Amphiphilic Hydrogels Constructed by Poly(ethylene glycol) and Shape-Persistent Dendritic Fragments[1]

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ABSTRACT: This paper describes the synthesis of amphiphilic hydrogels with highly shape persistent cross-link junctions using linear blocks, such as poly(ethylene glycol), PEG, and perfectly branched (dendritic) macromolecules. The synthetic strategy is based on the reaction of PEG with isocyanate or epoxy end groups as the hydrophilic component and hydrophobic dendritic poly(benzyl ethers) with amino groups at the periphery. It is found that the efficiency of the cross-linking reaction depends on the nature of chemical reaction used and the stoichiometric ratio of the two building blocks. The swelling of the gels formed is affected by the relative PEG content and by the polarity of the medium and the temperature, and it varies between 1.2 and 16.7 (by weight). The influence of various factors on the degree of crystallinity and phase segregation is also discussed.

Introduction

Synthetic hydrogels are versatile materials that are increasingly used as devices for controlled release of pharmacological substances,[2] as phase-transfer agents,[3] as supports for catalysts in different organic reactions,[4] as matrices for cell encapsulation,[5] and as size-selective polymerization media[6] and other uses. Poly(ethylene glycol), PEG, is widely employed as the major component in these water-swollen networks[7] because of its good biocompatibility and solubility in various solvents.

The procedures used in the formation of PEG hydrogels can be divided into three main groups: (1) The first is formation of physical networks by specific interactions of designated segments in the polymer chains or by entanglement of macromolecules with very high molecular weight.[8] This method yields materials that are usually free of impurities like residual cross-linking agents − an important requirement for any biomedical application. The deficiencies of the physical gels are in their easy disruption by relatively small mechanical forces or by changes in temperature and solvents. (2) Second is radiation-induced cross-linking of PEG and PEG derivatives and copolymers.[9] This approach also produces pure hydrogels and their degree of cross-linking can be conveniently controlled by the dose of irradiation. The disadvantages of the method are in the high limits in polymer molecular weights (M_w > 500 000) and the relatively high occurrence of defects in the network with pending linear chains. (3) Finally there is chemical cross-linking by copolymerization of PEG macromonomers and selected bifunctional comonomers or by modification of preformed functionalized polymers and copolymers.[10] In this method the network density can be controlled by the concentration of the cross-linking agent, but additional purification of the gel is necessary to remove the unreacted cross-linker. It should be mentioned that all three methods yield gels with a random distribution of cross-links (junctions) and interjunction molecular weights. Another common disadvantage of the hydrogels formed by all three methods is the relatively small size of their hydrophobic junctions and the ill-defined macromolecular organization in these domains. Both drawbacks ultimately affect not only the encapsulation and release rates into and from the gels, but also their binding capacity. While the randomness in the interjunction molecular weights could possibly be eliminated by a reaction of telechelic PEGs and multifunctional cross-linking agents, very few studies have been published on the incorporation of large well-structured hydrophobic domains in amphiphilic hydrogels despite the obvious advantages they might offer.[11] The data in these early publications reveal that networks containing PEG and linear or cyclic siloxane segments exhibit a much stronger affinity toward various hydrophobic molecules in comparison to conventional linear and cross-linked PEGs.[11]

Dendritic macromolecules would be the ideal candidates for cross-linking agents.[12] They have highly symmetrical, perfectly branched structures and multiple reactive sites placed in the interior and at the periphery of the macromolecules. The number (density) of the junctions and their chemical composition can be easily controlled by the generation of the dendrimer (i.e., the number of reactive groups therein) and the chemistry used in the construction. The fractal character of the dendritic interior provides unique possibilities for size-selective encapsulation, manipulation and release of different substrates. Surprisingly, publications on dendrimer networks are rather scarce.[13] In addition, in all published experiments involving dendritic fragments as the network junctions, only small molecules have been used to form the links between them.

The goal of this study is to explore the synthesis of amphiphilic hydrogels using telechelic PEG and surface-functionalized poly(benzyl ether) dendrimers. The selected linear (hydrophilic) and dendritic (hydrophobic) segments should be randomly distributed in the bulk of the networks formed, but their size and chemical composition would be precisely engineered (Figure 1).

Experimental Section

Materials. Poly(ethylene glycol) diisocyanate and poly(ethylene glycol)−bis(epoxide) with PEG molecular weight 3400 and M_w/M_n = 1.03 were obtained from Shearwater Polymers and were stored at −10 °C under nitrogen atmosphere prior to use. According to the manufacturer's data the

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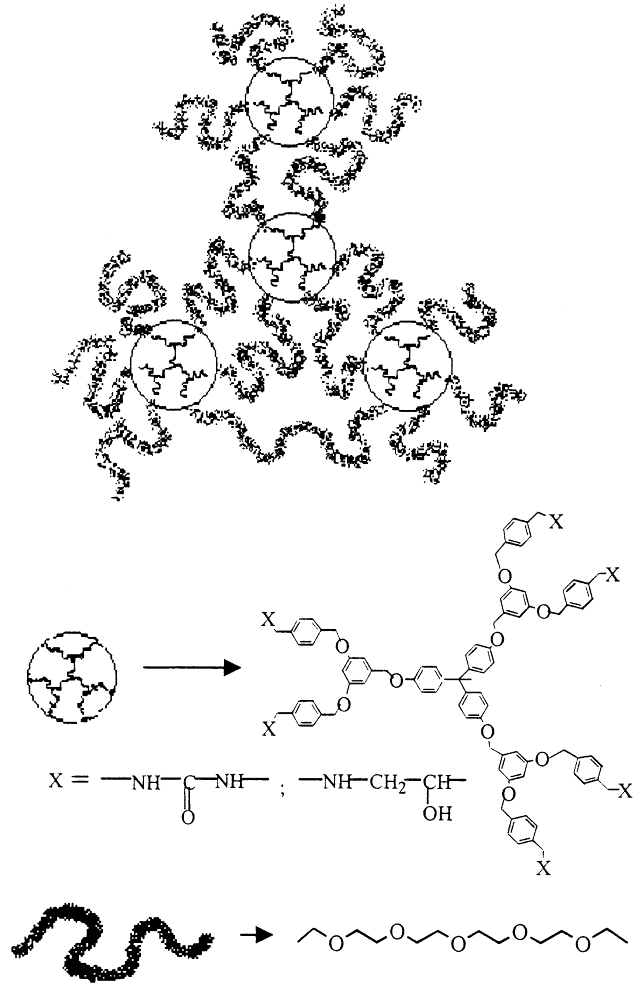


Figure 1. Schematic representation of a hydrogel, constructed by linear and dendritic fragments with precisely engineered size/length and hydrophilic/hydrophobic balance.

degree of functionalization was 86−88% for both materials and the content of higher molecular weight impurities (dimers and higher coupling products) was between 2 and 6%. Triethylamine, 3,5-dihydroxybenzyl alcohol, carbon tetrabromide (CBr_4), 18-crown-6, and 1,1,1-tris(4-hydroxyphenyl) ethane from Aldrich, while 4-(bromomethyl)benzonitrile, triphenylphosphine (PPh_3), ethyl acetate (EtOAc), $LiAlH_4$, and K_2CO_3 from ACROS (Fisher Scientific) were used without further purification. Dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were dried over P_2O_5 and benzophenone−sodium, respectively, and distilled immediately before use.

Instrumentation. Size-exclusion chromatography (SEC) analyses were performed on a SEC line consisting of a 510 pump, U6K universal injector, 486 tunable UV detector, and a R410 differential refractometer (all Waters). The separations were achieved at 40 °C across a set of three 5 μm columns (100 Å, 500 Å and Linear) from American Polymer Standards with THF eluting at 1 mL/min.

The FT-IR measurements of the lower-generation tridendrons and the starting functionalized PEGs were performed on a Nicolet 410 spectrophotometer from 500 to 4000 cm^{-1}. The materials were analyzed as thin films on disposable IR cards (3M, Type 62 TPFE films). The higher generation tridendrons and resulting networks therefrom were insoluble in common solvents and were analyzed in a powder/particle form on a Magna 750 FT-IR spectrometer (Nicolet) using a MTEC 300 photoacoustic module.

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6, when necessary, (both solvents being also used as internal standards) at room temperature on a Bruker Avance 300 instrument (^1H: 300 MHz).

DSC data were acquired on a Seiko DSC 220 calorimeter under nitrogen and in a heating/cooling/heating cycle between −100 and +100 °C with a scanning rate of 10 °C/min. The temperatures of the melting/crystallization transitions were determined at the intersection of the two tangents drawn at the baseline and the leading slope of the transition peak using indium (T_m = 156.6 °C) as the calibration standard. In all cases the calculations were made using the data from the second heating stage. The degree of crystallinity of the hydrogel (X_c) was obtained from the following equation:

$$X_c = \frac{\Delta H_f}{W \Delta H_{f0}} \times 100\%$$

where ΔH_f and ΔH_{f0} are the PEG enthalpies of fusion in the hydrogels and in a single PEG crystal (ΔH_{f0} = 197 J/g or 8.65 kJ/mol),[14] respectively, and W is the PEG weight fraction in the corresponding hydrogel.

Synthesis. Poly(benzyl ether) dendrimers with amino groups at the periphery were obtained from cyano-terminated precursors by modifications of known methods.[15] Ar, Ar′, and Ar″ stand for the 1,3,5-substituted aromatic rings from inside (i.e., close to the core) to outside monomer unit layers of the dendrimers. The generation number refers to the number of layers of monomer units.

Preparation of the Monomer $(NC)_2$[G-1]-OH (1). In a three-neck round-bottom flask, K_2CO_3 (4 equiv) was added to 150 mL of acetone under nitrogen atmosphere. One equivalent of 3,5-dihydroxybenzyl alcohol and 2.05 equiv of α-bromo-*p*-tolunitrile were added to the solution under stirring, followed by 0.3 equiv of 18-crown-6. The solution was stirred vigorously under nitrogen atmosphere and refluxed for 24 h. The evolution of the reaction was checked by thin-layer chromatography (TLC) with CH_2Cl_2. After the disappearance of the initial reagents spots in the TLC plates, the mixture was allowed to cool to room temperature, and K_2CO_3 was filtered off. The solvent was evaporated to dryness, the crude product was extracted three times with water and CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$. The solvent was removed under dynamic vacuum and the resulting white-brown solid was analyzed by ^1H NMR (yield: 95%). ^1H NMR ($CDCl_3$): δ 1.71 (1H, t, CH_2OH) 4.64 (2H, d, CH_2OH), 5.11 (4H, s, NCPhCH_2), 6.49 (1H, t, ArH), 6.62 (2H, d, ArH), 7.51 and 7.67 (8H, ABq, NCPhH).

General Procedure for the Synthesis of Dendritic Benzyl Bromides. These reactions were carried out on a scale of 0.5−10 g of dendritic benzyl bromide, depending on the generation number. CBr_4 (1.25 equiv) and PPh_3 (1.25 equiv) were added to a solution of the corresponding dendritic benzyl alcohol (1 equiv) in the minimum amount of THF. The reaction mixture was stirred at room temperature under nitrogen atmosphere. Typically, the reaction mixture changed from a colorless to a yellow solution with a precipitate forming over 1−5 min, depending on the generation number. The progress of the reaction was monitored by TLC. Additional amounts of CBr_4 and PPh_3 were added at 15-min intervals until the reaction was complete. The reaction was terminated by addition of a large amount of water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 three times and the combined CH_2Cl_2 portions were dried over $MgSO_4$. The solution was concentrated under low pressure. Decomposition was observed when the mixture turned bright yellow followed by green and then brown if the reaction was not promptly quenched.

$(NC)_2$[G-1]-Br (2). This was prepared from $(NC)_2$[G-1]-OH and 1.25 equiv of CBr_4 and PPh_3. The product was recrystallized in methanol to produce white crystals (yield: 90%). ^1H NMR ($CDCl_3$): δ 4.40 (2H, s, CH_2Br), 5.10 (4H, s, NCPhCH_2), 6.50 (1H, t, ArH), 6.64 (2H, d, ArH), 7.54 and 7.67 (8H, ABq, NCPhH).

$(NC)_4$[G-2]-Br. This was prepared from $(NC)_4$[G-2]-OH and 1.35 equiv of CBr_4 and PPh_3. The crude product was purified by flash chromatography eluting with solvent mixture (EtOAc: CH_2Cl_2 = 1:20) to produce a white powder (yield: 85%). ^1H NMR ($CDCl_3$): δ 4.40 (2H, s, CH_2Br), 4.97 (4H, s, Ar′CH_2),

5.11 (8H, s, NCPhCH_2), 6.43 (1H, t, ArH), 6.53 (2H, t, Ar′H), 6.61 (2H, d, ArH), 6.65 (4H, d, Ar′H), 7.53 and 7.64 (16H, ABq, NCPhH). ^{13}C NMR ($CDCl_3$): δ 33.34 (CH_2Br), 68.96, 69.70 (CH_2O), 101.74, 102.18 (ArC and Ar′C), 106.45, 108.07 (ArC and Ar′C), 111.74 (NCPhC), 118.48 (CN), 127.44, 132.30, 139.82 (NCPhC), 139.41, 141.98 (ArC and Ar′C), 159.57, 159.71 (ArC and Ar′C).

$(NC)_8$[G-3]-Br. This was prepared from $(NC)_8$[G-3]-OH and two consecutive additions of 1.25 equiv of CBr_4 and PPh_3 within 30 min. The crude product was purified by flash chromatography eluting with solvent mixture (EtOAc:CH_2Cl_2 = 1:15) to produce a white glass (yield: 80%). ^{1}H NMR ($CDCl_3$): δ 4.39 (2H, s, CH_2Br), 4.94 (4H, s, Ar′CH_2), 4.97 (8H, s, Ar″CH_2), 5.09 (16H, s, NCPhCH_2), 6.47 (1H, t, ArH), 6.52 (6H, m, Ar′H and Ar″H), 6.62−6.65 (12H, m, ArH and Ar′H and Ar″H), 7.50−7.61 (32H, ABq, NCPhH). ^{13}C NMR ($CDCl_3$): δ 33.41 (CH_2Br), 68.95, 69.68, 69.92 (CH_2O), 101.59, 101.66, 102.27 (ArC), 106.47, 108.08 (ArC), 111.70 (NCPhC), 118.49 (CN), 127.45, 132.28, 141.98 (NCPhC), 139.02, 139.54, 139.89 (ArC), 159.56, 159.84 (ArC).

General Procedure for the Synthesis of Dendritic Benzyl Alcohols. The reactions were carried out on a scale of 0.5−10 g dendritic benzyl alcohol, depending on the generation number. A mixture of the appropriate dendritic cyanobenzyl bromide (2.05 equiv), 3,5-dihydroxylbenzyl alcohol (1 equiv), K_2CO_3 (4 equiv) and 18-crown-6 (0.3 equiv) in acetone was heated at reflux and stirred vigorously under nitrogen atmosphere for 24−48 h (depending on the generation number). The reaction was monitored by TLC. The mixture was allowed to cool to room temperature, K_2CO_3 was removed by filtration, and the solvent was evaporated under low pressure. The residue was partitioned between water and CH_2Cl_2 and the aqueous layer extracted with CH_2Cl_2 three times. The combined organic portions were dried over $MgSO_4$ and evaporated to dryness.

$(NC)_4$[G-2]-OH. This was prepared from $(NC)_2$[G-1]-Br and purified by flash chromatography eluting with solvent mixture (EtOAc:CH_2Cl_2 = 1:5) to produce a white powder (yield: 90%). ^{1}H NMR ($CDCl_3$): δ 1.60 (1H, t, CH_2OH), 4.63 (2H, d, CH_2OH), 4.97 (4H, s, Ar′CH_2), 5.10 (8H, s, NCPhCH_2), 6.43 (1H, t, ArH), 6.52 (2H, t, Ar′H), 6.59 (2H, d, ArH), 6.64 (4H, d, Ar′H), 7.50 and 7.65 (16H, ABq, NCPhH). ^{13}C NMR ($CDCl_3$): δ 64.87 (CH_2OH), 68.94, 69.59 (CH_2O), 101.16, 101.63 (ArC and Ar′C), 105.58, 106.43 (ArC and Ar′C), 111.67 (NCPhC), 118.50 (CN), 127.45, 132.28, 142.02 (NCPhC), 139.69, 141.61 (ArC and Ar′C), 159.54, 159.78 (ArC and Ar′C).

$(NC)_8$[G-3]-OH. This was prepared from $(NC)_4$[G-2]-Br and purified by flash chromatography eluting with solvent mixture (EtOAc:CH_2Cl_2 = 1:8) to produce a white glass (yield: 75%). ^{1}H NMR ($CDCl_3$): δ 4.61 (2H, d, CH_2OH), 4.94 (4H, s, Ar′CH_2), 4.95 (8H, s, Ar″CH_2), 5.09 (16H, s, NCPhCH_2), 6.46 (1H, t, ArH), 6.51 (6H, m, Ar′H and Ar″H), 6.61−6.64 (12H, m, ArH and Ar′H and Ar″H), 7.50−7.67 (32H, ABq, NCPhH). ^{13}C NMR ($CDCl_3$): δ 64.94 (CH_2OH), 68.94, 69.64, 69.80 (CH_2O), 101.27, 101.49, 101.67 (ArC), 105.59, 106.34, 106.44 (ArC), 111.68 (NCPhC), 118.49 (CN), 127.44, 132.21, 141.98 (NCPhC), 139.29, 139.57, 143.70 (ArC), 159.54, 159.80, 159.91 (ArC).

General Procedure for the Synthesis of Cyano-Terminated Tridendrons. A mixture of the appropriate dendritic cyano-benzyl bromide (3.1 equiv), 1,1,1-tris(4-hydroxylphenyl)ethane (1.0 equiv), dry K_2CO_3 (4.0 equiv), and 18-crown-6 (0.3 equiv) in acetone was heated at reflux and stirred vigorously under nitrogen atmosphere from 36 to 48 h (depending on the generation). The reaction was monitored by TLC. The mixture was allowed to cool to room temperature, K_2CO_3 was removed by filtration, and the solvent was evaporated under low pressure. The residue was partitioned between water and CH_2Cl_2 and the aqueous layer extracted with CH_2Cl_2 three times. The combined organic portions were dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by flash chromatography.

{$(NC)_2$[G-1]}$_3$C—CH_3 (3). This was prepared from $(NC)_2$-[G-1]-Br and purified by flash chromatography, eluting with solvent mixture (EtOAc:CH_2Cl_2 = 1:18) to produce a white glass (yield: 85%). ^{1}H NMR ($CDCl_3$): δ 2.12 (3H, s, CH_3), 4.96 (6H, s, CH_2O), 5.11 (12H, s, NCPhCH_2), 6.52 (3H, t, ArH), 6.67 (6H, d, ArH), 6.85 (6H, d, core Ar′H), 6.99 (6H, d, core Ar′H), 7.53 and 7.65 (24H, ABq, NCPhH). ^{13}C NMR ($CDCl_3$): δ 30.78 (CH_3), 50.71 (CCH_3), 69.08 (ArCH_2O), 69.76 (NCPhCH_2O), 101.72, 106.65 (ArC), 111.88 (NCPhC), 114.04 (core Ar′C), 118.60 (CN), 127.59, 132.43, 140.10 (NCPhC), 129.66 (core Ar′C), 142.14, 156.71 (core Ar′C), 142.18, 159.67 (ArC). FT-IR, ν: 2908, 2203, 1606, 1505, 1166, 827 cm^{-1}.

{$(NC)_4$[G-2]}$_3$C—CH_3. This was prepared from $(NC)_4$[G-2]-Br and purified by flash chromatography, eluting with solvent mixture (EtOAc:CH_2Cl_2 = 1:15) to produce a white glass (yield: 80%). ^{1}H NMR ($CDCl_3$): δ 2.08 (3H, s, CH_3), 4.94 (6H, s, ArCH_2O), 4.97 (12H, s, Ar′CH_2), 5.10 (24H, s, NCPhCH_2), 6.45 (3H, t, ArH), 6.52 (6H, t, Ar′H), 6.64 (6H, d, ArH), 6.65 (12H, d, Ar′H), 6.85 (6H, d, core Ar′H), 6.97 (6H, d, core Ar′H), 7.50 and 7.61 (48H, ABq, NCPhH). ^{13}C NMR ($CDCl_3$): δ 30.71 (CH_3), 50.58 (CCH_3), 68.93 (ArCH_2O), 69.65, 69.81 (Ar′CH_2O and NCPhCH_2O), 101.50, 101.67 (ArC and Ar′C), 106.47 (ArC and Ar′C), 111.69 (NCPhC), 113.93 (core Ar′C), 118.50 (CN), 127.44, 132.28, 139.59 (NCPhC), 129.56 (core Ar′C), 139.53, 141.99 (ArC and Ar′C), 156.67 (core Ar′C), 159.55, 159.79 (ArC and Ar′C).

{$(NC)_8$[G-3]}$_3$C—CH_3. This was prepared from $(NC)_8$[G-3]-Br and purified by flash chromatography eluting with solvent mixture (EtOAc:CH_2Cl_2 = 1:10) to produce a white glass (yield: 75%). ^{1}H NMR ($CDCl_3$): δ 2.04 (3H, s, CH_3), 4.90−4.94 (42H, m, ArCH_2, Ar′CH_2 and Ar″CH_2), 5.05 (48H, s, NCPhCH_2), 6.49 (3H, t, ArH), 6.50 (18H, m, Ar′H and Ar″H), 6.62−6.65 (36H, m, ArH, Ar′H and Ar″H), 6.80 (6H, d, core Ar′H), 6.97 (6H, d, core Ar′H), 7.44−7.57 (96H, ABq, NCPhH). ^{13}C NMR ($CDCl_3$): δ 20.90 (CH_3), 60.25 (CCH_3), 68.90, 69.63 (CH_2O), 101.47, 101.62 (ArC), 106.44 (ArC), 111.65 (NCPhC), 113.91 (core Ar′C), 118.48 (CN), 129.53 (core Ar′C), 127.42, 132.24, 141.96 (NCPhC), 139.17, 139.54 (ArC), 156.64 (core Ar′C), 159.54, 159.81, 159.92 (ArC).

General Procedure for Synthesis of Amino-Terminated Tridendrons. The THF solution of the appropriate cyano-terminated tridendron was added to a solution of $LiAlH_4$ (2 equiv per CN function group) in dry THF drop by drop under vigorous stirring. The reaction mixture was heated at reflux overnight under nitrogen atmosphere. The mixture was allowed to cool and then quenched with several drops of water. Methanol was added (methanol:THF = 1:3), and after filtration, the solvent mixture was evaporated to dryness. The yellow glassy product was obtained by washing the crude product with a large amount of water. The product was characterized by ^{1}H NMR and FT-IR.

{$(H_2NCH_2)_2$[G-1]}$_3$C—CH_3 (4) (Yield: 70%). ^{1}H NMR (DMSO-d_6): δ 2.01, (3H, s, CH_3), 2.46−2.87 (12H, s broad, NH_2), 3.70 (12H, s, CH_2NH_2), 4.96 (6H, s, CH_2O), 5.03 (12H, s, NCPhCH_2), 6.58 (3H, t, ArH), 6.66 (6H, d, ArH), 6.88 and 6.91 (12H, m, core Ar′H), 7.32 and 7.33 (24H, m, NCPhH). FT-IR, ν: 3370, 3297, 3025, 2860, 1600, 1156, 831 cm^{-1}.

{$(H_2NCH_2)_4$[G-2]}$_3$C—CH_3 (Yield: 55%). ^{1}H NMR (DMSO-d_6): δ 1.98 (3H, s, CH_3), 2.47−3.08 (24H, s broad, NH_2), 3.67 (24H, s, CH_2NH_2), 4.96−5.00 (42H, m, ArCH_2O, Ar′CH_2 and NCPhCH_2), 6.45−6.66 (27H, m, ArH and Ar′H), 6.88 (12H, m, core Ar′H), 7.29 and 7.30 (48H, m, NCPhH). FT-IR, ν: 3370, 3297, 3025, 2860, 1600, 1156, 831 cm^{-1}.

{$(H_2NCH_2)_8$[G-3]}$_3$C—CH_3 (Yield: 35%). ^{1}H NMR (DMSO-d_6): δ 1.98 (3H, s, CH_3), 3.30 (48H, s broad, NH_2), 3.63 (48H, s, CH_2NH_2), 4.96−5.09 (90H, m, ArCH_2, Ar′CH_2, Ar″CH_2 and CNPhCH_2), 6.46−6.63 (63H, m, ArH, Ar′H and Ar″H), 6.83−6.90 (12H, m, core Ar′H), 7.26 (96H, m, NCPhH). FT-IR, ν: 3370, 3297, 3025, 2860, 1600, 1156, 831 cm^{-1}.

General Procedure for Synthesis of Hydrogel Formed by Reaction of Amino-Terminated Tridendron with PEG Diisocyanate (M_w = 3400). The solution of the diisocyanate PEG (ratio of isocyanate group to amino group = 1:2 or 1:1) in dry CH_2Cl_2 and several drops of triethylamine were added to the solution of the appropriate amino-terminated tridendron in DMF at 0 °C. The solution was allowed to warm to room temperature under stirring and nitrogen atmosphere in 1 h. Then the solvent was removed under low pressure. A yellow film was obtained.

Hydrogel Formed by Cross-Linking of First-Generation Amino-Terminated Tridendron with PEG Diisocyanate. ^{1}H NMR (DMSO-d_6): δ 2.02 (3H, s, CH_3), 3.49 (H, s, CH_2CH_2O), 3.73 (12H, s, CH_2NH$_2$), 4.96 (6H, s, core PhCH_2O), 5.03 (12H, s, PhCH_2), 6.58 (3H, t, ArH), 6.66 (6H, d, ArH), 6.88 and 6.90 (12H, m, core Ar′H), 7.34 (24H, m, PhH-CH$_2$-NH). FT-IR, ν: 3370, 2966, 1971, 1679, 1467, 837, 532 cm^{-1}.

Hydrogel Formed by Cross-Linking of Second-Generation Amino-Terminated Tridendron with PEG Diisocyanate. ^{1}H NMR (DMSO-d_6): δ 1.98 (3H, s, CH_3), 3.49 (H, s, CH_2CH_2O), 3.67 (24H, s, CH_2NH$_2$), 4.96−5.00 (42H, m, ArCH_2O, Ar′CH_2 and NCPhCH_2), 6.45−6.66 (27H, m, ArH and Ar′H), 6.88 (12H, m, core Ar′H), 7.29 and 7.30 (48H, m, PhH-CH$_2$NH). FT-IR, ν: 3370, 2966, 1971, 1679, 1467, 837, 532 cm^{-1}.

Hydrogel Formed by Cross-Linking of Third-Generation Amino-Terminated Tridendron with PEG Diisocyanate. ^{1}H NMR (DMSO-d_6): δ 1.98 (3H, s, CH_3), 3.49 (H, s, CH_2CH_2O), 3.63 (48H, s, CH_2NH$_2$), 4.96−5.09 (90H, m, ArCH_2, Ar′CH_2, Ar″CH_2 and NCPhCH_2), 6.46−6.63 (63H, m, ArH, Ar′H and Ar″H), 6.83−6.90 (12H, m, core Ar′H), 7.26 (96H, m, PhH-CH$_2$NH). FT-IR, ν: 3370, 2966, 1971, 1679, 1467, 837, 532 cm^{-1}.

General Procedure for Synthesis of Hydrogel Formed by Reaction of Amino-terminated Tridendron with PEG—Bis(epoxide) (M_w = 3400). The appropriate amino-terminated tridendron and PEG (ratio of epoxide group to amino group = 1:2 or 1:1) were mixed in DMF. This solvent was used to prepare a homogeneous dispersion of the tridendron in PEG. Then DMF was evaporated under low pressure and the resulting yellow mixture was subjected to a temperature gradient raising to 100 °C. The mixture was cooled after 5 h. A hard yellow product was formed. The product was refluxed with methanol, and dried after the solvent was filtered off.

Hydrogel Formed by Cross-Linking of First-Generation Amino-Terminated Tridendron with PEG—Bis(epoxide). ^{1}H NMR (DMSO-d_6): δ 3.49 and 3.31 (CH_2CH_2O). FT-IR, ν: 3490, 2890, 1980, 1600, 1470, 1350, 1280, 1120, 964, 841 cm^{-1}.

Hydrogel Formed by Cross-Linking of Second-Generation Amino-Terminated Tridendron with PEG—Bis(epoxide). ^{1}H NMR (DMSO-d_6): δ 3.49 and 3.31 (CH_2CH_2O). FT-IR, ν: 3500, 2890, 1980, 1600, 1470, 1300, 1280, 1130, 964, 845 cm^{-1}.

Hydrogel Formed by Cross-Linking of Third-Generation Amino-terminated Tridendron with PEG—Bis(epoxide). ^{1}H NMR (DMSO-d_6): δ 3.49 and 3.28 (CH_2CH_2O). FT-IR, ν: 3500, 2890, 1980, 1600, 1470, 1340, 1280, 1120, 964, 845 cm^{-1}.

Swelling Measurements. The weight swelling ratio was calculated as the ratio of the weight of the swollen hydrogel to the weight of the original dry gel according to the following procedure. The weight of the dry samples was recorded before they were immersed in a large excess of the corresponding solvent (water, toluene, THF, or CH_2Cl_2). After at least 12 h in the solvent, the swollen hydrogels were weighed again after the solvent droplets on the surface of samples were carefully blotted with lint-free paper towels. The temperature dependence of the swelling was studied by two methods. In method 1, the gel/solvent containers (kept initially at room temperature) were directly immersed in the water bath at the desired temperature, and the system was equilibrated for at least 12 h prior to measurement. In method 2, the swelling systems' temperatures were gradually increased within 1 h in the following sequence: 20 °C → 40 °C → 60 °C → 80 °C, and then the system equilibrated at least for 12 h at each desired temperature prior to measurement. The measurements cannot be performed above the boiling temperature of the solvent (THF, 65 °C; CH_2Cl_2, 40 °C).

Results and Discussion

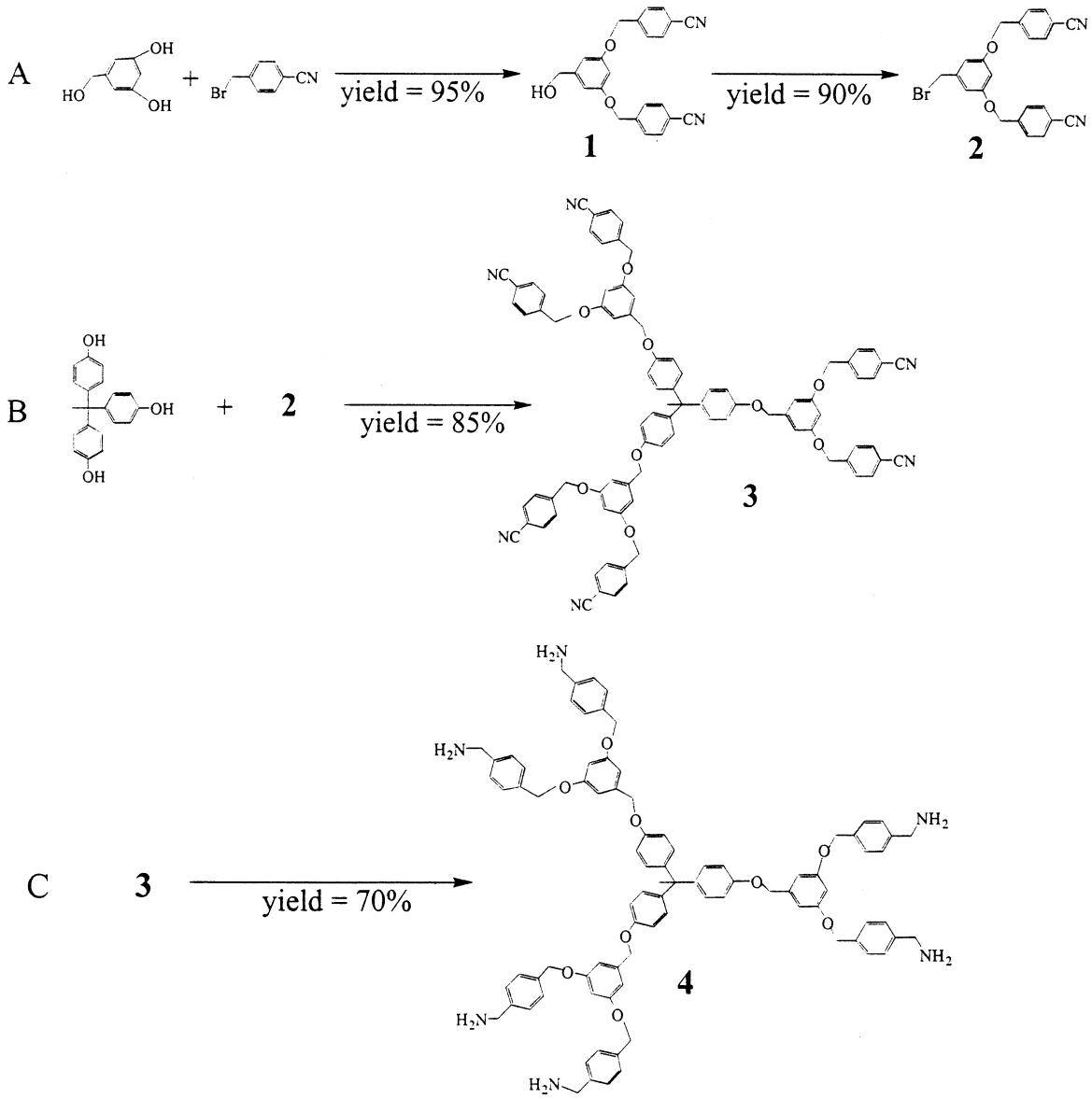
Synthesis of Amino-Terminated Tridendrons. Fréchet-type monodendrons containing CN termini at each peripheral group are prepared by the convergent growth method[15a] using 3,5-dihydroxybenzyl alcohol as the starting material, Scheme 1A. The cyano-terminated tridendrons are formed by a coupling reaction of the dendritic wedges to a core molecule: 1,1,1-tris(4-hydroxyphenyl)ethane (Scheme 1B). The efficiency of the coupling and the purities of those products are estimated by SEC and ^{1}H NMR techniques. SEC traces of the final products show only one peak that corresponds to the desired substance. ^{1}H NMR spectra show clearly the protons of the aromatic rings in the core as a pair of doublets at 6.97−6.99 and 6.80−6.85 ppm, well separated from the signals of the aromatic rings protons in the dendritic wedges, Figure 2b. The methyl group protons in the core appear as a singlet peak at 2.04−2.12 ppm. The ratio of the aromatic protons in the core to those of the dendritic wedges confirms the completeness of the coupling reaction. ^{13}C NMR analyses also provide useful information for the presence of all types of expected C atoms. The yield during the coupling and preparation of the cyano-terminated monodendrons follows the trend common for most of the dendrimer syntheses and decreases with the increase of the dendrimer generation.

In the final step, the CN termini in the tridendrons are reduced by $LiAlH_4$ (Scheme 1C). Reaction yields (first generation, 70%; second generation, 55%; third generation, 35%) are not as good as those of previous reactions. The difficulties arise during the isolation/purification of the final product and are due to the strong and increasing polarities of the amino-terminated tridendrons: the number of the amino groups rises from 6 in the first-generation tridendron to 24 in the third generation. The solubility of amino-terminated tridendrons in DMSO is fairly poor, especially for the higher generations. Flash chromatography, used previously to purify dendrimers containing a single benzylamino group,[16] does not work at all. We were able to obtain the desired products in pure form despite the relatively low yields by selective dissolution/precipitation sequence in a methanol/THF mixture (1:3 v/v) and subsequent filtration of the aluminum "cake". The ^{1}H NMR spectra of the products are recorded in DMSO-d_6 (Figure 2c). The fine structure of the peaks due to the aromatic protons disappears, but the integration yields the expected value. The new signal at 3.63−3.70 ppm can be attributed to the protons of the benzylic CH_2 group next to the peripheral amino groups. The broad peak of the protons in these groups can be seen between 3.0 and 3.5 ppm. The integration of the peaks corresponds to 12, 24, or 48 protons (i.e. 6, 12, or 24 NH_2 groups) respectively—a good indication for the complete reduction of the 6, 12, and 24 cyano groups of the initial first-, second- and third-generation tridendrons. The reduction is also clearly confirmed by the complete disappearance of the strong CN absorption band at 2230 cm^{-1} in the IR spectra of the initial tridendrons while the formation of the amino groups therein is evidenced by the absorption bands at 3370 and 3297 cm^{-1}.

Synthesis of the Hydrogels. The formation of the amphiphilic hydrogels is achieved by surface to surface connection of the dendritic globules and involves the reaction of functional end groups in the hydrophilic PEG with the reactive groups at the periphery of the hydrophobic dendritic poly(benzyl ether).

In this study, we focus on the synthesis of hydrogels by two types of chemical linkages. Initially we explored

Scheme 1. Synthetic Procedure for the Preparation of Amino-Terminated Tridendrons



the hydrogel formation based on the interaction of PEG diisocyanate with amino-terminated tridendrons. The coupling efficiency was monitored at two different ratios of the reactive groups: $[NH_2]/[NCO] = 1$ or 2 corresponding to full cross-linking and 50% reaction, respectively. The reaction does not proceed when the reaction mixture is kept at 0 °C, but it progresses rapidly when the clear homogeneous solution is allowed to warm to room temperature in the presence of the trace of triethylamine as the catalyst. Then the reaction mixture turns milky and its viscosity increases. For the first-generation amino-terminated tridendron, the gelation is observed within 10 min. After the removal of solvents, the hydrogel forms a yellow film with fairly strong adhesion to glass.

The cross-linking reaction can be conveniently monitored by FT-IR spectroscopy (Figure 3). The conversion is assumed to be complete after the disappearance of the characteristic isocyanate and primary amino group bands at 2265 cm^{-1} and 3370−3297 cm^{-1}, respectively. In the IR spectra of the cross-linked products, the distinctive peaks for the dendritic NH_2 groups are transformed almost quantitatively into absorptions characteristic of secondary amino groups (3410−3390 cm^{-1}). The appearance of peaks at 1700, 1680, and 1650 cm^{-1} (urea $\nu_{C=O}$) and 1560 and 1240 cm^{-1} (amide II and amide III $\delta_{N-H} + \nu_{OC-N}$, respectively) confirms the formation of urea linkages[17] (i.e., occurrence of the cross-linking reaction) (Figure 3c). ^1H NMR spectroscopy is not very useful in the quantitative evaluation of the cross-linking process (Figure 2e). The signal of the CH_2 protons in the PEG is rather strong and prevents the accurate integration of protons in the dendritic wedges. The aromatic protons from the dendrimer are still present in the gel while the broad peak for the amino groups in the region from 3.00 to 3.50 ppm is substantially reduced (Figure 2e).

To evaluate whether the hydrogel's properties are affected by the cross-linking chemistry, we explored the network formation based on the interaction of PEG−bis(epoxide) (PEG−2EP) with the same amino-terminated tridendrons. For the first- and second-generation tridendrons, DMF is added under stirring to promote the homogeneous mixing with PEG−2EP, and then the solvent is removed under low pressure. For the same purpose, the third-generation tridendron and PEG−2EP powders are initially blended before the reaction because we were not able to find a good solvent for the

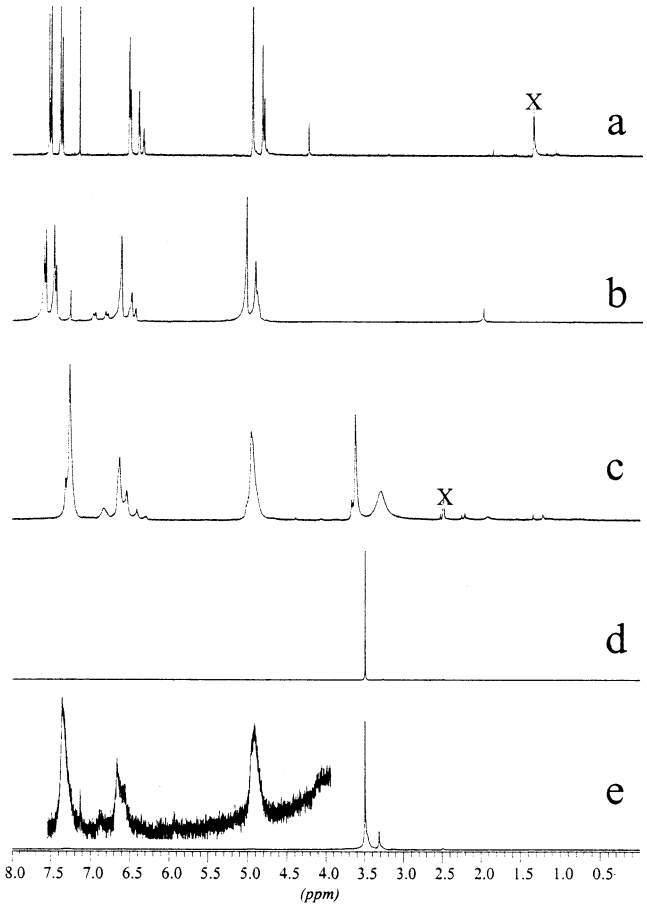


Figure 2. ^{1}H NMR spectra: (a) $(NC)_8$-[G-3]-Br in $CDCl_3$; (b) $\{(NC)_8$-[G-3]$\}_3-C-CH_3$ in $CDCl_3$; (c) $\{(H_2NCH_2)_8$-[G-3]$\}_3-C-CH_3$ in DMSO-d_6; (d) (OCN)-PEG3400-(NCO) in DMSO-d_6; (e) hydrogel synthesized from PEG−$(NCO)_2$ and $\{(H_2NCH_2)_8$-[G-3]$\}_3-C-CH_3$ and extracted consecutivelly with methanol and water (in DMSO-d_6).

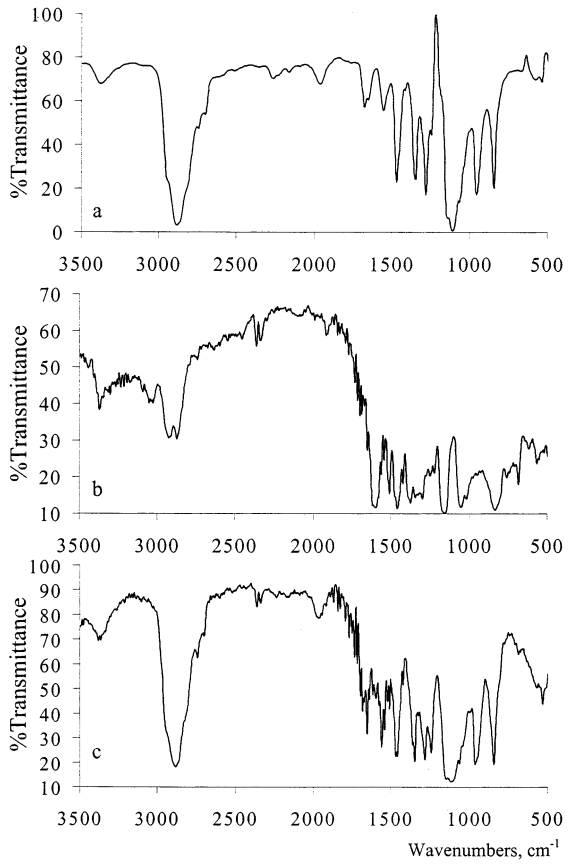


Figure 3. FT-IR spectra: (a) PEG−diisocyanate; (b) $\{(H_2NCH_2)_8$[G-3]$\}_3-C-CH_3$; (c) hydrogel synthesized from PEG−diisocyanate and $\{(H_2NCH_2)_8$[G-3]$\}_3-C-CH_3$.

tridendron. Then the solid mixture is placed in the oil bath at 100 °C. The resulting solid-melt mixture (T_m for PEG with molecular weight of 3400 is around 50 °C) was kept at this temperature for at least 5 h. After a methanol reflux, a yellow chunky hydrogel with good mechanical strength and adhesion to glass is collected.

The spectroscopic monitoring of this cross-linking reaction is rather difficult. Most of the epoxide group FT-IR absorption bands overlap with those of tridendrons and PEG and the only indication for the occurrence of the coupling is provided by the disappearance of two characteristic bands: for the primary amino group at 3370 cm^{-1} and for the oxirane ring at 764 cm^{-1}.[18] Surprisingly, the ^{1}H NMR signals of the aromatic protons from the dendrimers are also not visible in the hydrogels spectra beyond the first generation. The relatively high cross-linking density of the hydrogel is one of the possible explanations for this phenomenon. Since the dendritic wedge functions as the joint point in the cross-linking system, its mobility within the network matrix would be severely limited resulting in increasingly broader aromatic signals in ^{1}H NMR. When the mobility is sufficiently restricted, the aromatic NMR signals will practically disappear. A similar signal broadening in the aromatic protons region was previously observed with linear−dendritic copolymers containing PEG and dendritic poly(benzyl ether) blocks.[19]

It should be mentioned that the hydrogels synthesized by the reaction of amino-terminated tridendrons with PEG−diisocyanate, still show the aromatic protons from the dendrimer in their ^{1}H NMR spectra (Figure 2.e). Therefore, it could be assumed that these networks have relatively lower cross-linking density and/or that a part of the dendritic wedges is not fully incorporated as joint points. The use of reagents with the same molecular weight in the formation of both hydrogel families is a very useful approach to elucidate the factors that contribute to the observed differences in the cross-linking efficiency and density. The first one is related to the different chemistries involved in the network formation. Inherently the isocyanate group is more reactive toward NH_2 functionalities than the epoxide moiety. This is evidenced by the time for the onset of gel formation: 10 min for PEG−diisocyanate/tridendron mixtures at room temperature vs 2 h for PEG−2EP/tridendron mixtures at 100 °C. After the initial attachment on the surface of the tridendron, the second isocyanate functionality on the other end of the PEG chain would have lower mobility because of the increasing chain entanglements. The limited reaction opportunities caused by the relatively lower concentration of reaction partners (cross-linking in solution) constitute the second factor. Therefore, the probability for the second NCO end group to react with an amino group located at the same dendrimer before meeting another tridendron (i.e., intramolecular loop formation) will increase. The isocyanate groups in the PEG could also be inactivated by reactions with water since we do not strictly avoid moisture during the reaction. On the other hand, the lower reactivity of the epoxide groups enables them to remain intact and migrate through the forming network for a more efficient intermolecular coupling

Table 1. Weight Swelling Ratio of Hydrogels Formed by Cross-Linking of Amino-Terminated Tridendrons with PEG−Diisocyanate

feeding ratio	solvent	temp (°C) 20	40	60	80
[G-1][a]:PEG−diisocyanate = 1:1.5	water	5.5	5.8 (4.8)[b]	5.2 (4.9)	4.1 (4.1)
	toluene	1.3	5.0 (4.3)	4.7 (4.7)	5.0 (5.5)
	THF[c]	1.9	6.2 (5.4)	6.5 (6.0)	
	CH_2Cl_2[d]	16.2			
[G-1][a]:PEG−diisocyanate = 1:3	water	7.8	6.9 (7.6)	5.7 (5.4)	4.4 (4.7)
	toluene	1.7	6.0 (6.6)	5.8 (6.2)	5.9 (5.3)
	THF	2.1	5.5 (5.9)	5.8 (6.7)	
	CH_2Cl_2	16.7			
[G-2][a]:PEG−diisocyanate = 1:3	water	6.6	6.2 (6.2)	5.4 (3.7)	4.2 (5.7)
	toluene	1.6	5.4 (4.9)	5.4 (4.7)	5.4 (6.0)
	THF	2.3	4.7 (4.5)	5.3 (4.3)	
	CH_2Cl_2	10.6			
[G-3][a]:PEG−diisocyanate = 1:6	water	4.1	4.0 (4.4)	3.6 (4.0)	3.2 (3.6)
	toluene	2.7	2.7 (2.8)	3.0 (3.8)	3.0 (3.2)
	THF	2.9	3.0 (3.1)	3.0 (3.3)	
	CH_2Cl_2	8.8			

[a] [G-1]: first-generation amino-terminated tridendron. [G-2]: second generation. [G-3]: third generation. [b] All the data in the parentheses were obtained by method 2; the other data were obtained by method 1. See the Experimental Section for details. [c] The boiling temperature of THF is 65 °C. [d] The boiling temperature of CH_2Cl_2 is 40 °C.

with amino groups on different dendrimer molecules. The coupling efficiency could also be improved by the autocatalytic effect of the hydroxyl groups formed during the amine/epoxy reaction (Figure 1).[20] Hence, the lower reactivity (higher selectivity) of PEG−2EP and the melt-reaction conditions facilitate the formation of hydrogels with higher cross-linking density. Further evidence for this statement is provided by swelling and crystallinity measurements.

Swelling Behavior. Before the swelling measurements are performed, all hydrogel samples are extracted with methanol or water to remove the unreacted residual PEG fragments. In the series of networks, formed by equimolar amounts of PEG−diisocyanate and second- or third-generation tridendrons (feeding ratios PEG: tridendron = 1:6 and 1:12, respectively), the samples lose approximately 50% of their weight after extraction. In a swelling solvent, these hydrogels form brittle flocculates that can be split under a weak external force, such as stirring. The mechanical destruction of the gel's integrity prevents the precise evaluation of the swelling properties and therefore these materials were not further investigated. All other samples of this product line lose less than 5% weight and maintain their original shape in the swelling experiments. In the series of the hydrogels formed by PEG−2EP, all samples lose less than 5% weight after extraction and maintain their three-dimensional integrity under stirring regardless of the reagents feed ratio used for the network formation. These facts could be interpreted as an additional evidence for the lower cross-linking efficiency of PEG−diisocyanate due to the increased probability of intramolecular cyclizations and the possible side reaction with water. Obviously, these factors are not so dominant in the first generation and lower feeding ratios leading to the formation of well cross-linked products (low extraction yields).

The data from the swelling experiments are summarized in Tables 1 and 2. It should be emphasized that all hydrogels investigated rapidly reach the swelling equilibrium (within 10−30 min), a very important characteristic for their eventual application as drug delivery platforms and size-selective substrate harvesting media. The observed weight swelling ratios for both groups of materials are lower in comparison to other known hydrogels containing PEG segments with comparable molecular weights[10a,11b] indicating a higher degree of cross-linking (cross-linking density) for the networks in this study.

Since PEG is the dominant component in all networks their swelling behavior directly reflects its affinity toward the media studied (Tables 1 and 2). That is why the highest swelling ratio is observed in CH_2Cl_2 (good solvent for both gel constituents), followed by the ratio in water (good solvent only for the major phase—PEG chains) and toluene/THF (better solvents for the minor phase—dendritic fragments). The dissimilarity in the solution behavior of the linear and dendritic blocks is traceable in the temperature dependence of the swelling parameters. In toluene and THF, the hydrogels' swelling ratios increase with temperature (improved PEG solubility) in contrast to the aqueous system where the values are notably lower at temperatures exceeding 60 °C (decreased PEG solubility) (Tables 1 and 2). The more pronounced temperature dependency of the PEG−diisocyanate gels swelling is an indication for the occurrence of a reversible PEG chain entanglement as an additional contributing factor in the gelation process of these materials.

There are marked differences in the swelling behavior of the two hydrogel lines. With few exceptions the weight swelling ratios of hydrogels formed with PEG−2EP are lower in comparison to the values of the PEG−diisocyanate gels having identical linear−dendritic composition. The fact that the swelling parameters of PEG−2EP networks are only slightly affected by temperature changes from 20 to 80 °C (Table 2) could be considered as another proof for their higher degree of cross-linking and its chemical origin (i.e., lower degree of reversible physical entanglements).

DSC Measurements of the Hydrogels. The DSC measurements provide useful information not only for the thermal properties of hydrogels formed but also for their degree of crystallinity (i.e., the mobility of PEG segments within the network frame), compatibility of the linear and dendritic fragments, their phase organization, and interactions (Table 3). It is seen that the network building blocks have distinct differences in their solid-state properties. It is interesting to note that while the glass transition of the PEG occurs close to the

Table 2. Weight Swelling Ratio of Hydrogels Formed by Cross-Linking of Amino-Terminated Tridendrons with PEG−Bis(epoxide)

		temp (°C)			
feeding ratio	solvent	20	40	60	80
[G-1][a]:PEG−bis(epoxide) = 1:1.5	water	3.7	2.9 (3.2)[b]	2.7 (2.8)	2.2 (2.4)
	toluene	1.2	2.4 (2.2)	2.5 (2.5)	2.7 (3.0)
	THF[c]	2.7	2.7 (2.8)	3.0 (2.4)	
	CH_2Cl_2[d]	6.7			
[G-1][a]:PEG−bis(epoxide) = 1:3	water	2.9	2.9 (2.8)	2.4 (2.8)	2.1 (2.2)
	toluene	2.1	2.1 (2.3)	2.3 (1.9)	2.4 (2.3)
	THF	3.2	3.1 (2.8)	3.2 (2.7)	
	CH_2Cl_2	6.7			
[G-2][a]:PEG−bis(epoxide) = 1:3	water	3.2	2.7 (2.8)	2.7 (2.9)	2.0 (2.3)
	toluene	1.9	2.0 (2.0)	2.1 (2.0)	2.2 (2.1)
	THF	2.5	2.5 (3.0)	2.6 (2.4)	
	CH_2Cl_2	6.5			
[G-2][a]:PEG−bis(epoxide) = 1:6	water	3.7	3.3 (3.4)	2.9 (2.6)	2.5 (2.2)
	toluene	1.8	2.2 (2.4)	2.2 (2.5)	2.1 (2.2)
	THF	2.5	2.5 (2.6)	2.5 (2.4)	
	CH_2Cl_2	6.4			
[G-3][a]:PEG−bis(epoxide) = 1:6	water	3.5	3.1 (3.3)	2.8 (2.7)	2.3 (2.4)
	toluene	2.0	2.0 (2.0)	2.1 (2.2)	2.2 (2.1)
	THF	2.6	2.6 (2.8)	2.6 (2.9)	
	CH_2Cl_2	6.1			
[G-3][a]:PEG−bis(epoxide) = 1:12	water	4.1	3.4 (3.7)	3.1 (3.1)	2.4 (3.1)
	toluene	2.2	2.4 (2.5)	2.6 (2.6)	2.7 (2.3)
	THF	2.6	2.9 (3.0)	2.9 (2.9)	
	CH_2Cl_2	7.1			

[a] [G-1]: first-generation amino-terminated tridendron. [G-2]: second generation. [G-3]: third generation. [b] All the data in parentheses were obtained by method 2; the other data were obtained by method 1. See the Experimental Section for details. [c] The boiling temperature of THF is 65 °C. [d] The boiling temperature of CH_2Cl_2 is 40 °C.

Table 3. Chemical Composition Effects on the Thermal Characteristics and Degrees of Crystallinity of the Hydrogels

sample	T_g (°C)	T_g[a] (°C)	PEG (wt %)	T_m (°C)	ΔH_f (J/g)	T_c[b] (°C)	X_C^{PEG} (%)
PEG-3400	−51.2		100	46.2	129.0	32	65
[G-1][c]	50.5		0				
[G-2]	60.2		0				
[G-3]	73.1		0				
PEG−NCO[d]:[G-1] = 1.5	−18.0	−37.2	81	43.8	91.4	31.2	58
PEG−NCO:[G-2] = 3	−17.3	−36.2	81	44.1	98.6	37.4	62
PEG−NCO:[G-3] = 6	−14.9	−35.0	81	41.0	105.4	35.8	66
PEG-NCO:[G-1] = 3	−44.9	−44.0	90	42.6	110.9	35.0	63
PEG−NCO: [G-2] = 6	−46.9	−43.5	90	45.8	112.5	37.4	63
PEG−NCO:[G-3] = 12	−47.1	−42.1	89	48.5	115.7	38.0	66
PEG−EP[e]:[G-1] = 1.5	−16.0	−37.2	81	32.7	60.2	19.5	38
PEG−EP:[G-2] = 3	−21.4	−36.2	81	34.5	80.2	27.2	50
PEG−EP:[G-3] = 6	−30.8	−35.0	81	35.1	53.3	29.4	33
PEG−EP:[G-1] = 3	−37.7	−44.0	90	30.5	60.8	21.9	34
PEG−EP:[G-2] = 6	−28.9	−43.5	90	39.2	81.8	29.4	46
PEG−EP:[G-3] = 12	−45.4	−42.1	89	35.6	81.9	32.3	47

[a] The theoretical value of T_g as calculated by the Fox equation:[26] $1/T_g(\text{gel}) = W_{PEG}/T_g(\text{PEG}) + W_{dendr}/T_g(\text{dendr})$, where T_g(gel), T_g(PEG) and T_g(dendr) are the measured glass transitions of the gel, PEG, and the corresponding tridendron; W_{PEG} and W_{dendr} are the weight fractions of the two components in the network. [b] The crystallization temperature T_c, measured by DSC at a controlled cooling rate of 10 °C/min. See the Experimental Section for details. [c] [G-1]: first-generation amino-terminated tridendron. [G-2]: second generation. [G-3]: third generation. [d] PEG−NCO: PEG−diisocyanate. [e] PEG−EP: PEG−bis(epoxide).

known value (T_g = −52 °C[21]), the melting temperature is substantially lower than the reported data for polymers of similar molecular weights (T_m = 59.1−62.8 °C for PEG 4000[22]). This could be attributed to the influence of the reactive end groups leading to the formation of folded chain crystals of small size.[21a,23] On the other side, the tridendrons are completely amorphous (Table 3). The observed glass transitions are notably higher than their benzyl ether analogues, caused most probably by the increased polarity of the peripheral groups.[24]

Because of the relatively low content of amorphous dendritic components, all hydrogels have a clearly visible and single melting transition in their DSC traces (Figure 4). In all cases the melting temperatures (T_m) and the enthalpies of fusion (ΔH_f) are below the corresponding values of the initial PEG—an indication for the reduced chain end mobility (chain folding) in the linear segment after cross-linking. The networks formed by PEG−2EP have notably lower T_m and degrees of crystallinity, confirming again the higher cross-linking density in this series. In distinction to the previously reported data for linear−dendritic copolymers[25] of similar chemical and block compositions, all hydrogels show only a single glass transition temperature (T_g), positioned between the T_g of both constituents. The occurrence of single glass and melting transition events in all networks studied could be interpreted as a sign of the molecular miscibility of both components in this compositional range. It should also be mentioned that the measured glass transitions of all networks deviate from the T_g values predicted by the Fox equation (Table 3).[26] The discrepancy is notably larger at higher dendrimer concentrations and in the networks produced with PEG−diisocyanate. This increase in the T_gs of the

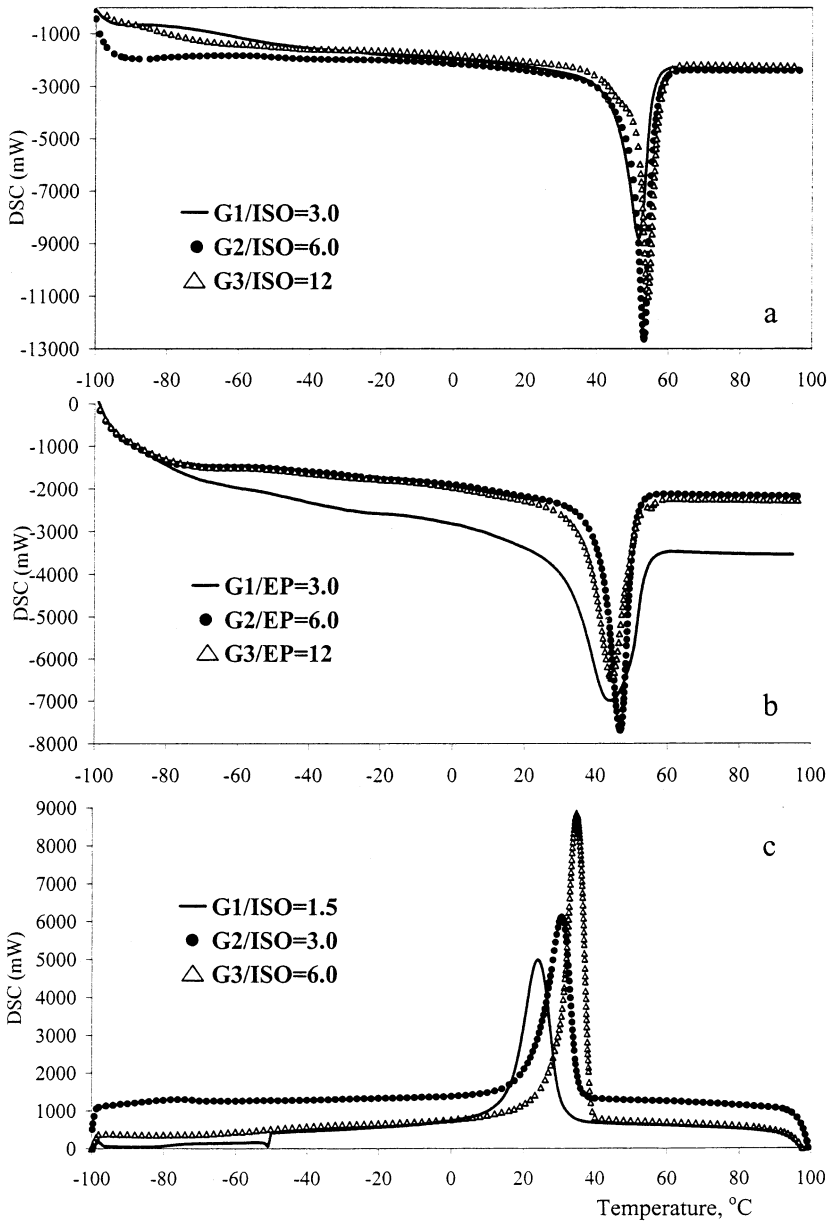


Figure 4. DSC traces of hydrogel samples. G1, G2, G3 are amino-terminated tridendrons of first, second, and third generation, respectively; ISO denotes PEG−diisocyanate, EP is PEG−bis(epoxide). Key: (a) melting transitions of PEG−diisocyanate based networks recorded at the second heating cycle; (b) melting transitions of PEG−bis(epoxide)-based gels recorded at the second heating cycle; (c) crystallization transitions of PEG−diisocyanate-based networks. See the Experimental Section and Table 3 for further details.

hydrogels is caused most probably not only by the cross-linking process but also by the additional immobilization of the PEG segments through hydrogen bonding with the urea anchoring groups at the surface of the tridendrons.[27] Evidence for these interactions is contained in the FT-IR spectra of the gels, where numerous absorption bands[17c] can be assigned to hydrogen-bonded groups: 3380, 3320, and 3290 cm^{-1} (NH); 1670 and 1650 cm^{-1} (C═O) (Figure 3c). The crystallization temperature visibly increases with the size of the dendritic component (Figure 4c, Table 3), due probably to the favorable nucleation effects exercised by the dense dendritic globules on the crystal growth.

Conclusions

The results obtained show that amphiphilic hydrogels with high degree of cross-linking can be successfully synthesized in high yields by the reaction of amino-terminated poly(benzyl ether) dendrimers with linear PEG (M_w = 3400) containing either isocyanate or epoxide functional groups at both ends. The high reactivity of the PEG−diisocyanate leads to a fast formation of relatively loose networks containing highly cross-linked domains weakly connected to one other. On the other side, the stability of the PEG−2EP under the reaction conditions used favors the production of more densely cross-linked structures. The actual cross-linking could proceed via three possible pathways: reversible physical entanglement of the PEG chains grafted on the periphery of the dendrimers, surface-to-surface linkage of the multifunctional tridendrons with PEG segments, and catenane formation by PEG loops formed on the individual dendritic fragments. The investigation of the swelling behavior and solid state properties of the hydrogels could not possibly differentiate the extent of the last two of the cross-linking modes. However, the

results clearly show that in the case of PEG−2EP physical entanglement plays a small role in the network formation while in the isocyanate gels this mode of cross-linking is evidently present. Both the swelling in selective solvents and the thermal characteristics of the hydrogels are affected by their mode of preparation (solution vs bulk), by the degree of cross-linking, by the nature of the anchoring groups at the surface of the tridendrons, and also by the polarity of the medium and the temperature.

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Supporting Information Available: Figures showing FT-IR spectra of $\{(CN)_2[G\text{-}1]\}_3-C-CH_3$, $\{(H_2NCH_2)_2[G\text{-}1]\}_3-C-CH_3$, PEG−bis(epoxide),$\{(H_2NCH_2)_4[G\text{-}2]\}_3-C-CH_3$, the hydrogel synthesized from PEG−bis(epoxide), and $\{(H_2NCH_2)_4[G\text{-}2]\}_3-C-CH_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

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