Rigid Calix[4]arene as a Building Block for the Synthesis of New Quaternary Ammonium Cation Receptors

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In memory of Prof. André Collet

Keywords: Molecular recognition / Pi Interactions / Calixarenes / Quaternary ammonium cations / Ion pairs

The synthesis of a new series of neutral hosts derived from the *head-to-head* linkage of two calix[4]arene-bis(crown-3) units fixed in the rigid *cone* conformation with bridges of different nature and length is described. The binding abilities of the new receptors towards tetraalkylammonium and *N*-methylpyridinium cations of different size and shape in $CDCl_3$ solution have been extensively investigated by ^1H NMR spectroscopy. In this solvent, ion-pairing is found to have a strong effect on the binding efficiency. In the more polar $CDCl_3/CD_3CN$ solvent mixture, a substantial decrease in the K_{ass} values is observed, which can be attributed, in part, to CD_3CN competing for the binding sites of the host. In all cases, the double calixarenes **2**, **7**, **8**, and **9** have been found to exhibit efficiencies much higher than that of the corresponding rigid calix[4]arene-bis(crown-3) **1**. The bridge present in these double calix[4]arenes dictates the orientation and distance between the two rigid caps and thus represents a new control element in determining the efficiency and selectivity of binding. The orientation and span imposed by the different bridges to the two calixarene subunits is responsible for the different binding modes observed with *N*-methylpyridinium and isomeric *N*-methylpicolinium cations.

Introduction

Among the more challenging objectives of supramolecular chemistry is the design and synthesis of hosts that efficiently and selectively bind a guest.[1] Moreover, structural studies of the complexes formed can provide useful information concerning the nature and role of the specific interactions that stabilize these supramolecular species, and allow an evaluation of the degree of matching between the host and guest.

Recognition phenomena of organic ammonium cations bound by specific receptors (enzymes) through cation−π interactions[2] have inspired research aimed at synthesizing hosts capable of recognizing organic ammonium cations[3] in both aqueous[4] and apolar media.[5] In recent literature, a number of calixarenes[6] have been reported to form, in apolar media, *endo*-cavity complexes with ammonium cations where cation−π interactions play an important role.[7]

In an early study, it was shown by Shinkai and coworkers that calix[4]arene derivatives bind *N*-methylpyridinium cations, albeit poorly, only when they are fixed in the *cone* conformation.[8]

More recently, in order to evaluate the inclusion of bulkier guests, the larger members of the calixarene series, i.e. calix[5]-,[9] calix[6]-,[10] and homooxacalixarenes[11] have also been employed, and their efficiencies in organic ammonium binding have usually been found to be appreciable, provided that their structural flexibility is to some extent restricted. For all neutral calixarene-based receptors capable of binding organic ammonium cations in media of low polarity, the association constants were found to be $< 10^3$ M^{-1}.

It thus appears that calix[4]arene, the conformational mobility of which can be more readily controlled, has an insufficiently large cavity, while for the larger calixarenes, more suited for hosting larger guests, the problem of rigidifying their structures has yet to be fully solved. Thus, the relationship between their structural flexibility and efficiency in molecular recognition processes has not yet been systematically studied. In this regard, it is also interesting to note that most authors consider a calixarene to be blocked when the groups introduced at the lower rim prevent the *cone-to-cone* ring inversion. Nevertheless, in a study aimed at correlating the structural flexibility of calix[4]arene-based cavitands with their binding abilities, we have recently demonstrated for the first time the role of rigidity as a control element on the efficiency of recognition processes.[12] The data obtained strongly support the idea that the design of a more complex receptor acting through weak host−guest interactions, where the *active binding site* is represented by the apolar cavity of a calix[4]arene, should contain its rigidity as structural information stored over the whole architecture.

An attractive target was thus the synthesis of rigid and cavity-extended receptors derived from calix[4]arenes for the recognition of tetraalkylammonium and *N*-methylpyrid-

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inium cations as models of the species central to biological processes or of environmental concern.

To this end, the structure of the calix[4]arene-bis(crown-3) **(1)**, in which the conformational flexibility of the molecular skeleton is prevented,[13] was chosen as a building block for the design and synthesis of more complex receptors.

We report herein on the synthesis of a series of new neutral hosts derived from the head-to-head linkage[14] of two rigid calix[4]arene subunits, with bridges that, by variation of their nature, geometry, and length, could be used as control elements to orientate and span the two cavities. We also report on the binding abilities of these new hosts, investigated by ^{1}H NMR in $CDCl_3$ and $CD_3CN/CDCl_3$ solutions, towards a set of simple ammonium and pyridinium cations of different shapes and sizes with the aim of clarifying the role of the host size and rigidity in the recognition of cations through cation−π interactions. The role of ion-pairing and solvent competition has also been studied.

Results and Discussion

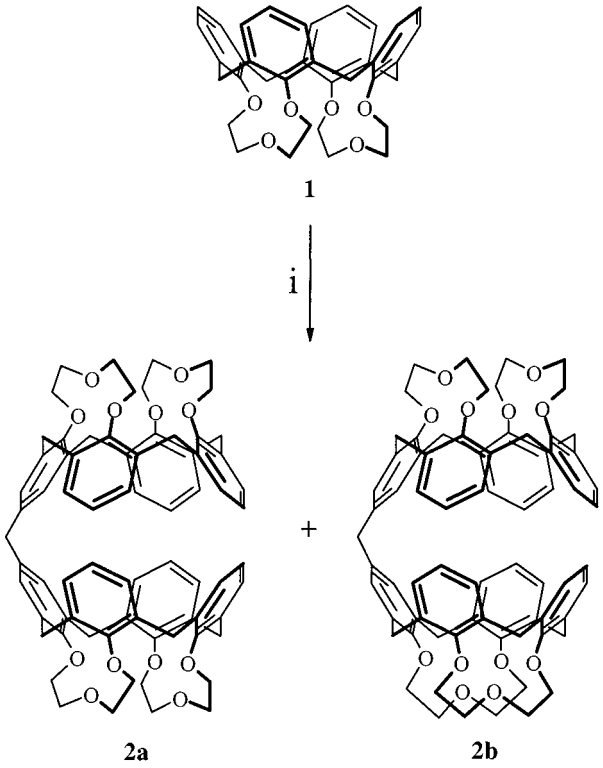
Design and Synthesis of the Hosts

Examination of molecular models showed that a methylene group linking the aromatic rings of two calix[4]arene-bis(crown-3) units **1** would result in sufficient separation and a convergent orientation between the subunits, which would then define an almost spherical cavity. On the other hand, incorporation of linear and rigid ethynyl and butadynyl groups would allow us to increase the span between the two hemispheres, which would then assume a quite divergent orientation and define a more elongated elliptical cavity. Furthermore, the azo group was considered as a spacer to assess the possibility of switching the mutual orientation of the two calixarenes photochemically.

In all double calix[4]arenes, the two subunits are still free to rotate about the bridge, thus allowing the two rigid caps to adapt in response to a potential guest and possibly cooperate in binding.

The molecular models of the various double calix[4]arenes show that the bridging of the two subunits can lead to isomers, where the crown moieties of the two different calixarenes are parallel (e.g. **2a**, Scheme 1), giving rise to a pair of enantiomers, or *anti*-parallel (e.g. **2b**, Scheme 1), giving a *meso* compound. This may open up new possibilities in the context of recognition of chiral quaternary ammonium cations.

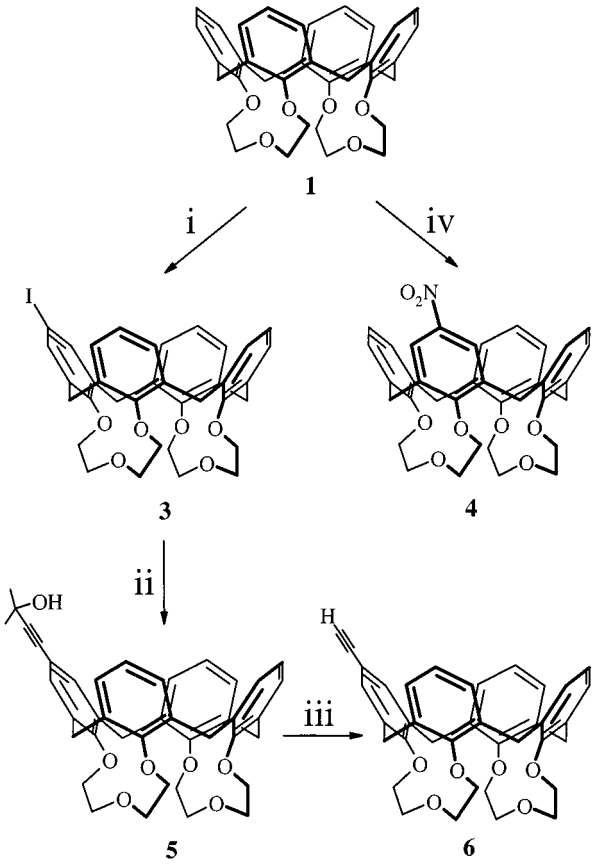
Thus, from the reaction of **1** with *para*-formaldehyde in dichloromethane using trifluoroacetic acid as catalyst, the mono-bridged dimeric fraction **2a**,**b** was isolated in 25% yield. Since all attempts to separate the diastereoisomers proved unsuccessful,[15] this fraction was characterized and studied as a mixture. In its ^{1}H NMR spectrum, compound **2** shows a diagnostic singlet correponding to two protons at δ = 3.62, while in the ^{13}C NMR spectrum a signal is seen at δ = 40.7. These signals are consistent with a mono-bridged compound. As a result of the bridge, the eight equatorial and eight axial methylene protons of the two calixarene units are seen as four sets of doublets (see Experimental Section).



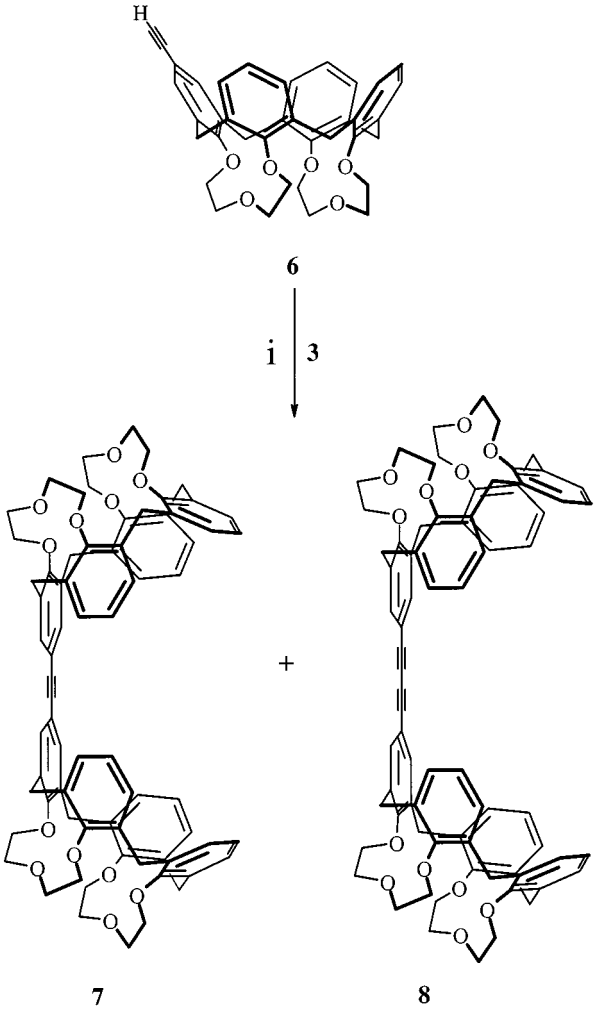
Scheme 1. (i) $(CH_2O)_n$, CF_3COOH, CH_2Cl_2, room temp.

The general synthetic challenge of obtaining double calixarenes connected by bridges that cannot be introduced directly by electrophilic aromatic substitution first required the development of procedures for the mono-functionalization of calix[4]arene-bis(crown-3) **1** with groups suitable for coupling reactions. Careful choice of the reaction conditions and the ratio of the reagents was chosen as a strategy for the mono-functionalization of **1**, rather than the introduction the two "crown" chains at the lower rim of an already mono-functionalized calix[4]arene at the upper rim and subsequent coupling. Thus, by applying methodologies already developed in our laboratories for the tetra-functionalization of flexible tetraalkyloxycalix[4]arene, the monoiodo derivative **3** was obtained in reasonable yield,[16] whereas the mononitro analogue **4** was obtained in 30% yield by reacting **1** with HNO_3 in CH_3COOH.

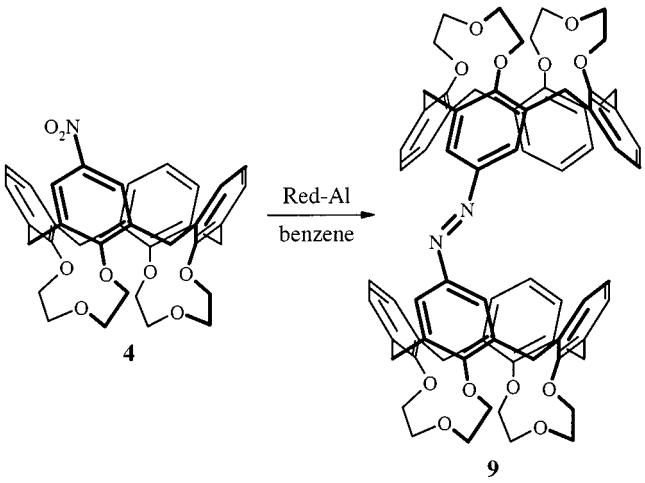
The double calix[4]arene incorporating an ethynyl spacer was then obtained by reacting the monoiodo derivative **3** with 3,3-dimethylpropargyl alcohol using $Pd(PPh_3)_4$/CuI as catalyst to give **5**, which was easily transformed into its ethynyl analogue **6** in almost quantitative yield using NaH as base in toluene solution (see Scheme 2). Coupling of **6** with **3** gave **7** in 80% yield (Scheme 3). As an interesting by-product of this Heck-type coupling reaction, the double calix[4]arene **8**, having a butadynyl spacer between the two subunits, was also obtained in 17% yield. The ^{1}H NMR spectra of **7** and **8** are very similar and thus they were characterized on the basis of their ^{13}C NMR spectra. Specifically, besides the upfield shift of the aromatic carbon in-



Scheme 2. (i) CF_3COOAg, I_2, $CHCl_3$, reflux; (ii) $HC{\equiv}CC(CH_3)_2OH$, $Pd[P(C_6H_5)_3]_4$, CuI, $N(C_2H_5)_3$; (iii) NaH, toluene, T = 80 °C; (iv) 65% aq. HNO_3, CH_3COOH



Scheme 3. (i) $Pd[P(C_6H_5)_3]_4$, CuI, $CH_2Cl_2/N(C_2H_5)_3$



Scheme 4. Red-Al (65% W/V in toluene), benzene, 0° C

volved in the bridge (δ = 116.7 in both hosts), which is also observed for the corresponding ethynyl derivative **6**, a signal at δ = 91.9 and two signals at δ = 81.2 and 72.8 due to the acetylenic carbon atoms are observed for **7** and **8**, respectively. The mass spectra confirmed the identities of these compounds.

The double calix[4]arene **9** incorporating an azo group as the bridging unit was obtained in 70% yield as a pale-yellow solid starting from the mononitro derivative **4** using Red-Al as a coupling agent in dry benzene solution (Scheme 4).[17] The *trans* geometry of the two calix[4]arene subunits about the nitrogen double bond was established by UV spectrophotometry. All attempts to switch from the *trans* to the *cis* form through UV irradiation proved unsuccessful.

Binding Studies

The complexing abilities of the double calix[4]arenes **2**, **7**, **8**, and **9** and the reference calix[4]arene-bis(crown-3) **(1)** towards a set of model ammonium cations chosen on the basis of their shape, size, and charge distribution were studied by ^1H NMR spectroscopy in $CDCl_3$ solution at 300 K. Thus, tetramethylammonium (TMA) and tetraethylammonium (TEA) were selected as representatives of spherical cations having a symmetrically distributed charge, while the more flat *N*-methylpyridinium (NMP) was chosen to model cations with a non-symmetrical charge distribution. In chloroform, however, these cations are present as tightly-bound ion pairs,[18] and thus in order to clarify the role of the anion on the extent of complexation, their halides (chloride or iodide, depending on solubility) and tosylates (Ts) were studied. To gain further insight into the bind-

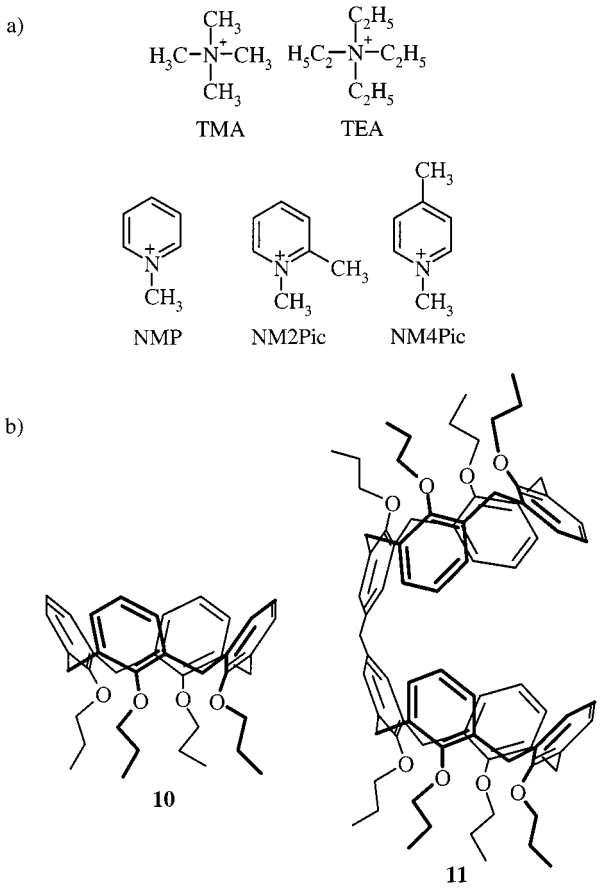


Figure 1. (a) Structural representations of the guests studied and (b) tetrapropyloxycalix[4]arene **10**[8a] and methylene-bridged double calix[4]arene **11**,[19] flexible analogues of rigid **1** and **2**, respectively

ing mode of the flat *N*-methylpyridinium iodide, the recognition of *N*-methyl-2-picolinium (NM2Pic) and *N*-methyl-4-picolinium (NM4Pic) iodides was also studied (see Figure 1a).

The binding abilities of hosts **1**, **2**, **7**, and **8** towards the pyridinium iodides were also tested in the more polar $CDCl_3/CD_3CN$ solvent mixture. This additional set of measurements allowed us to compare the present data with those obtained by Shinkai with the more flexible analogues **10**[8a] and **11**[19] (see Figure 1b).

By adding increasing amounts of a 5×10^{-2} M solution of the host to a 5×10^{-3} M solution of the guest in $CDCl_3$ or $CDCl_3/CD_3CN$, steadily increasing upfield shifts of the resonances were observed for all the guests examined. All the NMR spectra showed time-averaged signals for the free and the complexed species. Having verified a 1:1 stoichiometry for the association by means of continuous variation methods, the stability constants (K_{ass}), based on monitoring of the NCH_3 or NCH_2CH_3 methyl signal, were calculated using methods that have been described previously.[20] The results obtained in $CDCl_3$ and in $CDCl_3/CD_3CN$ are summarized in Table 1 and 2, respectively.

Cavitand **1** binds the flat NMP cation more efficiently than the other guests examined (see Table 1, entries 1−7). It is also clearly evident that this efficiency is strongly dependent on the nature of the counterion. The values of

Table 1. Association constants K_{ass} (M^{-1}), free energies of binding $-\Delta G°$ (kJ mol^{-1}), and guest limiting shift values δ_∞ (ppm) for 1:1 complexes (measured in $CDCl_3$) of tetramethylammonium tosylate (TMA tosylate), tetramethylammonium chloride (TMA chloride), tetraethylammonium tosylate (TEA tosylate), *N*-methylpyridinium tosylate (NMP tosylate), *N*-methylpyridinium iodide (NMP iodide), *N*-methyl-2-picolinium iodide (NM2Pic iodide), and *N*-methyl-4-picolinium iodide (NM4Pic iodide) with hosts **1**, **2**, **7**, **8**, and **9**

Entry	Guest	K_{ass} (M^{-1})[a]	$-\Delta G$ (kJ/mol)	δ_∞(N*Me*, ppm)
Host **1**				
1	NMP tosylate	113(12)	11.7(0.4)	2.8(0.1)
2	NMP iodide	418(78)	15.0(0.5)	2.3(0.3)
3	NM2Pic iodide	79(6)	10.9(0.2)	2.11(0.01)
4	NM4Pic iodide	98(24)	11.4(0.6)	−0.7(0.5)
5	TMA tosylate	33(10)[b]	8.7(0.3)	0.6(0.8)
6	TMA chloride	80(25)[b]	10.9(0.3)	1.6(0.5)
7	TEA tosylate	26(2)	8.1(0.1)	0.95(0.08)
Host **2**				
8	NMP tosylate	1405(123)	18.1(0.4)	0.8(0.2)
9	NMP iodide	> 10.000 [c]	> 23[c]	−
10	NM2Pic iodide	1167(69)	17.6(0.1)	0.85(0.08)
11	NM4Pic iodide	1935(149)	18.9(0.2)	1.2(0.3)
12	TMA tosylate	101(14)	11.5(0.2)	0.6(0.3)
13	TMA chloride	340(92)	14.4(0.5)	0.5(0.2)
14	TEA tosylate	191(61)	13.1(0.4)	0.2(0.1)
Host **7**				
15	NMP tosylate	1232(96)	17.7(0.1)	2.36(0.07)
16	NMP iodide	7260(850)	22.2(0.3)	1.55(0.06)
17	NM2Pic iodide	5713(950)	21.6(0.5)	1.7(0.5)
18	NM4Pic iodide	1632(112)	18.4(0.2)	−0.7(0.2)
19	TMA tosylate	1407(14)	18.08(0.02)	2.0(0.1)
Host **8**				
20	NMP iodide	657(120)	16.2(0.2)	3.0(0.1)
21	NM2Pic iodide	1473(334)	18.2(0.3)	3.8(0.2)
22	NM4Pic iodide	281(10)	14.06(0.05)	0.9(0.2)
23	TMA tosylate	233(50)	13.6(0.3)	1.4(0.1)
Host **9**				
24	NMP tosylate	927(309)	17.0(0.3)	2.0(0.2)
25	NMP iodide	797(275)	16.7(0.5)	0.7(0.3)
26	NM2Pic iodide	3693(668)	20.5(0.4)	1.48(0.04)
27	NM4Pic iodide	2450(325)	19.5(0.2)	0.1(0.1)
28	TMA tosylate	54(8)	9.9(0.1)	−0.5(0.2)

[a] Measured at $T = 300$ K by ^1H NMR spectroscopy, titrating a solution of the guest [$G_0 = 0.001 \div 0.0005$ M^{-1}], with a solution of the host [$H_0 = 0.001 \div 0.005$ M^{-1}], following the *N*−Me signal for the imminium salts and the *Me* group for the tetraalkylammonium guests. All values result from at least duplicate experiments, standard deviations are in brackets. − [b] See ref. [12a] − [c] the K_{ass} could not be accurately determined because of the extensive broadening of the guest's signals during titration.

$K_{ass} = 418$ M^{-1} and 113 M^{-1} measured for NMP iodide and NMP tosylate, respectively, together with the observation that the tosylate proton resonances are unaffected by complex formation during NMR experiments, are consistent with a binding process that does not involve separation of the ion pair. Although the observed difference may be rationalized by considering the different charge distributions on the cation as a result of its interactions with the two different anions, it is reasonable to assume that these binding processes are controlled by the steric requirements of the ion pair, in which the anion is tightly bound to the cation, and that this drives the host−guest interaction. As expected, no such large difference was observed in the case of the spherical TMA ion pair, which can bind with only minor steric adjustments.

Among the guests studied, TEA proved to be the least efficiently bound. It can thus be considered as being too

large, its charge probably also being too shielded for an efficient interaction with the cavity. A rather large difference is also seen in the binding efficiencies of receptor **1** towards NMP iodide and the two *N*-methylpicolinium iodides, which differ in the presence of a methyl group on the pyridine ring or in its relative position. The two *N*-methylpicolinium isomers (NM2Pic and NM4Pic) were found to be bound with comparable K_{ass} values, but less efficiently than NMP iodide. These results can be partially explained in terms of the respective binding modes (vide infra). The difference can also be attributed to greater charge dispersion over the heteroaromatic rings of the two picolinium cations due to the electron-donating ability of the methyl group.

As expected, all the double calix[4]arenes **2**, **7**, **8**, and **9** were found to bind the chosen guests more efficiently than the simple cavitand **1** (see Table 1), confirming the hypothesis that the extension of the calix[4]arene cavity with a larger number of π-donor binding sites strongly benefits complexation.

As also seen for **1**, they bind the spherical TMA tosylate less efficiently than the flat pyridinium guests, although a quite remarkable difference is apparent within the host series. Thus, compound **7** shows a K_{ass} = 1407 M^{-1} (entry 19, Table 1), while for **9** a value of K_{ass} = 54 M^{-1} is found (entry 28, Table 1). Although the bridge itself might act as an additional binding site, it is more likely that the observed efficiencies stem from the abilities of the hosts to allow the two hemispheres to converge around the guest. It can be hypothesized that in the case of **7** the span and orientation of the two calixarene caps is better suited for co-operative binding of the TMA tosylate, whereas in **8** the distance between the two caps probably exceeds the diameter of the guest, leading to less efficient binding. On the contrary (and unexpectedly), receptors **2** and **9**, despite seemingly possessing the requisite geometry on the basis of molecular models, exhibit lower efficiencies (Table 1, entries 12 and 28, respectively). This behaviour may be tentatively explained by considering that the angle imposed by the bridge in **2**, or the insufficient span between the hemispheres in both **2** and **9** prevents these hosts from spanning the two subunits upon binding and then relaxing to an unstrained, closed, occupied cavity, in which the cation is completely separated from its counterion. It thus seems likely that in these two receptors the two cavities do not co-operate efficiently with TMATs and, using only one cavity, they exhibit binding efficiencies comparable with that of cavitand **1**.

The varying degree of shape and size matching between the various double calix[4]arene cavities and the three *N*-methylpyridinium iodides probably accounts for the distribution of K_{ass} values, which range from 7260 M^{-1} (host **7** ⊃ NMP iodide; Table 1, entry 16) to 281 M^{-1} (host **8** ⊃ NM4Pic iodide; Table 1, entry 22). Except in the case of **9**, NMP iodide is the most efficiently bound of these three aromatic guests, while NM4Pic is least efficiently complexed. Interestingly, the hosts that exhibit the larger association constant with the NMP iodide cation (**2** and **7**) also show an enhanced difference (compared with cavitand **1**) between the NMP iodide and its tosylate (NMP tosylate).

Table 2. Association constants K_{ass} (M^{-1}), free energies of binding $-\Delta G°$ (kJ mol^{-1}), and guest limiting shift values δ_∞ (ppm) for 1:1 complexes (measured in $CDCl_3/CD_3CN$, 9:1) of *N*-methylpyridinium tosylate (NMP tosylate), *N*-methylpyridinium iodide (NMP iodide), *N*-methyl-2-picolinium iodide (NM2Pic iodide), and *N*-methyl-4-picolinium iodide (NM4Pic iodide) with hosts **1**, **2**, **7**, and **8**

Entry	Guest	K_{ass} (M^{-1})[a]	$-\Delta G$ (KJ/mol)	δ_∞(N*Me*, ppm)
Host **1**				
1	NMP iodide	28(10)	8.3(0.5)	2.7(0.3)
2	NM2Pic iodide	53(5)	9.9(0.1)	3.8(0.1)
3	NM4Pic iodide	27(5)	8.2(0.2)	2.5(0.3)
Host **2**				
4	NMP iodide	197(20)	13.2(0.1)	0.4(0.1)
5	NM2Pic iodide	100(22)	11.5(0.2)	2.4(0.3)
6	NM4Pic iodide	127(40)	12.1(0.3)	3.6(0.2)
Host **7**				
7	NMP iodide	497(45)	15.5(0.1)	1.7(0.1)
8	NM2Pic iodide	568(67)	15.8(0.2)	1.7(0.2)
9	NM4Pic iodide	451(29)	15.2(0.1)	1.2(0.1)
Host **8**				
10	NMP iodide	313(44)	14.3(0.2)	2.1(0.2)
11	NM2Pic iodide	257(30)	13.8(0.1)	2.9(0.1)
12	NM4Pic iodide	104(18)	11.6(0.2)	0.9(0.5)

[a] Measured at T = 300 K by ^{1}H NMR spectroscopy, titrating a solution of the guest [$G_0 = 0.001 \div 0.0005$ M^{-1}], with a solution of the host [$H_0 = 0.001 \div 0.005$ M^{-1}], following the *N*−Me signal for the imminium salts and the *Me* group for the tetraalkylammonium guests. All values result from at least duplicate experiments, standard deviations are in brackets.

Moreover, in the case of NMP tosylate complexed by **2** and **7**, a 0.1 ppm upfield shift of the ^{1}H NMR signals due to the protons in the 2- and 6-positions of the sulfonate anion is observed. As we demonstrated in our previous studies,[12a] such a shift can be considered as being indicative of ion-pair separation. It thus seems likely that receptors **2** and **7** bind the NMP cation with partial separation of the ion pair. Since no variation in the chemical shifts of the tosylate protons is observed for hosts **8** and **9**, it is reasonable to assume that they bind the NMP cation as a tightly-bound ion pair.

As expected, the association constants measured in $CDCl_3/CD_3CN$ were generally almost an order of magnitude lower for all the guests (see Table 2) owing to the presence of the more polar acetonitrile in the solvent mixture. The efficiency order was generally maintained. This marked decrease in the binding constants may be explained considering that the (relatively) acidic CD_3 group of the CD_3CN molecule could also act as a potential guest and thus compete for the receptor cavities. Indeed, it became apparent in our previous studies that the apolar cavity of rigid calix[4]arenes can host small neutral organic guests having acidic CH groups.[12a] In order to verify this hypothesis and to assess the extent of competition by acetonitrile, a blank titration was performed in $CDCl_3$ using **1** as the host and acetonitrile as the guest. On adding increasing amounts of CH_3CN to a $CDCl_3$ solution of **1**, an upfield shift of the guest signal (by up to 1 ppm) was observed, and a 1:1 association constant of 6 ± 1 M^{-1} could be determined.

The effect of solvent competition in molecular recognition phenomena has been quantitatively studied by Collet

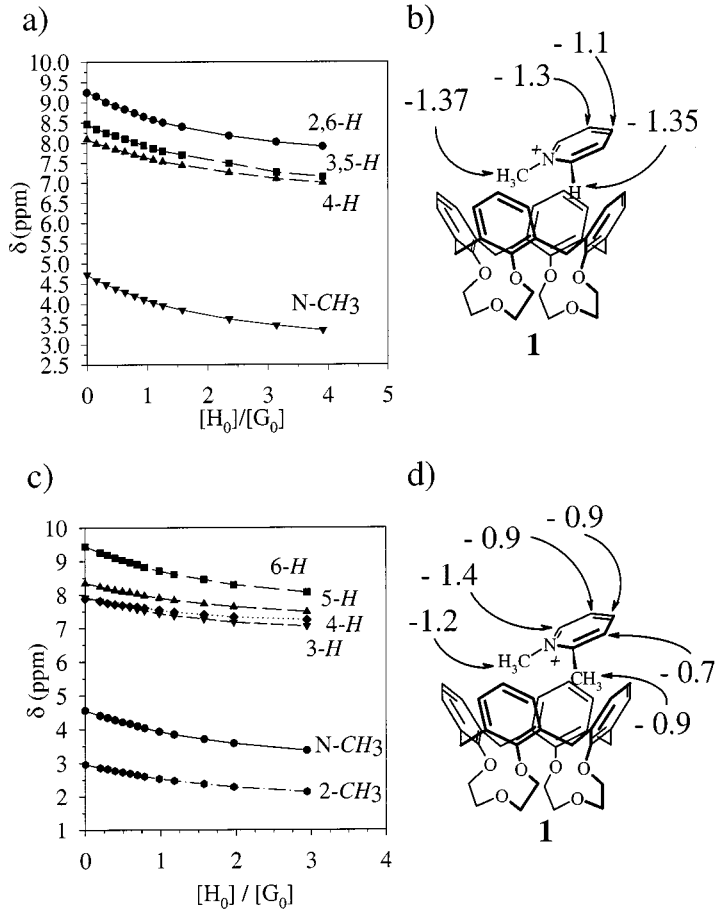


Figure 2. (a) ^{1}H NMR titration of NMP iodide with host **1** at T = 300 K in $CDCl_3$; symbols denote experimental data points relative to the signals of the guest (● = 2,6-H; ■ = 3,5-H; ▲ = 4-H; ▼ = *N*−Me); lines are best-fit curves calculated by non-linear regression; (b) proposed structure of the complex of **1** with NMP iodide; (c) ^{1}H NMR titration of NM2Pic iodide with host **1** at T = 300 K in $CDCl_3$; symbols denote experimental data points relative to the signals of the guest (■ = 6-H; ▲ = 5-H; ◆ = 4-H; ▼ = 3- H; ● = *N*−Me; ⬣ = 2-CH_3); lines are best-fit curves calculated by non-linear regression; (d) proposed structure of the complex of **1** with NM2Pic iodide

and co-workers.[21] They devised a simple relationship, $K_r = K_{ass}(1 + K_s[S])$, to correlate the "apparent" K_{ass} to the "real" K_r stability constant in cases where one of the components of the solvent mixture is a competing guest. In this equation, K_{ass} is the binding constant determined in the presence of the competing solvent and K_s is the association constant of the host with the competing solvent present at concentration [*S*]. By assuming that chloroform does not compete as a guest and considering that the data reported in Table 2 were obtained in solutions where [CH_3CN] = 1.91 M and K_s = 6 M^{-1}, the above equation was applied in the case of receptor **1** and NMP iodide. The calculated value of K_r = 347 indicated a very good agreement between the association constants measured in chloroform (Table 1, entry 2, K_{ass} = 418) and that calculated in acetonitrile/chloroform (Table 2, entry 1, K_{ass} = 28). Attempts to extend this ^{1}H NMR approach to **2** proved unsuccessful as it was found that this host forms complexes of variable stoichiometry with CH_3CN, thus precluding the determination of the binding constants and the possibility of quantifying the corresponding K_s.

Shinkai and co-workers[8a,19] have reported that, in the same solvent mixture, tetrapropyloxycalix[4]arene **10** (Figure 2), which represents a flexible analogue of **1**, binds NMP iodide with K_{ass} = 6.9 M^{-1}, while the double calix[4]arene **11**, which represents a flexible analogue of **2**, binds the same guest with K_{ass} = 480 M^{-1}. In the light of previous studies,[12a,22] which ruled out the possibility of flexible tetraalkyloxycalix[4]arenes forming stable inclusion complexes with neutral molecules, solvent competition can be excluded for both compounds **10** and **11**. The different efficiencies of **1** and **2** compared with **10** and **11**, respectively, can thus be ascribed to competition of acetonitrile in the case of the rigid hosts. The dissection of solvent competition in the case of **1** ⊃ NMP iodide in $CDCl_3/CD_3CN$ reveals that cavitand **1** exhibits an efficiency almost two orders of magnitude higher than that of **10**. This supports the hypothesis that rigidity of the host is among the most important structural requirements for enhanced efficiency.

Binding Mode

In contrast to the spherical TMA, where the positive charge is symmetrically dispersed over all four identical methyl groups, in the three flat aromatic cations the positive charge is mainly located on the NCH_3 moiety and on the

carbon atoms in the 2- and 6-positions of the heterocyclic ring.

By analysis of the upfield shifts ($\Delta\delta$) of the various proton signals of the three different *N*-methylpyridinium cations upon ^{1}H NMR measurements in $CDCl_3$ with hosts **1**, **2**, **7**, **8**, and **9**, some features of the structures of the complexes formed can be hypothesized. In particular, along with the protons of the $N-CH_3$ group, the more "acidic" aromatic protons in the 2- and 6-positions could indeed serve as a probe to obtain structural information on the complexes formed. Moreover, the methyl groups present in the 2- or 4-positions of the two picolinium isomers allowed further insight into steric effects and guest orientation within the cavity of the host.

A common feature of the trends in $\Delta\delta$ for all the hosts is that large upfield shifts in the signals of both the $N-CH_3$ groups and the aromatic 2-H and/or 6-H protons of the three guests are observed, thus indicating beyond doubt that they are in close proximity and are strongly bound in the host cavities through $CH_3-\pi$ and $=CH-\pi$ interactions. Moreover, the magnitude of the shielding effect is larger when the guests are bound by double calixarenes.

It was also observed that the protons in the 3-, 4-, and 5-positions of both the NMP (see Figure 2a) and NM2Pic (see Figure 2c) cations, as well as the 2-CH_3 protons of the latter, which were not expected to participate in binding on the basis of their acidities, exhibit upfield shifts with $\Delta\delta$ increments comparable with those seen for the $N-CH_3$ and 2- and/or 6-protons with all the hosts. Shinkai and coworkers[8a] made a similar observation on studying the complexation of NMP iodide with the flexible **10**. They hypothesized that in the complex the guest assumes an axial orientation with its $N-CH_3$ unit being deeply embedded in the host, a situation in which the aromatic cavity extends its shielding effect to all the other guest protons, even those not directly involved in binding. However, it appeared to us that this proposed binding mode is not wholly applicable in the present case, where rigid hosts are used. In fact, with such a model, the 2-CH_3 of NM2Pic should, for steric reasons, prevent the deep inclusion of its $N-CH_3$ moiety, which should thus exhibit only a minor upfield shift compared with that of NMP.

On the other hand (see Table 1), the differences between the K_{ass} values for NMP iodide and NM2Pic with all the hosts do not suggest that the 2-CH_3 group of NM2Pic has a significant effect on the extent of host–guest association. Moreover, in all cases, all the protons of both NMP and NM2Pic exhibit $\Delta\delta$ increments comparable with those seen for the corresponding $N-CH_3$ groups (see Figure 3a). On the basis of these observations, it is reasonable to assume

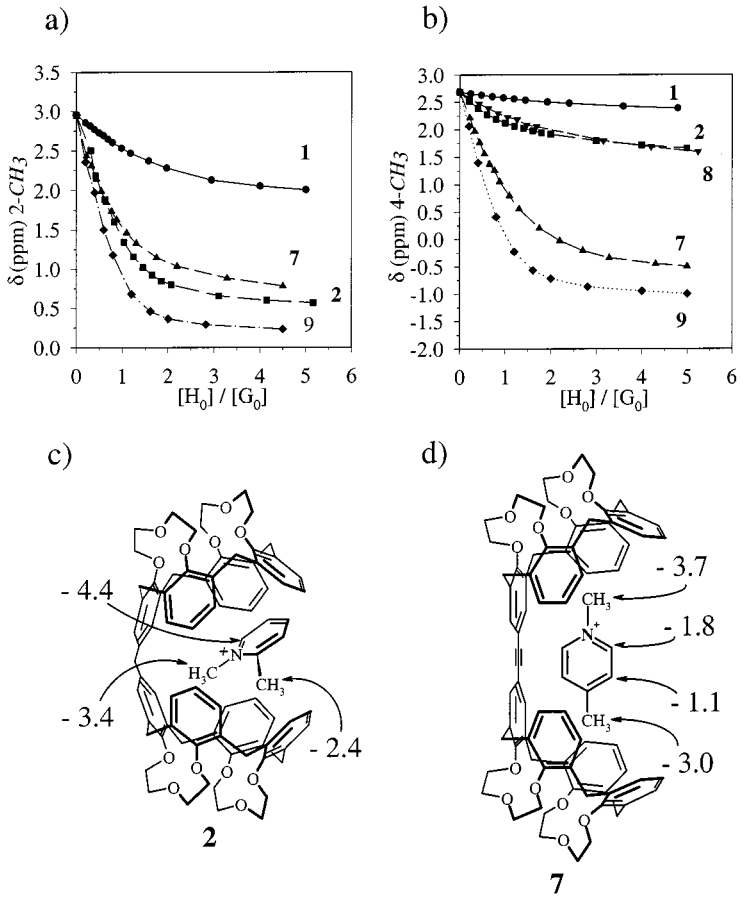


Figure 3. ^{1}H NMR titrations of (a) NM2Pic iodide and (b) NM4Pic iodide with host **1** (●), **2** (■), **7** (▲), **8** (▼), and **9** (◆) at T = 300 K in $CDCl_3$; symbols denote experimental data points relative to the 4-Me (a) and 2-Me (b) signals, respectively, of the guest; lines are best-fit curves calculated by non-linear regression; proposed structures of the complexes between (c) **2** and NM2Pic iodide and (d) **7** and NM4Pic iodide ($\Delta\delta$ are experimental chemical shift differences observed for the signals of the guest during titrations in $CDCl_3$)

that these two guests are bound in an almost equatorial orientation within the cavities of each of the receptors.

A further indirect confirmation of this hypothesis was provided by an examination of the 4-CH_3 group chemical shift variation of NM4Pic. The protons of the 4-CH_3 group resonate further upfield when NM4Pic is bound by the more elongated receptors **7** and **9** (see Figure 3b), while for the other hosts this shift is less pronounced. This indicates that NM4Pic minimizes its energy by assuming an axial orientation inside the cavities of **7** (see Figure 3d) and **9**. It is thus reasonable to assume that in the case of **2** ⊃ NM4Pic the 4-CH_3 cannot enter the host cavity and remains outside, distant from the receptors, whereas in **8** ⊃ NM4Pic the interaction with the N−CH_3 moiety holds the guest in close proximity to one of the calixarene caps, preventing close interaction of the 4-CH_3 group with the other.

In conclusion, new methodologies for the head-to-head bridging of two rigid bis(crown-3)-calix[4]arenes with bridges of varying length and nature have been devised. The bridge, by dictating the orientation and distance between the two calix[4]arene caps, constitutes a new control element in determining the efficiency of ammonium and pyridinium ion-pair complexation. All the synthesized double calix[4]arenes have been shown to exhibit binding efficiencies much higher than that of the reference cavitand **1**.

Experimental Section

General Remarks: All reactions were carried out under nitrogen; all solvents were freshly distilled under nitrogen and stored over molecular sieves for at least 3 h prior to use. All other reagents were of reagent grade quality as obtained from commercial suppliers and were used without further purification. − NMR: AMX 400 (400 MHz for ^1H), Bruker AC 300 (300 MHz and 75 MHz for ^1H and ^{13}C, respectively). For ^1H- and ^{13}C NMR, $CDCl_3$ as solvent, TMS as internal standard. − MS: Finnigan MAT SSQ 710 (CI mode, CH_4 as gas reagent). − Analytical thin-layer chromatography was performed on precoated silica gel plates (Merck, 60 F_{254}); column chromatography was performed on silica gel (ICN, particle size 63−200 and 32−63). − Compound **1** was synthesized according to literature procedures.[13] As observed by other authors,[23] the elemental analyses of calixarenes are very often incorrect. Nevertheless, the spectral data were in full agreement with the proposed structures of these new compounds.

Double Calix[4]arene 2: Paraformaldehyde (0.04 g, 1.33 mmol) was suspended in a mixture of CH_2Cl_2 (120 mL) and CF_3COOH (10 mL). The resulting suspension was stirred at room temp. until dissolution was complete, and then calix[4]arene **1** (1.0 g, 1.77 mmol) was added. The pale-purple mixture was stirred for 4 h at room temp. and then quenched with water (200 mL). The organic layer was separated, washed with saturated Na_2CO_3 solution (CAUTION!) until neutral, dried with Na_2SO_4, and the solvent was completely evaporated in vacuo. Purification of the residue by preparative TLC (ethyl acetate/hexane, 35:65) gave 0.25 g (25%) of **2**; m.p. 294 °C (dec.). − ^1H NMR (400 MHz, $CDCl_3$): δ = 3.10−3.28 (m, 8 H, H_{eq} of ArCH_2Ar), 3.58 (s, 2 H, ArCH_2Ar′), 3.81−3.94 and 4.16−4.38 (2 m, 16 H, OCH_2CH_2O), 4.43 and 4.49 (2 d, $J_1 = J_2$ = 12.1 Hz, 4 H, H_{ax} of ArCH_2Ar), 4.97 and 5.02 (2 d, $J_1 = J_2$ = 12.0 Hz, 4 H, H_{ax} of ArCH_2Ar), 6.40−6.46 (m, 4 H, Ar*H*), 6.72−6.81 (m, 10 H, arom.), 6.89 (d, J = 7.6 Hz, 4 H, Ar*H*), 7.06 (d, J = 8.0 Hz, 4 H, Ar*H*). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.7, 30.6, 40.7, 74.1, 75.2, 76.2, 115.8, 123.7, 127.8, 127.9, 128.0, 128.5, 128.7, 128.9, 129.0, 129.2, 134.9, 135.2, 135.5, 135.8, 136.1, 136.3, 153.6, 154.5, 155.5. − CI(+) MS: *m*/*z* = 1141 (100) [MH^+]. − $C_{73}H_{72}O_{12}$ (1141.4): calcd. C 76.82, H 6.36; found C 76.21, H 6.41.

5-Iodo-25,26-27,28-bis(crown-3)-calix[4]arene 3: To a solution of **1** (2.0 g, 3.54 mmol) in $CHCl_3$ (200 mL) was added CF_3COOAg (0.55 g, 2.49 mmol). The resulting mixture was refluxed with vigorous stirring for 30 min. and then iodine (0.64 g, 2.52 mmol) was added. After a further 30 min., the solid AgI formed was filtered off and the filtrate was treated with saturated aq. Na_2SO_3 solution until the purple colour had disappeared. The organic layer was separated, washed twice with water (2 × 100 mL), dried (Na_2SO_4), and the solvent was completely evaporated in vacuo. Purification of the residue by column chromatography (ethyl acetate/hexane, 40:60) gave 0.98 g (40%) of **3**; m.p. 285 °C (dec.). − ^1H NMR (300 MHz, $CDCl_3$): δ = 3.16, 3.22, 3.24, and 3.29 (4 d, $J_1 = J_2 = J_3 = J_4$ = 12.3 Hz, 4 H, H_{eq} of ArCH_2Ar), 3.8−3.9 and 4.2−4.3 (2 m, 16 H, OCH_2CH_2O), 4.43, 4.50, 4.99, and 5.05 (4 d, $J_1 = J_2 = J_3 = J_4$ = 12.3 Hz, 4 H, H_{ax} of ArCH_2Ar), 6.7−6.8 and 6.9−7.1 (2 m, 9 H, arom.), 7.32 and 7.34 (2 d, J = 2.1 Hz, 2 H, arom.). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 29.4, 29.7, 30.4, 30.7, 74.6, 74.8, 76.2, 76.3, 76.4, 97.3, 123.8, 123.9, 127.9, 128.1, 128.3, 129.0, 129.3, 134.5, 134.6, 135.5, 135.55, 135.6, 136.9, 137.7, 138.2, 138.4, 155.1. − CI(+) MS: *m*/*z* = 691.4 (20) [MH^+], 564.7 (30) [MH − I^+]. − $C_{36}H_{35}IO_6$ (690.6): calcd. C 62.61, H 5.11; found C 62.34, H 5.20.

5-Nitro-25,26-27,28-bis(crown-3)-calix[4]arene 4: To a solution of **1** (0.2 g, 0.35 mmol) in CH_2Cl_2 (35 mL) were added CH_3COOH (0.5 mL, 1.75 mmol) and 65% aq. HNO_3 (0.7 mL, 3.2 mmol). The resulting mixture was stirred at room temp. for 4 h, then poured into iced water (100 mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated, washed with water (2 × 100 mL) and brine (1 × 100 mL), dried (Na_2SO_4), and the solvent was completely evaporated in vacuo. Purification of the residue by column chromatography (ethyl acetate/hexane, 50:50) gave 0.065 g (30%) of **4**; m.p. 190 °C (dec.). − ^1H NMR (300 MHz, $CDCl_3$): δ = 3.24 and 3.29 (2 d, J = 12.1 and 12.2 Hz, 2 H, H_{eq} of ArCH_2Ar), 3.30 and 3.35 (2 d, J = 12.3 Hz, 2 H, H_{eq} of ArCH_2Ar), 3.80−4.38 and 4.10−4.40 (2 m, 16 H, OCH_2CH_2O), 4.48 and 4.56 (2 d, J = 12.3 Hz, 2 H, H_{ax} of ArCH_2Ar), 5.05 and 5.15 (2 d, J = 12.1 and 12.2 Hz, 2 H, H_{ax} of ArCH_2Ar), 6.72 (t, 1 H, J = 7.5 Hz, arom.), 6.81 and 6.82 (2 t, 2 H, J = 7.5 and 7.6 Hz, arom.), 6.9−7.1 (m, 6 H, arom.), 7.88 (s, 2 H, arom.). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 29.7, 30.7, 73.8, 74.4, 75.1, 76.1, 76.5, 76.9, 123.8, 124.2, 124.8, 128.0, 128.8, 129.1, 129.6, 134.1, 134.4, 135.0, 135.9, 136.2, 136.9, 143.5, 154.9, 155.4, 160.7. − CI(+) MS: *m*/*z* = 610.5 (100) [MH^+]. − $C_{36}H_{35}NO_8$ (609.7): calcd. C 70.92, H 5.79, N 2.30; found C 70.18, H 5.94, N 2.25.

5-(3,3-Dimethyl-3-hydroxy)propynyl-25,26−27,28-bis(crown-3)-calix[4]arene 5: To a solution of **3** (0.5 g, 0.72 mmol) in oxygen-free NEt_3 (20 mL) were added $Pd(PPh_3)_4$ (33 mg, 0.03 mmol), CuI (6 mg, 0.03 mmol), and 2-methyl-3-butyn-2-ol (0.12 g, 1.45 mmol). The resulting mixture was stirred at 50 °C overnight and then the solvent was completely evaporated. The residue was partitioned between ethyl acetate (100 mL) and 10% aq. HCl (50 mL). The organic layer was separated, washed with brine (2 × 100 mL), dried with Na_2SO_4, and the solvent was completely evaporated in vacuo. Purification of the residue by column chromatography (ethyl acetate/hexane, 40:60) gave 0.37 g (80%) of **5**; m.p. 203−205 °C. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.56 [s, 6 H, C≡CC(CH_3)$_2$OH],

3.17, 3.22, and 3.26 (3 d, J = 12.0 Hz, 4 H, H_{eq} of ArCH_2Ar), 3.8−3.9 and 4.2−4.3 (2 m, 16 H, OCH_2CH_2O), 4.45, 4.48, 5.00, and 5.03 (4 d, J = 12.0 Hz, 4 H, H_{ax} of ArCH_2Ar), 6.72−6.78 and 6.97−7.03 (2 m, 9 H, arom.), 7.07 and 7.09 (2 d, J = 2.0 Hz, 2 H, arom.). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 29.5, 30.4, 31.3, 74.7, 76.3, 123.5, 127.9, 128.9, 134.7, 135.3, 156.3. − CI(+) MS: m/z = 647.5 (100) [MH + 1$^+$], 646.2 (100) [M$^+$], 629.3 (60) [M$^+$ − OH]. − $C_{41}H_{42}O_7$ (646.8): calcd. C 62.61, H 6.54; found C 62.32, H 6.66.

5-Ethynyl-25,26−27,28-bis(crown-3)-calix[4]arene 6: To a solution of **5** (0.3 g, 0.46 mmol) in dry toluene (25 mL) was added NaH (0.022 g, 0.92 mmol) and the resulting heterogeneous mixture was stirred at 70 °C for 4 h. The solvent was then completely evaporated and the residue was partitioned between 10% aq. HCl (25 mL) and ethyl acetate (50 mL). The organic layer was separated, washed twice with water (2 × 100 mL), dried (Na_2SO_4), and the solvent was completely evaporated in vacuo. Purification of the residue by trituration with methanol gave 0.24 g (90%) of **6**; m.p. 186−189 °C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.90 (s, 1 H, C≡CH), 3.18, 3.22, 3.23, and 3.27 (4 d, 4 H, H_{eq} of ArCH_2Ar), 3.80−3.95 and 4.20−4.33 (2 m, 16 H, OCH_2CH_2O), 4.48, 4.50, 5.04, and 5.06 (4 d, J_1 = J_3 = 12.2, J_2 = J_4 = 12.1 Hz, 4 H, H_{ax} of ArCH_2Ar), 6.70−6.78 and 6.95−7.03 (2 m, 9 H, arom.), 7.15 and 7.17 (2 d, J = 2.0 Hz, 2 H, arom.). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 29.5, 29.7, 30.5, 30.7, 74.4, 74.6, 75.6, 76.2, 76.3, 76.4, 84.1, 116.9, 123.76, 123.80, 128.0, 128.1, 128.9, 129.0, 129.2, 123.1, 133.0, 134.7, 134.9, 135.5, 135.6, 135.7, 135.9, 155.1. − CI(+) MS: m/z = 589.3 (100) [MH$^+$], 563.4 (80) [M$^+$ − C≡CH]. − $C_{38}H_{36}O_6$ (588.7): calcd. C 77.53, H 6.16; found C 76.95, H 6.29.

Double Calix[4]arenes 7 and 8: To a solution of **3** (0.4 g, 0.68 mmol) in oxygen-free NEt_3 (50 mL) were added $Pd(PPh_3)_4$ (0.032 g, 0.028 mmol), CuI (0.005 g, 0.028 mmol), and derivative **6** (0.47 g, 0.68 mmol). The resulting mixture was stirred at 50 °C overnight and then the solvent was completely evaporated and the residue was partitioned between ethyl acetate (100 mL) and 10% aq. HCl (50 mL). The organic layer was separated, washed with brine (2 × 100 mL), dried with Na_2SO_4, and the solvent was completely evaporated. Purification of the residue by column chromatography (ethyl acetate/hexane, 40:60) gave 0.14 g (80%) of **7** (R_f = 0.24) and 0.068 g (17%) of **8** (R_f = 0.18).

7: m.p. > 320 °C. − ^{1}H NMR ($CDCl_3$): δ = 3.21−3.30 (m, 8 H, H_{eq} of ArCH_2Ar), 3.86−3.92 and 4.24−4.26 (2 m, 32 H, OCH_2-CH_2O), 4.46 and 4.50 (2 d, J = 11.9 Hz, 4 H, H_{ax} of ArCH_2Ar), 5.02 and 5.04 (2 d, J = 12.0 Hz, 4 H, H_{ax} of ArCH_2Ar), 6.74−6.80 (m, 6 H, arom.), 7.00−7.04 (m, 12 H, arom.), 7.13 and 7.15 (2 d, J = 1.8 Hz, 4 H, arom.). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 29.5, 29.7, 30.5, 30.7, 74.6, 76.2, 76.3, 76.4, 91.9, 116.7, 123.7, 128.0, 128.1, 128.2, 129.0, 131.4, 132.3, 134.8, 135.3, 135.5, 155.1. − CI(+) MS: m/z = 1152 (100) [MH + 1$^+$]. − $C_{74}H_{70}O_{12}$ (1151.4): calcd. C 77.20, H 6.13; found C 76.54, H 6.24.

8: m.p. 280 °C (dec.). − ^{1}H NMR ($CDCl_3$): δ = 3.16−3.30 (m, 8 H, H_{eq} of ArCH_2Ar), 3.82−3.92 and 4.27 (m and br. s, 32 H, OCH_2CH_2O), 4.47 and 4.50 (2 d, J = 12.1 Hz, 4 H, H_{ax} of ArCH_2Ar), 5.03 and 5.05 (2 d, J = 12.0 Hz, 4 H, H_{ax} of ArCH_2Ar), 6.74−6.79 (m, 6 H, arom.), 6.98−7.06 (m, 12 H, arom.), 7.16 and 7.17 (2 d, J = 1.8 Hz, 4 H, arom.). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 29.5, 29.7, 30.5, 30.6, 72.8, 74.3, 74.6, 74.7, 76.2, 76.3, 76.4, 82.1, 116.7, 123.8, 128.0, 128.3, 128.9, 129.0, 129.2, 132.4, 133.4, 134.6, 134.8, 135.2, 135.4, 135.5, 135.7, 135.8, 135.9, 155.1, 156.3. − CI(+) MS: m/z = 1176 (100) [MH + 1$^+$]. − $C_{76}H_{70}O_{12}$ (1175.4): calcd. C 77.66, H 6.00; found C 77.10, H 6.15.

Double Calix[4]arene 9: To a solution of **4** (0.12 g, 0.2 mmol) in dry benzene (12 mL) (CAUTION!) maintained at 0 °C was added Red-Al solution (65% *w/v* in toluene, 0.12 mL, 0.4 mmol). The resulting mixture was stirred at room temp. for 1 h and then the reaction was quenched by the slow addition of a small volume of methanol. The solvent was subsequently removed under reduced pressure and the residue was taken up in 10% aq. HCl (30 mL) and extracted with CH_2Cl_2 (50 mL). The organic layer was separated, washed with water (2 × 30 mL) and brine (30 mL), dried (Na_2SO_4), and the solvent was completely evaporated in vacuo. Purification of the residue by preparative TLC (ethyl acetate/hexane, 70:30) followed by trituration with methanol gave 0.08 g (70%) of **9**; m.p. > 300 °C. − ^{1}H NMR ($CDCl_3$): δ = 3.20 and 3.50 (m, 8 H, H_{eq} of ArCH_2Ar), 3.80−4.10 and 4.20−4.40 (2 m, 32 H, OCH_2CH_2O), 4.4−4.6 and 5.0−5.2 (2 m, 8 H, H_{ax} of ArCH_2Ar), 6.7−6.8 (m, 6 H, arom.), 6.9−7.1 (m, 12 H, arom.), 7.50 (s, 2 H, arom.), 7.8−8.0 (m, 2 H, arom.). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 29.7, 30.7, 74.4, 74.8, 76.2, 76.3, 76.4, 122.0, 122.9, 123.8, 123.9, 124.0, 125.5, 126.8, 128.1, 128.2, 128.4, 128.9, 129.1, 129.3, 134.6, 135.4, 135.6, 136.2, 155.0. − CI(+) MS: m/z = 1155 (100) [MH$^+$]. − UV/Vis ($CDCl_3$): λ_{max} (lg ε) = 351 nm (4.10). − $C_{72}H_{70}N_2O_{12}$ (1155.4): calcd. C 74.85, H 6.66, N 2.42; found C 74.32, H 6.73, N 2.35.

Acknowledgments

This work was partly supported by the Ministero dell'Università e Ricerca Scientifica (MURST) as part of the "Supramolecular Devices" project. We are grateful to the C.I.M. (Centro Interdipartimentale di Misure "G. Casnati") for NMR and mass measurements.

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Received December 3, 1999
[O99650]