Self-assembled dendrimers with uniform structure†

Yuliya Rudzevich,*[a] Valentyn Rudzevich,‡[a] Chulsoon Moon,[b] Gunther Brunklaus[b] and Volker Böhmer*[a]

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Calix[4]arenes substituted at their wide rim by four aryl urea residues (**1**) form hydrogen-bonded dimers in apolar solvents. Replacement of one urea residue by an acetamido moiety leads to calix[4]arene derivatives (**5**) which form hydrogen-bonded tetramers under the same conditions. Both self-assembly processes occur independently. Therefore, molecules have been prepared in which a tetra-urea calix[4]arene and a tri-urea mono acetamide derivative are covalently connected between their narrow rims by a long, mainly aliphatic chain [-O-$(CH_2)_n$-C(O)-NH-$(CH_2)_m$-O-] (**7**). In the presence of an equimolar amount of tetra-tosyl urea calix[4]arene (**2**) they form dendritic assemblies since the well known heterodimerization of tetra-tosyl and tetra-aryl urea calix[4]arenes prevents the formation of a cross-linked structure. Covalent connection of adjacent urea residues leads to tetra-loop derivatives (**3**) that cannot form homodimers, but instead form heterodimers with tetra-aryl or tetra-tosylureas. Therefore, similar dendrimers should be available using the selective dimerization observed for **3**. The formation of a single, structurally uniform dendrimer from eight building blocks is confirmed by ^{1}H NMR spectra, showing only peaks that are also found for respective model assemblies. Translational diffusion coefficients of the assemblies have been determined using ^{1}H DOSY NMR.

Introduction

Self-organisation on the molecular level is the driving force responsible for selective formation of essential assemblies in living systems. This principle is not only frequently used to construct rather intricate artificial arrangements but also to synthesize novel compounds or materials. Indeed, dimeric capsules,[1–3] tetramers,[4] hexamers,[5] rosettes,[6] supramolecular polymers[7] and dendrimers[8] have been obtained *via* self-assembly.

Among others, calix[4]arenes substituted by urea functions at their wide rim are often used as building blocks for such structures. In apolar, aprotic solvents they form dimeric capsules that are stabilized by a seam of hydrogen bonds between NH and C=O groups of the urea functions[9] (Fig. 1). A suitable guest (often a solvent molecule) is commonly included, filling the internal volume of the capsule.

The nature of residues connected to urea fragments strongly influences the dimerization. When two different aryl or alkyl ureas are mixed together, two possible homodimers and a heterodimer are usually obtained in a more or less statistical ratio.[10] However, a stoichiometric mixture of tetra-aryl and tetra-sulfonyl ureas **1** and **2** (Fig. 2) exclusively yields the heterodimeric assembly **1**·**2**.[11,12]

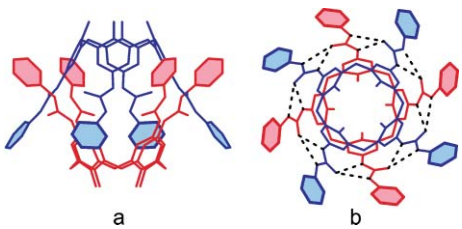

Fig. 1 Dimeric capsule formed by tetra-arylurea derivatives **1**; (a) side view, (b) top view; alkyl substituents are omitted for clarity.

This heterodimerization of **1** and **2** has been employed to construct various linear polymers from building blocks consisting of tetra-urea derivatives covalently connected *via* their narrow rims[13] and to characterise multiple tetra-urea calix[4]arenes[13,14] that could be used as cores for dendritic structures. In addition, it constitutes the basis for the controlled synthesis of calix[4]arene-based bis-, tris- and tetra-loop (**3a**) compounds *via* defined metathesis using **2a** as a template.[15]

Likewise, an exclusive heterodimerisation may be afforded by steric factors. The tetra-loop tetra-ureas **3** cannot homodimerise since this would require a sterically unfavourable overlapping of the loops.[15b,16] However, in the presence of stoichiometric amounts of "open-chain" tetra-ureas **1** or **2** it readily forms heterodimers **1**·**3** or **2**·**3**, thus facilitating the synthesis of topologically interesting catenanes[17] and rotaxanes.[18,19] We will show subsequently how these observations can be used to design and to realize well defined hydrogen-bonded dendrimers, uniform in size and in structure.

In most cases self-assembled dendrimers consist of (several) dendrons that are kept together by hydrogen bonding only in the core.[8d] To the best of our knowledge until now only two dendrimers were completely built up *via* self-organisation. The first reported example[20] was based on a system of two

[a]*Abteilung Lehramt Chemie, Fachbereich Chemie, Pharmazie und Geowissenschaften, Johannes Gutenberg-Universität Mainz, Duesbergweg 10-14, D-55099, Mainz, Germany. E-mail: rudzevic@mail.uni-mainz.de, vboehmer@mail.uni-mainz.de; Fax: +49 6131 3925419; Tel: +49 6131 3922319*
[b]*Max Planck Institut für Polymerforschung, Postfach 3148, D-55021, Mainz, Germany*

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‡ Permanent address: Institute of Organic Chemistry, NAS of Ukraine, Murmanska str. 5, 02094 Kyiv-94, Ukraine.

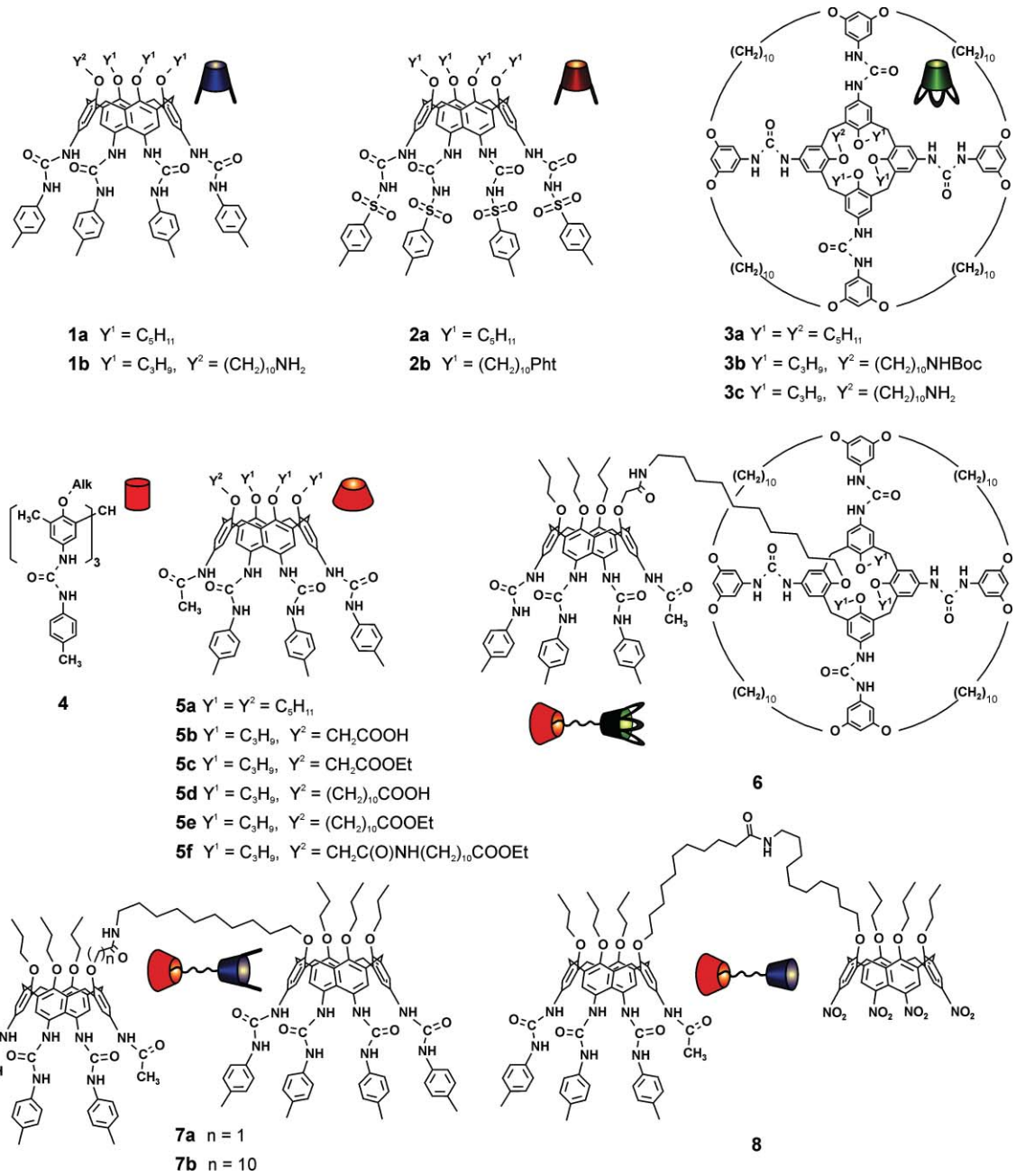

Fig. 2 General formulae and schematic representations of compounds **1–8**.

complementary hydrogen-bonding motifs. However, the molecular assemblies still may be different in size and structure, since the ratio of the building blocks determines only the *average* size.[21]

In contrast, the first structurally uniform hydrogen-bonded dendrimer was realized using three (self)-complementary units of types **1**, **2** and **4**.[8f] The formation of such an assembly was based on the homodimerisation of tri-urea triphenylmethanes **4** (as the core) and the exclusive heterodimerization of tetra-tolyl and tetra-tosyl ureas **1** and **2**, which obey the self-sorting principle.[16,22] Hence, a well defined dendrimer[8f] was formed upon mixing of building block **4**–**1**$_3$ and capping unit **2** in a 1 : 3 ratio.

In this paper we describe a second example of such a dendrimer which is also uniform in size *and* structure.

Results and discussion

General idea

Self-organisation leading to structurally uniform dendrimers (as described above) is based on the following rules:

– the core must be formed by self-assembly of a single, self-complementary unit;

– the exclusive heterodimerization of pairs of different units is needed to build up each subsequent shell;

– all units must obey the self-sorting principle.

The tri-urea triphenylmethane **4**, which was used as a core in the earlier example, forms homodimers independently from the dimerization of tetra-urea calix[4]arenes and thus fulfils the requirements for the central unit. This is due to the different number of urea functions and the different shape of compounds **4** and **1–3**.

Furthermore, mismatch of the corresponding hydrogen-bonding patterns of two assemblies allows for such selectivities. In apolar solvents, tri-urea monoacetamide **5a** yields tetramers whose stabilizing hydrogen-bonding network is entirely different from that observed for tetra-urea dimers (Fig. 3).[4] The four acetamide groups are placed in the middle of the assembly, while each amide oxygen is hydrogen-bonded to both an amide-NH and an urea-NH of two neighbouring calixarenes (Fig. 3a). Two of three urea carbonyl oxygens are connected with the urea protons of the neighbouring calixarenes by three-centred hydrogen bonds, while the remaining C=O and one NH are not involved in hydrogen bonding.

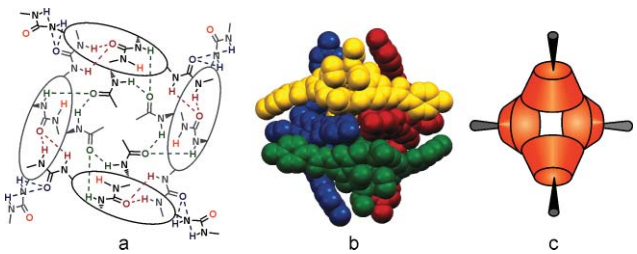

Fig. 3 Schematic drawing of (a) the hydrogen-bonding pattern of tetramer $\mathbf{5a}_4$, (b) a space-filling representation of tetramer $\mathbf{5a}_4$ based on its single crystal X-ray structure,[4] (c) a schematic representation of the tetrameric assembly $\mathbf{5a}_4$.

When tri-urea acetamide **5** and the tetra-urea **1** are mixed in an apolar solvent, both tetramerisation of **5** and homodimerization of **1** occur independently and simultaneously. This self-sorting principle holds also when a second (different) tetra-urea calix[4]arene is present in the mixture.[23] Therefore, when **5** is added to a 1 : 1 mixture of **1** and **2** (or **3**) only the tetramer $\mathbf{5}_4$ and the heterodimer **1**·**2** (or **1**·**3**) exist, as clearly proved by the ^{1}H NMR spectra shown in Fig. 4.

Using the approach outlined above, we have designed dendritic assemblies (Fig. 5) that are both uniform in size and structure and adopt a more spherical shape in comparison to the earlier example. Covalent connection of tri-urea monoacetamide **5b** with tetra-loop derivative **3c** or tetra-tolyl urea **1b**, respectively, forms the central building blocks **6** and **7**, while the tetra-ureas **2** are used as capping units. When these building blocks are mixed in a 1 : 1 ratio, dendritic assemblies as shown in Fig. 5 should be formed. The four functional groups (protected amino functions) at the narrow rim of **2b** could be either used to attach specific moieties (*e.g.* dyes to model light-harvesting systems) at the surface of the assembly or for further growth of the dendrimer to the next generation.

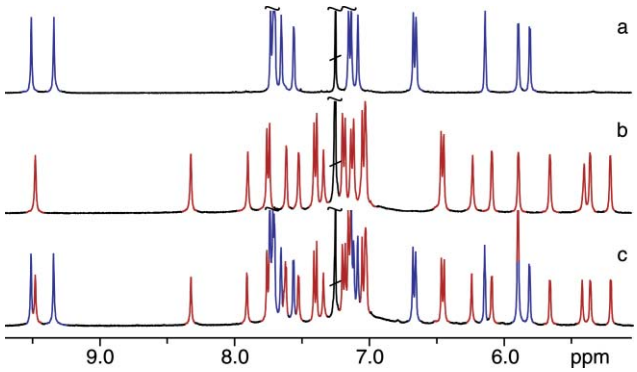

Fig. 4 Sections of the ^{1}H NMR spectra ($CDCl_3$, 400 MHz) of (a) the heterodimer **1a**·**3a**, (b) the tetrameric tritolyl urea monoacetamide $\mathbf{5a}_4$, (c) a 1 : 1 : 3 mixture of **1a**, **3a** and **5a** (an arbitrary amount), which shows only signals present in (a) and (b).

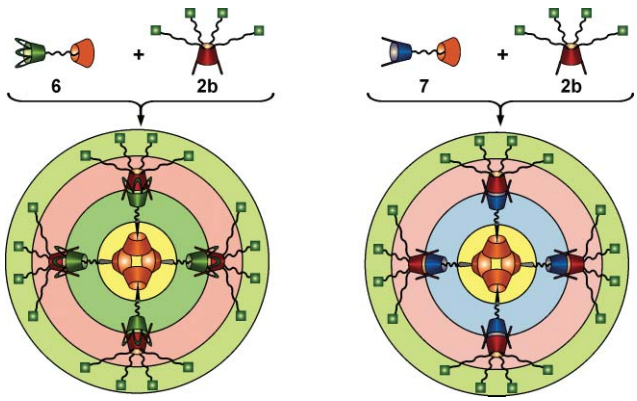

Fig. 5 Envisaged formation of dendritic structures *via* selective di- and tetramerization of urea derivatives of calix[4]arenes.

Synthesis and self-assembly studies

Coupling of tritolyl urea monoacetamides **5b** and **5d**[24] (bearing one acid function) and respective tetra-urea derivatives **1b**[14] or **3c**[25] (possessing one amino group) using PyBOP in DMF leads to the bis-calixarene building blocks **6** and **7** in 70–85% yield.

A representative ^{1}H NMR spectrum (DMSO-d_6) of building block **6** confirming its structure is partly presented in Fig. 6. One singlet of acetamide NH and the set of resonances for all remaining NH protons are found in the expected region. At 75 °C the characteristic NH signal of the amide bond connecting two calixarenes *via* their aliphatic arms (-CH_2NHC(O)CH_2-) can be observed separately at 7.78 ppm. In the aromatic part two doublets for the ArH protons of the tolyl residues in **5b** appear in a 1 : 2 ratio, while the other two are overlapping with one of the four singlets of the calixarene skeleton of **5b**. The remaining signals correspond to aromatic protons of the tetra-loop derivative **3c**.

Upon mixing of building block **6** with either tetra-tolyl urea **1a** or tetra-tosyl urea **2a** in a 1 : 1 ratio, formation of a dendritic assembly with 16 Y residues on the surface is anticipated (Fig. 5). However, no evidence for the correct assembly could be observed in the ^{1}H NMR spectrum of the mixture of **6** + **1a** in $CDCl_3$ or $C_2D_2Cl_4$ (Fig. 7a). All signals corresponding to a tetrameric structure were absent, while among the rest of the resonances, those corresponding to the homodimer **1a**·**1a** were detected. When tetra-tosyl urea **2a** was used instead of **1a** as a capping unit

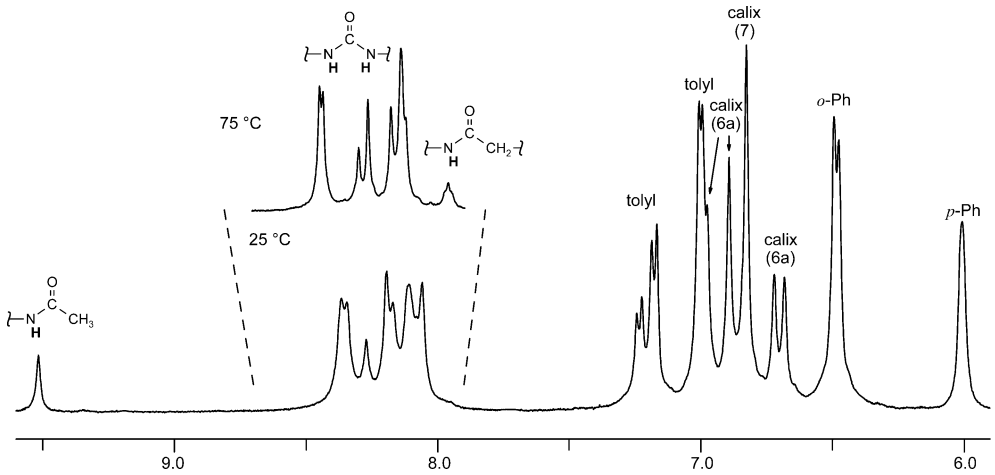

Fig. 6 Part of the ^{1}H NMR spectrum of **6** in DMSO-d_6.

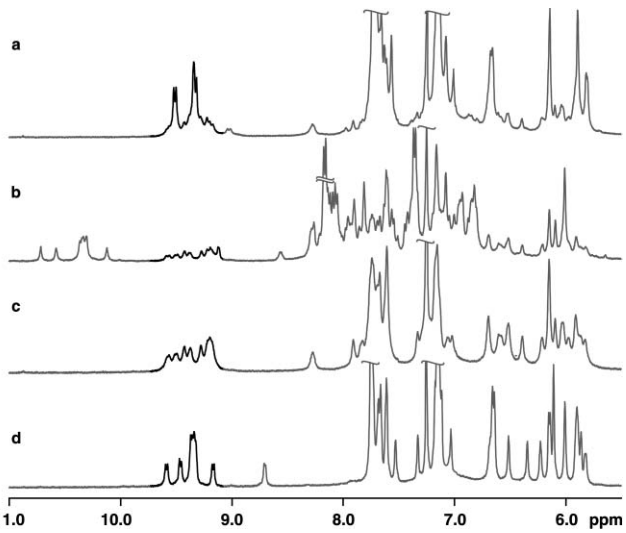

Fig. 7 Parts of the ^{1}H NMR spectra ($CDCl_3$, 400 MHz) of the stoichiometric mixtures of (a) **6** + **1a**, (b) **6** + **2a**, (c) **6**, (d) **3b** + **5c**.

the corresponding ^{1}H spectrum became even more complicated (Fig. 7b), but again no evidence for the tetramer was found.

Searching for an explanation we recorded the spectrum of building block **6** without addition of the capping units **1a** (or **2a**). Instead of the expected peaks of a tetramer we observed a different set of slightly broadened signals that were also present in the mixtures of **6** + **1a** and **6** + **2a** (Fig. 7a–c). This observation strongly suggests that the tri-urea monoacetamides **5**, which usually do not heterodimerize with "open-chain" tetra-ureas **1**, are able to form dimers with tetra-loop derivatives **3**. Indeed, when **3b** and **5c** were mixed together formation of the respective heterodimer was observed (Fig. 7d). This means that linear polymers are formed if only building block **6** is present in solution; however, it does not yet explain the absence of the desired assembly in the presence of **1a** or **2a**. Similar experiments with the building block **7a** lead to the same results.

Since in the model three-component mixtures of open-chain ureas **1a** or **2a**, tetra-loop urea **3a** and monoacetamide **5a** only the expected tetramer $\mathbf{5a}_4$ and the heterodimers **1a**·**3a** or **2a**·**3a** were observed (Fig. 4), the results obtained can be explained by two reasons. Either the spacer between the two calixarenes is too short and the dendrimer cannot be formed due to steric congestion, or the amide bonds connecting the two calixarenes in **6** and **7a** are placed too close to the hydrogen-bonding system of the envisaged tetramer and thus intervene with this assembly and prevent its formation.

The ^{1}H NMR spectrum of the model compound **5f**[26] in $CDCl_3$, showing only broad signals instead of the expected peaks of the tetramer, confirmed the latter assumption. To overcome this problem the building block **7b** was prepared, in which the amide bond is separated from the calixarene skeleton of tri-urea monoacetamide derivative by 10 carbon atoms.

The building block **7b** was mixed in a 1 : 1 ratio either with tetra-loop compound **3a** or tetra-tosyl urea **2b** to afford the respective assemblies. In the first case, formation of the desired dendrimer occurred, however, small additional signals were also present in the spectrum.[27] In contrast, in the mixture of **7b** with tetra-tosyl urea **2b** only the signals of the target assemblies $(\mathbf{7b}\cdot\mathbf{2b})_4$ were observed (Fig. 8). No identification for other assembly can be found by NMR. Taking into account that one $CHCl_3$ molecule may be included in each dimeric capsule, the calculated molecular mass of the structurally uniform dendritic assembly of 12 molecules $(\mathbf{7b}\cdot\mathbf{2b})_4$ is 20 206 g mol^{-1}.

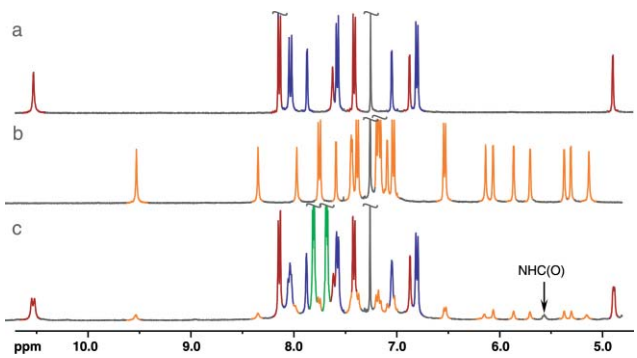

Fig. 8 Parts of the ^{1}H NMR spectra ($CDCl_3$, 400 MHz) of (a) the heterodimer **1a**·**2a**, (b) the tetramer formed by **5e**, (c) the stoichiometric mixture of **7b** and **2b** – the dendritic structure $(\mathbf{7b}\cdot\mathbf{2b})_4$.

^{1}H DOSY experiments[28] were performed for the tetramer formed by **5c**, for a bis-calixarene **8** (a model of the building block **7b**) and for the dendrimer (**7b**·**2b**)$_4$. The diffusion coefficients of 2.8×10^{-10}, 2.0×10^{-10}, 1.5×10^{-10} m^2 s^{-1} corresponding to hydrodynamic radii of 1.4, 2.0 and 2.6 nm respectively were found (Fig. 9). Thus the R_h of the new assembly is 0.5 nm larger than that of the previously published example[8f] (2.1 nm). Obviously the tetrahedral core in dendrimer (**7b**·**2b**)$_4$ leads to a less dense packing.

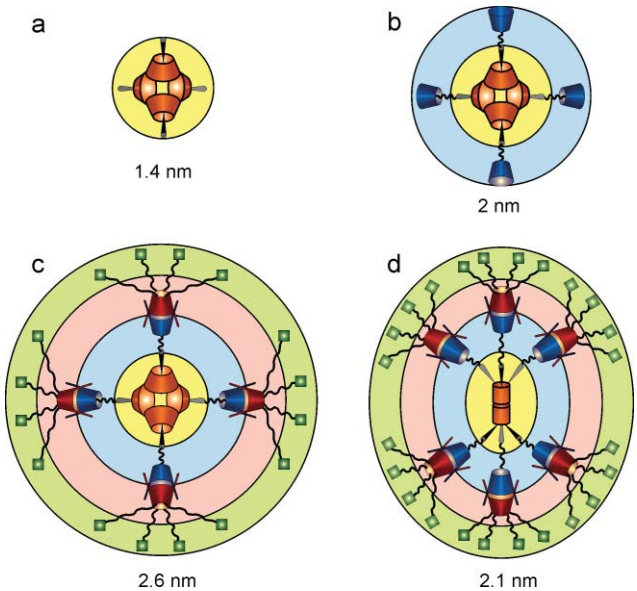

Fig. 9 Schematic representations and hydrodynamic radii of (a) the tetramer formed by **5c**, (b) the model tetramer **8**$_4$, (c) the dendrimer (**7b**·**2b**)$_4$, (d) the dendrimer[8f] having the dimeric triurea triphenylmethane **4**$_2$ as a core.

Conclusions

The well established preparative chemistry of calix[4]arenes allows the synthesis of specific derivatives which are not only able to self-assemble, but also to take part in self-sorting processes. Using these properties we constructed a dendrimer, which is uniform in size and structure and has molecular weight of more than 20 000 g mol^{-1}. The formation of the desired assembly was proved by ^{1}H and ^{1}H DOSY NMR spectroscopy. Moreover, it was shown that the formation of the correct aggregate may be supported and the undesired assemblies can be suppressed by only slight changes in the chemical structure of the dendrons.

In addition it was found that the triurea monoacetamides of type **5** (which usually tetramerize even in the presence of tetra-ureas of type **1**) form heterodimers with the tetra-loop tetra-ureas **3** if the latter has no other better partner.

Experimental

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer at 400 MHz. Chemical shifts are reported in δ units (ppm) with reference to the residual solvent peaks. Mass spectra were recorded on a Waters/Micromass QTof Ultima 3 mass spectrometer. All solvents were HPLC grade and used without further purification.

As previously verified,[29] data for elemental analyses of organic calixarenes are often misleading, due to inclusion of solvent molecules, and cannot be considered appropriate criteria of purity. Nevertheless, the identities of the reported compounds were unambiguously established by their spectroscopic data.

General procedure for the synthesis of building blocks 6–8

Et_3N (0.3 mL) was added to a solution of the respective acid[24] (0.15 mmol), amine[14,25] (0.13 mmol) and (benzotriazole-1-yloxy)trispyrrolidinophosphonium hexafluorophosphate (Py-BOP) (0.15 mmol) in DMF (peptide synthesis grade, 4 mL). The reaction mixture was stirred for 24 h at room temperature and then diluted with water (15 mL). The formed precipitate was filtered off, washed with MeOH (4 × 5 mL) and dried in air. In the case of the compound **7b** it was extracted with $CHCl_3$–THF (2 : 1, 3 × 30 mL). The organic layer was washed with brine, dried ($MgSO_4$), concentrated to a volume of 5–10 mL and the product was precipitated with MeOH.

Bis-calix[4]arene 6. Compound **6** was obtained as a white powder in 85% yield; m.p.: slow decomposition above 280 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 0.88–1.02 (18H, m, C*H*$_3$), 1.20–1.42 (64H, m, C*H*$_2$), 1.63 (16H, m, C*H*$_2$), 1.78–2.02 (15H, m, C*H*$_2$ and C(O)C*H*$_3$), 2.21 (9H, s, TolC*H*$_3$), 3.13 (8H, m, ArC*H*$_2$Ar), 3.27 (2H, br s, NHC*H*$_2$), 3.70–3.93 (30H, m, OC*H*$_2$), 4.36 (10H, m, OC*H*$_2$ and ArC*H*$_2$Ar), 6.04 (4H, s, Ar*H*), 6.51 (4H, s, Ar*H*), 6.52 (4H, s, Ar*H*), 6.71 (2H, s, Ar*H*), 6.75 (2H, s, Ar*H*), 6.86 (8H, s, Ar*H*), 6.92 (2H, s, Ar*H*), 7.01–7.04 (8H, m, ArH_{Tol} and Ar*H*), 7.21 (4H, d, $^3J = 7.8$ Hz, ArH_{Tol}), 7.26 (2H, d, $^3J = 7.8$ Hz, ArH_{Tol}), 8.06–8.44 (15H, m, NH_{urea} and CH$_2$C(O)N*H*), 9.54 (1H, s, N*H*C(O)CH$_3$); *m*/*z* (ESI) 3038.6 (5) [M$^+$ + Na], 1530.8 (63) [M^{2+} + Na].

Bis-calix[4]arene 7a. Compound **7a** was obtained as a white powder in 80% yield; m.p.: slow decomposition above 280 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 0.86–1.04 (18H, m, C*H*$_3$), 1.34 (12H, m, C*H*$_2$), 1.56 (2H, m, C*H*$_2$), 1.75–1.98 (17H, m, C*H*$_2$ and C(O)C*H*$_3$), 2.21 (21H, s, TolC*H*$_3$), 3.11 (8H, m, ArC*H*$_2$Ar), 3.26 (2H, br s, NHC*H*$_2$), 3.69–3.88 (14H, m, OC*H*$_2$), 4.27–4.45 (10H, m, OC*H*$_2$ and ArC*H*$_2$Ar), 6.68–6.89 (16H, m, Ar*H*), 7.02 (16H, br s, ArH_{Tol}), 7.22 (12H, br s, ArH_{Tol}), 8.04–8.33 (15H, m, NH_{urea} and CH$_2$C(O)N*H*), 9.55 (1H, s, N*H*C(O)CH$_3$); *m*/*z* (ESI) 2414.1 (3) [M$^+$ + Na], 1218.1 (79) [M^{2+} + Na].

Bis-calix[4]arene 7b. Compound **7b** was obtained as a white powder in 75% yield; m.p.: slow decomposition above 225 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 0.91–1.02 (18H, m, C*H*$_3$), 1.18–1.43 (26H, m, C*H*$_2$), 1.48 (2H, m, C*H*$_2$), 1.89 (19H, m, C*H*$_2$ and C(O)C*H*$_3$), 2.02 (2H, t, $^3J = 7.1$ Hz, C(O)C*H*$_2$), 2.21 (21H, s, TolC*H*$_3$), 2.97–3.14 (10H, m, ArC*H*$_2$Ar and NHC*H*$_2$), 3.69–3.85 (16H, m, OC*H*$_2$), 4.33 (8H, d, $^2J = 12.2$ Hz, ArC*H*$_2$Ar), 6.69–6.86 (14H, m, Ar*H*), 6.95–7.07 (16H, m, Ar*H*), 7.16–7.29 (14H, m, Ar*H*), 7.69 (1H, t, $^3J = 5.4$ Hz, C(O)N*H*), 8.07–8.31 (14H, m, N*H*), 9.47 (1H, s, N*H*C(O)CH$_3$); *m*/*z* (ESI) 2539.3 (26) [M$^+$ + Na], 1281.2 (100) [M^{2+} + Na].

Bis-calix[4]arene 8. Compound **8** was obtained as a white powder in 86% yield; m.p.: slow decomposition above 185 °C;

(400 MHz, DMSO-d_6), δ: 0.90–1.03 (18H, m, CH_3), 1.18–1.42 (26H, m, CH_2), 1.47 (2H, m, CH_2), 1.73 (2H, m, CH_2), 1.77–1.95 (17H, m, CH_2 and C(O)CH_3), 2.02 (2H, t, $^3J = 7.1$ Hz, C(O)CH_2), 2.21 (9H, s, TolCH_3), 2.61 (2H, m, NHCH_2), 2.97–3.12 (8H, m, ArCH_2Ar), 3.60–3.68 (4H, m, OCH_2), 3.70–3.82 (6H, m, OCH_2), 3.88–3.99 (6H, m, OCH_2), 4.28–4.39 (8H, m, ArCH_2Ar), 6.73 (2H, s, Ar*H*), 6.76 (2H, s, Ar*H*), 6.81 (2H, s, Ar*H*), 6.96–7.06 (8H, m, Ar*H*), 7.21 (4H, d, $^3J = 8.3$ Hz, Ar*H*), 7.26 (2H, d, $^3J = 8.3$ Hz, Ar*H*), 7.59 (4H, s, Ar*H*), 7.65 (2H, s, Ar*H*), 7.66 (2H, s, Ar*H*), 7.68 (1H, t, $^3J = 5.6$ Hz, C(O)N*H*), 8.13 (2H, s, N*H*), 8.15 (1H, s, N*H*), 8.23 (2H, s, N*H*), 8.30 (1H, s, N*H*), 9.47 (1H, s, N*H*C(O)CH_3); *m/z* (ESI) 2206.4 (100) [$M^+ + Et_3N$].

Acknowledgements

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