Highly diastereoselective self-assembly of chiral tris(*m*-ureidobenzyl)amino capsules†

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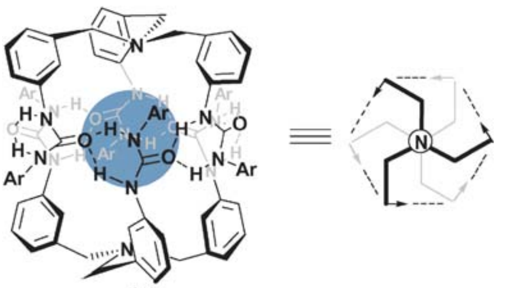
The self-assembly of chiral tris(*m*-ureidobenzyl)amines to give dimeric capsules is a highly diastereoselective process in solution, while in the solid state, the formation of the corresponding capsules is not only diastereoselective but also regioselective.

Self-assembled capsules are supramolecular structures made up of molecular bricks which are held together by weak intermolecular forces.[1–3] A great deal is known about the useful applications of capsules[4] as nanovessels,[5] as spaces inside where reagents are stabilized and new forms of stereochemistry can emerge.[2,6] We have recently recognized the role of tris(ureidobenzyl)amines as modular subunits in supramolecular chemistry.[7–11] Thus, two self-complementary tris(*m*-ureidobenzyl)amine molecules **1**, identical or not, associate by hydrogen bonding between their six urea units forming self-assembled capsules, wherein molecules of adequate size and shape are included (Fig. 1).[8,10] Although free monomers feature averaged C_{3v}-symmetries, the two tripodal modules adopt a chiral propeller arrangement in the capsule. The supermolecule is composed of two clockwise–anticlockwise tripods determining an overall S_6 symmetry.[8,10]



1·1

Fig. 1 Structure and schematic representation of capsules **1·1**.

We were interested in the design of chiral tribenzylamine monomers to examine the feasibility of diastereoselective self-assembling processes. Prediction and switching between self-assembled supramolecular diastereomers are relevant to diverse applications.[2,12,13] Triureas **2a–c** (Fig. 2) bearing a stereogenic carbon atom in one of the benzylic arms were easily synthesized from the corresponding α-methyl substituted tris(*m*-azidobenzyl)amines, previously reported[14] (see ESI for synthetic details†).

In the frozen conformation present in the capsules, triureas **2** may exist in two chiral diastereomeric forms, *R*,*M*/*S*,*P* and *S*,*M*/*R*,*P*, resulting from combining the stereogenic carbon atom and the propeller-like helicity (Fig. 2). There is a substantial difference in these two diastereomeric structures regarding the arrangement of the methyl group at the benzylic carbon atom, which is placed either in a pseudoaxial position in the *R*,*M*/*S*,*P* enantiomeric pair, or in a pseudoequatorial arrangement in the *S*,*M*/*R*,*P* pair (Fig. 2a and b).

Previous studies of our group on the preparation of macrobicyclic triphosphazides by tripod–tripod coupling of α-methyl substituted tris(*m*-azidobenzyl)amines, with tris(phosphanes) concluded that the configuration of the stereogenic benzylic carbon

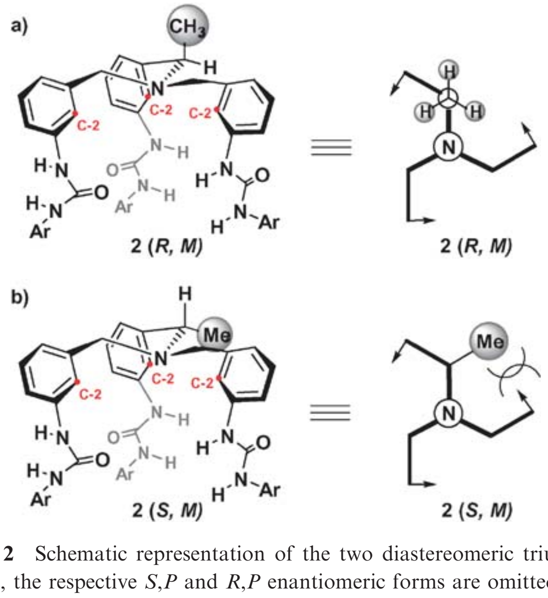


Fig. 2 Schematic representation of the two diastereomeric triureas **2a–c**, the respective *S*,*P* and *R*,*P* enantiomeric forms are omitted for simplicity.

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† Electronic supplementary information (ESI) available: Instruments, software and procedures used for data collection, structure solution and refinement of the crystal structure of **2b**. Experimental procedures for the synthesis of **2a–c** and **3**. Spectroscopic and analytical data for **2a–c** and **3** and their precursors. Schematic representation of all potential isomeric capsules **2·2** and their symmetry properties. ^{1}H NMR spectra of **3** in DMSO-d_6 and $CDCl_3$, electrospray ionization mass spectra of **2a** and **3** in $CHCl_3$. CCDC reference number 691454. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b809835b

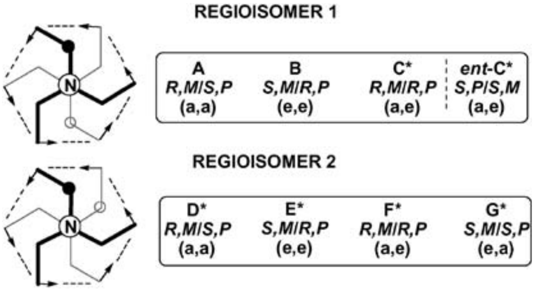


Fig. 3 Schematic representation of regioisomers 1 and 2 which can form by self-assembly of **2**. The stereogenic carbon atoms are indicated by circles on the propellers. Chiral capsules have been labelled by "*" (*ent*-**D***–**G*** have been omitted for simplicity). The configuration of each monomer and the arrangement of the methyl group, pseudoaxial (a) or pseudoequatorial (e), have been also specified.

atom at one arm of the triazide dictates the handedness of the propeller-like helicity of the final macrobicycle (point-to-helix chirality transfer).[14] This stereochemical bias can be traced down to a marked preference of the methyl group placed at this carbon atom for the pseudoaxial position to minimize steric crowding (compare Fig. 2a and b).

In principle, the self-assembly of racemic triureas **2** may lead to multiple dimeric capsules coming from the pairing of the four monomers (*R*,*M*), (*S*,*P*), (*S*,*M*) and (*R*,*P*), along with two regioisomeric assemblies depending on the relative position of the two arms bearing the stereogenic carbon atom, *i.e.* opposite or adjacent, which have been labelled as regioisomers 1 and 2, respectively in Fig. 3.[9] There are three different diastereomeric forms for regioisomeric capsule 1, two achiral centrosymmetric (**A** and **B**) and one chiral (**C***), schematically represented in Fig. 3 (for a more complete picture see ESI†). Similarly, regioisomeric capsule 2 may exist as four different chiral diastereoisomers (**D***–**G***). Summing up, a maximum of seven regio- and diastereoisomeric capsules may result from the self-dimerization of racemic **2**.

Notably, this somewhat puzzling and complex picture could be simplified by considering the expected preference of the methyl group for the pseudoaxial position (point-to-helix chirality transfer).[14] Taking into account this fact, the formation of capsules **A** and **D*** should be favoured over the rest (Fig. 4).

To our delight, the single-crystal X-ray analysis of **2b** ($CHCl_3$–*n*-pentane) showed one single regio- and diastereomeric capsule in the crystal lattice! (Fig. 5).‡ In the solid state, each dimer contains a disordered molecule of *n*-pentane as the guest species. The capsule is formed by two enantiomeric monomers with configurations *R*,*M* and *S*,*P*, and features the two stereogenic carbon atoms in opposite arms, that is, capsule **A** of Fig. 4.

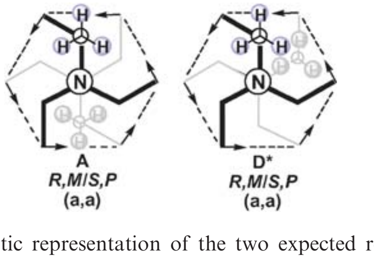


Fig. 4 Schematic representation of the two expected regioisomeric dimers from the self-assembly of **2**.

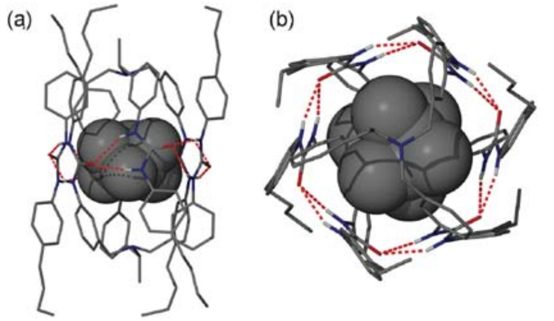


Fig. 5 X-Ray structure of **2b·2b@*n*-pentane**: (a) axial and (b) top view.

The structure depicted in Fig. 5 clearly shows that the two methyl groups are in a pseudoaxial arrangement providing an approximate S_6 symmetry for the dimeric core. Since **A** is formed by two enantiomeric subunits, the formation of **2b·2b** constitutes a chiral self-discrimination process.[15–20]

The self-assembly of triureas **2a,b** in solution was subsequently tested in noncompetitive solvents. Unfortunately, the low solubility of **2c** in $CDCl_3$, $C_2D_2Cl_4$ or toluene-d_8 hampered analogous studies. In a strongly hydrogen bonding solvent such as DMSO-d_6 **2a** exists as a monomeric, non-assembled species (Fig. 6a). The change to a noncompetitive solvent such as $CDCl_3$ causes significant alterations in the ^{1}H NMR spectrum (Fig. 6b). These variations concern not only the number of signals but also the chemical shifts of some resonances. The complexity and linewidth of the signals in this spectrum are indicative of a mixture of different species. Nevertheless, the spectra possess typical signatures of tribenzylamine-derived capsules such as significant shifts to lower frequencies of particular resonances, attributed to local anisotropic effects.[8,10] Thus, large shifts to lower frequencies were observed for the signals of the pendant *p*-tolyl protons (Fig. 6, in red) appearing as broad signals at 1.7–1.8, 6.5 and 6.7 ppm in $CDCl_3$. These protons resonate in DMSO-d_6 at 2.2, 7.1 and 7.3 ppm, respectively. Analogously, the aromatic protons located at the C-2 position (Fig. 2) in the tribenzylamine skeleton were also shifted around 2 ppm to lower frequencies in $CDCl_3$. Thus, whereas these protons resonate at 7.5 ppm in DMSO-d_6, they appear as a broad signal around 5.7 ppm in the halogenated solvent (Fig. 6, in blue). Finally, the broad signal around 8.2–8.3 ppm was assigned, as in capsules **1·1**, to the ureido NH

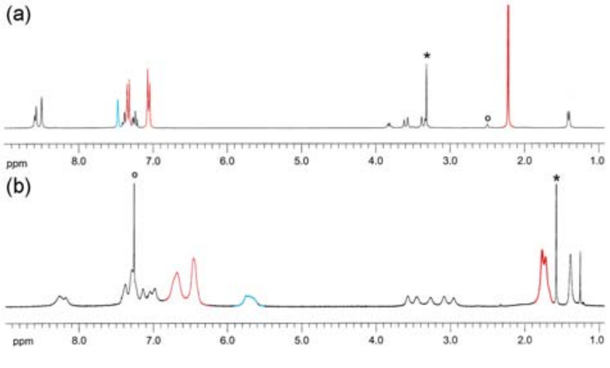


Fig. 6 ^{1}H NMR spectra of **2b**: (a) in DMSO-d_6 and (b) in $CDCl_3$. The signals of water and residual solvent have been labelled with an asterisk and a circle, respectively.

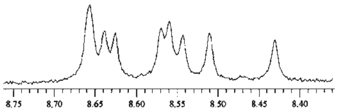
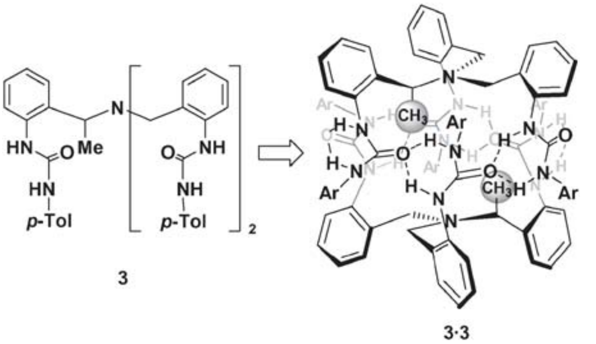


Fig. 7 Region of the ^{1}H NMR spectrum of **2b·2b@MeI** where NH protons of the *p*-butylamino fragments resonate ($CDCl_3$, −15 °C).

protons bearing the tolyl group.[10] The resemblance of the spectra of triureas **2** to those of triureas **1** in $CDCl_3$ suggests that capsules **2·2**, analogously to **1·1**, exist in solution and they contain a molecule of solvent inside the cavity.[10] A dimeric assembly **2a·2a** was also detected by electrospray ionization-MS experiments. The spectrum measured in $CHCl_3$ showed the corresponding molecular ion of the protonated dimer at m/z = 1491.4 (ESI†).

Subsequently, the regio- and diastereoselectivity for the self-assembly of **2** were scrutinized by analyzing the region where the NH protons of the *p*-tolylamino fragments resonate (8–9 ppm).[9] In principle, a statistical mixture of all the species would lead to 36 singlets of similar integration value in this region of the spectrum. On the contrary, the exclusive presence of capsule **A**, as observed in the solid state, would give only three peaks of similar intensity. Unfortunately, the broadness of the signals of the spectra of both **2a** and **2b** in $CDCl_3$, probably due dynamic processes within the capsule, hampered further analysis. The spectrum of **2b** recorded at low temperature (−10 and −60 °C) and measured in toluene-d_8 (also at low temperatures) did not provide a better resolution. To our delight, these resonances could be resolved into nine peaks of similar intensity (two of them overlapped, see Fig. 7) at −15 °C in the presence of an excess of MeI, where the capsule **2b·2b@MeI** is formed (the signal for encapsulated MeI was observed at 1.9 ppm).[10] We have applied Occam's razor to rationalize our findings for the assembly of triureas **2** in solution. Thus, the marked preference of the methyl group for being at the pseudoaxial position could direct the preference formation of capsules **A** and **D**, probably in a statistical ratio. In this case, three singlets may appear due to the resonances of the terminal NH protons of the centrosymmetric capsule **A**, and six due to those of the chiral capsules **D*** and *ent*-**D***, in agreement with the observed ^{1}H NMR spectrum.

As we have previously shown, tris(*o*-ureidobenzyl)amines self-assemble in solution although the resulting capsular dimeric aggregates, the *ortho* analogues of **1·1**, have very small cavities.[7,9] As part of the present study, we also synthesized the racemic "*ortho*" triurea **3** (see ESI for synthetic details†) for testing its dimerization ability. However, the triurea **3** has a low tendency to assemble in $CDCl_3$ (Fig. 8). Thus, the spectrum of **3** recorded in this solvent shows a mixture of monomer : dimer in a 84 : 16 ratio (see ESI for ^{1}H NMR and electrospray ionization mass spectra†). This behaviour has been rationalized taking into account the severe steric interactions in the putative aggregates **3·3** bearing pseudoaxial methyl groups. This steric hindrance would originate from the location of these methyl groups inside the small cavity of the dimeric aggregates **3·3** (Fig. 8).[21]



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3·3

Fig. 8 One of the possible isomeric structures for the dimer **3·3** (Ar = *p*-MeC_6H_4) with the methyl groups in pseudoaxial arrangement.

In summary, chiral tris(*m*-ureidobenzyl)amines **2** self-assemble in solution in a highly diastereoselective manner selecting only two isomeric capsules out of the seven possible by a double point-to-helix chirality transfer mechanism. In the crystal, a second level of discrimination occurs resulting in a highly regio- and diastereoselective process.

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Notes and references

‡ Crystal data for compound **2b**: $C_{57.5}H_{71}N_7O_3$, M = 908.21 g cm^{-3}, T = 120 K. Triclinic, space group $P\bar{1}$, unit cell dimensions: a = 14.856(2) Å, b = 16.166(3) Å, c = 22.046(4) Å, V = 4855.1(13) Å^3, Z = 4. Reflections collected/unique 42 719/17 078 [R(int) = 0.0392]. Final R indices [$I > 2\sigma(I)$] $R1$ = 0.0572, w$R2$ = 0.1417. CCDC 691454.

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