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Spherical Shape Complementarity as an Overriding Motif in the Molecular Recognition of Noncharged Organic Guests by *p*-Sulfonatocalix[4]arene: Complexation of Bicyclic Azoalkanes

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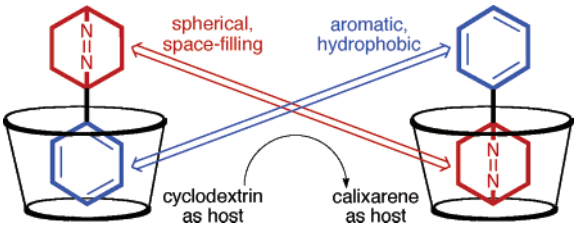

The complexation of *p*-sulfonatocalix[4]arene (CX4) with 2,3-diazabicyclo[2.2.1]hept-2-ene (**1**), 2,3-diazabicyclo[2.2.2]oct-2-ene (**2**), 2,3-diazabicyclo[3.2.2]non-2-ene (**3**), 1-methyl-4-isopropyl-2,3-diazabicyclo[2.2.2]oct-2-ene (**4**), and 1-phenyl-2,3-diazabicyclo[2.2.2]oct-2-ene (**5**) was studied in D_2O at pD 7.4 by ^1H NMR spectroscopy. The formation of deep inclusion complexes was indicated by large upfield ^1H NMR shifts of the guest protons (up to 2.6 ppm), which were also used to assign, in combination with 2D ROESY spectra, a preferential inclusion of the isopropyl group of **4** and a dominant inclusion of the azo bicyclic residue for **5**. The bicyclic azoalkanes **1**−**3** showed exceptionally high binding constants on the order of 1000 M^{-1}, 1−2 orders of magnitude larger than for previously investigated noncharged organic guest molecules. The strong binding was attributed to the spherical shape complementarity between the guest and the conical cavity offered by CX4. Interestingly, although the derivatives **4** and **5** are more hydrophobic, they showed a 2−3 times weaker binding, which was again attributed to the deviation from spherical shape in these bridgehead-substituted derivatives. The preferential inclusion of the hydrophilic but spherical bicyclic residue of **5** rather than the hydrophobic aromatic phenyl group provides a unique observation in aqueous host−guest chemistry and corroborates the pronounced spherical shape affinity of CX4.

Introduction

Water-soluble calixarenes of the *p*-sulfonato type have been under intense investigation for catalytic, biomimetic, sensor, and separation applications.[1−10] They are versatile macrocyclic host molecules with metal ion receptor properties, and additionally they provide, depending on their conformation, concave hydrophobic binding sites for organic residues. For *p*-sulfonatocalix[4]arene (CX4), a particularly common derivative, electrostatic and cation−π interactions are presumed to be the dominant driving force for complexation; this is reflected in the high binding constants of CX4 with organic (ammonium) cations (10^3−10^5 M^{-1}).[1−4] Binding of noncharged organic guest molecules by CX4 has also been intensively investigated, owing to, among others,

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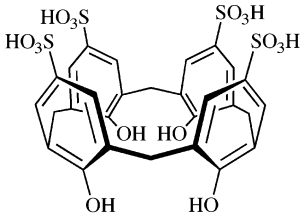
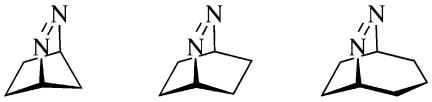
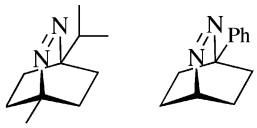
the potential of water-soluble calixarenes to serve as inverse phase-transfer catalysts.[5] However, the binding constants were consistently found to be undesirably low (10^1-10^2 M^{-1}),[5−8] implying a very low hydrophobic driving force for complexation.



CX4



1 **2** **3**



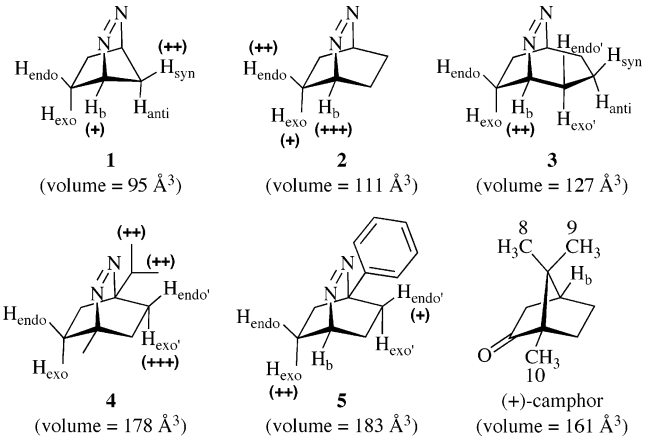
4 **5**

The present understanding of the complexation pattern of noncharged organic guests with CX4 in aqueous solution is such that (a) the binding should be weak[5−9] and (b) the selectivity should be low.[11−13] We questioned whether the binding constants of noncharged guests could be increased by employing bicyclic molecules, which match the spherical shape of the CX4 cavity in the molecular recognition process. Herein, we selected the azoalkanes **1**−**5** of the 2,3-diazabicyclo[x.2.x]alk-2-ene type, which have recently been established as versatile probe molecules for host−guest complexation phenomena in aqueous solution (e.g., for cyclodextrins and cucurbiturils).[14−20] They are, in particular, sufficiently water-soluble to obtain direct information on their binding constants and the structures of their complexes with CX4 by ^{1}H NMR spectroscopy.

Results and Discussion

Complexation-Induced Shifts. Addition of CX4 (0.4−8 mM) to an aqueous solution of **1**−**5** (0.5−1 mM) at pD 7.4 (adjusted by addition of NaOD) resulted in very large upfield ^{1}H NMR shifts for the azoalkane protons (up to 2.6 ppm, extrapolated to quantitative complexation; Chart 1, Table 1, Figure 1). These are characteristic for the formation of tight and deep host−guest inclusion complexes due to the shielding effect by the aryl groups.[4−7,21,22] It is well accepted that CX4 adopts a cone conformation in water, the flexibility of which is dependent on pH and the presence of metal ions or organic cations.[21−23] The methylene protons of CX4 appear as a broadened singlet at pD 7.4 in the absence of guest, consistent with a flexible cone conformation. The addition of an excess of azoalkane (e.g. **2**) resulted in a splitting of this peak (inset of Figure 1), which provides evidence for a rigidification of the cone conformation of the host upon inclusion of the guest (guest template effect).[22] As judged by the *averaged* complexation-induced shifts, the depth of immersion gradually decreases from **1** (ca. −1.9 ppm) to **2** (ca. −1.7 ppm) to **3** (ca. −1.5 ppm), as expected from the increasing guest size; the calculated van der Waals volumes increased from 95 to 111 to 127 Å^3 for azoalkanes **1**−**3** (Chart 1).

CHART 1. Proton Labelling and Calculated Molecular Volumes[a]



[a] Relative magnitudes (uncorrected) of 2D ROESY NMR cross-peaks in the corresponding CX4 complexes are added in parentheses.

The complexation-induced shifts for the virtually spherical azoalkanes **1**−**3** were insufficiently diagnostic to assign the structures of the host−guest complexes in more detail, because the shifts and splitting patterns for the individual bicyclic protons resembled qualitatively those observed upon changing from water to benzene as solvent, except that the shifts in the presence of CX4 were more exaggerated (Table 1). For example, the fact that the exo and anti protons displayed chemically induced shifts 0.3−0.8 ppm larger than those of the endo and syn protons cannot be necessarily interpreted in terms of their deeper immersion into the CX4 cavity, but can be similarly accounted for by the differential response of the chemical shifts toward any aromatic environment (i.e., the same effect is qualitatively observed in benzene as

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TABLE 1. Environment-Induced ^{1}H NMR Shifts Relative to D_2O Solution[a]

		Δδ/ppm					
guest	environment	H_{endo} [$H_{endo'}$]	H_{exo} [$H_{exo'}$]	H_{syn}	H_{anti}	H_b	other H's
1	CX4 complex	−1.44	−2.18	−1.89	−2.61	−1.63	
	benzene	−0.23	−0.82	−0.57	−0.96	−0.41	
2	CX4 complex	−1.46	−2.10	–	–	−1.25	
	benzene	−0.30	−0.75	–	–	−0.30	
3	CX4 complex	−1.25 [−1.28]	−1.66 [−1.65]		−2.04	−1.00	
	benzene					−0.17	
4	CX4 complex	−0.57	−0.54 [−0.96]	–	–	–	−0.59 (CH_3) −1.03 (CH) −1.39 (CH(CH_3)$_2$)
	benzene	−0.27	−0.65	–	–	–	−0.59 (CH_3) −1.03 (CH) −1.39 (CH(CH_3)$_2$)
5	CX4 complex	−1.49 [−0.75]	−1.90 [−0.87]	–	–	−1.96	−0.29 (ortho) −0.22 (meta) −0.28 (para)
	benzene	−0.37	−0.83 [−0.66]	–	–	−0.36	0.17 (ortho) −0.17 (meta) −0.20 (para)
(+)-camphor	CX4 complex					−1.74	−0.92 (8-CH_3) −1.62 (9-CH_3) −0.51 (10-CH_3)

[a] Complexation-induced shifts extrapolated to quantitative complexation.

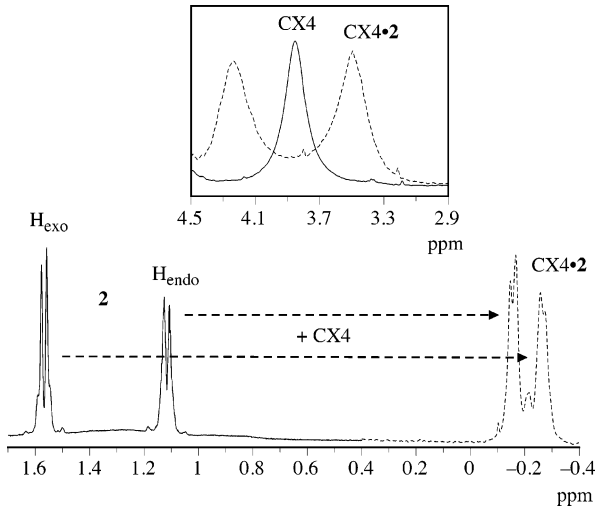

FIGURE 1. ^{1}H NMR shifts of the exo and endo protons of **2** (1 mM) upon addition of 8 mM CX4 at pD 7.4. The inset shows the ^{1}H NMR peak splitting of the methylene protons of CX4 (4 mM) upon addition of 20 mM **2** at pD 7.4.

solvent, where geometrical confinement effects do not apply).

2D ROESY NMR experiments were carried out to obtain complementary information on the inclusion geometries of the CX4 complexes of azoalkanes **1**−**3** (see relative magnitudes in Chart 1 and Supporting Information). Unlike complexation-induced shifts, ROESY cross-peaks are indicative of specific proximity relationships between host and guest protons (generally 4 Å or less).[17] In agreement with the cone conformation of CX4, the distances of the aromatic host protons to the guest are substantially shorter than those of the methylene protons, such that ROESY cross-peaks with included guest molecules were exclusively observed for the former. For azoalkanes **1**−**3**, NOE enhancements were observed with the bridgehead protons, particularly strong for azoalkane **2**, which renders an axial inclusion geometry (with the bridgehead protons pointing toward the open portals) unlikely.[17] Moreover, as observed for azoalkanes **1** and **2** (Chart 1), the cross-peaks for the endo and syn protons were larger than those for the respective exo and anti protons (no cross-peak was detected for the exo proton of **1**). These findings suggest that the endo and syn protons and therefore the azo group are located at the upper rim of CX4 near the aromatic host protons, while the exo and anti protons are more deeply immersed, which in turn is entirely consistent with the larger complexation-induced shifts of the latter (Table 1).

The combined NMR evidence for azoalkanes **1**−**3** suggests an equatorial complex geometry (Chart 2, top), where the polar azo group points toward the aqueous bulk and where the hydrophobic part of the bicycle can efficiently interact with CX4 through CH−π interactions.[24] NMR shift assignments have confirmed similar complexation modes (i.e., with the polar group displaced away from cavity of CX4) for small neutral guests such as ethanol and acetonitrile,[6] as well as substituted benzenes.[7] The equatorial complex structure is also consistent with the relatively moderate polarizability enhancement determined by solvatochromic effects on the absorption spectrum of **2** in its CX4 complex.[25] Due to the location of the azo chromophore, **2** reports more on the polarizability in the region of the hydrated sulfonato groups than near the highly polarizable aryl groups.

For azoalkanes **4** and **5**, an axial inclusion mode as that in Chart 2, bottom, is supported by ^{1}H NMR shifts (Table 1). Accordingly, the isopropyl group of **4** protrudes preferentially into the cavity (largest shifts for the isopropyl group), while for **5** the phenyl ring is displaced toward the aqueous bulk (very small shifts for the phenyl protons relative to those of the bicyclic ones). In this

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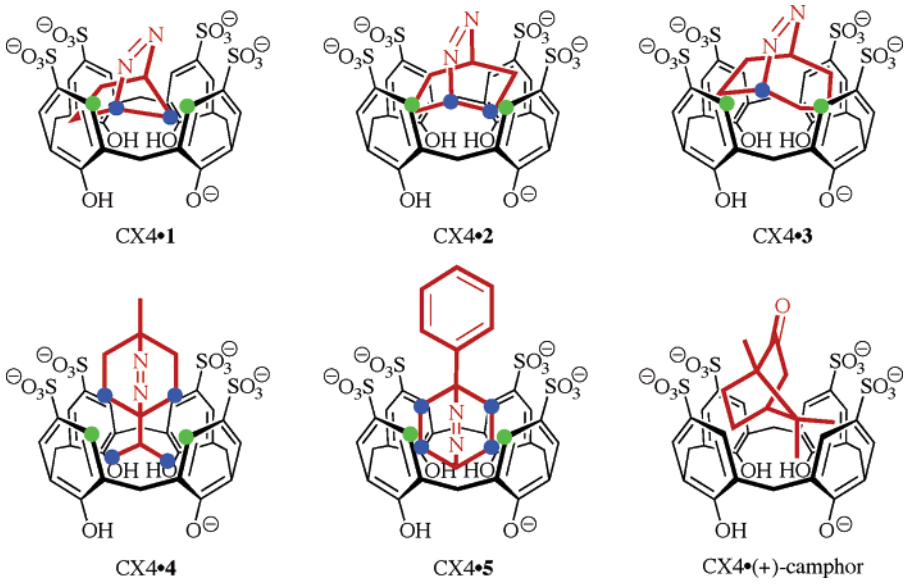
CHART 2. Suggested Structures for the CX4 Inclusion Complexes[a]



[a] Regions with significant 2D ROESY cross-peaks are marked in blue and green.

context, it is noteworthy that the small shifts of the phenyl protons of **5** are not the result of an intrinsically lower response of their chemical shift toward complexation by CX4, since the shifts observed for substituted benzenes upon complexation by CX4 (ca. 1−2 ppm upfield)[5,7] are otherwise known to be as large as those for the bicyclic azoalkanes.

Because the more deeply immersed bridge protons of **4** and **5** are expected to exhibit the larger complexation-induced shifts, the ^{1}H NMR signals of the exo and exo′ (resolved for **4** and **5**) as well as the endo and endo′ protons (resolved only for **5**) were assigned accordingly (Table 1 and Chart 1). The chemical shifts of the bridge protons of azoalkane **4** are also somewhat smaller than those for **2** and **5**, which suggests that the immersion of the isopropyl group displaces the bicycle somewhat away from the inner cavity. 2D ROESY NMR experiments further revealed a very strong cross-peak for the exo′ proton of azoalkane **4** and a strong one for the isopropyl methyl groups, while for azoalkane **5** a strong cross-peak with the exo proton and a weak one with the endo′ proton were observed (Figure 2). All other cross-peaks, in particular those with the bridgehead methyl protons of **4** and with the phenyl protons of **5**, were insignificant. The 2D ROESY NMR results are therefore fully in line with the structural assignments based on the complexation-induced shifts (Chart 2).

Binding Constants. The host concentration-dependent chemical shifts were employed to determine the binding constants by ^{1}H NMR titrations. In all cases, the experimental data could be well reproduced by a complexation model based on a 1:1 host−guest stoichiometry (Figure 3), such that higher-order complexes did not need to be postulated. The resulting binding constants for azoalkanes **1**−**5** were found to be on the order of 1000 M^{-1} (Table 2).

Bicyclic azoalkanes are very weak bases ($pK_a \leq 3$)[26] and therefore not protonated in neutral solution. Al-

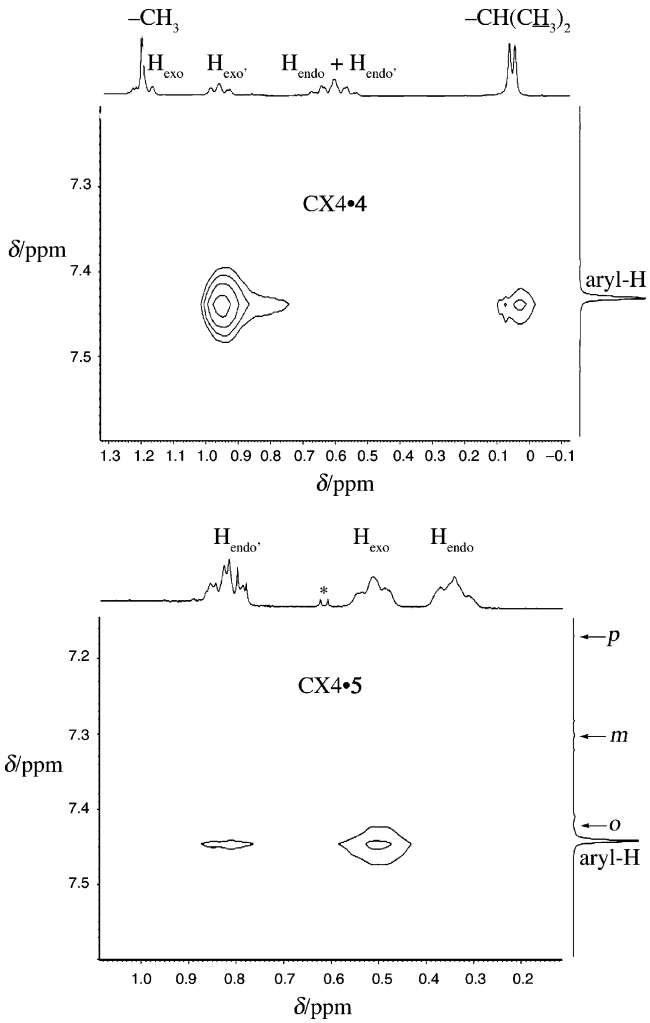


FIGURE 2. Diagnostic regions of the 2D ROESY spectra for the CX4 inclusion complexes of azoalkane **4** (top, 8 mM CX4, 5 mM **4**) and azoalkane **5** (bottom, 8 mM CX4, 1 mM **5**); asterisk marks an impurity.

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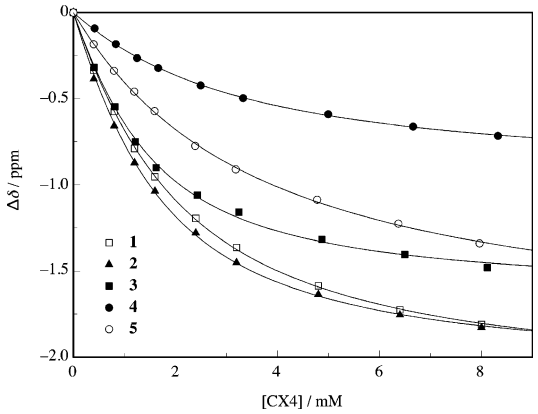

FIGURE 3. ^{1}H NMR titration plots for the complexation-induced shift of the exo protons of azoalkanes **1**−**5** (exo′ proton for **4**) at pD 7.4.

though macrocyclic hosts are known to shift pK_a values of included guest molecules,[11,27] a protonation of azoalkanes **1**−**5** in their complexes with CX4 can in fact be experimentally excluded at pD 7.4, since the corresponding UV spectra do not reveal the hypsochromically shifted absorption diagnostic for the protonated azo group, but rather a bathochromic and hyperchromic shift characteristic for the inclusion of the azo group into a more polarizable environment.[25] Electrostatic and cation−π interactions resulting from the formation of protonated guests therefore do not have to be considered in the interpretation of the presently reported binding constants. This renders the binding constants up to 1000 M^{-1} of the bicyclic azoalkanes truly exceptional, since they are 1 order of magnitude larger than those of all but one previously investigated small noncharged organic molecule (Table 2).[5−8,28]

The first binding constants for "small neutral organic molecules" with CX4 (as opposed to larger polycyclic aromatic hydrocarbons studied by solid−liquid extraction by Gutsche and Alam for a different type of water-soluble calixarenes)[29,30] were reported by Ungaro and co-workers;[6] they ranged from 15 to 65 M^{-1} for simple aliphatic ketones, alcohols, and acetonitrile. Schatz and co-workers studied binding of various aromatic compounds with CX4 and observed similarly low binding constants, between 20 and 80 M^{-1}.[5] Kunsági-Máté et al. have also reached the conclusion, when studying different types of calixarenes, that only very weak complexes with neutral aromatic guests are expected in water.[9] Kon et al. investigated recently a series of aromatic guests; their observation that electron-deficient aromatic guests display a higher binding (ca. 100 M^{-1}) than their electron-rich counterparts (ca. 10 M^{-1}) provided an indication that π−π electronic interactions, while weak, may be more important in the inclusion of substituted benzenes than unspecific hydrophobic interactions.[7] Interestingly, a recent investigation of π−π interactions in the complexation of substituted phenols with the larger *p*-sulfonatocalix[6]-arene (CX6) led to the observation of the opposite electronic substituent effect (i.e., *p*-nitrophenol formed a weaker complex with CX6 than *p*-methylphenol).[31]

In view of the previously reported low binding constants (Table 2), it is appropriate to state that azoalkanes **1**−**3**, in particular, are the first small noncharged organic guests to display a moderately strong binding with CX4; in fact, this substantial binding has provided the basis for a recently introduced fluorescence displacement assay employing azoalkane **2** for monitoring the binding of choline and carnitine derivatives.[25] The high affinity is the more surprising since azoalkanes **1**−**3**, in particular, are highly water-soluble, much more than the aromatic compounds in Table 2, such that hydrophobic interactions alone are unlikely to be held responsible. Rather, their strong binding reflects an improved goodness-of-fit, unquestionably due to the spherical shape complementarity, which is not fulfilled for the short aliphatic compounds such as ethanol or acetonitrile,[6] nor for the planar aromatic molecules[5,7] listed in Table 2. With a little hindsight, one may also note that the equatorial arrangement of the bicycles **1**−**3** (Chart 2) may optimize CH−π interactions[24] with *all four* aryl rings.

To allow further generalization, we have also studied the binding of (+)-camphor as an example of a structurally unrelated yet also bicyclic and spherical guest. The resulting complexation-induced shifts were about as large as those for azoalkanes **1**−**5** (Chart 1, Table 1), suggesting again the deep immersion of this bicyclic guest. On the basis of the relative magnitudes of the shifts, we tentatively assign a complex geometry, in which the bridgehead proton and the 9-methyl group protrude into the cavity, and where the polar carbonyl group points again to the aqueous bulk (Chart 2). Most importantly, the binding constant was also similarly high (ca. 650 M^{-1}), thereby corroborating the importance of the postulated spherical shape complementarity in the binding of CX4.[32] For comparison, a similar spherical shape matching, in favor of bicyclic guests over aromatic ones, has been previously inferred for calixarene-based capsules with ammonium ions from mass spectrometry studies.[33]

However, while the spherical shape of **2**, for example, appears to provide a very good match with the CX4 cavity (see above), the binding constants are less critically dependent on the size of the bicyclic system (Chart 1). The choice of the next smaller homologue **1** as guest resulted only in slightly weaker binding, while the next larger one **3** afforded a comparable binding constant, but the binding of (+)-camphor, which exceeds even **3** in size, was slightly lower again (Table 2). This reflects the ability of the conformationally flexible CX4 to adapt the inner conical cavity of CX4 through an induced fit,[1,2,22] which results in an overall poor to moderate guest *size*

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(32) As an additional control experiment, we also remeasured the binding of acetone to afford a low value of 58 M^{-1} (Table 2), similar to that found in the previous study (50 M^{-1}, ref 6). The latter result demonstrates that differences in experimental conditions (use of buffer, etc.) cannot account for the present observation of an increased binding of bicyclic guests.
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TABLE 2. Binding Constants of Noncharged Organic Guests with CX4 near Neutral pH

guest	K/M^{-1}	guest	K/M^{-1}
	bicyclic guests		
1	690[a]	**4**	480[a]
2	900[a] [1200][b]	**5**	350[a]
3	950[a]	(+)-camphor	650[a] [670][g]
	aromatic guests		
nitrobenzene	165[c]	phenylboronic acid	21[d]
benzonitrile	91[c]	iodobenzene	60[d]
chlorobenzene	28[c]	biphenyl	44[d]
methyl benzoate	20[c]	*p*-chlorobenzonitrile	40[d]
benzene	21[c]	benzaldehyde	79[d]
toluene	20[c] [25][d]	*trans*-cinnamaldehyde	78[d]
anisole	11[c]	benzyl *tert*-butyl nitroxide	13[h]
	aliphatic guests		
methanol	no complexation[e,f]	1,4-butanediol	19[e]
ethanol	11[e] [32][f]	1,5-pentanediol	27[e]
2-propanol	32[f]	acetone	50[f] [58][g]
n-propanol	22[e]	butanone	63[f]
n-butanol	38[e]	acetonitrile	16[f]
n-pentanol	43[e]		

[a] This work, determined by ^{1}H NMR titrations at pD 7.4, adjusted with NaOH; average value for different protons; 10% error. [b] From ref 25 by UV titration. [c] From ref 7 by ^{1}H NMR titrations at pD 7.3 with 0.1 M phosphate buffer. [d] From ref 5 by ^{1}H NMR titrations at pD 7.4 with buffer. [e] From ref 8 by microcalorimetry at pH 7.5, adjusted with NaOH. [f] From ref 6 by ^{1}H NMR titrations at pD 7.3 with 0.1 M phosphate buffer. [g] This work, determined by fluorescence regeneration, cf. ref 25, 10% error. [h] From ref 28 by EPR spectroscopy, in water.

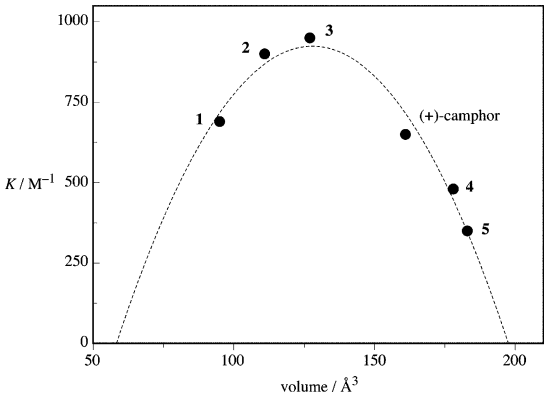
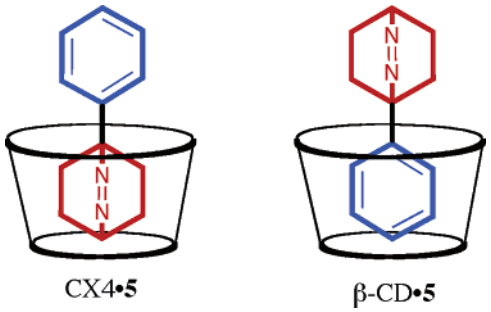


FIGURE 4. Apparent relationship between the binding constants of bicyclic guests with CX4 and the calculated volume of the guest.

selectivity.[11−13] For comparison, the binding constants of different tetraalkylammonium ions show also relatively small differences.[4,25] Apparently, the CX4 cavity can rather ideally provide a spherical space for 8−9 heavy atoms (carbon, nitrogen, or oxygen) or approximately 110−130 Å^3 accessible volume (those for **2** and **3**), or a cavity diameter of 6.0−6.3 Å (if approximated as a sphere). The "size" of the CX4 "cavity" is accordingly similar to that of β-cyclodextrin (β-CD)[18] and cucurbit-[7]uril,[19,34] and therefore larger than projected from studies employing aromatic probes.[7,11] The bicyclic guest size selectivity is qualitatively reflected in a plot of the binding constants versus the calculated volumes of the guests (Figure 4).

The importance of the spherical shape of **1**−**3** was corroborated through control experiments with the ellipsoidal derivatives **4** and **5**. Although these derivatives are more hydrophobic than the parent **2**, they showed

CHART 3. Preferred Inclusion Geometries of Azoalkane 5 with CX4 and β-CD



a weaker binding (Table 2). It should be noted that the elongated geometry of **4** and **5** requires an axial orientation of the guest inside the complex (Chart 2), which may be less favorable and account for the lower complex stability. For azoalkane **4**, the isopropyl group protrudes preferentially into the cavity, as borne out by the relative magnitude of the complexation-induced shifts (Table 1) and 2D ROESY cross-peaks (Chart 2, Figure 2); this situation is similar to the binding of **4** with β-CD.[16,17] Note that β-CD shows a comparable binding for **2** and **4** (ca. 1000 M^{-1}), suggesting similarly stabilizing intermolecular interactions for these two guests.[15−17] For azoalkane **5**, the complexation-induced ^{1}H NMR shifts as well as the 2D ROESY NMR spectra provide compelling evidence that it is the bicyclic azo residue *and not the phenyl group* that is included. This inclusion pattern is exactly opposite to that observed for β-CD as host (Chart 3), for which the phenyl group is preferentially included according to 2D ROESY spectral evidence.[18] In addition, the attachment of the phenyl group (**5** versus **2**) *increases* the binding with β-CD by a factor of about 3,[18] but *decreases* the binding with CX4 by a factor of 3!

Arimura et al. have previously concluded, on the basis of differential spectral shifts and binding constants reported by a solvatochromic probe, that the cavity of

(34) Márquez, C.; Hudgins, R. R.; Nau, W. M. *J. Am. Chem. Soc.* **2004**, *126*, 5806−5816.

CX6, the larger homologue of CX4, is more hydrophobic than β-CD.[35] Differential hydrophobic interactions were also held responsible for the increased (ca. factor 4) binding of the 1-adamantyltrimethylammonium versus the trimethylanilinium cation with CX4.[12,21] The present data for binding of azoalkanes **1**−**5** with CX4, in comparison with β-CD as host, demonstrate that the hydrophobicity of the guest is presumably not the dominant factor for CX4 but rather the spherical shape complementarity.

Particularly instructive is the consideration of the bifunctional guest **5**. The phenyl group must unambiguously be considered as the hydrophobic residue, while the bicyclic azo group presents the hydrophilic site. The hydrophilicity of azoalkane **2** is related to its high dipole moment (3.5 D)[36] and readily demonstrated by simple solubility considerations: The solubility of **2** in water is at least 1% or 100 mM, and its partition coefficient in water/*n*-pentane and water/diethyl ether is 6.7 and 1.6, respectively, *in favor of water*. Introduction of the hydrophobic phenyl group dramatically reduces the solubility of **5** to 0.5 mM, yet does not increase, but rather decreases, the binding constant with CX4. In addition, it is not the hydrophobic phenyl group that is preferentially included, as could be projected from the large difference in binding constants between toluene (ca. 20 M^{-1}) and azoalkane **2** (ca. 1000 M^{-1}). The spherical shape complementarity is therefore a sufficiently important criterion to entirely override hydrophobicity considerations in the complexation with CX4. To the best of our knowledge, this is the first example of a complexation process involving a water-soluble macrocyclic host with a hydrophobic cavity in which the inclusion of a hydrophilic spherical guest, in the absence of electrostatic or hydrogen-bonding interactions, is preferred over the inclusion of a similarly sized aromatic hydrophobic residue. A fundamentally different complexation affinity as that well established for cyclodextrins applies. This results in an unconventional inclusion pattern of the amphiphilic azoalkane **5**, for which the polar hydrophilic headgroup is buried in the hydrophobic cavity, while the hydrophobic phenyl group remains largely exposed to the aqueous phase.

The question arises why the shape matching is more important for CX4 than for β-CD, although it is well recognized that calixarenes are flexible and should be better able to adapt to the guest through an induced fit. We presume that the "function" of the guest in the case of CX4 is not only to optimize hydrophobic interactions by minimizing the degree of void space in the host cavity, but also to minimize the repulsive electrostatic interactions between the sulfonato groups. Guests that are too small, such as the aliphatic alcohols and ketones in Table 2 or planar aromatic guests, which may tend to form sandwich-type arrangements between two opposite aryl groups and the guest, may increase hydrophobic or $\pi-\pi$ interactions by a contraction of the CX4 cone, but only at the expense of increased electrostatic interactions, thereby resulting in an overall weak stabilization. Bicyclic substrates, on the other hand, appear to be sufficiently large to efficiently fill the inner conical cavity and remove high-energy water but at the same time serve as a spacer to keep all four sulfonato groups well separated. Finally, the "pinched" cone conformation required to optimize $\pi-\pi$ interactions with aromatic guests[37] must be achieved at a substantial entropic cost, the importance of which has recently been emphasized.[31]

Conclusions

p-Sulfonatocalix[4]arene has been demonstrated to display a relatively moderate guest size selectivity but a strong guest shape selectivity, namely a preference for inclusion of bicyclic (spherical) guests. Although azoalkanes **1**−**3** are highly water-soluble, they display substantially higher binding constants than previously investigated noncharged organic guest molecules. Most importantly, the spherical shape complementarity overrides other favorable factors, such as hydrophobic and $\pi-\pi$ interactions offered by aromatic guests, which was established through the complexation pattern of the amphiphilic derivative **5**. These results question the importance of $\pi-\pi$ interactions as a design criterion to optimize the binding of noncharged organic guests with *p*-sulfonatocalixarenes.

Experimental Section

Commercial *p*-sulfonatocalix[4]arene (CX4, >97%) and (+)-camphor were used as received. Azoalkanes **1**−**5** were available from previous studies on complexation with cyclodextrins.[17,18] All experiments were performed at ambient temperature in D_2O (99.8%). The pD value of the solutions was adjusted by addition of NaOD. pH readings were converted to pD by adding 0.40 units.[38] ^{1}H and 2D ROESY NMR spectra (400 MHz) were recorded by using the chemical shift of HOD in D_2O preset at 4.67 ppm as reference. The concentrations for the ROESY spectra varied from 8 to 12 mM CX4 and 1−30 mM azoalkane; they were adjusted to obtain a good peak separation (to avoid overlap for **2** and **3**) and sufficient signal strength (lowest for **1** and **3**); for **5**, the concentration was limited by its low solubility. Molecular volumes were estimated from van der Waals surfaces calculated with the QSAR module for structures optimized with the MM+ force field,[39] cf. ref 34.

Acknowledgment. This work was supported by the International University Bremen.

Supporting Information Available: ^{1}H NMR spectral assignments and 2D ROESY NMR spectra for azoalkanes **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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