

Articles

Ammonium Ion Binding Property of Naphtho-Crown Ethers Containing Thiazole as Sub-Cyclic Unit

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A short and efficient synthesis, solvent extraction and potentiometric measurements of new thiazole-containing naphtho-crown ethers are reported. The naphthalene moiety enhances the ammonium ion selectivity over potassium ion. The selectivity of NH_4^+/K^+ follows the trend $3 \approx 2 > 1$, indicating that the differences in conformational changes of **2** and **3** in forming ammonium complexes affect little on the resulting ammonium/potassium extraction selectivity ratio. The ammonium ion-selective electrodes were prepared with *n*-octylphenyl ether plasticized poly(vinyl chloride) membranes containing **1-4**; the effect of one naphthalene unit introduced on either right (**2**) or left (**3**) side of thiazolo-crown ether on their potentiometric properties (*e.g.*, ammonium ion selectivity over other cations, response slopes, and detection limits) were not apparent. However, the ammonium ion selectivity of **1**, **2** and **3** over other alkali metal and alkaline earth metal cations is 10-100 times higher than that of nonactin.

Key Words : Naphtho-crown ethers, Ammonium ion selective, Thiazole, Extraction, Potentiometric

Introduction

The design and synthesis of highly selective ammonium ionophore has been one of the goals in the development of membrane-based ion selective electrode (ISE) and optodes, due to the important role of the ammonium ion in biological and environmental systems.¹ Direct detection of ammonium ion in aqueous systems is essential for the development of ion sensors for application in clinical and environmental analyses.^{2,3} For potentiometric determination of ammonium ion concentration, nonactin, a natural product, has been widely used as an ion selective membrane electrode since 1970.¹ However, while nonactin-based membrane electrode show good selectivity towards the ammonium ion, they nevertheless suffer from other ions, particularly over potassium and sodium ions. To improve the selectivity for ammonium ion over other alkali metal ions, several synthetic ammonium ion selective ionophores were designed and synthesized.⁴⁻¹²

Recently we reported that thiazolo dibenzo-crown ether TDB18C6 provide enhanced ammonium ion selectivity over sodium ion ($\log K_{\text{NH}_4^+, \text{Na}^+}^{\text{POT}} = -3.9$) and slightly improved over potassium compared to nonactin.⁴ X-ray crystallography, ¹H NMR and theoretical studies suggested that the TDB18C6 form 2:1 complex with ammonium ion through hydrogen bonding.^{4,5} Similarly Suzuki showed that decalino-19-crown-6 (TD19C6) exhibited improved selectivity for ammonium

over sodium and other alkali metal ions.¹⁰ They proposed that a block-wall effect of the bulky docalino subunits is responsible for the increased ammonium ion selectivity over potassium and sodium ions by factors of 10 and 3000 times.

As the bulky subunits introduced in the crown ether cavity substantially seem to improve the ammonium ion selectivity over potassium and sodium ions, we examined such structural modification is also applicable to the derivatives of thiazole-containing crown ethers. We have synthesized thiazole-containing naphtho-crown ethers and examined their ion selectivity by extraction and potentiometric measurements.

Experimental Section

Melting points were measured on Thomas Hoover Melting point apparatus and are uncorrected. ¹H and ¹³C NMR spectra were recorded on a Varian Unity Spectrometer (¹H, 300 MHz; ¹³C, 75 MHz) with TMS as an internal standard. IR spectra were measured with a Galaxy FT-IR 7000 spectrophotometer. Mass spectra were recorded on a Shimadzu QP-1000 spectrometer. Elemental analyses were performed at Center for Scientific Instruments, Kyungpook National University. Flash column chromatography was performed with Merck silica gel 60 (70-230 mesh). All reactions were carried out under an atmosphere of argon. The solution was dried over anhydrous sodium sulfate. 2,3-Dihydroxynaphthalene, iodoacetamide, Lawesson's reagent, 1,3-dichloroacetone, ethyl bromopyruvate, lithium aluminum hydride, carbon tetrabromide, triphenylphosphine, catechol, and dibenzo-crown ether (DB18C6) were purchased from

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Aldrich. BTB18C6 (**1**) and BTN18C6 (**2**) were prepared by literature procedure.^{4,13} Metal, ammonium and amine picrates were prepared by the literature procedure.¹⁴

Synthesis of 2,3-bis(amidomethoxy)naphthalene (5). A mixture of 2,3-dihydroxynaphthalene (1.00 g, 6.24 mmol), iodoacetamide (2.43 g, 13.13 mmol), and K₂CO₃ (3.45 g, 24.96 mmol) was refluxed in 100 mL of acetone for 14 h. After the solvent was removed, diluted with water. The solid was collected by filtration and dried in an air to give **5** (2.99 g, 83%). Mp 236 °C (CH₂Cl₂-hexane); IR (KBr) 3439, 3377, 3227, 1682, 1479, 1250, 1031, 856, 758, 602 cm⁻¹; ¹H NMR (DMSO-d₆) δ 7.71 (dd, *J* = 3.3, 6.3 Hz, 1H), 7.52 (bs, 1H, CONH), 7.48 (bs, 1H, CONH), 7.32 (dd, *J* = 3.3, 6.3 Hz, 1H), 7.29 (s, 1H), 4.59 (s, 2H, OCH₂CONH₂); MS *m/z* 274 (M⁺, 72), 172 (100); Anal. Calcd for C₁₄H₁₄N₂O₄: C, 61.31; H, 5.14; N, 10.21. Found: C, 60.98; H, 5.20; N, 10.08.

Synthesis of 2,3-bis(thioamidomethoxy)naphthalene (6). A mixture of **5** (1.00 g, 3.65 mmol) and Lawesson's reagent (3.24 g, 9.10 mmol) was refluxed in THF (60 mL) for 7 h. After the solvent was removed, treated with dichloromethane (20 mL), and stirred for 30 min. The solid was filtered and dried to give **6** (816 mg, 73%). R_f 0.50 (EtOAc : hexane 1 : 1); mp 202 °C (CH₂Cl₂-hexane); IR (KBr) 3360, 3260, 3167, 1609, 1478, 1406, 1244, 1161, 850, 650 cm⁻¹; ¹H NMR (acetone-d₆) δ 9.22 (bs, 1H, CSNH), 8.91 (bs, 1H, CSNH), 7.78 (dd, *J* = 3.3, 6.3 Hz, 1H), 7.42 (s, 1H), 7.38 (dd, *J* = 3.3, 6.3 Hz, 1H), 5.01 (s, 2H, OCH₂CSNH₂); ¹³C NMR (acetone-d₆) δ 206.6 (CSNH₂), 148.7, 131.0, 127.9, 126.0, 111.0, 75.5; MS *m/z* 302 (M⁺, 4), 197 (100); Anal. Calcd for C₁₄H₁₄N₂O₂S₂: C, 54.88; H, 4.61; N, 9.14. Found: C, 54.85; H, 4.46; N, 8.85.

Synthesis of 2,3-bis[2(4-carbomethoxy)thiazolyl]methoxy-naphthalene (7). A mixture of **6** (2.46 g, 8.13 mmol) and ethyl bromopyruvate (4.00 g, 20.50 mmol) was refluxed in absolute ethanol (80 mL) for 5 h and the solvent was removed. The residue was extracted with dichloromethane, dried, concentrated, and was purified by column chromatography (EtOAc : hexane 1 : 2) to give **7** (2.96 g, 73%). R_f 0.30 (EtOAc : hexane 1 : 1); mp 168 °C (CH₂Cl₂-hexane); IR (KBr) 3079, 2982, 1732, 1705, 1485, 1248, 1213, 1097, 1022, 852, 754 cm⁻¹; ¹H NMR (CDCl₃) δ 8.23 (s, 1H, Thz-H), 7.70 (dd, *J* = 3.3, 6.3 Hz, 1H), 7.38 (dd, *J* = 3.3, 6.3 Hz, 1H), 7.25 (s, 1H), 5.60 (s, 2H, OCH₂Thz), 4.46 (q, *J* = 7.2 Hz, 2H, CO₂CH₂CH₃), 1.43 (t, *J* = 7.2 Hz, 3H, CO₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 169.5, 162.7, 148.8, 130.9, 129.5, 128.1, 126.6, 111.2, 69.7, 63.0, 15.8; MS *m/z* 498 (M⁺, 25), 171 (100); Anal. Calcd for C₂₄H₂₂N₂O₆S₂: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.97; H, 4.33; N, 5.44.

Synthesis of 2,3-bis[2(4-bromomethyl)thiazolyl] methyl-oxynaphthalene (9). To a solution of **7** (348 mg, 0.70 mmol) in dry THF (40 mL) was added LiAlH₄ in an ice bath and stirred for 6 h. The solvent was removed, and the residue was treated with 5% HCl solution, and extracted with ethyl acetate. The organic layer was dried and evaporated to give crude hydroxymethyl compound **8** (258 mg). The crude compound was treated with PPh₃ (556 mg, 2.12 mmol) and

CBR₄ (703 mg, 2.12 mmol) in dry dichloromethane (30 mL) at 5 °C for 1 h. The resulting mixture was extracted with dichloromethane, dried, and concentrated. The residue was purified by chromatography (EtOAc : hexane 1 : 4) to give **9** (310 mg, 82%). R_f 0.40 (EtOAc : hexane 1 : 2); mp 132 °C (CH₂Cl₂-hexane); IR (KBr) 3113, 3030, 1514, 1483, 1265, 1215, 1116, 856, 746 cm⁻¹; ¹H NMR (CDCl₃) δ 7.70 (dd, *J* = 3.3, 6.3 Hz, 1H), 7.37 (dd, *J* = 3.3, 6.3 Hz, 1H), 7.34 (s, 1H), 7.29 (s, 1H, ThzH), 5.54 (s, 2H, OCH₂Thz), 4.61 (s, 2H, ThzCH₂Br); ¹³C NMR (CDCl₃) δ 167.9, 152.0, 147.7, 129.5, 126.6, 125.0, 118.5, 110.0, 68.3, 26.9; MS *m/z* 542 (M+4, 4), 540 (M+2, 6), 538 (M⁺, 3), 111 (100); Anal. Calcd for C₂₀H₁₆Br₂N₂O₂S₂: C, 44.46; H, 2.98; N, 5.18; S, 11.87. Found: C, 44.73; H, 3.02; N, 4.94; S, 11.46.

Synthesis of 2,3-bis[2(4-chloromethyl)thiazolyl]methyl-oxynaphthalene (10) A mixture of **6** (1.00 g, 3.26 mmol) and 1, 3-dichloroacetone (912 mg, 7.18 mmol) in benzene (70 mL) was refluxed for 20 h with Dean-Stark column to remove water. After the solvent was removed, extracted with dichloromethane, dried, and concentrated. The residue was purified by column chromatography (EtOAc : hexane 1 : 2) to give **10** (1.28 g, 87%). R_f 0.58 (EtOAc : hexane 1 : 1); mp 137 °C (CH₂Cl₂-hexane); IR (KBr) 3110, 3030, 1514, 1448, 1264, 1117, 851, 744 cm⁻¹; ¹H NMR (CDCl₃) δ 7.71-7.68 (m, 1H), 7.39 (t, 1H), 7.35 (s, 1H, ThzH), 7.29 (s, 1H), 5.54 (s, 2H, OCH₂Thz), 4.72 (s, 2H, ThzCH₂Cl); ¹³C NMR (CDCl₃) δ 167.9, 151.9, 147.8, 129.5, 126.6, 125.0, 118.4, 109.9, 68.3, 40.7; MS *m/z* 450 (M⁺, 5), 146 (100); Anal. Calcd for C₂₀H₁₆Cl₂N₂O₂S₂: C, 53.22; H, 3.57; N, 6.21; S, 14.21. Found: C, 53.29; H, 3.54; N, 6.00; S, 14.05.

Synthesis of Naphtho-crown Ethers. After a mixture of catechol (1.1 eq) and K₂CO₃ (2.2 eq) was refluxed in acetone (200 mL) for 1 h, compound **9** (0.5 eq.) was added and continued to reflux for 15 h. After the solvent was removed, extracted with dichloromethane, dried, concentrated, and the residue was purified by flash chromatography (EtOAc : hexane 1 : 1) to give the product.

1,2-Naphthalene-5,16-dithiazolyl-10,11-benzene coronand 18C6 (3). This compound was obtained in 92% yield as a white solid: R_f 0.25 (EtOAc : hexane 1 : 1); mp 212 °C (CH₂Cl₂-hexane); IR (KBr) 3101, 3055, 2924, 2864, 1502, 1252, 1117, 1014, 845, 741 cm⁻¹; ¹H NMR (DMSO-d₆) δ 7.74 (dd, *J* = 3.3, 6.3 Hz, 1H), 7.42-7.40 (m, 1H), 7.40 (s, 1H), 7.36 (s, 1H, ThzH), 7.08-6.98 (m, 2H, Ph), 5.32 (s, 2H, NapCH₂O), 5.10 (s, 2H, ThzCH₂O); ¹³C NMR (DMSO-d₆) δ 163.8, 152.2, 148.7, 148.2, 129.3, 126.1, 124.4, 121.5, 118.0, 114.8, 111.1, 67.5, 66.8; MS *m/z* 488 (M⁺, 100); Anal. Calcd for C₂₆H₂₀N₂O₄S₂: C, 63.92; H, 4.13; N, 5.73. Found: C, 63.96; H, 4.23; N, 5.47.

Bis(5,16-thiazolyl-1,2,10,11-naphthalene) coronand 18C6 (4). This compound was obtained in 70% yield as a white solid: R_f 0.30 (EtOAc : hexane 1 : 1); mp 286 °C (CH₂Cl₂-hexane); IR (KBr) 3107, 3053, 2926, 2868, 1481, 1251, 1168, 995, 846, 742 cm⁻¹; ¹H NMR (DMSO-d₆) δ 7.95 (s, 1H, ThzH), 7.78 (dd, *J* = 3.3, 6.3 Hz, 2H), 7.51 (s, 1H), 7.49 (s, 1H), 7.33-7.39 (m, 2H), 5.38 (s, 2H, NapCH₂O), 5.18 (s,

2H, ThzCH₂O); ¹³C NMR (DMSO-d₆) δ 162.9, 152.0, 148.2, 147.8, 128.9, 126.3, 126.2, 124.3, 124.0, 121.6, 107.6, 107.0, 64.9; MS *m/z* 538 (M⁺, 100); Anal. Calcd for C₃₀H₂₂N₂O₄S₂: C, 66.89; H, 4.12; N, 5.20. Found: C, 67.19; H, 4.11; N, 5.14.

Extraction measurements.^{15,16} A 2.5 mL of aqueous picrate solution (3×10^{-4} mol/L) and 2.5 mL solution of naphtho-crown ethers in 1,2-dichloroethane (3×10^{-4} mol/L) was magnetically stirred in a stoppered glass tube at 25 °C. The equilibrium was reached after vigorous stirring for 1 h, and kept 12 h at same temperature. An aliquot of the 1,2-dichloroethane (0.5 mL) was taken with syringe and evaporated to dryness. The residue was diluted with acetonitrile to adjust the UV absorbance within 1.5. The UV absorbance of acetonitrile solution was measured at 376 nm. The extraction percentage was calculated according to the difference between the initial and final concentration of organic phase, and the values are the average of three parallel extraction results.

Preparation of electrodes and their potentiometric evaluation. Ion-selective membranes were prepared with four different ionophores **1-4** by the methods as reported earlier.^{4,6,17} Membrane cocktails were formulated by dissolving 2 mg ionophore, 66 mg PVC and 132 mg plasticizer (*n*-octylphenyl ether; NPOE) in 1 mL tetrahydrofuran (THF), poured into glass rings (i.d. = 22 mm) mounted on a slide glass, and dried overnight in a dust free chamber at room temperature. Membrane disks (d = 5.5 mm) were punched out of the master membranes and mounted in Philips electrode bodies (IS-561; Glasbläserei Möller, Zürich, Switzerland). The inner filling solution for all electrodes was 0.1 M NH₄Cl. An Orion (Cambridge, MA, USA) sleeve-type double-junction Ag/AgCl electrode (Model 90-02) was used as the external reference. The potential differences between the ion-selective electrode and the reference electrode were measured using a PC equipped with a 16-channel high-

impedance input voltmeter (Model KST101B, KOSENTECH, Busan, Korea). Dynamic response curves and calibration plots were obtained by adding calculated amounts of standard solutions to a 200 mL of stirred background electrolyte (0.05 M TRIS-HCl, pH 7.4) at room temperature; concentrations of primary and interfering ionic species were varied from 10⁻⁶ to 10⁻¹ M. The response of the electrodes to pH changes was tested by adding aliquots of NaOH solution to a buffer composed of 11.4 mM boric acid-6.7 mM citric acid-10.0 mM NaH₂PO₄ at room temperature. The solutions were magnetically stirred during all e.m.f. measurements. Selectivity coefficients were determined by using the matched potential method at an interfering ion concentration of 0.1 M.¹⁸ Other response characteristics, *e.g.*, detection limits, response slopes, and response times, were determined according to the IUPAC recommendation.¹⁹

Results and Discussion

We designed and synthesized a new class of ionophore by introducing a rigid naphthalene ring onto the crown ether skeleton. A simple molecular modeling study suggested that the compounds **2**, **3** and **4** which have rigid naphthalene units in the thiazolo-crown ether structure prefers the 1 : 1-complex with ammonium ion, while the previously known compound **1** form 2 : 1-complex.⁵ It was interesting to see if the change in complex structure would be beneficial for increasing the ammonium ion selectivity over other alkaline metal cations.

For the synthesis of NTB18C6 (**3**) and NTN18C6 (**4**), an efficient and short synthetic scheme for 2,3-bis[2(4-halomethyl)thiazoly]methoxynaphthalene was required. Previous synthesis of bromomethylthiazole (**9**) was achieved by three sequential steps from thioamide (**6**): reaction with ethyl bromopyruvate in dry ethanol to provide the thiazole (**7**), reduction of **7** with LiAlH₄ to give **8** and subsequent

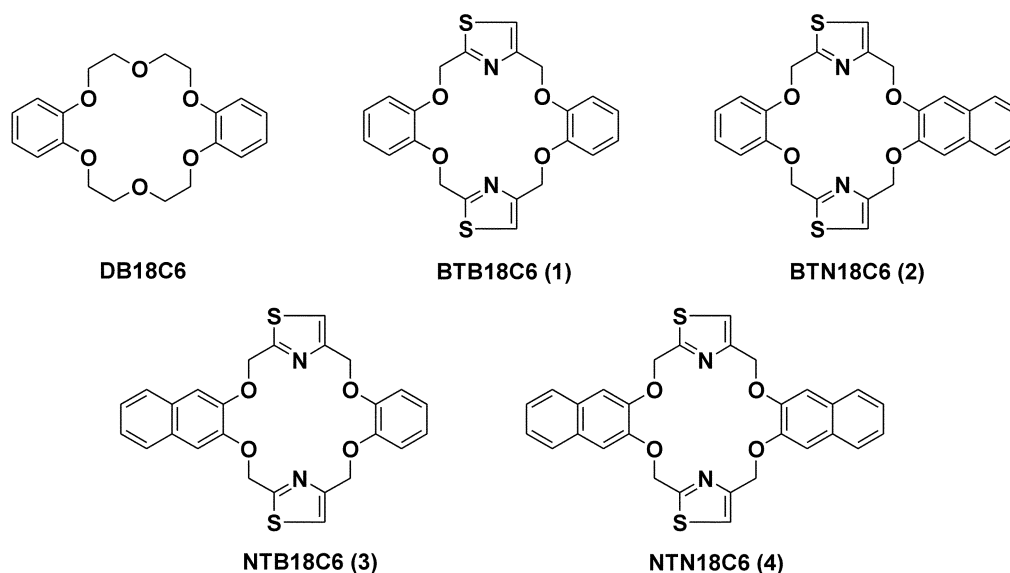
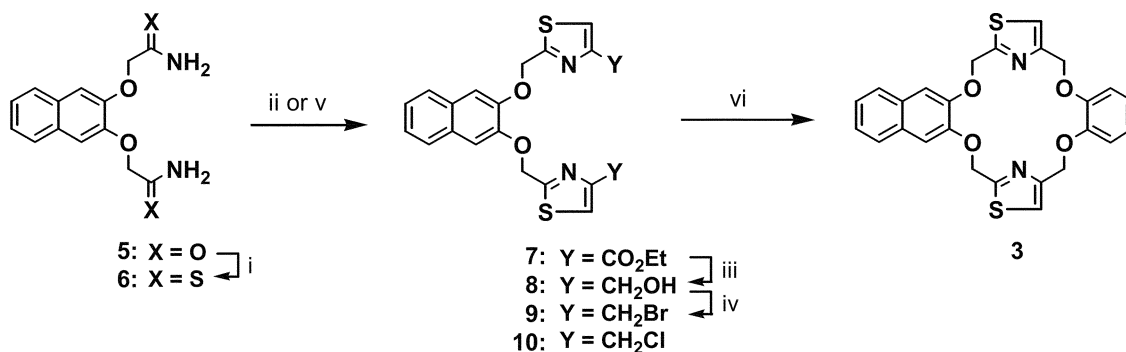


Figure 1. Structures of ammonium ion-selective neutral carriers.



Reaction conditions: i) Lawesson's reagent, THF; ii) BrCH₂COCO₂Et, EtOH; iii) LiAlH₄, THF; iv) CBr₄, PPh₃, CH₂Cl₂; v) 1,3-dichloroacetone, benzene; vi) K₂CO₃, acetone, catechol.

Scheme 1. Synthetic scheme for naphtho-crown ethers containing thiazole.

bromination with CBr₄-PPh₃ to yield **9** in 44% total yield. For the fast construction of halomethylthiazole, reaction of thioamide (**6**) with 1,3-dichloroacetone was investigated. Reaction of these two reagents in refluxing benzene provided chloromethylthiazole (**10**) in 87% yield. Cyclization of **9** or **10** with catechol or 2,3-dihydroxynaphthalene in the presence of K₂CO₃ in acetone yielded **3** and **4** in 92 and 70% yield, respectively as shown in Scheme 1.

The structure of compounds **3** and **4** were characterized by spectroscopic and elemental analysis. In the ¹H NMR spectra of **3**, thiazole proton appeared at δ 7.36 as singlet, a pair of singlets revealed at δ 5.32 and 5.10 corresponding to the methylene protons between naphthalene and thiazole, and thiazole and benzene moieties, which indicate that this compound has symmetric structure in CDCl₃. The mass spectrum of **3** also exhibited a peak at m/z 488 corresponding to the molecular ion.

In order to investigate the binding ability of these compounds towards different metal ions, and compare recognition selectivity, their extraction behavior towards Cs⁺, Rb⁺, K⁺, NH₄⁺, CH₃NH₃⁺ were carried out. The results of extraction experiments are summarized in Table 1; the selectivity ratio between NH₄⁺ and K⁺ follows the trend **3** \approx **2** > **1**. The extractability of compound **4** could not be accurately measured because of its poor solubility in 1,2-dichloroethane.

The potassium and ammonium ion extractability of compound **1** was 10 and 21%, respectively, yielding the NH₄⁺/K⁺ extraction selectivity ratio of 2.1. The naphthalene

unit on the thiazolo-crown ether frame provides enhanced ammonium extractability for compounds **2** (39%) and **3** (36%), which were almost twice compared to that of compound **1**, resulting in 1.2-1.3 times increased NH₄⁺/K⁺ extraction selectivity. It is supposed that the rigid structure of **2** and **3** increases the accessibility of ammonium ion to its nitrogen and oxygen in thiazolo-dibenzocrown ether unit without accompanying the steric hindrance in forming 2 : 1-complex between the ligands and ammonium ion. Molecular modeling of **2** and **3**, which have naphthalene unit on the right and left side of thiazole structure, respectively, converge to similar structures in the presence of ammonium ion, forming hydrogen bonds between ammonium ion and nitrogens in facially aligned thiazole rings (saddle-like structure). However, their equilibrium structures in the absence of ammonium ion are quite different; the two five membered thiazole rings in **3** are at opposite position with respect to nitrogen, while in **2** the same facial position. It means that the compound **3** may require additional energy for conformational change to form a complex with ammonium ion. However, the extraction experimental results indicate that such conformational change affect little on the ammonium ion binding ability of compound **3**.

To see if the enhanced ammonium ion extractability and selectivity in solution phase also reflected in their potentiometric selectivity of the compounds **1-4** doped in organic polymer phase, we prepared ammonium ion-selective ISEs with NPOE-plasticized PVC membranes. Potentiometric responses of the membranes to alkali metal and alkaline earth metal cations and to ammonium ion were measured. Figure 2 shows the responses of electrodes, and Table 2 summarizes the results: electrodes based on compounds **1**, **2**, and **3** exhibit Nernstian response to ammonium with detection limits below 10⁻⁵.

It was observed that the ammonium ion selectivity of **1**, **2** and **3** over other alkali metal and alkaline earth metal cations is 10-100 times higher than that of nonactin. It was possible to prepare the same PVC/NPOE-based membranes with compound **4** as it was dissolved well in THF. However, the very rigid structure of compound **4** greatly reduced the

Table 1. Extractability of naphtho-crown ethers for cations in picrate extraction

Ligand	Extractability (%) ^a					Selectivity
	Cs ⁺	Rb ⁺	K ⁺	NH ₄ ⁺	CH ₃ NH ₃ ⁺	
DB18C6	15	24	19	22	7	1.2
1	37	31	10	21	19	2.1
2	40	35	15	39	41	2.6
3	38	32	13	36	36	2.8

^aAverage and standard deviation for three samples in 1,2-dichloroethane.

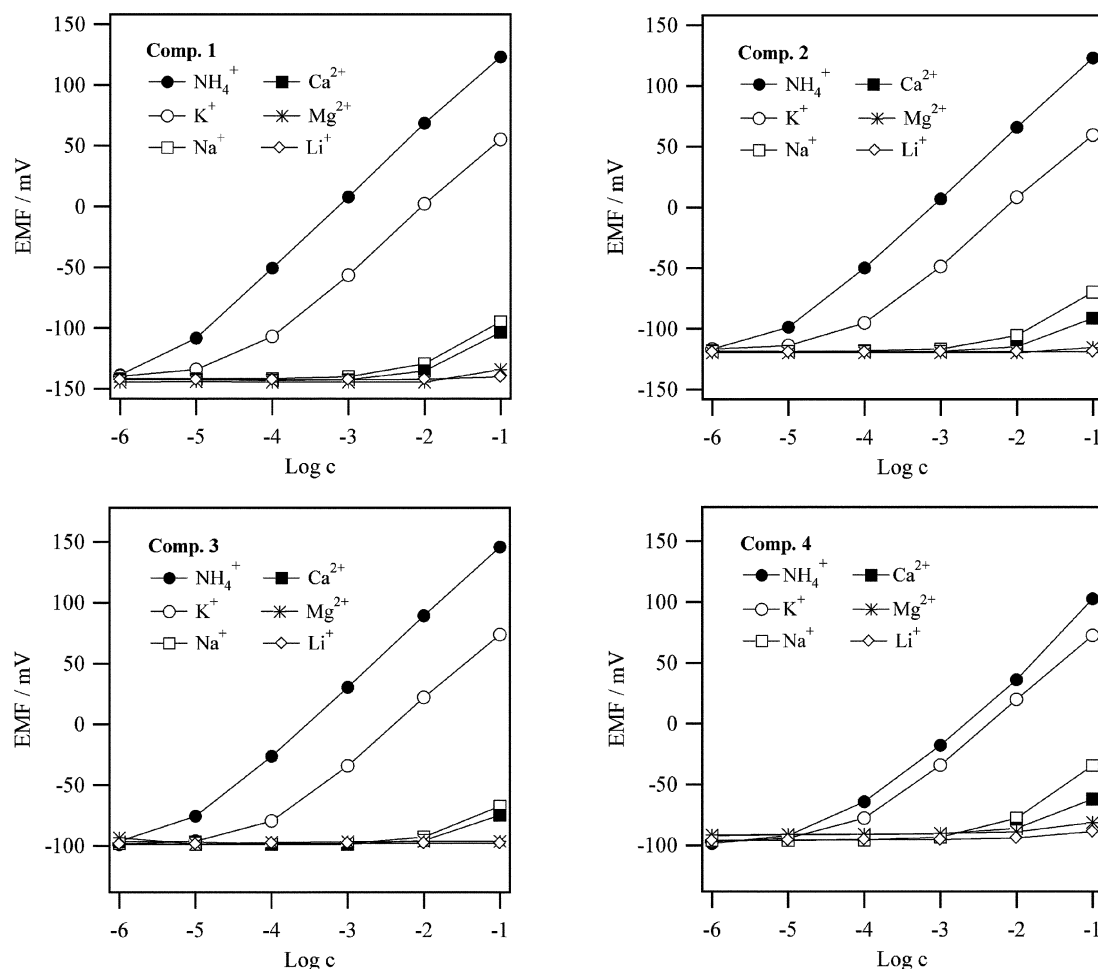


Figure 2. Potentiometric responses of the NPOE-plasticized PVC membranes prepared with naphtho-crown ethers containing thiazole.

Table 2. Potentiometric properties of ammonium ion-selective neutral carriers in NPOE-plasticized PVC membranes

Compound	slope ^a	detection limit ^b	selectivity coefficient ($\log K_{NH_4^+,j}^{pot}$)				
			Mg ²⁺	Li ⁺	Na ⁺	K ⁺	Ca ²⁺
1	58.7	-5.6	-4.9	-5.4	-3.8	-1.2	-3.9
2	57.8	-5.2	-4.9	-5.8	-3.4	-1.1	-3.8
3	57.6	-5.3	-4.0	-6.0	-3.8	-1.3	-4.9
4	55.5	-4.6	-3.6	-3.9	-2.4	-0.5	-3.0

^aSlopes from 10^{-5} to 10^{-1} M (mV/decade). ^bLog [NH₄⁺]

ammonium selectivity over potassium and sodium, indicating the loss of optimal conformation for hydrogen bonding formation with ammonium. Another plausible reason for reduced potentiometric performance is attributable to the reduced solubility of compound **4** in organic solvent; the effective concentration of compound **4** in solvent polymeric membrane may have not exceeded the critical concentration needed to exhibit theoretical behavior. Although we were not able to obtain new naphthothiazole-based ionophores that exhibit far enhanced ammonium selectivity compared to the ones reported in our previous work, the naphthalene unit containing compounds **2**, **3** and **4** provided valuable insights into the future design of ammonium-selective ionophores.

We are now examining the effect of various electron withdrawing or donating groups about the naphthothiazolo crown ether structures on the ammonium ion selectivity, and will be published elsewhere.

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