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Glycoluril Trimers: Selective Synthesis and Supramolecular Properties

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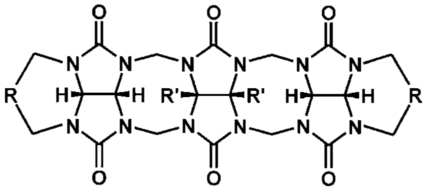
ABSTRACT



The first selective synthesis of glycoluril trimers is described. Trimers framed by *o*-xylylene walls represent new supramolecular hosts which are able to encapsulate bispyridinium ethylene and methylviologen guests in the solid state and aqueous solution.

Glycoluril and its derivatives are rigid heterocycles which are used as building blocks for the construction of various supramolecular objects. Glycolurils that are terminated by two xylylene units and contain a bulky substituent on their convex face are known to behave as molecular clips.[1] The connection of glycoluril units with aromatic spacers also leads to molecules which can self-assemble into pseudospherical structures.[2] Among these supramolecular objects, the most attention has been paid to the macrocyclic molecules known as cucurbit[*n*]urils (CB*n*).[3] These macrocycles are prepared by the polycondensation reaction between glycoluril and formaldehyde in mineral acid. With the exception of CB6, which can be readily prepared in conc. H_2SO_4 and temperatures above 100 °C as the sole macrocyclic product,[3c] mixtures of CB*n* homologues are obtained under milder reaction conditions, and difficult separation is required to obtain a unique macrocycle.[3e] Recently it was also demonstrated that the choice of a suitable formaldehyde/glycoluril ratio, reaction time, and other reaction conditions allows for the preparation of CB analogues as diastereomeric inverted CB[*n*],[4] bis-ns-CB[10],[5] and/or (±)-bis-ns-CB[6].[6] Using the same approach, Isaacs group has been able to isolate not only a previously described glycoluril dimer[7] but also higher acyclic oligomers with a number of glycoluril units ranging from 2 to 6.[6,8] They also demonstrated the ability of pentamers and hexamers to bind organic guests bearing positive charge. Inspired by these studies, we decided to investigate the possibility of creating a stepwise approach for the synthesis and characterization of glycoluril oligomers.

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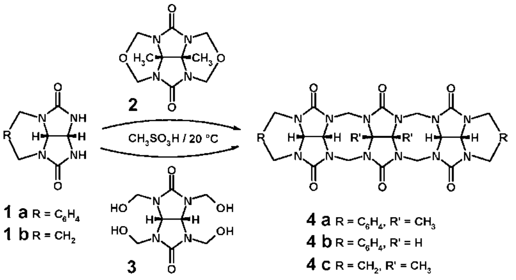
We believe that these oligomers can act as supramolecular host molecules and can be also used for the preparation of new cucurbiturils and their derivatives. As the first part of our approach, here we report the selective synthesis of glycoluril trimers and their supramolecular behavior in solid state and solution.

Our strategy is based on the selective connection of two 1,6-terminated glycolurils **1** through the central units **2**[9] and **3**[10] (Scheme 1). Convenient synthesis of 1,6-terminated glycolurils bearing hydrogen atoms on their convex face was recently reported.[11] Glycoluril diethers were selected as suitable bridging molecules; however, as the unsubstituted diether is unstable, tetrahydroxymethyl glycoluril was used as an additional bridge. The reaction was carried out in anhydrous methanesulfonic acid at room temperature under an inert atmosphere. Trimers were precipitated by addition of acetone or isopropanol from the resultant solution, purified by recrystallization, and characterized by ^1H and ^{13}C NMR spectroscopy and ESI mass spectrometry (see Supporting Information). Choice of solvent is crucial for the preparation of the trimer. With the exception of methanesulfonic acid, other tested solvent systems, including diluted HCl, lead to a mixture of products containing preferably a glycoluril dimer, which is formed by two terminated glycoluril units connecting through methylene bridges. In the presence of water, it has been demonstrated that cleavage of the N$-$CH$_2$ bond takes place during the interconversion of inverted CB6 to CB6. This cleavage could also permit the formation of the apparently more thermodynamically stable dimer in aqueous solution.[12] On the other hand, in anhydrous methanesulfonic acid, the cleavage events are suppressed, and the trimer is selectively obtained as a result. The influence of solvent system on trimer formation is currently under further investigation.

Scheme 1. Preparation of Glycoluril Trimers



We were able to measure the crystal structure of the trimer **4a** (see Figure 1), which crystallized in a convex C-shaped conformation. The xylylene walls close the molecule, leaving an opening measuring approximately 4 Å between the tips of the xylylene rings. The two mean planes of each terminal aromatic ring intersect each other at an angle of 89.7°. The plane defined by six equatorial glycoluril carbons intersect the mean plane of aromatic rings with identical angles of 89.2°.

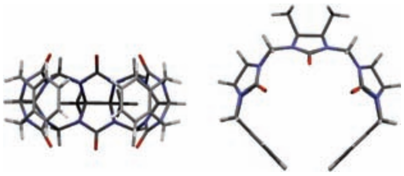


Figure 1. Wireframe representations of the crystal structures of trimer **4a**. Color coding: C, gray; H, white; N, blue; O, red.

The closed shape of the trimer containing three carbonyl oxygens on both sides of the molecule and the presence of the terminal xylylene unit indicate that these trimers (**4a**, **4b**) can act as host molecules for guests which are well-known to interact with CB*n* hosts. Typical examples of such molecules are organic guests bearing two positive charges (such as guests **5** and **6** in Figure 2).We therefore decided to investigate their complexation with the prepared trimers.

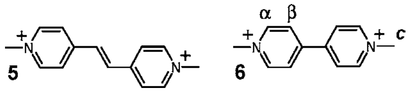


Figure 2. Structures of investigated guests.

Slow evaporation of an aqueous solution of trimer **4a** in the presence of **5** leads to yellow crystals which were characterized by X-ray crystallography. The crystal structure presented in Figure 3 reveals that in the solid state a single molecule of guest **5** is surrounded by two molecules of trimer **4a**. Upon formation of the complex, host **4a** adopts a helical

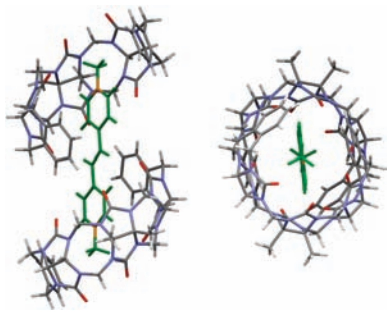


Figure 3. Wireframe representations of the crystal structures of complex **5·4a**. Color coding: C, gray; H, white; N, blue; O, red; except the guest molecule which is made green (C, H) and orange (N) for clarity.

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conformation. In the complex, each of the two host molecules is wrapped around one aromatic ring of the guest, one with a left-handed and the second with a right-handed helical orientation. Thus, the complex is assembled from the enantiomeric pair of helix shaped trimers which are held together by the supramolecular interaction with the guest. Two aromatic rings of the guest lie in the same plane.

Substitution of the two methyl units on the convex face of the central glycoluril unit of the trimer with hydrogen atoms plays a crucial role in the mode of binding between the trimers and guest **5** in the solid state. The crystal structure presented in Figure 4 shows the formation of a 1:1 inclusion complex between trimer **4b**, which lacks methyl substitution, and guest **5**. Trimer **4b** surrounds one-half of guest **5** with only minor distortion upon complexation. Also, the aromatic rings of the guest are twisted at an angle of 49.8°.

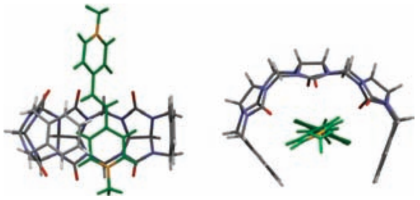

Figure 4. Wireframe representations of the crystal structures of complex **5·4b**. Color coding: C, gray; H, white; N, blue; O, red; except the guest molecule which is made green (C, H) and orange (N) for clarity.

The formation of a 1:1 complex between **6** and **4a** was also detected by X-ray crystallography (Figure 5). Methylviologen **6** contains two directly connected pyridinium rings and lacks a vinylene spacer which is present in guest **5**. Therefore, trimer **4a** wraps itself around both aromatic nuclei of the guest which induces helix distortion of the trimer.

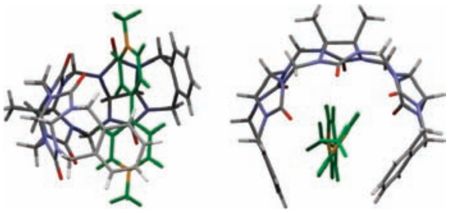

Figure 5. Wireframe representations of the crystal structures of complex **6·4a**. Color coding: C, gray; H, white; N, blue; O, red; except the guest molecule which is made green (C, H) and orange (N) for clarity.

We also investigated binding properties of prepared compounds in aqueous solution. Trimer **4b** is apparently insoluble in water, therefore we selected trimer **4a** and studied this interaction with methylviologen **6** using ^{1}H NMR spectroscopy (Figure 6). Upon addition of 1 equiv of trimer to methylviologen solution in D_2O, aromatic protons α and β of the guest undergo an upfield shift of 0.40 and 0.96 ppm, respectively. The upfield shifts of the aromatic protons of the guest correspond to the formation of the complex where guest **6** is included inside of trimer **4a**. One signal for each proton of the guest showed that the complexation is fast on the NMR time scale. Similar upfield shifts of the aromatic protons of methylviologen were previously described as a result of inclusion of the guest inside the CB7 macrocycle.[13] Dependence of the shift of guest proton signals on the amount of the host in the solution allowed us to determine the association constant of the **6·4a** complex. Experimental data afforded an association constant for the 1:1 complex of (7.5 ± 0.9) × 10^4 M^{-1}.

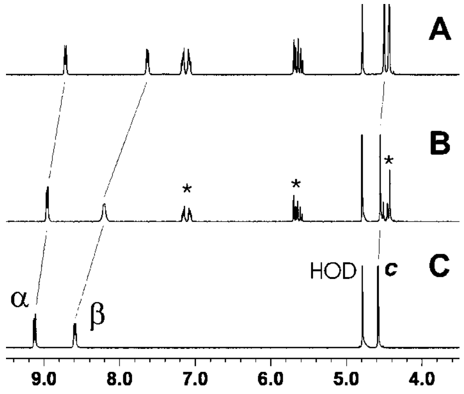

Figure 6. ^{1}H NMR spectra (300 MHz, D_2O) of **5** in the absence (C) and in the presence of 0.5 equiv (B) and 1 equiv (A) of **4a**. Signals of **4a** (*).

Binding features of guest **5** with host **4a**, such as upfield shift or aromatic protons and fast exchange on the NMR time scale, were similar to those observed for the binding of guest **6** with host **4a** (see Supporting Information). Surprisingly, experimental data obtained from ^{1}H NMR titration of a D_2O solution of **5** with trimer **4a** can be well fitted to 1:1 binding model to determine the association constant, which was found to be (8.4 ± 0.6) × 10^4 M^{-1}. The formation of a 1:1 complex between **5** and **4a** in solution is in direct contrast with the 1:2 binding ratio observed in the solid state. We therefore decided to conduct additional measurements to confirm our observations. The construction of a Job plot using ^{1}H NMR spectroscopy revealed a maximum at a molar ratio of the guest $\mathbf{5} = 0.5$, which clearly indicates a 1:1 binding stoichiometry between host and guest (see Supporting Information).

As glycoluril trimers **4a** and **4b** framed by xylylene walls act as good hosts, we decided to investigate how modification of the sidewalls of the trimers affects their supramolecular properties. To this end, we prepared trimer **4c**, which is terminated by propylene units on both sides. We were able to determine the crystal structure of **4c** which revealed a significantly more open C-shape structure when compared to host **4a**.

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All attempts to obtain monocrystals of the complexes between **4c** and guests **5** and **6** failed. Also, no association was observed between host **4c** and the guests in solution using NMR spectroscopy. Thus, these results suggest that the glycoluril trimers can act as good supramolecular hosts only when they are terminated by xylylene aromatic rings or possibly other spacious aromatic units.

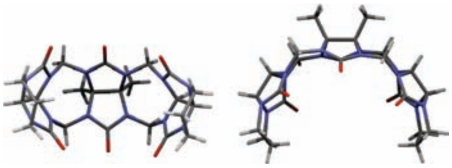

Figure 7. Wireframe representations of the crystal structures of trimer **4c**. Color coding: C, gray; H, white; N, blue; O, red.

In conclusion, for the first time the selective synthesis of glycoluril oligomers having more than two glycoluril units is reported. We have demonstrated that glycoluril trimers framed by xylylene walls **4a** can behave as a supramolecular host binding guests **5** and **6** with *K* values of (8.4 ± 0.6) × 10^4 M^{-1} and (7.5 ± 0.9) × 10^4 M^{-1} in 1:1 stoichiometry. In the solid state, however, guest **5** binds two trimer molecules of **4a**, while complex **6·4a** remains in 1:1 binding mode. In these complexes, **4a** adopts a helical conformation which is enhanced by the presence of methyl groups on the convex face of the central glycoluril unit of the trimer. Preparation of the additional trimers with various functional groups on the side walls as well as the selective synthesis of higher glycoluril oligomers is in progress.

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Supporting Information Available: Synthetic procedures, full characterization, and ^1H and ^{13}C NMR spectra of all new compounds, X-ray crystallographic files (CIF), and Job plot. This material is available free of charge via the Internet at http://pubs.acs.org.

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