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Remarkably Facile Ring-Size Control in Macrocyclization: Synthesis of Hemicucurbit[6]uril and Hemicucurbit[12]uril**

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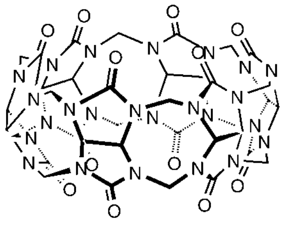
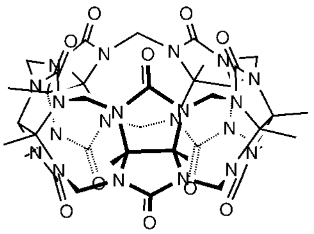
*Dedicated to Professor Leo A. Paquette
on the occasion of his 70th birthday*

Recent developments in the chemistry of cucurbit[*n*]urils (Cuc*N*: $n = 5$–10) reveal that their hydrophobic cavities are particularly useful for applications in supramolecular chemistry.[1]

As previously reported, decamethylcucurbit[5]uril (MeCuc5) behaves as a “molecular” sieve if the portals, which are frilled by carbonyl oxygen atoms, are not stoppered by cations.[2] Since the polar interactions of the portals with cations are well known,[3] we imagined that if the Cuc*N* molecules were cut in half along the equator, the resulting macrocycles, which we therefore call hemicucurbit[*N*]uril (hmCuc*N*), would capture a metal ion at the polar carbonyl side and an organic molecule at the hydrophobic ethylene side in the “cone” conformation.



Cuc6



MeCuc5

Since hmCuc*N* is simply a cyclic oligomer formed by condensation of ethyleneurea with formaldehyde we tried the reaction under the usual conditions used for synthesizing MeCuc5[2] and Cuc*N*.[4] However, the products of the reaction in concentrated acids at high temperatures were discolored syrups, from which no crystals could be isolated.

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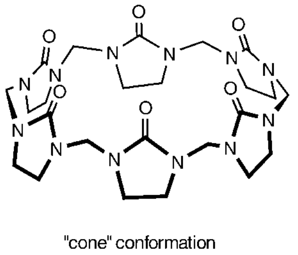
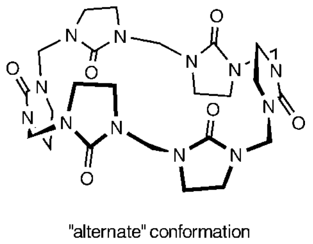




We found precedents for the condensation in the literature; for example, in 1955 Staudinger and Niessen reported linear oligomers with up to six ethyleneurea units.[5] The higher polymers were prepared for practical applications.[6] These studies indicate that the Mannich condensation itself proceeds even at pH 4 and suggest the possibility of forming hmCuc*n* under much milder conditions. This possibility is in sharp contrast to the synthesis of Cuc*n*, where the initially formed oligomers with random conformations must be transformed into the most stable cage structures by extensive bond scissions and recombinations under harsh conditions.[7]

We therefore reinvestigated the condensation under a wide range of acidic conditions. The products were analyzed by means of gel permeation chromatography (GPC) by taking advantage of the fact that all the components of the products could be dissolved in chloroform after the residual water had been removed azeotropically.

The condensation of ethyleneurea and 37 % formalin at pH 2 (72 h, 25 °C) provided a white powder which gave a GPC profile as shown in Figure 1. The product consists mainly of

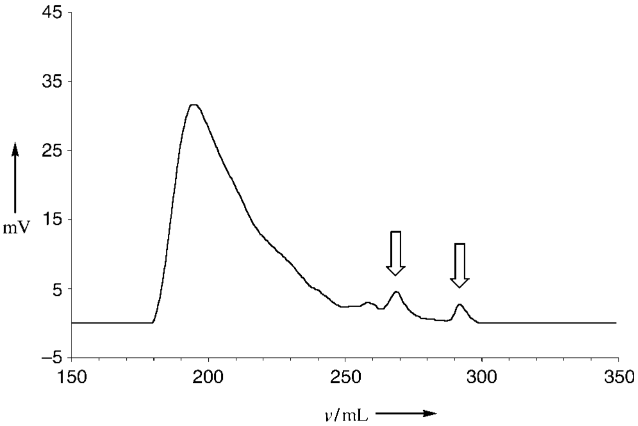
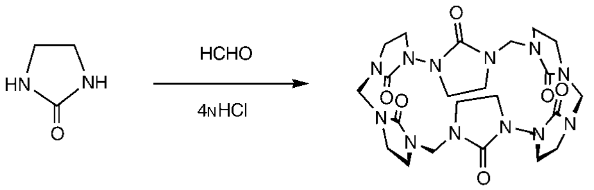


Figure 1. The GPC profile of the product after 72 h (RI detector response versus elution volumes).

polymers with number-averaged molecular weight ($\bar{M}_n$) of m/z 6345 which is higher than the reported value of m/z 4040 obtained by viscosity and osmometry measurements.[3b] The two small but distinct peaks at the low-molecular-mass end were readily identified as a cyclic hexamer (hmCuc6) and an unexpectedly large cyclic dodecamer (hmCuc12) by ESI mass spectroscopy. We then varied the acid concentrations and temperatures to identify the best conditions for producing either of these compounds on a preparative scale and thus enable the structures of these compounds to be established.

The best conditions to form hmCuc6 could be reached fairly readily. Simply mixing equimolar amounts of ethyleneurea and 37 % formalin in 4 N HCl at RT (Scheme 1)



Scheme 1. Synthesis of hmCuc6.

resulted in turbidity after a few minutes and then deposition of granular crystals. The mild exothermic reaction was complete in less than 30 min. The crystals contained HCl and water (see below) but HCl-free hmCuc6 was obtained in 94 % yield after drying in vacuo at 80 °C.[8]

The X-ray crystal structure of the HCl adduct determined at −180 °C (Figure 2a) indicates that the Cl^- ion is located at

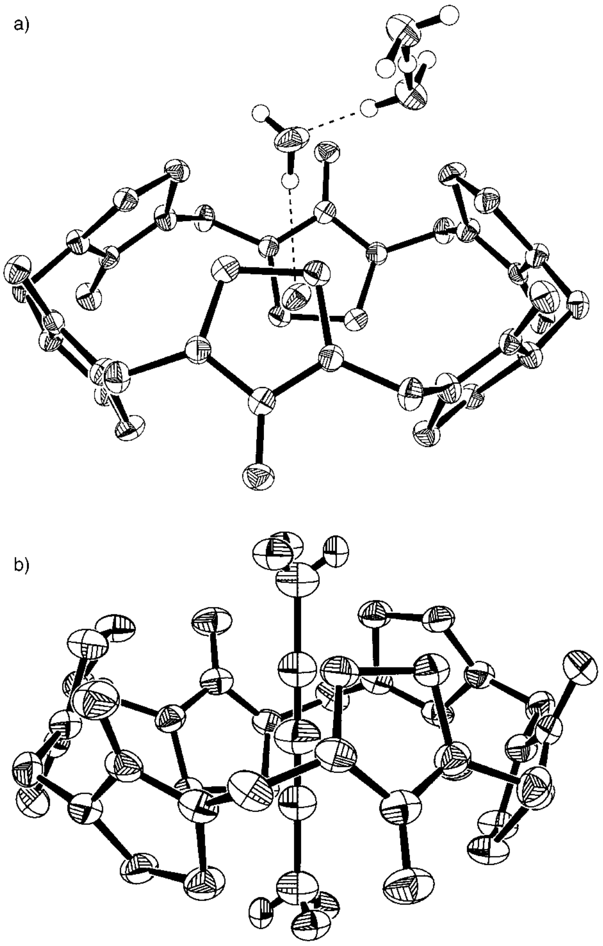


Figure 2. X-ray Structures of hmCuc6 including a) HCl and b) propargyl alcohol. Hydrogen atoms are omitted for clarity except for those attached to hydrogen-bonded water molecules. The propargyl alcohol is disordered over two symmetry related positions with further disorder of its oxygen atom.

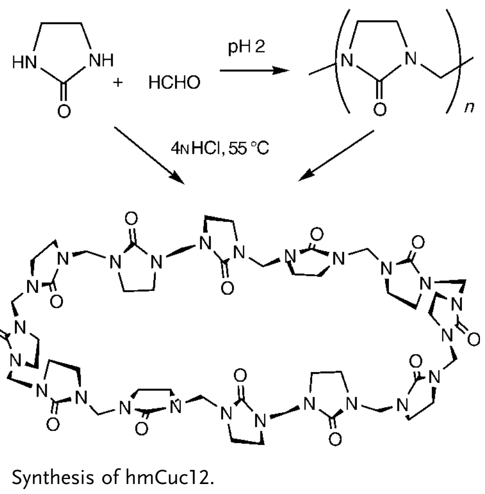
the center of the cavity in the “alternate” conformation of hmCuc6 and hydrogen bonded to a H_2O molecule, which in turn is hydrogen bonded to an external H_2O molecule. The H^+ ion is shared by the H_2O and another H_2O molecule belonging to the other hmCuc6, thus making a rigid hydrogen-bonding network.[8]

An acid concentration of 4N, therefore, appears to be the optimum conditions under which the cyclization occurs around a Cl^- ion template, and the resulting HCl adduct has the least solubility as a result of the hydrogen-bonding network.

Contrary to our expectations, hmCuc6 did not form complexes with common metal ions, possibly because of its “alternate” conformation. However, it can include an anion other than Cl^-, notably a thiocyanate. Although hmCuc6 is sparingly soluble in water (0.03 $mg\,mL^{-1}$ at 25 °C), the solubility was dramatically increased when metal or ammonium thiocyanate was added (250 $mg\,mL^{-1}$ if 150 mg of KNCS coexisted).[8]

Other than an anion, hmCuc6 can include a small molecule, such as water and formamide. Of particular interest is that propargyl alcohol has a greater affinity for hmCuc6 relative to water and can be taken up from an aqueous solution and included in the cavity as shown by the X-ray crystal structure (Figure 2b).[8,9] Further studies on its capability as a host molecule, along with its derivatization, are now in progress.

Finding the optimum conditions for the preparation of hmCuc12 met with considerable difficulty. However, once formation of a gel was found to be the key, the best procedure was readily found. Heating an equimolar mixture of ethyleneurea and 37% formalin in 1N HCl at 55 °C for 3 h furnished a white uniform gel (Scheme 2). Neutralization turned the gel to fine, but readily filterable, particles. The product proved to be pure hmCuc12 by GPC. It contained two H_2O molecules even after drying in vacuo at 80 °C for 18 h, as determined by elemental analysis.[8] The yield was as high as 93%. The same product was also obtained in 82% yield by depolymerization of the polymeric mixture described above under the same reaction conditions.



Scheme 2. Synthesis of hmCuc12.

The product was highly crystalline, as determined by powder X-ray diffraction studies, and sparingly soluble in common organic solvents except chloroform. Dissolving the powder in chloroform by rapid heating and cooling gave fine needles with a composition of hmCuc12·2H_2O·2$CHCl_3$.[8] Further heating with azeotropic removal of water furnished colorless prisms suitable for X-ray analysis.[8] As shown in Figure 3, the crystal contains three $CHCl_3$ molecules from above and three $CHCl_3$ molecules from below (not shown, symmetry-related) in the elongated cavity, and four $CHCl_3$ molecules in the lattice. The macro ring appears to be flattened out as a result of the inclusion of the $CHCl_3$ molecules and the packing forces in the solid state.

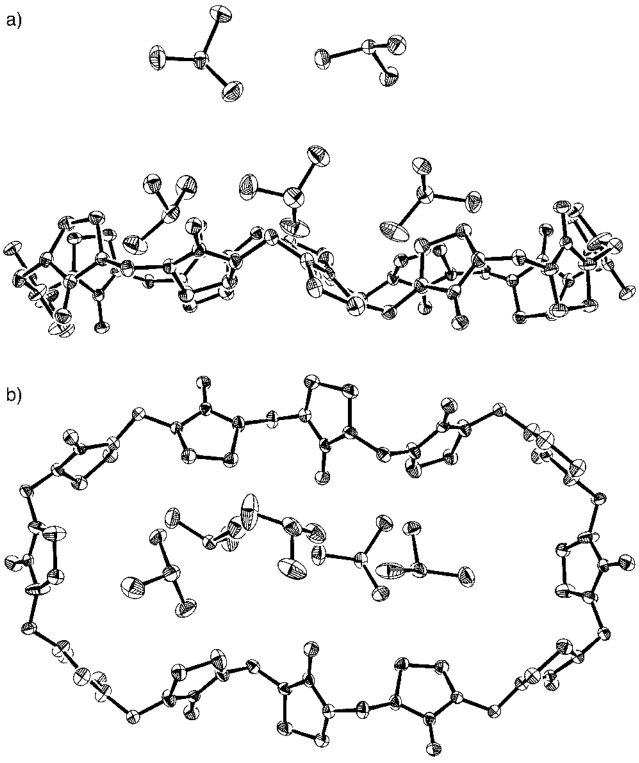


Figure 3. a) The side and b) top view of the X-ray structure of hmCuc12·10$CHCl_3$ (the H and disordered Cl atoms of minor occupancies are omitted for clarity).

The $CHCl_3$ solvate, however, formed good crystals only by chance and mostly amorphous solid was obtained after standing for a long time. The reason for this was elucidated by NMR spectroscopic studies. When the chloroform solvate was made $CHCl_3$-free and dissolved in meticulously dried $CDCl_3$, the singlet peak for the NCH_2CH_2N protons at $\delta =$ 3.40 ppm was accompanied by a shoulder at $\delta = 3.38$ ppm. The shoulder grew gradually larger with time and finally replaced the peak at $\delta = 3.40$ ppm after 5 h (see the Supporting Information). This new peak may be attributable to conformers with dissymmetric structures. A twisted, figure-of-eight conformation, as obtained by Monte Carlo searches (SpartanPro) and ab initio calculations (Gaussian98, B3LYP/STO-3G; Figure 4), may be one of the possible conformations in such solutions.[10]

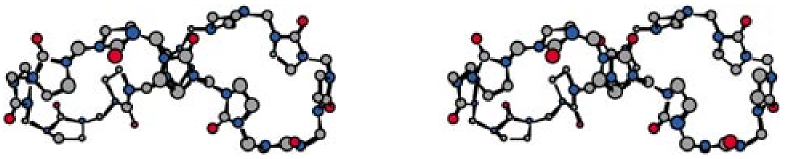


Figure 4. Stereoview of the B3LYP/STO-3G-optimized structure of hmCuc12.

In contrast, when hmCuc12 was dissolved in the usual $CDCl_3$ containing some water, the sharp singlet at $\delta = 3.40$ ppm did not change at all even when molecular sieves (3 Å) were added (see the Supporting Information). Interestingly, as the amount of water decreased, the water peak at $\delta = 1.91$ ppm decreased and a new peak appeared at $\delta = 1.25$ ppm, which increased until its integral reached the amount corresponding to 4H. Therefore, the two H_2O molecules included in hmCuc12 maintain the conformational structure by hydrogen bonding.

The unprecedented efficiency in forming the large hmCuc12 molecule[11] may not be explained solely by the stabilization of the macro ring by the intracavity H_2O molecules, but also by the formation of a stable gel by hydrogen-bonding interactions with intermolecular H_2O molecules. In fact, although the powder was insoluble in neutral H_2O, MeOH, or EtOH, it was dissolved in ethylene glycol by heating to 110–120 °C and formed a gel on cooling. Gel formation was observed over the concentration range of 0.5–5 %. The gel was fibrous when viewed under a microscope (Figure 5). We envisage that the fibers are formed by linking the hmCuc12·2 H_2O units linearly by intervening ethylene glycol molecules. Gel formation was also observed with diols such as propylene glycol and diethylene glycol.

Figure 5. HmCuc12-ethylene glycol gel (0.5 %) viewed under a phase-contrast microscope (20×).

In summary, we have developed facile methods for synthesizing two new macrocyclic polyurea compounds,[12] practical applications of which are currently under investigation.

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[1] For the latest review, see J. W. Lee, S. Samal, N. Selvapalam, H.-J. Kim, K. Kim, *Acc. Chem. Res.* **2003**, *36*, 621–630.

[2] Y. Miyahara, K. Abe, T. Inazu, *Angew. Chem.* **2002**, *114*, 3246–3249; *Angew. Chem. Int. Ed.* **2002**, *41*, 3020–3023.

[3] The complexation of Cuc6 with a variety of metal salts was studied without knowing its structure, see R. Behrend, E. Meyer, F. Rusche, *Justus Liebigs Ann. Chem.* **1905**, *339*, 1–37; for recent studies, see H.-J. Buschmann, E. Cleve, E. Schollmeyer, *Inorg. Chim. Acta* **1992**, *193*, 93–97 for Cuc6 and X. X. Zhang, K. E. Krakowiak, G. Xue, J. S. Bradshaw, R. M. Izatt, *Ind. Eng. Chem. Res.* **2000**, *39*, 3516–3520 for MeCuc5.

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[6] a) O. Cicchetti, S. Fontani, G. Landoni, R. Locatelli, G. Bertelli, P. Roma, Eur. Pat. EP-A2–37,706 Chem. Abstr. **1982**, *96*, P20900d; b) G. Camino, M. P. Luda, L. Costa, M. Guaita, *Macromol. Chem. Phys.* **1996**, *197*, 41–60.

[7] For the conditions and mechanisms of the Cucurbituril synthesis, see a) A. Day, A. P. Arnold, R. J. Blanch, B. Snushall, *J. Org. Chem.* **2001**, *66*, 8094–8100; b) A. Chakraborty, A. Wu, D. Witt, J. Lagona, J. C. Fettinger, L. Isaacs, *J. Am. Chem. Soc.* **2002**, *124*, 8297–8306.

[8] The properties and X-ray analyses of the compounds reported are given in the Supporting Information.

[9] The solubility of hmCuc6 in water was appreciably increased by addition of propargyl alcohol. However, the changes in chemical shift were too small to determine the association constant. The addition of propargyl alcohol in the more soluble $CDCl_3$ led to precipitation of the complex.

[10] The usual conformational search using molecular mechanics appears unreliable for polar urea derivatives. The B3LYP/STO-3G optimized structure is the best we could find so far, but the conformational problem in solution is apparently much more complex because of the flexibility and polar interactions. Internal thermal motion as found in supercoiled DNA may also be possible in this large macrocycle. For internal motion, see A. Stasiak in *Large Ring Molecules* (Ed.: J. A. Semlyen), Wiley, Chichester, UK, **1996**, pp. 43–97.

[11] For a variety of natural and synthetic macrocycles, see, *Large Ring Molecules* (Ed.: J. A. Semlyen), Wiley, Chichester, UK, **1996**. There seems to be no prior examples for such an efficient control of macrocyclization.

[12] Many macrocycles containing urea units have been synthesized by base-mediated S_N2 condensation, particularly when benzimidazol-2-one units are included; see J. Trepte, M. Czugler, K. Gloe, E. Weber, *Chem. Commun.* **1997**, 1461–1462; S. Kumar, D. Paul, G. Hundal, M. S. Hundal, H. Singh, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1037–1043; Z. Shi, R. P. Thummel, *Tetrahedron Lett.* **1995**, *36*, 2741–2744; O. Meth-Cohn, Z. Yan, *J. Chem. Soc. Perkin Trans. 1* **1998**, 423–436. Benzimidazol-2-one proved to be much less reactive in its condensation with formaldehyde than ethyleneurea under acidic conditions. Trimethyleneurea units have also been utilized in macrocyclic hosts: J. A. Bryant, S. P. Ho, C. B. Knobler, D. J. Cram, *J. Am. Chem. Soc.* **1990**, *112*, 5837–5843, and references therein. Trimethyleneurea, though reactive with formaldehyde under acidic conditions, failed to give readily identifiable products.