

New Potassium- and Cesium-selective Ionophoric Bis(crown ether)s Derived from Xanthene-4,5-dicarboxylic Acid

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Abstract. A series of bis(crown ether)s based-upon a xanthene-4,5-dicarboxylic acid skeleton was prepared and their ionophoric properties toward alkali metal cations were investigated. Bis(crown ether)s bearing 15-crown-5 and 18-crown-6 moieties exhibited pronounced extraction efficiencies toward K^+ and Cs^+ ions, respectively, and the extraction constant estimated by solvent extraction studies was as high as 10^9 for the **2**- K^+ and **3**- Cs^+ systems. Using UV titration of potassium picrate with **2** in THF, the complex was found to have a structure of a completely encapsulated guest in the host. In transport experiments, the bis(crown ether)s showed no significant selectivity pattern compared with extraction results, again implying the strong complexation of bis(crown ether)s. Ion-selective electrode studies also demonstrated that the selective ionophoric properties of **2** toward K^+ were reminiscent of the natural antibiotic valinomycin except for a somewhat slow response.

Key words: potassium-selective ionophore, bis(crown ether), ion selective electrode, solvent extraction.

1. Introduction

There have been numerous studies on the development of novel ionophores for the molecular recognition of biologically important ionic guests [1]. Formation of a sandwich type 2 : 1 complex of crown ether ring/cation by bis(crown ether)s is one of the basic principles for the design of some ionophoric molecular recognition systems for improved selectivity as neutral carriers for ion-selective electrodes (ISEs) [2]. In bis(crown ether) systems the geometry and spatial arrangements of two crown ether moieties are crucial factors for the efficient ionophoric behavior [3]. The structural properties of xanthene-dicarboxylic acid, which was developed as a motif for the construction of a rigid host framework by Rebek [4], are believed to be particularly suitable for the design of bis(crown ether)s. One reason is that its preorganized rigid framework of two carboxylic acids for the control of the spatial relationship between two pendant crown ether moieties and the separation between

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the two functional groups seem to be ideal for the design of bis(crown ether)s to form tight sandwich type complexes. The other reason is that the two *tert*-butyl groups as well as the xanthene backbone are lipophilic enough for the resulting ligands to work as an efficient analytical tool.

ISEs, which selectively measure ion concentrations of specific species, are generally welcomed in analytical chemistry. There are a number of sensors available for almost any cation of analytical and biological interest [5]. Extensive investigations have been made regarding the design of synthetic ionophores for use as neutral carriers, and crown compounds have received keen attention for this purpose. In this case, a remarkable improvement in the selectivity of crown ether based ISEs has been achieved with derivatives of bis(crown ether)s [6]. Here we report the development of new ionophoric bis(crown ether)s selective toward K^+ and Cs^+ ions, utilizing the structural features of 2,7-di-*tert*-butyl-9,9-dimethylxanthene-4,5-dicarboxylic acid.

2. Experimental

2.1. GENERAL

1H NMR spectra were obtained with a Varian VXR-200 NMR spectrometer using TMS as an internal standard. UV spectra were acquired with a Jasco V-500 spectrophotometer and IR spectra were recorded on a Jasco FT/IR-5300. FAB mass spectra were obtained by a JEOL AX505WA mass spectrometer. 2,7-Di-*tert*-butyl-9,9-dimethyl-4,5-xanthenedicarboxylic acid (Aldrich), aminomethyl crown ethers (Aldrich), 4'-aminobenzo-18-crown-6 (Fluka) and 4'-aminobenzo-15-crown-5 ether (Fluka) were purchased and used without further purification. 4'-Aminobenzo-12-crown-4 was prepared from benzo-12-crown-4 by nitration followed by hydrogenation with Pd/C according to known procedures [7]. Solvents were purified by standard methods. Column chromatography was carried out using Merck silica gel 60 (70-230 mesh, ASTM).

2.2. PREPARATION OF LIGANDS

Oxalyl chloride (4 mmol) was added to a suspension of 2,7-di-*tert*-butyl-9,9-dimethyl-4,5-xanthenedicarboxylic acid (1.0 mmol) in CH_2Cl_2 with one drop of DMF and stirred at room temperature under N_2 atmosphere for 2 h. After complete evaporation of solvent and excess oxalyl chloride under vacuum, the residue was dissolved in CH_2Cl_2 and added dropwise to a CH_2Cl_2 solution containing the respective amino crown ether and NEt_3 . After 2 h of reaction, the reaction mixture was treated with 1 N HCl. The aqueous phase was separated and the CH_2Cl_2 phase was washed again with water and concentrated under reduced pressure. The crude products **1–8** were purified by column chromatography (silica gel, eluent; CH_2Cl_2 : MeOH = up to 9:1, v/v). *N*-Phenylamide derivatives **1–3** and **7** were further purified by recrystallization from CH_2Cl_2 /hexane.

1. Yield: 58%; m.p. 140–142 °C; IR (NaCl): 3290, 2961, 1659, 1603, 1509, 1440, 1267, 1129 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): 8.90 (s, 2 H), 7.83 (d, $J = 2$ Hz, 2 H), 7.55 (d, $J = 2$ Hz, 2 H), 7.26 (d, $J = 2$ Hz, 2 H), 7.04 (dd, $J = 8.6$ Hz, $J = 2$ Hz, 2 H), 6.70 (d, $J = 8.6$ Hz, 2 H), 4.05 (m, 4 H), 3.98 (m, 4 H), 3.8–3.6 (m, 16 H), 1.67 (s, 6 H), 1.32 (s, 18 H); MS: $(\text{M})^+ = 853$, $(\text{M}+\text{Na})^+ = 876$.

2. Yield: 77%; m.p. 253–256 °C; IR (NaCl): 3534, 3291, 2952, 1656, 1604, 1513, 1239, 1133 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): 8.51 (s, 2 H), 7.80 (d, $J = 2$ Hz, 2 H), 7.56 (d, $J = 2$ Hz, 2 H), 7.11 (d, $J = 2$ Hz, 2 H), 7.01 (dd, $J = 8.5$ Hz, $J = 2$ Hz, 2 H), 6.60 (d, $J = 8.5$ Hz, 2 H), 4.06 (m, 4 H), 3.97 (m, 4 H), 3.88 (m, 8 H), 3.73 (m, 16 H), 1.69 (s, 6 H), 1.33 (s, 18 H); MS: $(\text{M})^+ = 941$.

3. Yield: 48%; m.p. 168–172 °C; IR (NaCl): 3324, 2960, 1653, 1606, 1516, 1122 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): 8.56 (s, 2 H), 7.80 (d, $J = 2$ Hz, 2 H), 7.56 (d, $J = 2$ Hz, 2 H), 7.07 (s, 2 H), 7.01 (d, $J = 8.5$ Hz, 2 H), 6.58 (d, $J = 8.5$ Hz, 2 H), 4.07 (m, 4 H), 3.99 (m, 4 H), 3.88 (m, 8 H), 3.70 (m, 24 H), 1.80 (s, 6 H), 1.33 (s, 18 H); MS: $(\text{M})^+ = 1029$.

4. Yield: 78%; oil; IR (NaCl): 3308, 2960, 1644, 1528, 1134 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): 7.82 (s, 2 H), 7.67 (d, $J = 2$ Hz, 2 H), 7.47 (d, $J = 2$ Hz, 2 H), 3.8–3.5 (m, 34 H), 1.60 (s, 6 H), 1.28 (s, 18 H); MS: $(\text{M})^+ = 785$.

5. Yield: 62%; oil; IR (NaCl): 3396, 2931, 1723, 1675, 1114 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): 8.02 (br s, 2 H), 7.74 (d, $J = 2$ Hz, 2 H), 7.50 (d, $J = 2$ Hz, 2 H), 3.8–3.4 (m, 42 H), 1.64 (s, 6 H), 1.32 (s, 18 H); MS: $(\text{M})^+ = 873$.

6. Yield: 52%; oil; IR (NaCl): 3386, 2875, 1723, 1676, 1111 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): 8.03 (br s, 2 H), 7.73 (d, $J = 2$ Hz, 2 H), 7.47 (d, $J = 2$ Hz, 2 H), 3.8–3.4 (m, 50 H), 1.62 (s, 6 H), 1.24 (s, 18 H); MS: $(\text{M})^+ = 961$.

7. Yield: 54%; m.p. 228–229 °C; $^1\text{H NMR}$ (CDCl_3): 7.82 (d, $J = 10$ Hz, 2 H), 7.70 (s, 1 H), 7.53–7.46 (m, 4 H), 6.97–6.82 (m, 2 H), 4.18–4.10 (m, 4 H), 3.91–3.87 (m, 4 H), 3.74 (s, 8 H); MS: $(\text{M})^+ = 387$.

8. Yield: 57%; oil; $^1\text{H NMR}$ (CDCl_3): 7.80–7.76 (m, 2 H), 7.46–7.36 (m, 3 H), 6.91 (s, 1 H), 3.84–3.49 (m, 21 H); MS: $(\text{M})^+ = 353$.

2.3. EXTRACTION EXPERIMENTS

Stock solutions (7.0×10^{-5} M) of alkali metal picrate salt were prepared in deionized water. An aqueous stock solution of metal picrate guest (3.0 mL) and a crown host solution (3.0 mL, 3.5×10^{-3} M in dichloromethane) were placed in a centrifuge tube equipped with a screw cap and equilibrated for an hour in a thermostat at 25 °C. After 1 h of equilibration the whole mixture was extracted with a Vortex-Genie for 1 min. The procedure was repeated twice to ensure thermal equilibration and complete extraction. The resulting mixture was then centrifuged to hasten phase separation, and the extraction efficiency was determined by measuring the absorbance of picrate salt in the aqueous phase at 356 nm using a UV spectrophotometer [8].

2.4. TRANSPORT EXPERIMENTS

Transport experiments across the CH_2Cl_2 liquid membrane were performed at 25 °C using a U-tube (1.8 cm, i.d.) apparatus. The source phase was aqueous alkali metal picrate solution (0.01 M, 15 mL) and the receiving phase was 15 mL of deionized water. The membrane phase was a 1.0×10^{-3} M solution of carrier in 15 mL of CH_2Cl_2 . The membrane phase was magnetically stirred at a constant speed of 200 rpm (with a tachometer) at 25 °C. The transport rate was obtained by measuring the concentration of co-transported picrate ion in the receiving aqueous phase by UV spectrophotometry (at 356 nm) after 24 h of experiment.

2.5. ISE EXPERIMENTS

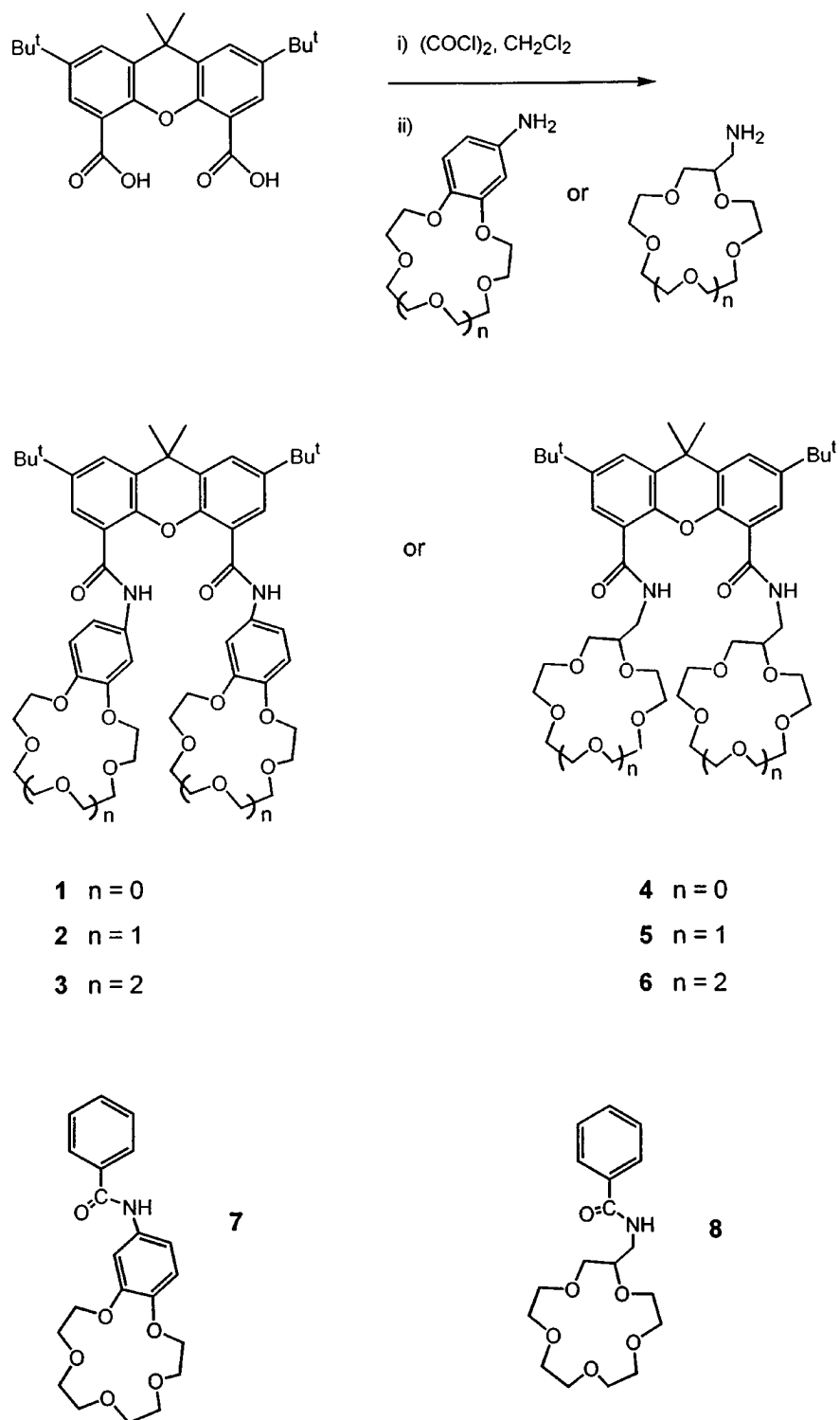
Potential measurements were carried out with a HP 3457A multimeter connected to a personal computer through a GPIB interface. For prevention of errors due to input impedance, a voltage follower and preamplifier were attached to the potentiometer terminal. The system of the cell is $\text{Ag}|\text{AgCl}|3 \text{ M KCl}||0.05 \text{ M Tris-HCl}||\text{sample}, 0.05 \text{ M Tris-HCl}||\text{membrane}|0.01 \text{ M KCl}|\text{AgCl}|\text{Ag}$. All reagents for fabricating the membrane were purchased from Fluka and the procedure of fabrication referred to the corresponding reports [9,10]. The membrane composition based on **2** was ionophore 2.5 mg, poly(vinyl chloride) (PVC) 66 mg, and dioctyl sebacate (DOS) 132 mg. After dissolving PVC and ionophore in THF (1.5 mL), DOS was added and stirred gently overnight. This mixture was poured into a cylindrical tube with 25.5 mm i.d. on a petri dish and dried for 24 h. The selectivity coefficients were determined by the fixed interference method employing Na^+ (5.0×10^{-2} M), Rb^+ (1.0×10^{-3} M), NH_4^+ (5.0×10^{-3} M), and Cs^+ (5.0×10^{-3} M) salt as the concentration level of interferents, respectively. The detection limit was measured according to the reference procedure [11]. All experiments were performed in 0.05 M Tris-HCl buffer (pH 7.2) at 25 °C.

3. Results and Discussion

3.1. SYNTHESIS AND ION-BINDING PROPERTIES

Bis(crown ether)s **1–3** and **4–6** were prepared by the reaction of xanthene-4,5-dicarboxylic acid dichloride, which was obtained by the treatment of dicarboxylic acid with oxalyl chloride, with the corresponding aminobenzo and aminomethyl-crown ethers (12-crown-4, 15-crown-5, and 18-crown-6 ethers), respectively, in the presence of NEt_3 in CH_2Cl_2 as shown in Scheme 1. The products were purified by column chromatography (silica gel, CH_2Cl_2 -MeOH) and/or by recrystallization (hexane- CH_2Cl_2 mixture, yield: 48–78%). The structures of **1–8** were satisfactorily characterized by NMR, IR, and mass (FAB) spectral data.

For the prepared bis(crown ether) hosts, along with the typical ^1H NMR resonances of xanthene and crown ether moiety, the resonance of the amide N–H protons



Scheme 1.

Table I. Solvent extraction of alkali metal picrates.^a

Ligand	% Extraction			
	Na ⁺	K ⁺	Rb ⁺	Cs ⁺
1	<1	<1	<1	<1
2	17.2	80.6	61.3	29.2
3	13.5	35.9	45.4	72.1
4	3.3	2.1	2.4	1.9
5	16.2	29.7	25.2	19.3
6	13.8	26.5	19.4	17.9
7	3.8	4.4	1.8	2.5
8	4.3	5.6	5.8	5.8
18-C-6	2.1	12.1	2.8	3.2

^a At 25 °C, CH₂Cl₂/H₂O = 5.0 mL/5.0 mL, [metal picrate] = 7.0 × 10⁻⁵ M in H₂O; [ligand] = 3.5 × 10⁻⁴ M in CH₂Cl₂.

appeared relatively down field, around δ 8.5–8.9 for benzocrown ethers and δ 7.8–8.1 for aminomethyl crown analogs. These values, when compared to the values of the monomeric analog of **7** (δ 7.70) and **8** (δ 6.91), which reflects a deshielding due to the formation of intramolecular hydrogen bonds between the amide N–H and carbonyl groups of bis(crown ether)s [12]. The formation of intramolecular hydrogen bonds in the present case is a somewhat unfavorable situation because the intramolecular hydrogen bonds must be broken and the two crown ether rings must be parallel with each other in order to effectively complex the metal ion guest in a sandwich type manner. However, the formation of intramolecular hydrogen bonds acts as additional means to control the complexation-decomplexation process, which may be critical to realize any type of responsive ionophoric functions.

The ionophoric properties of bis(crown ether) ligands toward alkali metal cations were assessed by the standard solvent extraction technique of metal picrate salt into CH₂Cl₂ at 25 °C [8]. The percent extraction values along with the results of the mono(crown ether) model compounds are summarized in Table I.

As can be seen in Table I, all the bis(crown ether)s derived from 15-crown-5 and 18-crown-6 ethers exhibit markedly pronounced extraction behavior with respect to their monomeric model compounds **7** and **8**. They are also much more efficient than 18-crown-6. Bis(crown ether) ligands **2**, **3**, **5**, and **6** exhibit a characteristic selectivity trend of sandwich type complexes with two crown ether rings in cooperative binding of guest ions. For example, bis(15-crown-5) ether **2** and bis(18-crown-6) ether **3** exhibit pronounced selectivities toward K⁺ and Cs⁺, respectively. This is a well known phenomenon for systems which can form sandwich type complexes. In particular, the selectivity of **2** is reminiscent of the well-known natural antibiotic valinomycin. The extraction equilibrium constants, obtained by the method of

Ungaro *et al.* [13], of **2** and **3** for the extraction of K^+ and Cs^+ picrate have values up to 10^9 ($\log K_{ex}$: 9.0 for **2**- K^+ and 8.6 for **3**- Cs^+ system), which are much higher than those of **5** and **6** as well as **7** and **8**. Furthermore, for ligand **2**, the selectivity ratio as defined by the ratio of $K_{ex}(K^+)/K_{ex}(Na^+)$ is as high as 100, suggesting its possible application as a selective ionophoric sensor material for potassium. One interesting observation to note is the fact that the *N*-alkylamide derivatives **5** and **6** show much inferior and reduced selectivity compared with **2** and **3**. This reduced selectivity may be due to a less organized structure resulting from the kinked nature of the *N*-methylamido linkage of **5** and **6** compared with the highly organized flat and parallel structural moiety of the *N*-phenylamide fragment of **2** and **3**. With 12-crown-4 derivatives, no significant formation behavior of a sandwich type complex was observed as evidenced by the results of **1** and **4**.

In order to elucidate the solution structure of the complexes formed, UV titration of the metal picrate salt with **2** was performed in THF, and the λ_{max} of the complexed metal picrate was determined. The λ_{max} of picrate ion complexed with ligand **2** varied as follows: Na^+ , 353; K^+ , 381; Rb^+ , 381; Cs^+ , 377 nm in THF. The λ_{max} of 381 nm for the **2**- K^+ and **2**- Rb^+ picrate system is comparable to the value obtained for some cryptand and calix[4]arene tetraester complexes in the same solvent [14], indicating that the complexed metal cations are completely encapsulated within two crown ether moieties [15]. The association constant obtained from the Scatchard plot of this titration in THF for the **2**- K^+ complex is 8.71×10^4 .

The strong ion binding properties of the bis(crown ether)s **2** and **3** toward K^+ and Cs^+ , respectively, were also revealed by transport behavior through a CH_2Cl_2 liquid membrane (U-tube). The trend of transport behavior summarized in Table II is quite confusing in view of the extraction results: the transport efficiency decreases in the order of $Na^+ > Cs^+ > Rb^+ > K^+$ for **2** and $K^+ > Na^+ > Rb^+ > Cs^+$ for **3** and, furthermore, the selectivity is not so pronounced. However, this rather inefficient transport behavior can be in part explained by the results obtained for a system which forms strong complexes with guest ions [16]. The complex formed in liquid membrane is too tight to release the complexed guest into the receiving phase, thus it retains the guest in the complexed form in the membrane phase.

3.2. ISE STUDIES

There has been much recent concern about the development of sensing materials for K^+ -selective electrodes [6,17,18]. Bis(15-crown-5 ether) **2** seems to have suitable ionophoric efficiency and selectivity for this purpose. For this reason, we carried out preliminary potentiometric studies of this ligand as a K^+ ion sensor material in PVC membrane using DOS as a plasticizer. As shown in Figure 1, the potential response of the polymeric liquid membrane upon treatment with alkali metal ions and ammonium ion shows near-Nernstian behavior. The maximum slope is 57 mV decade⁻¹ and the detection limit [10] is 6.2×10^{-6} M.

Table II. Transport of alkali metal cations through dichloromethane liquid membrane.

Carrier	Transport rate ($\times 10^{-8}$ mol cm $^{-2}$ h $^{-1}$)			
	Na $^{+}$	K $^{+}$	Rb $^{+}$	Cs $^{+}$
2	11.8	1.8	3.3	4.1
3	4.3	5.5	3.7	2.9

Source phase: [Metal picrate] = 0.01 M, in H $_2$ O (5.0 mL). Membrane phase: [Carrier] = 1.0×10^{-3} M, in CH $_2$ Cl $_2$ (15 mL). Receiving phase: Deionized water (5.0 mL). At 25 °C with a constant stirring of 200 rpm. Determined by UV spectrophotometry.

Table III. Selectivity coefficients for K $^{+}$ -selective electrode based on **2** and two representative ionophores.^a

Ionophores	K_{K^+,M^+}			
	Na $^{+}$	Rb $^{+}$	Cs $^{+}$	NH $_4^+$
2	3×10^{-4}	1×10^{-1}	4×10^{-3}	1×10^{-2}
Valinomycin ^b	2×10^{-4}	1.4	3×10^{-1}	1×10^{-1}
K $^{+}$ -ionophore ^c	6×10^{-4}	1×10^{-1}	3×10^{-3}	7×10^{-3}

^a Determined by fixed interference method, 0.05 M Tris-HCl buffer (pH 7.2).

^b Taken from Ref. [9].

^c Commercialized K $^{+}$ -ionophore reported by Kimura *et al.* [10].

The relevant selectivity coefficients of **2** for K $^{+}$ over alkali metal cations were determined by the fixed interference method [10] and are summarized in Table III. Comparing the selectivity values of valinomycin [9] and the K $^{+}$ -ionophore developed by Kimura *et al.* [10], Table III indicates that **2** exhibits an almost comparable selectivity pattern to these compounds. The selectivity ratio for the K $^{+}$ /Na $^{+}$ pair is found to be similar or even superior to the well-known K $^{+}$ -ionophore of Kimura *et al.* In comparison with the valinomycin-based electrode, the K $^{+}$ selectivity of **2** against Rb $^{+}$, Cs $^{+}$, and NH $_4^+$ ions is more favorable.

With regard to the response time, the ISE based on **2** shows a more sluggish response to the increase in K $^{+}$ concentration than that based on valinomycin. Figure 2 shows that the t_{90} and t_{99} values, the response times for the potential to reach 90% and 99% of the final value in the steady state, are 16 and 24 s, respectively. Completion of the stable response to the decrease of K $^{+}$ concentration also requires a relatively long time compared to the case of the valinomycin-based ISE. This slow response is serious in the very diluted concentration region below the 10^{-6} M level, and may be due to the slow dissociation of the tightly complexed form. Considering the results of the extraction and transport experiments described in

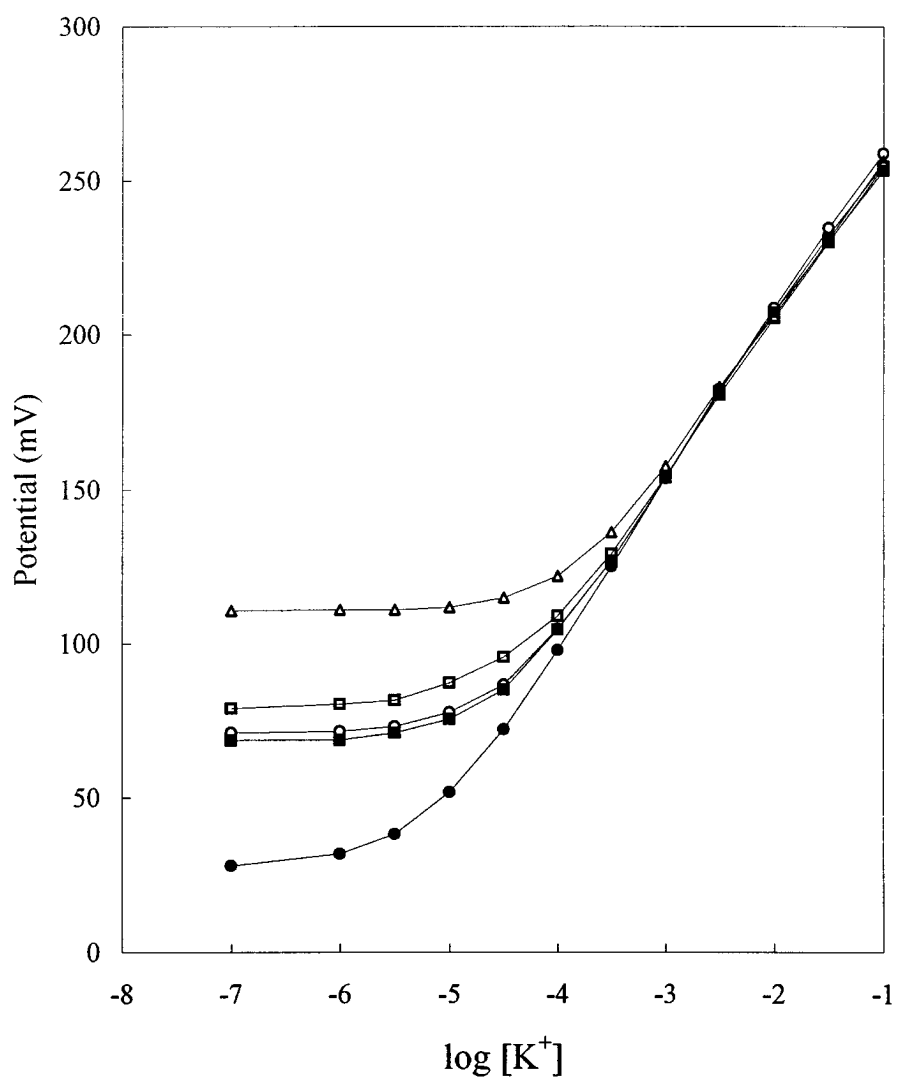


Figure 1. Response and selectivity of the K⁺-selective electrode based on **2** at 25 °C. Calibration plot for KCl without interferent (●), in the presence of 5.0×10^{-2} M of NaCl (○), 1.0×10^{-3} M of RbCl (Δ), 5.0×10^{-3} M of NH₄Cl (□) and 5.0×10^{-3} M of CsCl (■).

the previous section, this observation may be more evidence that supports the strong and relatively well organized structure of **2** for the complexation of K⁺ ion. Thereby, from the standpoint of the practical function of the ISE, the K⁺-selective electrode based on **2** has a drawback in its dynamic activity. However, a subsequent hysteresis test shows that a highly reproducible potential response is observed in the range of K⁺ ion concentration between 1.0×10^{-1} M and 3.1×10^{-5} M and that hysteresis is negligible. In addition, reproducible action of the electrode is

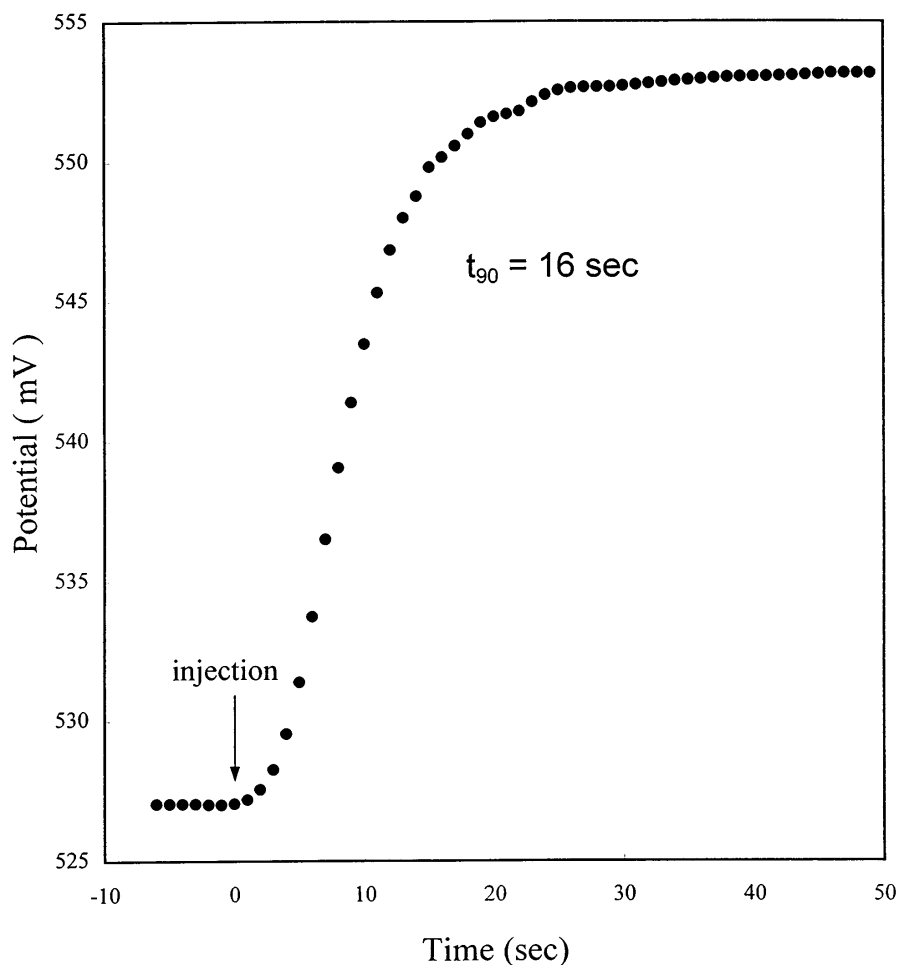


Figure 2. Traces of response to change in KCl concentration from 3.1×10^{-4} M to 1.0×10^{-3} M for K⁺-selective electrode based on **2**.

maintained without any deterioration for more than a week. Therefore, except for the slow response of about 10–15 s, the **2**-based ISE is thought to be comparable with the K⁺-ISE based on valinomycin or K⁺-ionophore [10] and even superior in selectivity over some interferents.

Ionophore **3** was also tested as a Cs⁺-selective ISE material under similar conditions. The preliminary results are satisfactory in that the electrode exhibited Nernstian behavior having a slope of 59 mV decade⁻¹ and the limit of detection for Cs⁺ ion was found to be 1.7×10^{-6} M. The response behavior was also satisfactory having a t_{90} value of 6 s. However, the selectivity coefficient K_{Cs^+, M^+} for **3** was moderate: 1×10^{-3} , 2×10^{-2} , 2×10^{-1} , and 0.4 for Na⁺, K⁺, Rb⁺, and NH₄⁺, respectively. This preliminary result is comparable to the

bis(benzo-18-crown-6) derivative-based ISE material, having a more flexible spacer of pentamethylene diester, reported by Kimura *et al.* [19] and somewhat inferior to the *p-tert*-butylcalix[6]arene ester-based ISE material [20]. Full details on these potential ISE sensory materials for the determination of K^+ and Cs^+ ion will be reported in due course.

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