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Water-soluble calixarenes—self-aggregation and complexation of noncharged aromatic guests in buffered aqueous solution

Marion Rehm (neé Baur) [a], Markus Frank [a], Jürgen Schatz [a,b,*]

[a] Division of Organic Chemistry I, University of Ulm, Albert-Einstein-Allee 11, 89081 Ulm, Germany
[b] Organic Chemistry 1, Friedrich-Alexander-University Erlangen-Nuremberg, Henkestr. 42, D-91054 Erlangen, Germany

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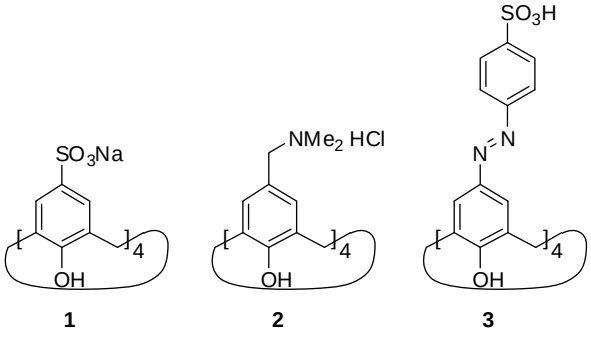
ABSTRACT

Water-soluble calix[4]arenes are useful receptors for hydrophobic substrates in aqueous buffered solution. The inclusion of 22 aromatic guests as well as the self-aggregation behavior of amphiphilic hosts was studied by ^{1}H NMR spectroscopy. The association constants obtained range from 10 to 1000 L mol^{-1}. In all cases, the aromatic moiety is included into the hydrophobic pocket of the calixarenes maximizing hydrophobic contacts. Additionally, substituents such as methyl or chlorine exhibit a preference for inclusion in the pocket of the macrocycles owing to CH/π or Cl/π interactions. In case self-aggregation is observed, millimolar CMC values are to be found.

The formation of host–guest complexes—the basis of supramolecular chemistry—especially in aqueous media is interesting not only from a mechanistic point of view, due to hydrophobic effects, but also from its possible applications, for example, in catalysis.[1] Water-soluble macrocycles such as cyclodextrins[2] or calixarenes[3] can encapsulate small organic compounds under physiological conditions. Here, a plethora of applications exploiting a supramolecular interaction are known. For example, sustained-release drug carriers,[4] cyclodextrins as active agents for 'odor eliminating' clothes,[5] or water soluble macrocycles as inverse phase transfer catalysts are current applications of such hosts.[6] Therefore, a principle study of host–guest interactions is of interest especially in pure water as the solvent.

Owing to our interest in polar calixarenes as receptor molecules, inverse phase transfer catalysts,[7] and enzyme mimics,[8] we choose conformationally flexible calixarenes **1–3** (Scheme 1), which exhibit high water solubility (>5 mmol L^{-1}), without any tendency to self-aggregation. Calixarene **3** is a chromophoric derivative of **1** with an extended hydrophobic cavity.[9] Binding studies with 22 mono-, di-, and tri-substituted benzenes **4–25** were performed in aqueous buffered solution by standard NMR titration experiments;[7] the results are summarized in Table 1.

In all cases, an up-field shift of the aromatic guest protons could be observed during the titration experiments indicating an inclusion of the aromatic moiety into the hydrophobic pocket of the water-soluble calix[4]arenes. Interestingly, throughout the titration experiments fixation of the calixarene host into the cone conformation by the included guest could be observed to some extent.[10] The typical AB doublets for the bridging methylene groups were re-established instead of the broad signals for the flexible hosts. For the formation of 1:1 host–guest complexes, association constants K_{ass} between 25 and 250 M^{-1} (mean value 80 M^{-1}) were determined for calix[4]arene **1**; host **2** usually exhibits higher values ranging from 50 to 530 M^{-1} (mean value 170 M^{-1}). Exceptions from this general trend are 2- and 3-nitro



Scheme 1. Polar calix[4]arenes used as receptor molecules.

* Corresponding author. Tel.: +49 9131 85 25766; fax: +49 9131 85 24707.
E-mail address: juergen.schatz@chemie.uni-erlangen.de (J. Schatz).

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Table 1
Association constants K_{ass} (M^{-1}) of hosts **1**–**3** with non-polar guests **4**–**25** and complexation-induced chemical shifts $\Delta\delta$ (ppm) obtained by NMR titration experiments measured in aqueous buffered solution

Guest		Host					
		1[a] K_{ass}	$\Delta\delta$	**2**[b] K_{ass}	$\Delta\delta$ (ppm)	**3**[a] K_{ass}	$\Delta\delta$
PhI	**4**	59.6	0.69 (*o*), 1.01 (*m*), 1.39 (*p*)	402	1.44 (*o*), 1.55 (*m*), 1.92 (*p*)	208	2.69 (*o*), 2.62 (*m*), 2.66 (*p*)
PhBr	**5**	30.0	0.68 (*o*), 1.24 (*m*), 1.76 (*p*)	243	1.51 (*o*), 1.71 (*m*), 2.03 (*p*)	97.1	3.67 (*o*), 3.51 (*m*), 3.52 (*p*)
PhCl	**6**	25.9	0.77 (*o*), 1.49 (*m*), 1.99 (*p*)	177	1.51 (*o*), 1.77(*m*), 2.04 (*p*)	25.3	7.91 (*o*), 6.92 (*m*), 6.77 (*p*)
PhF	**7**	26.2	0.79 (*o*), 1.52 (*m*), 2.09 (*p*)	74.5	1.50 (*o*), 1.93 (*m*), 2.03 (*p*)	11.4	9.63 (*o*), 10.50 (*m*), 15.56 (*p*)
PhCH=CH–CHO	**8**	77.8	1.03 (*o*), 2.05 (*m*), 3.53 (*p*)	80.2	0.98 (*o*), 1.90 (*m*), 2.61 (*p*)	n.d.	
PhCH=CHCH$_2$OH	**9**	n.d.		105	1.16 (*o*), 2.15 (*m*), 2.82 (*p*)	n.d.	
PhCH=CH–CO$_2$Me	**10**	n.d.		152	1.08 (*o*), 1.83 (*m*), 2.38 (*p*)	n.d.	
PhCH=CH–CO$_2$H	**11**	n.d.		146	1.27 (*o*), 2.04 (*m*), 2.60 (*p*)	n.d.	
PhCHO	**12**	79.2	1.10 (*o*), 2.06 (*m*), 2.61 (*p*)	82.4	1.23 (*o*), 1.98 (*m*), 2.60 (*p*)	212	3.54 (*o*), 4.30 (*m*), 4.92 (*p*)
PhCN	**13**	74.3	1.11 (*o*), 2.25 (*m*), 3.09 (*p*)	101	1.59 (*o*), 2.10 (*m*), 2.51 (*p*)	n.d.	
PhNO$_2$	**14**	95.5	1.32 (*o*), 2.88 (*m*), 3.94 (*p*)	97.0	1.26 (*o*), 1.92 (*m*), 2.55 (*p*)	n.d.	
4-H$_3$C–C$_6$H$_4$–CN	**15**	44.8	0.31 (*o*), 1.39 (*m*)	90.5	0.71 (*o*), 1.39 (*m*)	n.d.	
4-H$_3$C–C$_6$H$_4$–I	**16**	34.5	0.31 (*o*), 0.60 (*m*)	524	0.97 (*o*), 0.77 (*m*)	n.d.	
4-H$_3$C–C$_6$H$_4$–Cl	**17**	31.0	0.18 (*o*), 0.69 (*m*)	175	0.99 (*o*), 1.16 (*m*)	n.d.	
2-H$_3$C–C$_6$H$_4$–Cl	**18**	24.9	0.62 (6-H), 1.14 (5-H), .75 (4-H), 1.18 (3-H)	370	1.47 (6-H), 1.53 (5-H), 1.69 (4-H), 1.38 (3-H)	n.d.	
4-H$_3$C–C$_6$H$_4$–SO$_3$H	**19**	—		338	0.50 (*o*), 1.68 (*m*)	38.3	1.02 (*o*), 1.18 (*m*)
4-H$_3$C–C$_6$H$_4$–CO$_2$H	**20**	—		140	0.35 (*o*), 1.32 (*m*)	n.d.	
2-Cl–C$_6$H$_4$–CN	**21**	150	1.28 (6-H), 2.75 (5-H),				
3.13 (4-H), 1.88 (3-H)	122	1.45 (6-H), 2.23 (5-H),					
2.23 (4-H), 1.72 (3-H)	n.d.						
4-Cl–C$_6$H$_4$–CN	**22**	40.0	0.40 (*o*), 1.28 (*m*)	53.3	0.87 (*o*), 1.39 (*m*)	n.d.	
2.4-(NO$_2$)$_2$C$_6$H$_3$Cl	**23**	126	2.31 (6-H), 0.81 (5-H), 0.28 (3-H)	n.d.		n.d.	
2-NO$_2$-C$_6$H$_4$-CHO	**24**	287	1.33 (6-H), 3.35 (5-H), 3.64 (4-H), 1.93 (3-H)	79.5	1.30 (6-H), 2.49 (5-H), 2.65 (4-H), 1.67 (3-H)	676	2.88 (6-H), 4.08 (5-H), 4.89 (4-H), 3.95 (3-H)
3-NO$_2$-C$_6$H$_4$-CHO	**25**	210	3.04 (6-H), 3.66 (5-H), 2.68 (4-H), 0.59 (2-H)	69.8	2.14 (6-H), 2.60 (5-H), 2.08 (4-H), 0.28 (2-H)	511	6.32 (6-H), 4.50 (5-H), 3.72 (4-H), 2.55 (2-H)

Errors 5–13%.
[a] *p*D = 7.4.
[b] *p*D = 1.4, n.d. not determined.

benzaldehyde (**24** and **25**), respectively, for which aminocalix[4]arene **2** exhibits only 30% of the K_{ass} obtained with the anionic receptor **1**.

Diazocalix[4]arene **3** is a better receptor for the aforementioned nitrobenzaldehydes **24**, **25** compared to **1** or **2** presumably due to the extended size of the cavity. Association constants for host **3** range from 10 to 680 M^{-1} (mean value 220 M^{-1}).

The trend of the association constants obtained for the complexation of halobenzenes **4–7** can be compared with that of α- and β-cyclodextrins as hosts. For the bromo and iodo benzene K_{ass} of host **2** are about 50% of those of β-cyclodextrin, for fluoro and chloro benzene the binding strength is in the same order of magnitude.[11] For hosts **1**–**3** and α-/β-cyclodextrins the association constants decrease from PhI > PhBr > PhCl > PhF. In case of the cyclodextrins as hosts, the sizes of the halogen seem to play a dominant role in this series.[12] This cannot be true for the calixarenes, because the functionality points outside the cavity as indicated by the complexation-induced chemical shifts (see below). Here, in addition to the hydrophobic effect of the halogens, it is likely that inductive effects play an important role, because the π/π-interaction between host and guest is influenced.[13] The same tendency can be seen with toluene derivatives **15**–**17**, where the electronegative substituent is again outside the host molecule and the methyl-group points inside the cavity because of additional CH/π interactions.[14] Here again, the association constants decrease from iodine to chlorine/cyano.

In general, binding constants of calixarenes **1–3** are medium to weak. Here, a similar mechanism as reported before could play an additional role:[15] By inclusion of a noncharged aromatic guest, the calixarene skeleton is contracted. This assumption is in line with the observation that the *cone* conformation of the flexible hosts can be stabilized to some extent by the inclusion process as mentioned above. This contraction increases the electrostatic repulsion between the polar groups located at the upper rim partly compensating the energy gain of inclusion process.

Assignment of the host–guest geometry (Fig. 1) is based on the observed complexation-induced shifts (CIS, $\Delta\delta$, Table 1). Currently, the interpretation is only qualitative and based on 'chemical intuition',[16] however, structural models based on quantum chemical calculations of CIS values usually lead to very similar overall geometries.[17]

With monosubstituted guests **4–14**, the functional group points outside (Fig. 1, arrangement A). In these cases, π/π-interactions are the main source of binding energy.[18] Using the positively charged host **2**, fourfold additional favorable cation/π interaction increases the association constants but does not affect the binding geometry.[19]

Benzonitrile (**13**) is included in the cavity of both hosts **1** and **2** with a reasonable association constant (74 and 101 M^{-1}, respectively). Attaching a methyl group at the *para* position (4-methyl benzonitrile, **15**, arrangement B in Fig. 1) leads to a decrease in binding strength for the sulfonated calixarene **1.** Parallelly, the CIS is reduced significantly suggesting that 4-methyl benzonitrile is not immerged as deeply as the unsubstituted derivatives due to the bigger size of the methyl group compared to hydrogen. However, some of the unfavorable steric effect is compensated by an additional CH/π interaction between the methyl group and the aromatic calixarene bowl. Such a compensating interaction is lost when 4-chloro benzonitrile (**22**) is used as a guest. The association constant is dropping again. However, from the CIS it can be rationalized that the chlorine substituent is placed inside the hydrophobic cavity (arrangement C in Fig. 1). The arrangement exploiting Cl/π interactions seems to be energetically more favorable than complexation *via* the nitrile functionality.[20]

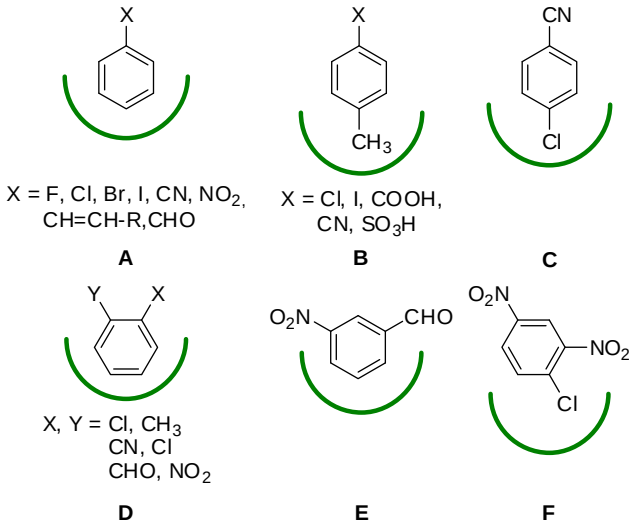
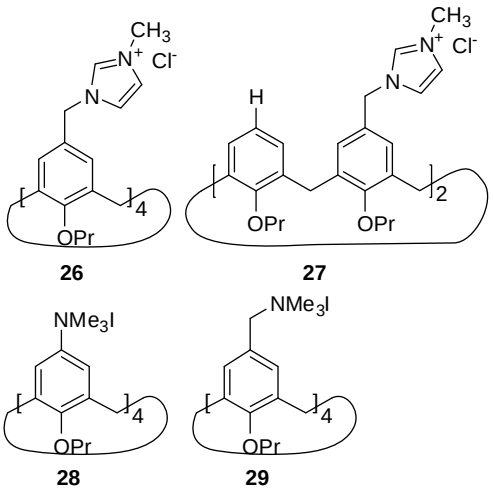


Figure 1. Geometries deducted from the induced chemical shifts (cf. Table 1) observed during the titration experiments.



Scheme 2. Cationic calixarenes fixed in the cone-conformation.

In case of the quite stable complexes of di- and tri-substituted benzenes **18**, **21**, **24**–**25** with host **1** (Fig. 1D–F), about half of a benzene ring is enclosed in the cavity with substituents pointing outside the calixarene cavity thus optimizing the hydrophobic contact (Fig. 1D–E).[21] For **23** (Fig. 1F), again, an additional attractive Cl/π interaction leads to inclusion of the chlorine substituent in the cavity.

As deducted from Table 1, cationic macrocycles are better host molecules for aromatic guest in pure water. Therefore, we wanted to expand this theme to different cationic calix[4]arenes and wanted to test them as receptors.

Imidazolium-substituted calix[4]arenes **26** and **27** (Scheme 2) were already used as precatalysts/inverse phase transfer catalysts for Suzuki cross-coupling reactions in water,[22] and ammonium calix[4]arenes **28**, **29** and β-cyclodextrin were included in the study for comparison. The solubilities of these compounds (Table 2) in pure water can be good to excellent.

Owing to the propyl groups located at the lower rim of calix[4]arenes **26**–**29** amphiphilic behavior can be expected. This would interfere with the 1:1 host–guest chemistry discussed here, because it would be difficult to differentiate between inclusion in a micelle and the host interior. Therefore, we performed standard NMR dilution experiments to get an estimate for critical micelle concentration (CMC).[23] The results are summarized in Table 2.

Tetra cationic host **26**, **28**, and **29** exhibit CMC values in the millimolar range. Tetraimidazolium calixarene **26** is—albeit its very good water solubility—an effective micelle builder via complexation of the propyl 'feet' in the cavity of a second macrocycle. In case of ammonium calixarenes **28** and **29**, the CMC parallels its solubility, the higher the solubility the higher the CMC value.

The solubility of diimidazolium calixarene 2**7** was not high enough to perform reliable NMR titration experiments and the ammonium host **28** proved not to be useful as a host molecule because aromatic guest is only weakly bound (K_{ass} < 5 M^{-1}) in water. Therefore, the complexation behavior of tetraimidazolium salt **26** with various guests was determined to illustrate the supramolecular chemistry of this class of compounds (Table 3).

Usually, the binding affinities are in the range of 20–120 M^{-1}. Surprisingly, iodo benzene is bound very tightly in the interior of macrocyclic host with an association constant (K_{ass} > 1000 M^{-1}), which is the highest one observed in this study. The methylene linker of the imidazolium groups of calixarene **26** leads to a quite flexible structure at the upper (wide) rim. Therefore, an easy interpretation of the CIS values is not possible as before. Currently, a capsule-like structure of the host maximizing additional cation/π interaction can be assumed. The observed CIS values for benzaldehyde as a guest molecule show an interesting feature supporting this assumption. Here, besides the aromatic protons, the aldehyde functionality is affected by the complexation process ($\Delta\delta$ = 0.36 ppm). This might be attributed to an additional CH/O hydrogen bridge of one imidazolium group with the carbonyl oxygen, a binding motif often found for imidazolium salt base anion receptors.[25]

Table 2
Solubilities S (g L^{-1}) and critical micelle concentration CMC (mmol L^{-1}) of macrocycles in pure water

	1	**26**	**27**	**28**	**29**	**β-CD**
S	>74.4	250	2.9	7.3	495	18.5[24]
CMC	—	1.4	—[a]	3.8	8.7	

[a] Not detectable owing to low solubility.

In summary, polar calixarenes are useful receptor molecules for nonpolar aromatic guests; association constants in buffered aqueous solution range from 10 to 1000 M^{-1}, and cationic host is more effective because of additional cation/π interactions. From the observed CIS the host–guest geometries of more than 50 complexes could be deduced. In general, the benzenes are included in such a way that the π/π interactions are maximized. Owing to the cavity size of calixarenes **1** and **2**, it is likely that about 50% of the benzene ring is included and the functionalities not providing any additional binding interaction are pointing outwards. In case the benzene ring is bearing functional groups such as methyl or chlorine, additional CH/ π or Cl/π interactions lead to encapsulation of these directing groups. Tetraimidazolium calix[4]arene 2**6** shows both

Table 3
Association constants K_{ass} (L mol^{-1}) of host **26** with non-polar guests and complexation-induced chemical shifts $\Delta\delta$ (ppm) obtained by NMR titration experiments measured in aqueous buffered solution, p*D* = 7.4

Guest	K_{ass}	$\Delta\delta$
Ph–$B(OH)_2$	38.8	0.41 (*o*), 0.78, (*m*), 0.76 (*p*)
Ph–CH_3	113	0.47 (*o*) 0.43 (*m*), 0.51 (*p*), 0.30 (CH_3)
4–Cl–C_6H_4–CN	71.7	0.55 (*o*), 0.49 (*m*)
Ph–CHO	28.3	0.57 (*o*), 0.55 (*m*), 0.52 (*p*), 0.36 (CHO)
Ph–CH=CH–CHO	128	0.76 (*o*), 0.51 (*m*), 0.53 (*p*)
PH–I	>1000	0.59 (*o*), 0.36 (*m*), 0.31 (*p*)

Errors < 10%.

self-aggregation and receptor properties, especially for iodo benzene as guest. Besides the inclusion in the cavity, additional interactions between the imidazolium groups and the included guest are a special feature of this host.

The presented data enable the appraisal of both the association constants and geometries of complexes between polar calixarenes and a wide range of benzene derivatives in aqueous solution. Such information can now be exploited in receptor design for applications such as supramolecular catalysis.

Experimental

All NMR titration experiments (400 MHz, $T = 293 \pm 2$ K) were performed in aqueous buffer solutions containing 0.83% methanol-d_4. Buffer concentrations were 0.2 (pD 1.4) and 0.1 mol L^{-1} (pD 7.4), respectively. For non-aggregating calixarenes **1–3**, the guest concentration—added as a stock solution in methanol-d_4 (5 μL)—was kept constant at 1.3–1.4 mmol L^{-1} and the calixarene host concentration was varied. In case of self-aggregating calix[4]-arene **26**, the host concentration was held constant well below its CMC at about 0.4 mmol L^{-1} and the guest concentration was varied. In all cases the aromatic signals of the guest were followed, and association constants (K_{ass}) were calculated using a nonlinear curve fit of the observed chemical shifts.

For the determination of solubilities, a suspension of the corresponding macrocycle in pure water was stirred for 24 h, the remaining solid was filtered off, and the residual material was dried. Solubilities were then determined just by differential weighing.

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