Anion Allosteric Effect in the Recognition of Tetramethylammonium Salts by Calix[4]arene *Cone* Conformers

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Rigid calix[4]arene *cone* conformers, which are efficient receptors for quaternary ammonium salts, are usually obtained through the functionalization of their lower rim with suitable groups. Using flexible *cone* conformer of calix[4]arene, bearing four 4-hydroxybenzyl groups as cooperative and rigidifying structural elements at the upper rim of the calix, which act as anion binding groups, a new heteroditopic cavitand, **7**, was synthesized. Whereas the tetramethoxy derivative **8** does not show any complexing ability, its tetrahydroxy analogue **7** recognizes tetramethylammonium salts with high efficiency. The binding abilities of this new receptor toward a series of tetramethylammonium salts (tosylate, chloride, acetate, trifluoroacetate, and picrate) have been investigated in $CDCl_3$ solution and compared to the monotopic and rigidified, through the lower rim, *cone* biscrown-3-calix[4]arene **9**. The results obtained confirmed that in $CDCl_3$ ion pairing strongly affects binding. In particular, the rigid monotopic receptor **9** experiences good efficiency toward tetramethylammonium salts having anions with low ion-pairing ability such as trifluoroacetate or picrate. On the contrary, for the new heteroditopic cavitand **7**, a reverse order of efficiency was found. In the latter case a different complexation mode was hypothesized in which the tetramethylammonium cation is deeply entrapped into the host cavity and its counteranion participates to the recognition process by coordination via hydrogen bonding by the four OH groups. To further support the role of the anion in the recognition process, a "dual host" approach, employing **7** or **9** in the presence of a specific receptor for chloride anion (**10**), was utilized. Molecular modeling studies confirmed that in the complexes formed by **7** and TMA salts the counteranion is involved in hydrogen bonding with the host OH groups and that the guests are bound as ligand-separated ion pairs.

Introduction

One of the main objectives of *supramolecular chemistry*[1] is the synthesis of receptors able to recognize charged species efficiently and selectively. In this context the synthesis of receptors for quats[2,3] is a topic of current and extensive investigations because of the important role these cations play in biological processes, in the environment, and in industrial applications.

With the aim of (1) determining the nature of the specific quats−host interactions which drive complex formation and (2) increasing efficiency, the extensive investigations carried out in the past decade have been performed in apolar media and usually the effect of the corresponding counteranion has been neglected. Only recently has the effect of the counterion on the whole recognition process been considered as the objective of specific investigations.[4,5] In fact, in apolar media ammonium ions are present as ion pairs or more likely as aggregates of ion pairs[6] and usually the host−ammonium cation interactions, when driven by the host aromatic cavity, do not afford sufficient energy gain to separate the cation from the ion pair,[4a,7] so that the host must necessarily recognize a tight ion pair. As a consequence, because of an extensive electrostatic interaction, the increase of the interacting power of the anion reduces the charge on the cation, thus decreasing the attractive host−guest interactions. These effects were elegantly studied by Roelens[4b] and Dalla Cort,[4d] who correlate the quats binding efficiency as a function of the counteranion interaction ability of cyclophanes and of calix[5]arene derivatives in chlorinated solvents, respectively.

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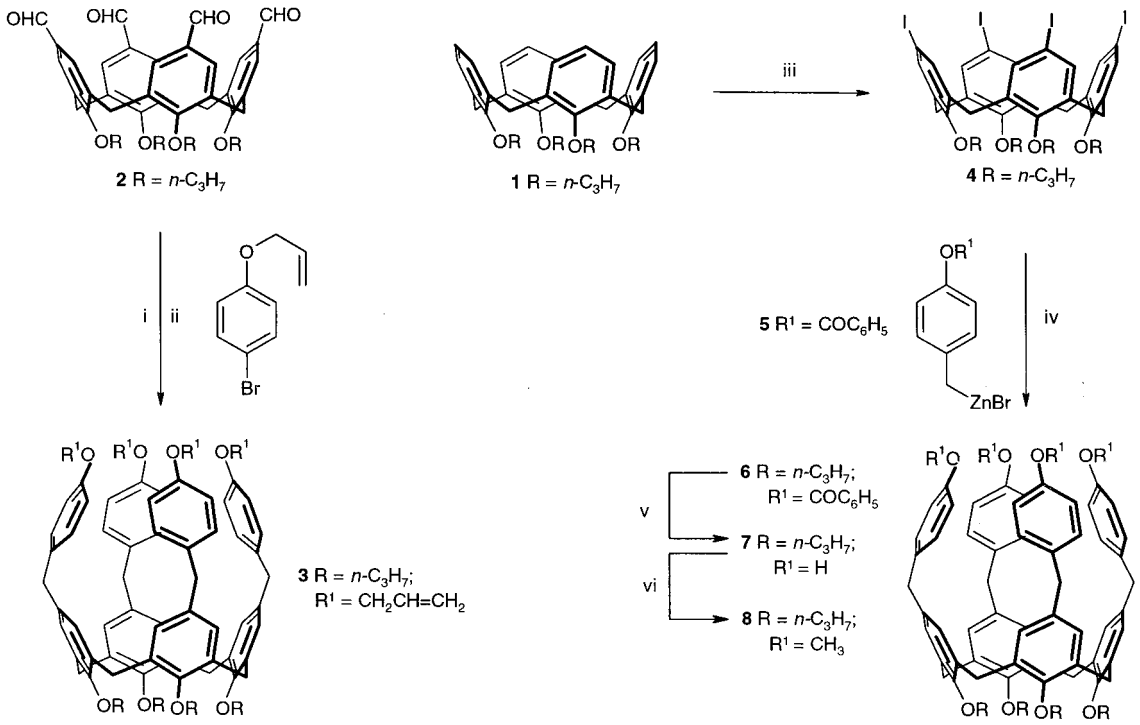
Scheme 1[a]



[a] Reagents and conditions: (i) Mg, THF dry; (ii) $NaBH_4$, CF_3COOH, $T = 0$ °C; (iii) CF_3COOAg, I_2, $CHCl_3$, reflux; (iv) $Pd[PPh_3]_4$, DMF, $T = 70$ °C; (v) CH_3ONa, THF; (vi) K_2CO_3, CH_3I, CH_3CN, $T = 40$ °C.

On the other hand, similar remarkable effects of the interacting power (ion-pairing strength) of the counterions on the ion-pair reactivity is well-established. For example, in apolar media the nucleophilicity of an anion is strongly influenced by the cation and it usually increases when the interacting ability of the counterion decreases.[8] However, in specific cases it is possible to utilize the interacting power of a cation as control element to determine, e.g., the regioselectivity in reactions involving nucleophilic polyfunctional compounds such as phenols, enols, pyrroles, and indoles.[9]

Similar positive results for the interaction power of the counterion have been recently obtained in the recognition process of ion pairs by some hosts.[10] For example, Kubik[10b] evidenced that a highly interacting anion such as *p*-toluensulfonate can strongly enhance the binding ability of quat ion pairs by preorganizing a cyclopeptide host skeleton.

These results prompted us to extend our previous studies on the recognition of quats using calix[4]arene derivatives as host. In early studies we found that in $CDCl_3$ the efficiency in the recognition of these guests by calix[4]arene-based derivatives is strongly dependent on both rigidity of the receptor and the nature of the counteranion.[4a] We thus envisaged that an interesting task could be the exploitation of the anion interacting power to tune the rigidity and the efficiency of complexation of these macrocycles toward quats. We therefore designed new flexible and adaptable *cone*-conformer calix[4]arenes derivative bearing additional binding sites which could participate to the recognition process through anion complexation. On this basis, a *heteroditopic* receptor, which can simultaneously bind both the cation and the anion,[11] derived from a tetrapropoxycalix[4]arene functionalized at the upper rim with 4-hydroxybenzyl groups (**7**) was synthesized. Its binding ability was investigated by ^1H NMR techniques in $CDCl_3$ toward a series of tetramethylammonium salts having different anions and compared to that of calix[4]arene-biscrown-3 (**9**) where the calixarene cavity is the only binding site.[4a]

In selected cases, to evidence a possible anion allosteric effect these studies were also performed in the presence of the specific anion ligand **10**.[10a]

Results and Discussion

Design and Synthesis of the Hosts. A calix[4]arene receptor functionalized with four 2,6-dimethyl-4-hydroxybenzyl groups at the upper rim was prepared in our laboratory a few years ago by Friedel−Crafts alkylation of 2,6-dimethylphenol with *p*-chloromethylcalix[4]arene.[12] However, to reduce the steric crowding over the cavity, new synthetic methodologies for the introduction of 4-hydroxybenzyl groups onto the upper rim of the *cone*-conformer of tetrapropoxycalix[4]arene (**1**) were studied. A first approach was based on the reaction of a Grignard reagent derived from 1-allyloxy-4-bromobenzene with tetraformylcalix[4]arene (**2**)[13] (see Scheme 1). The subsequent reduction of the diarylcarbinol intermediate

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mixture with sodium borohydride pellets in acidic media (CF_3COOH)[14] proceeds in 80% yield, giving the cavitand **3** in 37% overall yield. Unfortunately all attempts to remove the protective allyl groups (Pd/C−$HClO_4$, $NaBH_4$−I_2, and NaI−Me_3SiCl) to give **7** failed.

Better results were obtained using the more versatile and milder organozinc reagents[15] with halo-substituted calix[4]arenes. Thus **1** was transformed in 71% yield to its tetraiodo derivative **4**.[16] Then, when **4** was reacted with the organozinc reagent **5**, derived from benzoic acid 4-bromomethylphenyl ester, in the presence of tetrakis-triphenylphosphine palladium(0) as catalyst,[17] compound **6** was obtained in 32% yield. Methanolysis of the ester groups gave receptor **7**, having four hydroxyl functions, in 80% yield. With the aim of establishing the binding role of these OH groups toward the anion (see ahead), the methylated analogue **8** was synthesized by reacting **7** with methyl iodide using K_2CO_3 as base.

Receptor **7** shows the typical ^{1}H NMR spectrum of a tetrafunctionalized calix[4]arene blocked in the *cone* conformation in which the four equatorial and four axial methylene protons resonate as two distinct doublets at δ = 3.02 and 4.37 ppm, respectively, while the eight calixarene aromatic protons resonate as a singlet at δ = 6.44 ppm (see Experimental Section). In addition, in the spectrum a singlet at δ = 3.56 and two doublets at δ = 6.68 and 6.88 are present, which are consistent with the eight methylene and eight aromatic protons of the 4-hydroxybenzyl units, respectively. The four OH protons resonate as a broad singlet at δ = 4.99. Elemental analysis and mass spectrometry measurements fully agreed with the identity of **7**.

Binding Studies. The complexing abilities of the hosts having the benzyl groups with different substituents in the *para* position, **3**, **7**, and **8**, toward a set of tetraalkylammonium salts were studied by ^{1}H NMR in $CDCl_3$ solutions at 300 K. As reference hosts (see Introduction) the flexible *cone*-conformer **1** and the rigid calix[4]arene-biscrown-3 (**9**)[4a] were also tested.

In these experiments tetramethylammonium (TMA) salts having different counteranions (chloride, tosylate (TsO), acetate (Ac), trifluoroacetate (TFA), picrate (Pic)) and with a sufficient solubility in chloroform[3a] were employed as guests. Binding studies were carried out by adding increasing amounts of the appropriate host solution (c = 0.01 M) to a solution of the guest (c = 0.001 M). All the NMR spectra showed time-averaged signals for the free and the complexed species, except when TMAAc was titrated with host **7**. In this latter case extensive broadening of the signal for both host and guest was observed and this precluded an accurate evaluation of the association constant.

Having verified a 1:1 stoichiometry for the association by means of continuous variation methods, the stability constants (K_{as}), based on monitoring of the NCH_3 signal, were calculated using methods that have been previously described.[18] The results are summarized in Table 1.

Table 1. Association Constants K_{as} (M^{-1}) for 1:1 Complexes Measured in $CDCl_3$ of the Tetramethylammonium Salts $Me_4N^+X^-$ with Hosts 7 and 9[a]

entry	$Me_4N^+X^-$, X^- =	K_{as} (M^{-1})[b]
Host **7**		
1	TsO	4900(400)
2	Cl	3526(317)
3	Ac	>10 000[c]
4	TFA	1050(280)
5	Pic	368 (63)
6	Cl ⊂ **10**	440(97)
Host **9**		
7	TsO	33(10)[d]
8	Cl	80(25)[d]
9	Ac	247(30)[d]
10	TFA	362(75)
11	Pic	328(14)
12	Cl ⊂ **10**	428(88)

[a] TsO = *p*-toluensulfonate; Ac = acetate; TFA = trifluoroacetate; Pic = picrate. [b] Measured at T = 300 K by ^{1}H NMR titration; all values result from at least duplicate experiments, standard deviations are in parentheses. [c] Extensive broadening of the guest peaks; stability constant was estimated. [d] See ref 4a.

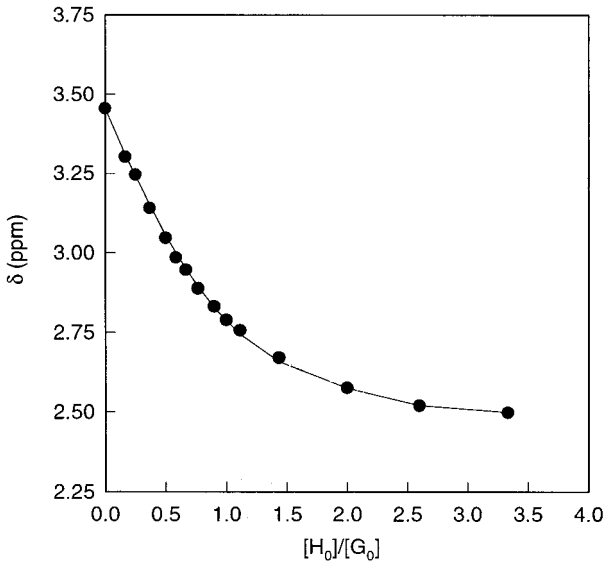

Figure 1. Titration of **7** with TMATsO in $CDCl_3$ (T = 300 K, initial concentration [7_0] = 9.0 × 10^{-3} M, [G_0] = 1.1 × 10^{-3} M), K_{as} = 4470 M^{-1} determined by monitoring the upfield of the guest N*Me* signal.

By monitoring the complexation induced shift (CIS) of the TMA signal, we observed that as expected **1**, **3**, and **8**, because of their flexibility, show negligible complexation toward all the salts studied. On the contrary, the TMA signal experiences extensive upfield CIS when **7** or **9** was used as host (see Figure 1). Despite its flexibility, **7** is the more efficient receptor and interestingly the extent of cation complexation is dependent on the type of counteranion. In addition, during titration experiments (Table 1, entries 1−6) the host OH groups experience extensive broadening and downfield shift ($\Delta\delta$ ca.5 ppm), while the aromatic signals of the sidearms tend to coalesce to δ = 6.80 ppm.

These data could be explained by hypothesizing a pivoting role of the anion that, depending on its ability

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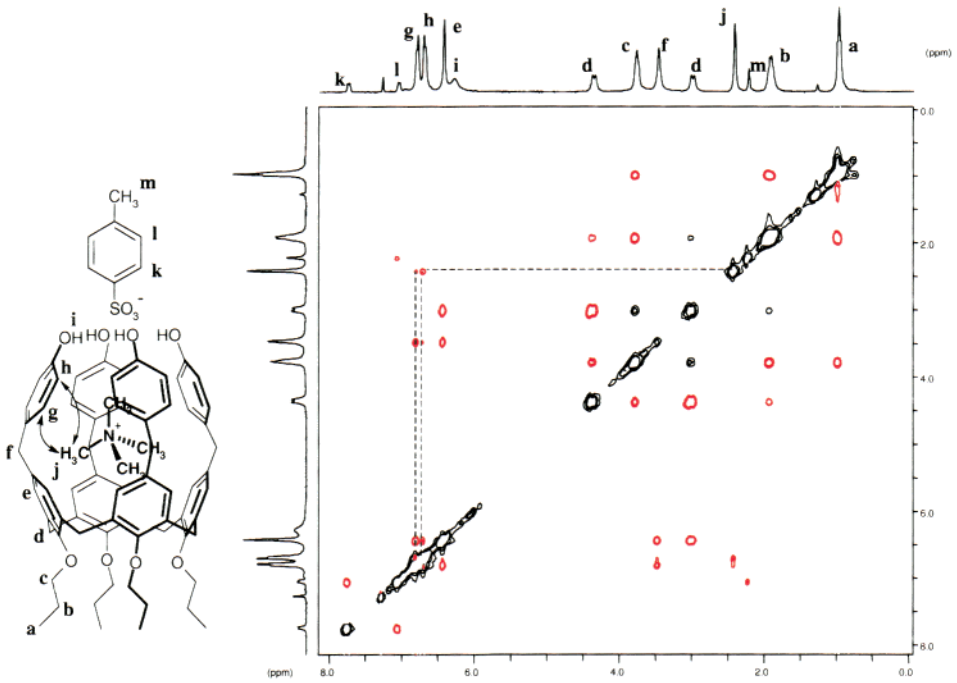
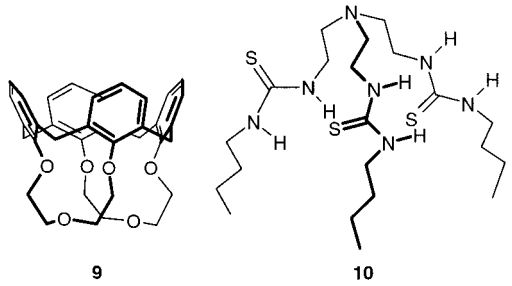


Figure 2. ROESY (300 MHz) spectrum for **7** (10 mM)/TMATsO (5 mM) complex in $CDCl_3$.

Chart 1



9 **10**

to act as hydrogen bond acceptor, interacts with the OH groups,[19] thus preorganizing the extended cavity of the host for cation binding. This is reflected by the efficiency order (Ac > TsO > Cl > TFA > Cl ⊂ **10** ≅ Pic) which support the hypothesis of a positive anion allosteric effect.[10b] This hypothesis is further confirmed by the lack of efficiency showed by **8** when the absence of the OH groups prevents any participation of the anion on the binding event (Chart 1).

The stability of the host−guest adducts is strongly dependent on the polarity of the media since the addition of even small amounts of polar deuterated solvents, such as CD_3OD, CD_3CN, or DMSO-d_6, to the $CDCl_3$ solutions of the different 1:1 complexes determines their disruption with release of the TMA cation which hence resonates as a free species.

Unfortunately, all attempts to obtain suitable crystals of **7** with TMA salts failed. However, from 2D ^{1}H NMR experiments some hypothesis of the structure of these complexes can be inferred. In fact, in the ROESY spectrum of TMATsO ⊂ **7** (see Figure 2) intermolecular NOEs between protons H(g) and H(h) belonging to the host sidearms and the methyl protons H(j) of the TMA were observed. Although this datum alone could be consistent with a different structure of the complex, together with the chemical shift variations observed in the 1D spectrum, it is in agreement with a situation where the TMA cation is inside the cage created through anion hydrogen bonding driven orientation of the host phenol groups.

To further support the hypothesis inferred from the data obtained in solution, theoretical calculations (in vacuo) based on the PM3 semiempirical methods,[20] using SPARTAN,[21] have been carried out to evaluate the relative stability of the complexes formed by **7** with TMA chloride, acetate, and tosylate. The modeling approach indicates, in all three cases, that the anion lies outside the intramolecular cavity which guests the cation. For the cation two different orientations inside the host cavity have been minimized, having respectively one (*up*-orientation) or three (*down*-orientation) methyl groups pointing toward the anion (see Figure 3). In the latter situation the remaining methyl group is deeply engulfed into the intramolecular cavity defined by the calixarene skeleton.

A comparison of the calculated complexation energies, summarized in Table 2, shows that the cation with *up*-orientation is the most stable of all investigated cases. Moreover, the energy difference among the two described orientations is noticeably anion dependent and reaches its maximum with the acetate anion (acetate > tosylate > chloride).

It must be emphasized that in all cases the anion is hydrogen bonded to the OH groups present in **7**, although the geometry of coordination depends on the anion nature and on the cation orientation in the host cavity. The latter factor is particularly important in complexes with TMAAc, for which the cation *down*-orientation determines the formation of only one hydrogen bond, whereas two hydrogen bonds, involving both acetate oxygens and two host OH groups, are formed in the *up*-orientation. This

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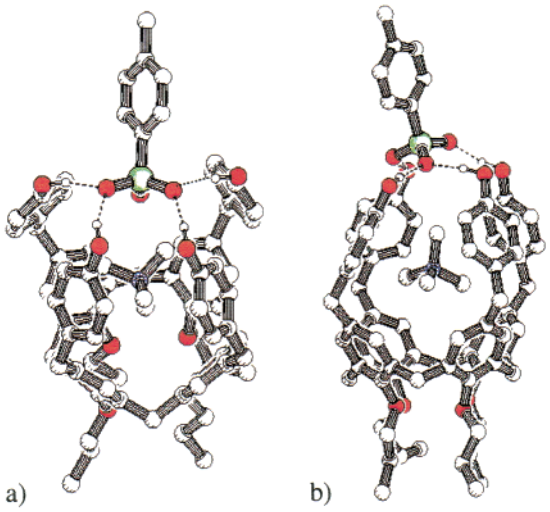

Figure 3. Proposed structures of TMATsO ⊂ **7**complex: (a) *down*-orientation and (b) *up*-orientation.

Table 2. Complexation Energy (kJ/mol) for 1:1 Complexes of Tetramethylammonium Salts ($Me_4N^+X^-$) with Host 7 Calculated Using PM3 Semiempirical Method

X^-	TMA *up*-orientation ($CH_3\uparrow$)	TMA *down*-orientation ($CH_3\downarrow$)
Cl	−306.28	−262.18
Ac	−219.03	−115.5
TsO	−283.24	−233.70

finding is reflected in a large energy difference for the two calculated structures (see Table 2).

The minor energy difference was calculated using chloride as counteranion, since we found two strong hydrogen bonds between chloride and two OH groups of the host (calculated Cl···H distances = 1.79 Å) both in the *up*- and *down*-orientations of the cation inside the cage.

In the case of the tosylate *down* complex, two bifurcated hydrogen bonds, involving two SO_3 oxygen atoms as acceptors and four host OH groups, link the anion to the host (Figure 3a). In the *up* complex the anion is linked to the host through two different hydrogen bonds: the first one involves one SO_3 oxygen as acceptor and one host OH hydrogen, the second one involves another tosylate oxygen as acceptor in a bifurcate hydrogen bond with two adiacent host hydroxy groups (Figure 3b).

These calculations suggest that the adaptability of the host is also an important factor. In fact the calixarene cavity remains unchanged in all cases, while the hydrogen bonding donor groups can assume different orientations to maximize the bonding interactions with the anions.

By looking at the cation−anion distance, some insight into the ion-pairing interaction for the three complexes can be inferred. In fact, in the chloride *up* complex all the three hydrogen atoms of the TMA methyl group interact at short distances with the anion in the range 2.66−2.72 Å, whereas in the *down* complex only two hydrogens interact with the anion at 2.47 Å.

In addition, in the *up* complex the two oxygens of the acetate interact strongly with two hydrogens of the methyl group (O···H distances 1.84 and 1.86 Å), whereas in the *down* complex these two oxygens interact (at 1.77 and 1.82 Å) with two hydrogen atoms on two different methyl groups of the TMA. In the case of the tosylate *up* complex, no short interactions have been found between the anion and the guest methyl group (the shortest $O_{Ts}\cdots H_G$ is 2.81 Å), whereas in the *down* complex one anion oxygen interacts strongly with one guest hydrogen atom ($O_{Ts}\cdots H_G$ = 1.76 Å). It is therefore reasonable to stress that receptor **7** binds these salts as ligand-separated ion pairs where both guest components participate in the overall stabilization of the complexes.

Although in these molecular modeling studies some discrepancies with the experimental anion effects are observed, the results concerning the calculated energy of the two possible complex orientations appears to be interesting. The more stable *up*-oriented complex can better explain the results obtained with the ROESY experiment and in particular the proximity between the guest methyl groups and the aromatic protons of the *p*-hydroxybenzyl substituents and the lack of NOE cross-peaks with the aromatic protons of the calix.

The monotopic host **9**, chosen as reference host, possesses a cone structure which is held rigid by the two diethyleneglycol chains present at the lower rim of the calix. Because of the hemispherical structure of the host and the lack of additional binding sites, it can bind the TMA cation as a tight ion pair and as a consequence it experiences a lower binding ability with respect to **7**. However, the efficiency order is opposite (Cl ⊂ **10** ≅ TFA ≅ Pic > Ac > Cl > TsO) and is larger when the anion is less interacting,[22] thus supporting the hypothesis that the ion-pairing ability of the anion controls efficiency as previously discussed.

Additional evidences, which support the opposite role of the counteranion of the recognition processes involving hosts **7** and **9**, were obtained by evaluating their binding ability toward TMACl in the presence of the specific ligand for chloride anion (**10**). These "dual host" complexation experiments were carried out by titrating a 1:1 TMACl−**10** $CDCl_3$ solution with **7** and **9**, respectively. As expected, the coordination of chloride by **10** causes an opposite effect on the two calixarene hosts in TMA binding. In fact, with **9** the loosening of the ion pair results in an increase of the K_{as} from 80 to 428 M^{-1} (Table 1, entries 8 and 12, respectively), while the lack of the anion allosteric effect with **7** strongly decreases binding from 3526 to 440 (Table 1, entries 2 and 6, respectively).

The comparison of the interacting power of the anion, as revealed by earlier reports, deserves some comments. The order Pic > TFA > Cl > TsO previously observed[4b−d] is similar to the results obtained with host **9**. However, with this host a leveling effect with the less interacting anions is observed. As expected, the interacting power of the acetate (Ac) anion is intermediate between the Cl and the TFA anion. Very promising is the possibility of decreasing the interactions of the anion with the cation with the dual host approach, without the use, e.g., of dangerous anions such as picrate.

Taking into account the results obtained with host **7**, a reverse order resulted, except with tetramethylammonium acetate for which the extensive complexation obtained, as demonstrate by the large upfield shifts of its signals, could be the result of a different structure of the ion-pair complex.

Conclusions

As verified in the nucleophile reactivity of ion pairs, the normal trend, based on pure electrostatic effects, of

the recognition of ions in apolar solvents is ion pair with low-interacting counterion > ion pair with high interacting counterion. Only in specific cases are positive effects of the interacting counteranion on the binding process efficiency observed, generally due to an increase of the preorganization of the host by hydrogen bonds with the anions of the ion pair. These results further support, using calix[4]arene receptors, the importance of the anion in determining the efficiency of the cation's complexation and the possibility to strongly increase the binding efficiency of ion pairs by this new approach which utilizes the allosteric effect of the anion.

Experimental Section

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 spectra (300 MHz) were recorded in $CDCl_3$ unless otherwise indicated. Mass spectra were determined in CI mode (CH_4). Melting points are uncorrected. Compounds **1**,[26] **2**,[13] 4-(benzoyloxy)benzyl bromide,[27] and 4-(allyloxy)-1-bromobenzene[28] were synthesized according to literature procedures.

5,11,17,23-Tetrakis-[(4-allyloxy)benzyl]-25,26,27,28-tetrapropoxycalix[4]arene (3). A mixture of magnesium turnings (66 mmol, 1.6 g) in dry THF (2 mL) was stirred in a 100 mL three-necked, round-bottomed flask equipped with a reflux condenser, a nitrogen inlet, and a dropping funnel containing a solution of 4-(allyloxy)-1-bromobenzene (66.0 mmol, 14.0 g) in dry THF (25 mL). After the addition of a 1 mL solution of the bromine derivative, the resulting mixture was gently heated until the reaction started. The remaining amount of the ethereal solution was then slowly added dropwise until all the magnesium turnings were dissolved. The resulting green dark colored solution was hence cooled to rt, and a solution of **2** (3.0 g, 4.3 mmol) in dry THF (25 mL) was added dropwise. After 30 min the reaction was cooled to 0 °C and quenched by means of slow addition of a saturated solution of NH_4Cl. The resulting yellow mixture was extracted with ethyl acetate (2 × 100 mL), the organic layer was separated, washed with brine, and dried (Na_2SO_4), and the solvent was completely evaporated in vacuo to give a pale yellow oil. This residue was triturated with *n*-pentane, dissolved in CH_2Cl_2 (100 mL), and added dropwise to a solution previously prepared by dissolving $NaBH_4$ pellets (ca. 1.6 g, pellets wt ~0.4 g) in CF_3COOH (150 mL) at 0 °C. During the addition the reaction temperature was maintained under 15 °C using an external ice bath. After 18 h the reaction was quenched by pouring the resulting orange solution into a flask containing ice water, maintained under a gentle nitrogen flow. The mixture was then diluted with CH_2Cl_2 (100 mL), the organic layer was separated and dried (Na_2SO_4), and the solvent was completely removed in vacuo. Purification of the residue by chromatography (ethyl acetate/hexane, 35:65) gave 1.84 g (37% overall yield) of **3**; mp = 121−122 °C. ^{1}H NMR (300 MHz) δ: 0.98 (t, 12H, J = 7.4 Hz); 1.9−2.0 (m, 8H); 3.03 (d, 4H, AX system, J = 13.0 Hz); 3.60 (s, 8H); 3.80 (t, 8H, J = 7.5 Hz); 4.38 (d, 4H, AX system); 4.4−4.5 (m, 8H); 5.24 (dd, 4H, J^1 = 10.5, J^2 = 1.4 Hz); 5.37 (dd, 4H, J^1 = 15.8, J^2 = 1.4 Hz); 5.9−6.0 (m, 4H); 6.46 (s, 8H); 6.79 (d, 4H, AB system, J = 8.6 Hz); 6.94 (d, 4H, AB system). ^{13}C (75 MHz) δ: 10.3, 23.2, 30.8, 40.4, 68.8, 76.5, 114.4, 117.7, 128.5, 129.5, 133.5, 134.1, 134.3, 134.7, 154.8, 156.7. CI(+) MS *m/e*: 1177 [MH^+]. Anal. Calcd for $C_{80}H_{88}O_8.H_2O$: C, 80.37; H, 7.59. Found: C, 80.43; H, 7.61.

5,11,17,23-Tetraiodo-25,26,27,28-tetrapropoxycalix[4]-arene (4). To a solution of **1** (6.8 mmol, 4.0 g) in $CHCl_3$ (200 mL) was added CF_3COOAg (29.9 mmol, 6.6 g). The resulting heterogeneous mixture was refluxed with vigorous stirring for 30 min; then iodine (29.9 mmol, 7.6 g) was added. After an additional 30 min, the yellow solid AgI formed was filtered off and filtrate was treated with a saturated aqueous $Na_2S_2O_5$ solution until the deep purple color had disappeared. The organic layer was separated, washed twice with water, and dried (Na_2SO_4), and the solvent was completely evaporated under vacuum. The solid was triturated with hot methanol to give 5.2 g (71%) of **4**; mp 290−291 °C. ^{1}H NMR (300 MHz) δ: 0.96 (t, 12H, J = 7.5 Hz); 1.8−1.9 (m, 8H); 3.05 (d, 4H, AX system, J = 13.4 Hz); 3.80 (t, 8H, J = 7.4 Hz); 4.29 (d, 4H, AX system, J = 13.4 Hz); 6.99 (s, 8H). ^{13}C (75 MHz) δ: 10.1, 23.0, 30.3, 76.9, 86.0, 136.7, 137.0, 156.3. CI(+) MS *m/e*: 1097 [MH^+]. Anal. Calcd for $C_{40}H_{44}I_4O_4$: C, 43.82; H, 4.04. Found: C, 43.92; H, 4.07.

5,11,17,23-Tetrakis[4-(benzoyloxy)benzyl]-25,26,27,28-tetrapropoxycalix[4]arene (6). The organozinc bromide reagent **5** was prepared according to a previously reported procedure:[17] to a suspension of Zn powder (5.0 mmol, 0.33 g, −100 mesh) in dry DMF (1 mL) was added 1,2-dibromoethane (0.4 mmol, 30 μL). The resulting mixture was heated at 70 °C, under vigorous stirring, for 10 min and cooled to room temperature, and then chlorotrimethylsilane (0.3 mmol, 40 μL) was added. The resulting activated zinc solution was allowed to stir for an additional 30 min and cooled to 0 °C; then the appropriate benzyl bromide derivative (5.0 mmol) in DMF (10 mL) was added dropwise within 2 h, maintaining the temperature below 5 °C. To the resulting organozinc bromide solution, tetraiodocalix[4]arene **4** (0.8 mmol) and $Pd(PPh_3)_4$ (0.03 mmol, 0.035 g) were added. After 18 h at 70 °C, the solvent was completely removed under vacuum and the residue taken up with ethyl acetate (100 mL) and with a saturated solution of NH_4Cl (100 mL). The organic layer was separated, washed with water, and dried (Na_2SO_4), and the solvent was completely evaporated under vacuum. Purification of the residue by column chromatography (eluent ethyl acetate/hexane, 2:8) gave 0.37 g (32%) of **6** as pure product; mp 195−196 °C. ^{1}H NMR (300 MHz) δ: 1.02 (t, 12H, J = 7.2 Hz); 1.9−2.0 (m, 8H); 3.10 (d, 4H, AX system, J = 13.2 Hz); 3.72 (s, 8H); 3.86 (t, 8H, J = 7.5 Hz); 4.44 (d, 4H, AX system, J = 13.2 Hz); 6.54 (s, 8H); 7.09 (s, 16H); 7.49 (t, 8H, J = 7.5 Hz); 7.5−7.6 (m, 4H); 8.18 (d, 8H, J = 7.5 Hz). ^{13}C (75 MHz) δ: 10.3, 23.2, 30.9, 40.7, 76.8, 77.4, 121.3, 128.5, 128.7, 129.6, 130.1, 133.4, 133.6, 134.9, 139.6, 149.0, 155.0, 165.2. CI(+) MS *m/e*: 1433 [MH^+]. Anal. Calcd for $C_{96}H_{88}O_{12}$: C, 80.42; H, 6.19. Found: C, 80.53; H, 6.17.

5,11,17,23-Tetrakis[4-hydroxybenzyl]-25,26,27,28-tetrapropoxycalix[4]arene (7). To a solution of **6** (0.2 mmol, 0.3 g) in dry THF (10 mL) was added a 2 M solution of CH_3ONa in CH_3OH (1 mL). The resulting mixture was then treated with water (25 mL), the solution pH was adjusted to neutrality, and finally the solution was extracted with ethyl

(22) The interaction of the counteranion with tetramethylammonium cation in apolar organic solvents is mainly electrostatic in nature, but other contributions may not be neglected.[23] However, a relative evaluation of such interaction is possible only when spherical anions[24] are compared or, at least, when they have the same geometry but different basicity, whereas it becomes problematic comparing anions such as, e.g., alkyl- or aryl-sulfonate and picrate. To the best of our knowledge, a systematic evaluation of the interacting power of anion in ion pairing does not exist. In fact, the Hofmeister series,[25] which is largely employed in biochemistry or in ion-selective electrodes (ISE) studies, does not represents a relative measurement of the electrostatic interactions between the ions of the ion pair, but it is rather correlated with their hydration energy. Other series, derived from anion exchange properties in organic solvents (e.g., CH_3CN) of tetralkylammonium ion−exchange resins, are more correlated to our results.[23] Therefore, the measurement of the interaction energy of ion pairs having different counteranion with an host with low steric hindrance can be employed as an additional experimental method to evaluate such interactions.

(23) See, for example: Okada, T. *J. Chromatogr. A* **1997**, *758*, 19−28.

(24) Marcus, Y. *Ion Solvation*; John Wiley & Sons Ltd.: Chichester, 1985. Marcus, Y. *Ion Solvation*; Dekker Inc.: New York, 1997.

(25) Hofmeister, F. *Arch. Ex. Pathol. Pharmakol.* **1888**, *24*, 247−260.

(26) Ikeda, A.; Nagasaki, T., Araki, K.; Shinkai, S. *Tetrahedron* **1992**, *48*, 1059−1070.

(27) Dimroth, K.; Laubert, G.; Blöcher, K. H. *Justus Liebigs Ann. Chem.* **1972**, *765*, 133−152.

(28) Bauld, N. L.; Aplin, J. T.; Yueh, W.; Endo, S.; Loving, A. *J. Phys. Org. Chem.* **1998**, *11*, 15−24.

acetate (2 × 25 mL). The organic layer was separated and the solvent completely removed under vacuum. Purification of the residue by column chromatography (eluent ethyl acetate/hexane, 7:3) gave 0.23 g (80%) of pure product; mp 203−204 °C. ^{1}H NMR (300 MHz) δ: 0.97 (t, 12H, J = 7.4 Hz); 1.8−1.9 (m, 8H); 3.02 (d, 4H, AX system, J = 13.0 Hz); 3.56 (s, 8H); 3.79 (t, 8H, J = 7.5 Hz); 4.37 (d, 4H, AX system, J = 13.0 Hz); 4.99 (s, var., 4H); 6.44 (s, 8H); 6.68 (d, 8H, J = 8.3 Hz); 6.88 (d, 8H, J = 8.3 Hz). ^{13}C (75 MHz) δ: 10.2, 23.1, 30.8, 40.4, 76.7, 115.1, 128.5, 128.7, 129.7, 134.1, 134.3, 134.8, 153.4, 154.7. CI(+) MS *m/e*: 1017 [MH^+]. Anal. Calcd for $C_{68}H_{72}O_8 \cdot H_2O$: C, 78.89; H, 7.20. Found: C, 78.65; H, 7.24.

5,11,17,23-Tetrakis[4-methoxybenzyl]-25,26,27,28-tetrapropoxycalix[4]arene (8). To a solution of **7** (0.3 mmol, 0.3 g) in dry CH_3CN (10 mL) were added K_2CO_3 (2.2 mmol, 0.3 g) and CH_3I (2.0 mmol, 0.28 g). The resulting heterogeneous mixture was heated, with vigorous stirring, at 40 °C. After 5 d the solvent was completely removed under vacuum and the yellow stiffening residue was taken up with a 10% HCl solution (50 mL) and CH_2Cl_2 (50 mL). The organic layer was separated, washed twice with water, and dried (Na_2SO_4), and the solvent was then completely evaporated under vacuum. Purification of the residue by column chromatography (eluent CH_2Cl_2/hexane, 6:4) gave 0.05 g (15%) of **8** as a viscous oil. ^{1}H NMR (300 MHz) δ: 0.97 (t, 12H, J = 7.4 Hz); 1.8−1.9 (m, 8H); 3.02 (d, 4H, AX system, J = 13.0 Hz); 3.60 (s, 8H); 3.74 (s, 12H); 3.79 (t, 8H, J = 7.5 Hz); 4.38 (d, 4H, AX system, J = 13.0 Hz); 6.46 (s, 8H); 6.78 (d, 8H, J = 8.4 Hz); 6.95 (d, 8H, J = 8.4 Hz). ^{13}C (75 MHz) δ: 10.2, 23.1, 30.8, 40.4, 55.1, 76.7, 113.6, 128.5, 129.5, 134.1, 134.2, 134.7, 153.8, 155.0. CI(+) MS *m/e*: 1073 [MH^+]. Anal. Calcd for $C_{72}H_{80}O_8$: C, 80.56; H, 7.51. Found: C, 80.69; H, 7.47.

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Supporting Information Available: ^{1}H NMR spectra of new compounds **6**−**8**, binding isotherms for the complexation of **7** with tetramethylammonium salts in $CDCl_3$, and graphical representations of inclusion complexes of **7** with TMAAc and TMACl, derived from molecular mechanics calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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