ORGANIC LETTERS

2008
Vol. 10, No. 12
2577−2580

Folding of Long-Chain Alkanediammonium Ions Promoted by a Cucurbituril Derivative

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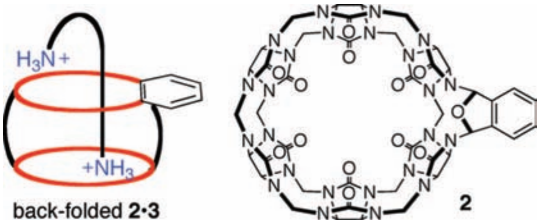
Received April 17, 2008

ABSTRACT



We report the isolation and characterization of two top−bottom differentiated CB[*n*]-type receptors, namely *ns*-CB[6] and cucurbituril derivative 2, which display diastereoselective recognition toward unsymmetrical guests. Compound 2 also promotes the back-folding of long chain alkanediammonium ions in water.

The supramolecular chemistry of the cucurbit[*n*]uril family[1] (CB[*n*]) of molecular containers has undergone rapid development in recent years due to the availability of a homologous series of molecular containers (n = 5, 6, 7, 8, 10)[2] with high binding affinity and high selectivity toward cationic species in aqueous solution. These unfunctionalized CB[*n*]s may be employed in a variety of intriguing applications including molecular machines, sensors, drug delivery, and the controlled release of gases.[3] In order to tailor the recognition properties toward specific applications—including supramolecular vesicles, artificial ion channels, sensors, and protein immobilization—several groups have pursued the preparation of CB[*n*] derivatives by direct functionalization[4] and building block strategies.[5] In this paper, we continue to develop an alternate approach toward novel CB[*n*]-type compounds based on CB[*n*] compounds lacking one or more

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(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) 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. (c) Day, A. I.; Arnold, A. P.; Blanch, R. J.; Snushall, B. *J. Org. Chem.* **2001**, *66*, 8094–8100. (d) Day, A. I.; Blanch, R. J.; Arnold, A. P.; Lorenzo, S.; Lewis, G. R.; Dance, I. *Angew. Chem., Int. Ed.* **2002**, *41*, 275–277. (e) Liu, S.; Zavalij, P. Y.; Isaacs, L. *J. Am. Chem. Soc.* **2005**, *127*, 16798–16799.

(3) (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) Henning, A.; Bakirci, H.; Nau, W. M. *Nature Methods* **2007**, *4*, 629–632. (c) Wheate, N. J.; Buck, D. P.; Day, A. I.; Collins, J. G. *Dalton Trans.* **2006**, *n/a*, 451–458. (d) Miyahara, Y.; Abe, K.; Inazu, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3020–3023. (e) Kellersberger, K. A.; Anderson, J. D.; Ward, S. M.; Krakowiak, K. E.; Dearden, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 11316–11317. (f) Bush, M. E.; Bouley, N. D.; Urbach, A. R. *J. Am. Chem. Soc.* **2005**, *127*, 14511–14517. (g) Sindelar, V.; Cejas, M. A.; Raymo, F. M.; Chen, W.; Parker, S. E.; Kaifer, A. E. *Chem. Eur. J.* **2005**, *11*, 7054–7059.

(4) (a) Kim, K.; Selvapalam, N.; Ko, Y. H.; Park, K. M.; Kim, D.; Kim, J. *Chem. Soc. Rev.* **2007**, *36*, 267–279. (b) Jon, S. Y.; Selvapalam, N.; Oh, D. H.; Kang, J.-K.; Kim, S.-Y.; Jeon, Y. J.; Lee, J. W.; Kim, K. *J. Am. Chem. Soc.* **2003**, *125*, 10186–10187. (c) Kim, J.; Ahn, Y.; Park, K. M.; Kim, Y.; Ko, Y. H.; Oh, D. H.; Kim, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 7393–7395. (d) Hwang, I.; Baek, K.; Jung, M.; Kim, Y.; Park, K. M.; Lee, D. W.; Selvapalam, N.; Kim, K. *J. Am. Chem. Soc.* **2007**, *129*, 4170–4171.

(5) (a) Zhao, J.; Kim, H.-J.; Oh, J.; Kim, S.-Y.; Lee, J. W.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4233–4235. (b) Lagona, J.; Fettinger, J. C.; Isaacs, L. *Org. Lett.* **2003**, *3*, 3745–3747. (c) Lagona, J.; Wagner, B. D.; Isaacs, L. *J. Org. Chem.* **2006**, *71*, 1181–1190. (d) Day, A. I.; Arnold, A. P.; Blanch, R. J. *Molecules* **2003**, *8*, 74–84. (e) 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.

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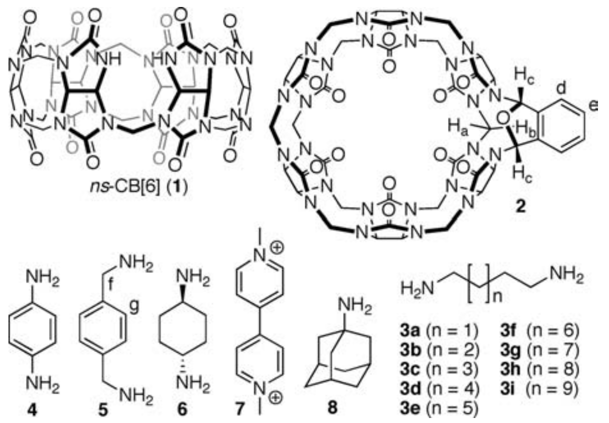

Figure 1. Compounds used in this study.

bridging CH_2-groups known as nor-seco-cucurbiturils.[6] In this paper, we report the isolation of *ns*-CB[6] (**1**), its chemical reactivity toward aldehydes, and the unique recognition properties of the top−bottom desymmetrized *ns*-CB[6] and **2** toward guests **3**−**20** (Figure 1).

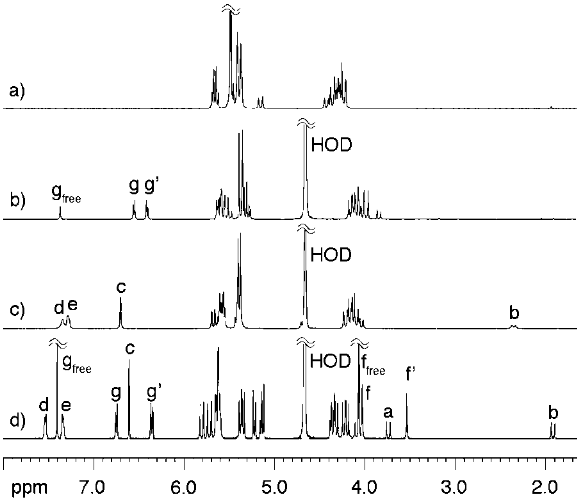

Figure 2. ^1H NMR spectra (400 MHz, D_2O, rt) recorded for (a) *ns*-CB[6] (4 mM, 20% DCl/D_2O), (b) a mixture of *ns*-CB[6] (4 mM) and **5** (5 mM), (c) **2** (3.6 mM), and (d) a mixture of **2** (3.6 mM) and **5** (7.2 mM).

From a reaction mixture comprising glycoluril (1 equiv) and paraformaldehyde (1.67 equiv) in concd HCl at 50 °C, we isolated *ns*-CB[6] (**1**). Although the ^1H NMR spectrum of **1** was uninformative (Figure 2a), its mass spectrum, and the ^1H NMR spectrum of *ns*-CB[6]·**5** (Figure 1b) allowed us to surmise its molecular formula and overall C_s-symmetry. To provide proof of structure we allowed *ns*-CB[6] to react with *o*-phthalaldehyde under acidic conditions and obtained **2** in 57% yield after recrystallization.[7] Although the ^1H NMR spectrum of **2** and its **2**·**5** complex (Figure 2c,d) allowed us to make an educated guess as to their structure, final proof was obtained in the form of an X-ray crystal structure (Figure 3). Several aspects of the ^1H NMR spectra and X-ray crystal structure are noteworthy: (1) the resonance for H_b is significantly upfield shifted due to its proximity to the face of the bridging aromatic ring, (2) the resonance for H_c appears at 6.6−6.7 ppm due to the combined deshielding effect of the bridging N−CH−O−CH−N and *o*-xylylene groups, (3) the presence of the new N−CH−O−CH−N bridge results in distinct upper and lower C═O lined rims of different diameter, and (4) the expansion at the upper rim, imposed by the bridging *o*-xylylene group, results in a pinching at the lower rim which promotes its solid state structure via C═O···K^+···O═C interactions (Figure 3b).

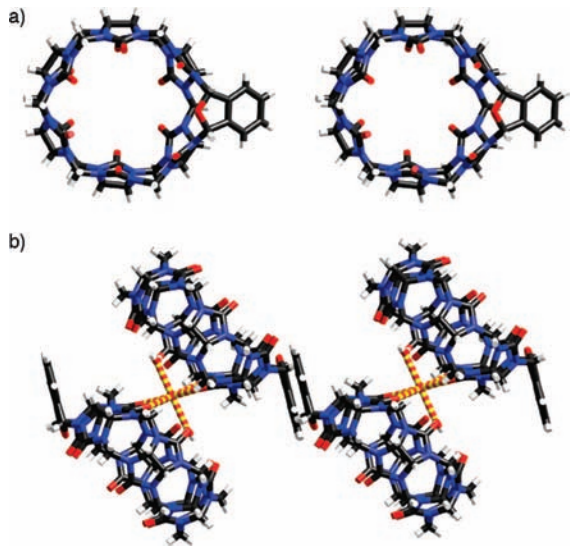

Figure 3. (a) Cross-eyed stereoview of **2** and (b) illustration of the packing of **2** in the crystal by C═O···K^+···O═C interactions. Color code: C, gray; H, white; N, blue; O, red; O···K^+ interactions, red-yellow striped. Solvating CF_3CO_2H and H_2O molecules have been removed for clarity.

Once the structures of *ns*-CB[6] and **2** had been established we decided to investigate their recognition behavior toward symmetrical diamines of increasing size (**3c**−**8**) to determine their effective cavity volumes. We found that both *ns*-CB[6] and **2** form inclusion complexes with **3c**−**7** but not with **8**. These experiments allow us to bracket the cavity volumes of *ns*-CB[6] and **2** between CB[6] (164 Å^3) and CB[7] (279 Å^3). Apparently, the expansion of the upper rim of **2** does not increase the cavity volume of **2** enough to allow complexation of the best guests for CB[7] (e.g., **8**). Complexation of symmetric guests like **3c**−**7** within hosts like *ns*-CB[6] and **2** with different upper and lower rims leads to

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[6] (a) Huang, W.-H.; Liu, S.; Zavalij, P. Y.; Isaacs, L. *J. Am. Chem. Soc.* **2006**, *128*, 14744–14745. (b) Huang, W.-H.; Zavalij, P. Y.; Isaacs, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7425–7427.

[7] The reaction between *ns*-CB[6] and (substituted) benzaldehydes was also conducted. We were unable to purify these reaction mixtures which consist of at least two compounds probably due to the potential for two diastereomeric orientations of the pendant Ar group.

reduction in guest symmetry upon complexation that is readily observed by ^{1}H NMR (e.g., Figure 2d, H_g, $H_{g'}$).

Compared to the electrostatic surface potential (ESP) map for CB[6] (Figure 4a), which has two equivalent ureidyl C═O portals, the ESP maps for *ns*-CB[6] (Supporting Information) and **2** (Figure 4b) are unsymmetrical. The upper rim of *ns*-CB[6] and the lower rim of **2** are significantly more negative. Given the fact that *ns*-CB[6] and **2** possess two different ureidyl C═O lined portals and that electrostatic potential at CB[*n*] portals is known to influence binding strength,[1b,8] we wondered whether the complexation of unsymmetrical amines and diamines (e.g., **9**−**20**) would favor one of the two conceivable diastereomers (Figure 4c; e.g. top-*ns*-CB[6]•guest versus bottom-*ns*-CB[6]•guest). Initially, we prepared the complexes between *ns*-CB[6] and **9** and observed a single diastereomer by ^{1}H NMR (Supporting Information).[9] Encouraged by this result, we decided to investigate the three series of guests (**10**−**13**, **14**−**17**, **18**−**20**) where Me and NH_3^+ groups are moved around the aromatic rings of aniline and benzylamine. For the *ns*-CB[6]**·10** (67:33) and *ns*-CB[6]**·11** (76:24) complexes we observed two sets of resonances that we assign to a mixture of top and bottom diastereomers. We next investigated the *meta*-substituted complex *ns*-CB[6]**·12**, which exists as a single diastereomer. The meta substitution in **12** (and **9**) does not allow strong ion-dipole interactions without imposing steric interactions between the CH_3-group and the wall of the *ns*-CB[6] cavity in one of the diastereomers.[10] Interestingly, meta-substituted **19** forms a mixture of top and bottom diastereomers with *ns*-CB[6] presumably because both portals are satisfied by ion−dipole interactions. Similar trends in top-bottom selectivity are seen for the benzylamine series (**14** − **17**). The complexes between ortho-substituted compounds **13**, **17**, and **20** and *ns*-CB[6] all exhibit fast exchange kinetics, which precludes a determination of the ratio of diastereomers in this series. Overall, we find that diastereoselective recognition inside *ns*-CB[6] can be achieved by combination of electrostatic and steric effects.

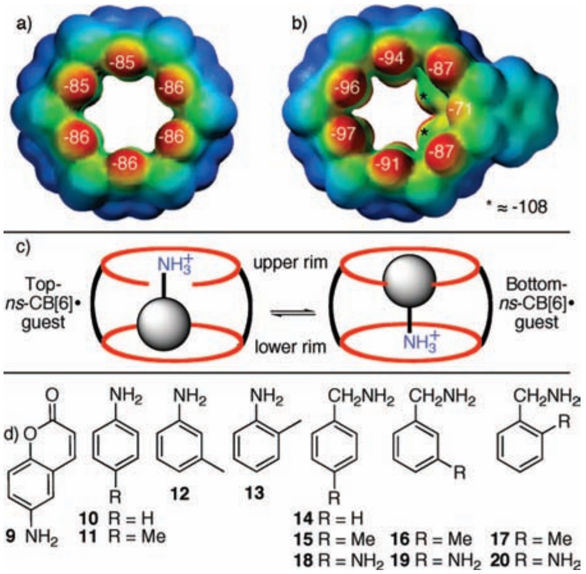

Figure 4. Electrostatic surface potential maps for (a) CB[6] and (b) **2**. The red to blue color range spans −85 to +35 kcal mol^{-1}. (c) Illustration of the two diastereomeric complexes possible with *ns*-CB[6] and **2** and (d) structures of guests for *ns*-CB[6].

We discovered an intriguing method of controlling diastereoselectivity for host **2** during our study of the complexes between **2** and the series of 1,*n*-alkanediammonium ions (**3a**−**i**, $n = 4, 5, 6, 7, 8, 9, 10, 11, 12$). For example, the ^{1}H NMR spectra for the **2·3c**, **2·3e**, and **2·3g** complexes (Figure 5) display a single set of resonances that correspond to a single diastereomer. Intriguingly, the symmetry equivalent CH_2 groups of the 1,*n*-alkanediammonium ion become nonequivalent in the complex and display *n*-resonances in their ^{1}H NMR spectra which reflect the asymmetric magnetic environment in the host−guest complex.[11] Of particular interest are the resonances for the CH_2 groups adjacent to the $^+NH_3$ groups (1 and 6, 1 and 8, and 1 and 10) that become widely separated (0.4−0.7 ppm) upon binding with

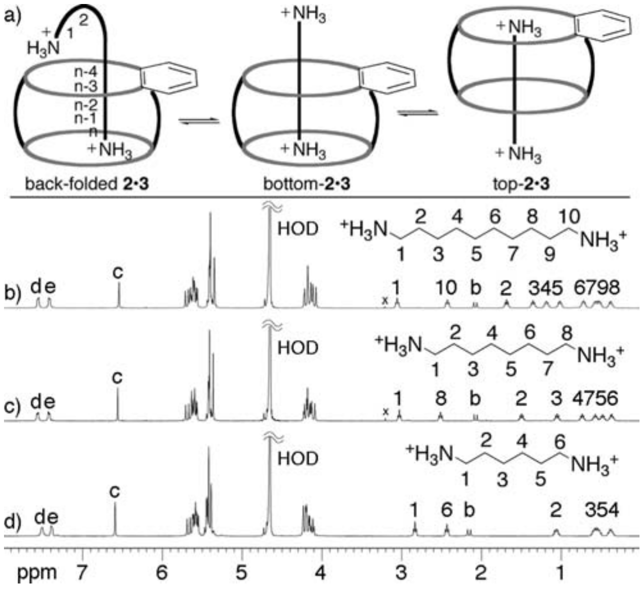

Figure 5. (a) Illustration of three possible diastereomers for **2·3** and ^{1}H NMR spectra (400 MHz, D_2O) for equimolar mixtures (3.6 mM) of **2** and (b) **3g**, (c) **3e**, and (d) **3c** (x = trace MeOH).

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(8) Ong, W.; Kaifer, A. E. *Organometallics* **2003**, *22*, 4181–4183.

(9) We did not observe intracomplex ROESY cross-peaks that would allow us to assign these complexes as a specific diastereomer. MMFF calculations (Supporting Information) suggest that the complex between *ns*-CB[6] and **9** is best formulated as bottom-*ns*-CB[6]**·9**.

(10) Mock previously showed that CB[6] binds to **11** but rejects isomeric **12** and **13** because only the geometry of **11** allows both substituents to pass through the C═O lined portals. See: Mock, W. L.; Shih, N. Y. *J. Org. Chem.* **1986**, *51*, 4440–4446.

(11) For examples of symmetrical CB[6]·alkanediammonium complexes, see ref 10 and: (a) Rekharsky, M. V.; Ko, Y. H.; Selvapalam, N.; Kim, K.; Inoue, Y. *Supramol. Chem.* **2007**, *19*, 39–46. (b) Buschmann, H.-J.; Mutihac, L.; Jansen, K.; Schollmeyer, E. *J. Inclusion Phenom. Macrocycl. Chem.* **2005**, *53*, 281–284.

one CH_2 downfield and one CH_2 upfield related to the free diammonium ion. The well-defined shielding region inside the cavity of CB[*n*]-type receptors and the deshielding region just outside the ureidyl C═O portals[10,12] allowed us to formulate the back-folding[13] that characterizes the geometry of the longer **2**·alkanediammonium ion (**3f**−**i**) complexes (Figure 5a). The pattern of the magnitude of complexation induced changes in chemical shift for the internal CH_2-groups are also consistent with the presence of this back-folded conformation. We conclude that the upper rim of **2**—in contrast to the lower rim—is wide enough to simultaneously permit the extension of the alkyl chain and allow ion-dipole interaction of a back-folded NH_3^+ group which drives the back-folding process. Related host-driven conformational changes of alkanes and alkylammonium ions were previously described by the groups of Rebek and Kim.[14,15] We were fortunate to obtain single crystals of **2·3f** and solve its X-ray structure (Figure 6). As predicted based on the ^1H NMR studies, **2·3f** exhibits a back-folded geometry in the crystal that benefits from the hydrophobic effect and ion-dipole interactions and H-bonds at both ureidyl C═O lined portals. Interestingly, the NH_3^+ group at the lower rim forms ion−dipole interactions/H-bonds with the C═O groups below the bridging *o*-xylylene group which have the highest ESP (Figure 4b).

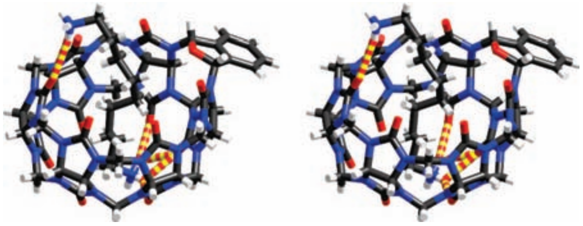

Figure 6. Cross-eyed stereoview of the X-ray crystal structure of **2·3f**. Color code: C, gray; H, white; N, blue; O, red; H-bonds, red-yellow striped.

In summary, we have reported the isolation of *ns*-CB[6], which is formally related to CB[6] by the removal of a single CH_2-group. *ns*-CB[6] functions as an aldehyde reactive cucurbituril synthon which allowed us to prepare CB[6]-derivative **2**. Both *ns*-CB[6] and **2** undergo top-bottom diastereoselective recognition processes toward ammonium and diammonium ions in water. Most intriguing is the ability of **2** to induce back-folding in the longer diammonium ions (e.g., **3f**−**i**). Beyond these recognition properties, the availability of *ns*-CB[6]—the first aldehyde reactive CB[*n*] synthon—has potentially widespread impact. For example, *ns*-CB[6] can undergo reaction with di-, tri-, and oligoaldehydes to deliver discrete well defined CB[6] dimers, trimers and oligomers as well as CB[6] derivatized surfaces, polymers, and separation materials. As such, we expect *ns*-CB[6] and its CB[6] derivatives to impact a range of application areas[4] including biochips, affinity chromatography, and drug delivery.

Acknowledgment. We thank the National Science Foundation (CHE-0615049) and the University of Maryland (Wylie Dissertation Fellowship to W.-H.H.) for financial support.

Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for *ns*-CB[6] and **2**, and ^1H NMR spectra for their host−guest complexes. Computational results for *ns*-CB[6], **2**, and selected host−guest complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] Buschmann, H.-J.; Wego, A.; Zielesny, A.; Schollmeyer, E. *J. Inclusion Phenom. Macrocycl. Chem.* **2006**, *54*, 241–246.

[13] For other examples of folding processes promoted by CB[*n*], see: (a) Ko, Y. H.; Kim, E.; Hwang, I.; Kim, K. *Chem. Commun.* **2007**, 1305–1315. (b) Liu, S.; Zavalij, P. Y.; Lam, Y.-F.; Isaacs, L. *J. Am. Chem. Soc.* **2007**, *129*, 11232–11241.

[14] A related phenomenon has been observed by Kim and co-workers for the complex of CB[8] with long-chain alkyltrimethylammonium ions Ko, Y. H.; Kim, H.; Kim, Y.; Kim, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 4106–4109.

[15] Rebek and co-workers have shown that *n*-alkanes exhibit helical conformations inside self-assembled capsules to maximize noncovalent interactions between host and guest. For a review, see Rebek, J. *Chem. Commun.* **2007**, 2777–2789.