Supramolecular self-assembly of dendrimers containing orthogonal binding motifs†

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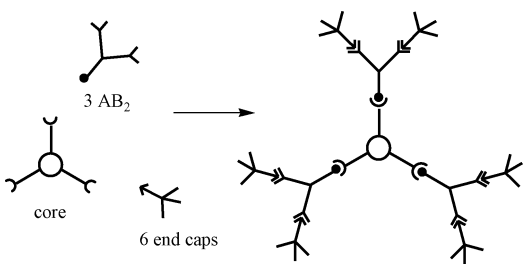
Two orthogonal non-covalent binding sites, namely metal–ligand complexation of Ru and bipyridine and intermolecular hydrogen bonding, facilitate the self-assembly of a new type of supramolecular dendrimers.

Self-assembly[1] involves the spontaneous and thermodynamically controlled formation of supramolecular architectures of suitable tailor-made molecular building blocks. Recently, we reported on the development of various self-assembled dendrimer prototypes,[2–4] which are based on the six-fold hydrogen bonding of Hamilton receptor[5] containing porphyrins or homotritopic core molecules and branched cyanuric acid derivatives. In another approach we used the complexation of depsipeptide functionalized 2,2′-bipyridine (bpy) ligands to ruthenium[6] for the assembly of a first type of chiral metallo dendrimers. These two non-covalent interactions are highly specific and do not interfere. A combination of two or more orthogonal binding motifs opens up the opportunity to self-assemble high hierarchically ordered architectures such as the supramolecular dendrimer schematically depicted in Scheme 1.

So far there is only one precedent for the construction of a supramolecular dendrimer involving orthogonal binding motifs, which was recently published by Böhmer *et al.*[7] On the other hand, triurea derivatives of triphenylmethanes and calix[4]arene derived tetraaryl- and tetratosylureas are capable of forming hydrogen-bonded homodimeric structures without mutual intervention.

Here, we report on the formation of a new type of supramolecular dendrimers based on a combination of the orthogonal Hamilton receptor–cyanuric acid and $Ru(bpy)_3$ metal–ligand interactions as outlined above.



Scheme 1 Self-assembly of a supramolecular dendrimer, consisting of core, 3 AB_2 branching units, and 6 end caps.

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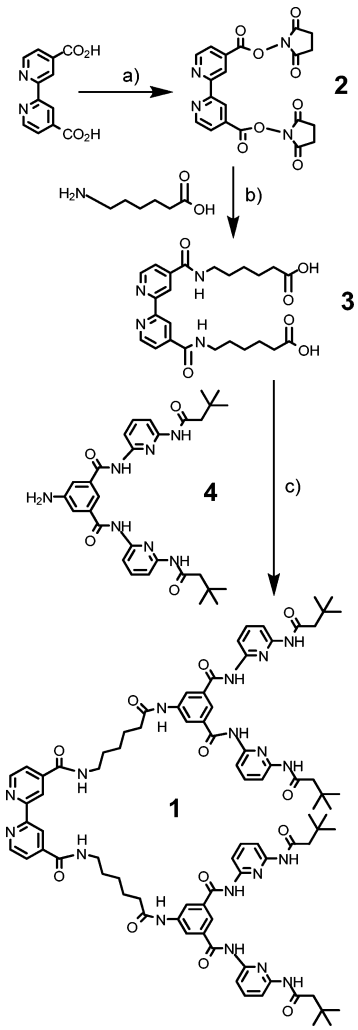
For this purpose we first synthesized the AB_2 building block **1**, consisting of a focal 2,2′-bipyridine moiety for metal complexation and two Hamilton receptor units for the binding of terminal cyanuric acid derivatives. The synthesis sequence started with 2,2′-bipyridinyl-4,4′-dicarboxylic acid,[8] which was treated with *N*-hydroxysuccinimide (NHS) and dicyclohexylcarbodiimide (DCC) to give the corresponding NHS-ester **2** in 69% isolated yield (Scheme 2).

The subsequent coupling with 6-aminohexanoic acid promoted by DCC in dry DMF afforded the bis-acid **3**, which was isolated in 62% yield. The final treatment of **3** with the amino Hamilton receptor **4**[9] under modified Steglich conditions (DCC, DMAP, HOBt) and purification *via* column chromatography (silica, CH_2Cl_2–MeOH 99 : 1, gradient slope to CH_2Cl_2–MeOH 95 : 5) afforded the desired AB_2 building block **1** in 53% yield as a colorless solid. The compound was characterized by ^{1}H-NMR, ^{13}C-NMR, UV/Vis, and IR-spectroscopy, by FAB mass spectrometry as well as by elemental analysis (see ESI†).

In order to evaluate the suitability of **1** to act as a key building block for the self-assembly of supramolecular dendrimers we started with the investigation of the first part of the overall process (Scheme 1), namely the formation of the core structure **5** (Fig. 1).

For this purpose $RuCl_3 \cdot xH_2O$ was refluxed under nitrogen atmosphere with 4 eq. of **1** in EtOH–$CHCl_3$. The formation of a ruthenium tris-bipyridine complex was attested by UV/Vis-spectroscopy. The spectrum shows a ligand centered band at 291 nm and a MLCT-band at 472 nm characteristic for $Ru(bpy)_3$ complexes,[10] which proves the coordination of 3 AB_2 ligands to the ruthenium core. Furthermore, the targeted structure could be verified by MALDI-TOF mass spectrometry, where the $[Ru(AB_2)_3]^+$-ion could be detected at m/z = 4761. As purification of the initially formed chloride of **5** by HPLC turned out to be very difficult due to aggregation and complexation of solvents and by-products, the Cl^- counter-ion was exchanged against PF_6^-. After subsequent purification by size-exclusion chromatography and recrystallization from acetone–diethyl ether the hexafluorophosphate of metallo-dendrimer **5** was obtained in 55% yield as red-orange microcrystals. It is readily soluble in aprotic polar solvents such as chloroform (in contrast to the uncoordinated building block **1**), but shows a strong tendency towards aggregation, as reflected by rather broad signals observed in the ^{1}H-NMR spectrum recorded in $CDCl_3$. In DMSO, however, no intermolecular hydrogen bonds take place and as a consequence further characterization of **5** by ^{1}H- and ^{13}C-NMR spectroscopy was possible.

Small amounts (<10%) of a purple by-product could be isolated *via* HPLC. The structure was determined as



Scheme 2 Synthesis of the AB_2 building block **1**: (a) NHS, DCC, DMF; (b) DCC, DMF; (c) DCC, DMAP, HOBt, CH_2Cl_2–DMF 1 : 1, 50 °C.

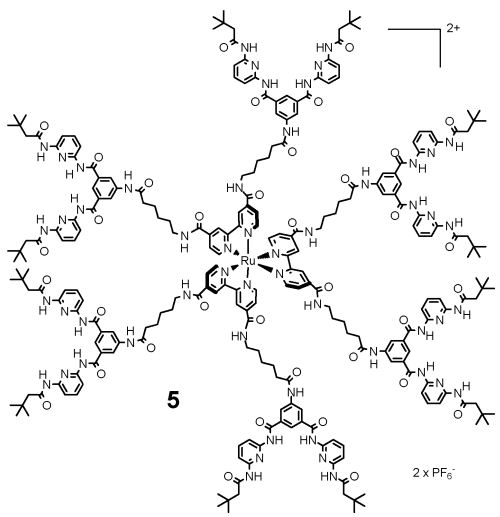
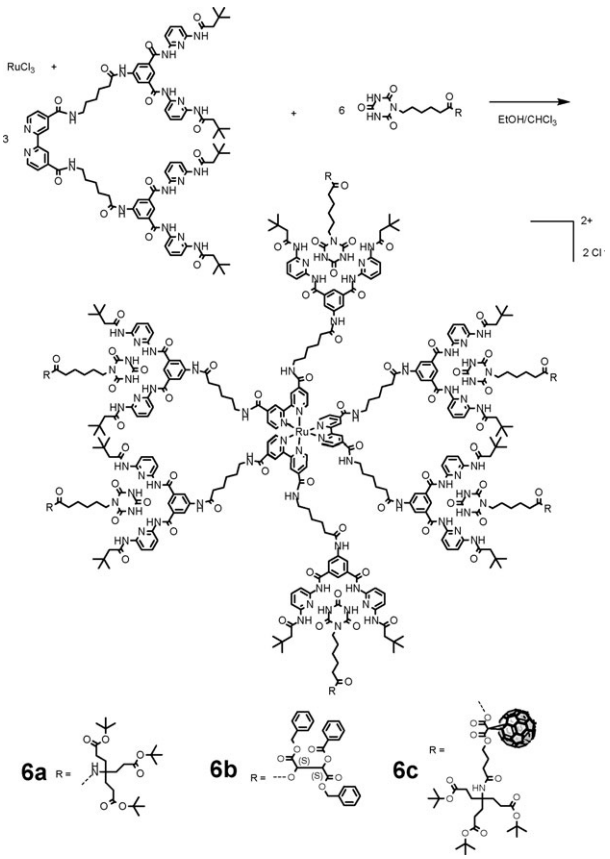


Fig. 1 Metallodendrimer $[Ru(\mathbf{1})_3](PF_6)_2$ **5**.

cis-ruthenium bis-bipyridine $[Ru(\mathbf{1})_2Cl_2](PF_6)_2$ due to the observation of characteristic MLCT absorption bands[10] at 397 and 556 nm. The MALDI-TOF mass spectrum (dithranol) displays the molecular ion peak at m/z = 3209).

The next step was the investigation of the binding of cyanuric acid derivatives to Hamilton receptor termini of **5** leading to self-assembled dendrimers **6a–c**. The corresponding hydrogen-binding as depicted in Scheme 3 was followed by NMR titration experiments.[3] For this purpose, three different end caps (Fig. 2) were used. The cyanuric acid derivative **7** was chosen as first generation dendritic ligand. The ligands **8**[3] and **9**[4] have already been applied successfully in supramolecular architectures and introduce either chirality (**8**) or the possibility for investigation of electronic communication (**9**).



Scheme 3 Complete self-assembly of supramolecular structures **6a–c**.

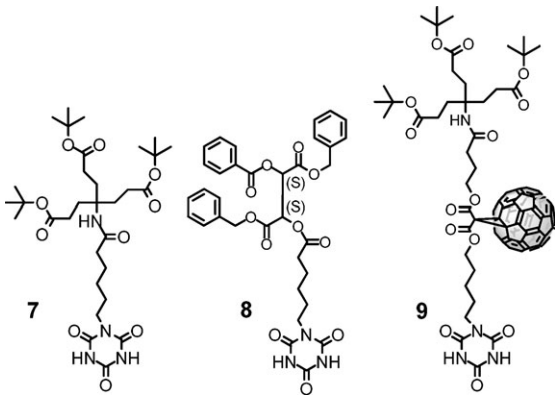


Fig. 2 End caps **7**, **8**, and **9**.

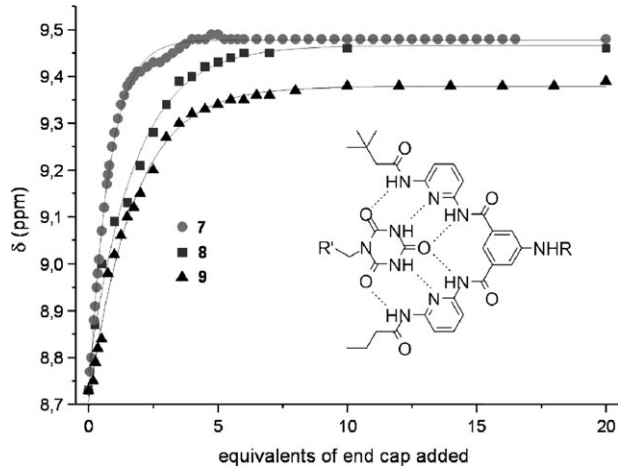


Fig. 3 Chemical shifts of ^{1}H-NMR titration (300 MHz, $CDCl_3$) of $Ru(AB_2)_3(PF_6)_2$ **5** with various end caps.

Table 1 Stepwise formation constants K_1–K_6 [L mol^{-1}]

Complex	(**5**)·(**7**)	(**5**)·(**8**)	(**5**)·(**9**)
log K_1	5.25	4.74	4.85
log K_2	4.91	4.47	4.24
log K_3	4.95	4.50	4.39
log K_4	3.12	4.02	3.88
log K_5	5.07	4.07	3.26
log K_6	5.30	3.80	3.63

Upon complexation of the Hamilton receptor with cyanuric acid derivatives, a complementary six-point hydrogen bonding motif between host and guest is formed. This leads to a significant downfield shift[3] of the Hamilton receptor's NH protons, which can be observed in the ^{1}H-NMR spectra. The subsequent resonance shifts of the amide protons of $[Ru(\mathbf{1})_3](PF_6)_2$ **5** after the addition of the end caps **7**, **8**, and **9** are shown in Fig. 3. The graph depicts saturation after the addition of about 6 equivalents of end cap, as all available binding sites of the macromolecule are occupied.

The characteristic downfield shift of the NH protons of the Hamilton receptor moiety was used to determine the stepwise association constants K_1–K_6 with the help of the program HypNMR,[11] and these are summarized in Table 1.

The calculated association constants are in good agreement with those we reported earlier for other Hamilton receptor–cyanuric acid complexes.[3,4]

Based on these calculations, the distribution of the various species **5**·L_1–**5**·L_6 (L = **7–9**) was determined with HypNMR. It shows that the **5**·L_6 prevails over the other species after the saturation is reached. After the addition of six equivalents of end cap, the amount of the **5**·L_6 complexes ranges between 98.4% for **8** and 99.9% for **6**.

As our final aim was to achieve a complete self-assembly of the multifunctional binding sites, the formation of supramolecular dendrimers **6** in a one-pot reaction was investigated (Scheme 3). For this purpose $RuCl_3{\cdot}xH_2O$, three equivalents of the AB_2 **1**, and 6 equivalents of the end cap **7** were refluxed in a one-pot procedure, yielding a vitreous, dark red solid after removal of the solvent. The formation of a $Ru(bpy)_3$ architecture was clearly demonstrated by the orange-red color of the solution and the characteristic absorption profile in the UV/Vis spectra. On the other hand the ^{1}H-NMR spectrum of **6a** is identical with the spectrum obtained after a stepwise procedure, namely the treatment of the metallodendrimer **5** with a six-fold excess of end cap **7**.

These findings attest the complexation of the ruthenium core by the bpy functionalities of the building block as well as hydrogen-bonding of latter to the end caps *via* the Hamilton receptor moiety and therefore prove the formation of the desired architecture in one single step.

In conclusion, we have introduced a new concept for the self-assembly of supramolecular dendrimers involving orthogonal Hamilton receptor–cyanuric acid and $Ru(bpy)_3$ metal–ligand binding motifs. Both a successive divergent reaction sequence as well as a one-pot reaction can be applied for the synthesis of such supramolecular dendrimers. Further extension of this concept by introducing three or more orthogonal binding motifs will allow for the facile construction of a supramolecular architecture with even higher complexity and hierarchical order. Work along these lines is currently under way in our laboratory.

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