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Head-to-Head Linked Double Calix[4]arenes: Convenient Synthesis and Complexation Properties

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Combination of calix[4]arenes functionalized at the upper rim at the 5- and 17-positions with amino and formyl groups, respectively, gives a new series of “head-to-head” linked double calix[4]arenes in nearly quantitative yield. The X-ray structure of a modified double calix[4]arene is reported. The novel, highly preorganized receptor molecules complex silver(I) ions ($K_{ass} = 9.5 \times 10^5$ M^{-1} in CDCl$_3$); the selectivity of complexation was studied by supported liquid membrane transport experiments and chemically modified field effect transistor measurements.

Introduction

Our general strategy for the design of receptor molecules with enforced cavities comprises the combination of two (or more) rigid building blocks.[1−3] Double calix[4]arenes[4] coupled “head-to-head” have been reported by Arduini, Böhmer, Shinkai, and Vögtle *et al.*[5−12] The respective yields are very low or not even reported probably due to the inherent conformational flexibility in the calix[4]arene skeleton.[5−12] Moreover, all these double calix[4]arenes with enforced cavities lack the ability to complex potential guest molecules due to the absence of suitable binding sites. The combination of such shielded cavities with preorganized inwardly pointing binding sites is interesting because such molecules meet the requirements for membrane transport and sensor materials for the detection of charged guest species.[13,14]

In this paper, we describe a convenient synthesis of doubly bridged double calix[4]arene receptors in excellent yield *via* simple Schiff-base formation starting from readily available calix[4]arenes selectively functionalized at the upper rim with amino and formyl groups, respectively. The X-ray crystal structure of a double calix[4]arene is described. Furthermore, the complexation properties, including selectivity of these lipophilic preorganized receptors toward silver(I) ions were investigated by ^{1}H NMR titration experiments, FAB-MS, SLM transport (supported liquid membranes), and CHEMFET (chemically modified field effect transistor) studies.

Results and Discussion

Synthesis of Double Calix[4]arenes. Nitration of 26,28-dipropoxycalix[4]arene (**1**)[15] with NaNO$_3$, LaNO$_3$·6H$_2$O (cat.) in a mixture of CH$_2$Cl$_2$, water, and HCl gave 5,17-dinitro-26,28-dipropoxycalix[4]arene (**2**) in 56% yield. Subsequent reduction of compound **2** with hydrazine monohydrate and a catalytic amount of Raney Ni in MeOH afforded 5,17-diamino-26,28-dipropoxycalix[4]arene (**3**) in quantitative yield. 5,17-Diaminotetrapropoxycalix[4]arene (**4**)[16] and the 5,17-diformylcalix[4]arenes **5**,[17] **6**,[11] and **7**[18] were prepared according to literature procedures (Chart 1).

The coupling reaction between 5,17-diaminocalix[4]arene (**4**) and diametrical dialdehyde **5** in CH$_2$Cl$_2$ as a

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(6) Siepen, A.; Zett, A.; Vögtle, F. *Liebigs Ann.* **1996**, 757.

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(8) Double calix[4]arenes linked *via* polymethene spacers were reported by Böhmer *et al.* The authors used a stepwise synthesis in which the calix[4]arene skeleton was built up in the final step. The reported yields are very low (1−13%): Böhmer, V.; Goldmann, H.; Vogt, W.; Vicens, J.; Asfari, Z. *Tetrahedron Lett.* **1989**, *30*, 1391.

(9) The synthesis of a symmetric double calix[4]arene (12% yield) covalently linked *via* four ethylene glycol spacers at the upper rim was described by Shinkai *et al.*: Araki, K.; Sisido, K.; Hisaichi, K.; Shinkai, S. *Tetrahedron Lett.* **1993**, *34*, 8297.

(10) The multistep synthesis of a mono-CH$_2$-bridged double calix[4]arene *via* the upper rim was recently reported: Araki, K.; Hisaichi, K.; Kanai, T.; Shinkai, S. *Chem. Lett.* **1995**, 569.

(11) The only exception was recently reported by Arduini *et al.* for the synthesis of a “head-to-head” linked double calix[4]arene (42% yield). However, the X-ray structure does not show a real head-to-head orientation of the two calix[4]arene cavities due to the two flexible three-atom-long CH$_2$OCH$_2$ bridges: Arduini, A.; Fanni, S.; Manfredi, G.; Pochini, A.; Ungaro, R.; Sicuri, A. R.; Ugozzoli, F. *J. Org. Chem.* **1995**, *60*, 1448.

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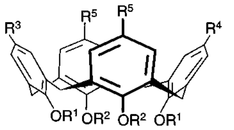
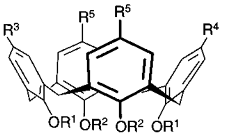
Chart 1

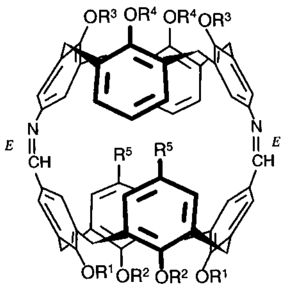


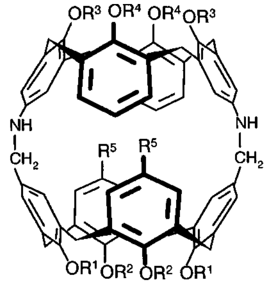
1 $R^1 = H, R^2 = Pr, R^3 = R^4 = R^5 = H$
2 $R^1 = H, R^2 = Pr, R^3 = R^4 = NO_2, R^5 = H$
3 $R^1 = H, R^2 = Pr, R^3 = R^4 = NH_2, R^5 = H$
4 $R^1 = R^2 = Pr, R^3 = R^4 = NH_2, R^5 = H$



5 $R^1 = R^2 = Pr, R^3 = R^4 = CHO, R^5 = NO_2$
6 $R^1 = R^2 = CH_2CH_2OEt, R^3 = R^4 = CHO, R^5 = H$
7 $R^1 = H, R^2 = Pr, R^3 = R^4 = CHO, R^5 = H$

Chart 2



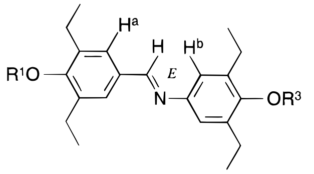


8 $R^1 = R^2 = R^3 = R^4 = Pr, R^5 = NO_2$
9 $R^1 = R^2 = Pr, R^3 = R^4 = CH_2CH_2OEt, R^5 = H$
10 $R^1 = R^3 = H, R^2 = R^4 = Pr, R^5 = H$
11 $R^1 = R^2 = R^3 = R^4 = Pr, R^5 = NO_2$
12 $R^1 = R^2 = Pr, R^3 = R^4 = CH_2CH_2OEt, R^5 = H$

solvent provided double calix[4]arene **8** in 92% yield after recrystallization from CH_2Cl_2/MeOH (Chart 2). High dilution conditions for the formation of this Schiff-base-based double calix[4]arene are not required, since different reaction concentrations (1.6 and 2.3 mM) gave the same result. When the reaction was performed with a 1:2 ratio (instead of 1:1) of diamine **4** and dialdehyde **5**, only double calix[4]arene **8** and unreacted dialdehyde **5** could be detected in the ^{1}H NMR spectrum of the crude evaporated reaction mixture. Double calix[4]arene **9** was prepared similarly starting from diaminocalix[4]arene **4** and dialdehyde **6** in 75% yield after recrystallization.[19] Compared to the NO_2-substituted derivative **8**, double calix[4]arene **9** provides larger portals.

The cone conformation of the calix[4]arene skeleton can be stabilized *via* intramolecular proximal OH···hydrogen bridges at the lower rim.[20] In order to make use of this stabilization effect, Schiff-base condensation of 5,17-diamino-26,28-dipropoxycalix[4]arene (**3**) and 5,17-diformyl-26,28-dipropoxycalix[4]arene (**7**), both diametrically substituted with OH groups at the lower rim, was carried out to give the double calix[4]arene **10** in 74% yield.[21]

Chart 3. Part of the Double Calix[4]arene Structures 8−10 To Point Out the *E* Stereochemistry



The two imine bridges of double calix[4]arenes **8** and **9** can easily be reduced with an excess of $NaBH_4$ at room temperature in a mixture of EtOH and THF to the more flexible amines **11** and **12**, respectively, in good yields (87% and 95%, respectively).[22] Reduction at higher temperatures also partly affected the nitro groups of **11**.

The structures of **2**, **3**, and **8**−**12** were confirmed by ^{1}H NMR, ^{13}C NMR, FAB-MS, and elemental analyses.

In the ^{1}H NMR spectra of **8**−**10** only one signal was observed for the imine hydrogens CH=N. The Schiff-base double calix[4]arenes **8**−**10** are exclusively present as *E,E* isomers with respect to the imine bonds. NOE experiments were performed for compound **9** as a representative example in $CDCl_3$ at −65 °C. The Schiff-base proton shows strong NOE contacts of almost the same intensity with the aromatic hydrogens H^a and H^b which unequivocally proves the *E* configuration.[23] CPK models confirm that the respective *Z,E* and *Z,Z* isomers are unlikely due to geometrical restrictions. ^{1}H ROESY and TOCSY experiments were performed for the ^{1}H NMR spectral assignments (for compounds **8** and **11** as representatives). In $CDCl_3$ the ^{1}H NMR spectra of the double calix[4]arenes **8** and **9** show two singlets for the aromatic hydrogens (H^a and H^b, Chart 3) bearing the imine bridges at unusually high field [$\delta = 6.40$ (H^a), $\delta = 5.83$ (H^b) for **8**, $\delta = 6.37$ (H^a), $\delta = 5.84$ (H^b) for **9**]. Also the imine protons of **8** and **9** absorb at high field ($\delta = 6.94$ for **8**, $\delta = 6.89$ for **9**). These characteristic shifts correspond to a pinched cone conformation of double calix[4]arenes **8** and **9** in solution, which is in agreement with the solid state structure (*vide infra*) of the reduced Schiff-base **11**.[24−26] The two opposite aromatic rings substituted with the imine groups are fixed in close proximity ("parallel") which results in shielding of these aromatic hydrogens.

The ^{1}H NMR spectrum of double calix[4]arene **10** shows the presence of cone conformations of the two calix[4]arene moieties, stabilized *via* OH···OR hydrogen bonds at the original lower rims. The aromatic hydrogen atoms

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[19] Besides 5,17-diformyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (**6**)—synthesized according to the literature procedure[11]—the respective proximal 5,11-diformyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene isomer was present in about 30% according to the ^{1}H NMR and the FAB-MS spectra.

[20] For the stabilization of the cone conformation of calix[4]arenes *via* proximal OH···OR hydrogen bonds at the lower rim, see for example: Bugge, K.-E.; Verboom, W.; Reinhoudt, D. N.; Harkema, S. *Acta Crystallogr.* **1992**, *C48*, 1848.

[21] As can be expected, the stability of double calix[4]arene **10** toward air oxidation is limited due to the formation of quinoid systems and probably as well due to the presence of acidic phenol protons in combination with the imine bonds. The ^{1}H NMR spectrum of a 4-week-old sample showed decomposition of **10**. Also diamine **3** decomposed (oxidation) by contact with air.

[22] The direct synthesis of double calix[4]arene **11** *via* reductive amination starting from diamine **4** and dialdehyde **5** with $NaBH_3CN$ in THF as a solvent resulted in many side products. Double calix[4]arene **11** could be isolated only in low yield (<10%) after several purification steps.

[23] In the case of a *Z* configuration, no NOE contact of the CH=N proton with the aromatic hydrogen H^b is possible due to the longer distance.

[24] For very recent discussions on the pinched cone conformation of calix[4]arenes in solution, see refs 17b and 25.

[25] Scheerder, J.; Vreekamp, R. H.; Engbersen, J. F. J.; Verboom, W.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 3476.

[26] A respective singly bridged double calix[4]arene was synthesized by following the same procedure as described for **8** using monoaldehyde− and monoamine−calix[4]arene derivatives. However, this model compound shows a conformationally mobile situation in $CDCl_3$ as a solvent. The respective aromatic hydrogens H^a and H^b and the imine proton absorb at the usual, lower field.

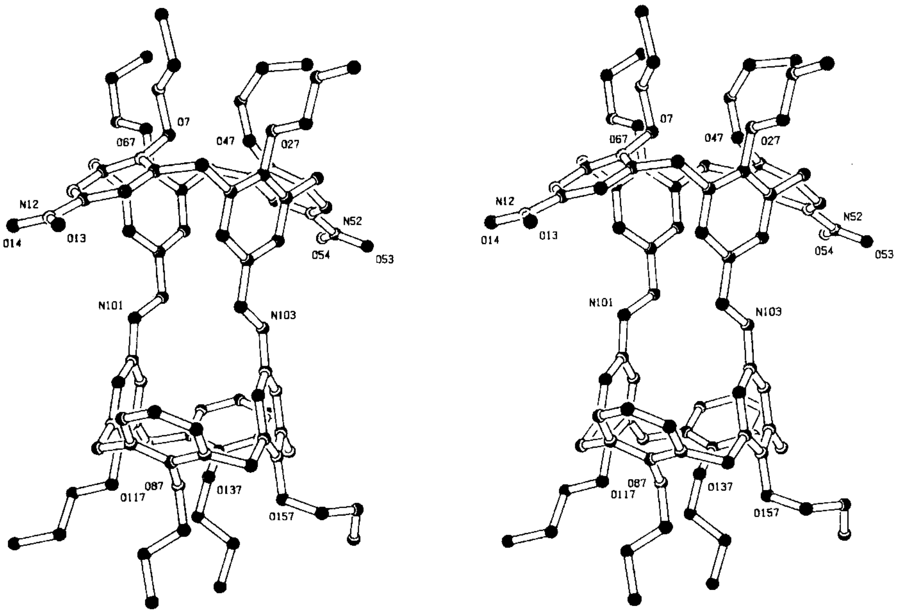

Figure 1. Stereoscopic view of the X-ray crystal structure of double calix[4]arene **11** (the H atoms and the cocrystallized solvent molecules are omitted for clarity).

H^a and H^b of **10** absorb at normal values of $\delta = 7.62$ and 7.02, respectively, and are not influenced by shielding effects as observed for the double calix[4]arenes **8** and **9** present in the pinched cone conformation. Therefore, the size of the present cavity of double calix[4]arene **10** can be controlled *via* the lower rim of the two calix[4]arene subunits.

X-ray Structure Analysis. The X-ray structure analysis unambiguously proves the structure of the "nonsymmetric" reduced Schiff-base **11** in the solid state (Figure 1). Suitable single crystals of double calix[4]arene **11** could be obtained by slow diffusion of MeOH into a CH_2Cl_2 solution of **11**. Both calix[4]arene moieties of double calix[4]arene **11** adopt a pinched cone conformation in the solid state in which the aromatic nuclei bearing the reduced Schiff-base bridges are oriented parallel (interplanar angles 19° and 16°) whereas the remaining aromatic units are "flattened" (interplanar angles 117° and 106°).[17b] The two calix[4]arene cavities are oriented head-to-head due to the short bridging spacers. The intramolecular N(101)···N(103) distance is 4.39(1) Å.

The two calix[4]arene subunits are slightly twisted around the CH_2NH bridges. Double calix[4]arene **11** has a noncrystallographic, approximate C_2 symmetry.[27]

Complexation Studies. The combination of two highly preorganized soft binding sites (imine units) surrounded by two lipophilic calix[4]arene moieties provides the requirements for the complexation of soft metal cations such as silver(I) ions.[28,29] Addition of increasing amounts of silver(I) triflate to a solution of **8** and **9** in $CDCl_3/CD_3OD$ (4/1 (v/v)) caused significant changes in the ^1H NMR spectra (Figure 2). The signals of the imine protons CH=N and the adjacent aromatic protons H^a shift significantly downfield and the aromatic protons H^b to higher field. The association constant of the complex $\mathbf{9}\cdot Ag^+$ is $9.5 \times 10^5\ M^{-1}$ in $CDCl_3/CD_3OD$ (4/1 (v/v)). The corresponding Job plot proved its 1:1 stoichiometry. In agreement with the ^1H NMR experiments, the FAB-MS spectra (*m*-NBA matrix) of receptors **8** and **9** in the presence of an excess of silver(I) triflate show peaks of 100% intensity for the silver(I) complexes at *m*/*z* 1433.5 ($[M + Ag]^+$) (calcd 1433.6) and 1463.8 ($[M + Ag]^+$) (calcd 1463.6), respectively.

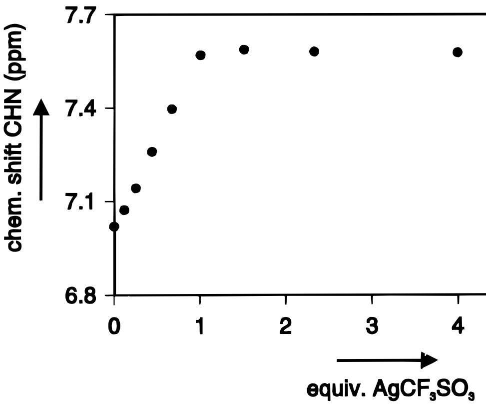

Figure 2. Curve of the titration experiment between receptor **9** and $AgCF_3SO_3$ in $CDCl_3/CD_3OD$ (4/1 (v/v)).

Membrane Transport. In order to evaluate the properties of receptor **9** as a carrier for Ag^+ in SLMs, the facilitated transport of different monovalent nitrate salts was carried out.[13,30] Transport of silver salts through SLMs has been reported previously by Tromp, Tsukube, Bromberg, and Nabeshima *et al.* because of industrial interest in the separation of silver from waste stream effluents.[31] The individual transport rates have been

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[27] For the first X-ray crystal structure of a self-assembled, hydrogen-bonded calix[4]arene dimer *via* the upper rim, see ref 17b.

[28] An X-ray structure of a double calix[4]arene in the 1,3-alternate conformation was very recently reported by de Mendoza *et al.* The authors also described qualitative studies of silver(I) ion complexation: Pérez-Adelmar, J.-A.; Abraham, H.; Sánchez, C.; Rissanen, K.; Prados, P.; de Mendoza, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1009.

[29] For a recent guest-binding study of pyridinium salts with a mono-CH_2-bridged double calix[4]arene, see ref 10 and literature cited therein.

[30] The solubility of double calix[4]arene **8** in the membrane matrix (*o*-NPOE) is limited; therefore, the more soluble double calix[4]arene **9** was used for the membrane transport studies.

[31] (a) Tromb, M.; Burgard, M.; Leroy, M. J. F.; Prefost, M. *J. Membr. Sci.* **1988**, *38*, 295. (b) Tsukube, H.; Adachi, H.; Morosawa, S. *J. Org. Chem.* **1991**, *56*, 7102. (c) Bromberg, L.; Levin, G.; Kedem, O. *J. Membr. Sci.* **1992**, *71*, 41. (d) Nabeshima, T.; Tsukada, N.; Nishijima, U.; Ohshiro, H.; Yano, Y. *J. Org. Chem.* **1996**, *61*, 4342.

Table 1. Transport Rates of Monovalent Cations as Nitrate Salts through Supported Liquid Membrane Containing Receptor 9[a]

salt	transport rate J_0 (10^{-8} mol m^{-2} s^{-1})
$AgNO_3$[b]	46
$NaNO_3$[b]	1.1
KNO_3[b]	1.4
$CsNO_3$[b]	<1

[a] The membrane phase consisted of a 0.01 [M] solution of the receptor in *o*-nitrophenyl *n*-octyl ether (*o*-NPOE) immobilized in Accurel as polymeric support. [b] The aqueous source phase consisted of a 0.1 [M] salt solution at neutral pH.

Table 2. Competitive Transport of $AgNO_3$ by Receptor 9 in the Presence of Alkali Metal Ions at Neutral pH

initial metal ion concentration in the source phase [M]		metal ion concentration in the receiving phase after 36 h of transport [M]	
Na^+	Ag^+	Na^+	Ag^+
0.52	5.1×10^{-3}	$<5 \times 10^{-6}$	2.9×10^{-4}
K^+	Ag^+	K^+	Ag^+
0.25	5.2×10^{-3}	$<5 \times 10^{-6}$	3.1×10^{-4}

determined from the initial flux J_0, which is related to the first derivative of the ion activity in the receiving phase as a function of time (eq 1). V_r is the volume of

$$J_0 = \frac{V_r}{A_m}\frac{da_r}{dt} \qquad (1)$$

the receiving phase, A_m is the area of the membrane surface, and a_r is the activity in the receiving phase. The initial fluxes are summarized in Table 1.

From Table 1 it can be seen that the transport rate for $AgNO_3$ is significantly higher than that for other monovalent cations. Repeated transport experiments with the same membrane did not result in a significant decrease of transport, which indicates that the membrane phase is stable under the experimental conditions. In competition experiments, the transport of Ag^+ was examined from a solution in which a large excess (50–100-fold) of alkali metal ions was present. After 36 h of transport, the aqueous receiving phase was analyzed by atomic absorption spectrometry. From these results (Table 2), it can be concluded that highly selective transport of $AgNO_3$ in the presence of $NaNO_3$ or KNO_3 can be achieved.

The transport mechanism was investigated in more detail.[32,33] In Figure 3 the transport rate J_0 is plotted as a function of the carrier concentration in the membrane. Without carrier, no transport of $AgNO_3$ is observed; however, upon addition of ligand **9** transport does occur and the transport rate J_0 increases linearly with the carrier concentration. This is indicative for carrier facilitated transport of the $AgNO_3$.

The transport rate J_0 as a function of the initial $AgNO_3$ concentration in the source phase is depicted in Figure 4. When the $AgNO_3$ concentration is increased, J_0 increases until it reaches a maximum at higher salt concentrations when the membrane at the source phase interface is "saturated" with Ag^+-complex.

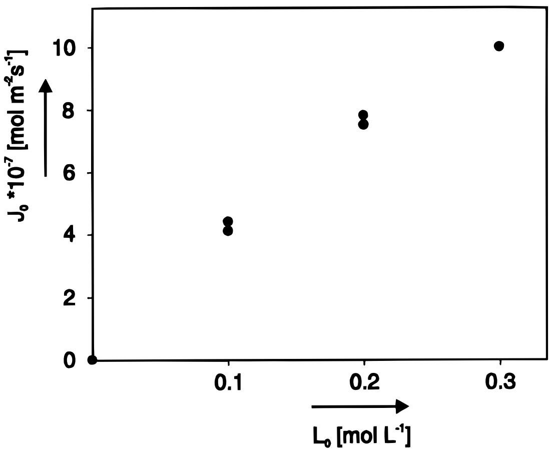

Figure 3. Transport rate J_0 as a function of the carrier concentration in the membrane phase.

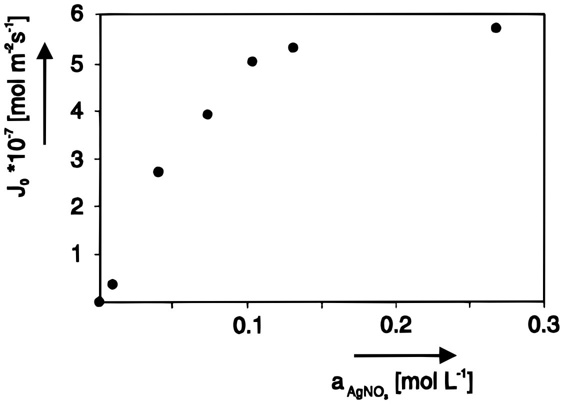

Figure 4. Transport rate J_0 as a function of the initial source phase concentration of $AgNO_3$.

A general expression for the transport rate J_0 in the case of diffusion limited facilitated transport of salts is given by eq 2.[32] J_0 is the initial flux at a certain salt

$$J_0 = \frac{D_m}{2d_m}\left(-K_{ex}[M^+]^2_{aq} + \sqrt{(-K_{ex}[M^+]^2_{aq})^2 + 4K_{ex}[M^+]^2_{aq}[L_0]_m}\right) \qquad (2)$$

concentration $[M^+]_{aq}$ in the aqueous phase, d_m is the membrane thickness, L_0 represents the total carrier concentration in the membrane, D_m is the apparent diffusion constant, and K_{ex} is the extraction constant. The function represented by eq 2 was fitted to the experimental data points that are depicted in Figure 4 to give the transport parameters $D_m = 6.3 \times 10^{-12}$ m^2 s^{-1} and $K_{ex} = 4.9$ M^{-1}. The diffusion coefficient was also determined independently from lag-time experiments.[31c,33] The lag time is defined as the time required for the complex to diffuse through the membrane from the source phase to the receiving phase. The corresponding diffusion constant D_m can be calculated according to eq 3, where θ is the porosity and d_m is the thickness of the membrane. A lag time of $t_{lag} = 620$ s corresponds to a diffusion coefficient of $D_m = 6.9 \times 10^{-12}$ m^2 s^{-1}. This is in good agreement with the diffusion coefficient obtained from the initial flux model ($D_m = 6.3 \times 10^{-12}$ m^2 s^{-1}).

$$D_m = \frac{\theta d_m^2}{6t_{lag}} \qquad (3)$$

The diffusion coefficient is a factor of 2 lower than that in the case of alkali metal ion transport by calix[4]arene

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[32] Nijenhuis W. F.; Buitenhuis, E. G.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 7963.

[33] Reichwein-Buitenhuis, E. G.; Visser, H. C.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 3913.

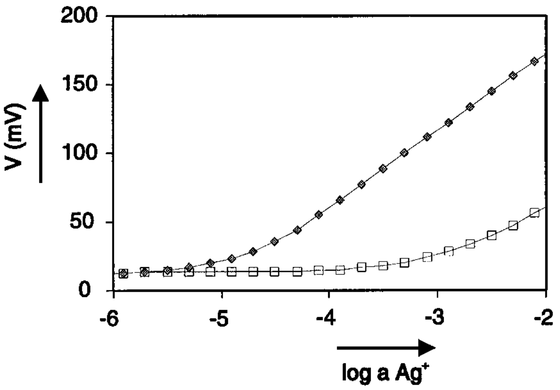


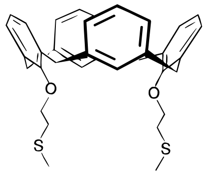
Figure 5. Ag^+ response of CHEMFETs containing ionophore **8** in the presence of $Cd(NO_3)_2$ at (□) pH = 4 (0.01 M Cd^{2+}) and (◆) pH = 5.5 (0.1 M Cd^{2+}).

Table 3. Response Characteristics of Ag^+-Selective CHEMFETs in the Presence of Various Interfering Ions *j*

	log $K_{Ag,j}^{pot}$ (slope mV/dec)		
interfering ion, *j*	**8** pH = 4	**8** pH = 5.5	**13** (ref 38)[c] pH = 4
0.1 M K^+	−1.7 (43)	−3.6 (55)	−4.7 (55)[a]
0.1 M Ca^{2+}	−2.0 (46)	−4.4 (55)	−4.5 (56)
0.1 M Cd^{2+}	−2.4 (48)[b]	−4.3 (57)	−4.2 (56)

[a] M interfering ion. [b] 0.01 M interfering ion.

[c]



13

crown carriers.[34,35] This can be explained by the increased size of the carrier, since **9** has two calix[4]arene units. The size is inversely related to the diffusion coefficient as described by the Stokes−Einstein relation.

CHEMFET Measurements. The selectivity of an ionophore may also be evaluated using the transduction of a selective recognition process into an electronic signal. This can be achieved by measurements with chemically modified field effect transistors (CHEMFETs).[14]

Calix[4]arene **8** incorporated in plasticized PVC CHEMFETs is selective for Ag^+ ions in the presence of excess of alkali or alkaline earth ions (K^+ and Ca^{2+}) with log $K_{Ag/K} = -3.6$ and log $K_{Ag/Ca} = -4.4$, respectively. The slopes of the response curves are near Nernstian at pH 5.5 (Table 3).[36−38]

The sensors are also selective for Ag^+ in the presence of 0.1 M cadmium ions (log $K_{Ag/Cd} = -4.3$, pH 5.5) which is comparable to a value of log $K_{Ag/Cd} = -4.2$ (pH 4) obtained for 25,27-bis[2-(methylthio)ethoxy]calix[4]arene[38] (**13**) (Table 3, Figure 5). The higher selectivity for Ag^+ is probably explained by a better fit of the cation and the nitrogen donating atoms of the ligand. In general the selectivities for Ag^+ are lower at pH 4 because of protonation of the nitrogen atoms of the ionophore **8** (Table 3).

Conclusions

It has been shown that the head-to-head condensation of upper-rim functionalized aminocalix[4]arenes with formylcalix[4]arenes comprises a convenient method for the synthesis of a new class of synthetic receptor molecules in high yield with highly preorganized binding sites for cations like silver(I). The short two-atom-long bridges are causing a relatively rigid head-to-head arrangement of the two calix[4]arene moieties. The double calix[4]arenes **8** and **9** show a very high affinity for silver(I) ions, which was proven by ^1H NMR titration experiments ($K_{ass} = 9.5 \times 10^5$ M^{-1} for receptor **9**) in $CDCl_3$. Membrane transport experiments and CHEMFET studies confirm the selective transport and complexation, respectively, of silver(I) ions also in the presence of interfering ions.

Experimental Section

Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless stated otherwise) at 250 and 400 MHz using residual solvent protons as internal standard. Chemical shifts are reported in ppm (δ). ROESY, TOCSY, and NOESY ^1H NMR spectra were recorded on the 400 MHz spectrometer. For the *n*-propoxy and ethoxyethoxy tails, no *J* values were determined. Fast atom bombardment (FAB) mass spectra were recorded using *m*-nitrobenzyl alcohol (*m*-NBA), *o*-nitrophenyl octyl ether (*o*-NPOE), or *threo*-1,4-dimercapto-2,3-butanediol (DTT)/*erythro*-1,4-dimercapto-2,3-butanediol (DTE) as a matrix. THF was freshly distilled from Na/benzophenone ketyl. Commercial CH_2Cl_2 was distilled over $CaCl_2$ and then stored for at least 1 day over molecular sieves (4 Å). All other solvents and chemicals were of reagent grade and were used without further purification. Flash chromatography was performed with silica gel 60 (0.040−0.063 mm, 230−400 mesh), and preparative LC were performed on precoated silica plates (SiO_2, 2 mm, Merck, $60F_{254}$). All reactions were carried out under an argon atmosphere unless otherwise stated. For reasons of clarity and to reduce space, the name calix[4]arene was used instead of the official IUPAC name: pentacyclo[$19.3.1.1^{3,7}.1^{9,13}.1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecane. Samples were prepared for elemental analysis by being dried overnight over P_2O_5 at 80 °C *in vacuo*. The presence of solvent in the analytical samples was confirmed by ^1H NMR spectroscopy. Dipropoxy- (**1**),[15] diamino- (**4**),[16] and diformylcalix[4]arenes (**5**),[17] **6**,[11] and **7**[18] were synthesized according to literature procedures. Aminophenol (**3**) was freshly prepared before use.

5,17-Dinitro-26,28-dipropoxycalix[4]arene (2). To a solution of 26,28-dipropoxycalix[4]arene (**1**) (1.00 g, 1.97 mmol) in CH_2Cl_2 (40 mL) was added a solution of $NaNO_3$ (0.66 g, 7.76 mmol) and a catalytic amount of $LaNO_3{\cdot}6H_2O$ in a mixture of H_2O (25 mL) and concentrated HCl (4 mL). The mixture was stirred at rt for 15 h. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with NH_4Cl solution (2 × 20 mL), dried over $MgSO_4$, and crystallized from CH_2Cl_2/MeOH. The crude product was purified by flash chromatography (CH_2Cl_2/hexanes, 1/1) to give pure **2** as a yellow powder in 56% yield: mp >320 °C dec; ^1H NMR δ 9.44 (s, 2 H), 8.05 (s, 4 H), 7.00 (d, 4 H, $J = 7.5$ Hz), 6.85 (d, 2 H, $J = 7.3$ Hz), 4.30 and 3.51 (ABq, 8 H, $J = 13.2$ Hz), 4.03 (t, 4 H), 2.11−2.03 (m, 4 H), 1.33 (t, 6 H); ^{13}C NMR δ 159.7, 151.7, 139.8, 131.9, 129.7, 128.3, 125.9, 124.6, 78.8, 31.3, 23.5, 10.9; FAB-MS (NBA) *m/z* 599.4 ([M +

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(37) Also more lipophilic thioethers have been described. Wróblewski, W.; Brzózka, Z. *Sens. Actuators B* **1995**, *26−27*, 183.

(38) Calix[4]arenes having two diametrically substitued thioether functionalities have also shown to be selective for Ag^+ even in the presence of Hg^{2+} ions. Cobben, P. L. H. M.; Egberink, R. J. M.; Bomer, G.; Bergveld, P.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1992**, *114*, 10573.

H]$^+$, calcd 599.2). Anal. Calcd for $C_{34}H_{34}N_2O_8$: C, 68.34; H, 5.72; N, 4.68. Found: C, 68.22; H, 5.84; N, 4.62.

5,17-Diamino-26,28-dipropoxycalix[4]arene (3). A suspension of 5,17-dinitro-26,28-dipropoxycalix[4]arene (**2**) (400 mg, 0.67 mmol), hydrazine monohydrate (1.5 mL), and a catalytic amount of Raney Ni in MeOH (100 mL) was refluxed for 7 h. The reaction mixture was allowed to cool to rt and filtered over Celite, and the solvent was evaporated under reduced pressure. The residue was taken up in CH_2Cl_2 (100 mL), washed with water (3 × 30 mL), and dried over Na_2SO_4. After filtration, the solvent was evaporated to give pure **3** in 98% yield: mp >320 °C; ^{1}H NMR δ 7.64 (s, 2 H), 6.93 (d, 4 H, $J = 7.5$ Hz), 6.75 (t, 2 H, $J = 7.0$ Hz), 6.46 (s, 4 H), 4.31 and 3.25 (ABq, 8 H, $J = 12.8$ Hz), 3.94 (t, 4 H), 3.18 (br s, 4 H), 2.06 (dt, 4 H), 1.28 (t, 6 H); ^{13}C NMR δ 152.1, 146.2, 138.1, 133.7, 129.1, 128.8, 125.1, 115.9, 78.3, 31.5, 23.4, 10.9; CI-MS (NH_3) *m*/*z* 538.3 (M$^+$, calcd for $C_{34}H_{38}N_2O_4$ 538.3). A satisfactory elemental analysis could not be obtained.

Double Calix[4]arene 8. A solution of dialdehyde **5** (369 mg, 0.50 mmol) and diamine **4** (311 mg, 0.50 mmol) in CH_2Cl_2 (250 mL) was refluxed for 3 days (Ott apparatus, molecular sieves (4 Å)). Subsequent evaporation of the solvent and crystallization of the residue from CH_2Cl_2/MeOH afforded double calix[4]arene **8** as light yellow microcrystals in 92% yield: mp >320 °C (from CH_2Cl_2/MeOH); ^{1}H NMR δ 8.17 (s, 4 H), 7.13 (d, 4 H, $J = 7.3$ Hz), 6.98 (t, 2 H, $J = 6.9$ Hz), 6.94 (s, 2 H), 6.40 (s, 4 H), 5.83 (s, 4 H), 4.46 and 3.29 (ABq, 8 H, $J = 13.8$ Hz), 4.39 and 3.10 (ABq, 8 H, $J = 13.2$ Hz), 4.16, 4.03, 3.64, 3.57 (t, 16 H), 2.04−1.80 (m, 16 H), 1.10, 1.07, 0.90, 0.87 (t, 24 H); ^{13}C NMR δ 163.9, 157.8, 157.2, 154.3, 153.3, 144.3, 142.3, 137.5, 136.8, 133.5, 132.2, 131.9, 128.8, 127.6, 124.7, 122.0, 119.7, 77.2, 77.1, 76.5, 31.0, 30.9, 23.5, 23.1, 22.9, 10.9, 10.8, 9.8, 9.7; FAB-MS (NBA) *m*/*z* 1326.2 ([M + H]$^+$, calcd 1325.7). Anal. Calcd for $C_{82}H_{92}N_4O_{12}\cdot 0.25H_2O$: C, 73.79; H, 7.02; N, 4.20. Found: C, 73.88; H, 7.02; N, 4.22.

Double calix[4]arene 9[19] was synthesized by following the same procedure as described for **8**, refluxing a solution of dialdehyde **6** (500 mg, 0.65 mmol) and diamine **4** (446 mg, 0.72 mmol) in CH_2Cl_2 (300 mL) for 3 days: light yellow microcrystalline powder; 75% yield (refered to 1,3-dialdehyde **6**); mp 294−296 °C (from CH_2Cl_2/MeOH); ^{1}H NMR δ 7.20 (d, 4 H, $J = 7.4$ Hz), 7.13 (d, 4 H, $J = 7.3$ Hz), 7.03 (t, 2 H, $J = 7.0$ Hz), 6.97 (t, 2 H, $J = 7.1$ Hz), 6.89 (s, 2 H), 6.37 (s, 4 H), 5.84 (s, 4 H), 4.47 and 3.13 (ABq, 8 H, $J = 13.5$ Hz), 4.40 and 3.10 (ABq, 8 H, $J = 13.0$ Hz), 4.28, 4.04 (t, 8 H), 3.91−3.84, 3.76−3.72, 3.60−3.45 (m, 24 H), 2.05−1.96, 1.88−1.80 (m, 8 H), 1.23, 1.15, 1.08, 0.88 (t, 24 H); ^{13}C NMR δ 158.1, 157.8, 156.9, 155.4, 152.9, 145.0, 136.9, 136.5, 133.6, 131.5, 129.2, 128.7, 127.5, 122.3, 121.8, 119.7, 77.4, 77.2, 73.8, 72.4, 69.7, 69.5, 66.6, 66.2, 31.1, 30.8, 23.5, 22.9, 15.4, 15.2, 10.9, 9.8; FAB-MS (NBA) *m*/*z* 1355.8 ([M + H]$^+$, calcd 1355.7). Anal. Calcd for $C_{86}H_{102}N_2O_{12}\cdot 0.5H_2O$: C, 75.69; H, 7.61; N, 2.05. Found: C, 75.57; H, 7.52; N, 1.99.

Double calix[4]arene 10[39] was synthesized by following the same procedure as described for **8**, reaction of dialdehyde **7** (150 mg, 0.27 mmol) and diamine **3** (140 mg, 0.27 mmol) in a mixture of $CHCl_3$ (50 mL) and CH_3CN (100 mL) for 2.5 days. The precipitate was isolated by filtration over a P4 glass filter to afford double calix[4]arene **10** as light yellow powder in 74% yield: mp >320 °C; ^{1}H NMR δ 8.87, 8.42, 8.32 (s, 6 H), 7.62 (s, 4 H), 7.02 (s + d, 12 H, $J = 7.4$ Hz), 6.76 (t, 4 H, $J = 7.4$ Hz), 4.35 and 3.49 (ABq, 8 H, $J = 12.5$ Hz), 4.32 and 3.41 (ABq, 8 H, $J = 12.9$ Hz), 4.10−3.98 (m, 8 H), 3.49, 3.41 (2 d, 8 H, $J = 13.1$ and 12.9 Hz), 2.20−2.03 (m, 8 H), 1.35 (t, 12 H); FAB-MS (DTT/DTE) *m*/*z* 1068.8 ([M + 2H]$^+$, calcd 1068.5). Anal. Calcd for $C_{70}H_{70}N_2O_8\cdot 0.25H_2O$: C, 78.44; H, 6.63; N, 2.61. Found: C, 78.38; H, 6.65; N, 2.49.

Double Calix[4]arene 11. A suspension of double calix[4]arene **8** (200 mg, 0.15 mmol) and $NaBH_4$ (400 mg, 10 mmol, added in three portions) in a mixture of EtOH (50 mL) and THF (50 mL) was stirred for 54 h at rt. Subsequently the reaction mixture was quenched with acetic acid (pH ≈ 5) and evaporated to dryness under reduced pressure. The residue was taken up in CH_2Cl_2 (50 mL), washed with water (3 × 25 mL), and dried over Na_2SO_4. After filtration, the solvent was evaporated and the crude product was purified by PTLC (CH_2Cl_2) to give pure **11** as a yellow-orange powder in 87% yield: mp >320 °C (from CH_2Cl_2/MeOH); ^{1}H NMR δ 8.11 (s, 4 H), 7.17 (d, 4 H, $J = 7.3$ Hz), 7.02 (t, 2 H, $J = 6.8$ Hz), 5.93 (s, 4 H), 5.39 (s, 4 H), 4.46 and 3.27 (ABq, 8 H, $J = 14.0$ Hz), 4.40 and 3.08 (ABq, 8 H, $J = 13.7$ Hz), 4.18, 4.03, 3.64, 3.59 (t, 16 H), 2.94 (s, 4 H), 2.03−1.77 (m, 18 H), 1.10, 1.08, 0.92, 0.87 (t, 24 H); ^{13}C NMR δ 163.8, 158.0, 154.2, 149.0, 142.7, 142.2, 137.8, 137.0, 133.9, 133.6, 131.7, 129.0, 125.9, 124.4, 121.7, 114.9, 77.4, 77.1, 76.4, 49.6, 31.1, 23.5, 23.1, 22.9, 10.9, 10.8, 9.8; FAB-MS (ONPOE) *m*/*z* 1329.9 ([M + H]$^+$, calcd 1329.7). Anal. Calcd for $C_{82}H_{96}N_4O_{12}\cdot 0.25H_2O$: C, 73.82; H, 7.29; N, 4.20. Found: C, 73.77; H, 7.16; N 4.11.

Double calix[4]arene 12 was synthesized by reaction of double calix[4]arene **9** (60 mg, 0.044 mmol) and $NaBH_4$ (100 mg, 2.64 mmol, added in three portions) in a mixture of EtOH (10 mL) and THF (10 mL) for 30 h at rt. Workup as described for **11** gave pure double calix[4]arene **12** as a white powder in 95% yield: mp 102−104 °C; ^{1}H NMR δ 7.14 (d, 8 H, $J = 7.3$ Hz), 7.04−6.96 (m, 4 H), 5.94 (s, 4 H), 5.39 (s, 4 H), 4.46 and 3.10 (ABq, 8 H, $J = 13.0$ Hz), 4.41 and 3.09 (ABq, 8 H, $J = 12.8$ Hz), 4.30, 4.04 (t, 8 H), 3.94−3.87, 3.79−3.75, 3.62−3.47 (m, 24 H), 2.93 (s, 4 H), 2.04−1.80 (m, 10 H), 1.84 (q, 8 H), 1.25, 1.17, 1.09, 0.88 (t, 24 H); ^{13}C NMR δ 158.1, 158.0, 153.8, 148.7, 143.2, 137.2, 136.9, 133.4, 133.3, 128.9, 128.8, 125.7, 122.0, 121.5, 114.5, 77.1, 76.5, 74.0, 72.4, 69.7, 66.5, 66.2, 50.0, 31.2, 30.9, 23.5, 22.9, 15.4, 15.3, 10.9, 9.8; FAB-MS (NBA) *m*/*z* 1359.7 ([M + H]$^+$, calcd 1359.8). Anal. Calcd for $C_{86}H_{106}N_2O_{12}\cdot 0.5H_2O$: C, 75.46; H, 7.88; N, 2.05. Found: C, 75.57; H, 8.02; N, 1.85.

Association Constant. The determination of the association constant was performed by mixing 1.14×10^{-2} mol dm^{-3} solutions of host and guest in $CDCl_3/CD_3OD$ (4/1 (v/v)) in nine different ratios (1:9−9:1) and monitoring the chemical shift. Quantitatively following the chemical shift differences of the imine proton signals as a function of the host−guest ratio gave a perfect fit to 1:1 binding isotherms. The K_{ass} value was obtained with a nonlinear two-parameter fit of the chemical shift of the complex and the association constant.[40]

Membrane Transport. The polymeric film Accurel was obtained from Enka Membrana. *o*-Nitrophenyl *n*-octyl ether (*o*-NPOE) was purchased from Fluka and was used without further purification. 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 published elsewhere.[41] Doubly distilled and deionized water was used as receiving phase. Supported liquid membrane consisted of a thin microporous polypropylene film (Accurel, thickness d = 100 μm, porosity 64%) immobilizing the solution of the carrier in *o*-NPOE. The measurements were performed at 25 ± 0.1 °C at least in duplicate. Salt activities were calculated according to the Debye−Hückel theory.[42]

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 nitrates used were of analytical grade (Merck-Schuchardt). All solutions were made with deionized, doubly distilled water.

CHEMFETs were prepared from ISFETs 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.[43,44] The modified

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[39] Due to the low solubility of **10** in $CDCl_3$, CD_2Cl_2, and DMSO-d_6 (also slow decomposition), no reliable ^{13}C NMR spectrum could be obtained.

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Table 4. Experimental Data for the X-ray Diffraction Study of 11

formula	$C_{82}H_{96}N_4O_{12}\cdot 2CH_2Cl_2$
crystal system	monoclinic
space group	$C2/c$
T	140 K
a (Å) [a]	22.763(1)
b (Å)	20.214(1)
c (Å)	35.292(2)
β (deg)	90.49(1)
V (Å^3)	16 237(3)
Z	8
D_{calc} (g cm^{-3})	1.23
mol wt	1499.6
radiation	Cu Kα
linear abs coeff, cm^{-1}	18.2
scan mode	$\omega/2\theta$
scan width ω (deg)	$(1.4 + 0.34 \tan\theta)$
θ range (deg)	$3 < \theta < 70$
index ranges	$h = -27$ to 27, $k = 0$ to 24, $l = 0$ to 43
total data measd	16 159
unique obsd data [b]	15 902
R (%)	0.091
R_w (%)	0.120

[a] Average of least-squares refinement of repeated measurements of 25 reflection angles. [b] $R_{merge} = 0.029$ (on F_o^2), after an empirical correction with DIFABS.[48] A total of 8254 reflections with $F_o^2 > 3\sigma(F_o^2)$ was used in the refinement.

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 an 0.01 M $AgNO_3$ solution (pH 4 or 5.5, HNO_3) for 1 h, prior to solvent casting. The ion-sensitive membrane was casted 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 milliliter of THF. The THF was allowed to evaporate overnight.

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 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 (V_{gs}) via the reference electrode. A saturated calomel electrode (SCE) was used as reference, connected to the sample solution via a salt bridge filled with 1.0 M KNO_3. Ten CHEMFETs were monitored simultaneously, and the data were collected and analyzed using an Apple IIGS microcomputer. Computer-controlled switches allowed disconnection of CHEMFETs which showed a too high 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). Before starting the measurements the CHEMFETs were conditioned in 0.01 M $AgNO_3$. CHEMFETs were stabilized for 20 min after immersion in the interfering cation solution before starting the titration.

X-ray Crystallography. The X-ray measurement was carried out on an Enraf-Nonius CAD4 diffractometer using graphite-monochromated Cu Kα radiation. The crystal data and the most relevant experimental parameters used in the X-ray measurement and crystal structure analysis are reported in Table 4. The structure was solved by direct methods[45] and refined with full-matrix least squares. Disorder was found for the terminal C atoms of two of the *n*-propoxy chains. This disorder could be solved by refining two atoms with partial occupancies of 0.5/0.5 and 0.75/0.25, respectively, using isotropic thermal parameters. Two methylene chloride solvent molecules were found in the structure. The carbon atom in one of these methylene chloride molecules was disordered over two positions with equal occupancy. In the difference Fourier synthesis made at this stage, a number of peaks attributed to disordered solvent molecules were found. These atoms have been refined as carbon atoms with isotropic thermal parameters. Hydrogen atoms for the ordered part of the double calix[4]arene molecule were put at calculated positions. Positions and thermal parameters of the 82 hydrogen atoms included were not refined. The number of parameters refined was 958 [scale factor, positional parameters of all non-hydrogen atoms, (an)isotropic thermal parameters]. All calculations were done with MOLEN.[46,47]

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(47) The authors have deposited atomic coordinates for compound **11** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1 EZ, U.K.

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