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Hydrogen-Bonded Dimers of Tetra-urea Calix[4]arenes Stable in THF

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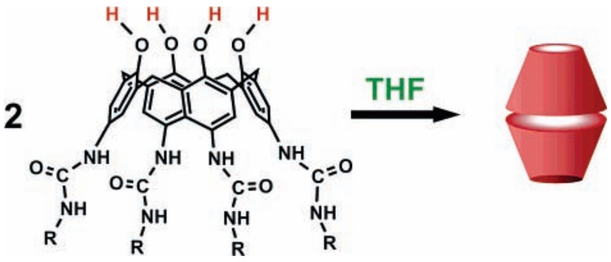
ABSTRACT



Whereas tetra-urea derivatives of tetra-alkoxy calix[4]arenes 1 exist as single molecules in THF, dimeric hydrogen-bonded capsules are exclusively found for the corresponding calix[4]arene derivatives 3 and 2 with two or four free hydroxyl groups. Comparison with the rigidified tetra-urea 5 suggests that this increased stability of the dimers is due to the stabilization of their four-fold symmetry by intramolecular hydrogen bonds between the phenolic hydroxyl groups.

Tetra-arylurea derivatives **1** form dimeric capsules in aprotic, apolar solvents (e.g. cyclohexane, benzene, chloroform, etc.) held together by a seam of intermolecular hydrogen bonds between the urea functions in the *p*-position of the calix[4]arene.[1] The internal volume of 190−200 Å^3 allows (and requires) the inclusion of various guests (neutral molecules[2] as well as organic cations[3]). However, this guest inclusion is not the only attractive property of dimers **1·1**. The structure of such a dimer, in which the two calixarenes are turned relative to each other by 45° around their common axis brings also the urea residues and the functional groups attached to them into a unique mutual position. This allows reactions between these functional groups that would not be possible with a similar selectivity for the single calixarenes.[1b] Bis- and tetraloop derivatives have been prepared by olefin metathesis in heterodimers with a tetra-tosylurea as template.[4] Hydrolysis of the tetraloop compounds led to huge macrocycles,[5] and their heterodimers with alkenyl ureas could be converted to multiple catenanes[6] and rotaxanes.[7]

For a comparative kinetic study of the guest release (or better guest exchange against the solvent),[8] we recently synthesized for the first time tetra-urea derivatives **2** and **3** having four or two free phenolic hydroxyl groups. (The

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(1) For reviews see: (a) Rebek, J., Jr. *Chem. Commun.* **2000**, 637−643. (b) Bogdan, A.; Rudzevich, Y.; Vysotsky, M. O.; Böhmer, V. *Chem. Commun.* **2006**, 2941−2952. (c) Böhmer, V.; Vysotsky, M. O. *Aust. J. Chem.* **2001**, *54*, 671−677.

(2) Castellano, R. K.; Kim, B. H.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 12671−12672. Vysotsky, M. O.; Böhmer, V. *Org. Lett.* **2000**, *2*, 3571−3574.

(3) Schlalley, C. A.; Castellano, R. K.; Brody, M. S.; Rudkevich, D. M.; Siuzdak, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 4568−4579. Vysotsky, M. O.; Pop, A.; Broda, F.; Thondorf, I.; Böhmer, V. *Chem. Eur. J.* **2001**, *7*, 4403−4410. Frish, L.; Vysotsky, M. O.; Matthews, S. E.; Böhmer, V.; Cohen, Y. *J. Chem. Soc., Perkin Trans. 2* **2002**, 88−93. Frish, L.; Vysotsky, M. O.; Böhmer, V.; Cohen, Y. *Org. Biomol. Chem.* **2003**, *1*, 2011−2014.

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(5) Cao, Y.; Wang, L.; Bolte, M.; Vysotsky, M. O.; Böhmer, V. *Chem. Commun.* **2005**, 3132−3134.

(6) Wang, L.; Vysotsky, M. O.; Bogdan, A.; Bolte, M.; Böhmer, V. *Science* **2004**, *304*, 1312−1314.

(7) Gaeta, C.; Vysotsky, M. O.; Bogdan, A.; Böhmer, V. *J. Am. Chem. Soc.* **2005**, *127*, 13136−13137.

(8) Manuscript in preparation.

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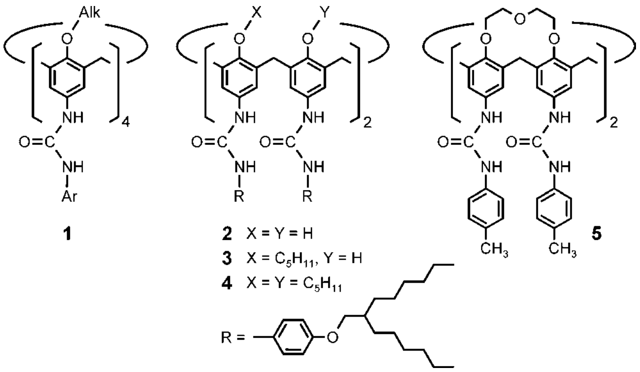
branched alkoxy group in the *p*-position of the urea-aryl residues was introduced to increase their solubility and does not influence the dimerization.) Compounds **2** and **3** were obtained by debenzylation (hydrogenation, 10% Pd/C) of the corresponding tetra-ethers with four or two benzylether groups in 51−95% yield.[9]



1

2 X = Y = H
3 X = C_5H_{11}, Y = H
4 X = Y = C_5H_{11}

5

Surprisingly we found that both compounds form dimers also in THF or dioxane, where tetra-ureas **1** in general (and tetra-ether **4** as a specific example) exist as monomers.[10] On the basis of the accumulated knowledge, the exclusive existence of dimers is unambiguously proved already by the signals of the calixarene aromatic protons, which appear as a pair of *m*-coupled doublets at 5.96 and 7.83 ppm (see Figure 1) in positions similar to those found in benzene (6.11 and 8.01 ppm). In DMSO-d_6 a single singlet for Ar-H (calix) reflects the C_{4v} symmetry of the monomeric calixarene.

Intermolecular cross-peaks found in the NOESY spectra of **2** in C_6D_6 and THF-d_8 (for example between the aromatic protons of the calix[4]arene and of the urea residue) are entirely consistent with the dimeric structure and are not observed in the case of DMSO-d_6.[11] The spectrum of **3** is more complex but in agreement with the expected C_2 symmetry of the dimer **3·3**.[12] The appearance of additional peaks in a mixture of **2** and **3** in THF-d_8 suggests the formation of heterodimers, although the spectrum is too complicated for a complete analysis.

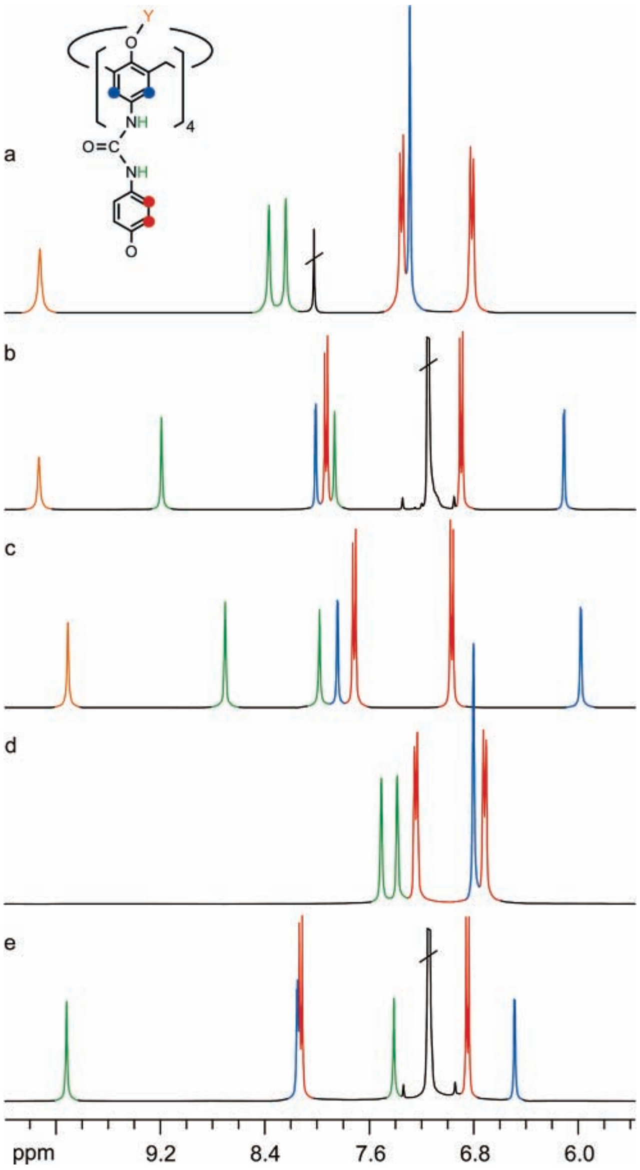


Figure 1. Sections of the ^{1}H NMR spectra of (a) **2** in DMSO-d_6 + $CDCl_3$ (20%); (b) **2** in C_6D_6; (c) **2** in THF-d_8; (d) **4** in THF-d_8; and (e) **4** in C_6D_6.

The reason why **2** dimerizes completely in THF (in contrast to its tetra-ether **4**) is not entirely clear. A tentative explanation might be found in the C_4-symmetrical conformation of the calix[4]arene required in the dimer. This conformation is stabilized by a cyclic array of O−H···O−H···O−H hydrogen bonds between the phenolic OH groups of **2**. Tetra-ethers, on the other hand, assume a pinched cone conformation with C_2 or C_{2v} symmetry, which must be rearranged to C_4 in the dimer, whereas for **2** such an energetically unfavorable rearrangement is not necessary. Two O−H···O−Y hydrogen bonds are present in 1,3-diethers such as **3**; they often assume a slightly pinched cone

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(9) Compound **2**: yield 95%; ^{1}H NMR (400 MHz, THF-d_8) δ 0.88 (t, 48H, ^3J = 6.8 Hz, CH_3), 1.3−1.4 (m, 160H, CH_2), 1.45 (m, 8H, CH), 3.05 (d, 8H, ^2J = 13.7 Hz, ArCH_2Ar), 3.81 (d, 16H, ^3J = 5.8 Hz, OCH_2), 3.91 (d, 8H, ^2J = 13.7 Hz, ArCH_2Ar), 5.96 (d, 8H, ^4J = 2.2 Hz, ArH), 6.95 (d, 16H, ^3J = 8.8 Hz, PhH), 7.70 (d, 16H, ^3J = 8.8 Hz, PhH), 7.83 (d, 8H, ^4J = 2.2 Hz, ArH), 7.96 (s, 8H, NH), 8.69 (s, 8H, NH), 9.89 (s, 8H, OH); *m/z* (ESI) 1833.2 (100%) [M + Na]$^+$ calcd for $C_{112}H_{160}NaN_8O_{12}$ 1832.2. Compound **3**: yield 51%; ^{1}H NMR (400 MHz, THF-d_8) δ 0.88 (t, 48H, ^3J = 6.8 Hz, CH_3), 0.98 (t, 12H, ^3J = 7.0 Hz, CH_3), 1.23−1.63 (m, 184H, CH and CH_2), 2.05 (m, 8H, CH_2), 2.85−3.03 (m, 8H, ArCH_2Ar), 3.81 (m, 24H, OCH_2), 4.02−4.17 (m, 8H, ArCH_2Ar), 5.90 (br s, 2H, ArH), 5.94 (br s, 2H, ArH), 6.06 (br s, 2H, ArH), 6.09 (br s, 2H, ArH), 6.93 (d, 8H, ^3J = 9.3 Hz, PhH), 6.95 (d, 8H, ^3J = 9.3 Hz, PhH), 7.53 (s, 2H, NH), 7.59 (s, 2H, NH), 7.65−7.85 (m, 28H, ArH, PhH and NH), 8.10 (s, 2H, OH), 8.11 (s, 2H, OH), 8.73 (s, 2H, NH), 8.90 (s, 2H, NH), 8.94 (s, 2H, NH), 9.13 (s, 2H, NH); *m/z* (ESI) 1973.4 (100%) [M + Na]$^+$ calcd for $C_{122}H_{180}NaN_8O_{12}$ 1972.4.

(10) A tetra-tritylurea calix[4]arene does not form dimers in apolar solvents. However, the dimerisation can be enforced under drastic conditions, offering tetramethyl ammonium cations as guest. These mechanically entangled dimers are rather stable in DMSO, decomposing with half-life times of several days, see: Vysotsky, M. O.; Thondorf, I.; Böhmer, V. *Chem. Commun.* **2001**, 1890−1891.

(11) A quantitative interpretation of NOESY spectra of **2** in C_6D_6 and THF-d_8 is given in the Supporting Information.

(12) For a symmetrically analogous example, compare: Mogck, O.; Pons, M.; Böhmer, V.; Vogt, W. *J. Am. Chem. Soc.* **1997**, *119*, 5706−5712. For general symmetry considerations, see: Pop, A.; Vysotsky, M. O.; Saadioui, M.; Böhmer, V. *Chem. Commun.* **2003**, 1124−1125.

conformation, but still it may take less energy to reach the regular cone conformation than for a tetra-ether.

In comparison to dimers of **1** and **4**, dimer **2·2** shows also an increased stability toward water. A solution of **2** in THF ($\sim 4 \times 10^{-3}$ M) still contains ~43% of the dimer after the addition of 2.5 vol % of water (~315 molecules per one molecule of **2**), and traces of **2·2** were seen in the NMR spectrum even with 7.7% water, when **2** starts to precipitate.

To get some further insight, we compared the dimerization of **2** and **3** with the tetra-urea derivative **5**, which is rigidified in a nearly perfect C_{4v}-symmetrical conformation by the two short crownether bridges.[13] Also **5** forms homodimers in THF, and a mixture with **2** contains in addition to the two homodimers **2·2** and **5·5** also the heterodimer **2·5**. This means the compounds **2**, **3**, and **5** show in THF the dimerization properties known from **1** (or **4**) in less polar solvents (chloroform, benzene). The dimerization of the rigid **5** with a flexible **1** (or **4**) is entropically disfavored.[14] Therefore it is not surprising that a solution of **2** and **1** (or **4**) in THF contains the homodimer **2·2** and the monomeric **1** (or **4**), whereas in $CDCl_3$ (or benzene) both homodimers are present.[14] Not entirely clear is the observation that "rigid/rigid" combinations like **2** and **5** or **2** and **3** contain only the homodimers in chloroform or benzene while heterodimers are not observed, in contrast to THF. Most probably this is a kinetic problem, since a mixture of **2·2**, **5·5** and **2·5**, obtained by evaporation of a THF solution, shows all three dimers after dissolution in chloroform.

In conclusion, we have found for the first time that tetra-urea calix[4]arenes **2**, **3**, and **5** form hydrogen-bonded dimeric capsules in THF with the solvent as guest. The rigidity of these calixarenes provides a reasonable explanation. The stability of hydrogen-bonded dimeric capsules in solvents such as THF or dioxane increases the scope of intramolecular reactions[4,6,7] that may be carried out, using a second tetra-urea calix[4]arene as template.

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Supporting Information Available: The quantitative interpretation of NOESY spectra of **2** and ^{1}H NMR spectra of compounds **2**−**5** in THF-d_8. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] This refers to the shape of the calix[4]arene skeleton. Of course the overall symmetry of **5** is C_{2v} due to these bridges.

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