Triple Linkage of Two Homooxacalix[3]arenes Creates Capsular Molecules and Self-Threaded Rotaxanes

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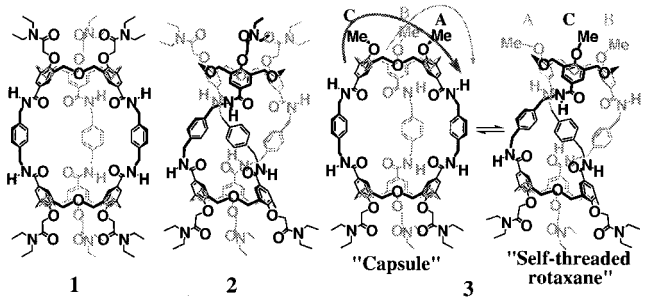
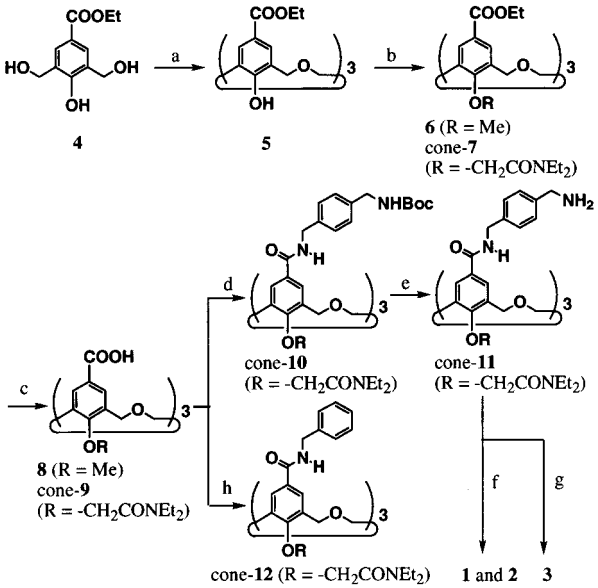
Half-bowl-shaped calixarenes and their analogues[1] are useful building units for constructing molecular capsules[2] which represent a very attractive type of host molecules with well-defined three-dimensional internal cavities. An early example is the sulfide-bonded calix[6]arene dimer reported in 1991.[3] It was later found that two complementarily functionalized calixarenes can dimerize to form molecular capsules cross-linked by hydrogen-bonding interactions.[4] For example, Rebek et al.[5] and Böhmer et al.[6] systematically studied this class of multiurea-functionalized calix[4]arene dimers and found that these dimers form hydrogen-bonded capsular architectures which can encapsulate small molecules under slow exchange with respect to the NMR time scale. Meanwhile, Reinhoudt et al.[7] successfully established a procedure to construct resorcinarene−calixarene capsules using covalent bonds. They demonstrated that these capsular compounds can also entrap small guest molecules. Very recently, we reported a novel homooxacalix[3]arene-based dimeric capsule cross-linked by a Pd(II)−pyridine interaction, which can include [60]fullerene in the three-dimensional cavity.[8] The historical background indicates that various bonds are useful to construct the dimeric capsules with various functions. Here, we report a novel type of triply cross-linked homooxacalix[3]arene dimers which show novel types of molecular motion and inclusion properties: capsular molecule **1**, self-threaded rotaxane **2**, and the conformationally changeable dimer **3**.



Capsular molecule **1** was designed considering that it has (i) a large internal hole to encapsulate large guest molecules, (ii) three windows large enough to allow the guests to get in and out, (iii) two ionophoric sites at the lower rims which can bind alkali metal cations and thus change the shape, rigidity, and charge state of the capsular hole, and (iv) amide moieties which may interact with guest molecules. We have unexpectedly found that the synthesis of capsular molecule **1** yields a very interesting isomer, self-threaded rotaxane **2**.[9] Theoretically, **1** and **2** should interconvert each other by inverting one of the two homooxacalixarene subunits. Actually, this inversion is prohibited by the diethylacetamide moieties on the phenolic oxygens.[10] The existence of the two isomers **1** and **2** prompted us to design and synthesize dimer **3**, in which three anisyl units can rotate to allow an equilibrium between "capsule **3**" with a large internal hole and "self-threaded rotaxane **3**" without the hole. Undoubtedly, to control the capsule−rotaxane equilibrium is a potential strategy to control the guest-including and -releasing properties in **3**.

Scheme 1[a]



[a] Conditions: (a) *p*-xylene, reflux, 47%. (b) **5** → **6**: NaH, MeI, DMF, 77%. **5** → **7**: NaH, $ClCH_2CONEt_2$/NaI, THF, 70%. (c) NaOH, EtOH/H_2O = 4:1 v/v, then dilute HCl, **8** 100%, **9** 77%. (d) *t*-$BocNHCH_2$-*p*-$C_6H_4CH_2NH_2$, BOP reagent, CH_3CN/Et_3N, 71%. (e) TFA, CH_2Cl_2, then dilute Me_4NOH, 98%. (f) **9**, BOP reagent, CH_3CN/Et_3N, 14% **1** and 7% **2**. (g) **8**, BOP reagent, CH_3CN/Et_3N, 14%. (h) benzylamine, BOP reagent, CH_3CN/Et_3N, 76%.

The syntheses of compounds **1**−**3** are depicted in Scheme 1. When tricarboxyl calixarene **9** reacts with triaminocalixarene **11** to form the triply linked dimers, there are two patterns for the first two linkages: the "syn pattern" with the unreacted carboxyl

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(9) A few examples of self-threaded molecules were reported: (a) Kanamathareddy, S.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 6572. (b) Siepen, A.; Zett, A.; Vögtle, F. *Liebigs. Ann.* **1996**, 757. (c) Canati, A.; Jacopozzi, P.; Pachini, A.; Ugozzoli, F.; Cacciapaglia, R.; Mandolini, L.; Ungaro, R. *Tetrahedron* **1995**, *51*, 591.

(10) The inversion of benzene ring in homooxacalix[3]arene is prohibited when the R group on the phenolic oxygen is *n*-butyl or larger groups: (a) Araki, K.; Inada, K.; Otsuka, H.; Shinkai, S. *Tetrahedron* **1993**, *49*, 9465. (b) Araki, K.; Hashimoto, N.; Otsuka, H.; Shinkai, S. *J. Org. Chem.* **1993**, *58*, 5958.

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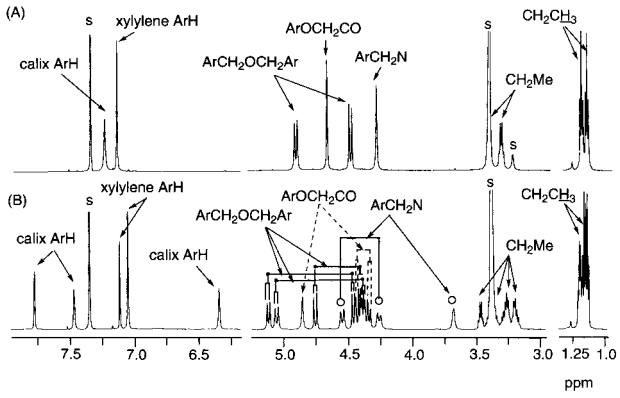

Figure 1. Partial ^{1}H NMR spectra of (A) **1** and (B) **2**: 600 MHz, $CDCl_3$/CD_3OD = 9:1 v/v, TMS, 25 °C. The peaks marked with "s" are attributed to undeuterated solvents.[11]

and amino groups on same side with respect to the macrocycle formed by the first two linkages, and the "anti pattern" with the unreacted carboxyl and amino groups on opposite sides. By the syn pattern, two calixarene cones are connected in a face-to-face manner, leading to capsular molecule **1**. The ^{1}H NMR spectrum (Figure 1A) shows four singlets for the calixarene ArH, xylylene ArH, $ArOCH_2CO$, and xylylene CH_2 protons, respectively, and a pair of doublets for the $ArCH_2OCH_2Ar$ protons, suggesting a D_{3h}-symmetrical structure of **1**. On the other hand, by the anti pattern, the third pair of carboxyl and amino groups has to react with each other, threading the macrocycle formed by the first two linkages, leading to the self-threaded rotaxane **2**. The complicated ^{1}H NMR spectrum of **2** (Figure 1B), which was assigned with a ^{1}H−^{1}H COSY spectrum, suggests a self-threaded structure with C_{2h} symmetry, in which one of the three xylylenediamide linkages threads through the cycle formed by the other two, and the calixarene benzene ring bearing the threading linkage orients toward the cavity formed by the other two benzene rings. The aromatic protons of the inward benzene shifts to unnormally high magnetic field (6.33 ppm), shielded by the other two benzenes, while the protons of the other two appear as a pair of singlets at lower magnetic field (7.77 and 7.46 ppm). The threading xylylenediamide linkage shows a singlet at 7.10 ppm for the aromatic protons and a singlet at 3.66 ppm for the methylene protons, while the other two linkages show a singlet at 7.04 ppm for the aromatic protons and a pair of doublets at 4.53 and 4.25 ppm (J = 14.6 Hz) for the methylene protons. The ESI-TOF MS spectra showed that **1** and **2** have the same expected molecular weight.

It is known that calixarenes[9c,12] or homooxacalixarenes[13] complex with quaternary ammonium ions by cation−π interactions operating in organic solvents. Capsular molecule **1** should be a host molecule suitable for complexation of large organic cations because it has a large internal hole consisting of two homooxacalixarene subunits and three xylylene linkages. Complexation properties of **1** with 1,1′-dimethyl-4,4′-bipyridinium ditosylate (methyl viologen) were investigated by a ^{1}H NMR spectroscopic method (600 MHz, $Cl_2CDCDCl_2$/CD_3OD = 100/2 v/v). Addition of **1** to a solution of the viologen did not generate separate signals for the complex and the free form but caused an upfield shift of the signals. The continuous variation plot[14] established that **1** forms a 1:1 complex with the viologen, and the association constant (K_{assoc}) was estimated to be 430 M^{-1}. The extrapolated upfield shift values of the complexed methyl viologen are −1.14, −1.54, and −0.76 ppm for the α, β, and methyl protons, respectively. To investigate whether the viologen was included into the internal hole of host **1**, the tris(benzylamide)-calixarene **12** was synthesized and used as a reference compound. Under the same conditions, the association constant between **12** and methyl viologen was estimated to be 120 M^{-1}, and the extrapolated upfield shift values are −0.53, −0.52, and −0.50 ppm for the α, β, and methyl protons of the complexed viologen, respectively. Compared with the reference, the much bigger association constant and, more cogently, the upfield shift values (especially that for the β-H) suggest that the complexed methyl viologen is located in the internal hole of capsular host **1**. This was further supported by the size selectivity of complexation of **1** with other dipyridinium guests. The estimated association constants of **1** with methyl viologen, ethyl viologen, propyl viologen, and 1,2-bis(1′-methyl-4′-pyridinio)ethylene ditosylate are 430, 116, 97, and 210 M^{-1}, respectively. Examination of CPK models showed that methyl viologen can be encapsulated by **1** with its two pyridinium heads inward toward the calixarene subunits, but propyl viologen cannot because of its longer size and the steric hindrance of the propyl groups. As predicted, the NMR spectrum revealed that the self-threaded rotaxane **2** has very poor (much poorer even than **12**) complexation ability to the viologen, as the cavity is self-filled.

Dimer **3** gave a very complicated ^{1}H NMR spectrum assignable to the mixture of the capsule form and the self-threaded rotaxane form, but all TLC, MS, and GPC analyses showed that it is a pure compound. The two conformers showed separate peaks on the ^{1}H NMR spectra from 0 to 120 °C in $Cl_2CDCDCl_2$, and the rotaxane/capsule ratio[15] decreased with the temperature rise, namely, 3.8, 2.6, and 1.8 at 0, 30, and 120 °C, respectively. Obviously, the two conformers interconvert at a rate slower than the NMR time scale.

In conclusion, this communication demonstrates a novel intramolecular threading phenomenon and the equilibrium between molecular capsule and self-threaded rotaxane through a conformational interconversion. We believe that in further research this equilibrium would be useful for controlling the complexation behavior of capsular host molecules, for example, in response to metal addition.

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Supporting Information Available: Syntheses and characterization of **1**−**3**, 600-MHz ^{1}H NMR spectrum of **3**, and estimated association constants and extrapolated chemical shift changes of the dipyridium guests complexed by **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Due to the hydrogen bond of the amide groups, **2** gave a broadened and very complicated ^{1}H NMR spectrum in $CDCl_3$ at room temperature. The spectrum was simplified and the signals were sharpened after addition of 10 vol % of CD_3OD. A multiamide tricyclic compound showed a similar phenomenon: Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed.* **1998**, *37*, 2270.

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(15) "Capsule **3**" shows one and "rotaxane **3**" shows two sharp singlets for the $ArOCH_3$ on the ^{1}H NMR spectra when the temperature is above 0 °C. Their ratio can be easily calculated from the integral intensity of the methyl peaks.