Poly(ethylene glycol)-*block*-poly(*N*-vinylformamide) Copolymers Synthesized by the RAFT Methodology

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Block copolymers where one block is poly(ethylene glycol) (PEG) are of interest in diverse applications ranging from commodity surfactants to biocompatible scaffolds for tissue engineering. PEG has many interesting physicochemical properties such as hydrophilicity[1] and solubility in both water and common organic solvents. Its biological properties include a lack of toxicity, antigenicity, and immunogenicity.[2−4] As such, investigation of new PEG-based block copolymers is continuing in both academia and industry.

Poly(*N*-vinylformamide) (PNVF) is a novel water-soluble polymer that,[5] because of previous monomer purification problems, has not received wide attention until recently. PNVF is not only a water-soluble polymer but also as an important precursor for preparing poly(vinylamine). To date, PNVF and its derivatives have been used in water treatment,[6] papermaking, and radiation cure coating.[7,8] Little published work exists regarding block copolymers containing NVF.

Traditionally, block copolymers are made by anionic,[9] cationic,[10] and group-transfer polymerization methods;[11] however, these polymerization methods can be successfully carried out only under controlled conditions (such as low temperature, inert atmosphere, or carefully purified monomers) and only for a limited number of monomers. NVF is not directly suitable for anionic and group transfer polymerization, while only oligomer is obtained via cationic polymerization.[12] Over the previous decade several types of living (controlled) free radical polymerization have been developed, enhancing our ability to easily generate block copolymers through sequential monomer addition. The most three common types of living radical polymerization systems are (1) stable free radical polymerization (SFRP) using nitroxides such as 2,2,6,6-tetramethyyl-1-piperdinyloxynitroxide,[13] (2) atom transfer radical polymerization (ATRP) using a transition metal complex, or (3) reversible addition−fragmentation chain transfer polymerization (RAFT) using dithioesters as chain transfer agents (RAFT agent).[14,15] The latter has proven to be a versatile method for controlled radical polymerization of a variety of monomers including vinyl acetate. The mechanism involves the chain transfer of active species such as the radicals from decomposition of the initiator and propagating polymer radicals to the RAFT agent, forming an unreactive adduct radical, followed by fast fragmentation to a polymeric RAFT agent and a new radical. The radical then continues polymerization. The equilibrium is established by subsequent chain transfer−fragmentation steps between the propagating radicals and polymeric RAFT agents and continues until all monomer is consumed, resulting in controlled growth of chains.

The RAFT method is a very convenient tool for preparation of block copolymers. The sequential polymerization of two monomers has given a number of copolymers such as poly(styrene-*b*-methyl methacrylate)[16] and poly(sodium 4-styrenesulfonate)-*b*-poly(sodium 4-vinylbenzoate).[17] In the present paper, we describe the synthesis and characterization of a new PEG macro-RAFT agent containing a xanthate end group and its application in the synthesis of PEG-*block*-PNVF copolymer. We focused on the use of the RAFT method after our attempts to employ ATRP methodology with NVF were unsuccessful.

Experimental Section

Materials. *N*-Vinylformamide was donated by BASF AG and distilled under reduced pressure before use. All other reagents used in this work were purchased from Aldrich. 4,4′-Azobis(4-cyanopentanoic acid) and 1,1′-azobis(cyclohexanecarbonitrile) (VAZO-88) were purified by recrystallization from methanol and ethanol, respectively. PEG monomethyl ether (MeOPEG) (M_n = 2000, M_w/M_n = 1.09 and M_n = 5000, M_w/M_n = 1.04) was dried in a vacuum at 40 °C for 24 h. All other reagents, including potassium ethyl xanthate, iodine, potassium iodide, and dicyclohexylcarbodiimide (DCC), were analytical grade and used as received. All solvents were purified using common methods.

4-Cyano-4-((thioethoxyl)sulfanyl)pentanoic acid was prepared according to the method described by Zard et al.[18] in 53% yield. IR (cm^{-1}): 3400−2500 (COO−H), 2235 (−CN), 1713 (C═O), 1040 (C═S). ^{1}H NMR ($CDCl_3$): δ 1.45 (t, CH_3CH$_2$O−, 3H), 2.18 (s, −C(CH_3)(CN)−, 3H), 2.36 (2 t, −CH_2CH$_2$COOH, 2H), 2.6 (t, −CH$_2$CH_2COOH, 2H), 4.75 (q, CH$_3$CH_2O−, 2H).

Synthesis of *O*,*O*-Diethyl Bisxanthate (2). *O*,*O*-Diethyl bisxanthate (**2**) was prepared by a method derived from that of Houben.[19] Potassium ethyl xanthate (**1**) (10.86 g, 0.067 mol) was dissolved in deionized water (50 mL), and the solution was transferred to a 500 mL Erlenmeyer flask equipped with a magnetic stir bar. Aqueous 10% iodine/potassium iodide solution (50 mL) was added dropwise to the xanthate solution via a dropping funnel over 30 min with strong stirring. The reaction mixture was allowed to stand overnight. Water (80 mL) was then added to the mixture, and the product was extracted with ether (3 × 60 mL). The combined ether extracts were washed with water (2 × 100 mL) and then with brine (100 mL). The resulting solution was dried over anhydrous $MgSO_4$ overnight. The product was recovered by evaporating the ether, and it crystallized to a solid mass on cooling. The yield was 84% (6.90 g, 0.028 mol). ^{1}H NMR ($CDCl_3$): δ 1.45 (t, CH_3CH$_2$O−, 6H); 4.75 (q, CH$_3$CH_2O−, 4H).

Synthesis of ω-Methoxy-α-[4-cyano-4-((thioethoxyl)-sulfanyl)pentanoyl]PEGs (5a,b). MeOPEG (M_n = 2000, 13.7 g, 6.84 mmol) was dissolved in 250 mL of ethyl acetate. 4-Cyano-4-((thioethoxyl)sulfanyl)pentanoic acid (4.23 g, 17 mmol) and DCC (3.52 g, 17 mmol) were added. After stirring at room temperature for 24 h, the precipitated dicyclohexylurea was removed by filtering. The remaining solution was placed in the refrigerator at 0 °C for 24 h, and the product was obtained by collecting the crystals and drying at 40 °C under vacuum. The yield was 94% (14.3 g). The product (**5a**) has M_n = 2100 and M_n/M_w = 1.09. Characterization: ^{1}H NMR ($CDCl_3$): δ 3.6 (−OCH_2CH_2O−); 3.9 (OCH_2CH$_2$OC(═O); 4.3 (−OCH$_2$CH_2OC(═O)−); 4.7 (−SC(═O)OCH_2CH$_3$). GPC: M_n = 2100, M_n/M_w = 1.09. The other ω-methoxy-α-[4-cyano-4-

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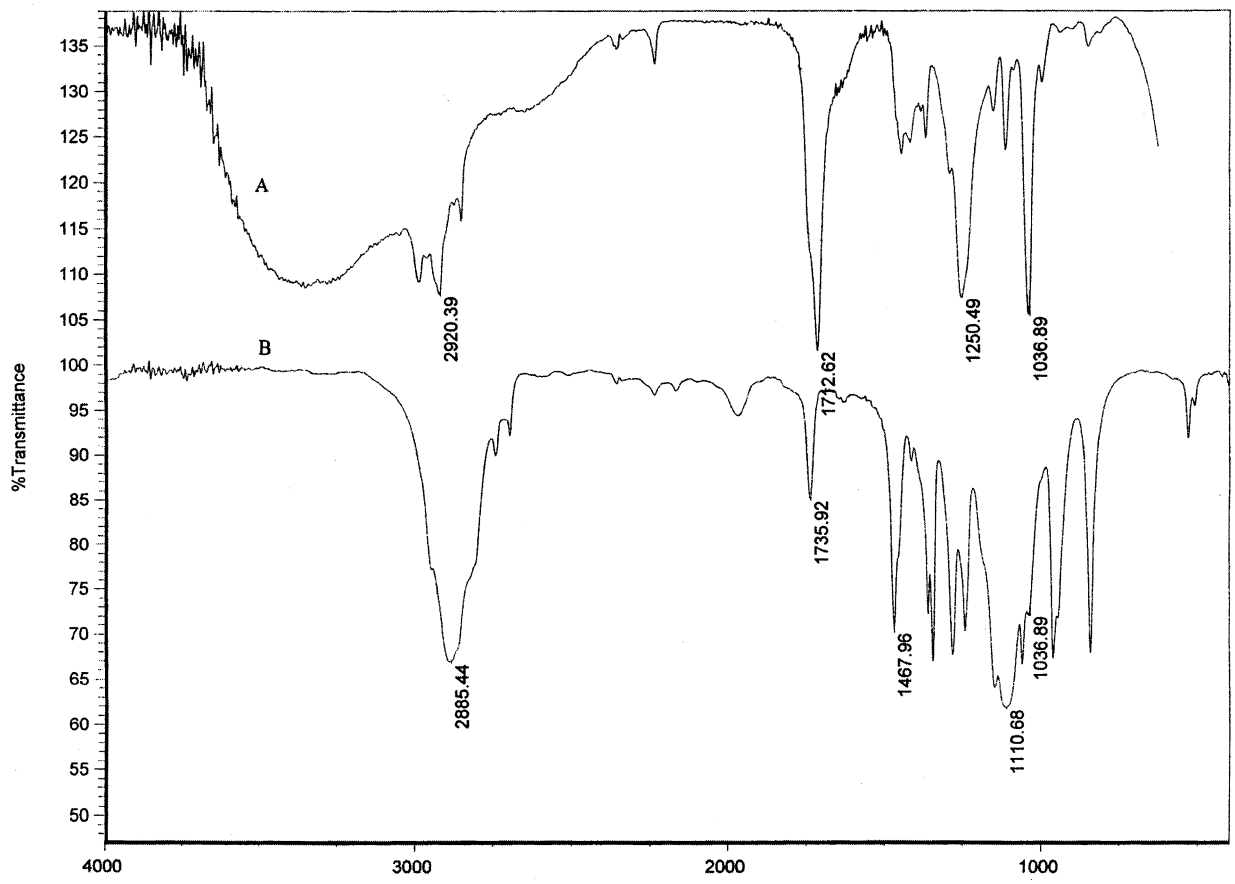
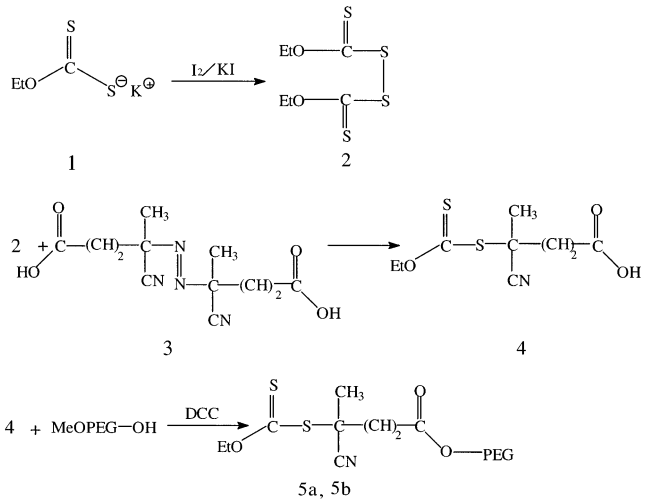


Figure 1. IR spectra of 4-cyano-4-((thioethoxyl)sulfanyl)pentanoic acid (A, upper) and PEG (M_n = 2000) after capping with it (B, lower).

Scheme 1. Synthesis of PEG Macro-RAFT Agent



((thioethoxyl)sulfanyl)pentanoyl]PEG (M_n = 5000) was prepared using a similar procedure (yield: 90%). The product (**5b**) has M_n = 5200 and M_n/M_w = 1.04.

Synthesis of PEG−PNVF Block Copolymers. A stock solution in DMSO containing (α-[4-cyano-4-((thioethoxyl)-sulfanyl)pentanoyl]PEG (6.2×10^{-2} M), *N*-vinylformamide (7.3 M), DMSO, and initiator VAZO-88 (7.0×10^{-3} M) was prepared. In a typical experiment, a 2 mL aliquot of the stock solution (0.124 mmol or 0.26 g of compound **5a**, 14.6 mmol or 1.04 g of NVF, and 0.014 mmol or 0.004 g of VAZO-88) was added to an ampule. Before sealing, the contents were carefully degassed by three freeze−pump−thaw cycles under oil pump vacuum. The polymerization was carried out in an oil bath at 100 °C for 30 min. To control the reaction accurately, the system was quickly frozen with liquid nitrogen after the given polymerization time. The product was diluted with water containing 10% ethanol (v/v) and precipitated from acetone. The copolymer was precipitated from DMSO into ether and then purified with diethyl ether in Soxhlet extraction for 8 h and then in ethyl acetate for 4 h to remove possible unreacted PEG. However, we only find a negligible amount of PEG during purification. The product was dried under vacuum at 40 °C for 24 h. The resulting copolymer was 0.38 g (NVF conversion: 12%). Characterization: ^{1}H NMR (D_2O): δ1.7 (broad, $-CH_2-CH$ (NH−)−); 3.3 (broad, $-CH_2-CH$(NH−)−); 3.6 (broad, $-CH_2CH_2O-$); 3.9 (broad, −N*H*CH(C═O); 8.0 (broad, −NHC*H*(C═O)).

Measurements. IR spectra were recorded on a Nicolet 360 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker MSL-300, using deuterium oxide or $CDCl_3$ as solvent and tetrmethylsilane as internal standard. UV spectra were taken on Perkin-Elmer Lambda 2 UV spectrometer. Vapor pressure osmometry (VPO) measurements for M_n determination were made with a vapor pressure osmometer, OSMOMAT 070-SA (Gonotec. Co) (cell temperature = 40 °C, solvent = double distilled water). An aqueous gel permeation chromatograph (GPC) for the characterization of M_n of block copolymer consisted of HPLC components from Waters Corp. (model 515 pump, detector: Viscotek triple detector array (TDA): model 300). The column was a Waters Ultrahydrogel (PEO) (pore size: 250 Å, exclusion limits: 8×10^4, length: 7.8 mm × 300 mm). An aqueous mobile phase was used consisting of 0.1 M $NaNO_3$ and 0.01% NaN_3 at a flow rate of 1.0 mL/min at 35 °C. Conversion was determined gravimetrically.

Results and Discussion

Synthesis of ω-Methoxy-α-[4-cyano-4-((thioethoxyl)sulfanyl)pentanoyl]PEGs (PEG Macro-RAFT Agents). The key to successful RAFT polymer-

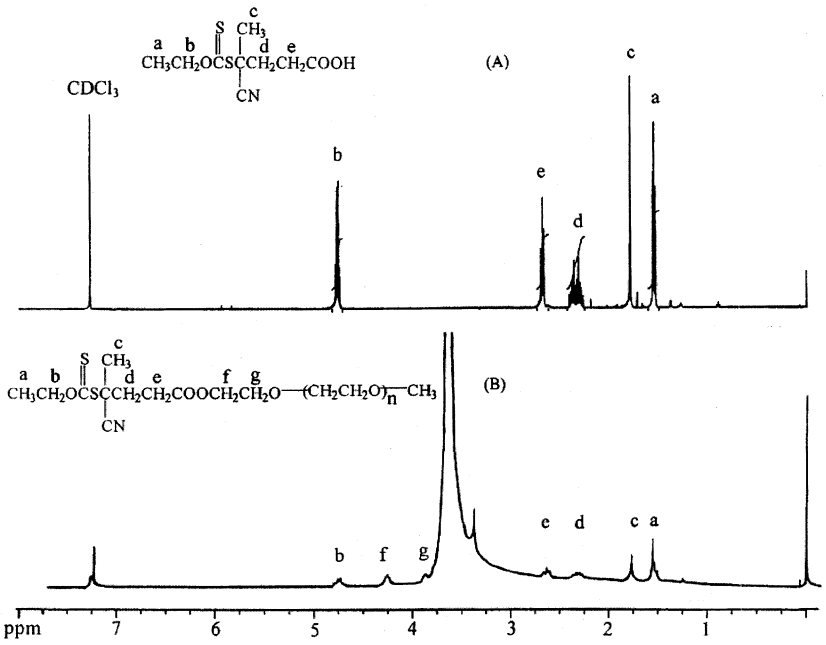


Figure 2. ^{1}H NMR spectrum recorded in $CDCl_3$ for 4-cyano-4-((thioethoxyl)sulfanyl)pentanoic acid (A, upper) and PEG (M_n = 2000) after capping with it (B, lower).

ization is the choice of an effective thiocarbonylthio reagent for each monomer. For example, the polymerization of vinyl acetate is completely inhibited in the presence of dithioesters, trithiocarbonates, and aromatic dithiocarbamates,[20] the preferred RAFT agents for methacrylates, acrylamides, and styrene. But xanthates and aliphatic dithiocarbamates, which show little or no activity with these monomers, function effectively in the RAFT polymerization of vinyl acetate.[20] Chong et al. synthesized a poly(styrene)−PEG block copolymer successfully by using *ω*-methoxy-α-[4-cyano-4-((thiobenzoyl)sulfanyl)pentanoyl]PEG.[21] Because *N*-vinylformamide exhibits reactivity characteristics and molecular structure similar to vinyl acetate,[22] we chose the xanthate type as the RAFT agent for this study.

The *O*-ethylxanthate group was attached to the end of MeOPEG (PEG with one terminal methoxy and one terminal hydroxy group) by the capping reaction of 4-cyano-4-((thioethoxyl)sulfanyl)pentanoic acid and MeOPEG in ethyl acetate in the presence of DCC (Scheme 1). *ω*-Methoxy-α-[4-cyano-4-((thioethoxyl)sulfanyl)pentanoyl]PEGs were characterized by IR and ^{1}H NMR spectra. Figure 1 shows the IR spectra of 4-cyano-4-((thioethoxyl)sulfanyl)pentanoic acid (A) and the product following esterification with MeOPEG (M_n = 2000 (B)). The spectra confirm the formation of the ester carbonyl group with the appearance of a new band at 1730 cm^{-1} and disappearance of the original carbonyl group at 1713 cm^{-1}. The large band at 1040 cm^{-1} represents the characteristic peak of C=S. In the ^{1}H NMR spectrum (Figure 2B), typical signals of both PEG and new end group were detected. New resonances at 3.9 ppm (OCH_2CH$_2$OC(=O)) and 4.3 ppm (−OCH$_2$CH_2-OC(=O)) also confirm the formation of the ester group. The peaks at 4.7, 2.6, 2.4, 1.7, and 1.5 ppm represent protons of the 4-cyano-4-((thioethoxyl)sulfanyl)pentanoic acid fragment.

The capping efficiency of the xanthate group on PEG could be obtained from the UV and/or NMR spectra. For a quantitative determination of the capping efficiency of the xanthate group on PEG, a calibration curve based on 4-cyano-4-((thioethoxyl)sulfanyl)pentanoic acid (λ = 294 nm) was used.[23] We also calculated the capping efficiency of the xanthate group on PEG with molecular weight (M_n = 2000) by comparing the peak area of the methyl protons of 4-cyano-4-((thioethoxyl)sulfanyl)pentanoic acid fragment at 1.8 ppm and the methylene protons of the PEG chain at the 3.6 ppm. Table 1 summarizes the characterization results of *ω*-methoxy-α-[4-cyano-4-((thioethoxyl)sulfanyl)pentanoyl]PEGs. This approach to forming the macro-RAFT agent is relatively efficient. Further, it is likely that this strategy could be used to form a variety of macro-RAFT agents, as it could easily be generalized to any number of precursor polymers with terminal OH groups.

Table 1. Preparation and Characterization of *ω*-Methoxy-α-[4-cyano-4-((thioethoxyl)sulfanyl)pentanoyl]PEGs

MeOPEG macro-RAFT agents	$M_n \times 10^{-3}$ [a]	M_n/M_w	yield (%)	capping efficiency	
				UV	NMR
5a	2	1.09	94	1.00	0.92
5b	5	1.04	90	0.98	

[a] M_n's of starting MeOPEG's.

Preparation and Characterization of PEG−PNVF Block Copolymers. The experimental results of the polymerization of *N*-vinylformamide in the presence of PEG macro-RAFT agents with different molecular weights are given in Table 2. Table 2 illustrates that the molecular weight of PNVF block copolymer and the conversion of the NVF monomer increased linearly with the polymerization time. This indicates that polymerization of NVF occurs from one end of PEG via a controlled radical polymerization as described by Rizzardo et al.,[15] resulting in the formation of PEG−PNVF block copolymers (Scheme 2). The broad polydispersities of NVF block copolymers might be attributed to the greater chain transfer of *N*-vinylformamide propagating radical to monomer and polymer.[24,25] The chain transfer constant of *N*-vinylformamide is $C_M = 9.53 \times 10^{-4}$ at 60 °C,[24] which is higher than that of common monomers such as vinyl acetate ($C_M = (1.75-2.85) \times 10^{-4}$), styrene

Table 2. Molecular Weight and Conversion Data for PEG−PNVF Copolymers[a] Prepared in the Presence of PEG Macro-RAFT Agent in DMSO at 100 °C

no. of block copolymer[b]	time (h)	M_n[c] × 10^{-3}	M_n[d] × 10^{-3}	M_n[e] × 10^{-3}	M_w/M_n	conv of NVF (%)
1	0.5	5.2 (3.2)[f]	5.8 (3.8)[f]	6.1 (4.1)[f]	1.7	13
2	1	9.2 (7.2)[f]				32
3	2	11.5 (9.5)[f]	10.4 (8.4)[f]			45
4	1	8.7 (3.7)[f]	9.2 (4.2)[f]	9.8 (4.8)[f]	2.3	10

[a] Polymerization conditions: [NVF] = 7.3 M, [PEG macro-RAFT agent] = 6.2 × 10^{-2} M, [VAZO-88] = 7.0 × 10^{-3} M for making samples 1−3 and 3.0 × 10^{-3} M for sample 4. [b] Samples 1−3 and 4 were prepared using PEG macro-RAFT agent with a molecular weight of 2000 (**5a**) and 5000 (**5b**), respectively. [c] Molecular weight was calculated from ^{1}H NMR data of block copolymer. [d] Molecular weight was determined via VPO. [e] Molecular weight was determined via GPC. [f] Parentheses show molecular weight (×10^{-3}) of PNVF block, which was calculated from the difference in M_n before and after the polymerization.

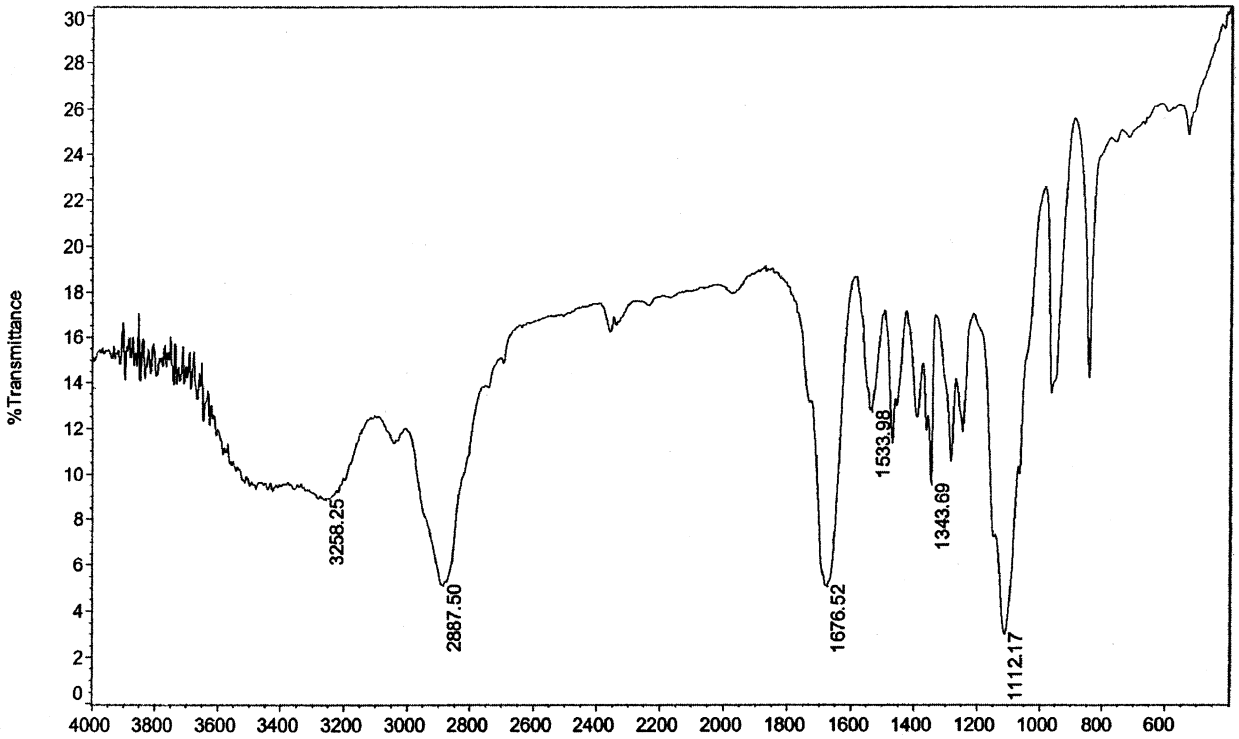


Figure 3. IR spectrum of PEG−PNVF block copolymer (M_n = 6.1 × 10^3, M_w/M_n = 1.7).

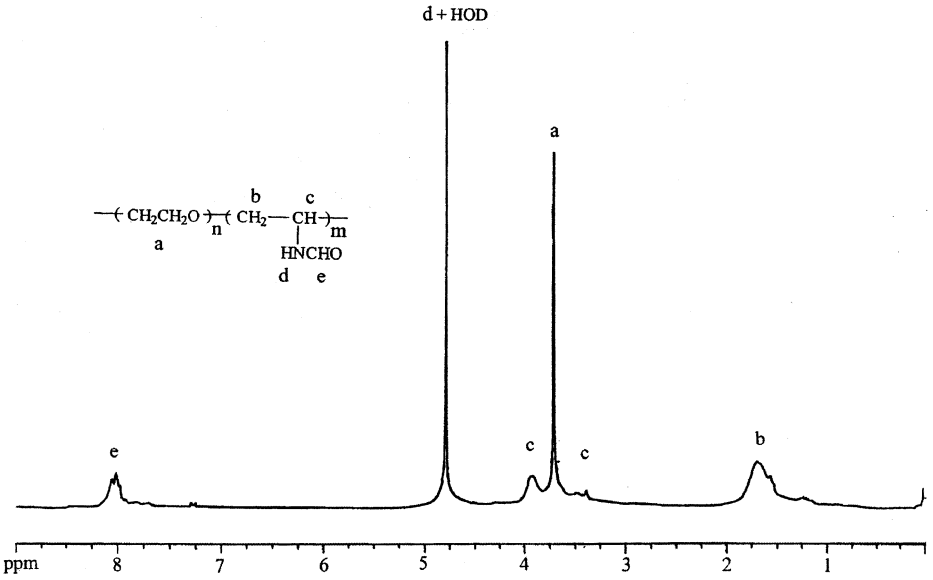


Figure 4. ^{1}H NMR spectrum recorded in D_2O for PEG−PNVF block copolymer (M_n = 6.1 × 10^3, M_w/M_n = 1.7).

(C_M = (0.3−0.6) × 10^{-4}), and methyl methacrylate (C_M = (0.07−0.25) × 10^{-4}).[26]

In addition, samples 1 and 4 have almost identical PNVF lengths under the same ratios of [NVF] to [macro-RAFT agent] at similar monomer conversions, whether the molecular weight of the PEG is high or low. Also, the yield and M_n of the poly-NVF parallel the reaction time, indexing for initiator concentration. This is additional evidence that the polymerization follows the controlled mode.

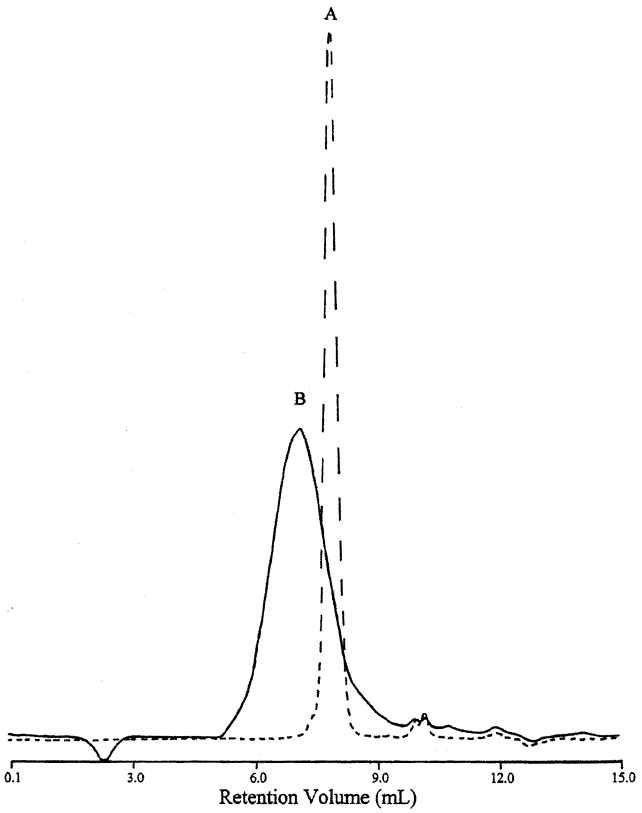
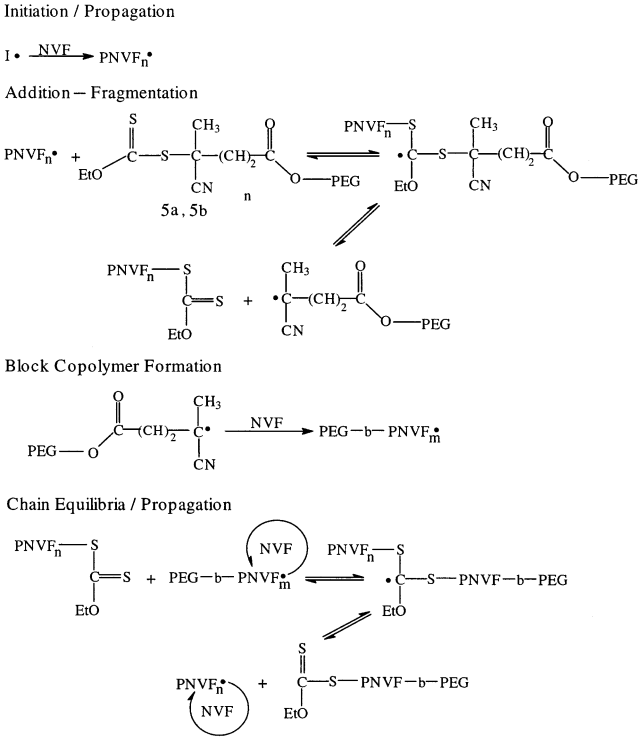


Figure 5. GPC chromatograms for MeOPEG macro-RAFT agent ($M_n = 2.1 \times 10^3$, $M_w/M_n = 1.09$) (A) and PEG−PNVF copolymer ($M_n = 6.1 \times 10^3$, $M_w/M_n = 1.7$) (B) after purification.

Scheme 2. Formation of PEG-*b*-NVF Copolymer



The copolymers were characterized by IR and ^{1}H NMR spectra. Figure 3 shows the IR spectrum of the block copolymer PEG-*b*-PNVF. The spectrum confirms the existence of two segments of the block copolymer with the key bands at ~3258 (N−H), 1676 (C═O), and 1112 (CH_2−O−CH_2) wavenumbers. A typical ^{1}H NMR spectrum of purified PEG−NVF block copolymer is shown in Figure 4. Peaks at 8.0 ppm (e), 3.9 and 3.3 ppm (c), and 1.7 ppm (b) also confirmed the formation of PNVF block. The peak at 3.6 ppm (a) is the characteristic peak of the protons of the PEG chain.

Figure 5 shows GPC chromatograms for the block copolymer made from MeOPEG (M_n = 2000) macro-RAFT agent (curve B), in which only one peak appeared after purification, as compared to the GPC trace for the PEG precursor (curve A). This further indicates that PEG−PNVF block copolymer, rather than homopolymer of NVF, was produced during the polymerization.

In summary, we have shown that the radical polymerization of *N*-vinylformamide can proceed in a controlled manner if an appropriate RAFT agent is employed. Use of a poly(ethylene glycol) macro-RAFT agent allowed for the generation of block copolymers of PEG and PNVF.

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