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Cross-Linked Hyperbranched Polyglycerols as Hosts for Selective Binding of Guest Molecules

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Abstract: The ring-closing metathesis reaction of dendrimers containing allyl ether end groups is known to rigidify them significantly. Herein we report that polyallylated hyperbranched polyglycerol (HPG) **1** complexes the sodium salt of rose Bengal in chloroform solution but releases it readily to water. In contrast, extensively cross-linking **1** with Grubbs catalyst provides **2** which similarly complexes rose Bengal, but does not release it despite 12 h of shaking with water. Both **1** and **2** also complex thymol blue and exhibit the same differential complex stability when extracted with water. Neither **1** nor **2** complex Congo red sodium salt and more weakly solubilize the cesium salt of rose Bengal and thymol blue. Larger loop size cross-linked analogs HPG **5** and **6** also bind rose Bengal (RB) and thymol blue and are able to bind Congo red, but both release the dye more readily when extracted with water. In addition, a bathochromic shift is observed in the UV spectra for complex **6**·RB, suggesting a changed microenvironment for the dye due to a tighter binding of the counteranion. Dihydroxylation of the alkene groups in **1**, **2**, **5**, and **6** produced HPGs **3**, **4**, **7**, and **8**, respectively. HPGs **3** and **4** are both water-soluble, but **7** and **8** were not and could not be studied further. In water, HPG **4** solubilized less than one nonpolar guest (Nimodipine, pyrene, or Nile red) per polymer at least in part because it forms very large aggregates. Dynamic light scattering (DLS) and size exclusion chromatography (SEC) indicate aggregates with diameters of ca. 100 nm in pure water. The aggregates dissociated in high salt concentrations suggesting applications in stimuli responsive materials.

Introduction

One of the key reasons dendritic polymers have found widespread use in science, medicine, and engineering is the possibility to readily modify their many peripheral groups. In this manner, their properties can be tuned or altered and more sophisticated functional architectures created.[1−5] An early analysis of the structure of dendritic polymers indicated the possibility of entrapping small molecules within a dense shell of peripheral groups.[6] Indeed, since their discovery, dendrimers have found numerous applications in host−guest chemistry.[7−9]

Amphiphilic dendrimers with hydrophobic interiors can function as unimolecular micelles and complex nonpolar guest molecules through a thermodynamically favored process.[10] Kinetic or mechanical entrapment has also been demonstrated by Meijer's dendritic box.[11] In this example, rose Bengal was trapped within a poly(propyleneimine) dendrimer with 64 peripheral amino groups by treatment with the activated ester of Boc-protected phenylalanine. The peripheral phenyl-alanine amide groups tightly pack creating a solid shell that imprisons the dye molecules. An alternative to this strategy would be to harden the shell of the dendrimer by intramolecular cross-linking prior to encapsulation. We recently demonstrated that the homoallyl and allyl ether end-groups of Fréchet-type dendrimers could be extensively cross-linked using the ring-closing me-

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tathesis (RCM) reaction[12] and this provided a means for creating rigidified organic nanoparticles,[13] including those with imprinted binding sites on their interiors.[14] An attractive feature of polyglycerol dendrimers is their lack of chromophores (UV−visible transparency), inherent water solubility, and ease of synthesis.[15] Additionally, analogous hyperbranched polymers can be made on a kilogram scale by the polymerization of glycidol.[16] We recently showed that both types of macromolecules could be allylated and cross-linked using a slightly modified RCM procedure.[17] The cross-linking process provides a unique architecture with a rigid shell which, upon full hydrogenation of the alkene groups (H_2, PtO_2), displays crown-type binding of picrate ions in organic phases.

Herein we report studies designed to probe whether cross-linked hyperbranched polyglycerols could serve as effective hosts for organic dyes. Particular attention is paid to the role played by rigidification of the peripheral shell and how different loop sizes affect the selective guest encapsulation. The results indicate that the RCM-mediated cross-linking increases the stability of the complexes, with the guest uptake dependent on both the loop size and the dye counterion. Finally, physical studies on these dendritic nanocarriers indicate that after dihydroxylation they form stable supramolecular aggregates that breakdown upon treatment with saturated salt solutions.

Results and Discussion

The surface hydroxyl groups of 5 kDa hyperbranched polyglycerol (HPG)[16a,18] were quantitatively etherified with allyl chloride using the previously reported phase-transfer procedure.[15a] The resultant polymer **1** was further converted into the closed-shell architecture **2** via ring-closing metathesis reaction (RCM) as described previously.[17] Finally, the organic soluble HPG were treated with osmium tetroxide to fully dihydroxylate the alkene groups producing water-soluble macromolecules **3** and **4** (Figure 1).

The ability of rigidified **2** and its open-shell precursor **1** to bind small molecules was determined by measuring their ability to extract solid hydrophilic ionic dyes into chloroform solution. Dyes of different sizes and counterions were examined to determine the effect of both on the extraction selectivity. Thus,

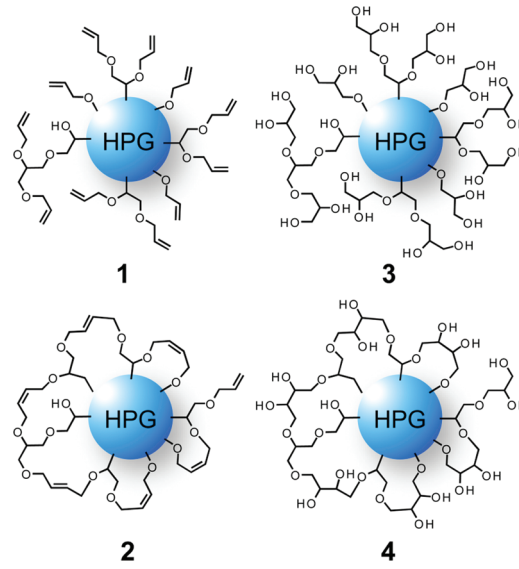

Figure 1. Schematic representation of allylated (**1**), RCM cross-linked (**2**), dihydroxylated (**3**), and RCM cross-linked and dihydroxylated (**4**) hyperbranched polyglycerols (HPG).

0.1 mM chloroform solutions of polymers **1** and **2** were stirred for 12 h with the sodium and cesium salts of rose Bengal and thymol blue and the sodium salt of Congo red. The resultant suspensions were filtered through a micro filter and the uptake of the dyes was calculated from the UV−visible absorption spectra in chloroform solution, as described in the experimental section. As shown in Table 1, polymers **1** and **2** exhibited similar loading capacities. The dye to polymer loading ratio for rose Bengal sodium salt and thymol blue sodium salt was found to be ca. 3.5:1 so that on average 3 or 4 dyes are bound to each polymer. The encapsulation of the cesium salt of these two dyes was significantly lower. Congo red was not effectively solubilized by either **1** or **2**.

To further investigate the host−guest stability, the polymer−dye solutions were extracted for five minutes with water. After phase separation the UV absorption of the organic phase was measured again (Figure 2 and Table 1). Now a clear difference between **1** and **2** was observed. Whereas the hydrophilic rose Bengal and thymol blue sodium salt transferred to the water layer from its organic soluble complex with **1**, the dye complex with **2** was sufficiently stable that the dye remained in the chloroform layer. Indeed, the cross-linked host **2** did not liberate the dye even after 12 h of shaking with water and the use of sonication. In contrast, the cesium salt of rose Bengal, fully transferred to the water layer.

These simple extraction experiments indicate that the cross-linked HPG **2** is more effective at encapsulating dye salts than the corresponding open-shell HPG **1** and that the complexation depends both on the dye structure and the counterion. One possibility for the poor binding of Congo red is its comparatively larger size making it more difficult to encapsulate in the rigidified, cross-linked shell of **2**. Thus, as seen in Figure 3, the longest dimension of Congo red is over twice that of the more compact rose Bengal and thymol blue.

To test the relationship between the cross-linking loop size, which in turn controls both the rigidity and cavity size, new polymers were synthesized using undec-10-enoyl chloride and

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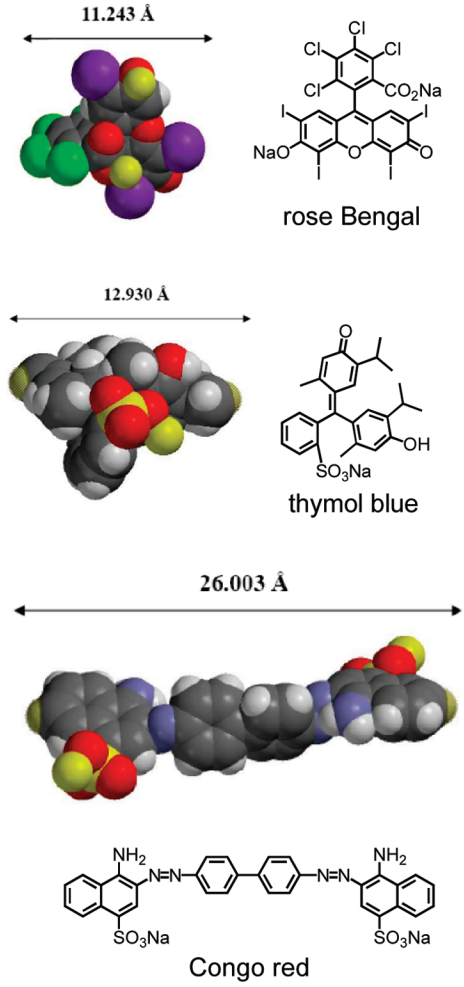
Table 1. Number of Dye Molecules Encapsulated Per One Polymer Molecule As Determined by UV−Vis Spectroscopy for Polymers **1**, **2** before and after Extraction with Water[a]

	chloroform after solid−liquid extraction		chloroform phase after extraction with water			
guest molecule	**1**	**2**	**1**	**2**	K_D (**1**)	K_D (**2**)
rose Bengal sodium salt	3.6	3.2	0.2	3.0	0.059	15
rose Bengal cesium salt	0.7	1.2	bdl	0.15	–	0.143
thymol blue sodium salt	3.5	3.0	0.3	3.0	0.094	>1000
thymol blue cesium salt	0.5	0.8	bdl	bdl	–	–
Congo red sodium salt	bdl	bdl	bdl	bdl	–	–

[a] Distribution constant ($K_D = [Dye]_{org}/[Dye]_{aq}$) for partitioning of dye between water and chloroform. Bdl is below detection limit.

5 kDa HPG (Figure 3). The esterification[19] was performed in DMF with triethylamine and produced **5** with a 79% yield and >98% conversion as determined by ^{1}H NMR analysis.



The ring-closing metathesis was effected with second generation Grubbs catalyst, but considerable effort was required to maximize the extent of cross-linking. As seen in Table 2, a minimum 8 mol % of catalyst loading per alkene unit was required to ensure a high conversion up to 80%. Not surprisingly the conversion rate was slower in comparison to the allyl analogue. Indeed, Astruc and co-workers showed in related systems that cross metathesis can be favored over the RCM process indicating that the competitive advantage of intramolecular cyclization is lost with the formation of large macrocycles.[20] As with the allylated HPG, **5** and **6** were dihydroxylated with osmium tetroxide to form **7** and **8**, respectively. Unfortunately, polymers **7** and **8** were not water soluble and were not studied further.

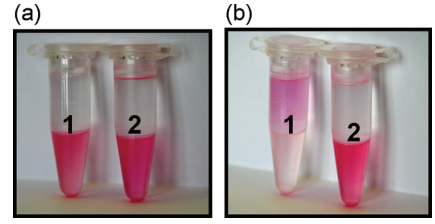


Figure 2. Photographs of encapsulated rose Bengal sodium salt in polymers **1** and **2** (a) before and (b) after 5 min extraction with water.

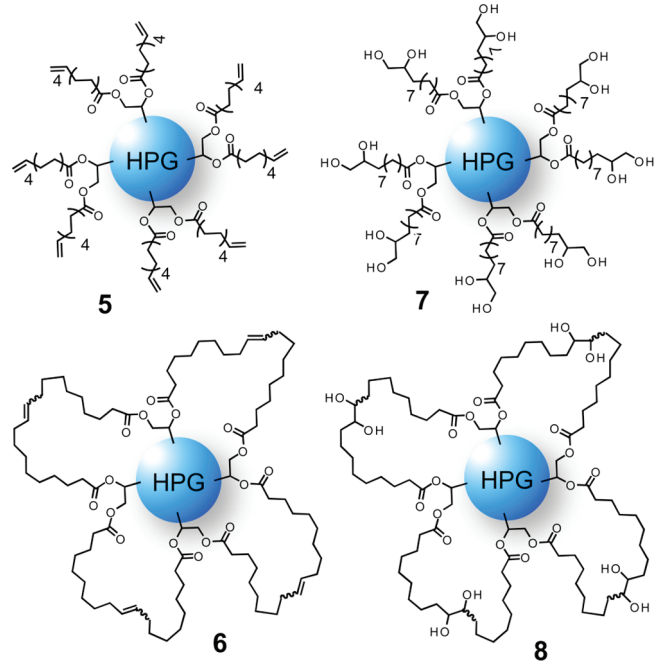


Figure 3. Structures and space filling models of the guest molecules. Schematic representation of polyester (**5**), RCM cross-linked (**6**), dihydroxylated (**7**), and RCM cross-linked and dihydroxylated (**8**) hyperbranched polyglycerols (HPG).

The binding abilities of cross-linked polymer **6** and its open-shell precursor **5** were assessed with the same solid−liquid extraction procedure used above. As seen in Table 3, the larger and more aliphatic HPG **5** and **6** were capable of extracting the sodium salts of rose Bengal and thymol blue and exhibited

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Table 2. Ring Closing Metathesis of **5** with Grubbs Second Generation Catalyst

time [h]	amount of cat.[a]	temp. [°C]	conversion [%][b]
7	4	rt	20
14	4	rt	45
24	4	40	45
24	8	rt	80
48	8	40	78

[a] All amounts of catalyst given as mol % relative to alkene units. [b] Conversion determined by ^{1}H NMR.

Table 3. Number of Dye Molecules Encapsulated Per One Polymer Molecule As Determined by UV−Vis Spectroscopy for Polymers **5**, **6** and Distribution Constant with Water[a]

	chloroform after solid−liquid extraction			
guest molecule	**5**	**6**	K_D (**5**)	K_D (**6**)
rose Bengal sodium salt	12	15	0.09	1.7
thymol blue sodium salt	19	17	0.12	1.5
Congo red sodium salt	0.5	1	−	−
5-aminofluorescein	bdl	0.1	−	−

[a] Distribution constant ($K_D = [Dye]_{org}/[Dye]_{aq}$) for partitioning of dye between water and chloroform. Bdl is below detection limit

significantly higher capacities. There was only a minor increase in particle size as exemplified for compound **6** upon dye loading (Figure 4). This strongly supports unimolecular transport of the dye molecules since no large aggregates were observed for these hydrophobic nanocarriers. Both HPG **5** and **6** also showed the ability to extract the Congo red dye, although only between a half and one equivalent per polymer **5** and **6**, respectively. The increased capacity did not correlate with higher complex stability as partitioning the chloroform layer with water led to a greater loss of the dye to the aqueous layer with the larger loop size polymer **6**, in comparison to the smaller loop size polymer **2**. The distribution constants are shown in Table 3.

The importance of the counterion was shown above when the sodium and cesium salts of the dyes exhibited quite different binding behavior. The ion effect is also demonstrated by the encapsulation of 5-aminofluorescein. Its size is comparable to that of rose Bengal and thymol blue, but it lacks the alkali metal cation. As seen in Table 3, the countercation is indeed required for efficient complexation. Thus, the encapsulation studies with 5-aminofluorescein showed very low affinity of the polymers, with minimal extraction observed for this dye.

Another difference between small and large loop sizes is seen in the UV−visible spectra. HPG **6** formed a complex with the sodium salt of rose Bengal (RB) in ethanol that produced a ca. 5 nm bathochromic shift in the dye ($\lambda_{max} = 562$, Figure 5b), whereas the dye spectra is unchanged in the presence of **2** (Figure 5a). The bathochromic shift for complex **6**·RB suggests a tighter complexation of the counterion that leads to a looser ion pair. The overall shift is small in comparison to that seen previously with cesium picrate.[17] The tighter complexation of the counterion is not accompanied by overall tighter binding indicating that the tight ion pair between the dye and countercation can be bound more tightly.

The fluorescence spectra of the sodium salt of rose Bengal in ethanol was examined at concentrations well below 10^{-4} M, where it is primarily monomeric. The spectra were taken with and without added HPG **2** and **6**. The emission spectra with and without **2** are essentially identical (Figure 5c). In the case of complex **6**·RB (Figure 5d) we observe again a significant shift in the λ_{em} but otherwise the spectra are minimally changed. These data suggest a large change in the microenvironment for the encapsulated dye in complex **6**·RB suggesting a tighter binding of the counteranion.

The ability to make the HPG water-soluble allowed comparative complexation studies of the open- and closed-shell **3** and **4**, respectively, to be extended to water. Because of the considerable interest in biocompatible polymers for drug solubilization and delivery, the effort was focused on the complexation of hydrophobic guest molecules. Thus, three apolar compounds were selected: the calcium channel blocker, Nimodipine, the fluorescent aromatic probe, pyrene, and the lipophilic stain, Nile red. The encapsulation results for polymers **3** and **4** in pure water (Table 4) indicated no uptake by HPG **3** and relatively poor uptake by **4**, with less than one guest per HPG host.

Although it is possible that the HPG have relatively polar interiors that may be partially hydrated, another explanation came from analyzing the size exclusion chromatography (SEC) and dynamic light scattering measurement (DLS) data. Thus, both techniques revealed that polymer **4** forms large aggregates with a diameter of approximately 100 nm in pure water. Thus, the rigidification created by the RCM cross-linking appears to lead to sections that are comparatively hydrophobic and prefer to aggregate. The net effect is to reduce the available surface area for encapsulation and to lower the binding capacity.

The ionophoric nature of the cross-linked HPG suggested that added salt might weaken the intermolecular contacts between molecules of polymer **4**. Indeed, as observed in the overlaid SEC chromatograms in Figure 6 the broad peak representing the large aggregate of polymer **4** disappears entirely when **4** is dissolved in 5 M NaCl solution. The resultant SEC chromatogram showed a decrease in the hydrodynamic volume with an elution time consistent with a single compound whose molecular weight is ca. 5 kDa.

The DLS measurements are consistent with the SEC data, indicating the presence of the particles in the range of around 100 nm in pure water (Figure 7), undergoing a breakdown to particles whose size is in the 1−2 nm range and consistent with fully contracted monomer. Although the addition of NaCl, in addition to breaking down the aggregates, could lead to a salting out effect that might increase binding, the ionophoric nature of the cross-linked HPG means that the guest must face additional competition. Polymer **4** was a somewhat more effective host when the encapsulation process was performed in saturated NaCl solution (Table 3) but the improvement is modest. For efficient, higher capacity encapsulation of apolar guests it appears that larger and well-defined hydrophobic loops will be necessary.

Conclusions

Cross-linked hyperbranched polyglycerols with different loop-sizes have been constructed applying a simple and efficient synthetic approach. The hosts are organic soluble before and after cross-linking, and can be rendered fully water-soluble by dihydroxylation. It has been shown that both, cross-linked and open-shell hyperbranched polyglycerols are able to bind small guest molecules. The binding selectivity of the guest correlates with its size but is also dependent on the counterion. In general the larger loop sizes exhibit better complexation properties (i.e., higher number of guests complexed) but the small cavities ensure higher stability of the host−guest complexes. Molecules with sodium as counterion showed higher binding abilities over larger or smaller cationic compounds. Consequently, they have more favorable binding interactions with the closed-shell hosts.

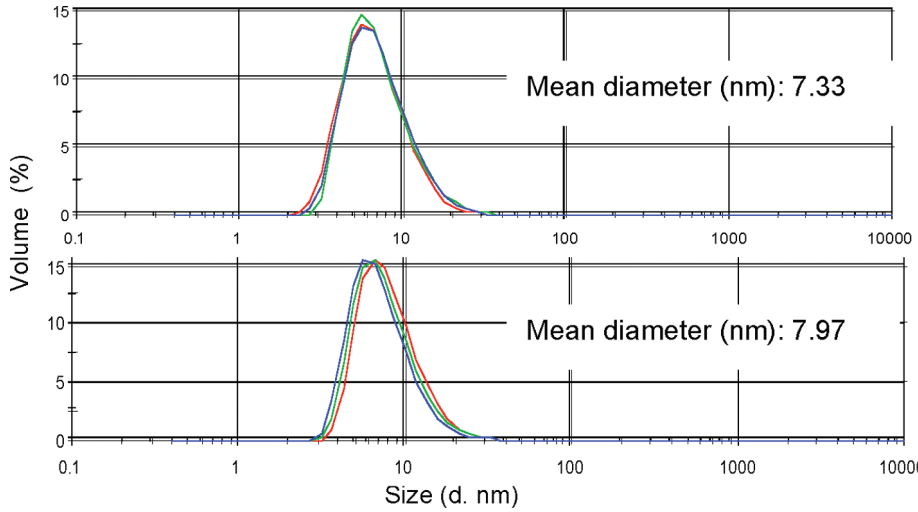

Figure 4. DLS plots by volume for cross-linked polymer **6** (top) before and (bottom) after binding of the dye rose Bengal in chloroform.

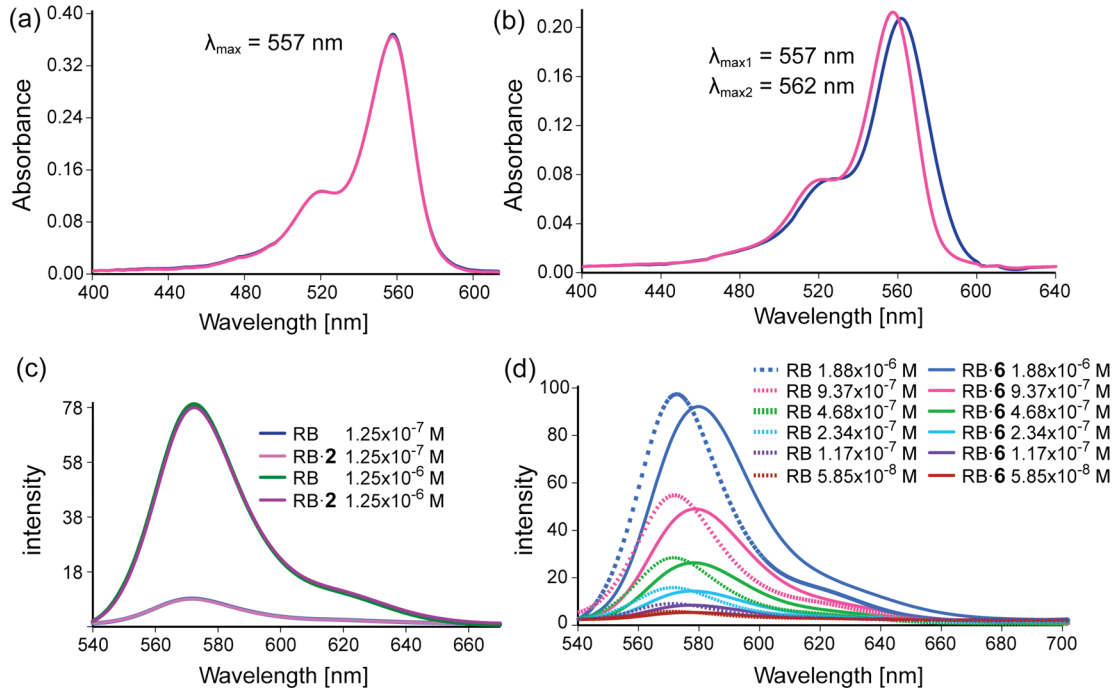

Figure 5. Absorption spectra of free rose Bengal sodium salt in ethanol (pink line) and rose Bengal sodium salt hosted in (a) polymer (blue line) **2** and (b) polymer **6**. Emission spectra of free rose Bengal sodium salt in ethanol and rose Bengal sodium salt hosted in (c) polymer **2** and (d) polymer **6**.

Table 4. Encapsulation of the Non-Polar Guest Molecules by Polymers **3** and **4** in Pure Water and in a 5 M NaCl Solution (**3*** and **4***)[a]

guest molecule	3	4	3*	4*
Nimodipine	0	0.1	0	0.5
pyrene	0	0.2	0	0.5
Nile red	0	0.6	0	1.2

[a] Results shown as the number of guest molecules per one host.

Furthermore, it has been shown that the dihydroxylated cross-linked hyperbranched polyglycerols tend to form stable supramolecular aggregates of about 100 nm diameter with narrow size distribution in pure water which break down in higher ionic strength solution. This property could lead to the development of some interesting stimuli responsive materials. On the basis of the results collected thus far, additional studies on these selective host nanotransport systems appear warranted and are underway.

Experimental Section

General. All solvents and reagents were of reagent quality, purchased commercially, and used without further purification, except as noted below. The following solvents were freshly distilled prior to use: methylene chloride (CH_2Cl_2) and chloroform ($CHCl_3$) from calcium hydride. *N*,*N*-Dimethylformamide (DMF) was stored over 4 Å molecular sieves. Water was deionized and purified in a Millipore-Q system. Hyperbranched polyglycerol 5 kDa (HPG) was prepared according to a published procedure[16,18] and analyzed by NMR, SEC and MALDI-TOF. Rose Bengal sodium salt and thymol blue sodium salt were of ACS reagent grade. Congo red sodium salt and 5-aminofluorescein were purchased from Sigma-Aldrich

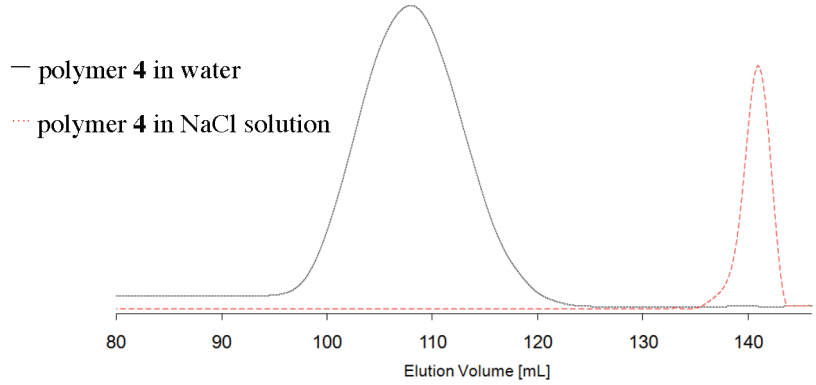

Figure 6. Size exclusion chromatography of polymer **4** in water and in NaCl solution.

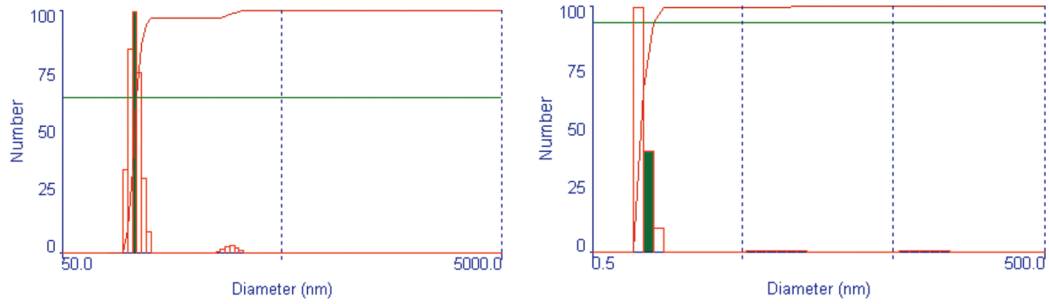

Figure 7. Dynamic light scattering of polymer **4** in (left) aqueous solution and (right) NaCl solution.

and the dye content was ≥85% (grade certified by the Biological Stain Commission). The rose Bengal cesium salt and thymol blue cesium salt were synthesized according to the procedure presented in experimental procedures.

Analytical size-exclusion chromatography (SEC) was performed on PSS Agilent 1100 system with three Suprema (10 μm) columns (3 × ID 8.0 × 300 mm) using 5% NaCl solution for the characterization of polymers **3** and **4** and PLgel Mixed-C (5 μm) columns, (3 × ID 7.5 × 300 mm) for the characterization of polymers **1**, **2**, **5**, and **6** using THF as eluent. For all analysis refractive index RI 1100 detector was used. The system was calibrated by narrow polystyrene standards (MW range: 200−4 × 10^6 Da) and polyethylene glycol standards (MW range: 106−4 × 10^5 Da) for aqueous analysis, respectively. Although, the standards used do not provide absolute molecular weights, the relative molecular weights in this molecular weight range are quite reliable.

Dynamic Light Scattering measurements were made using a Bio DLS 90 Plus/Bi-MAS from Brookhaven Instruments Corporation. UV−vis measurements were performed on Scinco S-3100 PDA UV−vis spectrophotometer at 25 ± 0.1 °C with wavelength from 190 to 850 nm. Fluorescence was recorded on Jasco FP-6500 fluorescence spectrophotometer at room temperature. The emission spectra were recorded from 540 to 800 nm with an excitation wavelength 525 nm and the bandwidth of 3 nm.

Polar Dye Encapsulation. To 10 mL of a chloroform solution saturated with an excess of each dye molecule was added polymer **2** or **6** at a concentration within the range of 0.1−1 wt % and the mixture stirred at room temperature for 12 h. These saturated solutions were centrifuged and filtered through a 0.2 μm filter. The absorbance was measured in a 0.1 cm path length quartz cuvette.

Nonpolar Guest Encapsulation. To 10 mL of an aqueous solution containing an excess of each guest molecule was added polymer **3** or **4** at a concentration within the range of 0.1−10 wt % and the mixture stirred at room temperature for 12 h. These saturated solutions were centrifuged and filtered through 0.2 μm filter. The absorbance was measured in a 0.1 cm path length quartz cuvette.

Synthetic Procedures. Rose Bengal Cesium Salt. An aqueous solution of rose Bengal sodium salt was acidified with 1 M HCl to pH 2 and extracted with chloroform. The organic layer was washed three times with water and the product was concentrated under reduced pressure. To 1 mL of an 11% cesium hydroxide solution was added 0.2 g of the product obtained above and the mixture stirred for 1 h. The product was lyophilized overnight to afford 0.22 g of rose Bengal cesium salt as pink solid.

Thymol Blue Cesium Salt. An aqueous solution of thymol blue sodium salt was acidified with 1 M HCl to pH 2 and extracted with chloroform. The organic layer was washed three times with water and the product was concentrated under reduced pressure. To 1 mL of a 15% cesium hydroxide solution was added 0.2 g of the product obtained above and the mixture stirred for 1 h. The product was lyophilized overnight to afford 0.21 g of thymol blue cesium salt as dark solid.

Polymer 5 - General Procedure. To a solution of 1.6 g (0.32 mmol) of HPG in 20 mL of dry DMF and 3.6 mL (26 mmol) of TEA was added slowly dropwise 5.6 mL (26.1 mmol) of 10-undecenoyl chloride. The reaction was stirred overnight. The DMF was evaporated under reduced pressure and the residue redissolved in chloroform and extracted three times with water and one time with brine. The organic layer was dried with $MgSO_4$ and purified via dialysis in chloroform to afford 4.1 g (79%, > 98% conversion by ^{1}H NMR analysis) of polymer **5** as a yellowish, highly viscous liquid. ^{1}H NMR 400 MHz ($CDCl_3$): δ (ppm) = 5.88−5.70 (m, 56H), 5.05−4.85 (m, 120H), 4.40−3.32 (m, 326H), 2.36−2.23 (m, 116H), 2.07−1.97 (m, 124H), 1.67−1.53 (bs, 126H), 1.45−1.20 (bs, 600H).

Polymer 6 - General Procedure. To a solution of 400 mg (0.023 mmol) of polymer **5** in 800 mL of methylene chloride (distilled from calcium hydride) was added 55 mg (8 mol %) of Grubbs' second generation catalyst. The mixture was stirred for 24 h and quenched with 20 mL of ethyl vinyl ether. The mixture was filtered through a plug of silica gel and the product was eluted with 800 mL of 5% methanol-methylene chloride. The solution was concentrated in vacuo to give 360 mg (94%) of polymer **6** as a light brown oil: ^{1}H NMR 400 MHz ($CDCl_3$): δ (ppm) = 5.88−5.70 (m,

7H), 5.50−5.22 (bs, 60H), 5.05−4.85 (m, 20H) 4.40−3.32 (m, 326H), 2.36−2.23 (m, 120H), 2.07−1.97 (m, 126H), 1.67−1.53 (bs, 128H), 1.45−1.20 (bs, 620H).

Polymer 7 - General Procedure. To a stirred mixture of 10 mL of *tert*-butyl alcohol and 10 mL of water was added sequentially 0.9 g AD-mix-beta at room temperature. Once the solids had dissolved the solution was cooled to 10 °C and 200 mg (0.011 mmol) of polymer **6** in 3 mL of THF was added. The slurry was vigorously stirred at 10 °C for 20 h and quenched with 1 g of Na_2SO_3. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was extracted three times with 30 mL with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give 198 mg (90%) of polymer **7** as yellow viscous liquid. ^{1}H NMR 400 MHz (CD_3OD): δ (ppm) = 4.0−3.50 (m, 988H), 1.70−1.60 (bs, 124H), 1.59−1.50 (bs, 116H), 1.46−1.35 (bs, 600H).

Polymer 8 - General Procedure. To a stirred mixture of 5 mL of *tert*-butyl alcohol and 5 mL of water was added sequentially 456 mg of AD-mix-beta at room temperature. Once the solids had dissolved, the solution was cooled to 10 °C, and a solution of 0.14 g (0.008 mmol) of polymer **7** in 3 mL of THF was added. The slurry was vigorously stirred at 10 °C for 20 h and quenched with 0.48 g of Na_2SO_3. The mixture was allowed to warm to room temperature with stirring overnight and extracted three time with 30 mL of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give 145 mg (92%) of polymer **8** as pale-yellow viscous liquid. ^{1}H NMR 400 MHz (CD_3OD): δ (ppm) = 4.07−3.43 (m, 666H), 1.75−1.50 (bs, 240H), 1.50−1.35 (bs, 600H).

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