ORGANIC
LETTERS

2000
Vol. 2, No. 6
755−758

Diastereoselective Formation of Methylene-Bridged Glycoluril Dimers

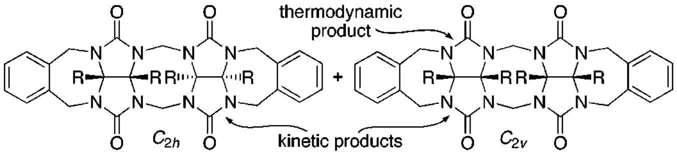
Dariusz Witt,[†,‡] Jason Lagona,[†] Fehmi Damkaci,[†] James C. Fettinger,[†] and Lyle Isaacs*,[†]

*Department of Chemistry and Biochemistry, University of Maryland,
College Park, Maryland 20742, and Chemical Faculty, Technical University of
Gdansk, Narutowicza St. 11/12, 80-952 Gdansk, Poland*

lI8@umail.umd.edu

Received December 21, 1999

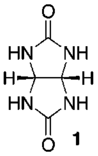
ABSTRACT

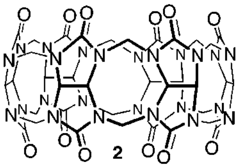


The acid-catalyzed formation of methylene-bridged glycoluril dimers yields the C_{2v}-diastereomer selectively. Product resubmission experiments establish that the selectivity is the result of thermodynamic control. A modified synthetic route is presented that allows for the preparation of unsymmetrically substituted dimers. We present the X-ray crystal structures of both diastereomers. This class of compounds is useful for studies of self-assembly in aqueous solution.

Derivatives of glycoluril (**1**) have been employed in many applications including polymer cross-linking, explosives, stabilization of organic compounds against photodegradation, textile waste stream purification, and combinatorial chemistry.[1] The groups of Rebek[2] and Nolte[3] have pioneered the use of glycoluril derivatives as building blocks for self-assembly, molecular recognition, and catalysis in chloroform. We have become interested in the preparation of self-complementary facially amphiphilic derivatives of glycoluril that self-assemble in water.[4] Our goal is to use the hydrophobic effect to prepare aggregates in water—in a predictable manner—that are both tightly associated and geometrically homogeneous.

We were intrigued by cucurbituril (**2**),[5] which is a macrocyclic compound composed of six glycoluril rings and 12 methylene bridges. Cucurbituril can be synthesized in one step by the condensation of **1** and formaldehyde in sulfuric acid. The straightforward synthesis of **2** has allowed its recognition properties toward alkyldiammonium ions in 1:1 formic acid/water ($K_d \approx 1\ \mu$M) to be studied[6] and used in supramolecular chemistry.[7−9] Two factors have prevented its more widespread use: (1) a current inability to access


1


2

[†] University of Maryland.

[‡] Technical University of Gdansk.

[1] (a) Jacobs, W.; Foster, D.; Sansur, S.; Lees, R. G. *Prog. Org. Coat.* **1996**, *29*, 127−138. (b) Parekh, G. G. U.S. Patent 4,105,708, 1978. (c) Wang, A.; Bassett, D. U.S. Patent 4,310,450, 1982. (d) Yinon, J.; Bulusu, S.; Axenrod, T.; Yazdekhasti, H. *Org. Mass Spectrom.* **1994**, *29*, 625−631. (e) Boileau, J.; Carail, M.; Wimmer, E.; Gallo, R.; Pierrot, M. *Propellants, Explos., Pyrotech.* **1985**, *10*, 118−120. (f) Krause, A.; Aumueller, A.; Korona, E.; Trauth, H. U.S. Patent 5,670,613, 1997. (g) Karcher, S.; Kornmuller, A.; Jekel, M. *Water Sci. Technol.* **1999**, *40*, 425−433. (h) Pryor, K. E.; Rebek, J., Jr. *Org. Lett.* **1999**, *1*, 39−42.

[2] (a) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1668. (b) Rebek, J., Jr. *Chem. Soc. Rev.* **1996**, *25*, 255−263. (c) Rebek, J., Jr. *Acc. Chem. Res.* **1999**, *32*, 278−286 and references therein.

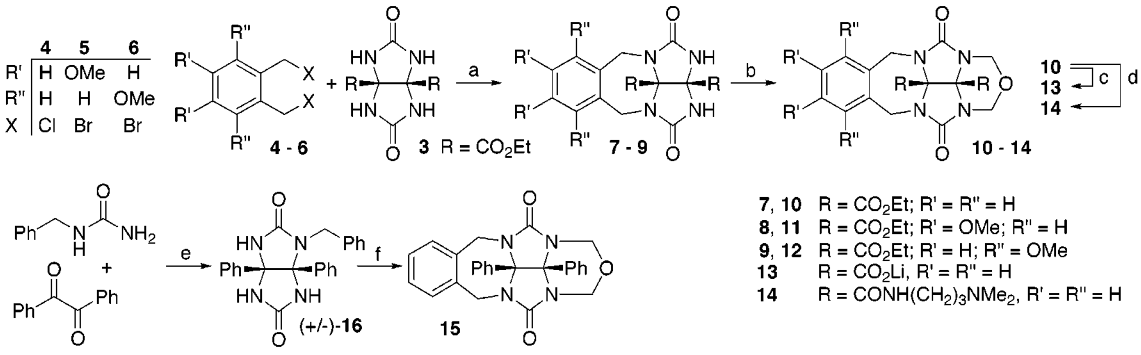
[3] (a) Rowan, A. E.; Elemans, J. A. A. W.; Nolte, R. J. M. *Acc. Chem. Res.* **1999**, 995−1006. (b) Sijbesma, R. P.; Nolte, R. J. M. *Top. Curr. Chem.* **1995**, *175*, 25−56 and references therein.

[4] Isaacs, L.; Witt, D.; Fettinger, J. C. *Chem. Commun.* **1999**, 2549−2550.

[5] (a) Behrend, R.; Meyer, E.; Rusche, F. *Justus Liebigs Ann. Chem.* **1905**, *339*, 1−37. (b) Freeman, W. A.; Mock, W. L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367−7368. (c) Buschmann, H.-J.; Fink, H.; Schollmeyer, E. German Patent DE 196 03 377 A1, 1996.

10.1021/ol991382k CCC: $19.00

Scheme 1

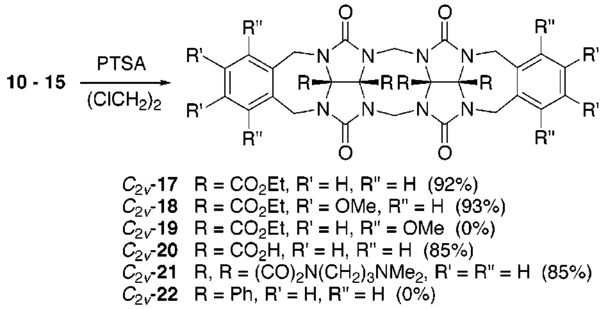


Conditions: a) DMSO, *t*-BuOK, 34-47%; b) TFA, $(CH_2O)_n$, 44-56%; c) LiOH, MeOH, H_2O, 98%; d) $H_2N(CH_2)_3NMe_2$, 92%; e) PhH, TFA, H_2NCONH_2, 36%; f) TFA, $(CH_2O)_n$, 63%.

functionalized derivatives[10] and (2) the poor solubility of **2** in water. We envisioned that both of these deficiencies could be alleviated if the extremely harsh conditions (H_2SO_4, 135−145 °C) used in the synthesis of **2** could be adapted to allow the use of glycoluril derivatives that incorporate hydrophilic functional groups. This paper describes our investigation of the synthesis, X-ray crystallographic characterization, and acid-catalyzed isomerization of nonmacrocyclic methylene-bridged glycoluril dimers.

As a first step toward the preparation of functionalized congeners of **2**, it was necessary to devise methods to prepare the methylene-bridged glycoluril dimer substructure of **2** (in bold). Scheme 1 shows starting materials **3**−**6**[11] and the synthesis of **7**−**16**. We chose **10** as our model substrate to develop conditions for the preparation of the methylene-bridged glycoluril dimer substructure for two reasons: (1) its ethyl ester groups could be readily transformed to water solubilizing carboxylate (**13**) or amidoamine (**14**) substituents in high-yielding reactions, and (2) the bridging xylylene ring protected two of the glycoluril nitrogen atoms that reduced the complexity of the reaction to the formation of *dimers*. After much experimentation, it was discovered that heating **10** under acidic conditions (PTSA) in refluxing dichloroethane for 24 h resulted in the formation of C_{2v}-**17** in 92% yield (Scheme 2).[12] Two equivalents of formaldehyde was formally extruded in this reaction with the formation of the methylene bridges. The C_{2h}-**17** diastereomer was not present in the reaction mixture.[13] This observation was surprising, especially since the relative stereochemistry of **17** was determined by the formation of the first covalent bond between the two equivalents of **10**. This stereochemical assignment was based on the observation of two doublets (6.01 and 4.58 ppm) for the diastereotopic methylene protons of the central eight membered ring.

Scheme 2



The X-ray crystal structure of C-shaped C_{2v}-**17**, obtained as the benzene solvate (Figure 1a), confirmed the stereochemical assignment. There were several interesting aspects of the structure of C_{2v}-**17**. First, C_{2v}-**17** was facially amphiphilic since all four ethyl ester groups are displayed on a single face of the molecule. Second, C_{2v}-**17** crystallized in a conformation where the two phenyl walls defined a hydrophobic cleft. Third, the distance between the centers of the substituted phenyl rings measured 7.4 Å; this distance is suitable for the complexation of an aromatic ring.[3,14]

Scheme 2 presents the results of several dimerization reactions that were performed. Compounds **13**−**15** were

---

(6) (a) Mock, W. L. *Top. Curr. Chem.* **1995**, *175*, 1−24. (b) Mock, W. L.; Shih, N.-Y. *J. Org. Chem.* **1983**, *48*, 3618−3619. (c) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Manimaran, T. L. *J. Org. Chem.* **1983**, *48*, 3619−3620. (d) Mock, W. L.; Shih, N.-Y. *J. Org. Chem.* **1986**, *51*, 4440−4446.

(7) (a) Heo, J.; Kim, S. Y.; Whang, D.; Kim, K. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 641−643. (b) Jeon, Y. M.; Kim, H.; Whang, D.; Kim, K. *J. Am. Chem. Soc.* **1996**, *118*, 9790−9791. (c) Whang, D.; Kim, K. *J. Am. Chem. Soc.* **1997**, *119*, 451−452. (d) Whang, D.; Heo, J.; Park, J. H.; Kim, K. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 78−80.

(8) Tuncel, D.; Steinke, J. H. G. *Chem. Commun.* **1999**, 1509−1510.

(9) (a) Buschmann, H. J.; Schollmeyer, E. *J. Incl. Phenom. Mol. Recogn. Chem.* **1992**, *14*, 91−99. (b) Meschke, C.; Buschmann, H. J.; Schollmeyer, E. *Macromol. Rapid Commun.* **1998**, *19*, 59−63.

(10) Flinn, A.; Hough, G. C.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1475−1477.

(11) (a) Branda, N.; Grotzfeld, R. M.; Valdés, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 85−88. (b) Kang, J.; Hilmersson, G.; Santamaría, J.; Rebek, J. Jr. *J. Am. Chem. Soc.* **1998**, *120*, 3650−3656. (c) Diederich, F.; Jonas, U.; Gramlich, V.; Herrmann, A.; Ringsdorf, H.; Thilgen, C. *Helv. Chim. Acta* **1993**, *76*, 2445−2453. (d) Ardecky, R. J.; Kerdesky, F. A. J.; Cava, M. P. *J. Org. Chem.* **1981**, *46*, 1483−1485.

(12) Fusco, A. M.; Del Franco, G. J.; Aronoff, E. J. *J. Org. Chem.* **1966**, *31*, 313−315.

(13) After 24 h all of the successful reactions shown in Scheme 2 lead to the exclusive formation of the C_{2v}-diastereomer.

(14) (a) Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362−386. (b) Jorgenson, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 4768−4774.

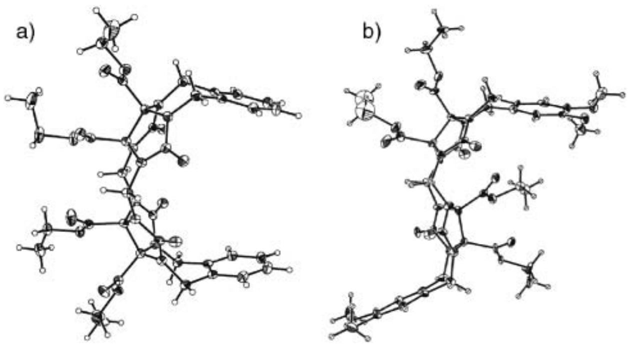
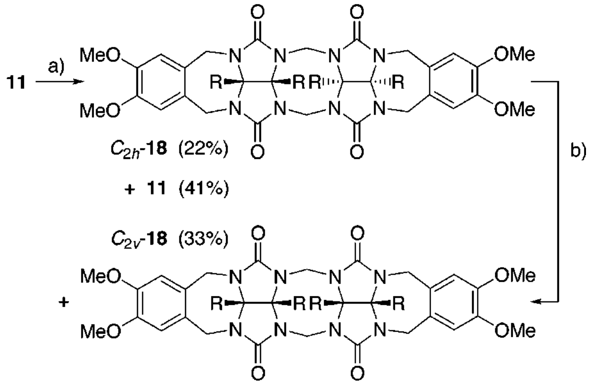


Figure 1. Crystal structures of (a) C-shaped **17**•$(C_6H_6)_2$ and (b) S-shaped **18** with 30% probability ellipsoids. The solvating benzene rings that partially fill the cleft of **17** have been removed for clarity.

prepared to assess the influence of the substituents on the convex face of the molecule on the dimerization reaction (Scheme 1). Compounds **13** and **14** dimerized smoothly, giving C_{2v}-**20** and C_{2v}-**21**[15] in high yield. The attempted dimerization of **15**, the diphenyl analogue of **10**, produced a complex reaction mixture that did not contain C_{2v}-**22**.[16] We do not currently understand the origin of this dramatic difference in product distribution; electronic differences should be minor because the quaternary carbon atom is present and steric differences between the ester and phenyl substituents are not apparent. Compounds **11** and **12** were prepared to determine the effect of substituents on the bridging xylylene ring. Compound **11** smoothly dimerized under the reaction conditions to yield C_{2v}-**18** in 93% yield. In contrast, isomeric **12** gave a complex reaction mixture that did not contain C_{2v}-**19**.[16]

The highly diastereoselective formation of the C_{2v}-stereoisomers was intriguing; this diastereoselectivity must be due to either kinetic or thermodynamic preferences. Since the transformation of **11** to **18** was a condensation reaction, we performed the reaction under wet conditions to attempt to isolate kinetic products along the pathway to C_{2v}-**18**. Scheme 3 shows the transformation of **11** into C_{2v}-**18** and C_{2h}-**18** at partial conversion. The structure of C_{2h}-**18** was apparent from its ^{1}H NMR spectrum that showed a singlet (5.04 ppm) for the four equivalent protons on the two methylene bridges of the central eight-membered ring. To prove the hypothesis that the high diastereoselectivity observed in these reactions was due to thermodynamic rather than kinetic factors a product resubmission experiment was performed (Scheme 3). When C_{2h}-**18** was heated at reflux in dichloroethane containing PTSA, the complete disappearance of C_{2h}-**18** was observed with concomitant formation of C_{2v}-**18**; we were able to isolate C_{2v}-**18** in 80% yield.

Scheme 3

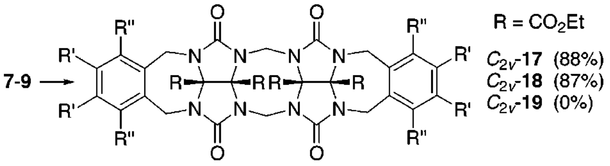


Conditions: a) H_2O•PTSA, $(ClCH_2)_2$; b) PTSA, $(ClCH_2)_2$, 80%

The crystal structure of C_{2h}-**18** was solved to provide structural details for the C_{2h}-symmetric dimers. Figure 1b shows the structure of one of the four independent molecules in the unit cell of crystals of **18**. Unlike C_{2v}-**17**, C_{2h}-**18** has two ethoxycarbonyl groups on one face of the molecule and two on the opposite face. In contrast to the time-averaged C_{2h}-symmetry deduced from its ^{1}H NMR spectrum, **18** did not crystallize in a conformation where the protons on the methylene bridges were symmetry equivalent.[17] This observation implies that the central eight membered ring undergoes fast conformational changes that result in C_{2h}-symmetry on the NMR time scale.

To expand the scope and utility of this dimerization reaction, two alternative methods were explored. Scheme 4 shows the reaction of **7**−**9** with PTSA and 1.5 equiv of $(CH_2O)_n$ in dichloroethane at reflux. When **7** and **8** were used as starting materials C_{2v}-**17** and C_{2v}-**18** were isolated in excellent yields. When **9** was used as substrate, however, C_{2v}-**19** was not produced. For the cases where it is applicable, this synthetic method (Scheme 4) is more expedient than that described in Scheme 2 since the preparation of cyclic ethers **10** and **11** is avoided.

Scheme 4



Conditions: PTSA, $(CH_2O)_n$, $(ClCH_2)_2$, reflux.

The synthetic methods described in Schemes 2 and 4 did not provide access to either C_{2v}-**19** or C_{2v}-**22**. Even though the direct dimerization of **9** (Scheme 4) and **12** (Scheme 2) both failed we hypothesized that the reaction of **9** and **12** might be successful (Scheme 5). Indeed, we were able to

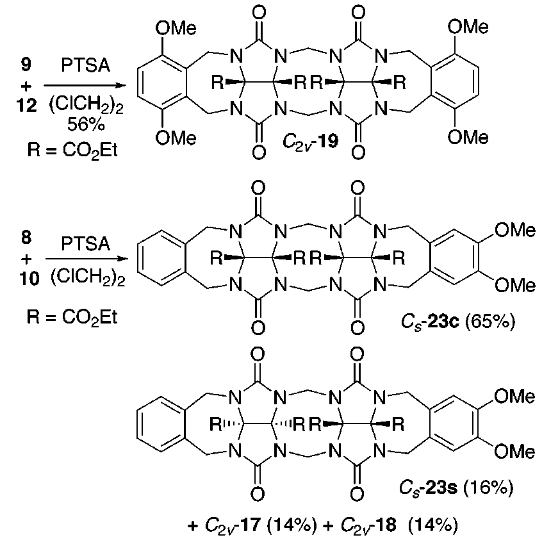
---

(15) The product of this reaction is not the expected tetraamide but rather the depicted diimide.

(16) The effect of substituents on the bridging xylylene rings and the nature of the solubilizing groups on the convex face of the molecule clearly have a dramatic effect on the dimerization reaction. We have conducted many experiments designed to address this issue but have not yet achieved a complete understanding of the scope and limitations of this reaction. We will report the results of our investigations in a full paper on this subject.

(17) This molecule can exist in eight distinct C_s-symmetric conformations that, when undergoing rapid interconversion, result in time averaged C_{2h}-symmetry.

Scheme 5



isolate C_{2v}-**19** although the yield was comparably low (56%). The ability to use two different glycoluril derivatives in the dimerization reaction suggested that it might be possible to perform a selective *heterodimerization* reaction. To demonstrate this possibility, 1 equiv of **8** and 1 equiv of cyclic ether **10** were allowed to react (Scheme 5). This reaction yielded the desired C-shaped heterodimer C_s-**23c** as the major product along with smaller quantities of the S-shaped heterodimer C_s-**23s** and the homodimers C_{2v}-**17** and C_{2v}-**18**. This result demonstrates the feasibility of selective heterodimerization reactions albeit with the competitive formation of the alternative homodimers.

Three related mild methods for the preparation of methylene-bridged glycoluril dimers were described. The reaction scope appears to be limited to the most useful substrates, namely those bearing carboxylic acid, ester, and amidoamine substituents. The more commonly employed diphenyl glycoluril derivatives are poor substrates. The C_{2v}-diastereomers are thermodynamically more stable than the C_{2h}-diastereomers. This observation provides an explanation for the high yield (82%) obtained in the formation of cucurbituril (**2**) and bodes well for the use of these reactions to create congeners of cucurbituril and related macrocyclic compounds under thermodynamically controlled conditions. Future papers will describe the successful use of this reaction in those applications as well as the self-association properties of the water-soluble self-complementary facial amphiphiles derived from C_{2v}-**17**−C_{2v}-**19**.

Acknowledgment. We thank the University of Maryland and the donors of the Petroleum Research Fund, administered by the ACS (PRF 33946-G4), for financial support of this work.

Supporting Information Available: Experimental procedures and characterization data for compounds **8**−**23**. Details of the X-ray diffraction studies for **17** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL991382K