

Synthesis of barbell-like triblock copolymers, dendritic triazine-*block*-poly(ethylene glycol)-*block*-dendritic triazine and investigation of their solution behaviors

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Abstract

New bis-globular triblock copolymers containing poly(ethylene glycol) (PEG) as a core and triazine dendrons were synthesized. First generation (G_1) was prepared by coupling of hydroxyl group of poly(ethylene glycol) with cyanuric chloride in different solvents through two routes, in the first route reaction was carried out in the presence of sodium hydride in dry DMF at low temperature and in another route water solution of sodium hydroxide in dichloromethane solvent was used. Reaction of compound G_1 with amino group of diethanolamine in dichloromethane resulted $G_{1.5}$. Second generation of linear-dendritic compounds (G_2) was synthesized using coupling reaction of hydroxyl groups of compound $G_{1.5}$ and **1** (compound **1** was prepared by reaction of cyanuric chloride with phenol in the presence of sodium hydroxide). Growth of dendrons on the PEG core and their structure was investigated using usual spectroscopy methods, SEC and CHN analysis. Critical micelle concentration and probable conformations of linear-dendritic compound G_2 was investigated using fluorescence and NMR spectroscopy in different solvents.

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1. Introduction

Linear-dendritic copolymers are hybrid structures that combine two types (linear and dendritic) of macromolecular architectures. Combining one or more dendritic moieties with one or more linear chain in a single macromolecule can have a profound effect on the ultimate properties of hybrid material that results. It is only within the past several years that a significant number of reports such true hybrid copolymers have appeared [1], as their widespread study was made possible [2] by the introduction of the highly versatile convergent method of synthesis of dendrimers [3]. The dendritic-linear copolymer hybrids may be divided into five major groups: AB diblock linear-dendritic copolymers containing a linear A block and dendritic B block [4], ABA triblock linear-dendritic copolymers containing B as the linear

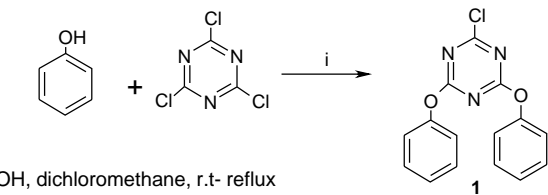
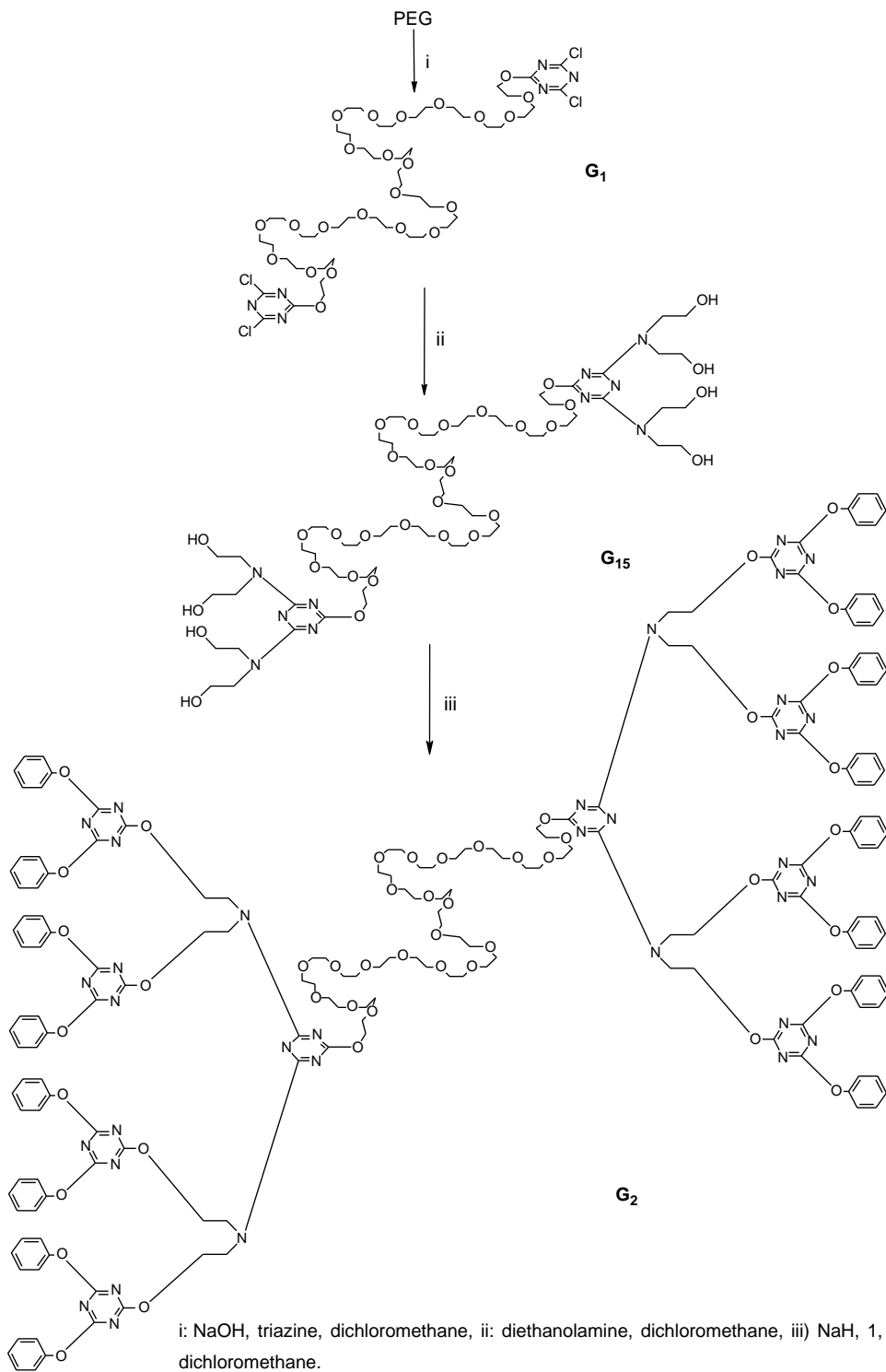
block and A as the dendritic block [5,6], side chain functionalized or dendronized linear-dendritic copolymers [7] and linear-dendritic star copolymers in which the dendritic blocks have connected to the end of arms of a star polymer [8]. Multiarm linear-dendritic block copolymers with dendrimer core and linear polymer arms [9].

ABA triblocks hybrids linear-dendritic copolymers containing PEG as the B block and A as the dendritic blocks were very well studied because of their interesting properties and applications. One of the most successful routes for synthesis of the ABA triblock linear-dendritic copolymers containing linear PEG block is Williamson coupling of hydroxy-terminated PEO or PEG with benzylic halide focal point of Fréchet-type dendrons [10].

The first linear-dendritic diblock copolymer through divergent growth on the PEG as the A block was synthesized by Chapman and co-workers [11]. This involved divergent dendritic growth of poly(lysine) dendritic block from an amine terminated PEO. Aqueous solutions of the G_4 linear-dendritic diblock copolymer were able to solubilize the water-insoluble dye Orange-OT. Recently Park and et al. prepared some of ABA

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Scheme 1. The synthesis of ABA-triblock copolymers.

triblock copolymers containing PEG as the A block and poly(lysine) as the B blocks by divergent growth [12]. These compounds were applied for transformation of DNA. One of the most important properties of linear-dendritic copolymers is self-assembling in aqueous media, that have been reported as the promising materials for many advanced applications [10]. In particular, linear dendritic copolymers based on poly(ethylene glycol) as the core, have a variety of potential applications in the fields of cell mimic systems, coatings, chemical sensors, hydrogels and drug delivery [11,1m,13].

Recently we reported the synthesis of some biodendrimers and star polymers containing citric acid and drug molecules that showed some interesting behaviors such as thermoreversible hydrogels [14a]. Also the application of biodendrimers as the drug delivery agents has been investigated [14b].

In general, the major difficulties in the synthesis of dendrimers are their protection and deprotection, purification process and their lower reaction yields, particularly in the higher generations. However, here we report a strategy for the preparation of these type compounds in excellent yield with elimination of protection and deprotection steps. We used the CHN analysis for confirmation the growth of dendrimers. The synthesized compounds showed some of interesting behaviors in solution. The critical micelle concentrations of these compounds in aqueous media were determined using fluorescence spectroscopy and pyrene as the molecular probe.

2. Experimental

2.1. Materials

Poly(ethylene glycol) 1000, cyanuric chloride, phenol, sodium hydride, sodium hydroxide and diethanolamine were purchased from Merck. Pyrene (Aldrich) was used without further purification.

2.2. Instrumental measurements

The NMR spectra were recorded on FT-NMR 400 MHz Bruker in CDCl₃, DMSO-*d*₆ and D₂O. IR spectra were measured on a Shimadzu Model FT-IR-8101M spectrometer. Elemental analysis was carried out in Oil Petroleum Research Center. All the fluorescence measurements were performed with an RF-5301 PC spectrofluorometer with a thermostate cell unit. Pyrene was used as fluorescence probe to analyze the block copolymers in the aqueous media. The excitation scans were performed at $\lambda_{em} = 393$ nm and the emission spectra was recorded at $\lambda_{ex} = 333$ nm. Both the spectral band widths of excitation and fluorescence spectra were 3 nm. Elemental analysis was carried out in Oil Petroleum Research Center. The molecular weight distributions were determined by size exclusion chromatography (SEC) using 100Å° column connected to a differential refractometer, RI and UV detector with DMF as the mobile phase at 25 °C. Poly(styrene) standard samples were used for calibration.

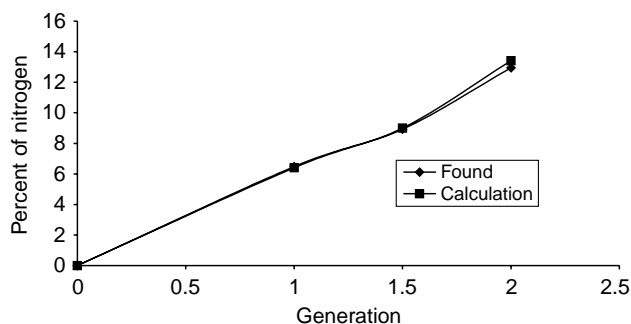


Fig. 1. N% vs. of the different generation of ABA triblock copolymers.

2.3. Synthesis of G₁

2.3.1. First procedure

A solution of poly(ethylene glycol) (4 g, 4×10^{-3} mol) and sodium hydroxide (0.32 g, 8×10^{-3} mol) in 10 mL of water was added to a solution of cyanuric chloride (3.69 g, 2×10^{-2} mol) in 50 mL dichloromethane at 0 °C. Mixture was stirred at 0 °C for 1 h then it was stirred at room temperature for 1 h and finally was refluxed for additional 6 h. Then mixture was cooled and filtered off and solvent was evaporated. The crude product was dissolved in 10 mL dichloromethane and was precipitated in diethyl ether at 0 °C several times. The purified product was obtained as a white solid (5.1 g, 4×10^{-3} mol, 100%). IR: 2877 (ν_{C-H}), 1755, 1714, 1669 ($\nu_{C=N}$), 1111 (ν_{C-O}) cm⁻¹. ¹H NMR (DMSO-*d*₆): (3.48–3.54, –OCH₂O–triazine), (3.63–3.68, PEG). ¹³C NMR (DMSO-*d*₆): (69, PEG), (71, –OCH₂O–triazine), (150, triazine part).

2.3.2. Second procedure

A solution of poly(ethylene glycol) (4 g, 4×10^{-3} mol) in 10 mL dry DMF was added to a mixture of cyanuric chloride (1.476 g, 8×10^{-3} mol) and sodium hydride (0.192 g, 8×10^{-3} mol) in 50 mL dry DMF at 0 °C. Mixture was stirred

Table 1
Solubility of ABA-triblock copolymers in different solvents

Compound	Solvent	Behavior
G ₁	Water	Thermoreversible hydrogel
G ₁	CH ₂ Cl ₂	Aggregation
G ₁	Et ₂ O	Insoluble < 0 °C, soluble > 0 °C
G ₁	Ethanol	Soluble
G ₁	DMF	Soluble
G ₁	THF	Aggregation
G _{1.5}	Water	Soluble
G _{1.5}	CH ₂ Cl ₂	Aggregation
G _{1.5}	Et ₂ O	Insoluble
G _{1.5}	Ethanol	Soluble
G _{1.5}	DMF	Soluble
G _{1.5}	THF	Aggregation
G ₂	CH ₂ Cl ₂	Aggregation
G ₂	DMF	Soluble
G ₂	Water	Insoluble

Table 2
N% of the different generations of ABA triblock copolymers

Compound	N% (Calculation)	N% (Found)
PEG	0	0
G ₁	6.41	6.1
G _{1.5}	8.92	9
G ₂	12.95	13.4
1	14.02	14.03

for 1 h at 0 °C and for additional 1 h at room temperature under argon atmosphere. Then mixture was filtered off and solvent was evaporated under vacuum, then the crude product was dissolved in 10 mL dichloromethane and was precipitated in diethyl ether at 0 °C several times. The product was obtained as a white solid (4.35 g, 3.36×10^{-3} , 84%).

2.4. Synthesis of G_{1.5}

2.4.1. First procedure

An excess of diethanolamine (1.88 g, 3×10^{-2} mol) was added to a solution of G₁ (2 g, 1.54×10^{-3} mol) in 20 mL dichloromethane dropwise at room temperature. Mixture was

stirred at room temperature for 1 h then was refluxed for additional 4 h. Mixture was cooled, solvent and excess of diethanolamine were evaporated under vacuum. For removing traces of diethanolamine, crude product was solved in 10×3 mL dichloromethane, solution was left 1 h then diethanolamine trace was separated by decanter. Solvent was evaporated and product was separated as a colorless viscose compound (4.7 g, 3×10^{-3} mol, 100%). IR: 3358 ($\nu_{\text{O-H}}$), 2874 ($\nu_{\text{C-H}}$), 1572, 1519 ($\nu_{\text{C=N}}$), 1104 ($\nu_{\text{C-O}}$) cm^{-1} . ¹H NMR (D₂O): (2.85–2.87, -NCH₂), (3.66–3.67, -CH₂OH) (3.60–3.64, PEG), (3.76–3.78, -OCH₂O-triazine). ¹³C NMR (D₂O): (49, -NCH₂), (59, -CH₂OH), (69, PEG), (165, 169, triazine part).

2.4.2. Second procedure

In the second procedure, diethanolamine were applied as the both reagent and solvent with refluxing G₁ in diethanolamine for 2 h. The crude compound was purified with successive repeating of the above-mentioned procedure.

2.5. Synthesis of compound 1

A solution of phenol (2 g, 2.1×10^{-2} mol) and sodium hydroxide (0.85 g, 2.1×10^{-2} mol) in 10 mL water was added

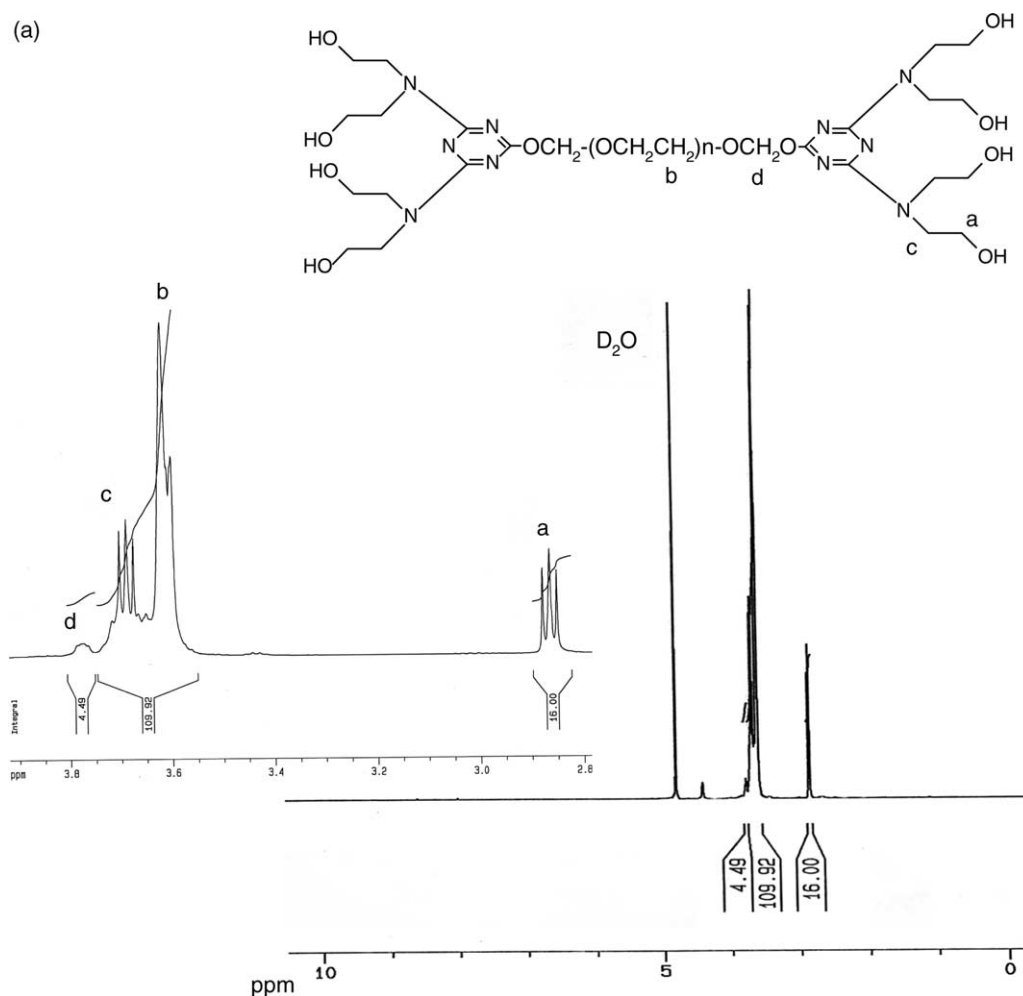


Fig. 2. (a) ¹H NMR spectra of G_{1.5} in CDCl₃, (b) ¹H NMR spectra of G_{1.5} in D₂O.

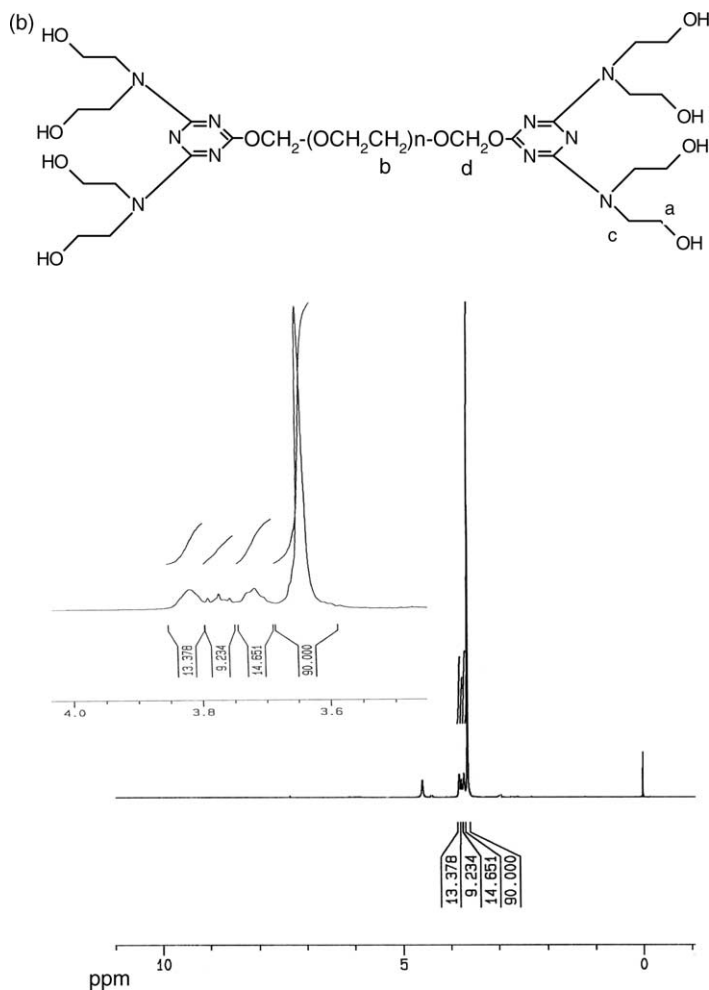


Fig. 2 (continued)

to a solution of cyanuric chloride (1.93 g, 1×10^{-2} mol) in 50 mL dichloromethane dropwise at 0 °C. Mixture was stirred at room temperature for 1 h then was refluxed for additional 6 h. Then mixture was cooled, filtered off and solvent was evaporated. For purification crude product was dissolved in 10 mL dichloromethane then a few drop of methanol was added to this solution, pure product was separated as a white solid gel (2.24 g, 7.5×10^{-3} mol, 75%). ^1H NMR (CDCl_3): (7.1–7.4). ^{13}C NMR (CDCl_3): (121, 126, 129, 151 phenolic), (172, 173 triazine part).

2.6. Synthesis of \mathbf{G}_2

A solution of $\mathbf{G}_{1.5}$ (2 g, 7×10^{-3} mol) in 5 mL of dry dichloromethane was added to a mixture of sodium hydride (0.8 g, 3.3×10^{-2} mol, excess) and compound **1** (1.82 g, 8×10^{-4} mol) in 10 mL of dry dichloromethane, dropwise at 0 °C. Mixture was stirred at room temperature for 1 h and refluxed for additional 12 h under argon atmosphere then it was cooled and filtered off. Product was extracted from water by 30 mL chloroform (three times), chloroform was removed and crude compound was dissolved in 5 mL chloroform, then product was precipitated in diethylether or cyclohexane

and purified compound was obtained as a yellow solid (18 g, 4.9×10^{-3} mol, 70%). IR: 3030, 2874 ($\nu_{\text{C-H}}$), 1729, 1668, 1574, 1529 ($\nu_{\text{C=N}}$ and $\nu_{\text{C=C}}$), 1098 ($\nu_{\text{C-O}}$) cm^{-1} . ^1H NMR ($\text{DMSO-}d_6$): (3.60, PEG), (3.86–3.91, $-\text{NCH}_2-$ and $-\text{CH}_2\text{O}-$), (7.0–7.9, aromatic portion). ^{13}C NMR ($\text{DMSO-}d_6$): (49, $-\text{NCH}_2-$), (70, PEG), (71, $-\text{CH}_2\text{O}-$), (120, 125, 128, 148, aromatic portion), (163, 164, 168, 171, triazine part).

2.7. Preparation the sample for fluorescence spectroscopy

For the fluorescence study, solutions of \mathbf{G}_2 in doubly distilled water with concentrations between 1.1×10^{-1} and 1.1×10^{-4} mol/L were prepared. The copolymer was dissolved gradually and left to equilibrate for 48 h at room temperature. A pyrene solution in THF (1.2×10^{-3} M) was prepared and added to the doubly distilled water to give a pyrene concentration of 12×10^{-7} M, and THF was removed under reduced pressure. The pyrene solution was mixed with the block copolymer solutions to obtained copolymer concentrations of 1.1×10^{-2} to 1.1×10^{-6} . The pyrene concentration of the samples was 6.0×10^{-7} M. All the samples were sonicated for 1 h at 30 °C and left to equilibrate for 24 h before fluorescence measurements.

3. Results and discussion

3.1. Synthesis

Compounds **G**₁, **G**_{1.5} and **G**₂ were synthesized through divergent method using PEG (1000) as a core. By means, compound **G**₁ was synthesized using variety of solvents and reagents with several routes. The reaction condition between PEG and cyanuric chloride was optimized in the presence of sodium hydroxide in dichloromethane as the solvent (Scheme 1) in which the yield of reaction was increased to 100%. Low temperature in preparation of **G**₁ is important, because at higher temperatures a crosslinked polymer containing cyanuric chloride and PEG is obtained. However, compound **G**_{1.5} was synthesized by reaction between compound **G**₁ and diethanolamine through two procedures (Scheme 1). In the first

procedure, the reaction was carried out in dichloromethane in the presence of excess diethanolamine. In the second procedure, diethanolamine was applied as the both reagent and solvent. For purification of product the solvent and excess of diethanolamine were evaporated and the product was extracted using dichloromethane. In the both reaction routes compound **G**_{1.5} was obtained in a quantitative yield as a colorless viscose compound.

For preparation of compound **G**₂, first compound **1** was synthesized using reaction of phenol with triazine (Scheme 1). In the purification step of compound **1**, an interesting phenomena was observed. When the crude compound was dissolved in dichloromethane with addition a little of methanol to this solution, it was suddenly changed to a gel. The simple filtration of gel gave a pure white solid product. The purity of the compound was confirmed using TLC, NMR and CHN.

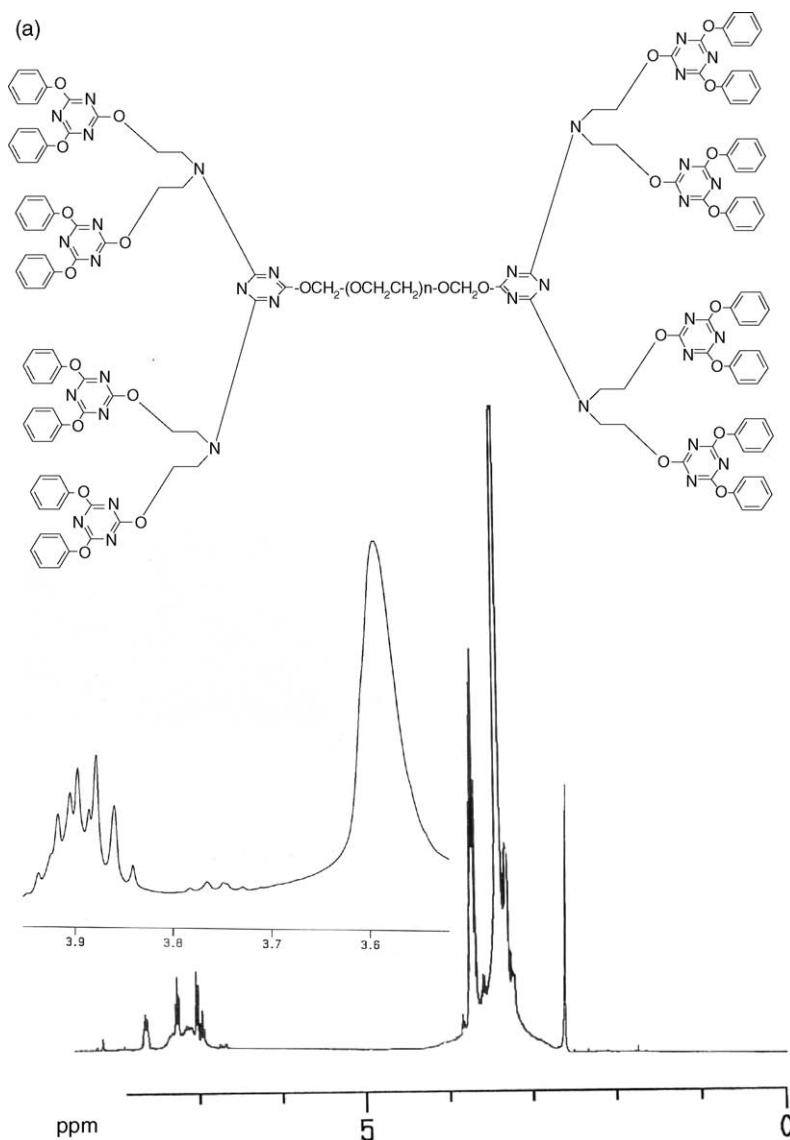


Fig. 3. (a) ¹H NMR spectra of **G**₂ in CDCl₃, (b) ¹H NMR spectra of **G**₂ in DMSO-*d*₆, (c) ¹³C NMR spectra of **G**₂ in CDCl₃, (d) ¹³C NMR spectra of **G**₂ in DMSO-*d*₆.

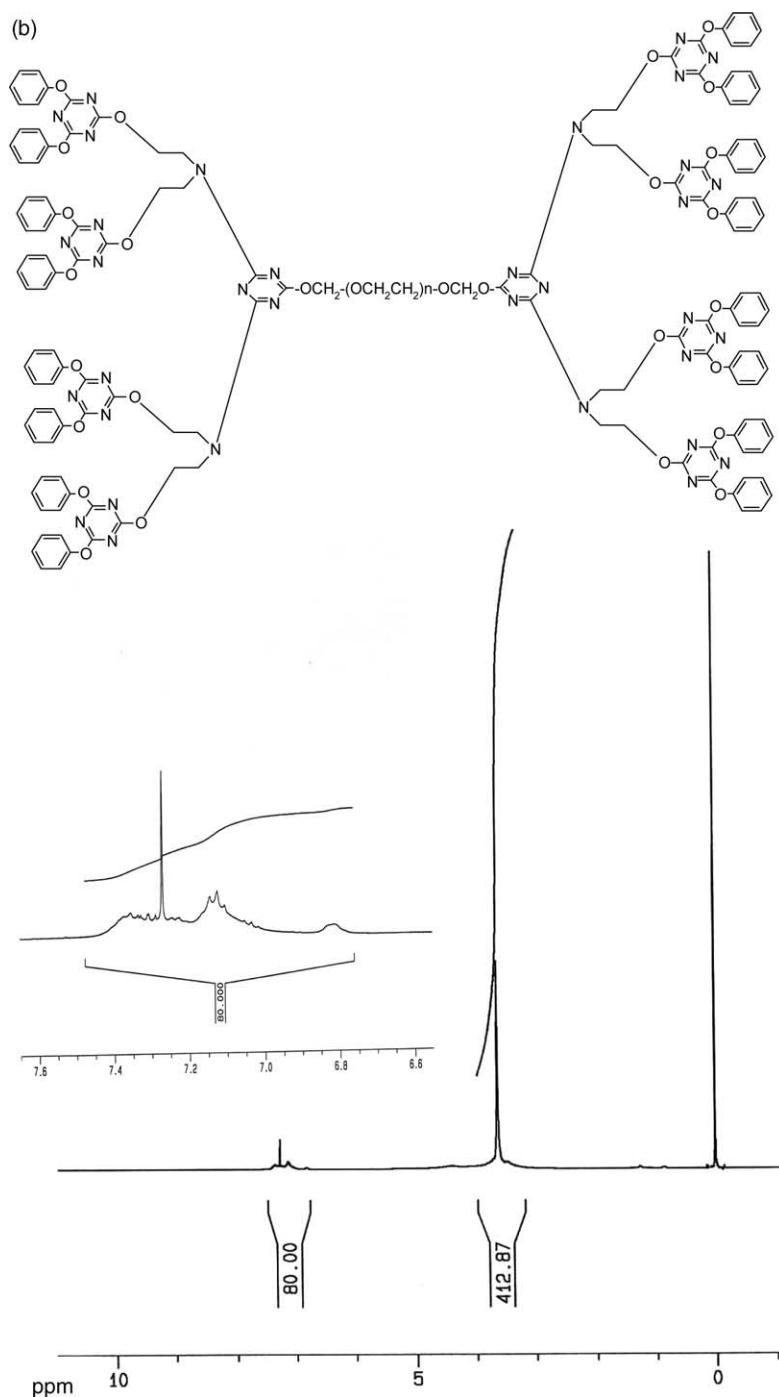


Fig. 3 (continued)

Compound **G₂** was prepared by reaction between compounds **G_{1.5}** and **1** in the presence of sodium hydride (Scheme 1) and the obtained product was purified as explained in the experimental section (Fig. 1).

3.2. Solubility behaviors

The ABA triblock copolymers are formed from different hydrophobic and hydrophilic fragments with totally different

solubility (Table 1). The aqueous solution of these compounds particularly **G₁** in different temperatures show one or two transition temperature and they behave as the thermoreversible hydrogels. Therefore, it seems that, investigation the solution behaviors of these compounds is interesting and more studies in our library relation to this work is in the way. The studying results of solubility behaviors of synthesized dendritic compounds in some of the solvents are shown in the Table 1.

(c)

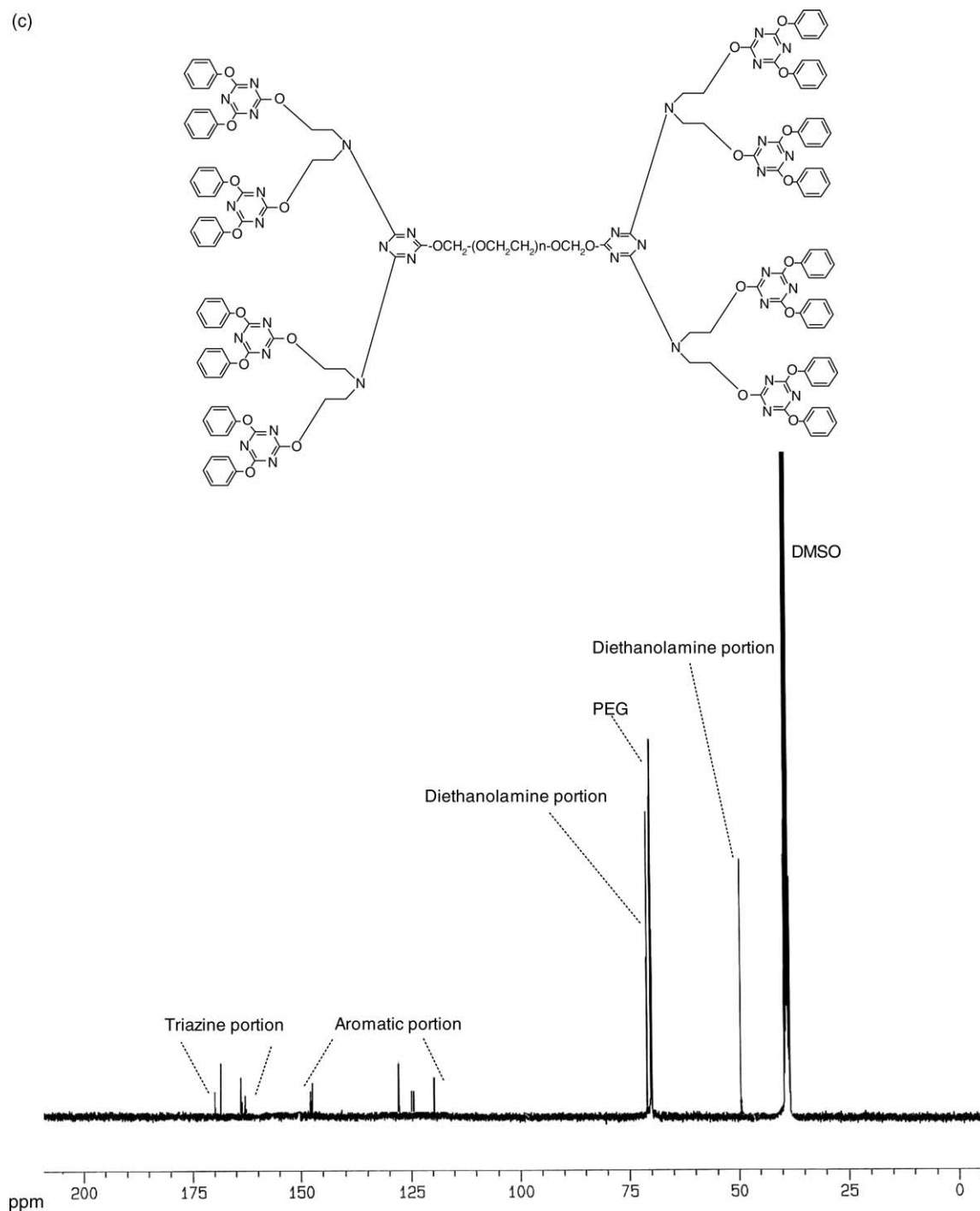


Fig. 3 (continued)

3.3. CHN investigations

In order to confirm the NMR data related to the growth of dendritic parts, CHN investigation was carried out for the prepared compounds. In theoretical view, the percent of nitrogen must be increased with growth of dendrimers. Because, the main portion of carbon percent of dendrimers is related to the PEG as the core, and with growth of triazine parts in ends of PEG the percent of nitrogen will increase.

Therefore, this method could be applied for the determination of the growth of dendrons on the PEG. Although, with increasing the dendrimer generations, the difference between calculated and experimental data is increased, however, as seen in Table 2 experimental results are in a good agreement with calculated results for the different dendrimer generations. Fig. 3 displays the increasing of percent nitrogen vs. the generations in comparison to the calculated values, as shown with increasing the generation of dendrimers

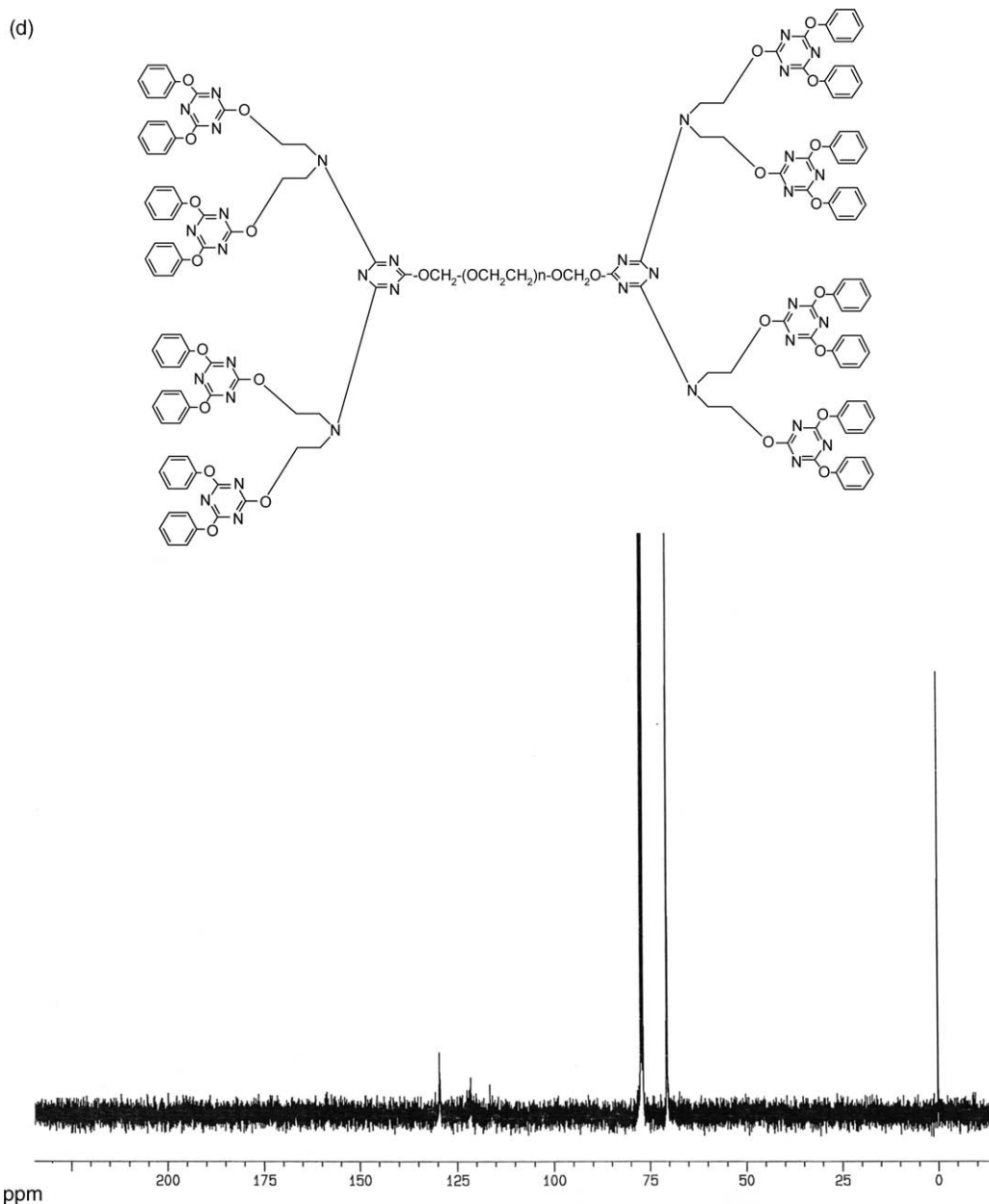


Fig. 3 (continued)

the nitrogen percent is increased which is evidence to the dendrimers growth.

3.4. NMR investigations

As above mentioned Fréchet et al. attached poly(benzyl ether) dendron units to PEO block and NMR investigation of hybrid copolymers showed their unusual solution behavior in organic solvents such as THF, methanol and chloroform [1,8, 10]. ^1H NMR spectra of ABA triblock copolymer showed that the ratio of peak area of the PEG to fourth generation dendrimer moiety in $\text{THF-}d_8$ was lower than the theoretical value, which can be obtained in CDCl_3 .

Whereas, in $\text{methanol-}d_4$, proton signals assignable to the dendritic wedge of fourth generation dendrimer were very

broad and weak. The results were closely related with the behavior of aggregation of block copolymers. In chloroform, the copolymer exists in an extended conformation while in THF, the PEG block was tightly packed, and conversely the dendrimer block is wrapped by an extended PEG chains in methanol. A similar behavior was observed earlier for the amphiphilic star copolymers.

Here we obtained some similar results for synthesized triblock copolymers containing triazine dendrons. Fig. 2(a) shows ^1H NMR spectra of $\text{G}_{1.5}$ in D_2O , signals of $-\text{CH}_2\text{O}-$ groups, PEG, $-\text{N}-\text{CH}_2-$ groups and end methylene groups of PEG are appeared at 2.85, 3.6, 3.7 and 3.8 ppm, respectively. In the ^1H NMR spectra of $\text{G}_{1.5}$ in CDCl_3 (Fig. 2(b)) the signal of methylene protons of PEG is appeared at 3.6 ppm and signal of methylene protons of $-\text{CH}_2\text{OH}$ group of diethanolamine which



Scheme 2. Proposed conformations of $G_{1.5}$ in DMSO and chloroform.

have been appeared at 2.85 ppm in ^1H NMR spectra of $G_{1.5}$ in D_2O (Fig. 2(a)) is disappeared, whereas three broad peaks related to these protons, $-\text{CH}_2-\text{N}-$ groups and protons of methylene end groups of PEG are appeared at 3.7–3.8 ppm. Therefore, it could be resulted, in the aqueous solvents $G_{1.5}$ expand to adapt its fully extended conformation because both of building blocks are readily soluble, but in the lower polar organic solvent such as chloroform $G_{1.5}$ form a monomolecular micelles containing PEG loops.

Fig. 3(a) display ^1H NMR spectra of G_2 , as seen signals of methylene protons of diethanolamine part and PEG protons are appeared at 3.5–4 ppm as overlapped signals, also signals of aromatic protons are appeared at 6.9–7.8 ppm. Fig. 3(b) shows the ^1H NMR spectra of G_2 in CDCl_3 . Signals of PEG and aromatic protons are appeared at 3.64 and 6.7–7.5 ppm, respectively, but peaks of protons of diethanolamine part are disappeared (compare to ^1H NMR spectra of G_2 in $\text{DMSO}-d_6$, Fig. 3(a)) and peaks of aromatic protons are broad and the ratio

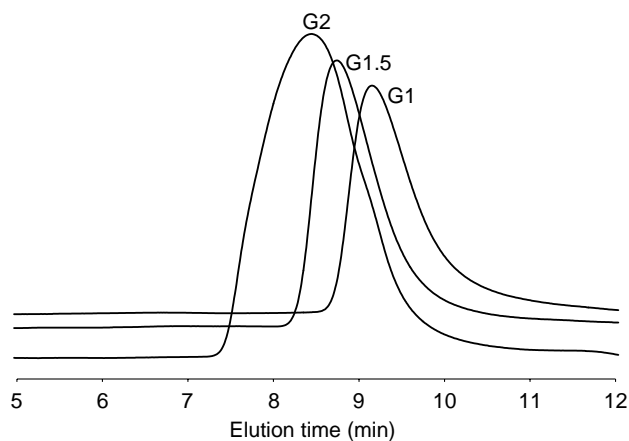


Fig. 4. GPC diagrams of linear-dendritic compounds.

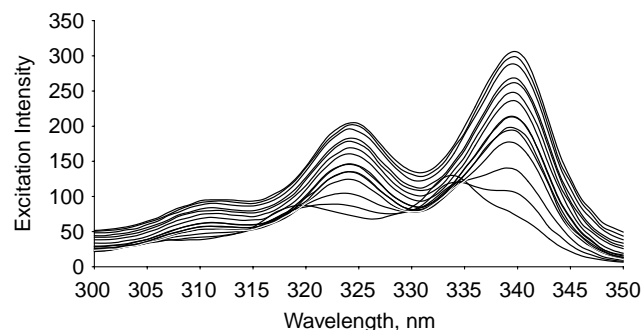


Fig. 5. Pyrene fluorescence excitation spectra in aqueous solutions of G_2 ; respectively, from top to down: 5×10^{-4} , 4×10^{-4} , 3.2×10^{-4} , 2.6×10^{-4} , 2×10^{-4} , 1.6×10^{-4} , 8×10^{-5} , 4×10^{-5} , 2.5×10^{-5} , 2×10^{-5} , 1.25×10^{-5} , 1×10^{-5} , 5×10^{-6} , 2.5×10^{-6} , 1.25×10^{-6} .

area peak of PEG to the aromatic part is higher than the calculated value. Fig. 3(c) display ^{13}C NMR of G_2 , signals at 48, 70 and 71 ppm are related to the carbon atoms of $-\text{NCH}_2-$ group, PEG and $-\text{CH}_2-\text{O}-$ group, respectively, also signals of aromatic and triazine carbons are appeared at 119–148 and 165–170 ppm, respectively. In the ^{13}C NMR of this compound in the chloroform solvent (Fig. 3(d)) the peak of carbons of PEG are exist at 70 ppm and the peaks of aromatic carbons are disappeared (compare to the ^{13}C NMR of G_2 in $\text{DMSO}-d_6$ Fig. 3(c)), this could be related to the aggregation behavior of G_2 in the chloroform. From the ^1H NMR and ^{13}C NMR data in the $\text{DMSO}-d_6$ and CDCl_3 , it could be resulted, in the polar solvents such as DMSO in which both building blocks are readily soluble, the triblock copolymer (G_2) expand to adapt their fully extended conformation, but in chlorinated solvents with lower polarity such as CDCl_3 the triblock copolymer form a monomolecular micelles with a hydrophobic dendrimer covered with hydrophilic outer PEG layer (Scheme 2).

3.5. GPC measurements

The fact that the measured molecular weights of dendritic and star copolymers by GPC are lower than the actual data

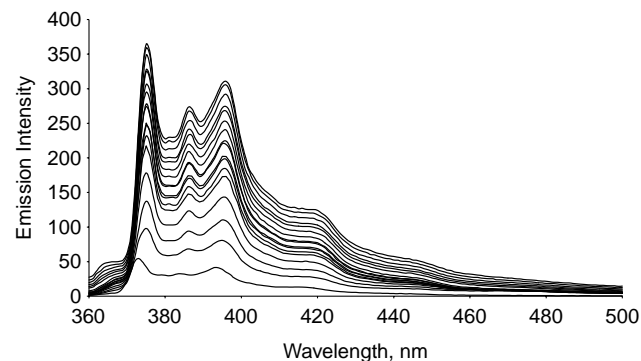


Fig. 6. Pyrene fluorescence emission spectra in aqueous solutions of G_2 ; respectively, from top to down: 5×10^{-4} , 4×10^{-4} , 3.2×10^{-4} , 2.6×10^{-4} , 2×10^{-4} , 1.6×10^{-4} , 8×10^{-5} , 4×10^{-5} , 2.5×10^{-5} , 2×10^{-5} , 1.25×10^{-5} , 1×10^{-5} , 5×10^{-6} , 2.5×10^{-6} , 1.25×10^{-6} .

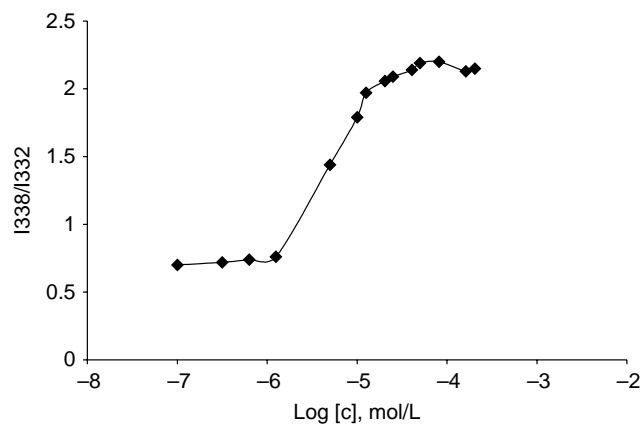


Fig. 7. Fluorescence intensity ratios of pyrene excitation bands (I_{338}/I_{332}) depending on the concentration of aqueous solutions of linear-dendritic copolymer (G_2).

(because of lower hydrodynamic volume of these types of compounds than linear analogs) is well known for several years [15]. However, for determination growth of dendrons and especially monomodality of copolymers GPC measurements for these compounds were performed and results are shown in Fig. 4. As seen in this figure molecular weight of linear dendritic compound with growth of dendrons is increased and all of the GPC diagrams are monomodal which display purity of compounds. Polydispersity index for G_1 , G_2 and G_3 is 1.2, 1.25 and 1.4, respectively, which is expectable for linear-dendritic supramolecules.

3.6. Fluorescence investigations

Fluorescence measurements were used for determination of cmc of G_2 in aqueous solutions. Clearly, the intensity of the spectra increases with increasing of copolymer concentration (Figs. 5 and 6) upon pyrene partition into a micellar hydrophobic core. Concentration dependence of pyrene fluorescence intensity (I_{375}) in aqueous solutions for copolymer is presented in Fig. 7. At a lower concentration range, a negligible change in the intensity was detected. However, at a certain concentration the intensity ratios exhibited a substantial increase, suggesting that pyrene molecules are incorporated into the hydrophobic core region upon micellar aggregation. The cmc value of G_2 was 4.07×10^{-5} .

4. Conclusions

A divergent method was applied for the growth of dendrimers on the PEG core. The reaction conditions were simple and protection and deprotection steps which are disadvantages of synthesize methods of dendritic supramolecules were avoided. Also the yields of reaction were high. Linear dendritic supramolecules are containing different parts with different solubility and they change their conformation in different solvents as the fully extent or tightly packed conformations for adaptation to medium and decreasing the undesirable interaction with solvent.

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