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Crowned Dendrimers: pH-Responsive Pseudorotaxane Formation

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With the end goal of incorporating the unique structural and physical properties of dendrimers into supramolecular assemblies, bis(*m*-phenylene)-32-crown-10-functionalized poly(propyleneimine) dendrimers of the first and third generations have been synthesized and their interaction with paraquat diol has been investigated. Using ^{1}H NMR, we determined that binding to the 4 or 16 crown ether sites occurred in an anti-cooperative fashion, most likely a result of steric influences. Upon protonation of the tertiary amines in the dendritic interior, binding became independent, i.e., statistical, and the average apparent association constant increased by nearly 5-fold; this effect is attributed to rigidification of the dendrimer, which makes its binding sites more accessible and less crowded.

Introduction

Among the many great contemporary areas of interest, dendritic and supramolecular chemistries have proven particularly appealing to the materials scientist. Whereas the ideal dendrimer is controlled synthetically as a monodisperse macromolecule with regularly branched three-dimensional architecture,[1] the ideal supramolecular entity is controlled at the molecular level via thermodynamic equilibrium considerations.[2]

Recent efforts in the dendritic arena have focused on the dendrimer's unique topology, which combines a high local density of active groups with a discrete number of functional groups.[1,3] Additional novel architectures such as rotaxanes and catenanes[4] have evolved independently, beginning with Frisch and Wasserman's preparation of physically interlocked rings over 40 years ago.[5] Of interest is the use of rotaxanes as templates in the construction of novel recognition motifs, particularly for the formation of supramolecular dendritic arrays assembled via crown ether cores.[6] Although such host−guest systems based on dendrimers abound in the literature,[7] few utilize recognition motifs at the periphery of the dendritic molecule.[8]

We here report on the preparation of pseudorotaxane[9] functionalized dendrimers,[10] fashioned from first and third generation poly(propyleneimine) (PPI) dendrimers[1c] end-capped with bis(*m*-phenylene)-32-crown-10

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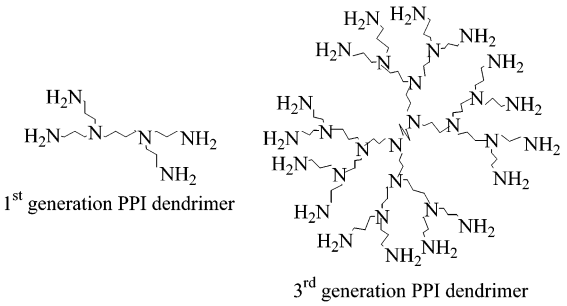
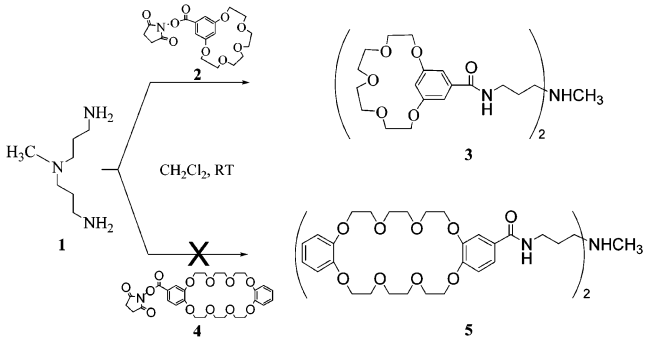
(BMP32C10) host macrocycles and *N*,*N*′-bis(*β*-hydroxyethyl)-4,4′-bipyridinium bis(hexafluorophosphate) (paraquat diol).



Results and Discussion

Synthesis of BMP32C10-Functionalized Dendrimers. Because the reaction between primary amines and succinimide esters is reportedly quantitative, even under mild conditions,[11] we employed this method in a model surface functionalization by coupling the primary amine end groups of *N*-methyl-*N*,*N*-bis(3-aminopropyl)amine (**1**) with the succinimide ester (**2**) of 1,3-phenylene-16-crown-5 to yield *N*-methyl-*N*,*N*-bis[*N*′-(5-carboxy-1,3-phenylene-16-crown-5)propylamino]amine (**3**, Scheme 1)

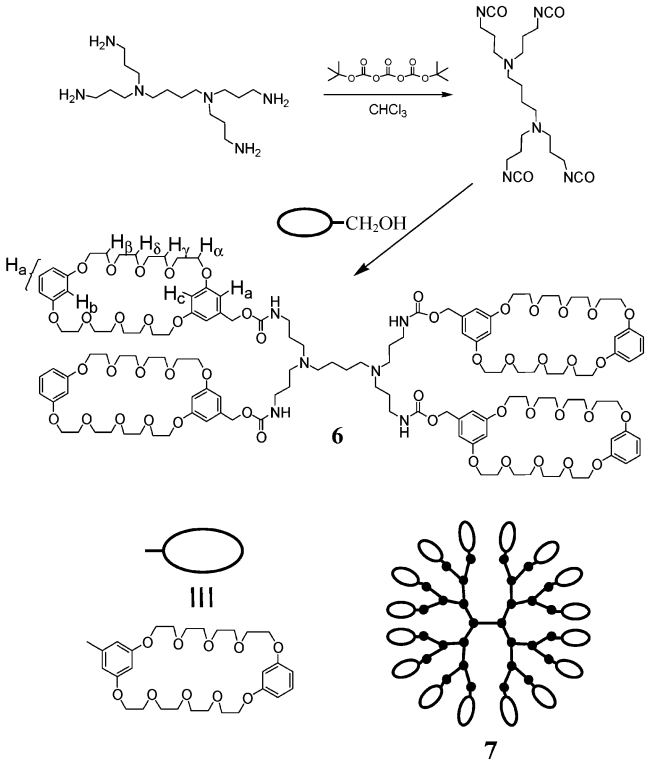
SCHEME 1. Preparation of Model Compounds for Formation of Crowned Dendrimers



with 100% conversion. Encouraged by these results, identical reactions were successfully conducted using the first, third, and fifth generation PPI dendrimers.

To integrate such receptor-functionalized dendrimers into pseudorotaxane arrays, the larger succinimide ester (**4**) of dibenzo-24-crown-8 was reacted with **1** under identical conditions (Scheme 1); however, analysis showed incomplete conversion to *N*-methyl-*N*,*N*-bis[*N*′-(2-carboxydibenzo-24-crown-8)propylamino]amine (**5**). The functionalization of the first generation PPI dendrimer with **4** was also attempted, again resulting in incomplete conversion of the endgroups.

SCHEME 2. Synthesis of Crowned PPI Dendrimers 6 and 7



We therefore converted the primary amine end groups of the dendrimers into isocyanates,[12] followed by in situ coupling to 5-hydroxymethyl-1,3-phenylene-1,3-phenylene-32-crown-10[13] (Scheme 2), yielding "crowned" PPI dendrimers **6** and **7**, in excellent yields.

Complexation of Neutral BMP32C10-Functionalized Dendrimers with Paraquat Diol. The BMP32C10-functionalized dendrimers were designed to be polyfunctional hosts for paraquat derivatives, as depicted in Scheme 3, leading sequentially to [2]-, [3]-, etc. pseudorotaxanes. A priori the relative values of the binding constants *K* for the sequential steps can (a) decrease statistically, (b) decrease more strongly than statistically predicted in an anti-cooperative manner or (c) decrease less than statistically predicted (or even increase) in a cooperative manner.[14]

Titration was employed to study the binding behavior of **6** and **7** with paraquat diol (**8**-2PF_6) using ^{1}H NMR spectroscopy in acetone-d_6 at 21.8 °C and a constant crown end group concentration of 3.0 mM. Upon mixing the host and guest components, a bright orange-colored solution resulted, indicating rapid complex formation via

(9) While we acknowledge the possibility that such a complex may adopt a folded or "taco" structure in solution [(a) Bryant, W. S.; Guzei, I. A.; Rheingold, A. L.; Gibson, H. W. *Org. Lett.* **1999**, *1*, 47−50. (b) Jones, J. W.; Zakharov, L. N.; Rheingold, A. L.; Gibson, H. W. *J. Am. Chem. Soc.* **2002**, *124*, 13378−13379], we choose to refer to the BMP32C10/paraquat complex as a pseudorotaxane, which must exist in light of the fact that catenanes have been prepared using this motif [Amabilino, D. B.; Anelli, P.-L.; Ashton, P. R.; Brown, G. R.; Cordova, E.; Godinez, L. A.; Hayes, W.; Kaifer, A. E.; Philp, D.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Tolley, M. S.; Williams, D. J. *J. Am. Chem. Soc.* **1995**, *117*, 11142−11170].

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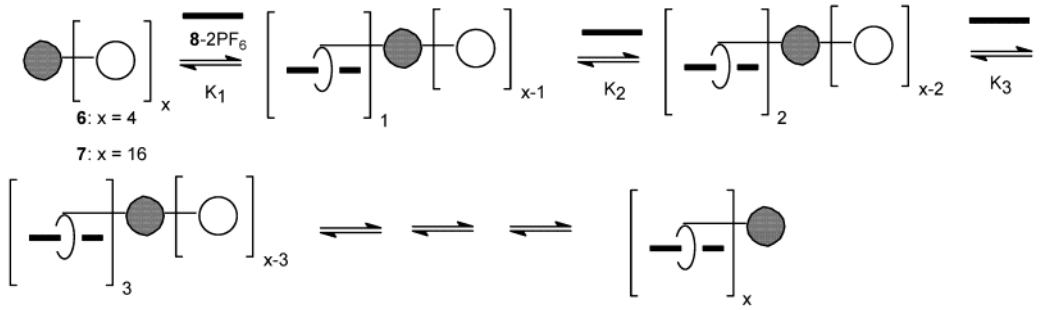
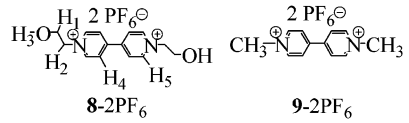
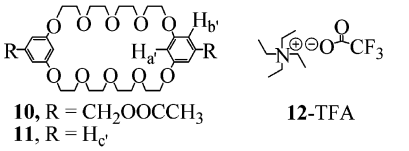
SCHEME 3. Representation of the Complexation of Monotopic Paraquat Diol (8-2PF$_6$) by Complementary Polytopic Dendrimers 6 and 7, Showing the Sequential Formation of [2]-, [3]-, [4]-, etc. Pseudorotaxanes with Association Constants K_1, K_2, K_3, etc.



hydrogen bonding and π-stacking interactions of host and guest.[15] Indeed, the time-averaged signals of H_a and H_b of the crown ether moiety were shifted upfield relative to those of pure **6** or **7** upon complexation with **8**-2PF$_6$. MALDI-TOF MS of the first generation dendrimer in the presence of 4 equiv of paraquat dihexafluorophosphate (**9**-2PF$_6$) also confirmed complex formation, showing a peak at *m*/*z* 3492 attributable to the [3]pseudorotaxane $\{[\mathbf{6}\cdot(\mathbf{9}\text{-}2PF_6)_2 - PF_6]^+\}$.





To analyze the chemical shift data, Δ_0, the difference in δ values for the aromatic protons of the uncomplexed and fully complexed crown ether, was assumed to be equivalent to that for the model system of bis(5-acetoxy-1,3-phenylene)-32-crown-10 (**10**) and **8**-2PF$_6$.[16] The fraction of total binding sites occupied, θ, and the equilibrium guest concentration, [**8**-2PF$_6$]$_{uc}$, were then estimated. Scatchard plots (Figure 1) are nonlinear for both the first (**6**) and third (**7**) generation crowned dendrimers, indicating that the binding is dependent upon neighboring occupied host moieties;[14] the concave slopes indicate anti-cooperative binding. Consequently, the data were interpreted using the Hill equation.[14c]

For both generations the Hill coefficient (i.e., the slope) is less than unity (Figure 2), indicating that binding is anti-cooperative: from the intercepts we determine $K_{AVE} = 23 \pm 3$ M^{-1} for **6** and $K_{AVE} = 15 \pm 2$ M^{-1} for **7**, values which are substantially lower than apparent K_a $= 61 \pm 5$ M^{-1} for the model system **11**/**8**-2PF$_6$ under these conditions. In addition, as can be seen from Figure 2, binding of **8**-2PF$_6$ is facilitated in **6** relative to **7**. This finding is not unexpected: theoretical calculations[18] as well as small-angle neutron-scattering studies[19] indicate that the importance of backfolding in PPI dendrimers increases with generation; intramolecular H-bonding of the CON-H moieties to the amine moieties may also be a factor. Furthermore, electrostatic repulsions among neighboring guest ions at the periphery of the larger

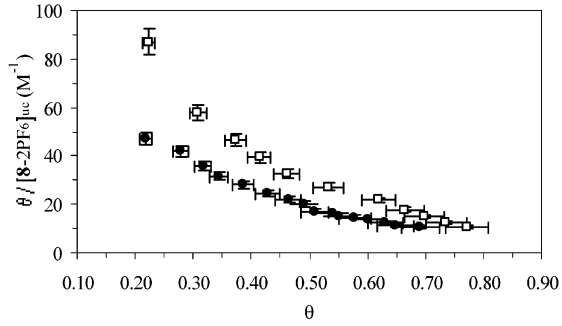


FIGURE 1. Scatchard plots for the binding of **6** (□) and **7** (●) with **8**-2PF$_6$ in acetone-d_6 at 21.8 °C and a constant crown end group concentration of 3.0 mM, based on H_a.[17]

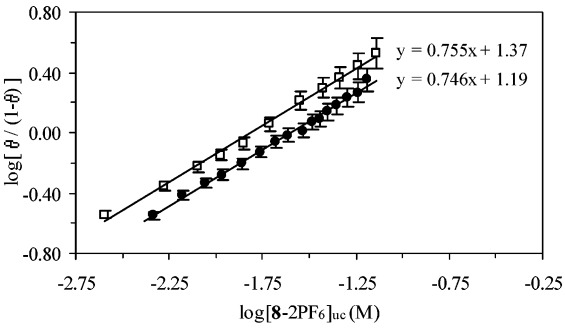


FIGURE 2. Hill plots for the binding of **6** (□) and **7** (●) with **8**-2PF$_6$ in acetone-d_6 at 21.8 °C, based on H_a.[17]

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(17) To determine error bars, we assumed an inaccuracy of ±5.0% in Δ_0 and calculated high and low values for θ, [**8**-2PF$_6$]$_{uc}$, and θ/[**8**-2PF]$_{uc}$ about this range.

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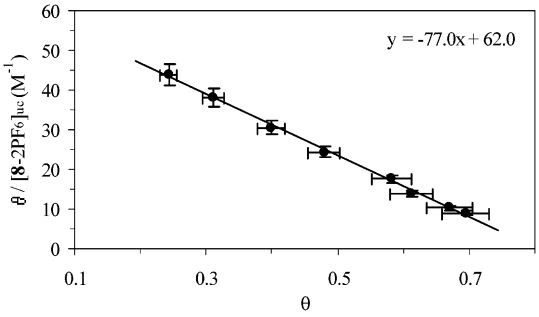

FIGURE 3. Scatchard plot for the binding of protonated **7**-H^+ with **8**-$2PF_6$ in acetone-d_6 at 21.8 °C, based on H_a, [TFA^-] = 2.62 mM (0.875 equiv relative to BMP32C10 moieties).[17]

crown ether functionalized dendrimer **7** may result in less efficient binding than for dendrimer **6**.

Complexation of Protonated BMP32C10-Functionalized Dendrimers with Paraquat Diol. The influence of folding on the nature of host/guest interaction was tested by protonation of the tertiary amines of the dendritic framework via addition of an equivalent amount of trifluoroacetic acid. A Scatchard plot for **7**-H^+/**8** (Figure 3, [end group] = 3.0 mM) is linear, indicating independence of binding sites; the slope and intercept yield an average apparent association constant of 70 ± 8 M^{-1}, which represents a 4.7-fold increase in K_{AVE} upon protonation. This value is within experimental error of apparent K_a = 61 ± 5 M^{-1} for the model system **11**/**8**-$2PF_6$ under identical conditions.

Effect of Trifluoroacetate Ions on a Model Complexation. To determine the impact of trifluoroacetate counteranions on the complexation, a model system consisting of BMP32C10 (**11**) complexed with **8**-$2PF_6$ was titrated with tetraethylammonium trifluoroacetate (**12**-TFA).[20] As we have previously observed in other systems,[9b] the addition of the trifluoroacetate salt hinders association of **11** with **8**: the upfield shifted host aromatic protons observed upon complexation of **11** with **8**-$2PF_6$ shift downfield upon addition of **12**-TFA (see Figure 4b vs 4c,d). Furthermore, the H_1−H_5 signals of **8** significantly broaden with increasing [**12**-TFA]. Again using Δ_0 from our model system,[16] we determine apparent K_a = 35 ± 5 M^{-1} when 3.75 equiv of **12**-TFA are present, a 43% reduction from **11**/**8**-$2PF_6$. Such a reduction in binding strength may be accounted for through counteranion exchange between the weakly paired PF_6 salt and the more tightly paired TFA salt.[21]

Conclusions

There exists an obvious "switch" in binding between unprotonated and protonated host macromolecules from an anti-cooperative regime to an independent one, despite the negative influence of added trifluoroacetate anion. Such a "switch" may be explained by rigidification of the protonated dendrimer in which the macromolecule is electrostatically forced to adopt a conformation that maximizes host binding site separation.[22] Coupled with

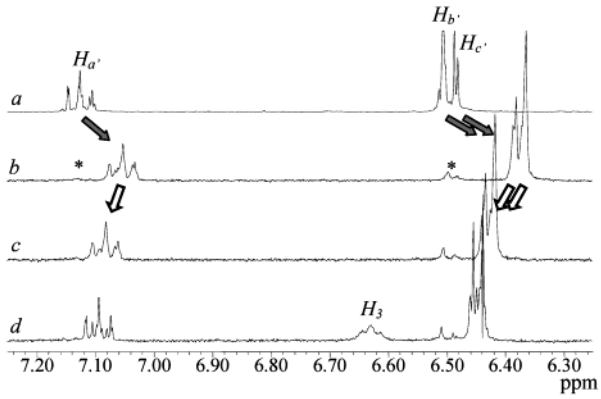

FIGURE 4. ^1H NMR spectra (400 MHz, acetone-d_6, 22.6 °C) of (a) **11**; (b) 3.05 mM **11** + 2.95 mM **8**-$2PF_6$; (c) 2.03 mM **11** + 1.97 mM **8**-$2PF_6$ + 2.50 mM **12**-TFA; (d) 2.03 mM **11** + 1.97 mM **8**-$2PF_6$ + 7.50 mM **12**-TFA. The asterisk denotes an impurity in **11** that is not involved in pseudorotaxane formation and is believed to be tetra(*m*-phenylene)-64-crown-20, a predicted byproduct of the cyclization reaction.

our recent report[6d] on cooperative[23] binding of positively charged tritopic guest core molecules with hydrophobic host dendrons, the above work foreshadows systems in which the binding can be made to be highly cooperative and thus mimic the foundation of DNA chemistry, wherein conformational changes brought about through an initial binding interaction, i.e., allosteric effects,[24] can serve to enhance or detract from the binding affinity of subsequent sites.[25]

Experimental Section

Unless otherwise noted, the starting PPI dendrimers,[1c] crown ether macrocycles,[13] and paraquat derivatives **8**[26] and **9**[15a] were prepared according to published procedures. All other reagents were purchased from commercial suppliers and used without further purification. ^1H NMR spectra were recorded on 300- or 400-MHz NMR spectrometers with the solvent proton signal as the reference and were collected immediately upon mixing the salt and crown solutions. To observe complex formation, a known volume of a specified concentration of crown macrocycle was added to an NMR tube. To these host solutions, measured volumes of a concentrated solution of salt were added and the tube was shaken vigorously for 30 s before data collection.

***N*-(5-Carboxy-1,3-phenylene-16-crown-5)succinimide (2).** 5-Carboxy-1,3-phenylene-16-crown-5[27] (2.087 g, 6.68 mmol)

(20) The addition of tetraethylammonium trifluoroacetate to BMP32C10 (**11**) had no influence on the ^1H NMR chemical shifts of **11**. Thus, tetraethylammonium ion does not bind to **11**.

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and *N*-hydroxysuccinimide (0.792 g, 6.88 mmol) were dissolved in 30 mL of glyme. Dicyclohexylcarbodiimide (1.516 g, 7.35 mmol) was added, and the solution stirred for 24 h at 0 °C. The resultant white precipitate was filtered under vacuum, washed with $CHCl_3$, and dried to yield an off-white oil. The oil was dissolved in hot isopropyl alcohol, and upon cooling a white powder was obtained, which was twice recrystallized from isopropyl alcohol. Yield: 2.36 g (86.2%). Mp = 112.0−115.3 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, ambient T) δ (ppm): 7.43 (1H, m); 7.29 (2H, d, J = 1.2 Hz); 4.33 (4H, m); 3.80 (4H, m); 3.62 (8H, m); 2.90 (4H, s). ^{13}C NMR (DMSO-d_6, 100 MHz, ambient T) δ (ppm): 170.7, 160.8, 126.1, 110.8, 110.6, 70.5, 70.3, 70.1, 68.8, 26.0 (10 peaks of 11 expected). Anal. Calcd: C 55.68, H 5.78; Found: C 55.74, H 5.66.

***N*-Methyl-*N*,*N*-bis[*N*′-(5-carboxy-1,3-phenylene-16-crown-5)propylamino]amine (3).** A solution of *N*-methyl-*N*,*N*-bis(3-aminopropyl)amine (**1**, 19.0 mg, 0.133 mmol) and **2** (110 mg, 0.0268 mmol) in CH_2Cl_2 (ca. 4−5 mL) was stirred at room temperature for 24 h, whereupon ∼4 mL of 1 M NaOH was added and the mixture stirred for 1 h. The organic layer was washed with a concentrated sodium bicarbonate solution followed by deionized H_2O and concentrated by rotoevaporation to give an oil. Yield: 105 mg (∼ 100%). ^{1}H NMR ($CDCl_3$, 300 MHz, ambient T) δ (ppm): 7.39 (2H, t, J = 4.2 Hz), 7.20 (2H, d, J = 2.1 Hz), 6.92 (4H, s), 4.29 (8H, t, J = 4.8 Hz), 3.76 (8H, t, J = 4.8 Hz), 3.60 (16H, m), 3.49 (4H, m), 2.50 (4H, t, J = 6.3 Hz), 2.27 (3H, s), 1.78 (4H, t, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, ambient T) δ (ppm): 167.6, 160.8, 137.1, 109.2, 107.4, 71.3, 71.2, 70.9, 69.4, 57.4, 42.4, 40.0, 27.0 (13 peaks as required). EI-MS (acetone): m/z 734.5 (**3** + H^+) (calcd m/z 734.4), m/z 1468.0 {2 × [**3** + H^+]}(calcd m/z 1468.8).

***N*-(2-Carboxydibenzo-24-crown-8)succinimide (4).** 2-Carboxydibenzo-24-crown-8[6b] (1.34 g, 2.73 mmol) and *N*-hydroxysuccinimide (0.323 g, 2.81 mmol) were dissolved in 50 mL of glyme. To this stirring solution was added dicyclohexylcarbodiimide (0.620 g, 3.00 mmol) at 0 °C, resulting in incomplete dissolution of the reactant species. The mixture was stirred for 48 h, whereupon the precipitate was filtered under vacuum and washed with $CHCl_3$. The filtrate was dried to yield an oil, which was dissolved in hot isopropyl alcohol. Upon cooling, a white powder was obtained and purified by column chromatography (SiO_2, 1. EtOH, 2. MeOH); **4** was recrystallized from isopropyl alcohol. Yield: 0.631 g, (39.2%). Mp = 81−90 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, ambient temp) δ (ppm): 7.71 (1H, d, J = 8.8 Hz); 7.48 (1H, s); 7.71 (1H, d, J = 8.8 Hz), 6.89 (4H, m); 4.21 (4H, m); 4.15 (4H, m); 4.05 (8H, m); 3.77 (16H, m); 3.66 (16H, m); 2.87 (4H, s). ^{13}C NMR (DMSO-d_6, 100 MHz, ambient temp) δ (ppm): 170.4, 161.3, 157.8, 154.3, 148.4, 148.3, 148.2, 124.8, 121.1, 116.2, 114.0, 113.9, 113.8, 112.8, 70.55, 70.47, 70.40, 69.2, 69.13, 69.0, 68.9, 68.74, 68.69, 68.66, 25.5. Anal. Calcd: C 59.11, H 6.08. Found: C 59.08, H 5.98.

***m*-Phenylene-16-crown-5 Functionalized Dendrimers.** *m*-Phenylene-16-crown-5 (MP16C5) functionalized PPI dendrimers were prepared using the same procedure described above for the synthesis of **3**. **DAB-*dend*-(CO-MP16C5)$_4$.**[28] Yield: 117 mg (∼100%). ^{1}H NMR ($CDCl_3$, 300 MHz, ambient temp) δ (ppm): 7.31 (4H, m), 7.19 (4H, t, J = 2.1 Hz), 6.92 (8H, d, J = 3.0 Hz), 4.26 (16H, t, J = 4.8 Hz), 3.74 (16H, t, J = 4.8 Hz), 3.58 (32H, m), 3.45 (8H, m), 2.48 (8H, m), 2.39 (4H, br s), 1.71 (8H, t, J = 6.9 Hz), 1.40 (4H, br s). ^{13}C NMR ($CDCl_3$, 75 MHz, ambient temp) δ (ppm): 167.1, 160.3, 136.4, 108.7, 106.9, 70.7, 70.6, 70.3, 68.8, 53.9, 52.6, 39.3, 26.7, 24.8 (14 peaks as required). **DAB-*dend*-(CO-MP16C5)$_{16}$.** Yield: 108 mg (∼100%). ^{1}H NMR ($CDCl_3$, 300 MHz, ambient temp) δ (ppm): 7.78 (16H, br s), 7.17 (16H, s), 7.03 (32H, s), 4.22 (64H, br s), 3.58 (224H, m), 2.38 (84H, m), 1.55 (60H, m). ^{13}C NMR ($CDCl_3$, 75 MHz, ambient temp) δ (ppm): 167.2, 160.2, 136.3, 108.9, 107.1, 70.7, 70.6, 70.2, 68.8, 52.1, 39.1, 30.9, 26.8, 24.5. **DAB-*dend*-(CO-MP16C5)$_{64}$.** Yield: 86.5 mg (84.2%). ^{1}H NMR ($CDCl_3$, 300 MHz, ambient temp) δ (ppm): 8.11 (64H, br s), 7.12 (64H, s), 7.06 (128H, s), 4.15 (256H, br s), 3.55 (896H, m), 2.39 (376H, br s), 1.60 (252H, br s). ^{13}C NMR ($CDCl_3$, 75 MHz, ambient temp) δ (ppm): 167.3, 160.2, 136.2, 109.1, 70.6, 70.2, 68.8, 54.3, 52.5, 40.6, 31.3, 25.4.

Bis(*m*-phenylene)-32-crown-10 Functionalized Dendrimers (6 and 7). BMP32C10-functionalized PPI dendrimers were prepared as described in the following typical procedure. The polyamine (114 mg) in $CHCl_3$ (5 mL) was injected into a stirred $CHCl_3$ solution (15 mL) of di-*tert*-butyltricarbonate (959 mg) and stirred at room temperature for 15 min under Ar. Formation of isocyanates was checked with IR spectroscopy (ν = 2265 cm^{-1}). Hydroxymethyl BMP32C10[13] (1.00 g) and zirconium(IV) acetylacetonate (0.1 mol %) were added; after 16 h the reaction mixture was precipitated in ice-cold heptane (250 mL). After size exclusion chromatography (Bio-Beads SX-1 column, CH_2Cl_2) and solvent removal in vacuo, yellowish highly viscous oils **6** and **7** were obtained and characterized as described below.

DAB-*dend*-(CO$_2$CH$_2$BMP32C10)$_4$ (6). Yield: 860 mg (93%). ^{1}H NMR ($CDCl_3$, 400 MHz, ambient temp) δ (ppm): 1.38 (4H, br s), 1.60 (8H, br s), 2.34 (4H, br s), 2.40 (8H, br s), 3.18 (8H, q, J = 6 Hz), 3.68 (64H, s), 3.81 (32H, quint, J = 5 Hz), 4.04 (32 H, quint, J = 5 Hz), 4.96 (8H, s), 5.68 (4H, br s), 6.40 (4H, s), 6.47 (20H, m), 7.11 (4H, t, J = 8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, ambient temp) δ (ppm): 25.1, 27.4, 40.3, 52.3, 53.8, 54.1, 66.5, 67.8, 69.9, 71.1, 101.1, 101.9, 106.8, 107.3, 129.9, 139.1, 156.5, 160.0. IR: ν_{max} 3339 (w.br), 2926 (m), 2871 (m), 1713 (s), 1594 (s), 1494 (s), 1125 (s), 1067 (s) cm^{-1}. MALDI-TOF MS m/z 2709 [M + Na]$^+$.

DAB-*dend*-(CO$_2$CH$_2$BMP32C10)$_{16}$ (7). Yield: 362 mg (83%). ^{1}H NMR ($CDCl_3$, 400 MHz, ambient temp) δ (ppm) 1.36 (4H, br s), 1.44−1.64 (56H, br s), 2.28−2.44 (84H, br s), 3.10−3.18 (32H, br s), 3.60−3.64 (128H, br s), 3.72−3.80 (128H, br s), 3.96−4.06 (128 H br s), 4.92 (32H, s), 5.76−5.90 (16H, br s), 6.37 (H, br s), 6.40−6.48 (112H, m, br s), 7.09 (16H, t, J = 8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, ambient temp) δ (ppm) 24.2, 27.3, 39.8, 51.7, 52.2, 66.2, 67.6, 69.7, 70.8, 100.9, 101.8, 106.7, 107.2, 129.9, 139.1, 156.6, 160.0. IR: ν_{max} 3339 (w.br), 2926 (m), 2870 (m), 1711 (s), 1594 (s), 1449 (s), 1125 (s), 1067 (s) cm^{-1}. MALDI-TOF MS m/z 11167 [M + H]$^+$.

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(28) Our crowned PPI dendrimers have been named according to convention (see ref 1c): the label DAB-*dend*-(X)$_y$ denotes a dendritic structure bearing a diaminobutane core surrounded by *y* endgroups of type X functionality. For example, DAB-*dend*-(CO$_2$CH$_2$BMP32C10)$_4$ represents molecule **6**, wherein a diaminobutane cored dendrimer has been functionalized at the periphery with four BMP32C10 macrocycles, which have been coupled to the PPI terminal groups by means of a CO_2CH_2 linker.