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METAL ION COMPLEXATION BY TETRAESTER DERIVATIVES OF BRIDGED CALIX[4]ARENES

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A series of bridged calix[4]arenes (5–10 methylene groups in the bridge) were synthesized and transformed into their tetraester derivatives by reaction with ethyl bromoacetate. The stability constants for complexes of the tetraester derivatives with sodium, potassium and silver cations, determined in methanol by spectroscopic or potentiometric techniques, show a drastic decrease (more than 10^5 for Na^+) for the shorter methylene chains. ^1H NMR studies demonstrate a conformational rearrangement of the calixarene part to fourfold symmetry to be necessary for the complexation of a cation, which is prevented by the shorter chains. This is further confirmed by the X-ray structure of a tetraester derivative with a $CH_2CH_2COCH_2CH_2$ bridge; crystals were monoclinic, space group $P2_1/c$, $a = 11{\cdot}847(2)$, $b = 39{\cdot}773(5)$, $c = 12{\cdot}127(2)$ Å, $\beta = 109{\cdot}24(1)^\circ$, $V = 5395{\cdot}1$ Å^3, $Z = 4$, $D_x = 1{\cdot}186$ Mg m^{-3}.

INTRODUCTION

Calixarenes, easily available in many cases by one-pot procedures,[1] may be used as platforms on which various ligating functions may be assembled.[2] In this way, numerous new ionophores have been prepared during the last decade.[3] By analogy with natural ionophores (such as valinomycin or enniatin), ester (**1**), amide (**2**) or keto functions (**3**) proved to be most effective.[4] In general, derivatives of calix[4]arenes show a high selectivity for sodium ion over the other alkali metal ions and for calcium (which has a similar ionic

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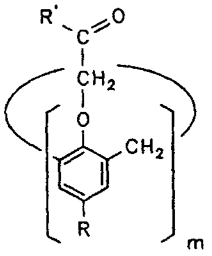


1 R' = O–alkyl
1a R = t–Bu , R' = OEt , m = 4

2 R' = N–(alkyl)$_2$, NH–alkyl
2a R = t–Bu , R' = N(CH$_2$)$_4$, m = 4
2b R = t–Bu , R' = N(Et)$_2$, m = 4

3 R' = alkyl

radius) among the alkaline earth metal cations.[5] Derivatives of calix[6]arenes prefer larger cations such as potassium, rubidium or caesium, but their selectivity is less pronounced, and derivatives of calix[8]arene in general are less efficient ionophores.[6] Thus, compound **1a** (R' = OEt, $m = 4$) shows a selectivity for sodium over potassium of $S_{Na/K} = 400$ and **2a** [R' = $N(CH_2)_4$, $m = 4$] a selectivity for calcium over magnesium of $S_{Ca/Mg} = 7 \times 10^7$.

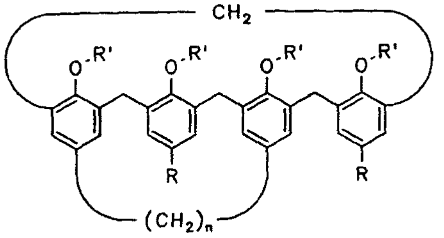
Probably one reason for the high complexation constants and for the radius-related selectivity is the high degree of preorganization which is found especially in the calix[4]arene derivatives fixed in the cone conformation. The molecular structures and conformations of various ligands of type **1**–**3** have been elucidated by X-ray analysis,[3,7] but remarkably only one metal complex, namely K^+ with **2b** (R' = NEt_2, $m = 4$), has been studied in this way.[8] Its beautiful structure with fourfold symmetry, the potassium ion being surrounded by the phenolic and the carbonyl oxygens, is tacitly assumed for all similar complexes. Indeed, it has been shown by ^1H NMR spectroscopy[9a] for the tetraester derivative of an asymmetrically substituted calix[4]arene that in solution also the complexation of a sodium ion imposes fourfold symmetry on the calixarene.[9b]

Recently, we have shown in a preliminary study[10] that the extraction of sodium picrate by tetraester derivatives of bridged calix[4]arenes, in which two opposite *para* positions are connected by an aliphatic chain, is strongly dependent on the length of this chain. Especially remarkable is a drastic change from extraction to non-extraction when the number of carbon atoms in the chain decreases from 7 to 6. To elucidate this observation more quantitatively (and to obtain in general a better insight into the conformational requirements for complexation), we have prepared an entire series of bridged calixarenes, and determined the complexation constants of their tetraester derivatives for Na^+, K^+ and Ag^+ in MeOH. To allow as close a comparison as possible with the corresponding derivative of (the unbridged) *tert*-butylcalix[4]arene, the *p*-*tert*-butyl group was chosen as substituent for the phenolic units not connected by the bridge.

SYNTHESIS AND GENERAL PROPERTIES

The bridged calixarenes **4** were obtained by condensation of diphenols [α,ω-bis(4-hydroxyphenyl)alkanes] with 2,6-bisbromomethyl-4-*tert*-butylphenol in dioxane using $TiCl_4$ as catalyst (and probably template) as described for **5**.[11] The best yields for the pure products (characterized by TLC and 400 MHz ^1H NMR and mass spectrometry) were in the range 13% ($n = 10$) – 34% ($n = 7$). It must be stated, however, that different runs to prepare the same compound sometimes resulted in different yields, even under the same conditions; the reason for these differences is unknown.

The distortion of the cone-shaped calix[4]arene nucleus, which is brought about by the shorter bridges, is nicely demonstrated by the chemical shift for the OH protons in the ^1H NMR spectra in $CDCl_3$. Whereas for $n = 16$ the singlet at 10·36 ppm is virtually identical with the value found for *tert*-butylcalix[4]arene, for the shorter chains shifts to higher field are observed (see Figure 1), indicating a continuous weakening of the intramolecular hydrogen bonds. Two different signals are observed for chain lengths of $n \leqslant 8$, their difference



4 R = t–Bu , R' = H
5 R = CH$_3$, R' = H
6 R = t–Bu , R' = CH$_2$–CO–OEt

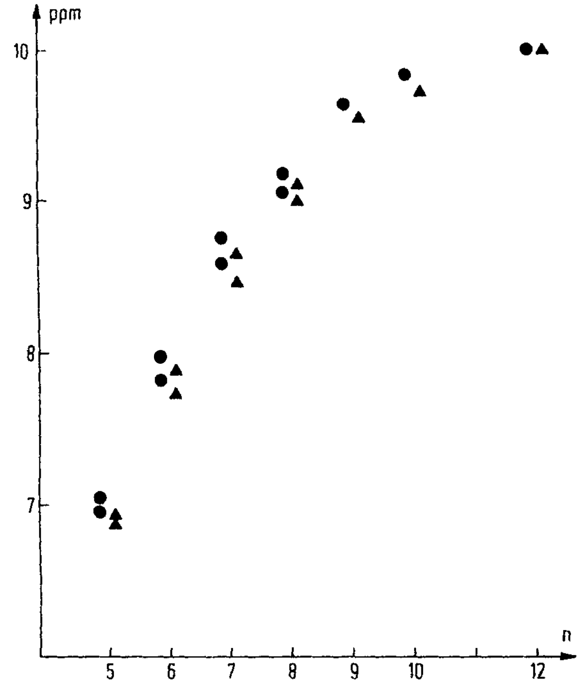


Figure 1. Chemical shifts for the OH protons for two series of bridged calix[4]arenes, (•) **4** and (▲) **5**, as a function of the chain length, *n*

being larger for $n = 6$ or 7 than for $n = 5$ or 8. This behaviour is similar for **4** [$R = C(CH_3)_3$] and **5** ($R = CH_3$), whereas the chemical shift for **5** in general is slightly lower.

Reaction of **4** with ethyl bromoacetate (refluxing acetone, K_2CO_3 as base) led to the tetraester derivatives **6**, isolated in 35–65% yield of pure product (characterized by TLC and ^1H NMR and mass spectrometry) after recrystallization from ethanol.

COMPLEXATION CONSTANTS AND EXTRACTION PROPERTIES

For the series of tetraester compounds **6** the stability constants for their complexes with sodium, potassium and silver ions have been determined in methanol by spectroscopic and/or potentiometric methods. Both techniques had already been employed for the simple *p-tert*-butylcalix[4]arene tetraethylester **1a**[4] and two tetraamide derivatives.[5] The results for β, defined as

$$\beta = c(ML^+)/[c(M^+)\,c(L)]$$

with $M^+ = Na^+$, K^+, Ag^+ and $L = 6$ are collected in Table 1 and plotted graphically in Figure 2, where for comparison the corresponding values for the tetraester of *tert*-butylcalix[4]arene (**1a**) are also given. The fol-

Table 1. Complexation properties of tetraester derivatives **6** (derived from bridged calix[4]arenes **4**) in comparison with the corresponding **1a** (derived from *tert*-butylcalix[4]arene)[a]

	Na^+		K^+		Ag^+:
Compound	Log β^b	*E*%	Log β^b	*E*%	Log β^b
6a ($n = 5$)	1^{s}	[0]	$1\cdot 3^{s}$	[0]	—
6b ($n = 6$)	$2\cdot 8^{s}$	[2]	$1\cdot 9^{s}$	[0]	$1\cdot 4^{s}$
6c ($n = 7$)	$4\cdot 6^{s}$	[24]	$2\cdot 4^{s}$	[5]	$3\cdot 6^{s}$
6d ($n = 8$)	$6\cdot 0^{p}$	[44]	$3\cdot 9^{s/p}$	[14]	$4\cdot 5^{s/p}$
6e ($n = 9$)	$5\cdot 5^{p}$	[25]	$2\cdot 7^{s}$	[8]	$4\cdot 1^{s/p}$
6f ($n = 10$)	$6\cdot 1^{p}$	[49]	$3\cdot 8^{s}$	[9]	$4\cdot 5^{p}$
1a[c]	5·0	[29]	2.4	[5]	4·0

[a] Stability constants are given as log β, and compared with *E*% (in brackets) for the extraction of picrates from water into CH_2Cl_2. All values are the arithmetic means of at least three independent experiments with the precision $2\delta_{N-1} = 0\cdot 1$–$0\cdot 2$ [0·5–1].

[b] s = spectrophotometric determination;
p = potentiometric determination.

[c] Taken from Reference 4.

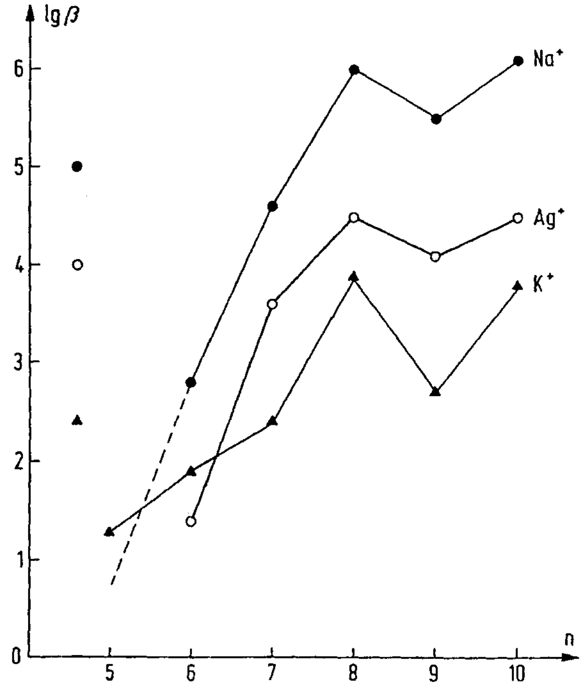


Figure 2. Stability constants (log β) as a function of the chain length (n) for tetraester derivatives **6** and (•) Na^+, (▲) K^+ and (○) Ag^+. For comparison, the values for **1a** are shown on the left

lowing features are evident:

(a) For all three cations the ligands with $n = 8$, 9 and 10 form stronger complexes than **1a**, the largest difference in log β being observed for K^+ and $n = 8$ with 1·5. This can be understood by a better 'preorganization' of the ligand, which is held in the optimum cone conformation (with approximately fourfold symmetry) by the bridging chain.
(b) For all cations the values for $n = 9$ are lower than those for $n = 8$ and 10, reflecting the fact that conformational preferences in the chain (staggered conformations of the CH_2 groups) also have some influence on the conformation of the calixarene part and consequently on the arrangement of the ligating ester functions.
(c) A continuous decrease in the complexation constant is found for all three cations on going from $n = 8$ to $n = 5$. Whereas the compound with $n = 7$ is still a reasonable ligand with β values slightly lower than for the *tert*-butylcalix[4]arene derivative **1a**, the complexation constants for $n = 5$ are lower than 10 in the case of Na^+ and probably Ag^+.
(d) Whereas for the longer chains ($n = 7$–10) the same sequence for the stability constants is found as for the *tert*-butylcalix[4]arene derivative ($Na^+ > Ag^+ > K^+$), this decrease is less pronounced for K^+ and there is a selectivity change for Ag^+/K^+ between $n = 7$ and $n = 6$ and for Na^+/K^+ between $n = 6$ and $n = 5$.

Table 1 also contains values for the extraction of sodium and potassium picrate from water into dichloromethane, determined according to Pedersen.[12] They reflect closely the trends in complexation mentioned above and need no further discussion.

Considering the structural similarity of all the compounds, these results suggest that there exist small, but obviously significant, differences in the mutual arrangement of ligating functions offered by the ligand, differences which must be caused by the different chain length of the bridge. X-ray structures are available for several bridged calix[4]arenes,[11,13] showing that the distance between the carbon atoms attached to the *para* positions decreases by 1·1–1·3 Å and 1·0–1·1 Å if the chain length decreases from 7 to 6 and from 6 to 5 carbon atoms, respectively. This necessarily leads also to a distortion of the arrangement of the phenolic oxygens, which in *tert*-butylcalix[4]arene[14] are found at the corners of a regular square with diagonal O—O distances of 3·78 Å. For these diagonal distances 4·13/3·48 Å (**5**, $R = CH_3$, $n = 7$), 4·32/3·45 Å (**5**, $R = CH_3$, $n = 6$), 4·46/3·39 Å (**4**, $R = t$-Bu, $n = 6$) and 4·76/3·31 Å (**5**, $R = CH_3$, $n = 5$) are found in bridged calix[4]arenes, where furthermore these oxygen atoms no longer lie within a plane. This situation is more or less fixed for $n = 5$ and $n = 6$, where the connecting chain assumes already a rather stretched conformation, whereas for longer chains a certain flexibility of the calixarene part remains.

^{1}H NMR SPECTROSCOPIC STUDIES

Further insight into the conformational requirements necessary for the complexation of a cation are obtained from ^{1}H NMR studies. *tert*-Butylcalix[4]arene at low temperature (where the cone conformation is fixed on the ^{1}H NMR time scale) shows the singlet for the Ar-H protons at 7·05 ppm, the two doublets for the methylene protons at 4·25 (axial) and 3·45 ppm (equatorial) and the singlet for the *tert*-butyl group at 1·15 ppm, while the corresponding signals in the tetraester derivative appear at 6·75 (ArH), 4·83 and 3·17 ($ArCH_2Ar$) and 1·05 ppm, respectively.[2] Complexation of an Na^+ cation leads to upfield and downfield shifts of these signals (in a complex kinetically stable on the ^{1}H NMR time scale), which then appear again in a range similar to that of the free calixarene [7·09 (ArH), 4·22 and 3·37 ($ArCH_2Ar$) and 1·12 ppm (*t*-Bu)].[3,9]

In the light of present knowledge (see also later), the changes in chemical shifts observed for the complexation of a sodium cation may be generally interpreted by the assumption of a conformation with fourfold symmetry (C_{4v}) in the complex, whereas the signals for the free ligand are due to a rapid interconversion of identical conformations with twofold symmetry (C_{2v}) as they are found also in the crystalline state. In fact, this conformation with twofold symmetry (C_2 in this case) is frozen at −90 °C on the ^{1}H NMR time scale for a tetraester derivative of a calix[4]arene with 3,4-dimethylphenol units.[15]

Table 2 contains the chemical shifts for the whole series of ligands **6** and for the Na^+ complexes of the compounds with $n = 7$–10, which are easily obtained by shaking a solution of **6** in $CDCl_3$ with solid NaSCN. For $n = 5$ and $n = 6$ kinetically stable complexes (on the 400 MHz ^{1}H NMR time scale) are not formed (although changes in the chemical shifts are observed also), which is in accordance with the low stability constants for these two compounds. The data, e.g. the two sets of signals for the CH_2COOEt groups (with differences between the two CH_2 singlets up to 0·72 ppm) clearly reveal the distorted cone conformation (C_{2v} symmetry), in which the two bridged phenolic units are pulled into the cavity, while consequently the two *p*-*tert*-butyl groups are pushed outwards. From the chemical shifts of the aromatic protons and from the protons of substituents attached to the *para* positions, it may be concluded that apparently the conformation for $n = 8$ in this series has the less distorted cone: the Ar_{chain}-H signal passes through a maximum at $n = 8$ (= lowest field, minimum shielding by the adjacent rings) whereas Ar_{Bu}-H here has a slight minimum. The

Table 2. Chemical shifts of tetraester derivatives **6** and of their Na^+ complexes ($CDCl_3$, 400 MHz)[a]

Proton	$n = 5$	$n = 6$	$n = 7$		$n = 8$		$n = 9$		$n = 10$	
ArH	7·082	7·082	7·070	(7·187)	7·068	(7·176)	7·081	(7·146)	7·082	(7·109)
	6·073	6·236	6·326	(6·691)	6·407	(6·769)	6·148	(6·862)	6·097	(6·878)
CH_2CO	5·022	5·106	5·157	(4·493)	5·173	(4·471)	5·034	(4·446)	5·014	(4·428)
	4·463	4·449	4·453	(4·424)	4·453	(4·426)	4·450	(4·425)	4·449	(4·428)
$ArCH_2Ar$	4·845	4·839	4·850	(4·217)	4·862	(4·214)	4·829	(4·217)	4·823	(4·221)
	3·149	3·159	3·180	(3·319)	3·187	(3·332)	3·150	(3·349)	3·148	(3·361)
CH_2CH_3	4·241	4·248	4·248	(4·351)	4·246	(4·357)	4·238	(4·357)	4·236	(4·357)
	4·134	4·125	4·120	(4·351)	4·118	(4·354)	4·122	(4·352)	4·120	(4·351)
$ArCH_2CH_2$	2·069	2·100	2·137	(2·265)	2·184	(2·352)	1·967	(2·353)	1·952	(2·406)
$C(CH_3)_3$	1·343	1·328	1·302	(1·256)	1·288	(1·236)	1·343	(1·189)	1·348	(1·165)
CH_2CH_3	1·300	1·307	1·311	(1·391)	1·315	(1·394)	1·298	(1·395)	1·297	(1·396)
	1·236	1·228	1·221	(1·391)	1·220	(1·394)	1·225	(1·391)	1·224	(1·391)
$CH_2CH_2CH_2$	0·983	1·128	1·035	(1·096)	1·093	(1·39)	1·2[c]	(1·305)	1·18[d]	(1·23)
	−0·140[b]	0·297	0·793[b]	(0·379[b])	0·936	(0·729)	1·16[b]	(0·666)		(0·93)
			0·410	(−0·222)	0·534	(0·013)	1·084	(0·342) (0·075[b])		(0·6[c])

[a] Compounds with $n = 5$ and $n = 6$ do not form kinetically stable complexes under these conditions.
[b] One CH_2 group.
[c] Four CH_2 groups.
[d] Eight CH_2 groups.

same is true for the Ar-CH_2 and *t*-Bu signals, respectively.

The uptake of the Na^+ cation enforces conformational changes on the ligand, which are demonstrated by the following changes in the ^1H NMR spectrum. First, the difference between the ether and ester chains disappears. The two signals for the CH_2CO protons merge completely on going from $n = 7$ to $n = 10$ ($\Delta\delta = 0{\cdot}069$, 0·045, 0·021 and 0·00 ppm). This rearrangement of the ester groups also affects the conformation of the calixarene part, which again becomes more and more evident on going from $n = 7$ to $n = 10$, with differences for the two ArH singlets from 0·496, 0·407, 0·284 and 0·231 ppm, the latter being entirely due to the different substituents.[9] It corresponds, for instance, exactly to the difference observed for the *ortho* protons in *tert*-butylbenzene and toluene. In the region of the $ArCH_2Ar$ protons the usual upfield shift for H_A and downfield shift for H_B is observed, confirming also the above-given interpretation for the tetraester derivatives of unbridged calix[4]arenes. Owing to the conformational rearrangement the *t*-Bu group is pulled into the cavity (upfield shifts of −0·046, −0·052, −0·154 and −0·183 ppm in comparison with the free ligand going from $n = 7$ to $n = 10$) and even more pronounced, the $ArCH_2CH_2$ is moved outwards (downfield shifts of 0·128, 0·168, 0·386 and 0·454 ppm are observed from $n = 7$ to $n = 10$). This movement is still found for the second CH_2 groups for $n = 7$ and 8 whereas the middle of the chain is pulled into the cavity, clearly visible by strong upfield shifts for the corresponding CH_2 protons, which now come into the shielding region of the *tert*-butylphenol units.

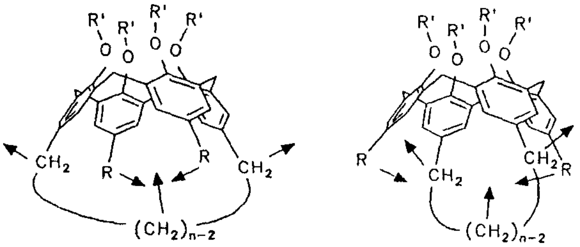


Figure 3. Schematic representation of the conformational changes of the calixarene part in tetraester derivatives **6**, necessary for the complexation of a Na^+ cation ($R' = CH_2COOEt$)

All these conformational changes of the calixarene part which are necessary for complexation are indicated schematically in Figure 3. Not only do they explain the inability (or low ability) to form complexes with the compounds with $n = 5$ and $n = 6$, where the short chain prevents this conformational change, they even explain the slight minimum in stability constants observed for $n = 9$. Obviously here the calixarene is not as 'preorganized' as for $n = 8$ and on the other hand not yet as 'flexible' as was for $n = 10$.

X-RAY STRUCTURE

Although single crystals have not yet been obtained from any of the tetraester derivatives **6** discussed here, the X-ray structure of a similar compound **7**, in which two opposite *para* positions are linked by a

$CH_2CH_2COCH_2CH_2$ bridge, may help in understanding the results. The effective distance of the *para*-substituting carbon atoms in this bridge, found in a bridged calix[4]arene with R = cyclohexyl,[16] is 5·04Å, whereas for a $(CH_2)_5$ bridge and $R = CH_3$ a slightly longer distance of 5·15Å was found,[13] which suggests that both bridges obviously should cause a similar distortion.

Crystal data for **7**, $C_{57}H_{70}O_{13}$, $M_r = 963{\cdot}2$ are monoclinic space group $P2_1/c$, $a = 11{\cdot}847(2)$, $b = 39{\cdot}773(5)$, $c = 12{\cdot}127(2)$ Å, $\beta = 109{\cdot}24(1)^\circ$, $V = 5395{\cdot}1$ Å^3, $Z = 4$, $F(000) = 2064$, $D_x = 1{\cdot}186$ Mg m^{-3}. Atomic coordinates for **7** are given in Table 3 and its molecular conformation is shown in Figure 4. The bond lengths and bond angles are close to the usual values. Remarkable deviations, which will be discussed in detail elsewhere, are found only in the bridge.

The calixarene moiety of **7** is similar to that of analogous derivatives of non-bridged calixarenes, including the tetradiethylamide of *tert*-butylcalix[4]arene (**2b**), the only ligand where also an X-ray structure of a complex (with K^+) is described.[8] Two opposite phenolic units (connected by the bridge) are nearly parallel (6·3°), whereas the other two units are almost perpendicular (95·6°). Interestingly, the above-mentioned distance between the *para*-substituting C atoms [C(25) and C(29)] is even shorter (4·85 Å) than in an analogous compound with free hydroxyl groups. The dihedral angles which the phenolic units include with the plane of the methylene carbons are 85·6/88·4° and 139·8/135·8°, respectively, a situation similar to that in **2b**. [According to a proposal of Ugozzoli and Andreetti,[17] the conformation of a calixarene is better described (especially in the case of the larger oligomers) by torsion angles for the $ArCH_2$ σ-bonds. For **7** these

Table 3. Fractional atomic coordinates ($\times 10^4$) of the non-hydrogen atoms of **7**[a]

Atom	*x*/*a*	*y*/*b*	*z*/*c*
C(1)	5167(4)	2858(1)	4327(4)
C(2)	4181(3)	2910(1)	3368(3)
C(3)	4121(3)	3172(1)	2579(3)
C(4)	2978(3)	3227(1)	1553(3)
C(5)	1912(3)	3280(1)	1982(3)
C(6)	1116(3)	3014(1)	1898(3)
C(7)	269(3)	3023(1)	2458(3)
C(8)	237(3)	3305(1)	3111(3)
C(9)	1007(3)	3573(1)	3220(3)
C(10)	1057(3)	3861(1)	4072(3)
C(11)	2151(3)	3838(1)	5121(3)
C(12)	2323(4)	3559(1)	5863(3)
C(13)	3349(4)	3518(1)	6806(3)
C(14)	4257(3)	3749(1)	6991(3)
C(15)	4119(3)	4034(1)	6274(3)
C(16)	5157(3)	4281(1)	6518(3)
C(17)	6262(3)	4102(1)	6422(3)
C(18)	7142(3)	3996(1)	7419(3)
C(19)	8061(3)	3780(1)	7415(3)
C(20)	8035(3)	3671(1)	6305(3)
C(21)	7192(3)	3770(1)	5283(3)
C(22)	7111(3)	3604(1)	4143(3)
C(23)	6107(3)	3349(1)	3794(3)
C(24)	6121(3)	3081(1)	4538(3)
C(25)	5179(5)	2560(1)	5148(4)
C(26)	5255(7)	2651(2)	6337(6)
C(27)	4127(13)	2778(3)	6394(9)
C(28)	4398(7)	2980(2)	7497(7)
C(29)	3490(5)	3219(1)	7588(4)
C(30)	3077(3)	4075(1)	5373(3)
C(31)	6335(3)	4004(1)	5352(3)
C(32)	5104(3)	3382(1)	2808(3)
C(33)	1816(3)	3562(1)	2616(3)
C(34)	−531(5)	2722(1)	2402(5)
C(35)	−1602(6)	2787(2)	2667(9)
C(36)	42(8)	2521(2)	3392(7)
C(37)	−750(6)	2505(2)	1452(6)
C(38)	8971(4)	3656(1)	8536(4)
C(39)	10125(4)	3537(1)	8408(4)
C(40)	9254(4)	3910(1)	9486(4)
C(41)	8437(4)	3361(1)	8968(4)
C(42)	2270(3)	4613(1)	5003(3)
C(43)	2196(4)	4916(1)	4268(4)
C(44)	1054(5)	5406(1)	3586(5)
C(45)	−31(5)	5513(2)	3282(7)
C(46)	5399(3)	4447(1)	4030(3)
C(47)	6067(5)	4568(1)	3255(4)
C(48)	7663(6)	4488(2)	2521(7)
C(49)	8478(6)	4399(3)	2599(9)
C(50)	5560(3)	3580(1)	1169(3)
C(51)	5462(5)	3873(1)	384(4)
C(52)	4436(6)	4380(2)	−349(6)
C(53)	3363(6)	4387(2)	−1204(5)
C(54)	2628(3)	4023(1)	1842(3)
C(55)	1898(4)	4339(1)	1701(3)
C(56)	1686(5)	4872(1)	801(5)
C(57)	2387(6)	5114(1)	534(6)
O(1)	2931(2)	4360(1)	4664(2)
O(2)	5489(2)	4099(1)	4302(2)
O(3)	5048(2)	3652(1)	2051(2)
O(4)	2636(2)	3825(1)	2807(2)
O(5)	2866(3)	4989(1)	3764(3)
O(6)	1266(3)	5102(1)	4253(3)
O(7)	5825(3)	4831(1)	2749(3)
O(8)	6946(3)	4383(1)	3246(3)
O(9)	6058(3)	3910(1)	−210(3)
O(10)	4606(3)	4079(1)	379(3)
O(11)	1075(3)	4390(1)	2011(3)
O(12)	2297(3)	4556(1)	1077(3)
O(13)	3091(5)	2735(1)	5804(5)

[a] The numbering scheme follows the rational name, which is tetraethyl[7,19-di-*tert*-butyl-27-oxohexacyclo[11.11.5.1^{3,23}.1^{5,9}.1^{11,15}.1^{17,21}]tritriaconta-1,3(30),5,7,9(33),11,13,15(32),17,19, 21(31), 23-dodecaen-30,31,32,33-tetra(yloxy)]tetraacetate.

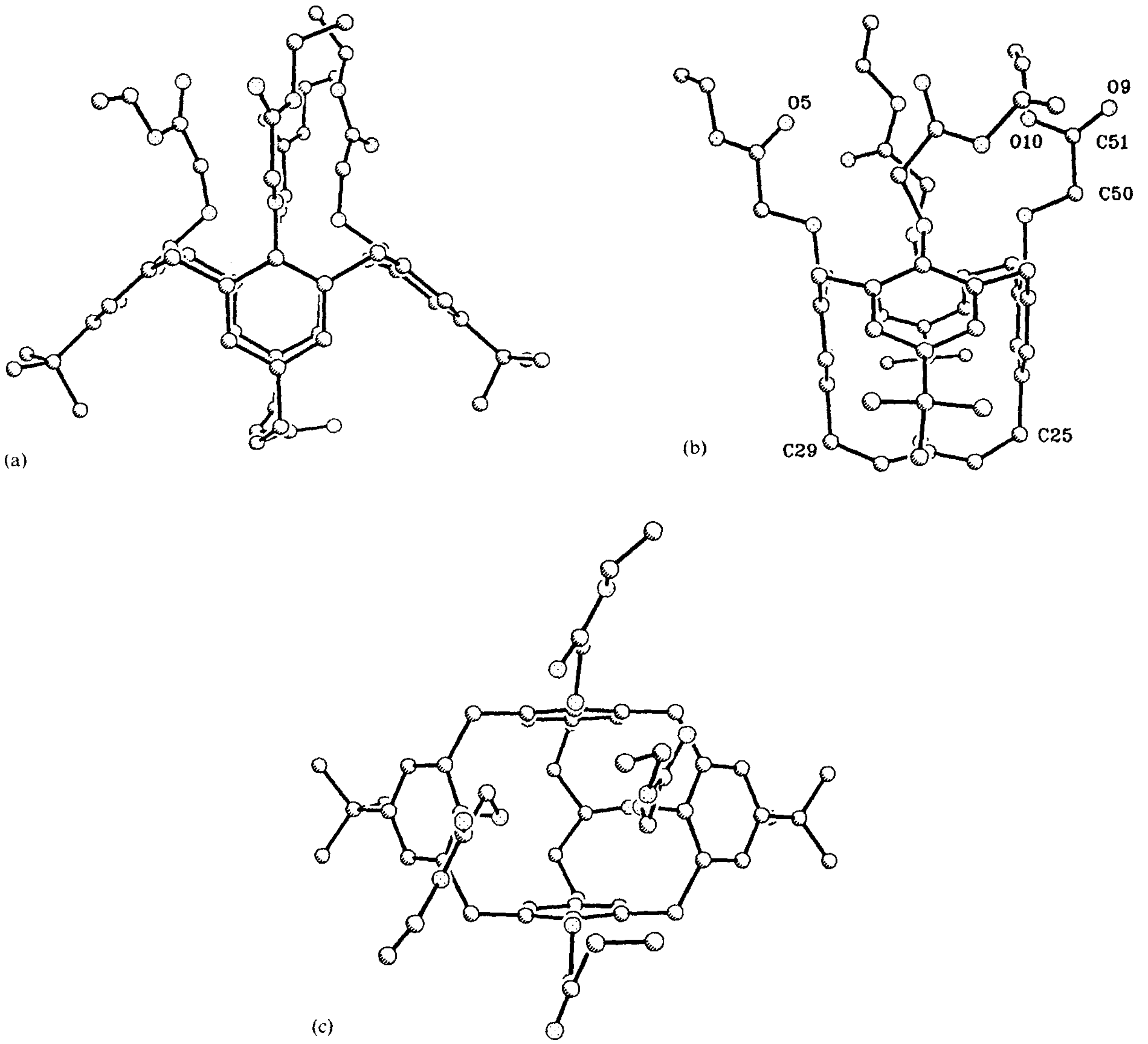


Figure 4. Molecular conformation of 7 in the solid state, seen from different directions. Hydrogen atoms are omitted for clarity

are (starting with the unbridged unit to which the carbonyl group points, and including always the carbon atoms carrying the phenolic oxygen) −68·8, 113·2, −118·9, 72·2, −72·3, 115·1, −119·8 and 66·9°. The alternating +/− sequence is characteristic for the cone conformation, and the deviation from 90° indicates its deformation.]

In its complex with K^+, however, **2b** assumes a conformation with fourfold symmetry and dihedral angles of 113·3° for all phenolic units. This rearrangement obviously is not possible for **7**, and for similar compounds such as **6**. The K^+ ion in {**2b**/K^+} is situated (sandwich-like) between two regular squares formed by the phenolic oxygens (distance of opposite O atoms = 4·70 Å) and the carbonyl oxygens (distance of opposite O atoms = 5·19 Å), which are twisted by 32° relative to each other. In contrast, the phenolic oxygen atoms of **7** are 'less coplanar' (the deviation from the best plane is ±0·14 Å), and (probably more important) their diagonal distances are 3·44 and 5·44 Å, a situation, which cannot be rearranged significantly, because it would require a further expansion of the bridge, which already assumes more or less its most stretched conformation. The closest possible distance of the opposite carbonyl oxygen at the bridged phenolic units cannot be derived unambigously from the X-ray structure, since in principal it is influenced by rotations around the $ArOCH_2CO$ σ-bonds. If, however, as in the K^+ complex, the CH_2 groups are assumed to be turned outwards, the situation illustrated in Figure 4(b) occurs, and the distance between O(5) and O(10) [rotation around C(50)—C(51) brings the carbonyl oxygen O(9) into a similar position] may be then taken as an approximate estimation. This distance (6·306 Å) is longer again by more than 1 Å than found in the K^+ complex of **2b**.

CONCLUSION

We have shown that small conformational changes imposed on the cone conformation of a calix[4]arene system by an aliphatic bridge have drastic influences on the stability constants of complexes of their tetraester derivatives. This observation may be used in numerous ways if compounds with a suitable bridge of variable length are available or if the distance of two opposite *para* positions in a calix[4]arene derivative can be varied by other means. This variation obviously must not be greater than 1–2 Å, which is just the length of a single covalent link. We are currently attempting to synthesize various new calixarenes capable of showing such allosteric effects.

EXPERIMENTAL

General procedure for the preparation of the bridged calix[4]arenes 4. The α,ω-bis(4-hydroxyphenyl)alkane (5 mmol) and 2,6-bis(bromomethyl)-4-*tert*-butylphenol (3·36 g, 10 mmol) were dissolved in 300 ml of dry dioxane (freshly distilled from sodium). The solution was warmed to 60 °C and $TiCl_4$ (2·85–4·55 g, 15–24 mmol) was added together with an additional 200 ml of dioxane. The mixture was heated at reflux under an argon atmosphere for 70–120 h, the progress of the reaction being monitored by TLC. The solvent was then removed under vacuum, the dark-red to brownish residue dissolved in 150 ml of CH_2Cl_2 and, after the addition of 50 g of silica gel, evaporated to dryness again. The dry silica gel was extracted by means of a Soxhlet apparatus with CH_2Cl_2 and the crude product thus obtained was purified, as indicated below for the individual compounds. Melting points reported were determined in sealed capillary tubes under argon.

4a ($n = 5$): Flash chromatography with $CHCl_3$ gave a crude product which was triturated and finally recrystallised from acetone to yield white crystals, m.p. 274–275 °C, yield 10–29%. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7·11 (s, 4H, ArH), 7·04 (s, 2H, ArOH), 6·96 (s, 2H, ArOH), 6·24 (s, 4H, ArH), 4·13 (d, $J = 14·3$ Hz, 4H, $ArCH_AHAr$), 3·30 (d, $J = 14·4$ Hz, 4H, $ArCHH_BAr$), 2·13 (m, 4H, $ArCH_2$), 1·35 (s, 18H, $C(CH_3)_3$), 0·87 (m, 4H, CH_2), −0·64 (m, 2H, CH_2). Electron impact mass spectrometry: *m*/*z* 604 (M^+, 100).

4b ($n = 6$): Repeated flash chromatography with $CHCl_3$ gave a crude product, which finally was triturated with acetone, m.p. 314–316 °C, yield 15–21%. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7·98 (s, 2H, ArOH), 7·82 (s, 2H, ArOH), 7·11 (s, 4H, ArH), 6·41 (s, 4H, ArH), 4·14 (d, $J = 14·1$ Hz, 4H, $ArCH_AHAr$), 3·34 (d, $J = 14·1$ Hz, 4H, $ArCHH_BAr$), 2·09 (m, 4H, $ArCH_2$), 1·32 (s, 18H, $C(CH_3)_3$), 0·82 (m, 4H, CH_2), −0·07 (m, 4H, CH_2). EI-MS: *m*/*z* 618 (M^+, 55), 382 (M^+, 100).

4c ($n = 7$): Flash chromatography with CH_2Cl_2 or $CHCl_3$ and trituration of the residue with acetone gave a product of m.p. 330 °C, yield 9–34%. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8·77 (s, 2H, ArOH), 8·59 (s, 2H, ArOH), 7·09 (s, 4H, ArH), 6·54 (s, 4H, ArH), 4·17 (d, $J = 13·9$ Hz, 4H, $ArCH_AHAr$), 3·38 (d, $J = 13·9$ Hz, 4H, $ArCHH_BAr$), 2·25 (m, 4H, $ArCH_2$), 1·28 (s, 18H, $C(CH_3)_3$), 0·97 (m, 4H, CH_2), 0·31 (m, 2H, CH_2), −0·27 (m, 4H, CH_2). EI-MS: *m*/*z* 632 (100).

4d ($n = 8$): Repeated flash chromatography with $CHCl_3$ and trituration with acetone gave a product of m.p. 378–380 °C, yield 23% ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 9·18 (br s, 2H, ArOH), 9·05 (br s, 2H, ArOH), 7·07 (s, 4H, ArH), 6·63 (s, 4H, ArH), 4·18 (d, $J = 13·8$ Hz, 4H, $ArCH_AHAr$), 3·39 (d, $J = 13·8$ Hz, 4H, $ArCHH_BAr$), 2·33 (m, 4H, $ArCH_2$), 1·25 (s, 18H, $C(CH_3)_3$), 1·13 (m, 4H, CH_2), 0·46 (m, 4H, CH_2), −0·02 (m, 4H, CH_2). EI-MS: *m*/*z* 646 (M^+, 100).

4e ($n = 9$): Repeated flash chromatography with $CHCl_3$ and trituration with acetone gave a product of m.p. 354 °C, yield 6–13%. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 9·64 (s, 4H, ArOH), 7·06 (s, 4H, ArH), 6·74 (s, 4H, ArH), 4·21 (d, $J = 13·7$ Hz, 4H, $ArCH_AHAr$), 3·42 (d, $J = 13·8$ Hz, 4H, $ArCHH_BAr$), 2·36 (m, 4H, $ArCH_2$), 1·22 (s, 18H, $C(CH_3)_3$), 1·22 (m, 4H, CH_2), 0·48 (m, 4H, CH_2), 0.12 (m, 4H, CH_2), −0·18 (m, 2H, CH_2). EI-MS: *m*/*z* 661 (M^+, 100).

4f ($n = 10$): Flash chromatography with $CHCl_3$ and subsequently with $CHCl_3$ – light petroleum (1 : 1) gave a product of m.p. 349 °C, yield 11%. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 9·84 (s, 2H, ArOH), 7·02 (s, 4H, ArH), 6·76 (s, 4H, ArH), 4·21 (d, $J = 13·7$ Hz, 4H, $ArCH_AHAr$), 3·41 (d, $J = 13·8$ Hz, 4H, $ArCHH_BAr$), 2·40 (m, 4H, $ArCH_2$) 1·21 (m, 4H, CH_2), 1·18 (s, 18H, $C(CH_3)_3$), 0·63 (m, 4H, CH_2), 0·44 (m, 4H, CH_2), 0·30 (m, 4H, CH_2). EI-MS: *m*/*z* 674 (M^+, 100).

General procedure for the preparation of the tetraethylester derivatives 6. The bridged calix[4]arene **4** (1 mmol) was dissolved with warming in 15 ml of dry acetone, 0·6 g (4·4 mmol) of K_2CO_3, a trace of KI and 0·735 g (4·4 mmol) of ethyl bromoacetate were added and the heterogeneous mixture was refluxed for 20 h in an argon atmosphere. The solvent was evaporated and the residue dissolved in water – CH_2Cl_2 (20 ml each). The aqueous phase was further extracted with CH_2Cl_2 and the combined organic phases were dried with $MgSO_4$ and evaporated to give a slightly yellow oil, which more or less rapidly crystallized. The following data refer to samples further purified by recrystallization from ethanol. ^{1}H NMR data are given in Table 2.

6a: Yield 64%; m.p. 165 °C; field desorption (FD) MS: *m/z* 948·6 (M^+, 100).

6b: Yield 31%; m.p. 122–124 °C; FD-MS: *m/z* 962·7 (M^+, 100).

6c: Yield 64%; m.p. 123–125 °C; FD-MS: *m/z* 976·4 (M^+, 100).

6d: Yield 44%; m.p. 120–121 °C; FD-MS: *m/z* 990·8 (M^+, 100).

6e: Yield 53%; m.p. 131–132 °C; FD-MS: *m/z* 1004·8 (M^+, 100).

6f: Yield 34%; m.p. 105–109 °C; FD-MS: *m/z* 1019.1 (M^+, 100).

Preparation of 7. The tetraester derivative **7** was obtained in an analogous way from the corresponding bridged calix[4]arene,[16] but using acetonitrile as solvent, which might be advantageous with respect to the yield.

The bridged calix[4]arene (0·2 g, 0·32 mmol), ethyl bromoacetate (0·22 g, 1·3 mmol) and K_2CO_3 (0·18 g, 1·3 mmol) were refluxed in 25 ml of dry acetonitrile for 20 h. After the usual work-up, the crude product was recrystallized from methanol to give 264 mg (85%) of colourless crystals, m.p. 128–130 °C. Analysis: calculated for $C_{57}H_{70}O_{13}$, C 71·10, H 7·27; found, C 71·28, H 7·02%. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7·13 (s, 4H, ArH), 6·14 (s, 4H, ArH), 4·99 (s, 4H, CH_2CO), 4·46 (s, 4H, CH_2CO), 4·83 (d, $J = 13{\cdot}2$ Hz, 4H, $ArCH_AHAr$), 4·24 (q, $J = 7{\cdot}2$ Hz, 4H, CH_2CH_3), 4·14 (q, $J = 7{\cdot}2$ Hz, 4H, CH_2CH_3), 3·15 (d, $J = 13{\cdot}3$ Hz, 4H, $ArCHH_BAr$), 2·34 (m, 4H, $ArCH_2$), 2·04 (m, 4H, $ArCH_2CH_2$), 1·42 (s, 18H, $C(CH_3)_3$), 1·31 (t, $J = 7{\cdot}2$ Hz, 6H, CH_2CH_3), 1·24 (t, $J = 7{\cdot}2$ Hz, 6H, CH_2CH_3). EI-MS: *m/z* 962 (M^+, 100).

X-ray structure analysis. Single crystals of **7** were grown from ethanol. A crystal of 0·5 mm × 0·4 mm × 0·2 mm was sealed in a Lindemann glass capillary. Twenty-five reflections with $\theta > 7°$ were used to determine the cell constants. Reflections with $|F| > 1\sigma(F)$ (12 114 of 13 011 unique reflections) were used for the structure analysis with a computer controlled diffractometer (Siemens), MoKα, $\mu = 0{\cdot}083$ mm^{-1}, $T = 293$ K.

The weighting system was $w = 1/\delta^2(|F|)$ according to the counting statistics; $S = 2{\cdot}04$; $-15 \leqslant h \leqslant 6$, $0 \leqslant k \leqslant 49$, $-16 \leqslant l \leqslant 16$, $R_{int} = 0{\cdot}041$. The phase problem was solved by direct methods.[18] Parameters were refined by least-squares analysis using the cascade method (631 parameters, 11 481 degrees of freedom). The coordinates of the H atoms were calculated according to theoretical considerations. In the last least-squares cycle the largest change of a parameter was smaller than 0·3% of its estimated standard deviation. The ten largest maxima of an electron density difference Fourier map were between 0·37 and 0·47 electrons per Å^3. The final values $R = 0{\cdot}179$ and $R_w = 0{\cdot}071$ are different, the main reason being that reflections as small as 1δ were used for the calculations.

Further details of the structure analysis are deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich technische Information mbH, D-W-7514 Eggenstein-Leopoldshafen, Germany. The full literature citation of this publication and the code number CSD-56234 should accompany the request.

Determination of stability constants. All measurements were done in pure methanol (Carlo Erba, maximum water content 0·01%). The following metal salts were used according to the method: the alkali metal chlorides NaCl (Prolabo, p.a.) and KCl (Merck, p.a.) or the perchlorates $NaClO_4$ (Fluka, purum), $KClO_4$ (Prolabo, Normapur) and $AgClO_4$ (Fluka, puriss.). They were dried for 24 h under vacuum at ambient temperature before use. In all cases the ionic strength was maintained at 0·01 M by use of Et_4NCl or Et_4NClO_4 (Fluka, purum).

Two protocols were used to follow the complexation by spectrophotometry: the spectra were recorded from 300 to 250 nm after addition of increasing amounts the metal salts (alkali metal chlorides or silver perchlorate) either to 2 ml of a methanolic solution of the ligand ($C_L = 1 \times 10^{-4}$–2×10^{-4} M) directly in the spectrophotometric cell of 1 cm path length or to 10 ml of the ligand solution in a series of volumetric flasks. The former method was generally preferred because it is less ligand consuming, although the complexation is better expressed by the latter as there is no dilution effect. Figure 5 illustrates the case for the complexation of Na^+ by ligand **6c**. The absorbances selected at different significant wavelengths were treated by the program Letagrop-Spefo[19] and interpreted on the basis of the formation of 1 : 1 complexes.

Potentiometric measurements with Ag^+ as auxiliary cation were performed at 25 ± 0·01 °C with the following electrochemical cell:

Ag_s | $AgClO_4$, $NaClO_4$ or $KClO_4$, Et_4NClO_4
0·01 M || Et_4NClO_4 0·01 M || $AgClO_4$ 0·01 M | Ag_s

The response of the working electrode was checked by adding increasing amounts of $AgClO_4$ ($c_{Ag} = 2 \times 10^{-4}$–$4 \times 10^{-4}$ M) in methanol to 10 ml of a solution of Et_4NClO_4 in MeOH in the presence of alkali metal perchlorate ($c_M = 2 \times 10^{-4}$–4×10^{-4} M). At the

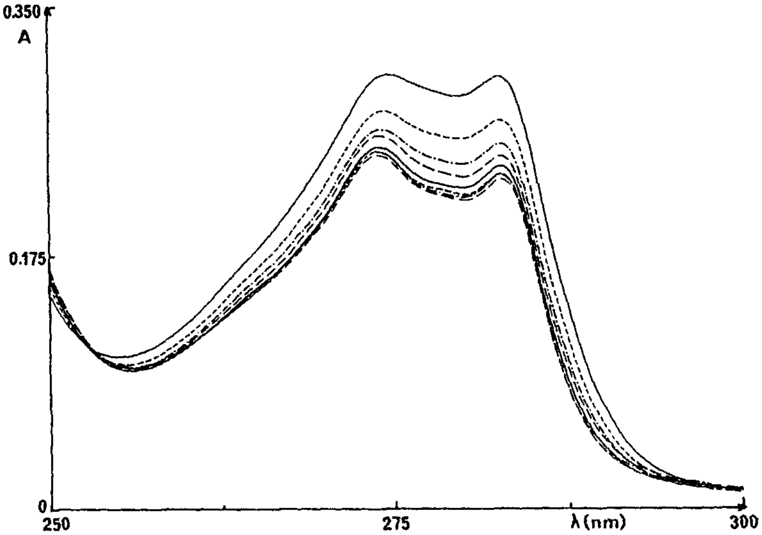


Figure 5. Spectral changes observed for **6c** ($n = 7$) in the presence of various amounts of NaCl: $c_L = 10^{-4}$ M, $0 \leqslant c_M/c_L \leqslant 3{\cdot}4$. The top curve is the spectrum of the ligand alone

end of the calibration, increasing amounts of ligand were added up to a metal to ligand molar ratio of at least 2. The corresponding potential changes were treated by the program Miniquad[20] using the stability constants for the corresponding silver complexes previously determined by potentiometry from solutions without alkali metal cations and/or by spectrophotometry.

Extraction measurements. The percentages of extraction, $E\%$, of alkali metal picrates from water into dichloromethane were determined according to the method of Pedersen.[12] The experimental details are described elsewhere.[4,5] In this case equal volumes (5 ml) of a $2{\cdot}5 \times 10^{-4}$ M aqueous solution of sodium or potassium picrate and of a $2{\cdot}5 \times 10^{-4}$M solution of the ligand in CH_2Cl_2 were placed in glass tubes and shaken manually and then magnetically for 5 and 30 min, respectively. After waiting 30 min to allow the two phases to settle, the absorbance A of the metal picrate in the aqueous phase was determined spectrophotometrically at 355 nm ($\varepsilon = 14\,416$ l mol^{-1} cm^{-1}). The extraction percentages are expressed as the ratios $E\% = 100(A_0 - A)/A_0$, where A_0 is the absorbance of the aqueous phase in blank experiments in the absence of a ligand in the organic phase.

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REFERENCES

1. C. D. Gutsche and M. Iqbal, *Org. Synth.* **68**, 234–237 (1989); C. D. Gutsche, B. Dhawan, M. Leonis and D. Stewart, *Org. Synth.* **68**, 238–242 (1989); J. H. Munch and C. D. Gutsche, *Org. Synth.* **68**, 243–246 (1989).
2. (a) C. D. Gutsche, *Calixarenes.* Royal Society of Chemistry, Cambridge (1989); (b) J. Vicens and V. Böhmer, *Calixarenes, A Versatile Class of Macrocyclic Compounds.* Kluwer, Dordrecht (1991).
3. R. Ungaro and A. Pochini, in *Calixarenes, a Versatile Class of Macrocyclic Compounds*, edited by J. Vicens and V. Böhmer, pp. 127–147. Kluwer, Dordrecht (1991); M.-J. Schwing and M. A. McKervey, in *Calixarenes, a Versatile Class of Macrocyclic Compounds*, edited by J. Vicens and V. Böhmer, pp. 149–172. Kluwer, Dordrecht (1991).
4. F. Arnaud-Neu, E. M. Collins, M. Deasy, G. Ferguson, S. J. Harris, B. Kaitner, A. J. Lough, M. A. McKervey, E. Marques, B. L. Ruhl, M.-J. Schwing-Weill and E. M. Seward, *J. Am. Chem. Soc.* **111**, 8681–8691 (1989).
5. F. Arnaud-Neu, M.-J. Schwing-Weill, K. Ziat, S. Cremin, S. Harris and M. A. McKervey, *New J. Chem.* **15**, 33–37 (1991).
6. V. Böhmer and M. A. McKervey, *Chem. in unserer Zeit* **25**, 195–207 (1991).
7. G. D. Andreetti and F. Ugozzoli, in *Calixarenes, A Versatile Class of Macrocyclic Compounds*, edited by J. Vicens and V. Böhmer, pp. 87–123. Kluwer, Dordrecht (1991).
8. A. Arduini, E. Ghidini, A. Pochini, R. Ungaro, G. D. Andreetti, G. Calestani and F. Ugozzoli, *J. Inclus. Phenom.* **6**, 119–134 (1988).
9. (a) For the first ^{1}H NMR spectroscopic studies of sodium complexation, see A. Arduini, A. Pochini, S. Reverberi, R. Ungaro, G. D. Andreetti and F. Ugozzoli, *Tetrahedron* **42**, 2089–2100 (1986); (b) L. Zetta, A. Wolff, W. Vogt,

R.-L. Platt and V. Böhmer, *Tetrahedron* **47**, 1911–1924 (1991).

10. V. Böhmer, W. Vogt, H. Goldmann, M. A. McKervey, M. Owens, S. Cremin and E. M. Collins, *J. Org. Chem.* **55**, 2569–2570 (1990).
11. H. Goldmann, W. Vogt, E. Paulus and V. Böhmer, *J. Am. Chem. Soc.* **110**, 6811–6817 (1988).
12. C. J. Pedersen, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **27**, 1305 (1968).
13. (a) E. Paulus, V. Böhmer, H. Goldmann and W. Vogt, *J. Chem. Soc., Perkin Trans. 2*, 1609–1615 (1987); (b) V. Böhmer, H. Goldmann, W. Vogt, E. F. Paulus, F. L. Tobiason and M. J. Thielman, *J. Chem. Soc., Perkin Trans. 2*, 1769–1775 (1990).
14. G. D. Andreetti, R. Ungaro and A. Pochini, *J. Chem. Soc., Chem. Commun.*, 1005–1007 (1979).
15. A. Wolff, V. Böhmer, W. Vogt, F. Ugozzoli, G. D. Andreetti, *J. Org. Chem.* **55**, 5665–5667 (1990).
16. B. Berger, V. Böhmer, E. Paulus, A. Rodriguez and W. Vogt, *Angew. Chem.* **104**, 89–92 (1992).
17. F. Ugozzoli and G. D. Andreetti, *J. Inclus. Phenom.* in press; see also, G. D. Andretti, F. Ugozzoli, Y. Nakamoto and S.-I. Ishida, *J. Inclus. Phenom.* **10**, 241–253 (1991).
18. G. M. Sheldrick, *SHELXTL-PLUS, an Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data*, University of Göttingen, Göttingen (1990).
19. L. G. Sillen and B. Warnquist, *Ark. Kemi* **31**, 377–390 (1968)
20. A. Sabbatini, A. Vacca and P. Gans, *Talanta* **21**, 53–77 (1974).