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Triple Molecular Recognition as a Directing Element in the Formation of Host−Guest Complexes with *p*-Sulfonatocalix[4]arene and *β*-Cyclodextrin

Roy N. Dsouza and Werner M. Nau*

School of Engineering and Science, Jacobs University Bremen, Campus Ring 1, D-28759 Bremen, Germany

w.nau@jacobs-university.de

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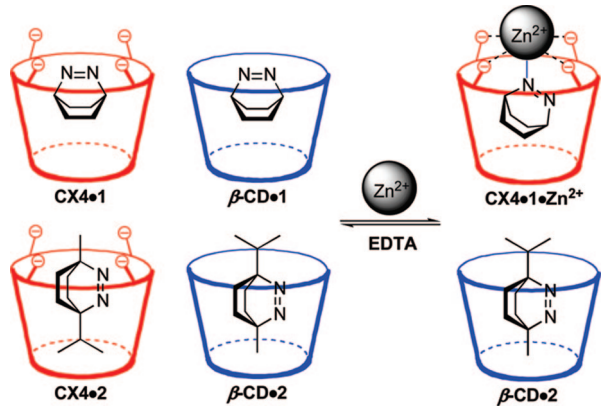

We have investigated a mixture consisting of *p*-sulfonatocalix[4]arene (CX4), *β*-cyclodextrin (*β*-CD), and 2,3-diazabicyclo[2.2.2]oct-2-ene (**1**) and its bridgehead-substituted derivative (**2**) in the absence and presence of Zn^{2+}. In the absence of Zn^{2+}, four equally populated host−guest complexes exist in solution, as projected from their comparable binding constants (ca. 1000 M^{-1}). However, upon the addition of Zn^{2+}, the formation of a ternary complex, CX4•**1**•Zn^{2+}, is induced by a synergy of three supramolecular interactions (Coulombic, hydrophobic, and weak metal−ligand bonding). Concomitantly, the CX4•**2** complex is destabilized by competitive binding, which drives the system toward a state where only two complexes predominate: namely, CX4•**1**•Zn^{2+} and *β*-CD•**2**. Known binding constants for the multiple equilibria were used to model the complex system, and the results were consistent with experimental data obtained from 1D and 2D NMR as well as induced circular dichroism (ICD) spectroscopy. The combined results demonstrate how a subtle interplay between cooperative and competitive binding can be exploited to design a complex multicomponent sorting system.

Introduction

The inclusion of bicyclic azoalkanes into macrocyclic molecular container compounds, such as cyclodextrins,[1–6] calixarenes,[7,8] and cucurbiturils,[9–13] has been studied in detail in our laboratory. Most recently, we have communicated the complexation of azoalkanes **1** and **2** with *p*-sulfonatocalix[4]arene (CX4),[14] a cone-shaped molecular container with cation-receptor properties.[15–18] We found that in the presence of divalent transition-metal ions, such as Zn^{2+}, an interesting interplay of cooperative vs competitive binding due to triple molecular recognition applied (Scheme 1).[19] Accordingly,

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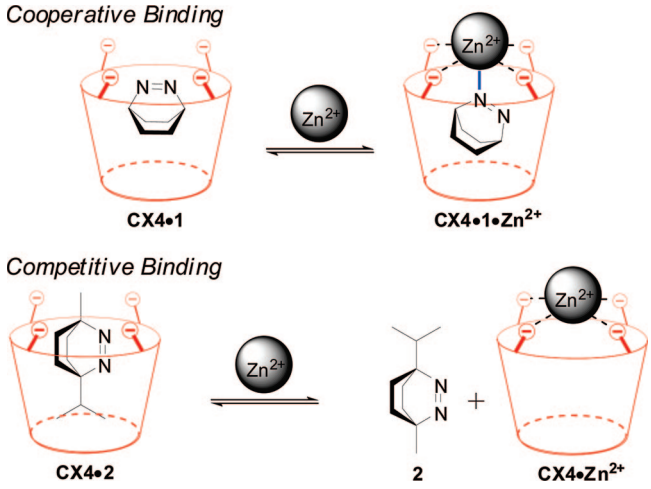
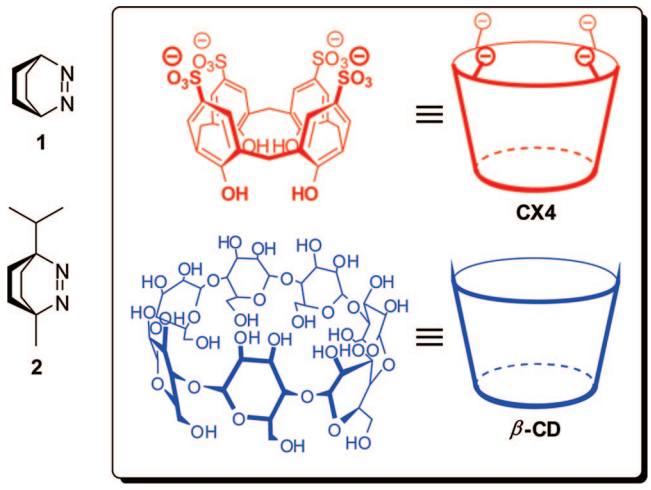
SCHEME 1



the organic guests are held in place inside the macrocycle by *hydrophobic* interactions, while the cations are preferentially bound by *Coulombic* interactions with the *p*-sulfonato groups at the upper rim. For azoalkane **1**, there is a sufficient vacant space at the upper rim to allow the cation to dock and to reinforce the resulting complex through the formation of a *weak metal−ligand* bond with the azo group (cooperative binding). Steric constraints prevent the formation of such a ternary complex for azoalkane **2**, such that the addition of larger amounts of Zn^{2+} led to the displacement of the organic guest in favor of the formation of the binary metal−calixarene complex. In this case, no metal−ligand bond can be formed inside the complex, which leads to a competitive binding situation. By utilizing the triple molecular recognition, namely by introducing the weak metal−ligand bonding as a third supramolecular motif, it should be possible to increase the selectivity for host−guest complexation significantly.



Thus, while in a neat mixture of azoalkanes **1** and **2** both guests should show a comparable affinity for CX4, the CX4·**1**·Zn^{2+} complex should predominate upon addition of the metal ion as a directing element. Moreover, it is interesting to investigate how such an already complex system would behave if an additional molecular container compound with distinctly different receptor characteristics would be added. *β*-Cyclodextrin (*β*-CD), for example, which also offers the possibility for hydrophobic binding but lacks the affinity for cations, also shows a comparable binding affinity with the two azoalkanes, and it would be challenging to understand how the presence of both hosts would respond to the stimulus of the added metal cation. As will be seen, the complexity of the multicomponent system is reduced because one complex (CX4·**1**·Zn^{2+}) is favored as a result of cooperative binding, while the second complex (*β*-CD·**2**) is indirectly populated through competitive binding. The net result of this process (shown in an exaggerated form in the abstract graphic) can be considered as "sorting", which presents a supramolecular phenomenon of considerable current interest. Notably, Isaacs and co-workers have described several impressive examples for sorting phenomena, particularly with cucurbiturils as macrocyclic hosts.[20–24] Herein, we describe a sorting phenomenon with cyclodextrins and calixarenes as hosts and introduce the triple supramolecular interaction with metal coordination as the directing element. This allows us to tune the selectivity of one host (CX4), which causes a redistribution of all complexes.

SCHEME 2

$$\begin{aligned}
\text{CX4} + \mathbf{1} &\rightleftharpoons \text{CX4}\bullet\mathbf{1} & K_{\text{CX4}\bullet\mathbf{1}} &\approx 1000\ \text{M}^{-1}\\
\text{CX4} + \mathbf{2} &\rightleftharpoons \text{CX4}\bullet\mathbf{2} & K_{\text{CX4}\bullet\mathbf{2}} &\approx 1000\ \text{M}^{-1}\\
\beta\text{-CD} + \mathbf{1} &\rightleftharpoons \beta\text{-CD}\bullet\mathbf{1} & K_{\beta\text{-CD}\bullet\mathbf{1}} &\approx 1000\ \text{M}^{-1}\\
\beta\text{-CD} + \mathbf{2} &\rightleftharpoons \beta\text{-CD}\bullet\mathbf{2} & K_{\beta\text{-CD}\bullet\mathbf{2}} &\approx 1000\ \text{M}^{-1}\\
\text{CX4}\bullet\mathbf{1} + \text{Zn}^{2+} &\rightleftharpoons \text{CX4}\bullet\mathbf{1}\bullet\text{Zn}^{2+} & K_{\text{CX4}\bullet\mathbf{1}\bullet\text{Zn}} &\approx 8000\ \text{M}^{-1}\\
\text{CX4} + \text{Zn}^{2+} &\rightleftharpoons \text{CX4}\bullet\text{Zn}^{2+} & K_{\text{CX4}\bullet\text{Zn}} &\approx 2000\ \text{M}^{-1}
\end{aligned}$$

Results

To evaluate the repercussions related to the complexity of the multicomponent system at hand, we decided to first model the equilibria of the known binding interactions among the hosts, guests, and metal cation with the binding constants in Scheme 2, which are rounded-up values from reported experimental data.[6,8,19]

These equilibria, along with the corresponding mass conservation laws, yield a set of 11 nonlinear equations which were numerically solved using a commercially available software package.[25] The full commented source code for the actual simulation program is provided in the Supporting Information.

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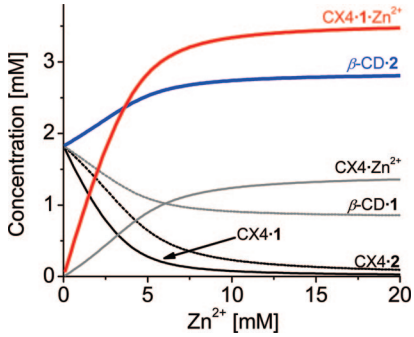

FIGURE 1. Simulated dependence of the concentrations of the various complexes according to Scheme 2 on the concentration of added Zn^{2+}. Initial concentrations of the four components were set to 5 mM.

The concentration dependence of the six distinct complexes formed in Scheme 2 on the concentration of added Zn^{2+} was generated and is presented in Figure 1. As can be seen, the addition of Zn^{2+} causes not only an evolution and systematic increase of the ternary (CX4·**1**·Zn^{2+}) and binary (CX4·Zn^{2+}) zinc-containing complexes but also of the β-CD·**2** complex (see the abstract graphic), which does not contain zinc and which is already present in the absence of this additive. The contributions of the remaining complexes decrease accordingly in order to maintain the mass balance. The concentrations reach a plateau region above ca. 10 mM, which can be traced back to the absolute magnitude of the binding constants (1000−8000 M^{-1}) and the employed initial concentrations (5 mM of hosts and guests).

On one hand, the selected 5 mM concentrations were sufficiently large to ensure large metal-induced variations in the concentrations of the various complexes (according to simulations) and to allow the planned 2D NMR and induced circular dichroism (ICD) measurements to be conducted with sufficient sensitivity and precision. On the other hand, the concentrations were sufficiently small to prevent precipitation from the multicomponent mixtures. For the same reason, the pH was adjusted to 4.8, namely to prevent the precipitation of zinc salts. A lower pH was not preferred, because the assumption related to the binding constants in Scheme 2 would become invalid. In particular, the binding constants of CX4 are known to increase in acidic solutions.[8]

^{1}H NMR spectra of the four-component mixture before and after the addition of Zn^{2+} were recorded to determine the chemically induced shifts (CIS) of the guest molecules, which are diagnostic for the inclusion of the azoalkanes into the two different host molecules (see Figure 2). Specifically, it is known that their inclusion into cyclodextrins gives rise to downfield shifts,[1,4,26–28] while their immersion in the calixarene cavity causes pronounced upfield shifts.[29–32] Upon the addition of Zn^{2+}, the protons of **1** showed upfield shifts, whereas those of **2** were shifted downfield, consistent with the projection from the

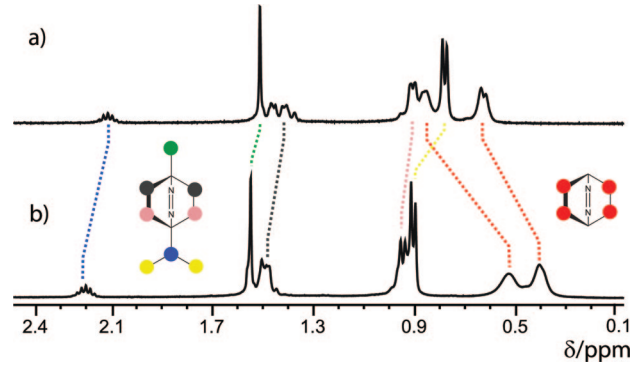

FIGURE 2. ^{1}H NMR spectra of a mixture of β-CD, CX4, **1**, and **2** (5 mM in D_2O at pD 5.2): (a) without Zn^{2+}; (b) with 20 mM Zn^{2+} (CIS for **1** in red and for **2** in other colors). Note that the bridgehead proton of **1** (not shown) also undergoes a similar upfield shift (from 4.53 to 4.39 ppm).

modeling studies that the CX4·**1**·Zn^{2+} and β-CD·**2** complexes are favored under those conditions. In detail, the characteristic protons of the ethano bridge in azoalkane **1** (marked in red) undergo the upfield shift, which is consistent with an increased probability of finding this guest in the calixarene cavity:[33] i.e., zinc "presses" this guest into this aromatic host. The downfield shifts observed for azoalkane **2** demonstrate that, on average, this guest resides with higher probability within the cyclodextrin: i.e., zinc apparently "forces" this guest from one host into another one.

2D ROESY NMR spectroscopy is a powerful qualitative method that has previously been used to monitor weak through-space proton coupling interactions in cyclodextrin and calixarene inclusion complexes.[27,34,35] In particular, the inclusion complexes of β-CD with bicyclic azoalkanes have been successfully studied using this technique.[1,4] Figure 3 shows the ROESY spectra of the four-component mixture before and after the addition of Zn^{2+}. Most diagnostic is the strengthening of the cross-peaks of azoalkane **2** with β-CD,[36] which is consistent with the increased population of the corresponding host−guest complex, as observed for the ^{1}H NMR shifts (Figure 2) and anticipated from the modeling results (Figure 1). The lowering of the cross-peak intensity of the endo protons of **1** (peaks shifted most upfield in Figure 3) provides circumstantial evidence that this complex is disfavored, presumably because this guest prefers to complex with the calixarene in the presence of Zn^{2+}. The cross-peaks with the calixarene were considerably weaker but showed a consistent trend (Supporting Information): namely, a relative weakening of the cross-peaks of **2** as compared to those of **1**. Consequently, the collective ROESY data, in combination with the clear-cut ^{1}H NMR chemical shift variations (Figure 2), support the repopulation of the individual complexes.

Induced circular dichroism (ICD) was also used to monitor the sorting process by taking advantage of the chiral environment provided by β-CD along with the corresponding types of signal

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(33) The NMR spectra reflect a fast host−guest exchange kinetics, such that only averaged signals are observed for both the calixarene and cyclodextrin complexes.[16,18]
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(36) While at lower concentrations of guest and host only cross-peaks with the inner protons are observable, very weak cross-peaks with the outer protons become observable at high concentrations, which may also be affected by experimental settings (mixing time of 250 ms) and the selected cutoff limits in the instrument software.

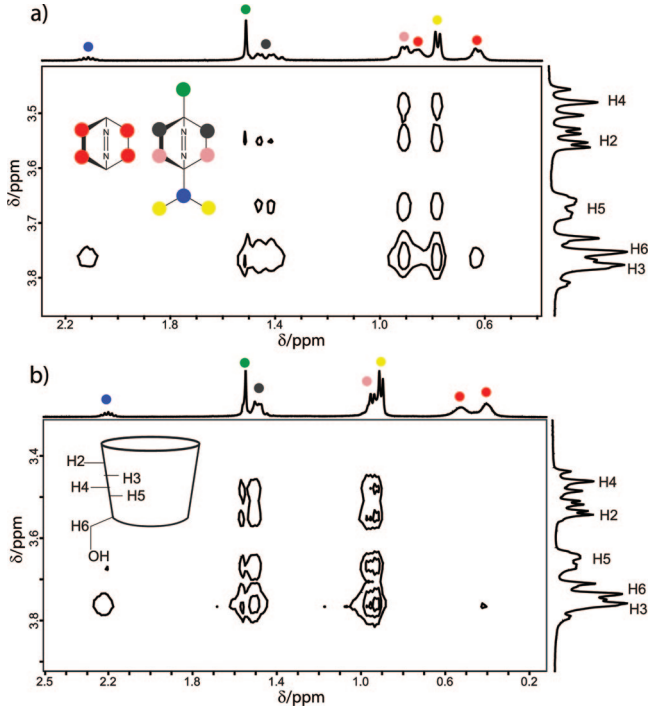

FIGURE 3. ROESY spectra of a mixture of β-CD, CX4, **1**, and **2** (5 mM in D_2O at pD 5.2): (a) without Zn^{2+}; (b) with 20 mM Zn^{2+}.

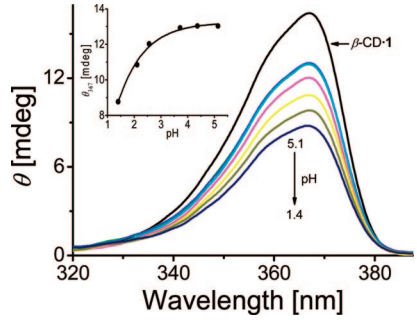

FIGURE 4. pH titration of an equimolar solution of β-CD, CX4, and **1** (5 mM). The inset shows the ICD intensity at 367 nm as a function of pH.

intensities of the encapsulated guests.[5,34,37] In particular, azoalkane **1** is known to produce a strong positive ICD signal of the near-UV n,π^* absorption band upon complexation, while azoalkane **2** gives a weaker negative signal.[1,6] Because ICD has, to the best of our knowledge, not yet been employed to monitor sorting phenomena in such complex systems, we decided first to investigate ICD effects in two simpler three-component systems, the first one comprised of β-CD, CX4, and azoalkane **1** in its dependence on pH and the second one comprised of β-CD, **1**, and **2**.

Figure 4 shows a pH titration of the molar ellipticity of a solution containing β-CD, CX4, and **1** as the first test case. Note that the affinity of **1** with CX4 can be fine-tuned with pH, because the binding constants increase significantly (from ca. 1000 to 12 500 M^{-1}) upon lowering the pH from ca. 7 to 1.4.[8] In contrast, the affinity of **1** with β-CD is insensitive to pH in the same range ($K \approx 1000\ M^{-1}$). Therefore, pH-dependent variations of the binding strength of CX4 with **1** should be indirectly observable in the ICD spectra. Indeed, the shift in

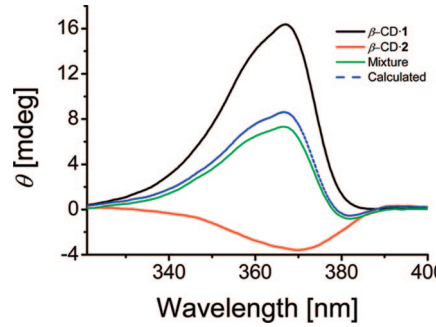

FIGURE 5. Experimental ICD spectra of β-CD·**1** (black), β-CD·**2** (red), and a mixture of β-CD·**1** and β-CD·**2** (green). The dotted blue line depicts the calculated spectrum of the mixture of β-CD·**1** and β-CD·**2**. The concentration of all individual components was 5 mM.

the equilibrium toward the formation of the CX4·**1** complex was observed in the form of a systematic lowering of the intensity of β-CD·**1** with decreasing pH. In other words, we "see" the preferential formation of the CX4·**1** complex at low pH through the depletion of the competing β-CD·**1** complex. Consequently, ICD can be used as a sufficiently sensitive technique to sound out complex equilibria via the observation of only one particular complex. A similar differential pH sensitivity of the binding constants of a guest with two different hosts has been previously documented by Isaacs and co-workers in the complexation of cucurbit[6]uril with two adamantyl amine derivatives, who employed NMR spectroscopy at the slow exchange limit to monitor the relocation.[24] NMR spectroscopy cannot be used in a similar manner to quantify such guest exchange phenomena with cyclodextrins and calixarenes, due to the more rapid host−guest exchange kinetics,[6,38] such that the ICD method presented an appealing alternative.

As a second test case, we investigated the ICD effects of two chromophoric and therefore ICD-active guests (**1** and **2**) in the presence of a single host (β-CD). The concentrations were selected to be the same as those used for the NMR and modeling studies. The experimental ICD results for this ternary system (green spectrum in Figure 5) can be understood as a composite signal of the ICD spectra of the individual binary complexes. The latter were recorded for comparison (black and red spectra) and were consistent with those previously reported at different concentrations.[6] Moreover, the experimental ICD spectra of the ternary mixture compared well with the "expected" spectrum (dashed blue spectrum), which was calculated by addition of the spectral components, corrected for the molar ellipticities, and weighted with the absolute concentration calculated for such a three-component mixture with the binding constants presumed in Scheme 2. As a third test case, we recorded the ICD spectra of guests **1** and **2** in the presence of β-CD and observed the variations upon the addition of CX4 (Supporting Information). In both cases, a decrease in the absolute ICD signal intensity was observed, consistent with a competitive binding situation where the formation of the ICD-silent CX4 complexes competes with that of the ICD-active β-CD ones.

In the next step, we proceeded to the four-component mixture by adding CX4 to the three-component mixture and measuring the resulting ICD spectrum. The addition of the second host caused a reduction in signal intensity (red vs blue spectrum in Figure 6a). This is expected for the addition of a competitive

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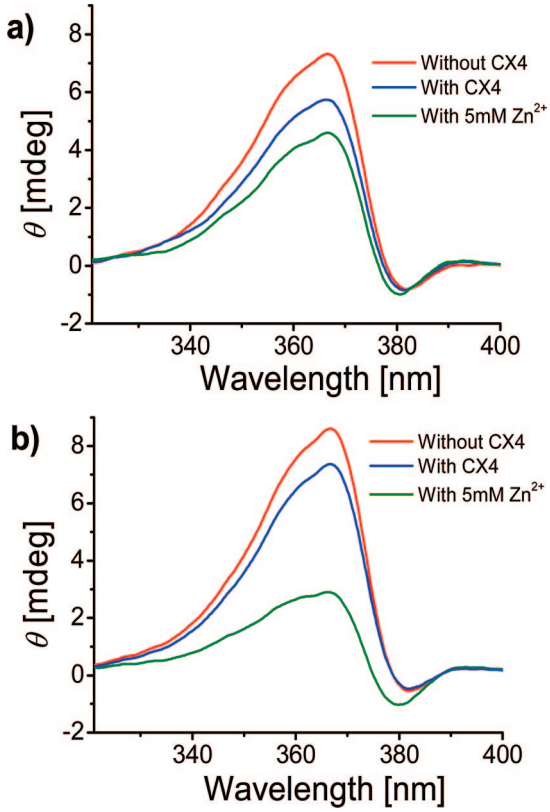

FIGURE 6. (a) Experimental ICD spectra of an equimolar mixture (5 mM) of β-CD, **1,** and **2** without CX4 (red), with 5 mM CX4 (blue), and with 5 mM CX4 and 5 mM Zn^{2+} (dark green). (b) Expected spectrum by addition of the spectral components, corrected for the molar ellipticities and weighted with the absolute concentrations calculated from the binding constants according to Scheme 2.

host, which competes with β-CD for the two guest molecules, thereby lowering the equilibrium concentration of both β-CD complexes. This was again compared with calculated spectra, which implied a slightly smaller decrease in ICD intensity than was experimentally observed (Figure 6b).

Finally, we proceeded to the most complex mixture consisting of the four components with the addition of Zn^{2+} (green spectra in Figure 6). The ICD intensity was further reduced near 367 nm but became more negative near 380 nm, signaling the preferential formation of a complex that not only depletes β-CD·**1** but also increases the relative concentration of β-CD·**2** in the solution. Our complexation model predicts this newly formed complex to be the ternary CX4·**1**·Zn^{2+} (cooperative binding). The CX4·**2** complex is destabilized in the presence of Zn^{2+} (competitive binding), thereby liberating **2** into solution and bolstering the formation of β-CD·**2**. Although the β-CD·**2** complex is expected to give rise to a negative ICD signal (Figure 5), a full inversion of the ICD signal upon the addition of Zn^{2+} was not observed experimentally. This is because (i) the intensity maxima for **1** (367 nm) and **2** (370 nm) are slightly shifted (Figure 5), (ii) the absolute signal intensity of **2** is only about one-fourth that of **1** (Figure 5), and, most importantly, (iii) the β-CD·**1** complex remains significantly populated even at high Zn^{2+} concentrations (see Figure 1).

Although the reduction in ICD signal intensity upon the addition of Zn^{2+} is readily detectable, the corresponding calculated spectrum shows a significantly larger change (green spectra in Figure 6). This quantitative discrepancy is presumably related to the approximations in our complexation model

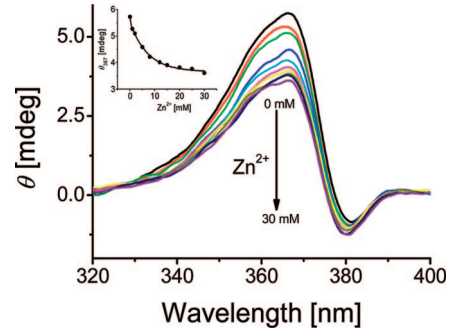

FIGURE 7. Titration of an equimolar solution of β-CD, CX4, **1**, and **2** (all 5 mM) with Zn^{2+}. The inset shows the ICD intensity at 367 nm as a function of Zn^{2+} concentration.

(Scheme 2). In particular, for simplicity, we set all binding constants of the binary host−guest complexes to be the same (1000 M^{-1}). Moreover, our model does not consider the formation of 2:1 complexes, for which we have no experimental evidence, but whose interference could affect the quantitative results. Nevertheless, all qualitative trends observed in both the NMR and ICD spectra are quite predictable. In view of the complexity of the multicomponent system and the delicate balance of the diverse supramolecular interactions, including the occurrence of both cooperative and competitive binding, the overall consistency is particularly gratifying.

The dependence on the absolute Zn^{2+} concentration was investigated in further detail. The ICD titration of the four-component mixture with Zn^{2+} (Figure 7) showed a systematic reduction in signal intensity upon successive addition of metal cation. As predicted by our modeling studies, the ICD intensity maxima of the multicomponent mixture reached an approximate plateau region at high concentrations of Zn^{2+} (20 mM). We have also conducted an additional experiment to test the reversibility of the transition-metal-induced sorting process. EDTA is known to form exceptionally strong complexes with metal ions. Indeed, upon the addition of EDTA (30 mM) to the four-component mixture with Zn^{2+} (30 mM), the signal intensity showed a virtually quantitative recovery (data not shown), indicating that the chelated Zn^{2+} loses its directing effect on the sorting process. It is therefore, principally, possible to "switch" reversibly between mixtures with either predominantly two or four equally populated host−guest complexes, as projected in the abstract graphic.

To summarize the outcome of the ICD experiments, it is generally a challenge (due to the multicomponent nature of all sorting experiments) to spectroscopically follow small variations in the course of titrations. While NMR spectroscopy remains the most instructive structural tool in such studies, we have shown that ICD spectroscopy constitutes a convenient tool to monitor such processes when chiral hosts and chromophoric guests can be selected.

Conclusions

We have introduced an additional noncovalent interaction, viz. a weak metal−ligand bond, to design chemically controlled sorting systems. Specifically, the complexation of bicyclic azoalkanes with structurally different host molecules has been mediated by a metal cation (Zn^{2+}). Naively, one would expect that the presence of an additional component in an already complex mixture would further increase its complexity. However, although rapid exchange equilibria exist between the

various components, it is the synergetic triple recognition between Zn^{2+} and a particular host−guest pair that drives these equilibria toward a state of simplification rather than increased complexity. With a little hindsight, the participation of metal ions in supramolecular systems as described herein may play a similar role in biological binding phenomena, particularly metalloproteins, which are also known to show selective binding under direct participation of, and ligation to, transition metals.[39,40]

Experimental Section

Commercially available zinc chloride, β-CD, and *p*-sulfonatocalix[4]arene sodium salt were used as received. Azoalkanes **1** and **2** were synthesized and purified according to previously reported methods.[1,41–43] ^{1}H and 2D ROESY NMR experiments (400 MHz) were performed at ambient temperature in D_2O (99.8%). The pD values of the solutions were adjusted by addition of NaOD and DCl. pH readings were converted to pD by adding 0.40 unit.[44] All experiments were performed at ambient temperature. ICD spectra were recorded with a Jasco J-810 circular dichrograph (0.2 nm resolution, 10 accumulations, 1 cm cell) by using a blank water solution for background correction.

Solutions were prepared by weighing out separately a known quantity of each of the components and sequentially mixing them to obtain the desired concentrations, after which the pH was adjusted to 4.8 (NaOH and HCl). A concentrated solution of $ZnCl_2$ (1 M) at pH 4.8 was also prepared for the titrations such that the addition of ca. 60 μL of this solution to 2 mL of the four-component mixture would give rise to a final Zn^{2+} concentration of 30 mM.

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Supporting Information Available: Text and figures giving experimental details of the ROESY data with calixarene cross-peaks and ICD control titrations, as well as the commented source code for the simulations in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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