Chiral Recognition

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Chiral Recognition inside a Chiral Cucurbituril**

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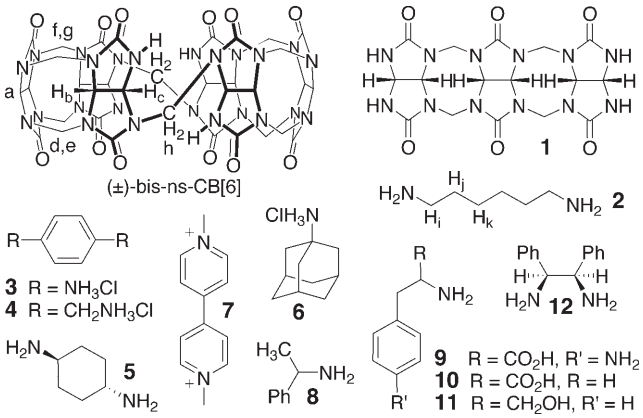
The supramolecular chemistry of the cucurbit[*n*]uril family[1] (CB[*n*]) of molecular containers has undergone rapid development in recent years including the development of a homologous series of CB[*n*] hosts ($n = 5$, 6, 7, 8, 10),[2] diastereomeric inverted CB[*n*],[3] and most recently bis-nor-seco-CB[10].[4] These new CB[*n*] compounds have cavity volumes ($V = 82$–870 Å^3) that span and exceed those available with α-, β-, and γ-cyclodextrin and are therefore capable of interacting with a wide range of chemically and biologically interesting guest species including gases, chromophores and fluorophores, anti-cancer agents, peptides, and neurotransmitters in water.[5] The extremely high affinity (K_a up to 10^{12} M^{-1}) and very high selectivity that are characteristic of CB[*n*] hosts[6] has been exploited in the creation of molecular machines, supramolecular vesicles, artificial ion channels, self-assembled dendrimers, and complex self-sorting systems.[7] Chiral recognition—a property readily achieved inside chiral cyclodextrins—has been challenging to reproduce using achiral CB[*n*].[2e,8] Herein we report the isolation of a chiral nor-seco-cucurbituril (±)-bis-ns-CB[6] and demonstrate its ability to undergo enantio- and diastereoselective recognition inside its cavity (Scheme 1).

The conversion of glycoluril (1 equiv) and formaldehyde (2 equiv) into CB[*n*][2] is a remarkably complex process involving the formation of 4*n* bonds and *n* rings with complete stereochemical control. Based on the hypothesis that the mechanism of CB[*n*] formation[2c,9] involved step-growth polymerization, we decided to starve the reaction of one of its monomers, namely formaldehyde, to access mechanistic intermediates on the path to CB[*n*] that might display exciting recognition properties. From a reaction mixture consisting of glycoluril (1 equiv) and paraformaldehyde (1.5 equiv) in concentrated hydrochloric acid at 80 °C we isolated the methylene-bridged glycoluril trimer **1** and (±)-bis-ns-CB[6] (Scheme 1). Fortunately, we were able to obtain X-ray crystal structures of **1** and (±)-bis-ns-CB[6] (Figure 1) which conclusively established their structures.[10] A number of features of the structure of (±)-bis-ns-CB[6] deserve comment: 1) the exclusive connection between homotopic NH groups of the two constituent glycoluril trimer fragments,[11] 2) the idealized presence of three mutually perpendicular C_2-axes which leads to overall D_2-symmetry, and 3) the presence of intramolecular hydrogen bonds between the NH groups and the C=O group on an adjacent glycoluril ring.



Scheme 1. Structures and numbering of compounds used in this study.

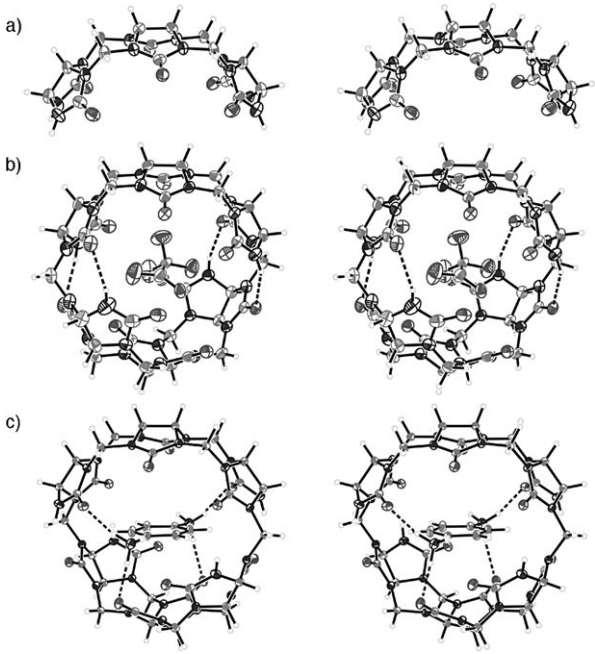


Figure 1. Cross-eyed stereoviews of the crystal structures of: a) **1**, b) (±)-bis-ns-CB[6]·CF_3CO_2H, and c) (±)-bis-ns-CB[6]⊂**3** with ellipsoids set at 30% probability. Solvating CF_3CO_2H and H_2O molecules have been removed for clarity.

After the structure of (±)-bis-ns-CB[6] was elucidated, we decided to study its abilities as a host in aqueous solution. We sought to experimentally determine the effective cavity volume of (±)-bis-ns-CB[6] by ^{1}H NMR spectroscopy com-

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plexation experiments. Similar to CB[6] itself, we found that (±)-bis-ns-CB[6] forms inclusion complexes with **2**–**5** but not with the larger adamantane amine **6** (see Scheme 1) which binds with high affinity to CB[7] (Supporting Information). Unlike CB[6], (±)-bis-ns-CB[6] does form an inclusion complex with methyl viologen (**7**) which allows us to bracket the cavity volume as follows (CB[6] < (±)-bis-ns-CB[6] < CB[7]). We measured the values of K_a for (±)-bis-ns-CB[6] toward guests **2**–**5** and **7**. For this purpose, we performed a UV/Vis spectroscopic titration between (±)-bis-ns-CB[6] and **3** ($K_a = 2.5 \times 10^3\,\text{M}^{-1}$, Figure 2). Taking advantage of the slow chemical exchange displayed by many (±)-bis-ns-CB[6] complexes, we performed ^{1}H NMR spectroscopy competition experiments[6a,b] (Supporting Information) to determine the affinity of (±)-bis-ns-CB[6] toward **2** ($1.3 \times 10^5\,\text{M}^{-1}$), **4** ($3.6 \times 10^4\,\text{M}^{-1}$), **5** ($320\,\text{M}^{-1}$), and **7** ($9.9 \times 10^3\,\text{M}^{-1}$).

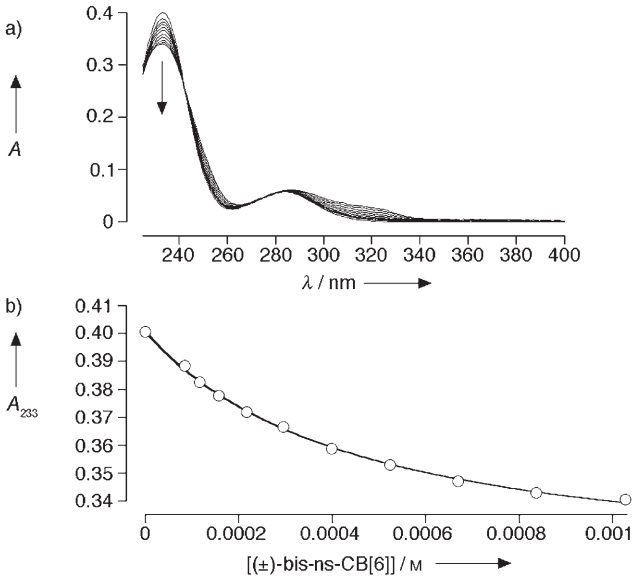

Figure 2. a) UV/Vis spectroscopic titration of **3** (60 μM) with (±)-bis-ns-CB[6] (50 mM NaO_2CD_3 buffered D_2O, pD 4.74), b) plot of absorbance versus [(±)-bis-ns-CB[6]] used to obtain K_a.

To probe the origin of the differences in binding strength of (±)-bis-ns-CB[6] toward guests **2**–**7** relative to CB[6][6a,b] we computed electrostatic surface potential maps for both CB[6] and (±)-bis-ns-CB[6] (Figure 3). The four intramolecular NH···OH bonds present in free (±)-bis-ns-CB[6] substantially narrow its carbonyl-lined portals and impart distinct electrostatic surface potentials to the three chemically nonequivalent C=O groups (L −66, M −77, H −98 kcal mol^{-1}). For comparison, the electrostatic surface potential on the C=O groups of CB[6] is approximately −87 kcal mol^{-1}. Consequently, the flexibility of (±)-bis-ns-CB[6] and its shape complementarity toward flatter guests (e.g. **4** and **7**) results in higher affinity for these guests than can be obtained with CB[6]. Conversely, the affinity of (±)-bis-ns-CB[6] toward **2** is 3400-fold lower than CB[6], which presumably arises from differences in the strength of ion–dipole interactions, the degree of aqueous solvation of the C=O portals, or both.

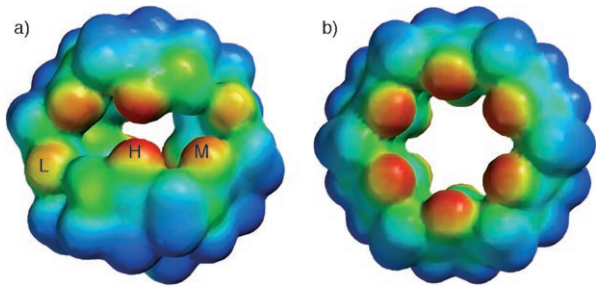

Figure 3. Electrostatic surface potential maps (red to blue: −90 to +31 kcal mol^{-1}) for: a) (±)-bis-ns-CB[6], and b) CB[6]. L low, M medium, H high electrostatic surface potentials.

The first hint that (±)-bis-ns-CB[6] would display useful levels of chiral recognition toward racemic guests came in our ^{1}H-NMR-spectroscopic studies of the binding of (±)-bis-ns-CB[6] with achiral guest **2**. Intriguingly, the ^{1}H NMR spectrum of (±)-bis-ns-CB[6]⊂**2** (Figure 4a) displays a pair of

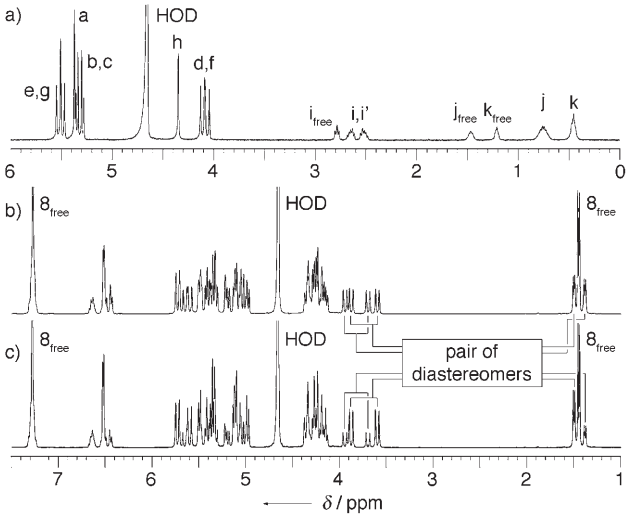

Figure 4. ^{1}H NMR spectra (400 MHz, D_2O) for: a) (±)-bis-ns-CB[6]⊂**2**; for numbering scheme see Scheme 1, b) a mixture of (±)-bis-ns-CB[6] and excess (+)-**8**, c) a mixture of (±)-bis-ns-CB[6] and excess (±)-**8**.

resonances for the diastereotopic CH_2 group (H_i, $H_{i'}$) of guest **2** which reflects the asymmetric magnetic environment within the chiral host–guest complex. Accordingly, we decided to investigate the ability of (±)-bis-ns-CB[6] to undergo diastereoselective complexation with guests containing one or more stereogenic centers. Although several chiral aliphatic amines bind to (±)-bis-ns-CB[6], they do so with fast exchange on the NMR spectroscopy timescale which precludes detection and quantitation of the degree of diastereoselectivity within (±)-bis-ns-CB[6] (Supporting Information). We turned, therefore, to guests **8**–**12** (see Scheme 1) which contain aromatic rings and exhibit slower kinetics of exchange. Figure 4b shows the ^{1}H NMR spectrum recorded for a mixture of (±)-bis-ns-CB[6] and excess (+)-**8** which shows resonances for a 50:50 mixture of diastereomers (+)-bis-ns-

CB[6]⊂**8** and (−)-bis-ns-CB[6]⊂**8**. When (±)-bis-ns-CB[6] is combined with excess (±)-**8**, however, a moderately diastereoselective process leads to a 72:28 ratio of the diastereomers (Figure 4c).[12] Further studies revealed that (±)-bis-ns-CB[6] displays moderate to very good levels of diastereoselectivity toward amino acids **9** (77:23) and **10** (88:12) and amino alcohol **11** (76:24). Interestingly, (±)-bis-ns-CB[6] is even able to distinguish between the enantiotopic groups of *meso*-compound **12** (74:26).[13]

In summary, we have reported the isolation of a new member of the CB[*n*] family—(±)-bis-ns-CB[6]—which is formally prepared by condensation of two equivalents of methylene bridged glycoluril trimer **1** with two equivalents of CH_2O by the exclusive connection between homotopic glycoluril NH groups.[14] The isolation of (±)-bis-ns-CB[6]—in combination with bis-ns-CB[10][4]—deepens our understanding of the mechanism of CB[*n*] formation[2c,9] by establishing the operation of a step-growth polymerization in this reaction. (±)-Bis-ns-CB[6] undergoes moderately diastereoselective complexation (up to 88:12) with chiral amines including amino acids and amino alcohols as well as *meso*-diamine **12**. Larger (±)-bis-ns-CB[*n*] (*n*=7, 8, 10) and N-functionalized derivatives can be readily envisioned and are expected to display even higher enantioselectivity.[15] Access to (±)-bis-ns-CB[6] and other chiral nor-seco-cucurbit[*n*]urils promises to dramatically broaden the scope of the applications to which the achiral members of the CB[*n*] family have already been applied[1,5,7] by enabling the creation of enantioselective molecular devices.

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[1] a) J. Lagona, P. Mukhopadhyay, S. Chakrabarti, L. Isaacs, *Angew. Chem.* **2005**, *117*, 4922–4949; *Angew. Chem. Int. Ed.* **2005**, *44*, 4844–4870; b) J. W. Lee, S. Samal, N. Selvapalam, H.-J. Kim, K. Kim, *Acc. Chem. Res.* **2003**, *36*, 621–630.

[2] a) W. A. Freeman, W. L. Mock, N.-Y. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 7367–7368; b) J. Kim, I. S. Jung, S.-Y. Kim, E. Lee, J.-K. Kang, S. Sakamoto, K. Yamaguchi, K. Kim, *J. Am. Chem. Soc.* **2000**, *122*, 540–541; c) A. I. Day, A. P. Arnold, R. J. Blanch, B. Snushall, *J. Org. Chem.* **2001**, *66*, 8094–8100; d) A. I. Day, R. J. Blanch, A. P. Arnold, S. Lorenzo, G. R. Lewis, I. Dance, *Angew. Chem.* **2002**, *114*, 285–287; *Angew. Chem. Int. Ed.* **2002**, *41*, 275–277; e) S. Liu, P. Y. Zavalij, L. Isaacs, *J. Am. Chem. Soc.* **2005**, *127*, 16798–16799.

[3] L. Isaacs, S.-K. Park, S. Liu, Y. H. Ko, N. Selvapalam, Y. Kim, H. Kim, P. Y. Zavalij, G.-H. Kim, H.-S. Lee, K. Kim, *J. Am. Chem. Soc.* **2005**, *127*, 18000–18001.

[4] W.-H. Huang, S. Liu, P. Y. Zavalij, L. Isaacs, *J. Am. Chem. Soc.* **2006**, *128*, 14744–14745.

[5] a) Y. Miyahara, K. Abe, T. Inazu, *Angew. Chem.* **2002**, *114*, 3146–3149; *Angew. Chem. Int. Ed.* **2002**, *41*, 3020–3023; b) K. A. Kellersberger, J. D. Anderson, S. M. Ward, K. E. Krakowiak, D. V. Dearden, *J. Am. Chem. Soc.* **2001**, *123*, 11316–11317; c) J. Mohanty, W. M. Nau, *Angew. Chem.* **2005**, *117*, 3816–3820; *Angew. Chem. Int. Ed.* **2005**, *44*, 3750–3754; d) N. J. Wheate, D. P. Buck, A. I. Day, J. G. Collins, *Dalton Trans.* **2006**, 5337–5344; e) Y. J. Jeon, S.-Y. Kim, Y. H. Ko, S. Sakamoto, K. Yamaguchi, K. Kim, *Org. Biomol. Chem.* **2005**, *3*, 2122–2125; f) M. E. Bush, N. D. Bouley, A. R. Urbach, *J. Am. Chem. Soc.* **2005**, *127*, 14511–14517; g) V. Sindelar, M. A. Cejas, F. M. Raymo, W. Chen, S. E. Parker, A. E. Kaifer, *Chem. Eur. J.* **2005**, *11*, 7054–7059; h) J. Lagona, B. D. Wagner, L. Isaacs, *J. Org. Chem.* **2006**, *71*, 1181–1190.

[6] a) W. L. Mock, N.-Y. Shih, *J. Org. Chem.* **1986**, *51*, 4440–4446; b) S. Liu, C. Ruspic, P. Mukhopadhyay, S. Chakrabarti, P. Y. Zavalij, L. Isaacs, *J. Am. Chem. Soc.* **2005**, *127*, 15959–15967; c) W. S. Jeon, K. Moon, S. H. Park, H. Chun, Y. H. Ko, J. Y. Lee, E. S. Lee, S. Samal, N. Selvapalam, M. V. Rekharsky, V. Sindelar, D. Sobransingh, Y. Inoue, A. E. Kaifer, K. Kim, *J. Am. Chem. Soc.* **2005**, *127*, 12984–12989.

[7] a) W. S. Jeon, E. Kim, Y. H. Ko, I. Hwang, J. W. Lee, S.-Y. Kim, H. J. Kim, K. Kim, *Angew. Chem.* **2005**, *117*, 89–93; *Angew. Chem. Int. Ed.* **2005**, *44*, 87–91; b) H. K. Lee, K. M. Park, Y. J. Jeon, D. Kim, D. H. Oh, H. S. Kim, C. K. Park, K. Kim, *J. Am. Chem. Soc.* **2005**, *127*, 5006–5007; c) S. Y. Jon, N. Selvapalam, D. H. Oh, J.-K. Kang, S.-Y. Kim, Y. J. Jeon, J. W. Lee, K. Kim, *J. Am. Chem. Soc.* **2003**, *125*, 10186–10187; d) K. Moon, J. Grindstaff, D. Sobransingh, A. E. Kaifer, *Angew. Chem.* **2004**, *116*, 5612–5615; *Angew. Chem. Int. Ed.* **2004**, *43*, 5496–5499; e) P. Mukhopadhyay, A. Wu, L. Isaacs, *J. Org. Chem.* **2004**, *69*, 6157–6164; f) P. Mukhopadhyay, P. Y. Zavalij, L. Isaacs, *J. Am. Chem. Soc.* **2006**, *128*, 14093–14102.

[8] M. V. Rekharsky, H. Yamamura, C. Inoue, M. Kawai, I. Osaka, R. Arakawa, K. Shiba, A. Sato, Y. H. Ko, N. Selvapalam, K. Kim, Y. Inoue, *J. Am. Chem. Soc.* **2006**, *128*, 14871–14880.

[9] a) A. Chakraborty, A. Wu, D. Witt, J. Lagona, J. C. Fettinger, L. Isaacs, *J. Am. Chem. Soc.* **2002**, *124*, 8297–8306; b) J. Lagona, J. C. Fettinger, L. Isaacs, *Org. Lett.* **2003**, *5*, 3745–3747; c) A. I. Day, R. J. Blanch, A. Coe, A. P. Arnold, *J. Inclusion Phenom. Macrocyclic Chem.* **2002**, *43*, 247–250; d) Y.-H. So, *Acc. Chem. Res.* **2001**, *34*, 753–758.

[10] CCDC-647412 (**1**), CCDC-647413 ((±)-bis-ns-CB[6]⊂**3**), and CCDC-647414 ((±)-bis-ns-CB[6]·CF_3CO_2H) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] (±)-bis-ns-CB[6] features connections between two pairs of homotopic NH groups of identical topicity whereas previously isolated bis-ns-CB[10] has connections between two pairs of homotopic NH groups of opposite topicity.

[12] The ROESY spectrum of the mixture of diastereomers did not provide information that would allow us to assign the major and minor resonances to a specific diastereomer. We are in the process of resolving this issue by separating the enantiomers of (±)-bis-ns-CB[6] by chromatography on a chiral stationary phase.

[13] Compound **12** and (±)-bis-ns-CB[6] form a 1:1 inclusion complex rather than a supramolecular polymeric exclusion complex.

[14] Product resubmission experiments confirm that trimer **1** is converted into (±)-bis-ns-CB[6] by condensation with CH_2O under acidic conditions.

[15] Several constitutional isomers of (±)-bis-ns-CB[*n*] are possible depending on the length of the glycoluril oligomer fragments that condense (e.g. (±)-bis-ns-CB[7] can be formed from tetramer and trimer fragments or from dimer and pentamer fragments).

