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Diastereoselective Formation of Glycoluril Dimers: Isomerization Mechanism and Implications for Cucurbit[*n*]uril Synthesis

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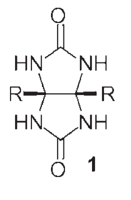
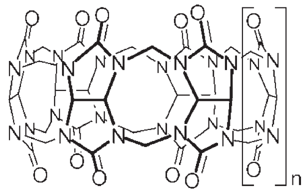
Abstract: Cucurbit[6]uril (**CB**[6]) is a macrocyclic compound, prepared in one pot from glycoluril and formaldehyde, whose molecular recognition properties have made it the object of intense study. Studies of the mechanism of **CB**[*n*] formation, which might provide insights that allow the tailor-made synthesis of **CB**[*n*] homologues and derivatives, have been hampered by the complex structure of **CB**[*n*]. By reducing the complexity of the reaction to the formation of S-shaped (**12*S*−18*S***) and C-shaped (**12*C*−18*C***) methylene bridged glycoluril dimers, we have been able to probe the fundamental steps of the mechanism of **CB**[*n*] synthesis to a level that has not been possible previously. For example, we present strong evidence that the mechanism of **CB**[*n*] synthesis proceeds via the intermediacy of both S-shaped and C-shaped dimers. The first experimental determination of the relative free energies of the S-shaped and C-shaped dimers indicates a thermodynamic preference (1.55−3.25 kcal mol^{-1}) for the C-shaped diastereomer. This thermodynamic preference is not because of self-association, solvation, or template effects. Furthermore, labeling experiments have allowed us to elucidate the mechanism of this acid-catalyzed equilibrium between the S-shaped and C-shaped diastereomers. The equilibration is an intramolecular process that proceeds with high diastereoselectivity and retention of configuration. On the basis of the broad implications of these results for **CB**[*n*] synthesis, we suggest new synthetic strategies that may allow for the improved preparation of **CB**[*n*] ($n > 8$) and **CB**[*n*] derivatives from functionalized glycolurils.

Introduction

In 1905, Behrend reported that the condensation reaction of glycoluril (**1a**) and formaldehyde in concentrated HCl yields an insoluble polymeric material.[1] To make the material more tractable, it was dissolved in concentrated sulfuric acid from which a crystalline substance could be obtained. In 1981, Mock et al.[2] reinvestigated Behrend's original report and discovered that the product of this reaction was cucurbituril, **CB**[6],[3] a remarkable macrocyclic compound comprising six glycoluril rings and 12 methylene bridges (Chart 1). In their syntheses of **CB**[6], neither Behrend nor Mock detected the presence of macrocyclic compounds comprising five, seven, or eight glycoluril rings (**CB**[5], **CB**[7], **CB**[8]). This result, when coupled with the high yield (82%) synthesis of **CB**[6] disclosed by Buschmann, suggested that the formation of **CB**[6] was governed by a thermodynamic preference for **CB**[6].[4] The first successful synthesis of an analogue of **CB**[6] was described by

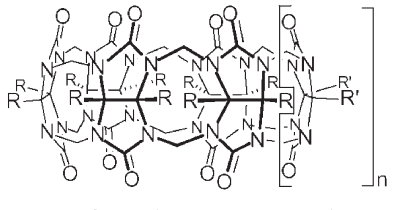
Chart 1





1a R = H
1b R = Me
1c R,R = $(CH_2)_4$
1d R = Ph
1e R = CO_2Et

CB[5] (n = 0)
CB[6] (n = 1)
CB[7] (n = 2)
CB[8] (n = 3)
CB[10] (n = 5)



Me$_{10}$**CB**[5] (R = R' = Me, n = 0)
Cy$_5$**CB**[5] (R,R = R',R' = $(CH_2)_4$, n = 0)
Cy$_6$**CB**[6] (R,R = R',R' = $(CH_2)_4$, n = 1)
Ph$_2$**CB**[6] (R = H, R' = Ph, n=1)

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(1) Behrend, R.; Meyer, E.; Rusche, F. *Liebigs Ann. Chem.* **1905**, *339*, 1−37.

(2) Freeman, W. A.; Mock, W. L.; Shih, N. Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367−8.

(3) Kim, J.; Jung, I.-S.; Kim, S.-Y.; Lee, E.; Kang, J.-K.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *J. Am. Chem. Soc.* **2000**, *122*, 540−541.

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