Cucurbit[*n*]uril Derivatives Soluble in Water and Organic Solvents[**]

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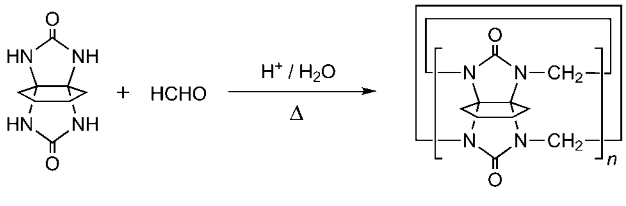
Cucurbituril (CB[6]), a macrocyclic cavitand comprising six glycoluril units, has a cavity of ~5.5 Å diameter that is accessible through two identical carbonyl-fringed portals.[1] Similar to cyclodextrins (CDs), the cavity can hold small organic molecules through hydrophobic interactions. Unlike CDs, however, the carbonyl groups at the portals allow CB[6] to bind ions and molecules through charge–dipole as well as hydrogen-bonding interactions.[1] The rigid structure and capability of forming complexes with molecules and ions make CB[6] very attractive as a synthetic receptor and as a building block for the construction of supramolecular architectures.[2, 3] Compared to the chemistry of CDs, however, that of CB[6] has developed slowly until recently which may be attributed mainly to its extremely poor solubility in common solvents, and the inability to functionalize these molecules. Our recent synthesis of higher CB homologues cucurbit[*n*]uril (CB[*n*], $n = 7$ and 8) with larger cavities, the dimensions of which are equivalent to those of β- and γ-CDs, respectively, opens up new possibilities in the chemistry of CB[*n*].[4] Nevertheless, the homologues also suffer the same shortcomings as CB[6].[5] Thus, synthesis of CB[*n*] derivatives having substituents at the peripheries that allow them to dissolve in common solvents, and to accept functionalization for further modifications would be a breakthrough in the chemistry of CB[*n*] and enable applications in many areas including separation, transport, and sensors. A straightforward approach to this goal may be condensation of glycoluril derivatives carrying alkyl or aryl groups at the "bridging" positions with formaldehyde, which would produce CB[*n*] derivatives with the corresponding substituents at the "equator". To date, however, the only successful synthesis of CB[*n*] derivatives from this approach (or by any other methods) is for decamethylcucurbit[5]uril (MeCB[5]),[6] synthesized from dimethylglycoluril, which nevertheless still suffers poor solubility in common solvents. After numerous unsuccessful attempts, we have finally succeeded in the synthesis of CB[*n*] derivatives from this condensation approach. Here we report the first CB[*n*] derivatives that are soluble in water as well as organic solvents.

Reaction of cyclohexanoglycoluril (**1**)[7] with formaldehyde in the presence of HCl produces a viscous solution, subsequent treatment of which with H_2SO_4 at 80 °C for 24 h yields a mixture of CB[*n*] derivatives containing *n* cyclohexanoglycoluril units (Scheme 1). The ^{1}H and ^{13}C NMR spectra reveal that the mixture contains cyclic pentamer ($n = 5$) and hexamer ($n = 6$) as major products (in a ~8:1 ratio), and a small amount of unidentified homologues. After a series of dissolution and fractional crystallizations, the pentamer (CB*[5]) and hexamer (CB*[6]) were isolated from the mixture in 16% and 2% yields, respectively.



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CB*[*n*] ($n = 5, 6$)

Scheme 1. Synthesis of CB*[*n*] ($n = 5, 6$).

The new CB derivatives CB*[5] and CB*[6] have been fully characterized by various methods including X-ray crystallography. Their X-ray analyses[8] reveal the expected structures with five and six fused cyclohexane rings, respectively, decorating the outside of the "equator" of CB[*n*] ($n = 5, 6$; Figure 1). The portal and cavity sizes of CB*[5] and CB*[6] are essentially the same as those of CB[5] and CB[6],

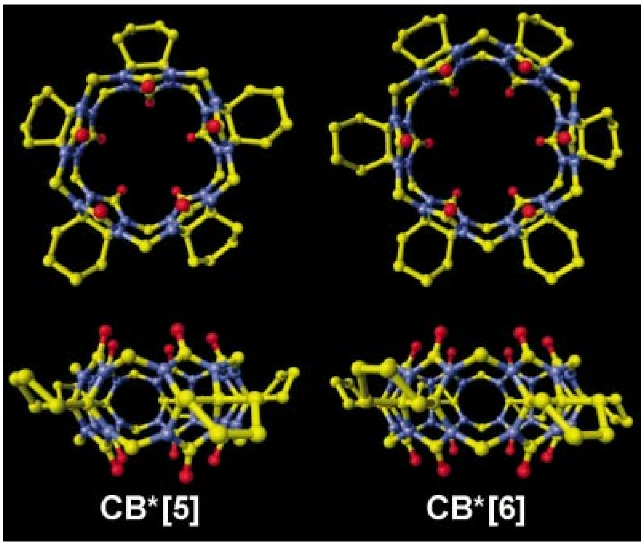

Figure 1. X-ray crystal structures of CB*[5] and CB*[6]. Water molecule(s) encapsulated in the cavities are omitted for clarity. Carbon: yellow, nitrogen: blue, oxygen: red.

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[**] We gratefully acknowledge Creative Research Initiative Program of the Korean Ministry of Science and Technology for support of this work and Brain Korea 21 Program of the Korean Ministry of Education for postdoctoral fellowship to J.Z. and graduate studentships to J.O. and S.-Y.K; $n = 5$ or 6.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

1433-7851/01/4022-4233 $ 17.50+.50/0

respectively: the mean cavity and portal diameters, 4.0 and 2.5 Å, respectively, for CB*[5], 5.4 and 4.0 Å, respectively, for CB*[6].

One of the most remarkable properties of these new cucurbituril derivatives CB*[5] and CB*[6] is their high solubility in common solvents such as water, methanol, DMSO, and reasonable solubility in ethanol, DMF, and acetonitrile.[9] Surprisingly, they are both more soluble in water ($\sim 2 \times 10^{-1}$ mol L^{-1}) than in organic solvents ($\sim 3 \times 10^{-2}$ mol L^{-1} or less) despite the presence of the equator-bound fused cyclohexane units. The solubility of CB*[6] in water is comparable to that of α-CD.

The remarkable solubility allowed us now to investigate the host–guest chemistry of CB*[5] and CB*[6] in *neutral* water. For example, a preliminary study on the complex formation of CB*[5] with K$^+$ ions in neutral water has been carried out using titration calorimetry. CB*[5] binds K$^+$ ions in a 1:2 stoichiometry with lgK_1 and lgK_2 values of 4.11 ± 0.06 and 2.16 ± 0.03 (pH 6.9), respectively.[10] This result is in contrast to the previous report[11] that MeCB[5] binds K$^+$ ions (and other alkali metal ions) in a 1:1 stoichiometry with lg$K$ of 3.48 in a 50 % formic acid/water solution. The acidic medium has been employed in most binding studies of CB[6] or MeCB[5] because of their poor solubility in neutral water.[1, 11–13] The reported 1:1 binding stoichiometry between MeCB[5] and alkali metal ions in the acidic medium has been attributed to the protonation of one of the receptor portals leaving only the other available for binding a metal ion.[11] The present binding study in neutral water, however, clearly demonstrates that the previously reported 1:1 binding stoichiometry and lower binding constant are a consequence of competition between metal ions and proton for the same binding site in the acidic medium. Comprehensive studies of the binding of CB*[5] and CB*[6] to metal and other ions in neutral aqueous solution are underway.[14]

The utility of water-soluble CB*[6] may be illustrated by the formation in neutral water of a stable 1:1 host–guest complex with acetylcholine, an important neurotransmitter. In the host–guest complex, the acetylcholine trimethylammonium groups are located outside CB*[6] whereas the rest of the molecule resides inside CB*[6] as determined by the NMR chemical shift changes upon complex formation. The formation constant and thermodynamic parameters associated with the inclusion phenomenon have been determined by NMR spectroscopy: lg$K = 3.11$, $\Delta H^0 = -2.7$ kcal mol^{-1}, and $\Delta S^0 = 3.6$ cal mol^{-1} K^{-1}.[15] On the other hand, choline exhibits little interaction with CB*[6] as shown by ^{1}H NMR spectroscopy. CB*[6] therefore behaves as an artificial receptor that can differentiate acetylcholine from choline in neutral water, a property that may find useful applications in neuroscience.

The good solubility of CB*[5] and CB*[6] in organic solvents allowed us to prepare membrane electrodes for ion sensing.[16] In particular, a membrane electrode prepared with CB*[5] was expected to function as an ion-selective electrode (ISE) for Pb^{2+} ions because MeCB[5] had been reported to bind Pb^{2+} ions exceptionally well.[11] A preliminary study revealed that CB*[5] indeed behaves as an ISE for Pb^{2+} ions with good sensitivity and selectivity (Figure 2a; see also Supporting Information). Furthermore, a membrane electrode prepared with CB*[6] is good for detecting acetylcholine with high selectivity over choline and other interfering ions such as Na$^+$, K$^+$, and NH$_4^+$ (Figure 2b), which may be useful in monitoring the neurotransmitter in biological samples.[17] Details of the applications of CB*[5] and CB*[6] in ISEs will be reported separately.

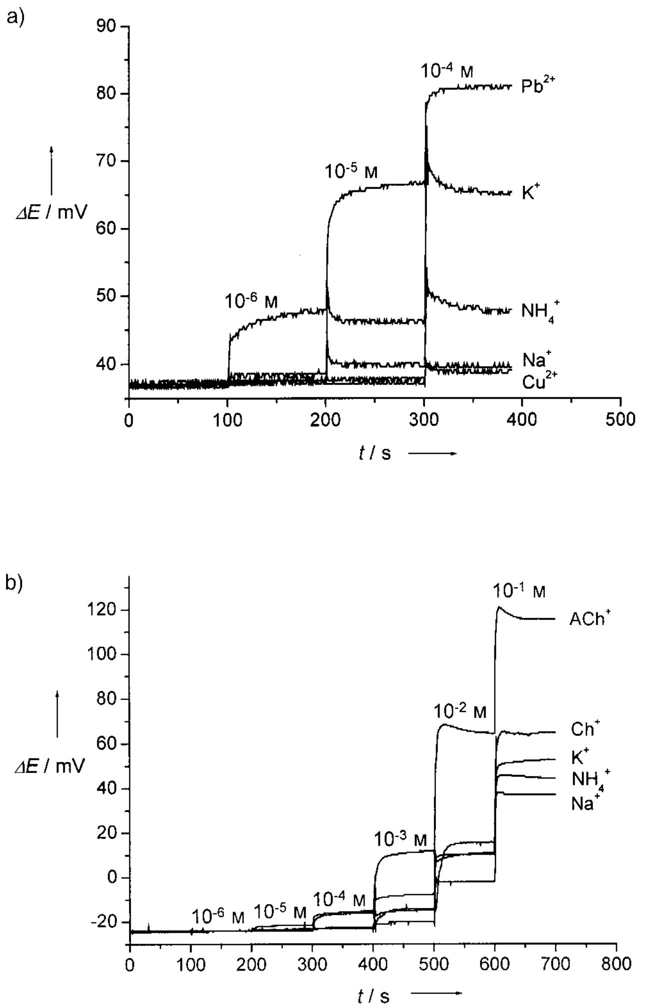

Figure 2. a) Responses of an ISE based on CB*[5] to Pb^{2+} and other ions (pH 4.0 with 1 mM Mg(OAc)$_2$/HCl buffer); b) Responses of an ISE based on CB*[6] to acetylcholine (ACh$^+$) and other interfering ions including choline (Ch$^+$) (pH 7.2 with 10 mM Tris buffer). All analytes were used as chloride salts except Pb(NO$_3$)$_2$ and Cu(NO$_3$)$_2$. OAc = acetate, Tris = 2-amino-2-(hydroxymethyl)-1,3-propanediol.

In conclusion, we have synthesized the first CB[n] ($n = 5, 6$) derivatives that are soluble in water as well as organic solvents. Their high solubility in common solvents should expand the utilities of CB*[n]. Moreover, it should be possible to introduce other functionalizable substituents at the equator of CB[n] by using the same synthetic method. We may also be able to synthesize other homologues containing higher numbers of substituted glycoluril units.

Experimental Section

CB*[n] ($n = 5$, 6): 37 % HCl (0.16 mL) was added to a mixture of **1** (see Supporting Information; 2.0 g, 10.2 mmol) and 30 % formaldehyde (1.9 mL, 23.4 mmol). The mixture was stirred and heated to 80 °C to give a purple viscous solution. After concentrated H$_2$SO$_4$ (2.5 mL) and water

(5.0 mL) were added, the purple solution was heated at 80 °C for 24 h. The solution was allowed to cool to room temperature, and then diluted with water (10 mL). The solution was poured into acetone (300 mL) to precipitate a solid, which was collected by filtration, and redissolved in water (50 mL). After the solution was neutralized with triethylamine, the solvent was removed under reduced pressure. The remaining solid was suspended in CH_3CN (20 mL) and the suspension filtered. The filter cake contains CB*[5] as a major product whereas the filtrate contains mostly CB*[6]. Recrystallization of the crude products from water produced colorless crystalline products CB*[5] (356.7 mg, 16 %) and CB*[6] (47.8 mg, 2 %). CB*[5]: ^1H NMR (300 MHz, D_2O): $\delta = 5.64$ (d, $J = 15.6$ Hz, 10 H), 4.33 (d, $J = 15.8$ Hz, 10 H), 2.20 (s, 20 H), 1.46 (s, 20 H); ^{13}C NMR (75 MHz, D_2O): $\delta = 156.33$, 76.45, 43.51, 23.56, 14.0; IR (KBr): $\tilde{\nu}_{CO}$ 1745 cm^{-1}; MS (ESI): m/z (%): 1123.5 (100) $[M+Na]^+$. CB*[6]: ^1H NMR (300 MHz, D_2O): $\delta = 5.73$ (d, $J = 15.9$ Hz, 12 H), 4.32 (d, $J = 16.0$ Hz, 12 H), 2.26 (s, 24 H), 1.49 (s, 24 H); ^{13}C NMR (75 MHz, D_2O): $\delta = 156.43$, 76.51, 44.1, 23.37, 14.07; IR (KBr): $\tilde{\nu}_{CO}$ 1734 cm^{-1}; MS (ESI): m/z (%): 1361.6 (100) $[M+Na+H_2O]^+$. Satisfactory elemental analyses were obtained for CB*[5] and CB*[6].

Received: June 12, 2001
Revised: September 10, 2001 [Z 17272]

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[1] Reviews on cucurbituril: a) W. L. Mock, *Top. Curr. Chem.* **1995**, *175*, 1; b) P. Cintas, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *17*, 205; c) W. L. Mock in *Comprehensive Supramolecular Chemistry*, *Vol. 2* (Ed.: F. Vögtle), Pergamon, Oxford, **1996**, p. 477.

[2] a) D. Whang, Y.-M. Jeon, J. Heo, K. Kim, *J. Am. Chem. Soc.* **1996**, *118*, 11 333; b) D. Whang, K. Kim, *J. Am. Chem. Soc.* **1997**, *119*, 451; c) D. Whang, K.-M. Park, J. Heo, K. Kim, *J. Am. Chem. Soc.* **1998**, *120*, 4899; d) S.-G. Roh, K.-M. Park, G.-J. Park, S. Sakamoto, K. Yamaguchi, K. Kim, *Angew. Chem.* **1999**, *111*, 672; *Angew. Chem. Int. Ed.* **1999**, *38*, 638; e) E. Lee, J. Heo, K. Kim, *Angew. Chem.* **2000**, *112*, 2811; *Angew. Chem. Int. Ed.* **2000**, *39*, 2699; f) E. Lee, J. Kim, J. Heo, D. Whang, K. Kim, *Angew. Chem.* **2001**, *113*, 413; *Angew. Chem. Int. Ed.* **2001**, *40*, 399; g) J. W. Lee, Y. H. Ko, S.-H. Park, K. Yamaguchi, K. Kim, *Angew. Chem.* **2001**, *113*, 769; *Angew. Chem. Int. Ed.* **2001**, *40*, 746.

[3] a) M. N. Sokolov, A. V. Virovets, D. N. Dybtsev, O. A. Gerasko, V. P. Fedin, R. Hernandez-Molina, W. Clegg, A. G. Sykes, *Angew. Chem.* **2000**, *112*, 1725; *Angew. Chem. Int. Ed.* **2000**, *39*, 1659; b) D. Tuncel, J. H. G. Steinke, *Chem. Commun.* **1999**, 1509; c) C. Meschke, H.-J. Buschmann, E. Schollmeyer, *Polymer* **1999**, *40*, 945.

[4] a) 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; b) H.-J. Kim, J. Heo, W. S. Jeon, E. Lee, J. Kim, S. Sakamoto, K. Yamaguchi, K. Kim, *Angew. Chem.* **2001**, *113*, 1574; *Angew. Chem. Int. Ed.* **2001**, *40*, 1526; c) S.-Y. Kim, I.-S. Jung, E. Lee, J. Kim, S. Sakamoto, K. Yamaguchi, K. Kim, *Angew. Chem.* **2001**, *113*, 2177; *Angew. Chem. Int. Ed.* **2001**, *40*, 2119.

[5] CB[*n*] compounds are appreciably soluble in neutral aqueous solutions only when the solutions contain alkali metal ions in high concentrations (> 0.1 M): a) Y.-M. Jeon, J. Kim, D. Whang, K. Kim, *J. Am. Chem. Soc.* **1996**, *118*, 9790; b) D. Whang, J. Heo, J. H. Park, K. Kim, *Angew. Chem.* **1998**, *110*, 83; *Angew. Chem. Int. Ed.* **1998**, *37*, 78.

[6] A. Flinn, G. C. Hough, J. F. Stoddart, D. J. Williams, *Angew. Chem.* **1992**, *104*, 1550; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1475.

[7] IUPAC name: 1*H*,4*H*-3a,6a-butanoimidazo[4,5-*d*]imidazole-2,5(3*H*,6*H*)-dione; G. I. Polozov, I. G. Tishchenko, *Vestsi Akad. Navuk BSSR Ser. Khim. Navuk* **1978**, *3*, 62.

[8] Crystals of CB*[*n*] ($n = 5, 6$) suitable for X-ray work were grown from aqueous solution in a refrigerator. Crystal data of CB*[5]: $[(C_{50}H_{60}N_{20}O_{10})\cdot 25\,H_2O]$, $M_r = 1551.58$, triclinic, $P\bar{1}$ (No. 2), $a = 15.0886(2)$, $b = 15.7065(1)$, $c = 17.8902(3)$ Å, $\alpha = 101.802(1)$, $\beta = 109.337(1)$, $\gamma = 108.471(1)^\circ$, $V = 3560.49(8)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.447$ g cm^{-3}, $T = 223$ K, $\mu = 1.22$ cm^{-1}. Siemens SMART diffractometer, $Mo_{K\alpha}$ ($\lambda = 0.71073$ Å), all non-hydrogen atoms were refined anisotropically (SHELXL-93). Final refinement on F^2 with all 10 651 reflections and 955 variables converged to $R1\,(>2\sigma(I)) = 0.0925$, $wR2$ (all data) = 0.2557, and GOF = 1.094. Crystal data of CB*[6]: $[(C_{60}H_{72}N_{24}O_{12})\cdot 18\,H_2O]$, $M_r = 1645.70$, $P\bar{1}$ (No. 2), $a = 12.7505(1)$, $b = 15.1302(3)$, $c = 19.3353(4)$ Å, $\alpha = 91.2977(8)$, $\beta = 92.8870(8)$, $\gamma = 92.9115(1)^\circ$, $V = 3719.39(11)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.469$ g cm^{-3}, $T = 223$ K, $\mu = 1.18$ cm^{-1}. Final refinement on F^2 with all 11 157 reflections and 1045 variables converged to $R1\,(I > 2\sigma(I)) = 0.0826$, $wR2$ (all data) = 0.2235, and GOF = 1.126. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-164887 (CB*[5]), and -164888 (CB*[6]). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[9] The solubility of CB*[*n*] ($n = 5, 6$) in a solvent was determined by ^1H NMR spectroscopy with an internal standard (see Supporting Information). Solubility (mol L^{-1}) of CB*[5] (CB*[6]): 2.6×10^{-1} (1.7×10^{-1}) in D_2O, 3.1×10^{-2} (4.3×10^{-2}) in [D$_4$]methanol, 1.8×10^{-2} (3.9×10^{-2}) in [D$_6$]DMSO, 1.3×10^{-3} (6.5×10^{-4}) in [D$_6$]ethanol, 2.5×10^{-3} (3.4×10^{-3}) in [D$_7$]DMF, 6.7×10^{-4} (2.1×10^{-3}) in [D$_3$]acetonitrile.

[10] $\Delta H_1 = -1.49 \pm 0.01$ kcal mol^{-1}, $\Delta S_1 = 13.89$ cal mol^{-1} K^{-1}; $\Delta H_2 = -1.49 \pm 0.04$ kcal mol^{-1}, $\Delta S_2 = 4.98$ cal mol^{-1} K^{-1}.

[11] X. X. Zhang, K. E. Krawowiak, G. Xue, J. S. Bradshaw, R. M. Izatt, *Ind. Eng. Chem. Res.* **2000**, *39*, 3516.

[12] a) H.-J. Buschmann, K. Jansen, C. Meschke, E. Schollmeyer, *J. Solution Chem.* **1998**, *27*, 135; b) H.-J. Buschmann, K. Jansen, E. Schollmeyer, *Thermochim. Acta* **1998**, *317*, 95; c) H.-J. Buschmann, K. Jansen, E. Schollmeyer, *Thermochim. Acta* **2000**, *346*, 33.

[13] R. Hoffmann, W. Knoche, C. Fenn, H.-J. Buschmann, *J. Chem. Soc. Faraday Trans.* **1994**, *90*, 1507.

[14] We performed a preliminary study on the complex formation of CB*[6] with Na^+ ions in neutral water by titration calorimetry, but failed to determine the binding stoichiometry unequivocally as the data can be fitted into 1:2, 1:3, and 1:4 binding models equally well. A further detailed study is needed to establish the binding stoichiometry and affinity.

[15] This inclusion process is accompanied by a positive entropy change, which has been observed in other systems: J. Kang, J. Rebek, Jr., *Nature* **1996**, *382*, 239.

[16] a) E. Bakker, P. Bühlmann, E. Pretsch, *Chem. Rev.* **1997**, *97*, 3083; b) P. Bühlmann, E. Pretsch, E. Bakker, *Chem. Rev.* **1998**, *98*, 1593.

[17] a) P. S. Bates, R. Kataky, D. Parker, *Chem. Commun.* **1993**, 691; b) O. Niwa, T. Horiuchi, R. Kurita, K. Torimitsu, *Anal. Chem.* **1998**, *70*, 1126.

Self-Assembly of a Mixed-Valence Copper(II)/Copper(III) Dithiocarbamate Catenane[**]

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During the past few decades the design and high-yielding syntheses of interlocked macrocyclic molecules, the catenanes,[1] have evolved mainly as a result of the elegant and inspirational transition metal and organic templated synthetic

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[**] We thank the EPSRC for a postdoctoral fellowship (O.D.F.) and the EPSRC and University of Reading for funds for the crystallographic image plate system.