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Electrochemical Cyanomethylation of Phenazines in Acetonitrile

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Cathodic reductions of phenazine (1) and 2,7-diethoxyphenazine (2) were carried out in acetonitrile containing trifluoroacetic acid (TFA) under air, and 2-(cyanomethy)phenazine (3) and 2-(cyanomethyl)-3,8-diethoxyphenazine(4) were obtained as final products, respectively. Cyclic voltammetry (CV) of 1 and 2 showed two cathodic peaks and these peaks had counterparts under N_2 and/or air. When CV was carried out under air, the current of the second cathodic peak of 2 was increased. Controlled potential electrolysis (CPE) of 1 under N_2 at the second cathodic peak gave a value of 1.8 for *n* (faradays per mole of substance electrolyzed) and 84% of the starting compound was recovered.

Dihydrophenazines produced by the electrochemical reduction of 1 and 2, activated dissolved oxygen. The activated oxygen oxidized the solvent, *i.e.*, acetonitrile, and gave a cyanomethyl radical, which attacked the 2-position of 1 and 2 to give 3 and 4, respectively. MO calculations of three putative intermediates were conducted to obtain their localization energy and heat of formation. The heat of formation of the intermediate radical appears to decide the direction of the reaction.

Key words phenazine; activated oxygen; cyclic voltammetry; molecular orbital method; electrolysis; cyanomethylation

Oxidation–reduction behaviors of phenazine have been studied extensively by means of electrochemical methods.1—15) Phenazine has a 1,4-diazine ring structure, which is similar to that of isoalloxazine existing in flavin adenine dinucleotide (FAD) as a redox site, and dihydrophenazine reacts with molecular oxygen to give hydrogen peroxide just like dihydroflavin. Therefore phenazine could be a useful model compound of FAD.

In the course of studies on phenazines as model compounds, an electrochemical cyanomethylation of phenazines was found.1) In order to elucidate the mechanism in detail, we have conducted electrochemical studies of phenazines and MO calculations.

Results

Cyclic Voltammetry (CV) Cyclic voltammograms of phenazine (**1**) are shown in Fig. 1.

Glassy carbon was used as a working electrode. In the absence of O_2, compound **1** showed two cathodic peaks at 0.21 and −0.07 V and these peaks had counterparts. In the range of −0.3 to −1.5 V, the voltammogram was flat. Under air, a new peak attributed to the presence of dissolved oxygen was observed at −1.0 V but no change of other peaks was found. In other words, the oxidation of dihydrophenazine, which is the two-electron reduction product of **1**, by dissolved oxygen was not observed.

Then the substrate was switched to 2,7-diethoxyphenazine (**2**), whose two-electron reduction product, 2,7-diethoxy-5,10-dihydrophenazine, has a lower oxidation potential than dihydrophenazine. Cyclic voltammograms of **2** are shown in Fig. 2.

In the absence of O_2, two cathodic peaks with counterparts were observed at 0.09 and −0.24 V. In the presence of air, the second cathodic peak was increased. The electrochemical reduction of phenazines in acidic solution is considered to proceed by a stepwise two-electron transfer mechanism to give 5,10-dihydrophenazines. The second cathodic wave corresponds the second electron transfer. Therefore, the change on the cyclic voltammogram suggests that 2,7-diethoxy-5,10-dihydrophenazine is oxidized by molecular oxygen in the time scale of CV to regenerate the substrate.

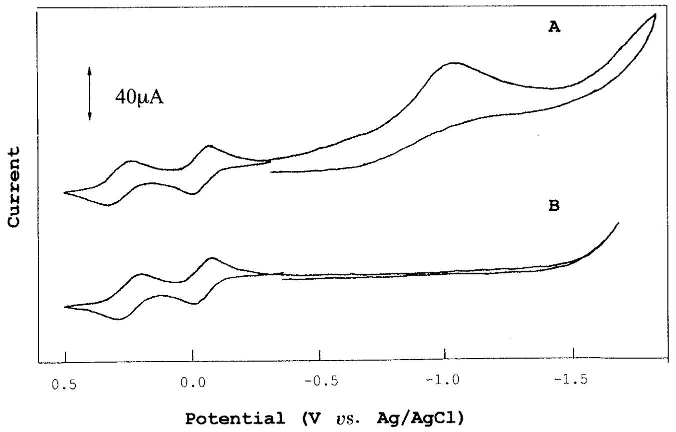

Fig. 1. Cyclic Voltammograms of 1 mM Phenazine (**1**) in Acetonitrile Containing 1% TFA and 0.1 M $NaClO_4$ under Air (A) and under N_2 Gas (B)

Glassy carbon cathode (diameter = 3.0 mm); voltage sweep rate, 50 mV/s.

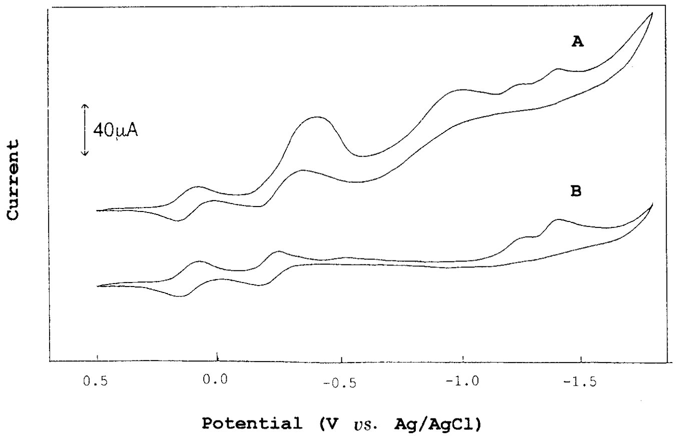

Fig. 2. Cyclic Voltammograms of 1 mM 2,7-Diethoxyphenazine (**2**) in Acetonitrile Containing 1% TFA and 0.1 M $NaClO_4$ under Air (A) and under N_2 Gas (B)

Glassy carbon cathode (diameter = 3.0 mm); voltage sweep rate, 50 mV/s.

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Table 1. Results of Controlled Potential Electrolysis of Phenazines in Acetonitrile

Compd. No.	Condition	TFA	Appl. Pot. (V)	$n^{a)}$	Products identified	Yield (%)
1	N_2	1%	−0.2	1.8	Phenazine	84%
1	Air	1%	−0.07	8.2	2-(Cyanomethyl)phenazine	40%
					Phenazine	30%
1	Air	1%	−0.2	8.4	2-(Cyanomethyl)phenazine	36%
					Phenazine	30%
1	Air	3%	−0.2	16.4	2-(Cyanomethyl)phenazine	50%
					Phenazine	Trace
2	Air	1%	−0.6	4.8	2-(Cyanomethyl)-3,8-diethoxyphenazine	7%
					2,7-Diethoxyphenazine	59%
2	Air	3%	−0.6	19.7	2-(Cyanomethyl)-3,8-diethoxyphenazine	17%
					2,7-Diethoxyphenazine	Trace

a) Faradays per mole of substance electrolyzed.

Controlled Potential Electrolysis (CPE) Glassy carbon electrodes and an H-Type cell were used. The results of CPE are summarized in Table 1.

Compound **1** was electrolyzed in acetonitrile containing 0.1 M $NaCl_4$ and 1% trifluoroacetic acid (TFA) at −0.07 V (*vs.* Ag/AgCl), which is the peak potential of the second wave. The quantity of electricity consumed corresponded to $n=8.2$. This n-value means that **1** suffered a two-electron transfer reduction more than 4 times. The electrolyte solution was added to benzene, washed with aqueous Na_2CO_3 solution, and then concentrated. Two compounds were separated from the residue by silica gel column chromatography. One was the recovered phenazine and the other was 2-(cyanomethyl)phenazine (**3**). Their yields were 30% and 40%, respectively, but the latter corresponded to 57% yield on the basis of consumed substrate.

In order to complete the electrolysis, the applied potential was decreased to −0.2 V but the n value and the yields of the phenazine and 2-cyanopmethylphenazine were not changed. Then the concentration of TFA was increased to 3%, and the electrolysis was completed. At this time n was 16.4, corresponding to consumption of 16.4 mmol of TFA. However, 1% TFA means only 13.4 mmol of TFA exists in the electrolysis cell. Therefore, it is the alkalization of the electrolyte following the electrolysis that prevents the completion of the electrolysis in acetonitrile containig 1% TFA. Although the electrolysis was carried out in a cathodic cell, the oxidation number of the product, 2-(cyanomethyl)phenazine, was higher than that of phenazine. Some oxidants must be generated during the electrolysis. In order to exclude the effect of dissolved oxygen, the electrolysis was carried out under an N_2 stream. The quantity of electricity consumed corresponded to $n=1.8$, indicating that 90% of **1** was reduced *via* a two-electron transfer mechanism. The electrolyzed solution was analyzed by HPLC and 84% recovery of **1** was obtained.

The electrolysis of **2** gave similar results.

Discussion

Few examples of electrochemical cyanomethylation are known. Takahashi *et al.* reported that triallylboranes were readily electrolyzed in an acetonitrle solution containing halide ion to give corresponding aliphatic nitriles in good yield.[17] These reactions can be explained in terms of nucleophilic attack of the initially formed acetonitrile anion. However, our reaction can not be explained by this mechanism, because the reaction proceeds without involvement of the halide ions.

The following scheme is proposed for the cyanomethylation of phenazine.

Phenazine is doubly protonated in an acidic solution, and reduced to dihydrophenazine by stepwise two-electron reduction on the cathode.[1] 5,10-Dihydrophenazine is oxidized by oxygen in the solution to doubly protonated phenazine, and the oxygen is reduced to hydrogen peroxide.[18−20] However, hydrogen peroxy radical may not oxidize acetonitrile, because acetonitrile has a high oxidation potential.[21] When hydrogen peroxide is reduced by the electrode or by 5,10-dihydrophenazine, a hydroxide ion and a hydroxyl radical are produced. The latter is the most reactive oxidant among the activated oxygens.[22] A cyanomethyl radical is produced by the oxidation of acetonitrile by a hydroxyl radical, and this attacks the 2-position of phenazine. The phenazine radical shown in Chart 1 is oxidized to **3** by hydrogen peroxide or hydroxyl radical.

In previous papers, it was reported that the nitrogen atom has the highest values of electron and spin density in ion radicals derived from phenazines.[1,23] The N-positions of phenazines are the most reactive, and indeed, no substitution reaction on a carbon atom in phenazine is known.

Coulson discussed the ease of addition of a methyl group to aromatic compounds in terms of localization energy attributed to the formation of a new bond that requires one π-electron to be removed from the conjugated system.[24] In order to elucidate why the substitution reaction occurred at the 2-position of **1**, MO calculations of all possible intermediates (A—C) were conducted, using modified neglect of diatomic overlap (MNDO) and Austin model 1 (AM1). The results are summarized in Table 2.

Localization energy was obtained by subtracting the total energy of diprotonated **1** from that of intermediates. The dication radical A that is generated from the attack of the cyanomethyl radical at the N-position of **1** has a localization energy comparable to that of C, which is generated from the attack of the cyanomethyl radical at the 2-position of **1**. The dication radical C is assumed to be a direct precursor of **3**. The dication radical B, generated from the attack of the cyanomethyl radical at the 1-position of **1**, has the lowest localization energy. Therefore, the localization energy can not account for the experimental results. Then the heats of formation of A—C were calculated. As we expected, C has the lowest value of the heat of formation. The difference of the value of the heat of formation between B and C is at least 7 kcal. The calculation results suggest that if this reaction proceeds by the mechanism shown in Chart 1, the heat of formation decides the direction of the reaction.

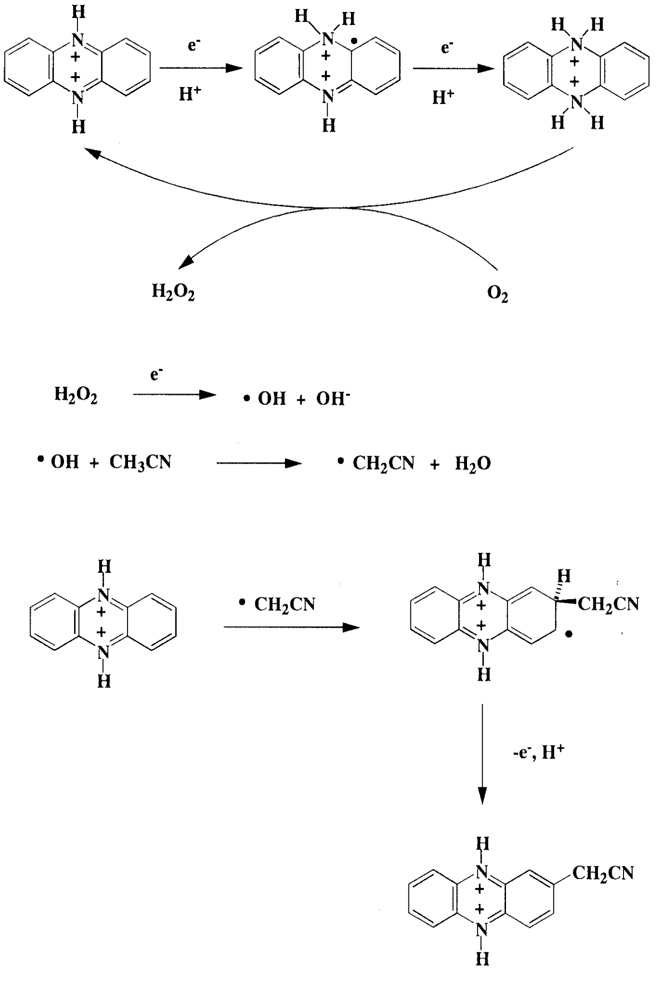


Chart 1

Experimental

Material Compound **2** was prepared from 4′-ethoxy-2-nitrobenzenesulfenanilide by the following method. 4′-Ethoxy-2-nitrobenzenesulfenanilide (1 g) was dissolved in acetonitrile (100 ml) containing TFA (1%), trifluoroacetic anhydride (1%), and $NaClO_4$ (0.1 M). The controlled potential electrolysis was carried out at 0.6 V (*vs.* saturated calomel electrode (SCE)) with a glassy carbon electrode. Solid Na_2CO_3 was added to the electrolyzed solution with stirring until the color of the solution changed. Water (150 ml) was added to the solution and the precipitates were filtered off and dried. The collected solid was chromatographed over silica gel using CH_2Cl_2 as a mobile phase. The corresponding yellow fractions were collected and concentrated using a rotary vacuum evaporator without heating. The precipitated yellow powder was collected and identified as 2,7-diethoxyphenazine by comparison of the spectral data with those of an authentic sample.[25] The yield was 15%.

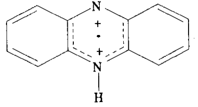
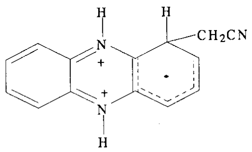
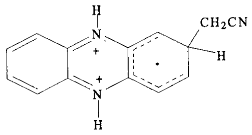
Acetonitrile was purified as described previously.[26] Other reagents were purchased and used without further purification.

Apparatus CV and CPE were carried out essentially as described previously.[1] Infrared (IR), nuclear magnetic resonance (NMR), and mass spectra (MS) were obtained on Hitachi 260-30, Brucker DPX-400, and Hitachi M-2000 spectrometers, respectively. HPLC was carried out using a Waters automated gradient controller model 680 equipped with a U6K universal injector and, a JASCO UVIDEC-II spectrometer. RCM 25 × 10 cartridge holder and two Nova-Pak HR C18 connected in series were used. MO calculation was carried out using a Hitachi FMV-Deskpower SII167 personal computer running HyperChem release 4.5 (Hypercube Inc., Canada).

Identification of Products from CPE Electrolysis was carried out in an H-Type divided cell. A glassy carbon plate (14 cm^2) was used as the working electrode. A typical example of the procedure is given below.

Compound **1** (1 mmol) was dissolved in acetonitrile (100 ml) containing 1% TFA and $NaClO_4$ (1.2 g) as a supporting electrolyte. Electrolysis was carried out at −0.2 V at room temperature until the value of current became less than 1% of the initial value. The electrolyzed solution was added to benzene (100 ml), and washed with 5% aqueous Na_2CO_3 solution (200 ml). The organic layer was dried with Na_2SO_4, and

Table 2. Results of Chemical Calculation of The Putative Intemediates

Structure	No.	Localization energy (kcal/mol)		Heat of formation (kcal/mol)	
		MNDO	AM1	MNDO	AM1
	A	−11286.031	−11281.751	527.671	524.657
	B	−6802.538	−6826.086	553.455	514.497
	C	−11305.367	−11298.822	508.335	507.587

evaporated under reduced pressure. The residue was purified on a silica gel column with benzene–$CHCl_3$ (1 : 1) to give **3** (79.5 mg). A part of **3** was further purified with HPLC and used for elemental analysis. mp 207—209 °C (dec.). IR (KBr) cm^{-1}: 2240 (CN). ^1H-NMR ($CDCl_3$) δ: 4.06 (2H, s, $-CH_2CN$), 7.76 (1H, dd, $J_1=9.0$ Hz, $J_2=2.1$ Hz, aromatic proton), 7.85—7.91 (2H, m, aromatic proton), 8.23—8.27 (3H, m, aromatic proton), 8.29 (1H, d, $J=9.0$ Hz, aromatic proton). *Anal.* Calcd for $C_{14}H_9N_3$: C, 76.70; H, 4.14; N, 19.17. Found: C, 76.86; H, 4.22; N, 19.10. MS *m/z*: 219 (M^+).

Compound **4** was obtained by essentially the same procedure. mp 233—243 °C (dec.). IR (KBr) cm^{-1}: 225 (CN). ^1H-NMR ($CDCl_3$) δ: 1.55 (3H, t, $J=7.0$ Hz, $-O-CH_2C\underline{H}_3$), 1.57 (3H, t, $J=7.0$ Hz, $-O-CH_2C\underline{H}_3$), 3.95 (2H, s, $-CH_2CN$), 4.26 (2H, q, $J=7.0$ Hz, $-O-C\underline{H}_2CH_3$), 4.29 (2H, q, $J=7.0$ Hz, $-O-C\underline{H}_2CH_3$), 7.39 (1H, d, $J=2.7$ Hz, aromatic proton), 7.43 (1H, s, aromatic proton), 7.51 (1H, dd, $J_1=9.4$ Hz, $J_2=2.7$ Hz, aromatic proton), 8.03 (1H, d, $J=9.4$ Hz, aromatic proton), 8.20 (1H, s, aromatic proton). HR-MS Calcd for $C_{18}H_{17}N_3O_2$: 307.1321. Found: 307.1309.

Semi-Empirical Calculation MNDO and AM1 were used. Before single point calculation, geometry optimization was carried out with UHF (spin unrestricted Hartree-Fock) calculation using Polak-Ribiere as the minimization algorithm until the total RMS (root-mean-square) gradient was reduced to 0.01 kcal/(Å mol).

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