Synthesis of Norbornahemicucurbiturils

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Abstract: Ethyleneurea fused with a norbornane ring was prepared. Acid-catalyzed polycondensation of the urea with paraformaldehyde yielded a new six-membered hemicucurbituril derivative. The presence of hemicucurbiturils containing from four to eight monomer units were also detected.

Key words: hemicucurbiturils, cucurbiturils, macrocycles, polycondensation, supramolecular chemistry

Hemicucurbit[*n*]urils (HmCB[*n*]) are macrocyclic compounds consisting of *n* ethyleneurea units linked together with *n* methylene bridges[1] (Figure 1). The name of HmCB[*n*]s was chosen because of their structural resemblance to cucurbit[*n*]urils (CB[*n*]s)[2,3] that have been divided in half along the equator. HmCB[*n*]s were introduced in 2004 by Miyahara et al., who prepared six- and twelve-membered rings, HmCB[6] and HmCB[12]. These compounds were synthesized by a Mannich-type[4] polycondenzation reaction of ethyleneurea with formaldehyde in aqueous HCl. The size of the prepared hemicucurbituril macrocycle can be controlled by the concentration of the acid, reaction time, and temperature. HmCB[6] was obtained in an excellent yield of 94% as a precipitate from 4 M HCl after stirring at room temperature for 30 minutes. Chloride anions act as a template and the resulting HmCB[6] is the kinetic product of the reaction. HmCB[12] requires 1 M HCl, a temperature of 55 °C, and is formed as a gel after three hours. The conformation of ethyleneurea units within HmCB[*n*] differs significantly from that of glycoluril in CB[*n*]s (Figure 1). Glycoluril units of CB[*n*]s are linked together with a pair of methylene bridges, resulting in a very rigid structure with only little conformational variability. On the other hand, only one row of CH_2 bridges connect the ethyleneurea units of HmCB[*n*]s, allowing rotations of the individual units with respect to each other. With this freedom, ethyleneurea units adopt an alternate conformation in which the carbonyl groups of adjacent urea units are directed towards opposite sides of the macrocycle plane. A similar conformation was previously described in a related family of macrocyclic compounds – bambus[*n*]urils (Figure 1).[5]

Until today, only two derivatives of HmCB[*n*]s have been reported.[6,7] The syntheses were performed according to the protocol for HmCB[*n*]s but *cis*- and *trans*-octahydro-2*H*-benzimidazol-2-one instead of ethyleneurea was used, and elevated temperature was required for the formation of the macrocyclic product. The resulting macrocycles contained six ethyleneurea units fused with cyclohexane rings.

Vladimir Sindelar (left) was born in Pelhrimov, Czech Republic, in 1975. He received his Ph.D. in polymer chemistry from the Institute of Chemical Technology, Prague, in 2002 under the supervision of Petr Sysel. After a period of postdoctoral research at the Heriot-Watt University with Graeme Cooke, and the University of Miami with Angel E. Kaifer, he joined Masaryk University, where he is now Associate Professor of Organic Chemistry. His research focuses on the synthesis of supramolecular host molecules including cucurbiturils and bambusurils and the investigation of their self-sorting processes.
Tomas Fiala (right) was born in Brno, Czech Republic, in 1990. He obtained his bachelor's degree from Masaryk University in 2013. He is currently pursuing his M.Sc. degree with Vladimir Sindelar at the same university.

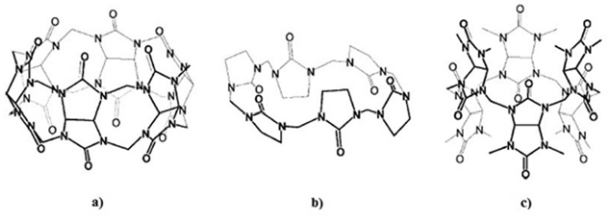

Figure 1 (a) Cucurbit[*n*]uril CB[6], (b) Hemicucurbit[*n*]uril HmCB[6], and (c) Me_{12}BU[6]

HmCB[*n*]s have been investigated for their ability to bind anions and cations,[7–9] and they have also been used in crystal engineering and catalysis.[6,10] The introduction of new substituents on the hemicucurbituril framework could modify their binding affinity as well as catalytic properties and could also tune their packing in the crystal structure. Therefore, we decided to investigate the preparation of a new HmCB[*n*] derivative.

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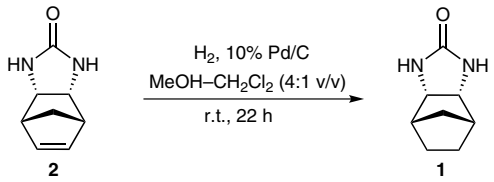
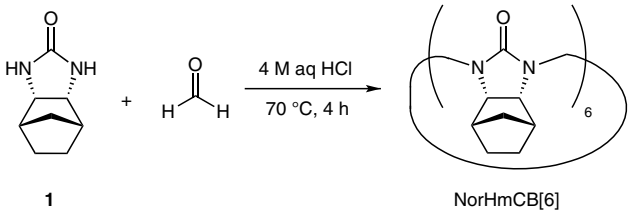


Scheme 1 Reduction of *endo*-3,5-diazatricyclo[5.2.1.0^{2,6}]dec-8-ene-4-one (**2**) to *endo*-3,5-diazatricyclo[5.2.1.0^{2,6}]decane-4-one (**1**)

We selected *endo*-3,5-diazatricyclo[5.2.1.0^{2,6}]decane-4-one (**1**) as a basic building block for the synthesis. This modified ethyleneurea is more spacious and rigid compared with those previously used. It was prepared by the reduction of *endo*-3,5-diazatricyclo[5.2.1.0^{2,6}]dec-8-ene-4-one (**2**) under hydrogen gas (1 atm) in the presence of 10% Pd/C (Scheme 1).[11] The starting material **2** was synthesized in several steps through the preparation of 2,3-dihydro-1*H*-imidazol-2-one, its conversion into the corresponding diacetyl, followed by Diels–Alder cycloaddition with cyclopentadiene and final deacetylation. All these methods, which were described in literature,[12–14] were optimized to increase the reaction yields (see the Supporting Information). Macrocyclization of ethyleneurea **1** with paraformaldehyde was performed in 4 M HCl at 70 °C for four hours (Scheme 2).[15] Hydrochloric acid was chosen because it proved to be most efficient for the preparation of this class of macrocyclic compounds.[7] After investigating various acid concentrations and temperatures, the given conditions were found to be optimal regarding the yield and purity of the product. The formation of macrocycles did not take place when an HCl concentration of less than 3 M was used. Higher reaction temperatures resulted in the formation of an impurity that was difficult to separate from the product.

Being inspired by the preparation of benzyl groups containing bambusurils,[16] we also attempted to prepare the target macrocycle in chloroform by using *p*-toluenesulfonic acid and trifluoroacetic acid. However, all attempts to prepare the products in organic solvent, both in the presence and in the absence of tetrabutylammonium iodide as a template, failed to give the desired macrocyclic product.



Scheme 2 Macrocyclization of **1**; synthesis of norbornahemicucurbit[6]uril (NorHmCB[6])

The macrocyclization in aqueous HCl provided a white precipitate that was collected by filtration and analyzed by MALDI-TOF MS and ^{1}H NMR spectroscopy. Although MS analysis revealed only signals corresponding to the hexameric hemicucurbituril (Figure 2), NMR spectra were more complex. This indicates the presence of low molecular weight oligomers that were not detected by MALDI-TOF mass spectrometry. The pure hexamer was obtained after silica gel column chromatography by using acetone–$CHCl_3$ (1:4 v/v) as the mobile phase. In accordance with the nomenclature used in cucurbituril chemistry, we named the new macrocycle norbornahemicucurbit[6]uril (NorHmCB[6]).

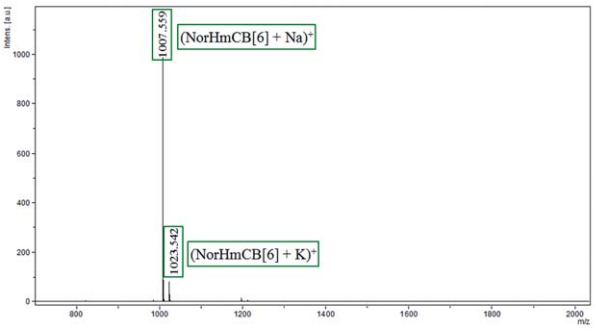


Figure 2 MALDI-TOF MS analysis (HCCA, positive mode) of the crude white precipitate after macrocyclization of **1**

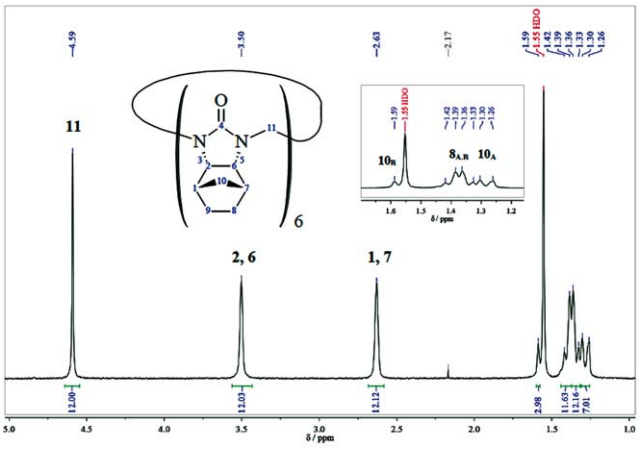


Figure 3 ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) spectrum of NorHmCB[6]

Ethyleneurea units within the macrocycle are relatively large, which prevents their free rotation. Among others, two probable arrangements of the units – alternate and cone – are possible. The ^{1}H NMR spectrum of the macrocycle showed a singlet at δ = 4.59 ppm corresponding to two chemically equivalent hydrogen atoms of the methylene bridges C(11)-H_2 (Figure 3). This signal is characteristic for the alternate arrangement of the ethyleneurea units, as known for all hemicucurbiturils and bambusurils.[1,5,6] Unique singlets of methanetriyl hydrogen signals from C(2,6)-H and C(1,7)-H prove that the orientation of all ethyleneurea units within the macrocycle are identical. The *endo*- configuration of the monomer units in NorHmCB[6] together with steric effects of the spacious norbornane rings ensure that the C(2,6)-H hydrogen atoms point

to the center of the macrocycle cavity whereas the norbornane groups are reversed out.

The filtrate that was left after collecting the precipitate from the reaction mixture was analyzed by MALDI-TOF MS. Surprisingly, not only the six-membered macrocycle was found but also macrocycles with 4, 5, 7, and 8 ethyleneurea units were detected in the spectrum (Figure 4). Until now, only six- and twelve-membered hemicucurbiturils have been reported. This unexpected result is currently under investigation.

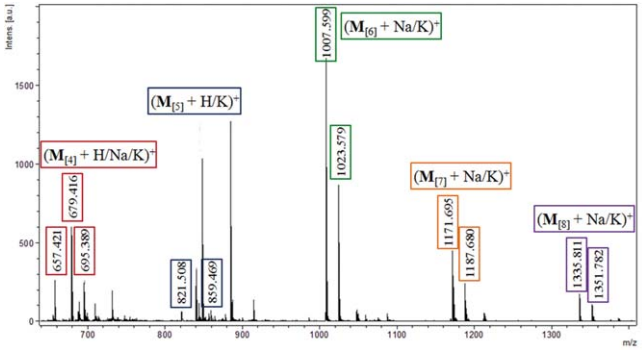


Figure 4 MALDI-TOF MS (HCCA, positive mode) of the filtrate after the macrocyclization of **1** ($\mathbf{M}_{[n]}$ = NorHmCB[*n*])

In conclusion, a new hexameric derivative of hemicucurbituril has been isolated and fully characterized. *endo*-3,5-Diazatricyclo[5.2.1.$0^{2,6}$]decane-4-one was used as an ethylene urea derivative for the macrocyclization. Hemicucurbiturils differing in the number of glycoluril units are side products of this reaction.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) ***endo*-3,5-Diazatricyclo[5.2.1.$0^{2,6}$]decane-4-one (1):** A solution of **2** (0.27 g, 1.8 mmol) in MeOH–CH_2Cl_2 (12 mL, 4:1 v/v) was stirred under an atmospheric pressure of H_2 in the presence of 10% Pd/C (0.12 g) for 22 h. The resulting mixture was filtered through Celite, washed with MeOH (15 mL) and the combined filtrates were concentrated in vacuo to give **1** (0.26 g, 1.7 mmol, 95%) as a white solid; mp 235.7–236.1 °C (dec.). IR (KBr): 710 (m), 774 (m), 1131 (m), 1252 (m), 1351 (m), 1466 (m), 1690 (s), 2871 (m), 2949 (s), 3067 (br. m), 3218 (br. s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 1.36 (d, *J* = 8 Hz, 2 H, C(8,9)-H_A), 1.39 (d, *J* = 11 Hz, 1 H, C(10)-H_A), 1.48 (d, *J* = 11 Hz, 1 H, C(10)-H_B), 1.71 (d, *J* = 8 Hz, 2 H, C(8,9)-H_B), 2.32 (s, 2 H, C(1,7)-H), 3.96 (s, 2 H, C(2,6)-H), 4.75 (br s, 2 H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ = 21.7 (C(8,9)-H_2), 36.4 (C(10)-H_2), 40.8 (C(1,7)-H), 57.7 (C(2,6)-H), 163.6 (C=O). HRMS: *m*/*z* calcd. for $[C_8H_{12}N_2O+H]^+$: 153.1022; found: 153.1022.
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(15) **Norbornahemicucurbit[6]uril (NorHmCB[6]):** Compound **1** (0.25 g, 1.6 mmol) was dissolved in 4 M aq HCl (20 mL) at 70 °C. Paraformaldehyde (0.054 g, 1.8 mmol of CH_2O) was added and the resulting mixture was heated at 70 °C for 4 h (during this period a white precipitate formed). The solid material was collected by filtration, washed with H_2O (10 mL), and dried in vacuo. The desired macrocyclic product was separated from the crude mixture by silica gel column chromatography (acetone–$CHCl_3$, 1:4 v/v). Yield: 0.024 g (0.024 mmol, 8.9%); mp >250 °C. IR (KBr): 614 (m), 760 (m), 813 (w), 1216 (s), 1372 (s), 1441 (s), 1699 (s), 2871 (m), 2961 (m), 3437 (br m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 1.28 (d, *J* = 13 Hz, 6 H, C(10)-H_A), 1.34 (d, *J* = 11 Hz, 12 H, C(8,9)-H_A), 1.40 (d, *J* = 11 Hz, 12 H, C(8,9)-H_B), 1.57 (d, *J* = 13 Hz, 6 H, C(10)-H_B), 2.63 (s, 12 H, C(1,7)-H), 3.50 (s, 12 H, C(2,6)-H), 4.59 (s, 12 H, C(11)-H_2). ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ = 21.9 (C(8,9)-H_2), 36.4 (C(10)-H_2), 39.4 (C(1,7)-H), 49.1 (C(11)-H_2), 57.0 (C(2,6)-H), 160.4 (C=O). HRMS: *m*/*z* calcd for $[C_{54}H_{72}N_{12}O_6+H]^+$: 985.5771; found: 985.5777. Anal. Calcd for $C_{54}H_{72}N_{12}O_6 \cdot 2\,H_2O$: C, 63.51; H, 7.50; N, 16.46. Found: C, 63.55; H, 7.55; N, 15.75.
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