Importance of intramolecular hydrogen bonding for preorganization and binding of molecular guests by water-soluble calix[6]arene hosts

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The binding affinity of calix[6]arene hexasulfonate hosts for ferrocene or cobaltocenium guests is highly dependent on the extent of intramolecular hydrogen bonding in the lower rim of the calixarene.

The calixarenes[1] are an interesting and extensively studied class of host molecules characterized by their aromatic character and conformational flexibility. Water-soluble calixarenes are commonly prepared by sulfonation of the aromatic rings, yielding a family of negatively charged hosts.[2] We have previously reported on the binding ability in aqueous solution of sulfonated calixarene hosts with different molecular guests.[3,4] Here, we concentrate our attention on calix[6]arenes **1** and **2** (Fig. 1) and report our findings on the striking differences in the binding affinity exhibited by these two calixarene hosts towards the same guests (ferrocene and cobaltocenium derivatives, Fig. 1). The differences observed can be rationalized on grounds of host preorganization due to intramolecular hydrogen bonding in the calixarene's lower rim.

Calixarene **1** exists in neutral aqueous solution as an octaanion due to the deprotonation of two of its phenolic OH groups. Atwood *et al.* reported the X-ray crystal structure of the sodium salt of $\mathbf{1}^{8-}$.[5] They found that this host exhibits a partial cone conformation with three adjacent sulfonate groups pointing to one side of the cavity and the remaining three sulfonates pointing to the opposite end. The structure is rigidified by hydrogen bonding of each negatively charged phenolate to the two neighboring phenolic OH groups, as shown in Fig. 1. This crystal structure was postulated to be very close to the average solution structure due to the high level of hydration of the crystal.[5]

The accessible electroactivity of the selected guests[‡] allowed us to readily examine the binding interactions between each calixarene–guest pair using voltammetric techniques. Relevant electrochemical data are given in Tables 1 and 2. Host **1** forms stable complexes in pH 7.0 aqueous media with all the guests surveyed. This is shown by the decreased current levels observed upon addition of $\mathbf{1}^{8-}$ on the voltammetric waves for the oxidation of the ferrocene guests as well as on those for the reduction of the cobaltocenium guests. This current decrease reveals the association of $\mathbf{1}^{8-}$ with all the guests prior to any electrochemical conversions. In addition to this, the half-wave potential ($E_{1/2}$) for the oxidation of the ferrocene guests shifts to less positive values in the presence of $\mathbf{1}^{8-}$ and the $E_{1/2}$ values for reduction of the cobaltocenium guests shift to more negative values. This is consistent with the octaanionic host binding more strongly to the oxidation states of the guests bearing a higher positive charge.

Similar experiments with $\mathbf{2}^{6-}$, the O-methylated analog of calixarene host $\mathbf{1}^{8-}$, yield very different results. First, addition of this calixarene does not affect the current levels of the voltammetric waves. Secondly the $E_{1/2}$ values also remain

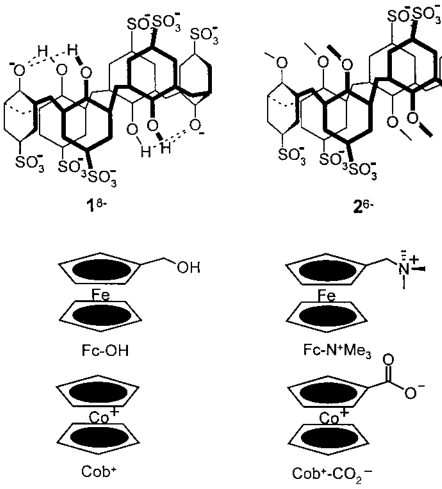

Fig. 1 Structures of calixarene hosts and molecular guests studied in this work

Table 1 Voltammetric data at 25 °C for different guests (1.0 mM) in the absence and in the presence of two calixarene hosts. Medium: 0.1 M phosphate buffer (pH 7)

		Host $\mathbf{1}^{8-}$		Host $\mathbf{2}^{6-}$	
Guest	[Host]/[Guest]	$E_{1/2}{}^a$/V	$i_p{}^b$/μA cm^{-2}	$E_{1/2}{}^a$/V	$i_p{}^b$/μA cm^{-2}
Fe–OH	0:1	0.234	336.5	0.229	350.1
	1:1	0.175	260.1	0.230	350.0
	4:1	0.114	274.2	0.224	350.1
Fc–N$^+$Me$_3$	0:1	0.446	216.4	0.445	223.0
	1:1	0.342	143.9	0.437	216.2
	5:1	0.331	139.9	0.421	209.6
Cob$^+$	0:1	-1.112^c	334.2^c	-1.112^c	336.4^c
	1:1	-1.228^c	149.5^c	-1.124^c	334.6^c
	4:1	-1.272^c	136.8^c	-1.128^c	320.6^c
Cob$^+$–CO$_2{}^-$	0:1	−0.992	210.9	−0.992	203.8
	1:1	−1.016	153.1	−0.996	204.2
	4:1	−1.044	142.6	−0.997	201.2

[a] V *vs.* Ag/AgCl reference electrode. [b] Peak current densities, cathodic for cobaltocenium and anodic for ferrocene derivatives. [c] These values are strongly affected by the precipitation of the reduced form (Cob); to minimize these effects, we determined the half-wave potentials using normal pulse voltammetry.

Table 2 Voltammetric data at 25 °C for ferrocene-based guests (1.0 mM) in the absence and in the presence of calixarene host $\mathbf{1}^{6-}$. Medium: 0.1 M chloroacetate buffer (pH 2.6)

Guest	[Host]/[Guest]	$E_{1/2}{}^a$/V	$i_p{}^b$/μA cm^{-2}
Fc–OH	0:1	0.227	183.5
	1:1	0.215	185.3
	4:1	0.191	165.2
Fc–N$^+$Me$_3$	0:1	0.441	175.4
	1:1	0.411	170.2
	5:1	0.393	142.0

[a] V *vs.* Ag/AgCl reference electrode. [b] Anodic peak current densities.

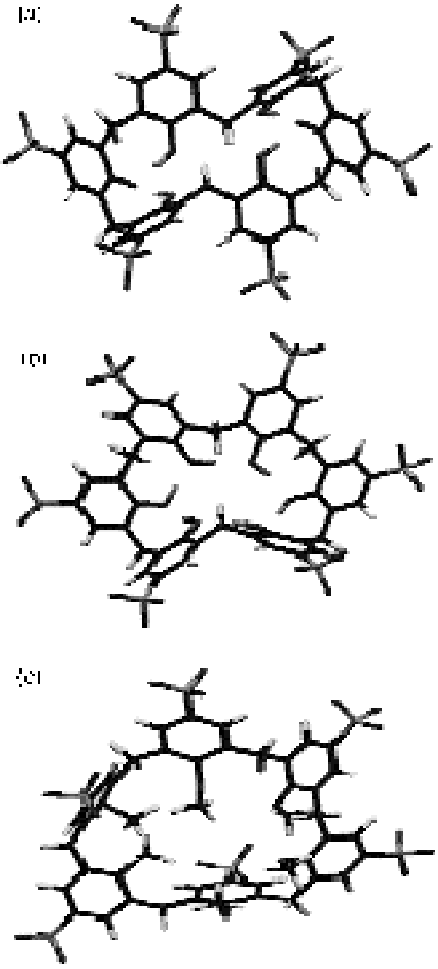

Fig. 2 Minimum energy conformations obtained with computational methods for (*a*) **1**$^{8-}$, (*b*) **1**$^{6-}$ and (*c*) **2**$^{6-}$§

essentially unchanged in the presence of **2**$^{6-}$. These data reveal that this hexaanionic calixarene host is ineffective at binding all these guests in any of their two accessible oxidation states. In an attempt to understand the striking binding ability differences between **1**$^{8-}$ and **2**$^{6-}$, we also performed experiments with **1**$^{6-}$, prepared by dissolving the unmethylated calixarene **1** in a solution buffered at pH = 2.6 to insure the full protonation of its phenolic lower rim.[6] The corresponding voltammetric results (Table 2) clearly indicate that this host loses a fraction of its binding ability under these conditions compared to the same host in neutral (pH = 7) media.

It seems dubious that these effects could be rationalized with electrostatic arguments. While calixarene **1** at neutral pH bears eight negative charges, both calixarene **2** at the two pH values surveyed here and calixarene **1** at pH = 2.6 are hexaanions. These less charged hosts still have six negative charges, certainly enough to attract positively charged guests if electrostatic forces were to control the host–guest interactions. To further clarify the observed binding properties we have run a series of molecular modeling calculations§ aimed at finding relevant conformational differences between these hosts. The computational results show that, at neutral pH, the most stable conformation of the octaanionic host **1**$^{8-}$ is very similar to the crystal structure reported by Atwood and coworkers [Fig. 2(*a*)]. After full protonation of its lower phenolic rim, the same host (now **1**$^{6-}$) adopts a very different, flattened and puckered conformation [Fig. 2(*b*)], which lacks well defined binding pockets in spite of its relative rigid character. This conformational change may be responsible for the diminished binding ability exhibited by this host in acidic media. Finally, the methylated host **2**$^{6-}$ exhibits a lot more flexibility since intramolecular hydrogen bonding in the lower rim is no longer possible. In this case, we could not locate a clearly defined energy minimum. The lowest energy conformation found is shown in Fig. 2(*c*), but many other equally disorganized conformations are readily accessible. The flexibility and absence of molecular preorganization are the key factors that determine the poor binding ability demonstrated by this host. Conversely, the octaanionic form of **1** (present at neutral pH) is an excellent host¶ for the guests surveyed here because of its preorganized and rigid character which is determined by the network of hydrogen bonds in its lower rim.

The authors are grateful to the US National Science Foundation for the support of this research work (to A. E. K., CHE-9633434).

Notes and References

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‡ The two ferrocene derivatives, Fc–OH and Fc–N$^+$Me$_3$, undergo reversible one-electron oxidation to the corresponding ferrocenium forms, Fc$^+$–OH and Fc$^+$–N$^+$Me$_3$, respectively. We have previously reported on the binding of these two guests by calixarene **1** in unbuffered aqueous media, see ref. 3(*a*). The two cobaltocenium derivatives, Cob$^+$ and Cob$^+$–CO$_2$$^-$, undergo reversible one-electron reduction to the corresponding cobaltocene forms, Cob and Cob–CO$_2$$^-$, respectively, at a potential which is accessible at neutral pH but inaccessible at pH = 2.6. The pK_a of Cob$^+$–CO$_2$H is *ca.* 1.3 so that complete ionization is expected in the pH range used in this work.

§ All calculations were run with the Macromodel software package (version 6.0) running on a O2 Silicon Graphics workstation. The energy of each calixarene was minimized, after setting the solvent option to water, using the OPLS force field. Conformtional searches were done using Monte Carlo simulations with an energy range of 100 kJ mol^{-1} (1 cal = 4.184 J). On average, 400–500 unique conformations were identified for each host *en route* to a global minimum. At least two full conformational searches were performed with each host.

¶ ^{1}H NMR spectroscopic experiments indicate that the complexes formed between the guests Fc–N$^+$Me$_3$ and Cob$^+$ with host **1**$^{8-}$ have 2:1 (guest:host) stoichiometry under these experimental conditions (see the following communication in this issue).

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Received in Columbia, MO, USA, 30th January 1998; 8/00846I