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Anodic Oxidation of Amines. IV.[1] Cyclic Voltammetry and Controlled Potential Electrolysis of 4-Diethylaminoantipyrine in Acetonitrile

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The anodic oxidation of 4-diethylaminoantipyrine (I) has been investigated in acetonitrile at a glassy-carbon electrode. The first step in the anodic oxidation of I is a quasi-reversible one-electron transfer to form the blue-violet cation radical (II) just as that of 4-dimethylaminoantipyrine (DMA). However, the lifetime of II is much longer than that of the cation radical of DMA (DMA$\cdot^+$). A slightly resolved ESR spectrum of II was obtained. In the absence of oxygen II decays in a first-order manner up to 50% decay, whereas in the presence of oxygen II decays in a second-order manner up to 60% decay. The difference in the behaviors between II and DMA$\cdot^+$ is interpreted on the basis of a much less reactivity of II towards disproportionation than that of DMA$\cdot^+$. A mechanism for the disappearance of II in the absence of oxygen is suggested.

Previously we reported on the anodic oxidation of 4-dimethylamino, 4-methylamino-, 4-amino-, and unsubstituted antipyrines at a glassy-carbon electrode in acetonitrile.[1] The first step in the anodic oxidation of 4-dimethylaminoantipyrine (DMA) was a quasi-reversible one-electron transfer from the lone-pair electrons on the dimethylamino-nitrogen atom to form the cation radical (DMA$\cdot^+$). The blue-violet cation radical decayed in a second-order manner with a rate constant of *ca.* $13\text{M}^{-1}\cdot\text{sec}^{-1}$ at 25° as determined by spectrophotometry. A well resolved electron spin resonance (ESR) spectrum of DMA$\cdot^+$ was obtained and interpreted on the basis of Hückel molecular orbital (HMO) calculation.

To obtain more detailed information on the stability and the decomposition of DMA$\cdot^+$ we studied the anodic oxidation of 4-diethylaminoantipyrine (I) and the kinetics of the decomposition of the cation radical which was generated electrochemically from I. Chemical and enzymatic oxidations of DMA,[3] and metabolism of DMA,[4a,d] sulpyrin,[4b] and 4-alkylamino-antipyrines[4c] have been studied extensively by many workers. However, no study has been made on I.

Results

Cyclic Voltammetry

Cyclic voltammetry of I in acetonitrile containing 0.1M $NaClO_4$ showed four anodic waves, with peak potentials (E_p) of 0.39, 0.88, 1.18 and 1.38 V *vs.* S.C.E., respectively at a potential scan rate (v) of 0.05 $V\cdot sec^{-1}$. Typical voltammograms are shown in Fig. 1. Upon reversal of the scan direction at 1.0 V, the first and the second waves gave cathodic counterparts with

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[1] Part III: H. Sayo and M. Masui, *J. Chem. Soc. Perkin II*, **1973**, 1640.

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[3] W. Awe and R. Buerhop, *Arch. Pharm.*, **293**, 462 (1960); W. Awe, E. Stoy-Geilich, R. Buerhop, and H. Bammel, *Arzneim. Forsch.*, **10**, 796 (1960); F. Pechtold, *ibid.*, **14**, 258 (1964); B.N. La Du, L. Gaudette, N. Trousof, and B.B. Brodie, *J. Biol. Chem.*, **214**, 741 (1955).

[4] *a*) H. Yoshimura, H. Shimeno, and H. Tsukamoto, *Yakugaku Zasshi*, **90**, 1406 (1970); *b*) H. Nogami, M. Hanano, S. Awazu, and K. Imaoka, *ibid.*, **90**, 378 (1970); *c*) H. Yoshimura, H. Shimeno, and H. Tsukamoto, *ibid.*, **88**, 89 (1968); *d*) H. Niwa, N. Hikichi, and H. Sasaki, *ibid.*, **95**, 1050 (1975).

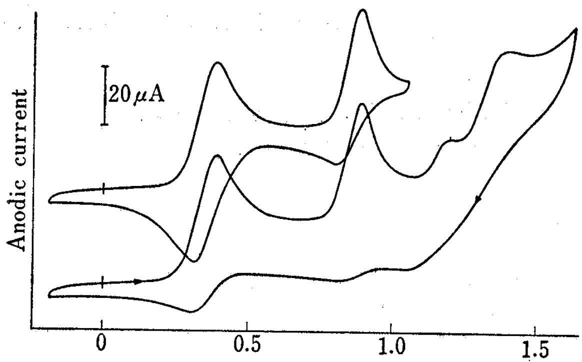

Fig. 1. Cyclic Voltammogram of 4-Diethylaminoantipyrine (2 mM) in Acetonitrile

scan rate 0.05 V·sec^{-1}

E_p of 0.30 and 0.80 V. Thus the first and the second waves had some reversibility. No extra wave was observed in a multiple sweep. The peak current (i_p) of the first and the second waves varied linearly with $v^{1/2}$ at v=0.0125—0.2 V·sec^{-1}. Therefore, no chemical complication was found for both waves in the time scale of voltammetry.

As shown in Fig. 2, the ratio of the cathodic to anodic current (i_{pc}/i_{pa}) of the first wave was independent of v, being 0.99—1.00, whereas that of the second wave increased with increasing v to a limiting value of *ca.* 0.66. As the scan rate increased from 0.0125 to 0.20 V·sec^{-1}, the separation in peak potentials of anodic and cathodic waves of the first wave increased from 80 to 130 mV, and that of the second wave increased from 70 to 130 mV, suggesting that both waves are quasi-reversible.

Cyclic voltammetry of 4-ethylaminoantipyrine in acetonitrile showed three anodic waves with E_p of 0.35, 1.40, and 1.60, respectively at v=0.05 V·sec^{-1}. Reversal of the scan direction at a potential positive to the first peak produced no cathodic wave.

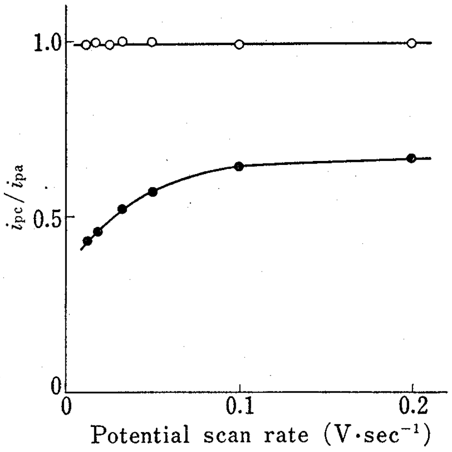

Fig. 2. Variation of the Ratio of the Cathodic to Anodic Current with Scan Rate for the First Wave (○) and the Second Wave (●) of 4-Diethylaminoantipyrine

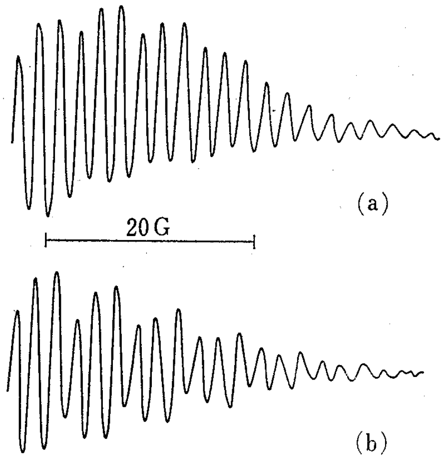

Fig. 3. (a) ESR Spectrum (low field one-half) of 4-Diethylaminoantipy rine Cation Radical; (b) Calculated Spectrum using Coupling Constants given in Table 1 and Line width of 0.7 Gauss (Lorentzian Line Shape)

Controlled Potential Electrolysis

A 2 mM solution of I in acetonitrile containing 0.1M sodium perchlorate was subjected to electrolysis at a glassy-carbon anode at 0.45 V. The solution turned blue-violet and the color deepened with a progress of electrolysis. The electrolysis current decayed steadily with time and reached less than 1% of the initial value (*ca.* 35 min). A coulometric *n*-value (number of Faradays passed per mole of I) of 0.95±0.01 was obtained. The absorption spectrum of the resulting solution had absorption maxima at 327 and 590 nm, and their absorbances decreased with time after electrolysis.

ESR Spectrometry

A 2 mM solution of I in acetonitrile was subjected to electrolysis at 0.45 V, and the solution was allowed to flow to a sample tube in the cavity of an ESR spectrometer. An ESR signal was observed, and its intensity increased with time and reached a maximum after *ca.* 20 min. When the flow of solution was stopped, the intensity of the ESR signal showed a very slow decay. The ESR spectrum of the radical was slightly resolved and had a total spectral width of *ca.* 90 G (Fig. 3). The spectrum was difficult to interpret owing to the large number of coupling constants. Considering the ESR data on DMA$\cdot^+$, a large number of spectra were computed from possible combinations of plausible coupling constants. The spectrum could not be interpreted unequivocally, but the computed one best fitting the experimental data is shown in Fig. 3, and the set of coupling constants used for the simulation is given in Table I together with the results on DMA$\cdot^+$.

TABLE I. ESR Coupling Constants in Gauss

Position	Nucleus	4-Diethylamino-antipyrine cation radical	4-Dimethylamino-antipyrine cation radical
2	N	2.2	2.2
2-Methyl	H(Me)	2.2	2.2
3-methyl	H(Me)	5.9	5.9
4-Amino	N	12.2	11.2
4-Dimethylamino	$H(Me_2)$		13.4
4-Diethylamino	$H((CH_2)_2)$	11.6	

Kinetics of Decomposition of 4-Diethylaminoantipyrine Cation Radical (II) in Acetonitrile

The variation of absorbance (A) of the solution after electrolysis with time was measured at 590 nm just after stopping the electrolysis of I at 0.45 V. The electrolysis was carried out for only 1—4 min to minimize the effect of the chemical and electron transfer reactions. The concentration of II was estimated from the numbers of coulombs consumed in the electrolysis assuming that $n=1$. As described below, the rate of disappearance of II was very slow, so a correction for decomposition of II during the electrolysis was unnecessary.

TABLE II. Data for Decay of 4-Diethylaminoantipyrine Cation Radical (II) measured by Spectrophotometry in Acetonitrile Containing 0.1 M $NaClO_4$ at 25°

C_i[a] (mM)	Time of electrolysis (min)	R_i[b] (mM)	ε $M^{-1}cm^{-1}$	10^5k_1[c] sec^{-1}	k_2[d] $M^{-1}sec^{-1}$	Remarks
1.54	1	0.20	2300	2.68		
1.98	1	0.21	2330	2.70		0.1% H_2O added
2.01	1	0.21	2310	2.57		
3.07	2	0.52	2260	4.33		
2.97	4	0.94	2260	6.37		
1.91	1	0.24	2270		0.78	O_2 present
3.05	1	0.39	2250		0.71	O_2 present
3.39	1	0.38	2300		0.72	O_2 present

a) initial concentration of 4-diethylaminoantipyrine
b) initial concentration of II
c) observed first-order rate constant
d) observed second-order rate constant

In the absence of oxygen plots of log A against time were linear up to 50% decay. However, the first-order rate constant obtained from the above plots, k_1, increased with increasing concentration of II as shown in Table II, indicating that the decomposition of II does not obey a simple first-order process. The molar extinction coefficient of II, ε, was calculated from the intercept of the plots. Addition of a small amount of water (0.1%) to the solution had little effect on the value of k_1, but the presence of oxygen greatly increased the rate of disappearance of II. Furthermore, in the presence of oxygen plots of 1/A against time were linear up to 60% decay, characterizing disappearance of II as a second-order process.

Product Identification

Large-scale controlled potential electrolysis of I in acetonitrile (10—20 mM) at 0.45 V gave an *n*-value of 0.94±0.01. The resulting blue-violet solution was allowed to stand for a day at room temperature. The blue-violet color faded very slowly, and it finally turned light red-brown. The red-brown solution was distilled under reduced pressure. From the distillate acetaldehyde (6.5 mole % of starting I) was determined as 2,4-dinitrophenylhydrazone. The residue was made alkaline by addition of sodium hydroxide solution and steam distilled. From the distillate a small amount of diethylamine (*ca.* 1%) was detected. The residue on distillation was extracted with $CHCl_3$. Evaporation of the extract gave I (72%).

Discussion

Comparing the results on I with those on DMA, it is concluded that the first step in anodic oxidation of I is a quasi-reversible one-electron transfer from the lone-pair electrons of the 4-diethylamino-nitrogen to form the cation radical (II). The differences between the results on I and those on DMA can be ascribed to a difference in the stabilities between two cation radicals. Since disproportionation was considered to be a major process in the decomposition of $DMA\cdot^+$ in acetonitrile, the substitution of diethylamino group for dimethylamino group will result in the enhanced stability of II. The facts that the half-life of II in acetonitrile (*ca.* 0.2 mM) in the absence of oxygen at 25° was more than 7 hours and the value of i_{pc}/i_{pa} of I was 0.995±0.005, compared with that of DMA, 0.88±0.04, substantiate the above consideration. The bulkiness of the diethylamino group is also reflected in the difference in the E_p value between I and DMA, that is, E_p value of the first wave of I is 0.05 V more positive than that of DMA.[1)]

In contrast with the results on $DMA\cdot^+$, the disappearance of II in acetonitrile did not decay in a second-order manner and accelerated in the presence of oxygen. However, this difference can be explained on the basis of a much lower reactivity of II towards disproportionation than that of $DMA\cdot^+$. That is, as to the disappearance of II, the rate of disproportionation of II is comparable to that of the reactions of II with oxygen and with other substances such as bases.

Anodic oxidation of aliphatic amines generally causes scission of a carbon-nitrogen bond and the products are the corresponding secondary amines and aldehydes.[5)] An aminium cation radical has been postulated as an intermediate in the anodic oxidation, but the cation radical was not detected by ESR spectroscopy during the electrolysis except for triethylenediamine.[6)] The relative amount of dealkylation in unsymmetrical amines is predominantly governed by the acidity and number of α-protons, but is also affected by the ease of oxidation of the radical $R_2N\overset{\cdot\cdot}{-}CHR'$.[5b)]

Aliphatic α,β-unsaturated tertiary amines very readily undergo electrochemical oxidation and generally the initial oxidation products are the cation radicals.[7)] The cation radicals derived from the less highly substituted species undergo rapid coupling reactions, whereas those derived from the highly substituted species decompose by some alternate pathway, which is assumed to be proton loss from methyl groups, with the resulting radicals undergoing various subsequent reactions.

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5) *a)* K.K. Barnes and C.K. Mann, *J. Org. Chem.*, 32, 1474 (1967); P.J. Smith and C.K. Mann, *ibid.*, 33, 316 (1968); *Idem, ibid.*, 34, 1821 (1969); *b)* M. Masui and H. Sayo, *J. Chem. Soc.* (*B*), **1971**, 1593.

6) T.M. McKinney and D.H. Geske, *J. Am. Chem. Soc.*, **87**, 3013 (1965).

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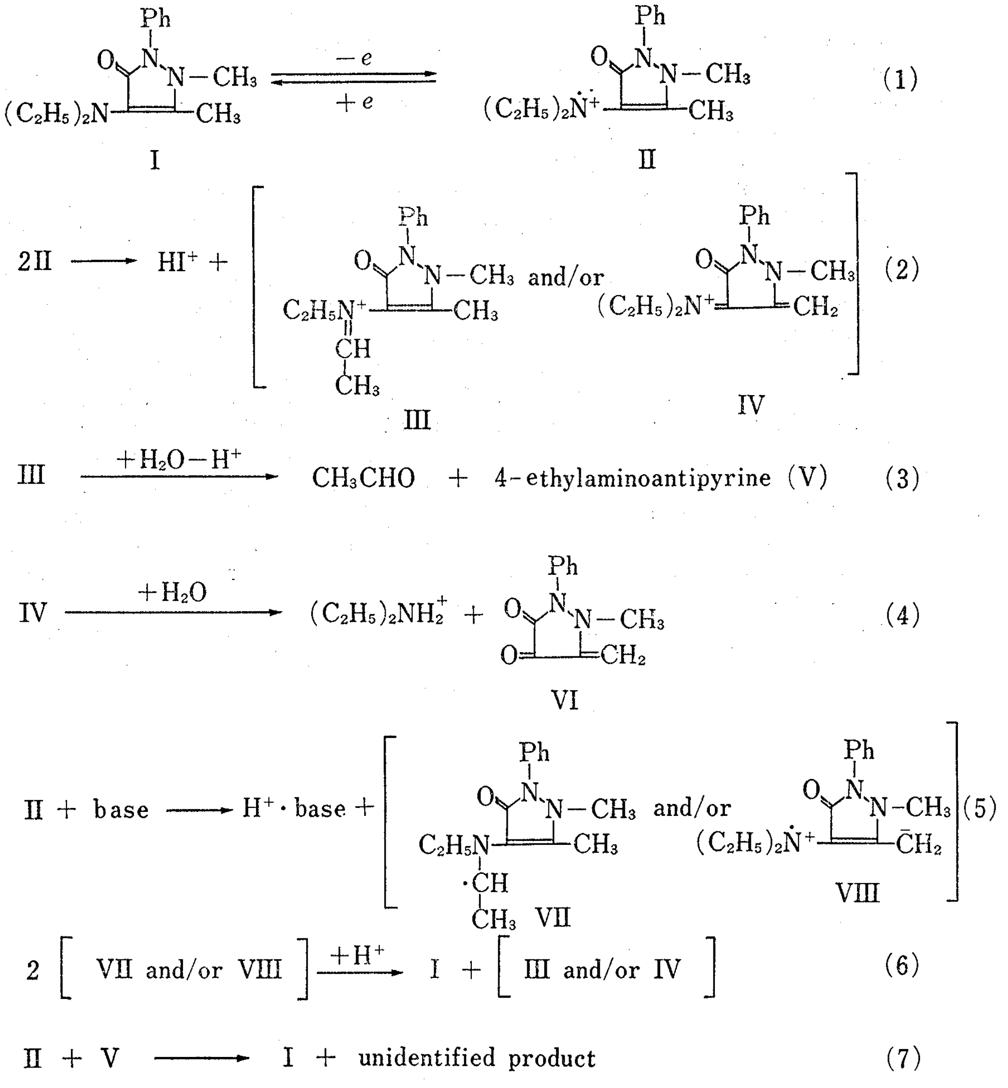
Aromatic tertiary amines generally undergo a one-electron oxidation to form the cation radicals.[8] Some cation radicals are extremely stable, making the electrode reaction appear entirely reversible. Decomposition of the cation radical occurs through coupling. Dealkylation is not observed for the anodic oxidation of N,N-dialkylanilines.

Anodic oxidation of I resembles that of aliphatic α,β-unsaturated tertiary amines and the fate of II resembles that of the cation radicals of aliphatic tertiary amines. This means the double-bond in the pyrazolone ring is fixed between 3 and 4 positions.

The following scheme is proposed for the anodic oxidation of I and the decomposition of II in the absence of oxygen.



Ph=phenyl

Chart 1

Acetaldehyde and diethylamine were detected as the products of decomposition of II (reactions 3 and 4), but V and VI were not detected. As E_p value of V is 0.08 V less positive than that of I, V can be oxidized further by II (reaction 7). The fate of VI is unknown at present. Deprotonation of II and disproportionation of VII and/or VIII are considered to

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[8] E.T. Seo, R.F. Nelson, J.M. Fritsch, L.S. Marcoux, D.W. Leedy, and R.N. Adams, *J. Am. Chem. Soc.*, **88**, 3498 (1966); M. Melicharek and R.F. Nelson, *J. Electroanal. Chem.*, **26**, 201 (1970); R. Hand, M. Melicharek, D.I. Scoggin, R. Stotz, A.K. Carpenter, and R.F. Nelson, *Collection Czech. Chem. Commun.*, **36**, 842 (1971).

cause the first-order decay of II (reactions 5 and 6). Since reaction 6 is a reaction between neutral molecules, it should be much faster than reaction 2. If the concentration of bases is much larger than that of II, the pathway through reactions 5 and 6 will proceed in a pseudo-first-order manner. I, V, and the further oxidized compounds are considered to act as base. The fact that I was recovered in a 72% yield, which is greater than that expected for reaction 2 alone, also substantiates reactions 5, 6, and 7.

The reason why II decays in a second-order manner in the presence of oxygen is not clear at present. Further studies are needed on this.

Experimental

Materials——4-Diethylaminoantipyrine was prepared from 4-aminoantipyrine and diethylsulfate, and recrystallized from *n*-hexane, mp 95—96°, which gave the correct analysis. 4-Ethylaminoantipyrine was prepared from 4-aminoantipyrine and acetaldehyde,[4c] and purified by column chromatography on alumina with benzene as eluant, pale yellow oil; picrate 168—169° (decomp.), (lit.[9] 169—171°). Acetonitrile and sodium perchlorate were purified as described previously.[1]

Apparatus——Cyclic voltammetry, controlled potential electrolysis, spectrophotometry, ESR spectrometry, and simulation of the ESR spectrum were carried out as described previously.[1] The kinetic studies were carried out at 25°±0.1°.

Controlled Potential Electrolysis——I (264.3 mg) was subjected to electrolysis in acetonitrile (100 ml) containing 0.1 M $NaClO_4$ at 0.45 V for 45 min at room temperature. Dissolved oxygen was removed by passing purified argon through the solution. The electrolysis consumed 91.7 coulombs, which corresponds to $n=0.93$. The solution was allowed to stand for 24 hours at room temperature. The resulting light red-brown solution was distilled under reduced pressure. The distillate was mixed with 2,4-dinitrophenylhydrazine dissolved in 2N HCl, and the mixture was concentrated to one-half of its original volume under reduced pressure. The yellow precipitate obtained was recrystallized from EtOH, mp 163—164° (14.5 mg) which was identified as 2,4-dinitrophenylhydrazone of acetaldehyde from its IR spectrum. The residue on distillation was made alkaline by addition of NaOH and steam distilled. The distillate was trapped with 0.1 N HCl. From the acidified distillate a small amount of diethylamine (*ca.* 1%) was detected by thin-layer chromatography as 1-dimethylamino-naphthalene-5-sulphonamide.[5b] The residue on steam distillation was extracted with $CHCl_3$. Evaporation of the extract gave a red-brown solid, which was extracted with hot *n*-hexane. Cooling of the hexane layer gave white crystals of I (191.6 mg), which were recrystallized from *n*-hexane, mp 95—96°, and identified from its infrared spectrum (Nujol). The identity of red-brown resinous substances which were insoluble into *n*-hexane could not be determined.

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9) A. Skita, F. Keil, and W. Stuhmer, *Chem. Ber.*, 75, 1696 (1942).