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An Investigation on Phase Behavior of ABA-type Block Copolymers Comprising of 2-Hydroxypropyl Acrylate and Poly (Ethylene Glycol)

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Abstract

ABA-type block copolymers consisting of 2-hydroxypropyl acrylate (HPA) and ethylene glycol (EG) segments were prepared by the RAFT polymerization method using two different lengths of macro-RAFT agents based on commercial poly(ethylene glycol)s with average molar masses of 400 and 1450 $gmol^{-1}$ (PEG400 and PEG1450). By extending the difunctional ends of PEG400 and PEG1450 vertebrate macro-RAFT agents with HPA units, it was aimed to synthesize three ABA type block copolymers of different lengths from each agent. Structural characterization of the copolymers was performed using FTIR and ^{1}H-NMR spectroscopy. In addition to confirming the chemical structures, signal integrations in the ^{1}H-NMR spectrum provided information about the relative proportions of individual repeating units in each copolymer. Six block copolymers were examined for critical dissolution temperatures based on the relative lengths of the blocks and their PEG content. It was determined that all block copolymer systems examined exhibited lower critical solution temperature (LCST) in the range of 17.2-23.9 ^oC, and as the ratio of EG units in the copolymers increased, the CST of the copolymers increased.

Keywords: RAFT polymerization, ABA type-block copolymer, phase transition, lower critical solution temperature

2-Hidroksipropil Akrilat ve Poli (Etilen Glikol)'den Oluşan ABA Tipi Blok Kopolimerlerin Faz Davranışlarının İncelenmesi

Öz

2-hidroksipropil akrilat (HPA) ve etilen glikol (EG) segmentlerinden oluşan ABA tipi blok kopolimerleri, 400 ve 1450 $gmol^{-1}$ ortalama mol kütlesine sahip ticari poli(etilen glikol)'lerden (PEG400 ve PEG1450) elde edilen iki farklı uzunlukta makro-RAFT ajanı kullanılarak RAFT polimerizasyon yöntemiyle hazırlandı. PEG400 ve PEG1450 omurgalı makro-RAFT ajanlarının difonksiyonel uçları HPA birimleri ile uzatılarak her ajandan üçer tane farklı uzunlukta ABA tipi blok kopolimer sentezlenmesi hedeflendi. Kopolimerlerin yapısal karakterizasyonu FTIR ve ^{1}H-NMR spektroskopisi kullanılarak yapıldı. Kimyasal yapıların doğrulanmasına ek olarak, ^{1}H-NMR spektrumundaki sinyal entegrasyonları, her bir kopolimerdeki ayrı ayrı tekrar eden birimlerin göreceli oranları hakkında bilgi verdi. Blokların bağıl uzunluklarına ve PEG içeriklerine bağlı olarak altı blok kopolimer kritik çözünme sıcaklıkları açısından incelendi. İncelenen tüm blok kopolimer sistemlerinin 17.2-23.9 ^oC aralığında düşük kritik çözelti sıcaklığı (LCST) sergilediği ve kopolimerlerdeki EG birimlerinin oranı arttıkça kopolimerlerin CST'sinin arttığı belirlendi.

Anahtar Kelimeler: RAFT polimerizasyonu, ABA-tipi blok kopolimer, faz geçişi, düşük kritik çözünme sıcaklığı

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Introduction

Stimuli-responsive polymers are a type of polymer that exhibit changes in their chemical and/or physical properties in response to changes such as pH (Kocak et al., 2017), temperature (Kim & Matsunaga, 2017), light (Lam et al., 2022; Stoychev et al., 2019), and redox reaction (Levit et al., 2020). Polymeric systems that are sensitive to any two of these factors have also often been reported (Babić et al., 2016; González et al., 2005; Huang et al., 2016; Kanazawa & Okano, 2011; Twal et al., 2024). Thermo-responsive polymers, main part of the class of stimuli-responsive polymers, undergo a reversible phase transition as a function of temperature. They are of great interest in biotechnological applications such as drug delivery systems (Yadav et al., 2019), polymer-drug conjugates (Fergie et al., 2024), and tissue engineering (Doberenz et al., 2020).

Thermoresponsive materials have a sharp transition temperature at which they become either soluble or insoluble. The temperature at which the phase transition occurs in solution is called the critical solution temperature. Polymers that become soluble with increasing temperature have an upper critical solution temperature (UCST) and those that become insoluble with increasing temperature have a lower critical solution temperature (LCST). Examples of polymers that exhibit LCST include PNIPAM, poly(N,N-diethyl acrylamide), poly(N-acryloylpyrrolidine), poly(2-isopropyl-2-oxazoline) and poly(vinyl methyl ether). Although PNIPAM is the most studied thermoresponsive polymer, it has the disadvantage of an irreversible phase transition. In addition, the presence of the tertiary amide function in PNIPAM can cause H-bonding interactions with peptide bonds in proteins. Such behaviour complicates the use of PNIPAM in some biotechnological applications.

Poly(2-hydroxypropyl acrylate) (PHPA) is one of the most common polymers exhibiting lower critical solution temperature (LCST)(Eggenhuisen et al., 2008; C. D. Vo et al., 2010) in water, *i.e.* it precipitates upon heating and dissolves if it is cooled. Many works (Eggenhuisen et al., 2008; C.-D. Vo et al., 2010) have been reported on the polymer since critical solution temperature of its 10% of solution has been first time reported as 16 ^{o}C (Taylor & Cerankowski, 1975). Since then, not only PHPA but also many copolymers of HPA (Babić et al., 2015; Chen et al., 2022; Christova et al., 2003; Eggenhuisen et al., 2008; Hoogenboom et al., 2009; Perera & Shanks, 1995; Topham et al., 2008; Zhao et al., 2012)has been investigated in the aspect of Tc. Because of the low LCST of PHPA, copolymerization with a more hydrophilic monomer is expected to lead to a library that covers a broad range of transition temperatures.

Another type of polymeric systems exhibiting LCST is the graft copolymers bearing PEG analogues as branches (Lutz, 2008; Vancoillie et al., 2014). The non-linear PEG analogues can be insoluble in water, readily soluble up to 100^{o}C, or thermo-responsive. In fact, the balance between hydrophilic and hydrophobic moieties in the molecular structure of the polymers is the key-parameter that determines their solution properties. In a study (Vancoillie et al., 2019), a polymer system based on HPA and non-linear PEG analogues has been reported as LCST exhibiting thermo-responsive polymer. Since the phase transition temperature is directly related to the hydrophilic/hydrophobic balance in a random copolymer, controlling the polymer composition provides a very effective way of tuning the LCST. By creating systematical libraries of random copolymers, the relationship between monomer composition and LCST can be studied in detail (Fournier et al., 2007).

In this study, a series of ABA-type block copolymers comprising PEG and HPA units with different PEG/HPA ratios were synthesized and investigated as a potential thermo-responsive copolymer system.

Material and Method

Material

2-Hydroxypropyl acrylate (HPA), which was bought from Aldrich, is an isomeric mixture of approximately 80% 2-hydroxypropyl acrylate and 20% 1-methyl-2-hydroxyethyl acrylate. HPA was

passed through a column filled with neutral alumina to remove inhibitors. THF and 1,4-dioxane were redistilled from sodium benzophenone ketyl to remove inhibitor and moisture. 2,2'-azoisobutyronitrile (AIBN) was recrystallized from methanol before use. PEG1450 (Sigma-Aldrich), PEG400 (Sigma-Aldrich), potassium ethyl xanthate (Sigma-Aldrich), P-toluenesulfonyl chloride (Sigma-Aldrich), Dichloromethane (Riedel-de Haën) and diethyleter (Riedel-de Haën) were used as purchased without further purification.

Method

Synthesis of Macro-RAFT agents

Terminally di-xanthate PEG1450 and PEG400 (α-Xanthate-ω-Xanthate PEG1450 and α-Xanthate-ω-Xanthate PEG400) were synthesized as difunctional macro-RAFT agents according to the literature (Raposo et al., 2020; Zalipsky et al., 1987). The two-step reaction to obtain the macro-RAFT agent was given in Figure 1. The procedure for the RAFT agent based on PEG1450 (PEG1450-RAFT) was outlined. Triethylamine (1.6 mL, 11.0 mmol) and tosyl chloride (4.8 g, 25.0 mmol) were added to the PEG1450 (7.25 g, 5 mmol) dissolved in DCM (50 mL) under a nitrogen atmosphere and the reaction mixture refluxed for 36 h. After cooling to room temperature, the mixture was washed with 1.0 N HCl (2x40 mL), water, and brine. The organic layer was dried over anhydrous $NaSO_4$, concentrated under vacuum, and purified by column chromatography (DCM to 9:1 DCM/MeOH gradient) afforded the tosylate (8.63 g, 98%) as pale-yellow wax.

Potassium ethyl xanthate (2.3 g, 14 mmol) was added in one portion to the tosylate (8.4 g, 4.8 mmol) dissolved in deionized water (35 mL) and the reaction stirred for 15 hours at room temperature under nitrogen atmosphere. The mixture is diluted with water (25 mL) and extracted with dichloromethane (3x50 mL) and brine. The organic layer was dried over anhydrous $NaSO_4$, concentrated under vacuo. The crude product was dissolved in a few mL of DCM and poured into cold stirring ether (100 mL). The provided white precipitate was filtered off and dried in vacuum. (7.0 g, 88% yield)

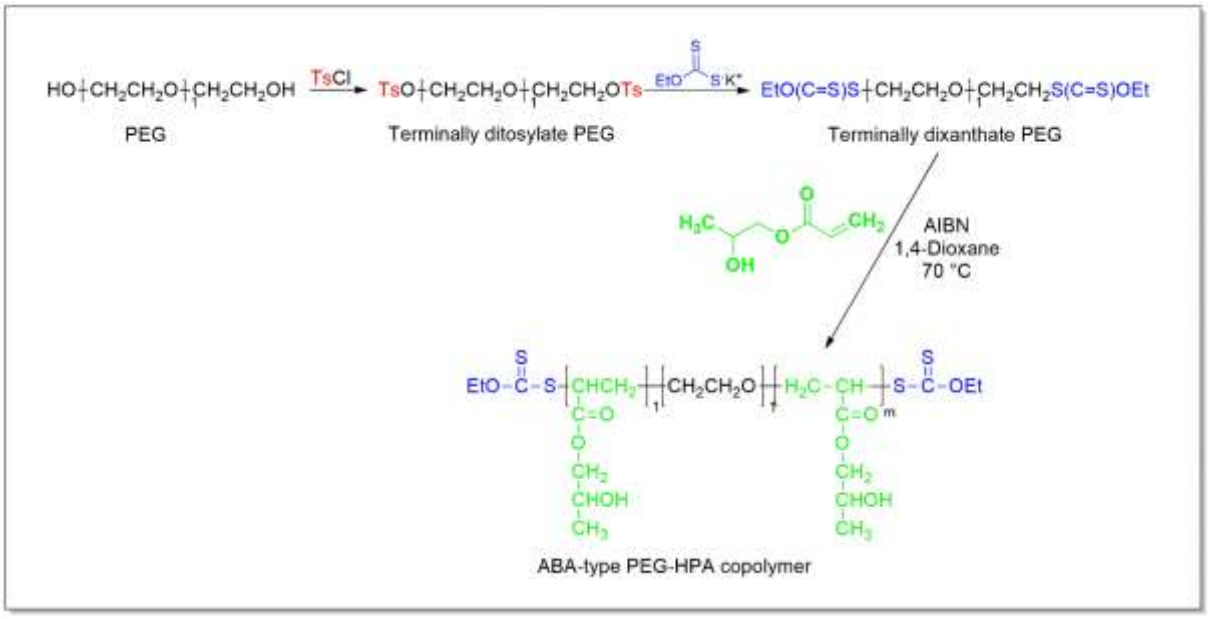

Figure 1. Reaction Pathway for the Synthesis ABA-Type PEG-HPA Block Copolymers

Polymerization

RAFT polymerization of 2-HPA was performed using the PEG-based difunctional RAFT agent as shown in Figure 1. The polymerization parameters outlined in Table 1 were applied to obtain a series of ABA-type block copolymers with different lengths as coded in Table 1. The reaction mixtures were poured

into 50 mL of cold diethyl ether to precipitate block copolymers. The yields of the polymerizations were calculated based on the weights of the diethyl ether-insoluble fractions for each copolymer.

Table 1. Polymerization Parameters

Code	Macro RAFT agent (g)	2-HPA (x10^3 mol)	AIBN (mg)	Yield (%)	Experimental ratio[1]
PEG1450-HPA-1	0.50	3.84	2	69	$PEG_{33}HPA_{36}$
PEG1450-HPA-2	0.50	7.68	2	78	$PEG_{33}HPA_{88}$
PEG1450-HPA-3	0.50	15.36	2	82	$PEG_{33}HPA_{125}$
PEG400-HPA-1	0.50	3.84	5	75	$PEG_{9}HPA_{21}$
PEG400-HPA-2	0.50	7.68	5	81	$PEG_{9}HPA_{32}$
PEG400-HPA-3	0.50	15.36	5	86	$PEG_{9}HPA_{40}$

Note. [1]Obtained from integrations in the ^{1}H-NMR spectra, Temperature: 70 Oc, Duration: 16 H, Solvent: 4 Ml 1,4-Dioxane

Characterization

FTIR spectra of PEG400, PEG1450, PEG400-RAFT, PEG1450-RAFT, and the copolymers (PEG400-HPA-1 and PEG1450-HPA-1) were recorded at ATR mode by using Shimadzu IR Affinity in the range of 600-4000 cm^{-1}. ^{1}H-NMR spectra of PEG1450-RAFT and the copolymers were received from Bruker AVANCE III 400 MHz NMR Spectrometer. MALDI-MS spectrum of the PEG1450-RAFT was attained using a Bruker Rapiflex MALDI- TOF/TOF mass spectrometer. The data were acquired in positive ion mode and DHB as the matrix.The copolymers prepared in 1.0 % solutions were heated and cooled in a controlled manner and their dissolution and precipitation temperatures were recorded (Güner & Ataman, 1994; Zhang et al., 2017). The isothermal environment required for the determination of precipitation (clouding) temperatures was provided by a water bath. Dissolution-precipitation cycles of the solutions prepared in the air jacketed tube were performed.

Results and Discussion

FTIR Spectroscopy

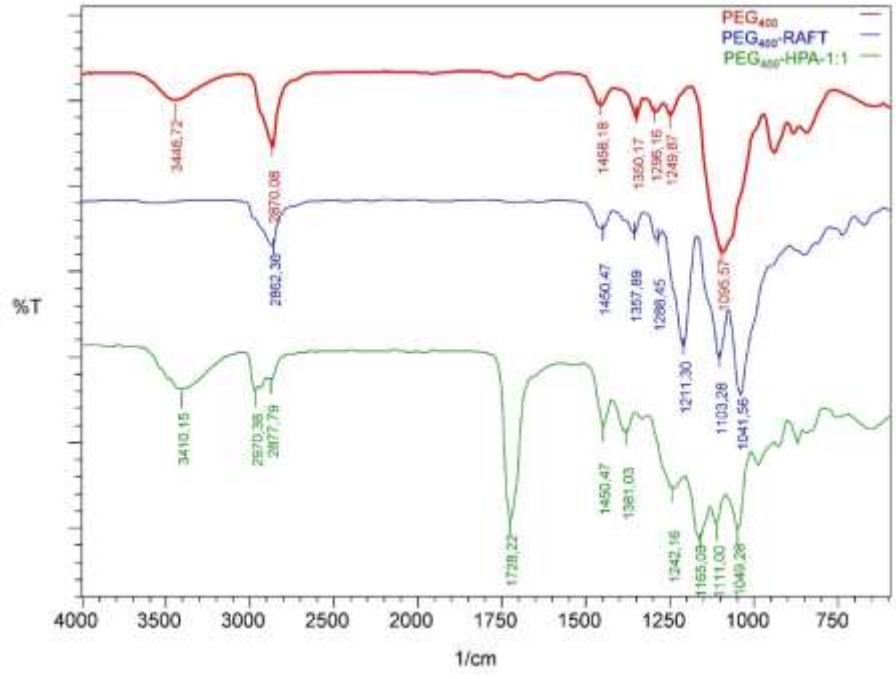

Figure 2. FTIR Spectra of PEG400, PEG400-RAFT and PEG400-HPA-1

FTIR spectra of pristine PEG400, PEG400-RAFT, and PEG400-HPA-1 were given in Figure 2 to easily compare the changes in the characteristic bands due to the chemical modifications. The full disappearance of the wide O-H stretching band at about 3449 cm^{-1} in the spectrum of PEG400 and the formation of the strong S-C-S bands at 1211 and 1041 cm^{-1} (Vorobyev et al., 2019) in the spectrum of the PEG400-RAFT are the basic indications of the RAFT-agent formation. The FTIR spectrum of PEG400-HPA-1 exhibited extra bands at about 3410, 1728, and 1165 cm^{-1} corresponding to the O-H, C=O, and C-O vibrations at HPA units, respectively.

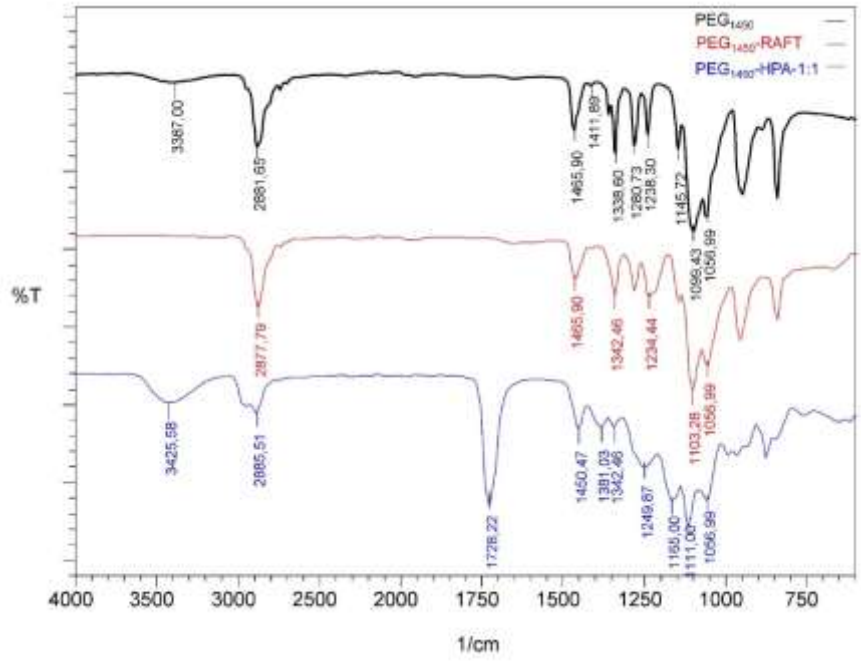

Figure 3. FTIR Spectra of PEG1450, PEG1450 RAFT and PEG1450-HPA-1

FTIR spectra of pristine PEG1450, PEG1450-RAFT and PEG1450-HPA-1 in Figure 3 were observed to be so like those for the PEG400 in Figure 2. The main differences between the corresponding spectra are due to the differences in the lengths of the PEG chains. Some examples are the longer PEG the weaker O-H (3387 cm^{-1}) and xanthate (1216 cm^{-1}) bands, the sharper bands of ethylene glycol units due to the self-crystallization of them.

MALDI Mass Spectrometry

MALDI mass spectrum of the PEG1450-RAFT sample in Figure 4 was recorded to assure that the end-group modification has been succeeded. The spectrum has well-distributed signals separated by 44 Da masses centered at about 1650 Da. The shift of the mass distribution of PEG1450 to the higher mass region at a degree of about 200 Da is a sign of successful end-group modification. Moreover, the signal with 1701.343 m/z completely corresponds to the structure of $[XM_{32}CH_2CH_2XNa]^+$. Here, X abbreviates the ethyl xanthate (C_2H_5O-CS-S-) group.

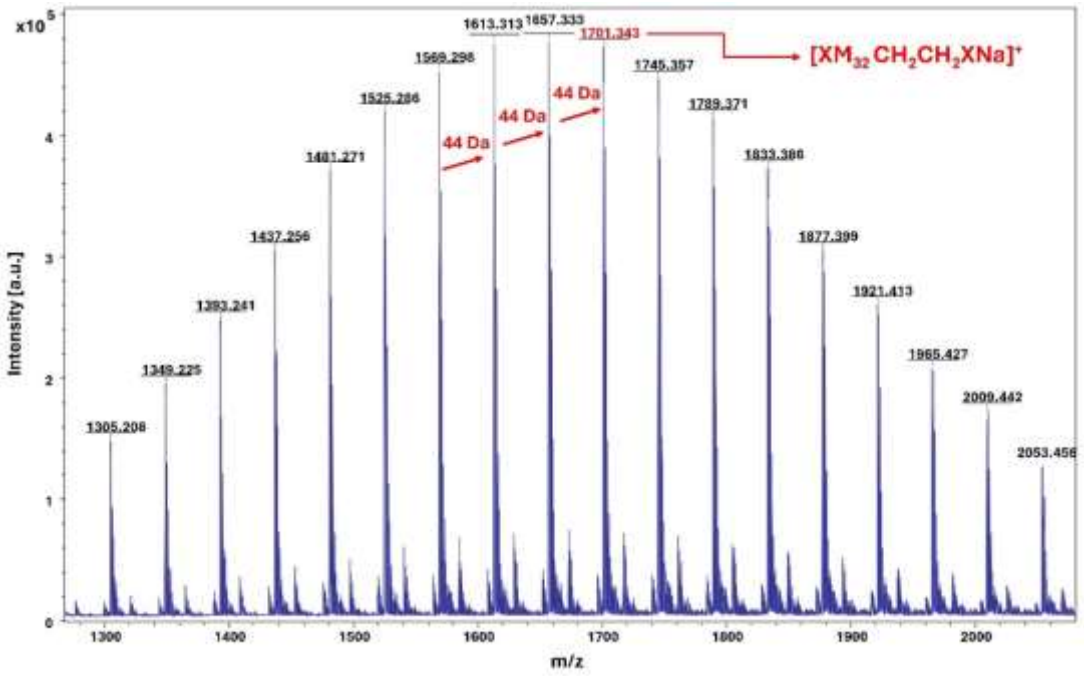

Figure 4. MALDI-MS TOF Spectrum of PEG1450-RAFT

Proton NMR Spectroscopy

^{1}H-NMR spectrum of the PEG1450-RAFT in Figure 5 has the split signals belonging to the protons at the end-groups and the huge signal belonging to the repeating units of ethylene glycol. As easily seen, the values of the integration and the chemical shift corresponding to each proton are consistent with the structure in Figure 5.

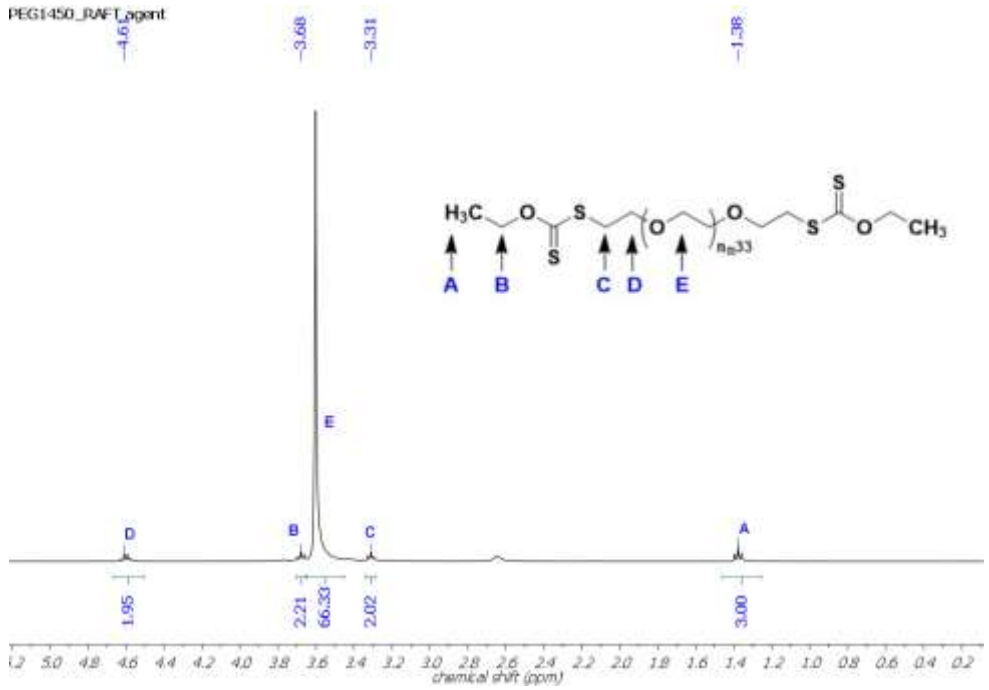

Figure 5. NMR Spectrum of The PEG1450-RAFT

^{1}H-NMR spectra of PEG400-HPA-1 was recorded both to confirm the structure, and to determine the HPA/EG ratio by mole in the block copolymer. As seen in Figure 6, the spectrum has signals belonging to the ethylene glycol and the HPA units. The integrations of the signals are consistent with the intra-

structure stoichiometry. The minor signals at 1.43, 3.35, 3.82 and 4.65 ppm belonging to the xanthate protons show the live character of the block copolymer. Because PEG400 has about average 9 repeating units, the intensity of the PEG signals at 3.65 and 3.70 ppm may be attributed to 36 protons to compare with the signal at 1.18 ppm belonging to the CH_3 protons of HPA. Since each repeating unit of HPA has only one CH_3 group the average number of HPA units may be estimated by dividing the intensity of CH_3 protons by three. As a result, the average number of HPA units was calculated as about 21 for the PEG400-HPA-1. Briefly, the copolymer may be defined as PEG_9-HPA_{21} as given in Table 1.

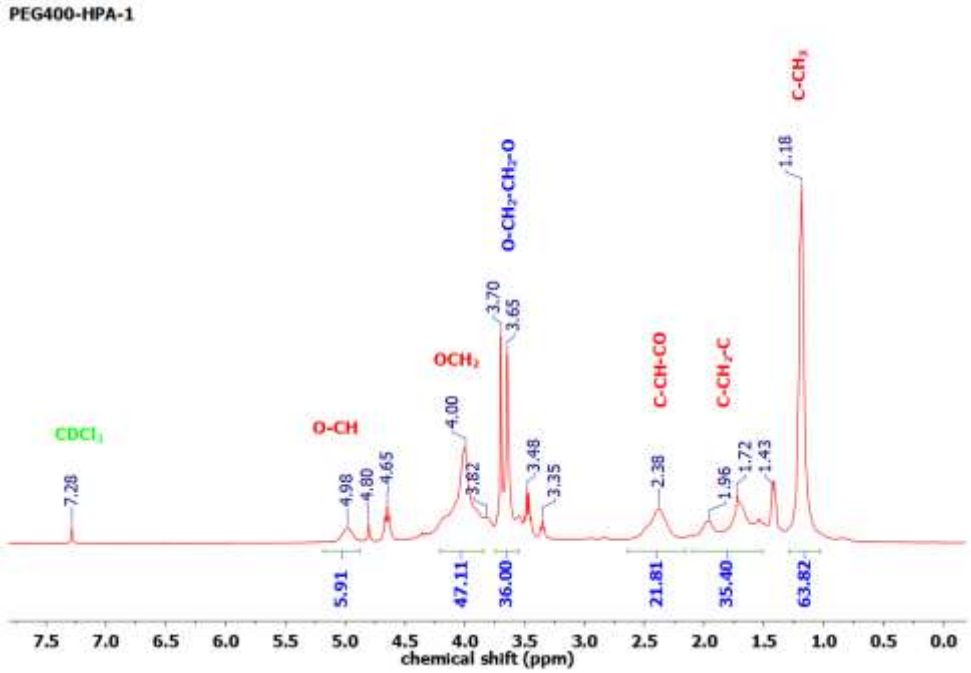

Figure 6. ^{1}H-NMR Spectra of PEG400-HPA-1

^{1}H-NMR spectra of PEG1450-HPA-1 was given in Figure 7. Evaluation of the spectrum is almost same as in the previous one. Briefly, the signals are consistent with the chemical structures of the repeating units with respect to chemical shifts and relative intensities. The spectrum has also trace signals of ethyl xanthate. Assuming that the PEG1450 has 33 repeating units, the signal at 3.59 ppm was attributed to 132 protons to compare with the signal of CH_3 protons in HPA units. The average number of repeating units of HPA in PEG1450-HPA-1 was found to be 36 using the approach above. As a result, the copolymer was defined as $PEG_{33}HPA_{36}$ as given in Table 1. The other copolymers were also defined in the same way and given in Table 1.

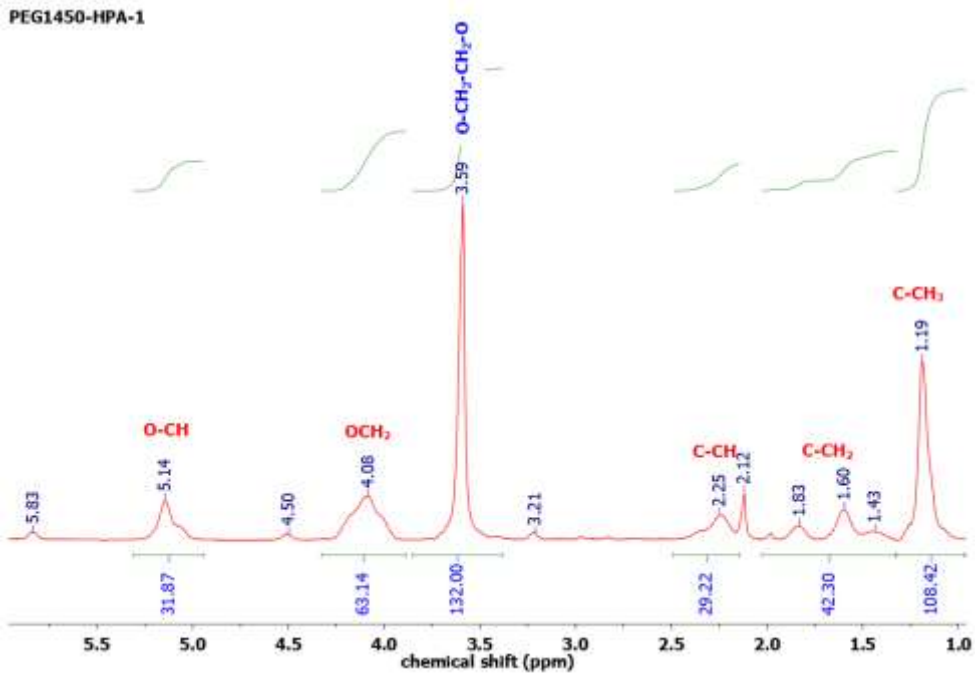

Figure 7. ^{1}H-NMR Spectra of PEG1450-HPA-1

Determination of Cloud-point Temperatures

The ABA-type PEG-HPA copolymers with different compositions were investigated in the aspect of their cloud-point temperatures. For this purpose, the 1.0 % (w/v) aqueous solutions of each copolymer were prepared, and heat-cool circle was applied to determine the cloud-point temperatures of the copolymers using the apparatus given in Figure 8.

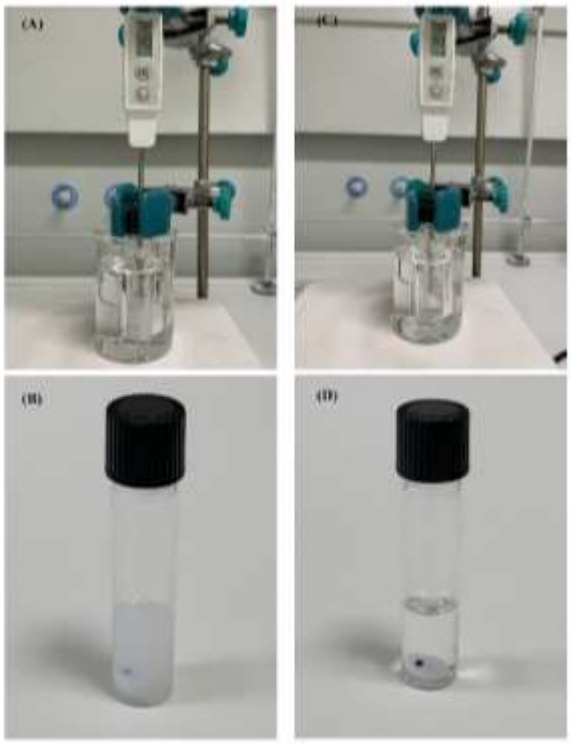

Figure 8. The Heat-Cool Circle Apparatus with Integrated Air-Jacket Tube and a Contact Thermometer (A and C). PEG1450-HPA-1 Sample above the Cloud-Point Temperature (B) and PEG1450-HPA-1 Sample below the Cloud-Point Temperature (D)

For the all copolymers, cloud-point temperature was measured values higher than that of HPA homopolymer, which was reported as 16 °C (Eggenhuisen et al., 2008). Moreover, the linear relationship between the PEG ratio and the cloud-point temperature is clearly seen for both polymer classes as shown in Figure 9. As well-known, thermo-responsive polymers in aqueous solution have strong intermolecular hydrogen-bond interactions at temperatures below the LCST. When the solutions are heated the intermolecular hydrogen bonds weaken and phase separation occurs. Since the phase transition temperature is related to the hydrogen bond capacity of this type of copolymer system, it seems that tuning the polymer composition causes the changes in the cloud-point temperature.

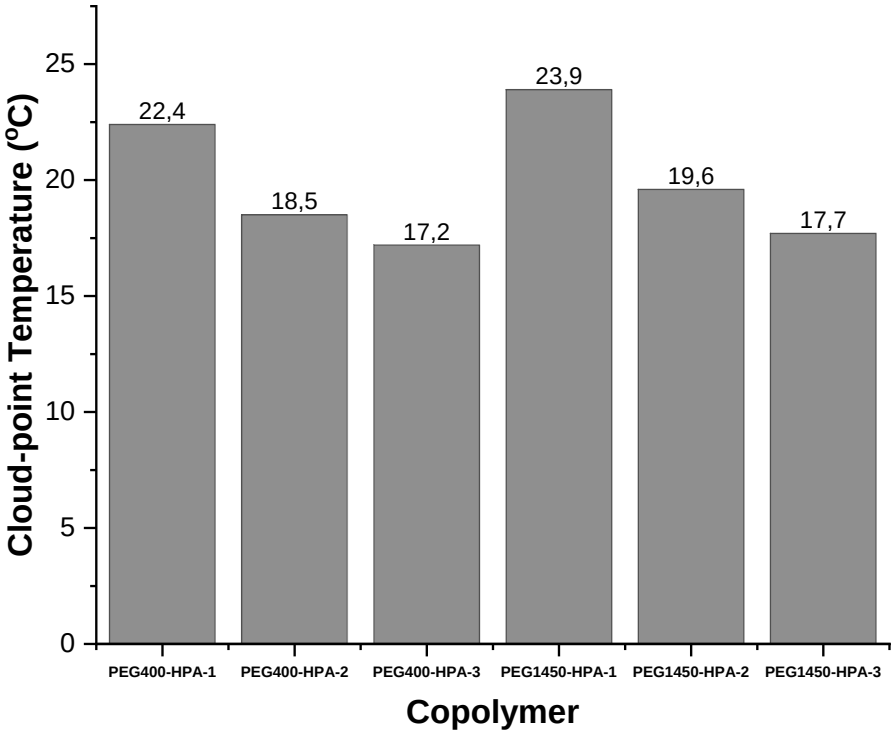

Figure 9. Cloud-Point Temperatures of the HPA-PEG Copolymers with Different Compositions.

Conclusion

PEG based difunctional macro-RAFT agents were successfully synthesized, characterized and used to prepare a series of ABA-type block copolymers of 2-hydroxypropyl acrylate. The copolymers and their compositions were determined through peak integration technique in ^{1}H-NMR analysis. Phase transition behavior of the copolymers in aqueous solution was conducted. The study shows that it is possible to tune the cloud-point temperature of the HPA based polymers by modifying the HPA chains with PEG moieties.

Author Contribution

Efkan Çatıker, conducted and directed the studies. *Abdullah Karanfil*, contributed to all the work as a researcher. Both authors participated in the laboratory work. Both authors made a direct contribution to the work and writing of the article. Both authors have read and approved the article.

Ethics Statement

There are no ethical issues with the publication of this article. Conflict of Interest The authors state that there is no conflict of interest.

Conflict of Interest

The authors state that there is no conflict of interest.

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