Journal of Inclusion Phenomena and Macrocyclic Chemistry (2006) 55:219–222
DOI 10.1007/s10847-005-9027-4

Unexpected Cyclization of Dipyridyl-glycoluril in the Presence of Formaldehyde and Strong Acid: A New Scaffold with a Potential as an Anion Receptor

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(Received: 6 June 2005; in final form: 4 October 2005)

Key words: cucurbituril, cucurbituril derivatives, glycolurils, molecular scaffolds

Abstract

In an attempted synthesis of peripherally pyridine-substituted cucurbituril, an unexpected cyclized product was obtained. A careful NMR analysis followed by mass spectrometry and preliminary crystallographic analyses, helped us in resolving the structure. The structure has two quaternized pyridine functionalities and a groove suitable as a potential receptor site. In addition, just like the parent glycoluril structure, two remaining urea-derived nitrogens can be alkylated by alkyl halides. Thus, we believe this high yielding reaction may become an entry point to a new class of anion receptors.

Introduction

Glycolurils are considered highly interesting molecular scaffolds due to their rigid concave structure [1–3]. In addition, many derivatives have found applications as biotin analogs, bleaching activators, radioiodination agents for biomolecules, psychotropic agents, and catalysts [4]. Glycolurils are also essential in the synthesis of cucurbiturils as molecular containers. The most common derivative is cucurbit[6]uril (CB6) which is based on six units of glycoluril linked by methylene units. CB6 offers a 5.5 Å wide and 6.0 Å high cavity which is only accessible by two portals of approximately 4.0 Å diameters [5–8]. Cucurbiturils have already been used successfully in catalytic processes in construction of polyrotaxanes and supramolecular switches [9–13]. There are also a few reports of modified cucurbiturils; decamethylCB5 [14], diphenylCB6 [15], a cyclohexane-fused CB6 [16] and very recently a dodecahydroxyCB6 [17], among others [18–19]. However, there is no doubt that a straightforward access to derivatized cucurbiturils would increase the number and variety of applications significantly, especially considering the low solubility of the unmodified cucurbiturils in any solvent except strongly acidic water [20] and a concentrated aqueous solution of sodium sulfate [21]. As a result, the synthesis of cucurbituril derivatives with improved solubility properties and a potential for further functionalization should be very valuable.

To this end, we targeted a cucurbituril derivative with peripheral pyridine units. Thus, we started with 2,2′-dipyridil (**1**); and with slight modifications to the literature procedure [22] and applying standard glycoluril synthesis procedures, we treated this compound with urea in benzene in the presence of a small amount of TFA. On cooling to room temperature di(2-pyridyl)glycoluril (**2**) was separated as a powder. Washing with ethanol and subsequent drying yields an analytically pure compound. In our attempted preparation of pyridine derivatized cucurbituril, we heated the glycoluril derivative **2** in concentrated sulfuric acid in the presence of formaldehyde. Again, cooling to room temperature yields a light green-beige powder which on washing with acetone and recrystallization from water, yielded colorless needles of a pure compound. ^{1}H NMR of this compound in D_2O (Figure 1) shows a striking similarity to an expected spectrum for a peripherally pyridine substituted cucurbituril. However, mass spectroscopic studies using various techniques (ESI, MALDI) clearly identified an unexpectedly low molecular weight parent peak at 419.4 amu. This molecular weight was in accordance with the structure of **3**. Further derivatization with methyl iodide or ethyl iodide resulted in derivatives of **4** and **5** which were also identified by NMR and mass spectrometry (Scheme 1).

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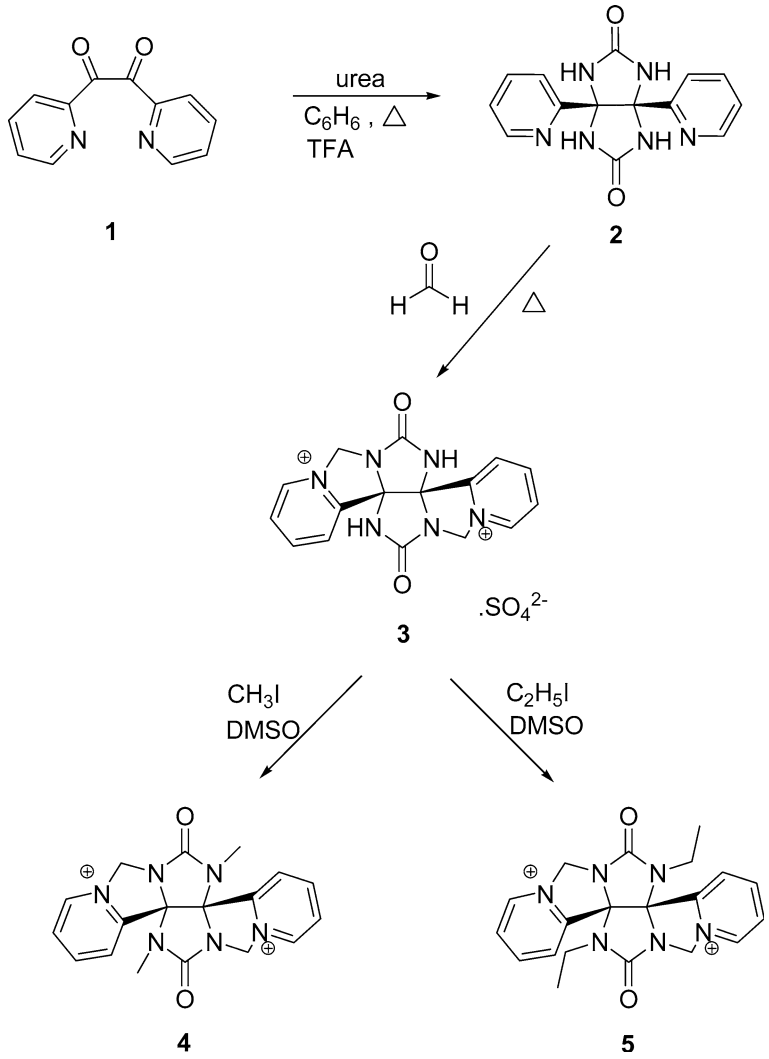

Scheme 1. Synthesis and structures of the cyclized glycoluril derivatives.

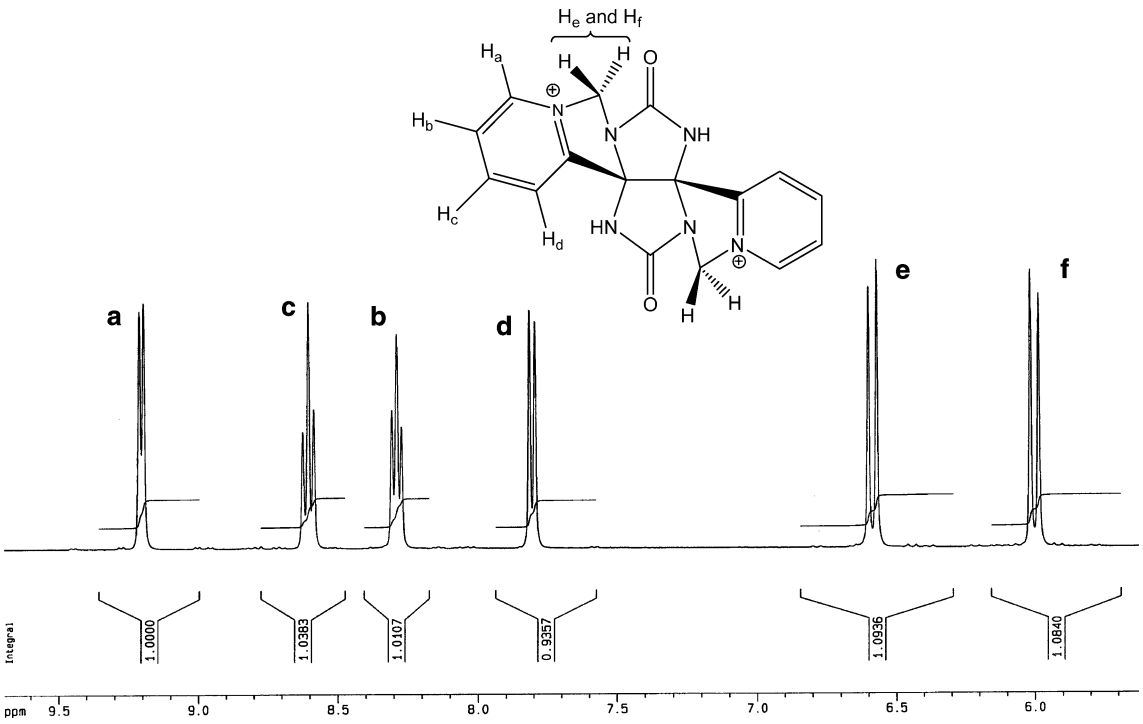

Figure 1. ^{1}H NMR spectrum and peak assignments for the compound (**3**).

Experimental

General

All chemicals and solvents purchased from Aldrich were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker DPX-400 in D_2O or DMSO-d_6 with TMS as internal reference. Reactions were monitored by thin layer chromatography using fluorescent coated aluminum sheets. Mass spectrometry was performed at Colorado State University Macromolecular Resources Facility, U.S.A. and University of Alberta, Mass Spectroscopy Laboratory, Canada.

Di(2-pyridyl)glycoluril (2)

To a suspension of 2,2′-Pyridil (3.18 g, 15 mmol), urea (1.8 g, 30 mmol) in benzene (50 ml) was added TFA (3 ml, 39 mmol). The resulting dark brown sticky mixture was refluxed under Dean–Stark apparatus overnight. Onto the reaction mixture, 30 ml of EtOH was added, the solid obtained was collected by suction filtration, and further washed with 50 ml of EtOH. After the completion of washing steps, di(2-pyridyl)glycoluril (**2**) was obtained as a brown powder. Yield 1.69 g (38%)

^{1}H NMR (400 MHz, DMSO-d_6), δ 2.5 (s, 4H, –NH), 7.08–7.02 (m, 2H), 7.17 (d, $J=7.9$ Hz, 2H), 7.49–7.44 (m, 2H), 8.32 (d, $J=4.6$ Hz, 2H). Mass spectrometry (ESI): m/z 297.1 ($M+H^+$).

Cyclization product (3)

To a heterogeneous solution of di(2-pyridyl)glycoluril (1.4 g, 4.7 mmol), 37% formaldehyde (1.4 ml) in 7.1 ml water, 0.7 ml concentrated sulfuric acid was added. The mixture was heated to 120 °C (during heating, a homogeneous solution was obtained) and kept at this temperature for 3 h. Then the temperature of the oil bath was increased to 150–160 °C and kept at this temperature for 1 h. To counteract the evaporation of water, 5 ml portions of water was added a few times. Then, the reaction mixture was cooled down to room temperature and 30 ml of acetone was added, the precipitated solid was collected by suction filtration, and further washed with 50 ml of acetone. The "cyclization product" (**3**) was obtained as a dark white powder. Yield 1.33 g (67%).

^{1}H NMR (400 MHz, D_2O), δ 6.01 (d, $J=11.8$ Hz, 2H), 6.60 (d, $J=11.8$ Hz, 2H), 7.82 (d, $J=8.07$, 2H), 8.30 (t, $J=7.0$ Hz, 2H), 8.60 (t, $J=7.92$ Hz, 2H), 9.22 (d, $J=6.04$Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 70.6 (–CH_2), 88.2 (q.C), 126.3 (Py.), 130.8 (Py.), 141.8 (Py.),145.3 (Py.), 148.9 (Py.), 159.7 (C=O). Mass spectrometry (ESI): m/z 419.4 (M^{2+} + HSO_4^-).

Methylation of the compound (3)

Into a mixture of compound (**3**) (1.0 g, 2.4 mmol), Na_2CO_3 (1.2 g, 11.3 mmol) in 10 ml DMSO was added CH_3I (1.0 ml, 16.1 mmol). The mixture was stirred at room temperature for overnight. After the reaction was completed, isopropyl alcohol was added onto the reaction mixture, and the desired product (**4**) was collected by suction filtration as brownish solid. Yield 0.76 g (52%).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.49 (d, $J=6.24$ Hz, 2H), 8.71 (t, $J=7.84$ Hz, 2H), 8.42 (t, $J=6.24$ Hz, 2H), 8.06 (d, $J=7.84$ Hz, 2H), 6.45 (d, $J=11.8$ Hz, 2H), 6.21 (d, $J=11.8$ Hz, 2H), 2.62 (s, 6H). Mass spectrometry (MALDI): m/z 605.0 ($M^{2+}+2I^-+H^+$).

Ethylation of the compound (3)

Into a mixture of compound (**3**) (1,0 g, 2.4 mmol), Na_2CO_3 (1.2 g, 11.3 mmol) in 10 ml DMSO was added C_2H_5I (0.8 ml, 9,6 mmol). The mixture was stirred at room temperature for overnight. After the reaction was completed, isopropyl alcohol was added onto the reaction mixture, and the desired product (**5**) was collected by suction filtration as brownish solid. Yield 0.91 g (60%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (d, $J=6.40$ Hz, 2H), 8.73 (t, $J=7.90$ Hz, 2H), 8.48 (t, $J=6.40$ Hz, 2H), 8.12 (d, $J=7.90$ Hz, 2H), 6.51 (d, $J=11.8$ Hz, 2H), 6.21 (d, $J=11.8$ Hz, 2H), 3.30 (m, 2H), 3.01 (m, 2H), 0.97 (t, $J=7.04$ Hz, 6H). Mass spectrometry (MALDI): m/z 633.0 ($M^{2+}+2I^-+H^+$), (ESI) m/z 505.4 ($M^{2+}+I^-$).

Results and discussion

Following the procedure detailed in the experimental section, compound **3** was obtained as a highly water-soluble sulfate salt. ^{1}H NMR spectrum is shown below, in addition to other peaks the spectrum shows an AB system very much reminiscent of cucurbituril exo and endo methylene hydrogens, a doublet at 6.01 and another doublet at 6.60 both with coupling constants of 11.8 Hz. This result was confusing at best, and misleading at worst. However, another ^{1}H NMR spectrum in DMSO-d_6 alerted us about the possibility of an unexpected product, this NMR spectrum had one more peak at 7.32 ppm with an integral corresponding to two hydrogens. Two other derivatives (**4**, **5**) obtained by alkylation using alkyl iodides had expected NMR spectra in DMSO-d_6, but in D_2O, highly acidic methylene peaks disappeared as a result of deuterium exchange in the protic solvent. This was also unexpected for a cucurbituril structure, but not for structures for **4** and **5**. Electrospray ionization and MALDI are two soft ionization mass spectrometry techniques. For this reason, we preferred mass spectrometric analyses using these techniques. The results were conclusive; largest molecular ion peaks corresponded to monosulfate salt of **3** and with the alkylated compounds diiodides of **4** and **5**. Preliminary crystallographic studies (details to be published elsewhere) also confirm the structure assignment. Energy-minimized structure of compound **3** is shown in Figure 2 The structure shows a very well defined binding groove with full positive charges on both ends. Thus, this mol-

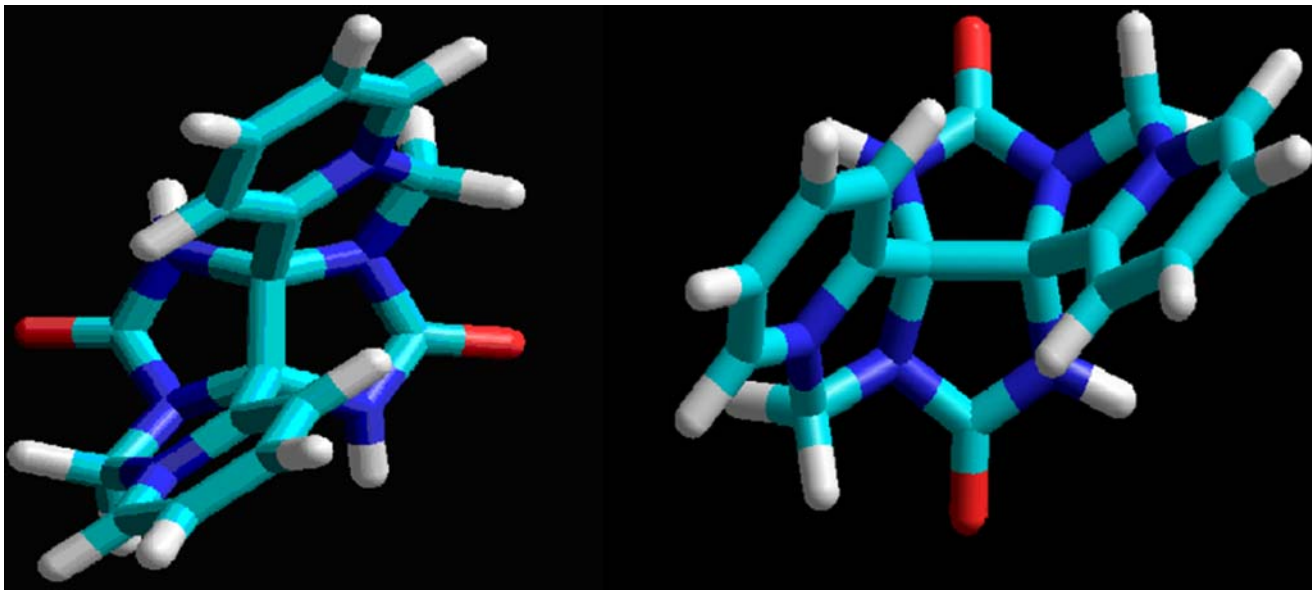

Figure 2. Two views of the energy minimized (Hyperchem v. 7.5, MM+ force field) structure of compound **3.** Preliminary X-ray diffraction studies also in full accordance with this structure.

ecule could be a very good receptor for negatively charged, electron-rich aromatic guests. The possibility of further functionalization as we demonstrated by methylation and ethylation increases the scope of this, and structurally related glycoluril derivatives even further. Our work along these lines is in progress.

Acknowledgements

We gratefully acknowledge support from Kocaeli University BAP Funds and METU University Research Funds.

References

1. J. Rebek Jr.: *Chem. Soc. Rev.* **25**, 255 (1996).
2. J. Rebek Jr.: *Acc. Chem. Res.* **32**, 278 (1999).
3. A.E. Rowan, J.A.A.W. Elemans, and R.J.M. Nolte: *Acc. Chem. Res.* **32**, 995 (1998).
4. S. Sun, J.F. Britten, C.N. Cow, C.F. Matta, and P.H.M. Harrison: *Can. J. Chem.* **76**, 301 (1998).
5. W.L. Mock: *Top. Curr. Chem.* **175**, 1 (1995).
6. J.W. Lee, S. Samal, N. Selvapalam, H.-J. Kim, and K. Kim: *Acc. Chem. Res.* **36**, 621 (2003).
7. J. Lagona, P. Mukhopadhyay, S. Chakrabarti, and L. Isaacs: *Angew. Chem. Int. Ed.* **44**, 4844 (2005).
8. K. Kim, N. Selvapalam, and D.H. Oh: *J. Incl. Phenom. Macro. Chem.* **50**, 31 (2004).
9. W.L. Mock and N.Y. Shih: *J. Org. Chem.* **48**, 3619 (1983).
10. D. Tuncel and J.H.G. Steinke: *Chem. Commun.* 253 (2001).
11. C. Meschke, H.J. Buschmann, and E. Schollmeyer: *Polymer* **40**, 945 (1999).
12. K.M. Park, D. Whang, E. Lee, J. Heo, and K. Kim: *Chem. Eur. J.* **8**, 498 (2002).
13. W.L. Lock: in F. Vögtle (ed.), *Comprehensive Supramolecular Chemistry*, Vol. 2, Elsevier Press, New York (1996), p. 477.
14. A. Flinn, G.C. Hough, J.F. Stoddart, and D.J. Williams: *Angew. Chem.* **104**, 1550 (1992).
15. H. Isobe, S. Sato, and E. Nakamura: *Org. Lett.* **4**, 1287 (2002).
16. J. Zhao, H. Kim, J. Oh, S. Kim, J.W. Lee, S. Sakamoto, K. Yamaguchi, and K. Kim: *Angew. Chem. Int. Ed.* **40**, 4233 (2001).
17. S.Y. Jon, N. Selvapalam, D.H. Oh, J.K. Kang, S.Y. Kim, Y.J. Jeon, J.W. Lee, and K. Kim: *J. Am. Chem. Soc.* **125**, 10186 (2003).
18. A.I. Day, A.P. Arnold, and R.J. Blanch: *Molecules* **8**, 74 (2003).
19. Y.J. Zhao, S.F. Xue, Q.J. Zhu, Z. Tao, J.X. Zhang, Z.B. Wei, L.S. Long, M.L. Hu, H.P. Xiao, and A.I. Day: *Chinese Sci. Bull.* **49**, 1111 (2004).
20. W.A. Freeman, W.L. Mock, and N.Y. Shih: *J Am. Chem. Soc.* **103**, 7367 (1981).
21. H.J. Buschmann, E. Cleve, K. Jansen, A. Wego, and E. Schollmeyer: *J. Incl. Phenom. Macro. Chem.* **40**, 117 (2001).
22. J.N.H. Reek, A. Kros, and R.J. Nolte: Chem. Commun. 245 (1996).