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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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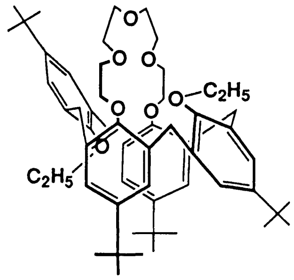
Several ionophores for the Na^+-selective electrode were developed from calix[4]arene crown ethers with a short -$(CH_2CH_2O)_2CH_2CH_2$- crown loop on the lower rim. The ionophoric cavities generated in these ionophores are much smaller and more rigid than those derived from calix[4]arene crown ethers with a long -$(CH_2CH_2O)_3CH_2CH_2$- 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



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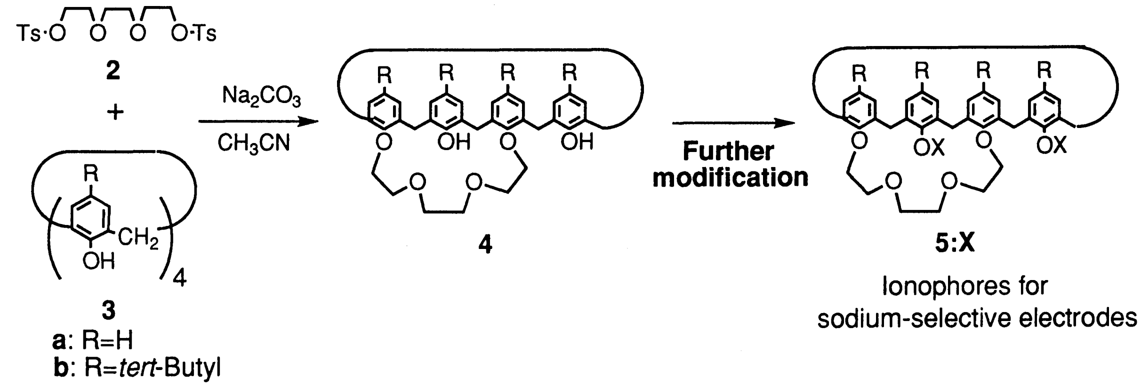
highest selectivity is not observed for K^+ but for Rb^+.11) This contrivance in nature teaches us that to efficiently discriminate larger K^+ from smaller Na^+ the ionophoric cavity should be adjusted in the size slightly larger than K^+. Provided that this working hypothesis is applied to discrimination 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 ^{1}H NMR spectral evidence and elemental analyses.14) The temperature-dependent ^{1}H 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

Table1. Sodium selectivity of 5-based electrodes$^{a)}$

	$\log K^{pot}_{Na^+,M^+}$ $^{b)}$										
Calix[4]arene	M^+=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/1×10^{-2} M NaCl/PVC membrane/sample solution /1×10^{-1} M NH_4Cl/ 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.

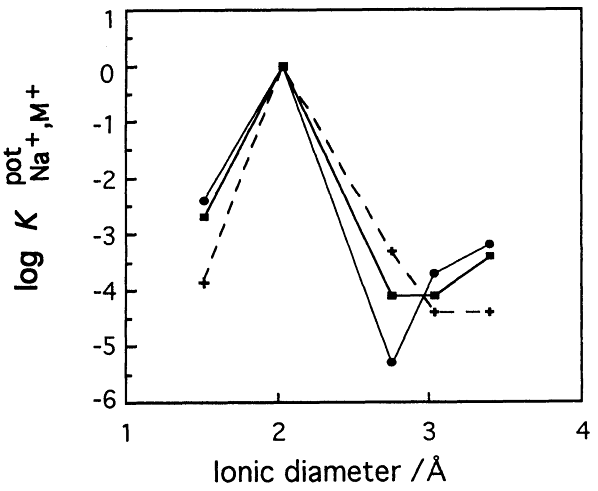


Fig. 1. Sodium selectivity against alkali metal cations, $\log K^{pot}_{Na^+,M^+}$, of the electrodes based on calix[4]arene derivatives (cone-**5a**:Et: —■— , partial-cone-**5a**:Et: —●— ,1,3-alternate-**5a**:Et: — + - -).

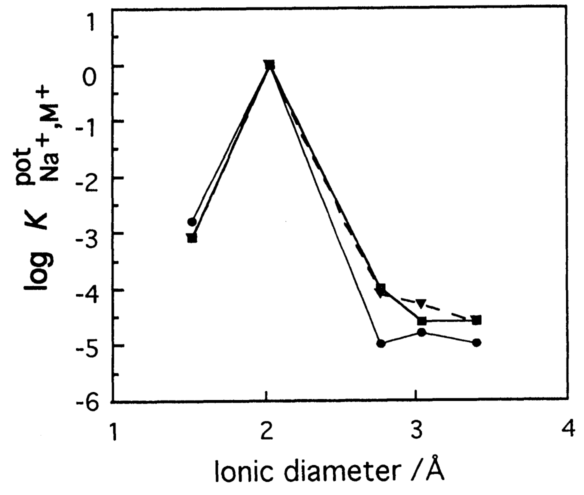


Fig. 2. Sodium selectivity against alkali metal cations, $\log K^{pot}_{Na^+,M^+}$, of the electrodes based or calix[4]arene derivatives (cone-**5b**:Et:—●—, cone-**5b**:AcOEt: —■— , cone-**5b**:EtOEt: — ▼ - -).

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 ($CDCl_3$, 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, $ArCH_2Ar$), 4.12 (dt, J= 6.0, 10.0 Hz, 2H, OCH_2), 3.95-3.71 (m, 12H, OCH_2, $ArCH_2Ar$, $OC\underline{H_2}CH_3$), 3.53 (dt, J= 5.9, 8.7 Hz, 2H, OCH_2), 3.29 (d, J= 12.6 Hz, 2H, $ArCH_2Ar$), 3.15 (dt, J= 6.0, 10.0 Hz, 2H, OCH_2), 1.48 (t, J= 6.9 Hz, 3H, $OCH_2C\underline{H_3}$), 1.42 (q, J= 6.9 Hz, 2H, $OC\underline{H_2}CH_3$), -0.11 (t, J= 6.9 Hz, 3H, $OCH_2C\underline{H_3}$). Cone-**5b:Et**; colorless crystal, mp 209-210.5 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.14 (s, 4H, ArH), 6.48 (s, 4H, ArH), 4.40 (t, J=6.2 Hz, 4H, $ArOC\underline{H_2}CH_2O$), 4.39 (d, J=12.5 Hz, 4H, $ArCH_2Ar$), 4.06 (t, J= 6.2 Hz, 4H, $ArOCH_2C\underline{H_2}O$), 3.89 (s, 4H, $CH_2OC\underline{H_2}C\underline{H_2}OCH_2$), 3.81 (q, J= 7.0 Hz, 4H, $OC\underline{H_2}CH_3$), 3.14 (d, J=12.5 Hz, 4H, $ArCH_2Ar$), 1.54 (t, J= 7.1 Hz, 6H, $OCH_2C\underline{H_3}$), 1.34 (s, 18H, $t\text{-}C_4H_9$), 0.82 (s, 18H, $t\text{-}C_4H_9$).
15) IUPAC Recommendation for Nomenclature of Ion-Selective Electrodes: see *Pure Appl. Chem.*, **48**, 129 (1976).

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