New Upper Rim Pyridine-Bridged Calix[4]arenes: Synthesis and Complexation Properties toward Neutral Molecules and Ammonium Ions in Organic Media

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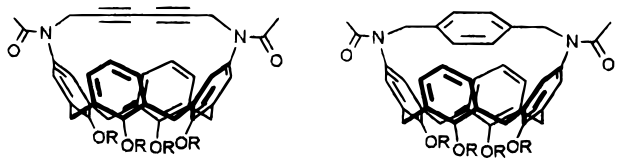
A new series of calix[4]arenes, diametrically bridged at the upper rim with pyridino systems, has been synthesized. The shape, rigidity, and chemical structure of the bridge influence the host-guest complexation properties of these systems in solution toward several neutral molecules having acidic C−H bonds. Additionally, selective complexation of methylammonium tosylate in comparison with other ammonium salts has been observed and the strength of this complexation enhanced by electron-donor ability of the *p*-substituent on the pyridine moiety of the calixarene host. X-ray crystal structures of *endo* complexes of host **5** with malononitrile and nitromethane have been resolved, verifying specific C−H bonding with the hard oxygen and nitrogen atoms of the bridge and the soft aromatic ring of the calixarene.

Introduction

Calix[4]arenes are cyclic molecules containing a hydrophobic cavity, extensively used in the study of host−guest interactions.[1] The formation of stable *endo*-cavity complexes with neutral molecules had been observed in the solid state[1,2] and subsequently studied by us in the gas phase[3] and in solution.[4] In particular, restriction of the conformational mobility of calix[4]arenes in solution leads to increased affinity toward neutral guests.[4] In fact, it has been recently shown that even *cone* tetraalkoxycalix[4]arenes are not completely blocked in solution, but instead experience residual conformational mobility between two C_{2v} flattened *cone* structures,[5] which adversely affects the molecular recognition properties of the cavitands. The reduction of conformational mobility and the preservation of the *cone* structure has been achieved as follows: (a) by functionalization at the lower rim with short ethereal bridges to immobilize the calixarene in a "rigid" *cone* conformation[4,5b] and (b) by introducing, at the upper rim, rigid bridges containing aromatic or other π-donor groups.[3,6]

In previous work we used mass spectrometric techniques to study the ability of a series of upper rim diametrically bridged calix[4]arenes with a xylyl or a 2,4-hexadiynyl moiety to complex neutral molecules in the gas phase.[3]



1 **2**

R= $CH_2CH_2OCH_2CH_3$

These cavitands showed high complexation efficiency and selectivity toward neutral guests containing acidic C−H groups. Our attempts to evaluate the complexation properties of the cavitands **1** and **2** in organic media toward neutral molecules, by ^{1}H NMR spectroscopy, were unsuccessful, probably because the type of interactions involved were too weak to overcome the solvation effects. Therefore, we decided to improve the complexation ability of this type of cavitands by introducing an additional binding site in the bridge, using a pyridine ring instead of xylyl or bisacetylenic groups.

Pyrido-crown ethers have already been extensively used to complex, for example, ammonium salts.[7] Typically, the basic pyridine nitrogen and two of the oxygen atoms in the crown system are involved in the complexation of ammonium ions. Although there is a general interest in the complexation of ammonium ions (especially quaternary[8]) because of their relevance to biological processes,[9] only recently some work on their complexation in organic media by calixarenes has been published.[4,10,11]

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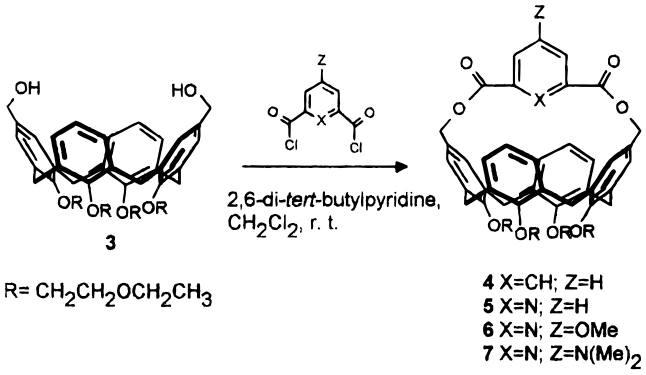
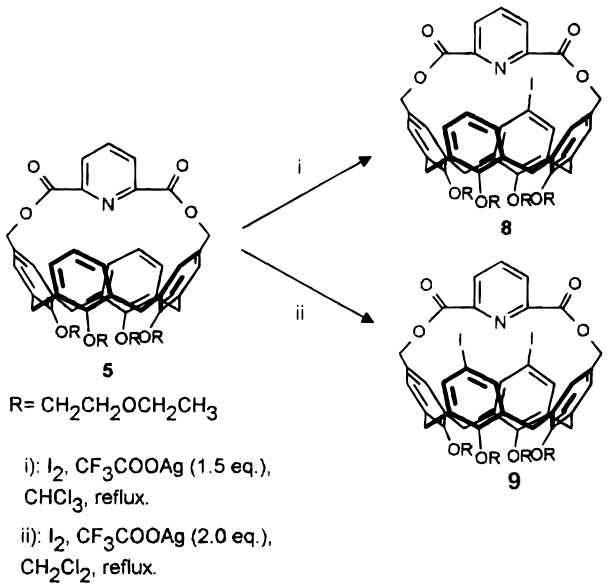
Scheme 1



Scheme 2



Results and Discussion

Synthesis of the Hosts. The major aim of this work was to investigate the cooperative effect of the lipophilic calixarene cavity and a basic group in close proximity, on the complexing ability of the hosts toward neutral molecules and ammonium ions.

The new upper rim bridged hosts **5**−**7**, having pyridine units of varying basicities,[12] were synthesized from the readily available diol **3**[6] and pyridino diacid chlorides[13] in high dilution conditions. For comparison, the synthesis of a corresponding isophtalic derivative **4** was also realized (Scheme 1).

As a final structural modification of these hosts one or two polarizable iodine atoms were introduced on the *para* position of the unbridged aromatic nuclei by iodination of **5** with iodine and silver trifluoracetate.[14] The extent of iodination was controlled by choosing the appropriate reagent molar ratio and by varying the solvent. In this way the monoiodo derivative **8** was obtained in 30% yield with a substantial recovery of starting material by using 1.5 equiv of iodine in $CHCl_3$, whereas the diiodo compound **9** was produced in 65% yield, operating in CH_2Cl_2 with 2 equiv of the reagent (see Scheme 2).

Complexation Studies. The complexation studies of some neutral molecules containing acidic C−H groups such as CH_3CN, CH_3NO_2, and $CH_2(CN)_2$ with the diametrically bridged calixarenes, **4**−**9**, in various apolar solvents, were performed by ^{1}H NMR spectroscopy. In these experiments, fast exchange conditions were observed, and therefore, the stability constants were easily calculated, having verified through continuous variation methods (Job plot)[15] a 1:1 stoichiometry for the complexes. ^{1}H NMR experiments also provide useful information on the structure of the complexes. A significant upfield shift on the methyl and methylene protons of the guest is observed on complexation, which implies that the acidic protons of the guest interact with the π-electrons of the host cavity. In fact, any interaction of these protons, involving only the nitrogen of the pyridine moiety and the oxygen atoms present in the bridge, should result in a downfield shift of these signals.

The values of the stability constants are listed in Table 1. As expected, the isophthalic derivative **4** shows no complexation for any of these guests, clearly demonstrating that the presence of the pyridine nitrogen in the bridge is essential.

To rationalize the value distribution of the stability constants several factors that can affect complexation phenomena must be taken into account: the acidity, shape and size of the guest, the basicity of the nitrogen of the pyridine ring, the accessibility of the host cavity, and the polarity of the solvent.

The influence of the solvent and the acidity of the guest on the extent of complexation has been extensively described by other authors using different hosts.[16] As expected, the stability of the complexes is higher in the less polar solvent CCl_4 and increases with the acidity of the guests[17] (malononitrile > nitromethane > acetonitrile). Moreover, our previous results[4] using some rigidified calix[4]arene cavitands as hosts showed a strong dependence of the complexation efficiency on the steric bulkiness of the guest (malononitrile > nitromethane > acetonitrile).

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Table 1. Association Constants $K_{1:1}$ (L mol^{-1}) of the Complexes of Hosts 4−9 with Several Guest Molecules in Various Organic Solvents at 300 K[a]

	cavitands					
guests	**4**[d]	**5**	**6**	**7**	**8**	**9**
CH_3CN (CCl_4)	n	36 ± 10	13 ± 2	*b*	30 ± 14	25 ± 2
CH_3NO_2 (CCl_4)	n	57 ± 5[c]	124 ± 10[c]	*b*	47 ± 22	29 ± 5
$CH_2(CN)_2$ ($CDCl_3$)	n	79 ± 20	50 ± 4	37 ± 2	77 ± 46	18 ± 2
CH_3NH_3OTs ($CDCl_3$)	n	131 ± 40	310 ± 55	1970 ± 277	142 ± 39	n

[a] No complexation was observed for di-, tri-, or tetramethylammonium tosylate. [b] The calixarene host was not appreciably soluble. [c] Negligible complexation in $CDCl_3$. [d] n indicates negligible complexation.

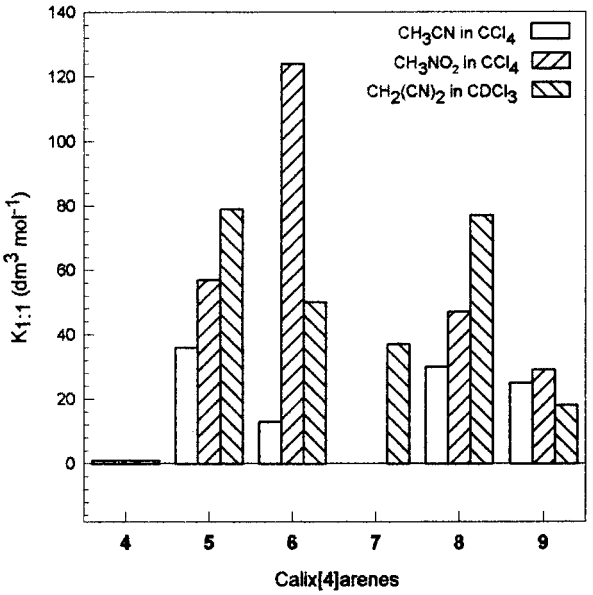

Figure 1. Plot of association constants for the complexation of neutral molecules by hosts **4**−**9** in various organic solvents.

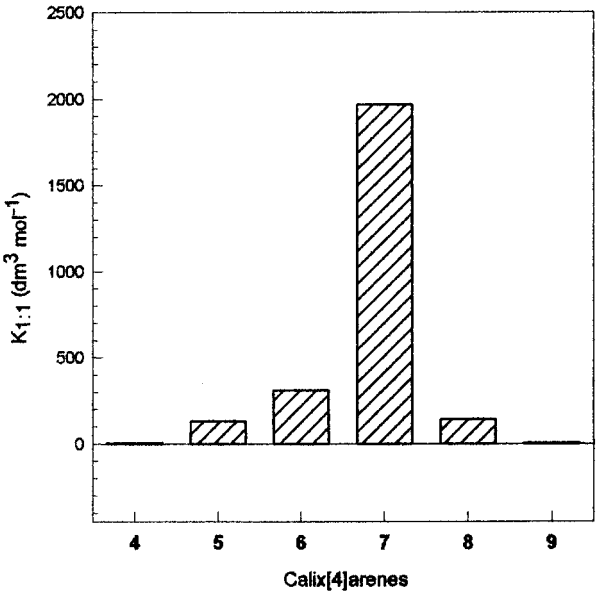

Figure 2. Plot of association constants for the complexation of methylammonium tosylate by hosts **4**−**9** in $CDCl_3$.

Cavitand **8** shows the same complexing efficiency as host **5** (see Figure 1). These results reveal that one side of the receptor cavity, not hindered by the iodine atom, is still available for complexation. On the contrary, cavitand **9** experiences very poor complexing ability with a reversed selectivity, showing that the predominant steric effect of the two iodine atoms reduces access to the host cavity.

Substituted methylammonium tosylates, which are sufficiently soluble in $CDCl_3$ to allow binding studies,[4] were also used as guests. No interaction was observed between dimethyl-, trimethyl-, and tetramethylammonium tosylates and any of our host molecules **4**−**9** (see Table 1).

Interestingly, methylammonium tosylate is the only guest complexed by our receptors. This remarkable selectivity is ascribed to the reduced dimension of the host cavity, which is too small to complex alkylammonium tosylate ion pairs larger than $CH_3NH_3^+OTs^-$, in agreement with our previous studies.[4] The most efficient host is the *p*-dimethylamino derivative **7** (K = *ca.* 2 × 10^3 L mol^{-1}), which, on the other hand, shows very little affinity toward neutral guests having acidic C−H groups, such as malononitrile (see Table 1).

Only the isophthaloyl derivative **4** and the diiodopyridino derivative **9** do not complex the methylammonium ion pair: the former because there is no nitrogen atom in the bridge and the latter because the two bulky iodine atoms prevent the access to the binding site. Figure 2 emphasizes the complexation trend of methyl ammonium on varying the pyridino-calix structure. As expected, the stability constants increase with the electron-donating ability of the *p*-substituent on the pyridine moiety of the host. The structure of the methylammonium complexes of hosts **5**−**8** seems to be different from that observed previously with other calixarene cavitands;[4] in fact, the tosylate counterion changes its chemical shift and CH_3-NH_3^+ signals broaden upon complexation. These data indicate that the ion pair breaks down and that the complex exists as a ligand-separated ion pair, probably through the interaction of the ligating sites with the NH_3^+ group.[18]

X-ray Studies. The structures of the complexes **5** ⊂ $CH_2(CN)_2$ and **5** ⊂ CH_3NO_2 obtained from the crystallographic study are reported in Figure 3a,b and in Figure 3c,d, respectively.

In both complexes the host molecule shows common general features. It possesses a "C_2 - like distorted cone conformation" with the pseudo 2-fold axes passing through N(1*) of the pyridine ring and to the center of mass of the methylene bridges of the calix[4]arene. The two opposite phenolic subunits A and C are almost orthogonal to each other—dihedral angles between their least-squares planes, 105.2(1) and 90.2(2)°—whereas the rings B and D are tilted away from each other with angles of 14.7(1) and 19.7(2)° in **5** ⊂ $CH_2(CN)_2$ and **5** ⊂ CH_3NO_2, respectively.

Table 2 provides a quantitative description of the calix[4]arene moiety conformations as a list of the dihedral angles between the least-squares planes of the phenolic rings and that through the four CH_2 bridging carbon

(18) For complexation at the methyl group of a methylammonium cation see ref 4.

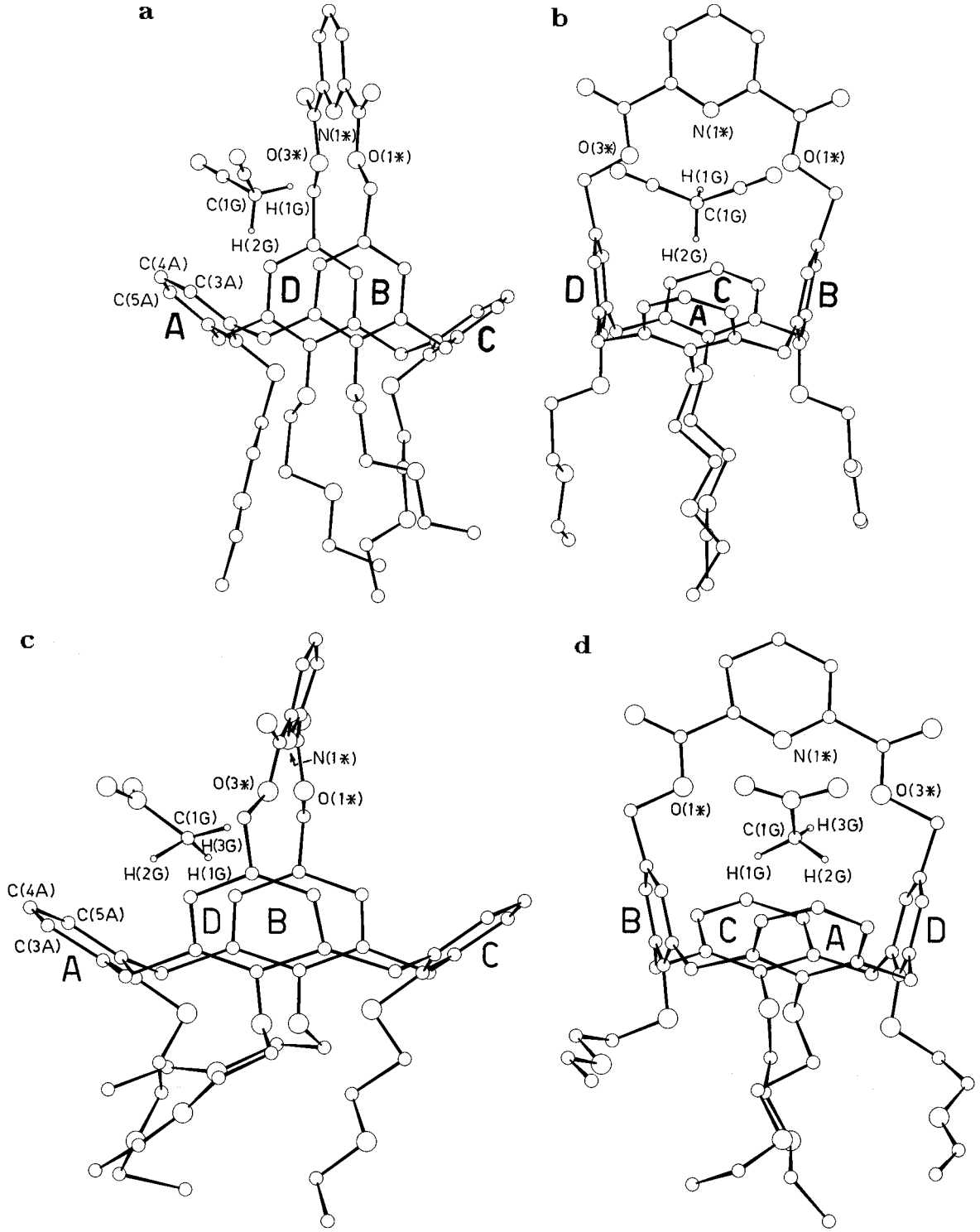

Figure 3. Perspective views of the complexes **5** ⊂ $CH_2(CN)_2$ (a and b) and **5** ⊂ CH_3NO_2 (c and d). The hydrogen atoms of the guest only have been reported for clarity.

atoms taken as molecular reference plane R[19] and from the Conformational Parameters,[20] respectively. For both complexes the Symbolic Representation of the conformation of the calix[4]arene is therefore C_1 + −,+ −,+ −, + −.

In the complex **5** ⊂ $CH_2(CN)_2$ the calix[4]arene is blocked in the observed "C_2 - like conformation" by the biscarbonyl pyridine bridge that links the two phenolic subunits B and D and whose plane is almost perpendicular to them and to the reference plane R (dihedral angles Py−B, 91.9(1)°, Py−D, 90.3(1)° and Py−R, 83.39-(8)°). Such orientation of the pyridine bridging group with respect to the aromatic nuclei of the calix[4]arene allows the host to act as "tongs" toward the malononitrile guest molecule, which is complexed *via* a trifurcate hydrogen bond involving the hydrogen atoms H(1G) of the malononitrile and the O(1*), N(1*), O(3*) acceptor atoms of the biscarbonyl pyridine bridge. The malononitrile guest forms a weaker bifurcate hydrogen bond[21]

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Table 2. *Conformational Parameters* (Deg) of the Calix[4]arene Moiety and Dihedral Angles (Deg) between the Least-Squares Planes through the Phenolic Rings and the Reference Plane R

	5 ⊂ $CH_2(CN)_2$		**5** ⊂ CH_3NO_2	
	φ	κ	φ	κ
A−D	110.7(4)	−70.5(4)	98.8(8)	−68.5(9)
D −C	66.2(4)	−104.4(4)	70.2(9)	−99.7(9)
C −B	105.9(4)	−70.5(4)	97.7(9)	−63.9(9)
B −A	68.9(4)	−108.9(4)	69.6(9)	−100.8(8)
	dihedral angles (deg)			
A−R	144.65(7)		135.8(2)	
B−R	98.74(9)		99.0(2)	
C−R	140.54(8)		135.1(2)	
D−R	95.96(9)		100.7(2)	

between H(2G) and the π orbitals on C(4A) and C(5A) atoms on the phenolic ring A.[22] Bond distances and angles of the H bonds are reported in Table 3.

The structural properties of the **5** ⊂ CH_3NO_2 complex are significantly different. The calix[4]arene host shows a more symmetric and less *flattened cone* conformation (see Table 2), whereas the biscarbonyl pyridine group is more flexed on the reference plane R of the calix[4]arene (dihedral angles Py−B, 95.5(2)°, Py−D, 90.9(2)°, Py−R, 79.2(2)°). The complexation of the guest occurs mainly *via* a bifurcated hydrogen bond involving the H(3G) of the nitromethane and the two acceptor atoms O(3*) and N(1*) of the biscarbonyl pyridine bridge as reported in Table 3. The guest is thus blocked in the observed position—with the two hydrogen atoms H(1G), H(2G) "astride" the phenolic unit A—by the hydrogen bonding[21] involving H(2G) and the π orbital on the C(3A) (see Table 3).[22] In both complexes the complexed guest is almost parallel to the phenolic unit A: the dihedral angles between the non-hydrogen atoms of the guest and the phenolic ring A are 3.9(2)° and 2.6(5)° for the malononitrile and nitromethane complexes, respectively, even if the interplane distances do not reveal specific stacking interactions.

The comparison of the molecular structure of the two complexes reveals that both guests are held by the host *via* the cooperation of two different hydrogen bonding mode: one "multifurcated" with the pyridine bridge and the other one with the aromatic ring of the calixarene *via* a CH−π interaction.[22] However, the contribution of the two different hydrogen bonding modes is different in the two complexes: the more acidic malononitrile shows a stronger multifurcated interaction with pyridine bridge, whereas the nitromethane shows a stronger CH−π interaction.

Conclusions

This new series of calix[4]arenes, diametrically bridged at the upper rim with pyridine units, shows interesting recognition properties toward molecules containing acidic C−H and N−H bonds. The strength of complexation is influenced by the acidity, shape, and size of the guest and by the presence of nitrogen in the bridge and the accessibility of the host cavity. X-ray crystal structures of the complexes **5** ⊂ $CH_2(CN)_2$ and **5** ⊂ CH_3NO_2 confirm the participation in the binding process of both "hard" donor groups of the bridge and the "soft" aromatic cavity. Specific complexation of methylammonium tosylate has been observed, and the stability of this complex was improved by structural modification of the calixarene host.

Experimental Section

General Procedures. All reactions were carried out under nitrogen. Dichloromethane was distilled and stored over 3 Å molecular sieves before use. All other reagents and solvents were of reagent grade quality, obtained from commercial suppliers, and used without further purification. NMR spectra were recorded in $CDCl_3$ unless otherwise indicated. Chemical shifts (δ) are expressed in ppm relative to internal tetramethylsilane (TMS). Mass spectra were determined in the CI mode (CH_4). Melting points are uncorrected. Elemental analyses were obtained from Dipartimento Farmaceutico at the University of Parma. The results with calixarenes are very often inaccurate;[23] however, the spectral data adequately confirm the structure of these new compounds (also see the supporting information). The calixarenes **1**,[3] **2**,[3] and **3**[6] were synthesized according to literature procedures.

General Method for the Synthesis of Upper Rim Bridged Calix[4]arenes 4−7. To a solution of appropriate diacid chloride (0.7 mmol) in 300 mL of CH_2Cl_2 were added 2,6-di-*tert*-butylpyridine (0.5 g, 2.6 mmol) and compound **3** (0.5 g, 0.65 mmol). The reaction mixture was stirred for 24 h and then quenched with water (100 mL). The organic layer was separated, washed twice with distilled water (2 × 100 mL), evaporated under reduced pressure, and dried in *vacuo* to remove the excess of 2,6-di-*tert*-butylpyridine entirely.

Isophthaloyl Derivative 4. Purification of the pale yellow residue by column chromatography (hexane:ethyl acetate = 70:30) and recrystallization from methanol afforded 120 mg (20% yield) of **4** as a white solid, mp 105 °C. ^{1}H NMR (300 MHz) δ: 1.22 and 1.26 (2t, 12H, J = 6.9 Hz); 3.22 (d, 4H, J = 12.6 Hz); 3.57 and 3.59 (2q, 8H); 3.77 (t, 4H, J = 4.8 Hz); 3.98 (t, 4H); 4.09 (t, 4H, J = 6.3 Hz); 4.42 (t, 4H); 4.59 (d, 4H); 4.81 (s, 4H); 6.71 (s, 4H); 6.77 (t, 2H, J = 7.5 Hz); 7.07 (d, 4H); 7.49 (t, 1H, J = 7.8 Hz); 7.91 (s, 1H); 8.18 (d, 2H). ^{13}C (75 MHz) δ: 15.2, 15.4, 33.7, 66.3, 66.5, 66.8, 69.4, 69.6, 72.0, 74.7, 123.2, 128.4, 128.7, 128.9, 130.0, 131.3, 133.4, 133.7, 135.9, 155.0, 156.6, 165.5. Mass spectrum m/e: 903 $(M + H)^+$. Anal. Calcd for $C_{54}H_{62}O_{12}$: C, 71.82; H, 6.92. Found: C, 70.51; H, 6.48.

Pyridine-2,6-dicarboxylate Derivative 5. Purification of the pale yellow residue by recrystallization from methanol afforded 290 mg (50% yield) of **5** as a white solid, mp 170−171 °C. ^{1}H NMR (300 MHz) δ: 1.19 and 1.25 (2t, 12H, J = 7.2 Hz); 3.17 (d, 4H, J = 12.6 Hz); 3.54 and 3.58 (2q, 8H); 3.77 (t, 4H, J = 6.0 Hz); 3.95 (t, 4H); 4.04 (t, 4H, J = 6.6 Hz); 4.40 (t, 4H); 4.55 (d, 4H); 4.98 (s, 4H); 6.62 (s, 4H); 6.64 (t, 2H, J = 7.5 Hz); 7.00 (d, 4H); 7.97 (t, 1H, J = 9.0 Hz); 8.25 (d, 2H). ^{13}C (75 MHz) δ: 15.2, 15.4, 30.9, 66.2, 66.4, 66.9, 69.4, 69.6, 72.0, 74.6, 123.0, 127.2, 128.7, 128.9, 129.8, 133.2, 135.8, 137.8, 147.6, 154.8, 156.8, 165.0. Mass spectrum m/e: 904 $(M + H)^+$. Anal. Calcd for $C_{53}H_{61}O_{12}N$: C, 70.41; H, 6.80; N, 1.55. Found: C, 69.01; H, 6.71; N, 1.38.

4-Methoxypyridine-2,6-dicarboxylate Derivative 6. Purification of the pale yellow residue by recrystallization from methanol afforded 300 mg (50% yield) of **6** as a white solid, mp 194−195 °C. ^{1}H NMR (300 MHz) δ: 1.20 and 1.25 (2t, 12H, J = 6.9 Hz); 3.18 (d, 4H, J = 12.6 Hz); 3.54 and 3.58 (2q, 8H); 3.77 (t, 4H, J = 5.1 Hz); 3.95 (t, 4H); 3.97 (s, 3H); 4.04 (t, 4H, J = 7.2 Hz); 4.40 (t, 4H); 4.55 (d, 4H); 4.94 (s, 4H); 6.62 (s, 4H); 6.68 (t, 2H, J = 7.5 Hz); 7.02 (d, 4H); 7.74 (s, 2H). ^{13}C (75 MHz) δ: 15.2, 15.4, 30.9, 66.2, 66.5, 66.6, 69.5, 69.6, 72.0, 74.6, 113.1, 123.0, 128.7, 129.2, 129.6, 133.2, 135.8, 149.3, 154.8, 156.8, 165.0. Mass spectrum m/e: 934 $(M + H)^+$. Anal. Calcd for $C_{54}H_{63}O_{13}N$: C, 69.44; H, 6.80; N, 1.50. Found: C, 68.40; H, 6.57; N, 1.21.

(21) For the van der Waals radii see: Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441−451.

(22) For the CH−π interactions see, e.g.: Nishio, M; Umezawa, Y; Hirota, M; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665−8701.

(23) Böhmer, V.; Jung, K.; Schon, M.; Wolff, A. *J. Org. Chem.* **1992**, *57*, 790−792. Gutsche, C. D.; See, K. A. *J. Org. Chem.* **1992**, *57*, 4527−4539.

Table 3. Interatomic Distances (Å) and Angles (Deg) of the Intermolecular Host−Guest Hydrogen Bonds

donor···acceptor (Å)		H···acceptor (Å)		donor-H···acceptor (Deg)	
		5 ⊂ $CH_2(CN)_2$			
C(1G)···O(1*)	3.370(4)	H(1G)···O(1*)	2.753(2)	C(1G)−H(1G)···O(1*)	120.2(2)
C(1G)···N(1*)	3.173(5)	H(1G)···N(1*)	2.401(4)	C(1G)−H(1G)···N(1*)	133.3(2)
C(1G)···O(3*)	3.255(4)	H(1G)···O(3*)	2.578(2)	C(1G)−H(1G)···O(3*)	124.8(2)
C(1G)···C(4A)	3.501(5)	H(2G)···C(4A)	2.857(4)	C(1G)−H(2G)···C(4A)	122.8(2)
C(1G)···C(5A)	3.608(5)	H(2G)···C(5A)	2.875(4)	C(1G)−H(2G)··· (5A)	130.8(2)
		5 ⊂ CH_3NO_2			
C(1G)···N(1*)	3.31(1)	H(3G)···N(1*)	2.68(1)	C(1G)−H(3G)···N(1*)	121.1(1)
C(1G)···O(3*)	3.24(1)	H(3G)···O(3*)	2.32(1)	C(1G)−H(3G)···O(3*)	151.4(9)
C(1G)···C(3A)	3.65(1)	H(2G)···C(3A)	2.71(1)	C(1G)−H(2G)···C(3A)	157.0(1)

4-(Dimethylamino)pyridine-2,6-dicarboxylate Derivative 7. Purification of the pale yellow residue by recrystallization from methanol afforded 245 mg (40% yield) of **7** as a white solid, mp 205−207 °C. ^{1}H NMR (300 MHz) δ: 1.20 and 1.25 (2t, 12H, J = 7.2 Hz); 3.10 (s, 6H); 3.18 (d, 4H, J = 12.6 Hz); 3.54 and 3.58 (2q, 8H); 3.77 (t, 4H, J = 5.4 Hz); 3.95 (t, 4H); 4.04 (t, 4H, J = 6.9 Hz); 4.41 (t, 4H); 4.55 (d, 4H); 4.90 (s, 4H); 6.64 (s, 4H); 6.73 (t, 2H, J = 7.5 Hz); 7.04 (d, 4H); 7.42 (s, 2H). ^{13}C (75 MHz) δ: 15.2, 15.4, 30.9, 39.5, 66.2, 66.4, 69.4, 69.6, 72.0, 74.5, 109.3, 123.1, 128.7, 129.3, 129.8, 133.1, 135.7, 147.9, 154.7, 156.8, 165.7. Mass spectrum m/e: 948 $(M + H)^+$. Anal. Calcd for $C_{55}H_{66}O_{12}N_2$: C, 69.57; H, 7.02; N, 2.96. Found: C, 67.32; H, 7.06; N, 2.03.

Upper Rim Bridged Calix[4]arene Pyridine-2,6-dicarboxylate Iodo Derivatives 8 and 9. Monoiodo Derivative 8. Compound **5** (0.17 mmol, 0.15 g) was dissolved in $CHCl_3$ (100 mL), and CF_3COOAg (0.25 mmol, 0.055 g) was added. The reaction mixture was refluxed for 30 min with vigorous stirring, and then iodine (0.25 mmol, 0.064 g) was added. After 2 h the precipitated AgI was filtered off and the organic solution treated with a 20% w/v $Na_2S_2O_5$ solution until the violet color had disappeared. The separated organic layer was then washed twice with distilled water and evaporated under reduced pressure to afford a crude product that was purified by column chromatography (hexane:ethyl acetate = 50:50); 75 mg (50%) of the starting reagent **5** and 52 mg (30% yield) of **8** as pale yellow solid were recovered. **8**. Mp: 181−183 °C. ^{1}H NMR (300 MHz) δ: 1.16−1.26 (m, 12H); 3.09 and 3.18 (2d, 4H, J = 12.9 and 12.6 Hz); 3.50−3.60 (m, 8H); 3.72−3.76 (m, 4H); 3.92−4.05 (m, 8H); 4.35−4.43 (m 4H); 4.51 and 4.53 (2d, 4H); 4.87 and 5.17 (2d, 4H, J = 11.4 Hz); 6.60 and 6.65 (2d, 4H, J = 1.8 Hz); 6.73 (t, 1H, J = 7.5 Hz); 7.05 (d, 2H); 7.30 (s, 2H); 7.97 (t, 1H, J = 7.8 Hz); 8.27 (d, 2H). ^{13}C (75 MHz) δ: 15.2, 29.7, 30.5, 30.9, 32.2, 62.7, 66.2, 66.4, 69.4, 69.6, 71.9, 72.2, 74.7, 123.1, 125.0, 127.4, 128.8, 129.4, 129.7, 129.9, 132.5, 133.2, 135.7, 137.1, 138.0, 138.5, 147.5, 154.8, 157.0, 164.6. Mass spectrum m/e: 1031 $(M + H)^+$. Anal. Calcd for $C_{53}H_{60}O_{12}NI$: C, 61.81; H, 5.87; N, 1.36. Found: C, 60.54; H, 5.32; N, 1.18.

Diiodo Derivative 9. Compound **5** (0.17 mmol, 0.15 g) was dissolved in CH_2Cl_2 (200 mL), and CF_3COOAg (0.37 mmol, 0.083 g) was added. The reaction mixture was refluxed for 30 min with vigorous stirring, and then iodine (0.37 mmol, 0.094 g) was added. After 4 h the precipitated AgI was filtered off and the solution treated with a 20% w/v $Na_2S_2O_5$ solution until the violet color had disappeared. The separated organic layer was then washed twice with distilled water, dried over Na_2SO_4, and evaporated under reduced pressure to afford a crude product that was purified by column chromatography (hexane:ethyl acetate = 50:50) and recrystallized from methanol to afford 127 mg (65% yield) of **9** as white solid, mp 181−183 °C. ^{1}H NMR (300 MHz) δ: 1.18 and 1.23 (2t, 12H, J = 7.2 Hz); 3.09 (d, 4H, J = 12.6 Hz); 3.51 and 3.55 (2q, 8H); 3.72 (t, 4H, J = 6.0 Hz); 3.91 (t, 4H); 3.97 (t, 4H, J = 6.0 Hz); 4.38 (t, 4H); 4.48 (d, 4H); 5.07 (s, 4H); 6.61 (s, 4H); 7.32 (s, 4H); 7.99 (t, 1H, J = 7.8 Hz); 8.29 (d, 2H). ^{13}C (75 MHz) δ: 15.2, 15.4, 30.4, 39.5, 66.0, 66.3, 66.5, 69.4, 69.6, 72.2, 74.8, 86.3, 127.4, 129.5, 130.1, 132.4, 137.2, 138.1, 138.5, 147.8, 154.8, 157.0, 164.8. Mass spectrum m/e: 1157 $(M + H)^+$. Anal. Calcd for $C_{53}H_{59}O_{12}NI_2$: C, 55.07; H, 5.14; N, 1.21. Found: C, 55.05; H, 5.30; N, 1.03.

Complexation Studies. $CDCl_3$ and CCl_4 were dried and stored over 3 Å molecular sieves before use. The NMR titrations with neutral molecules were performed at 300 K using published methods.[16] The ammonium tosylates are easily synthesized using known procedures.[24,25]

The NMR titrations with ammonium salts ($(5.00 \pm 0.05) \times 10^{-3}$ M) in $CDCl_3$ were performed at 300 K using methods reported elsewhere.[4] Fast exchange between complexed and free guest was observed, giving a single signal averaged between the two forms, the chemical shift of which varies with the ratio between host and guest. Stability constants were calculated using nonlinear regression analysis of the induced shifts on the low field protons of the tosylate counterion, because the methyl group of the ammonium ion becomes broad on complexation.

X-ray Crystallography. The X-ray measurements were carried out on a Siemens AED diffractometer using graphite-monochromatized Cu Kα radiation (1.541 78 Å) (**5** ⊂ $CH_2(CN)_2$) and on a Philips PW1100 diffractometer using graphite-monochromatized Mo Kα radiation (0.710 73 Å) (**5** ⊂ CH_3NO_2). The crystal data and the most relevant experimental parameters used in the X-ray measurements and in the crystal structure analyses are reported in Table 4. All the intensities were calculated by profile analyses according to the Lehmann and Larsen method.[26] For both complexes during the systematic data collection the intensity of one standard reflections, collected every 100, showed no significant fluctuations. The intensities were corrected for Lorentz and polarization but not for absorption effects. The approximate coordinates of all non-hydrogen atoms of the host molecule were obtained, for both compounds, from direct methods using SIR92.[27] The guest molecule was located in the subsequent cycles of the Fourier ΔF map. The crystal structure was refined by blocked full-matrix least-squares methods on F using SHELX76.[28] In both complexes parameters refined were as follows: the overall scale factor and the atomic coordinates and anisotropic thermal parameters for all the non-hydrogen atoms except the nitromethane, which was treated with isotropic temperature factors. All the hydrogen atoms in **5** ⊂ $CH_2(CN)_2$ were placed at their calculated positions with the geometrical constraint C−H 1.0 Å and refined "riding" on their corresponding carbon atoms, whereas in **5** ⊂ CH_3NO_2 the hydrogen atoms were found in the final Fourier ΔF map and refined with isotropic temperature factors, with the exception of those of the ether chains, which were placed at their calculated positions and refined, with a common temperature factor, "riding" on their corresponding carbon atoms. The atomic scattering factors of the non-hydrogen atoms were taken from Cromer and Waber;[29]

(24) (a) Cocivera, M. *J. Am. Chem. Soc.* **1966**, *88*, 672−676. (b) French, C. M.; Tomlinson, R. C. B. *J. Chem. Soc.* **1961**, 311−320.

(25) In a representative example, dry methylamine gas was bubbled through a concentrated solution of *p*-toluenesulfonic acid in diethyl ether, under nitrogen flow. The resultant precipitate was washed with ether and dried to give *N*-methylammonium *p*-toluenesulfonate (49%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (3H, s), 2.41 (3H, bs, NCH_3), 7.19 (2H, d, J = 7.7 Hz), 7.65 (3H, bs), 7.75 (2H, d, J = 7.7 Hz).

(26) Lehmann, M. S.; Larsen, F. K. *Acta Crystallogr.* **1974**, *A30*, 580−584.

(27) SIR92: Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Polidori, G. *J. Appl. Crystallogr.* **1994**, *27*, 435.

(28) Sheldrick, G. *SHELX76, Program for Crystal Structure Determinations*; University of Cambridge: England, 1976.

Table 4. Experimental Data for the X-ray Diffraction Studies

	5 ⊂ $CH_2(CN)_2$	**5** ⊂ CH_3NO_2
formula	$C_{53}H_{61}NO_{12}\cdot C_3H_2N_2$	$C_{53}H_{61}NO_{12}\cdot CH_3NO_2$
crystal syst	monoclinic	triclinic
space group	$P2_1/n$	$P\bar{1}$
cell param at 295 K[a]		
a (Å)	15.838(4)	12.831(3)
b (Å)	18.318(4)	11.979(3)
c (Å)	17.894(3)	19.264(3)
α (deg)	90	88.31(2)
β (deg)	93.01(2)	88.25(2)
γ (deg)	90	61.82(2)
V (Å^3)	5184(2)	2608(1)
Z	4	2
D_{calcd} (g cm^{-3})	1.243	1.229
F(000)	2064	1028
mol wt	970.127	965.105
linear abs coeff, cm^{-1}	7.131	0.886
scan type	$\theta/2\theta$	$\theta/2\theta$
scan speed (deg/min)	3 ÷ 12	3 ÷ 9.6
scan width (deg)	$[\theta - 0.65], [\theta + 0.65 + \Delta\lambda\lambda^{-1}tg\ \theta]$	$[\theta - 0.6], [\theta + 0.6 + \Delta\lambda\lambda^{-1}tg\ \theta]$
2θ range, deg	6 ÷ 140	6 ÷ 52
reflcns measd	$\pm h,+k,+l$	$\pm h,\pm k,\pm l$
total data measd	10497	10554
criterion for obsd	$I \geq 2\sigma(I)$	$I \geq 2\sigma(I)$
obsd data measd	7355	3324
unique obsd data	7020	3211
agreement between equiv obsd reflns	0.009	0.007
no. of variables[b]	241, 241, 178	273, 273, 176
max Δ/σ on last cycle	0.07	0.08
$R = \sum\|\Delta F\|/\Sigma\|F_o\|$	0.069	0.061
$R_w = \sum w^{1/2}\|\Delta F\|/\sum w^{1/2}\|F_o\|$	0.069	0.061
GOF $= [\sum w^{1/2}\|\Delta F\|^2/(NO - NV)]^{1/2}$	1.769	1.714

[a] Unit cell parameters were obtained by least-squares analysis of the setting angles of 30 carefully centered reflections found in a random search in reciprocal space. [b] In the blocked full-matrix least-squares refinement.

the values of $\Delta F'$ and $\Delta F''$ were those of Cromer and Ibers.[30] The geometrical calculations were obtained by PARST.[31] All the calculations were carried out on the Gould Encore91 of the Centro di Studio per la Strutturistica Diffrattometrica of C.N.R., Parma.

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Supporting Information Available: ^{1}H NMR spectra of all new compounds **4**−**9** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960937B

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(30) See ref 29, Table 2.3.1.
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