Novel Pseudorotaxane-Terminated Dendrimers: Supramolecular Modification of Dendrimer Periphery**

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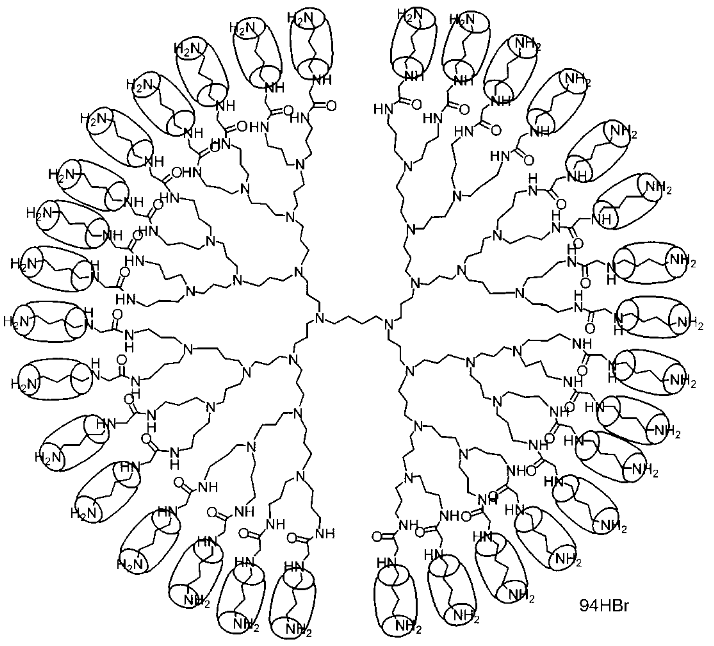
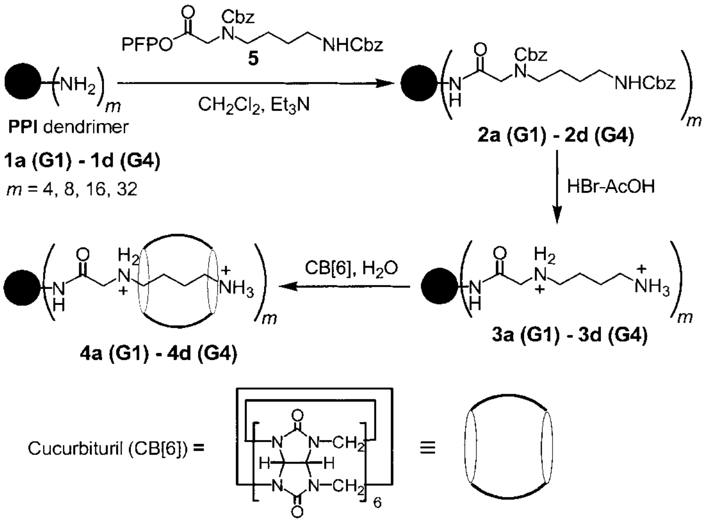
The chemistry of dendrimers is blossoming into an exciting field of research. A wide variety of dendrimers with different cores, branches, and end groups have been synthesized and applied in different areas, such as in drug delivery, catalysis, light-energy harvesting, and sensors, during the past decade.[1] Since many of the applications exploit functional groups at the periphery, the modification of terminal groups of dendrimers is of enormous current interest.[2] Most of these modifications are achieved through formation of a covalent bond to the terminal groups. However, modifications using noncovalent bonds/interactions[3] are more attractive as they offer many advantages, including reversibility. In fact, noncovalent bonds/interactions have been widely exploited in the self-assembly of supramolecular interlocked structures such as rotaxanes and catenanes.[4] Our interest in interlocked structures led us to develop a simple and efficient method to synthesize polyrotaxanes and molecular necklaces.[5] A key to the success of this method is to use cucurbituril (CB[6])[6, 7] as a molecular "bead" which has an ability to form remarkably stable pseudorotaxanes with "strings" derived from diaminoalkanes through multiple noncovalent interactions. Encouraged by this success, we decided to explore the formation of pseudorotaxanes at the termini of dendrimers with the aim of providing an interesting way of modifying the dendrimer exterior by noncovalent interaction. Herein we report the formation of novel pseudorotaxane-terminated dendrimers and their characteristics (Scheme 1).[8]



Scheme 1. Pseudorotaxane-terminated dendrimer **4d** (G4).

The synthesis of pseudorotaxane-terminated dendrimers **4a**(G1) – **d**(G4) is achieved in three steps (Scheme 2). Reaction of commercially available poly(propyleneimine) (PPI) dendrimers **1a**(G1) – **d**(G4) with **5**, which is easily synthesized from mono-Cbz-protected diaminobutane,[9] followed by column chromatography affords dendrimers **2a**(G1) – **d**(G4), respectively, in good yield. The deprotection of the diaminobutane units in dendrimers **2a** – **d** with HBr-AcOH produces dendrimers **3a**(G1) – **d**(G4) containing protonated diaminobutane units at the termini. Treating **3a** – **d** with CB[6] affords the target pseudorotaxane-terminated dendrimers **4a**(G1) – **d**(G4). The number of molecular beads bound in **4** is 4, 8, 16, and 32 for **4a** – **4d**, respectively.



Scheme 2. Synthesis of pseudorotaxane-terminated dendrimers **4a**(G1) – **d**(G4). All the internal imine nitrogen atoms of **3** and **4** are also protonated. Abbreviations: PFP = pentafluorophenyl; Cbz = benzyloxycarbonyl.

Figure 1 compares ^{1}H NMR spectra of the third generation dendrimers **3c** and **4c**. Note that the signals for the methylene groups (● and ▲) of the terminal diaminobutane units in **4c** which are located inside CB[6] are shifted upfield relative to those in **3c** while that of the methylene unit (*) adjacent to the carbonyl group in **4c** is shifted downfield. These observations are consistent with the structure of **4c** having pseudorotaxane units at the periphery of the dendrimers.[6] A similar NMR spectral behavior is observed in other generation pseudorotaxane-terminated dendrimers **4**.

Electrospray ionization mass spectrometry was successfully employed in the characterization of **2** and **3**. The observed

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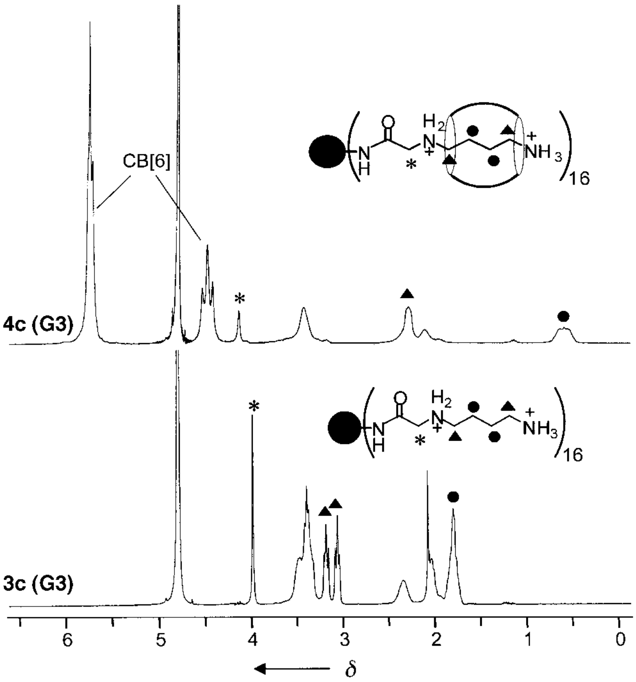

Figure 1. Comparison of the ^{1}H NMR spectra of the third-generation dendrimers **3c** and **4c**.

masses of the dendrimers are in excellent agreement with the calculated ones. The first-generation pseudorotaxane-terminated dendrimer **4a** also gave reasonable mass data.[9] However, we failed to obtain decent mass spectra for the pseudorotaxane-terminated dendrimer of higher generations (**4b**–**d**). This result is presumably a consequence of the high molecular weights and charges of the pseudorotaxane-terminated dendrimers: for example, the third-generation dendrimer **4c** with 16 molecular beads (CB[6]) and 46 counterions (Br$^-$), which balance the 46 positive charges of the fully protonated dendrimer body, has a molecular weight of 23408 Da. Similar difficulty in characterization of dendrimers with high molecular weights and charges by mass spectrometry has been reported.[2g, 10]

To understand the effect of threading CB[6] molecular beads onto the terminal groups of the dendrimer structures we decided to perform molecular dynamic (MD) simulation on the third-generation dendrimers **3c** and **4c**.[11] Figure 2 shows typical conformations of these dendrimers obtained by MD simulation. The MD simulation results indicate that there is some backfolding of the terminal groups before the molecular beads are threaded onto them. Some aggregation of the terminal groups in each dendron is also observed. However, when CB[6] molecular beads are threaded onto the terminal groups they adopt a fully extended conformation and segregate from each other. This conformational change increases the overall size of the third-generation dendrimers from 40 ~ 41 Å (for **3c**) to 44 ~ 49 Å (for **4c**). These large terminal pseudorotaxane units appear to form a rigid shell at the exterior of the dendrimer, which may behave as a barrier isolating the inner space of the dendrimer from the bulk solvents.

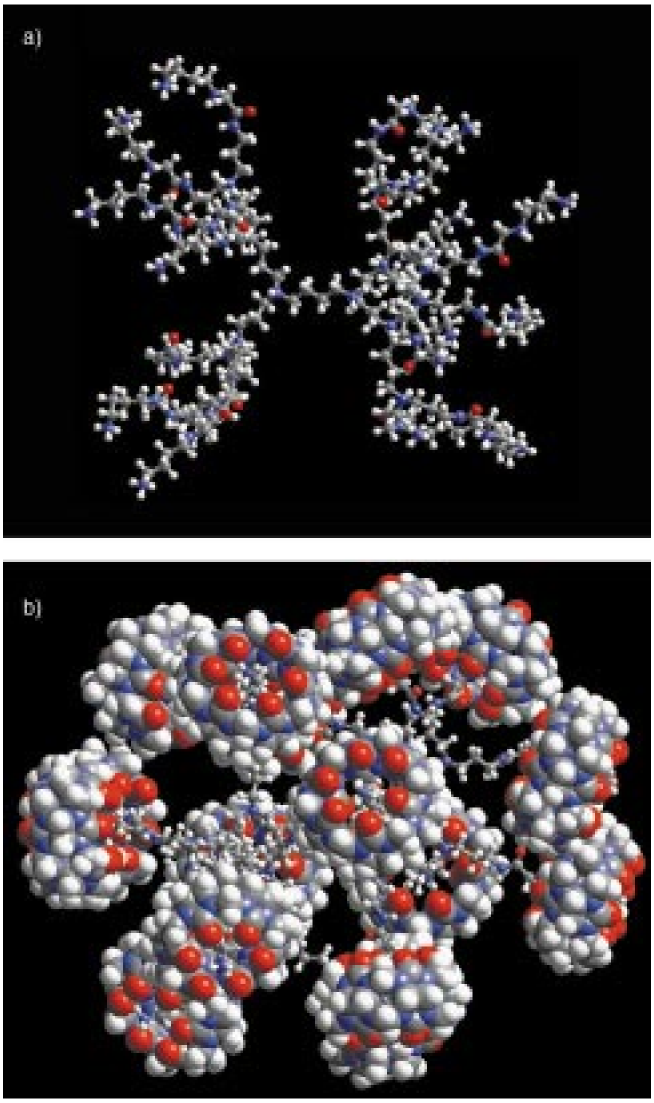

Figure 2. Structures of the third-generation dendrimers **3c** (a) and **4c** (b) obtained by MD simulation (after 520 ps). The dendrimer frameworks are represented with ball-and-stick models and the CB[6] molecular beads with a space-filling model. Color codes: oxygen: red; nitrogen: blue; carbon: gray; hydrogen: white. Solvent molecules and counterions are not shown.

The increased conformational rigidity arising from the threading of molecular beads at the dendrimer exterior has been confirmed by NMR spectroscopy. The ^{1}H and ^{13}C NMR signals of pseudorotaxane-terminated dendrimers **4** are broader than those of **3**. The line broadening becomes more pronounced in the higher generation dendrimers, which is attributable to a diminished molecular motion of the dendritic shells. ^{1}H NMR spin-lattice (T_1) relaxation measurements on **3** and **4** have been performed and the results are compared in Figure 3. The T_1 value for the methylene protons at the termini in **3** decreases slightly but steadily with increasing generations (Figure 3a). On the other hand, the T_1 value for the corresponding protons in **4** increases sharply with increasing generations (Figure 3b). Such an increase in the T_1 relaxation value with increasing generations indicates that the molecular motion in the outside dendritic shell of **4** resembles that in a solid phase.[15] This unusual behavior has been observed only once in a dendrimer with a highly congested exterior.[2i]

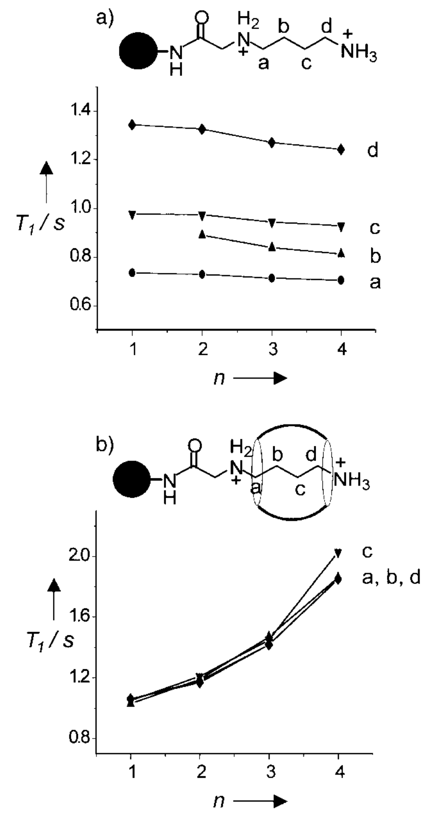

Figure 3. Generation (n) dependence of the ^{1}H NMR spin-lattice relaxation time (T_1) for the terminal diaminobutane unit of **3** (a) and **4** (b) in D_2O at 295 K. The proton relaxation data were recorded on a Bruker DRX500 at 500.23 MHz with a standard inversion–recovery pulse sequence.

In summary, we have synthesized novel pseudorotaxane-terminated dendrimers having a number of molecular beads threaded onto the periphery through noncovalent interactions. These pseudorotaxane-terminated dendrimers not only constitute a new class of topologically intriguing molecules but also provide a novel way of modifying the dendrimer exterior by noncovalent interactions. In addition, the large terminal pseudorotaxane units can form a rigid shell at the outer surface of the dendrimer which can potentially inhibit the escape of guest(s) trapped in the interior. If the beads can be de-threaded to make the exterior flexible once again and allow the escape of entrapped guests from the interior, such systems can potentially function as vehicles for translocating guests such as drug molecules. A preliminary experiment shows that all or a part of CB[6] molecular beads of **4** are de-threaded upon treatment with a base. We are currently investigating the threading/de-threading mechanisms as well as other properties of these novel dendrimers.

Experimental Section

Typical procedures for **2**, **3**, and **4** are illustrated with the third-generation dendrimers **2c**, **3c**, and **4c**.

2c: Dendrimer **1c** (124 mg, 0.074 mmol) and triethylamine (0.17 mL, 1.24 mmol) were added to activated ester **5** (0.7 g, 1.2 mmol) in dichloromethane (20 mL). The resulting solution was stirred for 24 h at room temperature. After addition of dichloromethane (50 mL) the solution was washed with water and $NaHCO_3$ solution, dried, and concentrated. Purification by column chromatography using EtOAc and then CH_2Cl_2:MeOH (1:1) containing 3% Et_3N as an eluent yielded the desired product **2c** (493 mg, 83%).

3c: A solution of **2c** (420 mg, 0.05 mmol) in 30% HBr–AcOH (10 mL) was stirred for 10 h at room temperature. Addition of diethyl ether (50 mL) to the solution precipitated **3c** (370 mg, 95%).

4c: CB[6] (128 mg, 0.13 mmol) was added in small portions to a solution of the dendrimer **3c** (50 mg, 6.7 μmol) in H_2O (30 mL) and the mixture was stirred for 10 h at room temperature. After excess cucurbituril was filtered, the volume of the solution was reduced to about 2 mL by evaporation. Addition of EtOH (30 mL) to the solution precipitated **4c** (152 mg, 97%).

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[11] All MD simulations were performed under constant-pressure periodic boundary conditions (NPT ensemble under PBC conditions) using the AMBER 5[12] suite of programs. The explicit solvent model of TIP3P[13] water was used. For each of the simulations, 46 Cl^- ions were added as counterions to neutralize the systems. We built a rectangular box of 5540 solvent molecules for **3c** and of 5991 solvent molecules for **4c** using the program XLEAP. The **3c** and **4c** systems are composed of 17398 and 20479 atoms, respectively. The SHAKE[14] procedure was employed to constrain all bonds involving hydrogen atoms. The time step of the simulations is 1 fs, with a nonbonded interaction cutoff of 8 Å. Details of the MD simulation will be reported elsewhere.

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Trinuclear Copper(I)-bipyridine Triskelion: Template/Bascule Control of Coordination Complex Stereochemistry in a Trefoil Knot Precursor**

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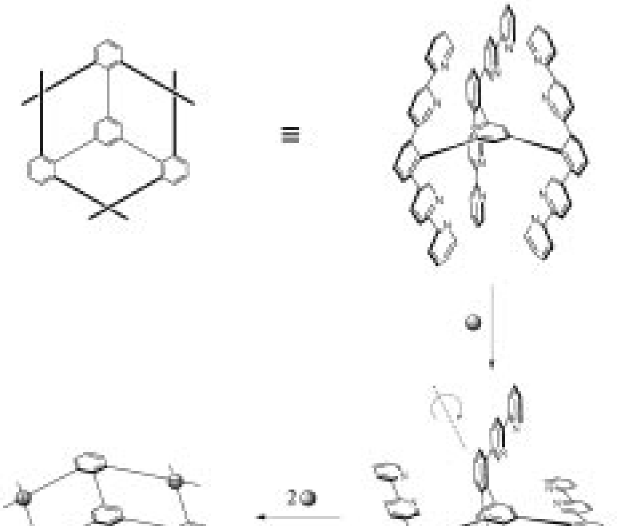
Projection of a knotted structure in the plane can be oriented to reveal a principal core "crossing structure" and a periphery of connecting arcs. From that perspective, the retrosynthesis of molecular knots and links can be divided into problems related to the control of a) macrocyclizations and b) stereochemistry of "crossing structures". Molecular designs that capitalize on symmetry and cooperativity lead to efficient control of stereochemistry.[1, 2] In the double helicates, the regular helical structure provides cooperative reinforcement for each new metallostereocenter to be of uniform configuration.[3] The identification of the double helix motif in a representation of the trefoil knot is key to understanding the rational synthesis where stereochemical control of helicity dictates the product identity, chirality, and yield.[4–9] An alternative representation of the trefoil knot has a D_3-symmetric core embedded within.[10] This core is also common to the Borromean link motif.[11–14] As such, synthesis and stereochemical control of an appropriate D_3 triskelion would provide a new class of stereoregular polynuclear coordination complexes and set the path to high-symmetry molecular knots and links.

Templating is a tried-and-true method for regulating the juxtaposition of molecular substructures.[15–20] A bascule mechanism pivots about the midpoint of a beam and couples the motion of the two ends such that as one end raises the other lowers.[21] Combining a tripodal template with tangential bascule beams readily evokes a D_3-symmetric construct in which neighboring beam-ends can cross. If these beam-ends were bidentate ligands, their crossing points would constitute binding sites for metals with tetrahedral ligand fields. Thus, emerges a design for a trinuclear copper(I)–bipyridine triskelion (**1**) (Scheme 1). The triskelion comes from three equivalents of a crescent-shaped polyaryl (**2**) and a 1,3,5-triethynyl core.



1-Cu$_3$

Scheme 1. Bascule mechanism for binding three metals in a triskelion. ● = Cu^I.

Synthesis of **1** depends heavily on the application of palladium-based Suzuki,[22–24] Stille,[25] and Sonagoshira[26] type aryl couplings (Scheme 2).[27–29] Although one begins from anisyl boronic acid (**3**) and 2,6-dibromopyridine to form 6-anisyl-2-bromopyridine (**4**), the coupling strategy rapidly builds much larger products. The stannylation of **4** occurs by reaction with butyllithium at −78 °C followed by quenching with trimethylchlorostannane. This stannyl reagent reacts

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