Container Molecules

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Aqueous Anion Receptors through Reduction of Subcomponent Self-Assembled Structures**

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Abstract: *To prepare new functional covalent architectures that are difficult to synthesize using conventional organic methods, we developed a strategy that employs metal–organic assemblies as precursors, which are then reduced and demetalated. The host–guest chemistry of the larger receptor thus prepared was studied using NMR spectroscopy and fluorescence experiments. This host was observed to strongly bind aromatic polyanions in water, including the fluorescent dye molecule pyranine with nanomolar affinity, thus allowing for the design of an indicator-displacement assay.*

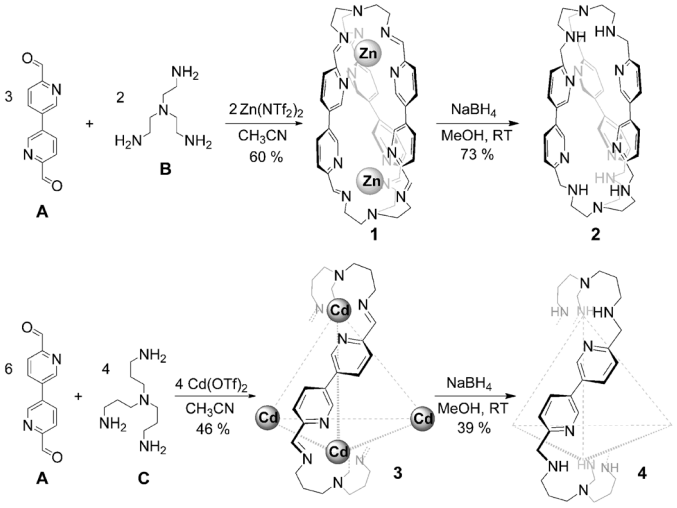
Subcomponent self-assembly allows the synthesis of increasingly complex architectures, from helicates[1] to metal–organic capsules,[2] wherein dynamic covalent imine bonds (C=N)[3] and coordinative nitrogen–metal bonds (N→M) are formed during the same self-assembly process. This approach offers several advantages: A large increase in molecular complexity can be achieved in a single reaction step; a structure can be rapidly modified with minimal synthetic effort to optimize a desired property, and the subcomponents employed are often either commercially available or straightforward to synthesize.[2f] This strategy is thus complementary to the use of metal–carbon bonds to generate complex organometallic structures.[4]

This work demonstrates the utility of subcomponent self-assembly as a means of preparing new functional covalent architectures that would be difficult to synthesize using conventional organic methods. Herein, metal–organic assemblies are used as precursors for the synthesis of metal-free complex organic structures. The imine linkages could be reduced to secondary amines through treatment with borohydride[5] to obtain purely covalent architectures. These robust new organic structures overcome some of the limitations of their metal–organic analogues, such as insolubility in water, poor stability in acidic or basic media, and lack of flexibility, thus enabling adaptive binding to prospective guest molecules.

This method thus builds upon and complements a recently reported strategy wherein dynamic imine structures that do not contain metal ion templates were hydrogenated.[6] The involvement of metal ion templates allows for additional structural complexity to be introduced[7] and provides additional information to guide the self-assembly process. Our method allows the "capture" of this additional structural complexity to achieve new functions: nanomolar affinity for the fluorescent dye molecule pyranine ($K_d = 1.2 \times 10^{-9}$ M), and the design of an indicator-displacement assay[8] involving the pyranine host complex.

The supramolecular chemistry of anions is a topic of continuing interest because of the vital role of anions in many chemical and biological processes.[9] In recent years, there have been many reports on the design and preparation of three-dimensional covalent receptors for anion binding.[9c,10] However, yield optimization and isolation of macroscopic amounts of products for further studies can be rendered difficult by the high-dilution techniques that are required for the syntheses of large-ring polycyclic cages.[11]

Two different covalent architectures (**2** and **4**) were obtained through reduction of the corresponding metal–organic precursors **1** and **3** (Scheme 1). Both **2** and **4** could easily be manipulated at 5 mM concentration in acidic or neutral water, and the host–guest chemistry of the larger cage **4** was probed in aqueous solution, thus demonstrating encapsulation of large and negatively charged aromatic guests.



Scheme 1. Synthesis of covalent architectures by reduction of the corresponding metal–organic precursors. For clarity, only one of the edges of the structure is shown for **3** and **4**.

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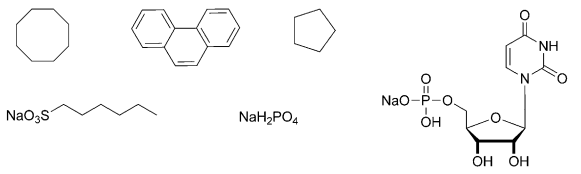
Zinc(II)-templated helicate **1** was synthesized from 3,3′-bipyridine-6,6′-dicarboxaldehyde (**A**), tris(2-aminoethyl)amine (**B**), and zinc trifluoromethanesulfonimide ($Zn(NTf_2)_2$) in acetonitrile solution (Scheme 1). The highest purity was obtained when a slight excess of the Zn^{II} salt was employed (Supporting Information, Figure S2). Helicate **1** was reduced using sodium borohydride (Scheme 1; for details, see the Supporting Information). Demetallated **2** was then isolated by precipitation from acetonitrile solution after acidifying with aqueous hydrochloric acid. NMR experiments revealed that **2** exists as a mixture of different conformers that are in slow exchange at room temperature (Figure S12). We reasoned that this behavior was consistent with a collapsed solution structure (modeled in Figure S28) of limited suitability for anion-binding studies, and we thus turned our attention to larger analogues.

The smaller building blocks Zn^{II} and triamine **B** in combination with precursor **A** appear to favor the formation of the approximately trigonal-prismatic coordination environment that is required for dimetallic compound **1**. In contrast, larger Cd^{II} ions and tris(3-aminopropyl)amine (**C**) are known to condense with **A** to form tetrahedron **3**,[12] which has been crystallographically characterized, and in which seven-coordinate cadmium(II) centers form the vertices. The coordination of the central nitrogen atoms of **C** to the cadmium(II) center appears to splay the residues of **A** in such a way as to favor the tetrahedral framework of **3**, disfavoring the formation of a structure analogous to **1**. When cage **3** was subjected to the same treatment as **1**, the new covalent structure **4** was obtained after precipitation from acetonitrile (Scheme 1). In this case, chromatographic purification was necessary (see the Supporting Information).

The reduction of iron(II)-containing analogues was also attempted; however, it proved unsuccessful. Instead, we observed a complex mixture of products, probably because of the difficulty that the reductant experiences when trying to access the tightly held ligands that surround the sterically crowded iron(II) centers. We infer that a structural reorganization may thus occur in the partially reduced structures. Based upon these observations and prior reports of the groups of Stoddart,[13] Schmittel,[7b] and our group[14] on borohydride reductions of subcomponent self-assembled structures, we infer that the pairing of labile metals with larger coordination radii, such as Cu^{I}, Zn^{II}, and Cd^{II}, with flexible chelating environments (here provided by aliphatic amines **B** and **C**) is a strategy likely to allow for successful, high-yielding imine reduction. Tighter, more restricted coordination environments may require rearrangement during the reduction process.

The organic cages **2** and **4** are more flexible and are thus more likely to encapsulate larger guests than their metal–organic precursors. Secondary amines of the type incorporated into **2** and **4** are protonated at neutral or acidic pH values (the pK_a value of 2-pyridinemethanamine has been measured to be 8.60),[15] thus leading to a high degree of water solubility for such compounds. Therefore, we set out to investigate the host–guest behavior of the larger of the two cages (i.e., **4**) in water with the aim of binding large anionic guests. Initial binding studies of guest molecules within capsule **4** were carried out using ^{1}H NMR spectroscopy; our prospective guests can be classified into three categories (Figure 1). The first category consists of molecules that were not observed to interact with the cage, such as uncharged molecules (e.g., phenanthrene, cyclooctane, cyclopentane) and hydrophilic or amphiphilic anions without aromatic groups (e.g., phosphate, monophosphate nucleotides, or hexane-1-sulfonate). The second class of molecules comprises those that were observed to interact with cage **4** and are in fast exchange between cavity and bulk solution on the NMR time scale (**G1**–**G4**); this class includes hexafluorophosphate and aromatic mono- and dianions. The last group consists of **G5** and **G6**, which undergo slow exchange with the cavity of **4** on the NMR timescale. These two guests are large aromatic molecules with three negative charges at neutral pH values.

a)



b)

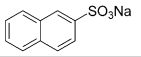
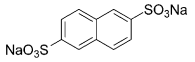
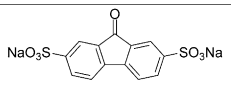
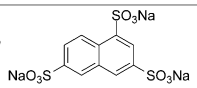
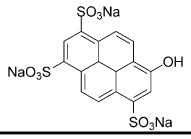
Guest		Type of exchange by NMR	K_a / M^{-1}
G1	KPF_6	Fast	110 ± 3 [a]
G2		Fast	387 ± 50 [a]
G3		Fast	540 ± 40 [a]
G4		Fast	650 ± 100 [a]
G5		Slow	(2 ± 1) x 10^6 [b]
G6		Slow	(8.3 ± 0.2) x 10^8 [b,c]

Figure 1. a) Molecules that did not show interactions with cage **4** by ^{1}H NMR spectroscopy in D_2O. b) Molecules for which ^{1}H NMR spectroscopy gave evidence of interactions with cage **4** in D_2O. [a] Affinity constant measured by ^{1}H NMR spectroscopy. [b] Affinity constant measured using fluorescence titration. [c] Affinity constant (K_{a1}) calculated for the interaction of cage **4** with the first molecule of **G6**.

Investigations of these prospective guests led us to propose three different factors, namely negative charge, molecular shape, and aromaticity, as key factors for determining the strength of encapsulation within **4**. The number of negative charges appears to be the most important factor. For example, **G2**, **G3**, and **G5** have the same naphthalene backbone, but differ in the number of anionic sulfonate groups. **G3**, which bears two sulfonate groups, has approximately twice the affinity of **G2**, which bears only one sulfonate group. However, guest affinity does not scale linearly with negative charge, as **G5**, which has three sulfonate

substituents, displays an affinity constant that is more than three orders of magnitude greater than that of **G3**. This observation was rationalized in terms of guest shape: The sulfonate moieties of **G5** and **G6** seem to be able to orient themselves within the cavity so as to maximize the attractive interactions between the anionic sulfonate groups and the cationic nitrogen atoms at three of the corners of the cage. Finally, the last factor that plays a role in the binding is the aromatic core of the guest, owing to favorable π-π stacking interactions with the pyridine rings of **4**. No binding was observed for aliphatic molecules, such as cyclopentane, cyclooctane, and sodium hexane-1-sulfonate, and a comparatively low affinity was measured for the hexafluorophosphate **G1**.

The guest molecule **G6**, having the trivial name pyranine, is an inexpensive, highly water-soluble, membrane-impermeable fluorescent pH indicator with a pK_a value of approximately 7.3.[16] It exhibits a pH-dependent absorption shift, allowing ratiometric measurements by using the excitation ratio between two wavelengths (450 and 405 nm). This property allows it to be used for measuring intracellular pH values in vivo.[17]

By ^{1}H NMR spectroscopy, two different sets of peaks were observed as **G6** was titrated into host **4** (Figure S24). The first set of peaks that appears was assigned to the 1:1 host–guest complex, as its complete formation was reached upon addition of one equivalent of **G6.** The addition of a second equivalent of **G6** led to the appearance of a second set of peaks, which was attributed to the formation of a 1:2 host–guest complex, with concomitant disappearance of the first set.

The affinity of **G6** for cage **4** was too high to be measured by NMR spectroscopy. Therefore, we decided to study its interaction with **4** using fluorescence measurements. Upon addition of cage **4** to an aqueous solution of **G6**, the fluorescence of **G6** was completely quenched (Figure 2a). We infer this quenching to be a result of photoinduced electron transfer (PET) from the amines of cage **4** to the encapsulated **G6** anion.[18] This phenomenon was used to calculate the affinity constant of the cage for **G6** through a fluorescence titration (Figure 2a), carried out in a phosphate buffer (10 mM) at pH 7.0. Under these conditions, the experimental data were best fitted with a 1:2 binding model (Figure 2c), which is consistent with the behavior observed by ^{1}H NMR spectroscopy (Figure S24).

The affinity constant (K_{a1}) for the interaction of one molecule of **G6** with one molecule of cage **4** (Figure 2b) was calculated to be $(8.3 \pm 0.2) \times 10^8\,M^{-1}$. The affinity constant (K_{a2}) between a second **G6** molecule and cage **4** (Figure 2d) was calculated to be $(11 \pm 5) \times 10^6\,M^{-1}$. The binding of **G6** to **4** thus follows anticooperative behavior, in which the second binding constant is two orders of magnitude smaller than the first one.

We envisaged using other guest molecules to displace **G6** from the cavity of **4**, which should result in partial recovery of fluorescence. Fluorescence measurements could then be used to calculate the affinity of those guests for cage **4** through competitive titration studies. Most importantly, this recovery of fluorescence through the displacement of **G6** could be

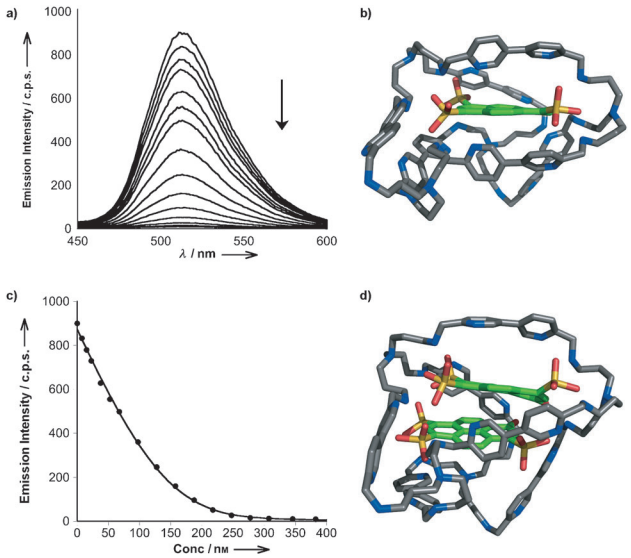


Figure 2. a) Fluorescence spectra for the titration of **G6** with cage **4** in phosphate buffer (pH 7). b) Molecular model of covalent cage **4** interacting with one molecule of **G6.** c) Curve fit for the titration of **G6** with **4**, representing the best fit to the experimental data using a 1:2 model ($K_{a1} = (8.3 \pm 0.2) \times 10^8\,M^{-1}$; $K_{a2} = (11 \pm 5) \times 10^6\,M^{-1}$). d) Molecular model of covalent cage **4** interacting with two molecules of **G6**. Models were optimized using the MM2 force field of CAChe.[19] Hydrogen atoms are omitted for clarity. c.p.s. = counts per second.

employed for the sensing of large anions in water in a displacement assay.[8a] A competitive displacement fluorescence titration was thus performed with **G5** (Figure S26). The fluorescence of free **G6** was fully recovered at the end of the titration, indicating its complete displacement by **G5.** The affinity constant of **G5** for cage **4** was thus calculated to be $(2 \pm 1) \times 10^6\,M^{-1}$ by using a 1:1 binding model.

Finally, we investigated the binding of **G6** to **4** in a buffer of higher ionic strength, to test its potential usefulness in biological media. The encapsulation of **G6** within cage **4** is inferred to occur mainly owing to electrostatic interactions; therefore, it was predicted that a high salt concentration would decrease the binding affinity. A fluorescence titration was thus performed in phosphate buffered saline (PBS), which is a buffer commonly used in biological research and which differs from a simple phosphate buffer because of its higher ionic strength from additional salt content (NaCl, 0.15 M). For this buffer, binding data were best fitted by using a 1:1 binding model, which gave an affinity constant of $2.0 \times 10^6\,M^{-1}$ (see the Supporting Information). Cage **4** thus appears to be capable of strongly binding large anions even in media with high ionic strengths.

In conclusion, two new covalent water-soluble architectures were prepared through the borohydride reduction of metal–organic assemblies that were synthesized using subcomponent self-assembly. The larger cage **4** was shown to be capable of encapsulating large anions with great affinity in aqueous media.[20] Our method should be applicable to the reduction of other metal–organic architectures that are prepared by subcomponent self-assembly having other ligands or that display other geometries, such as cubic

arrangements. Because of their high stability and solubility in water, studies on the use of these covalent architectures for applications[21] in catalysis[22] are ongoing. Furthermore, the robustness and positive charge of **4** suggest that it might be used for guest delivery within living cells.[23]

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