methods with the program SIR92.[17] Anisotropic least squares full matrix refinement was carried out on all non-hydrogen atoms using the program CRYSTALS.[18] The positions of the hydrogen atoms were determined geometrically. The disordered THF molecules in **3** were refined using appropriate restraints. Chebychev polynomial weights have been used to complete the refinement.[19] Scattering factors have been taken from *the International Tables*, *Vol. IV* (Ed.: T. Hahn), Kluwet Academic Publishers, London, **1995**, table 2.2B. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-127623, 127624, and 127625. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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## Molecular Nanocapsules Based on Amphiphilic Hyperbranched Polyglycerols

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Dendrimers have been shown to exhibit unusual properties in recent years,[1] such as the topological encapsulation of various guests,[2] and dendrimers with amphiphilic core – shell structures have shown micelle-like properties that have led to the picture of a "unimolecular micelle".[3] However, most systems reported in this context show aggregation in solution as a result of their amphiphilic nature.[4] Amphiphilic polymers with core – shell structures that are aggregation-free in solution offer the attractive potential to act as phase-transfer agents in both polar [5, 6] and apolar environments.[7, 8] To date, this solubilization effect is believed to be uniquely related to the structurally perfect, yet tedious to prepare, dendrimers. The compact dendrimer topology is promising for controlled release[9] and confined chemical nanoreactors.[10]

Hyperbranched polymers (prepared in a one-step reaction from $AB_m$-type monomers and thus randomly branched in contrast to the perfectly branched dendrimers) are generally considered to be poorly defined because of their broad polydispersity,[11] which is a consequence of the commonly used step-growth-type of synthesis. Furthermore, hyperbranched polymers are characterized by a random distribution of functional groups throughout their globular structure. We reported recently the first controlled chain-growth-type of approach to hyperbranched polymers based on the anionic ring-opening multibranching polymerization (ROMBP) of glycidol.[12] The polyglycerols obtained can be tailored in terms of their core functionality and molecular weight by the monomer/initiator ratio employed. As a consequence of the quasi-living nature of the polymerization these highly flexible aliphatic polyetherpolyols exhibit unprecedentedly narrow polydispersities ($M_w/M_n < 1.5$, mostly $< 1.3$).

Very few examples of amphiphilic hyperbranched structures have been reported.[13, 14] Herein we describe the use of hyperbranched polyglycerols for the preparation of amphiphilic "molecular nanocapsules" for hydrophilic guests. In contrast to dendrimer scaffolds where functional groups are exclusively located at the surface, polyglycerol scaffolds also contain hydroxyl groups throughout the structure. If only a certain fraction of these hydroxyl groups is modified with hydrophobic alkyl chains (43 – 93 %), thereby leaving residual hydroxyl moieties, the inner sphere of the molecule remains highly hydrophilic (Figure 1). The considerable flexibility of the polyether structure should permit the hydroxyl groups to arrange in a manner that represents a solvating environment for polar guest molecules in apolar solvents.

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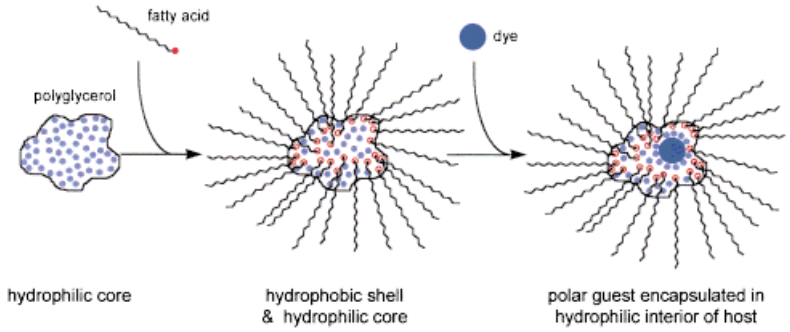
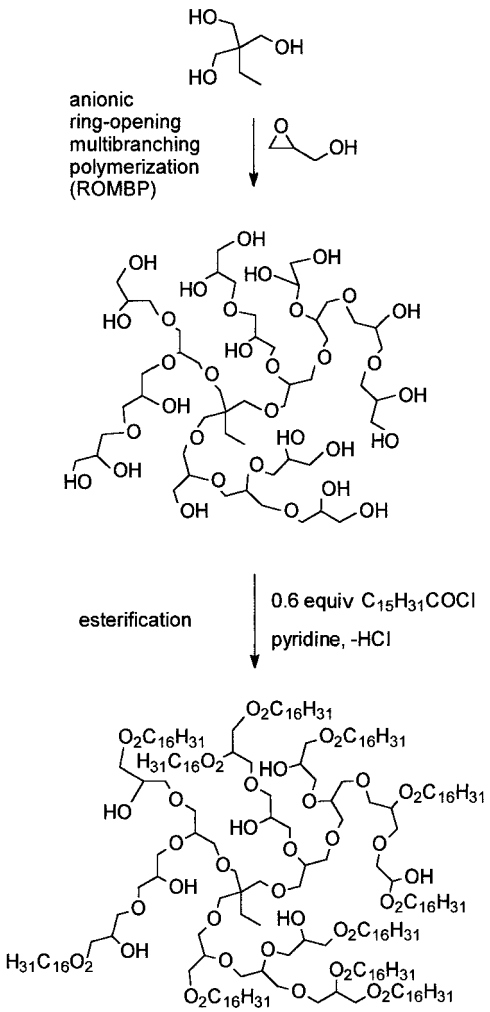



Figure 1. Synthesis of an inverted unimolecular micelle from a hyperbranched polyol by partial hydrophobization of the end groups and subsequent take-up of a water-soluble guest-molecule (small blue circles: free hydroxyl groups, small red rings: hydroxyl groups esterified with alkyl chains).

The polyglycerols with nonpolar shells were prepared by a straightforward two-step approach. In the first step we polymerized glycidol anionically by the method described previously using trimethylolpropane as the trifunctional initiator.[12] In the second step the polyetherpolyols were partially esterified using various fatty acid chlorides (Scheme 1).[15]




Scheme 1. Synthesis of partially esterified polyglycerols: step 1: controlled base-catalyzed ring-opening multibranching polymerization (ROMBP) of glycidol; step 2: partial esterification of the hyperbranched polyglycerol with a fatty acid chloride (for example, palmitoyl chloride).

Two polyglycerols with molecular weights of 1800 and 6300 with molecular weight distributions ($M_w/M_n$) of 1.2 and 1.5, respectively, were employed for this study. Four partially esterified polyols varying both in the the degree of alkyl substitution ($\alpha$) and the length of the alkyl chains were prepared from these two polymers. Palmitoyl (C16) and caprylic acid (C8) chlorides were used and between 43 % and 93 % of the hydroxyl groups were esterified. All products exhibited narrow polydispersities comparable to that of the substrates (Table 1).

The esterified polyglycerols are soluble in a large variety of nonpolar organic solvents (for example, toluene, chloroform, and hexane) in contrast to polyglycerol that is soluble only in extremely polar media, such as water or methanol. We chose Congo red as a representative anionic, water-soluble dye and chloroform as the apolar phase, in which this dye is not soluble (Figure 2, left sample tube) to investigate the phase-transfer properties of the esterified polyglycerols).

Table 1. Analytical data for the partially esterified polyglycerol samples from NMR, GPC, and UV/Vis measurements.

| sample[c] | Polyglycerol core | | Partially esterified polyglycerol | | | |
|---|---|---|---|---|---|---|
| | NMR | GPC[a] | NMR | | GPC[b] | UV/Vis |
| | $\bar{M}_n$ | $M_W/M_n$ | $\alpha$ [%][d] | $\bar{M}_n$ | $M_W/M_n$ | (Load) |
| $P(G_{23}C16_{0.6})$ | 1800 | 1.2 | 60 % | 5300 | 1.3 | 0.8 |
| $P(G_{23}C16_{0.9})$ | 1800 | 1.2 | 93 % | 7300 | 1.2 | 0.7 |
| $P(G_{84}C16_{0.6})$ | 6300 | 1.5 | 55 % | 17500 | 1.3 | 2.7 |
| $P(G_{84}C8_{0.4})$ | 6300 | 1.5 | 43 % | 10800 | 1.5 | 1.3 |

[a] Performed in DMF at 45 °C with poly(propylene glycol) standards. [b] Performed in $CHCl_3$ at 30 °C with polystyrene standards. [c] Nomenclature $P(G_xCY_\alpha)$: $x = DP_n$ of polyglycerol, $Y$: length of alkyl chain as measured by the number of carbon atoms. [d] $\alpha$: degree of alkyl substitution per hydroxyl group.

As a consequence of the spatially confined amphiphilic topology we expected to observe a point of saturation at which the maximum load of dye molecules per polymer

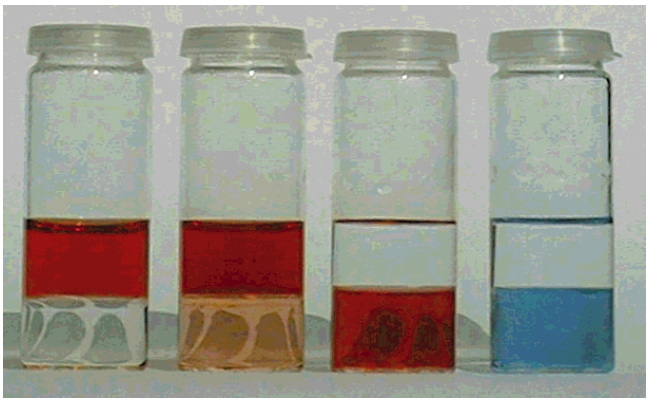


Figure 2. Demonstration of the solubilization effect (bottom layer: chloroform, upper layer: water). From left to right: 1) no polymer in organic layer; 2) molar ratio $P(G_{23}C16_{0.6})$:Congo red 1:4; 3) molar ratio $P(G_{23}C16_{0.6})$:Congo red 1:0.4; 4) organic layer from (3) transferred into a tube containing hydrochloric acid (pH 2).

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molecule is reached. Therefore we prepared chloroform solutions of the polymers and agitated them briefly with different concentrations of dye dissolved in the aqueous phase.[16] The organic phase was investigated, after phase separation, by UV/Vis spectroscopy as well as dynamic light scattering (DLS). In all cases a linear increase in the color intensity of the organic phase was observed below the saturation point. Once the saturation concentration of the dye in the organic phase was reached the absorption did not change with further increase of the dye concentration (Figure 2, second sample tube from left). The defined number of guests encapsulated is clearly supported by the results of the UV/Vis measurements shown in Figure 3 for three of the

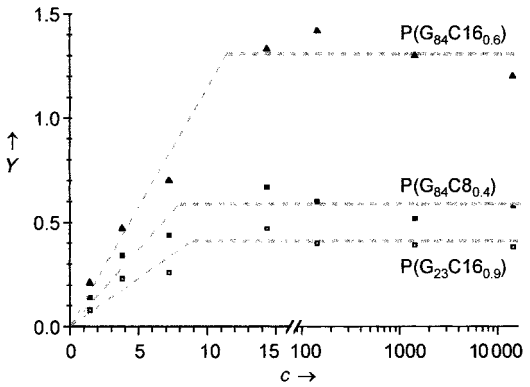


Figure 3. Determination of the average load of dye molecules per polymer from the absorption in the UV/Vis spectra (polymer concentration 0.01 wt% in chloroform). *c*: dye concentration ($10^{-6}$ M in aqueous phase); *Y*: average loading of dye molecules per polymer.

samples studied. Remarkably, Congo red was quantitatively extracted from the aqueous layer into $CHCl_3$ at dye concentrations below the saturation concentration (Figure 2, third sample tube from left). The average maximum load (that is, the saturation concentration) of dye molecules per polymer can be calculated from UV/Vis experiments by assuming the same absorption coefficient for the dye in water and in the amphiphilic structure. Calculation of the load from the determination of the saturation point gives similar values.

As shown in Table 1 the average maximum load depends on two factors: 1) the molecular weight of the polyglycerol used, and thus, the size of the hydrophilic hyperbranched topology and the related number of free hydroxyl groups (compare loadings of 0.7 and 2.7 for $P(G_{23}C16_{0.6})$ and $P(G_{84}C16_{0.6})$, respectively) and 2) on the length of the alkyl chains attached to the polyglycerol scaffold (compare loadings of 2.7 and 1.3 for $P(G_{84}C16_{0.6})$ and $P(G_{84}C8_{0.4})$, respectively). The degree of substitution $\alpha$ seems to play a minor role (compare loadings of 0.8 and 0.7 for $P(G_{23}C16_{0.6})$ and $P(G_{23}C16_{0.9})$, respectively).

Various light-scattering experiments with dye-loaded samples obtained from the solubilization procedure described above were carried out to clarify whether the host molecules are present as unimolecular species in the organic phase, that is, whether the solubilization observed is actually a consequence of the presence of an inverted unimolecular micelle type of structure (Figure 1). Static light-scattering experiments with the samples $P(G_{23}C16_{0.6})$ and $P(G_{23}C16_{0.9})$ at a concentration of $10^{-3}$ wt% showed no scattering intensity at any angle, which showed that no uncontrolled aggregation took place at the investigated concentration. Dynamic light-scattering measurements were performed with the sample $P(G_{23}C16_{0.9})$ at concentrations of 0.05 and 0.025 wt% at an angle of 90°. The hydrodynamic radius distribution was obtained by CONTIN analysis. In both cases an extremely weak scattering intensity was found below an average hydrodynamic radius of 100 nm. Thus, our experimental results point to a unimolecular nature of the solvating species. This is supported by the stability of the solutions of the dye-loaded polymers over extended periods that exceeded several months. It should be noted that our data cannot completely exclude the formation of small aggregates.

The solubilization described for Congo red appears to be general, namely similar behavior is observed with other water-soluble dyes (for example, bromophenol blue, rose Bengal) and other organic solvents (for example, toluene, *n*-hexane). For instance, when using *n*-hexane as the apolar solvent and rose Bengal as the hydrophilic dye, we observed an average load of 1.4 molecules of rose Bengal per polymer $P(G_{23}C16_{0.6})$. This slightly enhanced value relative to Congo red appears to be related to the somewhat more compact structure of rose Bengal in comparison to the extended rodlike structure of Congo red.

Two fundamental issues need clarifying: 1) whether the dye encapsulation is reversible and 2) whether chemical reactions of the solubilized species that take place in a polar environment can also be realized in the organic phase. Since Congo red is a pH-sensitive dye (pH > 3: red, pH < 3: blue), the most simple experiment concerning a chemical reaction in the molecular nanocapsule is the effect of a pH change in the aqueous phase on the dye solubilized in the chloroform phase. Therefore, we transfered the organic phase of a sample prepared as described above (neutral pH) into a new tube and added fresh water on top. Remarkably, after agitation and even ultrasonication no coloration of the aqueous phase was observed, which indicates irreversible encapsulation of the dye. The pH of the aqueous layer was lowered to a value of 2 by subsequent addition of hydrochloric acid and the sample agitated again. Interestingly, the color of the organic phase changed from red to blue, demonstrating that the dye solubilized in the hosting polymer is still accessible by protons and thus sensitive to pH changes (Figure 2, right sample tube). Release of the encapsulated dyes could only be observed after cleavage of the hydrophobic alkyl chains by ester hydrolysis. Since the presence of hydroxyl and ether groups in the core is a prime requirement for achieving irreversible encapsulation this unusual behavior can best be accounted for by hydrogen-bond formation.

In conclusion, the construction of molecular nanocapsules with hydrophilic interiors from hyperbranched polymers has been achieved for the first time using narrow polydispersity polyglycerols and simple esterification with fatty acids. Synthesis of these inverted micelle-type architectures requires only two synthetic steps and can conveniently be carried out on a multi-gram scale. The hyperbranched molecular nanocapsules are cabable of solubilizing a distinct average number of polar molecules in their interior, depending on the core size

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and substituents. This encapsulation based only on a hydrophobically shielded, hydrophilic solvating microenvironment represents a different principle in comparison to the topological entrapment observed for some dendrimer-based structures.[2] From light scattering measurements it was tentatively concluded that the solvating species are present in a unimolecular form in organic solvents, thus, representing "inverted unimolecular micelles". Since there appears to be no measurable release of encapsulated guests, the term "micelle" is slightly misleading; we favor the term "molecular nanocapsules". Release of the encapsulated dyes is achieved by means of cleaving the ester bond, thus, removing the hydrophobic molecular shield of the nanocapsules.

Molecular nanocapsules and their corresponding host/guest compounds offer an attractive potential for use in a wide variety of applications ranging from controlled drug release, solubilization of inorganic compounds in organic media, dispersion of polar dyes in hydrophobic polymers, preparation of inorganic/organic hybrid nanoparticles, to the design of microreactors and catalysts.[17]

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[16] In a typical experiment the respective aqueous dye solution (4 mL) was manually shaken for some seconds with 0.01 wt% solution (4 mL) of the partially esterified polyglycerol in chloroform. After phase separation (two experiments after 3 h and 24 h), an aliquot of the organic layer (2 mL) was transfered into a UV/Vis cuvette and its absorption spectrum measured. No difference between the 3 h and 24 h measurements was observed. The solutions remained unchanged for several months.
[17] The preparation of chiral polyglycerol based on the pure enantiomers of glycidol as a basis for chiral molecular nanocapsules has been investigated: A. Sunder, R. Mülhaupt, R. Haag, H. Frey, *Macromolecules*, in press.

# Biomimetic Explorations Towards the Bisorbicillinoids: Total Synthesis of Bisorbicillinol, Bisorbibutenolide, and Trichodimerol**

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*Dedicated to Professor Gerasimos J. Karabatsos on the occasion of his 67th birthday*

The bisorbicillinoids[1] are a growing family of novel natural products with interesting and diverse biological activities. Included within this class are bisorbicillinol (**1**),[2] bisorbibutenolide (**2**),[3] trichodimerol (**4**),[4] bisorbicillinolide (**5**),[3] and

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