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Toward Interlocked Molecules beyond Catenanes and Rotaxanes

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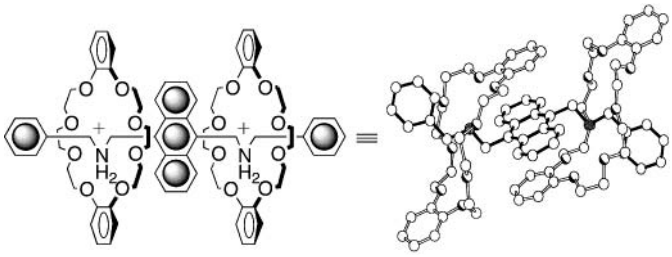
ABSTRACT



A linear bis secondary dialkylammonium ion-containing scaffold—based upon an anthracenyl core—has been synthesized. It has been demonstrated that it is possible to dock either one or two dibenzo[24]crown-8 (DB24C8) macrocycles onto this scaffold to afford either a [2]- or [3]pseudorotaxane, respectively. In solution, the association constants for the formation of each of these species has been quantified by employing ^{1}H NMR spectroscopy, and both species survive in the "gas phase" as evidenced by FAB mass spectrometry. Additionally, the X-ray crystal superstructure of the [3]pseudorotaxane has been determined.

During the past 35 years, several different protocols have been developed[1] for the synthesis of mechanically interlocked molecular compounds. These compounds, which include catenanes,[1,2] rotaxanes,[1,3] and carceplexes,[1,4] are constituted of molecules composed of two or more components that cannot be separated from each other for mechanical reasons. The synthetic protocols used by chemists have evolved[1] from being all but statistical[5] in the beginning to utilizing, successfully, covalent,[6] coordinative,[7] and noncovalent[8] templates under both kinetic[9] and thermodynamic[10] control.

We envisage the existence of a further class of interlocked molecules, beyond catenanes and rotaxanes, that are reminiscent of carceplexes, yet distinguishable from them. In their simplest forms, these molecules would consist of two components—a somewhat rigid *scaffold* and a reasonably flexible *net*—wherein the scaffold would be enmeshed by the net. With a judicious choice of cores and branches, a dendritic-like scaffold could be employed to template, under

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thermodynamic control, the formation of a matching net comprising macrocycles and links around the scaffold. These two components would be inseparable from each other prior to cleavage of at least one covalent bond somewhere in the molecular architecture. For example, the attempted departure of one macrocycle of the net from the scaffold would necessitate the passing of another macrocycle over the core of the scaffold which would be impossible for steric reasons. One of the simplest examples is portrayed in Figure 1 which

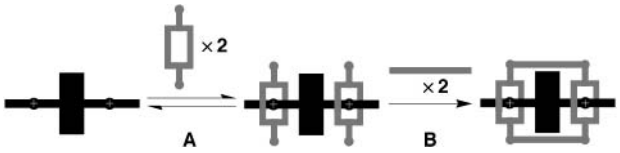
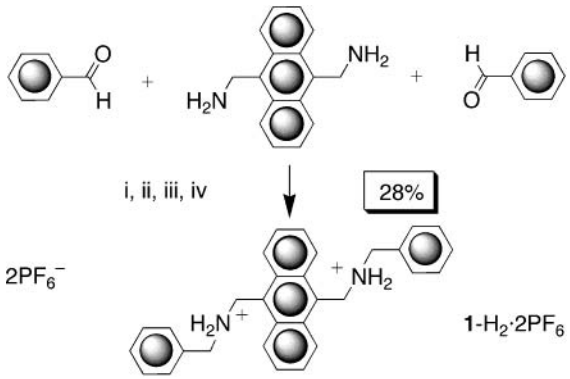


Figure 1. A schematic representation of the approach to be taken in the construction of a new class of interlocked molecular compounds. The "+" sign on the scaffold represents NH_2^+ centers, and the rectangles introduced at step **A** are crown ethers with [24]-crown-8 constitutions. In step **A**, noncovalent bonding leads to complexes (pseudorotaxanes) that are covalently linked in step **B**.

schematically illustrates the formation of an interlocked molecule containing (i) a linear rigid scaffold comprising a rod with a centrally located bulky core and (ii) a net-like macropolycycle built of two macrocycles joined by two rigid linkers. The first step toward making such an interlocked molecular compound is to identify and synthesize a ditopic scaffold and then demonstrate that it will form a 2:1 complex—namely, a [3]pseudorotaxane—which can subsequently be functionalized in order that the rigid linkers can be introduced during the covalent modification of the initially formed supermolecule. In this manner, the macrocycles can be covalently linked together after self-assembly of the [3]-pseudorotaxane, thus trapping the scaffold—which templates the formation of the net—inside the net.

The well-established[11] recognition motif that leads to the threading of secondary dialkylammonium centers through crown ethers, such as dibenzo[24]crown-8 (DB24C8), was chosen as the starting point for this research. Herein, we (a) report the synthesis (Scheme 1) of a bisammonium scaffold

Scheme 1[a]



[a] Reagents and conditions: i, PhMe, reflux; ii, $NaBH_4$, MeOH, H_2O, rt; iii, HCl, H_2O, rt; iv, NH_4PF_6, H_2O, rt.

based on a 9,10-anthracenyl core and (b) demonstrate its ability to form a [3]pseudorotaxane with DB24C8, both in the solid state and in solution.

9,10-Bis(aminomethyl)anthracene[12] was condensed with 2 equiv of benzaldehyde. The resulting diimine was reduced to yield the diamine which was protonated and subjected to counterion exchange to give the salt **1**-H_2·$2PF_6$[13] as a crystalline compound. X-ray quality single crystals of the [3]pseudorotaxane[14] $[(DB24C8)_2$·**1**-$H_2][PF_6]_2$ were obtained by vapor diffusion of *i*-Pr_2O into a 2:1 solution (CH_2Cl_2/

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(13) Synthetic details for, and characterization data relating to compounds **1** and **1**-H_2·$2PF_6$, can be found in the Supporting Information.

(14) The crystalline 2:1 complex was also examined using FABMS. In addition to a major peak at *m*/*z* 865, corresponding to a [2]pseudorotaxane that has lost two of its PF_6^- counterions, there is a significant peak at *m*/*z* 1459, corresponding to the [3]pseudorotaxane with the loss of one PF_6^- counterion, as well as a prominent peak at *m*/*z* 657, representing the doubly charged [3]pseudorotaxane without any counterions. A similar fragmentation pattern has been reported for a related [3]pseudorotaxane in which the 9,10-anthracenyl core of **1**-H_2^{2+} is replaced by a *p*-phenylene unit. See: ref 11b.

$MeNO_2$, 1:1) of DB24C8 and **1**-H_2·$2PF_6$. The X-ray analysis[15] of these crystals revealed (Figure 2) the anticipated

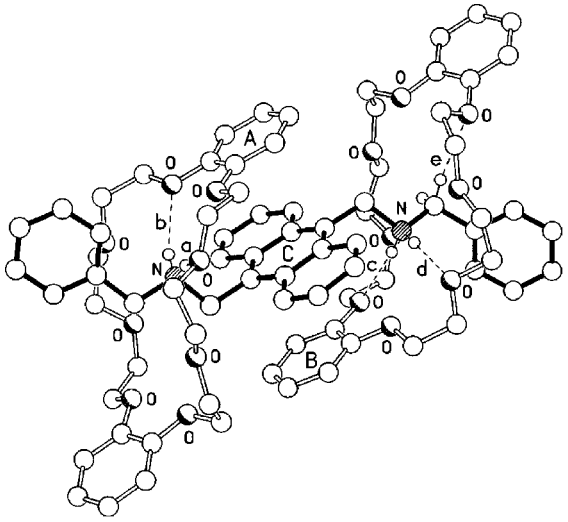

Figure 2. Solid-state superstructure of $[(DB24C8)_2$·**1**-$H_2]^{2+}$. The hydrogen bonding geometries are X−H···O, H···O distances (Å) and X−H···O angles (deg); (a) 2.94, 2.09, 159; (b) 3.05, 2.23, 152; (c) 3.17, 2.28, 174; (d) 3.00, 2.12, 167; (e) 3.41, 2.45, 172. The centroid···centroid and mean interplanar separations between ring A and ring C and between ring C and ring B are 3.72, 3.39 and 3.61, 3.45 Å, respectively.

threading of the benzylammonium portions of the dication through the centers of the two DB24C8 macrocycles to create a near C_i symmetric superstructure geometry. Intercomponent bonding is via a combination of N^+−H···O and C−H···O hydrogen bonds as well as $\pi-\pi$ stacking between one of the catechol rings of each of the DB24C8 units and the central portion of the anthracene unit of the dication **1**-H_2^{2+}. There are no interactions involving the terminal phenyl rings.

The complexation of **1**-H_2·$2PF_6$ by DB24C8 in CD_3CN solution has also been investigated by ^{1}H NMR spectroscopy starting with different stoichiometric ratios of macrocyclic polyether to scaffold. Since the equilibrium kinetics between complexed and uncomplexed species are slow on the ^{1}H NMR time scale at 400 MHz, sharp peaks for these species are observed (Figure 3) in the spectrum. In the ^{1}H NMR spectrum, obtained using a solution that is 50 mM in DB24C8 and 10 mM in **1**-H_2·$2PF_6$, only signals for the [3]-pseudorotaxane (2:1 complex) can be observed easily. Conversely, a solution that is 10 mM in DB24C8 and 50 mM in **1**-H_2·$2PF_6$ gives rise to an ^{1}H NMR spectrum of, almost exclusively, the [2]pseudorotaxane (1:1 complex). An

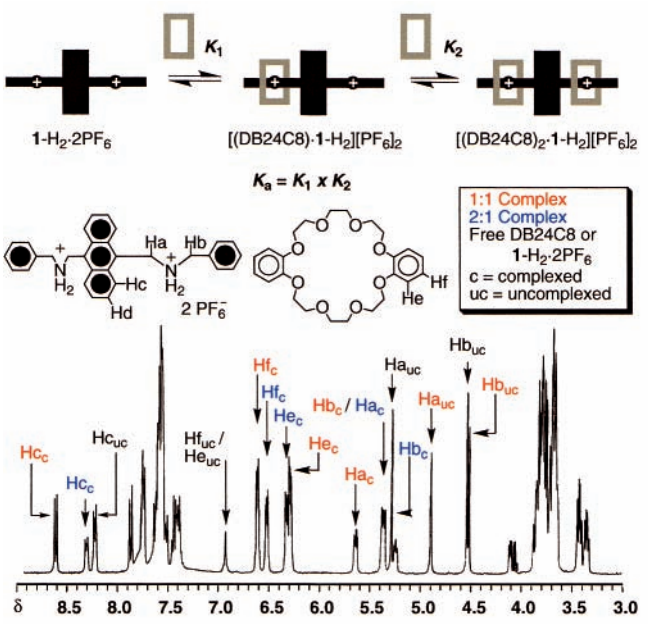

Figure 3. Partial ^{1}H NMR spectrum (400 MHz) of a 1:1 mixture of DB24C8 and **1**-H_2·$2PF_6$ (10 mM each) in CD_3CN at 298 K. The subscripts "c" and "uc" denote signals arising from protons that are complexed and uncomplexed, respectively. The resonances for the protons corresponding to the 1:1 $[(DB24C8)$·**1**-$H_2][PF_6]_2$ complex—which contains one complexed and one uncomplexed NH_2^+ center—are labeled in red while those corresponding to the 2:1 complex are in blue.

equimolar mixture (10 mM each) of DB24C8 and **1**-H_2·$2PF_6$ in CD_3CN gives rise to a ^{1}H NMR spectrum with all four species—the 1:1 and 2:1 complexes, in addition to the uncomplexed species—present. In this spectrum, downfield shifts, relative to the signals for **1**-H_2·$2PF_6$, are observed for the methylene protons (Ha and Hb) adjacent to the NH_2^+ centers in the 2:1 ($\Delta\delta = +0.02$ and $+0.83$ ppm for Ha_c and Hb_c, respectively) and 1:1 complexes ($\Delta\delta = +0.20$ and $+0.93$ ppm for Ha_c and Hb_c, respectively). Similar downfield shifts have been reported[16] for the resonances of the methylene protons in the ^{1}H NMR spectra of pseudorotaxanes formed between DB24C8 and a number of substituted dibenzylammonium cations, including the sterically analogous *N*-(9-anthracenylmethyl)-*N*-benzylammonium cation.[17] It is also evident that the downfield shift for the benzylic methylene protons (Hb) is more dramatic than that of the anthracenyl methylene protons (Ha). This larger shift for the former suggests that, upon complexation with DB24C8, the benzylic methylene protons interact with the crown ether through C−H···O hydrogen bonds. In the 1:1 complex, the signal for the anthracenyl methylene protons (Ha_{uc}) of the free ammonium site is shifted upfield, possibly as a

(15) Crystal data for $[(DB24C8)_2$·**1**-$H_2][PF_6]_2$·$2MeNO_2$: $C_{78}H_{94}N_2O_{16}$·$2PF_6$·$2MeNO_2$, $M = 1727.6$, monoclinic, $P2_1$ (No. 4), $a = 12.044(2)$, $b = 25.471(2)$, $c = 14.632(2)$ Å, $\beta = 113.52(1)°$, $V = 4115.7(8)$ Å^3, $Z = 2$, $D_c = 1.394$ g cm^{-3}, μ(Cu Kα) = 13.5 cm^{-1}, $F(000) = 1812$, $T = 183$ K; clear needles, 0.67 × 0.43 × 0.30 mm, refined based on F^2 to give $R_1 = 0.062$, $wR_2 = 0.163$ for 6389 independent observed absorption corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \le 128°$] and 1091 parameters. The absolute chirality of the structure was determined by an *R*-factor test [$R_1^+ = 0.0615$, $R_1^- = 0.0626$].

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consequence of shielding from a π-stacked catechol ring, while the signal for the other anthracenyl methylene protons (Ha_c) in the bound ammonium ion is shifted downfield (vide supra), presumably as a result of being encircled by a DB24C8 macrocycle. However, on complexation with a second macrocycle to give the 2:1 complex, the chemical shift changes are reversed so that the resonance corresponding to Ha_c is only slightly downfield (vide supra) from that for the free dication **1**-H_2^{2+}. The benzylic methylene protons (Hb) show a similar behavior. In summary, the chemical shifts of Ha and Hb depend on the conformations adopted by the DB24C8 macrocycles in the 1:1 and 2:1 complexes wherein the catechol rings can shield or not shield Ha and Hb as the case might be, while C−H···O interactions with the macrocycles has a direct and profound effect. It is also of interest to note that the resonances for the catechol ring protons (He and Hf) in DB24C8 are shifted upfield ($\Delta\delta = -0.65, -0.60$ ppm for He and $\Delta\delta = -0.30$ and -0.40 ppm for Hf) in the 1:1 and 2:1 complexes, respectively, as a consequence of their stacking with the anthracene core.

In solutions of known concentrations, the absolute concentrations of both complexes (2:1 and 1:1), DB24C8, and **1**-H_2·$2PF_6$ can be determined from integrations performed on resonances for suitable probe protons in the ^{1}H NMR spectra and thus the binding constants can be calculated[18] by the single point method. The overall association constant K_a for two DB24C8 macrocycles in equilibrium with **1**-H_2·$2PF_6$ was found[19] to be 7.4×10^6 M^{-2} in CD_3CN/CD_3NO_2 (1:1) and 1.4×10^6 M^{-2} in CD_3CN. The equilibrium constant, K_1, for the binding of one DB24C8 to one NH_2^+ center in the dication **1**-H_2^{2+} was calculated to be 6200 M^{-1} in CD_3CN/CD_3NO_2 (1:1) and 2800 M^{-1} in CD_3CN. Likewise K_2, the equilibrium constant for the binding of a second DB24C8 to the 1:1 complex, was found to be 1200 M^{-1} in CD_3CN/CD_3NO_2 (1:1) and 510 M^{-1} in CD_3CN. The $\Delta G°$ values arising from K_a, K_1, and K_2 (1:1 CD_3CN/CD_3NO_2) are -9.4, -5.2, and -4.2 kcal mol^{-1}, respectively. The fact that K_1 for the formation of the [2]pseudorotaxane is over five times larger than K_2 suggests that a small amount of negative cooperativity[20] is in operation for the binding of the second macrocycle. It appears that binding of the first macrocycle by an NH_2^+ center in the **1**-H_2^{2+} dication decreases very slightly the affinity of the other NH_2^+ center for the second macrocycle. A possible reason for this slight damping effect could be the fact that in the 1:1 complex both catechol rings in the macrocycle can $\pi-\pi$ stack with the anthracene core if it adopts a U-shaped conformation,[21] whereas when two macrocycles are bound to the dication **1**-H_2^{2+} in the 2:1 complex, only two of the four catechol rings can interact relatively strongly with the anthracene core. Nonetheless, despite the small amount of negative cooperativity, we have established that dications of the type **1**-H_2^{2+} do bind to DB24C8. With appropriately functionalized crown ethers, we hope to construct interlocked molecules of the type depicted in Figure 1.

We have noted that monofunctionalization of the catechol rings[22] of DB24C8—the obvious sites for functionalizing this macrocycle—will reduce its symmetry and therefore result in the production of a number of different isomeric compounds. Since this situation increases the complexity of the synthesis using DB24C8 macrocycles, we are looking to develop[23] macrocycles that retain the [24]crown-8 constitution yet can be functionalized in a symmetrical manner.

Acknowledgment. We thank the National Science Foundation for their support of this research.

Supporting Information Available: Synthetic procedure and relevant characterization data for **1**-H_2·$2PF_6$ and crystal data for [(DB24C8)$_2$·**1**-H_2][PF_6]$_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Association constants given for 1:1 DB24C8 and **1**-H_2·$2PF_6$ [CD_3CN/CD_3NO_2 (1:1)] were obtained at concentrations of 7.0 and 3.5 mM, respectively, while the K_a value given for CD_3CN was an averaged value for two different experiments, (a) 10 and 5 mM and (b) 20 and 10 mM in DB24C8 and **1**-H_2·$2PF_6$, respectively. The overall association constant, $K_a = K_1 \times K_2$ where K_a = [2:1]/([DB24C8][scaffold]), K_1 = [1:1]/([DB24C8][scaffold]), and K_2 = [2:1]/([1:1][DB24C8]).

(20) In a system where a substrate has two identical binding sites, $K_1 = 4K_2$ if the binding sites are independent. A system is positively cooperative if K_1/K_2 is smaller than 4, noncooperative if equal to 4, and negatively cooperative if greater than 4. See ref 12.

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(22) For an example of an asymmetric monofunctionalized DB24C8 derivative that results in diastereoisomeric mixtures of complexes, see: Ashton, P. R.; Baxter, I.; Cantrill, S. J.; Fyfe, M. C. T.; Glink, P. T.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1294−1297.

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