1,3-*Alternate* Calix[4]arenecrown-5 Conformers: New Synthetic Ionophores with Better K^+/Na^+ Selectivity than Valinomycin

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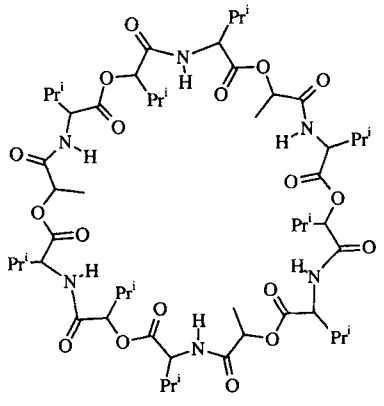
Abstract: New 25,27-dialkoxycalix[4]arenecrown-5 conformers **8**, **10**, and **11** have been synthesized and studied. The compounds **8a** and **8b**, fixed in 1,3-*alternate* structure, have been obtained in 57 and 40% yield, respectively, by reaction of the corresponding 25,27-dialkoxycalix[4]arenes **7a–b** with tetraethylene glycol di-*p*-toluenesulfonate in the presence of Cs_2CO_3. The *cone* **10a** and **10b** and the *partial cone* **11** conformers were obtained by selective demethylation of the 25,27-dimethoxycalix[4]arenecrown-5 (**6a**) and subsequent dialkylation with NaH/DMF and KO*t*Bu/THF, respectively. In the solid state (X-ray), compound **6a** adopts a *flattened cone* conformation, which is also found to be most abundant in CD_3CN and CD_3OD solution. Upon complexation with potassium picrate compound **6a** was converted quantitatively into the 1,3-*alternate* conformation. All new ligands synthesized were used in the extraction of alkali metal cations from H_2O into $CHCl_3$, and as active components in supported liquid membranes and in chemically modified field effect transistors. Results were compared to those obtained with with the natural antibiotic valinomycin **1**. All ligands showed high selectivity for potassium. Ligand **8a**, fixed in the 1,3-*alternate* conformation, is more selective than valinomycin and shows the highest K^+/Na^+ selectivity known so far.

Keywords
binding studies · calixarenes · crown ethers · ionophores · membranes

Introduction

The discovery that valinomycin (**1**) was able to facilitate the selective transport of K^+ cations through the mitocondria[1] and the synthetic efforts that followed to develop new potassium-selective ionophores mark the beginning of supramolecular chemistry. In spite of the numerous new ionophores synthesized (over a thousand),[2] valinomycin (**1**) is still used as the active component of choice, for example, in potassium-selective sensors.[3] This is because the K^+/Na^+ selectivity[4] of valinomycin-based devices is still higher than that found with other ionophores.



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We have previously reported the synthesis, complexation, and ion-sensing properties[5] of different conformers of calixcrown ethers derived from *p-tert*-butylcalix[4]arene. The ionophores, containing five oxygen atoms in the polyether ring (calix[4]arenecrown-5), selectively bind potassium ions with a selectivity (K^+/Na^+) that decreases in the order **3** (*partial cone* conformer) > **4** (1,3-*alternate* conformer) > **2** (*cone* conformer).

The corresponding crown-4 derivatives reported recently by Shinkai et al.[6] show a remarkable "inverse" selectivity for sodium over potassium ($\geq 10^5$). We have recently discovered that the larger calixcrown-6 derived from unsubstituted calix[4]arene (**5**, Scheme 1), which lacks the *p-tert*-butyl substituents and is fixed in the 1,3-*alternate* conformation, is very selective for ce-

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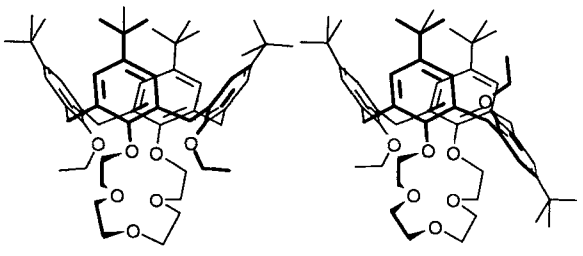
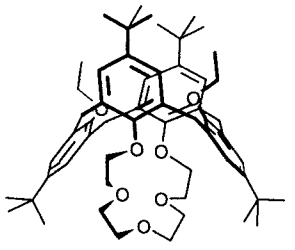


cone
2

partial cone
3



1,3-alternate
4

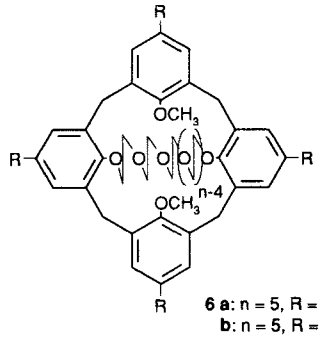
sium ions.[7, 8] This finding led to important applications in the field of cesium extraction from radioactive waste[7–9] and of cesium detection by chemically modified field effect transistors (CHEMFETs).[10] Moreover, these studies revealed that the 1,3-*alternate* conformation, being less polar than the other conformations,[11] reduces the stability of the sodium complex but increases that of the cesium complex, through cesium/π interactions. We have recently found that cation/π interactions are also present in potassium complexes of *partial cone* derivatives of 25,27-dialkoxy-*p*-*tert*-butylcalix[4]arenecrown-5 conformers (e.g., **3**).[12]

These results show that, in the family of calixcrown ethers, very small changes in substituents at the upper (aromatic nuclei) or at the lower rim (phenolic OH groups) and differences in the calix[4]arene conformation may result in dramatic changes in selectivity. In this respect calixarene-based ligands show distinct advantages over other classes of ionophores. They allow a stereoelectronic fine-tuning of the selectivity and efficiency of cation binding, because of their rigid framework, the different possible substitution patterns, and the fact that their conformation can be controlled during the synthesis.[5, 13]

In this paper we report that 25,27-dialkoxycalix[4]arenecrown-5 ethers, derived from unsubstituted calix[4]arene **5** and fixed in the 1,3-*alternate* conformation, are exceptionally selective for potassium ion with a K^+/Na^+ selectivity higher than valinomycin in extraction, membrane transport, and ion sensing by CHEMFETs.

Results and Discussion

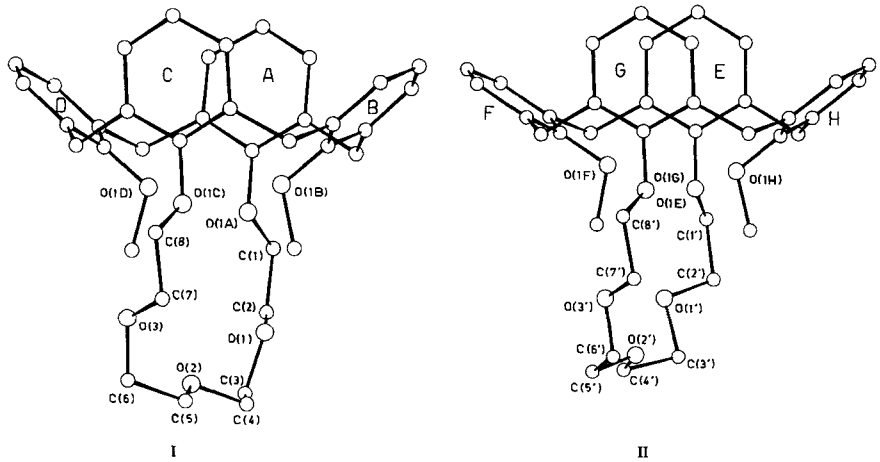
Synthesis and Conformational Properties of Ionophores and Their Complexes: We first synthesized the conformationally mobile 25,27-dimethoxycalix[4]arenecrown-5 (**6a**) by reacting the 25,27-dimethoxycalix[4]arene with tetraethylene glycol di-*p*-toluenesulfonate, for comparison with the previously reported *p*-*tert*-butyl derivative **6b**.



6a: n = 5, R = H
b: n = 5, R = t-Bu
c: n = 6, R = H
d: n = 7, R = H

Compound **6a** is present mainly in the *cone* conformation in solution, as is the *p*-*tert*-butyl derivative **6b**.[5b] This is evident from the two doublets of an AX system at $\delta = 4.41$ and 3.20 for the bridging methylenes in the ^1H NMR spectrum ($CDCl_3$, 25 °C, 400 MHz) of **6a**. At −35 °C low-intensity signals of the 1,3-*alternate* and of the *partial cone* are present in the spectrum as observed previously for the 25,27-dimethoxycalix[4]arenecrown-6 (**6c**).[8]

At −50 °C the ratio between *cone*, *partial cone*, and 1,3-*alternate* conformations is 86:7:7 in the case of **6a**. The ^1H NMR spectrum of **6a** appears to be much sharper at room temperature than those of 25,27-dimethoxy-26,28-dialkoxycalix[4]arenes,[14] including calixcrowns with longer bridges (**6c**,**d**).[8] Only when the samples are warmed to 80 °C is it possible to observe broadening (e.g., of the OCH_3 singlet and the two doublets of the AX system) due to the interconversion among the three conformations. This indicates that compound **6a** is conformationally more rigid than 25,27-dimethoxy-26,28-dialkoxycalix[4]arenes and 25,27-dimethoxycalix[4]arenecrown-6 (**6c**) and -crown-7 (**6d**). The X-ray crystal structure of compound **6a** (Fig. 1) clearly shows that only the *cone* conformation is present in the solid state.



I II

Fig. 1. X-ray crystal structure of compound **6a**: the two independent molecules **I** and **II** are shown.

Compound **6a** crystallizes in the monoclinic system, space group $P2_1/c$, with two independent calix[4]arene molecules (**I** and **II**, Fig. 1) and one chloroform solvent molecule in the asymmetric unit. Significant structural differences are observed between the two independent calix[4]arenecrown-5 molecules. Both have a distorted *cone* conformation: the two phenolic units bearing the crown chain are almost orthogonal to the reference plane (least-squares plane through the four methylene groups), and the other two almost parallel. For the two independent molecules the symbolic representation of the molecular conformation is C_1 +−, +−, +−, +−.[15] The conformational parameters ϕ and χ and the dihedral angles formed by the phenolic rings with respect to the molecular reference plane in the two independent calix[4]arene molecules are summarized in

Table 1. The most significant interatomic distances and torsion angles in the two molecules **I** and **II** are given in Tables 2 and 3, respectively.

Table1. Conformational parameters observed in the two independent molecules (**I**, **II**; Fig.1) of compound **6a** and in compound **6b** [5b].

a) Confromational parameters ϕ and χ (°), defined according to ref.[15].

	6a/I			**6a/II**		**6b**	
	ϕ	χ		ϕ	χ	ϕ	χ
A–B	66.8(6)	−102.0(5)	G–F	62.5(6)	−109.7(6)	66(2)	−92(2)
B–C	105.8(5)	−68.3(6)	F–E	110.2(5)	−64.0(6)	97(2)	−62(2)
C–D	62.9(6)	−99.7(5)	E–H	63.5(6)	−106.2(5)	62(2)	−106(2)
D–A	103.4(5)	−69.8(5)	H–G	106.7(5)	−64.5(6)	103(2)	−63(2)

b) Dihedral angles (°) between the least-squares planes through the CH_2 bridges (R) and the phenolic rings, as defined in ref.[15].

6a/I		**6a/II**		**6b**
R–A	100.9(1)	R–E	91.4(1)	93.7(4)
R–B	140.7(1)	R–F	146.5(1)	140.9(3)
R–C	98.6(1)	R–G	93.8(1)	94.1(4)
R–D	138.9(1)	R–H	142.8(1)	132.4(3)

Table 2. Interatomic O···O separations (Å) observed in the two independent molecules of compounds **6a** (**I**, **II**; Fig. 1) and in compound **6b**.

6a/I		**6a/II**		**6b**
O(1A)···O(1C)	5.085(4)	O(1E)···O(1G)	5.130(4)	5.12(2)
O(1B)···O(1D)	3.197(4)	O(1F)···O(1H)	3.178(4)	3.28(2)
O(1)···O(3)	5.258(4)	O(1′)···O(3′)	5.335(4)	5.29(2)

Table3. Torsion angles (°) in the polyether crown chains of the two independent molecules of compound **6a**.

Molecule **I**		Molecule **II**	
O(1A)-C(1)-C(2)-O(1)	−26(1)	O(1E)-C(1′)-C(2′)-O(1′)	55.4(7)
C(1)-C(2)-O(1)-C(3)	165.9(7)	C(1′)-C(2′)-O(1′)-C(3′)	−175.5(6)
C(2)-O(1)-C(3)-C(4)	−179.7(6)	C(2′)-O(1′)-C(3′)-C(4′)	167.5(7)
O(1)-C(3)-C(4)-O(2)	83.7(5)	O(1′)-C(3′)-C(4′)-O(2′)	−82.7(9)
C(3)-C(4)-O(2)-C(5)	169.2(5)	C(3′)-C(4′)-O(2′)-C(5′)	−177.2(7)
C(4)-O(2)-C(5)-C(6)	178.5(5)	C(4′)-O(2′)-C(5′)-C(6′)	176.1(6)
O(2)-C(5)-C(6)-O(3)	−69.3(7)	O(2′)-C(5′)-C(6′)-O(3′)	75.9(6)
C(5)-C(6)-O(3)-C(7)	−74.1(6)	C(5′)-C(6′)-O(3′)-C(7′)	−165.5(5)
C(6)-O(3)-C(7)-C(8)	−179.9(4)	C(6′)-O(3′)-C(7′)-C(8′)	−178.9(4)
O(3)-C(7)-C(8)-O(1C)	−66.1(5)	O(3′)-C(7′)-C(8′)-O(1G)	−61.2(5)

For comparison, the corresponding values[5b] for the analogous p-*tert*-butyl derivative **6b** are included. The deviations of ϕ and χ from the theoretical values expected for a perfect *cone* conformation ($\phi = +90$, $\chi = -90°$) show that molecule **I** has a more symmetrical structure than **II** and that compound **6b** is intermediate between the two independent molecules of **6a**. This indicates that the *tert*-butyl groups at the *para* position of the calix have only a minor influence on the solid-state conformational preference of this class of compounds. Large structural differences are observed between the crown chains of molecule **I** and **II**, although the size of the polar cavities created by their oxygens are not significantly different.

The molecular packing of the dimethoxycalix[4]arenecrown-5 (**6a**) molecules, which is consistent with the van der Waals interactions, leaves voids in the crystal lattice of suitable size to accommodate one chloroform molecule in a 2:1 stoichiometry.

^{1}H NMR (400 MHz) complexation studies of potassium picrate (KPic) with compounds **6a** and **6b** in CD_3CN reveal that, under saturation conditions, both ligands form 1:1 complexes, as determined from integration ratios between the protons of picrate anion and those of the aromatic nuclei of the calixarene. The potassium complex of **6a** shows a different structure, both in CD_3CN and in CD_3OD solution (Table 4), compared to that of the potassium complex of **6b**.

Table 4. Isomer distibution for potassium complexes of **6a** and **6b** in CD_3CN and CD_3OD at 25 °C (400 MHz) (*paco* = *partial cone*; 1,3-*alt* = 1,3-*alternate*).

Compound	Solvent	1,3-*alt*	*paco*	*cone*
6a·KPic	CD_3CN	80	20	–
6b·KPic	CD_3CN	–	75	25
6a·KSCN	CD_3OD	85	15	–
6b·KSCN	CD_3OD	[a]	>80	[a]

[a] Another conformer is clearly visible in the ^{1}H NMR spectrum but due to overlap with other signals it is not possible to assign its stucture unequivocally to the *cone* or 1,3-*alternate* conformation.

In acetonitrile, for example, the most stable conformation of the **6a**·KPic complex (Fig. 2a) is the 1,3-*alternate* (80%) followed by the *partial cone* (20%), but for *tert*-butylated analogue (**6b**) the situation is completely different (Fig. 2b). The 1,3-*alternate* conformer is not detected in the ^{1}H NMR spectrum of

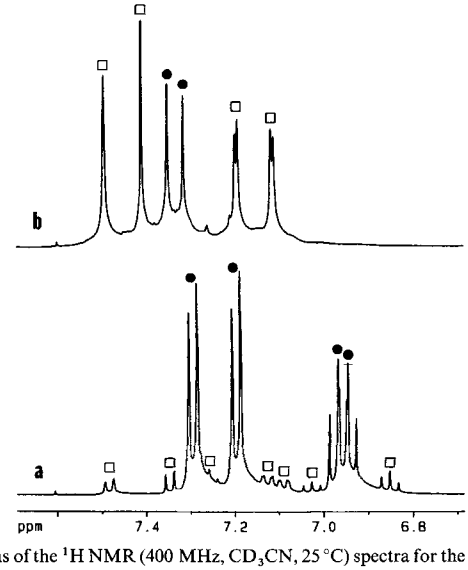


Fig. 2. Aromatic regions of the ^{1}H NMR (400 MHz, CD_3CN, 25 °C) spectra for the potassium picrate complexes with a) compound **6a** (□: *partial cone*; ●: 1,3-*alternate*) and b) compound **6b** (□: *partial cone*; ●: *cone*).

6b·KPic, and the *partial cone* and *cone* are present, respectively, in a ratio of 3:1 in agreement with the previously reported spectrum of the same complex in $CDCl_3$.[5a] These percentages were established by integration of the ^{1}H NMR signals in the aromatic region, assigned to the stereoisomers on the basis of the symmetry of the spectra and by comparison with those of compound **3**[5b] and **11** (vide infra) fixed in the *partial cone* conformation, and **4**[5b] and **8** (vide infra) fixed in the 1,3-*alternate* conformation.

These results indicate that, when *tert*-butyl groups are present at the *para* position of the calix[4]arene, the preferred conformation for binding potassium ion is the *partial cone*, whereas 1,3-*alternate* is favored for the unsubstituted calix[4]arene deriva-

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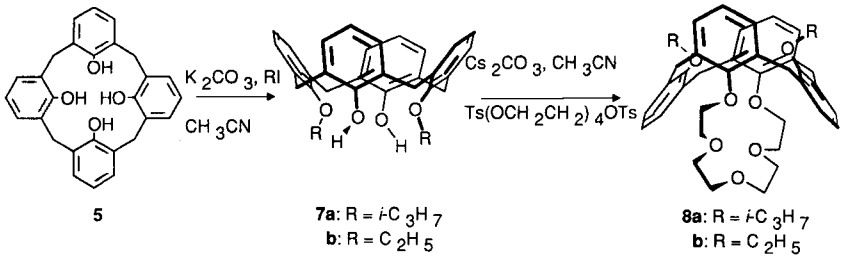
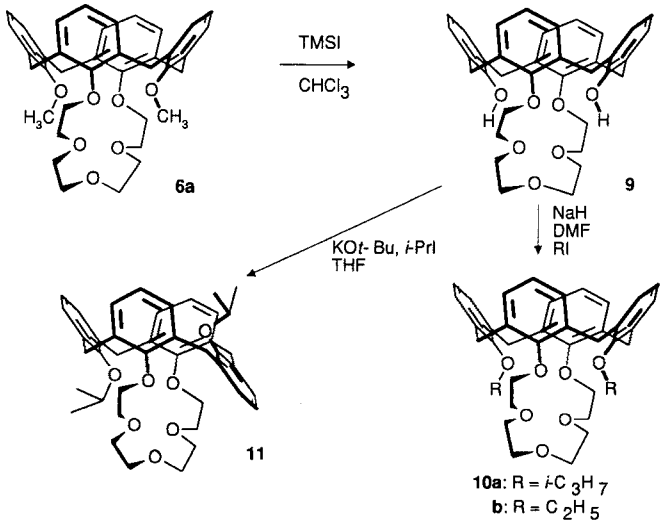
tives. This observation led us to synthesize the two crown-5 derivatives of calix[4]arene **8a** and **8b**, which are *fixed* in the 1,3-*alternate* conformation. A synthetic sequence previously successfully used for the synthesis of calix[4]arenecrown-6 in the fixed 1,3-*alternate* conformation was adapted for this purpose (Scheme 1).[8]



Scheme 1. Synthesis of **8a** and **8b** fixed in the 1,3-*alternate* conformation.

The isolated yields of **8a** and **8b** were 57 and 40%, and other isomers could not be detected in the reaction mixture. The ^{1}H NMR spectra of compounds **8a** and **8b** show a singlet at around $\delta = 3.8$ for the bridging methylene groups ($ArCH_2Ar$) of the calix[4]arene, and the ^{13}C NMR spectra a signal around $\delta = 39$; both are indicative for a 1,3-*alternate* structure.[16] For comparison we also synthesized compounds **10a** and **10b** both fixed in the *cone* and compound **11** fixed in the *partial cone*, starting from 25,27-dimethoxycalix[4]arenecrown-5 (**6a**) (Scheme 2). The ^{1}H and ^{13}C NMR data for compounds **10–11**



Scheme 2. Synthesis of **10a** and **10b** both fixed in the *cone* and **11** fixed in the *partial cone* structures.

are all in agreement with the proposed structures. The three-step synthesis (25,27-dimethylation, bridging, and demethylation) of calix[4]arenecrown-5 (**9**) was chosen rather than direct bridging[5b] of calix[4]arene **5** (with KO*t*Bu and tetraethylene glycol di-*p*-toluene sulfonate in dry benzene), because yields were better (73 vs. 30%) and purification more straightforward.

Complexation Studies: The association constants and binding free energies of complexation of the new ligands with alkali metal picrates in $CHCl_3$ saturated with water were determined by means of the picrate extraction method developed by Lein and Cram.[17] To allow a comparison we also determined the same data for valinomycin (**1**), since they have not previously been reported. The results are given in Table 5 and in Figure 3.

As anticipated from the preliminary NMR studies on the conformationally mobile 25,27-dimethoxycalix[4]arenecrown-5 (**6a**), the most efficient and selective ligands are **8a** and **8b**, which are fixed in the 1,3-*alternate* conformation. They show comparable binding properties and are both highly selective for potassium. This is mainly a consequence of the fact that the sodium ion is hardly complexed by the apolar 1,3-*alternate* conformation and that potassium ions can interact not only with the crown ether moiety but also with the two rotated aromatic nuclei—this is not possible with the smaller Na^+.[18] The three compounds **10a, b** and **11** bind alkali metal ions less strongly. Particularly ineffective is the *cone* diisopropoxy derivative **10a**, probably because the two bulky groups facing the polyether ring destabilize the complexes. A more

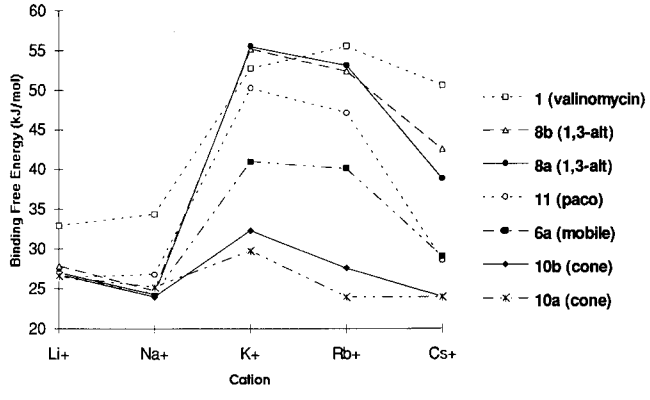


Fig. 3. Binding free energy (ΔG°, kJ mol^{-1}) of alkali picrate complexation in $CHCl_3$ saturated with H_2O at 22 °C (*paco* = *partial cone*; 1,3-*alt* = 1,3-*alternate*).

Table 5. Association constants (K_a) and binding free energies ($-\Delta G^\circ$) of complexes of hosts with alkali picrates in $CHCl_3$ saturated with H_2O at 22 °C [a].

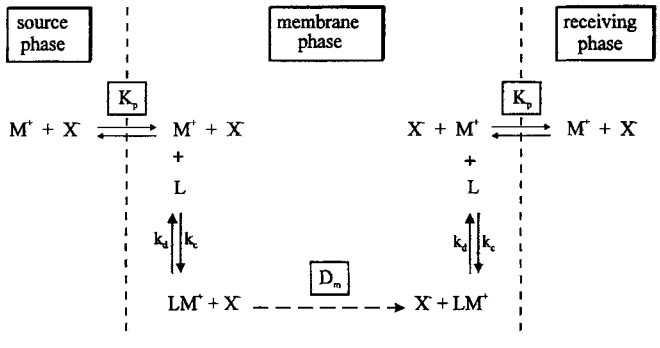
	$\log K_a$					$-\Delta G^\circ$ (kJ mol^{-1})				
	Li^+	Na^+	K^+	Rb^+	Cs^+	Li^+	Na^+	K^+	Rb^+	Cs^+
1	5.83	6.09	9.35	9.83	8.97	32.94	34.37	52.80	55.51	50.66
6a	4.71	4.31	7.20	7.09	5.13	26.58	24.37	41.03	40.07	29.01
8a	4.78	4.30	9.83	9.41	6.87	27.00	24.28	55.52	53.17	38.76
8b	4.93	4.38	9.77	9.29	7.52	27.84	24.75	55.23	52.42	42.50
10a	4.70	4.46	5.27	<4	<4	26.56	25.20	29.78	<24	<24
10b	4.74	<4	5.71	4.88	<4	26.79	<24	32.32	27.55	<24
11	4.67	4.74	8.90	8.36	5.05	26.38	26.79	50.28	47.18	28.55
4 [b]	[c]	5.46	8.15	7.73	5.97	[c]	31.40	48.15	43.96	33.91
2 [b]	[c]	5.11	7.08	5.60	4.99	[c]	28.89	40.19	31.82	28.47
3 [b]	[c]	5.87	9.95	9.18	6.20	[c]	33.49	56.52	52.33	35.59

[a] The association constants determination and the precision of the values obtained are described by Cram et al. [17]. [b] From ref. [5b]. [c] Not determined.

subtle steric effect of the alkyl substituents at the upper rim of the calix is also operating in these systems. The lower efficiency shown by the 1,3-*alternate* calixcrown derived from *p-tert*-butylcalix[4]arene (e.g., **4**)[5] compared with the corresponding stereoisomers **8a** and **8b** obtained from calix[4]arene ($\Delta\Delta G^\circ \approx 7.1-7.4$ kJ mol^{-1} for K^+) is explained by the steric bulk of the *tert*-butyl groups at the *para* position of the two rotated aromatic nuclei reducing the space around the binding region. This also explains why the efficiency in the *p-tert*-butylcalix[4]arene-crown-5 series[5] decreases in the order *partial cone* (**3**) > 1,3-*alternate* (**4**) > *cone* (**2**). The *partial cone* structure is the best compromise between negative steric effects of the *tert*-butyl groups at the upper rim (1,3-*alternate* structure) and the alkoxy groups at the lower rim (*cone* conformation), and positive cation/aromatic interactions.[12] Solvent effects operate in the same direction, since it has been shown by molecular dynamics that the *cone* conformation is the most solvated in methanol, water, and acetonitrile followed by *partial cone* and 1,3-*alternate*.[19] Therefore the high efficiency and selectivity shown by calixcrowns **8** in the 1,3-*alternate* conformation is a consequence of the simultaneous operation of several effects, namely, the polarity of the calix conformation and its solvation, the size of the polyether ring, the steric effects of the substituents on the rotated aromatic nuclei, and the cation/π interactions.

Table 5 and Figure 3 also show that the efficiency of ligands **8a** and **8b** in binding K^+ is higher than valinomycin (**1**), which actually binds Rb^+ slightly better than potassium, in agreement with the K_a values found in methanol[20] and acetonitrile.[21] Interestingly, the K^+/Na^+ selectivities exhibited both by ligands **8a** ($\Delta\Delta G^\circ = 31.2$ kJ mol^{-1}) and **8b** ($\Delta\Delta G^\circ = 30.5$ kJ mol^{-1}) are higher than for valinomycin (**1**) under the same conditions ($\Delta\Delta G^\circ = 18.4$ kJ mol^{-1}), and they are the highest values reported in literature so far.[20b] From our previous studies on calix[4]arenecrown-6 in 1,3-*alternate* conformation[8] and from what is generally known about solvent effects in complexation phenomena by macrocycles,[20b, 22] we can anticipate that the K^+/Na^+ selectivity of ligands **8a** and **8b** would be even higher in more polar solvents such as methanol.

Membrane Transport: In the evaluation of complexation properties of synthetic ionophores, we have extensively used carrier-mediated transport of alkali metal and guanidinium ions as well as urea through bulk liquid membranes (BLM)[23] and supported liquid membranes (SLM).[8, 24–27] SLMs have the advantage of a much smaller membrane volume. The facilitated transport of salts through an SLM can be described as a sequential process including the phase transfer of the salt, complexation/decomplexation reactions, and diffusion steps (Scheme 3).



Scheme 3. Transport of salts (M^+X^-) through a supported liquid membrane facilitated by ligand L.

Until recently[28] it was generally accepted that the rate of diffusion of the complex and the extraction constant determine both the flux of transport and the selectivity.[29] We have recently shown that for certain calix[4]arene crown ethers and calixspherands the slow rate of decomplexation influences the rate and selectivity of transport of salts.[28] In the same publication we describe a general model for transport of free ions through supported liquid membranes, which accounts both for the diffusion and the rate of cation release [Eq. (1)]. D_m is the apparent

$$J = \frac{D_m}{2d_m}\left\{\frac{-A + \sqrt{A^2 + 4AL_0 \cdot \frac{(1+2\alpha)}{(1+\alpha)}}}{1+2\alpha}\right\} \quad (1)$$

diffusion constant; L_0 represents the total carrier concentration in the membrane; d_m is the membrane thickness. The parameter α describes the ratio $D_m/kd_m\theta$, a dimensionless number, where k denotes the rate of release at the membrane–water interface and θ is the porosity of the membrane. The parameter A is defined as $A = K_{ex}a_s^2$, where K_{ex} is the product of the association constant of the complex in the membrane and the partition coefficient of the salt. The salt activity in the source phase is represented by a_s. When the carrier is fully loaded (by using a high salt concentration in the source phase), Equation (1) can be written as Equation (2). D_m and k can now be obtained by plotting L_0/J_{max} vs. d_m, and consequently α can be calculated at any membrane thickness.

$$J_{MAX} = \left(\frac{D_m}{d_m} \cdot L_0\right)\left(\frac{1}{1+\alpha}\right) \quad (2)$$

Because of its high polarity ($\varepsilon = 24$), *ortho*-nitrophenyl octyl ether (NPOE) was used as the membrane solvent. This means that the salt in the membrane is present as free ions. Fluxes were measured at different potassium perchlorate activities in the source phase for all calix[4]arenecrown ethers and valinomycin (Fig. 4). The initial fluxes were calculated from the increase in conductivity with time. By fitting the flux values from different source phase activities [using Eq. (1), under diffusion-limited conditions ($\alpha = 0$)], K_{ex} and D_m values for the carriers were obtained (Table 6). The very high K_{ex} values for both the 1,3-*alternate* conformers (**8a** and **8b**) are remarkable, and are in

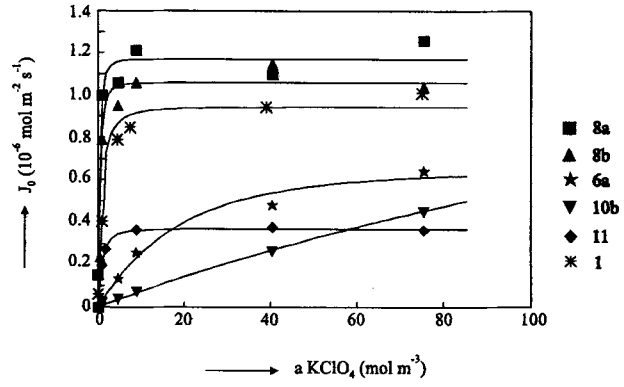


Fig. 4. $KClO_4$ flux as a function of the salt activity a in the source phase ([carrier]$_m$ $= 1 \times 10^{-2}$ M; $T = 298$ K). The lines drawn are calculated with the model; the points are measured values.

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Table 6. Calculated extraction constants and diffusion coefficients for different carriers in NPOE (T = 298 K).

Carrier	K_{ex} (M^{-1})	D_m (10^{-11} $m^2 s^{-1}$)
1	2900	1.06
6a	24	0.66
8a	40000	1.16
8b	28000	1.06
10a	$\ll$0.01	–
10b	0.32	1.33
11	6500	0.37

agreement with the high values of K_a obtained in $CHCl_3$ solution (see Table 5).

The lower apparent D_m values for the dimethoxy conformer **6a** and the *partial cone* diisopropoxycalix[4]arenecrown-5 (**11**) indicate that in these cases the transport is no longer diffusion-limited, but that the release of the potassium ion from the complex is also playing a role. By measuring the fluxes as a function of the membrane thickness, and plotting L_0/J vs. d_m (Fig. 5), it

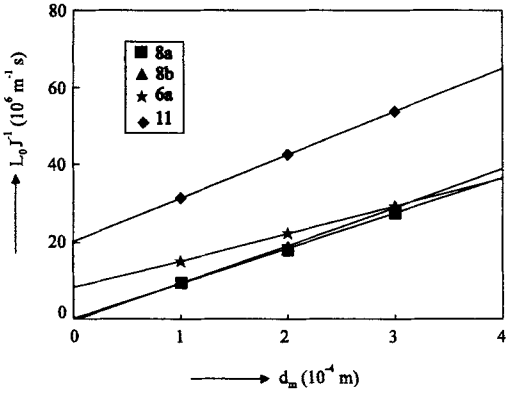

Fig. 5. Influence of the membrane thickness ($n \times 100$ μm) on L_0/J (See Eq. (2): $L_0/J = (1+\alpha)D_m^{-1}d_m$) [28]; [carrier]$_m$ = 1×10^{-2} M, source phase: 1×10^{-1} M $KClO_4$, T = 298 K.

was clearly shown that the transport of potassium ions by the 1,3-*alternate* conformers **8a** and **8b** is diffusion-limited (no intercept). The plots for the *partial cone* 25,27-diisopropoxy-calix[4]arenecrown-6 (**11**) and dimethoxy derivative **6a** show a substantial intercept; this indicates that kinetics is the limiting factor.

The D_m, k, and α values calculated with Equation (2) (Fig. 5, Table 7) also clearly show that transport is diffusion-limited for **8a–b** ($\alpha < 0.1$), and kinetically limited for **6a** and **11** ($\alpha > 0.1$).

Table 7. D_m, k, and α values calculated from L_0/J vs. d_m (Fig. 5).

Carrier	D_m (10^{-12} $m^2 s^{-1}$)	k (10^{-7} $m s^{-1}$)	α
6a	9.94	2.04	0.77
8a	11.0	61.1	<0.1
8b	10.2	−37.6	<0.1
11	8.94	0.778	1.80

The transport characteristics were also determined independently by measuring the flux as a function of temperature (Fig. 6). From these data the activation energies (E_a) for the transport were determined (Table 8). The E_a values for **8a–b** are also in agreement with diffusion-limited transport, whereas an

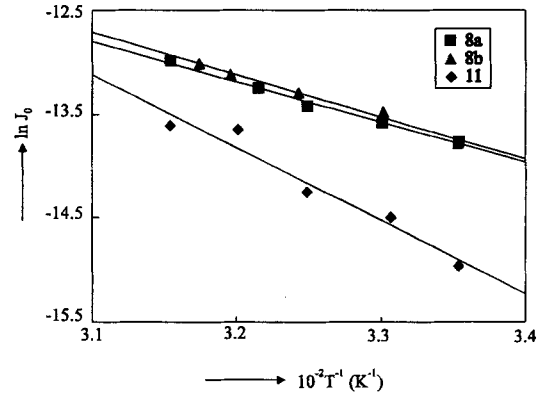

Fig. 6. Relationship between $\ln J_0(KClO_4)$ and $1/T$ for ionophores **8a,b** and **11** (source phase: 1×10^{-1} M $KClO_4$, [Carrier]$_m$ = 1×10^{-2} M). The symbols are measured values, and the lines drawn from linear least-squares analysis.

Table 8. Activation energies calculated from ln$J$ vs. $1/T$.

Carrier	E_a (kJ mol^{-1})
8a	32±2
8b	34±2
11	59±7

E_a value for **11** nicely corresponds with kinetically limited transport.

Correction for the kinetic component of the apparent transport parameters of **6a** and **11**, with the α values from Table 7, resulted in diffusion constants of 1.10×10^{-11} and 1.03×10^{-11} $m^2 s^{-1}$, respectively. These values are much more in line with the diffusion constants from the other calix[4]crowns (see Table 6), as expected, assuming the potassium complexes of all the calix[4]crowns will have approximately the same volume and therefore the same resistance in the membrane.

Comparison of the $\Delta G°$ values obtained for $CHCl_3$ from the extraction experiments with those for NPOE calculated from the transport measurements shows a very good correlation between the two experiments (Fig. 7).

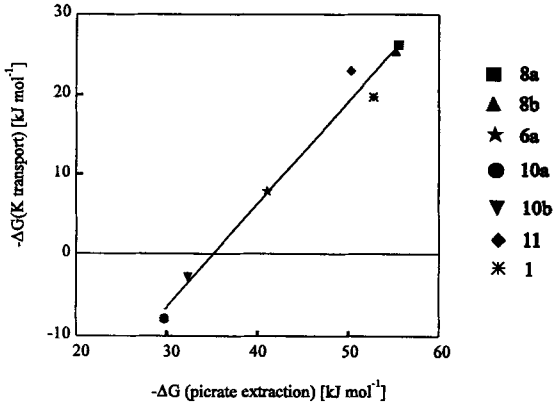

Fig. 7. Linear free energy relationship between ΔG_{ex} obtained from membrane transport through NPOE, and the association constant of K-picrates in $CHCl_3$.

To obtain high K^+/Na^+ selectivities by membrane transport, it is obvious that diffusion-limited transport is a prerequisite (see Table 9). Selectivity experiments were performed with 10^{-4} M $KClO_4/10^{-1}$ M $NaClO_4$ as source phase. When the measurements were recorded with a conductivity electrode, after

Table 9. Percentage of $KClO_4$ and $NaClO_4$ transported and K^+/Na^+ selectivity after 2 h (source phase: 10^{-4} M $KClO_4/10^{-1}$ M $NaClO_4$; T = 298 K).

Carrier	% $KClO_4$ transported	% $NaClO_4$ transported	Selectivity
8a	93.8	4.20×10^{-3}	22300
8b	94.8	4.72×10^{-3}	20100
11	25.1	27.0×10^{-3}	930
1	91.5	8.88×10^{-3}	10300

approximately 2 h a sharp leveling off in the conductivity was observed in the cases of **8a–b** and valinomycin (**1**); this might indicate that in these cases virtually all the $KClO_4$ had been removed from the source phase. Samples were therefore taken after 2 h and analyzed with atomic absorption spectroscopy. As can be seen from Table 9, almost all of the potassium ions had indeed been transported by **8a–b** and **1**. The difference in K^+/Na^+ selectivity between **8a–b** and valinomycin (**1**) is caused by the difference in Na^+ fluxes. To the best of our knowledge, the K^+/Na^+ selectivities for **8a–b** are the highest reported in literature so far.

CHEMFETs Measurements: Another way of evaluating the selectivities of new ionophores is the transduction of a chemical recognition process into an electronic signal. For this purpose we have developed CHEMFETs.[30–33]

The new calix[4]arene crown ethers (**8a–b**, **10a–b**, and **11**) and valinomycin **1**, incorporated into a plasticized PVC membrane, were studied by CHEMFET measurements. The potentiometric selectivities towards K^+ were determined in presence of different alkali and alkaline earth ions (Table 10). All the

Table 10. CHEMFET measurements with different K^+-selective ionophores [a]: potentiometric selectivity coefficients $K^{pot}_{K,j}$ [b], slope in parentheses (mV decade^{-1}) [c].

Ligand	0.1 M Ca^{2+}	0.1 M Li^+	0.1 M Mg^{2+}	0.1 M NH_4^+	0.1 M Na^+	1 M Na^+
1	−3.7 (59)	−3.5 (57)	−3.7 (59)	−2.0 (54)	−3.1 (57)	−3.9 (58)
8a	−4.0 (58)	−3.7 (56)	−4.0 (58)	−1.4 (46)	−3.2 (55)	−4.2 (56)
8b	−3.5 (53)	−3.7 (52)	−3.7 (53)	−1.4 (30)	−3.1 (52)	−3.9 (54)
10a	−3.9 (58)	−2.8 (56)	−3.8 (58)	−1.5 (54)	−2.5 (54)	[d]
10b	−3.6 (56)	−3.2 (56)	−3.8 (58)	−1.9 (53)	−2.0 (54)	−2.2 (50)
11	−3.6 (55)	−3.6 (56)	−3.7 (56)	−1.5 (54)	−3.2 (57)	−3.9 (58)

[a] 1 wt% ionophore and 50 mol% (with respect to ionophore) KTTFPB. [b] $\log K^{pot}_{K,j}$: ±0.1. [c] Slope: ±2 mV decade^{-1} [K^+]. [d] Not determined.

ligands show a high K^+ selectivity in presence of the alkaline earth ions Mg^{2+} and Ca^{2+} (≤ -3.5). These ions almost do not interfere at all. A rather low K^+ selectivity and a sub-Nerstian behavior is obtained in the presence of NH_4^+ ions. This can be explained by the higher partition coefficient of this ion compared to K^+. The differences in K^+ selectivity of CHEMFETs with the new ligands are more pronounced in presence of Na^+ ions. The *cone* conformers **10a** and **10b** are selective for K^+ ions in presence of Na^+ ions, but the discrimination between the ions is low. In contrast, a very high K^+/Na^+ selectivity is obtained for the *partial cone* conformer **11** and the 1,3-*alternate* conformers **8a** and **8b** (−3.9, −4.2, and −3.9, respectively; Table 10). The Na^+/K^+ selectivity for the calix[4]arene derivative **8a** in the 1,3-*alternate* conformation ($\log K_{K/Na} = -4.2$) (Fig. 8) is even better than that observed with CHEMFETs incorporating the natural ionophore valinomycin ($\log K_{K/Na} = -3.9$).

The results are in agreement with the data found for binding studies in chloroform (Table 5) and for the transport through

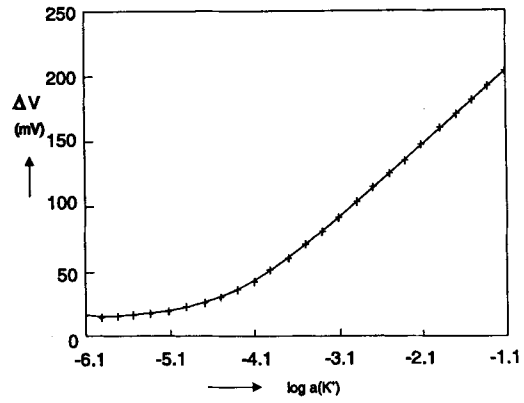

Fig. 8. K^+ response of CHEMFETs containing ionophore **8a** in the presence of 1 M NaCl.

SLMs. Although the difference in $\Delta\Delta G^\circ$ values between K^+ and Na^+ (Table 5) for the 1,3-*alternate* (**8a**) and *partial cone* (**11**) conformers (31.2 and 23.5 kJ mol^{-1}, respectively) is substantial for the picrate extraction experiments, this is not recognized with CHEMFETs measurements. In the case of CHEMFETs incorporating ligand **11**, a very high K^+/Na^+ selectivity is already obtained. A further enhancement of the selectivity by using ligand **8a** and **8b** can hardly be measured because of the detection limits of the sensors.

Conclusions

The antibiotic activity of the naturally occurring ionophore valinomycin (**1**) and the interest for this macrocycle in chemical technology are both due to the good lipophilicity of its cation complexes and the high K^+/Na^+ selectivity shown by the ligand. In this study we have synthesized new lipophilic ionophores, the 1,3-*alternate*-calix[4]arenecrown-5 conformers **8a** and **8b**, which are the first ligands to show a K^+/Na^+ selectivity consistently better than valinomycin in extraction experiments from H_2O to $CHCl_3$, in transport through supported liquid membranes (NPOE), and in ion detection by chemically modified field effect transistors (CHEMFETs). The efficiency and selectivity order found for the crown conformers derived from unsubstituted calix[4]arene (1,3-*alternate* > *partial cone* > *cone*) is different from that previously found (*partial cone* > 1,3-*alternate* > *cone*) for the crown-5 stereoisomers derived from *p-tert*-butylcalix[4]arene. This shows that the substituents at the *para* position of the calix also have a subtle steric influence.

Experimental Procedure

General [34]: Melting points were determined with an electrothermal melting-point apparatus in a sealed capillary and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with Bruker spectrometers of the Centro Interdipartimentale di Misure (C. I. M.) of the Parma University and of the Organic Laboratories of the Twente University. Mass spectra were obtained with a Finnigan MAT SSQ7 10 spectrometer (CH_4, DCI) and with a Finnigan MAT 90 (3-nitrobenzyl alcohol, FAB). Acetonitrile was dried over molecular sieves (3 Å). Tetraethylene glycol ditosylate [35], 25,27-dimethoxycalix[4]arenecrown-5 (**6a**) [8], 25,27-bis(2-propyloxy)calix[4]arene (**7a**) [36] and 25,27-diethoxycalix[4]arene (**7b**) [37] were prepared as described in literature. Analytical TLC were performed on precoated silica gel plates (SiO_2, Merck, $60F_{254}$). All reactions were performed in a nitrogen atmosphere. In the NMR spectra the phenolic oxygen is considered as the substituent to which the *ipso*, *ortho*, *meta*, and *para* positions refer.

General Procedure for the Preparation of 25,27-Dialkoxycalix[4]arenecrown-5 with 1,3-*Alternate* Structure (8): A suspension of 25,27-dialkoxycalix[4]arene **7**

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(3.02 mmol), Cs_2CO_3 (3.95 g, 12.12 mmol), and tetraethyleneglycol di-*p*-toluenesulfonate (1.67 g, 3.32 mmol) in CH_3CN (600 mL) was stirred for 24 h under reflux. Then CH_3CN was removed under reduced pressure and the residue treated with 50 mL of CH_2Cl_2 and 50 mL of 10% HCl. The organic phase was separated and washed three times with water. CH_2Cl_2 was removed under reduced pressure, and the product crystallized.

25,27-Bis(2-propyloxy)calix[4]arenecrown-5, 1,3-*alternate* (8a): Crystallized from ethanol (57% yield): M.p. 209–211 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.05 (d, ^3J(H,H) = 7.5 Hz, 4H; ArH *meta*), 7.00 (d, ^3J(H,H) = 7.6 Hz, 4H; ArH *meta*), 6.83 (t, ^3J(H,H) = 7.6 Hz, 2H; Ar *para*), 6.80 (t, ^3J(H,H) = 7.5 Hz, 2H; ArH *para*), 4.20 (sept, ^3J(H,H) = 6.1 Hz, 2H; $OCH(CH_3)_2$), 3.82 (s, 8H; $ArCH_2Ar$), 3.62–3.57 (m, 8H; $ArOCH_2CH_2OCH_2CH_2$), 3.20–3.10 (m, 8H; $ArOCH_2CH_2OCH_2CH_2$), 0.84 (d, ^3J(H,H) = 6.1 Hz, 12H; $OCH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 156.4, 154.9 (s; Ar *ipso*), 134.6, 133.6 (s; Ar *ortho*), 129.5 (d; Ar *meta*), 122.1, 121.9 (d; Ar *para*), 70.3 (d; $OCH(CH_3)_2$), 72.9, 70.5, 70.2, 68.0 (t; OCH_2), 39.1 (t; $ArCH_2Ar$), 21.7 (q; $OCH(CH_3)_2$); MS (CH_4, DCI): *m/z* (%): 667.2 (100) [M^+ + H]; $C_{42}H_{50}O_7$ (666.81): calcd C 75.65, H 7.55; found C 75.52, H 7.63.

25,27-Diethoxycalix[4]arenecrown-5, 1,3-*alternate* (8b): Crystallized from CH_2Cl_2/MeOH (1/4); (40% yield). For membrane transport measurements the product was purified by PTLC (SiO_2, CH_2Cl_2/EtOAc (4/1)): M.p. 188–190 °C; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.09 (d, ^3J(H,H) = 7.4 Hz, 4H; ArH *meta*), 7.03 (d, ^3J(H,H) = 7.5 Hz, 4H; ArH *meta*), 6.87 (t, ^3J(H,H) = 7.4 Hz, 2H; ArH *para*), 6.83 (t, ^3J(H,H) = 7.4 Hz, 2H; ArH *para*), 3.84 (s, 8H; $ArCH_2Ar$), 3.55 (s, 8H; $ArOCH_2CH_2OCH_2CH_2$), 3.45–3.34 (m, 8H; $ArOCH_2CH_3$; $ArOCH_2CH_2O$), 3.17 (t, ^3J(H,H) = 6.3 Hz, 4H; $ArOCH_2CH_2O$), 0.69 (t, ^3J(H,H) = 6.9 Hz, 6H; $ArOCH_2CH_3$); ^{13}C NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 156.8, 156.1 (s; Ar *ipso*), 134.5, 134.1 (s; Ar *ortho*), 129.4, 129.2 (d; Ar *meta*), 122.5 (d; Ar *para*), 72.6, 70.5, 70.1, 68.6, 65.1 (t; OCH_2), 38.2 (t; $ArCH_2Ar$), 14.6 (OCH_2CH_3); MS (NBA, FAB): *m/z* (%): 637.7 (100) [M^+]; $C_{40}H_{46}O_7$ (639.76): calcd C 75.21, H 7.25; found C 75.00, H 7.20.

25,27-Dihydroxycalix[4]arenecrown-5 (9):

Method A: To a solution of compound **6a** (0.46 g, 0.76 mmol) in $CHCl_3$ (30 mL), iodotrimethylsilane (0.22 mL, 1.52 mmol) was added under nitrogen. The reaction mixture was refluxed for 2 h, then quenched with 10% HCl (50 mL) and transferred to a separatory funnel. The organic phase was separated and washed with a saturated solution of $Na_2S_2O_3$ (30 mL) and with water (2 × 50 mL). Chloroform was removed under reduced pressure and the product crystallized from methanol (90% yield). M.p. 279–281 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.74 (s, 2H; OH), 7.07 (d, ^3J(H,H) = 7.5 Hz, 4H; ArH *meta*), 6.82 (d, ^3J(H,H) = 7.5 Hz, 4H; ArH *meta*), 6.70 (t, ^3J = 7.5 Hz, 2H; ArH *para*), 6.68 (t, ^3J(H,H) = 7.5 Hz, 2H; ArH *para*), 4.42 (d, ^2J(H,H) = 13.0 Hz, 4H; $ArCH_2Ar$), 4.08 (s, 8H; $ArOCH_2CH_2OCH_2CH_2O$), 4.0–3.8 (m, 8H; $ArOCH_2CH_2OCH_2CH_2O$), 3.35 (d, ^2J(H,H) = 13.0 Hz, 4H, $ArCH_2Ar$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 153.4, 152.0 (s; Ar *ipso*), 133.2, 128.1 (s; Ar *ortho*), 129.0, 128.5 (d; Ar *meta*), 125.3, 118.8 (d; Ar *para*), 76.8, 71.1, 70.2 (t; OCH_2), 31.1 (t; $ArCH_2Ar$); IR (KBr): $\tilde{\nu}$ = 3500–3100 cm^{-1} (bs, OH); MS (CH_4, DCI): *m/z* (%): 582.2 (100) [M^+]; $C_{36}H_{38}O_7$ (582.66): calcd C 74.21, H 6.57; found C 74.10, H 6.64.

Method B: A mixture of calix[4]arene (**5**) (3.50 g, 8.25 mmol) and KO*t*Bu (1.86 g, 16.6 mmol) in dry benzene (750 mL) was stirred for 0.5 h at room temperature. The mixture was then heated under reflux, and a solution of tetraethylene glycol di-*p*-toluene sulfonate (4.14 g, 8.25 mmol) in dry benzene (250 mL) was subsequently added dropwise over a 6 h period. After 48 h the reaction was cooled and washed with 1 N HCl (0.5 L). The aqueous layer was extracted twice with diethyl ether (0.5 L). The combined organic layers were washed with water, dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, CH_2Cl_2:EtOAc, 4:1 v/v) from which **9** was obtained as a white solid (30%).

25,27-Bis(2-propyloxy)calix[4]arenecrown-5, *cone* (10a): To a solution of **9** (0.35 g, 0.60 mmol) in dry DMF (25 mL), NaH (50% in oil, 0.29 mg, 6.0 mmol) and 2-iodopropane (1.20 mL, 12.0 mmol) were added under nitrogen. The reaction mixture was stirred at room temperature for 8 h. The reaction mixture was quenched by adding (CAUTION!) 10% HCl (50 mL) and extracted twice with dichloromethane (2 × 30 mL). The combined organic layers were washed twice with water, and dichloromethane was distilled off under reduced pressure. Pure product **10a** was obtained by crystallization of the residue from methanol (40% yield). M.p. 194–195 °C; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.13 (d, ^3J(H,H) = 7.4 Hz, 4H; ArH *meta*), 6.94 (t, ^3J(H,H) = 7.4 Hz, 2H; ArH *para*), 6.18 (t, ^3J(H,H) = 7.2 Hz, 2H; ArH *para*), 6.02 (d, ^3J(H,H) = 7.2 Hz, 4H; ArH *meta*), 4.36 (d, ^2J(H,H) = 13.5 Hz, 4H; $ArCH_2Ar$), 4.28 (t, ^3J(H,H) = 7.1 Hz, 4H; $ArOCH_2CH_2OCH_2CH_2O$), 4.06 (t, ^3J(H,H) = 7.1 Hz, 4H; $ArOCH_2CH_2OCH_2CH_2O$), 3.91 (sept, ^3J(H,H) = 6.1 Hz, 2H; $OCH(CH_3)_2$), 3.8–3.7 (m, 8H; $ArOCH_2CH_2OCH_2CH_2O$), 3.15 (d, ^2J(H,H) = 13.5 Hz, 4H; $ArCH_2Ar$), 1.34 (d, ^3J(H,H) = 6.1 Hz, 12H; $OCH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 158.6, 153.3 (s; Ar *ipso*), 136.8, 133.6 (s; Ar *ortho*), 129.1, 127.2 (d; Ar *meta*), 122.0 (d; Ar *para*), 76.8 (d; $OCH(CH_3)_2$), 72.6, 71.7, 70.5, 69.3 (t; OCH_2), 31.6 (t; $ArCH_2Ar$), 22.4 (q; $OCH(CH_3)_2$); MS (CH_4, DCI): *m/z* (%): 666.6 (100) [M^+]; $C_{42}H_{50}O_7$: calcd C 75.65, H 7.55; found C 75.57, H 7.64.

25,27-Diethoxycalix[4]arenecrown-5, *cone* (10b): Calixarene **9** (1.00 g, 1.72 mmol), NaH (55% in oil, 3.44 g, 17.2 mmol), and ethyl-*p*-toluenesulfonate (3.44 g, 17.2 mmol) were dissolved in DMF (50 mL) at 0 °C. The mixture was stirred at room temperature for 24 h. The reaction was quenched by adding a 10% HCl, and the resulting solid was filtered off. The residue was dissolved in CH_2Cl_2, washed twice with sat. NH_4Cl solution, and once with water, dried over $MgSO_4$ and filtered. The solvent was then removed under reduced pressure. The product was crystallized from CH_2Cl_2/MeOH (1/4); (81% yield). For membrane transport measurements the product was purified by PTLC (SiO_2, CH_2Cl_2/EtOAc (4/1)). M.p. 247–249 °C; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.13 (d, ^3J(H,H) = 7.4 Hz, 4H; ArH *meta*), 6.93 (t, ^3J(H,H) = 7.4 Hz, 2H; ArH *para*), 6.21 (t, ^3J(H,H) = 7.5 Hz, 2H; ArH *para*), 6.09 (d, ^3J(H,H) = 7.5 Hz, 4H; ArH *meta*), 4.38 (d, ^2J(H,H) = 13.4 Hz, 4H; $ArCH_2Ar$), 4.34–4.27 (m, 4H; $ArOCH_2CH_2O$), 4.14–4.07 (m, 4H; $ArOCH_2CH_2O$), 3.87–3.78 (m, 12H; $ArOCH_2CH_3$, $ArOCH_2CH_2OCH_2CH_2$), 3.17 (d, ^{2}J(H,H) = 13.4 Hz, 4H; $ArCH_2Ar$), 1.48 (t, ^3J(H,H) = 7.0 Hz, 6H; $ArOCH_2CH_3$); ^{13}C NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 158.5, 154.6 (s; Ar *ipso*), 136.6, 133.1 (s; Ar *ortho*), 129.0, 127.4 (d; Ar *meta*), 122.2 (d; Ar *para*), 72.7, 71.4, 70.6, 69.2 (t; OCH_2), 30.9 (t; $ArCH_2Ar$), 15.8 (q; OCH_2CH_3); MS (NBA, FAB): *m/z* (100): 637.8 (100) [M^+]; $C_{40}H_{46}O_7$ (638.808) calcd C 75.21, H 7.26; found C 75.62, H 7.36.

25,27-Bis(2-propyloxy)calix[4]arenecrown-5, *partial cone* (11): To a solution of **9** (0.40 g, 0.68 mmol) and 2-iodopropane (0.68 mL, 6.86 mmol) in dry THF (20 mL), a suspension of potassium *tert*-butoxide (0.31 g, 2.74 mmol) in dry THF (20 mL) was added. The reaction mixture was refluxed for 12 h. Then THF was removed under reduced pressure and the residue quenched with 3 N HCl. The aqueous phase was extracted with dichloromethane (2 × 25 mL). The combined organic extracts were washed with 1 M $Na_2S_2O_3$ (50 mL), 3 N HCl (2 × 50 mL), and water (3 × 50 mL). Dichloromethane was distilled off under reduced pressure and the residue treated with methanol to afford pure compound **11** as a white precipitate (48% yield). M.p. 197–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.18 (dd, ^3J(H,H) = 6.0, ^4J(H,H) = 2.0 Hz, 2H; ArH-6,16), 7.12 (d, ^3J(H,H) = 7.5 Hz, 2H; ArH-22,24), 6.93 (t, ^3J(H,H) = 7.5 Hz; ArH-23), 6.89 (dd, 2H; ArH-4,18), 6.86 (d, 2H; ArH-10,12), 6.85 (t, 2H; ArH-5,17), 6.56 (t, ^3J(H,H) = 7.6 Hz, 1H; ArH-11), 4.44 (d, ^2J(H,H) = 12.2 Hz, 2H; $ArCH_2Ar$, H_{ax}), 3.97 (d, ^2J(H,H) = 18.0 Hz, 2H; $ArCH_2Ar$, H_B), 3.94 (ddd, 2H; $ArOCHHCH_2$), 3.89 (d, ^2J(H,H) = 18.0 Hz, 2H; $ArCH_2Ar$, H_A), 3.86 (sept, ^2J(H,H) = 6.2 Hz; $CH(CH_3)_2$, H_G), 3.77 (ddd, J = 10.4, 8.5, 5.6 Hz, 2H; $ArOCHHCH_2$), 3.75 (sept, ^2J(H,H) = 6.4 Hz, 1H; $OCH(CH_3)_2$, H_H), 3.74–3.70 (m, 4H; OCH_2CH_2), 3.65 (d,d,d, J = 10.4, 8.5, 5.6 Hz, 2H; $ArOCHHCH_2$), 3.64–3.60 (m, 4H; OCH_2CH_2), 3.35 (ddd, J(H,H) = 9.7, 9.7, 5.6 Hz, 2H; $OCHHCH_2$, H_C), 3.26 (d, ^2J(H,H) = 12.2 Hz, 2H; $ArCH_2Ar$, H_{eq}), 1.33 (d, ^3J(H,H) = 6.0 Hz, 6H; $OCH(CH_3)_2$, H_D), 0.08 (d, ^3J(H,H) = 6.0 Hz, 6H; $OCH(CH_3)_2$, H_E); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 156.8, 155.4 (s; Ar *ipso*), 136.4, 134.2, 132.9, 132.6 (s; Ar *ortho*), 129.5, 128.8, 128.3, 127.6 (d; Ar *meta*), 122.7, 122.1, 121.3 (d; Ar *para*), 77.6 (d; $OCH(CH_3)_2$), 73.0, 71.1, 71.0, 70.0 (t; OCH_2), 40.0, 30.3 (t; $ArCH_2Ar$), 22.6, 21.3 (q; $OCH(CH_3)_2$); MS (CH_4, DCI): *m/z* 666.5 (100) [M^+]; $C_{42}H_{50}O_7$ (666.81): calcd C 75.65, H 7.55; found C 75.54, H 7.61. The complete peak assignment (Fig. 9) of the ^{1}H NMR spectrum for compound **11** has been

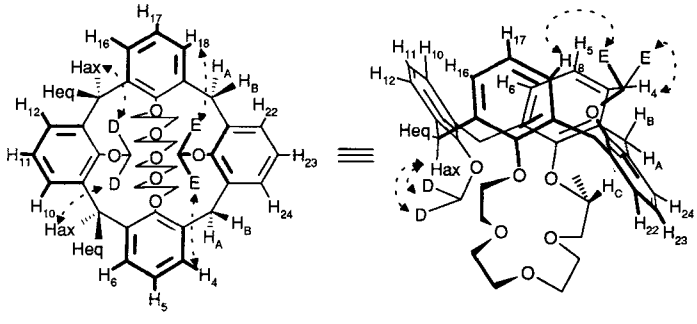

Fig. 9. Proton labeling and selected through-space correlations in compound **11**.

achieved unequivocally on the basis of 2D NMR experiments (COSY and NOESY). A clear through-space correlation of the doublet at δ = 1.33 (H_D) with the axial protons (H_{ax}) of the bridge indicates that this propyl group is oriented *syn* with respect to the crown moiety. The methyl signal of the *anti*-oriented isopropyl group (ΔH_E = 0.08) correlates in the NOESY spectrum with H_{18} and H_4 of the aromatic nuclei bearing the crown and experiencing the shielding effect of the calix cavity. A significant high-field shift (δ = 3.35) is also experienced by one (H_C) of the two $ArOCH_2$ protons of the crown, which is facing the *anti* oriented aromatic nucleus.

X-ray structure determination of compound 6a: A single crystal of $0.2 \times 0.1 \times 0.3$ mm suitable for X-ray diffraction measurements was mounted on a glass fiber without protection from the air. The crystal data and most relevant experimental parameters used in the crystal structure analysis are reported in Table 11. The intensities were

Table 11. Experimental data for the X-ray diffraction studies on **6a**.

formula	$C_{38}H_{42}O_7 \cdot 0.5\,CHCl_3$
cryst. system	monoclinic
space group	$P2_1/c$
cell parameters at 295 K [a]	
a, Å	18.498(4)
b, Å	12.901(3)
c, Å	29.175(6)
β, °	90.56(2)
V, Å^3	6962(2)
Z	8
D_{calcd}, g cm^{-3}	1.279
$F(000)$	2840
mol. wt	670.43
linear abs. coeff., cm^{-1}	17.21
diffractometer	Siemens AED
scan type	$\theta/2\theta$
scan speed, deg min^{-1}	3–12
scan width, °	$(\theta - 0.65), [\theta + (0.65 + \Delta\lambda\lambda^{-1}\,\mathrm{tg}\theta]$
radiation	$Cu_{K\alpha}$ (1.54178 Å)
2θ range, °	6–140
reflns measured	$\pm h, +k, +l$
total data measured	14148
criterion for observation	$I \geq 2\sigma(I)$
observed data measured	10376
unique observed data	10000
agreement between equiv. observed reflns	0.107
no. of variables	871
max. δ/σ on last cycle	0.07
$R = \sum\|\Delta F\|/\sum\|F_0\|$	0.097
$R_w = \sum w^{1/2}\|\Delta F\|/\sum w^{1/2}\|F_0\|$	0.097
GOF $= [\sum w\|\Delta F\|^2/(NO - NV)]^{1/2}$	2.31

[a] Unit cell parameters were obtained by least-squares analysis of the setting angles of 30 carefully centered reflections chosen from diverse regions of reciprocal space.

calculated by profile analysis according to Lehmann and Larsen [38] and corrected for Lorentz and polarization effects. One standard reflection, collected every 100 reflections, showed no significant fluctuation. The structure was solved by direct methods using SIR92 [39] and completed by successive Fourier syntheses using SHELX76 [40]. The chloroform solvent molecule was affected by severe static disorder with the CCl_3 group distributed over three different positions. The structure was refined by blocked full matrix least-squares methods, first with isotropic and then with anisotropic displacement parameters. All the hydrogen atoms were positioned on geometrical grounds (C–H = 1.0 Å) and refined "riding" on their C atoms. Different displacement parameters were used for the H atoms of each phenolic ring and for those of each crown chain. The atomic scattering factors of the non-hydrogen atoms were taken from Cromer and Waber [41]; the values of $\Delta f'$ and $\Delta f''$ were those of Cromer [42]. The geometrical calculations were obtained by PARST [43]. All the crystallographic calculations were carried out on the Gould Encore91 of Centro di Studio per la Strutturistica Diffrattometrica, CNR Parma. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1220/2. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (Fax: Int. code +(1223)336-033 or e-mail: teched@chemcrys.cam.ac.uk).

Membrane Transport: The polymeric film Accurel® was obtained from Enka Membrana. *o*-Nitrophenyl *n*-octyl ether (NPOE) was purchased from Fluka and was used without further purification. $KClO_4$ and $NaClO_4$ were of analytical grade and obtained from Janssen Chimica. The transport experiments were carried out in a permeation cell consisting of two identical cylindrical compartments (half-cell volume: ca. 50 mL; effective membrane area: ca. 13.5 cm^2). Details of this cell have been described elsewhere [44]. Aqueous solutions of $KClO_4$ and $NaClO_4$ were used as source phase. Doubly distilled and deionized water was used as receiving phase. Supported liquid membrane consisted of a thin microporous polypropylene film (Accurel®, thickness $d = 100$ mm, porosity 64%) immobilizing the solution of the carrier in NPOE. The measurements were performed at 25 ± 0.1 °C at least in duplicate. The transported perchlorate salts were determined by monitoring the conductivity (radiometer CDM 83 conductivity meter and Unicam 9550/60 electrode with a cell constant of 0.95 cm^{-1}) of the receiving phase as a function of time in the case of single-ion transport and by atomic absorption in case of competitive transport. The standard deviation in the transport measurements is about 15%. Salt activities were calculated according to Debye–Hückel theory [45].

Reagents for CHEMFETs: High molecular weight (HMW) PVC was obtained from Janssen Chimica; bis(2-ethylhexyl) sebacate (DOS), and potassium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (KTTFPB) were purchased from Fluka. The alkali and alkaline earth chlorides used were of analytical grade (Merck-Schuchardt), except potassium chloride and sodium chloride (Suprapur, Merck-Schuchardt). The pH 4 buffer was purchased from Yokogawa. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone ketyl before use. All solutions were made with deionized, doubly distilled water.

CHEMFETs: CHEMFETs were prepared from ISFETs (ion-sensitive field effect transistors) with dimensions of 1.2×3 mm. Details of the fabrication of the ISFETs modified with poly(hydroxyethyl methacrylate) hydrogel (polyHEMA) have been described previously [46,47]. The modified ISFETs were mounted on a printed circuit board, wire-bonded, and encapsulated with epoxy resin (Hysol H-W796/C8 W795). The polyHEMA-layer of the ISFETs was conditioned by immersion in a buffered (pH = 4) 0.1 M KCl solution for 1 h, prior to solvent casting. The ion-sensitive membrane was cast on the polyHEMA hydrogel by adding one drop of THF solution containing 100 mg of a mixture composed of HMW-PVC (33 wt%), plasticizer (65.5%), ionophore (1 wt%), and KTTFPB (50 mol%, with respect to the ionophore) per mL of THF. The THF was allowed to evaporate overnight.

CHEMFET Measurements: The output signal of the CHEMFETs was measured in a constant drain-current mode ($I_d = 100$ μA), with a constant drain-source potential ($V_{ds} = 0.5$ V). This was achieved by using a CHEMFET amplifier of the source-drain follower type (Electro Medical Instrumentation, Enschede, The Netherlands). The developed membrane potential was compensated by an opposite potential (ΔV_{gs}) via the reference electrode. A saturated calomel electrode (SCE) was used as reference, connected to the sample solution through a salt bridge filled with 1.0 M LiOAc. Ten CHEMFETs were monitored simultaneously and the data were collected and analyzed with an Apple IIGS microcomputer. Computer-controlled switches allowed disconnection of CHEMFETs that showed too high a leakage current ($I_d \geq 50$ nA). All equipment was placed in a dark and grounded metal box in order to eliminate any effects from static electricity and photosensitivity of the CHEMFETs. The potentiometric selectivity coefficients, $K_{i,j}^{pot}$, were determined by the fixed interference method (FIM) [48]. The constant background concentration of the interfering ion was 0.1 or 1 M. Before starting the measurements the CHEMFETs were conditioned in 0.1 M KCl. All measurements were carried out by titration of 25 mL of 0.1 or 1 M interfering cation with 0.01 and 1.0 M KCl solutions at a pH of 7. CHEMFETs were stabilized for 15 min after immersion in the interfering cation solution before starting the titration.

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