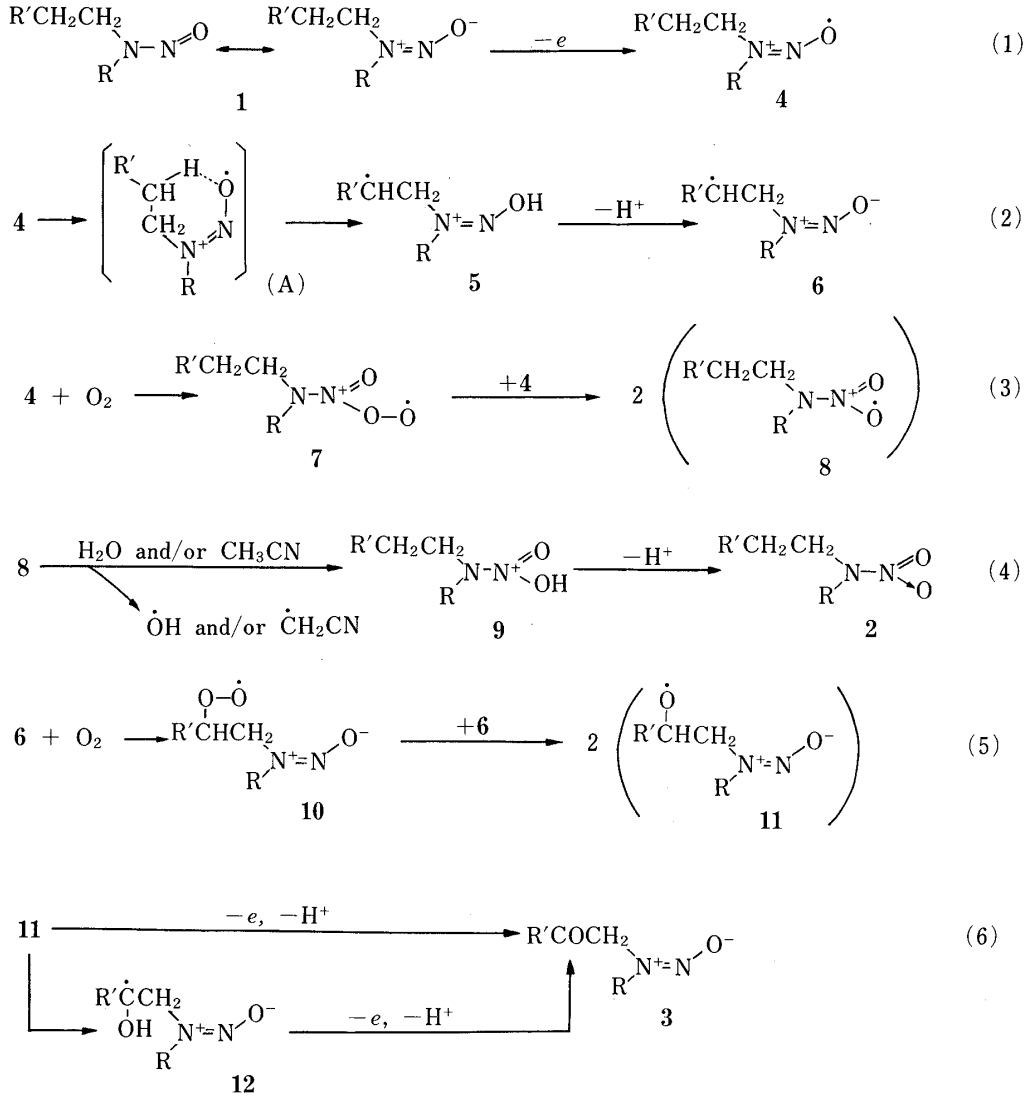
In order to confirm the source of oxygen incorporated into the products **2** and **3**, constant current electrolysis of **1e** was carried out in acetonitrile saturated with $^{18}O_2$ (see Experimental), and the products isolated were analyzed by mass spectroscopy. The labeled oxygen atom was incorporated in **2e** almost quantitatively, but it was not found in **3e**. Direct analysis of the electrolysis solution by mass spectrometry combined with gas chromatography (GC-MS) was attempted, but unambiguous evidence for the incorporation of ^{18}O into **3e** was not obtained owing to the thermal decomposition of **3e** under the experimental conditions. When the electrolysis was performed in acetonitrile containing 1% ^{18}O enriched water (50 atom%), the oxygen atom was not found in either of the products **2e** and **3e**. Thus, the origin of the oxygen atom in the carbonyl group of **3** could not be verified. However, the following observations suggest that it comes from the oxygen dissolved in the medium. In the constant current electrolysis of **1e** under an argon atmosphere, the formation of **3e** as well as **2e** was again negligible, though their detections were attempted directly by HPLC of the electrolysis solution. When **3e** (10 mg) was dissolved in a mixture of acetonitrile (0.4 ml) and $H_2{}^{18}O$ (99 atom%, 0.1 ml) containing 0.024 M HCl and the solution was allowed to stand for 24 h at ambient temperature, the oxygen atom of the carbonyl group of **3e** was completely exchanged with ^{18}O: no oxygen exchange was observed without HCl. Consequently, if a β-ketonitrosamine containing ^{18}O at the carbonyl group is formed in the electrolysis with $^{18}O_2$, the isotope can be lost during the work-up, for which preparative thin layer chromatography on

silica gel is required.[11] It is well known empirically that silica gel is acidic and a silica gel plate used for chromatography contains a considerable amount of water.

The amount of dioxygen consumed in the constant current electrolysis of **1e** (carried out at ambient temperature) was measured to be about one-half of the total amount of **2e** and **3e** produced (see Experimental), indicating that both of the atoms in one oxygen molecule are used to afford the products, or that the reaction regenerates half of the dioxygen consumed.

Discussion

From the results obtained, the pathway shown in Chart 2 can be proposed for the formation of the nitramines **2** and the β-ketonitrosamines **3**. It should be kept in mind, as suggested by the results of cyclic voltammetry, that all the reactions in Chart 2 will take place in the immediate vicinity of the electrode surface.



7+**6** ⟶ **8**+**11** (7)
2(**7**) ⟶ 2(**8**)+O_2 (9)
7+**10** ⟶ **8**+**11**+O_2 (11)

4+**10** ⟶ **8**+**11** (8)
2(**10**) ⟶ 2(**11**)+O_2 (10)

Chart 2

In the parent nitrosamine **1**, a predominant contribution of the dipolar structure has been well documented,[12] and the structure of the radical cation **4** has been confirmed for several nitrosamines.[3,13] Since the unpaired electron in **4** is strongly localized on the nitrosyl nitrogen,[3,13] the steps in Eq. 3, which are similar to those suggested for the reaction of aminyl radicals with oxygen to give nitroxide,[14] seem reasonable. Hydrogen abstraction from the solvent, such as that proposed in Eq. 4, has been concluded to occur in the electrochemical oxidation of amines[15] and amides[16] in acetonitrile, and in the silver (II)-catalyzed decarboxylation of carboxylic acids in acetonitrile–water mixture.[17] Succinonitrile is one of the possible products from the cyanomethylene radical,[15,16] and similarly hydrogen peroxide may be formed from the hydroxy radical. However, attempts to detect these species in the electrolysis solution were unsuccessful. Hydrogen peroxide, if formed, was found to be oxidized further under the electrolysis conditions. No other product characteristic of cyanomethylene and/or hydroxy radicals was detected. Thus, the step **8** to **9** in Eq. 4 is tentative.

The formation of the β-ketonitrosamines **3** should begin with the intramolecular hydrogen abstraction of the radical cation **4** through the six-membered-ring transition state (A), as suggested in the electrochemical oxidation of ketones,[18] to give the radicals **5** and/or **6** [Eq. 2]. Such a transition state is highly unfavorable for the radical cations of **1** derived from cyclic amines, and in the electrolysis of nitrosopiperidine (**1i**), the corresponding β-ketonitrosamine was not obtained. The reactions in Eq. 5 are proposed by analogy with those suggested in the autoxidation of organic substances. It is not clear whether the radical **11** directly undergoes electron transfer to give the final product **3** or whether **11** is first transformed to the alkyl radical **12** followed by further oxidation at the electrode. 1,2-Hydrogen shift of alkoxy radicals has been demonstrated in aqueous solutions by Gilbert *et al.*[19] In the case of **11**, water contaminating the medium may catalyze the transformation.

In addition to the reactions in Eqs. 3 and 5, Eqs. 7—11 are also feasible for the formation of the intermediate **8** and **11**. From the present results, it is not clear which processes are the best choice.

Intermediacy of β-hydroxynitrosamines, $RCH(OH)CH_2N(R')NO$ (**13**), might be considered in the pathway to β-ketonitrosamines **3**. However, the following observations suggest that this is unlikely. (i) A β-hydroxynitramine, which is expected to be formed by further oxidation of **13** [*cf.* Eqs. 1—4], was not detected in the products. (ii) When a β-hydroxynitrosamine, $CH_3CH_2CH(OH)CH_2N(Bu)NO$ (**13e**), prepared by a known method[20] was subjected to electrolysis under the conditions described in Fig. 3, the corresponding β-ketonitrosamine **3e** was formed in only 25% yield together with several unidentified products. On the other hand, the results in Fig. 3 require that the *Z*-isomer[12,21] in **13e** should be converted exclusively to **3e**. Thus, although the ratio of *E*- to *Z*-isomer in **13e** could not be determined, the yield of **3e** is expected to be at least 50% if the isomer ratio is 1 : 1.

The effects of added water on the electrochemistry of the nitrosamines derived from cyclic amines (**1i—k**) suggest another reaction of the radical cation **4** in addition to those shown in Chart 2. Hydrogen atoms on the carbon α to the nitrosamino group are known to be acidic, and the acidity is enhanced when the α-C–H bond is perpendicular to the plane of the nitrosamino group as in the case of nitrosopiperidines.[22] Since the radical cation **4** has a net positive charge, the α-hydrogens must be more acidic than those in the parent nitrosamine. Thus, in the case of **1i—k** with a sufficient amount of water, which will act as a base, the decomposition of **4** to give a neutral radical can take place in preference to the other reactions. The latter radical will undergo further electron transfer, leading to unidentified products. As expected from these considerations, the effects of water were markedly diminished in the electrochemistry of α-deuterated nitrosopiperidine **1i**-D.

In the absence of oxygen, the formation of *N*-cyclohexylacetamide and β-acetamidodi-

butylnitrosamine in the electrolysis of **1m** and **1e**, respectively (Table III), suggests the existence of electrode processes producing alkyl cations. Reactions of electrochemically generated alkyl cations with acetonitrile to give *N*-alkylacetamides are well known.[23] However, the low yields of the products suggest the possibility of other reactions, which should be elucidated by further investigations.

Experimental

Materials——The nitrosamines **1** were prepared by nitrosation of the corresponding amines with sodium nitrite in acidic solution, purified by recrystallization [**1d**, from petroleum ether, mp 48 °C; **1m**, from hexane, mp 105 °C] or by distillation, and gave the expected analytical results. α-Deuterated nitrosopiperidine (**1i**-D) was prepared as follows. A solution of **1i** (300 mg) in a mixture of D_2O (5 ml), MeOD (1 ml), and NaOD (50% in D_2O, 1 ml) was refluxed for 2 h. The solution was extracted with $CHCl_3$ (3 × 10 ml). The chloroform was removed under reduced pressure, and the residue was subjected to column chromatography on silica gel with $CHCl_3$ as the eluant. The mass spectrum of **1i**-D showed that it is composed of **1i** (1.4%), **1i**-d_1 (8.6%), **1i**-d_2 (27.5%), **1i**-d_3 (39.9%), and **1i**-d_4 (22.6%). Acetonitrile was purified as described previously.[24] TEAP was prepared from Et_4NBr and $HClO_4$, recrystallized from EtOH, and stored over P_2O_5 under reduced pressure. $^{18}O_2$ (99 atom%) and $H_2{}^{18}O$ (50 and 99 atom%) were obtained from CEA, France.

Apparatus——Cyclic voltammetry, controlled potential electrolysis, and constant current electrolysis were carried out essentially as described previously.[24] Infrared (IR), nuclear magnetic resonance (NMR), and mass spectra (MS) were obtained on JASCO A-202, Hitachi R-20A, and JEOL JMS-D300 spectrometers, respectively. Gas-liquid chromatography (GLC) was performed using a JEOL JGC-20K gas chromatograph connected with a Takeda Riken TR-2215A digital integrator: PEG-20M was used as the packing. HPLC was carried out using a Waters 6000-A solvent delivery system with a U6K universal injector and a Shimadzu SPD-2A spectrophotometric detector: Bondapack C_{18}-Corasil and 50—80% aqueous methanol were used.

Identification and Determination of Products from Macroscale Electrolysis——Electrolyses were carried out in an H-type cell with 50 ml capacity (anode compartment). A glassy carbon plate and a stainless steel plate were used as the anode and the cathode, respectively. Typical examples of the procedures are described below.

The nitrosamine **1m** (105 mg) was subjected to electrolysis in acetonitrile (40 ml) containing 0.1 M TEAP at 1.80 V at room temperature until the value of the current became <2% of the initial value (exhaustive electrolysis, see Table III). Before electrolysis the anolyte was saturated with oxygen, and during the course of electrolysis a slow stream of oxygen was passed over the anolyte. From the current–time curve 58 C, which corresponded to $n=1.2$, was found to have been consumed. The anolyte was adjusted to 50.0 ml by addition of acetonitrile in a volumetric flask. The resulting solution was subjected to GLC analysis. In a separate run with a larger amount of the substrate, the electrolyzed solution was evaporated under reduced pressure, and the residue was extracted with ether (3 × 50 ml). The ether was removed under reduced pressure, and the residue was subjected to preparative thin layer chromatography on silica gel with benzene–hexane (1 : 1) as the developing solvent. Three products were isolated. *N*-Nitrodicyclohexylamine (**2m**), mp 120 °C. *Anal.* Calcd for $C_{12}H_{22}N_2O_2$: C, 63.69; H, 9.80; N, 12.38. Found: C, 63.72; H, 9.99; N, 12.31. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1515 and 1290 (N-NO_2). NMR ($CDCl_3$) δ: 0.80—2.30 (20H, m), 4.00 (2H, m). MS *m/e*: 226 (M^+). *N*-Cyclohexyl-*N*-(2-oxocyclohexyl)nitrosamine (**3m**), solid.[25] *Anal.* Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.08; H, 8.76; N, 12.57. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1725 (C=O), 1450 (N–NO). NMR ($CDCl_3$) δ: 0.60—2.90 (16H, m), 3.00—4.80 (4H, m). MS *m/e*: 224 (M^+). *N*-Cyclohexylacetamide was identified by comparing its IR and NMR spectra with those of an authentic sample prepared from cyclohexylamine and acetyl chloride.

The following compounds[26] were obtained by essentially the same procedure.

N-Nitrodiethylamine (**2b**), oil. *Anal.* Calcd for $C_4H_{10}N_2O_2$: C, 40.67; H, 8.53; N, 23.71. Found: C, 40.66; H, 8.63; N, 22.91. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1510, 1290. NMR ($CDCl_3$) δ: 1.23 (6H, t, $J=8$ Hz), 3.76 (4H, q, $J=8$ Hz). *N*-Nitrodipropylamine (**2c**), oil. *Anal.* Calcd for $C_6H_{14}N_2O_2$: C, 49.30; H, 9.65; N, 19.16. Found: C, 48.94; H, 9.80; N, 18.83. IR ν_{max}^{film} cm^{-1}: 1520, 1270. NMR ($CDCl_3$) δ: 0.97 (6H, t, $J=7$ Hz), 1.75 (4H, m), 4.70 (4H, t, $J=7$ Hz). *N*-Nitrodiisopropylamine (**2d**), mp 106—109 °C. *Anal.* Calcd for $C_6H_{14}N_2O_2$: C, 49.30; H, 9.65; N, 19.16. Found: C, 49.14; H, 9.88; N, 19.13. IR ν_{max}^{KBr} cm^{-1}: 1510, 1300. NMR ($CDCl_3$) δ: 1.35 (12H, d, $J=7$ Hz), 4.40 (2H, br). *N*-Nitrodibutylamine (**2e**), oil. *Anal.* Calcd for $C_8H_{18}N_2O_2$: C, 55.15; H, 10.41; N, 16.08. Found: C, 55.32; H, 10.36; N, 16.11. IR ν_{max}^{film} cm^{-1}: 1520, 1290. NMR ($CDCl_3$) δ: 0.9—2.0 (14H, m), 3.73 (4H, t, $J=7$ Hz). *N*-Nitrodiamylamine (**2f**), oil. *Anal.* Calcd for $C_{10}H_{22}N_2O_2$: C, 59.38; H, 10.96; N, 13.85. Found: C, 59.58; H, 11.00; N, 13.83. IR ν_{max}^{film} cm^{-1} 1520, 1280. NMR ($CDCl_3$) δ: 0.7—2.0 (18H, m), 3.70 (4H, t, $J=7$ Hz). *N*-Nitrodihexylamine (**2g**), oil. *Anal.* Calcd for $C_{12}H_{26}N_2O_2$: C, 62.57; H, 11.38; N, 12.16. Found: C, 62.69; H, 11.38; N, 12.06. IR ν_{max}^{film} cm^{-1}: 1520, 1275. NMR ($CDCl_3$) δ: 0.7—2.0 (22H, m), 3.70 (4H, t, $J=7$ Hz). *N*-Nitropiperidine (**2i**), oil. *Anal.* Calcd for $C_5H_{10}N_2O_2$: C, 46.15; H, 7.75; N, 21.52. Found: C, 45.10; H, 7.55; N, 20.26. IR ν_{max}^{film} cm^{-1}: 1515, 1280. NMR ($CDCl_3$) δ: 1.30—2.00 (6H, m), 3.50—4.00 (4H, m). MS *m/e*: 130 (M^+).

N-Propyl-*N*-(2-oxopropyl)nitrosamine (**3c**), oil. *Anal.* Calcd for $C_6H_{12}N_2O_2$: C, 49.99; H, 8.39; N, 19.43. Found: C, 50.09; H, 8.51; N, 19.05. IR ν_{max}^{film} cm^{-1}: 1730 (C=O), 1430 (N–NO). NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7 Hz), 1.80 (2H, m), 2.18 (3H, s, CH_3–CO), 4.15 (2H, t, J=7 Hz, –CH_2–CH_2–N), 4.21 (2H, s, CO–CH_2–N): these spectra are for the *Z*-isomer.[12,21] The *E*-isomer is characterized by NMR signals at 2.25 (3H, s, CH_3–CO), 3.55 (2H, t, J=7 Hz, –CH_2–CH_2–N), and 4.93 (2H, s, CO–CH_2–N). The NMR spectra suggested that the product **3c** is a mixture of the two isomers with *E*/*Z* ratio of 1/6. *N*-Butyl-*N*-(2-oxobutyl)nitrosamine (**3e**), oil. *Anal.* Cacld for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.37; N, 16.26. Found: C, 54.87; H, 9.21; N, 15.79. IR ν_{max}^{film} cm^{-1}: 1730, 1460. NMR ($CDCl_3$) δ: 0.85—2.0 (10H, m), 2.48 (2H, q, J=7 Hz, CH_3–CH_2–CO), 4.15 (2H, t, J=7 Hz, –CH_2–CH_2–N), 4.18 (2H, s, CO–CH_2–N) (*Z*-isomer); 2.53 (2H, q, J=7 Hz, CH_3–CH_2–CO), 3.55 (2H, t, J=7 Hz, –CH_2CH_2–N), 4.89 (2H, s, CO–CH_2–N) (*E*-isomer); *E*/*Z*=1/8. *N*-Amyl-*N*-(2-oxoamyl)nitrosamine (**3f**), oil. *Anal.* Calcd for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99. Found: C, 59.97; H, 9.98; N, 13.73. IR ν_{max}^{film} cm^{-1}: 1730, 1460. NMR ($CDCl_3$) δ: 0.8—2.0 (14H, m), 2.43 (2H, t, J=7 Hz, –CH_2–CH_2–CO), 4.16 (2H, t, J=7 Hz, –CH_2–CH_2–N), 4.18 (2H, s, CO–CH_3–N) (*Z*-isomer); 2.48 (2H, t, J=7 Hz, –CH_2–CH_2–CO), 3.54 (2H, t, J=7 Hz, –CH_2–CH_2–N), 4.88 (2H, s, CO–CH_2–N) (*E*-isomer); *E*/*Z*=1/7. *N*-Hexyl-*N*-(2-oxohexyl)nitrosamine (**3g**), oil. *Anal.* Calcd for $C_{12}H_{24}N_2O_2$: C, 63.12; H, 10.59; N, 12.27. Found: C, 62.95; H, 10.47; N, 12.05. IR ν_{max}^{film} cm^{-1}: 1730, 1460. NMR ($CDCl_3$) δ: 0.8—2.0 (18H, m), 2.43 (2H, t, J=7 Hz, –CH_2–CH_2–CO), 4.16 (2H, t, J=7 Hz, –CH_2–CH_2–N), 4.18 (2H, s, CO–CH_2–N) (*Z*-isomer); 3.54 (2H, t, J=7 Hz, –CH_2–CH_2–N), 4.88 (2H, s, CO–CH_2–N) (*E*-isomer); *E*/*Z*=1/9.

N-Butylacetamide was identified by comparing its IR and NMR spectra with those of an authentic sample prepared from butylamine and acetyl chloride. *N*-Butyl-*N*-(2-acetylaminobutyl)nitrosamine was obtained in the electrolysis of **1e** under an Ar atmosphere (Table III, Run 3). Although this compound was not analytically pure, the spectroscopic data support the structure. IR ν_{max}^{film} cm^{-1}: 3300 (NH), 1660 (C=O), 1460 (N–NO). NMR ($CDCl_3$) δ: 0.7—1.9 (12H, m), 1.98 (3H, s, CO–CH_3), 2.5—4.5 (5H, m), 5.0—6.1 (1H, m, NH). MS (chemical ionization with NH_3) *m*/*e*: 216 [$(M+1)^+$], 233 [$(M+18)^+$].

The procedure of constant current electrolysis (Table IV and Fig. 3) was essentially the same as that of controlled potential electrolysis except that the electrolysis was carried out at a constant current at 0 °C and was interrupted when a pre-determined amount of electricity had been consumed. The anolyte was adjusted to 50.0 ml by addition of acetonitrile in a volumetric flask, and a part of the resulting solution was subjected to HPLC analysis. From the remainder of the solution, 10.0 ml aliquots were withdrawn and mixed with 40 ml of water. The mixture was subjected to potentiometric titration to determine the amount of protons liberated.

Electrolysis with $^{18}O_2$——The nitrosamine **1e** (195 mg) in acetonitrile (40 ml) containing 0.1 M TEAP was placed in the anode compartment of the H-cell. The anolyte was deoxygenated with Ar gas, and then equilibrated with $^{18}O_2$ (1 atom) supplied from a gas burette attached to the cell. The system was subjected to constant current electrolysis (10 mA; anode area, 5 cm^2) at room temperature for 4 h (144 C, 1.2 F per mol of the substrate). The products **2e** and **3e** isolated by preparative thin layer chromatography were analyzed by mass spectroscopy. The labeled oxygen atom was incorporated in **2e** almost quantitatively, but it was not found in **3e**. Oxygen consumption during the electrolysis of **1e** was measured in separate runs with unlabeled O_2: **1e**, 1.00 mmol; at room temperature; 10 mA, 2 h (72 C, 0.74 F per mol of **1e**). The following results were obtained. Run 1: **1e** recovered, 0.43; **2e**, 0.29; **3e**, 0.20; O_2 consumed, 0.28 mmol. Run 2: **1e**, 0.26; **2e**, 0.27; **3e**, 0.35; O_2, 0.35 mmol.

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References and Notes

1) A part of this paper was presented at the 7th International Symposium on *N*-Nitroso Compounds, Tokyo, September 1981.
2) M. Masui, K. Nose, A. Tanaka, E. Yamakawa, and H. Ohmori, *Chem. Pharm. Bull.*, **29**, 3758 (1981).
3) M. Masui, K. Nose, H. Ohmori, and H. Sayo, *J. Chem. Soc., Chem. Commun.*, **1982**, 879; M. Masui, H. Ohmori, C. Ueda, K. Nose, and H. Sayo, *Chem. Pharm. Bull.*, **31**, 3385 (1983).
4) See for example, C. J. Michejda, M. B. Kroeger-Koepke, S. R. Koepke, and R. J. Kupper, "*N*-Nitrosamines," ed. by J. P. Anseln, ACS Symposium Series 101, 1979, Chapter 5.
5) F. W. Kruger, *Z. Krebsforsch.*, **76**, 145 (1971); *idem, ibid.*, **79**, 90 (1973); *idem, ibid.*, **80**, 189 (1973).
6) At lower temperatures, some of the nitrosamines **1** showed a reversible or quasi-reversible anodic peak (ref. 3).
7) The peak potentials varied slightly with the identity of the working electrode. The anodic peaks at around 2.5 V reported previously (ref. 2) have been found to be due to the background.
8) The identification of the peaks due to **2** and **3** can be performed more clearly at this temperature than at 25 °C, though similar voltammograms were obtained at the latter temperature.
9) In some cases small amounts of **2** and **3** were detected in the electrolysis solution, probably because of incomplete deoxygenation of the medium.
10) Algebraically, the results suggest n=2 for **2** and n=1 for **3** as the better approximation. However, the opposite

case cannot be ruled out because of the possibility of experimental error.
11) In the exchange experiment, work-up by chromatography is not required.
12) C. E. Looney, W. E. Phillips, and E. L. Reilly, *J. Am. Chem. Soc.*, **79**, 6136 (1957); G. J. Karabatsos and R. A. Taller, *ibid.*, **86**, 4373 (1964); Y. L. Chow and C. J. Colon, *Can. J. Chem.*, **46**, 2827 (1968); R. K. Harris and R. A. Spragg, *J. Mol. Spectrosc.*, **23**, 158 (1967); *idem, ibid.*, **30**, 77 (1969); R. K. Harris, T. Pryce-Jones, and F. J. Swinbourne, *J. Chem. Soc., Perkin Trans. 2*, **1980**, 476; T. J. Hansen, R. M. Angeles, L. K. Keefer, C. S. Day, and W. Gaffield, *Tetrahedron*, **37**, 4143 (1981).
13) S. P. Mishra and M. C. R. Symons, *J. Chem. Soc., Perkin Trans. 2*, **1977**, 1449.
14) T. Toda, E. Mori, H. Horiuchi, and K. Murayama, *Bull. Chem. Soc. Jpn.*, **45**, 1802 (1972); J. R. Roberts and K. U. Ingold, *J. Am. Chem. Soc.*, **95**, 3228 (1973); M. B. Eleveld and H. Hogeveen, *Tetrahedron Lett.*, **1984**, 785.
15) C. D. Russell, *Anal. Chem.*, **35**, 1291 (1963); P. J. Smith and C. K. Mann, *J. Org. Chem.*, **34**, 1821 (1969).
16) J. F. O'Donnel and C. K. Mann, *J. Electroanal. Chem.*, **13**, 157 (1967).
17) W. E. Fristad, M. A. Fry, and J. A. Klang, *J. Org. Chem.*, **48**, 3575 (1983).
18) J. Y. Becker, L. R. Byrd, L. L. Miller, and Y.-H. So, *J. Am. Chem. Soc.*, **97**, 853 (1975); S. Hammerum and O. Hammerich, *Tetrahedron Lett.*, **1979**, 5027.
19) B. C. Gilbert, R. G. G. Holems, H. A. H. Laue, and R. O. C. Norman, *J. Chem. Soc., Perkin Trans. 2*, **1976**, 1047 and references cited therein.
20) M. Okada, E. Suzuki, and M. Iiyoshi, *Chem. Pharm. Bull.*, **26**, 3891 (1978).
21) N. Egger, L. Hoesch, and A. S. Dreiding, *Helv. Chim. Acta*, **65**, 2558 (1982); B. Libereck, J. Ciarkowski, K. Plucinska, and K. Stachowiak, *Org. Mag. Resonance*, **18**, 143 (1982).
22) D. Seebach and D. Enders, *Angew. Chem. Int. Ed. Engl.*, **14**, 15 (1975) and references therein.
23) L. Eberson and J. H. P. Utley, "Organic Electrochemistry," 2nd ed., ed. by M. M. Baizer and H. Lund, Marcel Dekker, Inc., New York, 1983, Chapter 13.
24) H. Ohmori, A. Matsumoto, and M. Masui, *J. Chem. Soc., Perkin Trans. 2*, **1980**, 347.
25) The value of mp could not be determined because the compound gradually decomposed on heating.
26) The values of mp or bp for most of the products were not determined, but the analytical and spectroscopic data were consistent with the proposed structures.