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Integrative Self-Sorting: Construction of a Cascade-Stoppered Hetero[3]rotaxane

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Nature efficiently uses the principles of noncovalent self-assembly[1] together with self-sorting phenomena to generate complex, functional architectures from many different building blocks. Self-sorting thus integrates different subunits into the architecture with precise positional control. In contrast, most synthetic self-assembled architectures repetitively use ever the same building blocks thus severely restricting the implementation of function. Self-sorting will certainly contribute to solving this problem.[2]

The more similar the building blocks become, the more difficult self-sorting is to achieve. Here, we report two self-sorting systems based on two very similar crown ethers. When two binding sites are integrated in one axle component, self-sorting almost quantitatively generates a hetero[3]pseudorotaxane with a defined sequence of two different wheels. Stoppering gives rise to the corresponding "cascade-stoppered" hetero[3]rotaxane.

Recently, Huang et al.[3] reported secondary di*alkyl* ammonium ions to thread through the cavity of benzo-21-crown-7 (**C7**) to form pseudorotaxanes. Phenyl groups suffice as stoppers to trap **C7** on the axle. In contrast, dibenzo-24-crown-8 (**C8**) forms pseudorotaxanes even with secondary di*benzyl* ammonium ions showing the phenyl groups not to be efficient stoppers for **C8**.[4]

On the basis of this literature knowledge, we have designed a four-component self-sorting system consisting of **1**-H$\cdot$PF$_6$, **2**-H$\cdot$PF$_6$, **C7**, and **C8** (Figure 1, inset). The corresponding association constants[5] indicate [**1**-H@**C8**]$\cdot$PF$_6$ and [**2**-H@**C7**]$\cdot$PF$_6$ to be more stable than [**2**-H@**C8**]$\cdot$PF$_6$. Thermodynamic properties thus control the preference of **C8** for **1**-H$\cdot$PF$_6$. Because of two stoppers anthracenyl and phenyl groups attached to **1**-H$\cdot$PF$_6$, a too high barrier exists for **C7** to slip onto axle **1**-H$\cdot$PF$_6$. The ESI mass spectrum (Figure 1) of an equimolar mixture of all four components in dichloromethane (DCM) shows the result of both effects: Only two intense peaks are observed, one for [**2**-H@**C7**]$^+$ (*m*/*z* 550) and one for [**1**-H@**C8**]$^+$ (*m*/*z* 746). A signal for [**2**-H@**C8**]$^+$ is hardly visible at *m*/*z* 642, while no complex ion of **1**-H$^+$ and **C7** is detected at all (*m*/*z* 654). This high-fidelity self-sorting is clearly confirmed by ^{1}H NMR experiments (Supporting Information, Figures S12−S18).

The above self-sorting system is *nonintegrative* because it merely leads to a smaller than possible set of discrete complexes from subunits each equipped with just one binding site. In contrast, an *integrative* self-sorting system is characterized by the formation of one complex, in which more than two *different* subunits are bound in two or more recognition events with positional control.[6] As a prerequisite, more than one binding site must be integrated in at least one of the components. This strategy ensures programmability and correct positioning of all distinct subunits in the final complex.

An integrative self-sorting system can conceptually be derived from the one above by combining the two axles **1**-H$\cdot$PF$_6$ and **2**-H$\cdot$PF$_6$ into divalent counterpart **3**-2H$\cdot$2PF$_6$ (Figures 2 and S19). Axle **3**-2H$\cdot$2PF$_6$ is equipped with two binding sites **A** and **B**, of which site **A** is inherited from **1**-H$\cdot$PF$_6$, and site **B** from **2**-H$\cdot$PF$_6$.

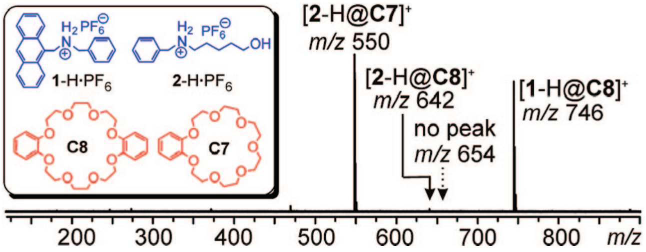

Figure 1. Electrospray-ionization Fourier-transform ion-cyclotron-resonance (ESI-FTICR) mass spectrum of an equimolar mixture of **1**-H$\cdot$PF$_6$, **2**-H$\cdot$PF$_6$, **C7**, and **C8** in DCM and their chemical structures (inset).

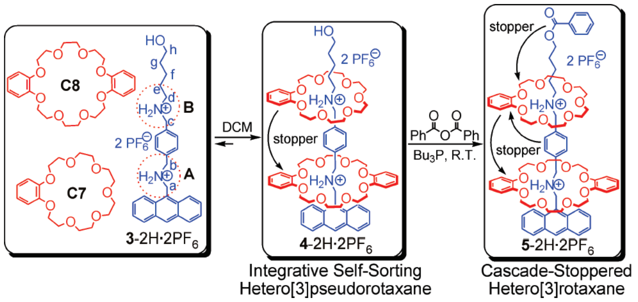

Figure 2. Sequence-specific formation of hetero[3]pseudorotaxane **4**-2H$\cdot$2PF$_6$ based on an integrative self-sorting process and the synthesis of "cascade-stoppered" hetero[3]rotaxane **5**-2H$\cdot$2PF$_6$.

In noncompetitive solvents, the sequence-specific hetero[3]-pseudorotaxane **4**-2H$\cdot$2PF$_6$ is expected to prevail in an equimolar solution of **3**-2H$\cdot$2PF$_6$, **C7**, and **C8**. The ^{1}H NMR spectrum (Figure 3a) of a 1:1 mixture of **3**-2H$\cdot$2PF$_6$ and **C7** confirmed **C7** to bind exclusively at site **B**. While the signals for H$_c$, H$_d$, and H$_e$ experience significant complexation-induced shifts, H$_a$ and H$_b$ remain almost unaffected with respect to the free axle (Figure 3b). Adding 1 equiv of **C8** to **3**-2H$\cdot$2PF$_6$ (Figure 3c) caused changes for all protons on both sites **A** and **B**, but the changes for the protons on site **A** are more obvious, indicating **C8** to equilibrate between **A** and **B** with a clear preference for **A** in agreement with the binding constants discussed above. In the equimolar mixture of **3**-2H$\cdot$2PF$_6$, **C7**, and **C8**, site **B** is occupied by **C7** as most clearly seen from the shift of H$_e$ to the same position observed in Figure 3a. Site **A** is bound to **C8** as characterized by downfield shifts of H$_a$ and H$_b$ almost identical to those observed in Figures 3c (also see Figures S21 and S22). In line with expectation, **C8** and **C7** are thus bound almost quantitatively to **A** and **B**, respectively. Furthermore, irrespective of the mixing order of the three components, the ^{1}H NMR spectrum is always the same. This implies the equilibrium of all accessible complexes to be reached with **4**-2H$\cdot$2PF$_6$ being the only major component.

An ESI mass spectrum of the equimolar mixture of **3**-2H$\cdot$2PF$_6$, **C7**, and **C8** in DCM confirmed the integrative self-sorting: In the

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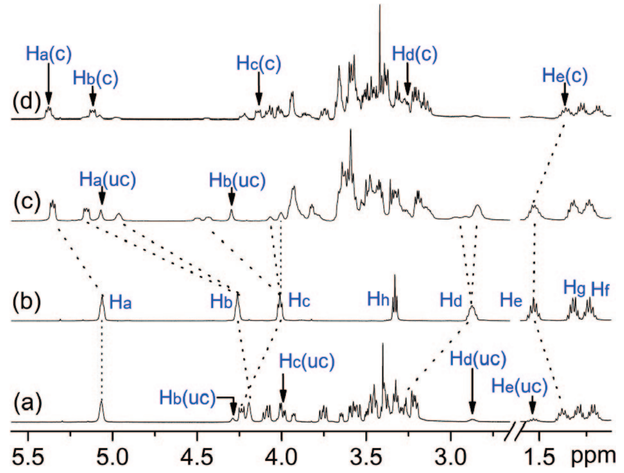

Figure 3. Partial ^{1}H NMR spectra (500 MHz, 298 K, CDCl$_3$:CD$_3$CN = 2:1, 10.0 mM) of (b) **3**-2H·2PF$_6$ alone and equimolar mixtures of (a) **3**-2H·2PF$_6$ and **C7**; (c) **3**-2H·2PF$_6$ and **C8**; (d) **3**-2H·2PF$_6$, **C7**, and **C8**. Complexed and uncomplexed species are denoted by "c" and "uc" in the parentheses, respectively.

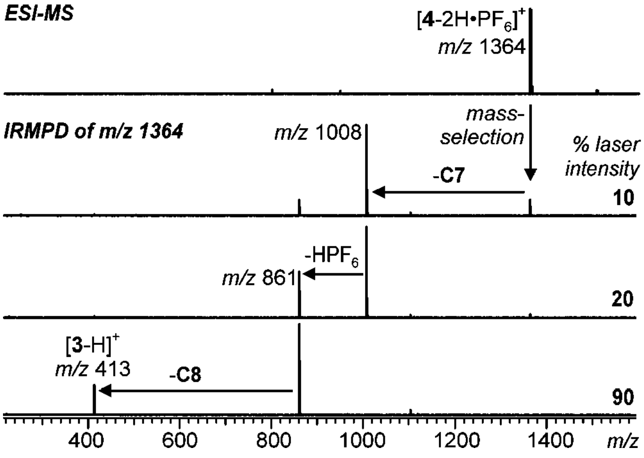

Figure 4. (Top) ESI-FTICR mass spectrum of a 1:1:1 DCM solution of **3**-2H·2PF$_6$, **C7**, and **C8**; (bottom) infrared-multiphoton dissociation (IRMPD) experiments (MS/MS) of mass-selected [**4**-2H·PF$_6$]$^+$.

clean spectrum (Figure 4), only one intense peak appears at *m/z* 1364 which corresponds to [**4**-2H·PF$_6$]$^+$. Moreover, the fragmentation reactions of mass-selected pseudorotaxane ions confirm the sequence of wheels: Infrared-multiphoton dissociation (IRMPD) experiments[7] with [**4**-2H·PF$_6$]$^+$ reveal the loss of **C8** to occur only at higher laser intensities as a consecutive fragment after losing **C7** and HPF$_6$. This fragmentation pattern is only in agreement with **C8** occupying site **A** and **C7** site **B**. Thus, NMR and MS experiments agree that an integrative self-sorting system with a well-organized structure has successfully been constructed from the equimolar mixture of **3**-2H·2PF$_6$, **C7**, and **C8**.

A phenyl group is an efficient stopper for **C7**.[3] Thus, the hetero[3]rotaxane **5**-2H·2PF$_6$ (Figure 2) can be synthesized by treating the hetero[3]pseudorotaxane **4**-2H·2PF$_6$ with benzoic anhydride in the presence of tributyl phosphine as the catalyst[8] in 70% yield. In this rotaxane, the phenyl groups at the end and middle of the axle trap **C7**. **C8** can still slip over the central phenyl group, but certainly not over **C7** so that it is also trapped by what could be considered as a "stopper cascade".

The cascade-stoppering strategy in **5**-2H·2PF$_6$ has been tested by heating its DMSO-d_6 solution at 80 °C for 2 days in the presence of excess Et$_3$N (Figure S27). Afterward, no free components or deprotonated products have been detected by ^{1}H NMR experiments providing evidence for the rotaxane structure and quite a high stability of the [3]rotaxane against dethreading of one of the wheels. In an IRMPD experiment conducted with mass-selected [**5**-2H·PF$_6$]$^+$ (Figure S28 and S29), a complex fragmentation pattern was observed. In contrast to the pseudorotaxane, the rotaxane first loses HPF$_6$ indicating the dethreading of **C7** now to be more energy-demanding than the HPF$_6$ loss because of the phenyl stopper's presence. When the resulting [**5**-H]$^+$ fragment is reisolated in an MS^3 experiment and again irradiated with the IR laser, **C7** first slips over the phenyl group.[9] Only after **C7**, **C8** can dissociate. Finally, an IRMPD experiment conducted with the mass-selected dication [**5**-2H]$^{2+}$ at *m/z* 661 (Figure S30) displays the cleavage of the anthracenyl methyl-nitrogen bond which is driven by charge repulsion and leads to the simultaneous loss of the anthracenyl methyl cation (*m/z* 191) and neutral **C8**. The second fragment (*m/z* 683) is a rotaxane with **C7** still trapped on the remainder of the axle. All these experiments confirm the rotaxane structure as well as the sequence of wheels.

In conclusion, we have successfully demonstrated the concept of integrative self-sorting with a hetero[3]pseudorotaxane as a model system. Conceptually, it is derived from a self-sorting system with four discrete components. We applied this concept to the synthesis of a hetero[3]rotaxane with an efficient cascade-stoppering system. We believe integrative self-sorting, as an important "programming language" in nature, will be highly useful in constructing complex supramolecular assemblies and various artificial smart materials with well-organized structure, distinct topology, and function.

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Supporting Information Available: Synthesis and characterization of **3**-2H·2PF$_6$ and **5**-2H·2PF$_6$; ^{1}H NMR spectra, ^{1}H−^{1}H-COSY spectra; ESI-FTICR mass spectra of **5**-2H·2PF$_6$; Figures S1−S30. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Association constants (acetone-d_6): [**1**-H@**C8**]·PF$_6$, 496 ± 18 M^{-1} (Figure S11); [**2**-H@**C7**]·PF$_6$, 615 ± 36 M^{-1}; and [**2**-H@**C8**]·PF$_6$, 155 ± 8 M^{-1} (ref 3).
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