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Controlled Radical Polymerization of *N*-Vinylpyrrolidone by Reversible Addition-Fragmentation Chain Transfer Process

Renjith Devasia,[1] *Raveendra L. Bindu,*[1] *Redouane Borsali,*[1] *Nathalie Mougin,*[2] *Yves Gnanou**[1]

Summary: Poly(*N*-vinylpyrrolidone) (PNVP) was polymerized by RAFT process using diphenyldithiocarbamate of diethylmalonate (DPCM) as the reversible chain transfer agent in the presence of a small percentage of a conventional radical initiator (AIBN). The molar mass of the polymers synthesized by this method was found to increase with conversion and time. The presence of end group in the polymer chain could be confirmed by ^{1}H NMR spectra. The molar masses calculated using ^{1}H NMR spectroscopy and static light scattering (SLS) showed good agreement with the theoretical molar masses. The RAFT compound was fully consumed during the initial stages of the polymerization itself. The controlled nature of these polymers was further confirmed by generating diblock copolymers by sequential addition of monomers such as styrene or *n*-butyl acrylate (*n*-BA). PNVP efficiently participated as a macro-RAFT reagent, and cross-over reaction between the two blocks efficiently occurred. The successful diblock copolymer synthesis using PNVP as macro-transfer reagent further confirms the ‘‘controlled’’ nature of such synthetic procedure.

Keywords: amphiphilic diblock copolymers; controlled radical polymerization; dithiocarbamate; RAFT; *N*-vinylpyrrolidone

Introduction

Poly(*N*-vinylpyrrolidone) (PNVP) is an industrially important polymer that is utilized in a variety of applications, specially in biomedical sectors and in the cosmetic industry.[1–4] Its solubility in aqueous and non-aqueous solvents and its excellent biotolerance make this polymer one of the most used chemicals in bio-related applications. PNVP is generally obtained by free radical polymerization of *N*-vinylpyrrolidone (NVP).[5–7] To the best of our knowledge no study of its radical polymerization by one of the methodologies known to bring about ‘‘living’’/‘‘controlled’’ propagation has been reported so far.[8–15] In our studies we found that neither nitroxide-mediated polymerization (NMP) nor atom transfer radical polymerization (ATRP) was indeed found suitable for NVP and vinyl amides in general, whose controlled/living polymerization has been quite a challenge. Direct ATRP of NVP was unsuccessful due to its peculiar structure, the polar lactam group present in the monomer disrupting the catalyst-ligand system used whatever its nature. The polar lactam group present in the monomer is indeed responsible for the complexation to the metal catalyst used in ATRP.

The recently developed reversible addition-fragmentation chain transfer (RAFT) process is a breakthrough in the field of controlled radical polymerization

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[1] Laboratoire de Chimie des Polymères Organiques (LCPO)-CNRS-ENSCPB, Université Bordeaux 1, 16 Avenue Pey Berland, 33607 Pessac Cedex, France
E-mail: gnanou@enscpb.fr

[2] L’Oréal, 1 Av E Schueller, Aulnay/sous/Bois, 93601 Paris, France

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because it can be successfully applied to functional vinylic monomers.[10,13] Dithiocarbonates and dithioesters were indeed shown to control the chain growth of a wide range of monomers.[10] However, the polymerization of vinyl esters is inhibited in presence of dithioesters and that of methacrylates could hardly be controlled using dithiocarbonates, which limits the scope of that particular class of RAFT reagents.[10] As an attempt to overcome these limitations CSIRO[10] and Rhodia[13] simultaneously proposed the use of dithiocarbamates as RAFT reagents. In the presence of the latter a variety of monomers could be polymerized under controlled conditions, including vinyl acetate.[10,16] This prompted us to investigate the potential of dithiocarbamates as RAFT reagents for the controlled radical polymerization of NVP. The advantages of RAFT over ATRP and other methodologies are known: (a) no metal catalysts are needed and (b) conventional radical initiators can be used to initiate the reaction. This paper gives an account of the results obtained with the polymerization of NVP using diphenyldithiocarbamate of diethylmalonate (DPCM) as reversible chain transfer (CT) reagent and describes the synthesis of the corresponding amphiphilic diblock copolymers by sequential addition of monomers.

Materials and Methods

Chemicals Used

N-Vinylpyrrolidone (Aldrich) was vacuum-distilled before use. Styrene (Acros, 99% purity), and *n*-butyl acrylate (*n*-BA) (Aldrich) were dried over CaH_2 and distilled under vacuum. α,α'-Azobisisobutyronitrile (AIBN) (Aldrich, 99% purity) was recrystallized from methanol and dried under vacuum. Solvent 1,4-dioxane was dried by distilling over CaH_2 prior to use.

Instrumentation

Size exclusion chromatography (SEC) was used to determine the apparent molar mass distribution of the samples with respect to poly(ethylene oxide) standards for water-methanol SEC (Varian® 9012) and polystyrene standards for THF SEC (Varian® 9040). Gas chromatography (Varian® 3350) was used to determine the polymer conversions performed in 1,4-dioxane solution. ^{1}H NMR spectra of the polymers were recorded using Bruker® AC-400 spectrometer. The light scattering measurements were performed on an ALV® DLS/SLS-5000 spectrometer/goniometer equipped with an ALV®-5000 digital time correlator and a helium-neon laser. We used static light scattering (SLS) to measure the mass average molar mass using a standard Zimm plot analysis from the Rayleigh ratio $R_{vv}(q)$ determined from the time-averaged scattered intensity.[17]

Synthesis of Diphenyldithiocarbamate of Diethylmalonate (DPCM)

DPCM was synthesized by a slightly modified procedure described elsewhere.[18] The purity of the product was checked by ^{1}H NMR spectroscopy (Figure 1).

^{1}H-NMR (CD_2Cl_2)
$\delta = 1.32$ ppm [–COO–CH_2–CH_3, two methyl groups]
$\delta = 4.12$ ppm [–COO–CH_2–CH_3, two methylene groups]
$\delta = 4.2$ ppm [–S–CH–(COO–CH_2–CH_3)$_2$, one methine group]
$\delta = 7.36$–7.44 ppm [(Ar–*H*), two phenyl rings]

Polymerizations

In a typical experiment NVP (1 ml, 9.357×10^{-3} mol), DPCM (M/50, 0.07355 g), AIBN (10% of CT), and 1,4-dioxane (1 ml) were taken in a Schlenk tube. The reaction mixture was degassed by four freeze-vacuum-thaw cycles, sealed under vacuum, and heated in an oil bath thermostated at 80 °C for the required time. The polymer obtained was dissolved in dichloromethane, purified by repeated precipitations in diethyl ether, and was dried under vacuum.

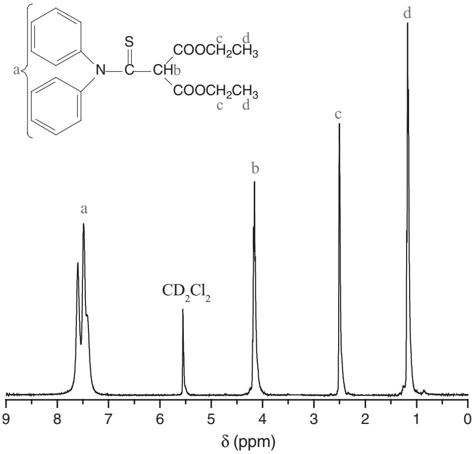


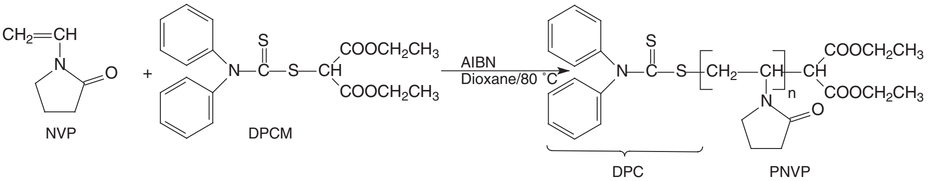
Figure 1.
400 MHz ^{1}H-NMR spectrum (CD_2Cl_2) of the RAFT agent DPCM.

Block copolymers were synthesized as described below. PNVP-*b*-PS block copolymers, for example, were synthesized by polymerizing 0.25 g of styrene in 1.5 ml of 1,4-dioxane in the presence of 0.5 g of PNVP-6 (Table 2, entry 2) as the macro-CT agent and AIBN (0.1 mol-% with respect to styrene) as initiator. The reaction mixture was subjected to four freeze-pump-thaw cycles and heated in an oil bath under stirring at 60 °C for 20 h. The reaction mixture was precipitated in ether and then precipitated in water. The slightly turbid water solution was centrifuged at a lower temperature (5 °C) to obtain the insoluble polymer. The polymer obtained by centrifugation from water was completely soluble in methanol confirming the absence of any homopolymer in the purified block copolymer. The purity of the block copolymer was further confirmed by SEC analysis using THF as eluent.

Results and Discussion

N-Vinylpyrrolidone has been polymerized by RAFT process in 1,4-dioxane using DPCM as CT agent in the presence of a small percentage of conventional radical initiator AIBN. Upon addition of a growing radical to DPCM, fragmentation should occur and diethylmalonate radicals be released. Chains grown under these conditions should normally contain a diphenyldithiocarbamate (DPC) moiety at one end and a diethylmalonate fragment (M) at the other end (Scheme 1).

The polymerization of NVP was carried out at 80 °C under conditions mentioned in Table 1. In the first series of experiments the [NVP]/[DPCM] ratio was maintained constant and taken equal to 100 whereas the initiator concentration was varied. It could be observed that the yield of polymer decreased with a decrease in the



Scheme 1.
Polymerization of NVP in 1,4-dioxane by RAFT process using DPCM as the CT agent and AIBN as initiator.

Table 1.
Experimental conditions for the homopolymerization of NVP in 1,4-dioxane solution in the presence of DPCM at 80 °C, and effect of AIBN concentration on the conversion and polydispersity ([M]/[CT] = 100).

Sample[a]	[AIBN]/[DPCM] (molar ratio)	Time	Conversion	$\overline{M}_n$		PDI (SEC)[d]
		h	%	Expected[b]	^{1}H NMR[c]	
				g/mol	g/mol	
PNVP-1	0.5000	44	93	10 700	14 500	1.5
PNVP-2	0.2500	27	89.4	10 300	14 000	2.3
PNVP-3	0.1250	37	64.3	7 500	9 800	1.3
PNVP-4	0.0625	55	Negligible	–	–	–

[a] Abbreviations: PNVP—poly(*N*-vinylpyrrolidone), AIBN—α,α'-azobis(isobutyronitrile), DPCM—diphenyldithiocarbamate of diethylmalonate.

[b] The theoretical molecular weight was calculated from the expression $([M]_i/[CTA]_i) \cdot f \cdot M_o + M_{CTA}$ where $[M]_i$ and $[CTA]_i$ are the initial concentrations of the monomer NVP and the CT agent DPCM respectively, f is the fractional conversion, and M_o and M_{CTA} are the molecular weights of the monomer NVP and the RAFT agent used.

[c] Determined by end group analysis using ^{1}H NMR spectroscopy.

[d] Determined by SEC using H_2O/CH_3OH (80/20) containing 0.1 M $NaNO_3$ as eluent on the basis of poly(ethylene oxide) calibration curve.

concentration of AIBN (Table 1). This is due to a lesser concentration of radicals generated at a lower concentration of the initiator, which resulted in a slower rate of polymerization. The number of chains that originated directly from the azo initiator and did not contain the two moieties of DPCM at chain end was then reduced. Another effect of a low concentration in initiator was seen on the polydispersity of the samples (Table 1) which was found equal to 1.3 for the optimal [AIBN]/[DPCM] ratio of 0.125.

Narrow molar mass distributions could be obtained with a careful choice of reaction conditions. In the next series of experiments the [NVP]/[DPCM] molar ratio was taken equal to 100 and the [AIBN]/[DPCM] molar ratio was set to 0.125. The evolution of molar masses as a function of reaction time was monitored by sampling out aliquots that were characterized by SEC and ^{1}H NMR. The conversion of the monomer was determined from gas chromatography and the polymer was purified by precipitation from ether. Figure 2 shows the pseudo-first-order kinetic plot with respect to the monomer concentration observed within 20–80% conversion. The corresponding time-conversion plot is linear which is characteristic of living radical systems (Figure 2).

The polymerization also witnessed a linear increase in molar mass with conversion. The number average molar mass $\overline{M}_n$ of the polymer formed was determined by end group analysis using ^{1}H NMR spectroscopy. Apart from the signal due to the proton resonance of the PNVP chain "–N–C*H*–" at δ 3.6–4.1 ppm, "–COO–CH_2–" at δ 3–3.4 ppm, and four "–CH_2–" groups between δ 1.4 and 2.4 ppm the ^{1}H NMR spectra also showed a signal at δ 6.75–7.4 ppm attributable to phenyl "C_6H_5–" end groups of DPCM (Figure 3).

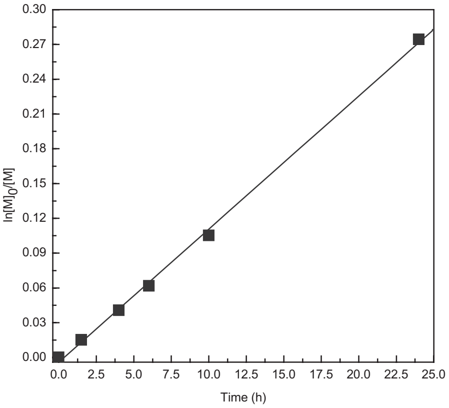


Figure 2.
Pseudo-first-order kinetic plot of ln$[M]_o/[M]$ with time for PNVP homopolymerization in 1,4-dioxane at 80 °C using DPCM as the CT agent.

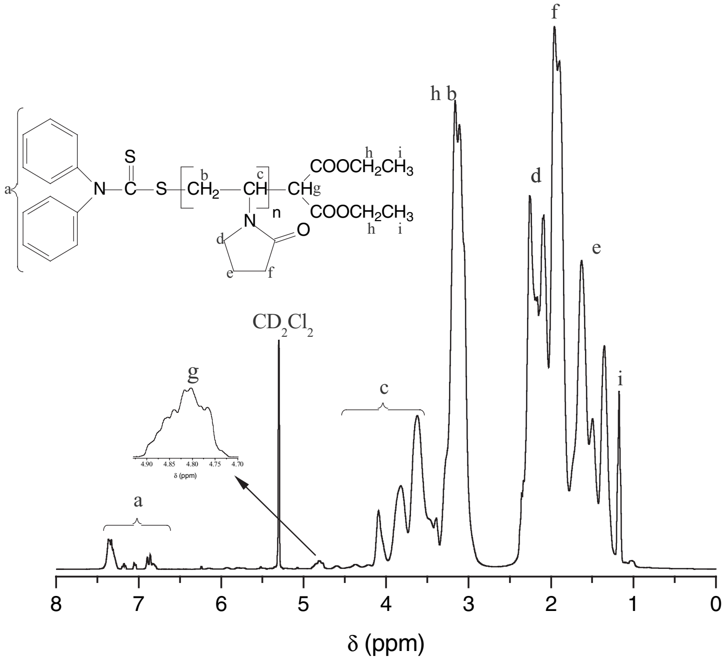


Figure 3.
^{1}H-NMR spectrum of PNVP in CD_2Cl_2 synthesized in 1,4-dioxane using DPCM as the CT agent and AIBN as initiator.

Upon integration of the peak corresponding to the end group and comparison with that of the repeating units, the $\overline{M}_n$ of the polymer samples could be calculated. These $\overline{M}_n$ values were found to increase with conversion and to correspond almost ideally with the expected values except at higher monomer conversions (Figure 4). The evolution of molar mass is clearly observed in the SEC profile as the peak shifts to shorter elution time as seen in Figure 5. However, the polydispersity

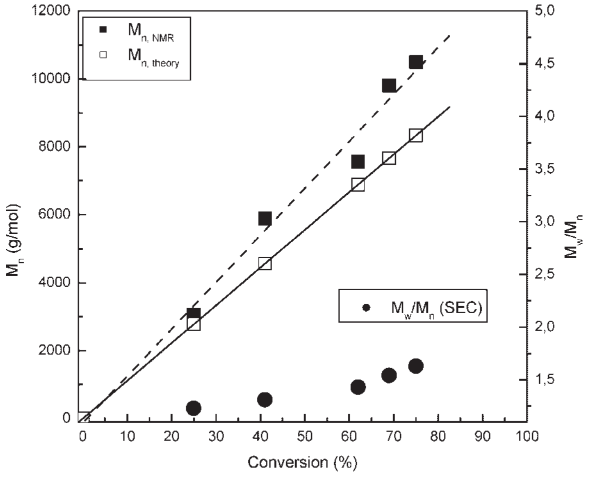


Figure 4.
Variation of $\overline{M}_n$ with conversion for PNVP homopolymerization in 1,4-dioxane at 80 °C using DPCM as the CT agent.

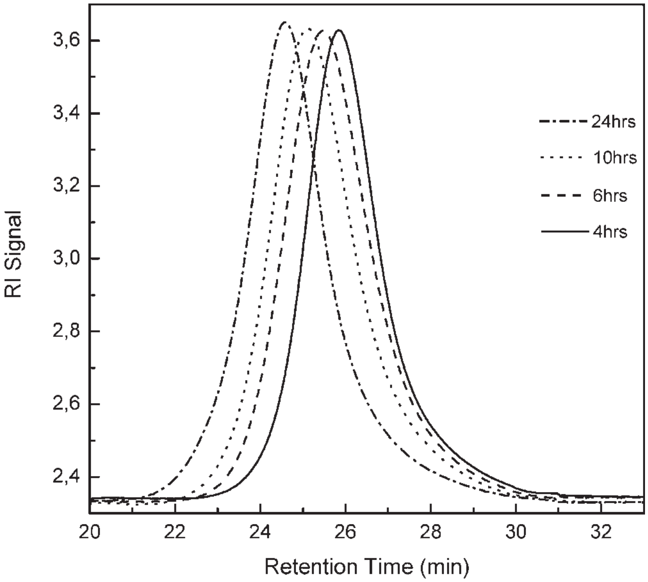


Figure 5.
SECs of PNVP homopolymers — variation of $\overline{M}_n$ with time determined by SEC using H_2O/CH_3OH (80/20) containing 0.1 M $NaNO_3$ as eluent on the basis of poly(ethylene oxide) calibration curve.

increased with conversion and almost leveled off at ≅1.5–1.6 after about 50% conversion (Figure 4). This type of increase in polydispersity with conversion was also observed in the RAFT polymerization of NIPAM using the cumyl dithiobenzoate/AIBN initiation system in 1,4-dioxane.[19]

The slight deviation observed from the theoretical values of $\overline{M}_n$ as conversion increases may well be due to bimolecular terminations which could not be fully avoided at higher conversions. This explains the broadening of the molar mass distribution with conversion and the depletion of the living character with time.

Experiments corresponding to a constant [AIBN]/[DPCM] molar ratio as equal to 0.125 but different [NVP]/[DPCM]

Table 2.
Experimental conditions for the homopolymerization of NVP in 1,4-dioxane solution in the presence of DPCM at 80 °C, and effect of [NVP]/[DPCM] molar ratio on the conversion and polydispersity ([AIBN]/[DPCM] = 0.125).

Sample	[NVP]/[DPCM] (molar ratio)	Time	Conversion	$\overline{M}_n$			PDI (SEC)[c]
		h	%	Expected[a]	^1H NMR[b]	SLS	
				$g \cdot mol^{-1}$	$g \cdot mol^{-1}$	$g \cdot mol^{-1}$	
PNVP-5	50	24	61.4	3 800	4 200	4 900	1.3
PNVP-6	125	33	83.3	11 900	11 500	10 800	1.5
PNVP-7	200	37	85.3	19 300	20 300	23 200	1.2
PNVP-8	400	49	75.2	33 800	45 800	43 800	1.4
PNVP-9	500	24	82.5	46 200	—	—	1.5

[a] The theoretical molecular weight was calculated from the expression $([M]_i/[CTA]_i) \cdot f \cdot M_o + M_{CTA}$ where $[M]_i$ and $[CTA]_i$ are the initial concentrations of the monomer NVP and the CT agent DPCM, respectively, f is the fractional conversion, and M_o and M_{CTA} are the molecular weights of the monomer NVP and the RAFT agent used.

[b] Determined from ^1H NMR spectroscopy.

[c] Determined by SEC using H_2O/CH_3OH (80/20) containing 0.1 M $NaNO_3$ as eluent on the basis of poly(ethylene oxide) calibration curve.

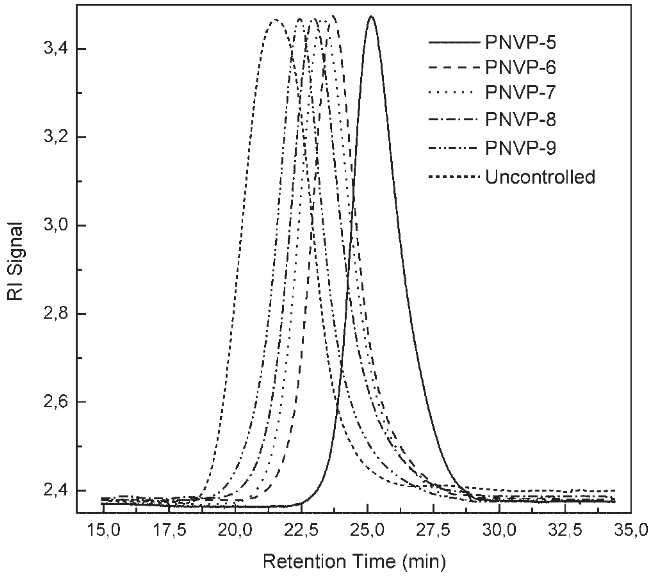


Figure 6.
SECs of PNVP homopolymers prepared in 1,4-dioxane at 80 °C with AIBN as an initiator and varying amounts of DPCM as CT agent determined by SEC using H_2O/CH_3OH (80/20) containing 0.1 M $NaNO_3$ as eluent on the basis of poly(ethylene oxide) calibration curve.

molar ratios were also carried out. The corresponding results are shown in Table 2. In the case of a [NVP]/[DPCM] ratio of 500 (Table 2, PNVP-9) the initiator was added in two equal portions at two different intervals of time: the first at the beginning of the reaction and the second after 8 h of polymerization. This method led to a higher conversion and thus to a higher molar mass within a comparatively short duration of reaction time. The $\overline{M}_n$ values given in Table 2 were drawn from the ^{1}H NMR and SLS of the samples. A good agreement between the experimental and theoretical values of molar masses for these polymers could be observed. In the case of the samples corresponding to an [NVP]/[DPCM] of 500, its molar mass could not be determined by NMR because of the lack of accuracy of the latter technique. The polydispersity of the polymers obtained varied between 1.2 and 1.5. The SEC profiles in water/methanol (80:20) of the PNVP homopolymers of varying molar masses synthesized using DPCM as the CT agent in comparison with a conventionally polymerized PNVP are given in Figure 6.

A blank experiment was indeed conducted without CT agent under the same conditions, which resulted in a high molar mass polymer exhibiting a broad polydispersity ≅8.4 (Figure 4). From these observations it could be concluded that the growth of polymer chain in the presence of DPCM is by RAFT process.

Block Copolymers from DPC-PNVP

The living nature of these polymers was confirmed by synthesizing block copolymers of PNVP by sequential addition of monomers. Block copolymers of PNVP with different hydrophobic monomers (styrene and *n*-BA) were synthesized by sequential addition of monomers in the presence of a small percentage of AIBN. PNVP-6 (entry 2, Table 2) was used as a macro-CT agent for the synthesis of diblock copolymers. The blocking efficiencies were rather poor in this case but amphiphilic

Table 3.
Characteristics of PNVP-*b*-STY, PNVP-*b*-PBA diblock copolymers synthesized in 1,4-dioxane solution in the using PNVP-6 (DPCM) as macro-CT agent at 60 °C. (AIBN = 0.1 mol-% with respect to styrene/*n*-BA, PNVP-6 $\overline{M}_n$ = 11 500).

Sample	mol-% of styrene/*n*-BA		$\overline{M}_n$	Solubility in CH_3OH	PDI[a]
	Feed	Copolymer	^{1}H NMR		
			g · mol^{-1}		
PNVP-*b*-PS_1	20	6.1	12 200	Soluble	–
PNVP-*b*-PS_2	33.3	13.7	13 100	Soluble	1.44
PNVP-*b*-PBA_1	15	8.3	12 600	Soluble	1.23
PNVP-*b*-PBA_2	20	12.1	13 200	Soluble	1.30

[a] Determined by SEC using THF as eluent on the basis of poly(styrene) calibration curve.

diblock copolymers could be isolated after being freed from the homopolymer by precipitation in water or methanol, followed by centrifugation at lower temperature (5 °C). The purified block copolymers were insoluble in water even for small percentages of hydrophobic part in the copolymer chain. In contrast, its solubility in methanol was found to depend on the percentage of hydrophobic part incorporated in the polymer chain. The purity of the block copolymers was further confirmed by SEC analysis, which showed a single peak attesting to the absence of homopolymers. The SEC data gave only apparent molar mass in the case of block copolymers as the instrument was calibrated using homopolymer standards. The real molar mass of the block copolymers could be calculated from ^{1}H NMR measurements, knowing the molar mass of the macro-CT agent. The characteristics of the block polymers are given in Table 3.

The polymer PNVP-*b*-PS_1 was completely soluble in methanol and it did not show a peak in SEC (THF); this was attributed to the very low styrene incorporation and a d*n*/d*c* value of the PNVP block close to 0 in THF. The SEC curves of all the other copolymers showed a single peak due to the formation of amphiphilic block copolymers as shown in Figure 7(A) and (B).

The ^{1}H NMR spectra of PNVP-*b*-PS and PNVP-*b*-PBA are shown in Figure 8(a) and (b), respectively. These spectra clearly indicate the presence of two blocks in these copolymers. The complete solubility of the copolymers with a low content of PS or

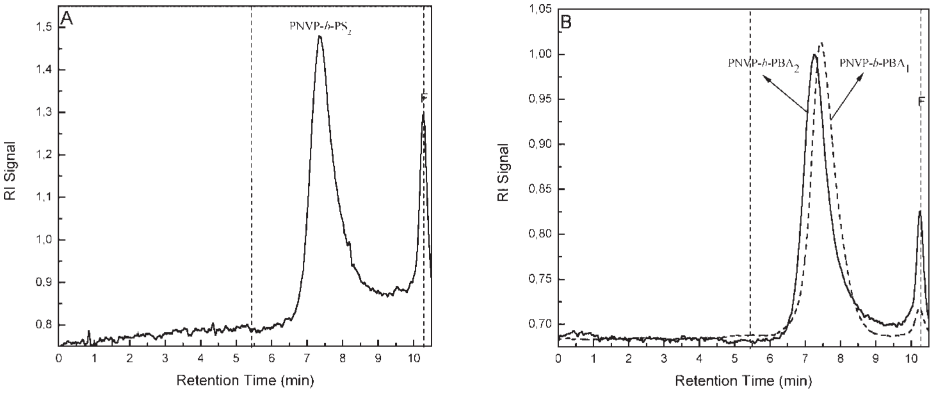


Figure 7.
SECs of PNVP-*b*-PS, PNVP-*b*-PBA prepared in 1,4-dioxane at 60 °C with AIBN as an initiator and PNVP-6 as the macro-CT agent (THF was used as the eluent and was calibrated using polystyrene standards).

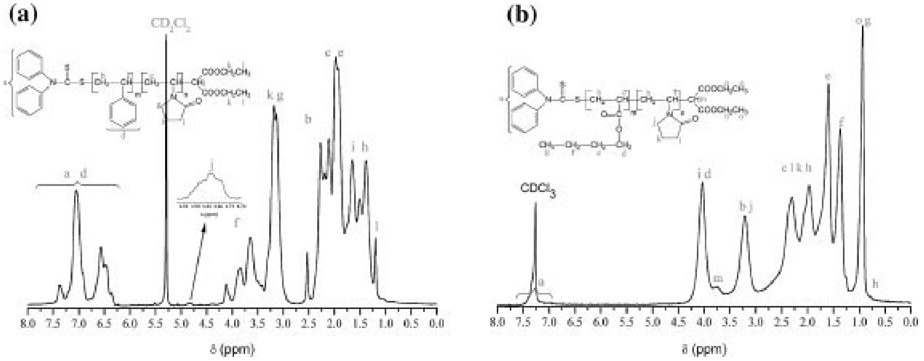


Figure 8.
^{1}H-NMR spectra (a) PNVP-*b*-PS and (b) PNVP-*b*-PBA, synthesized in 1,4-dioxane at 60 °C with AIBN as an initiator and PNVP-100 as the macro-CT agent.

PBA in methanol confirms the absence of any PS and PBA homopolymers. The percentage of each block present in the diblock copolymers as well as the overall $\overline{M}_n$ was derived from ^{1}H NMR spectra by integrating the corresponding peaks, and the composition thus calculated is given in Table 3. The successful synthesis of diblock copolymers using PNVP-6 as macro-CT agent demonstrates that growing $PS^\bullet$ and $PBA^\bullet$ macroradicals efficiently add to the macro-CTA and that the intermediate radicals formed fragment as expected, confirming the controlled/living nature of such synthetic procedure.

Conclusion

N-Vinylpyrrolidone has been successfully polymerized by RAFT process using DPCM as CT agent in the presence of small percentage of a conventional radical initiator (AIBN). The molar mass of the polymers synthesized by this method was found to increase with conversion and time. The presence of diphenyldithiocarbamate end group in the polymer chain could be confirmed by NMR. The molar mass calculated using ^{1}H NMR and SLS showed good agreement with the expected molar mass values. The controlled nature of these polymers was further confirmed by generating diblock copolymers by sequential addition of monomers such as butyl acrylate or styrene. The block copolymers were finally characterized by SEC and ^{1}H NMR.

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