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Reinvestigation of Supramolecular Complexes with Cyclophanes of the Stetter and Koga Type: Agreement and Disagreement with Solid-State Structures

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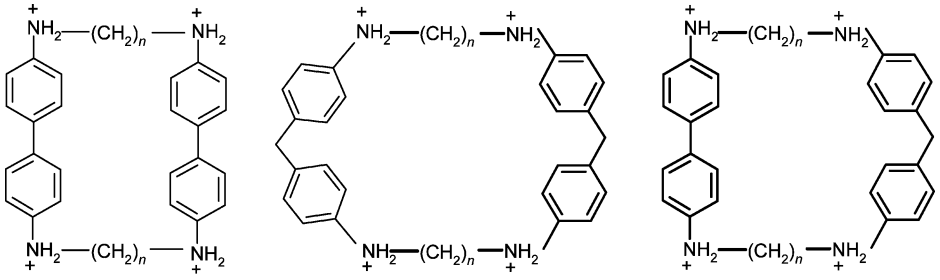
In this paper we reinvestigate the historically oldest complexations with cyclophanes of the Stetter and Koga type (**1** and **2**), and new macrocycle **3**, which is a hybrid of the two former. NMR titrations in aqueous solution reveal that benzene forms, as known, strong complexes with Koga-type host **2**, but also weaker ones with Stetter cyclophane **1**, in contrast to earlier observations with the corresponding crystals. Tosylate forms weak complexes with **1**, but stronger ones with **2** and **3**. The binding free energy difference (ΔG = 7 kJ mol^{-1}) between tosylate and benzene as guest and **2** or **3** as host agrees well with the salt bridge increment found earlier with many supramolecular complexes.

Introduction

Large cyclophanes, which were synthesized a long time ago,[1] exhibit a sizeable cavity that has been the starting point for many studies of supramolecular complexes.[2,3] Many new publications illustrate the continuing interest in cyclophanes; they lead to more insight in the mechanisms of the corresponding noncovalent interactions,[4] as well as to many new applications.[5] Generally, one assumes that cavity size determines which guest molecules will be complexed, for aromatic molecules driven π–π interactions, in aqueous solution also by hydrophobic contributions. Comparison with cyclophanes bearing no positive charge in the cavity have shown early that in the presence of positively charged host centres cation–π interactions are the major driving force;[6] the same was concluded from the observation of much lower affinity of saturated versus aromatic guest molecules.[7] Cation–π interactions dominate at least in aqueous media where the low polarizability of water lowers the competition of van der Waals contributions by the bulk medium. The complexation of benzene itself has been addressed in relatively few papers.[8]

Cyclophanes containing biphenyl units bridged by at least four methylene groups provide a cavity seemingly large enough for the complexation of benzene derivatives. The earliest report on such a complexation goes back to the investigation of Stetter with biphenyl host **1** shown in Figure 1.[9] Stetter et al. observed that crystals obtained from **1** and benzene contained both molecules always with a 1:1 stoichiometry, and they concluded that in line with the seemingly perfect fitting with CPK models the expected intracavity inclusion did occur. Related complexes were reported 25 years later by Koga et al. with cyclophanes such as **2** containing aryl units separated by one methylene



1 (*n* = 4) **2** (*n* = 4) **3** (*n* = 4)

Figure 1. Structures of the cyclophanes.

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group; here it was secured for the first time by NMR spectroscopic measurements in solution and by X-ray analysis in the solid state that even the more bulky tetramethylben-

zene unit is bound within the cavity.[10] More than 25 years after Stetter's initial report, Hilgenfeld and Saenger analyzed the crystals from **1** by X-ray and found that, in contrast to the earlier conclusions, the benzene is in fact outside the cavity of **1**; this is explained by the repulsion between the *o,o′*-hydrogen atoms of the phenyl units, which turns one of the aryl rings inside the cavity with the result of a then too-small space for the accommodation of a phenyl guest molecule.[11] The hindered rotation of the aryl units in such cyclophanes was later studied in more detail,[12] but could be overcome if an intracavity inclusion would provide enough driving force towards an induced fit. In this paper we investigate whether the Stetter picture of intracavity inclusion with **1** comes true in solution; for comparison we also measured properties with hybrid cyclophane **3**, which contains both the biphenyl units used by Stetter and the diphenylmethane units used in Koga's complex.

Results and Discussion

The cyclophanes were obtained by slight variation of the procedure by Stetter et al.[9] for **1**, for **2** as described earlier,[13] and for **3** by first building up the trimer from the *p*-bisaminodiphenylmethane unit and dibromobutane, described already by Koga et al.[13] and then treating this with bistosylbenzidin. The composition and purity was controlled by NMR spectroscopy (Tables 1 and 2) and TLC, and the molecular weight was determined by mixed melting points with camphor, securing that no smaller or larger macrocycles were formed.

Table 1. NMR spectroscopic data of Stetter cyclophane **1**.[a]

Position	Multiplicity	*J*(H,H) [Hz]	$\delta(^1H)$ [ppm]	$\delta(^{13}C)$ [ppm]
4	m	10	1.54	25.31
5	m	18	3.13	41.45
6	s	–	5.46	–
7				146.95
8	AB	7.9	6.40	112.17
9	AB	7.9	7.05	125.43
10				127.36

[a] In $[D_6]$DMSO/TMS.

Table 2. NMR spectroscopic data of hybrid cyclophane **3**.[a]

Position	Multiplicity	*J*(H,H) [Hz]	$\delta(^1H)$ [ppm]	$\delta(^{13}C)$ [ppm]
2	m	22	3.14	44.11
5				47.75
3	m	19	1.71	25.42
4				27.2
7				146.23
8	AB	8.4	6.49	111.73
9			6.98	129.51
10				131.37
13	s		3.77	40.07
32				128.84
33	AB	8.3	7.03	127.14
34			6.54	115.47
35				146.78

[a] In $[D_6]$DMSO/TMS.

NMR titrations were performed as described before[14] in D_2O/CD_3OD solution (80:20) at pH = 7.0, where the nitrogen atoms of the macrocycles are protonated. With benzene as guest the observed complexation-induced NMR shifts (CIS) and equilibrium constants *K* (Table 3) are large for Koga-type cyclophane **2**, where immersion of the aryl rings is known to occur without distortion of the cavity.[10] With the hybrid Koga–Stetter macrocycle **3** both indicators become smaller, as distortion of the biphenyl units is already necessary for accommodation of the guest. This effect increases with Stetter macrocycle **1**, where full immersion of benzene would require coplanar orientation of the host biphenyl parts. Nevertheless, the observed CIS and *K* values clearly indicate that in contrast to the crystal a sizeable intracavity complexation of benzene with the Stetter macrocycle occurs in solution. CIS values of benzene are small also, as they are the average of all benzene protons, including those that are not, as in Koga host **2**, directly in the shielding cone of the host phenyl rings. With tosylate as guest and host **1** the CIS values are smaller than with benzene, as are the *K* values (Table 4). With evaluation of the different signals the *K* values are also more scattered than usual, suggesting that the salt bridge between then host ^+N centres and the guest sulfonate leads to additional complex geometries, although the titration curves agreed with a 1:1 complex stoichiometry. In contrast, the Koga cyclophane with tosylate gave a ΔG value of 19.7 kJ mol^{-1} (Table 5), which is 7 kJ mol^{-1} more than with benzene (12.6 kJ mol^{-1}). The same difference was observed with hybrid macrocycle **3**, with either 12.0 (tosylate) or 4.9 kJ mol^{-1} (benzene). It is gratifying that the constant binding energy difference of 7 kJ mol^{-1} agrees within $\pm$1 kJ mol^{-1} with the salt bridge increment derived from measurements of many other supramolecular complexes,[15] including the binding energy difference between, for example, nucleotides and nucleosides to azoniacyclophanes of the Koga type.[16]

Table 3. Complexation of benzene with macrocycles **1**–**3**.[a]

Host	**1**	**2**	**3**
CIS	0.20	1.12	0.41
K	6.5 ± 0.2	160 ± 8	7.1 ± 0.7
$-\Delta G$	4.6	12.6	4.9

[a] In D_2O/CD_3OD solution (80:20), pH = 7.0; CIS of benzene signal (δ =7.6 ppm) for 100% complexation in ppm; equilibrium constants *K* as [M^{-1}]; ΔG in kJ mol^{-1}.

Table 4. Complexation of tosylate with macrocycle **1**.[a]

Signal of **1**	$-CH_2-$	$N-CH_2-$	aryl-1	aryl-2
δ_o	1.64	3.55	7.46	7.64
CIS	0.53	0.34	0.20	0.63
K	1.2 ± 0.1	1.7 ± 0.2	4.0 ± 0.7	2.7 ± 0.2
$-\Delta G$	0.5	1.3	3.4	2.5

[a] See footnotes to Table 3; δ_o: shift [ppm] before complexation.

Table 5. Complexation of tosylate with macrocycles **2** and **3**.[a]

Signal of tosylate	H2	H3	CH_3
δ_o	7.76	7.44	2.48
with **3**: CIS	0.53	0.34	0.20
K	142 ± 10	118 ± 8	101 ± 7
ΔG	12.3	11.8	11.4
with **2**: CIS	1.57	1.91	0.65
K	2990 ± 20	3010 ± 20	3010 ± 20
$-\Delta G$	19.8	19.9	19.5

[a] See footnotes to Table 4.

Conclusions

The results demonstrate that care should be taken with conclusions from structures obtained from X-ray analyses in the solid state or from simple model considerations with respect to the more free state in solution. Crystal structures are to a large degree determined by symmetry requirements and lattice forces between the single molecules. These dominate over an intracavity inclusion if the latter is characterized by much smaller energies as in the present case. Also, for these reasons very weak interactions do not usually show up in crystals, but in solution.[17] It should be noted, however, that even with relatively strong metal complexes the metal ion may be found within a cavity in the solid state, but not in solution.[18]

Experimental Section

General Methods: NMR measurements were performed at 400 MHz (^1H) or 100.6 MHz (^{13}C). NMR titrations for measuring equilibrium constants were performed and processed as described,[14] with the addition of the host compound in usually 8 steps, in D_2O/CD_3OD solution (80:20), pH = 7.0 adjusted with NaOD and/or CF_3COOD. The purity of the macrocycles (>97%) was controlled not only by NMR spectroscopy and TLC, but also by ^1H NMR signal integration with comparison to a calibrated internal reference such as nitromethane of known concentration.

Stetter Cyclophane 1 (1,6,19,24-Tetraaza[6.0.6.0]paracyclophane): A solution of bistosylbenzidine (15 g, 31 mmol) and 1,4-dibromobutane (6.70 g, 31 mmol) dissolved in absolute DMF (600 mL) was added dropwise over 18 h at 100 °C to a suspension of potassium carbonate (waterfree, 30 g, 217 mmol) in absolute DMF (500 mL). After filtration of the hot solution, concentration of the filtrate under reduced pressure to 250 mL, and subsequent cooling to –30 °C, one obtained a colourless precipitate, which was washed with cold DMF, suspended in weak HCl, stirred, and after filtration washed again with water to neutral pH. The tosylate (3.68 g, 23%; ref.[9] 24%) was detosylated without further purification.

Detosylation: The tosylate (3.68 g, 3.37 mmol) was heated at reflux for 6 h in the presence of phenol (10 g) and HBr (48% solution, 80 mL). After cooling, the yellow sublayer was discharged, and the oily red phase was extracted several times with ether. The resulting precipitate was filtered off, washed with small amounts of methanol and ether, and dried in vacuo. The solid compound was heated at reflux for 1 h in the presence of NaOH (20% solution, 50 mL), and the crystalline residue was filtered off and washed with hot MeOH. After renewed filtration, washing with ether and drying, the free azacyclophanone (1.42 g, 88%) was obtained. M.p. 245 °C (ref.[9] 90%, 242 °C). See Table 1 for the NMR spectroscopic data.

Hybrid Stetter–Koga Cyclophane 3: The precursor "trimer" *N*,*N*-bistosyl-*N*,*N*-bis(4-bromobutyl)-*p*-diaminodiphenylmethane was obtained similar to the literature protocol (71%, m.p. 111 °C; ref.[13] 72%, m.p. 110–111 °C). A solution of the trimer (8.0 g, 10.3 mmol) and bistosylbenzidine (5.1 g, 10.3 mmol) dissolved in absolute DMF (500 mL) was added with a pump over 18 h to a suspension of potassium carbonate (waterfree, 10 g, 72 mmol) in absolute DMF (700 mL) at 100 °C. The hot solution was filtered, and the DMSO of the filtrate was evaporated down to 100 mL; after cooling to –30 °C over 24 h a colourless precipitate was obtained, which was suspended in weak aqueous HCl at pH 3, stirred for 1 h, and after filtration was washed again with water to neutral pH. The solid was dissolved as far as possible into chloroform, dried with Na_2SO_4, and after removal of the solvent the residue was eluted on a short silica column. The main fractions were collected and washed with diethyl ether. The material (2.0 g, 18%) was then detosylated without further purification.

Detosylation: The tosylate (2.0 g, 1.86 mmol) was treated with phenol (10 g) and HBr (48% solution, 100 mL) as described for **1**. After cooling, the yellow sublayer was discharged, and the oily red phase was extracted several times with ether. The residue was heated at reflux for 1 h with NaOH (20%) to yield a colourless solid, which was purified by repeatedly taking it up in ethyl acetate and adding ether. Yield: 666 mg (73%) of the free azacyclophane. See Table 2 for the NMR spectroscopic data.

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