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Nor-Seco-Cucurbit[10]uril Exhibits Homotropic Allosterism

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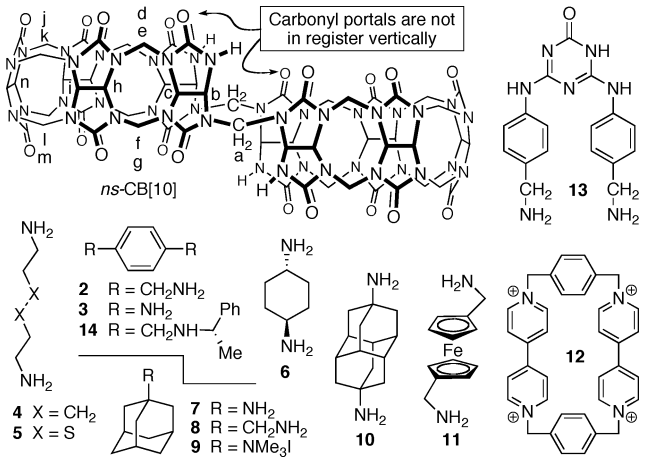
Cucurbit[6]uril (CB[6]), the prototypical member of the CB[n] family[1], has outstanding recognition properties toward aliphatic and aromatic amines in aqueous solution.[2] In recent years, a homologous series of hosts (CB[*n*]: $n = 5, 7, 8, 10$)[3] has been isolated and investigated. These new CB[*n*]—with their increased cavity volumes—bind to a wide range of chemically and biologically important guests and therefore participate in a variety of interesting applications including fluorophore photostabilization,[4] gas binding,[5] chemical sensing,[6] supramolecular vesicles,[7] supramolecular dendrimers,[8] molecular machines,[9] and complex self-sorting systems.[10] Stimulated by the discovery of inverted CB[*n*] ($n = 6, 7$),[11] we postulated that other kinetically controlled structures might be formed as stable mechanistic intermediates[12] during CB[*n*] formation. We report the isolation and recognition properties of nor-seco-cucurbit[10]uril (*ns*-CB[10]) which results from formal extrusion of two CH_2 bridges from CB[10] along with bond reorganization.

We discovered that heating a mixture of glycoluril (**1**) and paraformaldehyde at 50 °C in concentrated HCl delivers a reaction mixture that contains CB[*n*] and *ns*-CB[10] (Chart 1). We isolated *ns*-CB[10] as a white solid in 15% yield by washing and recrystallization. The ^{1}H NMR spectra of free *ns*-CB[10] (Figure 1a) was not informative because of significant signal overlap, although the resonance for the inwardly directed CH_2 bridge (H_a) appeared in a distinctive region of the spectrum. In contrast, the NMR spectrum of *ns*-CB[10]·$\mathbf{2}_2$ was relatively well dispersed which allowed unambiguous assignment of its structure by 2D NMR methods (Supporting Information). Of particular diagnostic utility are the resonances for H_a and H_n which appear as singlets due to the overall C_{2h}-symmetry of *ns*-CB[10]·$\mathbf{2}_2$.

Fortunately, we obtained single crystals of *ns*-CB[10] as its *p*-phenylenediamine (**3**) complex (*ns*-CB[10]·$\mathbf{3}_2$) which were suitable for X-ray structure determination (Figure 2). Several structural features are intriguing including: (1) the absence of two CH_2 bridges and the internal disposition of the two single CH_2 bridges, (2) two symmetry equivalent cavities and their lack of vertical registration (Chart 1), and (3) infinite guest filled channels defined by the stacking of *ns*-CB[10]·$\mathbf{3}_2$ in the crystal (Supporting Information). Interestingly, the solvating H_2O molecules in the ureidyl carbonyl region of *ns*-CB[10]·$\mathbf{3}_2$ act as bridges between guest NH and host C═O groups.

Although *ns*-CB[10] has poor solubility in D_2O and strongly acidic solution, its complexes are nicely soluble in D_2O which allowed us to investigate its recognition properties. The two cavities of *ns*-CB[10] are comparable in size to those of CB[6] and CB[7] and therefore bind guests commonly used with these hosts. For example, *ns*-CB[10] forms ternary (1:2) complexes with alkyl, cycloalkyl, aryl, and adamantyl amines (**2**−**10**) although some of these complexes display fast exchange on the NMR time scale.[13] *ns*-CB[10] also binds some more chemically and biologically interesting species (Supporting Information) like dyes (e.g., coumarins, acridines, nile blue), amino acids (tryptophan, 4-aminophenylalanine, and arginine), and electrochemically active substances

Chart 1. Structure of *ns*-CB[10] and Guests Used in This Study.



(ferrocenes (e.g., **11**) and viologens). More sizable guests (e.g., **12** and **13**) that are too large for the individual CB[6]−CB[7] sized cavities of *ns*-CB[10] instead form binary (1:1) complexes that fill both cavities simultaneously.

Several types of selectivity are observed within ternary complexes of *ns*-CB[10]. For example, when unsymmetrical guests are bound within *ns*-CB[10] three diastereomers are possible (Figure 3: top−top, center−center, and top-center).[14] For some guests a single diastereomer is observed (e.g., *ns*-CB[10]·$\mathbf{7}_2$) which we tentatively assign the top−top conformation. In the top−top conformation, the NH_3^+ groups bind at the more flexible C═O portals which lack a CH_2-bridge. For other guests (e.g., **8**) all three conformations can

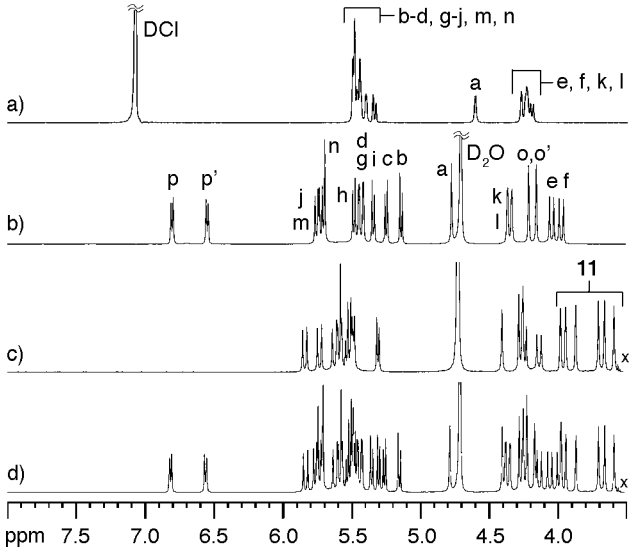


Figure 1. ^{1}H NMR spectra for (a) *ns*-CB[10] (400 MHz, 20% DCl), (b) *ns*-CB[10]·$\mathbf{2}_2$, (c) *ns*-CB[10]·$\mathbf{11}_2$, (d) 2:2:2 mixture of *ns*-CB[10], **2**, and **11:** (b−d) 500 MHz, D_2O; x = trace EtOH impurity.

10.1021/ja064776x CCC: $33.50

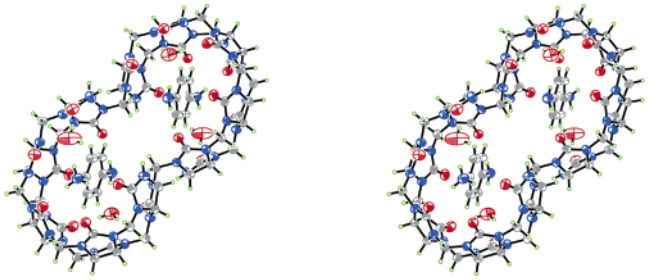


Figure 2. Cross-eyed stereoview of the crystal structure of *ns*-CB[10]·$\mathbf{3}_2$. Solvating H_2O molecules have been removed for clarity. Color code: C, gray; H, green; N, blue; O, red.

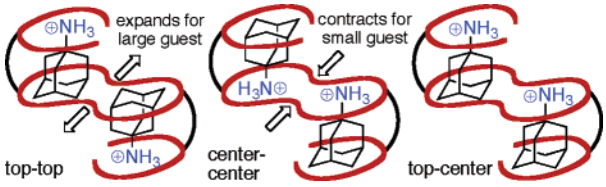


Figure 3. Three potential diastereomers of *ns*-CB[10]·$\mathbf{7}_2$. The arrows illustrate the key $CH_2\cdots CH_2$ nonbonded distance that changes according to guest size.

be observed by ^{1}H NMR (Supporting Information). A second type of selectivity is possible during the binding of chiral but racemic guests. For example, when a mixture of **14** and *ent*-**14** is offered to *ns*-CB[10] two homochiral forms (*ns*-CB[10]·$\mathbf{14}_2$ and *ns*-CB[10]·*ent*-$\mathbf{14}_2$) and one heterochiral form (*ns*-CB[10]·**14**·*ent*-**14**) are observed as a statistical mixture. Further studies are needed to understand the structural features that allow an efficient transmission of chiral information.

Interestingly, during our binding studies we never observed the formation of binary complexes concomitant with ternary complexes, which suggests a sizable positive cooperativity in the system. To demonstrate its potential for homotropic allostery,[15] we offered *ns*-CB[10] guest mixtures containing two (e.g., **2** and **11**, **5** and **7**, **2** and **5**, or **7** and **10**) different guests. When guests of quite different sizes are used (**2** and **11**, Figure 1b−d) allosteric control leads to a mixture of homomeric complexes (e.g., *ns*-CB[10]·$\mathbf{2}_2$ and *ns*-CB[10]·$\mathbf{11}_2$). In contrast, mixtures of similarly sized guests (e.g., **2** and **5** or **7** and **10**) result in mixtures of the homomeric and heteromeric ternary complexes. These results show that binding of the first guest to *ns*-CB[10] preorganizes the second cavity for binding of a *similarly sized guest.* Computational results suggest that the allosteric structural change is transmitted between binding sites in the putative 1:1 complex via the central $H_2C\cdots CH_2$ separation (5.5−9.3 Å) and overall cavity volume (450−740 Å^3) which varies systematically with the size of the guest (Figure 3 and Supporting Information).

In summary, we have reported the isolation of a new member of the CB[*n*] family, *ns*-CB[10], which is both structurally and functionally intriguing. For example, *ns*-CB[10] retains much of the binding profile of CB[*n*] but also (1) binds larger guests than expected given that its two cavities are each shaped by only five glycoluril rings which highlights the structural responsiveness of the *ns*-CB[10] cavity, (2) displays unusual top−center isomerism, and (3) displays homotropic allostery based on a guest size induced preorganization mechanism. As an intermediate in the formation of CB[*n*] with reactive NH groups, we believe that *ns*-CB[10] will enable straightforward access to CB[*n*] derivatives, surface immobilized CB[*n*], and CB[*n*] dimers.[16] The isolation of *ns*-CB[10] deepens our understanding of the mechanism of CB[*n*] formation and presages the formation of CB[*n*] hosts of even higher complexity. In combination, these results promise to broaden both the structural range of CB[*n*] that can be accessed and the applications (e.g., biomimetic allosteric systems, supramolecular polymers, and covalent multivalent CB[*n*] scaffolds) to which CB[*n*] can be applied.

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Supporting Information Available: Procedures and characterization data for *ns*-CB[10], NMR spectra for *ns*-CB[10]·guest complexes, and details of the X-ray structure of *ns*-CB[10]·$\mathbf{3}_2$ (cif). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4844−4870. (b) Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H.-J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621−630.
(2) (a) Freeman, W. A.; Mock, W. L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367−7368. (b) Mock, W. L. *Top. Curr. Chem.* **1995**, *175*, 1−24.
(3) (a) Kim, J.; Jung, I. S.; Kim, S.-Y.; Lee, E.; Kang, J.-K.; Sakamoto, S; Yamaguchi, K.; Kim, K. *J. Am. Chem. Soc.* **2000**, *122*, 540−541. (b) Day, A. I.; Arnold, A. P.; Blanch, R. J.; Snushall, B. *J. Org. Chem.* **2001**, *66*, 8094−8100. (c) Day, A. I.; Blanch, R. J.; Arnold, A. P.; Lorenzo, S.; Lewis, G. R.; Dance, I. *Angew. Chem., Int. Ed.* **2002**, *41*, 275−277. (d) Liu, S.; Zavalij, P. Y.; Isaacs, L. *J. Am. Chem. Soc.* **2005**, *127*, 16798−16799.
(4) Mohanty, J.; Nau, W. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3750−3754.
(5) (a) Miyahara, Y.; Abe, K.; Inazu, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3020−3023. (b) Kellersberger, K. A.; Anderson, J. D.; Ward, S. M.; Krakowiak, K. E.; Dearden, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 11316−11317.
(6) Zhao, J.; Kim, H.-J.; Oh, J.; Kim, S.-Y.; Kim, J. W.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4233−4235. Sindelar, V.; Cejas, M. A.; Raymo, F. M.; Chen, W.; Parker, S. E.; Kaifer, A. E. *Chem.−Eur. J.* **2005**, *11*, 7054−7059. Bush, M. E.; Bouley, N. D.; Urbach, A. R. *J. Am. Chem. Soc.* **2005**, *127*, 14511−14517. Lagona, J.; Wagner, B. D.; Isaacs, L. *J. Org. Chem.* **2006**, *71*, 1181−1190.
(7) Lee, H.-K.; Park, K. M.; Jeon, Y. J.; Kim, D.; Oh, D. H.; Kim, H. S.; Park, C. K.; Kim, K. *J. Am. Chem. Soc.* **2005**, *127*, 5006−5007.
(8) (a) Moon, K.; Grindstaff, J.; Sobransingh, D.; Kaifer, A. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 5496−5499.
(9) (a) Jeon, W. S.; Kim, E.; Ko, Y. H.; Hwang, I.; Lee, J. W.; Kim, S.-Y.; Kim, H. J.; Kim, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 87−91. (b) Ko, Y. H.; Kim, K.; Kang, J.-K.; Chun, H.; Lee, J. W.; Sakamoto, S.; Yamaguchi, K.; Fettinger, J. C.; Kim, K. *J. Am. Chem. Soc.* **2004**, *126*, 1932−1933. (c) Jeon, W. S.; Ziganshina, A. Y.; Lee, J. W.; Ko, Y. H.; Kang, J. K.; Lee, C.; Kim, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4097−4100.
(10) (a) Mukhopadhyay, P.; Wu, A.; Isaacs, L. *J. Org. Chem.* **2004**, *69*, 6157−6164. (b) Liu, S.; Ruspic, C.; Mukhopadhyay, P.; Chakrabarti, S.; Zavalij, P. Y.; Isaacs, L. *J. Am. Chem. Soc.* **2005**, *127*, 15959−15967.
(11) Isaacs, L.; Park, S.-K.; Liu, S.; Ko, Y. H.; Selvapalam, N.; Kim, Y.; Kim, H.; Zavalij, P. Y.; Kim, G.-H.; Lee, H.-S.; Kim, K. *J. Am. Chem. Soc.* **2005**, *127*, 18000−18001.
(12) Chakraborty, A.; Wu, A.; Witt, D.; Lagona, J.; Fettinger, J. C.; Isaacs, L. *J. Am. Chem. Soc.* **2002**, *124*, 8297−8306.
(13) The 1:2 host/guest stoichiometry was established by ^{1}H NMR integration in the presence of excess guest under conditions of slow exchange. Competition experiments establish that the affinity of the *ns*-CB[10]·$\mathbf{2}_2$ complex is comparable to that of CB[7]·**2** ($K_a = 1.8 \times 10^9$ M^{-1}; ref 10b).
(14) For a related isomerism, see Timmerman, P.; Verboom, W.; van Veggel, F. C. J. M.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2345−2348.
(15) Shinkai, S.; Ikeda, M.; Sugasaki, A.; Takeuchi, M. *Acc. Chem. Res.* **2001**, *34*, 494−503.
(16) (a) Zhao, Y.; Xue, S.; Zhu, Q.; Tao, Z.; Zhang, J.; Wei, Z.; Long, L.; Hu, M.; Xiao, H.; Day, A. I. *Chin. Sci. Bull.* **2004**, *49*, 1111−1116. (b) Nagarajan, E. R.; Oh, D. H.; Selvapalam, N.; Ko, Y. H.; Park, K. M.; Kim, K. *Tetrahedron Lett.* **2006**, *47*, 2073−2075.

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