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Selective Complexation and Membrane Transport of Guanidinium Salts by Calix[6]arene Amides

ALESSANDRO CASNATI,[a] PATRIZIA MINARI,[a] ANDREA POCHINI,[a] ROCCO UNGARO*[a]
WILMA F. NIJENHUIS,[b] FEIKE DE JONG [b] AND DAVID N. REINHOUDT*[b]
[a]Istituto di Chimica Organica dell' Universita, Viale delle Scienze, I-43100 Parma, Italy
[b]Laboratory of Organic Chemistry, University of Twente, P. O. B. 217, 7500 AE Enschede, The Netherlands

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Abstract. The *p-tert*-butylcalix[6]arene hexamide **2** and *syn*-1,3,5-trimethoxy-2,4,6-triamide **4** were synthesized by reaction of α-chloro-*N,N*-diethylacetamide and the corresponding calix[6]arenes **1** and **3**, respectively. ^{1}H NMR spectroscopy shows that **2** is a mixture of different conformations whereas **4** is fixed in a cone conformation. Extraction experiments, (S–L) and (H_2O–$CDCl_3$) with picrate salts, indicate that **2** complexes both alkali metal (1:2 complex) and guanidinium salts (1:1 complex) but **4** complexes only guanidinium (1:1 complex). Incorporated in supported liquid membranes (Accurel® / *o*-nitrophenyl *n*-octyl ether) the calixarenes **2** and **4** transport guanidinium salts. The hexamide **2** is a more efficient carrier of guanidinium but the *syn*-1,3,5-trimethoxy-2,4,6-triamide **4** is much more selective. Both **2** and **4** are sufficiently lipophilic to give membranes that are stable over longer periods (weeks).

INTRODUCTION

The recognition of guanidinium cations has been the subject of several investigations in supramolecular or host–guest chemistry.[1-4] The interest is justified by the important role that this cation plays in biological systems, being present in arginine residues as binding sites for anionic substrates in enzymes[5] and antibodies.[6] Moreover, the guanidinium cation has been used as a model for the complexation of urea because it is isoelectronic with the uronium cation. We have previously studied the transport of guanidinium cations through bulk[3a] and supported liquid membranes [7] mediated by crown ethers.

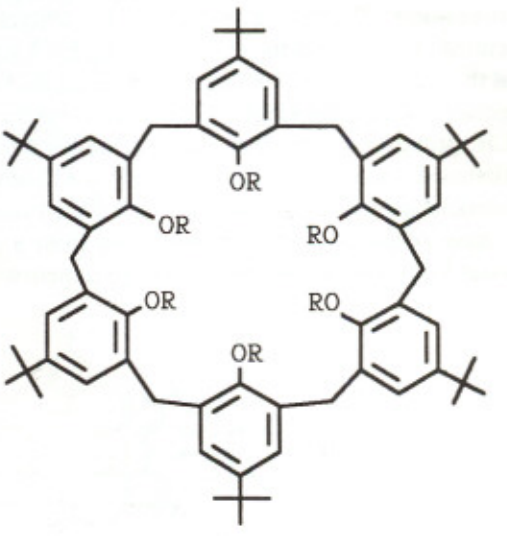
Our extensive studies on supported liquid membranes show that the transport efficiency depends on the lipophilicity of the carrier, which is incorporated in the membrane.[8] Calixarenes[9] offer a highly lipophilic backbone and therefore calixarene-based ionophores are attractive to use in supported liquid membranes. Previously, we have used calix[4]arene crown ethers as selective K^+-ionophores.[10] Other derivatives have been shown to be efficient and selective complexing agents for a variety of cations.[11]

In this paper we describe the synthesis of novel ionophores bearing amide substituents based on *p-tert*-butylcalix[6]arene (**1**), their complexation with alkali and guanidinium cations, and their transport properties.[12]

RESULTS AND DISCUSSION

Synthesis and Solution Structure of the Ligands

The hexamide **2** has been obtained in 90% yield by reaction of *p-tert*-butylcalix[6]arene (**1**) with α-chloro-



1, R = H
2, R = $CH_2CON(CH_2CH_3)_2$

*Authors to whom correspondence should be addressed.

N,N-diethylacetamide (NaH, THF/DMF). The ^{1}H NMR spectrum of **2** recorded at 25 °C in $CDCl_3$ (Fig. 1a) shows a rather complex pattern, indicating the presence of different conformations. In DMSO, **2** is conformationally more mobile, and at 110 °C for most of the signals only singlets are present (Fig. 1b), indicating a fast interconversion between the different conformers.

In $CDCl_3$ at –25 °C the signal at δ 6.95 ppm has disappeared, and in the aromatic region other sharp singlets appear, indicating a freezing of the ligand in a mixture of conformers which was not further identified. In the solid state **2** is present in a *syn*-1,2,3-*anti*-4,5,6 conformation which has a center of symmetry.[12a]

The *syn*-1,3,5-trimethoxy-2,4,6-triamide **4** was obtained in 20% overall yield from *p-tert*-butylcalix[6]arene **1** by reaction of **1** with three equivalents methyl iodide (K_2CO_3, acetone), followed by reaction of **3** with α-chloro-*N,N*-diethylacetamide (NaH,THF/DMF) (see Scheme).

Whereas compound **3** is conformationally very mobile, the triamide **4** exhibits spectroscopic data that are in agreement with a fixed cone structure. The ^{1}H NMR spectrum of ligand **4** (Fig. 2) remains virtually unchanged between –70 °C and +120 °C with exception of the ethyl groups of the amides which are present as two sets of signals of equal intensity at room temperature. This indicates restricted rotation around the C–N bonds. At T > 100 °C one quartet (δ = 3.47 ppm) and one triplet (δ = 1.20 ppm) are present. This spectrum further shows two sharp singlets for the *tert*-butyl and the aromatic protons, a singlet for the OCH_2CO and the methoxy groups, and an AB quartet for the bridging methylene groups at all temperatures. These data and the large difference in chemical shift between the *equatorial* (H_{eq}: δ = 3.43 ppm) and the *axial* (H_{ax}: δ = 4.53 ppm) protons of the bridge, together with the abnormally high field absorption of the OCH_3 groups (δ = 2.21 ppm) suggest that **4** is present in a flattened cone conformation according to Gutsche's nomenclature (up-out-up-out-up-out).[9a,13] Very recently, we have obtained the preliminary data from a single crystal X-ray analysis and these are in agreement with the proposed structure.

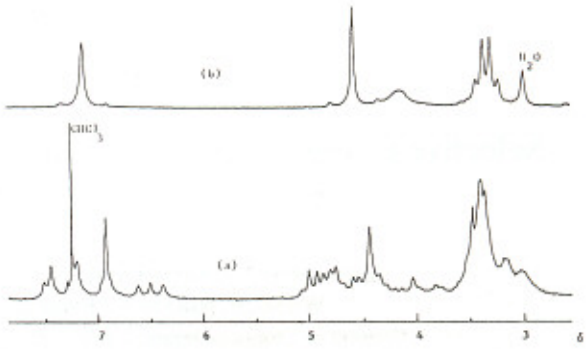


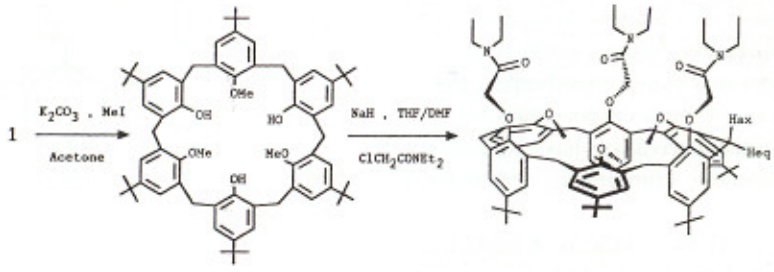
Fig. 1. ^{1}H NMR spectrum of hexamide **2**: (a) in $CDCl_3$ at 298 K; (b) in DMSO-d_6 at 383 K.

In this conformation the methoxy groups point into the shielding π cloud of the apolar cavity of the calix, which is rigidified by the three bulky acetamide groups. Compared with the mobile hexamide **2**, the conformational rigidity of compound **4** is rather surprising. It is possible that specific weak (OCH_3...π)[14] interactions are responsible for this different conformational behavior. We are currently carrying out a more detailed conformational analysis and molecular mechanics calculations to clarify this observation.

The three converging chelating amide groups in a rigid cleft offer an attractive possibility to study the complexation of polar guests with a C_3 symmetry such as a guanidinium cation.

Complexation of Alkali Metal and Guanidinium Cations

Preliminary solid–liquid ($CDCl_3$) and liquid–liquid (H_2O–$CDCl_3$) extraction experiments using picrates (10-fold excess) already indicated that ligand **2** is able to complex both alkali metal and guanidinium cations, whereas the triamide **4** complexes only guanidinium. The guanidinium cation is complexed by both ligands **2** and **4** with a 1:1 stoichiometry. The hexamide **2** forms 1:2 complexes with Na^+ and K^+. Evidence for the presence of two alkali metal ions per molecule of ligand **2** was also obtained from FAB+ mass spectrometry (see Experimen-



3 4

Scheme

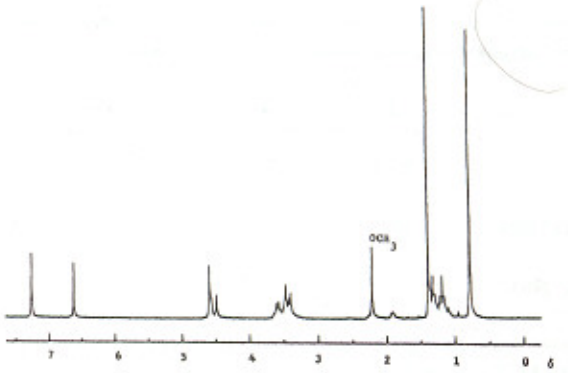


Fig. 2. ^{1}H NMR spectrum (200 MHz) of triamide **4** in $CDCl_3$ at 298 K.

tal section). Interestingly, the ^{1}H NMR spectrum of the 1:2 complex of hexamide **2** and Na^+Pic^- shows a very simple and symmetrical pattern (Fig. 3), indicating that the complexed ligand is in the cone conformation, in contrast to the free ligand which is present as a mixture of conformers.

When the molar ratio between **2** and Na^+ is equal to 1.6, the 25 °C ^{1}H NMR spectrum is very broad. At –25 °C it sharpens, showing only separate signals corresponding to the free ligand and the 1:2 complex, respectively. This indicates that in $CDCl_3$ only one type of complex is formed (1:2), which at room temperature exchanges with the free ligand at a rate comparable to the frequency difference between the complex and the free ligand. Therefore, the first complexed sodium cation acts as a template to bring the ligand in the cone conformation suitable for complexation of a second sodium cation.[15]

The ^{1}H NMR spectrum of the 1:2 complex of hexamide **2** with K^+ shows a different and more complex pattern which rules out the formation of a cone structure for the complexed ligand. This means that binding of the larger potassium cation is different from that of the sodium cation.

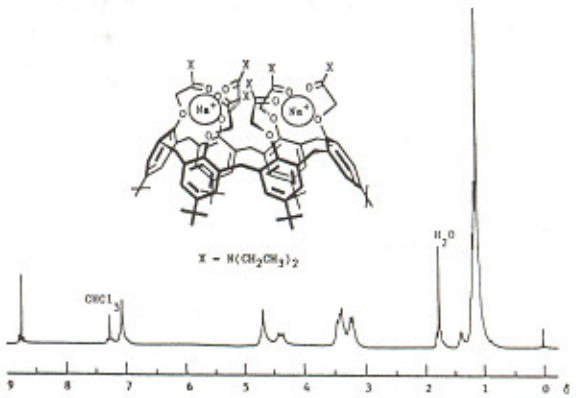


Fig. 3. ^{1}H NMR spectrum (200 MHz) of **2**-sodium picrate (1:2) complex in $CDCl_3$ at 298 K.

These are the first examples of calix[6]arene ligands that are able to host simultaneously two alkali metal cations, although it is known that calix[6]arene derivatives form bimetallic complexes with titanium (IV).[12a,16]

The guanidinium cation is complexed by the hexamide **2** with a 1:1 stoichiometry. Although this induces some conformational changes in the ligand, a precise structure is difficult to define.

The ^{1}H NMR spectrum of the 1:1 complex of the triamide **4** and the guanidinium cation is very similar to that of the free ligand, and this indicates that **4** is rigid. The complexed guanidinium cation absorbs at δ_H = 7.0 ppm and δ_C = 158.8 ppm, as observed in the corresponding crown ether complexes.[1,3b]

A more quantitative evaluation of the binding properties of ligands **2** and **4** was obtained by extraction of metal picrates from water to $CDCl_3$.[17] The equations used to calculate the association constants have been modified to take into account the fact that in chloroform, hexamide **2** forms only 1:2 complexes with Na^+ and K^+. The partition of the free salt is defined by the partition coefficient P_M:

$$P_M = \frac{[MX]_o}{[M^+]_w[X^-]_w} \qquad (1)$$

in which o denotes the organic phase and w the aqueous phase. The association constant (K_a) in the organic phase is defined as:

$$K_a = \frac{[CAM_2X_2]_o}{[MX]_o^2[CA]_o} \qquad (2)$$

The extraction constant (K_{ex}) from the aqueous to the organic phase is defined as:

$$K_{ex} = \frac{[CA\ M_2X_2]_o}{[M^+]_w^2[X^-]_w^2[CA]_o} \qquad (3)$$

Using eqs 1–3 and the mass balances of the carrier and the salt gives:

$$K_{ex} = \frac{R}{(2-R)([M^+]_w^0 - RV_r[CA]_o^0)^4} \qquad (4)$$

in which:

$$R = \frac{[M^+]_{o,tot}}{[CA]_{o,tot}} \text{ and } V_r = \frac{V_o}{V_w}$$

By using:

$$K_a = \frac{K_{ex}}{P_M^2}$$

K_a can be calculated from eq 4.

The data show (Table 1) that hexamide **2** is 350 times more efficient than triamide **4** in the complexation of the guanidinium picrate in $CDCl_3$. However, like most of the guanidinium receptors known so far,[3] the hexamide **2** also complexes alkali metal cations, showing selectivity for sodium over potassium. The triamide **4**, with its three chelating chains organized in a C_3 symmetry, does not complex alkali metal cations significantly and is therefore selective for the highly complementary guanidinium cation.

Cation Transport Through Supported Liquid Membranes

Single cation transport. As described in our earlier studies,[7,8,10] the membrane consisted of a 10^{-2} M solution of carrier (**2** or **4**) in NPOE (*o*-nitrophenyl *n*-octyl ether) immobilized in a porous polymeric support (Accurel®). The source phase was a 0.1 M aqueous solution of alkali metal or guanidinium thiocyanate, the receiving phase was bidistilled water. In all cases only initial transport (< 5%) was observed. The fluxes are summarized in Table 2.

Table 2 shows that both ligands **2** and **4** are able to facilitate the transport of guanidinium thiocyanate through the membrane, which is low in the absence of the carrier. This is more clearly indicated by the observed increase of the cation flux with the carrier concentration in NPOE (Fig. 4) and with the salt activity in the source phase (Fig. 5).

These data also indicate that under these conditions

Table 1. Association Constants (K_a) and Binding Free Energies ($-\Delta G^0$) of Complexes of Hosts **2** and **4** with Alkali and Guanidinium Picrates in $CDCl_3$ Saturated with H_2O at 22 °C [a]

Compound		2	4
Na^+	K_a(1:2) (M^{-2})	3.6×10^{17}	–
	$-\Delta G^0$ (kcal mol^{-1})	23.7	–
K^+	K_a(1:2) (M^{-2})	9.3×10^{16}	–
	$-\Delta G^0$ (kcal mol^{-1})	22.9	–
Gu^+	K_a(1:1) (M^{-1})	9.6×10^9	1.7×10^7
	$-\Delta G^0$ (kcal mol^{-1})	13.2	9.7

[a] The association constants were determined as described by Cram et al.[17a] The precision of the values is as described by Cram et al.[17b]

Table 2. Guanidinium, Sodium, and Potassium Cation Fluxes[a] for Carriers **2** and **4** in Single Cation Transport

Compound	2	4	none[b]
Gu^+ flux	25.9	5.3	0.9
Na^+ flux	18.4	0.7	0.3
K^+ flux	17.7	1.3	0.5

[a] (10^{-8} mol cm^{-2} h^{-1}); $[thiocyanates]_{s.p.}$ = 0.1 M; $[carrier]_m$ = 10^{-2} M; T = 298 K.
[b] Fluxes in absence of carrier.

both ligands do not show saturation, which generally limits the flux at high salt concentrations in the source phase.[10] Therefore ligands **2** and **4** are ideal carriers for guanidinium salts. The hexamide **2** is more efficient than the triamide **4**, in agreement with the values of the stability constants in $CDCl_3$ (*vide supra*). The triamide **4** hardly transports potassium or sodium salts through the membrane and should render **4** much more selective towards guanidinium cations than **2**. The guanidinium cation flux of hexamide **2** ($J = 25.9 \times 10^{-8}$ mol cm^{-2} h^{-1}), is comparable with that of the lipophilic *n*-decyl-benzo-27-crown-9 ($J = 26.1 \times 10^{-8}$ mol cm^{-2} h^{-1}), one of the best carriers for this cation through supported liquid membranes.[7]

Previous studies with this type of membrane have shown that the membrane stability is related to the NPOE/water partition coefficient of the carrier. When $\log P_{NPOE/water}$ is higher than 5, leaching of the free carrier to the aqueous phases is negligible. The stability of the membrane has been determined by measuring the flux after replacing both aqueous phases after 24 h (Table 3).

In most cases the flux does not change after two

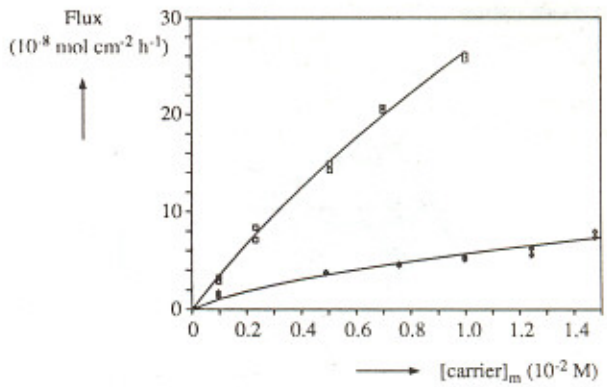


Fig. 4. Guanidinium thiocyanate flux as a function of the carrier concentration in NPOE. $[Gu^+]_{s.p.}$ = 0.1 M; T = 298 K. □ = carrier **2**, ◇ = carrier **4**. The lines shown are calculated according to the model;[10] the points are measured values.

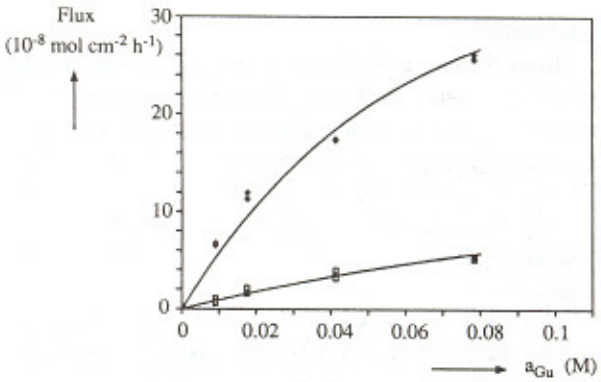


Fig. 5. Guanidinium thiocyanate flux as a function of the salt activity in the source phase. $[carrier]_m = 0.01$ M; $T = 298$ K.◇ = carrier **2**, □= carrier **4**. The lines shown are calculated according to the model;[10] the points are measured values.

Table 3. Cation Flux Stability for Different Carrier–Cation Systems [a]

Carrier–Cation	Flux (10^{-8} mol cm^{-2} h^{-1}) no. of replacements[b] 0	1	2
2-Gu^+	25.9	26.7	26.3
2-Na^+	18.4	16.6	14.7
2-K^+	17.7	17.3	17.0
4-Gu^+	5.3	5.2	5.0

[a] $[thiocyanates]_{s.p.} = 0.1$ M; $[carrier]_m = 10^{-2}$ M; T = 298 K. [b] Of the source and receiving phase after 24 h.

replacements, except for sodium transport by hexamide **2** where a decrease of the flux (ca. 10% per replacement) was observed. This means that the ligands **2** and **4** and their complexes do not leach into the aqueous phases in most cases. In the case of hexamide **2** the formation of a rather hydrophilic ligand/Na^+ complex or a strong Na^+ complexation in water causes leaching of the complex to the source phase.

Previously, we have proposed a mathematical model which describes carrier-mediated transport through a supported liquid membrane by the different equilibria that can be defined at both interfaces of the membrane. By applying this model to the present case it has been possible to evaluate the extraction equilibrium constant K_{ex}:

$$K_{ex} = \frac{[M^+CA]_m[X^-]_m}{[M^+]_w[X^-]_w[CA]_m} = P_M K_a \qquad (5)$$

(m denotes the membrane phase (NPOE), where free ions are present) and the diffusion coefficient $\mathbf{D}_m$ for the different complexes in NPOE (Table 4), using the equation for the flux derived from Fick's first law for diffusion-limited transport (no leaching of the carrier):

$$J = \frac{\mathbf{D}_m}{d}\left(\frac{-1 + \sqrt{(1+4T)}}{2Q}\right) \qquad (6)$$

in which:

$$T = \frac{[CA]_m^0}{K_{ex}\, a_M^2}$$

$$Q = \frac{1}{K_{ex}\, a_M^2}$$

The model assumes a 1:1 complexation. Although in $CDCl_3$ hexamide **2** forms a 1:2 complex with K^+ and Na^+, there is no evidence that this is the case in NPOE. While in $CDCl_3$ *ion pairs* are present, in NPOE the salts exist as *free ions*. Therefore, a 1:2 complex with two cations at a very close distance without the shielding of an anion seems very unlikely in NPOE. Also, the fact that the 1:1 transport model fits the results very well gives us reason to believe that, indeed, in NPOE there is a 1:1 complexation in all cases.

The data show that in the case of hexamide **2**, where the diffusion coefficients are very similar for all complexes, the difference in transport rates is mainly determined by the high extraction constant of this ligand towards guanidinium thiocyanate. The low flux values observed for the triamide **4** are only partly due to the lower K_{ex}; they are also due to the lower $\mathbf{D}_m$.

Competitive transport. The transport selectivity in membrane transport can be defined as the ratio of fluxes measured in single-cation experiments or in competitive experiments (J_{Gu+} / J_{M+}). We have previously shown that significant selectivity data in membrane transport are only obtained in competitive, rather than in single-ion experiments.[10] For two competing cations a mathematical model has been developed which predicts the observed selectivities using the K_{ex} and $\mathbf{D}_m$ of single-ion experiments and the following flux equations:

$$J_1 = \frac{\mathbf{D}_{m1}}{d}\left(\frac{-1 + \sqrt{(1+4T')}}{2Q'_1}\right) \qquad (7)$$

$$J_2 = \frac{\mathbf{D}_{m2}}{d}\left(\frac{-1 + \sqrt{(1+4T')}}{2Q'_2}\right) \qquad (8)$$

Table 4. Calculated Extraction and Diffusion Coefficients of Different Complexes in NPOE[a]

Compound	$K_{ex}(M^{-1})$	$D_m(cm^2h^{-1})$
2–Gu^+	2.9	3.7×10^{-4}
2–Na^+	0.21	5.9×10^{-4}
2–K^+	0.32	4.6×10^{-4}
4–Gu^+	0.56	1.3×10^{-4}

[a] T = 298 K.

in which:

$$T' = \frac{[CA]_m^0}{(a_{M1}K_{ex,1} + a_{M2}K_{ex,2})(a_{M1}+a_{M2})}$$

$$Q_1' = \frac{1}{(a_{M1}+a_{M2})K_{ex,1}\,a_{M1}}$$

$$Q_2' = \frac{1}{(a_{M1}+a_{M2})K_{ex,2}\,a_{M2}}$$

From this it follows that:

$$\frac{J_1}{J_2} = \frac{D_{m,1}K_{ex,1}a_{M1}}{D_{m,2}K_{ex,2}a_{M2}}$$

The triamide **4** has been shown to transport only guanidinium cations. Therefore we checked only hexamide **2** in competitive experiments by measuring the transport selectivity using thiocyanate salts, keeping the concentration of the competing cation (K^+ or Na^+) constant and varying the guanidinium cation concentration. The results are reported in Table 5 together with the fluxes calculated with K_{ex} and D_m obtained from single-ion experiments according to the model. As expected, the selectivity measured in competitive experiments is higher than in single-ion experiments, and guanidinium cations are transported better even in the presence of a 10-fold excess of potassium or sodium cations. Moreover, the calculated fluxes are in good agreement with the observed values.

CONCLUSIONS

The reaction of *p-tert*-butylcalix[6]arene **1** with α-chloro-*N,N*-diethylacetamide produces a fully-alkylated hexamide derivative **2**, which is conformationally mobile. The selective 1,3,5-methylation of **1** followed by alkylation with the same reagent produces the *syn*-1,3,5-trimethoxy-2,4,6-triamide **4**, which is fixed in the cone conformation.

Both ligands complex guanidinium cations and are able to transport their salts through a supported liquid membrane. The hexamide **2** shows a transport efficiency comparable with the most complementary crown ethers (ring size 27–30). The triamide **4** is less efficient but exhibits a much higher guanidinium/alkali metal cation selectivity. Both ligands are sufficiently lipophilic to give stable fluxes.

Hexamide **2** complexes sodium and potassium picrates in $CDCl_3$ with a 1:2 stoichiometry. In the sodium complex, the ligand is fixed in a cone conformation with the two cations complexed at the lower rim.

Because of these promising results in the complexation of guanidinium cations, these calix[6]arenes (**2** and **4**) are attractive receptors for the selective complexation and transport of amino acids[18] and/or other polar organic molecules.

EXPERIMENTAL SECTION

Melting points are uncorrected. Mass spectra (FAB+) were recorded on a Finnigan MAT 90 using *m*-nitrobenzyl alcohol as a matrix. ^1H NMR spectra (200 and 250 MHz) and ^{13}C NMR spectra (25 and 63 MHz) were recorded on Bruker instruments. Chemical shifts (δ) are expressed in ppm from Me_4Si. IR spectra were performed on a FT-IR Nicolet 5 SCX FT spectrophotometer. Elemental analyses were carried out at the Istituto di Chimica Farmaceutica of the University of Parma. All solvents were purified by standard procedures. All reactions were carried out under a nitrogen atmosphere. Analytical TLC was performed on precoated silica gel plates (SiO_2, Merck, 60 F_{254}), while silica gel 60 (Merck, particle size 0.040–0.063 mm, 230–240 mesh) was used for preparative column chromatography. *p-tert*-Butylcalix[6]arene was prepared as described in the literature.[19]

37,38,39,40,41,42-Hexakis(N,N-diethylaminocarbonylmethoxy)-5,11,17,23,29,35-hexakis(1,1-dimethylethyl)-heptacyclo[31.3.1.1 3,7.1 9,13.1 15,19.1 21,25.1 2 7,31]octetraconta-1(37),3,5,7(42),9,11,13(41),15,17,19(40),21,23,25(39),27,29,31(38),33,35-octadecaene (2)

To a solution of *p-tert*-butylcalix[6]arene **1** (1.0 g, 1.02 mmol) in a mixture of 8 mL dry DMF and 40 mL dry THF,

Table 5. Comparison of Measured and Calculated Fluxes in Combined Experiments: Guanidinium vs Sodium and Potassium Cation Fluxes for Carrier **2**

Cations	Source Phase $[Gu^+]$–$[M^+]$ (M)	Measured J_{Gu+}	Measured J_{M+}	Calculated J_{Gu+}	Calculated J_{M+}
		(10^{-8} mol $cm^{-2}h^{-1}$)		(10^{-8} mol $cm^{-2}h^{-1}$)	
Gu^+–Na^+	0.1–0.1	22.7	3.3	27.8	3.1
	0.01–0.1	8.2	8.1	9.3	10.5
Gu^+–K^+	0.1–0.1	24.8	2.8	27.1	3.5
	0.01–0.1	9.1	7.2	8.2	10.8

$[carrier]_m = 10^{-2}$ M; T = 298 K.

sodium hydride (NaH 50% in oil, 0.59 g, 12.24 mmol) and α-chloro-*N,N*-diethylacetamide (1.83 g, 12.24 mmol) were added, and the reaction mixture was kept at 80 °C for 6 h. THF was removed by rotary evaporation, the residue quenched with 2N HCl (50 mL) and extracted with 2 × 50 mL dichloromethane. The combined organic layers were washed twice with water (100 mL). Dichloromethane was removed under reduced pressure and the product precipitated after addition of hexane (yield = 90%). The pure compound **2** was obtained as a white crystalline solid after crystallization from CH_2Cl_2–MeOH: mp 238–240 °C; IR υ_{max} (KBr) 2960, 1665(vs), 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.7–1.4 (m, 90H, $C(CH_3)_3$ and $N(CH_2\underline{C}H_3)_2$), 3.1–5.1 (m, 48H, $N(\underline{C}H_2CH_3)_2$, $ArCH_2Ar$ and OCH_2CO), 6.41, 6.52, 6.63, 6.95, 7.24, 7.26, 7.46, 7.53 (bs, 12H, ArH); ^{13}C NMR ($CDCl_3$) δ 13.1, 13.7, 14.1, 14.6, 14.8 (q, $N(CH_2\underline{C}H_3)_2$), 29.7, 30.4, 34.8 (t, $ArCH_2Ar$), 31.2, 31.6 (q, $C(\underline{C}H_3)_3$), 33.9, 34.1 (s, $\underline{C}(CH_3)_3$), 39.4, 40.3, 41.4, 42.3 (t, $N(\underline{C}H_2CH_3)_2$), 71.9 (t, $O\underline{C}H_2CO$), 123.9, 124.6, 126.0, 126.9, 127.6, 128.3, 129.2 (d, Ar meta), 131.4, 132.6, 133.1, 145.2, 145.9, 146.3 (s, Ar), 152.5, 153.7, 154.1 (s, Ar ipso), 167.1, 167.8, 168.3 (s, C=O); ^1H NMR (DMSO-d_6, T = 383 K) δ 1.01 (t, 36H, $N(CH_2\underline{C}H_3)_2$, J = 7.1 Hz), 1.07 (s, 54H, $C(\underline{C}H_3)_3$), 3.26 (q, 24H, $N(\underline{C}H_2CH_3)_2$), 4.09 (bs, 12H, $ArCH_2Ar$), 4.52 (s, 12H, OCH_2CO), 7.08 (s, 12H, ArH); mass spectrum, 1650.9 (M^+, calcd 1651.1). Anal. calcd for $C_{102}H_{150}N_6O_{12}$: C, 74.14; H, 9.15; N, 5.08. Found: C, 73.72; H, 9.04; N, 4.80.

5,11,17,23,29,35-Hexakis(1,1-dimethylethyl)-37,39,41-trimethoxy-heptacyclo[31.3.1.1^{3,7}.1^{9,13}.1^{15,19}.1^{21,25}.1^{27,31}]octetraconta-1(37),3,5,7(42),9,11,13(41),15,17,19(40),21,23,25(39),27,29,31(38),33,35-octadecaene-38,40,42-triol (**3**)

To a stirred solution of *p-tert*-butylcalix[6]arene 1 (3.0 g, 3.1 mmol) in dry acetone, potassium carbonate (K_2CO_3, 1.28g, 9.3 mmol) was added. The reaction mixture was heated to reflux, and methyl iodide (1.76 g, 12.4 mmol) was added. After 18 h, acetone was removed under vacuum, the residue quenched with 2N HCl (70 mL), and extracted twice with 50 mL CH_2Cl_2. The combined extracts were washed with distilled water (2×100 mL). Dichloromethane was removed under reduced pressure and the white raw product was purified on a silica gel column (eluent: hexane–THF = 9:1). The product was crystallized from CH_2Cl_2–methanol to afford 0.86 g of compound **3** (yield = 27%): mp 273–274 °C; IR υ_{max} (KBr) 3400, 2990, 1620, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (s, 27H, $C(CH_3)_3$), 1.19 (s, 27H, $C(CH_3)_3$), 3.46 (s, 9H, OCH_3), 3.87 (s, 12H, $ArCH_2Ar$), 6.77 (s, 3H, OH), 6.89 (s, 6H, ArH), 6.99 (s, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ 31.3, 31.6 (q, $C(\underline{C}H_3)_3$), 31.2 (t, $ArCH_2Ar$), 34.0, 34.1 (s, $\underline{C}(CH_3)_3$), 61.4 (q, OCH_3), 125.8 (d, Ar meta), 126.8, 132.6, 142.4, 146.9 (s, Ar), 150.0, 152.5 (s, Ar ipso); mass spectrum, 1015.0 (M^+, calcd 1014.7). Anal. calcd for $C_{69}H_{90}O_6$: C, 81.61; H, 8.93. Found: C, 81.20; H, 9.15.

37,39,41-Tris(N,N-diethylaminocarbonylmethoxy)-38, 40,42-trimethoxy-5,11,17,23,29,35-hexakis(1,1-dimethylethyl)heptacyclo-[31.3.1.1^{3,7}.1^{9,13}.1^{15,19}.1^{21,25}.1^{27,31}]octetraconta-1(37),3,5,7(42),9,11,13(41),15,17,19(40),21,23,25(39),27,29,31(38),33,35-octadecaene (**4**)

A sample of **3** (0.51 g, 0.5 mmol) was dissolved in 60 mL dry THF and 7 mL dry DMF. After addition of sodium hydride (NaH 50% in oil, 0.14 g, 3 mmol), the reaction mixture was heated at 90 °C for 0.5 h. Then α-chloro-*N,N*-diethylacetamide (0.9 g, 6 mmol) was added and the reaction mixture was refluxed for 24 h. THF was distilled off and the residue quenched with 2N HCl (50mL) and extracted twice with dichloromethane (2 × 50 mL). The organic phase was washed twice with distilled water and dichloromethane was removed under reduced pressure. The residue was crystallized from methanol to give 510 mg of white crystals (75% yield): mp 279–280 °C; IR(KBr) υ_{max} 2990, 1650 (vs), 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (s, 27H, $C(CH_3)_3$), 1.18 (t, 9H, $N(CH_2\underline{C}H_3)_2$, J = 7.0 Hz), 1.32 (t, 9H, $N(CH_2\underline{C}H_3)_2$, J = 7.0 Hz), 1.38 (s, 27H, $C(CH_3)_3$), 2.21 (s, 9H, OCH_3), 3.43 (d, 6H, H_{eq}, J = 15.3 Hz), 3.45 (q, 6H, $N(\underline{C}H_2CH_3)_2$), 3.58 (q, 6H, $N(\underline{C}H_2CH_3)_2$), 4.53 (d, 6H, H_{ax}, J = 15.3 Hz), 4.59 (s, 6H, OCH_2CO), 6.67 (s, 6H, ArH), 7.27 (s, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ 12.9, 14.6 (q, $N(CH_2\underline{C}H_3)_2$), 30.0 (t, $ArCH_2Ar$), 31.2, 31.7 (q, $C(\underline{C}H_3)_3$), 34.1, 34.3 (s, $\underline{C}(CH_3)_3$), 40.3, 42.0 (t, $N(\underline{C}H_2CH_3)_2$), 60.2 (q, OCH_3) 72.8 (t, $O\underline{C}H_2CO$), 123.8, 128.3 (d, Ar meta), 133.0, 133.6, 146.0, 146.4 (s, Ar), 152.0, 154.6 (s, Ar ipso), 167.6 (s, C=O); mass spectrum, 1353.5 (M^+, calcd 1353.9). Anal calcd for $C_{87}H_{123}N_3O_9$: C, 77.12; H, 9.15; N, 3.10. Found: C, 76.75; H, 9.52; N, 3.0.

General Procedure for the Preparation of Cation Complexes of Hexamide **2** *and Triamide* **4**

A solution of 0.02 mmol of ligand (**2** or **4**) in 1.5 mL of $CDCl_3$ was stirred with 0.1 mmol of salt picrate or thiocyanate for 24 h. The resulting suspension was filtered and the ratio between ligand and picrate was determined from intensities in the ^1H NMR spectra. To the filtrate ca. 1 mL *n*-hexane was added, and after slow evaporation the precipitate was filtered and characterized.

2·Sodium picrate (1:2) complex. ^1H NMR ($CDCl_3$) δ 1.1–1.2 (bs, 90H, $C(CH_3)_3$ and $N(CH_2\underline{C}H_3)_2$), 3.21 (q, 12H, $N(\underline{C}H_2CH_3)_2$), 3.4–3.5 (m, 18H, H_{eq} and $N(\underline{C}H_2CH_3)_2$), 4.37 (d, 6H, H_{ax}, J = 14.20 Hz), 4.68 (s, 12H, OCH_2CO), 7.06 (s, 12H, ArH), 8.75 (s, 4H, picrate); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.1 (q, $N(CH_2\underline{C}H_3)_2$), 28.8 (t, $ArCH_2Ar$), 31.3 (q, $C(\underline{C}H_3)_3$), 34.3 (s, $\underline{C}(CH_3)_3$), 40.4, 40.8 (t, $N(\underline{C}H_2CH_3)_2$), 71.6 (t, $O\underline{C}H_2CO$), 125.3, 126.3, 141.9, 162.4 (picrate), 126.5 (d, Ar meta), 132.0, 147.4 (s, Ar), 151.5 (s, Ar ipso), 168.1 (s, C=O); mass spectrum 1926.4 ((L·2Na·1 picrate)$^+$, calcd 1925.1), 1674.3 (L·Na^+, calcd 1674.1). Anal. calcd for $C_{114}H_{154}N_{12}Na_2O_{26}$: C, 63.56; H, 7.20; N, 7.80. Found: C, 63.00; H, 7.32; N, 8.05.

2· Potassium picrate (1:2) complex. ^1H NMR ($CDCl_3$) δ –1.39 and –0.73 (t, 3.4H, $N(CH_2\underline{C}H_3)_2$), 1.1–1.4 (m, 88.8H, $C(\underline{C}H_3)_3$, $N(\underline{C}H_2CH_3)_2$ and $N(CH_2\underline{C}H_3)_2$), 2.41 (s, 2.2H, OCH_2CO), 3.1–3.6 and 4.3–4.7 (m, 43.6H, $ArCH_2Ar$, $N(\underline{C}H_2CH_3)_2$, and OCH_2CO), 7.01, 7.12, 7.19, 7.26, 7.36, 7.50, 7.56 (s, 12H, ArH), 8.71 (s, 4H, picrate); mass spectrum 1729.2 (L·2K$^+$, calcd 1729.4), 1691.2 (L·K$^+$, calcd 1690.3). Anal. calcd for $C_{114}H_{154}K_2N_{12}O_{26}$: C, 62.62; H, 7.09; N, 7.68. Found C, 61.95; H, 7.30; N, 7.95.

2-Guanidinium thiocyanate (1:1) complex. IR (KBr) υ_{max} 3600–3200 (bs), 2965, 2045, 1650 (vs), 1480 cm^{-1}; ^1H NMR

($CDCl_3$) δ 1.05, 1.07, 1.39 (s, 54H, $C(CH_3)_3$), 1.1–1.2 (m, 36H, $N(CH_2C\underline{H}_3)_2$), 3.2–4.8 (m, 54H, $ArCH_2Ar$, $N(C\underline{H}_2CH_3)_2$, OCH_2CO and $C(NH_2)_3^+$), 6.48, 6.91, 7.29, 7.58 (m, 12H, ArH); mass spectrum 1711.5 ($L{\cdot}Gu^+$, calcd 1711.1). Anal. calcd for $C_{104}H_{156}N_{10}O_{12}S$: C, 70.56; H, 8.88; N, 7.9. Found C, 70.25; H, 8.62; N, 8.3.

4-Guanidinium thiocyanate (1:1) complex. IR (KBr) υ_{max} 3600–3200 (bs), 2047, 1645 (vs), 1482 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (s, 27H, $C(CH_3)_3$), 1.19 (t, 9H, $N(CH_2C\underline{H}_3)_2$), 1.27(t, 9H, $N(CH_2C\underline{H}_3)_2$), 1.38 (s, 27H, $C(CH_3)_3$), 2.26 (s, 9H, OCH_3), 3.46 (m, 18H, H_{eq} and $N(C\underline{H}_2CH_3)_2$), 4.51 (d, 6H, H_{ax}, $J = 13.8$ Hz), 4.62 (s, 6H, OCH_2CO), 6.65 (s, 6H, ArH), 7.06 (s, 6H, $N(C\underline{H}_2)_3^+$), 7.27 (s, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ 12.9, 14.4 (q, $N(CH_2\underline{C}H_3)_2$), 29.9 (t, $ArCH_2Ar$), 31.1, 31.6 (q, $C(\underline{C}H_3)_3$), 34.0, 34.3 (s, $\underline{C}(CH_3)_3$), 40.6, 41.6 (t, $N(\underline{C}H_2CH_3)_2$), 60.1 (q, OCH_3), 71.5 (t, OCH_2CO), 123.8, 128.2(d, Ar meta), 132.4 (s, SCN), 132.8, 133.5, 146.2, 146.6 (s, Ar), 151.4, 154.4 (s, Ar ipso), 158.8 (s, $\underline{C}(NH_2)_3^+$), 167.5 (s, C=O); mass spectrum 1414.3 ($L{\cdot}Gu^+$, calcd 1414.0). Anal. calcd for $C_{89}H_{129}N_7O_9S$: C, 72.56; H, 8.83;N, 6.65. Found C, 72.05; H, 8.96; N, 6.84.

Transport Measurements

Guanidinium, sodium, and potassium thiocyanates were obtained from Fluka. The guanidinium content was checked by titration, while for the sodium and potassium salts atomic absorption was used. The polymeric film Accurel® was obtained from Enka Membrana, while *o*-nitrophenyl *n*-octyl ether (NPOE) was obtained from Fluka and used without further purification.

Transport experiments were performed in thermostated (T = 25 °C) cells consisting of two identical cylindrical compartments (half-cell volume: 50 mL; effective membrane area 12.4 cm^2) previously described.[8]

The supported liquid membrane was prepared by adsorbing the solution of carrier in NPOE in a thin microporous polypropylene film (Accurel®; thickness d = 100 μm, porosity = 64%) under a high vacuum. Aqueous solutions of guanidinium, potassium, or sodium thiocyanate were used as source phase while the receiving phase consisted of double-distilled water. Every measurement was repeated at least twice. The amount of salt transported was monitored in time by measuring the conductivity (Philips PW 9527 conductivity meter and a Philips PW 9512/61 electrode with a cell constant of 0.76 cm^{-1}) in the receiving phase for single-cation transport or by atomic absorption and titration of samples taken after 24 h in the case of competitive transport. Standard deviations in transport measurements are about 15%.

Determination of the Partition Coefficient of Guanidinium Picrate between Water and $CHCl_3$

In a separatory funnel 200 mL of an aqueous solution (0.002 M) of guanidinium picrate was vigorously shaken with 300 mL of ethanol-free $CHCl_3$. After 12 h the chloroform phase was carefully separated, and evaporated to dryness. The residue was dissolved in a flask with 5 mL CH_3CN and the absorption at λ = 378 nm was measured (ε = 17700). A P_{Gu} value of 4.2×10^{-4} M^{-1} was obtained.

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