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Glycoluril Dimer Isomerization under Aqueous Acidic Conditions Related to Cucurbituril Formation

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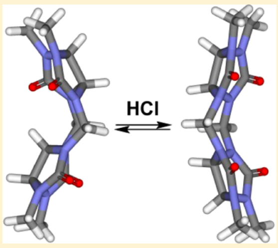
Supporting Information

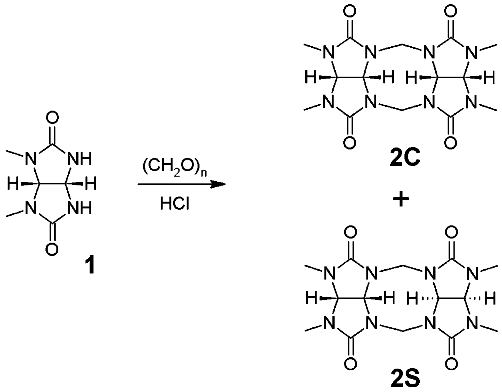
ABSTRACT: A water-soluble methylene-bridged glycoluril dimer **2S** was isolated. It was shown that **2S** is the only kinetic product of the reaction between glycoluril derivative **1** and paraformaldehyde. Compound **2S** is subsequently intermolecularly transformed into its diastereomer **2C**. The kinetics and thermodynamics of the S- to C-shaped dimer isomerization were investigated under reaction conditions similar to those for cucurbituril synthesis.



The importance of cucurbiturils (CBn) as host molecules in supramolecular chemistry has increased rapidly in the last two decades.[1] Although the supramolecular properties of these macrocycles have been extensively studied for a long time, the synthesis of modified cucurbiturils and their analogues with tailored properties has started to develop only recently. Understanding the mechanism of CBn formation is key to allowing the synthesis of new cucurbiturils. Among others, Day and Isaacs contributed to the majority of these mechanistic studies.[2,3] Day and colleagues studied the CBn-forming reaction between glycoluril and formaldehyde and monitored the influence of reaction conditions as well as the presence of a template on the ratio of the CBn homologues in the resulting reaction mixture. On the other hand, Isaacs and co-workers focused on glycolurils protected with a xylylene unit which react with formaldehyde in 1,2-dichloroethane under acidic conditions, resulting in the kinetic products S- and C-shaped glycoluril dimers. It was demonstrated that under these conditions the S-shaped diastereomer is intramolecularly transformed to a thermodynamically more stable C-shaped diastereomer. Further mechanistic studies were based on the conversion of inverted CBn, which contain a motif resembling the S-shaped dimer.[4] It was shown that inverted CBn are kinetic products that are converted into cucurbiturils. Conversion of S- into a C-shaped unit during the CBn transformation proceeded intramolecularly under anhydrous conditions. In contrast, intermolecular conversion was suggested when the reaction took place under aqueous acidic conditions.[3]

Differences in the mechanism of the CBn-forming reaction caused by the choice of solvent led us to further investigate this system. As previously described, the dimerizations of glycolurils were studied in a nonpolar solvent, but we decided to design a system that would closely resemble the real conditions used in CBn synthesis. We selected glycoluril **1** (Scheme 1), which differs from glycoluril only in the presence of two methyl groups in positions 2 and 8. We previously reported on the preparation of a C-shaped glycoluril dimer **2C** in 90% yield which was synthesized by condensation of **1** and formaldehyde in concd HCl at 80 °C for 4 h.[5] We decided to test this reaction under milder conditions in order to detect the presence of the S-shaped dimer **2S**, which was expected to be a kinetic product of the reaction. The reaction was carried out in 5 M HCl at 5 °C for 24 h until all formaldehyde was consumed by the reaction. Conversion of the S- to the C-shaped dimer, which is known to take place under acidic conditions, was inhibited by the neutralization of the resulting solution using a strongly basic anion-exchange resin in OH^- form. After evaporation, we obtained a solid that contained 88% of the **2S** and only 12% of the **2C** diastereomer based on ^1H NMR spectra. When the same experiment was carried out for 127 days, we determined the **2S** and **2C** diastereomer ratio to be 39:61. These experiments clearly show that under acidic aqueous conditions

Scheme 1. Synthesis of C- and S-Shaped Dimers 2C and 2S



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the S-shaped dimer **2S** is the only kinetic product of the reaction which is then converted into its C-shaped diastereomer. This finding is in contrast with the previously reported dimerization of glycolurils in a less polar solvent, where both S- and C-shaped diastereomers were described as kinetic products of the reaction.[3a]

The S-shaped dimer **2S** was isolated in 48% yield from the solid containing both diastereomers based on its better solubility in methanol compared to the C-shaped dimer. Monocrystals of **2S** were obtained by diffusion of diethyl ether vapors into a solution of the dimer in methanol. X-ray diffractometry confirmed that the isolated compound is the S-shaped dimer **2S** in which the methine hydrogen atoms of each glycoluril unit went to opposite sides of the molecule (Figure 1).

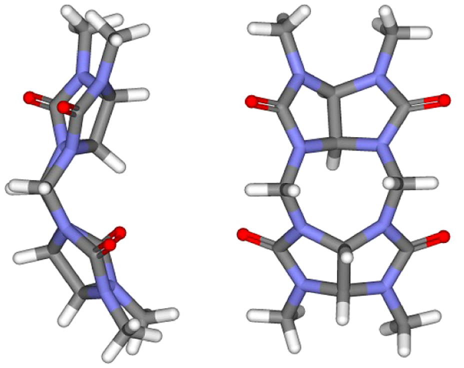
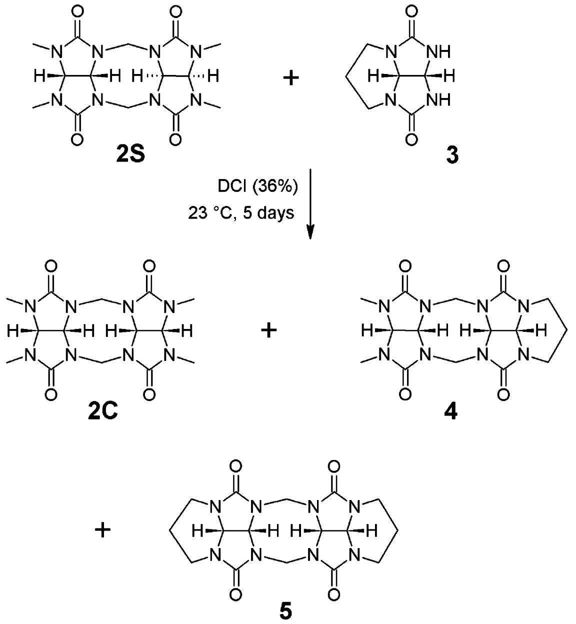


Figure 1. Wireframe representations of side and top views of the crystal structures of **2S**. Color coding: C, gray; H, white; N, blue; O, red.

Scheme 2. Detected Products from the Reaction of 1S and 3



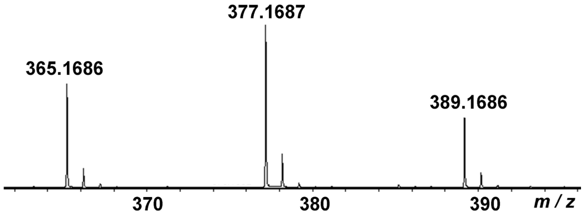


Figure 2. Detail of ESI MS spectrum of the resulting solution obtained after reaction of **2S** and **3** showing the presence of **2C** (m/z 365.1686), **4** (m/z 377.1687), and **5** (m/z 389.1686).

Study of the conversion of inverted CBn into CBn previously indicated that the S- to C-shaped dimer transformation is an intermolecular process when the reaction takes place in an acidic aqueous environment.[4] To test the validity of this hypothesis, we designed a reaction in which an S-shaped dimer **2S** reacted with propylene protected glycoluril **3** (Scheme 2). We expected that in the intermolecular process, two glycoluril units of the S-shaped dimer would be separated via cleavages of two methylene bridges. These separated units would subsequently recombine into a C-shaped dimer. However, in the presence of protected glycoluril **3**, they should form not only the C-shaped dimer **2C** but also a heterodimer **4**. On the other hand, if the S- to C-shaped dimer conversion is an intramolecular process, only one CH_2 bridge cleaves at a time. Thus, isomerization will dominate the reaction with distant molecules of glycoluril **4**, and only the C-shaped dimer will be detected at equilibrium.

In the experiment, we dissolved an equimolar amount of the S-shaped dimer **2S** and glycoluril **3** in 36% DCl, and the reaction mixture was left at 23 °C for 5 days. Then the solution was analyzed by ^{1}H NMR spectroscopy and ESI mass spectrometry. Despite the complexity of the NMR spectra we were able to identify signals of not only the C-shaped dimer, but also heterodimer **4** and homodimer **5**. Moreover, ESI mass spectra showed three significant signals corresponding to **2C**, **4**, and **5** (Figure 2). These experiments thus confirmed the previously hypothesized intermolecular nature of the S- to C-shaped dimer conversion.

The above-described experiments illustrate that during the CBn synthesis, two glycoluril units react with two formaldehyde molecules, yielding a S-shaped methylene-bridged dimer. This dimer is probably intermolecularly converted to a C-shaped diastereomer while further oligomerization of both diastereomers takes place at the same time. The resulting oligomer, called Behrend's polymer, is then converted to a mixture of cucurbituril homologues. As demonstrated, the transformation of the S- to C-shaped diastereomer is closely related to processes which take place during the CBn synthesis. Therefore, we decided to investigate the kinetics and thermodynamics of this transformation. We prepared a 27.45 mM solution of S-shaped dimer **2S** in 10 M DCl and monitored its transformation to C-shaped diastereomer **2C** at different temperatures 10, 22, 30, 38, 45, and 70 °C. NMR spectroscopy was used as a suitable technique, as the ^{1}H NMR spectra of the two diastereomers differ significantly (Figure 3). The actual concentration of the two diastereomers was based on integration of the corresponding signals (see the Supporting Information).

The kinetics of the **2S**–**2C** transformation are significantly influenced by temperature (Figure 4). The half-life of the transformation at 10 °C is 17.7 h, compared to 12 min at 45 °C. The experiment performed at 70 °C failed, as the S-shaped dimer undergoes decomposition at this temperature.[6]

The isomerization is an acid-catalyzed reaction. As H^+ ions are present in large excess in the reaction mixture, we treated the obtained data using pseudo-first-order rate equations.[7] Rate constant for the forward reaction (k_1) and the backward

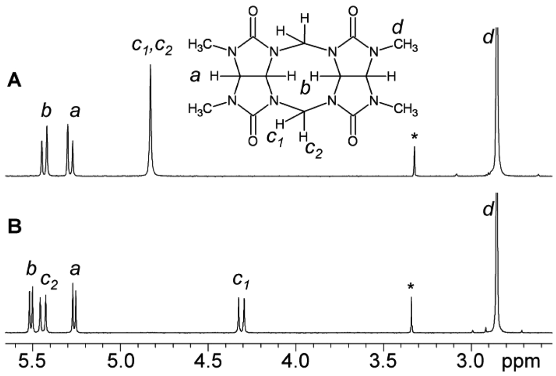


Figure 3. ^{1}H NMR spectra (300 MHz, 10 M DCl in D_2O) of (A) **2S** and (B) **2C**. *Signal of methanol used as an internal standard.

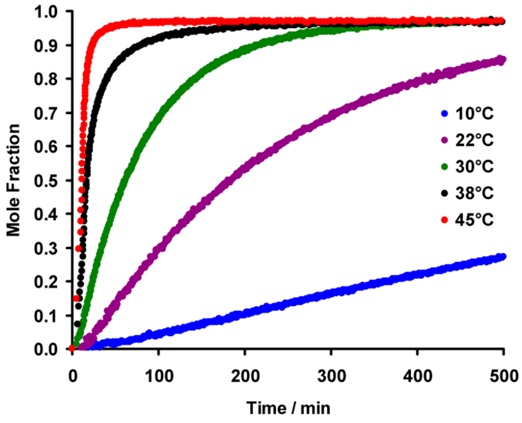


Figure 4. Mole fraction of **2C** over time for the isomerization of **2S** into **2C** (10 M DCl in D_2O) measured at various temperatures.

reaction (k_{-1}) (Table 1) were determined as a solution of a two equations system of the value ($k_1 + k_{-1}$) and the equilibrium constant (K), expressed as the ratio k_1/k_{-1}. The sum of the rate constants was obtained by a linear regression for the kinetic equation $(k_1 + k_{-1})t = \ln\{[\mathbf{2C}]_e/([\mathbf{2C}]_e - [\mathbf{2C}])\}$ describing a time dependence of the rate constants sum on the actual and equilibrium concentration of **2C**. To obtain this value we selected kinetic data that are not influenced by backward reaction in the late stages of the process. Equilibrium constants (K) were calculated from the concentrations of the C- and S-shaped diastereomers in the equilibrium ($[\mathbf{2C}]_e/[\mathbf{2S}]_e$ ratio). As is shown in Table 1, both rate constants naturally increase with temperature, although k_1 is more than 1 order of magnitude higher than k_{-1}.

The rate constants for the reaction at 10 °C were not determined due to the low concentration of the S-shaped product in equilibrium which was beneath the detection limit of the NMR spectroscope. The dependence of rate constants on temperature fits well to the Arrhenius equation, yielding activation energy (E_a) (Supporting Information). Similarly, the Eyring equation allowed us to calculate the enthalpy and entropy of the activation (ΔH_a and ΔS_a) (Table 2). The E_a of the forward reaction is about 50 kJ·mol^{-1} lower than the backward reaction. The enthalpy factor is the one which contributes most to the E_a value compared to the small contribution of the entropy factor. The ratio of C- and S-shaped diastereomers in the equilibrium ($[\mathbf{2C}]_e$:$[\mathbf{2S}]_e$) shifts in the yield of the S-shaped diastereomer with increasing reaction temperature (Table 1). The increasing content of the S-shaped diastereomer in equilibrium is caused by the lower E_a of the backward reaction, which assumes greater importance at higher reaction temperatures. As K was used for the calculation of Gibbs free energy ($\Delta G°$) of the isomerization, it was not surprising that $\Delta G°$ also increases with increasing reaction temperature. Depending on temperature, $\Delta G°$ values range from −6.65 to −9.43 kJ·mol^{-1}. The obtained $\Delta G°$ values are similar to those determined by Isaacs and co-workers for the isomerization of the S- into the C-shaped dimer in organic solvents.[3a] Finally, we calculated the enthalpy and entropy of the reaction ($\Delta H°$ and $\Delta S°$) to be −50.54 kJ·mol^{-1} and −0.14 kJ·K^{-1} mol^{-1} ($-T\Delta S° = 42$ kJ·mol^{-1}, if $T = 295.1$ K). These results revealed that the transformation of the C- into the S-shaped diastereomer is favored by enthalpy, while the entropy factor disfavors the reaction.

Table 2. Activation Energy (E_a) and Enthalpy and Entropy of the Activation (ΔH_a and ΔS_a) of the Isomerization of 2S into 2C

	E_a (kJ·mol^{-1})	ΔH_a (kJ·mol^{-1})	ΔS_a (kJ·mol^{-1}·K^{-1})
forward reaction	108.9 ± 2.8	106.3 ± 2.8	0.004 ± 0.009
backward reaction	159.4 ± 11.0	156.4 ± 11.0	0.143 ± 0.036

In conclusion, we performed dimerization of the protected glycoluril **1** under the same conditions as used for the synthesis of CBn. We demonstrated that the S-shaped dimer **2S** is the only kinetic product of the reaction and is subsequently transformed into the C-shaped dimer **2C**. This experiment demonstrated the determining influence of the reaction media, as the previous mechanistic study performed in an organic solvent showed that the formation of both the S- and C-shaped diastereomers are kinetic products of the reaction. The S-shaped dimer was isolated in 48% yield, and its crystal structure was determined. The C-shaped dimer is thermodynamically more stable than the S-shaped isomer by 6.65−9.43 kJ·mol^{-1}. The S- to C-dimer isomerization is an enthalpy-driven process. The isomerization is an intermolecular process, as illustrated by the formation of heterodimer **4** in the reaction between S-shaped dimer **2S** and glycoluril **3**.

Table 1. Rate Constants of the Forward (k_1) and Backward (k_{-1}) Reactions, Diastereomer Ratio in Equilibrium ($[\mathbf{2C}]_e$:$[\mathbf{2S}]_e$), Equilibrium Constants (K), and Gibbs Free Energy ($\Delta G°$) of Isomerization of 2S into 2C in 10 M DCl Measured at Various Temperatures

temp/°C	k_1 (10^{-6} s^{-1})	k_{-1} (10^{-6} s^{-1})	$[\mathbf{2C}]_e$:$[\mathbf{2S}]_e$	K	$\Delta G°$ (kJ·mol^{-1})
22	69.6 ± 0.1	1.5 ± 0.1	98:2	46.7 ± 2.6	−9.43 ± 0.14
30	204.5 ± 0.3	5.9 ± 0.2	97:3	34.5 ± 1.3	−8.93 ± 0.09
38	629.4 ± 1.9	47.6 ± 1.5	93:7	13.2 ± 0.5	−6.68 ± 0.09
45	1722.7 ± 6.3	139.5 ± 3.4	92:8	12.4 ± 0.3	−6.65 ± 0.07

■ EXPERIMENTAL SECTION

S-Shaped Tetramethylglycoluril Dimer (2S). 1,6-Dimethylglycoluril (**1**) (1.00 g, 5.8 mmol) was mixed with paraformaldehyde (175 mg, 5.8 mmol) in precooled 5 M HCl (5.0 mL), and the resulting mixture was stirred at 3−5 °C for 24 h. The reaction mixture was neutralized by passing it through a column filled with a strongly basic anion exchange resin in OH^- form (Amberlyst A26). The aqueous solution was evaporated in vacuo at 45 °C to afford a solid which was then triturated with methanol (60 mL) at rt for 10 min. The undissolved solid was removed by filtration, and the filtrate was evaporated to dryness resulting in an amorphous solid (0.73 g). A pure compound (0.50 g, 48%) was obtained as white crystals after recrystallization from methanol (25 mL): mp > 300 °C dec; ^{1}H NMR (300 MHz, D_2O) δ 5.41 (d, J = 8.5, 2H, C*H*), 5.33 (d, J = 8.5, 2H, C*H*), 4.94 (s, 4H, CH_2), 2.97 (s, 12H, CH_3); ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.22−5.16 (m, 4H, C*H*), 4.83 (s, 4H, CH_2), 2.85 (s, 12H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.5 (C=O), 71.2 (CH), 66.2 (CH), 51.8 (CH_2), 29.6 (CH_3); IR (Nujol, cm^{-1}) 2945, 2929, 2904, 2868, 1709, 1492, 1380, 1231, 1200, 1039, 991, 808, 780, 748; HRMS (ESI+) *m*/*z* calcd for ($C_{14}H_{20}N_8O_4$ + H^+) 365.1686, found 365.1691.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and procedures, crystallographic data for the compound **2S**, and copies of ^{1}H and ^{13}C NMR spectra of compound **2S**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(7) Validity of the expected pseudo-first-order conditions was confirmed by a set of additional experiments. S- to C-dimer conversion was monitored at constant temperature (30 °C) and various DCl concentrations (6, 8, 10, and 12 M). We treated the obtained data using pseudo-first-order rate equations to obtain rate constants for the forward reaction (k_1). Dependence of k_1 on the activity of H^+ ions showed a good linear fit which proved the relevance of the selected model.