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Dimerization of tris(*o*-ureidobenzyl)amines: a novel class of aggregates†

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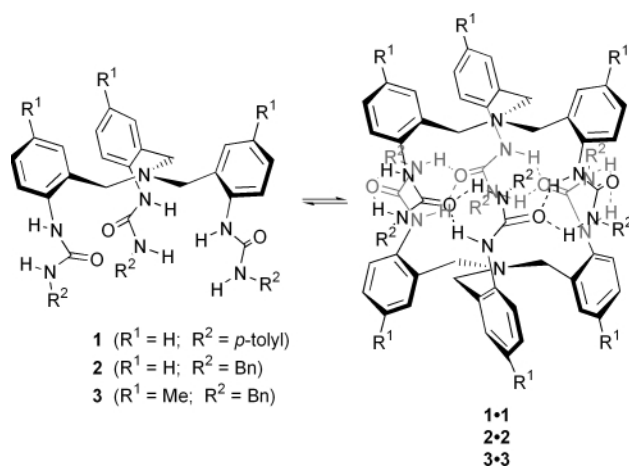
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Dimeric aggregates are formed by the assembly of two tripodal moieties which are held together, both in solution and in the solid state, by a belt of 6 hydrogen-bonded urea functions.

When two or more identical subunits are geometrically and functionally complementary, they may self-assemble to form a super molecule.¹ Urea or thiourea functionalities are excellent candidates to construct molecules that self-assemble by hydrogen-bonding not only in the solid state but are able to persist in solution.² Rebek³ and Böhrer⁴ have independently established that calix[4]arenes containing four urea functions at the upper rim form dimers by interdigitation of the all eight ureas in a head-to-tail directional array of 16 hydrogen bonds. Mendoza and coworkers have described dimeric capsules derived from tris(ureido)calix[6]arenes.⁵ Herein we report a novel type of self-assembled dimeric aggregate derived from tris(*o*-ureidobenzyl)amines which resemble the structure of ureidocalixarenes.

The tris(ureas) **1–3**⁶ shown in Scheme 1, easily available⁷ from previously reported tris(*o*-azidobenzyl)amines,⁸ showed dramatic differences in their ¹H NMR spectra when recorded in CDCl₃ or DMSO-*d*₆. While the spectra of **1–3** in DMSO-*d*₆ displayed the expected patterns consistent with averaged C_{3v} symmetries (Fig. 1a), by changing the solvent to CDCl₃ a new set of signals corresponding to a dimer (see below) emerged in each case. The ratio in which both species, monomer and dimer, were present in CDCl₃ depended on the substituent R² to a great extent. Thus, while for the tris(urea) **1** (R² = *p*-tolyl) only the signals attributed to the dimer were apparent, for the tris(ureas) **2** and **3** (R² = Bn) their spectra were interpreted as



Scheme 1

† Electronic supplementary information (ESI) available: ¹H NMR spectra. See <http://www.rsc.org/suppdata/cc/b0/b007955n/>

corresponding to equilibrium mixtures of both compounds (Fig. 1b).

The dimeric species featured two well separated doublets assigned to the diastereotopic methylenic protons of the (ArCH₂)₃N fragment ($J_{gem} = 14.5–15.7$ Hz), instead of the singlet observed for the same nuclei in DMSO-*d*₆. In the dimers emerging from **2** and **3** the ABX systems formed by the three protons of the –CH₂NH– fragments were clearly evident. The signals assigned to the NH protons of the dimers (near 6.0 and 7.6 ppm, in **2·2** and **3·3**) appeared significantly sharp and shifted to lower field when compared to those attributed to the monomers (near 5.2 and 6.3 ppm). The involvement of the urea carbonyl groups as hydrogen bonding acceptors is supported by the δ value of their carbon atoms in the ¹³C NMR spectra, which were shifted to downfield in CDCl₃ ($\Delta\delta = 2.8–3.2$ ppm). FT-IR of CHCl₃ solutions of **1** (13.7 mM) and **2** (16.4 mM) revealed typical hydrogen-bonded NH-stretching bands⁹ at 3317–3327 cm⁻¹.

All those data revealed that the dimers **1·1**, **2·2** and **3·3** should possess a highly ordered, hydrogen-bonded structure. Further indication of the existence of **1·1** and **3·3** in solution came from ESI-MS experiments. This technique was used in virtue of its gentle ionization and has been reported to reflect, at least qualitatively, solution phenomena.¹⁰ The spectra in CHCl₃ showed the molecular ions of the protonated dimers **1·1** (1463) and **3·3** (1547).

Thus, monomers and their dimeric aggregates coexist in equilibrium in CDCl₃. Preliminary calculations of the dimerization constant of **1** by ¹H NMR experiments at three concentrations (in the range 1–10 mM in CDCl₃) following known equations¹¹ showed values (82518, 83832 and 84755 M⁻¹) which are comparable within the experimental error margin.

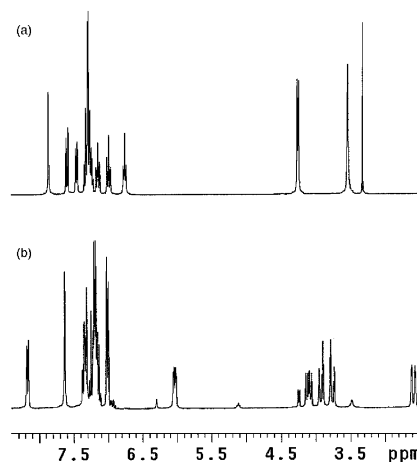


Fig. 1 (a) ¹H NMR spectrum (300 MHz) of the tris(urea) **2** in DMSO-*d*₆ (the singlet at 3.39 ppm is H₂O from the solvent), (b) ¹H NMR spectrum measured in CDCl₃ showing a mixture of **2** and **2·2**.

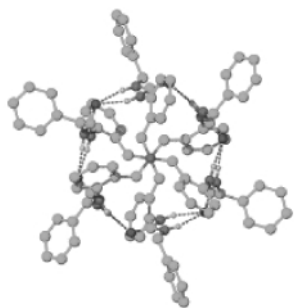


Fig. 2 A perspective view of the molecular structure **2·2**, as projected along the pseudothreefold axis containing the two pivotal nitrogen atoms.

Since DMSO- d_6 is able to disrupt the intermolecular hydrogen bonds, only the monomeric species could be observed in this solvent. The thermodynamic stability of the dimeric aggregate **1·1** proved to be higher than **2·2** and **3·3**. The dimer **1·1** is virtually the only species observed ($\geq 98\%$) in a 30 mM CDCl₃ solution of **1**. In contrast, the ¹H NMR spectra of **2·2** and **3·3** in CDCl₃ solutions of the same concentration displayed considerable amounts of their respective monomers (15–20%). These dimerization equilibria were concentration dependent, and could be shifted toward the monomer by decreasing the concentration. These equilibria could be also totally shifted to the monomeric tris(urea) by adding DMSO- d_6 (40%) to the CDCl₃ solution. Finally, the composition of a mixture of **2** and **2·2** was found to be temperature dependent; an increase in the temperature shifted the equilibrium toward the monomer. Thus, the 85:15 ratio of **2·2** to **2** measured at 296 K decreased to 72:28 at 323 K (38 mM in CDCl₃).

A single crystal X-ray structure¹² of **2·2** confirmed unambiguously the existence of the hydrogen-bonded dimers in the solid state, and provided an exact description of their geometry (Fig. 2). The dimer is composed of two enantiomeric units entangled *via* their urea residues, which form a belt of 12 hydrogen bonds with N...O distances ranging from 2.897(4) to 3.024(4) Å. The dimeric core is of approximate S_6 symmetry, although this is broken by the pendant phenyl substituents. The centre of the capsule is empty and is too small to contain any guest species, however extensive disordered solvent exists in external pockets formed by the aryl groups of the dimer. On the basis of the NMR data (CDCl₃) we believe that the conformation shown by the solid state structure of **2·2** is retained in solution.

The formation of heterodimers by the combination of two homodimeric species is a well-known phenomenon in uridocalixarenes.^{3,4} In our case, a mixture of equimolecular amounts of the dimers **1·1** and **2·2** in CDCl₃ did not show the formation of heterodimers. However, the ¹H NMR spectrum of an equimolecular mixture of **2·2** and **3·3** revealed the appearance of signals attributable to the heterodimer **2·3**, besides those of homodimers **2·2** and **3·3** and monomers **2** and **3**. In this experiment the region of the aryl-NH protons (7.45–7.80 ppm) was especially informative (Fig. 3). Thus, four NH singlets appeared (Fig. 3c), two of them due to the homodimers **2·2** ($\delta = 7.63$ ppm) and **3·3** ($\delta = 7.61$ ppm), and the other two to both aryl-NH protons of the heterodimer **2·3** ($\delta = 7.51$ ppm and $\delta = 7.73$ ppm). The integration revealed a nearly statistical mixture of the three dimers.

In summary, we have shown that tris(*o*-ureidobenzyl)amines **1–3** self assemble to form dimeric aggregates in which six urea groups constitute a cyclic array involving a closed network of 12 hydrogen bonds.

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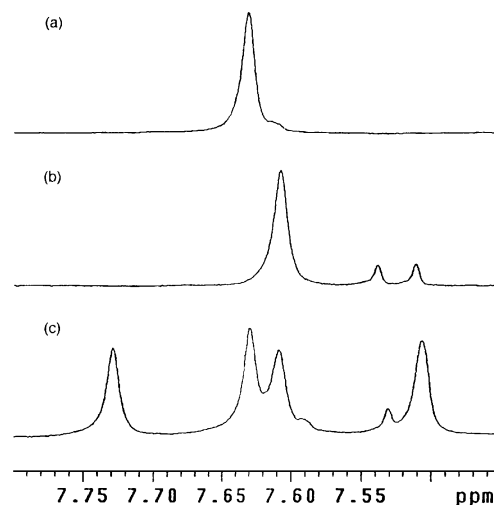


Fig. 3 Partial ¹H NMR spectra (300 MHz, CDCl₃) showing the NH-aryl region: (a) **2·2**; (b) **3·3** (the doublet at 7.53 ppm was assigned to the monomer **3**); (c) mixture of equimolecular quantities of **2·2** and **3·3**.

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- Crystallographic data for **2·2**: Formula: C₅₀H₅₁Cl₂N₇O₃, triclinic crystal, space group $P\bar{1}$, $a = 13.936(3)$, $b = 13.985(3)$, $c = 14.350(3)$ Å, $\alpha = 117.719(3)$, $\beta = 94.551(3)$, $\gamma = 108.840(3)^\circ$. $T = 100(2)$ K, $U = 2253.4(8)$ Å³, $D_c 1.281$ mg m⁻³, 7864 independent reflections used in refinement, 498 parameters, $R1 (I > 2\sigma(I)) = 0.0805$, $wR2$ (all data) = 0.2211. CCDC 182/1878.