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LETTERS

Synthesis of Molecular Clefts Derived from Glycoluril

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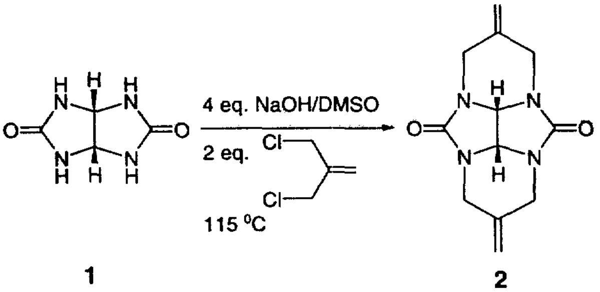
Abstract:

The alkylation of glycoluril with methallyl dichloride and further functionalization of the resultant tetracyclic molecule to synthesize different molecular clefts is described. © 1998 Elsevier Science Ltd. All rights reserved.

The rigid concave shape of glycoluril **1**, coupled with facile tetrafunctionalization of its ring nitrogen atoms and the availability of two urea carbonyl hydrogen bond acceptors make it an ideal scaffolding on which to build synthetic host molecules.[1] Several macrocyclic receptor units based on diphenyl glycoluril have been synthesized and their complexation with a variety of guest molecules have been studied by Rebek[2] and Nolte.[1] We report facile syntheses of functionalized tetracyclic molecules based on glycoluril.

The reaction of **1** with two equivalents of methallyl dichloride in the presence of four equivalents of sodium hydroxide in dry DMSO resulted in the formation of the tetracyclic product **2** in 45% isolated yield.[3]



Interestingly, under identical conditions except for the presence of an additional equivalent of sodium hydroxide, the only products resulting from the rearrangement of the exo double bond, **3** and **4**, were formed in a ratio of 4.6 to 1. These were obtained in

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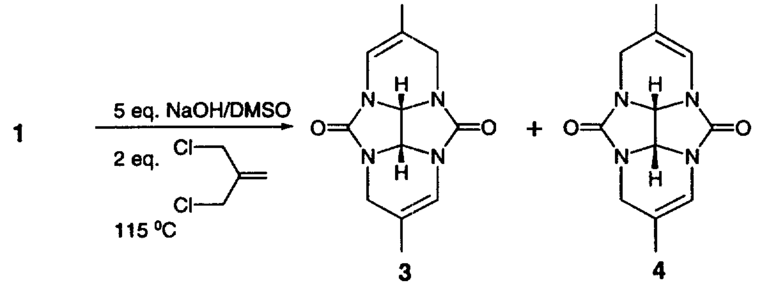
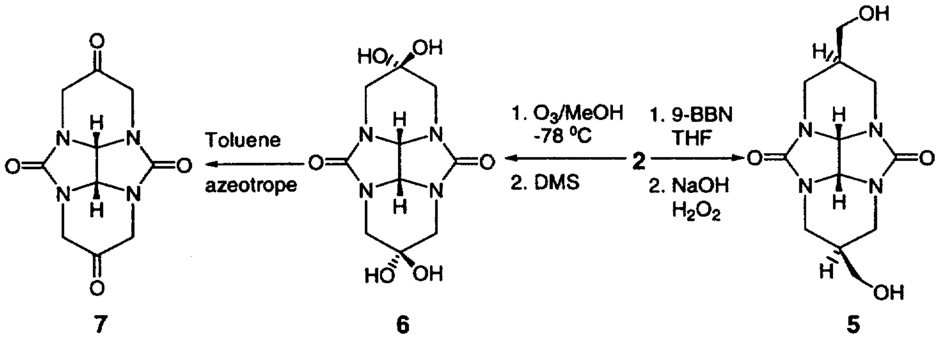
pure form by repeated chromatographic separation and the structure of the major compound 3, was derived from its NMR and mass spectral data and established by X-ray crystallography. The structure of isomeric compound 4 was established by its NMR and mass spectra.[4]



With a facile synthesis of 2 in hand we proceeded to utilize the exomethylene to further functionalize the rim of this molecule. Hydroboration with 9-BBN (excess) in THF resulted in the formation of a single product whose structure was derived from NMR data and confirmed by X-ray crystallography to be as shown for 5.[5] This is a result of the reaction of 9-BBN exclusively from the concave face of the molecule.



Ozonolytic cleavage of the exomethylene units was carried out in methanol at –78 °C followed by treatment with dimethyl sulfide at –78 °C to decompose the ozonide. Workup of the reaction afforded 6, the dihydrate of the expected diketone 7. The structure of 6 was established by NMR data and X-ray crystallography.[6] Compound 6 was easily dehydrated to 7 by azeotropic removal of water. Although 7 could be stored in solid state in a sealed container indefinitely, solutions in acetone slowly get turbid due to formation of the dihydrate, which is insoluble in acetone.

The structures of compounds 3, 5, and 6 in solid state determined by X-ray crystallography are depicted in Figure 1.

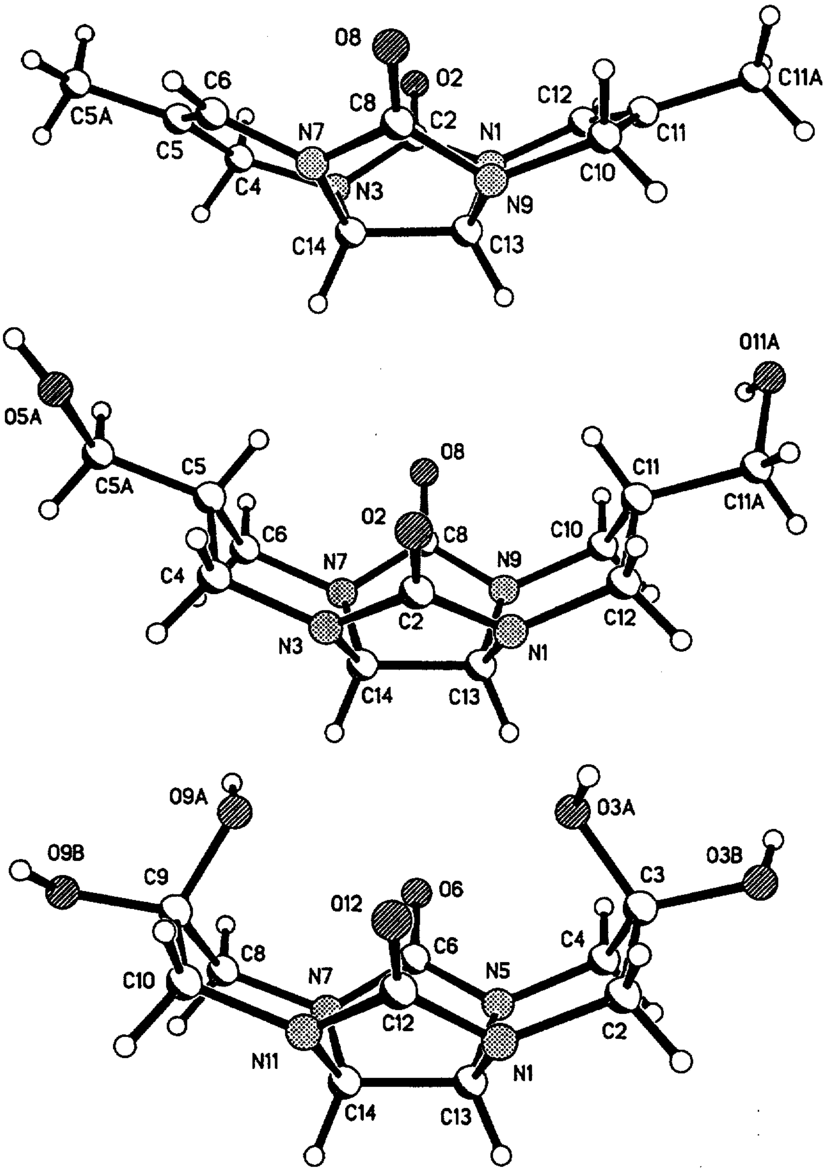


Fig. 1 ORTEP views of compounds **3**, **5**, and **6**.

Each of the molecules is bowl shaped cavities of different size. The distances between the two urea carbonyl units in molecules **3**, **5**, and **6** are 3.52, 3.46 and 3.51 A° respectively.

Molecules **5** and **6** have requisite peripheral functionalization that would allow for further elaboration of these macrocycles. Investigation of complexation properties of these molecules and the synthesis of more complex macrocycles based on these tetracyclic clefts is under study.

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References and Footnotes:

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2. Rivera, J.M.; Martin, T.; Rebek, Jr. J. *J. Am. Chem. Soc.* **1998**, *120*, 819; Valdes, C.; Spitz, U.P.; Toledo, L.M.; Kubik, S.W.; Rebek, Jr. J. *J. Am. Chem. Soc.* **1995**, *117*, 12733; Meissner, R.S.; Rebek, Jr. J.; de Mendoza, J. *Science*, **1995**, *270*, 1485; Wyler, R.; de Mendoza, J.; Rebek, Jr. J. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1699.
3. A mixture of glycoluril (4.0 g, 28mmol), NaOH (4.5 g, 112 mmol), methallyl dichloride (7.0 g, 56 mmol) and 100 mL DMSO was heated at 115 ^{0}C overnight. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The organic extract was washed with water, dried over Na_2SO4, concentrated under reduced pressure and the residue recrystallized from CH_2Cl_2/EtOAc to give 3.0 g (44%) of crystalline **2**. Mp >250 °C dec.; ^{1}H NMR ($CDCl_3$): δ 5.3 (s, 2H), 5.0 (s, 4H), 4.4 (AB, J_{A-B} = 15.0 Hz, 4H), 3.7 (AB, J_{A-B} = 15.0 Hz, 4H); ^{13}C NMR ($CDCl_3$): δ 158.7, 135.3, 114.6, 65.3, 46.2; IR cm^{-1}: 1699 (s), 1432 (m), 1100 (m). Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.51; H, 5.73; N, 22.76. Found: C, 58.68; H, 5.82; N, 22.75.
4. Spectral data for: **3**: ^{1}H (CD_3COCD_3): δ 6.38 (m, 2H), 5.43 (s, 2H), 4.07 (AB, J_{A-B} = 18.0 Hz, 2H), 3.67 (AB, J_{A-B} = 18.0 Hz, 2H), 1.69 (m, 3H); ^{13}C NMR (CD_3COCD_3): δ 157.08, 117.80, 116.34, 63.68, 43.08, 17.06; IR cm^{-1}: 1713 (s), 1669 (m), 1451 (s); MS (EI): 246 (M^+), 231 (M^+ -CH3), 150, 96. **4**: ^{1}H NMR (CD_3COCD_3): δ 6.34 (m, 2H), 5.42 (s, 2H), 4.08 (AB, J_{A-B} = 18.0 Hz, 2H), 3.63 (AB, J_{A-B} = 18.0 Hz, 2H), 1.69 (m, 3H); ^{13}C NMR (CD_3COCD_3): δ 157.39, 119.46, 118.68, 63.28, 42.42, 17.06; IR cm^{-1}: 1716 (s), 1436 (s), 1240 (m); MS (EI): 246 (M^+), 231 (M^+ -CH3), 202, 150, 96. HRMS (EI) Calcd. for $C_{12}H_{14}N_4O_2$ 246.1117: Found 246.1109.
5. Spectral data for **5**: ^{1}H NMR (CD_3OD): δ 5.3 (s, 2H), 4.0 (dd, 4H, J=14.4 Hz, J=4.5Hz), 3,4 (d, 4H, J=6.0 Hz), 2.9 (m, 4H), 1.6 (m, 2H); ^{13}C NMR (CD_3OD): δ 159.3, 65.5, 61.9, 42.4, 36.4; IR cm^{-1}: 3665-3030 (m, br), 1686 (s), 1482 (s), 1242 (m). HRMS Calcd. for $C_{12}H_{18}N_4O_4$: 282.1328: Found 248.1337.
6. Spectral data for **6**: ^{1}H NMR (CD_3OD): δ 5.35 (s, 2H), 3.82 (AB, J_{A-B} = 14.1 Hz, 4H), 3.08 (AB, J_{A-B} = 14.1 Hz, 4H); **7**: ^{1}H NMR (CD_3COCD_3): δ 5.93 (s, 2H), 4.22 (AB, J_{A-B} = 18.9 Hz, 4H), 3.95 (AB, J_{A-B} = 18.9 Hz, 4H).