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New Chiral Cyclohexylhemicucurbit[6]uril

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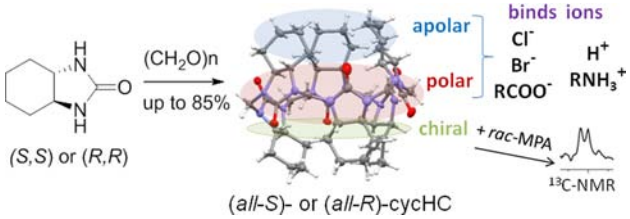
ABSTRACT



The first enantiomerically pure members of the cucurbituril family, (*all-S*)- and (*all-R*)-cyclohexylhemicucurbit[6]urils (cycHC), were synthesized in good yield (up to 85%). The crystal structure of this new macrocycle clearly shows its ball-like shape. CycHC monomers adopt a "zigzag" conformation, having apolar cyclohexyls around the openings and polar ureas in the middle. Cyclohexylhemicucurbit[6]urils formed complexes with halides, carboxylic acids and amines and diastereomeric complexes with methoxyphenylacetic acid in organic media. The association constants of cycHC with small organic compounds were evaluated by diffusion NMR in chloroform.

The first synthesis of macrocyclic ureas was reported by Behrend et al. in 1905; later they were named cucurbiturils[1] by Mock et al. in 1981.[2] The pioneering work on the characterization of the first cucurbituril, CB[6], and its complexation studies performed by Mock were taken further by Kim and co-workers, who isolated new members of the cucurbituril family, CB[5], CB[7] and CB[8],[3] in 2000. Less than two years later, Day et al. isolated the host–guest pair CB[5]@CB[10].[4] Since then studies of cucurbiturils have dramatically grown in number, especially with respect to their host–guest chemistry. Cucurbiturils form complexes with inorganic species (metallic cations and their counteranions) and with various organic guests, binding especially well with diammonium compounds.[5]

Not only has the family of cucurbiturils grown in the ring size of homologues, which differ in the number of monomers in the macrocycle, but also there has been progress in the synthesis of new relatives of cucurbiturils: inverted cucurbiturils (*i*CB[*n*]s),[6] *ns*-cucurbit[*n*]urils,[7] and various cyclic[8] and acyclic congeners.[9] Soon after the discovery of the usefulness of the cucurbituril family, Miyahara et al.

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synthesized hemicucurbiturils, HC[6] and HC[12], which can be viewed as cucurbiturils that are cut in half along the equator.[10] Li et al. synthesized and reported the crystal structure of a substituted hemicucurbituril *meso*-cyclohexylhemicucurbit[6]uril.[11] Hemicucurbiturils have, because of their "zigzag" conformation, a significantly different complexation ability from cucurbiturils. Hemicucurbit[6]urils form complexes with selected anions, cations, and small molecules (water and formamide).[10,12]

In the most recent development in the member list of the cucurbituril family, the research group of Sindelar[13] introduced bambus[*n*]urils, which combine the structural properties of cucurbiturils (glycouril monomers) and hemicucurbiturils (zigzag conformation). The list of bambus[*n*]urils was increased by Rivollier et al.[14] this year. Compared to cucurbiturils, bambusurils have enhanced structural flexibility and good solubility in organic solvents.

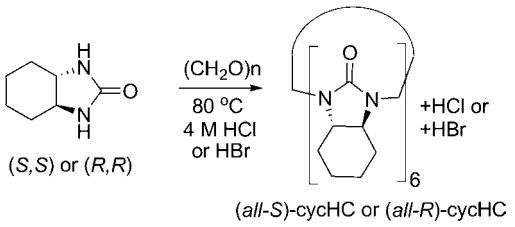
These given examples complete the list of known cucurbituril congeners, of which only one has been shown to exhibit chiral recognition toward an enantiomerically pure guest, the *nor-seco*-cucurbituril (±)-*bis-ns*-CB[6], which was synthesized from achiral monomers in racemic form.[7b]

In this paper, we describe the synthesis, structure, and complex formation of the new chiral (*all-R*)- and (*all-S*)-cyclohexylhemicucurbit[6]urils.

Enantiomerically pure hemicucurbit[6]urils ((*all-S*)- and (*all-R*)-cycHC, Scheme 1) can be synthesized from (*S*,*S*)- and (*R*,*R*)-cyclohexane ureas. Both enantiomers of starting ureas can be easily derived from 1,2-cyclohexanediamine by stereoselective crystallization with L- or D-tartaric acid[15] and subsequent carbonylation with diphenylcarbonate.[16] The enantiomeric purity of derived hemicucurbiturils is inherited from the *trans*-1,2-cyclohexanediamines.

Cyclohexylhemicucurbit[6]urils (cycHC) are formed by heating the starting urea and formaldehyde in 4 M aqueous hydrochloric or hydrobromic acid. CycHC is the main product formed in thermodynamically controlled conditions and precipitates from the reaction mixture as HCl or HBr complex in good yield (85% of cycHC+HCl and 64% of cycHC+HBr) (Scheme 1). The existence of such reaction products as 1:1 halogenide complexes was determined by ESI-MS and quantitative NMR analysis. So far our attempts to isolate macrocyclic products from the reactions catalyzed by other acids, namely, sulfuric, trifluoroacetic, and hydroiodic acids, have failed.

Scheme 1. Synthesis of Cyclohexylhemicucurbit[6]urils



CycHC formed carbon tetrachloride solvate monocrystals from a mixture of CCl_4 and diisopropylethylamine. The crystal structure showed that 6 monomers incorporated into cycHC adopted zigzag conformations, as with all single-bridged members of the cucurbituril family (Figure 1). Strongly basic diisopropylethylamine abstracted/neutralized the hydrogen chloride during crystallization; therefore, halogenide was not incorporated in the crystal structure of cycHC. The cyclohexyl rings leaned toward each other, closing the opening of the macrocycle, so the shape of this macrocycle was more similar to cucurbiturils' pumpkin or ball shape than to the bambusurils, with cavity shrinkage in the middle of the macrocycle.

The size of the opening of cycHC was found to be 2.2 Å, which is comparable to the corresponding value of 2.4 Å for cucurbit[5]uril.[17] The cavity size of cycHC was wider, and the distance between the two opposite carbonyl carbons was 5.3 Å, comparable to the cucurbit[6]uril cavity size of 5.8[17] and 5.3 Å in α-cyclodextrin.[18] The height of cycHC was 12.1 Å. The given distances take into account the van der Waals radii of relevant atoms. In spite of the resemblance of the general shapes of cucurbituril and cyclohexylhemicucurbit[6]uril, their polar and lipophilic regions were arranged in opposite formations. CycHC had a polar belt bearing urea functionalities in the middle and nonpolar cyclohexyls around the openings. The monomers were linked to each other in cycHC via one methylene bridge; thus, cyclohexyl rings that were further apart from this bridge were flexible, and the size of the opening could increase. Therefore, cycHC could serve as a chiral host molecule that has unique complexation ability.

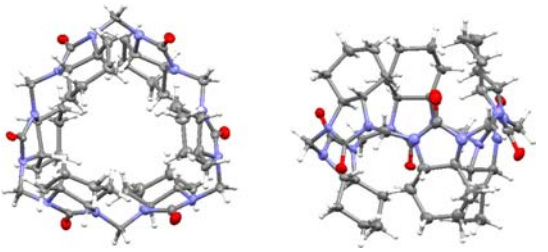


Figure 1. Crystal structure of (*all-S*)-cyclohexylhemicucurbit[6]uril.

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The interaction of cycHC with small organic compounds was studied by NMR and MS analysis. Mixing cycHC and the compounds **1**–**5** as shown in Figure 2 in chloroform in equimolar ratios caused a ^{13}C NMR chemical shift change of small molecules. As a representative example, the ^{13}C NMR spectra of monoethylfumarate **1** with and without cycHC are shown in Figure 2. The nonequal direction of the ^{13}C NMR chemical shift change of different monoethylfumarate **1** carbons supports the postulate of the existence of a host–guest complex between cycHC and acid **1**. In ESI-MS analysis of mixtures of **1**–**4** and cycHC, the molecular ions of complexes cycHC+carboxylic acids **1** and **2** were detected in negative mode (as carboxylates) and complexes cycHC+amino compounds **3** and **4** in positive mode (in protonated form), confirming the existence of 1:1 complexes. Also a 2:1 (cycHC:**4**) complex with diamine **4** was detected by MS.

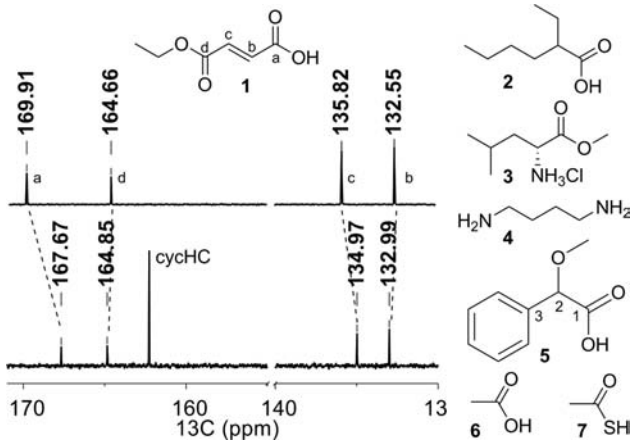

Figure 2. ^{13}C NMR spectra of carboxylic acid **1** without (upper) and with (lower) (*all-R*)-cycHC and structures of **1**–**7**, whose complexes with cycHC were studied in this work.

The formation of diastereomeric complexes with methoxyphenylacetic acid (MPA) **5** and (*all-R*)-cycHC was detected in ^{13}C NMR spectra. Mixtures of MPA and cycHC in ratios of 5:1, 1:1, and 1:5 were analyzed, and the splitting of *rac*-MPA ^{13}C NMR signals along with an accompanying chemical shift change was observed. Figure 3 shows representative ^{13}C NMR fragments with MPA signals at C3.

The complexed MPA signal of C3 was shifted downfield compared to the uncomplexed MPA C3 signal (Figure 3 spectrum d). Complexed and uncomplexed MPA did not give isolated signal pairs in spectra of MPA and cycHC mixtures, because of an exchange within the NMR time span. Nevertheless, diastereomeric complexes of (*R*)-MPA+(*all-R*)-cycHC and (*S*)-MPA+(*all-R*)-cycHC were distinguishable in all analyzed *rac*-MPA and (*all-R*)-cycHC mixture ratios. The mixtures of (*all-R*)-cycHC with enantiomerically pure MPA gave single peaks resonating at different frequencies, confirming the formation of diastereomeric complexes.

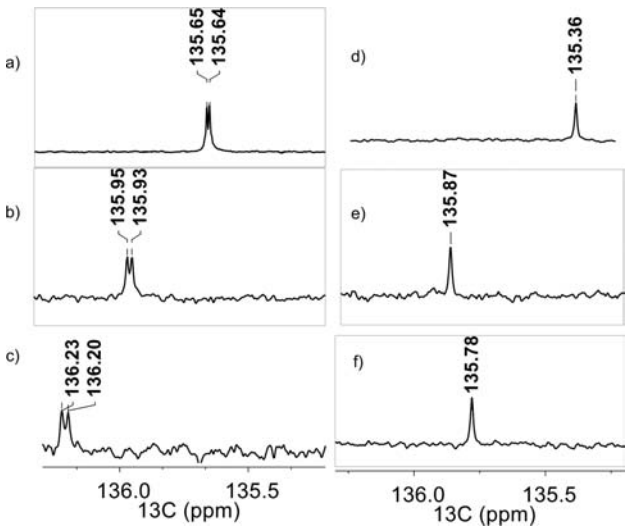

Figure 3. Fragments of ^{13}C NMR spectra of MPA: C3 signals measured with and without (*all-R*)-cycHC: (a) *rac*-MPA and (*all-R*)-cycHC in 5:1 ratio; (b) *rac*-MPA and (*all-R*)-cycHC in 1:1 ratio; (c) *rac*-MPA and (*all-R*)-cycHC in 1:5 ratio; (d) MPA without cycHC; (e) (*S*)-MPA and (*all-R*)-cycHC in 1:1 ratio; (f) (*R*)-MPA and (*all-R*)-cycHC in 1:1 ratio.

Diffusion NMR measurements of cycHC with guests **1**–**5** and additionally with acetic acid **6** and thioacetic acid **7** were performed to confirm that NMR chemical shift changes are caused by complexation. Diffusion NMR can be used to evaluate the mobility of different dissolved species in solution and has been exploited for studying intermolecular complexation and solution state aggregates. Moreover, diffusion methods allow to get an estimate for the binding constant K_a from a single measurement, and it is an acceptable alternative to titration studies.[20]

As seen in Table 1, the self-diffusion coefficients (*D*) of small molecules, which reflect the rate of thermal translational motion of dissolved species, decrease in the presence of cycHC. Although these preliminary measurements need further elaboration, they clearly indicate intermolecular interaction and support the earlier observations from ESI-MS and 1D NMR that compounds **1**–**6** form complexes with cycHC.

In the case of 1:1 host–guest complex formation and full inclusion of the guest, the host *D* value should not change upon complexation. The relation between molecular size and diffusion coefficient predicts that the self-diffusion coefficient of the host dimer should decrease at least 26% compared to the monomeric host *D* value.[20c] However, the small decrease of the complexed host's *D* (for example 11%

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Table 1. Diffusion Coefficients D (10^{-10} m^2/s) and Association Constants K_a (M^{-1}) of Guests with (*all-R*)-cycHC Host in 1:1 Mixtures in $CDCl_3$

guest	D_{free}	D_{bound}	D_{cycHC}	K_a
none			5.26 ± 0.01	
1	9.09 ± 0.01	6.91 ± 0.01	4.68 ± 0.01	73.2 ± 0.5
2	9.66 ± 0.01	8.66 ± 0.01	5.27 ± 0.01	14.4 ± 0.1
3	5.18 ± 0.01	4.87 ± 0.01	5.11 ± 0.01	NA
4	13.94 ± 0.01	12.17 ± 0.01	5.16 ± 0.01	11.9 ± 0.5
***S*-5**	10.34 ± 0.01	8.94 ± 0.01	5.29 ± 0.01	20.1 ± 0.2
***R*-5**	[a]	8.59 ± 0.01	4.99 ± 0.01	27.2 ± 0.8
6	15.48 ± 0.02	13.85 ± 0.02	4.83 ± 0.01	8.0 ± 0.5
7	18.45 ± 0.07	18.56 ± 0.02	5.27 ± 0.01	0.0 ± 0.5

[a] D_{free} of *S*-MPA was used.
D_{free} denotes uncomplexed guest, D_{bound} complexed guest, and D_{cycHC} complexed macrocycle. All samples were prepared in $CDCl_3$ at 26.5 mM concentration of each component and measured at 288 K in neat solutions or in 1:1 mixtures of guest and cycHC. Association constants K_a were calculated according to Rymden et al.[19] Binding of **3** could not be reliably determined, as diffusion methods are not suitable for binding evaluation when the D of guests and macrocycles are very close.

in case of guest **1**) can also be caused by simultaneous existence of complexes with different host−guest ratios, in addition to 1:1 ratio or by partial inclusion of the guest molecule.

It is important to note that association constants between organic molecules were measured in an organic solvent ($CDCl_3$), and therefore lower affinities compared to the organic molecule complexes in aqueus solutions can be expected. Nevertheless, the determined K_a values reflect organic molecules' relative affinities toward cycHC. The nature of complexation with amino-substituted guests needs further elaboration, but preliminary conclusions on carboxylic acids can be drawn. The highest binding is observed with the most planar carboxylic acid **1**, and introduction of branching to the α position of carboxylic acids **2** and **5** decreases K_a. There is a small difference in the association constants of (*all-R*)-cycHC with *S*- and *R*-MPA, indicating minor chiral recognition. The K_a for acetic acid **6** is an order of magnitude lower than for the guest **1**, suggesting that polar and apolar regions of the host and guest do not match in this case. The absence of complexation with thioacetic acid **7**, which incorporates a bulkier sulfur atom, indicates that complexation is dependent on the size and shape of the guest. Therefore the existence of inclusion complexes of cycHC and carboxylic acids is proposed. Studies on the exact nature of complexation will be the subject of our further research.

New (*all-S*)- and (*all-R*)-cyclohexylhemicucurbit[6]urils were synthesized: the first enantiometrically pure members of the cucurbituril family. These hemicucurbiturils formed complexes with either HCl or HBr, depending on the acid used for their formation. Complexation of cycHC with carboxylic acids and amines was detected, and their association constants were determined in organic media. Formation of inclusion complexes with carboxylic acids was proposed. CycHC formed diastereomeric complexes with enatiomers of methoxyphenylacetic acids, binding affinities of which were distinguishable. Detailed studies on the complexation and on the synthesis of homologues are currently underway in our group.

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Supporting Information Available. Experimental procedures, characterization of cycHC and its complexes, and crystal data (CIF). These materials are available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.