

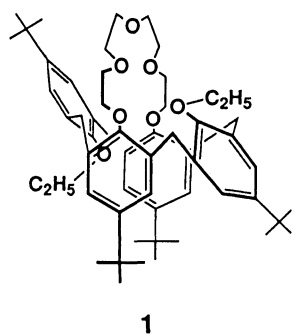
Molecular Design of Calix[4]arene-Based Sodium-Selective Electrodes
Which Show Remarkably High $10^{5.0}$ - $10^{5.3}$ Sodium/Potassium Selectivity

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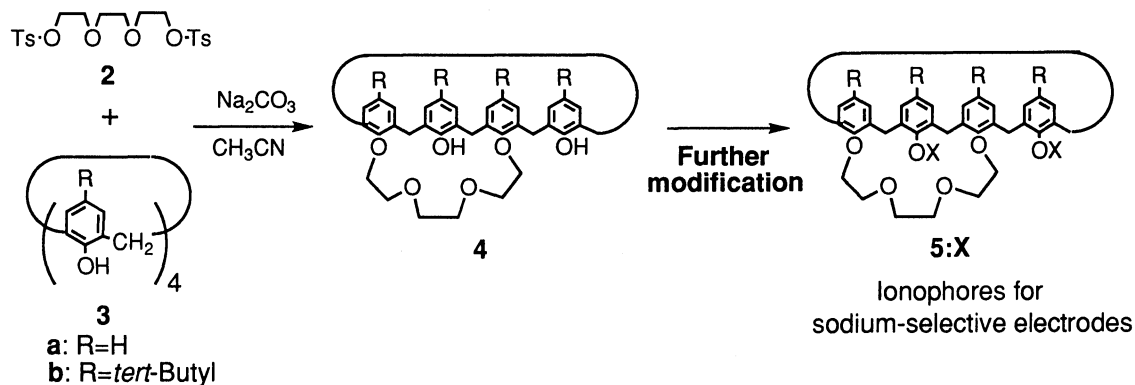
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Several ionophores for the Na^+ -selective electrode were developed from calix[4]arene crown ethers with a short $-(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_2\text{CH}_2-$ crown loop on the lower rim. The ionophoric cavities generated in these ionophores are much smaller and more rigid than those derived from calix[4]arene crown ethers with a long $-(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2-$ crown loop. It was shown that *two electrodes possess Na^+ selectivity (with respect to K^+) exceeding a factor of 10^5 which is higher by more than two orders of magnitude than that of the former calix[4]arene-based Na^+ -selective electrodes!*

Among alkali metal cations Na^+ and K^+ play particular roles in regulation of many biological events. Hence, in analytical and biological chemistry fields extensive research efforts have so far been devoted toward precise discrimination between Na^+ and K^+ . To selectively recognize K^+ with respect to Na^+ the nature gives us a splendid ionophore, valinomycin which shows very high K^+ selectivity. One can devise practical K^+ -selective electrodes from a poly(vinyl chloride)(PVC)-plasticizer system using valinomycin as an ionophore.¹⁾ In contrast, there exists in nature no such useful ionophore for selective recognition of Na^+ with respect to K^+ . Hence, one has to develop some artificial ionophores for Na^+ -selective electrodes which show high Na^+ selectivity. In the first stage Na^+ -selective electrodes were prepared from crown ethers.²⁾ For example, Shono *et al.*³⁾ devised a Na^+ -selective electrode using a bis(12-crown-4) ethers which showed 10^2 Na^+/K^+ selectivity. However, the Na^+/K^+ selectivity attainable with crown ethers has been saturated at the 10^2 order. In the second stage Na^+/K^+ selectivity was further improved by using calix[4]aryl esters and amides as ionophores.⁴⁻¹⁰⁾ For example, Kimura *et al.*⁴⁾ realized $10^{2.4}$ Na^+/K^+ selectivity with a PVC-2-fluoro-2'-nitrodiphenyl ether (FNDPE)-5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(decyloxycarbonyl)methoxy]-calix[4]arene system and Sakaki *et al.*⁵⁾ attained $10^{3.1}$ Na^+/K^+ selectivity with a PVC-FNDPE-5,11,17,23-tetra-*tert*-octyl-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene system. The superiority of calix[4]aryl esters over crown ethers is ascribed to the ionophoric cavity size exactly fit to the size of Na^+ and to the rigid calix[4]arene skeleton supporting the cavity as a platform.⁵⁾ To further improve Na^+/K^+ selectivity we synthesized various ionophores from calix[4]arene-25,26,27,28-tetrol but could not come across the ionophore that exceeds $10^{3.1}$ Na^+/K^+ selectivity.⁵⁾ Is there any potential strategy to break this selectivity? Valinomycin is produced by nature so as to selectively recognize K^+ in the presence of Na^+ . It is known, however, that the



highest selectivity is not observed for K^+ but for Rb^+ .¹¹⁾ This contrivance in nature teaches us that to efficiently discriminate larger K^+ from smaller Na^+ the ionophoric cavity should be adjusted in the size slightly larger than K^+ . Provided that this working hypothesis is applied to discrimination of smaller Na^+ from larger K^+ , it follows that the ionophoric cavity should be adjusted in the size slightly smaller than Na^+ . Recently, Ghidini *et al.*¹²⁾ reported a calix[4]arene crown ether **1** which shows high K^+ selectivity. Examination of the CPK molecular models reveals that as reported by them,¹²⁾ the length of the crown loop suitable to the cross-link of the two distal OH groups is a $-(CH_2CH_2O)_3CH_2CH_2-$ chain. We considered that if one could synthesize a calix[4]arene capped with a shorter $-(CH_2CH_2O)_2CH_2CH_2-$ chain, it should result in a smaller ionophoric cavity which fits Li^+ or Na^+ . We thoroughly examined the reaction products yielded from the reaction of 3,6-dioxaoctane-1,8-ditosylate (**2**) with calix[4]arene-25,26,27,28-tetrol (**3a**)¹³⁾ or 5,11,17,23-tetra-*tert*-butylcalix[4]arene-25,26,27,28-tetrol (**3b**) and eventually found out the reaction conditions which give conformational isomers of $-(CH_2CH_2O)_2CH_2CH_2-$ bridged calix[4]arene crown ethers. By suitable modification of these calix[4]arene crown ethers we have succeeded in the design of Na^+ -selective electrodes which show *unbelievably high* $10^{5.0}$ - $10^{5.3}$ Na^+ selectivity.



Preparation of **4a** was described previously.¹³⁾ **4b** (mp 259-262 °C) was synthesized in a manner similar to that described for **4a**. These compounds were treated with ethyl bromide, bromo acetate, or 2-bromoethyl ethyl ether in THF (but in DMF for 1,3-alternate-**5a:Et** and 1,3-alternate-**5b:Et**) in the presence of NaH (but in the presence of KH for 1,3-alternate-**5a:Et** and 1,3-alternate-**5b:Et**). The products were identified by IR and 1H NMR spectral evidence and elemental analyses.¹⁴⁾ The temperature-dependent 1H NMR spectra (0-145 °C, tetrachloroethane- d_2) established that the rotation of the phenyl units are suppressed, indicating that the ethyl group is bulky enough to inhibit the oxygen-through-the-annulus rotation in **5**. Preparation of ion-selective electrodes was described in detail previously.⁵⁾ The selectivity coefficients were determined by a mixed solution method (FIM). The results are summarized in Table 1 and Figs.2 and 3.

Examination of Table 1 tells us several intriguing characteristics of **5**-based ion-selective electrodes: that is, (i) six electrodes show the highest selectivity for Na^+ , (ii) Na^+/K^+ selectivity of two electrodes exceeds a factor of 10^5 which is higher by more than two orders of magnitude than the past champion data,⁵⁾ (iii) the highest Na^+/K^+ selectivity ($10^{5.3}$) is realized with partial-cone-**5a:Et**, (iv) cone-**5b:Et** also shows $10^{5.0}$ selectivity but that for 1,3-alternate-**5b:Et** is reduced to $10^{2.0}$, and (v) introduction of ester or ethereal groups

Table 1. Sodium selectivity of 5-based electrodes^{a)}

Calix[4]arene	$\log K_{\text{Na}^+, \text{M}^+}^{\text{pot}}$ b)										
	$\text{M}^+=\text{Li}^+$	Na^+	K^+	Rb^+	Cs^+	NH_4^+	Mg^{2+}	Ca^{2+}	Ba^{2+}	Sr^{2+}	H^+
Cone-5a:Et	-2.7	0	-4.1	-4.1	-3.4	-4.4	-4.3	-4.3	-4.8	-4.1	-4.7
Partial-cone-5a:Et	-2.4	0	-5.3	-3.7	-3.2	-3.9	-5.1	-4.6	-4.6	-4.2	-4.7
1,3-Alternate-5a:Et	-3.8	0	-3.3	-4.4	-4.4	-4.5	-4.5	-4.4	-5.0	-4.1	-3.4
Cone-5b:Et	-2.8	0	-5.0	-4.8	-5.0	-4.4	-4.5	-4.4	-5.5	-4.1	-5.4
1,3-Alternate-5b:Et	-3.0	0	-2.0	-2.8	-1.4	-2.3	-4.7	-4.6	-4.4	-4.4	-3.1
Cone-5b:AcOEt	-3.1	0	-4.0	-4.6	-4.6	-4.3	-4.4	-4.4	-5.1	-4.1	-4.2
Cone-5b:EtOEt	-3.1	0	-4.1	-4.3	-4.6	-4.5	-4.3	-4.2	-5.1	-4.1	-4.7
Reference ^{c)}	-3.6	0	-3.0	-4.4	-4.6	-4.3	-5.5	-5.5	-6.1	-5.2	-4.6

a) The PVC membranes consist of 3.2% (in weight) calix[4]arene derivative, 64.1% *o*-nitrophenyl octyl ether as a plasticizer, 32.1% PVC, and 0.6% potassium tetrakis(*p*-chlorophenyl) borate. The emf measurements were carried out at 25 °C with an electrochemical cell of Ag-AgCl/1x10⁻² M NaCl/PVC membrane/sample solution /1x10⁻¹ M NH₄Cl/ sat. KCl/Ag-AgCl. b) Data were obtained by the FIM method with back ground concentrations of 0.05M for Li⁺ and K⁺ (in the case of log*K* values smaller than -4) and 0.5 M for other cations (Rb⁺, Cs⁺, etc.) and K⁺ (in the case of log*K* values larger than -4). The selectivity coefficients were determined according to the recommendation of IUPAC.¹⁵⁾ c) 5,11,17,23-Tetra-*tert*-octyl-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene.

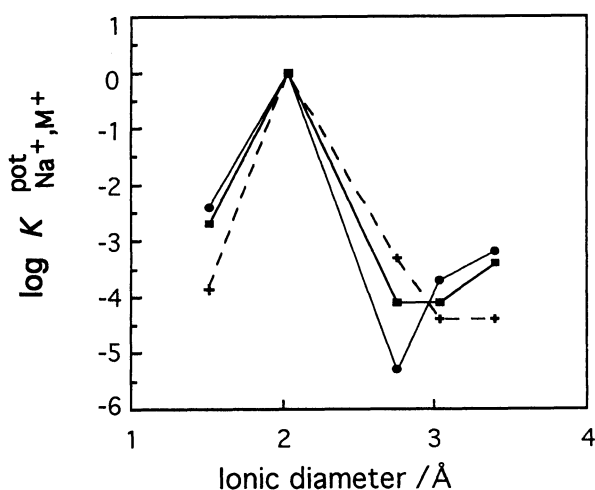


Fig. 1. Sodium selectivity against alkali metal cations, $\log K_{\text{Na}^+, \text{M}^+}^{\text{pot}}$, of the electrodes based on calix[4]arene derivatives (cone-5a:Et: —■—, partial-cone-5a:Et: —●—, 1,3-alternate-5a:Et: —○—, 1,3-alternate-5a:Et: —△—).

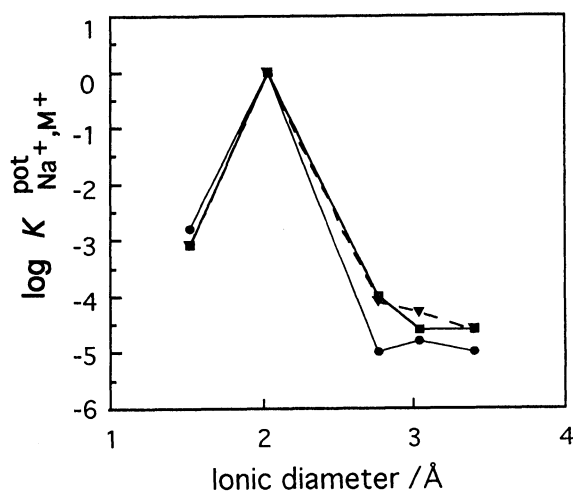


Fig. 2. Sodium selectivity against alkali metal cations, $\log K_{\text{Na}^+, \text{M}^+}^{\text{pot}}$, of the electrodes based on calix[4]arene derivatives (cone-5b:Et: —●—, cone-5b:AcOEt: —■—, cone-5b:EtOEt: —○—, cone-5b:EtOEt: —△—).

reduces Na⁺/K⁺ selectivity about one order of magnitude (see cone-5b:AcOEt and cone-5b:EtOEt vs. cone-5b:Et). These findings suggest that a size of the ionophoric cavity and a surrounding of the cavity seriously influence the performance of the electrode.

In conclusion, the present study demonstrated that the Na⁺-selective electrode can be devised by preparing a calix[4]arene crown ether having a rigid, small ionophoric cavity. To the best of our knowledge, Na⁺/K⁺ selectivity of 10^{5.3} is the highest value achieved so far. The results imply that the working hypothesis described in Introduction is pertinent. We are now investigating the Na⁺-binding mode of these calix[4]arene crown ethers by ¹H NMR spectroscopy. The preliminary ¹H NMR study indicates that in partial-cone-**5a:Et** Na⁺ resides in the crown loop and is sandwiched by the two EtO oxygens. This binding mode is similar to that proposed by Ghidini *et al.*¹²⁾ for **1** with a partial-cone conformation. We believe that his research eventually leads to further improvement of Na⁺ selectivity.

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- 14) Mp's and yields from **4** are 208-209.5 °C and 11% for cone-**5a:Et**, 220-221.5 °C and 27% for partial-cone-**5a:Et**, >400 °C and 14% for 1,3-alternate-**5a:Et**, 209-210.5 °C and 31% for cone-**5b:Et**, 312-314 °C and 50% for 1,3-alternate-**5b:Et**, 186-189 °C and 60% for cone-**5b:AcOEt** and 172.5-174 °C and 60% for cone-**5b:EtOEt**. According to the referee's advice, we here record the ¹H NMR data for partial-cone-**5a:Et** and cone-**5b:Et**. Partial-cone-**5a:Et**: white powder, mp 220-221.5 °C; ¹H NMR (CDCl₃, 300 MHz) δ 7.22 (br. d, J= 7.6 Hz, 2H, ArH), 7.18 (d, J= 7.6 Hz, 2H, ArH), 7.08 (br d, J= 7.5 Hz, 2H, ArH), 7.01 (t, J= 7.5 Hz, 1H, ArH), 6.94 (t, J= 7.6 Hz, 2H, ArH), 6.76 (d, J= 7.5 Hz, 2H, ArH), 6.56 (t, J= 7.5 Hz, 1H, ArH), 4.42 (d, J= 12.6 Hz, 2H, ArCH₂Ar), 4.12 (dt, J= 6.0, 10.0 Hz, 2H, OCH₂), 3.95-3.71 (m, 12H, OCH₂, ArCH₂Ar, OCH₂CH₃), 3.53 (dt, J= 5.9, 8.7 Hz, 2H, OCH₂), 3.29 (d, J= 12.6 Hz, 2H, ArCH₂Ar), 3.15 (dt, J= 6.0, 10.0 Hz, 2H, OCH₂), 1.48 (t, J= 6.9 Hz, 3H, OCH₂CH₃), 1.42 (q, J= 6.9 Hz, 2H, OCH₂CH₃), -0.11 (t, J= 6.9 Hz, 3H, OCH₂CH₃). Cone-**5b:Et**: colorless crystal, mp 209-210.5 °C; ¹H NMR (CDCl₃, 300 MHz) δ 7.14 (s, 4H, ArH), 6.48 (s, 4H, ArH), 4.40 (t, J=6.2 Hz, 4H, ArOCH₂CH₂O), 4.39 (d, J=12.5 Hz, 4H, ArCH₂Ar), 4.06 (t, J= 6.2 Hz, 4H, ArOCH₂CH₂O), 3.89 (s, 4H, CH₂OCH₂CH₂OCH₂), 3.81 (q, J= 7.0 Hz, 4H, OCH₂CH₃), 3.14 (d, J=12.5 Hz, 4H, ArCH₂Ar), 1.54 (t, J= 7.1 Hz, 6H, OCH₂CH₃), 1.34 (s, 18H, t-C₄H₉), 0.82 (s, 18H, t-C₄H₉).
- 15) IUPAC Recommendation for Nomenclature of Ion-Selective Electrodes: see *Pure Appl. Chem.*, **48**, 129 (1976).

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