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REVIEW COMMENTARY
CATION–π INTERACTIONS IN CALIX[*n*]ARENE AND RELATED SYSTEMS

PAVEL LHOTÁK[1]* AND SEIJI SHINKAI[2]

[1]*Department of Organic Chemistry, Institute of Chemical Technology, Technická 5, Prague 6, Czech Republic*
[2]*Department of Chemical Science and Technology, Faculty of Engineering, Kyushu University, Fukuoka 812, Japan*

Non-covalent intermolecular forces have been recognized as a very important part of molecular interactions in complex biological systems. The fundamental functions of living matter such as transcription of genetic information in DNA, spatial arrangement of protein molecules, enzymatic functions or immunity system response are enabled owing to the presence of weak non-covalent forces based on hydrogen bonding interactions, van der Waals interactions, electrostatic interactions, hydrophobic effects, etc. Recently, among them so-called 'cation–π' interactions have been proved to contribute to the overall binding process in various artificial or biological systems. Calix[*n*]arenes have emerged as an important family of molecules with promising applications in many branches of chemistry. Because of their suitable molecular preorganization with aromatic units being 'concentrated' in a relatively small space, calix[*n*]arenes represent interesting compounds exhibiting an enhanced ability for cation–π interactions. The importance of such forces in calix[*n*]arene chemistry is demonstrated here on several recent examples.

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INTRODUCTION

During recent decades, much interest has been focused on the design and synthesis of artificial receptors and related compounds. Molecules possessing an ability for selective interactions with defined ions or other molecules are of great importance in supramolecular chemistry, where they can be used for the construction of host–guest type receptors. Because of their easy large-scale preparation and excellent capability of derivatization, calix[*n*]arenes ($\mathbf{1}_n$) (Figure 1) have emerged[1,2] (in addition to cyclodextrins and crown ethers) as a third generation[3] of supramolecules with a variety of applications in the complexation of cations, anions and even neutral molecules.[1–5] Their unique concave molecular architecture and tunable size of the inner cavity make the calix[*n*]arenes very attractive building blocks[6] for supramolecular chemistry, where the combination of the defined size, conformation (Figure 2), preorganization of molecular shape, rigidity and suitable non-covalent interactions can lead to the design of very sensitive and specific sensors.

Non-covalent intermolecular forces have been recognized as a very important part of molecular interactions in complex biological systems. The fundamental functions of living matter such as transcription of genetic information in DNA, secondary (and higher) structures of proteins, enzymatic functions and immunity system response are enabled owing to the presence of weak non-covalent forces based on hydrogen bonding interactions, van der Waals interactions, electrostatic interactions, hydrophobic effects, etc. Among them, so-called 'cation–π interactions' (Figure 3) have been considered to be extremely weak (if present at all), contributing minimally to the overall binding process. The determination of an active site of acetylcholine esterase, published recently,[7] has completely changed this opinion. It was demonstrated that the $N(CH_3)_3^+$ group of acetylcholine is held not by negatively charged anionic groups of the enzyme, but rather by aromatic residues creating a suitable

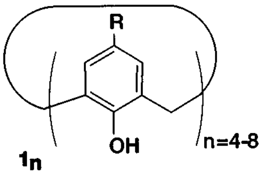

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Figure 1. Calix[*n*]arenes

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* *Correspondence to:* P. Lhoták. E-mail:lhotakp@vscht.cz.

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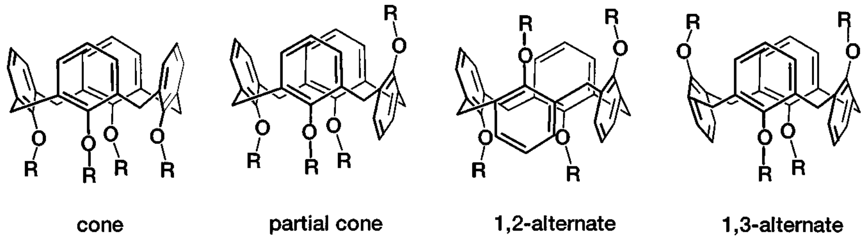


Figure 2. Four main theoretically possible conformations of calix[4]arene

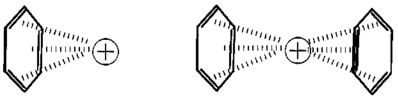


Figure 3. Cation–π interactions

'π-capsule' for binding of the quaternary ammonium salt by cation–π interactions. This development attracted great interest from organic and theoretical[8–11] chemists, and many papers dealing with cation–π interactions, including an excellent review,[12] have appeared in recent years.

In this paper we have attempted to collect the literature sources concerning calix[*n*]arene chemistry, with the intention of demonstrating the importance of cation–π interactions in the host–guest chemistry of calixarene derivatives.

INTERACTIONS WITH QUATERNARY AMMONIUM IONS

Water-soluble calixarenes

As was reported by Dougherty and co-workers[12–17] and others,[18–20] cyclophane hosts could be suitable agents for the recognition of quaternary ammonium salts even in aqueous solutions.[9] It was found that the positive charge of the guest is held by attractive cation–π interactions (Figure 4) provided by the electron-rich faces of host aromatic rings. The possible biomimetic application of the above-mentioned cyclophanes was demonstrated on the effective catalysis of the S_N2 alkylation of pyridine, quinoline and isoquinoline substrates by alkyl halides.[13,14] The partial positive charge of the transition state is stabilized by cation–π interactions, which results in substantial acceleration of the reaction rate (100 ×).

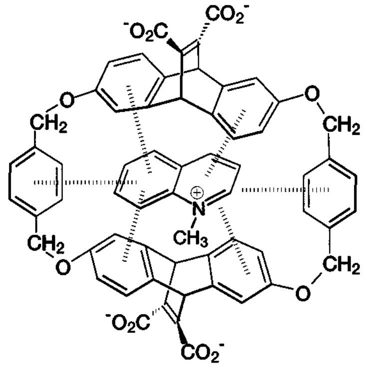


Figure 4. Water-soluble macrocycle

The design and synthesis of water-soluble, synthetic macrocycles as biomimetic models for enzymes and artificial receptors have been the subject of interest in recent years. Simple bowl-shaped resorcinarenes (Figure 5), prepared by the acid-catalyzed condensation[21] of resorcinol with aldehydes, were found to be partly water soluble in the form of a tetraphenolate structure. Their concave architecture (supported by four intramolecular hydrogen bonds) with a cavity inside and electron-rich aromatic walls around was recognized as a suitable structural moiety for the binding of quaternary ammonium cations in aqueous solution.[22–25] Based on ^1H NMR experiments (complexation-induced chemical shifts, Job plots), it was concluded that resorcinarenes create a 1:1 complex with an ammonium head immersed in the cavity as indicated in Figure 5. This binding mode does not represent typical (pure) cation–π interactions. The main binding forces are rather electrostatic attractive interactions between tetraanionic host and cationic guest molecules; nevertheless, the cation–π interactions are believed to contribute greatly to this system.

Because of the high complexation constants, the resorcinol system was used for the binding study of acetylcholine[26]

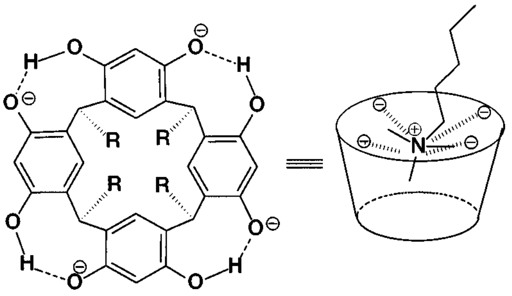


Figure 5. Water-soluble resorcinarene derivative

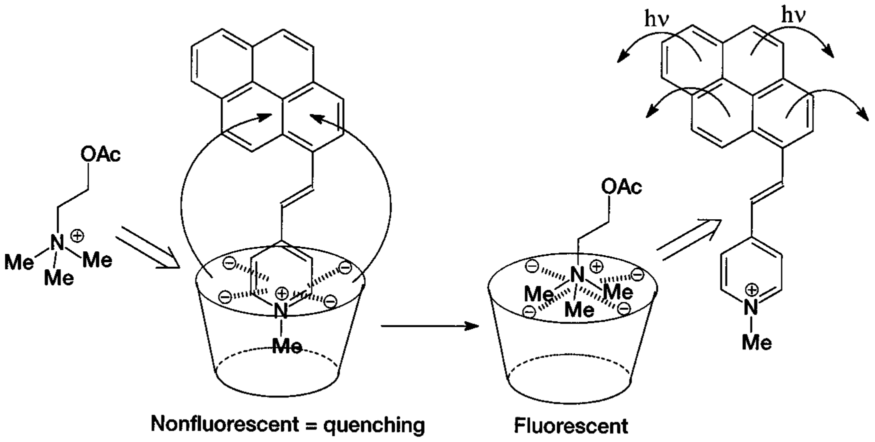


Figure 6. Receptor for acetylcholine

and related ammonium compounds,[24] which led to the design of a non-destructive system for detection of acetylcholine in protic media. The selective recognition process of acetylcholine is based on the finding[27] that a pyrene-appended pyridinium salt (used as a fluorescence probe) is complexed by resorcinarene tetraphenolate and can be ‘substituted’ by an acetylcholine derivative under the measuring conditions. While it is in the complex, the fluorescence of the pyrene part is negligible owing to quenching (electron transfer from phenolate anions), whereas its liberation from the complex leads to a dramatic enhancement of fluorescence (Figure 6). Hence the presence of acetylcholine could be easily detected by measuring the increased fluorescence intensity. However, the measuring conditions are far from biological ones (0·01 M KOH/MeOH), which prevents this system from being used in really interesting medical applications (see later).

Another water-soluble class of calixarene is represented by *p*-sulfonatocalix[*n*]arenes ($\mathbf{2}_n$), which were prepared by sulfonation of the parent de-*tert*-butylated calix[*n*]arenes.[1–3] To evaluate the possible shape (hole-size) selectivity of these calixarenes, the complexation ability of $\mathbf{2}_n$ towards ammonium cations[3,23,28,29] **3** and **4** was studied in D_2O by a ^{1}H NMR method. It was found that $\mathbf{2}_4$ and $\mathbf{2}_6$ create 1:1 complexes whereas $\mathbf{2}_8$ with a larger cavity size can form 1:2 complexes. The association constants *K* and thermodynamic parameters ΔH and ΔS are collected in Table 1. From a comparison of entropic factors we can conclude that the binding mode in the case of $\mathbf{2}_4$ ($\Delta S<0$) might be different from that in $\mathbf{2}_6$ and $\mathbf{2}_8$ ($\Delta S>0$). Moreover, the ^{1}H NMR spectrum of the **3**:$\mathbf{2}_4$ system in acidic aqueous solution (pH 0·4) showed that only the signals assignable to aromatic protons of **3** are shifted to higher magnetic field, whereas the same spectrum in neutral conditions (pH 7·3) exhibits a non-specific upfield shift of both the aromatic and methylammonium parts of **3**. The results imply that under acidic conditions the aromatic part of the guest molecule is preferentially ‘immersed’ in the calix[4]arene cavity, while the binding mode under neutral conditions is non-specific as indicated in Figure 7. It seems to be obvious that under acidic conditions the OH groups are not dissociated and thus the main driving forces for inclusion of the guest molecule are hydrophobic interactions. At neutral pH the presence of dissociated phenolate anions causes enhancement of the electron density in calix[4]arenes aromatic walls, enabling the ammonium part to bind competitively to the cavity by hydrophobic and cation–π interactions. The change in the binding mode is accompanied by a change in the sign of ΔS.[3,23,28] The above-mentioned binding modes have also been directly observed by x-ray measurements of complex $\mathbf{2}_4$ with tetramethylammonium[30] and trimethylanilinium[28] ions.

The stabilizing effect of cation–π interactions in the complex of acetylcholine with $\mathbf{2}_4$ has been demonstrated by x-ray determination of the structure,[31] where the positively charged trimethylammonium group is inserted inside the cavity of calix[4]arene. Recently, Koh *et al.*[32] have shown that the acetylcholine-signalling system based on resorcin[4]arene[27] suffers from several drawbacks: (i) very hard conditions for biological systems, 0.01 M KOH/MeOH, (ii) acetylcholine undergoes base-catalyzed methanolysis at

Table 1. Association constants *K* (D_2O, 25 °C, pH 7·3) and thermodynamic parameters ΔH and ΔS for the complexation of ammonium salts

Guest	Thermodynamic parameter	$\mathbf{2}_4$	$\mathbf{2}_6$	$\mathbf{2}_8$	
				1:1	1:2
3	K(mol^{-1} dm^3)	5600	550	5200	4600
	ΔH (kcal mol^{-1})	−6·2	−0·25	0·0	0·0
	ΔS (kcal mol^{-1})	−3·6	11·7	17·0	16·7
4	K (mol^{-1} dm^3)	2100	1000	19000	17000
	ΔH (kcal mol^{-1})	−5·7	−0·15	0·0	0·0
	ΔS (kcal mol^{-1})	0·65	13·3	19·6	19·3

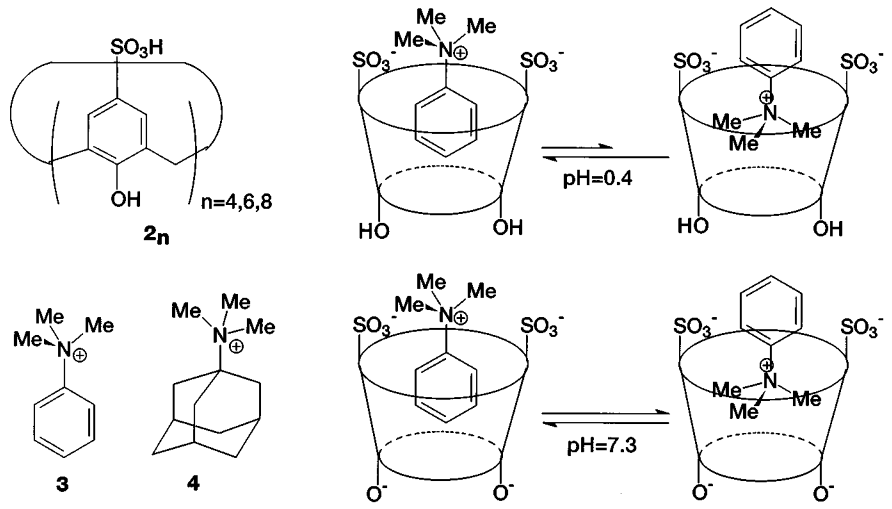


Figure 7. Binding modes for ammonium guests at various pH

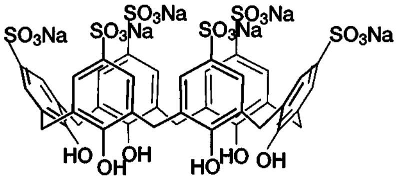
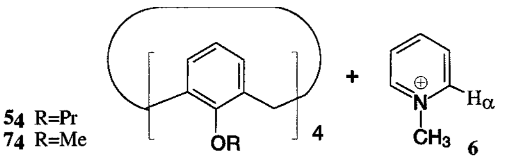


Figure 8. Acetylcholine receptor

room temperature, (iii) the pyrene-appended pyridinium marker is susceptible to nucleophilic addition and under the measuring conditions is transformed into 1,2- or 1,4-dihydropyridines.[32] Therefore, the sodium salt of $\mathbf{2}_6$ (Figure 8) has been recommended as a novel, very specific artificial receptor for acetylcholine that works on a similar principle[27,32] to Inoue's. Because the pK_a values of the OH groups in $\mathbf{2}_6$ are very low, this receptor is really useful even in neutral aqueous solution and thus can be used, for the first time, for the non-destructive histochemical analysis of acetylcholine. Moreover, the interaction with acetylcholine is so specific that the determination of this neurotransmitter is possible even in the presence of amino acids.

Interactions in organic media

Araki *et al.*[33] have studied the interactions of various calix[4]arenes with quaternary ammonium salts in organic solvents to find which conformation is most suitable for cation–π interactions. It was revealed that among series of immobilized conformers $\mathbf{5}_4$ the best inclusion ability was shown by the cone conformer, whereas the 1,2- and 1,3-alternates showed almost no complexation ability. This difference could be demonstrated by the induced ^{1}H NMR chemical shifts [$CDCl_3$–CD_3CN(10:1)] of *N*-methylpyridinium iodide (**6**) after addition of appropriate calix[4]arene $\mathbf{5}_4$ (Figure 9).[33] It is obvious that only cone conformer possesses a π-base cavity geometrically suitable for inclusion of guest molecules; in other words, suitable preorganization of the host molecule is necessary for the observation of cation–π interactions. This conclusion was further corroborated from the conformational behavior of the tetramethoxy derivative $\mathbf{7}_4$. At -50 °C $\mathbf{7}_4$ exists as a mixture of cone (31%) and partial cone (69%) conformers, whereas the addition of 1 equiv. of **6** results in an increased content of cone (67%) isomer due to the complexation induced change in the equilibrium process (Figure 9).



Induced chemical shifts (H-α):

5$_4$ cone => -0.707 ppm
5$_4$ part.cone => -0.049 ppm
5$_4$ 1,2-alt. => -0.019 ppm
5$_4$ 1,3-alt. => -0.018 ppm

$$\mathbf{7}_4\ (31\%\ \text{cone} + 69\%\ \text{partial cone}) \xrightleftharpoons{\mathbf{6}(1\ \text{eq.})} \mathbf{7}_4\ (67\%\ \text{cone} + 33\%\ \text{partial cone})$$

Figure 9. Cation–π interactions of various conformers

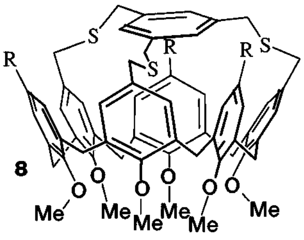


Figure 10. Capped calixarene

The importance of preorganization for cation–π interactions can be demonstrated on the calix[6]arene derivative **8** (Figure 10.).[34] The immobilization of the calix[6]arene skeleton by capping on the upper rim leads to a rigid derivative exhibiting C_3 symmetry. This symmetry is considered to be ideal for the recognition of trimethylammonium ions. Indeed, the association constant for trimethylanilinium iodide (CD_2Cl_2) is several times higher than that for the reference compound hexamethoxy-*tert*-butylcalix[6]arene.

It is known[35,36] that cone conformers of tetraalkoxycalix[4]arenes apparently exhibit rigid C_4 symmetry in solution, but in fact this is the result of time averaging of the interconversion between two C_{2v} structures (Figure 11). It is believed that such a conformational equilibrium can affect the molecular recognition process in solution. To suppress this type of motion, and thus enhance the complexation ability of the host compound, Arduini *et al.*[37] introduced short diethylene glycol bridges into calix[4]arene. The resulting derivative **9** was successfully used for the cation–π complexation study of methylammonium and tetramethylammonium ions.

Another possible strategy to increase the complexation ability through cation–π interactions is the use of conformationally immobilized calix[4]arene as a building block for the construction of a more sophisticated molecular assembly. This method allows suitable preorganization of target molecules with an appropriate π-basic cavity. For instance, bis-calix[4]arenes **10**[38] and **11**[39] were found to be much better host molecules for pyridinium and related cations than the model compound tetrapropoxycalix[4]arene **5**$_4$ (cone). The inner cavity of both derivatives is composed of two calix[4]arene subunits connected via upper rims that can cooperatively catch the host molecule as tweezers with the help of cation–π interactions, as indicated in Figure 12 (although the contribution of charge-transfer interactions cannot be ruled out). As shown in Table 2, the inner space of derivative **10** exactly satisfies[38] the steric requirements of guest **6**, which results in a substantial enhancement of the association constant, whereas the larger cavity of **11** matches the size of quinolinium salt **15**[39] An interesting feature of **11** is the fact that the CH=CH bridge can contribute to the overall binding process by additional cation–π and/or π–π interactions. This is corroborated by a dramatic induced upfield shift of the double-bond signal in the ^{1}H NMR spectrum after the addition of the guest molecule. Another noteworthy phenomenon is the shape recognition ability of **11** (compare the association constants for quinolinium and isoquinolinium[40] host molecules **14** and **15**).

Recently, we have found[41] that an extended conjugated π-system based on calix[4]arene can significantly influence the complexation of quaternary ammonium salts. For instance, the vinyl-substituted derivative **16** can enhance the association constants for methylpyridinium iodide **6** [$K = 18.4\ \mathrm{dm^3\ mol^{-1}}$, $CDCl_3$–CD_3CN (4:1, v/v), 298 K] by additional cation–π (π–π) interactions (Figure 13). On the other hand, calix[4]arene **17** with reduced double bonds cannot ‘use’ any such additional forces, and therefore the association constant ($K = 4.2\ \mathrm{dm^3\ mol^{-1}}$) is fully comparable to that for the model tetrapropoxy (cone) derivative **5**$_4$ ($K = 4.0\ \mathrm{dm^3\ mol^{-1}}$).

Although all the above-mentioned complexation studies of quaternary ammonium salts have been carried out in solution, there have also been two studies dealing with the gas phase. Inokuchi *et al.*[42] have used positive secondary ion mass spectrometry (SIMS) of various calix[n]arenes in *m*-nitrobenzyl alcohol as a matrix for the detection of cation–π interactions in the gas phase. By measuring the relative calix[n]arene–ammonium cation cluster intensities, they estimated the selectivity of calix[n]arenes towards ‘cation–π’ based complexes. The host–guest selectivity thus obtained is largely different from that measured in solution, which indicates the important role of solvation effects in solution. A similar method[43] (fast atom bombardment mass spectrometry) was also successfully applied to the detection of calix[4]arene complexes with Et_3S^+ and Et_3O^+ cations.

The recognition and complexation of quaternary ammonium salts by several homooxacalixarenes[44–46] or calix[4]crowns[47,48] in $CDCl_3$ solution have been described, where cation–π interactions could be recognized as one of the driving forces of this process.

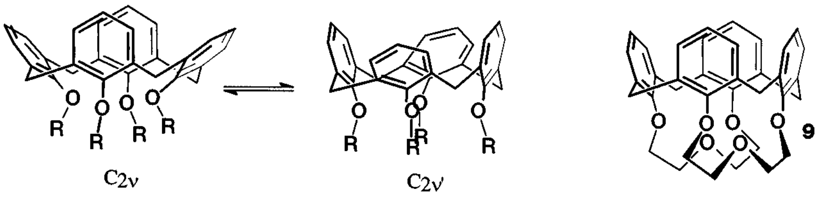


Figure 11. C_2–C_2 interconversion of calix[4]arene cone conformers

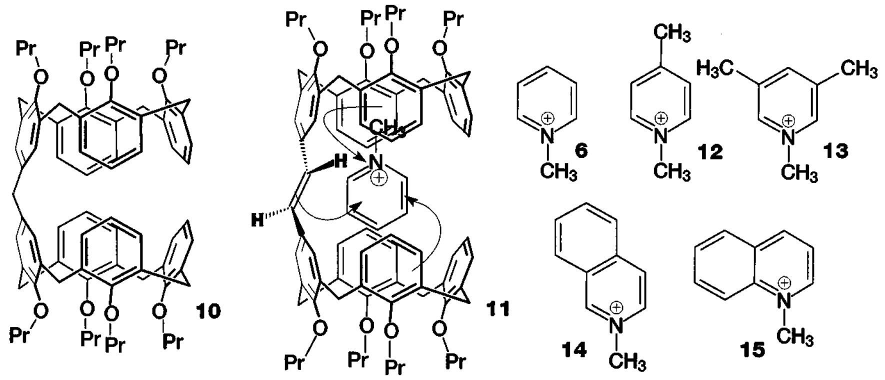


Figure 12. Bis-calix[4]arene systems

COMPLEXATION OF ALKALI METAL CATIONS

Cation–π interactions have been studied theoretically (*ab initio* 6–31G** level) by Dougherty and co-workers[8,10] on a simple model based on benzene–alkali metal cation interactions. It was shown that in the gas phase the binding sequence $Li^+ > Na^+ > K^+ > Rb^+$ corresponds to the normal electrostatic interactions, whereas in an aqueous environment the order is rearranged and K^+ exhibits the strongest binding energy for the 2:1 (Ar–K^+–Ar) complex. In the light of the above-mentioned computations the cation–π interactions are understood to constitute the main electrostatic part (ion–quadrupole interactions) with additional terms, such as dispersion forces, charge transfer, induced dipoles, polarizabilities, etc.[8,10–12] In calix[*n*]arene chemistry there is another very important factor influencing the strength of cation–π interactions, namely the size of the cavity preorganized by the calix[*n*]arene used and a given conformation.

During the study of the influence of added metal ions on the conformational isomerism of tetramethoxycalix[4]arenes,[49,50] it was found that the partial cone isomer **18** interacts with potassium cation. The ^{1}H NMR-induced changes show that the cation is probably held by the π-base cavity created by three aromatic subunits and one oxygen atom offered from one inverted phenyl ring (see Figure 14).[49] This binding mode resembles interactions with the Ag^+ cation (see later). The examination of CPK models confirmed that the lower rim cavities of partial cone or cone conformers are too small to include the large K^+ ion by common electrostatic interactions of ethereal oxygen atoms. On the other hand, Li^+ and Na^+ are small enough to be bound in such a ‘classical’ way.[49,51]

Table 2. Association constants K ($dm^3\,mol^{-1}$) for bis-calix[4]arenes [$CDCl_3$–CD_3CN (10:2), 24 °C]

Host calixarene	Guest molecule				
	6	**12**	**13**	**14**	**15**
5$_4$	6·9 (4·0[a])	3·5	2·0	18[a]	47(91[a])
10	480	36	2·0	–	97
11	108[a]	–	–	22[a]	440[a]

[a]Measured in $CDCl_3$–CD_3CN (4:1, v/v), 25 °C.

Similarly, it was found that 1,3-alternates **19a,b** exhibit a surprisingly high affinity towards the K^+ cation, as was proved by the enhanced exctractibility for potassium picrate in the CH_2Cl_2–water system.[51,52] In the ^{1}H NMR spectrum of **19** [$CDCl_3$–CD_3OD (4:1)] the signals of complexed and uncomplexed species appeared separately at −50 °C, indicating that the rate of the complexation–decomplexation is slower than the NMR (400 MHz) time-scale. The non-symmetrical splitting pattern and the induced chemical shifts imply the binding mode depicted in Figure 14. Potassium cation exactly matches the size of a cavity composed of two upper rims of aromatic units and two ethereal oxygens, and it was therefore concluded that the cation is bound by two cooperative effects of cation–π interactions and electrostatic forces. A similar binding mode has been observed in the x-ray structure of the sodium complex of 1,3-alternate tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene, where the contribution of π-electron clouds from two opposite aromatic rings is less significant because of the strong coordination ability of the ethoxycarbonyl groups.[53]

Since the first reported synthesis[54] of so-called calixcrowns in 1983, this new family of macrocyclic compounds has attracted great attention. The conjunction of ethylene glycol units (crowns) with the calix[4]arene moiety led to very useful host molecules[36] with an unexpectedly

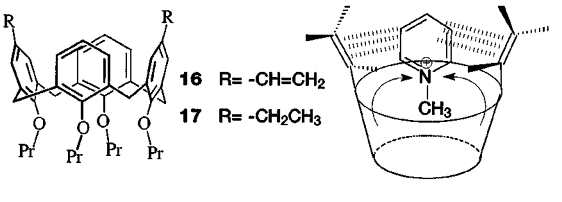


Figure 13. Additional cation–π interactions

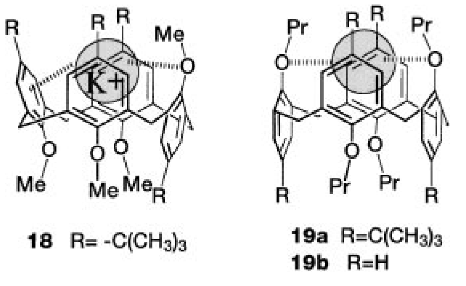
high recognition ability, especially towards alkali and alkaline earth metal cations. The well known complexation properties of crowns together with the ‘tunable’ size and shape of calixarene were recognized as two main factors influencing the overall binding properties of calixcrowns. It was reported that the selectivity of calixcrowns depends strongly both on the length of the ethylene glycol unit and on the conformation of the basic calixarene.[55]

Selective bridging of *p-tert*-butylcalix[4]arene with appropriate ethylene glycol ditosylates followed by alkylation with an alkyl halide gives three isomers (cone, partial cone and 1,3-alternate) of *p-tert*-butylcalix[4]arenecrowns (**20**) (Figure 15). A complexation study[55] revealed that the most selective agent for potassium cation is partial cone **20** ($R{=}Bu^t$, $R_1{=}Et$). A suitably preorganized cavity, corresponding to the radius of the K^+ cation, allows the selective recognition of the potassium cation even in the presence of sodium cation. The association constant in $CHCl_3$ for potassium picrate ($K{=}8{\cdot}9\times10^9$ mol^{-1} dm^3) is much higher than that for sodium picrate ($7{\cdot}5\times10^5$ mol^{-1} dm^3), which represents a K^+/Na^+ selectivity factor of $1{\cdot}1\times10^4$, the highest ever observed in artificial receptors. Based on x-ray analyses of several isomers, the driving forces of the binding process were recognized as electrostatic interactions from oxygen lone pairs with synchronous cation–π interactions from inverted aromatic units.[55,56] This conclusion has also been corroborated by theoretical calculations.[56]

The 1,3-alternate isomer **21** bearing substituents on the upper rim ($R{=}Bu^t$, $R_1{=}Et$) complexes K^+ only moderately[56] ($CHCl_3$, $1{\cdot}4\times10^8$ mol^{-1} dm^3) because of the steric hindrance of two *tert*-butyl groups. Being located in proximity, they can interact with the binding region in the crown moiety, which results in decreased complex stability. Recently, the selectivity has been improved by using the similar 1,3-alternate derivatives **21** without substitution on the upper rim.[57] Such crowns were found to be highly selective towards K^+ cation because of very efficient cation–π interactions from both rotated phenyl rings (Figure 15).[57] Isomers **21a** ($R{=}H$, $R_1{=}Pr^i$) or **21b** ($R{=}H$, $R_1{=}Et$) possess the highest K^+/Na^+ selectivity factor (**21a**, $3{\cdot}38\times10^5$; **21b**, $2{\cdot}45\times10^5$) that has been ever achieved, even higher than that for the natural ionophore valinomycin.[57] The selective recognition of K^+ by calixcrowns-5 was used for the construction of chemically modified field effect transistors (CHEMFETs)[58] and for the selective transport of cations through supported liquid membranes.[35]

Yamamoto and Shinkai[59] observed that the Nature, to recognize K^+ selectively in the presence of Na^+, uses valinomycin with a cavity slightly larger than potassium, which means that the highest selectivity of valinomycin is actually observed for the Rb^+ cation.[57] Using a similar strategy, they designed the novel ionophoric calixcrown-4 **22**. With this molecule (Figure 15), we can demonstrate that the complexation properties of calixcrowns depend strongly on the length of the crown moiety. A derivative bearing a shorter ethylene glycol chain (**22**, $R_1{=}Et$, $R{=}H$) can selectively recognize sodium even in the presence of potassium cations, with an incredibly high Na^+/K^+ selectivity factor of $10^{5.0}$–$10^{5.3}$. Compared with the above-mentioned examples of crown-5 derivative **20**, the selectivity towards sodium cation is entirely reversed. In this system, however, spectroscopic evidence for π-base participation was not obtained.[59]

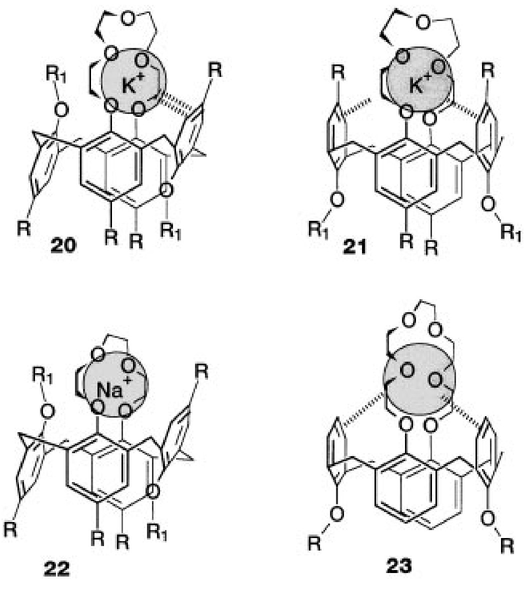
The substantial environmental problem of the selective removal of radioactive $^{137}Cs^+$ from waste water led to the design of calix[4]crowns-6 (Figure 15).[60–62] In accordance with the expectation, the selectivity of crowns is strongly dependent on the conformation[60] of the calix[4]arene skeleton, and the order of complexation is cone < partial cone < mobile calixarene < 1,3-alternate.[61] For instance, the Cs^+/Na^+ selectivity factor in $CHCl_3$ for **23**[60] ($R{=}Pr^i$) is $3{\cdot}98\times10^3$ and the Cs^+/K^+ selectivity factor is 2500. As was shown by x-ray crystallography, the Cs^+ cation is again included in the crown moiety with a cation–π contribution from two inverted phenyl units.[62]



18 R= -C(CH$_3$)$_3$

19a R=C(CH$_3$)$_3$
19b R=H

Figure 14. Interactions with potassium cation



20 **21** **22** **23**

Figure 15. Calix[4]arene crown derivatives

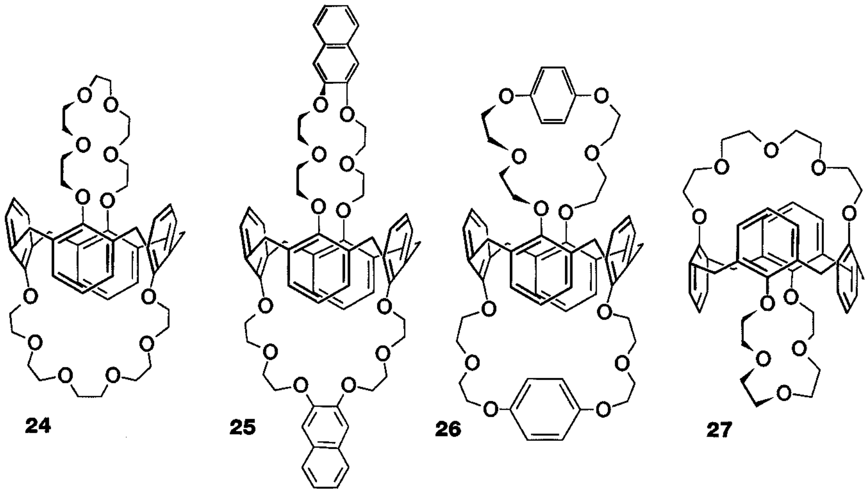


Figure 16. Examples of 1,3-alternate bis-crowns

NMR[63,64] and x-ray diffraction studies[65] of single crystals have revealed that the calix[4]arene-bis-crowns **24**–**27** (Figure 16) can form either 1:1 or 1:2 complexes with alkali metal cations, depending on the calix[4]arene to metal ratios. Especially, bis-crowns-6 were found to complex Cs^+ cation selectively, and **25**[63,66] possesses a Cs^+/Na^+ selectivity factor of $4{\cdot}5\times10^4$. In all cases, a substantial contribution of cation–π interactions to the stabilization of complexes has been proposed.[67]

Positive secondary ion mass spectrometry (SIMS) of tetrapropoxycalix[4]arenes was used by Inokuchi *et al.*[68] to study the selective recognition of alkali metal cations by a π-basic molecular cavity in the gas phase. The selectivity observed is completely consistent with that observed in solution. Recently the complexation of alkali metal cations by calix[4]crowns in the gas phase, in water and at the $CHCl_3$–water interface has been studied with the help of molecular dynamics.[69]

INCLUSION OF SILVER

Despite the similar atomic radius and similar chemical behavior to alkali metals, it seems preferable to consider the silver cation in a separate section. The main reason is the well known pronounced capability[70] of Ag^+ to create cation–π complexes with aromatic systems[71–73] (**28**) or even with suitably substituted double[74,75] (**29, 30**) and triple bonds[76] (**31**). As can be seen in Figure 17, the preorganization and rigidification of the cavities can lead to interesting 1:1 complexes with silver or other transition metals.[77,78]

X-ray and NMR studies of deltaphane **28**[71] revealed that the silver cation does not reside in the inner space of the rigid cavity, but is rather bound to the edge of the aromatic system. This phenomenon might be general also in calix[4]arene chemistry, as was indicated by x-ray analysis of single crystals of calix[4]arene–silver complexes. Ikeda and Shinkai[51] have shown that Ag^+ is complexed by cation–π interactions in cone **32** and partial cone **33**[79] conformers of $\mathbf{5_4}$, and in both cases the ion is held by the upper rim of calix[4]arene. The structure of the silver complexes with the partial cone derivative (similar to **33**) has been proved recently by x-ray measurements.[80,81]

Although a single crystal of the 1,3-alternate–Ag^+ complex has not been successfully isolated, ^1H NMR measurements imply the same binding mode as proposed in Figure 18.[51,52] Moreover, the temperature-dependent ^1H

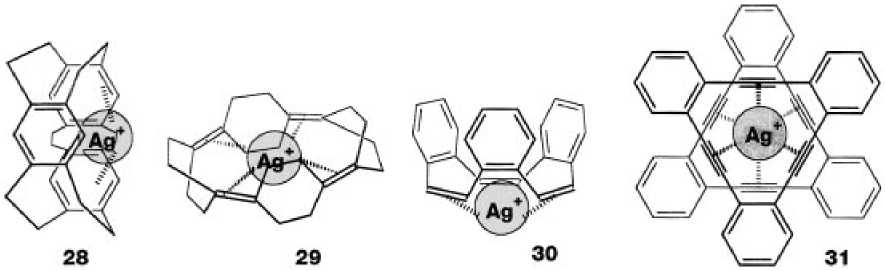


Figure 17. Examples of Ag^+ complexes based on cation–π interactions

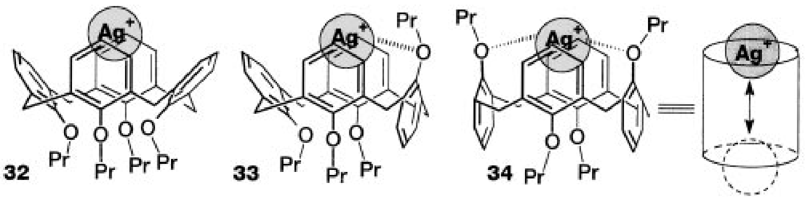


Figure 18. Cation–π complexes with calix[4]arenes and silver tunneling

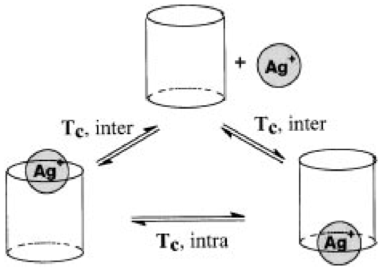


Figure 19. Metal tunneling in 1,3-alternate derivative

NMR spectra showed that the binding position of the silver cation changes on the NMR time-scale by two main mechanisms. Whereas the intermolecular complexation–decomplexation process gives $T_{c,inter}$ which is highly concentration dependent, the other mechanism, intramolecular equilibrium, is characterized by a concentration-independent $T_{c,intra}$ as depicted in Figure 19. Two such different coalescence temperatures for derivative **34** [CD_2Cl_2–$CDCl_3$(4:1, v/v); $T_{c,intra} = -70$ °C; $T_{c,inter} = 0$ °C] and their concentration dependence thus clearly support this assumption.[51] Similar metal tunneling has been observed also for the 1,3-alternate bis-crown derivative **27**.[67]

Very recently we have found[41] that the upper rim vinyl-substituted calix[4]arenes **35** and **36** can bind silver cation much better that those without appropriate substituents (Figure 20). ^{1}H NMR titration experiments corroborated the assumption that the wider π-system can more efficiently bind Ag^+ owing to the additional cation–π interactions from double bonds.

Molecules with a spherical concave surface such as **37** and **38** (Figure 21) were recognized as suitable host molecules for the complexation of Ag^+ or Ga^+ cations with the help of cation–π interactions.[82,83] These hydrocarbons represent not only molecules with aesthetic structures, but also a very promising kind of cyclophane exhibiting high preorganization and enhanced complexation ability.

We recently found a direct route leading from calix[4]arene to cyclophane chemistry.[39] The McMurry reaction of tetraformylcalix[4]arene in a 1,3-alternate conformation leads to the intramolecularly double-bridged molecule **39** (Figure 22) with an ideal cage-like structure. SIMS in the presence of silver triflate revealed that this compound forms a 1:1 complex with silver cation, which was also validated by ^{1}H NMR experiments. A basic question concerning cage derivative **39** is whether it is too small to include silver (or any other cation) inside its cavity. We were interested in solving this problem and hence we attempted to prove the binding mode of the **39**–Ag^+ system. Obviously, there are two basic possibilities: (a) the Ag^+ cation is bound inside the cage molecule and held by cation–π interactions from all four aromatic subunits, or (b) binding occurs outside the cage, where the silver cation can be held by cation–π interactions (possibly with some participation of oxygen atoms) either from aromatic units or from double bonds.

To establish the real binding mode for **39** we prepared similar structures (half-cages) based on diformyl derivatives of 1,3-alternate or cone conformers **40** and **41**. The catalytic reduction of these derivatives then yielded the corresponding compounds with saturated bonds (**42**–**44**), which were used for the elucidation of the role of the double bond in the binding of silver cation. The complexation ability towards silver triflate was studied by ^{1}H NMR titration and dynamic NMR spectroscopy in $CDCl_3$–CD_3OD (4:1, v/v) solvent. It was found that the simplest situation is in the 1,3-alternate half-cage structures **40** and **43**. As expected, the binding

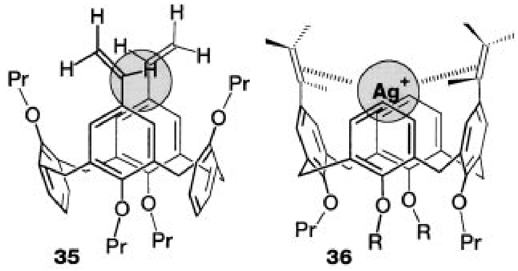


Figure 20. Vinyl-substituted calix[4]arenes

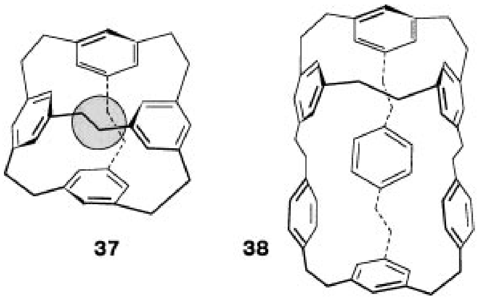


Figure 21. Concave hydrocarbons

mode is very similar to that already described above for complex **34**. Based on the complexation-induced chemical shifts (Figure 23), we can conclude that the silver cation resides in the cavity created by two oxygens from inverted phenyl rings and the two upper rims of the remaining distal aromatic units (depicted in Figure 24). This cooperative effect of cation–π and electrostatic interactions leads to comparatively high association constants for **40** (log $K=2{\cdot}52$) and **43** (log $K=2{\cdot}85$).

Cone derivative **41** creates a 1:1 complex with silver cation (log $K=0{\cdot}74$); on the other hand, the chemical shifts of the derivatives are with a reduced double bond are scarcely influenced by the addition of silver triflate. This indicates that the double bond is crucial and necessary for the binding of Ag^+ in the case of **41**. The CPK models showed that this derivative actually has no suitable cavity for the inclusion of silver, and therefore the only possible binding mode is to keep the metal cation outside by cation–π interactions from a double bond with possible additional interactions from the edge of aromatic ring(s).

Finally, the two cage molecules **39** and **42** possess similar association constants for silver cation, log $K=1{\cdot}25$ and $1{\cdot}15$, respectively. This implies that the double bonds are not necessary for binding. Moreover, the induced chemical shifts (Figure 23) exhibit the same changes in all parts of molecule, indicating a similar influence (distance) of the silver cation. A likely conclusion is that silver is caught in the middle of the cavity because of cation–π interactions from the aromatic surfaces. Of course, such a binding mode is much weaker than that in **40**, because only pure cation–π interactions can operate here in derivatives **39** and **42**. Figure 24 shows all three proposed binding modes for

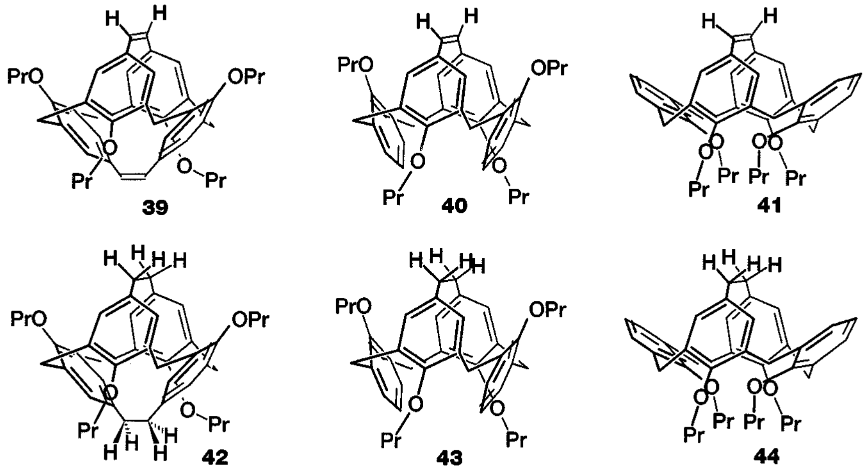


Figure 22. Cage-like derivatives prepared by McMurry reactions

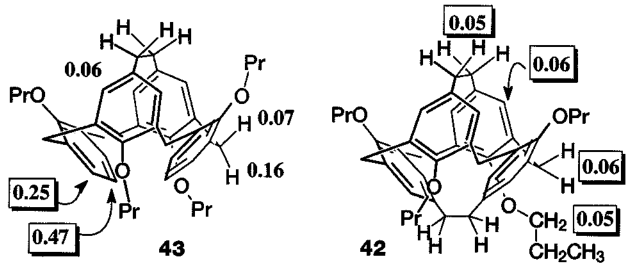


Figure 23. Induced chemical shifts after addition of 10 equiv. of AgTfl

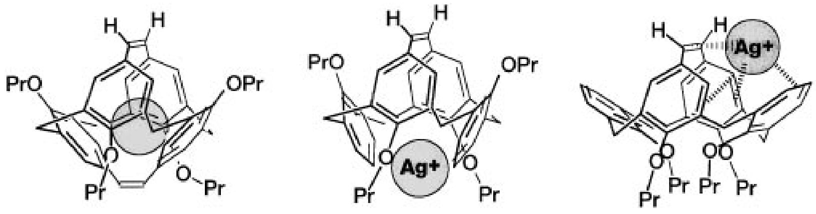


Figure 24. Proposed binding modes for Ag^+ complexes of calix[4]arenes **39**–**41**

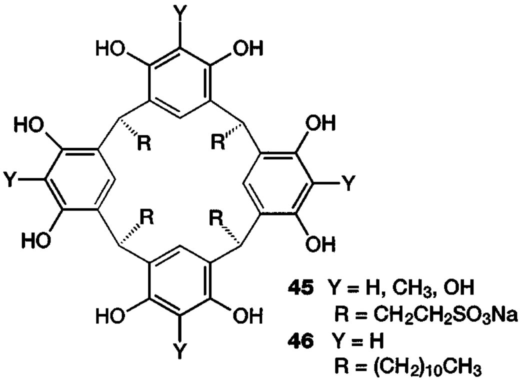
derivatives **39**–**41**, demonstrating nicely the importance of molecular preorganization (conformation, number of bridges) for the resulting complexation capability.

MISCELLANOUS (C—H. . .π INTERACTIONS)

C—H · · · π interactions have recently been recognized[84] as weak non-covalent forces that are assumed to contribute (to a certain extent) to the binding process in many solid complexes as determined by x-ray crystallographic measurements. Especially the presence of several such weak interactions inside a molecular framework can significantly influence the conformational preferences and three-dimensional structures of a variety of molecules. *Ab initio* calculations have revealed that under some circumstances their energy can be comparable to or even stronger than that of common hydrogen bonds.[85]

We are aware that C—H · · · π interactions are different from the subject reviewed in this paper, i.e. cation–π interactions. Nevertheless, we believe that their relatively weak interaction force along with the similar physical essence of the phenomenon (the participation of electron-rich aromatic systems) can justify a brief discussion here.

Kikuchi and Aoyama[86] have shown that calix[4]resorcinarenes (**45**) (Figure 25) can form 1:1 complexes with hydrophilic guest molecules in water. The guests exhibit the general formula CH_3—X—CH_3, where X = O, CH(OH), C = O or S = O, and the binding constants increase in the same order. The thermodynamic parameters, coupled with NMR data, indicate that the driving force of the complexation is a C—H · · · π interaction between the C—H bonds of a guest molecule (soft acids) and aromatic rings of a resorcinarene host (soft base). The complexation study[87,88] of alkyl benzoates with derivative **46** resulted in the same conclusions and gave proof of the selective inclusion of the alkyl group in the cavity of the host molecules.



45 Y = H, CH_3, OH
R = $CH_2CH_2SO_3Na$
46 Y = H
R = $(CH_2)_{10}CH_3$

Figure 25. Calix[4]resorcinarenes host molecules

C—H · · · π interactions are believed to operate also in the solid-state complexes of *tert*-butylcalix[4]arenes with aromatic compounds. Based on the crystallographic results it was proposed that aromatic guests are stabilized by the interactions of the aromatic ring with methyl groups of *tert*-butyl.[84] Although only a few examples of cone conformations either in the solid state[84,89] or in solution,[84,90] have been described, recently partial cone 'self-inclusion' complexes driven by C—H · · · π interactions have also been reported.[91]

CONCLUSIONS

This paper has reviewed cation–π interactions observable in the field of calix[n]arene chemistry. It is obvious that this force appears distinctly only when host molecules are well preorganized for inclusion of cationic guest metals or molecules. The association energy (ΔG) is compensated between ΔH and ΔS. Even though one can expect some ΔH gain for the association process, a large conformational change in the host molecule usually requires a negative ΔS change and, as a result, the ΔH gain is offset by the ΔS loss. This situation explains the importance of 'preorganization' where the ΔS decrease is suppressed to a minimum value. In this context, a calix[n]arene family is an ideal class of host molecules: it can not only provide various conformationally different π-basic cavities to examine the suitability of cation–π interactions, but can also allow us to design well preorganized π-basic receptor sites. We believe that the investigation of cation–π interactions will further accelerate the skilful design of calix[n]arene-based receptors and derivatives useful for molecular recognition processes.

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