CH_2Cl_2 at -5 °C (-40 °C for *cis*-**6**-d_3). The butenes were in 30–50% excess, and the end of the reaction was indicated by complete decolorization of the reaction mixture (within a few minutes to 1 h). The ^1H NMR spectra of PTAD ene adducts with *cis*-**6**-d_3 and *trans*-**6**-d_3 are shown in Figure 4. MS calcd for *cis*-**6**-d_3-PTAD, $C_{12}H_{10}D_3N_3O_2$, 234.1196, found 234.1190. MS calcd for *trans*-**6**-d_3-PTAD, $C_{12}H_{10}D_3N_3O_2$, 234.1196, found 234.1197. Isobutylene-d_3-PTAD ene isomeric adducts: ^1H NMR δ 1.65 (s, CH_3), 4.05 (s, CH_2), 4.85 (d, J = 2 Hz, $=CH_2$), 7.45 (m, Ph); MS calcd for $C_{12}H_{10}D_3N_3O_2$: 234.1196, found 234.1208.

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Self-Assembly of a Threaded Molecular Loop

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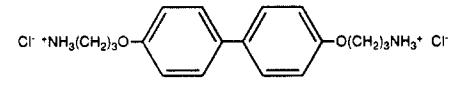
Abstract: An efficient (71% yield) synthesis of a threaded molecular loop is described. The synthetic approach is notable in that it is a template-directed self-assembly process in aqueous solution. The structure of the threaded molecular loop is unprecedented since it is held intact solely by noncovalent interactions. The high yield, mild conditions, and convergent nature of the assembly process suggest that a variety of highly organized supramolecular entities can be efficiently prepared from appropriately designed subunits via noncovalent forces.

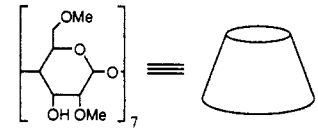
Noncovalent attractive forces are commonly employed in biological systems to drive the assembly of highly organized supramolecular entities (e.g., membranes, ribosomes, and multicomponent enzyme complexes) from relatively simple subunits.[1] In addition, the self-assembly phenomenon is proposed to have been an essential component in the molecular events that comprised protobiogenesis.[2] It is apparent that a process that plays such a fundamentally important role in biology must offer several synthetic advantages. These include (1) a reduction in structural errors in the final product by rejection of defective subunits during self-assembly, (2) synthetic economy by virtue of the convergent nature of the assembly process, and (3) facile formation of the stable end product, facilitated by rapidly established noncovalent interactions. Clearly, such attractive features should prove useful in the synthesis of artificial biologically relevant assemblies as well. Indeed, we have recently achieved an efficient template-driven self-assembly of a prototype for a heme-dependent protein mimic.[3] In addition, the advantages of the multicomponent assembly process should be useful in the construction of compounds that have no counterpart in nature. In the present paper, we describe the self-assembly of a threaded molecular loop.[4]

The diammonium salt **1** was synthesized from biphenyldiol by alkylation of the hydroxyl moieties with *N*-(3-bromopropyl)-phthalimide (71.5%) and subsequent hydrazinolysis (83.0%). The



1

resultant free diamine was dissolved in trifluoroethanol and, upon addition of concentrated hydrochloric acid, precipitated out of solution as the desired diammonium salt in quantitative yield. In spite of its doubly charged character, compound **1** is only sparingly soluble in aqueous solution. However, upon addition of 1.5 equiv of heptakis(2,6-*O*-methyl)-β-cyclodextrin (Me-CD, **2**),[5,6] the diammonium salt was rendered freely water soluble. The radical change in solubility signals the likely formation of an inclusion complex (**3**; since primary ammonium ions tend to be well solvated, we suspect that it is the free amine of **1** that threads the cavity of Me-CD). ^1H NMR (300 MHz, D_2O as solvent) confirmed the formation of **3**, since compound **1** induces upfield chemical shifts for the Me-CD C_3 (18 Hz) and C_5 (102 Hz) protons. Such chemical shifts are a generally recognized manifestation of cyclodextrin-based inclusion compound formation.[7]



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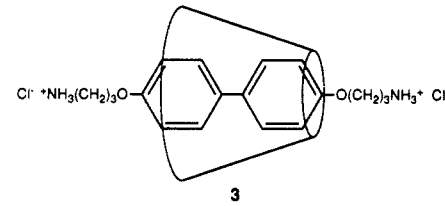

3

Species **3** (a threaded molecular loop) was sequestered at pH 7.0 by the addition of an aqueous solution of sodium tetraphenylboron (4.0 equiv). The resultant precipitate, which formed instantaneously, proved to be species **4**. The structure of this complex bears resemblance to the class of compounds known as rotaxanes, threaded molecular loops whose structural integrity is maintained by the presence of steric impediments. The structural assignment of **4** is based on the following considerations: (1) ^1H and ^{13}C NMR of the complex are consistent with a compound that contains the requisite number of components in the proper ratios [tetraphenylboron (two subunits), Me-CD (one subunit), and compound **1** (one subunit)]. (2) Fast atom bom-

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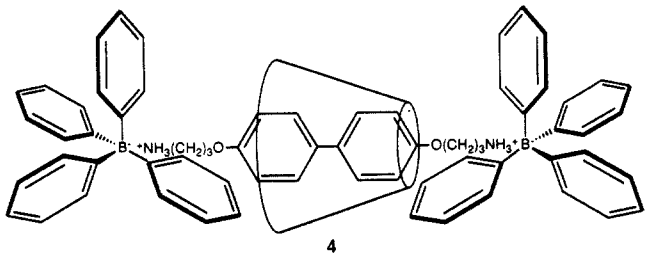

4

bardment mass spectrometry produced several high molecular weight species that are chemically reasonable fragments of **4** (MW 2271 g/mol). (3) Thin-layer chromatography of the complex on cellulose analytical plates (80:20, benzene/acetone) revealed a single spot which was UV-active ($R_f = 0.5$). In contrast, the free Me-CD ($R_f = 0.0$), diammonium salt **1** ($R_f = 0.0$), and sodium tetraphenylboron ($R_f = 1.0$) displayed vastly different migratory aptitudes in this system.[8] (4) NOE experiments in DMSO-d_6 confirmed that the diammonium salt is closely associated with the Me-CD component in **4**. Irradiation of the aromatic protons ortho to the ether linkage resulted in a dramatic reduction (−11%) in the combined C_3 and C_5 proton resonances of the Me-CD moiety. Similarly, irradiation of the protons meta to the ether linkage produced a pronounced effect (−17%) on the resonances of the same nuclei. The observed negative NOEs are most likely a consequence of the relatively large size of the complex.[9]

Interestingly, the complex **4** appears to be relatively stable in acetone, as determined by thin-layer chromatography (vide supra). We do not observe the formation of free cyclodextrin, in spite of the fact that acetone and the corresponding chromatography eluent (benzene/acetone, 80:20) are not conducive to complex formation. Furthermore, ammonium tetraphenylboron salts are known to be primarily solvent-separated ion pairs in polar aprotic solvents.[10] We do observe the dissociation of the cyclodextrin component from the biphenyl moiety when the complex is heated in acetone at reflux. This suggests that a barrier does exist which precludes loss of the cyclodextrin molecular loop. One possibility is that the positively charged ammonium salt functional groups are solvated to such an extent in acetone that they cannot readily pass through the cyclodextrin cavity. Indeed, we found that, upon treatment of **4** in acetone with a trace of triethylamine, the biphenyl thread dissociates from the cyclodextrin loop.

A noteworthy aspect of the self-assembly process is the high yield (71.2%) in which the threaded molecular loop was obtained. We are unaware of any rotaxane synthesis that exceeds 30% (indeed, yields are rarely above 5%).[4,6] This supports the notion that template-directed self-assembly processes, based upon noncovalent interactions, are unusually facile.

In summary, we have constructed a rotaxane-like molecule in aqueous media, at room temperature, and in high yield via noncovalent interactions. We therefore conclude that such interactions not only are useful in promoting the formation of transient complexes but can drive the assembly of stable, highly organized entities as well.

Experimental Section

All commercial grade reagents were employed without purification. DMSO was distilled under reduced pressure from CaH_2. Tetrahydrofuran was distilled from sodium/benzophenone ketyl. All experiments were performed under a nitrogen atmosphere, except for the self-assembly of **4**, which was conducted in air. NMR spectra were recorded on a Varian Gemini-300 instrument. DMSO-d_6 and $CDCl_3$ were employed as NMR solvents, with tetramethylsilane serving as internal standard. Chemical shifts are reported in parts per million. Mass spectra were recorded on a VG-70SE mass spectrometer.

Preparation of *N,N'*-(4,4'-Biphenyldiyldioxydi-1,3-propanediyl)bis(phthalimide). 4,4'-Biphenyldiol (1.15 g, 2.14 mmol) in 2.0 mL of DMSO was added dropwise to a dispersion of sodium hydride (0.17 g, 7.1 mmol) in DMSO (9 mL) at room temperature. After 3 h, a solution of *N*-(3-bromopropyl)phthalimide (1.15 g, 4.3 mmol) in DMSO (3.5 mL) was added to the reaction mixture and stirred for 72 h at 25 °C. The mixture was carefully poured into 200 mL of ice water, and the resulting solid was collected and dissolved in chloroform. The solution was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure, to provide a light yellow solid. This material was recrystallized from ethyl acetate, to give a white fluffy material (0.44 g, 71.5%), mp 190–193 °C. Thin-layer chromatography (silica gel): $R_f = 0.4$, 40:60 ethyl acetate/hexanes. ^{1}H NMR (DMSO-d_6): 7.85-7.78 (m, 8 H), 7.43 (d, 4 H), 6.81 (d, 4 H), 4.01–3.97 (t, 4 H), 3.75–3.71 (t, 4 H), 2.06–1.98 (p, 4 H). ^{13}C NMR ($CDCl_3$): 169.1, 158.5, 134.5, 134.2, 132.8, 128.2, 123.8, 115.3, 66.1, 35.8, 28.6. FABMS: *m/z* 560.6

Preparation of 3,3'-(4,4'-Biphenyldiyldioxy)bis(propylamine) and the Diammonium Salt 1. *N,N'*-(4,4'-Biphenyldiyldioxydi-1,3-propanediyl)-bis(phthalimide) (0.10 g, 0.34 mmol) was suspended in tetrahydrofuran (3 mL). The mixture was warmed to 50 °C, and upon addition of hydrazine hydrate (2.0 mL, 64.2 mmol), the solution became homogeneous. The reaction mixture was subsequently heated to reflux for 10 h. The solution was then cooled to room temperature, and 1.5 mL of distilled water was added dropwise. The mixture was cooled in an ice bath. After 4 h, the product appeared as platelets, which were filtered, washed with 50 mL of tetrahydrofuran, and placed under high vacuum overnight (yield 0.045 g, 83%). Mp: 161–164 °C. ^{1}H NMR ($CDCl_3$): 7.46 (d, 4), 6.93 (d, 4), 4.07–4.03 (t, 4), 2.91–2.89 (t, 4), 1.95–1.86 (m, 4). ^{13}C NMR (DMSO-d_6): 158.2, 132.8, 127.5, 119.8, 64.7, 38.6, 32.5. FABMS: *m/z* 301.0. The free diamine (0.050 g, 0.134 mmol) was added to 2,2,2-trifluoroethanol (5 mL), and the mixture was warmed in a hot water bath until a homogeneous solution was obtained. Upon the dropwise addition of concentrated hydrochloric acid, the desired diammonium salt precipitated in quantitative yield.

Preparation of the Threaded Molecular Loop 4. Ten milligrams (0.02 mmol) of **1** was suspended in 2 mL of water. Me-CD (42 mg, 0.032 mmol) was added portionwise to the above suspension with vigorous stirring, and a clear solution was obtained. The pH of the mixture was then adjusted to 7.0 with 0.02 N sodium hydroxide. An aqueous solution (2.3 mL) of sodium tetraphenylboron (36 mg, 0.105 mmol) was introduced in a dropwise fashion, and the resulting white precipitate was collected by centrifugation and dried under high vacuum overnight. Yield: 43 mg (71.2%). The compound proved to be pure as assessed by NMR, combustion analysis, and thin-layer chromatography. ^{1}H NMR (DMSO-d_6): 7.13 (br), 6.88 (t), 6.75 (t) (40 H, phenyl of tetraphenylboron), 7.49 (d, 4 H, ortho H of **1**), 6.94 (d, 4 H, meta H of **1**), 4.93 (br, 7 H, anomeric H of Me-CD), 4.03 (t, 4 H, OCH_2 of **1**), 3.63–3.69 (m, 14 H, H_3 and H_5 of Me-CD), 3.51 (br, 7 H, H_6 of Me-CD), 3.45 (s, 21 H, C_2-OCH_3 of Me-CD), 3.30 (br, 7 H, H_4 of Me-CD), 3.26 (s, 21 H, C_6-OCH_3 of Me-CD), 3.14–3.18 (dd, 7 H, H_2 of Me-CD), 2.90 (t, 4 H, $CH_2NH_3^+$ of **1**), 1.92 (m, 4 H, $OCH_2CH_2CH_2NH_3^+$ of **1**). ^{13}C NMR (DMSO-d_6): 163.3–165.5 (q, BC of tetraphenylboron), 158.2 (aromatic CO of **1**) 137.5, 125.7, 122.0 (unsubstituted C of tetraphenylboron), 133.6 (aromatic bridge C of **1**), 127.7 (aromatic ortho C of **1**), 115.9 (aromatic meta C of **1**), 102.3 (C_1 of Me-CD), 83.7 (C_4 of Me-CD), 81.9 (C_2 of Me-CD), 72.9 (C_3 of Me-CD), 71.1 (C_6 of Me-CD), 69.9 (C_5 of Me-CD), 64.5 (OCH_2 of **1**), 59.6 (C_2-OCH_3 of Me-CD), 58.1 (C_6-OCH_3 of Me-CD), 36.1 (CH_2N of **1**), 27.5 ($OCH_2CH_2CH_2N$ of **1**). FABMS: *m/z* 2235.5 ($M + H^+ - CH_3OH$), 1632.3 [$M + H^+ - 2B(C_6H_5)_4$], 1616.6 [$M + H^+ - 2B(C_6H_5)_4 - NH_3$], 1515.5 [$M + H^+ - 2B(C_6H_5)_4 - 2C_3H_9N$]. Combustion analysis: found (calcd for $C_{122}H_{162}N_2O_{17}B_2 \cdot H_2O$): C, 63.98 (63.88); H, 7.25 (7.06).

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Registry No. **1**, 124992-42-3; **1** free base, 98397-26-3; **2**, 51166-71-3; **3**, 124992-43-4; **4**, 124992-44-5; 4,4'-biphenol, 92-88-6; *N*-(3-bromopropyl)phthalimide, 5460-29-7; *N,N'*-(4,4'-biphenyldiyldioxydi-1,3-propanediyl)bis(phthalimide), 124992-45-6.

(8) Formation of $(C_6H_5)_4B \cdot \mathbf{1} \cdot B(C_6H_5)_4$ during the assembly of the threaded molecular loop can be ruled out on the following grounds: (a) The diammonium salt is nearly insoluble in water (1 mg of **1** will dissolve in 3 mL of water only after extensive sonication). Consequently, under the self-assembly conditions employed, only Me-CD-entrapped **1** should be present in solution. (b) The ^{1}H NMR spectrum of the threaded molecular loop integrates to 1:1:2 Me-CD:**1**:tetraphenylboron. (c) $(C_6H_5)_4B \cdot \mathbf{1} \cdot B(C_6H_5)_4$ is not observed in the TLC of the rotaxane; R_f(rotaxane) = 0.5; $R_f[(C_6H_5)_4B \cdot \mathbf{1} \cdot B(C_6H_5)_4] = 0.44$.

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