JOC Article

Methylene-Bridged Glycoluril Dimers: Synthetic Methods

Anxin Wu,[†,‡] Arindam Chakraborty,[†] Dariusz Witt,[†,§] Jason Lagona,[†] Fehmi Damkaci,[†] Marie A. Ofori,[†] Jessica K. Chiles,[†] James C. Fettinger,[†] and Lyle Isaacs*[,†]

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, and National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

LI8@umail.umd.edu

Received May 2, 2002

Methylene-bridged glycoluril dimers are the fundamental building blocks of cucurbituril (**CB**[6]), its homologues (**CB**[*n*]), and its derivatives. This paper describes three complementary methods for the synthesis of C- and S-shaped methylene-bridged glycoluril dimers (**29**−**34** and **37**−**44**). For this purpose, we prepared glycoluril derivatives (**1a**−**d**) bearing diverse functionalities on their convex face. These glycoluril derivatives were alkylated under basic conditions (DMSO, *t*-BuOK) with 1,2-bis(halomethyl)aromatics **6**−**15** to yield **4a**−**d** and **16**−**24**, which contain a single aromatic *o*-xylylene ring and potentially nucleophilic ureidyl NH groups. Glycoluril derivatives bearing potentially electrophilic cyclic ether groups (**5a**−**f**) and **25**−**28** were prepared by various methods including condensation reactions in refluxing TFA containing paraformaldehyde. The condensation reactions of **4a**−**d** and **16**−**24** with paraformaldehyde under anhydrous acidic conditions (PTSA, $ClCH_2CH_2Cl$, reflux) give, in most cases, the C-shaped and S-shaped methylene-bridged glycoluril in good to excellent yields. In many cases, the C-shaped compound is formed preferentially with high diastereoselectivity. Cyclic ethers **5a**,**d**−**f** and **25**−**26** undergo highly diastereoselective dimerization reactions to yield methylene-bridged glycoluril dimers with the formal extrusion of formaldehyde. Last, it is possible to perform selective heterodimerization reactions using both cyclic ethers and glycoluril derivatives bearing ureidyl NH groups. These reactions deliver the desired C- and S-shaped heterodimers with low to moderate diastereoselectivities. This heterodimerization route is the method of choice in cases where the homodimerization reactions fail. The formation of side products (±)-**35b** and (±)-**35d** helps clarify the electronic requirements for a successful **CB**[*n*] synthesis. The X-ray structures of **30*C***, **38*C***, and **38*S*** allow for a discussion of the structural features of this class of compounds.

Introduction

Cucurbituril (**CB**[6]) is a an intriguing macrocyclic compound comprising six glycoluril (**1f**) rings and twelve methylene bridges whose structure was established by Mock in 1981.[1] **CB**[6] possesses a hydrophobic cavity with carbonyl-lined portals that results in remarkable molecular recognition properties (Chart 1). For example, Mock and co-workers found that **CB**[6] binds tightly ($K_d \approx 1$ μM) to alkyldiammonium ions in aqueous solution by a combination of the hydrophobic effect and ion−dipole interactions.[2] It was also demonstrated that **CB**[6] is an efficient enzyme mimic capable of catalyzing the dipolar cycloaddition between azide and acetylene-derivatized ammonium ions by their simultaneous binding within the cavity of **CB**[6].[3] The synthetic method used to prepare cucurbituril is equally impressive; simply heating glycoluril (**1a**) and formaldehyde under strongly acidic conditions (H_2SO_4, 135−145 °C) results in the formation of **CB**[6] in high yield.[4] This straightforward synthetic method has allowed the use of **CB**[6] in many elegant studies including molecular necklaces,[5] bowls,[6] polyrotaxanes,[7] DNA complexes,[8] molecular switches,[9] removal of contaminants from aqueous waste streams,[10] studies of molecular polarizability,[11] and ion and molecular complexation studies.[2,12]

In efforts to expand the range of applications, several groups have been investigating the preparation of congeners of cucurbituril that display enhanced properties. This line of inquiry was first pursued by Stoddart, who prepared Me_{10}**CB**[5] by condensation of **1e** with formaldehyde.[13] More recently, Kim and co-workers[14,15] as well as Day and co-workers[16,17] isolated homologues of cucurbituril comprising five, seven, eight, and ten glycoluril

* To whom correspondence should be addressed.
† University of Maryland.
‡ Lanzhou University.
§ Current address: Chemical Faculty, Technical University of Gdansk, Narutowicza 11/12, 80-952 Gdansk, Poland.

(1) Freeman, W. A.; Mock, W. L.; Shih, N. Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367−7368.

(2) Mock, W. L.; Shih, N. Y. *J. Org. Chem.* **1983**, *48*, 3618−3819. Mock, W. L.; Shih, N. Y. *J. Org. Chem.* **1986**, *51*, 4440−4446. Mock, W. L.; Shih, N. Y. *J. Am. Chem. Soc.* **1988**, *110*, 4706−4610. Mock, W. L.; Shih, N. Y. *J. Am. Chem. Soc.* **1989**, *111*, 2697−2679.

(3) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Manimaran, T. L. *J. Org. Chem.* **1983**, *48*, 3619−3820. Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Adhya, M. *J. Org. Chem.* **1989**, *54*, 5302−5308.

(4) Buschmann, H.-J.; Fink, H.; Schollmeyer, E. Preparation of Cucurbituril. German Patent DE 196 03 377 A1, 1997.

(5) Whang, D.; Park, K.-M.; Heo, J.; Ashton, P.; Kim, K. *J. Am. Chem. Soc.* **1998**, *120*, 4899−4900. Roh, S.-G.; Park, K.-M.; Park, G.-J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 638−641. Lee, E.; Kim, J.; Heo, J.; Whang, D.; Kim, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 399−402.

(6) Jeon, Y.-M.; Kim, J.; Whang, D.; Kim, K. *J. Am. Chem. Soc.* **1996**, *118*, 9790−9791. Whang, D.; Heo, J.; Park, J. H.; Kim, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 78−80.

10.1021/jo0258958 CCC: $22.00
Published on Web 07/03/2002