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Chapter 5

Hybrid Dendritic Capsules: Properties and Binding Capabilities of Amphiphilic Copolymers with Linear Dendritic Architecture

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This chapter describes the synthesis and the characterization of amphiphilic hybrid ABA block copolymers that self-assemble in aqueous media. The materials under investigation are constructed of poly(ethylene glycol) (PEG), as the water-soluble B block and poly(benzyl ether) monodendrons as the hydrophobic A fragments. The copolymers could be formed by different synthetic schemes that are briefly discussed. The process of self-assembly in aqueous media is investigated by size-exclusion chromatography (SEC. The data obtained indicate that the critical micelle concentrations (cmc) for these systems are between 1×10^{-7} and 5×10^{-6} mol/L and depend on the dendron/PEG ratio. The character of the micellar core is investigated by UV-Vis and fluorescence spectroscopy using different polyaromatic hydrocarbons (PAHs). The PAHs encapsulation results can also serve as a preliminary evaluation of the binding capabilities of the linear-dendritic amphiphiles and their potential application in the biomedical and environmental fields.

Polymers that are capable of association and self-assembly in aqueous media are an important class of materials with significant and diverse application potentials. They can be found in numerous biological processes including molecular recognition, encapsulation and delivery, and also play an important role in many advanced technologies. Self-assembling molecules can be used for the complexation and transport of different substrates into and through hostile environments, they can change the mechanism and stereoselectivity of chemical reactions and enhance their

In Associative Polymers in Aqueous Media; Glass, J.;
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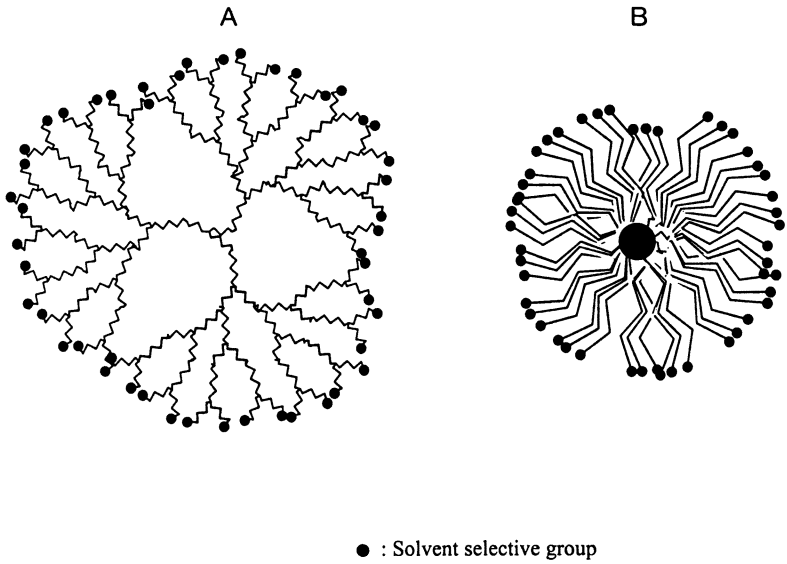
rates (*1*). Amphiphilic block- and graft copolymers are intensively investigated for this purpose because of their distinctive micellar behavior in selective solvents, interesting surface activity and complexation capabilities. The utilization of these materials as emulsifiers in different coatings, as drug carriers with membrane recognition and specific cell targeting, phase-transfer agents and polymer electrolytes is progressing rapidly (*2*). In addition, polymeric amphiphiles form aggregates that tend to be more stable than the micelles assembled of low molecular weight surfactants. Despite their numerous advantages as micelle forming materials, these polymers have also certain limitations. Some of the most difficult problems arise from the uncontrollable flexibility and the relatively broad molecular weight distribution of the building linear blocks resulting in ill defined, compact and entangled cores. This negatively affects their complexation and release capacity and hampers the quantitative evaluation of the structure-properties relationship for these systems.

Recently several groups reported their studies on unimolecular dendritic micelles and offered an ingenious and promising solution to this problem (*3*). Certain unique features distinguish these dendritic systems from the conventional macromolecular amphiphiles - the perfectly branched structure that emanates from a central core, the highly organized interior and the ever-increasing number of functional groups at the periphery (*4*), Scheme 1. A good example for the potential of the dendritic micelles is the entrapment of different "guest" molecules by appropriate modification of the exterior of the "host" dendrimer (*5*). This approach is rather spectacular and encouraging, but it also has limitations. Interestingly, the application of dendritic amphiphiles as phase-transfer agents, drug carriers and nanoscale reactors could be hampered by a feature considered one of their advantages. The highly organized interior of the dendritic unimolecular micelles has a semi-rigid molecular construction with prearranged geometry and void size, Scheme 1; this greatly reduces the number of substrates capable of penetration. In addition, chemical modification of the periphery of the dendrimer is imperative for the entrapment and subsequent release.

It would be interesting to design and test a self-assembling amphiphilic copolymer that combines the advantageous properties of both linear and dendritic amphiphiles. The first attempt in this direction was reported by Newkome et al. in 1986 with the synthesis of dumbbell-shaped dendritic alcohols ("arborols") containing hydrophilic dendritic groups attached to a short hydrophobic alkyl chain (*6*). These compounds exhibit interesting supramolecular behavior and form extended ribbon structures. In our studies we chose poly(ethylene glycol), PEG, as the hydrophilic block because of its proven biocompatibility and solubility in a broad variety of media. A series of hybrid amphiphilic ABA copolymers were produced with PEG as the B block and poly-3,5-dihydroxybenzilic dendrimers as the A blocks (*7*). The structure of the copolymer containing two second-generation monodendrons and PEG is presented in Scheme 2. It was shown that these hybrid macromolecules aggregate in unimolecular or multimolecular micelles depending on the size of the dendritic segments and the length of the PEG block (*7,8*). According to their behavior in aqueous media these systems belong to the group of amphiphilic copolymers that self-assemble through their end-blocks. This class of material is important both from



Scheme 1.
Unimolecular Dendritic Micelle (A) *vs* Conventional Micelle (B)

theoretical and practical points of view because of the entropy constraints, the variety of possible macromolecular assemblies (stars, rosettes, physical networks and others) and the resulting final characteristics of the systems (*9*).

The first part of the chapter reviews the synthesis of the hybrid linear-dendritic amphiphiles composed of PEG and poly-3,5-dihydroxybenzyl ether monodendrons, and the solution and solid-state properties that are related to their association behavior. The second portion concentrates on the encapsulation studies and information on the character of the dendritic core that can be derived from them.

Experimental Details

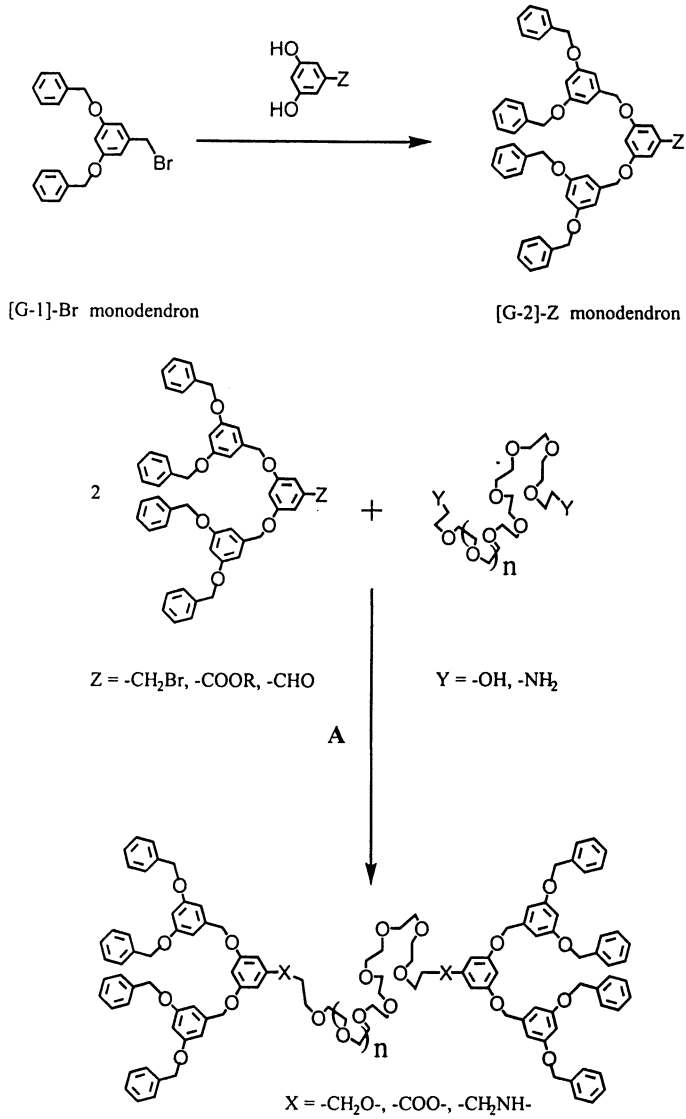
Materials. The hybrid linear-dendritic block copolymers, [G-2]-PEG5000-[G-2] were synthesized from poly(ethylene glycol), PEG, with nominal molecular weight 5,000 (Shearwater Polymers, Inc.) and two second-generation poly(benzyl ether) monodendrons (Scheme 2.A) with a benzyl bromide moiety at their 'focal' points (*10*). The experimental details are given elsewhere (*7*). The polyaromatic hydrocarbons (PAHs) - phenantrene, pyrene and perylene (all from Aldrich), and fullerene C_{60} (Southern Chemical Group) were used without further purification. The experiments were performed in deionized (DI) water (18.3 MΩ).

Instrumentation. The solubilization experiments were performed in an Aquasonic model 75D sonicator (VWR Scientific), the solutions were clarified by centrifugation using a Sorvell TC6 swingarm centrifuge (DuPont) and the spectroscopic measurements were made in a DU 640B UV-Vis spectrometer (Beckman) and SPEX Fluorolog-3 spectrophotometer (Instruments CA). Size-exclusion chromatography (SEC) analyses were performed in methanol-water (1:1, v/v, with 0.1 M NaN_3) at a nominal flow rate 1 ml/min and 30°C. The SEC system consisted of a Waters 510 pump, a U6K universal injector (Waters), a differential viscometric detector R 110 (Viscotek) and a differential refractive index (dRI) detector Refractomonitor IV (Milton-Roy) connected in parallel. The separations were achieved across a set of two Shodex PROTEIN KW 802.5 and 804 columns.

Dissolution of PAHs in water. An excess of the PAH, finely ground was placed in a 25 ml volumetric flask and DI water was added to the full volume of the flask. The mixture was sonicated in the water bath of the sonicator for 6 h at 30°C and was left at the same temperature to equilibrate for 48 h. The clear solution above the PAHs particles was analyzed by UV-Vis spectroscopy in several 24-hour intervals.

Hybrid Copolymer solutions. Solutions of [G-2]-PEG5000-[G-2] in DI water with concentrations 1.1×10^{-7}, 1.1×10^{-6}, 1.1×10^{-5}, 1.1×10^{-4}, and 1.1×10^{-3} mol/L were prepared. The copolymer dissolved gradually and was left to equilibrate for 48 h at room temperature. After that period the resulting clear colorless solutions were analyzed by UV-Vis and fluorescence spectroscopy.

Encapsulation studies. To each solution of the hybrid was added 50 mg of a finely ground PAH. The heterogeneous mixtures were sonicated for 6 h at 30°C and left to equilibrate for 24 h. After recording the UV-Vis and fluorescence spectra the solutions were sonicated for one hour and left to equilibrate for additional 48 h. Spectroscopic analyses were performed again. The mixtures were left at 30°C for 9 days and final spectral analyses were made with each mixture.



Scheme 2. A
Synthesis of Second-Generation Monodendrons, [G-2]-Z, and Subsequent Formation of ABA Copolymers by Reaction of Preformed Blocks

Spectroscopic procedures. All UV-Vis analyses were made at 30°C from 190 to 600 nm with a scanning speed of 600 nm/min. The changes in the concentrations of the PAHs were calculated using the following molar extinction coefficients: pyrene - $\varepsilon = 32{,}300\ L\times mol^{-1}\times cm^{-1}$ at $\lambda = 319$ nm (*11*); phenantrene - $\varepsilon = 14{,}400\ L\times mol^{-1}\times cm^{-1}$ at $\lambda = 293$ nm (*11*), perylene - $\varepsilon = 27{,}200\ L\times mol^{-1}\times cm^{-1}$ at $\lambda = 418$ nm (*11*) and C_{60} - $\varepsilon = 175{,}000\ L\times mol^{-1}\times cm^{-1}$ at $\lambda = 254$ nm (*12*). The steady-state fluorescence spectra were recorded on SPEX Fluorolog-3 spectrophotometer (Instruments CA) from 300 nm to 500 nm with both excitation and emission slits set at a 4 nm bandpass. The excitation wavelengths were: 335.5 nm (pyrene); 282 nm (phenantrene) and 408 nm (perylene).

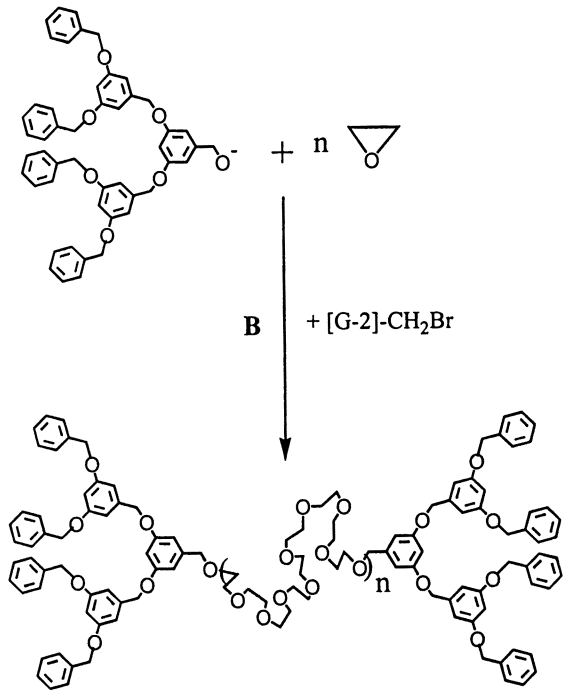
Results and Discussion

This report will discuss only a selected member of this copolymer series, namely [G-2]-PEG5000-[G-2]. It contains second-generation poly(benzyl ether) monodendrons with well developed branching structure that are easy to make in large quantities and PEG with molecular weight 5,000 that is commercially available from several vendors.

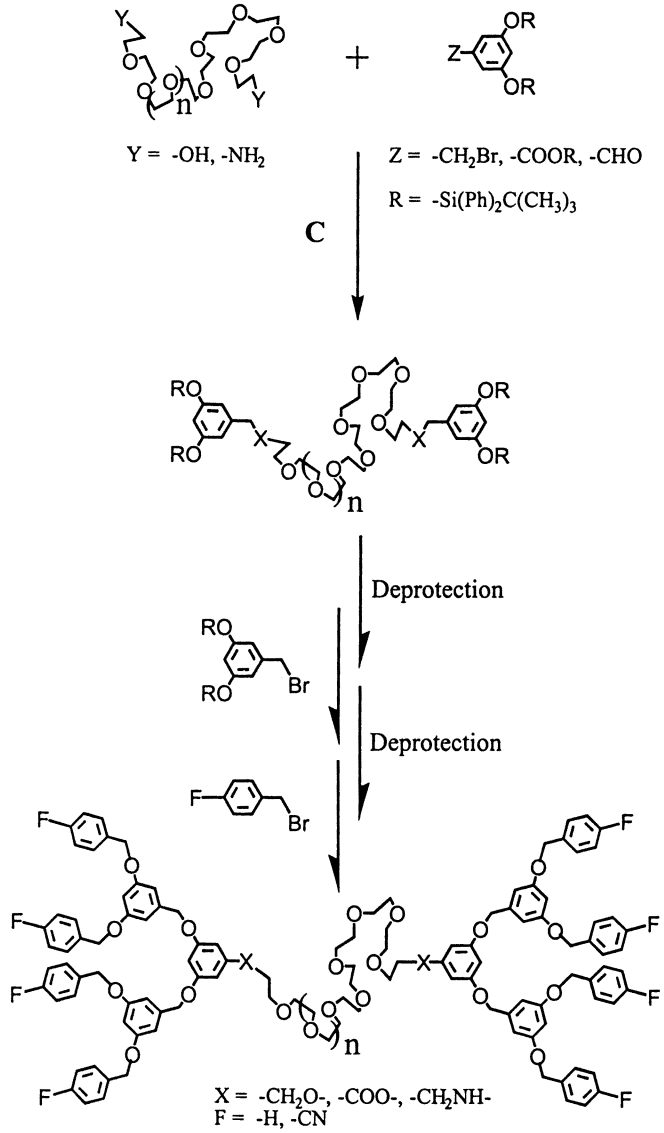
Synthesis of linear-dendritic block copolymers containing PEG. Three distinct methods can be used for the preparation of the linear-dendritic hybrids. The first one is based on the coupling of preformed blocks - PEG and two Fréchet-type monodendrons using different chemical reactions (Scheme 2A). The most effective reaction is the Williamson ether synthesis using a dendritic wedge with a benzyl bromide moiety at the 'focal' point and telechelic PEG containing two hydroxyl end-groups. Within 3 hours the reaction leads practically to full conversion even at only slight excess of the dendritic bromide (*13*). The process can be easily monitored by size-exclusion chromatography with dual (dRI/UV) detection. A transesterification reaction between the dendritic ester and PEG can also be used to form a block copolymer that differs from the previous one only by the nature of the link between the two fragments - an ester *vs* ether group. The reaction is performed under dynamic vacuum in the melt and in the presence of catalytic amounts of tin or cobalt salts (*13*). Alternatively, a reductive amination (*14*) between a dendritic aldehyde and PEG with two peripheral amino groups (Jeffamine® polymers have also been tested) can be employed to produce the targeted hybrid copolymer (*15*). However, the last two methods afford the desired compounds in much lower yields (50 - 80 %). The construction of linear dendritic hybrids based on the reaction of activated PEG and protected monodendrons was also reported (*16*).

The second approach (Scheme 2B) is based on the assumption that dendritic alcoholates, previously reported to initiate the polymerization of ε-caprolactone (*17*), can also trigger the ring-opening polymerization of ethylene oxide. Then the "living" polyether chain can be terminated by a dendritic bromide affording the same ABA block copolymer (*18*). Potential advantages of this method are the ability to grow the hydrophilic block to a specific chain length that is not commercially available and attach dissimilar dendritic fragments at the PEG ends.

The third strategy, Scheme 2C, uses telechelic PEG as the starting block and protected dihydroxybenzyl bromides can be added to grow the dendritic fragments in a typical protection/deprotection sequence (*19*). This approach was initially employed



Scheme 2. B
Synthesis of ABA Copolymers Using Monodendrons as Initiators and End-capping Agents



Scheme 2. C
Synthesis of ABA Copolymers using PEG as a Template for Divergent Dendrimer Growth

by Chapman and coworkers for the formation of AB copolymers containing PEG and dendritic poly(α,ε-L-lysine) (*20*). Methoxy-terminated PEG was used as a template for the growth of the hydrophobic dendritic fragment. One of the advantages of this method is the possibility of forming hybrid amphiphilic copolymers with reactive functional groups at the periphery of the dendritic blocks that can be used later for the attachment of biologically active compounds or fluorescent tags.

It should be noted that so far, very few of the properties of the published linear-dendritic amphiphiles have been tested and very little is known about the mechanism of micelle formation for these systems, the number and position of the segments forming the core and the corona. The character of the microenvironment in the core of the assemblies is completely unknown. All this information is of paramount importance for the future practical application of dendritic amphiphiles as encapsulating agents, platforms for sustained drug release and vessels for chemical reactions on a nanometer scale.

Solution behavior of [G-2]-PEG5,000-[G-2]. It is known that the solubility of the amphiphilic linear-dendritic copolymers in aqueous media depends on the PEG/dendrimer ratio (*8*). [G-2]-PEG5000-[G-2] dissolves easily in methanol and water forming clear slightly opalescent solutions. SEC in methanol/water reveals that the composition of these solutions is concentration dependent. It should be mentioned that an extensive mass balance study was performed to verify that the composition picture provided by SEC is not obscured by adsorption and retention of fractions on the column packing. In all cases the injected materials could be recovered with an average yield of 99.8 %. At concentrations 1.5×10^{-4} mol/L and higher two distinct fractions are clearly visible in the SEC traces, Figure 1A. The first one that appears at 15.2 mL has an apparent molecular weight of 53,000 (related to PEG standards) indicating the presence of a multimolecular micelle. The second entity is a broad peak between 18 and 22 mL most probably consisting of ill-defined micelles with aggregation numbers between 2 and 4. Decreasing the concentrations of the copolymer from 5×10^{-5} mol/L down to the detection limit (1.5×10^{-6} mol/L) does not change the eluograms drastically, Figure 1B. The high molecular weight peak is still clearly visible along with increasing amounts of unimolecular micelles (21.5 mL). The limited sensitivity of the refractive index detector prevents the detection of the critical micelle concentration (cmc) of [G-2]-PEG5000-[G-2] by SEC. Static surface tension measurements performed in water at 24°C reveal that the onset of the self-assembly for this copolymer (cmc) appears at 1.3×10^{-6} mol/L (*21*). Heating the solutions at 60°C over extended periods of time does not change their composition, Figure 2. It could be assumed that at these conditions the micellar organization of the copolymer molecules is thermodynamically stable with the majority of the dendritic blocks concentrated in the core.

Solid state properties of [G-2]-PEG5,000-[G-2]. The peculiar organization of the hybrid amphiphile in aqueous medium is further evidenced by crystallization studies. Often the morphology of films cast from solution is a direct result of the specific organization of the polymer in the liquid medium. It can be fine-tuned by the pre-arrangement of the amphiphilic copolymer in selective solvents and by the nature of the substrate. This is an issue of growing importance because of the increased utilization of polymeric surfactants for surface modification (*21*). Crystals grown on

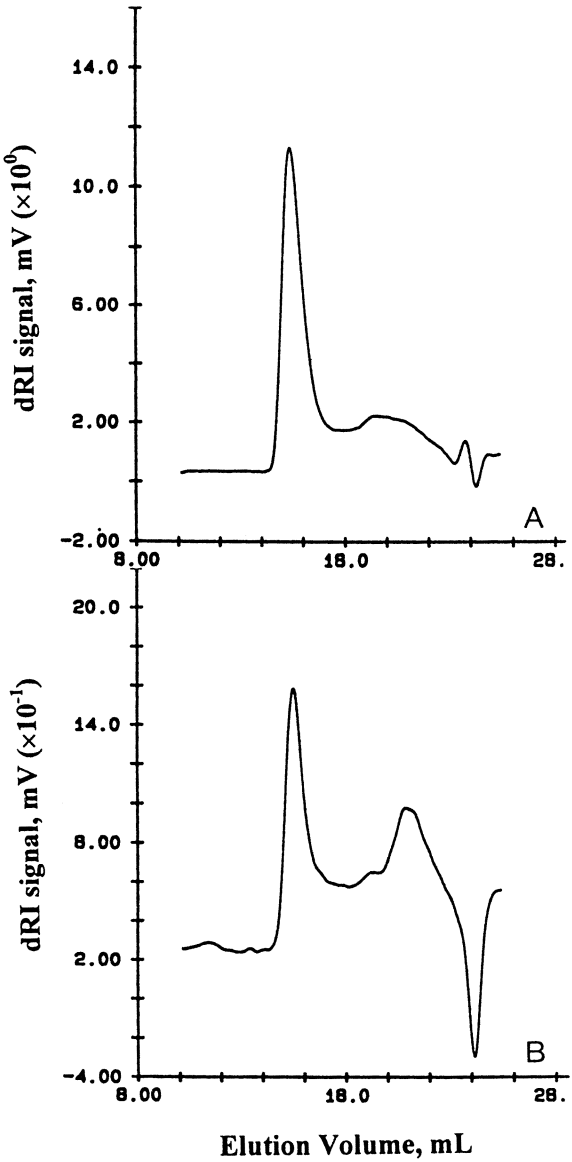


Figure 1. Aqueous size-exclusion chromatography of [G-2]-PEG5000-[G-2] at different concentrations. A - 1.5×10^{-4} mol/L; B - 5×10^{-5} mol/L.

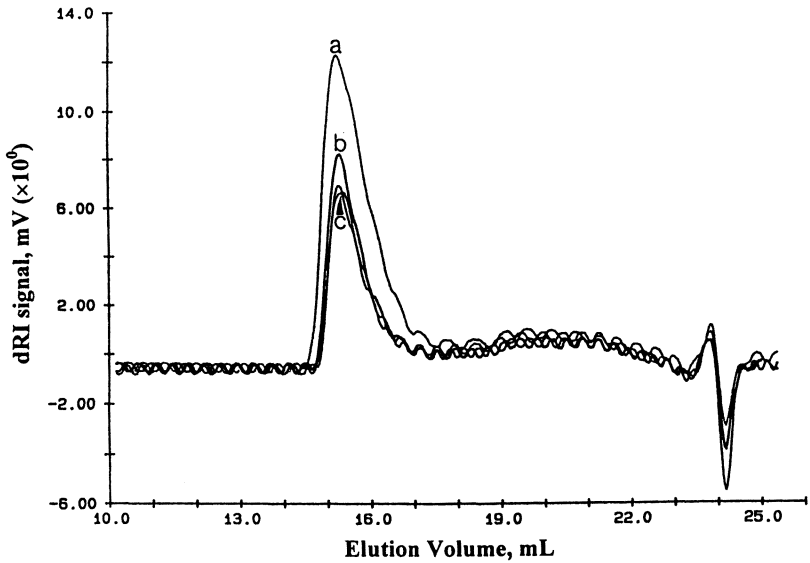


Figure 2. Aqueous size-exclusion chromatography of [G-2]-PEG5000-[G-2] solutions in water after heating at 60°C. a - initial solution; b - after 3 h; c - after 24 h and 7 days.

glass substrates from the melt (Figure 3) or from solutions in solvents good for both blocks (*8*) have a spherulite form and show a typical Maltese-cross pattern when analyzed by optical microscopy under crossed polarizers. Aqueous solutions with low concentrations (1×10^{-7} - 1×10^{-5} mol/L) yield thin films with similar surface morphology. When the experiment is repeated at higher concentrations in a chamber with controlled humidity the results are surprisingly different. The linear-dendritic hybrid crystallizes in unique star-like structures with sizes between 1 and 7 mm, and platelet morphology (Figure 4). It could be speculated that these formations are superaggregates constructed by a large number of micellar entities. It is evident that the self-assembly of [G-2]-PEG5000-[G-2] in water significantly affects the nucleation of the matrix mesophase (PEG) and the characteristics of its crystallization. This statement, however, needs further verification. The structure of the semi-diluted solutions and the crystals therefrom are currently being investigated by a combination of microscopy and scattering methods.

Encapsulation of polyaromatic hydrocarbons (PAHs) by [G-2]-PEG5000-[G-2] in water. Fluorescence and UV-Vis measurements are probably the most widely used methods to monitor the micellization process, evaluate the character of the core of the assemblies and study the binding of organic molecules to micellar systems in aqueous media. Pyrene and derivatives are the standard probes used in the studies (*22-24*). The vibronic fluorescence spectra of these compounds and more specifically the intensity ratio of the fourth and first peak in them (I_4/I_1) are very sensitive indicators for the local polarity of the environment surrounding the probe (*25*). Figure 5 shows the dependence of the pyrene fluorescence on the concentration of [G-2]-PEG5000-[G-2]. It is seen that at concentrations 1.1×10^{-4} mol/L and higher, the normalized spectra undergo a clear shift to longer wavelengths with a simultaneous change in the I_4/I_1 values. At low concentrations the probe is exposed to a relatively polar environment (I_4/I_1 = 0.79 - 0.83). It should be noted, that these values are still significantly higher than the reported values for pure water (0.71) and compounds similar to PEG and the linear-dendritic amphiphile: ethylene glycol (0.62), Brij 35 (0.69) and Triton X-100 (0.72) (*25*). It is seen, that at higher concentrations the I_4/I_1 ratio increases markedly up to 1.03, a value characteristic for entirely hydrophobic surroundings (*25*). Surprisingly, no eximer formation ($\lambda_{ex} \approx 480$ nm) is observed in the concentration range studied (Figure 5). The results obtained indicate that pyrene is encapsulated predominantly in the core of the micelles as it is shown schematically in Figure 6. Previous studies by Fréchet and coworkers have proven that poly(benzyl ether) dendrimers show little tendency to interpenetrate (*26*) and therefore they can form a *non-entangled* highly ordered entity in the center of the assembly. In this way the micellar core is capable of accommodating a *large number of molecules* that can be isolated (compartmentalized) in the internal voids of the dendrimers as well as in the space between the individual dendritic "wedges". This positioning of the pyrene molecules obviously prevents to a large extent their association and logically hampers the eximer formation. The I_4/I_1 value at high concentration clearly excludes the possibility that in the process of self-assembly water molecules might be partially entrapped in the voids between the monodendrons.

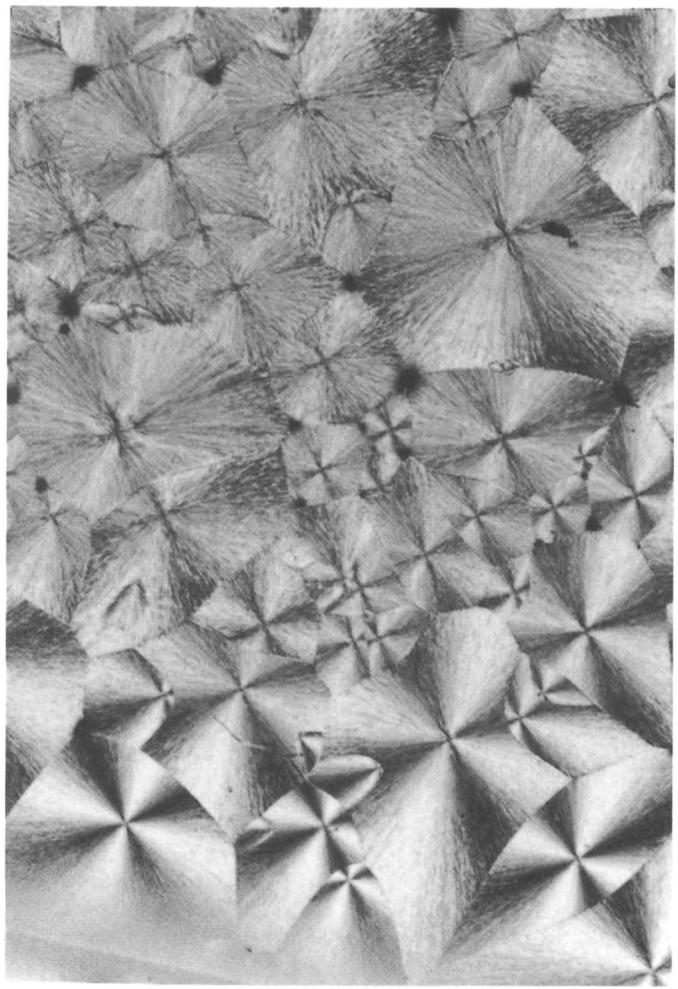


Figure 3. Polarized optical micrograph of [G-2]-PEG5000-[G-2] crystallized from the melt. Magnification 25×.

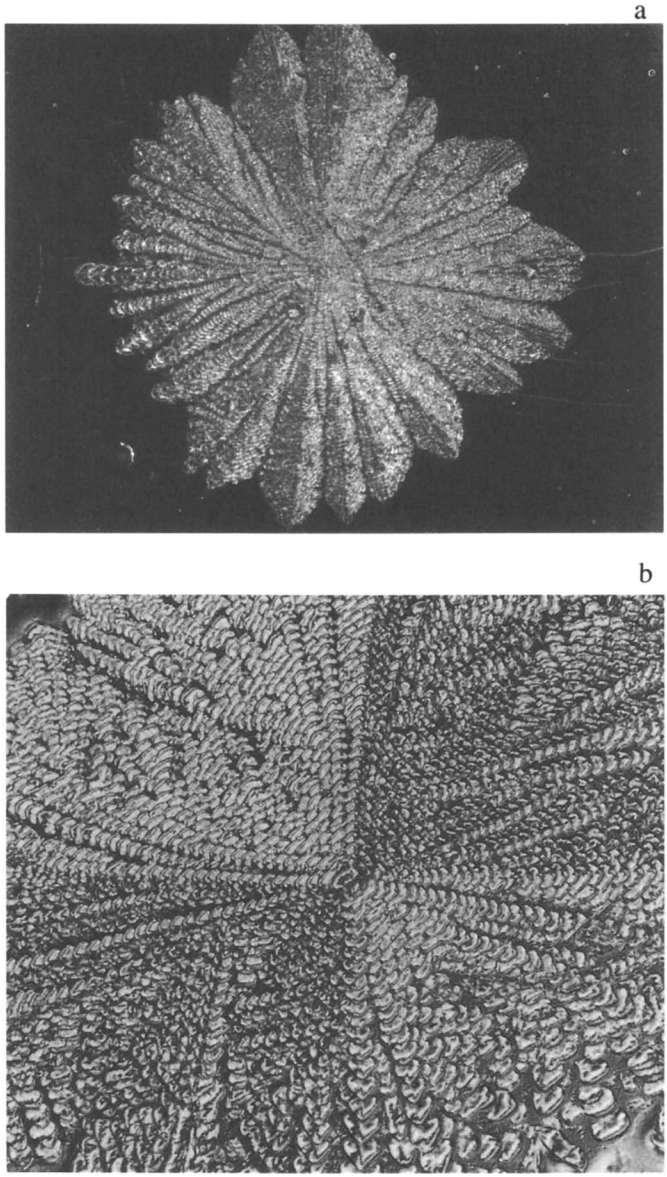


Figure 4. Optical microscopy of [G-2]-PEG5000-[G-2] crystallized from aqueous solutions. Concentration 1×10^{-3} mol/L. A - Dark-field micrograph, magnification 15×; B - polarized micrograph of the same crystal, magnification 25×.

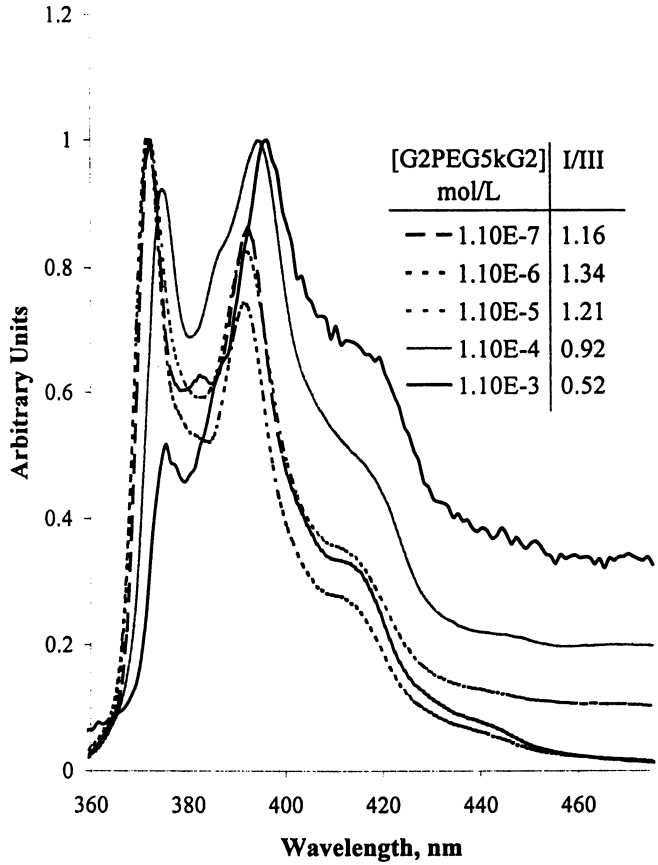


Figure 5. Fluorescence spectroscopy of mixtures of [G-2]-PEG5000-[G-2] and pyrene in water at different concentrations of the hybrid copolymer.

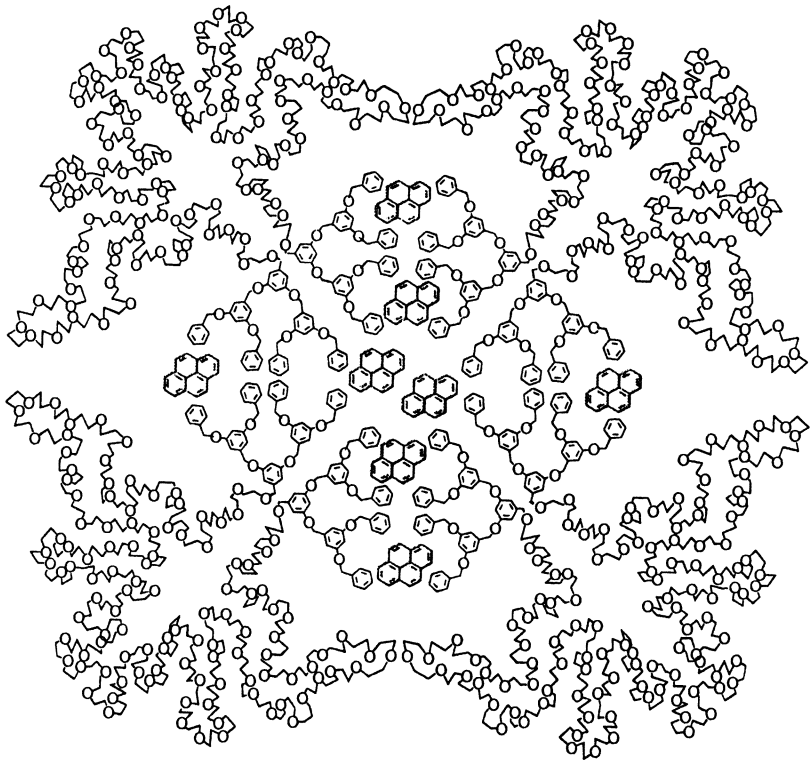


Figure 6. Schematic illustration of pyrene encapsulation by [G-2]-PEG5000-[G-2] in water.

The fluorescence studies can be extended further with binding experiments in order to evaluate the potential of the amphiphilic hybrids as encapsulating agents for removal of dangerous trace contaminants in aqueous waste (*27*). UV-Vis spectroscopy is used to investigate the entrapment of pyrene and other polycyclic aromatic compounds - phenantrene and perylene, Figure 7. Naturally, the smaller size of phenantrene and its geometry allow the accommodation of more molecules in the core of the micelles, while perylene is obviously excluded from the interior voids of the monodendrons and the quantities that can be bound are significantly lower. Quantitative information for the amounts of PAHs bound in similar systems is rather scarce. However, the data available indicate that the linear-dendritic amphiphiles compare favorably with their dendritic or linear analogues. The aqueous solubility of pyrene achieved with [G-2]-PEG5000-[G-2] is 5×10^{-5} mol/L (0.5 mol per mol polymer) against 9.5×10^{-5} mol/L obtained with surface functionalized fourth-generation poly(benzyl ether) dendrimer (*28*) (0.45 mol per mol dendrimer) and 1 mol per mol of comb-grafted polystyrene-polyethylene oxide with molecular weight 120,000 (*29*).

The encapsulation capability of [G-2]-PEG5,000-[G-2] is demonstrated further by the solubilization of large carbon clusters (fullerenes) in water. Incorporation of C_{60} and C_{70} into micelles and vesicles has recently attracted considerable attention (*30*) because of their potential use as artificial redox mediators in biological systems. The initial experiments show that amphiphilic hybrid linear dendritic copolymers are able to encapsulate significant amounts of C_{60} in water (Plate 1) in sharp contrast to dendritic unimolecular micelles which are not capable of C_{60} binding.

Micellar solutions containing high loads of pyrene and C_{60} are still capable of forming large crystalline structures (Plates 1 and 2). The typical color of the encapsulated compounds is visibly concentrated in the platelets of the crystals, indicating again their incorporation within the frame of the [G-2]-PEG5000-[G-2] assemblies. Their morphology, however, is significantly less organized in comparison with the pure crystals grown of the same copolymer under identical conditions (Figure 4).

Conclusions

The results of this study indicate that amphiphilic linear-dendritic copolymers could successfully complement the common low molecular weight surfactants and amphiphilic block copolymers. In contrast to the known micelle forming linear copolymers the novel hybrid macromolecules have perfectly branched globular segments that form the core of the micelle. This new approach for multimolecular micelles offers the distinct advantage of introducing a highly organized and restrictive entity in the center of the associating system. The potential benefits from this novel design could include increased selectivity to different organic substrates, improved solubility in aqueous and organic media of polycyclic aromatic compounds including fullerenes, a broad array of complexation capabilities, enhanced surface activity and catalytic potential. There is little doubt that such micelles containing dense and highly organized globular fragments will enable the development of novel unique devices and technologies that will find applications in biotechnology, environmental protection and the biomedical field.

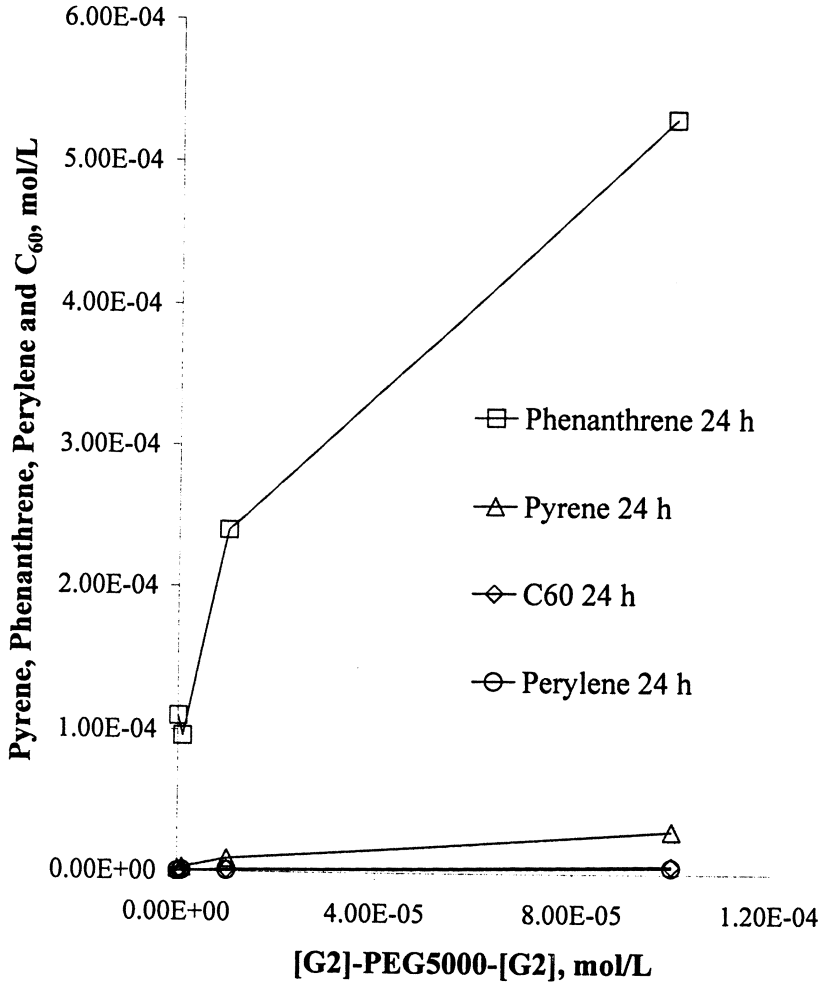


Figure 7. Binding of PAHs and C_{60} by [G-2]-PEG5000-[G-2] in water.

Acknowledgments

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