ORGANIC LETTERS

2010
Vol. 12, No. 7
1392−1395

Piperazine Bridged Resorcinarene Cages

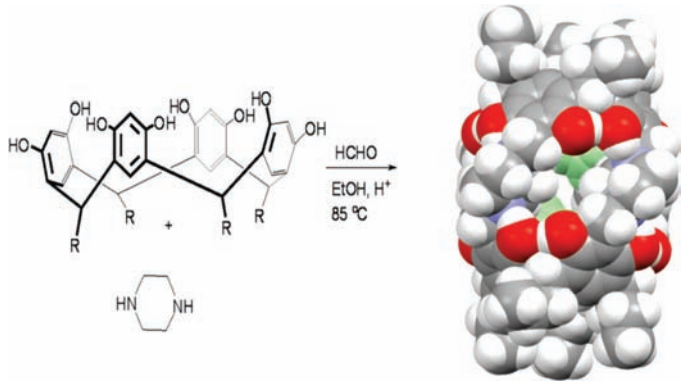
N. Kodiah Beyeh, Arto Valkonen, and Kari Rissanen*

NanoScience Center, Department of Chemistry, University of Jyväskylä, P.O.Box 35, 40014 Jyväskylä, Finland

kari.t.rissanen@jyu.fi

Received November 2, 2009

ABSTRACT



The one-pot Mannich condensation of resorcinarenes with piperazine and an excess of formaldehyde under high dilution conditions results in a helical cage, namely, a covalently linked dimer of two resorcinarenes connected via four piperazine bridges in yields ranging from 20 to 40%. The compounds were analyzed by NMR spectroscopy, ESI mass spectrometry, and single crystal X-ray diffraction. The helical cages can encapsulate small guest molecules by adapting the cavity volume by changing the helical pitch according to the guest size.

The seminal work by Baeyer[1] on the studies of condensation reactions between benzaldehyde and resorcinol in acidic medium resulted in the first synthesis of resorcinarenes in 1872. Resorcinarenes,[2] commonly referred to as one of the pillars in supramolecular chemistry, are readily available mainly in the form of their *rccc* isomer by acid-catalyzed cyclocondensation of resorcinol with various aliphatic and aromatic aldehydes.[3] The possibility of modifying these resorcinarenes either via nucleophilic aromatic substitutions at position 2 on the aromatic ring or the phenol hydroxyl groups or the lower rim increases their potential for forming multifunctional compounds. Resorcinarenes are important tools in the synthesis of, for example, cavitands[4] and dendrimers[5] and in the building of even larger supramolecular and tubular assemblies.[6] The multipurpose scaffold possessed by resorcinarenes are useful in various applications such as their ability to act as hosts in forming open inclusion complexes[7] and dimeric[8] and hexameric[9] capsules.

Mannich[10] condensation is without a doubt the most common and most important synthetic procedure in functionalizing resorcinarenes at the aromatic ring. With excess formaldehyde in ethanol, tetrabenzoxazines are formed in

(1) (a) Baeyer, A. *Ber Dtsch. Chem. Ges.* **1872**, *2*, 25. (b) Baeyer, A. *Ber Dtsch. Chem. Ges.* **1872**, *5*, 280.

(2) (a) Timmerman, P.; Verboom, W.; Reinhoudt, D. *Tetrahedron* **1996**, *52*, 2663. (b) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931.

(3) (a) Tunstad, M.; Tucker, A.; Dalcanale, E.; Weiser, J.; Bryant, A.; Sherman, C.; Helgeson, C.; Knobler, B.; Cram, J. *J. Org. Chem.* **1989**, *54*, 1305. (b) Högberg, S. *J. Org. Chem.* **1980**, *45*, 4498.

(4) Cram, D.; Karbach, S.; Kim, E.; Knobler, B.; Maverick, F.; Ericson, L.; Helgeson, C. *J. Am. Chem. Soc.* **1988**, *110*, 2229.

(5) (a) Luostarinen, M.; Laitinen, T.; Schalley, C. A.; Rissanen, K. *Synthesis* **2004**, 255. (b) Luostarinen, M.; Salorinne, K.; Lahteenmaki, H.; Mansikkamaki, H.; Schalley, C. A.; Nissinen, M.; Rissanen, K. *J. Incl. Phenom. Mac. Chem.* **2007**, *58*, 71.

(6) (a) Orr, G. W.; Barbour, L. J.; Atwood, J. L. *Science* **1999**, *285*, 1049. (b) Mansikkamaki, H.; Nissinen, M.; Rissanen, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1243. (c) Mansikkamäki, H.; Busi, S.; Nissinen, M.; Åhman, A.; Rissanen, K. *Chem.—Eur. J.* **2006**, *12*, 4289.

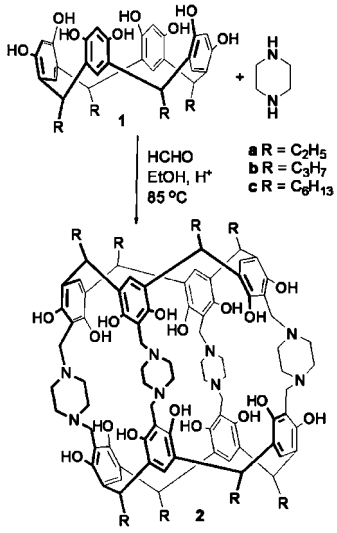
(7) (a) Rudkevich, D.; Rebek, J., Jr. *Eur. J. Org. Chem.* **1999**, 1991. (b) Nissinen, M.; Rissanen, K. *Supramol. Chem.* **2003**, *15*, 581. (c) Vuorimaa, E.; Vuorinen, T.; Tkachenko, N.; Cramariuc, O.; Hukka, T.; Nummelin, S.; Shivanyuk, A.; Rissanen, K.; Lemmetyinen, H. *Langmuir* **2001**, *17*, 7327. (d) Falábu, D.; Shivanyuk, A.; Nissinen, M.; Rissanen, K. *Org. Lett.* **2002**, *4*, 3019.

10.1021/ol100407f
Published on Web 03/05/2010

quite high yields in the presence of primary amines while the use of secondary amines results in the formation of tertiary amines. Mannich condensation has been employed to connect a pair of adjacent[11] and opposite[12] benzoxazine rings on a single resorcinarene unit by aliphatic arms forming single- and double-handled baskets. Cage-like dimer formation via weak interactions of resorcinarenes carrying morpholine and hydroxyethyl-piperazine substituents have been reported.[13]

Mannich condensation under high dilution conditions has been used to covalently connect two resorcinarenes via four flexible ethylene diamine moieties acting as the bridges in a 15% yield.[14] By tuning this procedure, the more rigid piperazine was used as a linker to covalently connect two resorcinarene units via four piperazines. The desired resorcinarene cages **2** (Scheme 1) were purified via Flash chromatography and isolated with yields ranging from 20 to 40% (see Supporting Information).

Scheme 1. Synthesis of Covalent Resorcinarene Cages via Four Piperazine Linkers



The ^{1}H NMR spectra of cages **2a**−**c** show the compounds to be symmetrical in solution with overlapping signals

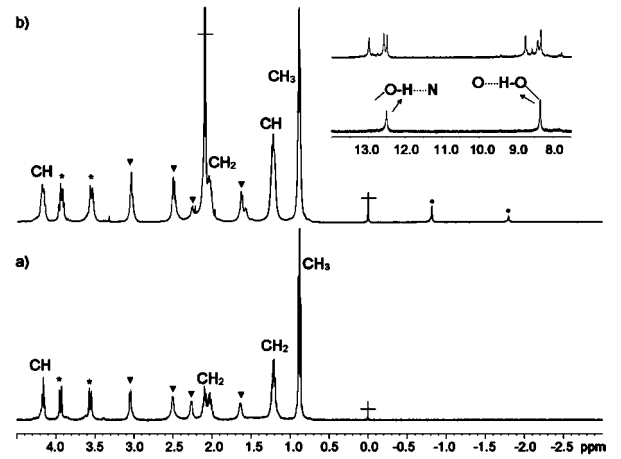


Figure 1. ^{1}H NMR spectra of **2b** in $CDCl_3$ at 303 K (a) after chromatography, revealing two doublets for the diastereotopic Ar−CH_2-N (*), and four doublets for the equally diastereotopic piperazine protons (▼), (b) after boiling in distilled MeCN for 2 h and drying. The highly upfield shifted signals (•) refer to the encapsulated MeCN. (Inset) Change in the hydrogen bonding behavior from the nonencapsulating cage (bottom) to the MeCN encapsulating cage (top).

corresponding to the upper and lower part of the molecule. Taking cage **2b** as an example (Figure 1a), the methine protons of the resorcinarene scaffold appear around 4.15 ppm as a triplet. The diastereotopic protons of the Ar−CH_2-N group are easily identified as the two doublets between 3.5 and 4.0 ppm. Four doublets are observed between 1.5 and 3.3 ppm corresponding to the piperazine protons NCH_2-N. The diastereotopic nature of the piperazine protons can be seen from the fact that they all form doublets. The methylene groups of the resorcinarene appear as multiplets at 2.1 ppm and 1.2 ppm, while the methyl groups appear as a triplet at 0.9 ppm. Two different broad peaks corresponding to the hydroxyl groups appear at 12.5 ppm and 8.3 ppm. This confirms the two different intramolecular hydrogen bonds in solution. The peak at 12.5 ppm corresponds to the hydroxyl groups involved in intramolecular hydrogen bonds with the nitrogens (O−H···N) of the adjacent piperazine unit while the peak at 8.3 ppm corresponds to the hydroxyl groups involved in intramolecular hydrogen bonding with the oxygens (O−H···O) of the adjacent hydroxyl group.

The cages have a tendency to encapsulate solvent molecules from synthesis (ethanol) and during the purification process (methanol and CH_2Cl_2). The elimination of all the solvent molecules from **2b** was achieved during the purification phase and the nonencapsulating "empty" **2b** was used in the NMR studies to probe the small guest encapsulation. The "empty" **2b** was boiled in distilled MeCN for 2 h and

(8) (a) Shivanyuk, A.; Rissanen, K.; Kolehmainen, E. *Chem. Commun.* **2000**, 1107. (b) Shivanyuk, A.; Paulus, E. F.; Rissanen, K.; Kolehmainen, E.; Böhmer, V. *Chem.—Eur. J.* **2001**, *7*, 1944. (c) Mansikkamäki, H.; Nissinen, M.; Rissanen, K. *Chem. Commun.* **2002**, 1902. (d) Mansikkamäki, H.; Nissinen, M.; Schalley, C. A.; Rissanen, K. *New J. Chem.* **2003**, *27*, 88. (e) Mansikkamäki, H.; Schalley, C. A.; Nissinen, M.; Rissanen, K. *New J. Chem.* **2005**, *29*, 116. (f) Mansikkamäki, H.; Nissinen, M.; Rissanen, K. *CrystEngComm.* **2005**, *7*, 519. (g) Åhman, A.; Luostarinen, M.; Rissanen, K.; Nissinen, M. *New J. Chem.* **2007**, *31*, 169. (h) Beyeh, K.; Valkonen, A.; Rissanen, K. *Supramol. Chem.* **2009**, *21*, 142.

(9) (a) Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 3432. (b) Atwood, J.; Babour, L.; Jerga, A. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4837. (c) Beyeh, N. K.; Kogej, M.; Åhman, A.; Rissanen, K.; Schalley, C. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5214. (d) Rissanen, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3652. (e) MacGillivray, L. R.; Atwood, J. L. *Nature* **1997**, *389*, 469. (f) Gerkensmeier, T.; Iwanek, W.; Agena, C.; Frohlich, R.; Kotila, S.; Nather, C.; Mattay, J. *Eur. J. Org. Chem.* **1999**, 2257.

(10) (a) Iwanek, W.; Mattay, J. *Liebigs Ann. Chem.* **1995**, 1463. (b) Airola, K.; Böhmer, V.; Paulus, E. F.; Rissanen, K.; Schmidt, C.; Thondorf, I.; Vogt, W. *Tetrahedron* **1997**, *53*, 10709.

(11) Schmidt, C.; Airola, K.; Böhmer, V.; Vogt, W.; Rissanen, K. *Tetrahedron.* **1997**, *53*, 17691.

(12) Arnott, G.; Heaney, H.; Hunter, R.; Page, P. C. B. *Eur. J. Org. Chem.* **2004**, 5126.

(13) Becker, R.; Reck, G.; Radeglia, R.; Springer, A.; Schulz, B. *J. Mol. Struct.* **2006**, *784*, 157.

(14) Schmidt, C.; Thondorf, I.; Kolehmainen, E.; Böhmer, V.; Vogt, W.; Rissanen, K. *Tetrahedron Lett.* **1998**, *39*, 8833.

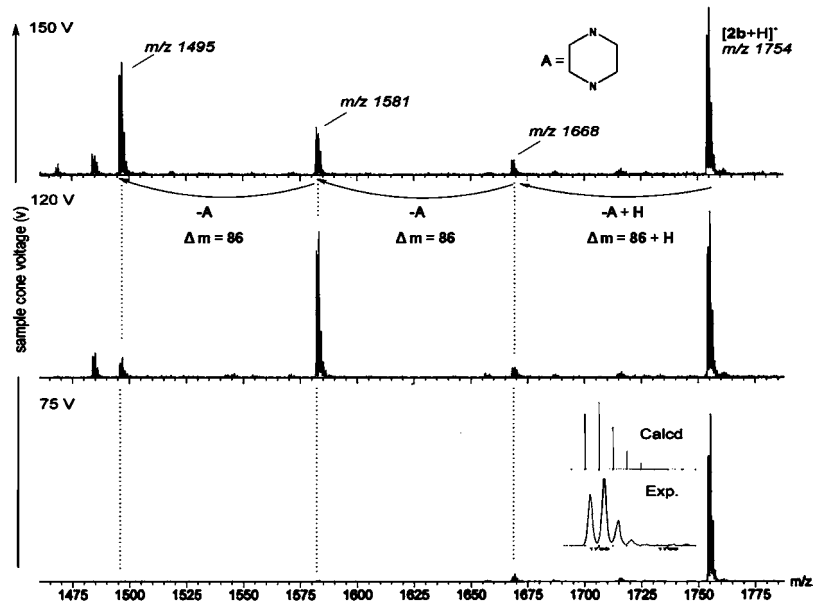


Figure 2. Positive ion ESI mass spectra of **2b**. Signal for the protonated compound appears at *m*/*z* 1754. A series of consecutive fragments appear at equal distances of Δm = 86 Da corresponding to the loss of a piperazine moiety via 1,4-amine elimination. (Inset) Measure isotope pattern is in line with the calculated pattern on the basis of natural abundance.

dried and the ^{1}H NMR was measured. Two new peaks were clearly seen at −0.74 and −1.72 ppm corresponding to the encapsulated MeCN (Figure 1b). The OH groups (Figure 1, inset) of the resorcinarene moieties clearly form hydrogen bonds to the encapsulated MeCN molecules resulting in the two observed upfield shifted signals. Similar experiments with residual solvent encapsulating **2a** and **2c** were performed to see if the encapsulated solvents could be replaced. It was observed that MeCN replaces a part of the encapsulated solvent molecules in **2a** and **2c**. Nitromethane was also tested for **2a** and similar partial replacement as for MeCN was observed (see Supporting Information Figure 2 and Supporting Information Figure 13).

The cages **2a**−**c** can easily be ionized and transferred intact into the gas phase by an electrospray ionization (ESI) mass spectrometric technique using CH_2Cl_2/methanol as the spray solvent. In this case, protonated ions are formed presumably protonated at one of the tertiary nitrogens. The isotope patterns obtained by experiment agree well with those simulated on the basis of natural abundances. With an increase in sample cone voltage, intense peaks appear at repetitive distances of $\Delta m = 86$ Da, which corresponds to the loss of a piperazine moiety (Figure 2). Intramolecular hydrogen bonding between one of the OH groups on a resorcinol ring and the amine nitrogen supports a 1,4-elimination proceeding through a six-membered transition structure. All four piperazine moieties were successfully fragmented at higher voltages. Encapsulated solvent did not survived the high vacuum of the mass spectrometer and hence could not be seen in the gas phase.

The crystallization of **2b** from two different solvents resulted in two X-ray structures (see SI) of the cage with solvent encapsulation. Single crystals suitable for crystal structure analysis for **2b_I** were obtained from a methanol/acetone solvent mixture. The resorcinarene skeleton in **2b_I** (Figure 3) adopts a near perfect cone conformation (the distances between the centroids of the opposite resorcinol rings are 6.92 and 6.83 Å and due to the crystallographic symmetry [space group *C*2/*c* with $Z = 4$], the upper and lower resorcinarene skeleton are similar) stabilized by four (x 2) intramolecular hydrogen bonds each between neighboring hydroxyl groups with an average hydrogen bond distances of 2.72 Å. In addition to the eight O−H···O hydrogen bonds, the eight remaining OH hydrogens form a strong O−H···N hydrogen bonds (average bond distance of 2.60 Å) to the adjacent nitrogens of the piperazine moiety locking the cage into a helical conformation (Figure 3). The distances between adjacent piperazine nitrogens in the upper and lower layer are nearly equal (7.08, 7.22, 7.43, and 7.15 Å). The helical turn between the upper (up) and lower (lo) part of the cage is measured as the torsion angle of the upper and lower part [defined as Bz(up)(centroid) − CH(up) − Bz(lo)(centroid) − CH(lo)] of the piperazine connected benzene rings. For **2b_I**, the helix turn is 54.3°. The cavity volume of 166 Å^3 measured using PLATON VOIDS module[15] encapsulates two highly disordered methanol molecules in the upper and lower part of the cavity. Due to the severe disorder, the orientation and possible interactions (H-bonding) between the methanol guests could not be verified.

Crystallizing **2b** from propanol solution, a cage with slightly different overall structure was obtained. The **2b_II** is not as symmetrical [space group $P2_1/c$ with $Z = 4$] as **2b_I** and the two crystallographically independent resor-

(15) Spek, A. L. *J. Appl. Crystallogr.* **2003**, *36*, 7.

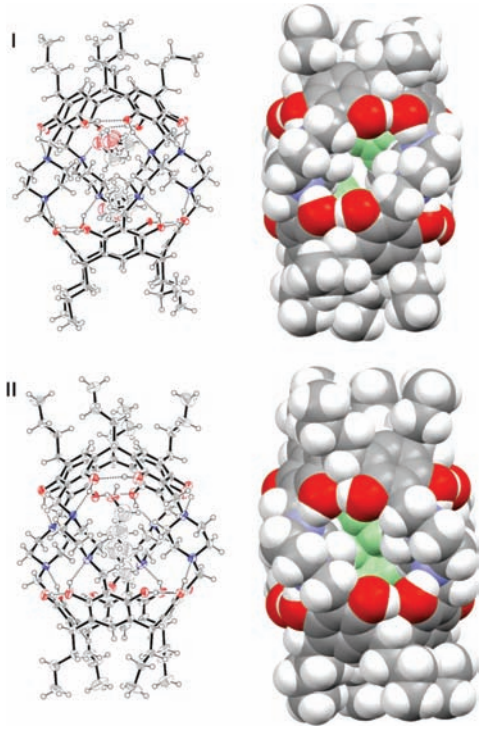


Figure 3. Ortep and CPK plots of the X-ray structures of covalently linked resorcinarene cage **2b** with encapsulated methanol **I** and propanol **II**. The encapsulated solvent molecules are highly disordered. Noncoordinating solvent molecules are omitted and the disordered encapsulated solvent molecules in the CPK model are colored for clarity.

cinarene skeletons in **2b_II** (Figure 3) show nearly identical cone conformation with **2b_I**, the distances between the centroids of the opposite resorcinol rings being 6.92 and 6.92 Å for the upper and 6.89 and 6.90 Å for the lower resorcinarene moieties. The O−H···O hydrogen bonds are slightly longer than in **2b_I** with the average H-bond distance being 2.74 Å. The O−H···N hydrogen bonds are also slightly longer with average H-bond distance of 2.61 Å. The slight asymmetry of **2b_II** is manifested by the unequal distances between the adjacent nitrogens in the upper/lower [7.12/7.09, 7.62/7.63, 7.09/7.00 and 7.33/7.39 Å] parts of the cage. The helix twist in **2b_II** is 52.6°; thus, the cavity is slightly more open than in **2b_I**. One highly disordered propanol molecule is encapsulated into the cavity, the volume of which is 177 Å^3. Compound **2b** has the ability to open and close the helical conformation, therefore opening the windows for solvent inclusion in methanol and in propanol. The sizes (3d-volumes[16]) of the solvent molecules [V_{MeOH} = 41 Å^3, V_{PrOH} = 78 Å^3] are sufficiently small to be encapsulated by the cage leading to the cavity volume and helix turn changes. The Rebek 55% rule[17] is nicely followed by 49% PC_{cavity} for **2b_I** and 44% for **2b_II**.

In conclusion, four piperazine units were successfully used as linkers, to covalently connect two resorcinarene molecules. The ^{1}H NMR show these compounds to be fairly symmetrical in solution with overlapping peaks corresponding to the upper and lower part of the dimeric cage. Encapsulated solvent molecules during synthesis and purification could be replaced with other solvent molecules. The single crystal X-ray structure of **2b_I** and **2b_II** shows that, the helical cages are able to encapsulate suitably small solvent molecules by adapting to the size of the guest via modulating the helix turn leading to a larger cavity for a larger guest. The nature of the encapsulated solvent is thus partly responsible for the difference in volume size and twist angle of the different structures. In our future studies, we aim to investigate the possibility of incarceration[18] of a specific larger guest inside the cavity of the dimeric cage during the synthetic process.

Acknowledgment. We gratefully acknowledge the Academy of Finland (proj. no. 212588) and the University of Jyväskylä for financial support.

Supporting Information Available: Analytical methods, experimental details for **2a**−**c** and a crystallographic information file (CIF) for **2b_I** and **2b_II**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100407F

(16) *Spartan 04*; Wavefunction Inc.: Irvine, CA, 2004.
(17) Mecozzi, S.; Rebek, J., Jr. *Chem.—Eur. J.* **1998**, *4*, 1016.
(18) Mal, P.; Breiner, B.; Rissanen, K.; Nitschke, J. R. *Science* **2009**, *324*, 1697.