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Water-Soluble Dendritic Core–Shell-Type Architectures Based on Polyglycerol for Solubilization of Hydrophobic Drugs

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Abstract: Since many potential drugs are poorly water soluble, there is a high demand for solubilization agents. Here, we describe the synthesis of dendritic core–shell-type architectures based on hyperbranched polyglycerol for the solubilization of hydrophobic drugs. Amphiphilic macromolecules containing hydrophobic biphenyl groups in the core were synthesized in an efficient three- or four-step procedure by employing Suzuki-coupling reactions. These species were then used to solubilize the commercial drug nimodipine, a calcium antagonist used for the treatment of heart diseases and neurological deficits. Pyrene was also used as a hydrophobic model compound. It turned out that the transport properties of the dendritic polyglycerol derivatives, which are based on hydrophobic host–guest interactions, depend strongly on the degree and type of core functionalization. In the case of the multifunctional nimodipine, additional specific polymer–drug interactions could be tailored by this flexible core design, as detected by UV spectroscopy. The enhancement of solubilization increased 300-fold for nimodipine and 6000-fold for pyrene at a polymer concentration of 10 wt%. The sizes of the polymer–drug complexes were determined by both dynamic light scattering (DLS) experiments and transmission electron microscopy (TEM), and extremely well-defined aggregates with diameters of approximately 10 nm in the presence of a drug were observed. These findings together with a low critical aggregate concentration of 4×10^{-6} mol L^{-1} indicate the controlled self-assembly of the presented amphiphilic dendritic core–shell-type architectures rather than a unimolecular transport behavior.

Keywords: core–shell architectures · dendrimers · drug-carrier systems · hydrophobic interactions · supramolecular chemistry

Introduction

One of the major problems faced by the pharmaceutical industry is the poor solubility of many existing and novel drugs in the body's aqueous environment. Very often the therapeutic effectiveness of these drugs is diminished by their inability to gain access to the site of action in an appropriate dose. Therefore, these drugs are either abandoned, delivered in large volumes of aqueous or ethanolic solutions, delivered in conjunction with surfactants, or chemically derivatized to afford soluble prodrugs. Unfortunately, all of these modifications can result in reduced efficacy or harmful side effects.

Many approaches to deliver hydrophobic compounds using polymeric carriers, such as block copolymers and dendritic polymers, have been explored.[1,2] Polymeric micelles (PM) based on amphiphilic block copolymers have attracted much attention as promising drug-delivery agents because their sizes and structures are similar to those of some viruses and lipoproteins that are natural carriers in biological sys-

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tems.[3] Block-copolymer micelles exhibit spherical, core–shell structures and diameters of about 20–50 nm. In contrast to micelles formed from low-molecular-weight amphiphiles, micelle-forming block-copolymer–drug conjugates and block copolymers can exhibit very slow rates of micelle dissociation to free polymer chains.[4] However, because micelle formation is a thermodynamic phenomenon, even PM can be unstable in high dilutions, such as those encountered after oral administration.[5] Polymers that consist of covalently bound amphiphilic polymer chains and which are referred to as unimolecular polymeric micelles (UPM)[6] can overcome these problems as their formation is independent of polymer concentration. Such UPMs have been obtained from both dendritic polymers[2,7,8] and star polymers.[5,9]

Dendritic polymers are spherical, branched macromolecules possessing a specific topology: the interior branching scaffold, the *core*, and the end groups in the periphery, the *shell*.[10] Both the perfectly branched dendrimers with their regular, well-defined unimolecular architecture and the hyperbranched polymers possessing a molecular-weight distribution are currently attracting much interest as dendritic nanocarriers for applications in drug solubilization and delivery.[2,7,8,11] These branched macromolecules can be further tailored by postsynthetic chemical modification of the shell to increase hydrophilicity. However, for the generation of hydrophobic cores, only hyperbranched polymers with their remaining functional core groups due to unreacted linear units can be further functionalized. In previous studies, paclitaxel (PTX), a poorly water-soluble drug, was solubilized in water by using polyglycerol dendrimers[12] with four or five generations and with tremendous synthetic effort (8–10 synthetic steps).[13,14] Pyrene was complexed within poly(propylene imine) (PPI) dendrimers,[15] pegylated benzylether dendrimers,[16] and pegylated poly(amido amine) (PAMAM) dendrimers.[17] Modification of PAMAM dendrimers led to water-soluble nanocontainers that were able to solubilize small organic molecules.[18] Reichardt's dye and the anticancer drug 10-hydroxycamptothecin were complexed within poly(glycerol-succinic acid) dendrimers.[19] Furthermore, pegylated polyester dendrimers bearing pH-sensitive acetal groups in the periphery were synthesized and employed as nanotransporters with non-unimolecular behavior but defined structures (diameter of micelles ca. 25 nm) in the solubilization and pH-controlled release of doxorubicin, a hydrophobic anticancer drug.[20,21] It was also reported that water-soluble, hyperbranched core–shell architectures that could be obtained in a one-pot synthesis by copolymerization of ethylene and an alkene derivative bearing a poly(ethylene glycol) tail in the presence of a Brookhart catalyst were successfully investigated for the encapsulation of nile red.[22,23]

Hyperbranched polyglycerol (PG) **1** (Figure 1) is a readily available, well-defined polymer with dendritic (treelike) branching obtained by controlled anionic polymerization of glycidol.[24–26] The molecular weight of hyperbranched PG (1000–20000 g mol^{-1}) and degree of polymerization (DP) can be tailored by the monomer/initiator ratio to obtain

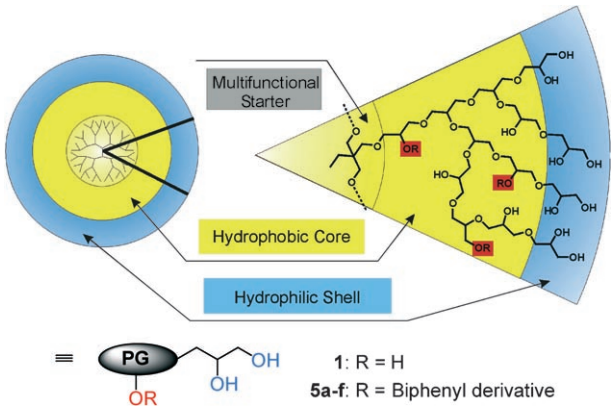


Figure 1. Core–shell-type architectures with the functionalized core hydroxy groups (red) and the terminal 1,2-diol groups (blue). R represents different biphenylmethyl ether groups that lead to tailormade nonpolar PG cores (see Table 1). The depicted idealized structure shows only a small fragment of the large PG molecules (ca. 114 glycerol units).

narrow polydispersities (typically <2.0).[25] PG **1** has a degree of branching of 60% relative to the fully branched perfect glycerol dendrimers.[12] Nevertheless, the physicochemical properties are very similar. With regard to the biocompatible properties of the aliphatic polyether polyols in general (e.g., polysaccharides, polyethylene glycols), similar properties are observed for polyglycerol.[27,28] Furthermore, oligoglycerols (2–10 monomer units) have been studied in detail with respect to their toxicological properties and have been approved as food and pharma additives.[29] Dendritic architectures based on polyglycerol **1** should, therefore, be well suited for the generation of spherical amphiphilic macromolecules for applications in drug solubilization and delivery.

In contrast to glycerol dendrimers,[12] hyperbranched PG possesses linear OH groups in the core as well as terminal OH groups in the periphery of the macromolecule.[30] The linear OH groups, however, lead to a more polar core of the unfunctionalized PG **1**, and no transport of hydrophobic drugs, as was reported for perfect polyglycerol dendrimers,[13,14] can be observed. On the other hand, these linear OH groups allowed us to modify the core with specific functional groups such as aromatic systems.

Herein, we report a simple and efficient approach towards water-soluble dendritic core–shell-type architectures based on hyperbranched polyglycerol (PG)[24–27] containing functional biphenyl units in their core for the efficient solubilization of hydrophobic drugs, such as nimodipine, and hydrophobic fluorescent dyes, such as pyrene. In contrast to our previous work in which we selectively modified the shell of PG to transport water-soluble guest molecules into the organic phase,[31] we now have specifically modified and tailored the core of PG with hydrophobic biphenyl groups by employing Suzuki-coupling reactions. The resulting amphiphilic core–shell-type architectures **5a–f** were designed to solubilize the poorly soluble commercial drug nimodipine (a calcium antagonist used for the treatment of heart diseases and neurological deficits) and pyrene as a model compound

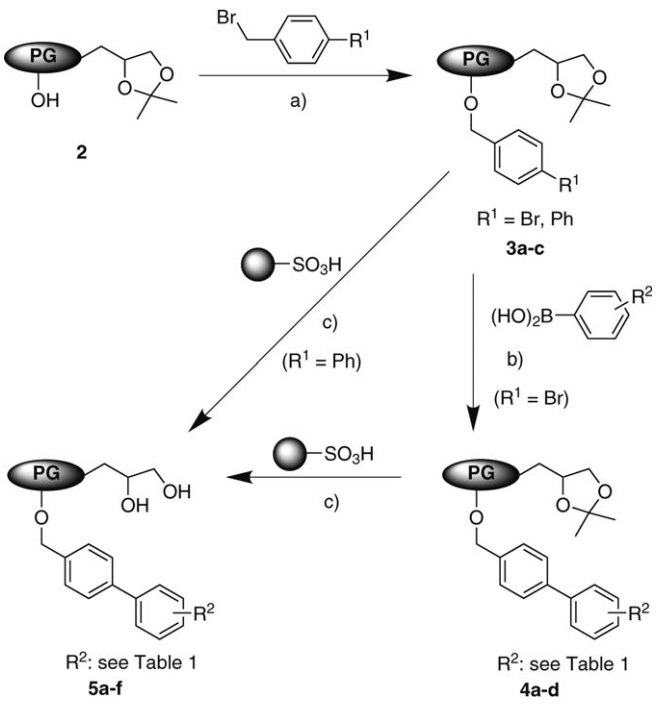
for hydrophobic fluorescent dyes. The biphenyl group was chosen after preliminary transport tests of nimodipine and pyrene with a wide range of analogous core-functionalized polyglycerol derivatives, from which it turned out that only macromolecules with aryl groups (and especially biphenyl groups) in the core were suitable for high solubilization efficiencies of both guest molecules.[32]

Results and Discussion

Structural design and synthetic approach: The synthesis of the amphiphilic polyglycerol derivatives was carried out in a three- or four-step procedure on a multigram scale. Dialysis was used for the purification of all derivatives and, in contrast to tedious dendrimer syntheses, chromatographic methods could be avoided. Starting from hyperbranched polyglycerol **1** with a molecular weight (M_n) of 5000 g mol^{-1}, all terminal 1,2-diol groups were selectively protected as 2-propylidene acetals by using acetone dimethylacetal as reagent in a large excess and 4-toluenesulfonic acid (PTSA) as catalyst. This starting material **2** is readily available on a 100-g scale, as previously reported.[30]

In the polyglycerol acetal **2**, a given percentage of the remaining linear OH groups were either directly converted into biphenylmethyl ether groups by using sodium hydride and 4-phenylbenzyl chloride in dry DMF as solvent, or first converted into 4-bromobenzyl ether groups by using sodium hydride and 4-bromobenzyl bromide in dry DMF (Scheme 1).[33] In the latter case, 0.25 equivalents of 4-bromobenzyl bromide were employed, resulting in the polyglycerol derivative **3a** with a core functionalization of 25%. This corresponds to an average of seven hydrophobic groups per molecule, considering all accessible linear OH groups, as determined by ^{1}H NMR spectroscopy. In the case of the direct formation of biphenyl groups in the polyglycerol core, 0.25 and 0.50 equivalents of alkylation reagent per OH group were employed, respectively, resulting in two different polymers: polyglycerol derivative **3b** with a degree of functionalization of 25% and polyglycerol derivative **3c** with 44% functionalization (this corresponds to an average of seven and twelve hydrophobic groups per molecule, respectively). These results show that the degree of functionalization can be easily adjusted by variation of the molar ratio of the alkylation reagent per OH group, as the etherification reaction is almost quantitative (>90%). The protected polyglycerol ethers (**3a–c**) were obtained in high purities (>98% according to ^{1}H NMR analysis) after dialysis in chloroform and in good yields (>90%, except derivative **3b** due to problematic dialysis).

To selectively modify the core with specific functionalities, the polyglycerol derivative **3a** bearing aryl bromide groups in the core was then reacted with differently substituted phenyl boronic acids in Suzuki-coupling reactions by using tetrakis(triphenyl phosphine) palladium(0) as catalyst[34] to tailor the core of the macromolecules with various hydrophobic substituents. Four different boronic acids (4-methoxyphenyl, 3,4-dimethoxyphenyl, 2,3,4-trimethoxyphenyl, and 4-acetylphenyl boronic acid) were employed, respectively, to generate biphenyl functionalities with acceptor or donor groups in the core of polyglycerol. All derivatives **4a–d** were obtained in good yields (61–88%) after dialysis in chloroform. The conversion of aryl bromide derivative **3a** with 2,3,4-trimethoxyphenyl boronic acid was difficult, however, due to steric hindrance (*ortho* substitution); therefore, the reaction was carried out by using double amounts of reagents to reach a similar degree of core functionalization (23% according to ^{1}H NMR analysis).



Scheme 1. Synthesis of core–shell structures **5a–f** starting from polyglycerol-2-propylidene acetal **2** by using a sequence of ether formation, Suzuki-coupling reactions, and deprotection; a) NaH, DMF, 80°C, 24 h; b) 2 mol% $[Pd(PPh_3)_4]$, K_2CO_3, 140°C, 72 h; c) MeOH, reflux, 24 h. For yields see text, for structures and properties see Table 1.

In the last step, all core-functionalized macromolecules **3b**,**c** and **4a–d** were deprotected in their shell by treating a methanolic solution with acidic ionic-exchange resin (Lewatit K1131) as catalyst in an orthogonal fashion to simplify the workup procedure.[35] After quantitative conversion (>98% according to ^{1}H NMR analysis) and subsequent purification by dialysis in methanol the final products **5a–f** were obtained as pale-yellow liquids in good yields (46–72%). All dendritic architectures **5a–f** showed high solubility in water.

Attempts were made to synthesize other polyglycerol derivatives containing unsubstituted and substituted biphenyl groups in the core with a degree of functionalization >45%. Unfortunately, all of them were insoluble in water, indicating that the sample **5f** with 44% functionalization represents the derivative with the maximum hydrophobic/hydrophilic ratio in this type of core–shell architecture.

Detailed analysis of polyglycerol acetal **2**, intermediates **3a–c**, **4a–d**, and products **5a–f** by NMR spectroscopy con-

firmed the structure and degree of functionalization of these dendritic core–shell-type architectures. The molecular weights (M_n) of the products **5a–f** (Table 1) were calculated based on the degree of functionalization from their ^{1}H NMR spectra and by using the known original molecular weight of polyglycerol **1** as reference, which was independently determined by size exclusion chromatography (SEC) and ^{1}H NMR spectroscopy (see Supporting Information).[24–26]

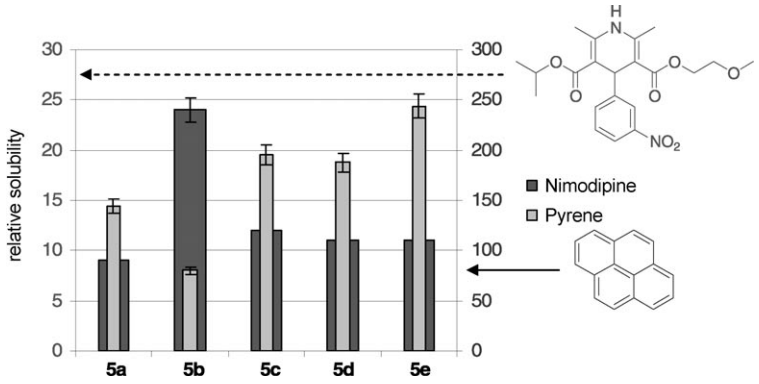


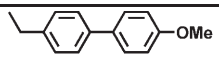
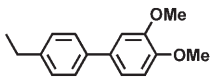
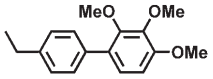
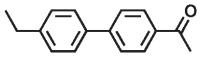
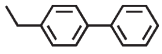
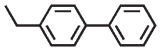
Figure 2. Solubility of nimodipine and pyrene in 1 wt% solutions of polymers **5a–e** relative to their solubility in pure water (1.1 mg L^{-1} and 0.1 mg L^{-1}, respectively).

Formation of polymer–drug complexes: For the evaluation of the solubilization properties of the synthesized polymeric structures **5a–f** we used pyrene as a model compound and the commercially available drug nimodipine. Nimodipine (Figure 2) is a drug of the 1,4-dihydropyridine type and was developed by Bayer AG in 1983.[36] Nimodipine is a calcium antagonist used for a variety of applications, for example, for the treatment of heart diseases and neurological deficits. Its poor water solubility (0.4 mg L^{-1})[37] necessitates the development of solubility enhancers to avoid the use of ethanolic and poly(ethylene glycol) solutions. For 50 mg of nimodipine, 37.5 g ethanol and 62.5 g poly(ethylene glycol) are currently used to yield the commercial formulation.[38] Another approach is the addition of 2.5 g of phospholipids for the same amount of nimodipine to achieve a higher solubility.[39]

For the drug solubilization measurements, 1 mL of an aqueous solution of the respective polymer **5a–f** at a concentration within the range of 0.1–10 wt% with an excess of each drug molecule was stirred at room temperature for 18 h. These saturated solutions were filtered and centrifuged to remove all solids. Then UV spectroscopy measurements were carried out at 25 °C with the corresponding drug-free polymer solution as reference. In the UV spectra, the absorption at 335 nm (≈340 nm in complex) for pyrene and the absorption at 355 nm (≈365 nm in complex) for nimodipine were used for our transport experiments (see Supporting Information). Calibration curves for pyrene in ethanol and for nimodipine in methanol were recorded by using known concentrations of each drug molecule in the respective solvent. Assuming that the extinction coefficients of both drug molecules in the respective alcohol and in water are the same, the amount of solubilized pyrene and nimodipine molecules in the polymer solutions can be calculated (see Table 1).

All saturated, aqueous solutions prepared by stirring as described above showed good long-term stability (several months). Higher transport capacities (up to a factor of two), but a lower long-term stability of the complex were obtained by treating the polymer–drug mixtures with ultrasonification for 30 min at room temperature prior to filtration and UV measurement.

Table 1. Solubilization of pyrene and nimodipine in 1 wt% solutions of the dendritic polymers.

Polyglycerol derivative	Core functionality (R in Figure 1)	Degree of functionalization [%][a]	M_n [g mol^{-1}][b]	Solubility of pyrene		Solubility of nimodipine	
				[mg per g polymer]	[mmol per mol polymer]	[mg per g polymer]	[mmol per mol polymer]
5a		25	6400	1.6	50	1.0	15
5b		25	6600	0.9	29	2.6	41
5c		23	6750	2.2	72	1.3	21
5d		25	6500	2.1	67	1.2	19
5e		25	6000	2.7	80	1.2	18
5f		44	6900	5.7	193	5.2	85

[a] According to ^{1}H NMR spectra. [b] Calculated from the functionalization data of ^{1}H NMR spectra and original SEC/^{1}H NMR data of polyglycerol.

Evaluation and characterization of the polymer–drug complexes: For polymers **5a–e** with a degree of functionalization of 25%, significant effects of the designed core substituents (biphenyl derivatives) on the transport behavior could be detected. For pyrene it was found that the polymer **5b** with two methoxy substituents on the biphenyl group had very low transport capacity (29 mmol per mol polymer, Table 1, Figure 2), whereas all other compounds **5a**,**c–e** showed much higher values of solubilized pyrene (50–80 mmol per mol polymer). In the case of pyrene solubilization, a clear dependence on the different donor or acceptor substituents could not be detected. This is in good agreement with its structure, because pyrene has no donor or acceptor groups attached to the aromatic system. The highest transport capacity in this series was detected for the polymer **5e** with the unfunctionalized biphenyl groups. For nimodipine, the situation is completely different. In this case, the polyglycerol derivative **5b** with the two methoxy substituents on the aromatic core group showed the highest transport capacity (Table 1, Figure 2).

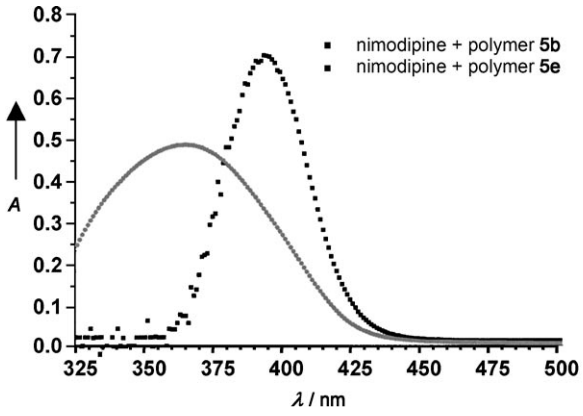
Because nimodipine bears a 3-nitrophenyl group on the dihydropyridine unit, a specific π–π interaction of the electron-poor aromatic ring with the electron-rich biphenyl derivative in the dendritic polymer **5b**, in addition to common hydrophobic interactions, can be the origin for this high transport capacity (Figure 3). This assumption is strengthened by strong bathochromic shifts (up to 28 nm) in the UV spectra of the polymer **5b**–nimodipine complex, especially at higher concentrations (Figure 3). The other derivatives **5a**,**c–e** showed much lower values of solubilized nimodipine (Table 1) due to the lack of specific interactions. The relatively low transport capacity of polymer **5c** with even three methoxy substituents on the biphenyl group (Table 1) could be explained by twisted aromatic rings due to sterical hindrance (*ortho* substitution). Therefore, a plain overlapping of the nimodipine and the trimethoxybiphenyl unit was disturbed and did not lead to strong additional donor–acceptor interactions.

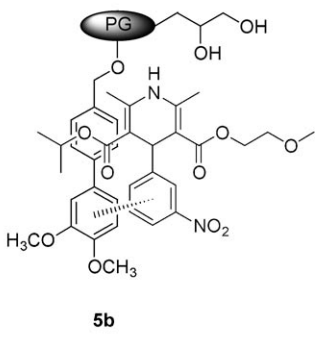
The transport experiments also revealed that for both unpolar guest molecules (pyrene and nimodipine) the polymer **5f** with the highest degree of functionalization of the inner shell (44%) showed the best transport properties, which are based on hydrophobic host–guest interactions (Table 1). Up to 193 mmol of pyrene molecules and 85 mmol of nimodipine molecules could be solubilized by 1 mol of dendritic core–shell-type architecture (1 wt% aqueous solutions). This indicates that a high degree of functionalization of the inner shell is the most important factor in a series of similar functionalization groups. The upper limit for the degree of core functionalization (experimentally determined to 45%) is the water solubility of the amphiphilic polymer.

The dependency of the transport behavior on the concentration of the dendritic polymers was studied by using the polyglycerol derivative **5f** with the highest solubilization factor for both pyrene and nimodipine (Table 2). Although the concentration of the polymer was varied from 0.1 to 10 wt%, the transport capacity (mmol drug molecules per mol polymer) was almost the same. Within this concentration range, 174–290 mmol pyrene and 52–85 mmol nimodipine molecules per mol polymer were solubilized by using solutions of polymer **5f**. This indicates an almost linear relationship between the concentration of the dendritic polymer and the complexed drug molecule, which is in good agreement with other polymer–drug systems.[4,14] It also shows that by increasing the concentration of the polymer to 10 wt%, the relative solubility of pyrene could be increased 6000-fold relative to pure water. This is significantly higher than the results obtained for the perfect glycerol dendrimers (solubility factor: 100) used for taxol solubilization.[14] Relative to pegylated polyether dendrimers reported by Fréchet et al., a slightly lower encapsulation of pyrene for the dendritic core–shell-type architecture **5f** was observed. However, the use of ultrasonification and heating during the sample preparation results in higher drug-to-polymer ratios, but, no long-term stable complexes were obtained in the case of **5f**.[7]

Table 2. Concentration dependency of the solubility of drug-loaded polymeric micelles.

Polyglycerol derivative	Conc. [wt%]	Solubility of pyrene		Solubility of nimodipine	
		[mg per g polymer]	[mmol per mol polymer]	[mg per g polymer]	[mmol per mol polymer]
5f	0.1	8.5	290	3.3	55
5f	1.0	5.7	193	5.2	85
5f	5.0	5.1	174	3.1	52
5f	10.0	7.0	238	3.5	58





5b

Figure 3. a) UV spectra of the specific complex of nimodipine with polymer **5b** (black square) and the unspecific complex of nimodipine with polymer **5e** (gray circle). b) Assumed π–π interactions between nimodipine and 3′,4′-dimethoxybiphenyl-4-methyl ether groups in polymer **5b**.

The solubilization results obtained clearly indicate that no 1:1 complexes of drug and polymers are formed for all

systems. In the case of polymer **5f**, a ratio of 5:1 for the polymer–pyrene complex and 12:1 for the polymer–nimodipine complex shows that the previous reported behavior of amphiphilic dendrimers to act as unimolecular micelles,[6] in which one or more drug molecules were complexed in one polymer molecule due to hydrophobic host–guest interactions, could not be verified for these core–shell-type architectures. Nevertheless, it is already known from the literature that molar host-to-guest ratios >1 can often be observed in case of macromolecular nanotransporters with molecular weights of less than $10^4\,g\,mol^{-1}$.[23]

Based on these polymer-to-drug ratios (>1), larger aggregates are likely. The sizes of these polymeric aggregates were measured by performing dynamic light scattering (DLS) experiments (Table 2). No significant concentration effect for the transport of both pyrene and nimodipine could be observed, as studied for polymer **5f** (see Table 2). Therefore, all polyglycerol derivatives **5a–f** were used in 1 wt% concentrations. DLS was carried out for both the drug-free and the drug-loaded nanoparticles (Table 3). The results obtained show that the particles without encapsulated drug molecules had diameters of 6–13 nm, depending on the different functionalization groups of the polymer core. These aggregates were already relatively defined, because the error of the measurements was small ($<10\%$). The nimodipine-loaded polymeric aggregates had diameters of 6–9 nm and were more defined (error of measurements $<5\%$) and smaller if the polyglycerol derivative bears substituted biphenyl groups in the core (**5a–d**). The nanoparticles containing pyrene show a similar behavior, also with diameters of 6–9 nm and errors $<5\%$.

It has been reported that amphiphilic dendritic polymers can self-assemble to form supramolecular aggregates with sizes in the range of 100 nm to several μm,[40] and that specifically tailored structures based on dendronized calixarene derivatives result in defined micellar structures in water.[41] However, both reported systems have not been measured in the presence of guest molecules. Recently, it has been shown that biarylether dendrimers of different generations bearing polar carboxylate and unpolar decyl groups are able to encapsulate Reichardt's dye in water, resulting in aggregates with particle sizes of 22–42 nm.[42] Furthermore, pegylated polyester dendrimers bearing pH-sensitive acetal groups in the periphery were successfully employed by Fréchet et al. in the solubilization of doxorubicin, exhibiting defined supramolecular aggregates with diameters of approximately 25 nm.[21] In the case of our flexible, amphiphilic polyglycerol derivatives **5a–f**, we also observe supramolecular aggregates in the presence of a hydrophobic guest. These aggregates are extremely well defined and in some cases are even smaller than the respective drug-free polymer particles. This might be due to attractive interactions between the biphenyl groups in the core of the polymer and the aromatic guest molecules. These interactions can be seen best for the polyglycerol derivative **5b**, whose complexes with nimodipine already showed strong and specific π–π interactions under UV spectroscopy (Figure 3). Here, the drug-free particles had diameters of 12.8 nm and the polymer particles loaded with pyrene or nimodipine showed diameters of 8.4 nm and 8.0 nm, respectively.

To confirm the results obtained from DLS experiments, the polymer–drug complexes were also analyzed by transmission electron microscopy (TEM). TEM images of nimodipine-loaded nanotransporters based on polymer **5f** (Figure 4) clearly show that the polymer–drug complexes exhibit defined supramolecular aggregates with diameters of 10–15 nm. The values obtained from the TEM images are slightly higher than those obtained from DLS measurements (7.2 nm, see Table 3). This can be explained by surface effects, for example, flattening and aggregation of several nanoparticles to bigger species during sample preparation. This again demonstrated the formation of supramolecular aggregates instead of unimolecular nanoparticles (2–4 nm)[14,43] of these amphiphilic dendritic architectures **5a–f**.

The formation of aggregates could also be confirmed by measurements of the critical aggregate concentration (cac). However, in case of unimolecular nanoparticles, a cac should not exist. The appropriate measurements resulted in a cac value of $0.028\,g\,L^{-1}$ for polymer **5f**, which corresponds to $4\times10^{-6}\,mol\,L^{-1}$. This value is much lower than the critical micelle concentration (cmc) of classical surfactants such as SDS ($7\times10^{-3}\,mol\,L^{-1}$), and it is within the same range as the cmc values of block-copolymer micelles or micelles based on dendritic polymers,[44] although linear-dendritic block copolymers with a cmc of even $3\times10^{-8}\,mol\,L^{-1}$ but with relatively big particle sizes of around 100 nm have been reported recently.[45] Therefore, the very low cac value of the amphiphilic dendritic core–shell-type architecture **5f**, together

Table 3. Particle sizes of drug-free and drug-loaded polymeric aggregates.

Polyglycerol derivative	Conc. [wt%]	Diameter of nanoparticles [nm][a]		
		drug-free polymeric aggregates	pyrene-loaded polymeric aggregates	nimodipine-loaded polymeric aggregates
5a	1.0	10.1±0.7	8.6±0.4	9.1±0.5
5b	1.0	12.8±0.5	8.4±0.1	8.0±0.2
5c	1.0	7.3±0.1	6.9±0.1	6.9±0.1
5d	1.0	10.0±0.3	9.3±0.2	9.2±0.3
5e	1.0	5.7±0.1	5.7±0.1	5.6±0.1
5f	1.0	6.9±0.1	7.0±0.1	7.2±0.1

[a] Data from dynamic light scattering experiments obtained by using a biexponential fitting method.

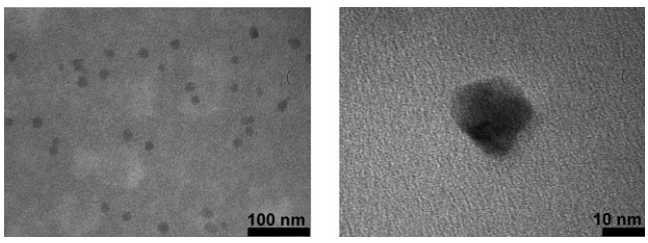


Figure 4. TEM images of polymer **5f**–nimodipine complexes. Defined nanoparticles with diameters of 10–15 nm can be observed.

with the formation of defined supramolecular aggregates, gives rise to promising further applications, as a low cac in combination with controllable particle sizes is a key feature for the development of new drug-delivery systems.

Drug release: For further applications in medicine it is also very important to achieve a release of solubilized and transported drug molecules from the nanocarrier. Therefore, the release of nimodipine from the amphiphilic polyglycerol nanotransporters presented was evaluated by using chromatographic methods. The polyglycerol derivative **5e** was used in a concentration of 10 wt% for the transport of nimodipine. The drug-loaded nanoparticles were separated on a Sephadex LH20 column by using water and water/methanol mixtures (gradient) as eluents. In all cases the first fractions already contained the whole amount of the corresponding polymer employed, which was analyzed further by UV spectroscopy. The respective polymer contained no nimodipine. These experiments demonstrate that the drug can be released from the dendritic nanocarrier by high dilution, which is in contrast to some known systems based on block-copolymer micelles.[4]

Conclusions

A new type of biocompatible dendritic architecture has been developed that can serve as a nanocarrier for nonpolar drugs. For this purpose, readily available polyglycerol was functionalized in a simple three- or four-step protocol with unsubstituted and donor-/acceptor-substituted biphenyl groups in the core by employing etherification and Suzuki-coupling reactions. A major advantage of these amphiphilic polyglycerol derivatives is the possibility to design a hydrophobic core tailored for specific polymer–drug interactions. Consequently, it is possible to design dendritic architectures with a specific interaction profile for functional drug molecules. Here, the core–shell polyglycerol derivative **5b** with 3′,4′-dimethoxybiphenyl-4-methyl ether groups in the core showed specific π–π interactions as detected by UV spectroscopy in the case of nimodipine complexation, in addition to nonspecific hydrophobic host–guest interactions. The complexes formed from the dendritic polymers and the drug molecules showed long-term stability for several months if they were prepared by simple stirring at room temperature, rather than under harsh conditions such as ultrasonification and heating. However, all polymer-to-drug ratios were higher than a value of one. These observations already indicated the formation of aggregates. Detailed analysis using DLS, TEM, and cac measurements revealed that these flexible, amphiphilic macromolecules self-assemble to extremely defined supramolecular structures with diameters of around 10 nm in the presence of the drug at very low concentrations (cac typically ca. 10^{-6} mol L^{-1}). Although we could not detect unimolecular transport behavior, we observed defined aggregates in which the modified dendritic polymers are assumed to self-assemble around the drug molecules in a controlled manner. This led to even smaller and more-defined particles than the drug-free aggregates, especially in the case of the polyglycerol derivative **5b** with 3′,4′-dimethoxybiphenyl-4-methyl ether groups in the core. This phenomenon can be explained by strong and specific π–π interactions, as detected by UV spectroscopy. In addition to the transport of different drug molecules, we demonstrated that the release of nimodipine can occur upon SEC column filtration in which high dilution conditions are mimicked. Further studies to analyze the three-dimensional structure of these supramolecular aggregates are in progress.

Experimental Section

Materials: Polyglycerol (PG) **1** ($M_n \cong 5000$ g mol^{-1}, $M_w/M_n = 1.6$; data from ^{1}H NMR and SEC, see Supporting Information Figures S1, S2) was prepared as described previously by using 1,1,1-tris(hydroxymethyl)propane (TMP) as initiator.[24,25] Acetone dimethylacetal and 4-toluenesulfonic acid (PTSA) were purchased from Fluka. Sodium hydride (95%), 4-bromobenzyl bromide, 4-phenylbenzyl chloride, 4-acetylphenyl boronic acid, 4-methoxyphenyl boronic acid, 3,4-dimethoxyphenyl boronic acid, and 2,3,4-trimethoxyphenyl boronic acid were received from Aldrich. Tetrakis(triphenylphosphine)palladium(0) was obtained from Merck, potassium carbonate from Grüssing, and Lewatit K1131 acidic ionic-exchange resin from Bayer. PTSA was dried in vacuo prior to use. All other reagents were used without further purification. The solvent *N*,*N*-dimethylformamide (DMF) (ultradry quality, water <50 ppm, stored over molecular sieve and p.a. quality, respectively) as well as methanol and chloroform (both p.a. quality) were purchased from Acros. Dialysis (benzoylated cellulose tubing, Sigma–Aldrich, MWCO 1000) in either methanol or chloroform was performed in a 2-L beaker by changing the solvent three times over a period of 24 h.

Analysis: ^{1}H NMR spectra were recorded at concentrations of 20 mg mL^{-1}, ^{13}C NMR spectra at concentrations of 100 mg mL^{-1} in $CDCl_3$ and CD_3OD, respectively, by using Bruker spectrometers ARX 300, DRX 400, and DRX 500 operating at 300, 400, 500 MHz and 75.4, 100.5, 125.7 MHz, respectively.

UV measurements were carried out by using a Specord S100 UV/Vis spectrometer (Analytik Jena) at 25 °C. 1 mL of saturated solutions of the drug molecules (nimodipine or pyrene) in polymer/water mixtures with specific concentrations were prepared, and the UV/Vis spectra were recorded from 220 to 800 nm with the corresponding drug-free polymer solutions in water as the reference.

Dynamic light scattering was performed on aqueous solutions by photon correlation spectroscopy using a Malvern Instruments Zetasizer-Nano. A 4-mW HeNe laser module (633 nm) was used and the measurements were carried out at a 173° scattering angle at 25 °C. The critical aggregate concentration (cac) was measured by a commercially available pendant drop tensiometer PAT1 SINTECH constructed by Surface & Interface Technologies (Germany).

Size exclusion chromatography (SEC) was performed for polyglycerol **1** by using a Knauer microgel set C11 with DMF as the eluent at 45 °C. An evaporative mass detector (EMD 960, Polymer Laboratories) operating at 110 °C was employed for detection, poly(propylene oxide) standards were used for calibration.

Synthesis of polyglycerol acetal (2): Dry PTSA (420 mg, 2.4 mmol) was added to a mixture of polyglycerol **1** (40.0 g, 169.3 mmol of diol units) and acetone dimethylacetal (200 mL, 169.4 g, 1.63 mol). The reaction was performed under ultrasonication over 3 h at 40 °C. After about 15 min a homogeneous solution was obtained. The crude product was diluted in chloroform and then extracted three times with saturated Na_2CO_3 solution to remove the remaining PTSA. The organic phase was dried over $MgSO_4$. Dialysis in chloroform was performed for 24 h to remove traces of remaining acetone dimethylacetal and PTSA. The purified product

was dried in vacuo. Polyglycerol acetal **2** (41.85 g: 89%, >95% conversion by ^{1}H NMR analysis) was obtained as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.77$ (t, 3H; $CH_3CH_2C(CH_2O)_3$-PG), 1.29 (s, 3H; PG-C(CH_3)CH_3), 1.35 (s, 3H; PG-C(CH_3)CH_3), 3.35–3.80 (m, *PG*), 3.86 (m, 1H; C*H*(H)-PG (1,3-dioxolane)), 3.99 (m, 1H; CH(*H*)-PG (1,3-dioxolane)), 4.19 ppm (m, 1H; C*H*-PG (1,3-dioxolane)); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 25.4$ (PG-C(CH_3)CH_3), 26.8 (PG-C(CH_3)CH_3), 62.1 (PG), 66.7 (*C*H(H)-PG (1,3-dioxolane)), 69.4, 71.6, 72.5, 74.7, 78.6, 79.7 (*PG*-C(CH_3)CH_3), 109.4 ppm (PG-*C*(CH_3)CH_3).

Alkylation of core OH groups (general procedure I): Ether formation of the desired amount of linear OH groups in the core of polyglycerol acetal **2** was performed with different alkylating agents by using sodium hydride in dry DMF. Polyglycerol acetal **2** (4.50 mmol core OH groups per g polymer) was dissolved in dry DMF and sodium hydride was added to the solution under vigorous stirring and cooling in an ice bath (0°C) under an argon atmosphere. After hydrogen formation ceased, the respective alkyl halide (0.25 and 0.50 equiv, respectively, corresponding to the desired degree of functionalization), dissolved in dry DMF, was slowly added to the reaction mixture over 4 h at room temperature. The suspension was then heated at 60°C for 18 h to reach quantitative conversion. After cooling to room temperature, the reaction mixture was quenched with methanol and water. All solvents were removed in vacuo; the residue was dissolved in chloroform and extracted three times with water. The organic phase was dried over $MgSO_4$, concentrated in vacuo, and purified by dialysis in chloroform.

Core functionalization (25%) with 4-bromobenzyl ether groups (3a): This product was obtained according to general procedure I. Polyglycerol acetal **2** (18.00 g, 81.0 mmol OH groups), dissolved in dry DMF (60 mL) was partially deprotonated by using sodium hydride 95% (510 mg, 20.2 mmol sodium hydride). A solution of 4-bromobenzyl bromide (5.05 g, 20.2 mmol) in dry DMF (60 mL) was slowly added to the reaction mixture. After purification by dialysis in chloroform, 21.33 g (98%, 25% conversion of core OH groups by ^{1}H NMR analysis) of core-functionalized polyglycerol acetal **3a** was isolated as a pale yellow, highly viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.79$ (t, 3H; $CH_3CH_2C(CH_2O)_3$-PG), 1.32 (s, 3H; PG-C(CH_3)CH_3), 1.38 (s, 3H; PG-C(CH_3)CH_3), 3.35–3.80 (m, *PG*), 3.88 (m, 1H; C*H*(H)-PG (1,3-dioxolane)), 4.00 (m, 1H; CH(*H*)-PG (1,3-dioxolane)), 4.21 (m, 1H; C*H*-PG (1,3-dioxolane)), 4.44 (m, PG-$O_{prim}CH_2$Ar), 4.58 (m, PG-$O_{sec}CH_2$Ar), 7.19 (m, 2H; 2-*H*, 6-*H*), 7.41 ppm (m, 2H; 3-*H*, 5-*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 25.4$ (PG-C(CH_3)CH_3), 26.9 (PG-C(CH_3)CH_3), 63.7 (PG), 66.7 (*C*H(H)-PG (1,3-dioxolane)), 69.4, 70.3, 70.8, 71.6, 72.6, 74.7, 78.7, 79.7 (*PG*-$O_{prim/sec}$-*C*H_2Ar), 109.4 (PG-*C*(CH_3)CH_3), 121.4 (4-*C*), 129.4 (2-*C*, 6-*C*), 131.5 (3-*C*, 5-*C*), 132.7, 135.0 ppm (PG-$O_{prim/sec}CH_2C_{ar,quart}$).

Core functionalization (25%) with biphenyl-4-methyl ether groups (3b): This product was obtained according to general procedure I. Polyglycerol acetal **2** (4.30 g, 19.4 mmol OH groups), dissolved in dry DMF (25 mL), was partially deprotonated by using sodium hydride 95% (125 mg, 4.9 mmol sodium hydride). A solution of 4-phenylbenzyl chloride (1.00 g, 4.9 mmol) in dry DMF (20 mL) was slowly added to the reaction mixture. After purification by dialysis in chloroform, 2.61 g (52%, 25% conversion of core OH groups by ^{1}H NMR analysis) of core-functionalized polyglycerol acetal **3b** was isolated as a pale yellow, highly viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.81$ (t, 3H; $CH_3CH_2C(CH_2O)_3$-PG), 1.33 (s, 3H; PG-C(CH_3)CH_3), 1.39 (s, 3H; PG-C(CH_3)CH_3), 3.35–3.80 (m, *PG*), 3.89 (m, 1H; C*H*(H)-PG (1,3-dioxolane)), 4.01 (m, 1H; CH(*H*)-PG (1,3-dioxolane)), 4.22 (m, 1H; C*H*-PG (1,3-dioxolane)), 4.55 (m, PG-$O_{prim}CH_2$Ar), 4.69 (m, PG-$O_{sec}CH_2$Ar), 7.28–7.45 (m, 5H; 3-*H*, 3′-*H*, 4′-*H*, 5-*H*, 5′-*H*), 7.55 ppm (m, 4H; 2-*H*, 2′-*H*, 6-*H*, 6′-*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 25.5$ (PG-C(CH_3)CH_3), 26.9 (PG-C(CH_3)CH_3), 63.7 (PG), 66.8 (*C*H(H)-PG (1,3-dioxolane)), 69.4, 70.4, 71.7, 72.6, 74.7, 78.6, 79.8 (*PG*-$O_{prim/sec}CH_2$Ar), 109.5 (PG-*C*(CH_3)CH_3), 127.2, 127.4, 128.2 (2-*C*, 2′-*C*, 3-*C*, 5-*C*, 6-*C*, 6′-*C*), 128.9 (3′-*C*, 4′-*C*, 5′-*C*), 138.0 (4-*C*), 140.5, 140.9 ppm (1-*C*,1′-*C*).

Core functionalization (44%) with biphenyl-4-methyl ether groups (3c): This product was obtained according to general procedure I. Polyglycerol acetal **2** (3.00 g, 13.5 mmol OH groups), dissolved in dry DMF (10 mL), was partially deprotonated by using sodium hydride 95% (170 mg, 6.7 mmol sodium hydride). A solution of 4-phenylbenzyl chloride (1.36 g, 6.7 mmol) in dry DMF (10 mL) was slowly added to the reaction mixture. After purification by dialysis in chloroform, 3.90 g (97%, 44% conversion of core OH groups by ^{1}H NMR analysis) of core-functionalized polyglycerol acetal **3c** was isolated as a pale yellow, highly viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.81$ (t, 3H; $CH_3CH_2C(CH_2O)_3$-PG), 1.33 (s, 3H; PG-C(CH_3)CH_3), 1.38 (s, 3H; PG-C(CH_3)CH_3), 3.35–3.80 (m, *PG*), 3.90 (m, 1H; C*H*(H)-PG (1,3-dioxolane)), 3.99 (m, 1H; CH(*H*)-PG (1,3-dioxolane)), 4.21 (m, 1H; C*H*-PG (1,3-dioxolane)), 4.53 (m, PG-$O_{prim}CH_2$Ar), 4.69 (m, PG-$O_{sec}CH_2$Ar), 7.28–7.45 (m, 5H; 3-*H*, 3′-*H*, 4′-*H*, 5-*H*, 5′-*H*), 7.54 ppm (m, 4H; 2-*H*, 2′-*H*, 6-*H*, 6′-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 25.5$ (PG-C(CH_3)CH_3), 26.9 (PG-C(CH_3)CH_3), 62.2 (PG), 66.8 (*C*H(H)-PG (1,3-dioxolane)), 69.4, 70.5, 71.7, 72.1, 72.5, 74.7, 78.8, 79.8 (*PG*-$O_{prim/sec}CH_2$Ar), 109.4 (PG-*C*(CH_3)CH_3), 127.1, 127.3, 128.2 (2-*C*, 2′-*C*, 3-*C*, 5-*C*, 6-*C*, 6′-*C*), 128.8 (3′-*C*, 4′-*C*, 5′-*C*), 137.4, 137.9 (4-*C*), 140.5, 140.9 ppm (1-*C*,1′-*C*).

Suzuki-coupling reactions on the shell-protected bromobenzyl polyglycerol derivative 3a (general procedure II): The formation of the desired substituted biphenyl groups in the core of bromoaryl-functionalized polyglycerol acetal **3a** was performed by employing Suzuki-coupling reactions using different aryl boronic acids as reagents and tetrakis(triphenylphosphine)palladium(0) as catalyst. Bromobenzyl polyglycerol acetal **3a** (1.01 mmol bromoaryl groups per g polymer) was dissolved in p.a. DMF and potassium carbonate (4.0 equiv). The respective aryl boronic acid (3.2 equiv), and tetrakis(triphenylphosphine)palladium(0) (3.2 mol%) were added to the solution at room temperature under an argon atmosphere. The reaction mixture was then heated at 140°C for 72 h to achieve quantitative conversion. After cooling to room temperature, the solvent DMF was removed in vacuo, the residue dissolved in chloroform and filtered, and the filtrate extracted three times with water. The organic phase was dried over $MgSO_4$, concentrated in vacuo, and purified by dialysis in chloroform.

Core functionalization with 4′-methoxybiphenyl-4-methyl ether groups (4a): This product was obtained according to general procedure II. Potassium carbonate (2.85 g, 20.6 mmol), 4-methoxyphenyl boronic acid (2.54 g, 16.7 mmol), and tetrakis(triphenylphosphine)palladium(0) (190 mg, 0.16 mmol) were added to bromoaryl-functionalized polyglycerol acetal **3a** (5.00 g, 5.1 mmol bromoaryl groups) dissolved in p.a. DMF (125 mL) and the mixture was heated at 140°C for 72 h. After purification by dialysis in chloroform, 3.99 g (78%, >95% conversion by ^{1}H NMR analysis) of biphenyl-functionalized polyglycerol acetal **4a** was isolated as a brownish, highly viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.80$ (t, 3H; $CH_3CH_2C(CH_2O)_3$-PG), 1.33 (s, 3H; PG-C(CH_3)CH_3), 1.39 (s, 3H; PG-C(CH_3)CH_3), 3.35–3.80 (m, *PG*), 3.81 (s, 3H; 4′-OCH_3), 3.91 (m, 1H; C*H*(H)-PG (1,3-dioxolane)), 4.01 (m, 1H; CH(*H*)-PG (1,3-dioxolane)), 4.22 (m, 1H; C*H*-PG (1,3-dioxolane)), 4.52 (m, PG-$O_{prim}CH_2$Ar), 4.67 (m, PG-$O_{sec}CH_2$Ar), 6.93 (m, 2H; 3′-*H*, 5′-*H*), 7.35 (m, 2H; 3-*H*, 5-*H*), 7.49 ppm (m, 4H; 2-*H*, 2′-*H*, 6-*H*, 6′-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 25.5$ (PG-C(CH_3)CH_3), 26.9 (PG-C(CH_3)CH_3), 55.4 (4′-OCH_3), 62.3 (PG), 66.8 (*C*H(H)-PG (1,3-dioxolane)), 69.4, 70.3, 71.7, 72.6, 72.9, 74.7, 78.7, 79.8 (*PG*-$O_{prim/sec}CH_2$Ar), 109.4 (PG-*C*(CH_3)CH_3), 114.3 (3′-*C*,5′-*C*), 126.7, 128.1, 128.3 (2-*C*, 2′-*C*, 3-*C*, 5-*C*, 6-*C*, 6′-*C*), 133.3 (1′-*C*), 136.7, 137.1 (4-*C*), 140.2 (1-*C*), 159.2 ppm (4′-*C*).

Core functionalization with 3′,4′-dimethoxybiphenyl-4-methyl ether groups (4b): This product was obtained according to general procedure II. Potassium carbonate (2.85 g, 20.6 mmol), 3,4-dimethoxyphenyl boronic acid (3.04 g, 16.7 mmol), and tetrakis(triphenyl phosphine) palladium (0) (190 mg, 0.16 mmol) were added to bromoaryl-functionalized polyglycerol acetal **3a** (5.00 g, 5.1 mmol bromoaryl groups), dissolved in p.a. DMF (125 mL), and the mixture was heated at 140°C for 72 h. After purification by dialysis in chloroform, 4.68 g (88%, >95% conversion by ^{1}H NMR analysis) of biphenyl-functionalized polyglycerol acetal **4b** was isolated as a brownish, highly viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.81$ (t, 3H; $CH_3CH_2C(CH_2O)_3$-PG), 1.32 (s, 3H; PG-C(CH_3)CH_3), 1.38 (s, 3H; PG-C(CH_3)CH_3), 3.35–3.80 (m, *PG*), 3.89 (m, 3′-OCH_3, 4′-OCH_3, C*H*(H)-PG (1,3-dioxolane)), 4.01 (m, 1H; CH(*H*)-PG (1,3-dioxolane)), 4.21 (m, 1H; C*H*-PG (1,3-dioxolane)), 4.53 (m, PG-

$O_{prim}CH_2Ar$), 4.67 (m, PG-$O_{sec}CH_2Ar$), 6.90 (m, 1H; 2′-*H*), 7.07 (m, 2H; 5′-*H*, 6′-*H*), 7.36 (m, 2H; 3-*H*, 5-*H*), 7.49 ppm (m, 2H; 2-*H*, 6-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 25.5$ (PG-C(CH_3)*C*H_3), 26.9 (PG-C(*C*H_3)CH_3), 56.0 (3′-O*C*H_3, 4′-O*C*H_3), 62.4 (PG), 66.8 (*C*H(H)-PG (1,3-dioxolane)), 69.4, 70.3, 71.7, 72.6, 72.9, 74.7, 78.7, 79.9 (*PG*-$O_{prim/sec}$-*C*H_2Ar), 109.4 (PG-*C*(CH_3)CH_3), 110.4 (2′-*C*), 111.5 (5′-*C*), 119.4 (6′-*C*), 126.8 (3-*C*, 5-*C*), 128.2 (2-*C*, 6-*C*), 133.8 (1′-*C*), 136.8, 137.2 (4-*C*), 140.4 (1-*C*), 148.7 (4′-*C*), 149.2 ppm (3′-*C*).

Core functionalization with 2′,3′,4′-trimethoxybiphenyl-4-methyl ether groups (4c): This product was obtained according to general procedure II, but by using double amounts of reagents as high conversion was difficult to achieve. Potassium carbonate (1.12 g, 8.1 mmol), 2,3,4-trimethoxyphenyl boronic acid (1.42 g, 6.7 mmol), and tetrakis(triphenyl phosphine) palladium (0) (80 mg, 0.07 mmol) were added to bromoaryl-functionalized polyglycerol acetal **3a** (1.00 g, 1.01 mmol bromoaryl groups) dissolved in p.a. DMF (30 mL), and the mixture was heated at 140 °C for 72 h. After purification by dialysis in chloroform, 660 mg (61 %, 90 % conversion by ^{1}H NMR analysis) of biphenyl-functionalized polyglycerol acetal **4c** was isolated as a brownish, highly viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.81$ (t, 3H; C*H*$_3$CH$_2$C(CH$_2$O)$_3$-PG), 1.33 (s, 3H; PG-C(CH$_3$)C*H*$_3$), 1.39 (s, 3H; PG-C(C*H*$_3$)CH$_3$), 3.35–3.80 (m, *PG*), 3.83–3.95 (m, 2′-OC*H*$_3$, 3′-OC*H*$_3$, 4′-OC*H*$_3$, *C*H(H)-PG (1,3-dioxolane)), 4.02 (m, 1H; CH(*H*)-PG (1,3-dioxolane)), 4.22 (m, 1H; C*H*-PG (1,3-dioxolane)), 4.55 (m, PG-$O_{prim}CH_2Ar$), 4.69 (m, PG-$O_{sec}CH_2Ar$), 6.71 (m, 1H; 5′-*H*), 6.98 (m, 1H; 6′-*H*), 7.30–7.50 ppm (m, 4H; 2-*H*, 3-*H*, 5-*H*, 6-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 25.5$ (PG-C(CH$_3$)*C*H$_3$), 26.9 (PG-C(*C*H$_3$)CH$_3$), 56.2 (4′-O*C*H$_3$), 61.1 (2′-O*C*H$_3$, 3′-O*C*H$_3$), 62.3 (PG), 66.8 (*C*H(H)-PG (1,3-dioxolane)), 69.5, 70.2, 71.7, 72.6, 72.9, 74.7, 78.8 (*PG*-$O_{prim/sec}CH_2Ar$), 107.6 (5′-*C*), 109.5 (PG-*C*(CH$_3$)CH$_3$), 124.9 (6′-*C*), 127.6 (2-*C*, 6-*C*), 128.5 (1′-*C*), 129.2 (3-*C*,5-*C*), 131.5, 132.2 (4-*C*), 137.7 (1-*C*), 142.6 (3′-*C*), 151.5, 153.2 ppm (2′-*C*,4′-*C*).

Core functionalization with 4′-acetylbiphenyl-4-methyl ether groups (4d): This product was obtained according to general procedure II. Potassium carbonate (2.85 g, 20.6 mmol), 4-acetylphenyl boronic acid (2.74 g, 16.7 mmol), and tetrakis(triphenyl phosphine) palladium (0) (190 mg, 0.16 mmol) were added to bromoaryl-functionalized polyglycerol acetal **3a** (5.00 g, 5.1 mmol bromoaryl groups), dissolved in p.a. DMF (125 mL), and the mixture was heated at 140 °C for 72 h. After purification by dialysis in chloroform, 3.92 g (75 %, >95 % conversion by ^{1}H NMR analysis) of biphenyl-functionalized polyglycerol acetal **4d** was isolated as a brownish, highly viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.79$ (t, 3H; C*H*$_3$CH$_2$C(CH$_2$O)$_3$-PG), 1.32 (s, 3H; PG-C(CH$_3$)C*H*$_3$), 1.38 (s, 3H; PG-C(C*H*$_3$)CH$_3$), 2.61 (s, 3H; 4′-C(O)C*H*$_3$), 3.35–3.80 (m, *PG*), 3.90 (m, 1H; C*H*(H)-PG (1,3-dioxolane)), 4.01 (m, 1H; CH(*H*)-PG (1,3-dioxolane)), 4.21 (m, 1H; C*H*-PG (1,3-dioxolane)), 4.55 (m, PG-$O_{prim}CH_2Ar$), 4.70 (m, PG-$O_{sec}CH_2Ar$), 7.41 (m, 2H; 3-*H*, 5-*H*), 7.48–7.71 (m, 4H; 2-*H*, 2′-*H*, 6-*H*, 6′-*H*), 8.00 ppm (m, 2H; 3′-*H*, 5′-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 25.5$ (PG-C(CH$_3$)*C*H$_3$), 26.8 (4′-C(O)*C*H$_3$), 26.9 (PG-C(*C*H$_3$)CH$_3$), 62.2 (PG), 66.8 (*C*H(H)-PG (1,3-dioxolane)), 69.4, 71.7, 72.6, 73.0, 74.7, 78.7, 79.9 (*PG*-$O_{prim/sec}CH_2Ar$), 109.4 (PG-*C*(CH$_3$)CH$_3$), 127.2, 127.3 (2-*C*, 2′-*C*, 6-*C*, 6′-*C*), 128.3 (3-*C*, 5-*C*), 129.0 (3′-*C*,5′-*C*), 131.7, 132.1 (4-*C*), 135.9 (4′-*C*), 139.2 (1′-*C*), 145.4 (1-*C*), 197.8 ppm (4′-*C*(O)CH$_3$).

Acetal cleavage (general procedure III): Acidic ionic-exchange resin Lewatit K1131 was added to a diluted solution of the acetal-protected core-functionalized polyglycerols **3b**, **3c** and **4a–d** in methanol. The mixture was stirred and heated at reflux for 24 h. The crude product was filtered and the clear methanol solution was concentrated in vacuo. For further purification, dialysis in methanol was performed for 24 h.

Polyglycerol with 4′-methoxybiphenyl-4-methyl ether groups (25 %) in the core (5a): This product was obtained according to general procedure III. Acidic ionic-exchange resin Lewatit K1131 (2.0 g) was added to biphenyl-functionalized polyglycerol acetal **4a** (2.0 g, 5.8 mmol of diol units) dissolved in methanol (30 mL, 0.74 mol) and the mixture was refluxed under gentle stirring for 24 h. After purification by dialysis in methanol, 1.1 g (62 %, >98 % conversion by ^{1}H NMR analysis) of biphenyl-functionalized polyglycerol **5a** was isolated as a yellowish, highly viscous liquid. ^{1}H NMR (500 MHz, CD_3OD): $\delta = 0.77$ (t, 3H; C*H*$_3$CH$_2$C-(CH$_2$O)$_3$-PG), 3.30–3.75 (m, *PG*), 3.79 (s, 3H; 4′-OC*H*$_3$), 4.43 (m, PG-$O_{prim}CH_2Ar$), 4.58 (m, PG-$O_{sec}CH_2Ar$), 6.86 (m, 2H; 3′-*H*, 5′-*H*), 7.15–7.55 ppm (m, 6H; 2-*H*, 2′-*H*, 3-*H*, 5-*H*, 6-*H*, 6′-*H*); ^{13}C NMR (125.8 MHz, CD_3OD): $\delta = 54.9$ (4′-O*C*H$_3$), 61.9, 63.5, 69.7, 70.1, 71.5, 72.0, 73.0, 78.9, 80.4 (*PG*-$O_{prim/sec}CH_2Ar$), 114.4 (3′-*C*, 5′-*C*), 126.5, 128.0, 128.6 (2-*C*, 2′-*C*, 3-*C*, 5-*C*, 6-*C*, 6′-*C*), 133.4 (1′-*C*), 137.1, 137.5 (4-*C*), 140.4 (1-*C*), 159.8 ppm (4′-*C*).

Polyglycerol with 3′,4′-dimethoxybiphenyl-4-methyl ether groups (25 %) in the core (5b): This product was obtained according to general procedure III. Acidic ionic-exchange resin Lewatit K1131 (2.0 g) was added to biphenyl-functionalized polyglycerol acetal **4b** (2.0 g, 5.7 mmol of diol units) dissolved in methanol (30 mL, 0.74 mol) and the mixture was refluxed under gentle stirring for 24 h. After purification by dialysis in methanol, 810 mg (46 %, >98 % conversion by ^{1}H NMR analysis) of biphenyl-functionalized polyglycerol **5b** was isolated as a yellowish, highly viscous liquid. ^{1}H NMR (500 MHz, CD_3OD): $\delta = 0.81$ (t, 3H; C*H*$_3$CH$_2$C-(CH$_2$O)$_3$-PG), 3.30–3.75 (m, *PG*), 3.82 (m, 3′-OC*H*$_3$, 4′-OC*H*$_3$), 4.40–4.55 (m, PG-OC*H*$_2$Ar), 6.60–7.60 (m, 7H; Ar-*H*); ^{13}C NMR (100.6 MHz, CD_3OD): $\delta = 56.6$ (3′-O*C*H$_3$, 4′-O*C*H$_3$), 62.8, 64.4, 70.7, 71.0, 72.2, 72.4, 72.9, 74.0, 79.9, 81.4 (*PG*-$O_{prim/sec}CH_2Ar$), 111.8 (2′-*C*), 113.3 (5′-*C*), 120.6 (6′-*C*), 127.7, 128.8, 129.4, 130.6 (2-*C*, 3-*C*, 5-*C*, 6-*C*), 135.0 (1′-*C*), 138.0 (4-*C*), 141.9 (1-*C*), 150.0 (4′-*C*), 150.7 ppm (3′-*C*).

Polyglycerol with 2′,3′,4′-trimethoxybiphenyl-4-methyl ether groups (23 %) in the core (5c): This product was obtained according to general procedure III. Acidic ionic-exchange resin Lewatit K1131 (1.0 g) was added to biphenyl-functionalized polyglycerol acetal **4c** (660 mg, 1.8 mmol of diol units) dissolved in methanol (10 mL, 0.25 mol) and the mixture was refluxed under gentle stirring for 24 h. After purification by dialysis in methanol, 420 mg (72 %, >98 % conversion by ^{1}H NMR analysis) of biphenyl-functionalized polyglycerol **5c** was isolated as a yellowish, highly viscous liquid. ^{1}H NMR (400 MHz, CD_3OD): $\delta = 0.77$ (t, 3H; C*H*$_3$CH$_2$C(CH$_2$O)$_3$-PG), 3.30–3.71 (m, *PG*), 3.71–3.86 (m, 2′-OC*H*$_3$, 3′-OC*H*$_3$, 4′-OC*H*$_3$), 4.48 (m, PG-$O_{prim}CH_2Ar$), 4.62 (m, PG-$O_{sec}CH_2Ar$), 6.73 (m, 1H; 5′-*H*), 6.93 (m, 1H; 6′-*H*), 7.10–7.42 ppm (m, 4H; 2-*H*, 3-*H*, 5-*H*, 6-*H*); ^{13}C NMR (125.8 MHz, CD_3OD): $\delta = 56.6$ (4′-O*C*H$_3$), 61.5 (2′-O*C*H$_3$, 3′-O*C*H$_3$), 62.8, 64.5, 70.6, 70.9, 71.2, 72.2, 72.4, 73.0, 74.0, 79.9, 81.4 (*PG*-$O_{prim/sec}CH_2Ar$), 109.2 (5′-*C*), 126.1 (6′-*C*), 128.9 (2-*C*, 6-*C*), 129.5 (1′-*C*), 130.2 (3-*C*, 5-*C*), 132.5, 133.1 (4-*C*), 139.0 (1-*C*), 143.8 (3′-*C*), 152.5, 154.6 ppm (2′-*C*, 4′-*C*).

Polyglycerol with 4′-acetylbiphenyl-4-methyl ether groups (25 %) in the core (5d): This product was obtained according to general procedure III. Acidic ionic-exchange resin Lewatit K1131 (1.5 g) was added to biphenyl-functionalized polyglycerol acetal **4d** (1.4 g, 4.0 mmol of diol units) dissolved in methanol (20 mL, 0.49 mol) and the mixture was refluxed under gentle stirring for 24 h. After purification by dialysis in methanol, 630 mg (51 %, >98 % conversion by ^{1}H NMR analysis) of biphenyl-functionalized polyglycerol **5d** was isolated as a yellowish, highly viscous liquid. ^{1}H NMR (500 MHz, CD_3OD): $\delta = 0.76$ (t, 3H; C*H*$_3$CH$_2$C(CH$_2$O)$_3$-PG), 2.50 (4′-C(O)C*H*$_3$), 3.30–3.85 (m, *PG*), 4.50 (m, PG-$O_{prim}CH_2Ar$), 4.63 (m, PG-$O_{sec}CH_2Ar$), 7.10–7.75 (m, 6H; 2-*H*, 2′-*H*, 3-*H*, 5-*H*, 6-*H*, 6′-*H*), 7.92 ppm (m, 2H; 3′-*H*, 5′-*H*); ^{13}C NMR (125.8 MHz, CD_3OD): $\delta =$ 26.9 (4′-C(O)CH_3) 62.7, 64.5, 70.6, 70.9, 72.2, 72.4, 72.9, 73.9, 79.8, 81.4 (*PG*-$O_{prim/sec}CH_2Ar$), 128.1 (2-*C*, 2′-*C*, 6-*C*, 6′-*C*), 129.5 (3-*C*, 5-*C*), 130.2 (3′−*C*,5′−*C*), 132.5, 133.1 (4-*C*), 137.0 (4′-*C*), 140.1 (1′-*C*), 146.6 (1-*C*) 200.0 ppm (4′-*C*(O)CH$_3$).

Polyglycerol with biphenyl-4-methyl ether groups (25 %) in the core (5e): This product was obtained according to general procedure III. Acidic ionic-exchange resin Lewatit K1131 (3.0 g) was added to biphenyl-functionalized polyglycerol acetal **3b** (2.6 g, 8.0 mmol of diol units) dissolved in methanol (30 mL, 0.74 mol) and the mixture was refluxed under gentle stirring for 24 h. After purification by dialysis in methanol, 1.5 g (66 %, >98 % conversion by ^{1}H NMR analysis) of biphenyl-functionalized polyglycerol **5e** was isolated as a yellowish, highly viscous liquid. ^{1}H NMR (400 MHz, CD_3OD): $\delta = 0.76$ (t, 3H; C*H*$_3$CH$_2$C(CH$_2$O)$_3$-PG), 3.30–3.85 (m, *PG*), 4.47 (m, PG-$O_{prim}CH_2Ar$), 4.61 (m, PG-$O_{sec}CH_2Ar$), 7.15–7.40 (m, 5H; 3-*H*, 3′-*H*, 4′-*H*, 5-*H*, 5′-*H*), 7.50 ppm (m, 4H; 2-*H*, 2′-*H*, 6-*H*, 6′-*H*); ^{13}C NMR (125.8 MHz, CD_3OD): $\delta = 62.7$, 64.4, 70.6, 71.0, 72.2, 72.4, 72.9, 73.9, 79.8, 81.4 (*PG*-$O_{prim/sec}CH_2Ar$),

127.9, 128.4, 129.5 (2-*C*, 2′-*C*, 3-*C*, 5-*C*, 6-*C*, 6′-*C*), 129.9 (3′-*C*, 4′-*C*, 5′-*C*), 138.6, 139.0 (4-*C*), 141.5, 141.9 ppm (1-*C*,1′-*C*).

Polyglycerol with biphenyl-4-methyl ether groups (44%) in the core (5f): This product was obtained according to general procedure III. Acidic ionic-exchange resin Lewatit K1131 (4.0 g) was added to biphenyl-functionalized polyglycerol acetal **3c** (3.9 g, 10.6 mmol of diol units) dissolved in methanol (20 mL, 0.49 mol) and the mixture was refluxed under gentle stirring for 24 h. After purification by dialysis in methanol, 2.4 g (69%, >98% conversion by ^{1}H NMR analysis) of biphenyl-functionalized polyglycerol **5f** was isolated as a yellowish, highly viscous liquid. ^{1}H NMR (500 MHz, CD_3OD): $\delta = 0.74$ (t, 3H; $CH_3CH_2C(CH_2O)_3$-PG), 3.30–3.85 (m, *PG*), 4.41 (m, PG-$O_{prim}CH_2$Ar), 4.57 (m, PG-$O_{sec}CH_2$Ar), 7.13–7.37 (m, 5H; 3-*H*, 3′-*H*, 4′-*H*, 5-*H*, 5′-*H*), 7.46 ppm (m, 4H; 2-*H*, 2′-*H*, 6-*H*, 6′-*H*); ^{13}C NMR (125.8 MHz, CD_3OD): $\delta = 62.8$, 64.5, 70.6, 71.2, 72.2, 72.4, 72.8, 74.0, 79.8, 81.4 (*PG*-$O_{prim/sec}CH_2$Ar), 128.0, 128.5, 129.5 (2-*C*, 2′-*C*, 3-*C*, 5-*C*, 6-*C*, 6′-*C*), 130.0 (3′-*C*, 4′-*C*, 5′-*C*), 138.6, 139.1 (4-*C*), 141.6, 141.9 ppm (1-*C*,1′-*C*).

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