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

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[**] This work was supported by the Office of Science, Office of Basic Energy Sciences, of the U. S. Department of Energy under contract No. DE-AC02-05CH11231. We thank Dr. Christian G. Canlas and Dr. Rudi Nunlist from University of California, Berkeley for their help on NMR measurements.

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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] nanoelectromechanical systems (NEMS),[4] photo controllable 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 of the common strategies of making [2]rotaxanes involves the clipping of a macrocycle around a preformed dumbbell-shaped template in a [1+1] or [2+2] manner. (Scheme 1) While early examples were based on irreversible kinetic pathway[8] through covalent bond formation, recent advances on reversible dynamic covalent chemistry (DCC)[9] has 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 in the category of DCC reactions,[9,10] the imine formation has proven[11] to be very versatile in macrocyclization to give complex interlocked molecular compounds.

Cryptands are three dimensional bicyclic hosts with preorganized cavities capable of inclusion of ions and small molecules.[12] Replacing 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, resulting in novel metal sandwiches,[13] fluoride receptors,[14] and host-guest complexes.[15] In particular, the seminal work by Gibson, Huang and coworkers[15] on cryptand complexation with paraquat and diquat guests have 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 in high-dilution conditions, which often suffered from low yield and tedious workup. Thus, a one-step, five-component [2+3] clipping reaction that can give the desired macrobicycle is highly desirable.[17]

We are motivated by a π-guest templating protocol, because not only π-π interactions can contribute to the formation of macrobicycles, but also the resulting host-guest system holds great promise as a forerunner in the construction of interlocked molecules.[18] (Scheme 1c) Very simple precursors, namely 1,3,5-benzenetrialdehyde (**1**) and 2,2'-(ethylenedioxy)diethylamine (**2**) were chosen as the components for desired macrobicycle. (Scheme 2) 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, proper spacing, and polar binding sites to assist guest encapsulation. Initial screening of π-templates engaged[19] several C_3 symmetric aromatic compounds in order to match the symmetry of the desired macrobicycle, which only resulted in 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.

Mixing trisaldehyde **1** (30 mmol) and diamine **2** (45 mmol) in CD_3CN/CD_3OD (1 mL, v/v 1:1) in the absence of any template resulted in a complicated mixture, as indicated by ^{1}H NMR spectrum (Figure 1a). Addition of 2 equiv. *N*,*N*'-dimethyl

bipyridinium (**3**•2PF_6) led to progressive spectroscopic changes that evolved to give a simple spectrum within two hours (Figure 1b-d). The disappearance of aldehyde protons, as well as the emerging imine protons were consistent with the formation of a symmetrical polyimine macrobicycle. A comparison with the spectrum of $\mathbf{3}^{2+}$ (Figure 1e) revealed upfield shifts for the H_α and H_β aromatic protons of BPY, an indication of BPY being 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 time scale. A yellow color corresponding to a charge-transfer band at λ 420 nm in the UV-vis spectrum was observed, 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]

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 **5**•2PF_6 (Scheme 3), where the macrobicycle should be sterically hindered from slipping off the dumbbell. **5**•2PF_6 alone was insoluble in $CDCl_3$. In the presence of 2 equiv. trisaldehyde **1** (30.0 mM) and 3 equiv. diamine **2** (45.0 mM), **5**•2PF_6 gradually dissolved in $CDCl_3$ within one hour to give a yellow solution. The ^{1}H NMR spectrum indicated (Figure 2c) the formation of one single, symmetric species that was identified as the desired [2]rotaxane **6**•2PF_6. In contrast to the pseudo[2]rotaxane **4**•2PF_6 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 splitting into a set of two singlets in a ratio of 1:2. The H_β resonance of **6**•2PF_6 showed significant upfield shift in comparison to that of the dumbbell **5**•2PF_6 (Figure 2b), consistent with a shielding effect in addition to minor solvent effects.[21] The formation of [2]rotaxane was further confirmed by high resolution electrospray mass spectrometry (ESI-MS). An intense molecular ion at *m/z* 995.6 was observed in the ESI-MS of **6**•2PF_6, corresponding to the loss of two PF_6^- anions and is consistent with the theoretical predictions. In comparison, the mixture of **1** and **2** in the absence of **5**•2PF_6 only resulted in a nonspecific mixture (Figure 2a).

Two-dimensional Nuclear Overhause Effect Spectroscopy (2D NOESY) ^{1}H NMR spectra provided (Figure 3) unequivocal evidence for the interlocked structure of **6**•2PF_6. For example, the H_α protons of the BPY in the dumbbell component showed 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}, consistent with the relative spatial arrangements of the aromatic units. In addition, protons of ethylene glycol side loops showed correlations to H_α and H_β of the BPY (Figure 3) as well as to H_g on the dumbbell (See Supporting Information). The cross-peaks between the dumbbell and the macrobicyclic components are indicative of threaded species, i.e., **6**•2PF_6, as opposed to nonthreaded complexes.

Multiple noncovalent interactions were identified from the lowest energy *co*-conformation of **6**•2PF_6 (Figure 4) computed by force-field modeling.[22] As expected, the imine bonds of the macrobicyclic component were nearly coplanar with the phenylene cores to give the “ceiling” and the “floor” with extended π surfaces. The distance

between the centroids of the "ceiling" and the "floor" to the mean plane of BPY unit was 3.6 Å, 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 Gibson–Huang cryptand-BPY systems.[15,16] In accordance to 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**•2PF_6.

We reported a highly efficient one-pot [2+3] clipping method to obtain a macrobicycle and a related [2]rotaxane through six-fold imine bond formation. A linear BPY-based π-template has been shown for the first time to effectively induce the cage-like, C_3 symmetrical cyrptand around itself, despite the symmetry mismatch between the host and the guest. Based on this π-templating protocol, a novel [2]rotaxane **6**•2PF_6 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**•2PF_6 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 opens up a window for the assembly of incrementally more complex interlocked systems with 3D 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•2PF$_6$. A mixture of **1** (5.3 mg, 32 μmol) and **2** (7.2 mg, 48 μmol) in $CDCl_3$ (1 mL) was stirred at RT for 1 hour. After the addition of **5**•2PF$_6$ (26 mg, 16 μmol), the mixture was further stirred for 2 hours. The resulting yellow solution was filtered through a short plug of cotton, followed by evaporation of the filtrate to give **6**•2PF$_6$ as a pale yellow solid (36.0 mg, 97%). ^{1}H NMR ($CDCl_3$, 500 MHz, 298 K): 8.78 (d, *J* = 6.0 Hz, 4 H), 8.10 (s, 4 H), 7.89 (s, 2 H), 7.77 (s, 2 H), 7.22 (d, *J* = 8.5 Hz, 12 H), 7.13 (s, 4 H), 7.07 (d, *J* = 8.5 Hz, 16 H), 6.75 (d, *J* = 8.5 Hz, 4 H), 4.70 (t, *J* = 6.5 Hz, 4 H), 4.00–3.54 (m, 40 H), 2.34 (br s, 4 H), 1.89 (br s, 4 H), 1.69 (br s, 8 H), 1.31 (s, 54 H); ^{13}C NMR ($CDCl_3$, 125 MHz, 298 K): 161.8, 161.0, 1568, 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; HRMS (ESI): $[M - 2PF_6]^{2+}$: calcd 995.6409, found 995.6414.

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[18] Although π-donor/acceptors were widely used as kinetic templates in the synthesis of interlocked molecules, no π-templates have been shown for rotaxane synthesis using a dynamic clipping protocol.

[19] The following C_3-symmetrical aromatic compounds were attempted as templates but failed: mesitylene, 1,3,5-trihydroxybenzene, 1,3,5-tris(4-pyridyl)benzene, coronene.

[20] Rigid macrobicyclic molecular cages based on metal-ligand coordination have been synthesized by Fujita and coworkers. See: a) K. Kumazawa, K. Biradha, T. Kusukawa, T. Okano, M. Fujita, *Angew. Chem.* **2003**, *115*, 4039-4043; *Angew. Chem. Int. Ed.* **2003**, *42*, 3909-3913; b) M. Yoshizawa, J. Nakagawa, K. Kumazawa, M. Nagao, M. Kawano, T. Ozeki, M. Fujita, *Angew. Chem.* **2005**, *117*, 1844-1847; *Angew. Chem. Int. Ed.* **2005**, *44*, 1810-1813; c) Y. Yamauchi, M. Yoshizawa, M. Fujita, *J. Am. Chem. Soc.* **2008**, *130*, 5832-5833.

[21] Although the ^{1}H NMR spectra of **5**•2PF_6 and **6**•2PF_6 were taken in different solvent system due to solubility limitations, the large upfield shift of H_β resonance (0.7 ppm) cannot be accounted for by solvent effect alone, because only insignificant shifts (<0.1 ppm) were observed for the resonances of aromatic protons (H_c, H_d, H_e and H_f) on the stopper.

[22] The *co*-conformation was minimized with MOE2006 using MMFF94x force field and the implemented solvation model for $CHCl_3$. MOE2006 is a product of Chemical Computing Group, Montreal, Canada.

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[24] The high reactivity of bipyridinium towards common reductants posed a problem in our attempts to reduce the imine bonds to kinetically lock the [2]rotaxane. While trying other mild reducing agents, we are also searching for other π-acceptor based templates,

such as pyromellitic diimide, which is more compatible with the reducing conditions for the imine bonds.

Captions to Figures

Figure 1. 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. $\mathbf{3}^{2+}$ after b) 5 min, c) 10 min, and d) 2 hours. e) Partial ^{1}H NMR spectrum of **3**•2PF_6 under the same conditions.

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

Figure 3. Partial 2D NOESY spectrum ($CDCl_3$, 298 K, 500 MHz) of **6**•2PF_6.

Figure 4. a) Space-filling representation of computed lowest energy *co*-conformation of **6**•2PF_6. b) Multiple [C–H···O] hydrogen bonding interactions indicated by the stick model. Hydrogen bonding geometries [C···O], [H···O] (Å), [C–H···O] (^{o}): a: 3.49, 2.61, 138.6; b: 3.45, 2.87, 147.5; c: 3.59, 2.59, 154.1; d: 3.47, 2.64, 133.6.

Captions to Schemes

Scheme 1. Illustrations of the Clipping Methods toward [2]Rotaxanes through a) [1 + 1], b) [2 + 2], and c) [2 + 3] Reactions.

Scheme 2. Templated Formation of Pseudorotaxane **4**•2PF_6.

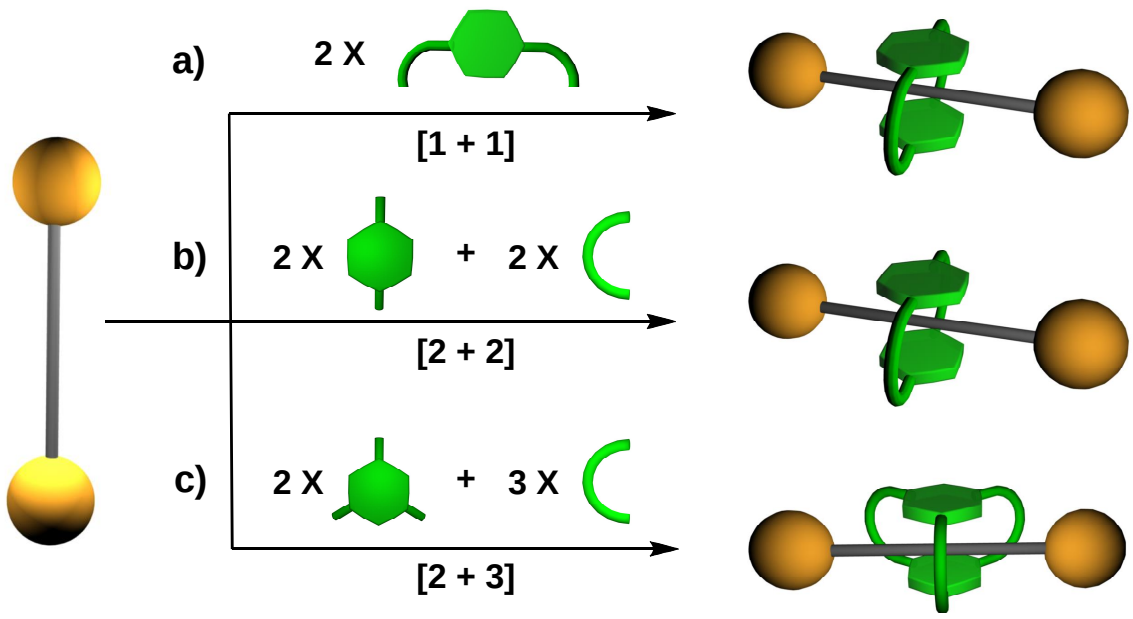
Scheme 3. Templated Formation of [2]Rotaxane **6**•2PF_6.

Table of Contents

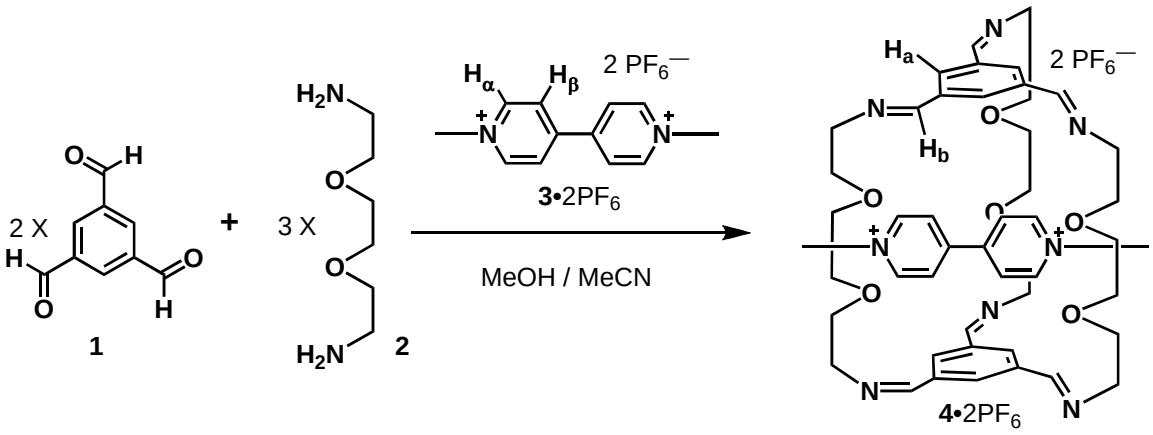
Cage me! A linear dumbbell shaped bipyridinium molecule can template the cage formation around itself through six-fold imine bond formation to give an interlocked [2]rotaxane as the single product, despite the symmetry mismatch between the template and the formed macrobicycles.

Keywords

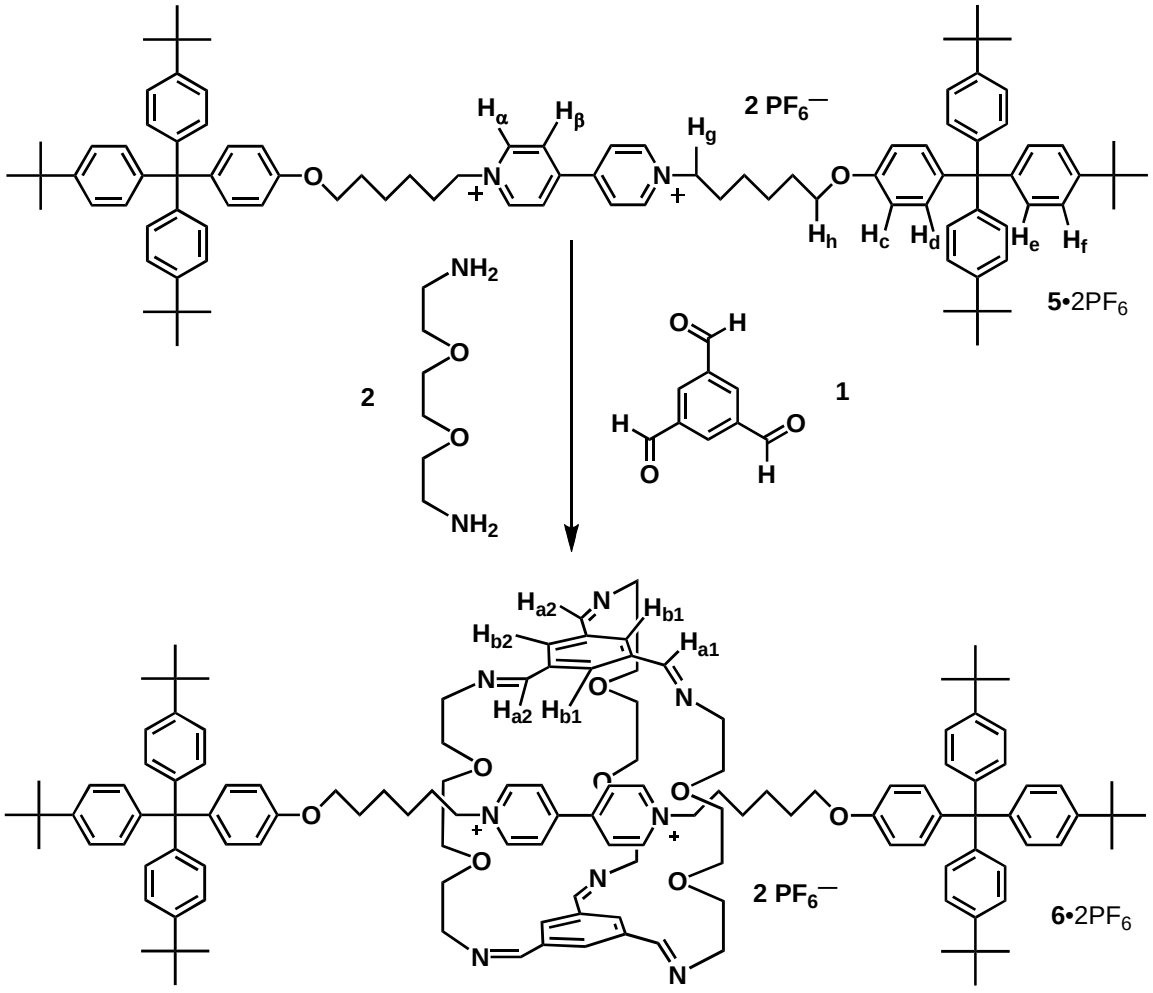
dynamic covalent chemistry · imine formation · π interactions · rotaxanes · templated synthesis



Scheme 1



Scheme 2



Scheme 3

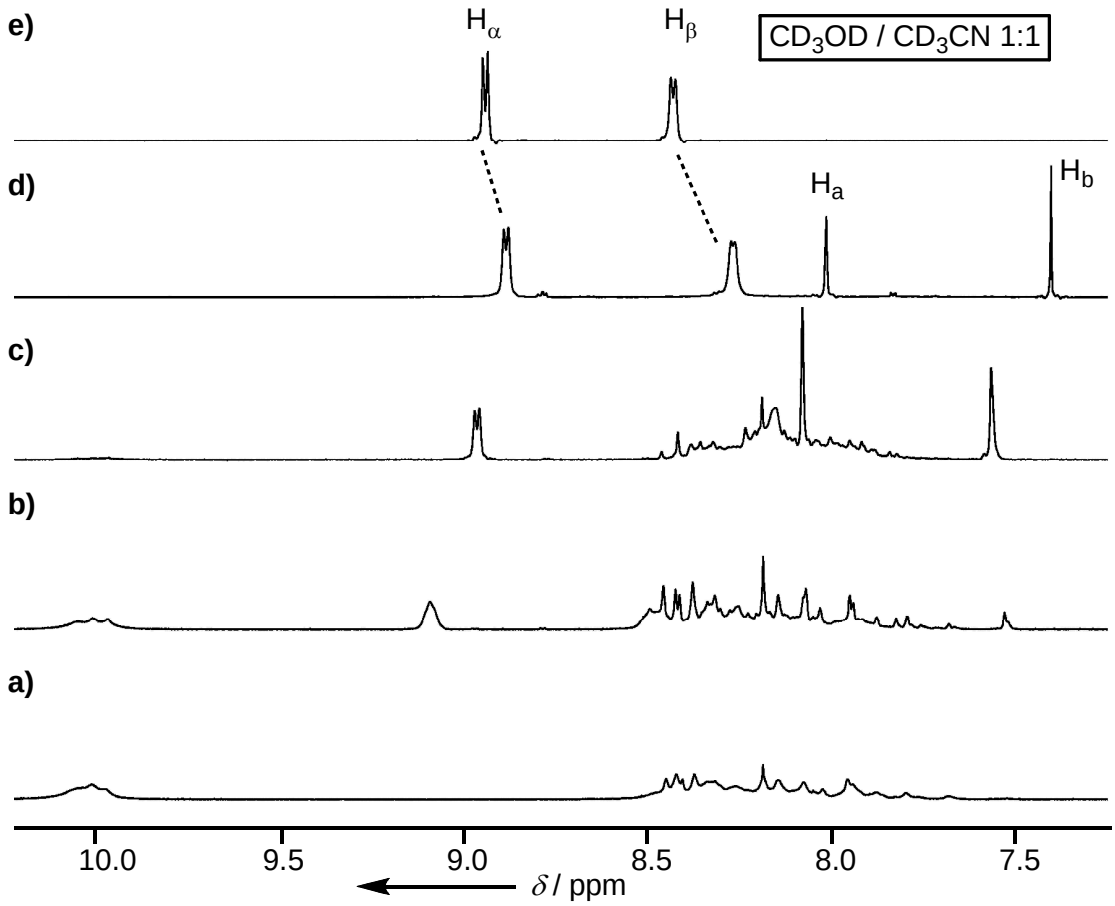

e)
H_α
H_β
CD_3OD / CD_3CN 1:1
d)
H_a
H_b
c)
b)
a)
10.0
9.5
9.0
8.5
8.0
7.5
δ / ppm

Figure 1

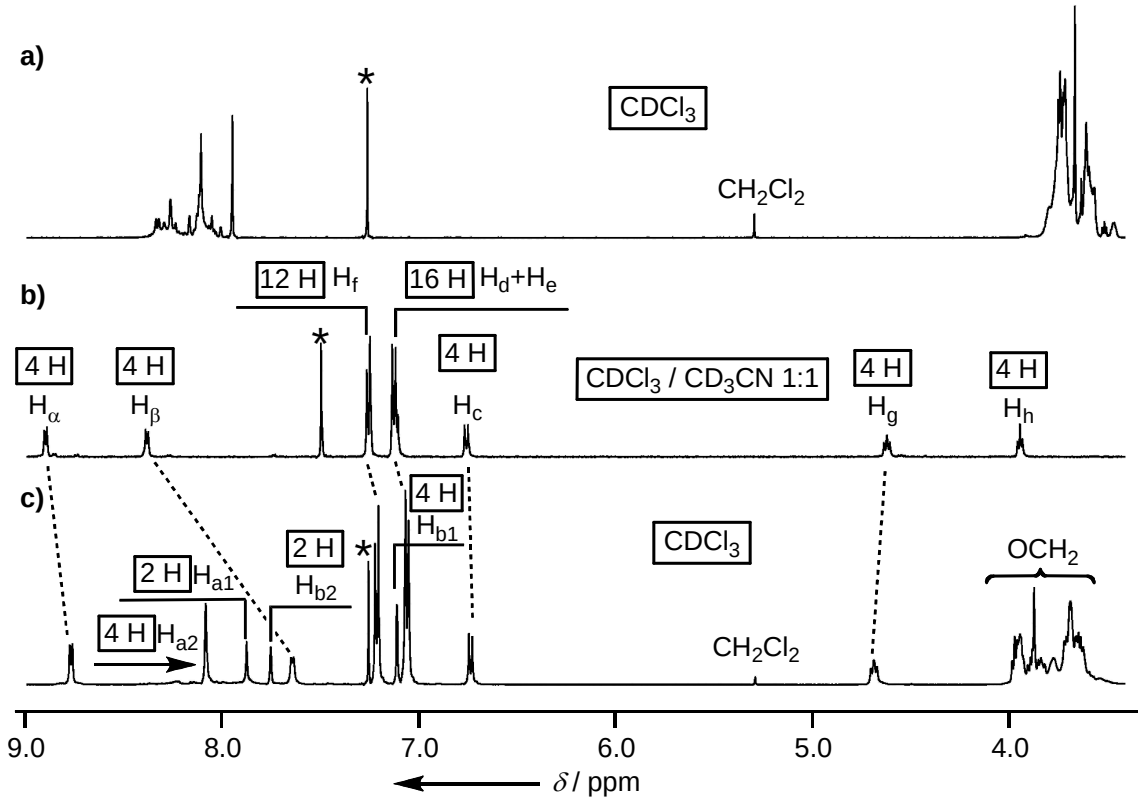


Figure 2

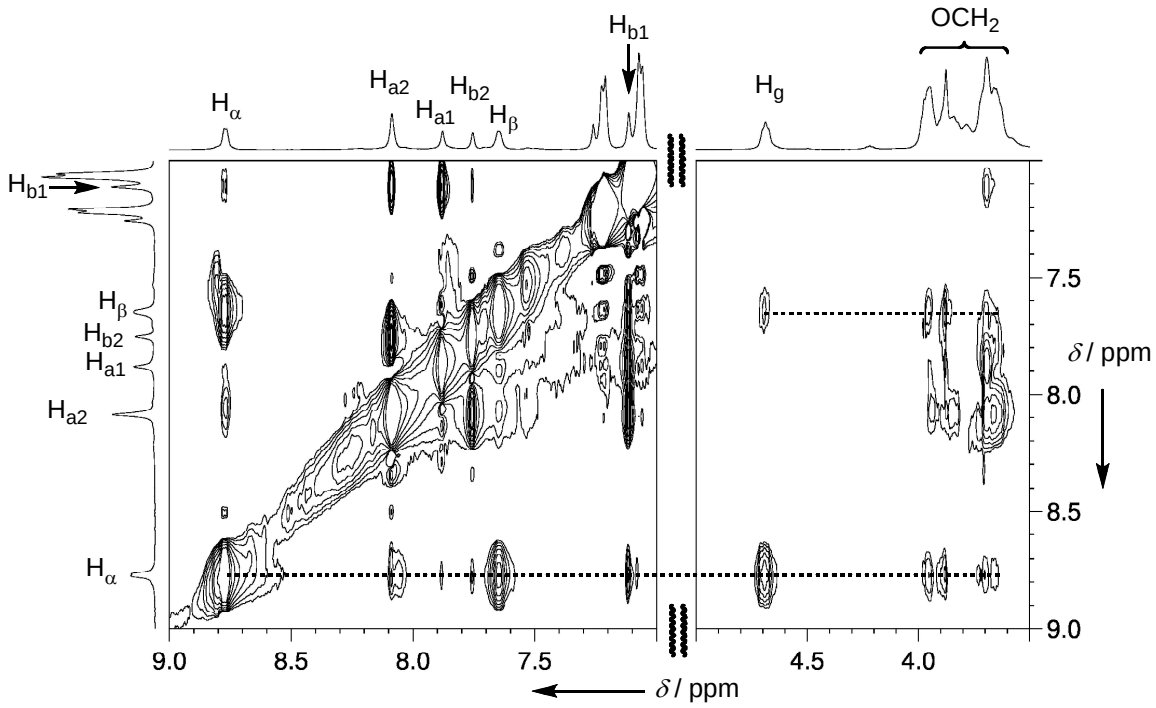


Figure 3

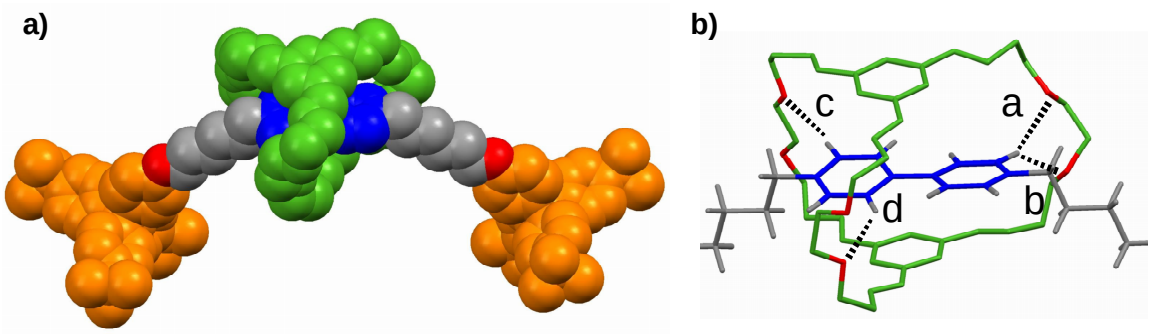


Figure 4

TOC Figure