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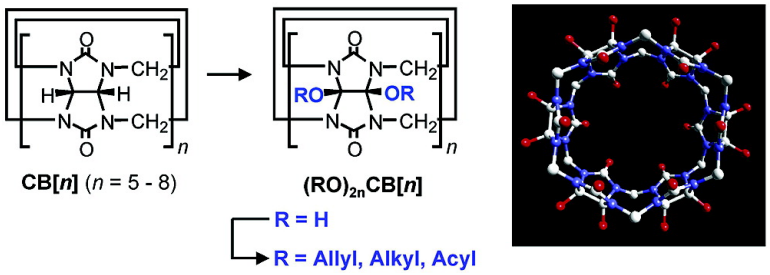

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Facile Synthesis of Cucurbit[*n*]uril Derivatives via Direct Functionalization: Expanding Utilization of Cucurbit[*n*]uril

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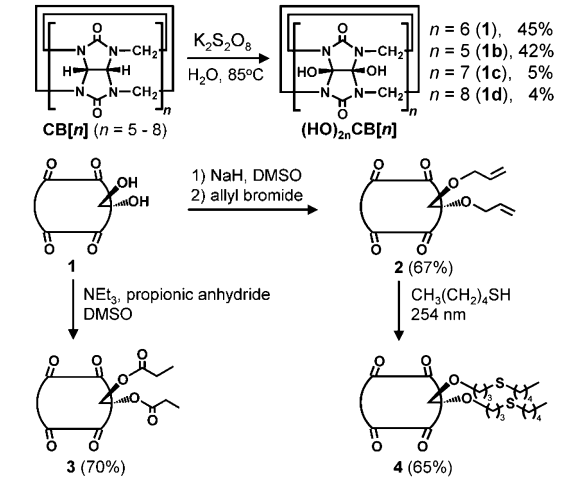
Cucurbituril (CB[6]), a macrocyclic cavitand comprising six glycoluril units, has a hydrophobic cavity that is accessible through two identical carbonyl-fringed portals.[1] The rigid structure and capability of forming complexes with molecules and ions make CB[6] attractive not only as a synthetic receptor but also as a building block for supramolecular assemblies such as rotaxanes, catenanes, and molecular machines.[2,3] Recent synthesis of CB homologues cucurbit[*n*]uril (CB[*n*], $n = 5$, 7, and 8)[4] has broadened the scope of the cucurbituril chemistry. Their host−guest chemistry as well as novel supramolecular assemblies based on CB[*n*] has been studied[5,6] and summarized in a topical review article.[7] Although the cucurbiturils (CBs) are potentially as useful as well-known host molecules such as crown ethers, cyclodextrins (CDs), and calixarenes, their practical applications have been limited[8] mainly due to their poor solubility in common solvents, and difficulty in introducing functional groups on their surfaces. In particular, unlike other molecular hosts, functionalization of these molecules has been a daunting task. Introduction of substituents at the "equator" of CBs by condensation of substituted glycoluril with formaldehyde has been achieved with only limited success. So far, only methyl and 1,2-cyclohexyl groups have been successfully introduced, and, furthermore, only or mostly cyclic pentamers (i.e., CB[5] derivatives) have been produced.[9] Reaction of a mixture of methyl- or phenyl-substituted glycoluril and unsubstituted glycoluril with formaldehyde produces a complicated mixture of unsubstituted and substituted CBs, separation of desired products from which is practically impossible or laborious.[10] Furthermore, no method of direct functionalization has been reported, which may be attributed to the high chemical stability of CBs. Therefore, appending functional groups, particularly reactive ones, directly on the CB[*n*] surface remains a challenge as well as an important goal because such functionalization would pave the way to applications of CBs, in the same manner as the upsurge in applications of CDs after they were functionalized. Herein, we report the facile synthesis of CB[*n*] derivatives with a wide variety of functional groups via direct functionalization, which sets the stage for extensive utilization of CBs in many different fields. Several novel applications of such functionalized CBs are also demonstrated.

Reaction of CB[6] with $K_2S_2O_8$ in water at 85 °C for 6 h followed by crystallization produces perhydroxycucurbit[6]uril (**1**) in 45% yield as a potassium ion complex (Scheme 1).[11] The new CB derivative **1** has been fully characterized by various methods including X-ray crystallography. The X-ray analysis of **1** reveals the expected structure with hydroxy groups at the periphery of the CB[6] framework (Figure 1).[12] The portal and cavity sizes of **1** are essentially the same as those of CB[6] with mean cavity and portal diameters of 5.5 and 3.9 Å, respectively. In a similar fashion, $(HO)_{2n}$CB[*n*] ($n = 5$, 7, and 8) are produced from the corresponding CB homologues.[13] The mechanism of the perhydroxylation of CB-[*n*] is not clear, although OH radical generated by $K_2S_2O_8$ appears to be involved.[14]

Scheme 1



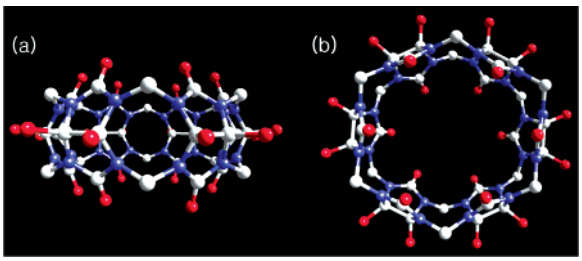


Figure 1. X-ray crystal structure of **1**: (a) side view and (b) top view. Color codes: carbon, white; nitrogen, blue; oxygen, red.

The new cucurbituril derivative **1** is soluble in DMSO and moderately soluble in DMF. Most importantly, **1** allows further functionalization by conventional methods (Scheme 1).[12] For example, alkyl ethers of **1** can be prepared by treatment with NaH in DMSO followed by reaction with alkyl bromides. Similarly, esters of **1** are prepared in moderate yields by reaction with acid anhydrides in the presence of triethylamine. In most cases, the products are isolated by the addition of water followed by washing with ether or hexane to remove the unreacted alkyl bromides or anhydrides. Among these derivatives, perallyloxycucurbit[6]uril (**2**), which can be easily prepared from the reaction of **1** with allyl bromide in the presence of NaH, is useful for further transformation because of its good solubility in organic solvents as well as the reactive functional group. For example, photoinitiated reaction[15] of **2** with alkylthiol produces thioether-substituted CB[6] (Scheme 1).[12] The synthesis of other derivatives of **1** and **2** is currently in progress.

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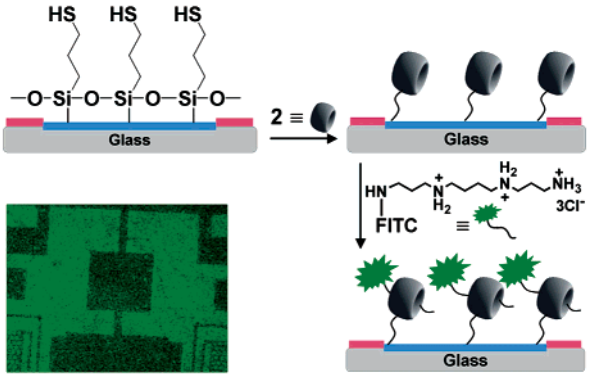
Scheme 2. Anchoring **2** onto a Patterned Glass and Detection of Fluorescent Guest by the CB[6] Modified Surface[a]



[a] The photograph shown is the fluorescence microscopic image of the patterned glass after binding of the fluorescent guest.

To demonstrate the utilities of these derivatives, we have anchored a CB[6] derivative on a glass surface. Immersing a patterned thiol-terminated glass substrate, prepared by the microcontact printing technique,[16] in a chloroform solution of **2** in a quartz tube followed by irradiating UV light (254 nm) for 12 h under N_2 atmosphere produces a CB[6] modified glass (Scheme 2). The CB[6] modified glass recognizes small molecules such as spermine which is known to form a stable host−guest complex with CB[6]. A fluorescence microscopic image (Scheme 2) of the CB[6] modified glass plate taken after brief immersion of the plate in an aqueous solution containing a spermine derivative carrying a fluorophore at the terminal followed by thorough washing with water gives clear evidence of the complex formation between the fluorescent guest and the CB[6] unit anchored on the surface.[12] Thus, such a CB[6] modified surface may be useful in designing sensors and biochips. Similarly, CB[*n*] can be attached on silica surfaces which can be utilized as a stationary phase in chromatography. Details of these studies will be published separately.

The CB[6] derivative with a long alkyl chain, $[CH_3(CH_2)_7S(CH_2)_3O]_{12}$CB[6], forms nanospheres when emulsified.[12] The SEM measurement of the emulsion shows nanospheres with diameters in the range of ca. 50−150 nm (Figure S1).[12] Because CB[6] has a high binding affinity toward alkylammonium groups, the nanospheres may have practical applications in protein and peptide drug delivery.[17] We are currently investigating the mechanism of formation of the nanospheres and their potential use.

In conclusion, a long-standing problem in cucurbituril chemistry is answered through the first direct functionalization of CB[*n*] leading to perhydroxyCB[*n*] which can be further modified to provide tailored CB[*n*] derivatives with desired functional groups and good solubility in common solvents. In a way similar to how functionalized CDs and calixarenes have been utilized, the new CB[*n*] derivatives should enable applications in many areas including sensor, transport, separation, catalysis, drug delivery, artificial ion channels, and nanomaterials. Work along these lines is in progress in our laboratory.

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Supporting Information Available: Procedures for the synthesis of perhydroxyCB[*n*] and their derivatives, anchoring of $(allyl\text{-}O)_{12}$CB-[6] on a patterned glass, and nanosphere preparation (PDF), and an X-ray crystallographic file (CIF) for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) A slurry of CB[6] (1.0 g, 1.0 mmol) and $K_2S_2O_8$ (3.9 g, 14.4 mmol) in water (50 mL) was heated at 85 °C for 6 h under inert atmosphere. After being cooled to room temperature, the resulting precipitate was removed by filtration, and the filtrate was concentrated to 25 mL. Acetone diffusion to the resulting solution gave a white precipitate which was collected by filtration, washed with acetone, and dried in a vacuum to give **1** $[(HO)_{12}CB[6](K_2SO_4)_2]$ (690 mg, 45%). ^{1}H NMR (500 MHz, DMSO): δ = 7.83 (s, 12H), 5.33 (d, J = 14.9 Hz, 12H), 4.42 (d, J = 14.9 Hz, 12H). ^{13}C NMR (125 MHz, DMSO): δ = 152.7, 93.8, 40.2. MS (MALDI-TOF): m/z 1227.1 $[M + K^+]$, 1266.1 $[M + 2K^+]$; satisfactory elemental analysis was obtained for compound **1**.
(12) See Supporting Information.
(13) The same procedure also produces perhydroxyCB[5] from CB[5] in a moderate yield (42%) (see Supporting Information). In the case of CB[7] and CB[8], however, it produces the corresponding perhydroxyCB[*n*] (n = 7 or 8) only in ~5% yield, which may be due to a much lower stability of the products. The perhydroxy derivatives $(HO)_{14}$CB[7] and $(HO)_{16}$CB-[8] have been characterized by NMR and mass spectrometry (see Supporting Information). The improved synthesis and further characterization of the compounds are in progress.
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