Supramolecular Chemistry

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Linear π-Acceptor-Templated Dynamic Clipping to Macrobicycles and [2]Rotaxanes**

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Functional rotaxanes[1] are one of the representative nanoscale molecular machines[2] that have found applications in many areas, including molecular electronics,[3] nano-electromechanical systems (NEMS),[4] photocontrollable smart surfaces,[5] and nanovalves.[6] With the advent of molecular recognition and self-assembly, such molecular compounds can now be obtained efficiently through template-directed synthesis.[7] One common strategy for the formation of [2]rotaxanes involves the clipping of a macrocycle around a preformed dumbbell-shaped template in a [1+1] or [2+2] manner (Figure 1). While early examples were based on

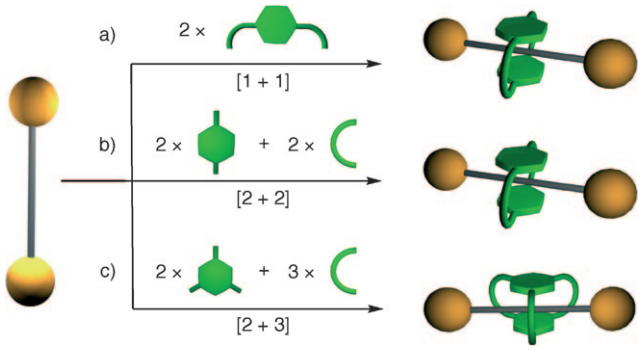
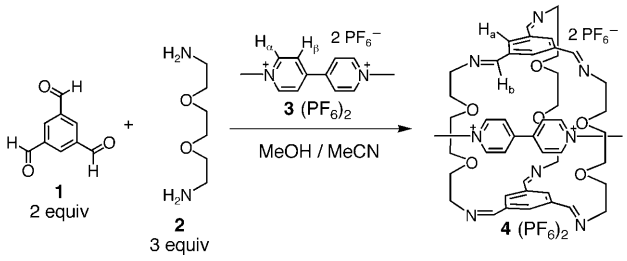


Figure 1. Clipping methods for [2]rotaxane formation through a) [1+1], b) [2+2], and c) [2+3] reactions.

irreversible kinetic pathways[8] and covalent bond formation, recent advances in reversible dynamic covalent chemistry (DCC)[9] have attracted great attention to this field. By virtue of thermodynamically controlled equilibria, DCC has provided highly efficient and versatile synthetic routes in the selection of specific products from a complex system. Among the several reversible reactions used in DCC,[9,10] imine formation has proved[11] highly versatile in macrocyclization reactions that produce complex interlocked molecular compounds.

Cryptands are three-dimensional bicyclic hosts with preorganized cavities that are capable of including ions and small molecules.[12] Replacement of the nitrogen bridgeheads in common cryptands with aromatic ring systems gives cyclophane-based macrobicycles. The introduction of aromatic ring systems into a preorganized cage-like geometry facilitates ion–π interactions and π–π interactions, which result in novel metal sandwiches,[13] fluoride receptors,[14] and host–guest complexes.[15] In particular, the seminal work by Gibson, Huang and co-workers[15] on cryptand complexation with paraquat and diquat guests has resulted in the efficient synthesis of mechanically interlocked rotaxanes.[16] The synthesis of cyclophane-based macrobicycles, however, was mostly realized through multiple reaction steps and under high-dilution conditions, which often suffered from low yields and involved tedious workup. Thus, a one-step, five-component [2+3] clipping reaction that can give the desired macrobicycle is preferred.[17]

We were motivated by a π-guest templating protocol, not only because π–π interactions can contribute to the formation of macrobicycles, but also because the resulting host–guest system has great potential as a precursor for the construction of interlocked molecules (Figure 1c).[18] Very simple precursors, namely 1,3,5-benzenetrialdehyde (**1**) and 2,2′-(ethylenedioxy)diethylamine (**2**) were chosen as the components for the desired macrobicycle (Scheme 1). The formation of six imine bonds would connect the five components to give a macrobicycle, while extending the conjugation in the C_3-symmetric aromatic "ceiling" and "floor", which is suitable for enhancing the π–π interactions with a complementary aromatic template. Meanwhile, the ethylene glycol "pillars" can provide sufficient flexibility, appropriate spacing, and polar binding sites to assist guest encapsulation. Initial screening of π templates[19] used several C_3-symmetric aro-



Scheme 1. Templated formation of pseudorotaxane **4**$(PF_6)_2$.

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matic compounds in order to match the symmetry of the desired macrobicycle but resulted in only nonspecific mixtures. It was found instead that linear bipyridinium (bpy) containing guests effectively templated the [2+3] clipping reaction. Based on this protocol, a [2]rotaxane was successfully assembled as the single product from the six-component reaction.

When trialdehyde **1** (30 mmol) and diamine **2** (45 mmol) were mixed in CD_3CN/CD_3OD (1 mL, 1:1 v/v) in the absence of any template, a complicated mixture was formed, as shown by ^{1}H NMR spectroscopy (Figure 2a). Addition of two equivalents of *N*,*N*′-dimethyl bipyridinium ($\mathbf{3}(PF_6)_2$) led to progressive spectroscopic changes that evolved to give a simple spectrum within two hours (Figure 2b–d). The disappearance of the signals corresponding to the aldehyde protons, as well as the appearance of signals corresponding to the imine protons were consistent with the formation of a symmetrical polyimine macrobicycle. Comparison of this spectrum with the ^{1}H NMR spectrum of $\mathbf{3}^{2+}$ (Figure 2e) revealed upfield shifts for the H_α and H_β aromatic protons of bpy, which indicated that bpy was shielded by the polyimine aromatic cores of the macrobicyclic host. The absence of unbound free species suggested that the pseudorotaxane $\mathbf{4}^{2+}$ was in fast exchange with $\mathbf{3}^{2+}$ and the macrobicyclic host on the ^{1}H NMR timescale. A yellow color that corresponds to a charge-transfer band at $\lambda = 420$ nm in the UV/Vis spectrum was observed, which is consistent with charge-transfer interactions between the aromatic units. To the best of our knowledge, this is the first example of three-dimensional cryptand templated by a lower-symmetry linear π guest.[20]

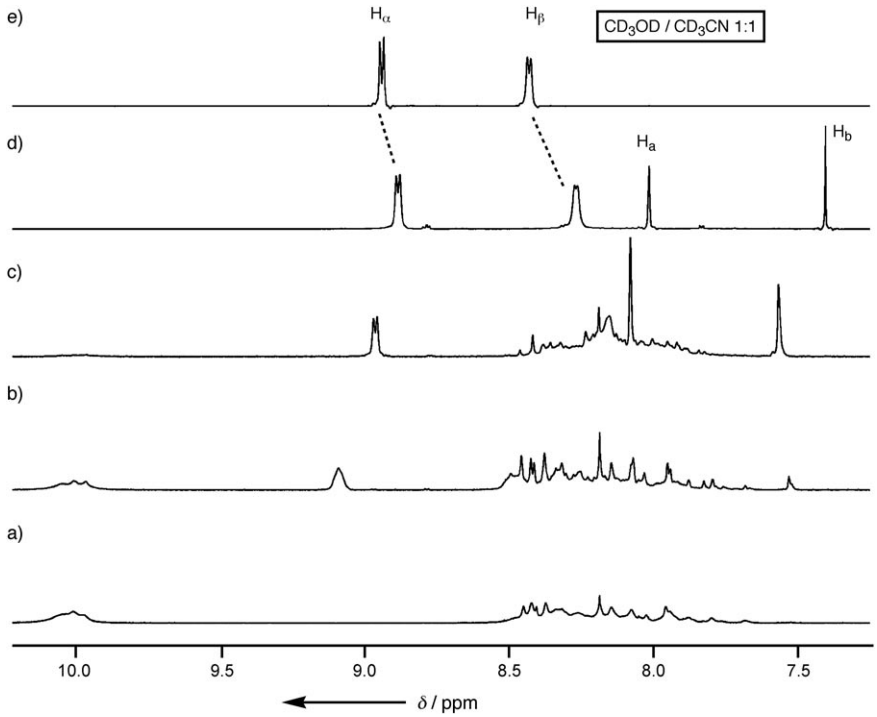
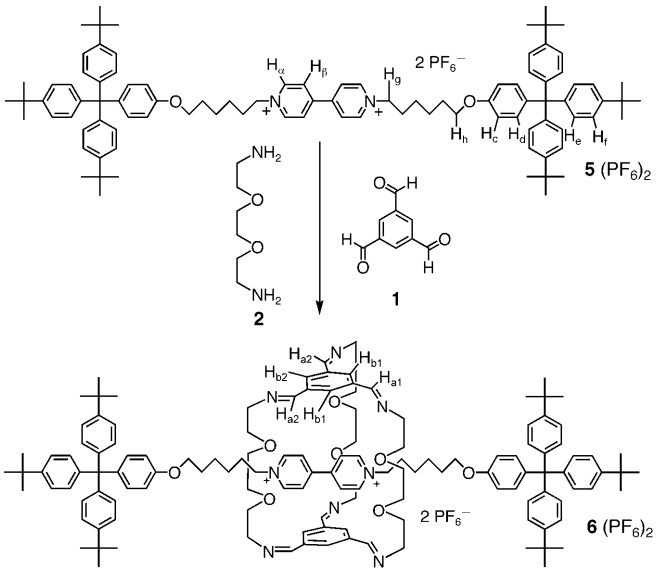


Figure 2. Partial ^{1}H NMR spectra (298 K, 500 MHz) of the mixture of a) **1** and **2**, and the time-evolved spectra in the presence of 2 equiv of $\mathbf{3}^{2+}$ after b) 5 min, c) 10 min, and d) 2 h. e) Partial ^{1}H NMR spectrum of $\mathbf{3}(PF_6)_2$ under the same conditions.



Scheme 2. Templated formation of [2]rotaxane $\mathbf{6}(PF_6)_2$.

Encouraged by the successful templated formation of pseudorotaxane $\mathbf{4}^{2+}$ from six components, we decided to test the efficiency of [2]rotaxane formation using the dumbbell-shaped bpy-containing $\mathbf{5}(PF_6)_2$ (Scheme 2), where the macrobicycle should be sterically hindered from slipping off the dumbbell. $\mathbf{5}(PF_6)_2$ alone was insoluble in $CDCl_3$. In the presence of two equivalents of trialdehyde **1** (30.0 mM) and three equivalents of diamine **2** (45.0 mM), $\mathbf{5}(PF_6)_2$ gradually dissolved in $CDCl_3$ over one hour to give a yellow solution. The ^{1}H NMR spectrum (Figure 3c) indicated the formation of one single, symmetric species that was identified as the desired [2]rotaxane $\mathbf{6}(PF_6)_2$. In contrast with the pseudo[2]-rotaxane $\mathbf{4}(PF_6)_2$ that was in fast equilibrium with its components, the macrobicycle was held in place around the dumbbell component and no free components were observed. Consequently, the symmetry of the macrobicyclic component was lowered so that the six imine protons and six phenylene protons became nonequivalent, each signal thus split into a set of two singlets with an intensity ratio of 1:2. The H_β resonance of $\mathbf{6}(PF_6)_2$ showed a significant upfield shift compared to that of the dumbbell $\mathbf{5}(PF_6)_2$ (Figure 3b), which is consistent with a shielding effect in addition to minor solvent effects.[21] The formation of a [2]rotaxane was further confirmed by high-resolution electrospray mass spectrometry (ESI-MS). An intense molecular ion peak at *m/z* 995.6 was observed in the ESI mass spectrum of $\mathbf{6}(PF_6)_2$, this peak corresponds to the loss of two PF_6^- anions from the rotaxane and is consistent with the predicted spectrum. In

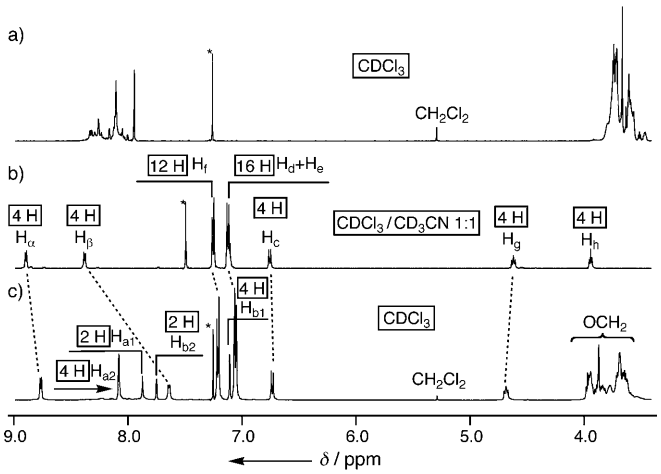


Figure 3. Partial ^{1}H NMR spectra (298 K, 500 MHz) of a) **1** and **2** (2:3) in $CDCl_3$, b) **5**$(PF_6)_2$ alone in $CDCl_3/CD_3CN$ (1:1), and c) **1**, **2**, and **5**$(PF_6)_2$ (2:3:1) in $CDCl_3$. The asterisk indicates residual $CHCl_3$.

comparison, the mixture of **1** and **2** in the absence of **5**$(PF_6)_2$ resulted in a nonspecific mixture only (Figure 3a).

Two-dimensional nuclear Overhauser effect spectroscopy (2D NOESY) ^{1}H NMR spectra (Figure 4) provided unequivocal evidence for the interlocked structure of **6**$(PF_6)_2$. For example, the H_α protons of the bpy unit in the dumbbell

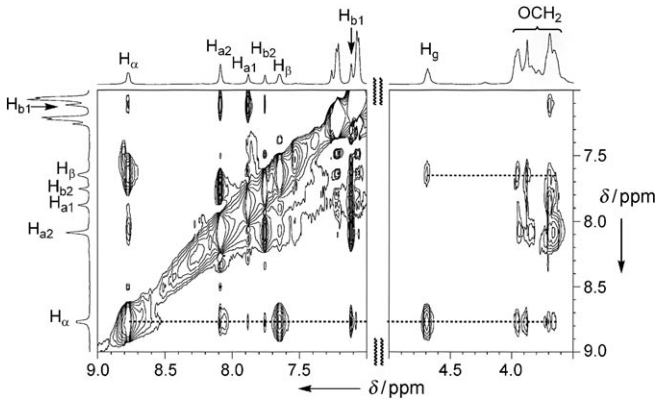


Figure 4. Partial 2D NOESY spectrum ($CDCl_3$, 298 K, 500 MHz) of **6**$(PF_6)_2$.

component show strong NOEs with the imine protons H_{a2} and the aromatic protons H_{b1} of the macrobicyclic component while weakly correlating to H_{a1} and H_{b2}; this correlation is consistent with the relative spatial arrangements of the aromatic units. In addition, the protons of ethylene glycol side-loops show correlations to H_α and H_β of the bpy (Figure 4) as well as to H_g on the dumbbell (see the Supporting Information). The cross-peaks between the dumbbell and the macrobicyclic components are indicative of threaded species, that is, **6**$(PF_6)_2$, as opposed to nonthreaded complexes.

Multiple noncovalent interactions were identified from the lowest energy co-conformation of **6**$(PF_6)_2$ (Figure 5) computed by force-field modeling.[22] As expected, the

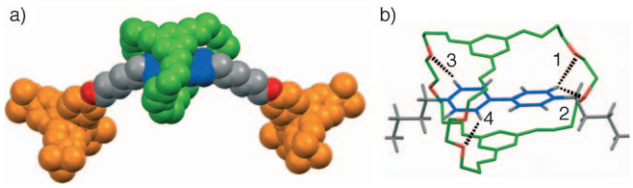


Figure 5. a) Space-filling representation of computed lowest energy co-conformation of **6**$(PF_6)_2$. b) Multiple C–H···O hydrogen bonding interactions indicated by the stick model. Hydrogen-bonding distances C···O, H···O [Å] and angles C–H···O [°]: 1) 3.49, 2.61, 138.6; 2) 3.45, 2.87, 147.5; 3) 3.59, 2.59, 154.1; 4) 3.47, 2.64, 133.6.

imine bonds of the macrobicyclic component were nearly coplanar with the phenylene cores to form the "ceiling" and the "floor" that have extended π surfaces. The distance between the centroids of the "ceiling" and the "floor" and the mean plane of bpy unit is 3.6 Å, which is indicative of π–π interactions. The co-conformation was further stabilized by multiple C–H···O hydrogen bonds between 1) H_αs of the bpy unit and the oxygen atoms on the two nearby ethylene glycol loops on the back and 2) H_β of the bpy unit and the oxygen atom on the front ethylene glycol loop. Similar interactions were also present in the aforementioned cryptand–bpy systems reported by Gibson, Huang, and their respective co-workers.[15,16b–e] In accordance with our original design, the modeling results confirmed the combination of π–π stacking and hydrogen-bonding interactions as the origin of the thermodynamic selectivity expressed in the exclusive formation of [2]rotaxane **6**$(PF_6)_2$.

We have reported a highly efficient one-pot [2+3] clipping method to obtain a macrobicycle and a related [2]rotaxane through sixfold imine bond formation. A linear bpy-based π template has been shown for the first time to effectively induce the formation of the cage-like, C_3-symmetrical cryptand, despite the symmetry mismatch between the host and the guest. Based on this π-templating protocol, a novel [2]rotaxane **6**$(PF_6)_2$ was assembled as the only product from a six-component mixture. The high efficiency is reminiscent of enzymatic catalysis,[23] in that the binding of **5**$(PF_6)_2$ with an intermediate, either acyclic or monocyclic, leads to a preorganization of substrates into a conformation suitable for macrobicyclization. The current method not only provides facile access to cyclophane-based macrobicyclic hosts, but also provides further opportunities for the assembly of incrementally more complex interlocked systems with three-dimensional structural features from simple starting materials. Its application to the template-directed synthesis of catenanes and suitanes[10d] is currently underway.[24]

Experimental Section

Synthesis of [2]rotaxane **6**$(PF_6)_2$. A mixture of **1** (5.3 mg, 32 μmol) and **2** (7.2 mg, 48 μmol) in $CDCl_3$ (1 mL) was stirred at room temperature for 1 hour. After the addition of **5**$(PF_6)_2$ (26.0 mg, 16 μmol), the mixture was stirred for a further 2 h. The resulting yellow solution was filtered through a short plug of cotton wool, followed by evaporation of the filtrate to give **6**$(PF_6)_2$ as a pale yellow solid (36.0 mg, 97%). ^{1}H NMR ($CDCl_3$, 500 MHz, 298 K): $\delta = 8.78$ (d, $J = 6.0$ Hz, 4H), 8.10 (s, 4H), 7.89 (s, 2H), 7.77 (s, 2H), 7.22 (d, $J = 8.5$ Hz, 12H), 7.13 (s,

4H), 7.07 (d, $J = 8.5$ Hz, 16H), 6.75 (d, $J = 8.5$ Hz, 4H), 4.70 (t, $J = 6.5$ Hz, 4H), 4.00–3.54 (m, 40H), 2.34 (br s, 4H), 1.89 (br s, 4H), 1.69 (br s, 8H), 1.31 ppm (s, 54H); ^{13}C NMR ($CDCl_3$, 125 MHz, 298 K): $\delta = 161.8$, 161.0, 156.8, 148.3, 145.1, 144.1, 139.6, 136.6, 135.8, 133.1, 132.3, 130.7, 127.0, 125.1, 124.1, 112.9, 71.6, 71.1, 70.8, 70.7, 67.3, 63.0, 61.3, 60.6, 60.0, 34.3, 31.4, 31.1, 29.1, 26.2, 25.8 ppm; HRMS (ESI): $[M-2PF_6]^{2+}$: calcd 995.6409, found 995.6414.

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