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Novel Capsular Aggregates from Flexible Tripodal Triureas with C_s Symmetry

Mateo Alajarin,*[a] Raul-Angel Orenes,[a, b] Judith A. K. Howard,[c] Elinor C. Spencer,[c] Jonathan W. Steed,[c] and Aurelia Pastor*[a]

Abstract: Tris(2- and 3-ureidobenzyl)-amines with C_s symmetry self-assemble in solution forming mixtures of regioisomeric capsular aggregates, one of which is chiral and the other centrosymmetric. Under certain conditions, a predominance of the centrosymmetric regioisomer is found before equilibrium, that is, a mixture close to the statistical ratio of the two species is reached. In the solid state, there is a preference for the centrosymmetric capsules. Molecular models of both regioisomeric aggregates have been built and analyzed for comparison. Guests inside capsules formed by self-assembly of desymmetrized tris(3-ureidobenzyl)-amines feel different magnetic environments, depending on whether they are inside a chiral or an achiral regioisomeric container. Of special significance are the experiments with a more flexible triurea endowed with an ureidopropylic arm, which self-assembles with the same efficiency as the more rigid tris(ureidobenzyl)amines.

Keywords: host–guest systems · hydrogen bonds · self-assembly · supramolecular chemistry · triureas

Introduction

The ability of molecules to spontaneously generate order through self-assembly is one of the most attractive phenomena investigated in the last decade.[1,2] The design of self-assembling systems with potential applications needs a profound knowledge of the rules that govern supramolecular chemistry.[3] Organizational rigidity has been frequently invoked for the design of efficient supramolecular assemblies to minimize entropy losses.[4] However, that the efficiency of molecular recognition processes suffers less than generally assumed from the presence of single bonds has been proved in supramolecular systems based on hydrogen bonds[5,6] or electrostatic interactions.[7]

In recent years much attention has been paid to self-assembled capsules, nanoscale structures made up of several synthetic subunits and connected through noncovalent interactions.[8–10] These systems exhibit the key properties of selective guest recognition and reversible encapsulation.[11] A range of capsules have been constructed from modules with rigid and preformed concave geometries, such as resorcarenes,[12,13] calixarenes[14,15] and calixpyrroles.[16,17] Tris(2- and 3-ureidobenzyl)amines **1** and **2** have proved to be useful scaffolds in supramolecular chemistry despite their flexibility. They form capsular dimeric aggregates held together by a seam of six hydrogen-bonded urea groups (Figure 1).[18] Whereas assemblies **1·1** exist as solvent-free capsular aggregates,[19,20] assemblies **2·2** are able to encapsulate guests of appropriate size and shape.[21,22] The tribenzylamine core provides a high degree of flexibility to triureas **1** and **2**, which adopt averaged C_{3v} symmetry in competitive solvents with hydrogen bonds. In non-competitive solvents, aggre-

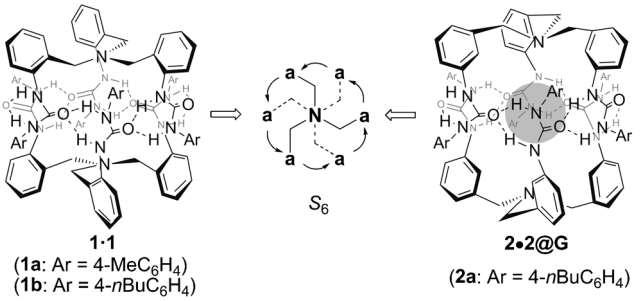


Figure 1. Structure and schematic representation of capsular aggregates **1·1** and **2·2** formed by self-assembly of tris(2- and 3-ureidobenzyl)amines **1** and **2**.

[a] Prof. Dr. M. Alajarin, Dr. R.-A. Orenes, Dr. A. Pastor
Departamento de Quimica Organica, Facultad de Quimica
Universidad de Murcia, Campus de Espinardo, Murcia-30.100 (Spain)
E-mail: alajarin@um.es
aureliap@um.es

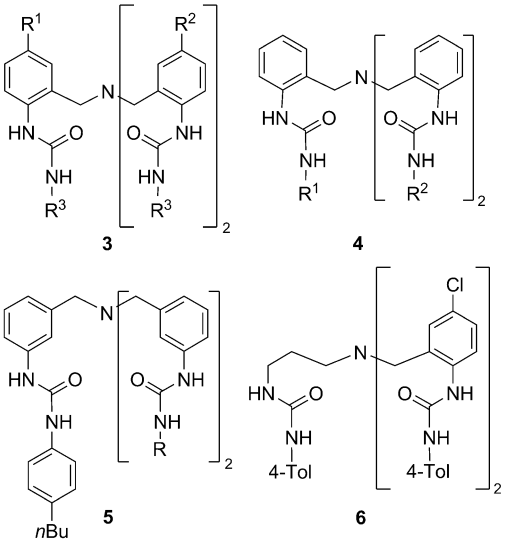
[b] Dr. R.-A. Orenes
Servicio Universitario de Instrumentacion Cientifica
Universidad de Murcia, Campus de Espinardo, 30.100 Murcia (Spain)

[c] Prof. Dr. J. A. K. Howard, Dr. E. C. Spencer, Prof. Dr. J. W. Steed
Department of Chemistry, University of Durham
University Science Laboratories, South Road
Durham DH1 3LE (UK)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201102246 or from the author. It contains experimental procedures and spectroscopic and analytical data of precursors **7**–**12** and **14** and of triureas **3c**–**e**, ^{1}H NMR spectra of **1a**,**b**, **2**, **3a**, **4a** and **5a** in [D$_6$]DMSO and CDCl$_3$, high-frequency region of the ^{1}H NMR spectra of **4a**–**c** (CDCl$_3$) and **5a** (CD$_2$Cl$_2$) and electrospray ionization mass spectra of **5a** and **6**.

gates **1·1** or **2·2** are formed by assembly of two self-complementary and enantiomeric tripods of C_3 symmetry offset by 60° to each other, resulting in a global achiral S_6 symmetry for the supermolecule (self-discrimination).

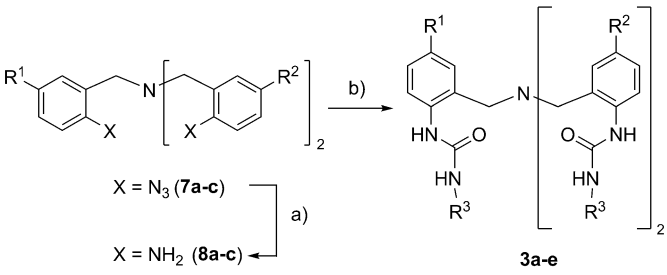
Although more complex systems are known, capsular aggregates **1·1** and **2·2** are attractive and challenging due to their special geometry. Moreover, the modular structure of the tribenzylamine skeleton has great potential for modification. The sequential construction "arm-to-arm" of the tertiary amine core would provide access to new triureas of C_s symmetry with variation of both the pendant ureido positions[20] and the substitution at the tribenzylamine skeleton. Moreover, triureas with even more flexible branches would be easily available. Herein we present a detailed study of the self-assembly of desymmetrized tris(2- and 3-ureidobenzyl)amines **3**–**5**. New capsules derived from the **5·5** assembly have been characterised in solution and the solid state. Of special significance is the self-assembly of the more flexible supramolecular tecton **6** endowed with a ureidopropylic arm. The formation of regioisomeric aggregates from triureas **3**–**6** has also been examined.



Results and Discussion

Tris(2-ureidobenzyl)amines **3a**–**e**, with different substituents at one of the arylic groups of the tribenzylamine skeleton, were synthesised from key triazides **7a**–**c** (Scheme 1, Table 1). Intermediate azides **7** were prepared by following a synthetic route previously reported by us.[23]

Tris(2-ureidobenzyl)amines **3** feature overall C_s symmetries in competitive solvents, and thus are not chiral. Figure 2a shows the exchange equilibrium by inverting the rotation sense of the propeller of the tribenzylamine skeleton in C_s-symmetric triureas. Accordingly, ^{1}H, ^{13}C{^{1}H} and ^{19}F{^{1}H} NMR spectra of triureas **3a**–**e** in [D$_6$]DMSO exhibit the expected resonances for C_s-symmetric monomers. The spectra display two sets of signals in a 2:1 ratio corresponding to the two differently substituted branches of the tripodal molecules. This pattern is clearly evident in Figure 3a, in which the high-frequency region of the ^{1}H NMR spectrum of **3b** shows the resonances for the NH protons bearing the R^3 groups (full spectrum of **3a** included in the Supporting Information).



Scheme 1. General procedure for the synthesis of triureas **3**. Reagents and reaction conditions: a) $LiAlH_4$, Et_2O, 0→20°C, 6 h; b) R^3NCO, CH_2Cl_2, 20°C, 18 h (R^1, R^2 and R^3 in Table 1).

Table 1. Synthesis of triamines **8** and triureas **3**.

Entry	Compound	R^1	R^2	R^3	Yield
1	**8a**	H	Me	–	92[a]
2	**8b**	Me	H	–	61[a]
3	**8c**	Cl	H	–	76[a]
4	**3a**	H	Me	4-MeC_6H_4	84[b]
5	**3b**	H	Me	4-$CF_3C_6H_4$	92[b]
6	**3c**	Me	H	4-MeC_6H_4	81[b]
7	**3d**	Cl	H	4-MeC_6H_4	71[b]
8	**3e**	Cl	H	4-$CF_3C_6H_4$	73[b]

[a] After chromatography. [b] Precipitated from the reaction mixture.

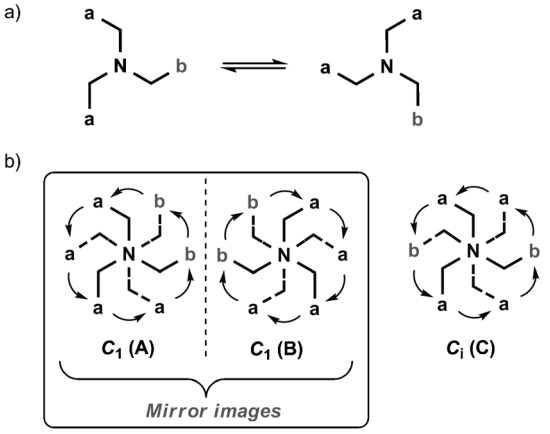


Figure 2. Schematic representation of a) the exchange equilibrium between the two enantiomeric conformations of a triurea with C_s symmetry by inverting the rotation sense of the propeller and b) the three putative dimeric aggregates derived from the assembly of C_s-symmetric triureas (the arrows symbolize the directionality of the belt of hydrogen bonds).

The self-assembly of **3a**–**e** was subsequently investigated in a non-competitive solvent such as $CDCl_3$ (20–40 mM). The ^{1}H NMR spectra of **3a**–**e** in $CDCl_3$ are very complex compared to those of **3a**–**e** in [D$_6$]DMSO and to those of the C_{3v}-symmetric triureas **1** and **2** in the same halogenated

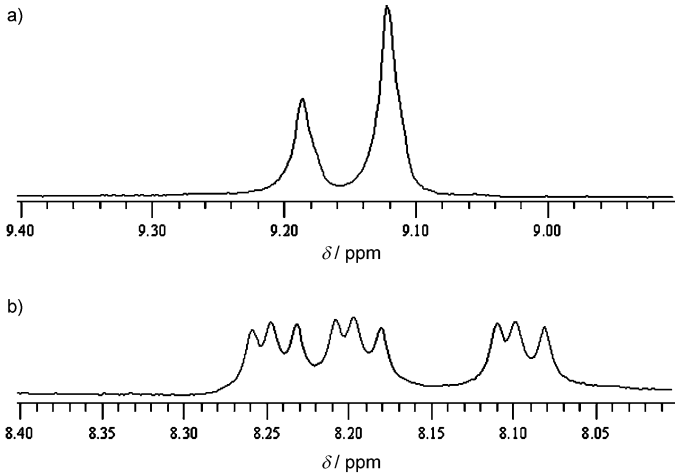


Figure 3. High-frequency regions of the ^{1}H NMR spectra of **3b** (300 MHz, 20 °C) in a) [D$_6$]DMSO and b) $CDCl_3$, at which the NH groups bearing the pendant R^3 groups resonate.

solvent (Supporting Information). In spite of their complexity, the diagnostic features for the dimeric aggregates **3·3** can be clearly distinguished: 1) shifts to higher frequencies for the resonances of the NH protons with respect to those of diphenylurea used as reference,[24] and 2) anisotropic effects for the protons of the pendant aromatic groups and the methylenic protons of the $(ArCH_2)_3N$ fragments. The resonances for the monomeric species are not observed at the concentrations used for measurements. The complexity of the spectra of **3** may be due not only to the loss of symmetry by formation of dimeric assemblies **3·3**, but also to the presence of two regioisomeric species: one enantiomeric pair of C_1 symmetry, labelled **A** and **B** in Figure 4, and one C_i-symmetric species, denoted **C** (Figure 4). Aggregates **A** and **B** are schematically represented in Figure 2b and they feature supramolecular chirality.[25–27] Since separate signals for the two regioisomers are observed, their interconversion by a dissociation/recombination process may be slow on the NMR timescale. The relative proportions of the two regioisomers was determined by analyzing the resonances of the NH groups bearing the pendant substituents R^3 in the region of 7.8–8.3 ppm. Nine signals of similar area are observed in this region of the spectra, as illustrated for **3b** in Figure 3b. Six singlets were attributed to the chiral regioisomer and three singlets to the *meso* aggregate, and the three assemblies are present in statistical ratio (33:33:33). An analogous conclusion can be drawn for the self-assembly of **3a** and **3c**,**d** although the corresponding high-frequency regions of their NMR spectra display more significant overlap. The self-assembly of **3b** and **3e** was further analyzed by ^{19}F{^{1}H} NMR spectroscopy. By analogous reasoning, the statistical ratio of C_1- and C_i-symmetric regioisomers should give rise to nine signals of equal integration, as in fact is observed in the region around −62.6 ppm for **3e**.

As we previously reported,[20] triureas **4a–c** (**4a**: R^1 = 4-*n*BuC_6H_4, R^2 = 4-$CF_3C_6H_4$; **4b**: R^1 = 4-*n*BuC_6H_4, R^2 = 4-FC_6H_4; **4c**: R^1 = 4-MeOC_6H_4, R^2 = 4-$CF_3C_6H_4$), differently substituted at one of the pendant aryl groups, are easily available from a common intermediate. Taking into account that a 66:33 ratio of C_1- and C_i-symmetric regioisomers corresponds to the statistical arrangement, **4a** (57:43) and **4c** (60:40) display some degree of selectivity in favour of the C_i-symmetric dimeric species **4a·4a** and **4c·4c**. The ^{1}H NMR spectra of triureas **4b** and **4c** remain invariant over time. Conversely, when a sample of **4a** obtained by slow evaporation of a $CDCl_3$ solution was redissolved in the same solvent and its ^{1}H NMR spectrum immediately recorded, it showed a 36:64 ratio of C_1- and C_i-symmetric regioisomers. After about 20 min, the mixture of species equilibrated and reached a 57:43 ratio. After 5 d a value close to the statistical ratio was reached (Table 2).[20] This result seems to be an indication of a predominance of the centrosymmetric dimer in the solid state.

Table 2. Ratio of C_1- and C_i-symmetric regioisomers of **4a·4a** over time.

Entry	Time[a]	C_1:C_i[b]
1	1 min	36:64
2	20 min	57:43
3	2 d	59:41
4	5 d	62:38

[a] From the preparation of the sample ($CDCl_3$, 20 °C) until the spectrum was measured. [b] Determined by integration of selected signals in their ^{1}H NMR spectra (400 MHz); error ±5% of the stated value.

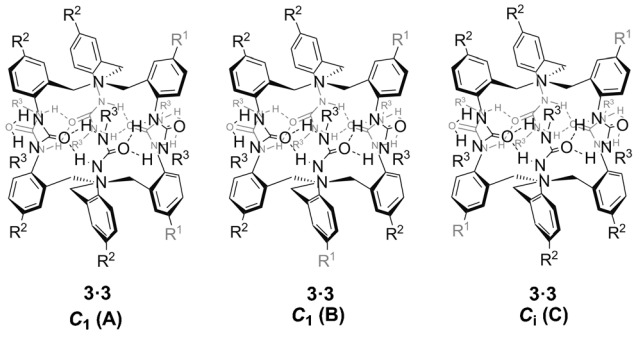


Figure 4. Structure of the three isomeric aggregates of C_1 and C_i symmetry of **3·3**, labelled as **A**, **B** and **C** (R^1, R^2 and R^3 shown in Table 1).

The influence of temperature and the solvent on the distribution of regioisomers was also investigated. Thus, the ^{1}H NMR spectra of triurea **4a** in $C_2D_2Cl_4$ at −30, 25 and 89 °C and in [D$_8$]toluene at −60, 25 and 90 °C were measured. However, the effect of these parameters in the aggregates ratio was found to be minimal.

To evaluate subtle differences in the structures of the two regioisomeric aggregates **4a·4a**, we used the program MacroModel 8.1 (AMBER* force field) to build the two molecular models. Molecular modelling in the gas phase and in chloroform led to similar structures (Figure 5). A detailed analysis of the two energy-minimized structures reveals that there are no significant differences. The belt of hydrogen-bonded urea moieties is very symmetric with N···O=C dis-

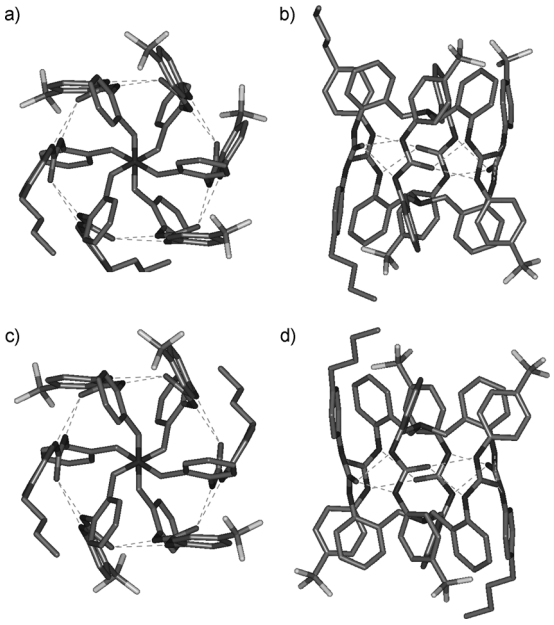
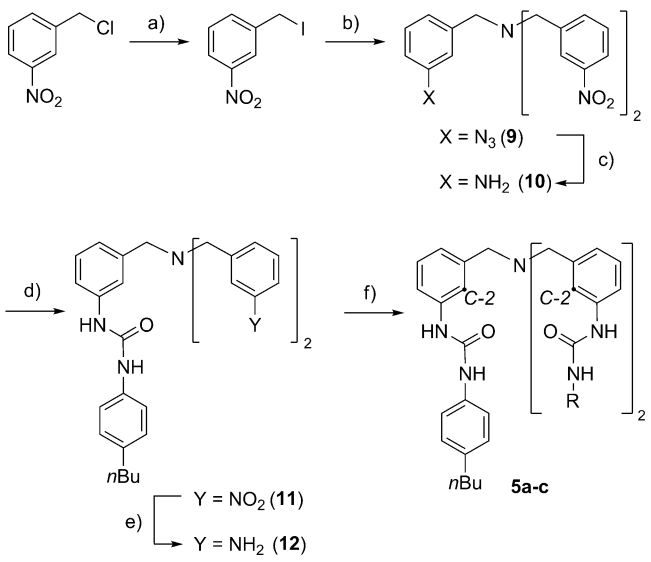


Figure 5. Minimum-energy structures of **4a·4a** calculated in chloroform. Top (a) and side (b) views of the chiral regioisomer. Top (c) and side (d) views of the centrosymmetric regioisomer. The belt of hydrogen-bonded urea moieties is indicated by dashed lines.



Scheme 2. Reagents and reaction conditions for the synthesis of triureas **5a–c**: a) NaI, acetone, 20 °C, 20 h; b) 3-azidobenzylamine, Na_2CO_3, MeCN, reflux, 24 h; c) i) PMe_3, THF, 0 °C, 30 min; ii) H_2O/THF, 20 °C, 16 h; d) 4-*n*BuC_6H_4NCO, CH_2Cl_2, 20 °C, 24 h; e) H_2, PtO_2, THF, 20 °C, 16 h; f) RNCO, solvent, temperature, 24 h (see Table 3).

Table 3. Reaction conditions and yields for the synthesis of triureas **5a–c**.

Entry	Compound	R	Solvent	*T* [°C]	Yield [%]
1	**5a**	4-$CF_3C_6H_4$	CH_2Cl_2	20	72
2	**5b**	4-$MeOC_6H_4$	CH_2Cl_2	20	92
3	**5c**	Bn	$CHCl_3$	reflux	80

tances of 2.84–2.89 Å for the urea nitrogen atoms bearing the pendant aromatic substituents very similar to those of the urea nitrogen atoms attached to the tribenzylamine skeleton (N···O=C 2.82–2.88 Å). The distances between the two pivotal nitrogen atoms are almost coincident: 5.18 Å and 5.22 Å for the chiral and centrosymmetric regioisomer, respectively. The structural resemblance of the two dimeric suprastructures would explain their similar stability and thus the statistical ratio observed in solution.

The synthesis of the tris(3-ureidobenzyl)amines **5a–c**, differing in the pendant substituents, is depicted in Scheme 2. Treatment of 3-nitrobenzyl chloride with NaI led to the corresponding iodide (99% yield), which was then treated with 3-azidobenzylamine in the presence of Na_2CO_3 yielding tertiary amine **9** (57%). Formation of the corresponding iminophosphorane by reaction of **9** with trimethylphosphine followed by hydrolysis in THF/H_2O led to amine **10** (96%). Tribenzylamine **11** was isolated in 97% yield after the reaction of **10** with 4-*n*-butylphenyl isocyanate. Compounds **5a–c** were obtained from **11** by sequential catalytic hydrogenation (75%) and reaction with the corresponding isocyanate (Table 3).

Subsequently, the self-assembly of triureas **5a–c** in $CDCl_3$ was tested. The complexity and line width of the signals once more indicate the presence of a mixture of species. Whereas the spectrum of **5c** is too complex to extract any conclusion, the ^{1}H NMR spectra of **5a–b** show typical signatures of tribenzylamine-derived capsules (Figure 6).[21,22] Large shifts to lower frequencies were observed for the signals of the protons of the pendant aromatic substituents as well as the protons located at the C2 position of the tribenzylamine skeleton (labelled in Scheme 2), the latter shifted as much as 2 ppm to lower frequencies. Thus, whereas protons at C2 resonate at 7.5 ppm in [D_6]DMSO, they appear as broad signals at 5.7–5.9 ppm in the halogenated solvent. The benzylic protons of the $(ArCH_2)_3N$ fragment resonate as two multiplets at $\delta = 2.6$–2.7 and $\delta = 3.2$–3.6 ppm. Finally, the broad signals around 7.9–8.6 ppm were assigned, as in capsules **2·2**, to the ureido NH protons bearing the pendant aromatic groups. The dimeric assembly **5a·5a** was also detected by ESI-MS experiments. The spectrum measured in $CHCl_3$ shows the corresponding molecular ion of the protonated dimer at *m*/*z* 1764 (Supporting Information).

Molecular models of both regioisomeric aggregates **5a·5a** (Figure 7) were computed in both gas phase and chloroform by using MacroModel 8.1 (AMBER* force field). The two energy-minimized structures reveal no significant differences. The separations between the two pivotal nitrogen atoms are 10.11 and 10.12 Å for the chiral and the centrosymmetric species, respectively. The N···O=C distances (2.77–2.79 Å) for the urea nitrogen atoms bearing the pendant aromatic substituents are slightly shorter than the N···O=C distances (2.90–3.00 Å) for the urea nitrogen atoms attached to the tribenzylamine skeleton.

The regioselectivity in the self-assembly of triureas **5a** and **5b** was examined by analyzing the region in which the

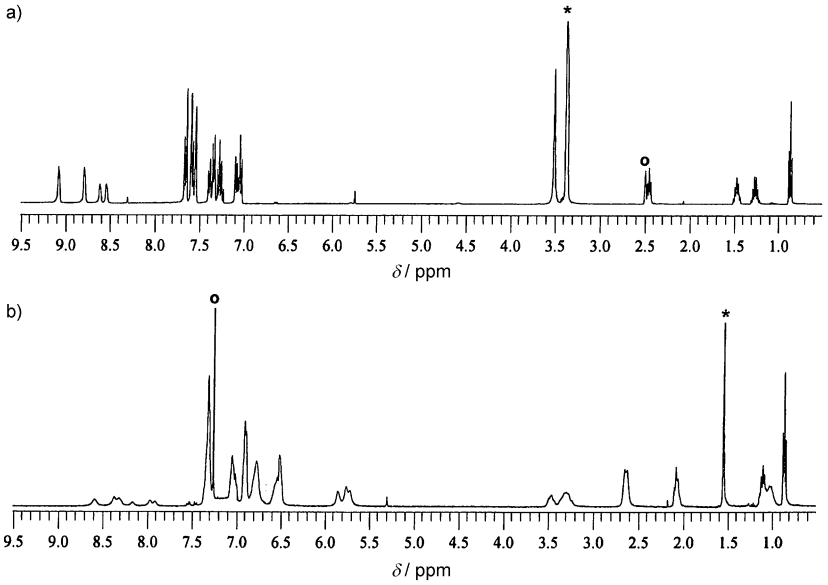


Figure 6. ^{1}H NMR spectra (400 MHz, 25 °C) of **5a** in a) [D$_6$]DMSO and b) $CDCl_3$. *) Water and ○) residual peaks of the solvent.

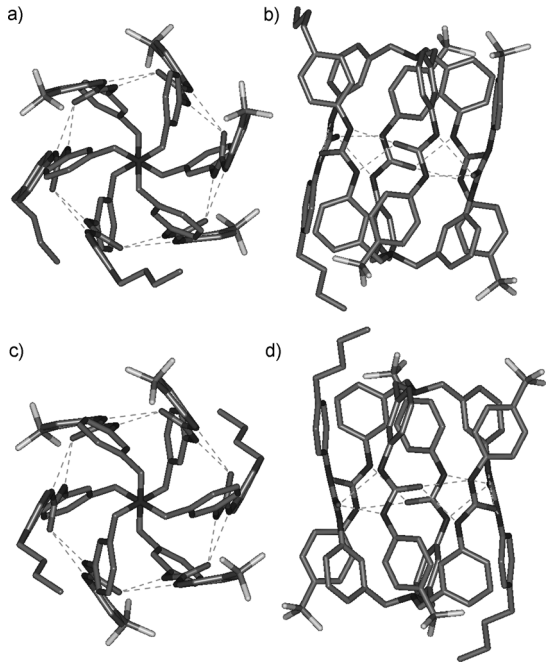


Figure 7. Minimum-energy structures of **5a·5a** calculated in the gas phase. Top (a) and side (b) views of the chiral regioisomer. Top (c) and side (d) views of the centrosymmetric regioisomer. The belt of hydrogen-bonded urea moieties is indicated by dashed lines.

NH protons bearing the terminal substituents resonate. Nevertheless, the broadness and overlap of these signals hampered this analysis. The spectrum of **5a** in $CDCl_3$ recorded at −10 and −60 °C, as well as that measured in [D$_8$]toluene also at low temperatures, did not provide a better resolution. The resonances were resolved as nine peaks by using CD_2Cl_2 as solvent, in which the capsule **5a·5a@CD$_2$Cl$_2$** exists (Supporting Information). The observed ratio for C_1- and C_i-symmetric regioisomers was 62:38, very close to the statistical distribution.

Tris(3-ureidobenzyl)amines **2** (Figure 1) form dimeric aggregates with cavities that are able to encapsulate guests of appropriate shape and size.[21,22] The resemblance of the spectra of triureas **5** with those of triureas **2** in $CDCl_3$ suggests the presence of capsules **5·5@CDCl$_3$**. Previously, we demonstrated that dimeric aggregates **2·2** are excellent containers for MeI, CH_2Cl_2 and $MeNO_2$.[22] At −15 °C, the ^{1}H NMR spectra of **5a** in the presence of an excess of MeI, CH_2Cl_2 and $MeNO_2$, show the resonances for the capsules **5a·5a@MeI**, **5a·5a@CH$_2$Cl$_2$**, **5a·5a@MeNO$_2$** as well as the encapsulated guests, shifted 0.3–0.4 ppm to lower frequencies with respect to those of the free ones (Figure 8). The high-frequency regions of the ^{1}H NMR spectra support a distribution of regioisomers close to statistical (Figure 8, left), which indicates that the presence of these guests inside the cavity may not influence the regioselectivity of the self-assembly process.[27] Interestingly, the spectra reveal two different resonances for MeI and $MeNO_2$ inside **5a·5a**, with slightly different chemical shifts in a 2:1 ratio (Figure 8a and 8c, right). The most intense signals were assigned to the guests inside the chiral capsules, since they exist as a 50:50 mixture of two enantiomers, and the less intense signal to the guest inside the achiral one. Clearly, the guests feel a different magnetic environment depending on whether they are inside the chiral container or the achiral one.

We succeeded in growing single crystals of **5a** suitable for X-ray analysis ($CHCl_3$/*n*-pentane). The structure comprises two independent molecules **5a·5a**, each of which forms a unique capsule by symmetry, as we have described previously (Figure 9).[21,28] The belt of hydrogen-bonded urea residues is rather symmetrical, as expected from the computed structures, with N···O=C distances ranging from 2.86 to 3.09 Å. Inside the capsule, a disordered molecule of *n*-pentane was found as guest species. Notably, the crystal shows the exclusive presence of the C_i-symmetric regioisomeric capsule. The preference for the centrosymmetric arrangement in the solid state suggests that crystal packing forces must play a significant role.[28,29]

Intrigued by the self-assembly abilities of more flexible triureas, we designed triurea **6** with an ureidopropylic arm. Rigid molecules have been frequently designed to minimize entropy losses and favour their self-assembly processes.[4] However, the presence of flexible regions is less of a disad-

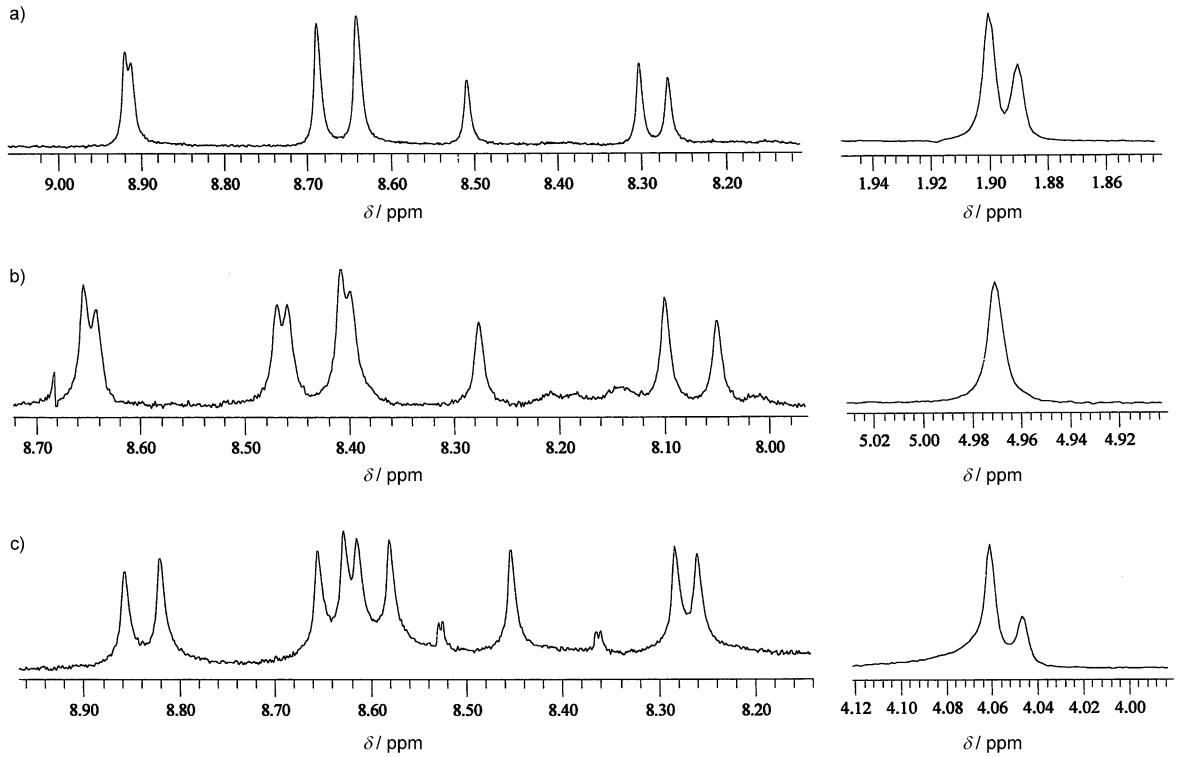


Figure 8. Selected regions of the ^{1}H NMR spectra (400 MHz, $CDCl_3$, −15 °C) of a) **5a·5a@MeI**, b) **5a·5a@CH_2Cl_2** and c) **5a·5a@$MeNO_2$**, at which the NH moieties bearing the pendant aryl groups (left part) and the encapsulated guest (right part) resonate.

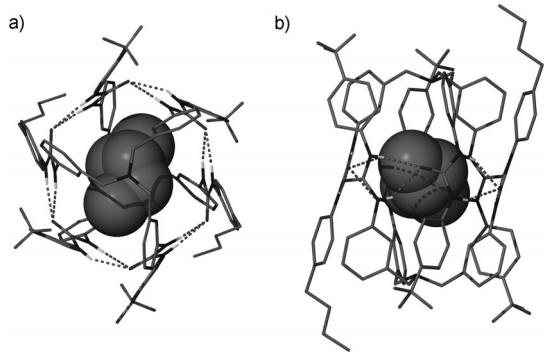
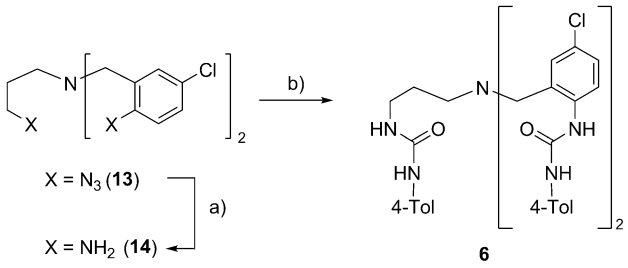


Figure 9. X-ray structure of **5a·5a**@*n*-pentane. a) Top and b) side view. The belt of hydrogen-bonded urea moieties is indicated by dotted lines. A molecule of pentane is located inside the cavity.



Scheme 3. Synthesis of triamine **14** and triurea **6**. Reagents and reaction conditions: a) i) PMe_3, THF, 0 °C, 5 h; ii) H_2O/THF, 20 °C, 18 h; b) 4-MeC_6H_4NCO, $CHCl_3$, 20 °C, 20 h.

vantage than previously supposed, since single bonds can better accommodate strain.[3,5,6] The synthesis of **6** was conducted from triazide **13**[30] by reduction to triamine **14** and subsequent reaction with 4-methylphenyl isocyanate (Scheme 3).

The pattern of signals in the ^{1}H NMR spectrum of **6** in [D_6]DMSO is consistent with the presence of an averaged C_s-symmetric monomer (Figure 10a). However, a more complex picture is present in $CDCl_3$. The ^{1}H NMR spectrum of **6** in this solvent reveals a large number of sharp signals, ruling out the presence of oligomeric associations (Figure 10b). The spectrum was interpreted as being due to an equilibrium mixture of C_1- and C_i-symmetric regioisomers (Figure 11). The resonances appearing around 7.5–8.5 ppm were assigned to the NH groups bearing the pendant aromatic groups. Additionally, the signals around 6.10-7.00 ppm were attributed to the arylic protons of the pendant 4-methylphenyl groups, and those appearing at 1.89-2.28 ppm to the methyl protons of the same fragments. The lack of a singlet around 3.6 ppm points to an undetectable amount of monomeric species at this concentration (40 mM). The dimeric assembly **6·6** was also detected by ESI-MS experiments. The spectrum measured in $CHCl_3$ shows the corresponding molecular ion of the protonated dimer at *m*/*z* 1505 (Supporting Information).

The appearance of nine signals with a similar integration in the high-frequency region of the ^{1}H NMR spectrum of **6** ($CDCl_3$) would be in agreement with the presence of the two regioisomeric aggregates in 66:33 (statistical) ratio

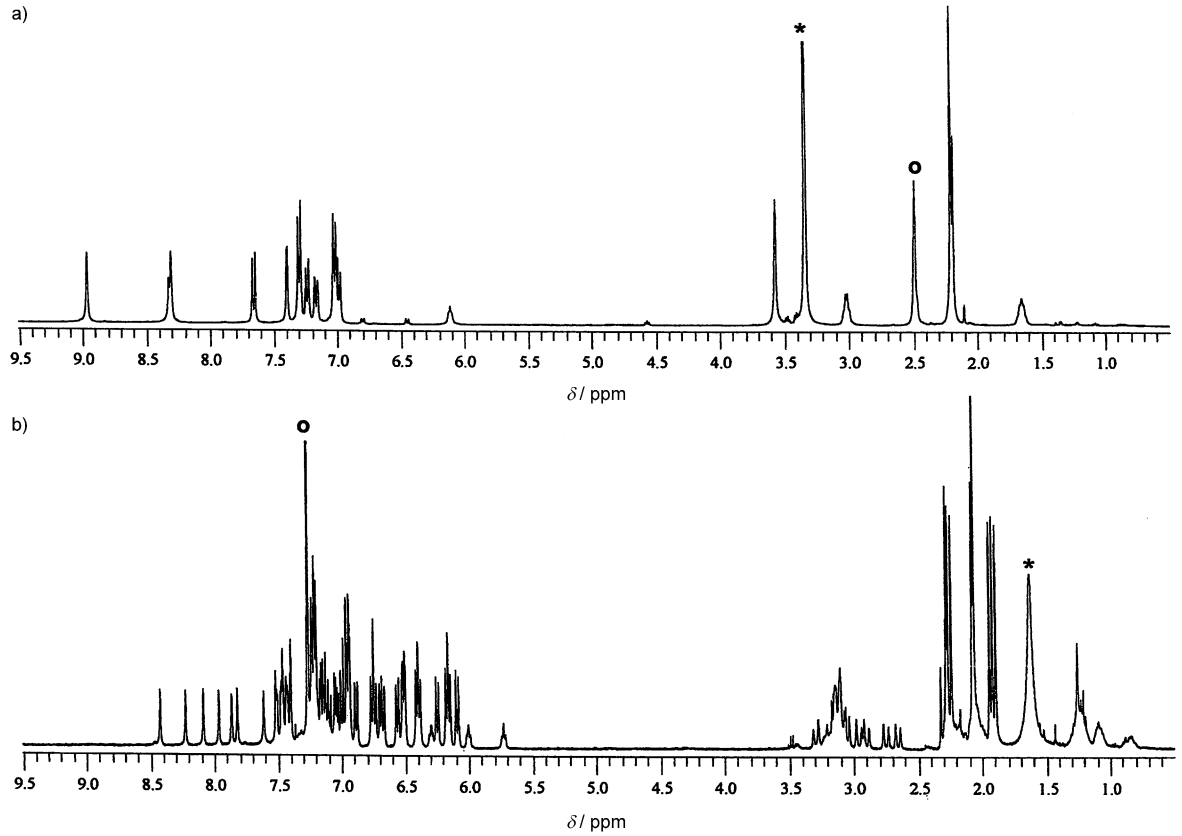


Figure 10. ^{1}H NMR spectra (400 MHz, 25 °C) of **6** in a) [D_6]DMSO and b) $CDCl_3$; *) Water and ○) residual peak of the solvent.

(Figure 11). In fact, this is the overall picture, although only seven signals are clearly visible; the two missing resonances may be overlapped by the aromatic region (Figure 12a). The analysis of the region between 1.86 and 2.30 ppm is even more revealing (Figure 12b). Thus, the spectrum displays eight singlets, one of them of double intensity, for the resonances of the methyl groups of the pendant 4-methylphenyl substituents. Compared to the resonances of the C_{3v}-symmetric aggregates **1·1**, the resonances attributed to these protons are spread out over a wider region. This fact can be rationalized on the basis of a more different environment experienced by the six methyl groups within **6·6** depending on their location, that is, either between two ureidobenzylic branches or between one ureidopropylic and one ureidobenzylic arms (Figure 11).

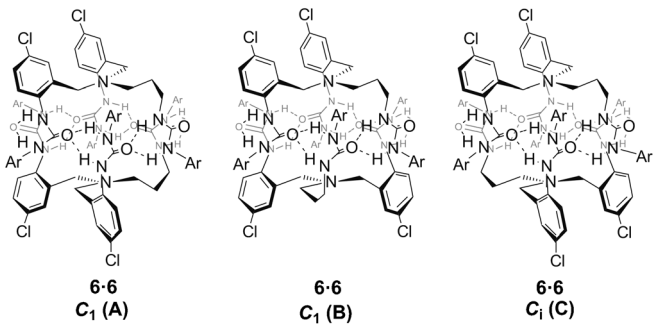


Figure 11. Structure of the three isomeric aggregates of C_1 and C_i symmetry of **6·6** labelled as **A**, **B** and **C** (Ar = 4-MeC_6H_4).

Conclusion

Flexible tris(2- and 3-ureidobenzyl)amines with C_s symmetry are synthetically accessible and able to self-assemble to form capsular dimeric aggregates. In solution, the dimeric aggregates exist as a mixture of regioisomers, one chiral and one centrosymmetric. Under certain conditions, predominance of the centrosymmetric dimers is observed before the equilibrium, that is, a distribution close to the statistical ratio of the two regioisomers, is reached. Computed molecular models point to the two regioisomeric structures having a similar stability. Interestingly, the guests inside capsules derived from desymmetrized tris(3-ureidobenzyl)amines feel different magnetic environments depending on whether they are inside a chiral or an achiral container. Moreover, there is a preference for the centrosymmetric capsule in the solid state, probably due to crystal packing effects. Finally, a triurea endowed with an ureidopropylic arm has the ability to self-assemble with the same efficiency as the tris(ureidobenzyl)amines do. These results further authenticate the use of tris(ureidobenzyl)amines and their derivatives as versatile frameworks for the rational design of more sophisticated supramolecular systems in the foreseeable future.

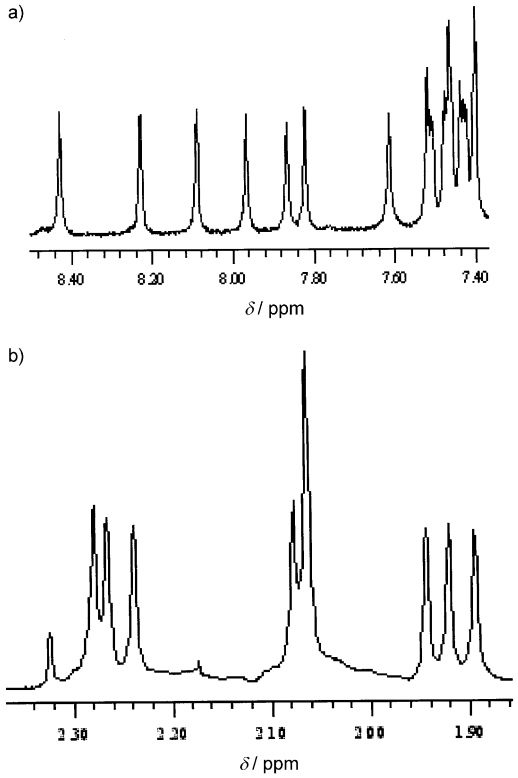


Figure 12. Selected regions of the ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 25 °C) of triurea **6** where a) the NH moieties bearing the pendant aryl groups and b) the methyl groups of the 4-methylphenyl substituents resonate.

Experimental Section

General: See the Supporting Information for experimental procedures and spectroscopic and analytical data of precursors **7**–**12** and **14** and of triureas **3c**–**e**, ^{1}H NMR spectra of **1a**,**b**, **2**, **3a**, **4a** and **5a** in [D_6]DMSO and $CDCl_3$, high-frequency region of the ^{1}H NMR spectra of **4a**–**c** ($CDCl_3$) and **5a** (CD_2Cl_2) and electrospray ionization mass spectra of **5a** and **6**.

Molecular mechanics calculations: All molecular mechanics calculations were carried out by using the AMBER* force field as implemented within Maestro/MacroModel 8.1. Standard potentials and atomic charges, as provided by the AMBER* force field, were employed without modifications. AMBER* and OPLAA force fields produce essentially the same results in related structures. Calculations were initially performed under vacuum and then in chloroform solution (GB/SA solvation model). Most complex structures were virtually identical under both conditions. Energy minimizations were conducted over 500 iterations on a Silicon Graphics Computer. Minimized structures were then subjected to conformational searches with 5000-step Monte Carlo multiple minimum simulations. All conformations within 15 kJ mol^{-1} of the computed global minimum were stored and the representative lowest-energy structure was analyzed.

Data collection, structure solution and refinement of the crystal structure of 5a: $C_{53}H_{57.5}Cl_{1.5}F_6N_7O_3$; M_r = 1007.74; 0.17 × 0.11 × 0.10 mm; triclinic, space group $P\bar{1}$ (No. 2); a = 14.7822(6), b = 18.1191(7), c = 18.4515(7) Å; α = 94.795(2), β = 93.989(2), γ = 98.372(2)°; V = 4855.5(3) Å^3; Z = 4; ρ_{calcd} = 1.379 g cm^{-3}; F_{000} = 2112; Bruker SMART 1000, $Mo_{K\alpha}$ radiation, λ = 0.71073 Å; T = 120(1) K; $2\theta_{max}$ = 46.6°; 25 611 reflections collected, 13 904 of which were unique (R_{int} = 0.0758). The structure was solved and refined by using the programs SHELXS-97[31] and SHELXL-97,[31] respectively. The program X-Seed[32] was used as an interface to the SHELX programs and to prepare the figures. Final GOF = 0.865, R_1 = 0.0861, wR_2 = 0.2201, R indices based on 5164 reflections with $I > 2\sigma(I)$ (refinement on F^2), 1227 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.182 mm^{-1}. CCDC 813383 (**5a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for synthesis of triureas 3a–e: The corresponding isocyanate (0.90 mmol) was added to a solution of the corresponding triamine **8** (0.30 mmol) in dry CH_2Cl_2 (8 mL) under N_2. After stirring at 20 °C for 18 h, the solvent was removed under reduced pressure and the residue triturated with Et_2O (5 mL). The white solid was filtered and dried under vacuum. Further purification was carried out by recrystallization.

*Bis{5-methyl-2-[N′-(4-methylphenyl)ureido]benzyl}{2-[N′-(4-methylphenyl)ureido]benzyl}amine (**3a**)*: Colourless prisms (from 1:1 $CHCl_3$/Et_2O), 84% yield. M.p. 234–236 °C; ^{1}H NMR (300 MHz, [D_6]DMSO, 20 °C): δ = 2.13 (s, 6H), 2.21 (s, 9H), 3.59 (s, 6H), 6.91–6.97 (m, 3H), 7.01–7.04 (m, 6H), 7.12 (t, ^3J(H,H) = 7.2 Hz, 1H), 7.19 (s, 2H), 7.26–7.31 (m, 6H), 7.34 (d, ^3J(H,H) = 8.1 Hz, 2H), 7.43 (d, ^3J(H,H) = 7.2 Hz, 1H), 7.54 (d, ^3J(H,H) = 8.1 Hz, 1H), 7.83 (s, 2H), 7.98 (s, 1H), 8.60 (s, 2H), 8.66 ppm (s, 1H); ^{13}C NMR (50 MHz, [D_6]DMSO, 20 °C): δ = 20.4 (q), 20.6 (q), 54.8 (t), 118.3 (d), 123.2 (d), 123.4 (d), 124.3 (d), 127.1 (d), 127.8 (d), 129.1 (d), 129.5 (s), 129.9 (d), 130.2 (s), 130.5 (s), 132.8 (s), 134.5 (s), 137.2 (s), 137.3 (s), 153.0 (s), 153.4 ppm (s); IR (Nujol): $\tilde{\nu}$ = 3319 (s), 1665 (vs), 1607 (vs), 1557 (vs), 1516 (s), 1316 (m), 1287 (m), 1244 (m), 1208 (m), 819 (s), 746 (w), 721 (w), 695 cm^{-1} (w); elemental analysis calcd (%) for $C_{47}H_{49}N_7O_3$ (760.0): C 74.28, H 6.50, N 12.90; found: C 73.91, H 6.84, N 12.99.

*Bis{5-methyl-2-[N′-(4-trifluoromethylphenyl)ureido]benzyl}{2-[N′-(4-trifluoromethylphenyl)ureido]benzyl}amine (**3b**)*: Colourless prisms (from 1:1 $CHCl_3$/Et_2O) 92% yield. M.p. 248–251 °C; ^{1}H NMR (300 MHz, [D_6]DMSO, 20 °C): δ = 2.11 (s, 6H), 3.61 (s, 6H), 6.90 (dd, ^3J(H,H) = 8.1 Hz, ^4J(H,H) = 1.5 Hz, 2H), 6.96 (t, ^3J(H,H) = 7.2 Hz, 1H), 7.11 (t, ^3J(H,H) = 7.2 Hz, 1H), 7.20 (s, 2H), 7.31 (d, ^3J(H,H) = 8.4 Hz, 2H), 7.43 (d, ^3J(H,H) = 7.2 Hz, 1H), 7.50 (d, ^3J(H,H) = 7.2 Hz, 1H), 7.53–7.62 (m, 12H), 8.01 (s, 2H), 8.16 (s, 1H), 9.12 (s, 2H), 9.18 ppm (s, 1H); ^{13}C NMR (75 MHz, [D_6]DMSO, 20 °C): δ = 20.4 (q), 54.7 (t), 117.9 (d), 121.6 (q, ^2J(C,F) = 31.6 Hz) (s), 123.8 (d), 123.9 (d), 124.5 (q, ^1J(C,F) = 269.5 Hz) (s), 124.8 (d), 125.9 (q, ^3J(C,F) = 3.6 Hz) (d), 127.2 (d), 127.8 (d), 129.3 (d), 130.1 (d), 130.3 (s), 130.9 (s), 133.4 (s), 134.0 (s), 136.8 (s), 143.5 (s), 152.8 (s), 153.2 ppm (s); ^{19}F NMR (188 MHz, [D_6]DMSO, 20 °C): δ = −59.8 ppm; IR (Nujol): $\tilde{\nu}$ = 3329 (s), 1666 (vs), 1605 (vs), 1563 (vs), 1410 (w), 1325 (vs), 1249 (m), 1168 (s), 1125 (vs), 1068 (s), 850 (m), 833 cm^{-1} (w); elemental analysis calcd (%) for $C_{47}H_{40}F_9N_7O_3$ (921.9): C 61.24, H 4.37, N 10.64; found: C 61.17, H 4.47, N 10.68.

General procedure for the synthesis of triureas 5a,b: The corresponding isocyanate (1.10 mmol) was added to a solution of **12** (0.28 g, 0.55 mmol) in dry CH_2Cl_2 (10 mL) under N_2. After stirring at 20 °C for 24 h, the solvent was removed under reduced pressure and Et_2O (5 mL) was added. The white solid was filtered and dried under vacuum.

*Bis{3-[N′-(4-trifluoromethylphenyl)ureido]benzyl}{3-[N′-(4-butylphenyl)ureido]benzyl}amine (**5a**)*: Colourless prisms (an analytical sample was obtained by recrystallization from 1:3 $CHCl_3$/*n*-pentane), 72% yield. M.p. 179–181 °C; ^{1}H NMR (401 MHz, [D_6]DMSO, 20 °C): δ = 0.86 (t, ^3J(H,H) = 7.3 Hz, 3H), 1.25 (sext, ^3J(H,H) = 7.3 Hz, 2H), 1.47 (quint, ^3J(H,H) = 7.5 Hz, 2H), 2.45 (t, ^3J(H,H) = 7.5 Hz, 2H), 3.50 (s, 6H), 7.02–7.09 (m, 5H), 7.23–7.29 (m, 3H), 7.32–7.35 (m, 3H), 7.38 (d, ^3J(H,H) = 8.0 Hz, 2H), 7.54 (s, 3H), 7.58 (d, ^3J(H,H) = 8.7 Hz, 4H), 7.62 (d, ^3J(H,H) = 8.6 Hz, 4H), 8.54 (s, 1H), 8.61 (s, 1H), 8.79 (s, 2H), 9.08 ppm (s, 2H); ^{13}C NMR (101 MHz, [D_6]DMSO, 20 °C): δ = 13.7 (q), 21.7 (t), 33.2 (t), 34.1 (t), 57.0 (t), 57.1 (t), 116.8 (d), 117.1 (d), 117.8 (d), 118.26 (d), 118.33 (d), 118.7 (d), 121.7 (q, ^2J(C,F) = 32.1 Hz) (s), 121.9 (d), 122.4 (d), 124.5 (q, ^1J(C,F) = 269.4 Hz) (s), 126.0 (q, ^3J(C,F) = 3.7 Hz) (d), 128.5 (d), 128.7 (d), 135.7 (s), 137.3 (s), 139.3 (s), 139.7 (s), 139.8 (s), 143.5 (s), 152.2 (s), 152.6 ppm (s); IR (Nujol): $\tilde{\nu}$ = 3329 (s), 1668 (vs), 1608 (vs), 1565 (vs), 1488 (m), 1415 (m), 1331 (vs), 1251 (s), 1165 (s), 1118 (vs), 1076 (s), 853 (m), 778 (w), 703 cm^{-1} (m); MS (FAB$^+$): *m*/*z* (%): 882 (74) [*M*+1]$^+$, 881 (34) [*M*]$^+$, 880 (63), 600 (27), 588 (32), 294 (26), 293 (100), 237 (26); ele-

mental analysis calcd (%) for $C_{48}H_{45}F_6N_7O_3$ (881.9): C 65.37, H 5.14, N 11.12; found: C 64.91, H 5.13, N 11.11.

*Bis{3-[N′-(4-methoxyphenyl)ureido]benzyl}{3-[N′-(4-butylphenyl)ureido]-benzyl}amine (**5b**)*: Colourless prisms (an analytical sample was obtained by recrystallization from 10;1 $CHCl_3/Et_2O$), 92% yield. M.p. 141–146°C; ^{1}H NMR (401 MHz, [D$_6$]DMSO, 20°C): δ = 0.89 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.29 (sext, ^3J(H,H) = 7.4 Hz, 2H), 1.50 (quint, ^3J(H,H) = 7.2 Hz, 2H), 2.49 (t, ^3J(H,H) = 7.5 Hz, 2H), 3.51 (s, 6H), 3.70 (s, 6H), 6.86 (d, ^3J-(H,H) = 6.8 Hz, 4H), 7.06–7.08 (m, 5H), 7.25–7.28 (m, 3H), 7.36–7.38 (m, 9H), 7.50–7.52 (m, 3H), 8.47 (s, 2H), 8.56 (s, 1H), 8.60 (s, 2H), 8.64 ppm (s, 1H); ^{13}C NMR (101 MHz, [D$_6$]DMSO, 20°C): δ = 13.8 (q), 21.7 (t), 33.3 (t), 34.2 (t), 55.1 (q), 57.1 (t), 114.0 (d), 116.8 (d), 118.3 (d), 120.0 (d), 121.8 (d), 121.9 (d), 128.5 (d), 128.7 (d), 132.7 (s), 135.7 (s), 137.3 (s), 139.7 (s), 139.8 (s), 139.9 (s), 152.6 (s), 152.7 (s), 154.4 ppm (s); IR (Nujol): $\tilde{\nu}$ = 3326 (s), 1654 (vs), 1606 (vs), 1555 (vs), 1511 (vs), 1489 (vs), 1311 (s), 1247 (vs), 1181 (m), 1113 (w), 1036 (w), 834 (m), 780 (w), 700 cm^{-1} (m); MS (FAB$^+$): *m/z* (%): 806 (42) $[M+1]^+$, 805 (20) $[M]^+$, 804 (33), 550 (21), 255 (45), 237 (28), 133 (22), 132 (100), 124 (37), 123 (78), 122 (32), 120 (20); elemental analysis calcd (%) for $C_{48}H_{51}N_7O_5$ (806.0): C 71.53, H 6.38, N 12.17; found: C 71.90, H 6.42, N 12.47.

Bis{3-[*N*′-(benzyl)ureido]benzyl}{3-[*N*′-(4-butylphenyl)ureido]benzyl}amine (5c): Benzyl isocyanate (0.05 g, 0.40 mmol) was added to a solution of **12** (0.10 g, 0.20 mmol) in dry $CHCl_3$ (10 mL) under N_2. After stirring at reflux for 24 h, the solvent was removed under reduced pressure and *n*-pentane (5 mL) was added. The white solid was collected by filtration and dried under vacuum to give **5c** in 80% yield; colourless prisms (an analytical sample was obtained by recrystallization from 1/1 acetone/*n*-pentane). M.p. 155–158°C; ^{1}H NMR (401 MHz, [D$_6$]DMSO, 20°C): δ = 0.88 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.28 (sext, ^3J(H,H) = 7.2 Hz, 2H), 1.50 (quint, ^3J(H,H) = 7.2 Hz, 2H), 2.45 (br s, 2H), 3.43 (s, 6H), 4.28 (d, ^3J-(H,H) = 5.5 Hz, 4H), 6.57 (t, ^3J(H,H) = 6.0 Hz, 2H), 6.97–7.08 (m, 5H), 7.12–7.41 (m, 22H), 8.54 (s, 2H), 8.60 ppm (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 20°C): δ = 13.8 (q), 21.7 (t), 33.3 (t), 34.2 (t), 42.7 (t), 57.05 (t), 57.13 (t), 116.4 (d), 116.7 (d), 118.0 (d), 118.3 (d), 121.3 (d), 121.9 (d), 126.7 (d), 127.0 (d), 127.1 (d), 128.3 (d), 128.5 (d), 128.6 (d), 135.7 (s), 137.3 (s), 139.6 (s), 139.8 (s), 140.3 (s), 140.4 (s), 152.6 (s), 155.2 ppm (s); IR (Nujol): $\tilde{\nu}$ = 3312 (s), 1647 (vs), 1606 (s), 1552 (vs), 1490 (s), 1315 (s), 1239 (s), 1131 (w), 1083 (w), 888 (w), 784 (w), 696 cm^{-1} (s); MS (FAB$^+$): *m/z* (%): 774 (100) $[M+1]^+$, 773 (29) $[M]^+$, 772 (50), 534 (42), 492 (26), 147 (26), 132 (78), 108 (23); elemental analysis calcd (%) for $C_{48}H_{51}N_7O_3$ (774.0): C 74.49, H 6.64, N 12.67; found: C 74.70, H 6.71, N 12.77.

Preparation of bis{5-chloro-2-[*N*′-(4-methylphenyl)ureido]benzyl}{3-[*N*′-(4-methylphenyl)ureido]propyl}amine (6): 4-Methylphenyl isocyanate (0.06 g, 0.48 mmol) was added to a solution of **14** (0.06 g, 0.16 mmol) in dry $CHCl_3$ (15 mL) under N_2. After stirring at 20°C for 20 h, the solvent was removed under reduced pressure and Et_2O (2 mL) was added. The white solid was collected by filtration and dried under vacuum. The corresponding triurea was purified by recrystallization from $CHCl_3/Et_2O$ (2:1) (yield: 77%). M.p. 218–220°C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 20°C): δ = 1.65 (quint, ^3J(H,H) = 6.1 Hz, 2H), 2.19 (s, 3H), 2.21 (s, 6H), 2.49 (m, 2H), 3.01 (q, ^3J(H,H) = 5.9 Hz, 2H), 3.57 (s, 4H), 6.11 (t, ^3J-(H,H) = 6.0 Hz, 1H), 6.97–7.03 (m, 6H), 7.16 (dd, ^3J(H,H) = 8.6 Hz, ^4J-(H,H) = 2.1 Hz, 2H), 7.23 (d, ^3J(H,H) = 8.2 Hz, 2H), 7.29 (d, ^3J(H,H) = 8.2 Hz, 4H), 7.39 (d, ^4J(H,H) = 1.9 Hz, 2H), 7.65 (d, ^3J(H,H) = 8.7 Hz, 2H), 8.31 (s, 2H), 8.32 (s, 1H), 8.96 (s, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 20°C): δ = 20.35 (q), 20.39 (q), 26.4 (t), 37.4 (t), 51.9 (t), 54.4 (t), 118.0 (d), 118.8 (d), 124.3 (d), 127.0 (s), 127.1 (d), 129.0 (d), 129.1 (d), 129.8 (s), 130.8 (s), 131.5 (s), 136.7 (s), 137.1 (s), 137.9 (s), 152.9 (s), 155.6 (s); IR (Nujol): $\tilde{\nu}$ = 3340 (s), 1656 (vs), 1599 (vs), 1555 (s), 1514 (s), 1410 (w), 1318 (m), 1289 (m), 1247 (m), 1184 (w), 1116 (w), 823 cm^{-1} (m); MS (FAB$^+$): *m/z* (%): 754 (21) $[M+3]^+$, 753 (15) $[M+2]^+$, 752 (27) $[M+1]^+$, 373 (17), 308 (28), 290 (18), 275 (26), 274 (21), 273 (79), 271 (34), 266 (17), 241 (30), 219 (26); HRMS (ESI): *m/z* calcd for $C_{41}H_{43}Cl_2N_7O_3+H^+$: 752.2877; found: 752.2883 $[M+H]^+$.

Acknowledgements

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