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Synthesis of Disubstituted Cucurbit[6]uril and Its Rotaxane Derivative

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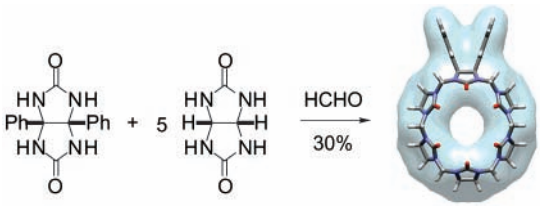
ABSTRACT



Synthesis of diphenyl cucurbit[6]uril (CB[6]) has been achieved via co-oligomerization of diphenyl glycoluril and unsubstituted glycoluril. The unsymmetrically substituted CB[6], Ph_2CB[6], was further converted to a rotaxane incorporating bis(dinitrophenyl)spermine.

Almost a century has passed since the first synthesis of cucurbit[*n*]uril (CB[*n*]) was reported.[1,2] CB[*n*] is a cyclic oligomer of *n* units of glycoluril (GU, **4**) linked by 2*n* methylene bridges derived from formaldehyde. Several symmetrical homologues of CB[*n*] have been synthesized by homo-oligomerization of unsubstituted GU **4** or substituted GU.[3,4] Cyclic hexamer CB[6] (**1**, $n = 6$, R = H) is uniquely important because of its ability to take up a molecule of linear polyamine in the internal cavity. The result is the formation of pseudorotaxane,[2,5] which is interesting not only purely for its intriguing shape but also for possible use in molecular machines.[6] Our interest in the development of chemical substances that control biological activities through DNA targeting[7,8] directed us to investigate the synthesis of substituted CB[6]. After unsuccessful attempts to synthesize the cyclic homohexamer, dodecasubstituted CB[6], from disubstituted GU, we envisioned that the persubstituted homohexamer may suffer from steric strain between substituents. Indeed, recently Kim showed that although a symmetrical persubstituted CB[6] is obtainable in a certain case, the yield of the product is far less than satisfactory.[4b] In addition, it has not been demonstrated whether this cyclic homo-oligomer can form a rotaxane by inclusion of a polyamine molecule. As the result of extensive optimization studies, we found that the disubstituted cyclic hexamer forms more readily than unsubstituted CB[6]. We report herein the first synthesis of unsymmetrically substi-

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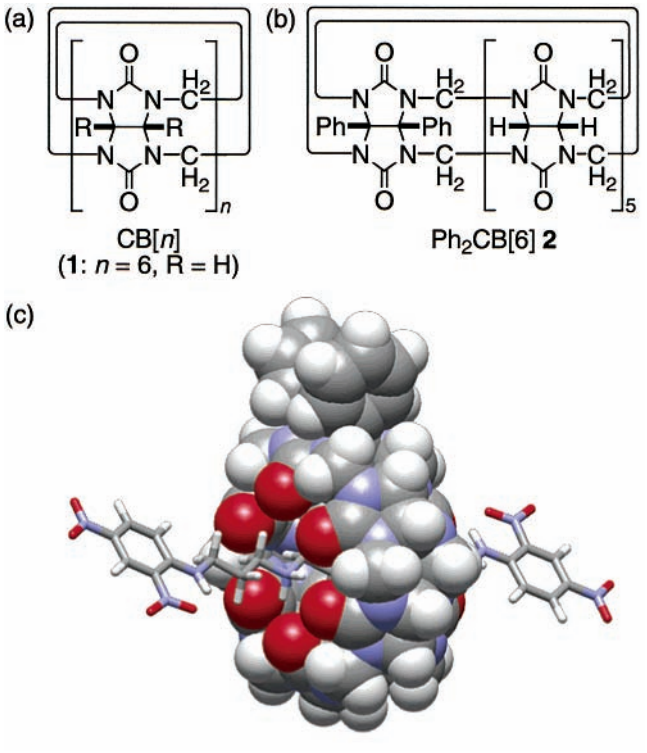
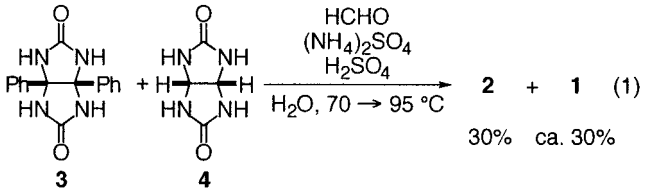


Figure 1. (a) Structure of cucurbit[*n*]uril. (b) Structure of Ph_2-CB[6] **2**. (c) AM1 optimized structure of rotaxane dication part of **6**. CB moiety is shown in a CPK model, and bis(dinitrophenyl)-spermine is shown in a stick model (C = gray, H = white, N = blue, O = red).

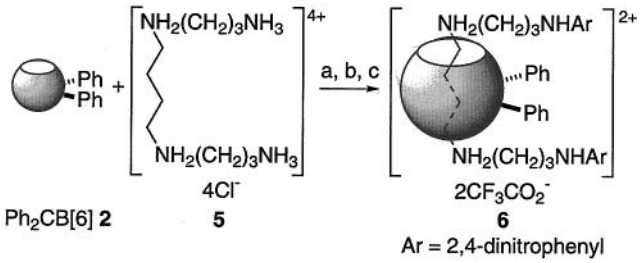
tuted cucurbit[6]uril, Ph_2CB[6] (**2**, Figure 1), by co-oligomerization of substituted GU **3** and unsubstituted GU **4**. The molecule that we synthesized is capable of forming pseudorotaxane and rotaxane with polyamine.

The optimized synthesis of Ph_2CB[6] **2** is very simple, requiring only near stoichiomeric amounts of necessary reactants. Thus, we heated a mixture composed of 1 equiv of Ph_2GU **3**,[9] 5 equiv of GU **4**, 14 equiv of formaldehyde, and 3.0 equiv of ammonium sulfate in 6.7 M aqueous sulfuric acid first at 70 °C for 24 h and then at 95 °C for 12 h and, after purification with gel permeation chromatography, obtained the desired co-hexamer **2** in 30% isolated yield together with unsubstituted CB[6] **1** in ca. 30% yield. There formed a small amount of tetraphenyl cucurbituril (Ph_4CB[6]) as detected by mass spectral analysis of the crude reaction mixture but none of the more substituted cohexamers or decaphenyl CB[5], a product expected by analogy with the previous synthesis of homopentamers.[3] The desired Ph_2CB-[6] **2** exhibits characteristic signals at δ 4.99 observed in D_2O containing 6 M H_2SO_4 and 0.8 M trifluoroacetic acid as the result of the shielding effect of the phenyl group (vide infra).



Unlike CB[5] derivatives whose internal cavity is very small,[10] Ph_2CB[6] **2** was found to form a pseudorotaxane with polyamine. Full structural characterization of **2** was achieved by further conversion to rotaxane **6** made by end-capping with bulky dinitrophenyl groups.[5] The rotaxane **6** was isolated as a trifluoroacetic acid salt by reverse-phase chromatography and characterized by electron spray mass and ^{1}H, ^{13}C, and ^{19}F NMR spectra (Figure 2 and Supporting Information). Molecular formula of $C_{70}H_{74}N_{32}O_{20}$ for di-cationic rotaxane was obtained by ESI-MS spectra [$(M - 2CF_3CO_2^-)^{2+}$, *m*/*z* 842.295; found 842.294], which confirmed the structure of the desired rotaxane composed of Ph_2CB[6] and bis(dinitrophenyl)spermine. The "bead and thread" structure of **6** was evident from the significantly upfield-shifted signals of the methylene protons enclosed in the CB cavity (circled a and b in Figure 2).[11] Further analysis of the ^{1}H NMR signals of the spermine moiety in **6** revealed that the internal amine atoms (N^c) bear two protons and the N^g atoms bear only one proton on each nitrogen atom, indicating that only the N^c atoms are protonated. All ^{1}H and ^{13}C NMR signals of the spermine moiety including those in the dinitrophenyl groups have been assigned. The ^{13}C and ^{19}F NMR analyses showed the presence of $CF_3CO_2^-$ counter-anion in **6**.

Scheme 1[a]



[a] Reagents and conditions: (a) H_2O, 25 °C, 1 h; (b) 2,4-dinitrophenyl fluoride, 2,6-lutidine, H_2O, 25 °C, 19 h; (c) HPLC purification (0.1% TFA in MeCN/H_2O).

The most characteristic feature of the CB moiety of **6** is C_{2V} symmetry, and hence the majority of the ^{1}H and ^{13}C NMR signals integrate twice as much as those located in planes of the symmetry, whose ^{1}H and ^{13}C signals integrate for two atoms. The connectivity for hydrogen and carbon atoms in the CB skeleton of **6** has been determined by HMBC correlations (Figure 2). Assignment of ^{1}H and ^{13}C NMR signals was made first for the phenyl groups. Starting

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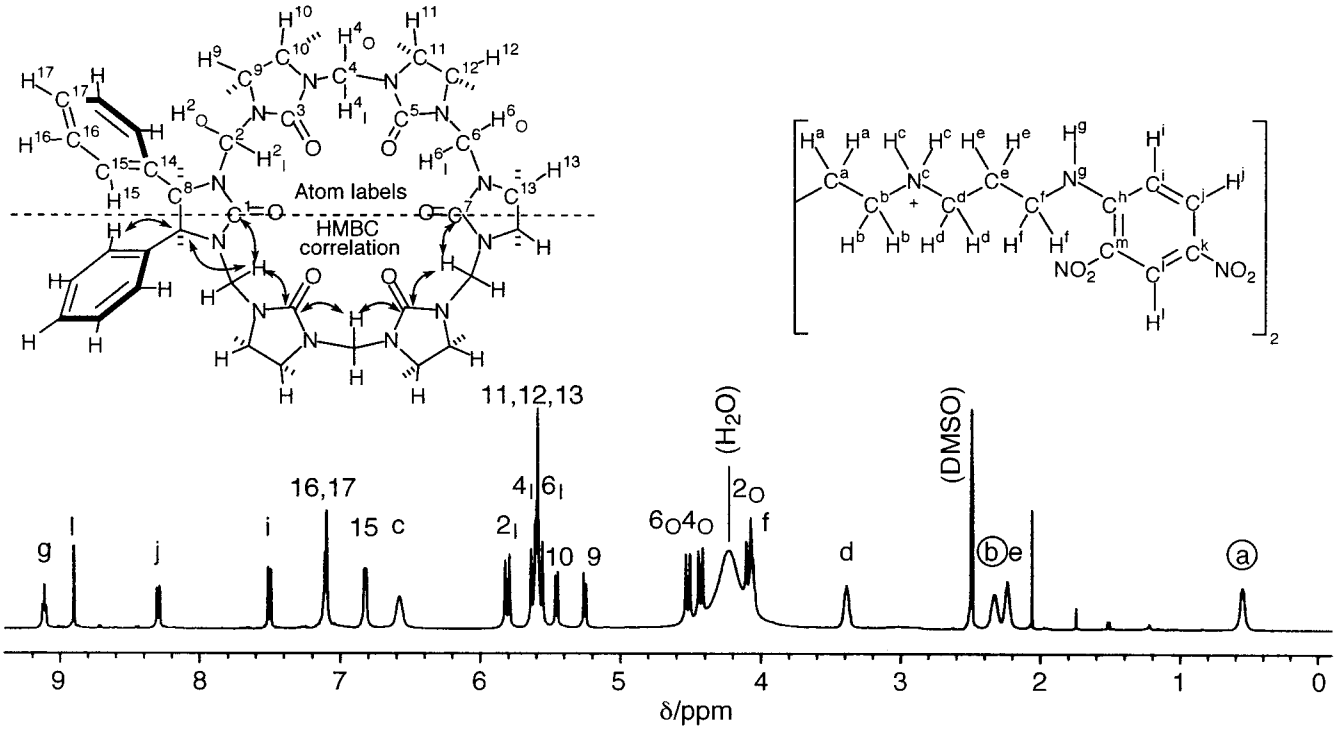

Figure 2. ^{1}H NMR spectrum (500 MHz) of rotaxane **6** in DMSO-d_6. Atom labels and key HMBC correlations are shown in the molecular structures. Structures of CB and spermine are shown separately for clarity. CB moiety is viewed along the spermine molecule and only the front half of the molecule is shown. ^{13}C NMR and 2D spectra are reported in Supporting Information.

from the C^2_I methylene proton, HMBC correlations through $^3J_{C,H}$ established the connectivity in the CB framework from the C^1 carbonyl carbon to the most distant carbonyl C^7 carbon. The most characteristic is the upfield shift of H^2_O, H^4_O, H^9, and H^{10} atoms located right above the phenyl group (Figure 3). In contrast, H^2_I located in the deshielding region undergoes marked downfield shift. The shielding increment ($\Delta\delta$) relative to the chemical shift of the corresponding rotaxane of unsubstituted CB[6][5] is in good agreement with the theoretical calculations assuming restricted rotation of the phenyl groups.[12] The synthesis of unsymmetrically substituted cucurbit[6]uril and its rotaxane derivative **6** has thus been achieved. Since the phenyl group may be amenable to further elaboration and the synthetic route is simple and flexible, we expect that the present synthesis will lead the cucurbituril chemistry toward new directions.

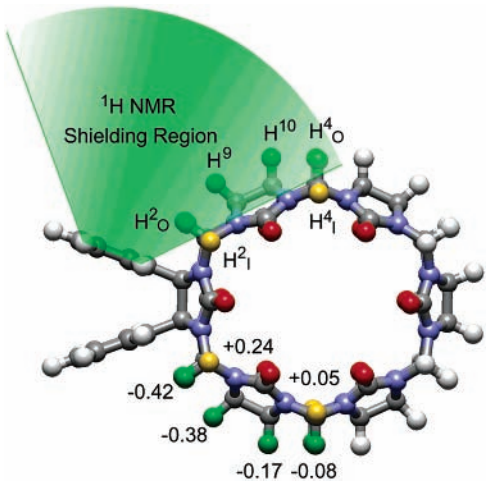

Figure 3. Upfield and downfield shifted chemical shift values ($\Delta\delta$) observed in the ^{1}H NMR spectrum of rotaxane **6**. Hydrogens colored in green shifted upfield and those in yellow shifted downfield. Chemical shift increments and decrements are relative to the rotaxane complex of **1**.[5]

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Supporting Information Available: Experimental procedures and details of mass and NMR spectra analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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