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Ozonization of Phenothiazine and Its Analogues

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When phenothiazine and phenoxazine were ozonized in dichloromethane, the cation radicals and the ozonate anion radical were detected, whereas, in the ozonization of phenoxathiin and thianthrene, these radicals were not observed. Formation of these radicals was more favorable as greater was the polarity of the solvent and lower was the oxidation potential of the substrate. Ozonization of phenothiazine and phenoxazine in polar solvents was explained by the electron-transfer mechanism accompanied by the electrophilic ozone attack, and that of phenoxathiin and thianthrene by the electrophilic ozone attack alone.

Reactions of ozone are classified into four types; (1) a 1,3-dipole represented by the Criegee ozonolysis mechanism,1) (2) an electrophile in the ozonization of phosphines,2) (3) a nucleophile as was reported by Olah *et al.*,3) and (4) an electron acceptor which was reported in the ozonization of *p*-phenylenediamines4) and amines.5—7)

Ozonization of phenothiazine, phenoxathiin, thianthrene, and phenoxazine which possibly involves the electron-transfer was discussed.

Experimental

General. Ozone was generated by a Nihon Ozon 0-1-2 type ozonizor. Mass spectra were recorded with Hitachi M-52 and RMU-6M spectrometers. NMR, IR, and visible spectra were recorded on a Hitachi R-24 spectrometer, a Hitachi EPI-S2 spectrometer, and a Hitachi EPS-3T spectrometer, respectively. Gas and liquid chromatography was performed on a Shimadzu 4C-PF gas chromatograh and a Japan Spectroscopic Co. Familic 100N liquid chromatograph, respectively. Melting points were measured with a Yamato MP-21 melting point apparatus. Oxidation potential was measured with Niko NPGS-301 and NPS-2 apparatuses. Purity of the materials used was confirmed by gas and liquid chromatography.

Materials. Phenothiazine (**1a**) (Nakarai Chemicals, Ltd.) was recrystallized from ethanol; mp 185.4 °C (lit, 185.1 °C);8) MS (20 eV) *m/z* (rel intensity) 199(M$^+$; 100), 198 (17), 167 (41), 166 (16), and 100 (10); ^{1}H NMR (DMSO-d_6) δ=6.5—7.1 (m, 8H) and 8.51 (s, 1H); IR (KBr disk) 3300 cm^{-1} (NH). Phenoxathiin (**1b**) was synthesized according to the literature;9) mp 55.8 °C (lit, 56.5—57.5 °C);9) MS (20 eV) *m/z* (rel intensity) 200 (M$^+$; 100), 171 (25), and 168 (30). Thianthrene (**1c**) (Tokyo Chemical Industry Co., Ltd.) was recrystallized from ethanol; mp 155.0 °C (lit, 155—157 °C);10) MS (20 eV) *m/z* (rel intensity) 216 (M$^+$; 100), 184 (52), and 171 (12). Phenoxazine (**1d**) (Aldrich Chemical Co., Inc.) was used without further purification; mp 156.0 °C (lit, 154.5—156.0 °C);11) MS (20 eV) *m/z* (rel intensity) 183 (M$^+$; 100), 154 (31), and 127 (8); IR (KBr disk) 3380 cm^{-1} (NH). Phenothiazine 5-oxide (**2a**) was synthesized according to the literature;12) mp 252—254 °C (lit, 251—253 °C);12) MS (70 eV) *m/z* (rel intensity) 215 (M$^+$; 56), 199 (31), 186 (92), 167 (100), and 153 (25); IR (KBr disk) 3170 (NH) and 1075 cm^{-1} (S=O). Phenoxathiin 10-oxide (**2b**) was synthesized by the oxidation of phenoxathiin with an equivalent molar amount of ozone, and recrystallized from ethanol; mp 152.4 °C (lit, 153—154 °C);13) MS (20 eV) *m/z* (rel intensity) 216 (M$^+$; 62), 200 (100), 187 (59), and 168 (97); IR (KBr disk) 1035 cm^{-1} (S=O). Thianthrene 5-oxide (**2c**) was synthesized by the ozonization of thianthrene and recrystallized from ethanol; mp 141.8 °C (lit, 143.0—143.5 °C);10) MS (20 eV) *m/z* (rel intensity) 232 (M$^+$; 20), 216 (22), 203 (15), 184 (100), 171 (12), and 152 (8); IR (KBr disk) 1075 cm^{-1} (S=O). 3*H*-Phenothiazin-3-one (**3a**) was synthesized according to the literature;14) mp 164—166 °C (lit, 165—166 °C);14) MS (20 eV) *m/z* (rel intensity) 213 (M$^+$; 37), 185 (100), and 141 (17); IR (KBr disk) 1630 cm^{-1} (C=O). 3*H*-Phenoxazin-3-one (**3d**) was synthesized by the ozonization of phenoxazine and purified by column chromatography (silica gel, dichloromethane); mp 213—215 °C (lit, 216—217 °C);15) MS (20 eV) *m/z* (rel intensity) 197 (M$^+$; 100), 169 (94), 140 (19), and 114 (16); IR (KBr disk) 1615 cm^{-1} (C=O). 2-Chlorophenothiazine (**4a**) (Tokyo Chemical Industry Co., Ltd.) was employed without further purification; mp 193.0—194.5 °C (lit, 194—195 °C);16) MS (20 eV) *m/z* (rel intensity) 235 (39), 233 (M$^+$; 100), 201 (22), and 198 (56); IR (KBr disk) 3300 cm^{-1} (NH). Thianthrene 5,10-dioxides (**5c** and **5′c**) were synthesized by the ozonization of thianthrene and purified by thin layer chromatography (silica gel, dichloromethane : hexane=5:1); *trans*-Thianthrene 5,10-dioxide (**5c**); mp 276—277 °C (lit, 284 °C);17) MS (20 eV) *m/z* (rel intensity) 248 (M$^+$; 53), 232 (17), 216 (43), 200 (53), 184 (100), and 171 (33); IR (KBr disk) 1085 cm^{-1} (S=O). *cis*-Thianthrene 5,10-dioxide (**5′c**); mp 234.5—235.5 °C (lit, 249 °C);17) MS (20 eV) *m/z* (rel intensity) 248 (M$^+$; 35), 232 (13), 216 (54), 200 (42), 184 (100), and 171 (46); IR (KBr disk) 1075 cm^{-1} (S=O).

Ozonization Reaction. Ozonization was carried out with an ozone-nitrogen mixture. The products were identified by comparing the retention time in the gas and liquid chromatography and mass spectra with those of authentic samples. The products were determined by GLC using a 2% Silicone OV-1 column, 3 mm×1 m, programmed from 80 to 240 °C at 10 °C min^{-1}. The conditions in LC were (1) SS-10 column, 0.5 mm×0.15 m, eluted with the mixed solution (dichloromethane : ethanol=25:1) and detection at 254 nm, and (2) SS-10 column, 0.5 mm×0.15 m, eluted with the mixed solution (dichloromethane : acetone=40:1) and detection at 254 nm.

Results and Discussion

The results of the ozonization reactions are shown in Table 1. Materials employed are shown in Fig. 1.

When phenothiazine (**1a**) was ozonized in dichloromethane, phenothiazine 5-oxide (**2a**), 3*H*-phenothiazin-3-one (**3a**), and 2-chlorophenothiazine (**4a**) were detected. Since the ozonization of phenothiazine 5-oxide gave 3*H*-phenothiazin-3-one (Run 9), it was concluded that phenothiazine reacted with one molar equivalent of ozone to give phenothiazine 5-oxide and 2-chlorophenothiazine, and further ozonization gave 3*H*-phenothiazin-3-one. Though the reactivity of phenothiazine with ozone increaed with the rise of the reaction temperature, the distribution of the products was scarcely affected (Runs 1,2,3, and 4). Since chlori-

TABLE 1. RESULTS OF THE OZONIZATION REACTION[a]

Run	Substrate	Solvent	Temp / °C	Ozone (consumed) / 10^{-4} mol	Conv / %	Ozone[b] (consumed) / Substrate (reacted)	Yield[c]/%		
							2	3	Others
1	**1a**	CH_2Cl_2	20	1.71	68	1.00	47	13	**4a**(6%)
2	**1a**	CH_2Cl_2	0	1.27	48	1.05	46	12	**4a**(Trace)
3	**1a**	CH_2Cl_2	−20	2.79	70	1.59	49	16	**4a**(2%)
4	**1a**	CH_2Cl_2	−78	3.57	62	2.29	51	11	**4a**(2%)
5	**1a**	$CHCl_3$	0	2.91	77	1.51	55	12	**4a**(8%)
6	**1a**	CCl_4	0	5.62	72	3.11	23	8	**4a**(11%)
7	**1a**	CH_3COOH	15	2.41	59	1.63	68	10	
8	**1a**	C_6H_{14}	0	0.23	55	1.05	25	3	
9	**2a**	CH_2Cl_2	0	0.15	64	0.99	—	14	
10	**1b**	CH_2Cl_2	0	17.88	67	1.07	97	—	
11	**1b**	CCl_4	0	17.81	72	0.99	90	—	
12	**1c**	CH_2Cl_2	0	5.35	72	0.80	92	—	
13	**1c**	CCl_4	0	7.27	78	1.01	88	—	**5c**(Trace)
14	**2c**	CH_2Cl_2	0	1.89	95	0.92	—	—	**5c**(81%), **5'c**(2%)
15	**1d**	CH_2Cl_2	0	7.73	92	1.03	—	5	Polymer

a) Ozonization was carried out with an ozone-nitrogen mixture on 0.251 mmol of phenothiazine (**1a**), 0.023 mmol of phenothiazine 5-oxide (**2a**), 2.50 mmol of phenoxathiin (**1b**), 0.926 mmol of thianthrene (**1c**), 0.216 mmol of thianthrene 5-oxide (**2c**), and 0.82 mmol of phenoxazine (**1d**) in 20 ml of solvent, respectively. b) Molar ratio. c) Yield was based on the substrate reacted with ozone.

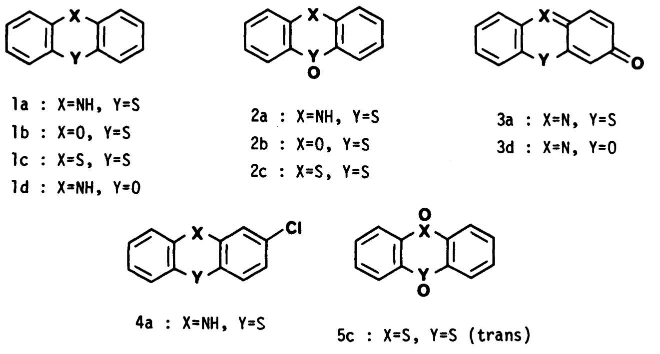


Fig. 1. Materials employed.

nated product **4a** was not formed, the yield of phenothiazine 5-oxide in acetic acid was greater than that in the chlorinated solvents (Runs 2,5, and 7). Since the yields of phenothiazine 5-oxide and 3*H*-phenothiazin-3-one in carbon tetrachloride and hexane were low compared with that in the other solvents (Runs 2,5,6,7, and 8), the electron-transfer mechanism during ozonization is suggested.

Phenoxathiin (**1b**) reacted with one molar equivalent of ozone to give phenoxathiin 10-oxide (**2b**) quantitatively. The reaction was scarcely affected by the polarity of the solvent (Runs 10 and 11).

When thianthrene (**1c**) was ozonized, thianthrene 5-oxide (**2c**), and a trace amount of *trans*-thianthrene 5,10-dioxide (**5c**) were detected. Ozonization of thianthrene 5-oxide gave *trans*-thianthrene 5,10-dioxide and *cis*-thianthrene 5,10-dioxide (**5'c**) in the ratio 97:3. The yield of thianthrene 5-oxide was scarcely affected by the solvent (Runs 12 and 13).

When phenoxazine (**1d**) was ozonized in dichloromethane, the reaction was complex and the product isolated was 3*H*-phenothiazin-3-one (**3d**), accompanied by unidentified polymers (Run 15).

When phenothiazine was ozonized in dichloromethane, the reaction mixture turned red in color. The visible absorption spectra during the reaction are shown in Fig. 2. The spectra showed the absorption maxima at 435 and 519 nm, which are close to those of the phenothiazine cation radical reported by Hason *et al.*,[18] and Brown *et al.*[19] The spectra have smaller peaks at 481 and 502 nm which are attributed to the uncharged radical.[20] Since an ozonate anion radical has been reported to undergo the hydrogen abstraction reaction,[21] cumene and triphenylmethane were added to the ozonized solution, and the mixture was allowed to stand for 0.5 h. The control experiment was also carried out. When cumene was ozonized, 2-phenyl-2-propanol was detected as was reported by Pryor *et al.*[22] However, since (1) the yield in the presence of phenothiazine (8%) was clearly greater than that in the absence of phenothiazine (trace), and (2) triphenylmethanol was not detected from the ozonized solution in the absence of phenothiazine, it was concluded that cumene and triphenylmethane reacted with the ozonate anion radicals to give 2-phenyl-2-propanol and triphenylmethanol, respectively. Since the reactivity of cumene with radicals is smaller than that of triphenylmethane,[23] yield of the ozonate anion radical with four molar equivalents of cumene gave only a trace amount of 2-phenyl-2-propanol. The result is shown in Table 2. As was expected, the ozonate anion radical was trapped in dichloromethane, chlorform, and acetic acid, in which the phenothiazine cation radical was detected (Runs 1,

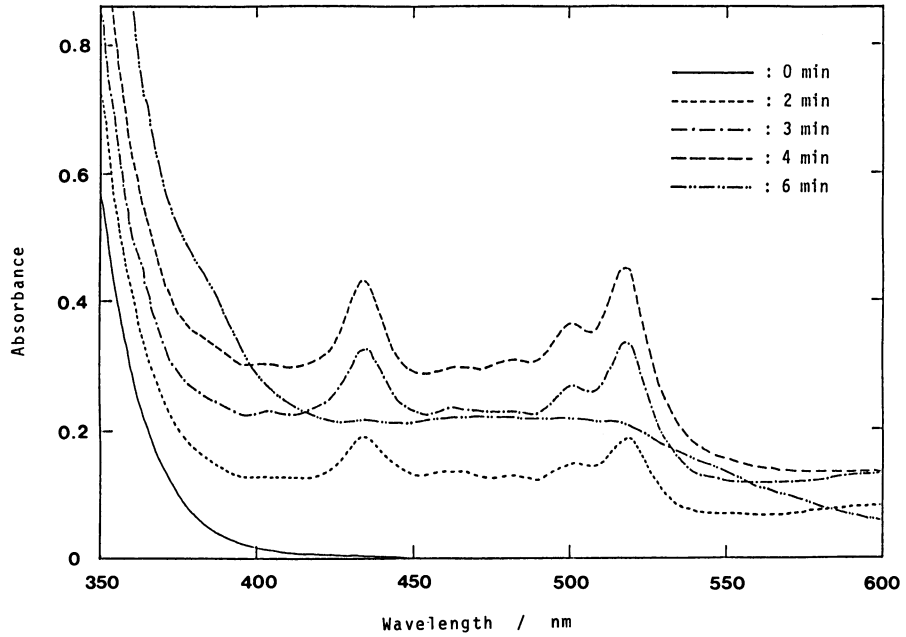


Fig. 2. Change in the visible spectrum of phenothiazine during ozonization.
Ozonization was carried out with an ozone–nitrogen mixture (ozone: 0.3 mmol, nitrogen: 50 cm^3 min^{-1}) on 0.251 mmol of phenothiazine in 50 ml of dichloromethane at 0 °C.

Table 2. Relation between the formation of a phenothiazine cation radical and the yield of the ozonate anion radical during the ozonization of phenothiazine[a)]

Run	Solvent	Formation[b)] of a cation radical	Yield[c)]/%	
			2-Phenyl-2-propanol	Triphenylmethanol
1	CH_2Cl_2	+	8	3
2	$CHCl_3$	+	7	3
3	CH_3COOH	+	7	2
4	CCl_4	–	0	0
5	C_6H_{14}[d)]	–	0	0

a) Ozonization was carried out with an ozone-nitrogen mixture (ozone: 1.0 mmol, nitrogen: 50 cm^3 min^{-1}) on 1 mmol of phenothiazine in 40 ml of solvent at 0 °C. To the ozonized solution, 140 and 4 molar equivalents of cumene and triphenylmethane were added, respectively. b) The cation radical was detected by the visible spectrum. c) Yield was based on the phenothiazine reacted. d) Ozonization was carried out with an ozone-nitrogen mixture (ozone: 0.3 mmol, nitrogen: 50 cm^3 min^{-1}) on 0.25 mmol of phenothiazine in 40 ml of solvent.

2, and 3). The greater the polarity of the solvent is, the easier is the formation of the ozonate anion radical. Such a tendency is similar to the solvent effect reported in the reaction of a superoxide ion.[24)]

Bailey *et al.* reported that *t*-butylamine cation radical produced in the ozonization underwent hydrogen abstraction reaction from 2,2,4-trimethylpentane to give 2,4,4-trimethyl-2-pentanol.[25)] However, since (1) an ozonate anion radical produced on magnesium oxide underwent hydrogen abstraction reaction,[21)] and (2) addition of cumene and triphenylmethane decreased the absorbance of phenothiazine cation radical, we have modified Bailey's mechanism, as shown in Eqs. (1)—(3),

$$O_3^{\cdot-} + RH \rightarrow R^{\cdot} + O_2 + OH^-, \tag{1}$$

$$R^{\cdot} + PTH^{+\cdot} \rightarrow R^+ + RTH, \tag{2}$$

$$R^+ + OH^- \rightarrow ROH, \tag{3}$$

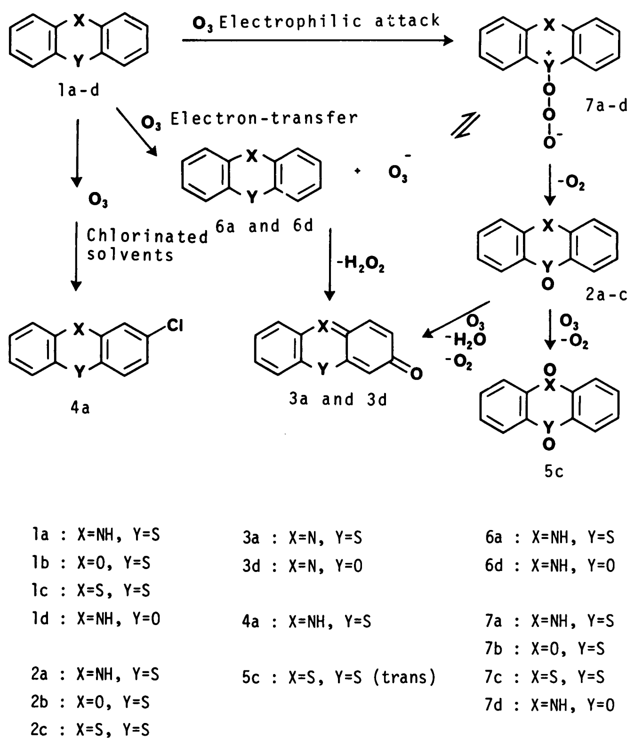
where RH is cumene and triphenylmethane, and PTH is phenothiazine.

Relations among oxidation potential ($E^{ox}_{1/2}$), formation of the cation radicals and yield of the ozonate anion radical in the ozonization of *N,N′*-diphenyl-*p*-phenylenediamine, phenothiazine, phenoxazine, phenoxathiin, and thianthrene are shown in Table 3. When *N,N′*-diphenyl-*p*-phenylenediamine, whose ozonization has been explained by the electron-transfer mechanism, was ozonized in dichloromethane, formation of the cation radical was observed, and the ozonate anion radical was also trapped (Run 1). In the ozonization of phenoxazine the solution turned red in color and visible spectrum showed the absorption maxima at 404 and 522 nm which are similar to that of the phenoxazine cation radical.[26)] The ozonate anion radical was also trapped in the yield of 6 and 2%, respectively (Run 3). Bailey *et al.* reported that ozonization of thianthrene in the presence of dilute sulfric acid gave the cation radical.[27)] When ozonization of phenoxathiin and thianthrene was carried out in dichloromethane, formation of the cation radicals and the ozonate anion radical were not observed (Runs 4 and 5). The result that the lower the oxidation potential is, the easier is the formation of the cation radical and the ozonate anion radical suggests that the electron-transfer process is the major path during the ozonization of phenothiazine and phenoxazine. On the other hand,

Table 3. Relations among the oxidation potential of the substrate, formation of the cation radicals, and the yield of an ozonate anion radical during ozonization[a)]

Run	Substrate	$E_{1/2}^{\mathrm{ox}\,b)}$/V	Formation of the[c)] cation radical	Yield[d)]/%	
				2-Phenyl-2-propanol	Triphenyl-methanol
1	*N*,*N*′-Diphenyl-*p*-phenylenediamine	0.35	+	19	4
2	Phenothiazine	0.59	+	8	3
3	Phenoxazine	0.60	+	6	2
4	Phenoxathiin	1.17	—	0	0
5	Thianthrene	1.21	—	0	0

a) Ozonization was carried out with an ozone-nitrogen mixture (ozone: 1.0 mmol, nitrogen: 50 cm^3 min^{-1}) on 1.0 mmol of substrate in 40 ml of dichloromethane. To the ozonized solution, 140 and 4 molar equivalents of cumene and triphenylmethane were added, respectively. b) *vs.* SCE in acetonitrile. c) The cation radical was detected by the visible spectrum. d) Yield was based on the substrate reacted.



Scheme 1.

ozonization of phenoxathiin and thianthrene is explained by the electrophilic ozone attack.

The probable ozonization mechenism is shown in Scheme 1. When phenothiazine (**1a**) and phenoxazine (**1d**) are ozonized in the polar solvents, the cation radicals **6a** and **6d** are formed *via* the electron-transfer reaction. They are in equilibrium with the substrate-ozone adducts **7a** and **7d** in solution. Ozonization of phenothiazine (**1a**) in the chlorinated solvents gives 2-chlorophenothiazine (**4a**). Recombination of **6d** with the ozonate anion radical gives 3*H*-phenoxazin-3-one (**3d**). The substrate-ozone adducts **7a**—**d** were also formed *via* the electrophilic attack of ozone on the substrate and the adducts lose an oxygen molecule and give the S-oxides **2a**—**c**. Thianthrene 5-oxide (**2c**) is further ozonized to give thianthrene 5,10-dioxide (**5c**).

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