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Hydrogen Bonded Dimers of Triurea Derivatives of Triphenylmethanes

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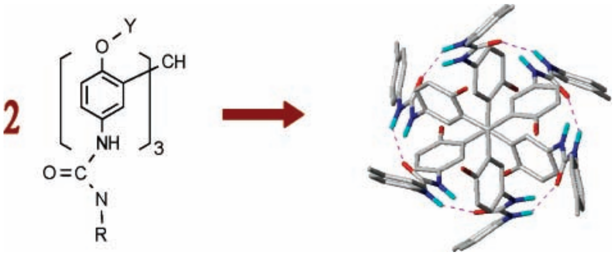
ABSTRACT



Tri-(2-alkoxy-5-ureido-phenyl)methanes represent a novel self-complementary motif forming hydrogen bonded homo- and heterodimers in nonpolar, aprotic solvents as evidenced by ^{1}H NMR and ESI-mass spectra and by the formation of heterodimers. MD simulations suggest the formation of hydrogen bonds of different strength in agreement with NMR data. The dimerization does not interfere with that of tetraurea calix[4]arenes. A combination of both motifs may be used therefore to build up larger structures via self-assembly processes.

Calix[4]arenes substituted at their wide rim by four urea functions form dimeric capsules in nonpolar, aprotic solvents, held together by a seam of hydrogen bonds formed alternatingly between urea groups of the two calix[4]arenes.[1,2] Although attempts to form analogous dimers from calix[5]-arenes failed so far, this hydrogen bonding motif[3] seems to possess some "general" importance, since dimers are formed also between triurea derivatives of tribenzylamines[4] and calix[6]arenes.[5] If, on the other hand, one of the four urea functions in a tetraurea calix[4]arene is replaced by acetamide, the molecules assemble to S_4-symmetrical tetramers, unless the dimerization is induced by a favorable guest such as tetraethylammonium.[6]

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(1) For a short review, see: Rebek, J., Jr. *Chem. Commun.* **2000**, 637−643.

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(3) Analogous hydrogen bonds were found in numerous X-ray structures of di-(aryl/alkyl)-ureas. For examples, see: Lortie, F.; Boileau, S.; Bouteiller, L. *Chem. Eur. J.* **2003**, *9*, 3008−3014. Schwiebert, K. E.; Chin, D. N.; MacDonald, J. C.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996**, *118*, 4018−4029. Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415−8426.

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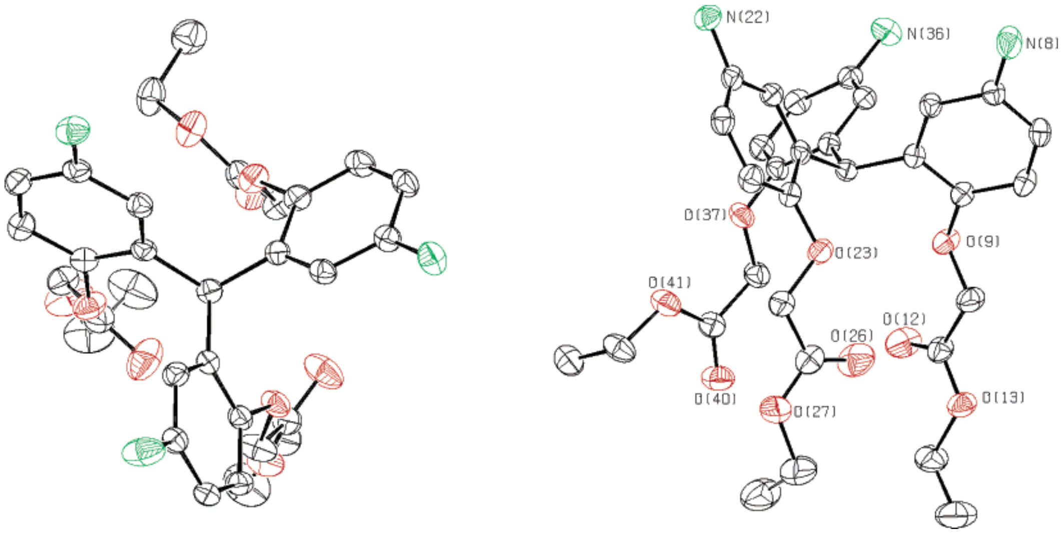
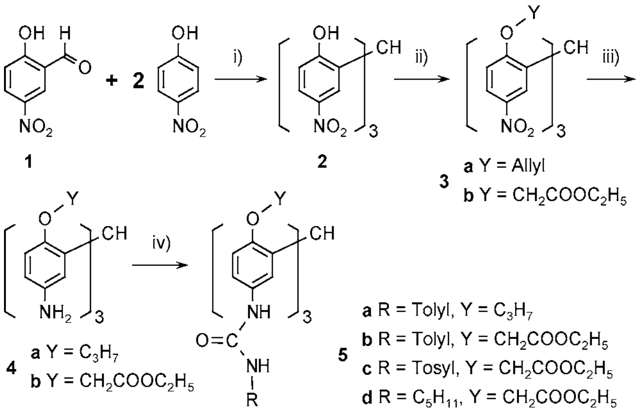


Figure 1. Molecular conformation of **4b** seen from two different perspectives. Angles between least-squares planes through the aromatic rings: 83.6, 88.3, and 89.7°. Intramolecular N···N distances: 6.75, 7.29, and 6.41 Å.

Searching novel platforms for the "tripodal" arrangement of ligating functions, we recently developed a simple synthesis for tri-(2-alkoxy-5-aminophenyl)methanes, which is indicated in Scheme 1.

Scheme 1. Synthesis of the Target Triureas[a]



[a] Key: (i) H_2SO_4, 155 °C; (ii) YBr, K_2CO_3, acetone; (iii) H_2, Raney-Ni, THF/EtOH; (iv) RNCO, CH_2Cl_2.

Acid-catalyzed condensation of 2-hydroxy-5-nitro-benzaldehyde **1** with a 2-fold excess of *p*-nitrophenol leads to **2** (89%),[7,8] which can be O-alkylated with reactive alkylhalogenides such as allylbromide or bromoethyl acetate. The triethers **3** are reduced to the triamines **4** by catalytic hydrogenation, which in the case of **3a** leads to the tripropyl ether **4a**. A single-crystal X-ray analysis of **4b**[9] confirms its structure and reveals an interesting conformation, resembling a three-bladed propeller (Figure 1), in which all CH_2COOEt and all NH_2 groups are found in a syn arrangement relative to each other.

Triurea derivatives **5** are formed from **4** by reaction with the respective isocyanates.[10] Their ^1H NMR spectra in DMSO-d_6 demonstrate the expected pattern of a molecule with (dynamic) C_{3v} symmetry (Figure 2a), showing for instance one singlet for the enantiotopic $-O-CH_2$ protons in **5b**. In solvents such as $CDCl_3$ or benzene, this signal splits into a pair of doublets ($\Delta\delta = 1.1$ ppm) with geminal coupling ($^2J = 16$ Hz) (Figure 2b), indicating that these CH_2 protons experience now a chiral environment, rendering them diastereotopic. The strong splitting of the two NH singlets sug-

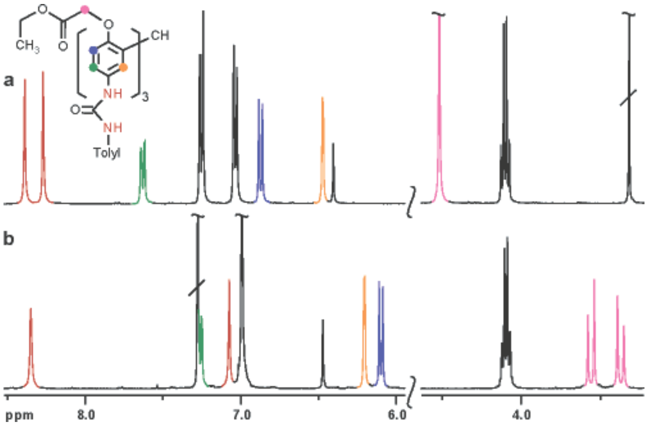


Figure 2. Sections of the ^1H NMR spectra (400 MHz) of **5b** in DMSO-d_6 (a) and in $CDCl_3$ (b).

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(7) Grüttner, C.; Böhmer, V.; Assmus, R.; Scherf, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 93−94. Dinger, M. B.; Scott M. J. *Eur. J. Org. Chem.* **2000**, 2467−2478.

(8) For the synthesis of similar triphenylcarbinol derivatives, see: Kelderman, E.; Starmans, W. A. J.; van Duynhoven, J. P. M.; Verboom, W.; Engbersen, J. F. J.; Reinhoudt, D. N. *Chem. Mater*. **1994**, *6*, 412−417.

gests that one of the NH groups forms a hydrogen bond, and the whole spectrum is in agreement with a C_3-symmetrical conformation, e.g., in a kinetically stable dimer with S_3 symmetry.

Dimerization was unambiguously proved by the formation of heterodimers in 1:1 mixtures of two triureas **5**. While the spectrum of such a mixture in DMSO-d_6 consists of a superimposition of the two single spectra, in $C_2D_2Cl_4$ an additional double set of signals corresponds to the heterodimer, as demonstrated in Figure 3. Simultaneously, the formation of a larger assembly is excluded by this still simple spectrum.

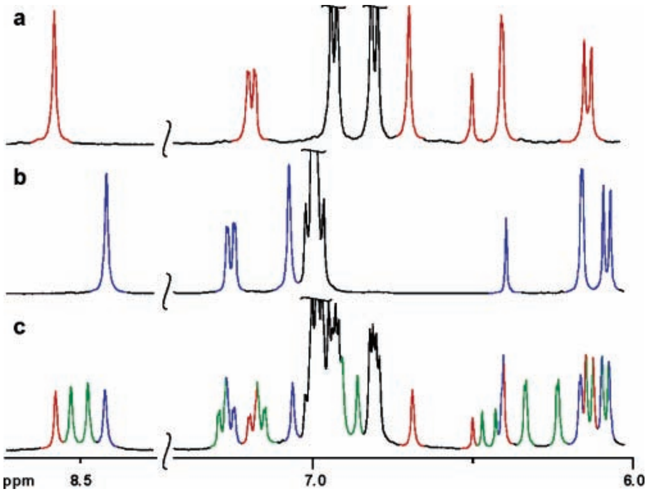
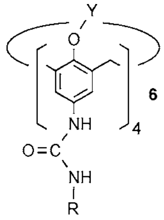
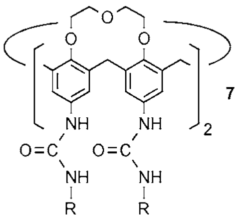


Figure 3. Sections of the ^{1}H NMR spectra (400 MHz) of **5a** (a), **5b** (b), and of their stoichiometric mixture (c) in $C_2D_2Cl_4$. The signals for the heterodimer are shown in green.

In contrast to tetraureas **6** and **7**, the dimerization could be demonstrated also by ESI-MS. A mixture of **5b** and **5d** shows the peak for the heterodimer with 100% abundance, the two peaks for the homodimers with ~30−35% abundance, and the peaks for the single molecules with 25−100% abundance (all peaks with one Na^+). It is unclear if this is due to a greater stability of dimers **5·5**[11] or to their lower mass in comparison to **6·6**.



6 **a** R = Tolyl **b** R = Tosyl



7 R = Tolyl

Molecular dynamics simulations were used to obtain an idea of the conformation of the dimers. Selected geometric parameters derived from these calculations are collected in Table 1.[12] The average structure of the dimer can best be described by two triangular pyramids whose vertexes are the carbonyl and methine carbon atoms that are rotated by 60° against each other.[13] An estimation of the internal space of such a "capsule" leads to a volume of ~80−90 Å^3, which explains that an inclusion of guests is not observed.

Table 1. Geometric Parameters Obtained by MD Simulation

radius of gyration of the C═O groups (Å)	4.02 ± 0.08
distance of the methine C atoms (Å)	9.97 ± 0.23
intermolecular N_α···O distances (Å)[a]	2.99 ± 0.19
intermolecular N_β···O distances (Å)[b]	3.35 ± 0.29
intermolecular N_α−H···O distances (Å)	2.46 ± 0.39
intermolecular N_β−H···O distances (Å)	2.90 ± 0.43
intramolecular distances of the carbonyl C atoms (Å)	4.28 ± 0.33
intramolecular N_α···N_α distances (Å)	6.57 ± 0.23
torsion angles around the Ar−C bonds (°)	83 ± 9/−84 ± 9
interplanar angles between trityl phenyl residues (°)	81.7 ± 8

[a] N_α: nitrogen atom attached to R. [b] N_β: nitrogen atom attached to the trityl group.

As illustrated in Figure 4, only the NH groups attached to the urea residues R seem to be involved in NH···O═C hydrogen bonds; see also the distances in Table 1. Shorter NH···O distances by about 0.44 Å in comparison to the NH

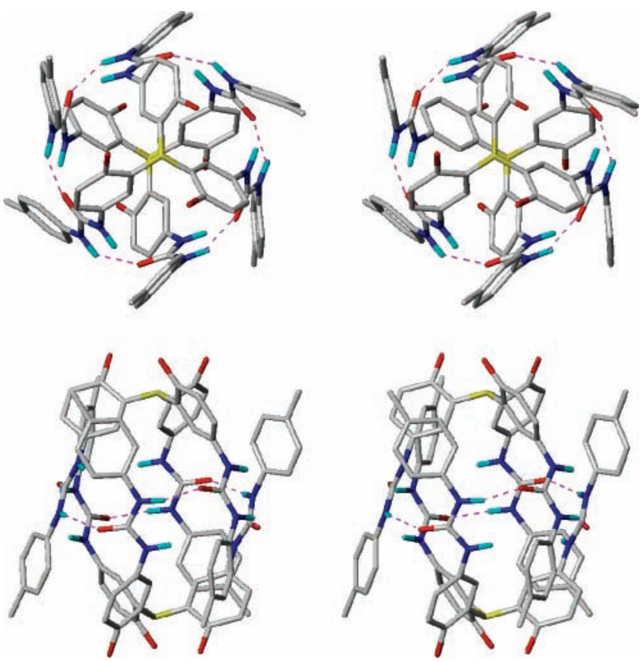


Figure 4. Minimized average structure obtained from molecular dynamics simulation of **5** (R = Tol, Y = Et). Two stereoviews from different directions are shown, the ether substituents have been omitted for clarity.

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(9) Crystal data for compound **4b** at 193 K: $C_{31}H_{37}N_3O_9$, M = 595.63, space group P-1 (No.2), $a = 9.860(4)$, $b = 12.351(2)$, $c = 13.171(2)$ Å, $\alpha = 100.79(1)$, $\beta = 103.51(2)$, $\gamma = 103.50(2)°$, $V = 1466.1(7)$ Å^3, $d_{calcd} = 1.349$ g cm^{-3}, $Z = 2$. For the 5904 unique reflections collected ($2 \leq \theta \leq 74°$) with Cu Kα ($\lambda = 1.54178$ Å), the 5249 with $F_o^2 > 2.0\sigma(F_o^2)$ were used in the final least-squares refinement to yield $R_1 = 0.0757$ and w$R_2 = 0.2050$ for all reflections. CCDC reference number: 248 044.

groups attached to the trityl skeleton are in agreement with the NMR results.

The average geometry of the trityl groups obtained from the MD simulation is very similar to those of the monomer in the crystal (Figure 1), as indicated by the interplanar angles (88.5 ± 3° vs 81.7 ± 8°), the intramolecular $N_\alpha \cdots N_\beta$ distances (6.57 ± 0.23 Å), and the overall rms value of 0.27 Å for the aromatic and methane carbon atoms and the oxygen and nitrogen atoms.

From tetraureas **6**, it is known that in a stoichiometric mixture of aryl (**6a**) and tosyl (**6b**) ureas heterodimers **6a·6b** are formed exclusively.[14] The analogous combination **5b** and **5c** leads to the formation of all possible dimers. As expected, ^{1}H NMR spectra of the solutions of **5** and **6** in $CDCl_3$ show only the presence of both homodimers. Since also **6a** and the more rigid **7** do not form heterodimers,[15] a mixture of all three urea derivatives (**5b**, **6a**, **7**) contains only the three possible homodimers (Figure 5).

A similar self-sorting process has been recently observed for mixtures consisting of molecules with rather different hydrogen bonding motifs,[16] such as linear AADD molecules,[17] "rosettes" formed by triazine triamides and barbiturates,[18] and tetraurea calixarenes.[19] It must be emphasized that the hydrogen bonding systems involved in the present case are much more similar, since they consist only of diarylurea systems that are arranged in a (slightly) different way or different number on different platforms. Self-sorting selectivities such as these may be used to build up well defined larger structures via self-assembly processes from molecules containing two (or more) tri- and/or tetraurea units.

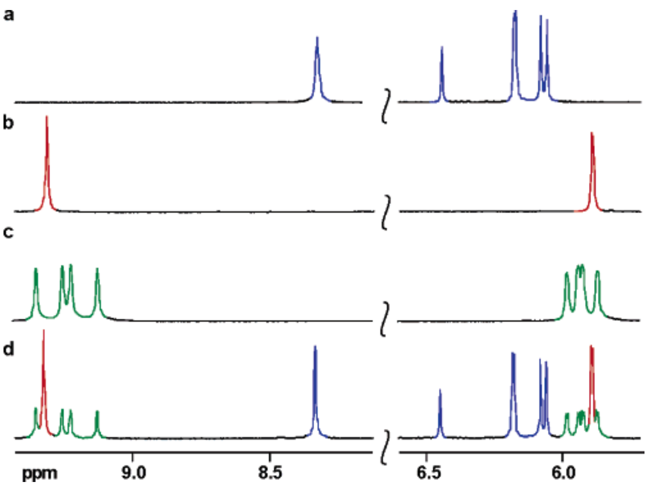

Figure 5. Sections of the ^{1}H NMR spectra (400 MHz) of **5b** (a), **6a** (b), and **7** (c) and of their stoichiometric mixture (c) in $CDCl_3$.

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Supporting Information Available: Selected ^{1}H NMR of triphenylmethane derivatives and crystallographic details for **4b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] Anion binding by triureas **5** will be described elsewhere.

[11] Titration experiments show that dimers **5·5** are present up to 9% DMSO-d_6 in a $C_2D_2Cl_4$ solution, which is comparable to dimeric capsules of calix[4]arenes **7** while dimers of **6a** are less stable.

[12] MD simulations were performed for 60 ns in vacuo using the AMBER force field, see: Case, D. A.; Pearlman, D. A.; Caldwell, J. W.; Cheatham, T. E., III; Wang, J.; Ross, W. S.; Simmerling, C. L.; Darden, T. A.; Merz, K. M.; Stanton, R. V.; Cheng, A. L.; Vincent, J. J.; Crowley, M.; Tsui, V.; Gohlke, H.; Radmer, R. J.; Duan, Y.; Pitera, J.; Massova, I.; Seibel, G. L.; Singh, U. C.; Weiner, P. K.; Kollman, P. A. *AMBER 7*; University of California, San Francisco: San Francisco, CA 2002.

[13] Structure is in agreement with the preliminary results of an X-ray structure that could not yet be sufficiently refined.

[14] Castellano, R. K.; Kim, B. H.; Rebek, J., Jr. *J. Am. Chem Soc.* **1997**, *119*, 12671−12672.

[15] Vysotsky, M. O.; Mogck, O.; Rudzevich, Y.; Shivanyuk, A.; Böhmer, V.; Brody, M. S.; Cho, Y. L.; Rudkevich, D. M.; Rebek, J., Jr. *J. Org. Chem.* **2004**, *69*, 6115−6120.

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[17] A and D denote hydrogen bond acceptors and donors; see for instance: Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761−6769.

[18] For examples, see: Félix, O.; Crego-Calama, M.; Luyten, I.; Timmerman, P.; Reinhoudt, D. N. *Eur. J. Org. Chem.* **2003**, 1463−1474. Prins, L. J.; Neuteboom, E. E.; Paraschiv, V.; Crego-Calama, M.; Timmerman, P.; Reinhoudt, D. N. *J. Org. Chem.* **2002**, *67*, 4808−4820. Prins, L. J.; Verhage, J. J.; de Jong, F.; Timmerman, P.; Reinhoudt, D. N. *Chem. Eur. J.* **2002**, *8*, 2302−2313. Prins, L. J.; Hulst, R.; Timmerman, P.; Reinhoudt, D. N. *Chem. Eur. J.* **2002**, *8*, 2288−2301.

[19] Rudzevich, Y.; Vysotsky, M. O.; Böhmer, V.; Brody, M. S.; Rebek, J., Jr.; Broda, F.; Thondorf, I. *Org. Biomol. Chem.* **2004**, *2*, 3080−3084.