Dendritic Macromolecules Containing Several Types of Functional Groups

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ABSTRACT: Dendritic macromolecules containing several types of functional groups were successfully synthesized through divergent method. Poly(ethylene glycol) was functionalized using cyanuric chloride and it was reacted with *p*-toluidine at room temperature and a macromolecule containing chloride and methyl functional groups (PEG-Cl_2-Me_2) was obtained. Substitution of chloride functional groups of PEG-Cl_2-Me_2 by hydroxyl functional groups led to a macromolecule containing methyl and hydroxyl functional groups (PEG-Me_2-OH_4). Hydroxyl functional groups of PEG-Me_2-OH_4 were reacted with cyanuric chloride and PEG-Me_2-Cl_8 was obtained. Finally, PEG-Me_2-Cl_8 was reacted with *p*-aminophenol at room temperature and a macromolecule containing methyl, hydroxyl, and chloride functional groups (PEG-Me_2-$(PhOH)_4$-Cl_4) was obtained. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 115: 9–14, 2010

Key words: dendrimer; functional group; triazine; poly(ethylene glycol); diethanolamine

INTRODUCTION

Multifunctional macromolecules such as dendrimers,[1–8] polyrotaxans,[9] and hyperbranched polymers[10–17] are caused an explosion in the scientific interest in the recent years. Because of their controllable and well known structures, dendrimers are one of the best candidates to make nanodevices.[18–26] Nanocarriers,[26] nanoreactors,[27–30] nanoextractions,[31] nanomembranes,[32] nanocomposites,[33] and nanoparticles[34] are only few examples of nano-objects constructed based on dendrimers. Dendritic macromolecules containing active sites on their surface or core could be used as multidisciplinary materials in the atomic or molecular level,[35–37] and actually high functionality and cavity of dendrimers is the most important reason to be novel tools for constructing nanodevices.[19,38–41]

A nanodevice is containing several different segments which are connected together with a precise in atomic or molecular level.[42–44] Multifunctional macromolecules are able to deliver several segments in the same time and are good candidates to construct the nanodevices. However due to their synthesis routes, perfect dendrimers are containing only one or two types of functional groups on their surfaces[19,38–41] which have the same reactivity and selective reactions for constructing nanodevices is difficult. Based on this idea, macromolecules containing several types of functional groups in which number and place of each type of functional groups are controllable are recognized as good candidates for molecular architecture and finally preparation of nanodevices.

In this work, poly(ethylene glycol) was functionalized using cyanuric chloride. Then chloride functional groups of functionalized PEG were substituted using different reagents step by step and different macromolecules containing different types of functional groups were obtained.

EXPERIMENTAL

Characterization

^{1}H-NMR spectra were recorded in $CDCl_3$ solution, on a Bruker DRX 500 (500 MHz) apparatus with the solvent proton signal for reference. ^{13}C-NMR spectra were recorded at 125.721 MHz on the same instrument using the solvent carbon signal as a reference. IR spectra of samples as KBr pellets were recorded using a Nicolet 320 FTIR. CHN analyses were recorded in Institute of Polymer and Petrochemical.

HPLC experiments were carried out by Shimadzu GC-17A using DB5 column and a UV detector, the length of column was 25 cm and the elution solvents were ammonium acetate buffer and acetonitril with a 0.8 mL/min flow rate.

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MATERIALS

Poly(ethylene glycol) ($M_n = 1000$), cyanuric chloride, *p*-toluidine, diethanoamine, *p*-aminophenol, and solvents were purchased from Merck and used without further purification. PEG-Cl_4 was prepared according to reported procedure in the literature.[45]

Synthesis of PEG-Cl_2-Me_2

PEG-Cl_4 (2 g, 1.5×10^{-3} mmol) was added to a reaction flask containing 20 mL dichloromethane and equipped with magnet, argon, and vacuum inlets. *p*-toluidine (1 g, 4×10^{-3} mmol) dissolved in 10 mL dichloromethane was added to reaction flask at 0°C dropwise. Solution was stirred at 0°C for 4 h, then it was filtered and solvent was evaporated using vacuum at 15°C. Product was precipitated in diethylether as a brown solid compound in 70% yield (Scheme 1).

IR (cm^{-1}): *N*—H (3200), aromatic C—H (3100), C=N (1650), C=C (1611, 1640). ^{13}C-NMR (ppm): C=N (175), C=C (141, 132, 129, 127), PEG (69), CH_3 (27).

Synthesis of PEG-Me_2-OH_4

PEG-Cl_2-Me_2 (1 g, 7×10^{-4} mmol) was added to a reaction flask containing 20 mL dichloromethane and equipped with magnet, argon, and vacuum inlets. Subsequently, diethanolamine (0.7 mL, 1.4×10^{-3} mmol) was added to it at room temperature dropwise and mixture was stirred at room temperature for 1 h and then refluxed for 24 h. Then, it was filtrated and diethanolamine was separated using decanter. Solvent was evaporated and product was precipitated in diethylether as a yellow viscose compound in 60% yield (Scheme 1).

IR (cm^{-1}): O—H (3200–3500), C=N (1660), C=C (1611, 1640). ^{13}C-NMR (ppm): C=N (177, 175), C=C (141, 134, 130, 128), PEG (69), CH_3 (27), —CH_2OH (44), —NH—CH_2— (20).

Synthesis of PEG-Me_2-Cl_8

Cyanuric chloride (1.5 g, 8.1×10^{-3} mmol) was dissolved in 20 mL dichloromethane and added to a reaction flask equipped with magnet, argon, and vacuum inlets. Then, a mixture of PEG-Me_2-OH_4 (1 g, 6.3×10^{-4} mmol) and sodium hydroxide (0.1 g, 2.5×10^{-3} mmol) in 4 mL water was added to this solution at 0°C dropwise. Mixture was stirred at 0°C for 1 h and refluxed for 6 h. Then, it was cooled and filtered and solvent was evaporated. Product was precipitated in diethylether as a white solid compound in 50% yield (Scheme 1).

IR (cm^{-1}): *N*—H (3310), aromatic C—H (3100), aliphatic C—H (2900), C=N (1670–1730), C=C (1611, 1640). ^{13}C-NMR (ppm): C=N (176–170), C=C (144, 139, 135, 128), PEG (69), CH_3 (27), —CH_2O— (32), —NH—CH_2— (20).

Synthesis of PEG-Me_2-$(PhOH)_4$-Cl_4

PEG-Me_2-Cl_8 (1 g, 4.7×10^{-4} mmol) was added to a reaction flask containing 20 mL methanol and equipped with magnet, argon and vacuum inlets. *p*-aminophenol (0.4 g, 3.7×10^{-3} mmol) dissolved in 10 mL dichloromethane was added to reaction flask at 0°C dropwise and it was stirred at 0°C for 4 h. Then it was filtrated and solvent was evaporated at 15°C using vacuum. Product was precipitated in diethylether as a brown solid compound in 55% yield (Scheme 1).

IR (cm^{-1}): O—H (3500–3100), C=N (1650–1730), C=C (1611, 1640). ^{13}C-NMR (ppm): C=N (176–170), C=C (146–124), PEG (69), CH_3 (27), —CH_2O— (32), —NH—CH_2— (20).

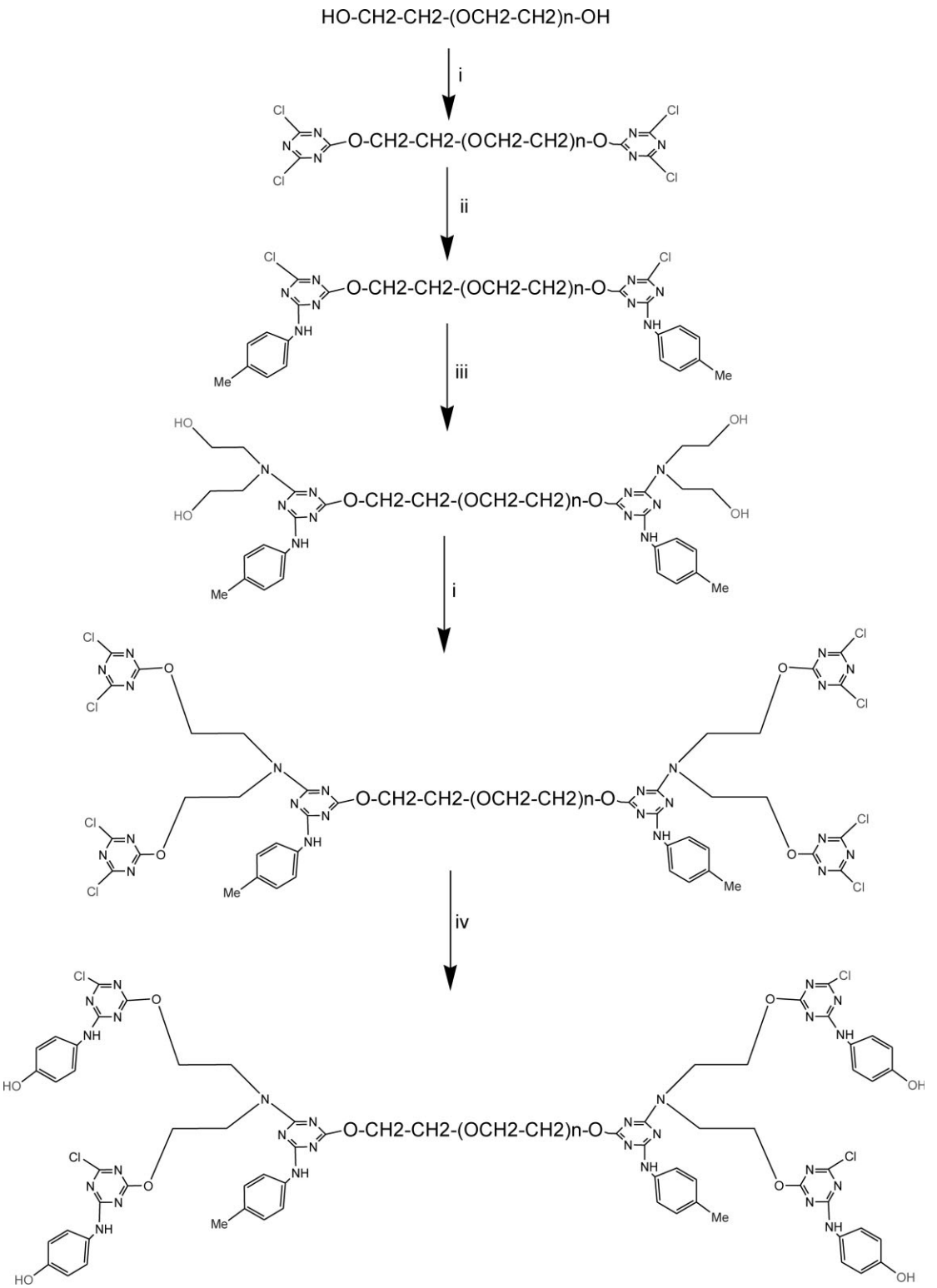
Synthesis of amphiphilic copolymer using PEG-Me_2-$(PhOH)_4$-Cl_4

One milliliter of 1×10^{-3} M toluene solution of $Sn(Oct)_2$ was added to a polymerization ampule equipped with a magnetic stirrer and vacuum inlet. Toluene was evaporated by vacuum at 60°C for 30 min. One milliliter of ε-caprolactone and 12 mg of PEG-Me_2-$(PhOH)_4$-Cl_4 were added to polymerization ampule. Polymerization ampule was left under vacuum for 1 h at 60°C. Then, it was sealed and stirred at 120°C for 10 h. Polymerization ampule was cooled and ampule contents were dissolved in chloroform. Solution was filtered and product was precipitated in diethylether. Twenty milligrams of dried copolymer was dissolved in 30 mL of acetonitril and 20 mL of 2-ethy-2-oxazoline was added to reaction flask. Mixture was stirred at 100°C for 24 h. Then reaction was cooled and solvent was evaporated and product was precipitated in diethylether.

IR (cm^{-1}): O—H (3400–3150), C=O (1710 and 1640). ^{1}H-NMR (ppm) (—^{a}CO—^{b}CH_2—^{c}CH_2—^{d}CH_2—^{e}CH_2—^{f}CH_2—O—): *f* (4), *b* (2.2), *c*, *d*, and *e* (1.3–1.7), PEG (3.6), —N—CH_2 and —CH_2— (3.8 and 3.56), —CH_2—N(CH_2)$_2$— and —CH_2— (3.1), —CO—CH_2— (2.2), —CH_3 (2.3 and 1), aromatic protons (6.9–7.6). ^{13}C-NMR (ppm): *a* (173.41), *f* (63.93), *b* (33.92), *c*, *d*, and *e* (28.25, 25.34, 24.38), C=O_{PEO} (167), C=C (120–147), C=N (155), PEG (69), —CH_2— (41, 34, and 23).

RESULTS AND DISCUSSION

Dendritic macromolecules containing several types of functional groups were successfully synthesized



Scheme 1 Synthesis of different dendritic macromolecules. Reagents: (i) triazine, dichloromethane, NaOH, 0°C: reflux; (ii) dichloromethane, *p*-toluidin, 0°C; (iii) diethanolamine, reflux; (iv) *p*-aminophenol, methanol, 0°C.

by divergent method. Scheme 1 shows the synthesis route of dendritic macromolecules in which PEG was functionalized using cyanuric chloride and PEG-Cl_4 was obtained. Substitution of second chloride functional groups of cyanuric chloride segments by *p*-toluidine was led to a macromolecule containing methyl and chloride functional groups (PEG-Cl_2-Me_2). Figure 1 shows the IR spectra of different dendritic macromolecules from 4000 to 2250 cm^{-1}. In the IR spectra of PEG-Cl_4 [Fig. 1(a)] the absorbance

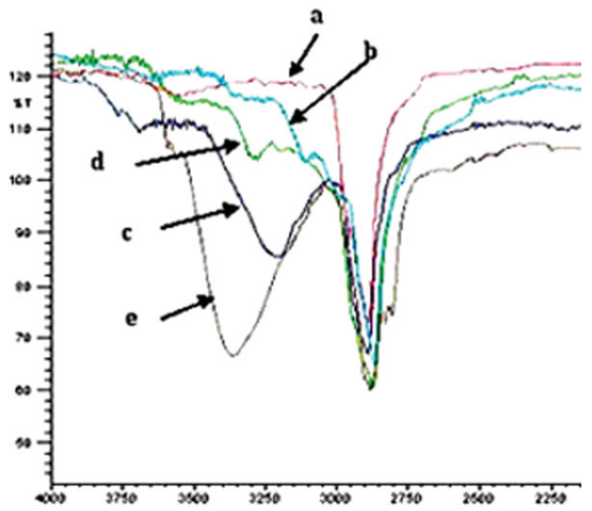


Figure 1 IR spectra of (a) PEG-Cl_4, (b) PEG-Cl_2-Me_2, (c) PEG-Me_2-OH_4, (d) PEG-Me_2-Cl_8, and (e) PEG-Me_2-$(PhOH)_4$-Cl_4 from 4000 to 2250 cm^{-1}. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

band of C—H bonds of PEG protons is appeared at 2850 $cm^{-1}$and the absorbance band of C—Cl bond of cyanoric chloride part is appeared at 730 cm^{-1}. IR spectra of PEG-Cl_2-Me_2 [Fig. 1(b)] is containing the same absorbance bands and a shoulder at 3100 cm^{-1} which is related to the aromatic protons of *p*-toluidine segments. On the other hand in the ^{1}H-NMR spectra of PEG-Cl_2-Me_2, signals of aromatic protons of *p*-toluidine segments, protons of PEG and methyl groups are appeared at 7.3, 7.1, 3.6, and 2.3 ppm, respectively, [Fig. 2(a)]. Nucleophilic substitution of chloride functional groups of PEG-Cl_2-Me_2 by diethanolamine led to a macromolecule containing methyl and hydroxyl functional groups (PEG-Me_2-OH_4) (Scheme 1). In the IR spectra of this macromolecule, appearing an absorbance band at 3500–3200 cm^{-1} which is related to the hydroxyl functional groups of diethanolamine segments [Fig. 1(c)] proved that the chloride functional groups are substituted by diethanolamine. ^{1}H-NMR spectra of PEG-Me_2-OH_4 is displayed in Figure 2(b). In this figure, the signals of aromatic protons can be seen at 7.4 and 7.1 ppm and signals at 4.6 and 3.85 ppm are related to the diethanolamine segments and signals of PEG and methyl groups can be seen at 3.6 and 2.3, respectively.

PEG-Me_2-Cl_8 was synthesized through reaction between cyanuric chloride and PEG-Me_2-OH_4 (Scheme 1). In the IR spectra of this compound [Fig. 1(d)], the absorbance band of hydroxyl functional groups of PEG-Me_2-OH_4 is disappeared and absorbance bands of *N*—H and aromatic and aliphatic protons can be seen at 3310, 3100, and 2900 cm^{-1} respectively. In these spectra, the appearing new absorbance bands at 1730–1670 cm^{-1} and 750 cm^{-1} which are related to the C=N and C—Cl bonds, respectively, proved the conjugation of cyanuric chloride segments to the PEG-Me_2-OH_4. Figure 2(c) shows the ^{1}H-NMR spectra of PEG-Me_2-Cl_8 in which signals at 7.5 and 7.1 ppm are related to the aromatic protons of *p*-toluidine segments and signals at 3.85 and 3.1 ppm are related to the diethanolamine segments. Signals of PEG and methyl groups are also appeared at 3.6 and 2.3 ppm, respectively.

Reaction between PEG-Me_2-Cl_8 and *p*-aminophenol in the mild condition leads to a macromolecule containing methyl, chloride, and phenolic hydroxyl functional groups (PEG-Me_2-$(PhOH)_4$-Cl_4) (Scheme 1).

Appearance of an absorbance band at 3500–3100 cm^{-1} in its IR spectra which is assigned to the phenolic hydroxyl groups shows that chloride functional groups of PEG-Me_2-Cl_8 are substituted by *p*-aminophenol. Figure 2(d) display the ^{1}H-NMR spectra of PEG-Me_2-$(PhOH)_4$-Cl_4 in which signals of different segments of PEG-Me_2-$(PhOH)_4$-Cl_4 are shown.

Elemental analysis was used to investigate the growth of dendritic parts on PEG core. Table I shows the carbon, nitrogen, and oxygen analysis data for macromolecules. Good agreement between them and calculated data show that compounds are synthesized successfully and free from impurities.

For investigations, the growth of dendritic parts and purity of compounds the HPLC experiments were also done. Figure 3 shows the HPLC diagrams for different generations. In this experiment, column was hydrophobic and the retention time was directly dependent on the polarity of compounds. The signal (a) is related to the methanol which is a high polar solvent and has a weak interaction with the hydrophobic column. The signal (b) is related to the PEG-Me_2-$(PhOH)_4$-Cl_4 which is a polar compound and have a weak interaction with the column. The third signal (signal c) is related to the PEG-Me_2-OH_4 compound which is also a hydrophilic compound and also has a weak interaction with hydrophobic column. The signal (d) is related to the PEG-Cl_2-Me_2 which has lower polarity. The signals (a) and (f) are almost in the same region and are related to the PEG-Me_2-Cl_8 and PEG-Cl_4 compounds which their dendritic parts are similar and are also hydrophobic. In this figure, the monomodality of diagrams prove the purity of products.

Because of the presence of different functional groups in these dendritic macromolecules, they can be used to make hybrid materials. In this work, PEG-Me_2-$(PhOH)_4$-Cl_4 was used to synthesize amphiphilic copolymer containing PEG core and poly(caprolactone) (PCL) and poly(2-ethyl-oxazoline) (PEO) arms. In this synthesis, —OH functional groups were used to initiate the polymerization of ε-caprolactone monomer and chloride functional groups of cyanuric parts were used to polymerize

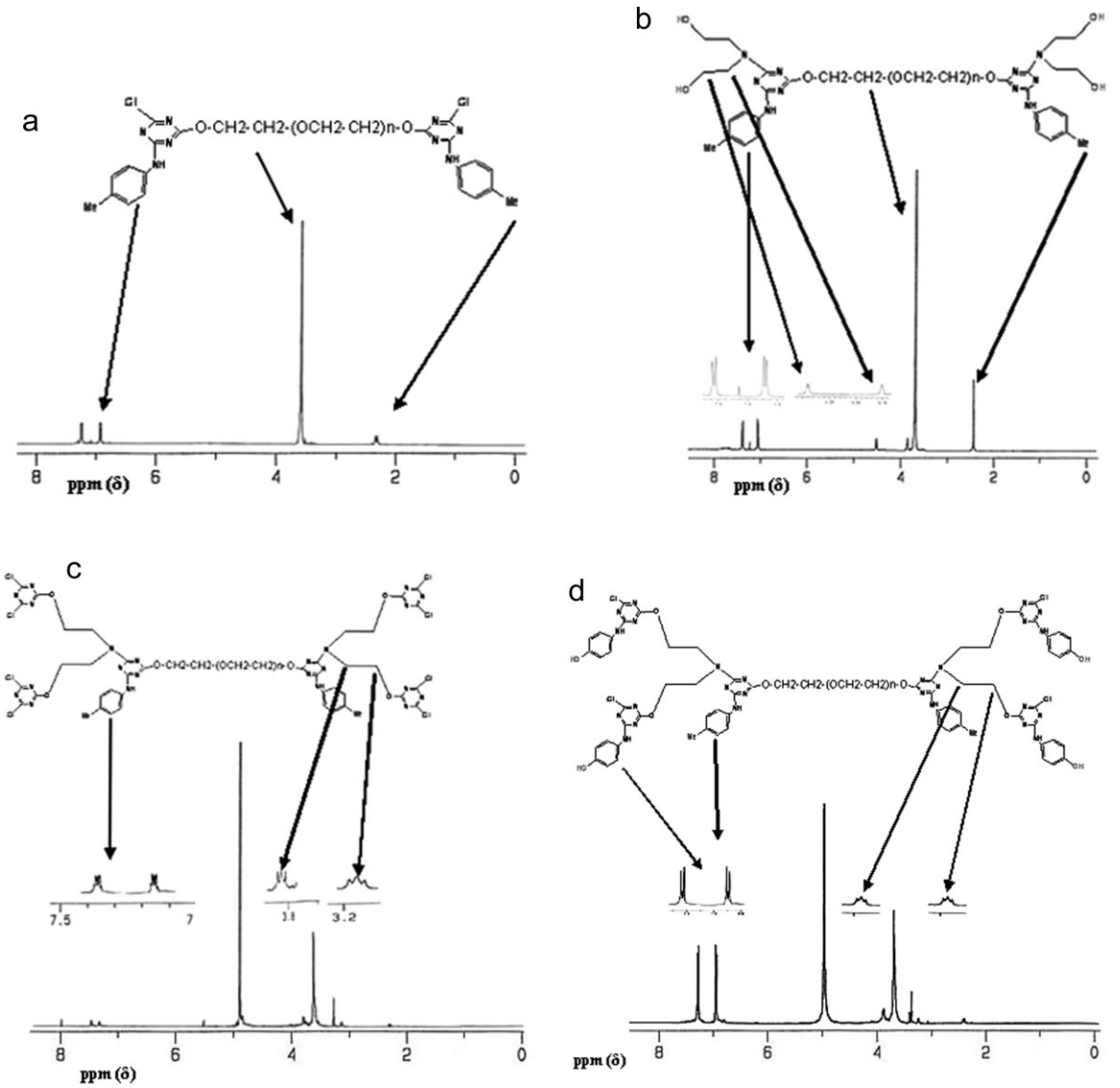


Figure 2 ^{1}H-NMR spectra of (a) PEG-Cl_2-Me_2, (b) PEG-Me_2-OH_4, (c) PEG-Me_2-Cl_8, and (d) PEG-Me_2-$(PhOH)_4$-Cl_4.

oxazoline monomer. Synthesized copolymer was containing three blocks in which PEG is a hydrophilic and biocompatible block, PCL is a hydrophobic and biocompatible block and PEO is a hydrophilic and biocompatible block. Because of the presence of PEO and two other biocompatible blocks in this macromolecule and its amphiphilic property, it can be used to deliver different biological molecules in the biological systems.

CONCLUSIONS

Poly(ethylene glycol) was functionalized using cyanuric chloride in a high yield. Stepwise substitution

TABLE I
Elemental Analysis Results for Different Macromolecules

Sample	%N		%O		%C	
	Exp.	Cal.	Exp.	Cal.	Exp.	Cal.
PEG	0	0	38.35	38.4	54.5	54.54
PEG-Cl_4	6.4	6.4	29.65	29.6	47.45	47.64
PEG-Cl_2-Me_2	7.73	7.79	26.1	26.7	54.56	54.37
PEG-Me_2-OH_4	8.74	8.89	28.51	28.46	45.1	45.33
PEG-Me_2-Cl_8	13.31	14.21	20.44	20.69	40.8	39.59
PEG-Me_2-$(PhOH)_4$-Cl_4	14.15	14.82	21.2	20.84	47.2	46.64

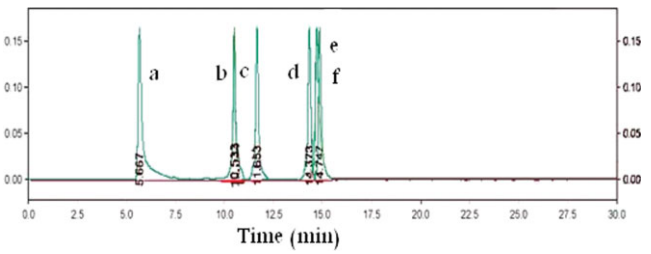


Figure 3 HPLC diagrams of (a) MeOH, (b) PEG-Me_2-$(PhOH)_4$-Cl_4, (c) PEG-Me_2-OH_4, (d) PEG-Cl_2-Me_2, (e) PEG-Me_2-Cl_8, and (f) PEG-Cl_4. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

of chloride functional groups of cyanuric chloride segments lead to macromolecules containing several types of functional groups. The type of functional groups in the synthesized macromolecules depends on the reagent.

However, multidisciplinary materials containing several types of functional groups are new class of macromolecules which can be synthesized through selective and step by step reactions. Because of their multitype functional groups, they are suitable building blocks for preparation of materials in the nano- and atomic scale.

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