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CHEMICAL MODIFICATIONS OF *N,N*-DIMETHYLALKYLAMINO-SUBSTITUTED 2-CHLOROPHENOTHIAZINE AND THEIR ELECTROCHEMICAL BEHAVIOR

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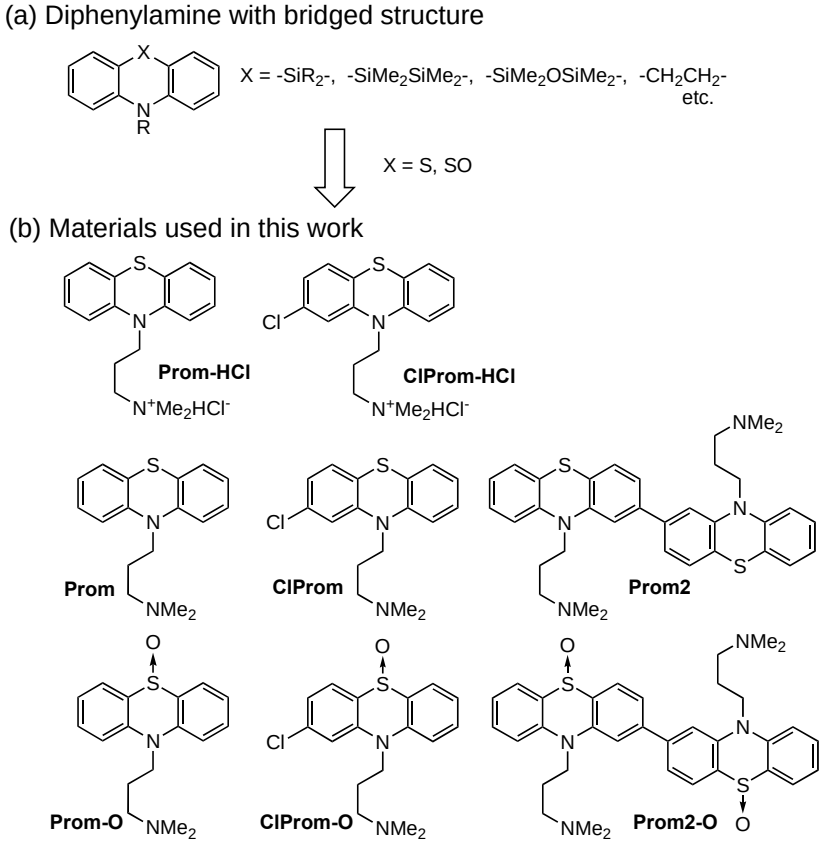
Abstract – The effects of the introduction of Cl to promazine and its oxide analogue were investigated. Cyclic voltammetry (CV) of Cl-substituted promazine derivatives (chlorpromazine (**ClProm**) and chlorpromazine-*S*-oxide (**ClProm-O**)) showed a negative oxidation and reduction potential compared to non-substituted promazine derivatives, whereas their optical properties were not affected by Cl. The Ni-promoted coupling reaction of **ClProm** and **ClProm-O** afforded phenothiazine dimers. It was observed that optical and electrochemical properties were affected by dimerization.

INTRODUCTION

Diphenylamines with a bridging structure are widely studied due to their interesting chemical and physical properties for functional materials. We previously reported the preparation, properties, and applications of silylene,[1-7] disilylene,[1,2] disiloxane-1,3-diyl,[1-3] and ethylene[8,9] unit-bridged diphenylamine derivatives (Scheme 1(a)). On the other hand, we also reported the preparation of poly(dibenzazepine)s ((**PAzep**)s) by oxidative polymerization of the corresponding dibenzazepines ((**Azep**)s). However, our efforts to synthesize poly(phenothiazine)s using the same method failed to give the desired polymer.[9] In the case of phenothiazine, we hypothesized that the oxidation of phenothiazine occurred prior to the oxidative polymerization. The mass and IR spectral data of the oxidation product strongly indicated that phenothiazine oxide is produced under the oxidative polymerization conditions of phenothiazine.[10] Therefore, we investigated the possibility of phenothiazine oxide for the functional material. We found that phenothiazine oxide is potentially applicable as an n-type semiconductor.[11] We used promazine

(10-(3-(dimethylamino)-1-propyl)phenothiazine, **Prom**) and its hydrochloride salt (**Prom-HCl**) as phenothiazine derivatives (Scheme 1(b)) which are readily available, because they are studied for medical use.[12,13]



Scheme 1

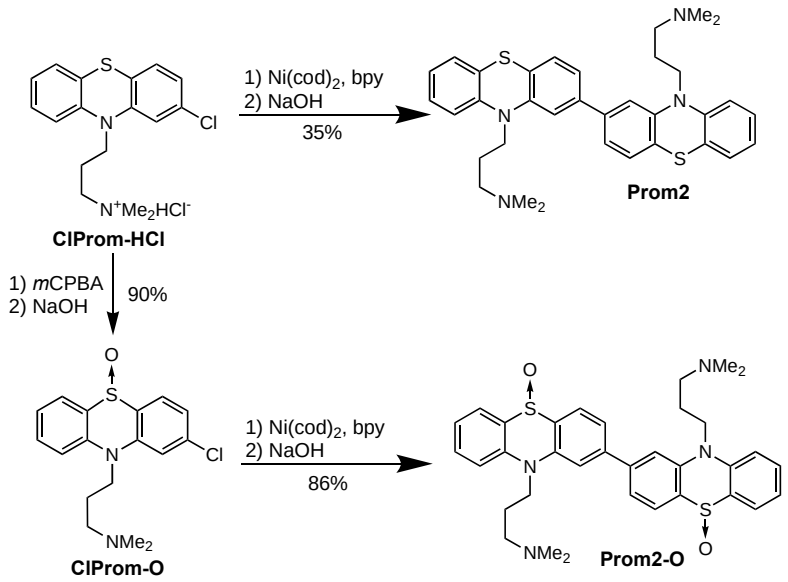
In this article, we focused on chlorpromazine (2-chloro-10-(3-(dimethylamino)-1-propyl)phenothiazine, **ClProm**, Scheme 1(b)), a 2-chloro-substituted promazine derivative that has been reported in medical applications.[12,14] It is a promazine that can be functionalized not only by chemical conversion of the **ClProm** skeleton but also by utilizing the electron-withdrawing property and reactivity of the Cl atom.

We prepared *S*-oxide and an ammonium analogue of **ClProm**. In addition, 2,2'-biphenothiazine derivatives (promazine dimer-type compounds, **Prom2** and **Prom2-O**, Scheme 1(b)) were also synthesized from **ClProm** and its *S*-oxide analogue, **ClProm-O**, respectively. In this paper, we will report the synthesis of new **Prom** and **Prom-O** derivatives, and compare the optical and electrochemical properties of these compounds.

RESULTS AND DISCUSSION

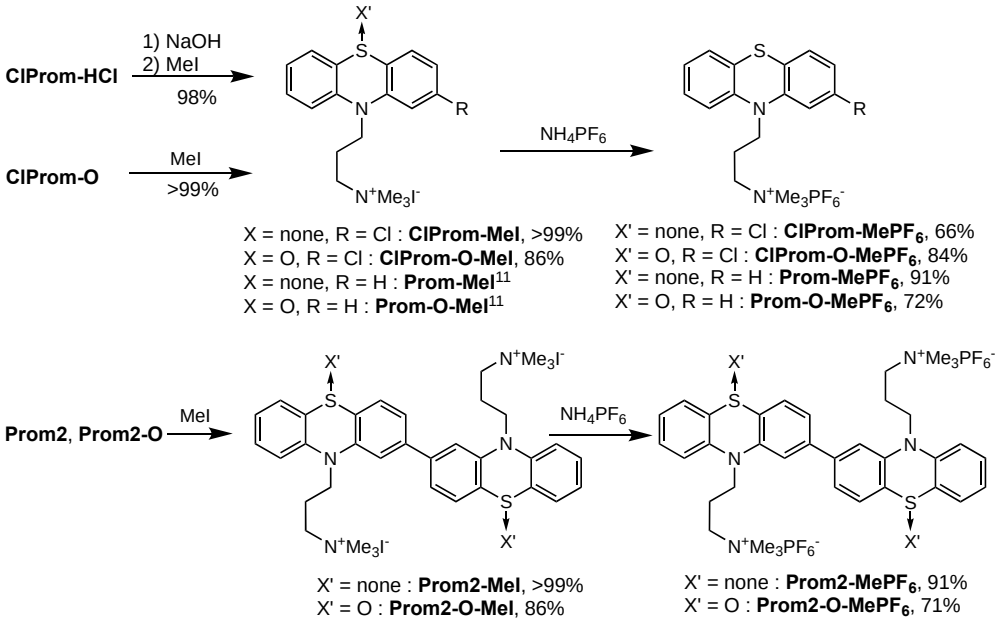
*Chemical modification of **ClProm***

We synthesized several compounds from commercially avaliable **ClProm-HCl** as shown in Scheme 2. The oxidation of **ClProm-HCl** using *m*-chloroperoxybenzoic acid (*m*CPBA)[11,12] afforded **ClProm-O**. It is known that the organometallic compound-mediated dehalogenative coupling reaction of aromatic halide affords an aromatic-aromatic compound.[15,16] Usually, aromatic bromide or iodide has been used for such a reaction. However, in some cases, aromatic chloride can be used; for instance, crown ethereal subunit-containing polythiophenes were prepared from corresponding dichlorothiophene.[16] Therefore, we tried to prepare promazine dimer-type compounds (**Prom2** and **Prom2-O)** by the Ni-promoted coupling reaction of **ClProm-HCl** and **ClProm-O**, respectively (Scheme 2).



Scheme 2

The dimethylamino group in **ClProm**, **ClProm-O**, **Prom2** and **Prom2-O** was converted to a trimethyl-ammonium group by the treatment of methyl iodide as shown in Scheme 3.[5,11,17] Next, the counter ion (I^-) of the compounds were exchanged to PF_6^- by a modified reported method (Scheme 3)[18] because iodide prevents us from observing the oxidation potential of the phenothiazine unit.[11,19] In addition, I^- of **Prom-MeI**[11] and **Prom-O-MeI**[11] were also exchanged to PF_6^- for comparison of optical and electrochemical properties (Scheme 3). Figure 1 shows ESI-MS spectra of the promazine dimer-type compounds. In the spectra, molecular ion peaks of **Prom2** and **Prom2-O** were observed as $[M+H]^+$, whereas those of **Prom2-MeZ** and **Prom2-O-MeZ** (Z = I^- and PF_6^-) were observed as $[M-2Z]^{2+}$, suggesting that dication was formed.



Scheme 3

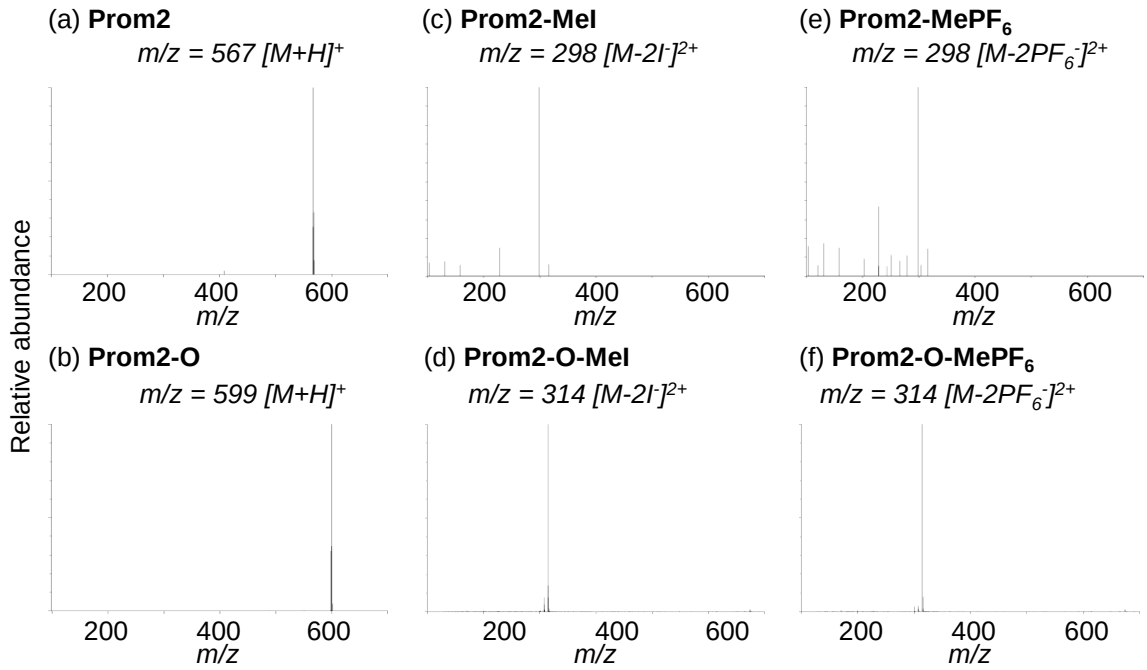


Figure 1. ESI-MS of (a) **Prom2**, (b) **Prom2-O**, (c) **Prom2-MeI**, (d) **Prom2-O-MeI**, (e) **Prom2-MePF6**, and (f) **Prom2-O-MePF6**

In the ^{19}F and ^{31}P NMR spectra of PF_6^- salts (**ClProm**, **ClProm-O**, **Prom2** and **Prom2-O**), the signals appear almost the same region and the same coupling constant.[20] As shown in Figure 2, the IR spectra of these compounds also suggested formation of PF_6^- salt (# marks in the Figure).

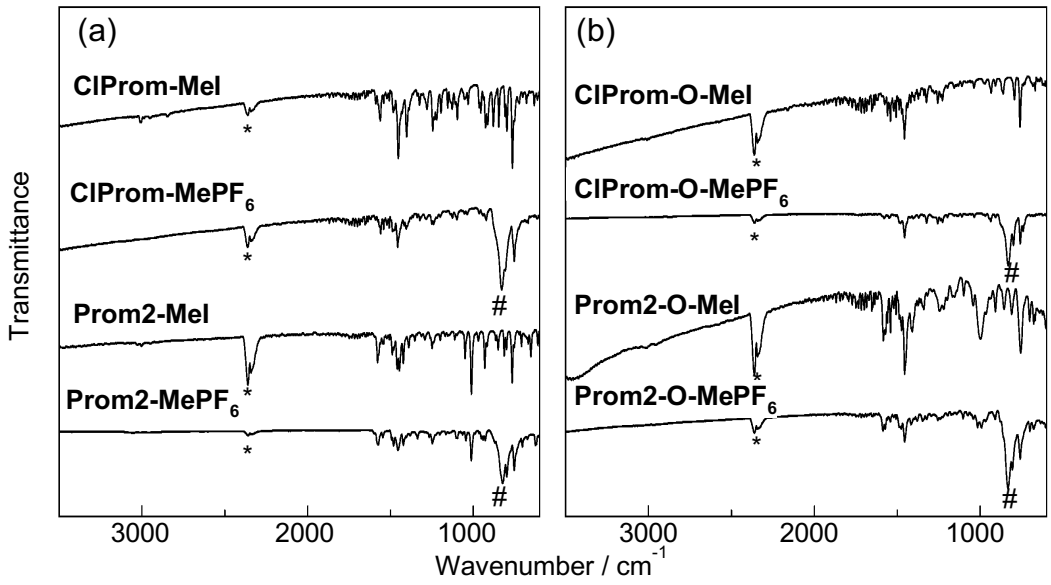


Figure 2. IR spectra of (a) **ClProm-MeZ** and **Prom2-MeZ** and (b) **ClProm-O-MeZ** and **Prom2-O-MeZ** (**Z** = **I** or $\mathbf{PF_6}$). The * marks is due to CO_2.

Electrochemical behavior

The electrochemical behavior of the products was studied using cyclic voltammetry (CV). The redox responses of the compounds are shown in Figure 3, and the data are summarized in Table 1. As shown in Figure 3(e), **Prom-MePF$_6$** showed a three-step oxidation process, whereas **Prom-O-MePF$_6$** showed one irreversible oxidation process (Figure 3(f)). The first oxidation process of **Prom-MePF$_6$** (reversible, $E_{pa}^{1/2}$ = +0.32 V *vs.* Fc^+/Fc) indicates oxidation of diphenylamine,[2,4,21] and the second (+0.89 V *vs.* Fc^+/Fc) and the third (+1.04 V *vs.* Fc^+/Fc) irreversible oxidation processes indicate oxidation of S[21,22] and *S*-oxide,[23] respectively. The third oxidation potential of **Prom-MePF$_6$** is almost same as the first oxidation potential of **Prom-O-MePF$_6$** (+1.04 V *vs.* Fc^+/Fc). These results show that oxidative polymerization of **Prom** did not afford the polymer due to the formation of promazine oxide.[9,10]

Next, the effect of the introduction of Cl group to **Prom** was investigated. The oxidation potential of **ClProm-MePF$_6$** (+0.46 V *vs.* Fc^+/Fc) is observed at higher potential than that of **Prom-MePF$_6$**. No oxidation response was observed in the CV of **ClProm-O-MePF$_6$**, therefore the oxidation potential of **ClProm-O-MePF$_6$** is considered to appear more positive than that of **Prom-O-MePF$_6$**. The electrochemical properties of **Prom**[21] and **ClProm**,[23] which are the former compounds of the quaternized products, were investigated in an acidic solution. According to the reports, $E_{pa}^{1/2}$ values of **Prom** and **ClProm** are observed at +0.51 V (*vs.* SHE)[21] and +0.54 V (*vs.* SHE),[23] respectively, suggesting that the Cl group acts as an electron-withdrawing substituent.

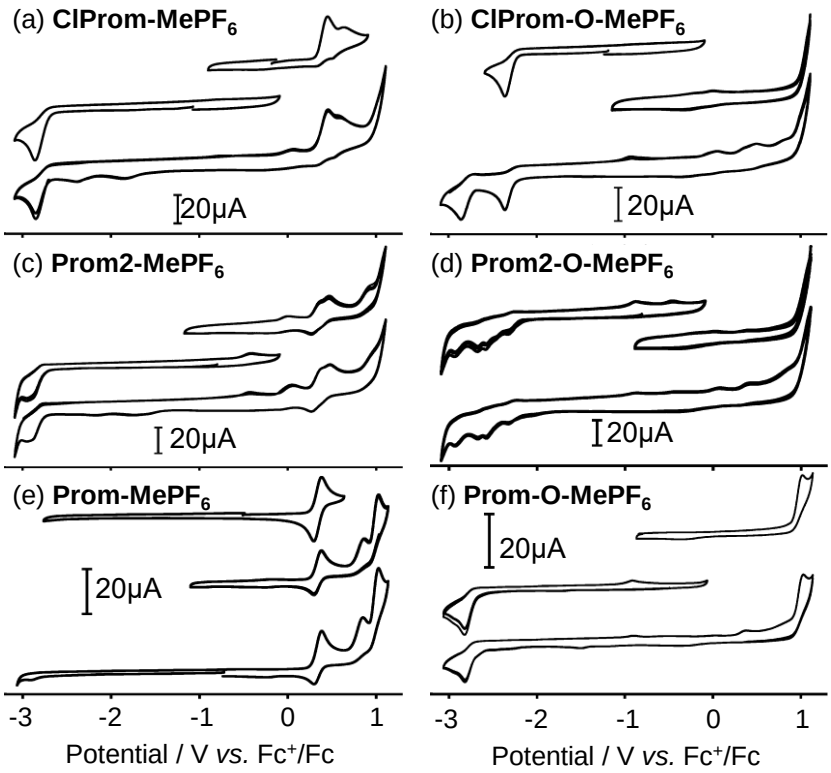


Figure 3. CVs of dissolved (a) **Prom2**, (b) **Prom2-O**, (c) **Prom2-MeI**, (d) **Prom2-O-MeI**, (e) **Prom2-MePF6**, and (f) **Prom2-O-MePF6**

Table 1. Electrochemical data of the promazine derivatives

compound	Oxidation		Reduction	
	E_{pa}[a]	E_{pc}[a]	E_{pc}[a]	E_{pa}[a]
ClProm-MePF6	0.46	[b]	-2.85	[b]
ClProm-O-MePF6	Not observed		-2.36 -2.86	[b]
Prom2-MePF6	0.48	0.27	-2.95	[b]
Prom2-O-MePF6	Not observed		-2.33 -2.57 -2.67 -2.94	[b]
Prom-MePF6	0.38 0.89 1.04	0.27 [b] [b]	Not observed	
Prom-O-MePF6	1.03	[b]	-2.82	[b]

[a] *vs.* Fc^+/Fc. [b] Irreversible.

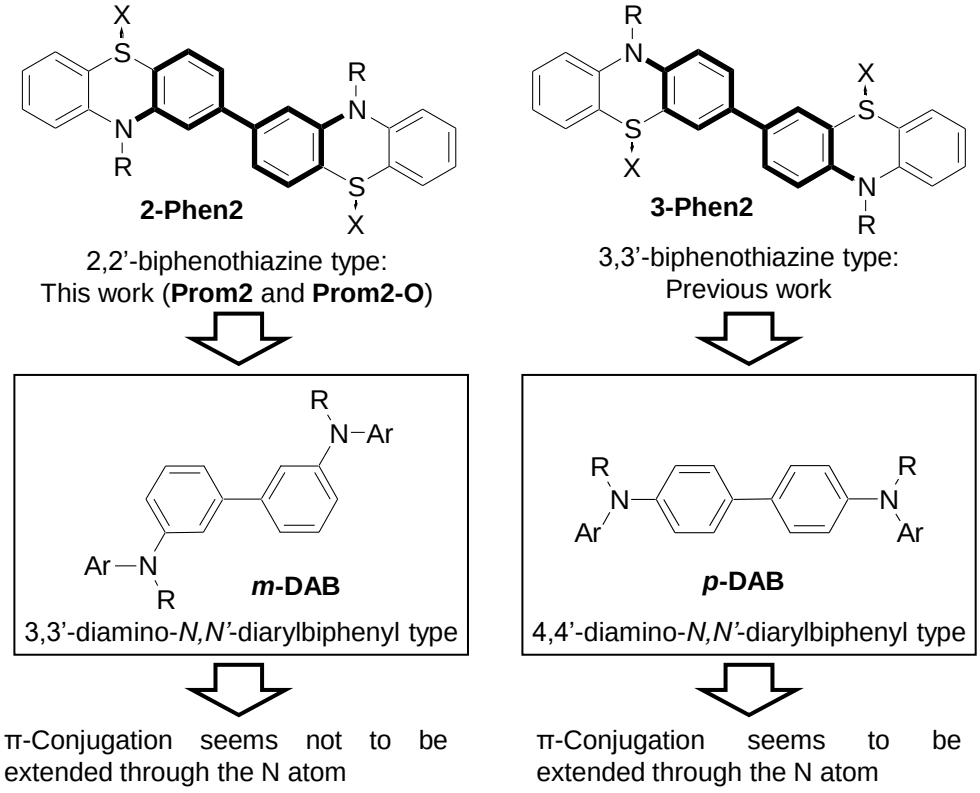
In the oxidation region, the CV of **ClProm-MePF6** showed irreversible behavior. This was different from CV of **Prom-MePF6** which showed reversible oxidation behavior. The CV of **ClProm-MePF6** was also observed differently from the previously reported CV of **ClProm** which showed reversible oxidation

behavior.[23] These differences seem to be due to the interaction between oxidized **ClProm** compounds and the counter anion of the electrolyte.

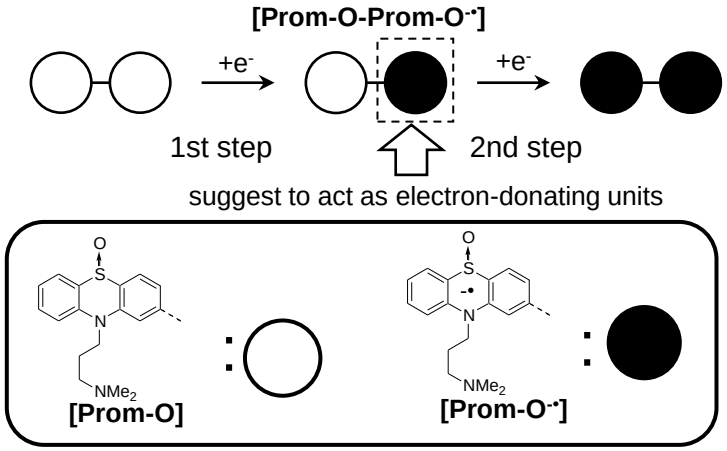
As described above, the electrochemical properties of **ClProm** have been reported previously,[23] however, only the oxidation properties of the compounds have been described in the articles.[21,23] We tried to investigate the reduction behavior of **ClProm**-type compounds. As shown in Figure 3(a), negative scan of **ClProm-MePF$_6$** shows an irreversible reduction peak at E_{pc} = -2.85 V (*vs.* Fc^+/Fc) although **Prom-MePF$_6$** shows no reduction peak in the reduced region (Figure 3(e)). Similarly, the first reduction potential of **ClProm-O-MePF$_6$** (-2.36 V *vs.* Fc^+/Fc) appears at a higher potential than that of **Prom-O-MePF$_6$** (-2.82 V *vs.* Fc^+/Fc). These results indicate that the Cl group introduced into the phenothiazine unit of **Prom** works as an electron-withdrawing group, and shifts the reduction potential of the compound to the negative side. Next, the effect of dimerization on the electrochemical properties was examined. The first oxidation potential of **Prom2-MePF$_6$** ($E_{pa}^{1/2}$ = +0.38 V) is observed at a more positive potential than that of **Prom-MePF$_6$** ($E_{pa}^{1/2}$ = +0.33 V). Such a positive shift also appeared between **Prom2-O-MePF$_6$** (E_{pa} > +1.2 V) and **Prom-O-MePF$_6$** (E_{pa} = +1.03 V). As bis(*N*-substituted phenothiazine)s, derivatives bonded at the 3,3'-position have been reported (**3-Phen2**, Scheme 4).[24-26] The electrochemical behavior of 2,2'-bis(*N*-substituted phenothiazine) (**2-Phen2**, Scheme 4) derivatives (**Prom2** and **Prom2-O**, this work) was different from that of **3-Phen2**. The first oxidation potential of **3-Phen2** (+0.64 V *vs.* Fc^+/Fc) appears more positive than that of monophenothiazine (+0.73 V *vs.* Fc^+/Fc).[24] CV of **Prom2-MePF$_6$** did not show two-step clear reversible oxidation process like **3-Phen2**. This result suggests the second oxidation potential was not so different from the first oxidation potential. As shown in Scheme 5, **3-Phen2** contains 4,4'-diamino-*N*,*N*'-diarylbiphenyl (***p*-DAB**) structure (bold line in **3-Phen2**), therefore, **3-Phen2** can be regarded as having a π-conjugated system extended through the N atoms. On the other hand, **Prom-2** and **Prom2-O** have a 3,3'-diamino-*N*,*N'*-diarylbiphenyl (***m*-DAB**, Scheme 4) structure, therefore it is considered that there is no extension of the π-conjugated system like **3-Phen2**. These structural differences in the compounds appear to have a great influence on the electrochemical oxidation behavior of each compound. Oxidative scan of **Prom2-MePF$_6$** (Figure 3(c)) is similar to those observed in ***m*-DAB**-type compounds which show one oxidation process.[27]

On the other hand, in the negative scan of **Prom2-MePF$_6$**, an irreversible reduction peak appeared at -2.95 V (*vs.* Fc^+/Fc, (Figure 3(c)), which was not observed in **Prom-MePF$_6$** (Figure 3(e)). The first reduction potential of **Prom2-O-MePF$_6$** (-2.33 V *vs.* Fc^+/Fc, Figure 3(d)) is observed at a more positive potential than that of **Prom2-MePF$_6$**, suggesting that the formed *S*-oxide unit was electron-withdrawing. Negative scan of **Prom2-O-MePF$_6$** showed complicated peaks which were not observed in **Prom2-MePF$_6$**. This result can be explained as follows. The electrochemical reduction of **Prom2-O-MePF$_6$** forms the species [**Prom-O-Prom-O**$^{-\cdot}$] (Scheme 5), in which one of the two **Prom-O**

units is an anionic radical. The radical anion unit acts as an electron donating group for the next **Prom-O** unit, making it less susceptible to the second reduction. Similar behavior has been observed with electrochemical oxidation of ***p*-DAB** compounds (such as *N,N'*-dimethyl-*N,N'*-diphenylbenzidine (**MPBz**)[28] and biphenazasiline (**Phz2**)[4]). Therefore, the CV on the reduction side of **Prom2-O-MePF$_6$** is considered to have exhibited a reduction process of two or more steps.



Scheme 4. Juncture of biphenothiazines



Scheme 5

Optical properties

The absorption spectra of the PF_6 salts are shown in Figure 4, and the data are summarized in Table 2. The absorption λ_{max} of **Prom-MePF$_6$** (256 and 307 nm) and **Prom-O-MePF$_6$** (276, 296, and 339 nm) are almost the same as the corresponding iodides (254 and 307 nm (**Prom-MeI**) and 275, 295, and 341 nm (**Prom-O-MeI**).[11] This suggests that absorption λ_{max} of the compounds was not affected by the sort of the counter anion. Usually, *N*-substituted diphenylamines show absorption λ_{max} corresponding to the π-π* transition at ca. 300 nm: for example, diphenylamine (λ_{max} = 297 - 305 nm);[29] phenazasiline (λ_{max} = 295 nm).[4,6] In agreement with the literature, the π-π* transition of monopromazine derivatives is observed at λ_{max} = ca. 305 nm. However, the π-π* transition in monopromazine oxide derivatives is red-shifted by ca. 30 nm due to the narrow π-π* gap resulting from the electron-withdrawing *S*-oxide unit. In contrast, the introduction of the Cl group had a less significant effect on the spectroscopic properties of the compound (Table 2). The $\Delta\lambda_{max}$ value between **Prom-MePF$_6$**, **Prom-O-MePF$_6$** and their dimerized analog, **Prom2-MePF$_6$**, **Prom2-O-MePF$_6$**, is about 10 nm. This value is smaller than those of ***p*-DAB**-type compounds, **3-Prom2** ($\Delta\lambda_{max}$ = 38 nm vs. corresponding monomer)[24] and **Phz2** ($\Delta\lambda_{max}$ = 46 nm vs. corresponding monomer).[6] This result indicates that π-conjugation of bis(promazine) type compounds (**Prom2-MePF$_6$** and **Prom2-O-MePF$_6$**) were not extended through the N atom of the diphenylamine unit, because the two **Prom** units in **Prom2** form a ***m*-DAB**-type structure (Scheme 4).

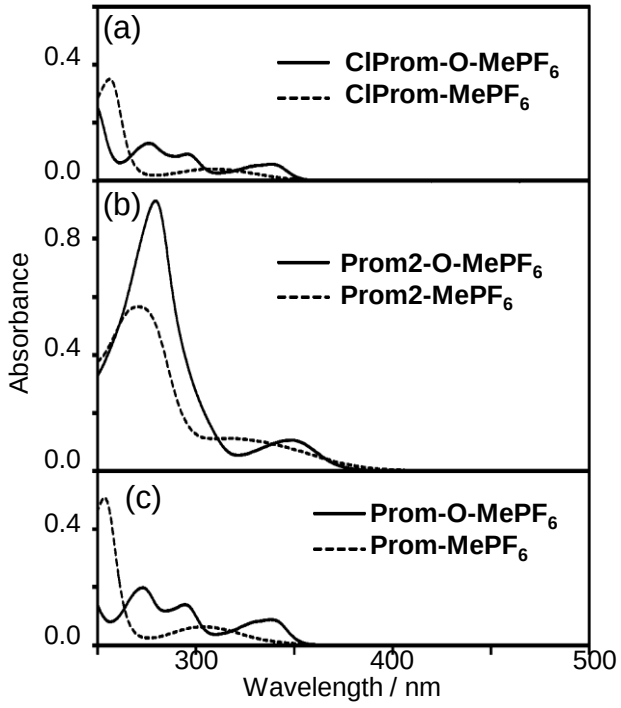


Figure 4. Absorption spectra of (a) chlorpromazine derivatives, (b) promazine-dimer type compounds, and (c) promazine derivatives in a 10 μM MeCN solution.

Table 2. Optical data of the promazine derivatives

Compound	UV λ_{max}/ nm [a]	FL λ_{max}/ nm [a,b]
ClProm-MePF$_6$	256, 307	450
ClProm-O-MePF$_6$	276, 296, 339	369
Prom2-MePF$_6$	271, 315	480
Prom2-O-MePF$_6$	280, 348	430
Prom-MePF$_6$	254, 306	442
Prom-O-MePF$_6$	273, 294, 338	370

[a] MeCN solution. [b] Excited at UV λ_{max}.

Figure 5 displays the fluorescent spectra of a 10 μM acetonitrile solution of the promazine derivatives. As shown in Figure 5 and Table 2, fluorescent λ_{max} of *S*-oxide-type compounds appeared at shorter wavelength than that observed with *S*-type compound like previously reported bis(phenylethynyl)phenothiazine.[30] The observed fluorescence intensities of the promazine dimer-type compounds (**Prom2-MePF$_6$** and **Prom2-O-MePF$_6$**) are stronger than those of corresponding monopromazine derivatives (**Prom-MePF$_6$** and **Prom-O-MePF$_6$**), respectively. This result was also observed in **3-Phen2** type compound.[25] As described above, π-conjugation of **3-Phen2** was extended through N atom in contrast to **Prom2-MePF$_6$** and **Prom2-O-MePF$_6$** (**2-Phen2** type compound). This suggests that the formation of the biphenyl structure caused an increase in the fluorescence intensity of **Prom2-MePF$_6$** and **Prom2-O-MePF$_6$**.

As shown in Figure 5, the fluorescence intensities of **Prom-O-MePF$_6$** and **ClProm-O-MePF$_6$** are stronger than those of **Prom-MePF$_6$** and **ClProm-MePF$_6$**. These are same results as the relationship between **Prom-MeI** and **Prom-O-MeI**,[11] suggesting that formation of *S*-oxide cause the fluorescence intensity stronger. But in contrast to the monomeric compounds, the dimeric *S*-oxide, **Prom2-O-MePF$_6$**, exhibits weaker fluorescence intensity than that of the promazine dimer compound, **Prom2-MePF$_6$**. This relationship was also observed in bis(phenylethynyl)phenothiazine and bis(phenylethynyl)phenothiazine oxide.[30] These results suggest that effect of formation of biphenyl seems to be stronger than that of *S*-oxide for fluorescence intensity of **Prom2-MePF$_6$** and **Prom2-O-MePF$_6$**.

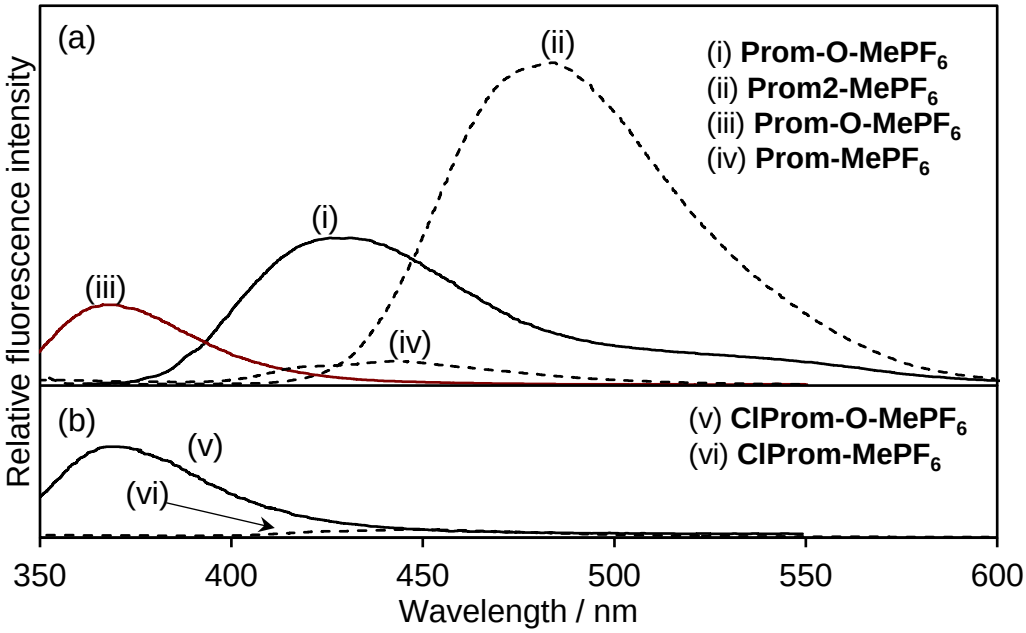


Figure 5. Fluorescence spectra of promazine derivatives in a 10 μM MeCN solution.

In summary, we reported the effects of the Cl group on chlorpromazine, **ClProm**, and chlorpromazine-*S*-oxide, **ClProm-O**, which are *N*-aminoalkyl-substituted phenothiazine derivatives containing a chloro group. The Cl group of **ClProm** can act not only as an electron-withdrawing group but also as a reactive unit for preparing **Prom2** with a dimeric structure. Further chemical modification of promazine is expected to develop into highly functional materials.

EXPERIMENTAL

Reagents 10-(3-(trimethylammonio)-1-propyl)-10*H*-phenothiazine iodide **(Prom-MeI)** and 10-(3-(trimethylammonio)-1-propyl)-10*H*-phenothiazine-5-oxide iodide (**Prom-O-MeI**) were prepared by previously described methods.[11] Other chemicals were used as purchased.

Measurement

^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H} and ^{31}P{^{1}H} NMR spectra were taken by using a Bruker AVANCEIII400HD spectrometer. Absorption spectra were measured by using a JASCO V-570 spectrometer. Fluorescence spectra were measured by using a Hitachi 4010 spectrometer and were excited at the absorption λ_{max} light. ESI-MS were measured by LC-MS system: Shimadzu Nexera X2 was used for LC and Shimadzu LCMS-8040 was used for MS.

Electrochemical measurements

Cyclic voltammetry (CV) was measured as follows. A conventional three-electrode configuration was used, with a glassy carbon electrode (BAS PFCE 3 carbon electrode), a platinum wire auxiliary electrode

(Niraco, special order), and 0.1 M $AgNO_3$/Ag reference (BAS RE-7). Cyclic voltammograms were recorded at a scan rate of 100 mV s^{-1}. The sample concentration was 1 mM in CH_2Cl_2 containing 0.1 M *n*-Bu_4NPF_6 as the supporting electrolyte.

Preparation of 2-chloro-10-(3-(dimethylamino)-1-propyl)-10*H*-phenothiazine-5-oxide (ClProm-O)

Under N_2 atmosphere, 4.29 g (12.1 mmol) of **ClProm-HCl** was dissolved in 50 mL of $CHCl_3$; then, 2.49 g (14.1 mmol) of *m*-chloroperoxybenzoic acid was added to the solution at 0 °C and stirred overnight. The reaction was quenched by the addition of aqueous NaOH, and the solution was extracted by $CHCl_3$. The organic phase was dried over $MgSO_4$, then the solvent was removed by evaporation. The residue was purified by alumina column chromatography (eluent: $CHCl_3$) and dried in vacuo to afford **ClProm-O** as a colorless powder in 90% yield (3.64 g, 10.9 mmol).

^{1}H NMR ($CDCl_3$) *δ*:7.94 (dd, 1H, *J* = 7.7 and 1.6 Hz, Ar), 7.86 (d, 1H, *J* = 8.2 Hz, Ar), 7.6-7.8 (m, 2H, Ar), 7.52 (d, 1H, *J* = 8.1 Hz, Ar), 7.1-7.3 (m, 2H, Ar), 4.31 (t, 2H, *J* = 7.8 Hz, ArN-C*H*$_2$-), 2.46 (t, 2H, -C*H*$_2$-NMe$_2$), 2.31 (s, 6H, -N*Me*$_2$), 1.9-2.2 (m, 2H, -CH_2-C*H*$_2$-CH_2-). ^{13}C{^{1}H} NMR ($CDCl_3$) *δ*:139.32, 138.99, 137.84, 133.03, 132.82, 131.69, 124.25, 122.50, 122.25, 121.91, 116.06, 115.94, 56.51, 46.05, 45.72, 24.55.

IR (ATR) 2943, 2768, 1577, 1450, 1418, 1249, 1095, 1025, 922, 834, 795, 747, 710, 664 cm^{-1}. ESI-MS: *m/z* = 335 $[M+H]^+$.

Preparation of 10,10'-bis(3-(dimethylamino-1-propyl)-10*H*,10'*H*-2,2'-biphenothiazine (Prom2)

Under N_2 atmosphere, **ClProm-HCl** (0.71 g, 2.0 mmol) was added to a mixture of [Ni(cod)$_2$] (0.98 g, 3.6 mmol, cod = 1,5-cyclooctadiene), cod (1 mL), and 2,2'-bipyridyl (0.56 g, 3.6 mmol) in DMF (10 mL), and the mixture was heated at 80 °C for 48 h. The reaction was quenched by the addition of NaOH aqueous solution and the mixture was extracted with $CHCl_3$. The organic layer was successively washed with water and saturated NaCl aqueous solution, and dried over anhydrous $MgSO_4$. After removing the drying agent by filtration, the organic layer was purified by alumina column chromatography (eluent: $CHCl_3$) and dried in vacuo to afford **Prom2** as a brown oil in 53% yield (0.30 g, 0.53 mmol).

^{1}H NMR ($CDCl_3$) *δ*:7.1-7.3 (m, 6H, Ar), 7.07 (dd, 2H, *J* = 7.9 and 1.7 Hz, Ar), 7.02 (d, 2H, *J* = 1.6 Hz, Ar), 6.8-7.0 (m, 4H, Ar), 3.97 (t, 4H, *J* = 7.0 Hz, Ar$_2$N-C*H*$_2$-), 2.41 (m, 4H, *J* = 2.4 Hz,-C*H*$_2$-NMe$_2$), 2.19 (s, 12H, -N*Me*$_2$), 1.8-2.1 (m, 4H, -CH_2-C*H*$_2$-CH_2-). ^{13}C{^{1}H} NMR ($CDCl_3$) *δ*:145.69, 145.05, 140.43, 127.52, 127.44, 127.24, 125.04, 124.50, 122.51, 121.16, 115.68, 114.27, 57.16, 45.59, 45.46, 25.25. IR (ATR) 2937, 2815, 2763, 2361, 1581, 1547, 1453, 1398, 1243, 1216, 1152, 1129, 1107, 1038, 803, 744 cm^{-1}. ESI-MS: *m/z* = 567 $[M+H]^+$.

Preparation of 10,10'-bis(3-(dimethylamino)-1-propyl)-10*H*,10'*H*-2,2'-biphenothiazine-5,5'-dioxide (Prom2-O)

Under N_2 atmosphere, **ClProm-O** (0.40 g, 1.2 mmol) was added to a mixture of [Ni(cod)$_2$] (0.39 g, 1.4 mmol), cod (1 mL), and 2,2'-bipyridyl (0.21 g, 1.3 mmol) in toluene (5 mL) and the mixture was heated at 80 °C for 4 days. The reaction was quenched by the addition of NaOH solution and the mixture was extracted with $CHCl_3$. The organic layer was successively washed with water and saturated NaCl aqueous solution, and dried over anhydrous $MgSO_4$. After removing the drying agent by filtration, the organic layer was evaporated and dissolved to $CHCl_3$ and reprecipitated by hexane. The precipitate was dried in vacuo to afford **Prom2-O** as a colorless powder in 86% yield (0.30 g, 0.51 mmol).

^{1}H NMR ($CDCl_3$) δ:8.05 (d, 2H, J = 8.9 Hz, Ar), 7.98 (dd, 2H, J = 7.7, 1.6 Hz, Ar), 7.75 (dd, 2H, J = 4.6, 1.3 Hz, Ar), 7.6-7.7 (m, 2H, Ar), 7.56 (d, 2H, J = 8.6 Hz, Ar), 7.47 (d, 2H, J = 8.0 Hz, Ar), 7.29 (t, 2H, J = 7.4 Hz, Ar), 4.4-4.5 (m, 4H, ArN-CH_2-), 2.4-2.6 (m, 4H, -CH_2-NMe$_2$), 2.24 (s, 12H, -NMe_2), 2.0-2.2 (m, 4H, -CH$_2$-CH_2-CH$_2$-). ^{13}C{^{1}H} NMR ($CDCl_3$) δ: 145.45, 138.31, 133.00, 132.24, 131.71, 122.05, 121.04, 121.01, 115.93, 115.23, 115.20, 56.65, 46.15, 45.75, 24.68. IR (ATR) 2943, 2817, 2767, 1585, 1541, 1458, 1408, 1369, 1254, 1219, 1158, 1100, 1019, 896, 876, 831, 803, 774, 748, 706, 676, 650 cm^{-1}. ESI-MS: m/z = 599 [M+H]$^+$.

Preparation of 2-chloro-10-((3-trimethylammonio)-1-propyl)-10*H*-phenothiazine iodide (ClProm-MeI)

Iodomethane (3 mL) was added to a benzene solution (20 mL) of **ClProm**, which was prepared by the neutralization of **ClProm-HCl** (2.35 g, 6.6 mmol) using NaOH, and stirred for 24 h to yield a colorless precipitate. The precipitate was collected by filtration, washed with hexane, and dried in vacuo to afford **ClProm-MeI** as a yellow powder in 97% yield (2.98 g, 6.5 mmol, from **ClProm-HCl**).

^{1}H NMR ($CDCl_3$) δ 7.2-7.3 (m, 1H, Ar), 7.19 (d, 1H, J = 7.6 Hz, Ar), 7.10 (m, 1H, Ar), 6.95-7.05 (m, 3H, Ar), 6.91 (d, 1H, J = 2.0 Hz, Ar), 4.08 (t, 2H, J = 5.9 Hz, ArN-CH_2-), 3.7-3.8 (m, 2H, -CH_2-NMe$_3$), 3.26 (s, 9H, -NMe_3), 2.2-2.4 (m, 2H, -CH$_2$-CH_2-CH$_2$-). ^{13}C NMR ($CDCl_3$) δ 146.11, 143.35, 133.86, 128.44, 128.18, 128.00, 125.99, 124.67, 123.99, 123.41, 116.97, 116.65, 64.60, 53.75, 43.60, 20.80. IR (ATR) 3010, 1588, 1561, 1541, 1453, 1403, 1484, 1280, 1245, 1325, 1222, 1195, 1155, 1128, 1096, 1053, 1032, 964, 955, 927, 913, 879, 846, 809, 797, 764, 722, 702, 679, 633, 613 cm^{-1}. ESI-MS: m/z = 333 [M-I$^-$]$^+$.

Preparation of 2-chloro-10-((3-trimethylammonio)-1-propyl)-10*H*-phenothiazine-5-oxide iodide (ClProm-O-MeI)

Iodomethane (3 mL) was added to a benzene solution (20 mL) of **ClProm-O** (1.09 g, 3.3 mmol) and stirred for 24 h to yield a pale-yellow precipitate. The precipitate was collected by filtration, washed

with hexane, and dried in vacuo to afford **ClProm-O-MeI** as a pale-yellow powder in 94% yield (1.46 g, 3.1 mmol).

^{1}H NMR ($CDCl_3$) δ:7.9-8.1 (m, 2H, Ar), 7.87 (d, 4H, J = 1.7 Hz, Ar), 7.6-7.85 (m, 2H, Ar), 7.3-7.4 (m, 2H, Ar), 4.47 (t, 2H, J = 7.0 Hz, ArN-CH_2-), 3.43 (t, 2H, J = 8.4 Hz, -CH_2-NMe_3), 2.97 (s, 9H, -NMe_3), 2.0-2.4 (m, 2H, -CH_2-CH_2-CH_2-). ^{13}C NMR ($CDCl_3$) δ:139.22, 137.88, 137.45, 133.38, 132.56, 130.81, 125.37, 123.97, 122.80, 122.21, 117.34, 116.79, 62.20, 52.35, 43.63, 20.18. IR (ATR) 1577, 1490, 1447, 1422, 1250, 1050, 1011, 930, 849, 814, 766, 653, 610 cm^{-1}. ESI-MS: m/z = 349 [M-I$^-$]$^+$.

Preparation of 10,10'-bis(3-(trimethylammonio)-1-propyl)-10*H*,10'*H*-2,2'-biphenothiazine diiodide (Prom2-MeI)

Iodomethane (1 mL) was added to a benzene solution (5 mL) of **Prom2** (0.12 g, 0.21 mmol) and stirred for 24 h to yield a precipitate. The precipitate was collected by filtration, washed with hexane, and dried in vacuo to afford **Prom2-MeI** as a pale-yellow powder in 87% yield (0.15 g, 0.18 mmol).

^{1}H NMR (DMSO-d_6) δ:7.2-7.4 (m, 10H, Ar), 7.13 (d, 2H, J = 7.7 Hz, Ar), 7.0-7.1 (m, 2H, Ar), 4.66 (t, 4H, J = 6.7 Hz, ArN-CH_2-), 3.3-3.5 (m, 4H, -CH_2-NMe_3), 3.01 (s, 18H, -NMe_3), 2.0-2.3 (m, 4H, -CH_2-CH_2-CH_2-). ^{13}C NMR (DMSO-d_6) δ: 145.31, 144.15, 139.60, 127.80, 127.63, 127.44, 124.16, 123.85, 123.08, 121.49, 116.30, 114.28, 63.31, 52.35, 43.55, 20.42. IR (ATR) 1457, 1324, 1256, 1227, 934, 862, 794, 760, 668 cm^{-1}. ESI-MS: m/z = 298 [M-2I$^-$]$^{2+}$

Preparation of 10,10'-bis(3-(trimethylammonio)-1-propyl)-10*H*,10'*H*-2,2'-biphenothiazine-5,5'-dioxide diiodide (Prom2-O-MeI)

Iodomethane (2 mL) was added to a benzene solution (35 mL) of **Prom2-O** (0.17 g, 0.29 mmol) and stirred for 24 h to yield a pale-yellow precipitate. The precipitate was collected by filtration, washed with hexane, and dried in vacuo to afford **Prom2-O-MeI** as a pale-yellow powder in 76% yield (0.19 g, 0.22 mmol).

^{1}H NMR (DMSO-d_6) δ: 8.16 (dd, 2H, J = 8.0, 2.3 Hz, Ar), 7.95-8.1 (m, 4H, Ar), 7.7-7.9 (m, 6H, Ar), 7.3-7.5 (m, 2H, Ar), 4.66 (4H, ArN-CH_2-), 3.4-3.6 (m, 4H, -CH_2-NMe_3), 2.96 (s, 9H, -NMe_3), 2.95 (s, 9H, -NMe_3), 2.1-2.4 (m, 4H, -CH_2-CH_2-CH_2-). ^{13}C NMR ($CDCl_3$) δ: 144.20, 144.15, 138.78, 138.08, 133.25, 131.35, 131.25, 130.66, 125.71, 125.21, 125.14, 122.54, 121.83, 121.78, 117.39, 116.23, 62.26, 52.32, 43.50, 20.48. IR (ATR) 1717, 1654, 1584, 1541, 1507, 1456, 1410, 1246, 998, 908, 856, 810, 756, 702 cm^{-1}. ESI-MS: m/z = 314 [M-2I$^-$]$^{2+}$

Preparation of 2-chloro-10-((3-trimethylammonio)-1-propyl)-10*H*-phenothiazine hexafluorophosphate (ClProm-MePF$_6$)

NH_4PF_6 (0.47 g, 2.9 mmol) was added to a mixture of MeOH-water (50:50 v/v, 40 mL) and **ClProm-MeI** (0.54 g, 1.2 mmol). The generated white precipitate was collected by filtration, washed with MeOH,

and dried in vacuo. **ClProm-MePF$_6$** was obtained as a colorless powder in a 66% yield (0.47 g, 0.98 mmol).

^{1}H NMR (acetone-d_6) δ 7.15-7.4 (m, 5H, Ar), 6.9-7.1 (m, 2H, Ar), 4.16 (t, 2H, ArN-CH_2-), 3.6-3.8 (m, 2H, -CH_2-NMe$_3$), 3.28 (s, 9H, -NMe_3), 2.3-2.5 (m, 2H, -CH$_2$-CH_2-CH$_2$-). ^{13}C NMR (acetone-d_6) δ 147.54, 144.95, 134.10, 129.12, 128.84, 128.40, 125.98, 125.15, 124.42, 123.61, 117.45, 117.01, 65.21, 53.73, 44.67, 44.65, 21.65. ^{19}F NMR (acetone-d_6) δ -72.11 (d, J = 707.8 Hz). ^{31}P NMR (acetone-d_6) δ -144.24 (sep, J = 708.2 Hz). IR (ATR) 1559, 1541, 1508, 1488, 1457, 1405, 1239, 1098, 923, 828, 753 cm^{-1}. ESI-MS: m/z = 333 [M-PF$_6^-$]$^+$.

Preparation of 2-chloro-10-(3-(trimethylammonio)-1-propyl)-10*H*-phenothiazine-5-oxide hexafluorophosphate (ClProm-O-MePF$_6$)

NH_4PF_6 (0.54 g, 3.3 mmol) was added to a mixture of MeOH-water (50:50 v/v, 50 mL) and **ClProm-O-MeI** (0.74 g, 1.5 mmol). The generated precipitate was collected by filtration, washed with MeOH, and dried in vacuo. **ClProm-O-MePF$_6$** was obtained as a colorless powder in an 84% yield (0.64 g, 1.29 mmol).

^{1}H NMR (acetone-d_6) δ:7.9-8.1 (m, 2H, Ar), 7.7-7.85 (m, 3H, Ar), 7.3-7.5 (m, 2H, Ar), 4.66 (m, 2H, ArN-CH_2-), 3.5-3.6 (m, 2H, -CH_2-NMe$_3$), 3.06 (s, 9H, -NMe_3), 2.40-2.60 (m, 2H, -CH$_2$-CH_2-CH$_2$-). ^{13}C NMR ($CDCl_3$) δ:141.11, 139.22, 139.11, 134.00, 132.55, 130.95, 128.80, 127.31, 123.95, 123.38, 118.91, 118.56, 63.73, 53.41, 44.50, 22.13. ^{19}F NMR (acetone-d_6) δ: -72.34 (d, J = 708.2 Hz). ^{31}P NMR (acetone-d_6) δ -144.27 (sep, J = 707.9 Hz). IR (ATR) 3045, 1574, 1546, 1481, 1455, 1422, 1336, 1248, 1096, 1045, 1012, 941, 929, 823, 798, 753, 704, 626 cm^{-1}. ESI-MS: m/z = 349 [M-PF$_6^-$]$^+$.

Preparation of 10,10'-bis(3-(trimethylammonio)-1-propyl)-10*H*,10'*H*-2,2'-biphenothiazine bis(hexafluorophosphate) (Prom2-MePF$_6$)

NH_4PF_6 (0.16 g, 0.98 mmol) was added to a mixture of MeOH-water (50:50 v/v, 40 mL) of **Prom2-MeI** (0.10 g, 0.12 mmol). The generated precipitate was collected by filtration, washed with water, and dried in vacuo. **Prom2-MePF$_6$** was obtained as a colorless powder in a 91% yield (0.098 mg, 1.1 mmol).

^{1}H NMR (acetone-d_6) δ:7.3-7.5 (m, 10H, Ar), 7.1-7.2 (m, 2H, Ar), 7.0-7.1 (m, 2H, Ar), 4.27 (t, 4H, J = 6.6 Hz ArN-CH_2-), 3.60-3.8 (m, 4H, -CH_2-NMe$_3$), 3.28 (s, 18H, -NMe_3), 2.4-2.6 (m, 4H, -CH$_2$-CH_2-CH$_2$-). ^{13}C NMR (acetone-d_6) δ:146.80, 145.53, 141.26, 128.69, 128.65, 128.44, 126.50, 126.07, 124.15, 122.66, 117.37, 115.51, 65.42, 53.77, 44.65, 21.80. ^{19}F NMR (acetone-d_6) δ -72.20 (d, J = 708.2 Hz). ^{31}P NMR (acetone-d_6) δ -144.25 (sep, J = 708.2 Hz). IR (ATR) 1579, 1550, 1456, 1323, 1256, 1227, 1037, 936, 831, 800, 759, 741 cm^{-1}. ESI-MS: m/z = 298 [M-2PF$_6^-$]$^{2+}$.

Preparation of 10,10'-bis(3-(trimethylammonio)-1-propyl)-10*H*,10'*H*-2,2'-biphenothiazine-5,5'-dioxide bis(hexafluorophosphate) (Prom2-O-MePF$_6$)

NH_4PF_6 (0.27 g, 1.6 mmol) was added to a mixture of MeOH-water (62.5:37.5 v/v, 40 mL) of **Prom2-O-MeI** (0.28 g, 0.32 mmol). The generated precipitate was collected by filtration, washed with water, and dried in vacuo. **Prom2-O-MePF$_6$** was obtained as a gray powder in a 72% yield (0.21 g, 0.23 mmol).

^{1}H NMR (acetone-d_6) δ:8.1-8.2 (m, 4H), 8.03 (dd, 2H, Ar), 7.7-7.9 (m, 6H, Ar), 7.3-7.5 (m, 2H, Ar), 4.7-5.0 (m, 4H, ArN-CH_2-), 3.5-3.7 (m, 4H, -CH_2-NMe$_3$), 3.06 (s, 9H, -NMe_3), 3.05 (s, 9H, -NMe_3), 2.40-2.60 (m, 4H, -CH$_2$-CH_2-CH$_2$-). ^{13}C NMR (acetone-d_6) δ:145.47, 140.85, 139.85, 133.98, 131.66, 131.06, 129.16, 128.61, 123.82, 122.88, 119.06, 117.93, 63.81, 53.48, 44.54, 22.44. ^{19}F NMR (acetone-d_6) δ: -72.36 (d, J = 708.2 Hz). ^{31}P NMR (acetone-d_6) δ: -144.26 (sep, J = 707.7 Hz). IR (ATR) 1586, 1573, 1542, 1508, 1475, 1456, 1417, 1380, 1348, 1323, 1256, 1197, 1173, 1103, 1075, 1042, 1016, 992, 909, 833, 806, 759, 701, 677, 606 cm^{-1}. ESI-MS: m/z = 314 [M-2PF$_6^-$]$^{2+}$.

Preparation of 10-(3-(trimethylammonio)-1-propyl)-10*H*-phenothiazine hexafluorophosphate (Prom-MePF$_6$)

NH_4PF_6 (0.17 g, 1.0 mmol) was added to a mixture of MeOH-water (50:50 v/v, 20 mL) of **Prom-MeI** (0.22 g, 0.51 mmol). The generated precipitate was collected by filtration, washed with MeOH, and dried in vacuo. **Prom-MePF$_6$** was obtained as a colorless powder in a 93% yield (0.21 g, 0.48 mmol).

^{1}H NMR (acetone-d_6) δ 7.15-7.30 (m, 4H, Ar), 7.05-7.15 (m, 2H, Ar), 6.9-7.05 (m, 2H, Ar), 4.15 (t, 2H, J = 6.7 Hz, ArN-CH_2-), 3.6-3.8 (m, 2H, -CH_2-NMe$_3$), 3.29 (s, 9H, -NMe_3), 2.3-2.6 (m, 2H, -CH$_2$-CH_2-CH$_2$-). ^{13}C NMR (acetone-d_6) δ 145.86, 128.62, 128.34, 126.34, 123.96, 116.99, 65.36, 53.78, 44.53, 21.66. ^{19}F NMR (acetone-d_6) δ -72.34 (d, J = 707.8 Hz). ^{31}P NMR (acetone-d_6) δ -144.26 (sep, J = 708.2 Hz). IR (ATR) 1474, 1456, 1330, 1253, 1220, 1164, 1128, 1039, 967, 934, 877, 829, 761, 732, 670 cm^{-1}. ESI-MS: m/z = 299 [M-PF$_6^-$]$^+$.

Preparation of 10-(3-(trimethylammonio)-1-propyl)-10*H*-phenothiazine-5-oxide hexafluorophosphate (Prom-O-MePF$_6$)

NH_4PF_6 (0.17 g, 1.0 mmol) was added to a mixture of MeOH-water (50:50 v/v, 10 mL) of **Prom-MeI** (0.22 g, 0.50 mmol). The generated precipitate was collected by filtration, washed with MeOH, and dried in vacuo. **Prom-MePF$_6$** was obtained as a colorless powder in a quantitive yield (0.20 g, 5.04 mmol).

^{1}H NMR (acetone-d_6) δ:7.9-8.0 (m, 2H, Ar), 7.60-7.80 (m, 4H, Ar), 7.3-7.4 (m, 2H, Ar), 4.73 (t, 2H, J = 6.1 Hz, Ar$_2$N-CH_2-), 3.5-3.6 (m, 2H, -CH_2-NMe$_3$), 3.24 (s, 9H, -NMe_3), 2.4-2.6 (m, 2H, -CH$_2$-CH_2-CH$_2$-). ^{13}C NMR (acetone-d_6) δ: 139.88, 133.76, 130.98, 128.66, 123.35, 118.63, 63.68, 53.37, 44.26, 22.10.

^{19}F NMR (acetone-d_6) δ: -72.20 (d, J = 707.3 Hz). ^{31}P NMR (acetone-d_6) δ -144.26 (sep, J = 707.9 Hz). IR (ATR) 3392, 1641, 1589, 1489, 1462, 1378, 1256, 1177, 1056, 985, 922, 828, 768, 747, 704, 670, 627 cm^{-1}. ESI-MS: m/z = 315 [M-PF_6^-]$^+$.

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