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## Selectivity of Calix[4]arene-crown-6 for Cesium Ion in ISE: Effect of the Conformation

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A new series of calix-crowns were used in ion-selective electrodes with two solvents (dibutyl sebacate and onitrophenyl octyl ether). As ionophores, the 1,3-dimethoxy and the three different conformers of the 1,3-diisopropoxycalix[4]arene-crown-6 (i.e., 1,3-alternate, partial cone, and cone) were considered. Their behavior toward cesium ion was studied in terms of detection limit (DL), sensitivity (S, mV/pCs), and selectivity toward protons, ammonium, alkali, and alkaline earth metal ions. The lowest DL value was obtained for membranes containing the 1,3-diisopropoxy derivative in the 1,3-alternate conformation. To correlate the analytical results with the structural properties of the ligand and with the nature of the polymeric membrane, a multifactor ANOVA with interactions was carried out on selectivities toward univalent and divalent ions. As for the alkali metal ions, a highly significant negative correlation (p < 0.01) between the  $pK_{Cs/M}^{pot}$  values and the ionic radius was found; in addition, for the smaller ions H<sup>+</sup>, Li<sup>+</sup>, and Na<sup>+</sup>, the four ionophores showed higher differences in selectivity than for the larger ions K<sup>+</sup> and Rb<sup>+</sup> as well as for alkaline earth metal ions. Better results than those previously reported with other ligands in terms of DL (5  $\times$  10<sup>-7</sup> M) and  $pK_{C_S/M}^{pot}$  (4.46) were found for the 1,3-diisopropoxycalix-[4]arene-crown-6 in the 1,3-alternate conformation.

Calixarene-based ionophores have been widely studied because of their structural and electronic features,<sup>1,2</sup> which allow a tridimensional control of metal ion complexation, resulting in a high efficiency and selectivity. Moreover, the presence of alkyl groups at the upper rim (aromatic nuclei) of the calix make it possible to modulate the lipophilicity of the ligands.

The ability of the calixarene compounds to act as carriers has been widely exploited for the construction of alkali and alkaline earth metal ion-selective electrodes; good selectivities have been obtained for sodium<sup>3,4</sup> and potassium.<sup>5</sup> Recently, a new class of calixarene derivatives having a polyether chain bridging the 1,3-position of the lower rim of the calix (OH groups) has been synthesized.

p-tert-Butylcalix[4]arene-crown-5 compounds have been used for the complexation of alkali metal ions and as carriers in electrodes.<sup>6,7</sup> Some of them have high selectivity toward potassium; in particular, the 1,3-diisopropoxy-p-tert-butylcalix[4]arenecrown-5 has a  $pK_{K/Na}^{pot} = 3.6$ . The most effective stereoisomers are those fixed in a partial cone structure. Selectivity toward sodium has been obtained by Yamamoto and Shinkai using calix-[4]arene-crowns-4.8 The highest values of Na/K selectivity constants ( $pK_{Na/K}^{pot} = 5.0$  and 5.3) have been obtained with ethoxy derivatives, which have different structures and substituents, i.e., a cone structure with *tert*-butyl groups on the aromatic nuclei in the first case and partial cone structure without substituents in para position in the second one. These results suggest that, even though the length of the crown ether chain is the most important factor, the structural features and the presence of bulky substituents also play a relevant role in determining selectivity.

With the aim of obtaining new ionophores for larger alkali metal ions such as rubidium and cesium, a series of new calix-[4]arenes bridged with a longer crown ether chain has been synthesized and characterized.<sup>9</sup> Thermodynamic and membrane transport data have shown that the most efficient and selective ligands are those fixed in 1,3-alternate conformation, which allows also interaction of the complexed cesium cation with the aromatic rings of two rotated nuclei.

On the basis of these results, we have examined in this work the behavior of compounds I-IV (see Chart 1) as carriers in liquid membrane electrodes, considering cesium as primary ion and

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other alkali and alkaline earth ions as interferents. Detection limits, sensitivities, and selectivity coefficients were determined through potentiometric measurements. To correlate the analytical results with the features of the ionophores and with the conditions of preparation of the membrane, the analysis of variance was carried out, following the approach used in previous work.<sup>4</sup> The nature of the ionophore, membrane solvent, and interfering ion were considered as factors.

#### **EXPERIMENTAL SECTION**

Synthesis and characterization of compounds I, II, and IV are described in ref 9.

Synthesis and Characterization of 25,27-Bis(2-propyloxy)calix[4]arene-crown-6, Partial Cone (III). A suspension of potassium tert-butoxide (0.31 g, 2.74 mmol) in 20 mL of dry THF was added to a solution of 25,27-dihydroxycalix[4]arene-crown-69 (0.25 g, 0.4 mmol) and 2-iodopropane (0.2 mL, 2.7 mmol) in 20 mL of dry THF. The reaction mixture was refluxed for 24 h, and THF was removed under reduced pressure, and the residue was quenched with 3 M HCl. The aqueous phase was extracted with dichloromethane  $(2 \times 25 \text{ mL})$ , and the combined organic extracts were washed with 1 M Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (50 mL), 3 M HCl ( $2 \times 50$  mL), and water  $(3 \times 50 \text{ mL})$ . Dichloromethane was distilled off under vacuum, and the residue was treated with methanol to afford pure III as a white precipitate in 43% yield. Melting point 184.5-185.5 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 25 °C, TMS):  $\delta$  7.46 (d, J = 7.5Hz, 2 H, ArH meta), 7.1-6.8 (m, 6 H, ArH), 6.70 (t, I = 7.5 Hz, 1 H, ArH para), 6.55-6.43 (m, 3 H, ArH), 4.36 (ept, J = 6.0 Hz, 1 H, Ar-O-CH), 4.22 (d,  $J_{AX-EQ} = 12.6$  Hz, 2 H, Ar-CH<sub>2</sub>-Ar, H<sub>AX</sub>), 4.20-4.07 (m, 4 H, Ar-CH2-Ar), 3.92-3.60 (m, 21 H, O-CH2-CH2-O, Ar-O-CH), 3.02 (d,  $J_{AX-EQ} = 12.6$  Hz, 2 H, Ar-CH<sub>2</sub>-Ar, H<sub>EQ</sub>), 1.21 (d, J = 6.1 Hz, 6 H, Ar-O-CH-(CH<sub>3</sub>)<sub>2</sub>), 1.07 (d, J = 6.1 Hz, 6 H, Ar-O-CH-(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR  $\delta$  155.3, 154.8 (s, Ar ipso), 137.6, 133.6, 133.5, 132.7 (s, Ar ortho), 131.7, 129.7, 128.7, 128.6 (d, Ar meta), 122.8, 121.9, 121.7 (d, Ar para), 74.6 (d, Ar-O-CH), 72.6 (t, O-CH<sub>2</sub>-CH2-O), 72.0 (d, Ar-O-CH), 71.6, 71.4, 70.9 (t, O-CH2-CH2-O), 37.2, 30.9 (t, Ar-CH<sub>2</sub>-Ar), 22.6, 22.2 (q, O-CH-(CH<sub>3</sub>)<sub>2</sub>). MS (CH<sub>4</sub>, DCI): m/z 710.2 (M<sup>+</sup> calculated 710.4). Anal. Calcd for C<sub>44</sub>H<sub>54</sub>O<sub>8</sub>: C, 74.33; H, 7.65. Found: C, 74.19; H, 7.75.

**Membranes.** Experimental details on the procedure of preparation of the membrane are reported in ref 4. High molecular weight PVC (Aldrich, Milan, Italy) was used as matrix; dibutyl sebacate (DBS) or *o*-nitrophenyl octyl ether (NPOE) (Fluka, Milan, Italy) was used as plasticizer, and potassium tetrakis(*p*-chlorophenyl) borate (KtCIPB) (Fluka, Milan, Italy) was used as the lipophilic salt.

# Table 1. Detection Limits $(-\log [Cs^+])$ and Sensitivities (mV/pCs) Found for Four lonophores in Two Solvents (Mean of Four Independent Measurements with SD in Parentheses)

solvent	I	II	III	IV
DBS	6.1 (0.3) -61.1 (0.6) 6.0 (0.2)	6.33 (0.08) -58.2 (0.7) 6.3 (0.1)	5.3 (0.2) -60 (1) 5 4 (0.3)	4.6 (0.1) -50 (2) 4.48 (0.08)
NIOL	-60.9(0.4)	-58.2(0.7)	-58.2(0.1)	-54 (1)

emf Measurements and Calculations. Determination of detection limits (DL), sensitivities (S = mV/pCs), and selectivity constants have been described previously.<sup>4</sup>

### **RESULTS AND DISCUSSION**

**Detection Limit and Sensitivity.** The response of the electrodes was first checked with respect to the detection limit and sensitivity toward cesium ion. The detection limit values were obtained by applying a nonlinear regression to the Eisenmann–Nikolsky function; in this way, the points of the nonlinear area of the calibration curve were also used. The results expressed as mean values of four independent determinations for the four calixarenes and the two solvents are given in Table 1. The lowest value ( $5 \times 10^{-7}$  M) was obtained with the diisopropoxy ionophore **II**, which has the fixed 1,3-alternate structure, for both plasticizers.

Similar values, even though slightly higher, were obtained using the dimethoxy derivative I. This compound can assume all three conformations, since rotation is not hindered by the small methoxy groups. Thus, when complexed with cesium, I is likely to be in the 1,3-alternate conformation, as observed in the solid state for cesium picrate–I complex<sup>9</sup> and as deduced from NMR spectra in solution. Small and statistically insignificant differences were observed between the two solvents, both for the detection limit and sensitivity (two-way ANOVA tests). The sensitivity toward cesium obtained with ligand II is 58.2 (0.7) mV/pCs. This value is slightly but significantly lower (p < 0.01, *t*-test) than the theoretical value of 60.15 mV/pCs at 30 °C.

**Selectivity.** The selectivity coefficients were determined toward the following cations:  $H_3O^+$ ,  $NH_4^+$ ,  $Li^+$ ,  $Na^+$ ,  $K^+$ ,  $Rb^+$ ,  $Mg^{2+}$ ,  $Ca^{2+}$ ,  $Sr^{2+}$ ,  $Ba^{2+}$ . These coefficients, measured using the fixed interference method, are given in Table 2 and are presented graphically in Figures 1 and 2. Each determination was replicated four times.

Also with respect to selectivities, the best results were obtained using the 1,3-alternate ionophore II; high selectivities were also obtained with conformationally mobile dimethoxy derivative I. Particularly noteworthy is the Cs/Na selectivity of ionophore II  $(pK_{Cs/Na}^{pot} = 4.36 \text{ and } 4.46 \text{ with DBS and NPOE as plasticizers,}$ respectively). These values are higher than those reported for ISEs<sup>10</sup> and for CHEMFETs<sup>11</sup> based on calixarene derivatives.

The highest values of  $pK_{Cs/M}^{pot}$  are obtained for alkaline earth ions, due to the difference in charge, while the most interfering ions are K<sup>+</sup>, Rb<sup>+</sup>, and NH<sub>4</sub><sup>+</sup>, since their size is close to that of cesium. A more systematic and accurate examination of the data was performed with ANOVA. This procedure allowed us to detect

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Table 2. Selectivity Coefficients ( $pK_{CSM}^{oo}$ ) (Mean of Four Independent Measurements with SD in Parentheses)

solvent DBS				solvent NPOE			
I	II	III	IV	I	II	III	IV
3.35 (0.15)	4.32 (0.07)	2.28 (0.10)	1.0 (0.4)	3.86 (0.17)	4.32 (0.05)	2.88 (0.08)	1.0 (4)
1.91 (0.03)	1.86 (0.03)	0.76 (0.11)	0.66 (0.07)	1.96 (0.02)	1.98 (0.02)	0.82 (0.16)	1.01 (1)
3.51 (0.05)	5.03 (0.03)	2.98 (0.17)	1.38 (0.06)	3.54 (0.11)	4.81 (0.05)	3.81 (0.10)	2.22 (4)
2.95 (0.13)	4.36 (0.08)	2.09 (0.10)	1.3 (0.4)	3.10 (0.08)	4.46 (0.10)	2.47 (8)	1.43 (5)
2.06 (0.05)	2.14 (0.08)	0.71(0.19)	0.5 (0.4)	2.05 (0.14)	2.18 (0.03)	0.74 (9)	0.60 (7)
0.90 (0.02)	0.81(0.06)	0.1 (0.1)	0.17 (0.03)	0.91(0.11)	0.89(0.12)	0.15 (8)	0.33 (12)
5.1 (0.3)	5.32 (0.13)	4.60 (0.12)	3.8 (0.3)	5.4 (0.5)	5.5 (0.5)	5.0 (4)	3.92 (13)
5.43 (0.14)	5.56 (0.18)	4.6 (0.3)	3.4(0.4)	5.2 (0.6)	5.4 (0.4)	4.8 (4)	3.5(2)
5.37 (0.06)	5.5 (0.2)	4.7 (0.3)	3.5 (0.3)	5.2 (0.6)	5.3 (0.6)	4.7 (7)	3.5 (2)
5.42 (0.10)	5.1 (0.5)	4.5 (0.4)	3.3 (0.3)	5.0 (0.3)	5.2 (0.3)	4.6 (3)	3.28 (7)
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**Figure 1.** Cs<sup>+</sup> selectivities  $(-\log K_{CsM}^{\text{pot}})$  of liquid membrane ISEs containing ionophores I–IV (see Chart 1): fixed interference method, 0.1 M concentration level of chlorides, 1 M for H<sup>+</sup>; membrane solvent DBS.

the significant effects of the parameters that affect the selectivities and thus to propose interpretations and mechanisms on the basis of truly significant differences in effects.

Since selectivity coefficient values for cesium versus the alkaline earth metal ions were very similar and, in addition, much smaller than those toward alkali metal ions, two separate statisticalanalyses were applied to the uni- and divalent ions. First, a three-way ANOVA with interactions was performed on selectivities toward univalent ions. The three classification factors were as follows: (a) the nature of the interfering ion (six levels); (b) the nature of the ionophore (four levels); and (c) the solvent of the membrane (two levels).

A set of 194 calibrations was carried out for this purpose. Since the third-order interaction was found to be highly significant (p < 0.01%), a general inference can be made either on the main



Figure 2. Same as Figure 1; membrane solvent NPOE.

effects (ions, ligands, and solvents) or on the second-order interactions. Therefore, the 194 calibrations for selectivities toward univalent ions were split into two sets. The first (98 calibrations) was obtained with DBS as the solvent, and the second (96 calibrations) was obtained with NPOE as the solvent. Two ANOVAs were then performed. Each set of data gave highly significant differences for the main effects (for a and b, p < 0.01) and for the second-order interaction (p < 0.01).

In both solvents, for the four ionophores, the highly significant effect of the nature of the interfering ions gave rise to a highly significant negative correlation (p < 0.01) between the values and the ionic radius: Rb < K = NH<sub>4</sub> < Na < Li (Figure 3). This indicates that ion size and the related charge density are the most important factors affecting the interfering power of the univalent ions. It can be thus asserted that the main effect of ligands on selectivity in the case of both solvents leads to an increasing order of values: fixed-cone < partial cone < mobile < 1,3-alternate. This effect will be discussed in detail later. The order is roughly the



**Figure 3.** Cs<sup>+</sup> selectivity vs ionic radius for the four ionophores obtained with different methods: (a) ionophore I; (b) ionophore II; (c) ionophore III; (d) ionophore IV. ( $\Box$ ) ISE, fixed interference method, membrane solvent DBS. (x) ISE, fixed interference method, membrane solvent NPOE. For a and b: (\*) calculated from extraction data in CHCl<sub>3</sub>, ref 9; (•) calculated from stability constants in methanol, ref 9.

same for all of the univalent ions. For the smaller ions  $H^+$ ,  $Li^+$ , and  $Na^+$ , the different ligands show higher differences in selectiv-

ity than for the larger ions  $K^+$  and  $Rb^+$ . This accounts for the low significance level for the a-b interaction.

A good basis for the interpretation of these trends is offered by a comparison with the extraction constants (H<sub>2</sub>O/CHCl<sub>3</sub>) and the thermodynamic parameters of complex formation in methanol that were reported recently9 for the same ligands and alkali metal ions. Good agreement is found between the selectivity coefficients determined in this work and those determined from the stability and extraction constants (Figure 3). The interpretation proposed9 is easily extensible to other ions and ligands and accounts for the solvent effect as well. On this basis, the fact that the coneshaped calixarene IV has the lowest selectivity seems to be due to the extensive solvation experienced by this ligand and to the destabilization of its cesium complex due to the steric effect of the alkyl groups that face the polyether ring. Moreover, in the cesium complex of the cone isomer IV, there is no contribution of cation/ $\pi$  interaction, which occurs in the 1,3-alternate isomer H.

An intermediate selectivity is observed with the partial-cone ligand III, in which one phenyl group can possibly interact with the complexed cesium cation. Selectivities higher than those for III and IV are shown by the mobile ligand I, which can assume the 1,3-alternate conformation in the cesium complex, although the conformational rearrangement reduces the efficiency of this ligand compared with II.

The enhancement of selectivity for smaller ions takes place in both solvents, but is higher in NPOE. This explains the low significance level for the third-order interaction a-b-c in the first ANOVA performed on the whole set of selectivity data for univalent ions. In fact, if the ANOVA is repeated after excluding the data for protons and lithium ion, no effect of the solvent, be it a primary, second, or third-order interaction, is seen to be significant. As it is known that the  $pK^{\text{pot}}$  for univalent ions should not depend on the solvent for 1:1 complexes,<sup>12</sup> this could indicate a different stoichiometry for the proton and lithium ion complexes. The 6-oxygen chain could allow for some interaction with a second small ion. This interaction seems to be higher in NPOE solvent, which has a higher dielectric constant.

With respect to the alkaline earth ions, the multifactor ANOVA with interactions on the same three classification factors considered for alkali metal ions gave low significance levels for the ion (p = 0.02) and ligand (p < 0.01) factors. The first *p* value accounts for the increase as the ion size decreases, as seen for alkali ions. The second one is due to the much lower selectivity of the cone-shaped calixarene. Thus, lower selectivity could be explained by the low stability of the complex with cesium ion. Contrary to what is already known about the liquid membrane ISE,<sup>12</sup> no significant effect for divalent ions was observed for solvent variation (p > 0.1). The variability of our results made it impossible for us to detect the significance of small differences in selectivities for the two solvents.

In conclusion, it can be stated that, for calixarene-based ISEs, selectivity is determined by preorganization of the ligand. Preorganization of the ligand in the 1,3-alternate conformation increases the  $-\Delta H$  of the complexation since no energy has to be paid for conformational interconversion. Moreover, no entropy decrease is determined by tightening the ligand in the complex-

<sup>(12)</sup> Morf, W. E. The principles of ion-selective electrodes and of membrane transport; Elsevier: Amsterdam, 1981; Chapter 12, p 294.

ation. A lower detection limit for cesium ion than those found in literature is observed for the 1,3-alternate and mobile ligands in both solvents, as are higher selectivity coefficients ( $pK_{Cs/Na}^{\text{pot}}$ ) for the same ligands.

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