Investigation of the Telomerization Kinetics of *N*-Isopropylacrylamide Using 3-Mercaptopropionic Hydrazide as Chain Transfer Agent

Matteo D. Costioli,[†] D. Berdat,[†] Ruth Freitag,[*,†,‡] Xavier André,[§] and Axel H. E. Müller[§]

Laboratory of Chemical Biotechnology, Faculty of Basic Science, Swiss Federal Institute of Technology, Lausanne, Switzerland, Process Biotechnology, University of Bayreuth, 95440 Bayreuth, Germany, and Macromolecular Chemistry II, University of Bayreuth, 95440 Bayreuth, Germany

Received July 23, 2004; Revised Manuscript Received December 16, 2004

ABSTRACT: The telomerization (chain transfer polymerization) kinetics of *N*-isopropylacrylamide were investigated in various (hydro)organic solvents using 3-mercaptopropionic hydrazide as chain transfer agent (telogen). Except for the dioxane/water system telogen consumption rates were similar for all cases, while solvent effects could be observed for the monomer consumption rates. Chain transfer constants, as defined by the ratio of the rate constants for chain transfer and chain propagation ($C_T = k_{tr}/k_p$), were highest in DMF (10.3), a solvent unable to form hydrogen bonds or dipole−dipole interactions with the monomer, while a more promising value of $C_T = 1.7$ was found for the 6:4 methanol/water mixture. The highest monomer consumption rates were observed for the 1:1 dioxane/water mixture. However, in this particular case the telogen consumption was also found to increase, as we propose due to a "hydrophobic effect" whereby polymer microaggregates serve to locally increase the concentration of telogen and/or monomer once a certain water concentration has been passed. As a result a comparatively high C_T of 3.2 characterizes the dioxane/water system.

Introduction

Controlled chain transfer, i.e., the calculated shift of the radical from the growing polymer chain to another molecular species, which in turn can reinitiate chain growth, is a convenient way to control the molar mass and the polydispersity of polymers produced by free radical polymerization.[1−4] If the rate of reinitiation is in the same order of magnitude as the original rate of propagation, the overall polymerization rate is not affected, while a larger number of polymers (or oligomers) albeit with smaller molecular mass, is formed. When the reinitiation rate is slow compared to the propagation, the size of the polymers as well as the rate of the polymerization is decreased in chain transfer polymerization (also called telomerization) compared to the same reaction in the absence of the chain transfer agent. Many compounds can be used as chain transfer agents (telogens) in free radical polymerization; the most popular are halogens and mercaptans. Besides their capacity to react as chain transfer agents, these molecules also supply a well-defined end group to the final polymer (telomer). Vinyl monomers that are suitable for conventional radical chain polymerization, such as ethylene, styrenes, acrylamides, or (meth)acrylates, can be used in telomerization.[4−7]

Chain transfer polymerization of *N*-isopropylacrylamide (NIPAAm) is increasingly used for the synthesis of defined oligomers bearing a particular functional (ester, carboxylic acid, amino) end group that can be conveniently employed for the construction of bioconjugates.[8−12] For such applications, the ability to control the size and heterogeneity of the polymer is the most important aspect besides the presence of a reactive end group. It is known that the degree of polymerization and therefore the molecular mass of the telomer can be controlled via the initial ratio of the telogen and monomer concentration.[5,6] However, to take advantage of this, the kinetics of a given telogen/monomer couple and in particular their chain transfer constants have to be known. To date, few kinetic studies on telomerization reactions have been reported, mostly by Boutevin and co-workers, cf. Tables 1 and 2.[5,7,13−20] In particular, these authors studied the behavior of various telogens in the telomerization of (meth)acrylates. A detailed study of PNIPAAm is still missing, which is unfortunate given the overwhelming importance of this compound in the area of stimuli-responsive macromolecules and materials.[8−10]

The mechanistic steps of chain transfer polymerization differ little from those in conventional radical polymerization; cf. Scheme 1. Ideally, chain growth starts with the addition of the telogen radical to the first monomer rather than a radical stemming from the initiator. Propagation is by the addition of a certain number of monomers, while chain termination is typically by chain transfer. The higher the growth rate relative to the transfer rate, the higher the number of monomer units present in the telomer before chain transfer occurs. To produce macromolecules the reaction rates of chain growth, R_p, and chain transfer, R_{tr}, should differ by one to 2 orders of magnitude. If $R_p \gg R_{tr}$, predominantly conventional polymers are formed and the chain transfer effect on the size is lost. If R_p is too small compared to R_{tr}, 1:1 adducts and oligomers are formed. In addition to these reactions, all reactions known from conventional free radical polymerization

---

[*] Corresponding author. Chair for Process Biotechnology, Faculty of Engineering Science, University of Bayreuth, 95440 Bayreuth, Germany. Fax: 0049 921 55-7375. E-mail ruth.freitag@uni-bayreuth.de.

[†] Swiss Federal Institute of Technology.

[‡] Process Biotechnology, University of Bayreuth.

[§] Macromolecular Chemistry II, University of Bayreuth.

10.1021/ma0484882 CCC: $30.25 © 2005 American Chemical Society
Published on Web 04/09/2005

Table 1. Chain Transfer Constants of Linear Thiols with Alkylacrlyamides, Alkylmethacrylamide, and Acrylic Acids

monomer	thiols	C_T	T (°C)	solvent	ref
acrylic acid	thioglycolic acid	3.2	65	THF	14
	thioglycolic acid	0.5–3.2	65	THF/water	14
	3-mercaptopropionic acid	0.49		water	42
	1-ethyldecanethiol	0.38	70	dichlorobenzene	43
	1-dodecanethiol	1.7–2.3	45	2-propanol	44
acrylamide	1-dodecanethiol	1.7	45	methanol	44
	1-octanethiol	1.65–1.70	45	methanol	44
	1-octadecanethiol	1.70	45	methanol	[44
	$C_6F_{13}-C_2H_4-SH$	0.65	80	acetonitrile	15
N-(2-hydroxypropyl)methacrylamide	2-mercaptoethylamine	0.08	50	methanol	31
	3-mercaptopropionic acid	0.32	50	methanol	31
	methyl 3-mercaptopropionate	0.38	50	methanol	31
	3-mercaptopropionic hydrazide	0.8	50	methanol	31
tris(hydroxymethyl)acrylamidomethane	*n*-alcanethiols	1	60	methanol	45
N-isopropylacrylamide	3-mercaptopropionic acid	0.006 63	70	DMF	33
	methyl 3-mercaptopropionate	4.1	65	ethanol	32
	3-mercaptopropionic hydrazide	6.0	65	dioxane	this study
	3-mercaptopropionic hydrazide	10.3	65	DMF	this study
	3-mercaptopropionic hydrazide	5.5	65	methanol	this study
	3-mercaptopropionic hydrazide	1.7	65	methanol/water 6:4	this study
	3-mercaptopropionic hydrazide	3.2	65	dioxane/water 1:1	this study

Table 2. Values of the Propagation/Termination Rate Constant Ratio Determined from Telomerization Different Monomers in Different Solvents

monomer	thiols	$k_p/\sqrt{k_t}$ [(L mol s)$^{-0.5}$]	T [°C]	solvent	ref
acrylic acid	thioglycolic acid	5	50^a	water	42
	thioglycolic acid	2.02	29^a	water	14
	thioglycolic acid	0.42	29^a	formamide	14
	thioglycolic acid	0.11	29^a	DMSO	14
	thioglycolic acid	0.75	80	CH_3CN	46
	thioglycolic acid	0.48	65	THF	14
	thioglycolic acid	0.54	65	THF/water 9:1	14
	thioglycolic acid	1.56	65	THF/water 5:5	14
	thioglycolic acid	2.09	65	THF/water 2:8	14
	thioglycolic acid	2.48	65	water	14
alkylacrylamide	1-dodecanethiol	2.5	45	methanol	44
	1-dodecanethiol	0.66	80	CH_3CN	47
	1-dodecanethiol	0.23	80	CH_3CN	47
N-isopropylacrylamide	methyl 3-mercaptopropionate	0.53	65	ethanol	32
	3-mercaptopropionic hydrazide	0.24	65	DMF	this study
	3-mercaptopropionic hydrazide	0.58	65	dioxane	this study
	3-mercaptopropionic hydrazide	0.53	65	methanol	this study
	3-mercaptopropionic hydrazide	1.42	65	methanol/water 6:4	this study
	3-mercaptopropionic hydrazide	8.30	65	dioxane/water 1:1	this study

[a] H_2O_2 was used as initiator.

can also take place, e.g., the direct initiation of a polymer chain by an initiator rather than a telogen radical. Several other side reactions, e.g., a termination by recombination of a chain initiated by a telogen radical and a chain initiated by an initiator radical further add to the complexity of chain transfer polymerization. The kinetics of a telomerization are hence extremely complicated. Moreover, the rate constants of the early events in telomerization, which are the most crucial ones, are difficult to access experimentally.[4,21]

In the case of a homopolymerization, the chain transfer constant C_T ($=k_{tr}/k_p$) can be used to characterize the system. In such a case the chain propagation rate, R_p, is proportional to $(k_p/(k_i/k_t))^{0.5}$, i.e., the rate constants for the chain propagation, initiation, and termination reactions respectively, while the chain transfer rate, R_{tr}, is proportional only to k_{tr}, i.e., the rate constant for chain transfer. Since initiation and termination show little dependency on the solvent, save for a possible viscosity effect, they can be assumed to be constant and the ratio of chain propagation and chain transfer is proportional to the ratio of the two remaining rate constants, i.e., C_T.

O'Brien et al.[25] proposed a method for the determination of the chain transfer constant C_T in which the telogen concentration is connected to the reaction progress. From the average degree of polymerization, $\overline{DP_n}$, and under the assumption that termination is exclusively due to the transfer of the radical to the telogen, we can formulate

$$\overline{DP_n} = \frac{d[M]/dt}{d[T]/dt} = \frac{k_p[M][P_n^\bullet]}{k_{tr}[T][P_n^\bullet]}$$

which in turn allows the determination of C_T from the following relationship:

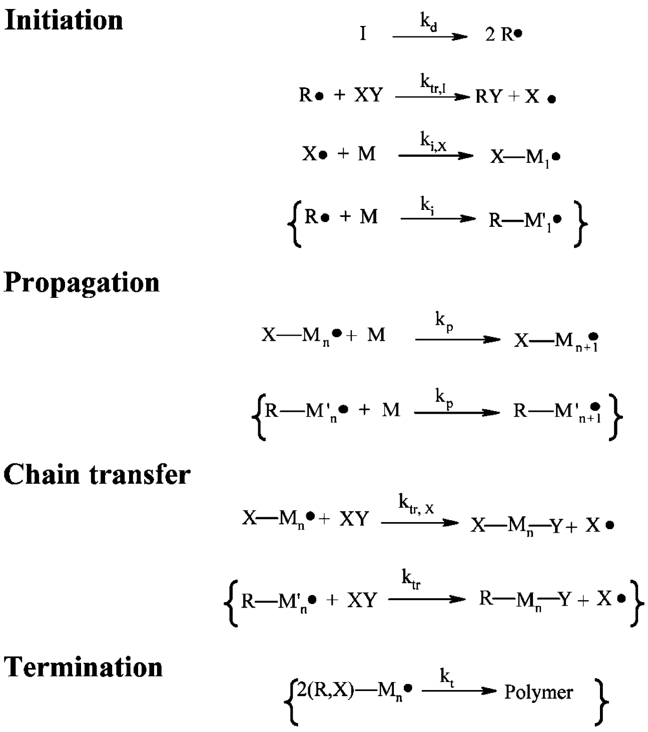
$$\ln\frac{[T]_0}{[T]} = C_T \ln\frac{[M]_0}{[M]}$$

or

$$\ln(1 - \alpha_T) = C_T \ln(1 - \alpha_M)$$

where the subscript of 0 denotes initial concentrations and α_M (α_T) is the monomer (telogen) conversion.

Scheme 1. Schematic Presentation of the Reactions Involved in Chain Transfer Polymerization (Telomerization)[a]



[a] Key: I = initiator, R = radical, XY = chain transfer agent, and M = monomer. Possible competitive reaction steps due to conventional radical polymerization are indicated in brackets.

Experimental Procedures

Materials. Chemicals were obtained from Sigma-Aldrich. The initiator 2,2′-azoisobutyronitrile (AIBN) and the monomer *N*-isopropylacrylamide (NIPAAm) were recrystallized from methanol and hexane, respectively, prior to use. Solvents were from Fluka and Carlo-Erba. Diethyl ether was dried by reflux over sodium using benzophenone as indicator. DMF and dichlomethane were dried on calcium hydride and distilled over 3 Å molecular sieves. Water was purified with an Elix-3 water purification system (Millipore, USA). Deuterated solvents were from Deutero, Germany.

Syntheses. The chain transfer agent 3-mercaptopropionic hydrazide was prepared as follows. First, 10 g (83 mmol) of methyl 3-mercaptopropionate was added dropwise to an excess of hydrazine monohydrate (10 g, 200 mmol) dissolved in 30 mL of methanol at ambient temperature. The reaction mixture was stirred at room-temperature overnight. Thin-layer chromatography was used to follow the reaction (R_f = 0.62; methanol/diethyl ether 1:4). Methanol was removed under vacuum by rotary evaporator and the product purified by chromatography on a silica gel column eluted with methanol/diethyl ether (1:4). The fraction containing the product was collected and the solvent removed under vacuum by rotary evaporator. The final oily 3-mercaptopropionic hydrazide was dried under vacuum; yield 8.4 g (84%). ^{1}H NMR ($CDCl_3$, ppm): 1.57 (t, 2H, SH), 2.43 (t, 2H, $COCH_2$), 2.76 (m, 2H, CH_2SH), 3.96 (sh, 1H, NH). ESI−MS, *m/z*: 121.54 (H^+).

For the synthesis of poly(*N*-isopropylacrylamide), PNIPAAm, 12.0 g of the monomer (0.11 mol) was dissolved in 70 mL of the indicated degassed solvent. The mixture was heated to 65 °C. Then, 174.0 g AIBN (1.06 mmol) and 318.1 g of the chain transfer agent (2.65 mmol) were dissolved together in 1 mL of the same solvent. Both solutions were injected into the reaction vessel (N_2 atmosphere) with a syringe. The reaction was monitored by FT-NIR. In the case of ^{1}H NMR monitoring 1.7 g of monomer (15.02 mmol) were dissolved in the indicated degassed solvent and heated to 65 °C. 24.7 g AIBN (0.15 mmol) and 72.1 g chain transfer agent (0.60 mmol) were individually dissolved in a minimal volume of the same solvent and added with a syringe to the reaction vessel (N_2 atmosphere). In both cases, samples were taken at different time intervals using a disposable syringe. The samples were immediately immersed in liquid nitrogen and stored at −20 °C until analysis.

Analytics. The consumption of the chain transfer agent, 3-mercaptopropionic hydrazide, was followed by the Ellman test.[26] Briefly, 50 μL of sample from the reaction mixture was diluted several times in a 0.1 M phosphate buffer pH 8 to reach a final concentration of approximately 0.1 μmol/mL in terms of the sulfhydryl group in a total volume of 1.5 mL. Then 50 μL of a freshly prepared 5,5′-dithio(2-nitrobenzoic acid) (DTNB) solution (4 mg/mL) was added to the sample mixture and the mixture left to stand for 20 min. The concentration of the sulfhydryl group was calculated from the UV signal recorded at 410 nm using 1.5 mL buffer containing 50 μL of the DTNB solution as reference.

^{1}H NMR spectra for monitoring of the monomer conversion were obtained on a Bruker AC 250 at an operating frequency of 250 MHz. As an internal standard, the residual proton signal of the deuterated solvent was used. Samples were analyzed after dilution in deuterated DMSO (telomerization in DMF) or methanol (telomerization in methanol or dioxane). The degree of conversion, α_M, was determined by a comparison of the signal stemming from the three vinylic protons of the monomer (Ha′, 5.7 ppm and Hb′, 6.3 ppm) with the broad peak stemming from the methin proton of the polymer (Hc, between 2.05 and 2.35 ppm), according to the following formula:

$$\alpha_M = \frac{Hc}{\frac{(Ha' + Hb')}{3} + Hc}$$

Fourier transform near-infrared (FT-NIR) spectroscopy was performed in situ using a Nicolet Magna 560 FT-IR optical bench equipped with a white-light source and a PbS detector. The fiber-optic immersion probe (Hellma, quartz glass Suprasil 300) with an optical path length of 10 mm was connected to the FT-NIR instrument by 2 m fiber-optical cables. Data processing was performed with Nicolet's OMNIC Series software. Each spectrum was constructed from 32 scans with a resolution of 4 cm^{-1}. The total collection time per spectrum was approximately 22 s. Prior to the measurements, a blank spectrum was recorded with the solution of the corresponding chain transfer agent in the indicated solvent. FT-NIR spectra were recorded every 30 s and the variation in time of the intensity of the NIPAAm monomer bands at 6157 cm^{-1} (the vinylic stretching overtone of NIPAAm) was followed for the evaluation of the monomer consumption. The monomer conversion, α_M, was extrapolated from the intensities of the FT-NIR absorbance peaks at zero monomer conversion and at total conversion using the following equation:

$$\alpha_M = \frac{A_0 - A_t}{A_0 - A_\infty}$$

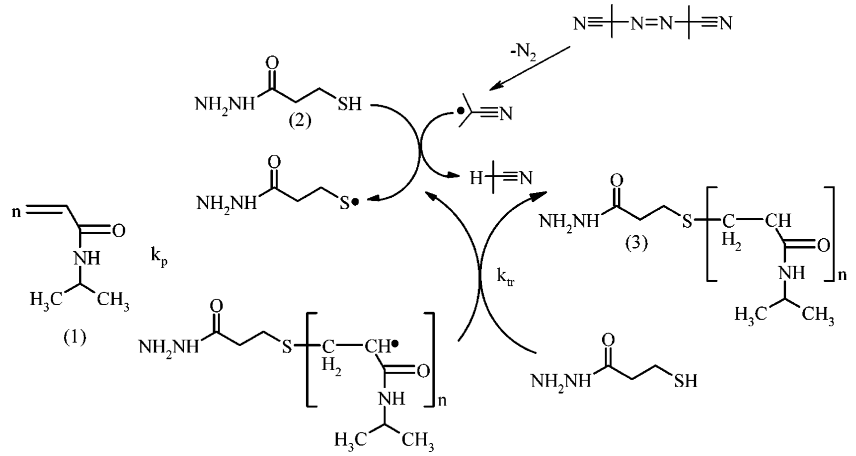
Here A_t is the absorbance at time t, A_0 is the initial absorbance, and A_∞ is the absorbance at full conversion.

ESI−TOF mass spectra were acquired on a LCT mass spectrometer from Micromass (Manchester, U.K.). This instrument combines an electrospray ionization source with a TOF (time-of-flight) mass analyzer. The LCT mass spectrometer was used in the positive ionization mode for all experiments. The ES+ Source parameters were adjusted as a function of the tested products.

Results

We undertook an investigation of the telomerization kinetics of NIPAAm considering mainly the possible effect of various solvents. Since we have recently introduced 3-mercaptopropionic hydrazide as a chain transfer agent particularly suitable for bioconjugate synthesis by chemical ligation,[27] telomerization of

Scheme 2. Idealized Scheme of Telomerisation of NIPAAm Using 3-Mercaptopropionic Hydrazide as Chain Transfer Agent



NIPAAm using this particular chain transfer agent was taken as an example in our studies. However, the conclusions drawn in regard to the influence of the solvent on the telomerization kinetics of NIPAAm should be of general applicability.

The reactions involved in the telomerization of NIPAAm using 3-mercaptopropionic hydrazide as chain transfer agent are shown in Scheme 2. In principle, any solvent should be suitable for telomerization as long as the monomer and the telogen are well dissolved and, more importantly, as long as the solvent does not act itself as chain transfer agent. When an efficient chain transfer agent, e.g., a thiol, is chosen, the chain transfer properties of most solvents should be negligible by comparison. However, as in any radical polymerization, the solvent may exert a pronounced effect on the monomer reactivity, especially in the case of polar monomers, monomers containing atoms with a free electron pair, and/or those capable of forming hydrogen bonds. Examples include acrylates, methacrylates, and acrylamides such as the NIPAAm central to this study.[28]

The influence of the nature of the solvent on the telomerization kinetics was investigated by calculating the respective chain transfer constants, $C_T = k_{tr}/k_p$, according to the method proposed by O'Brien outlined in the Introduction. For this purpose, the consumption of the monomer and chain transfer agent were followed as a function of time. In the case of the monomer this was achieved by in situ FT-NIR and/or by ^{1}H NMR. FT-NIR is a powerful tool for this type of investigation, as it allows the in situ monitoring of the monomer conversion.[29,30] The intensity of the NIPAAm monomer bands at 6157 cm^{-1} (the vinylic stretching overtone of NIPAAm) was followed with time. This band does not significantly overlap with those at other wavelengths, in particular those of the polymer (e.g., the band at 6727 cm^{-1}, which increases during the telomerization) or more importantly, the bands of most of the investigated solvents. As an example of the FT-NIR measurements, the evolution of the spectra with time for a telomerization of NIPAAm in dioxane as solvent is shown in Figure 1. ^{1}H NMR was used for the determination of the monomer conversion, especially when the solvent employed in the telomerization showed NIR absorption bands overlapping with those of the monomer. Figure 2 shows an example of an ^{1}H NMR spectrum recorded for a NIPAAm

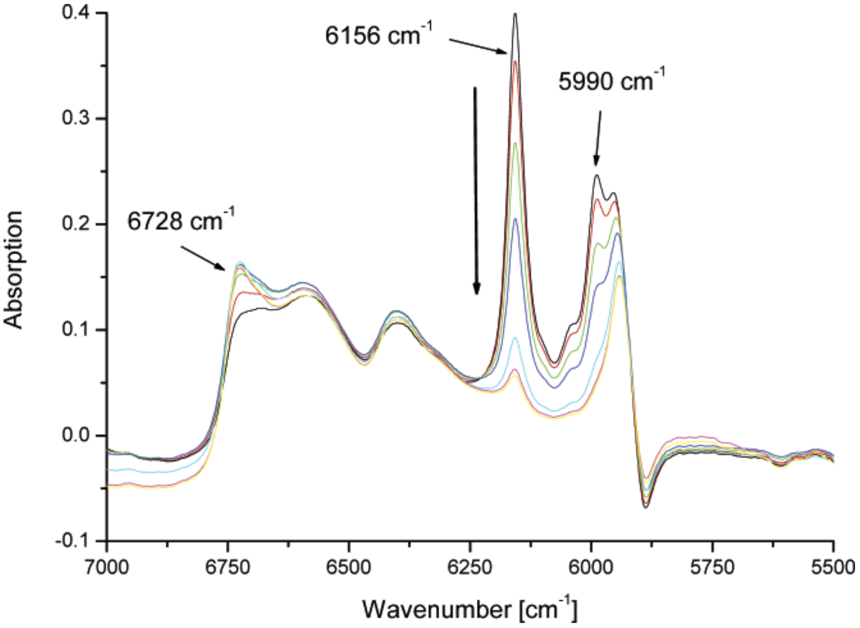


Figure 1. Evolution of the FT-NIR-spectrum (after 0.4, 4, 9, 21, 36, and 80 min) in the telomerization of NIPAAm in dioxane, using 3′-mercaptopropionic hydrazide as chain transfer agent.

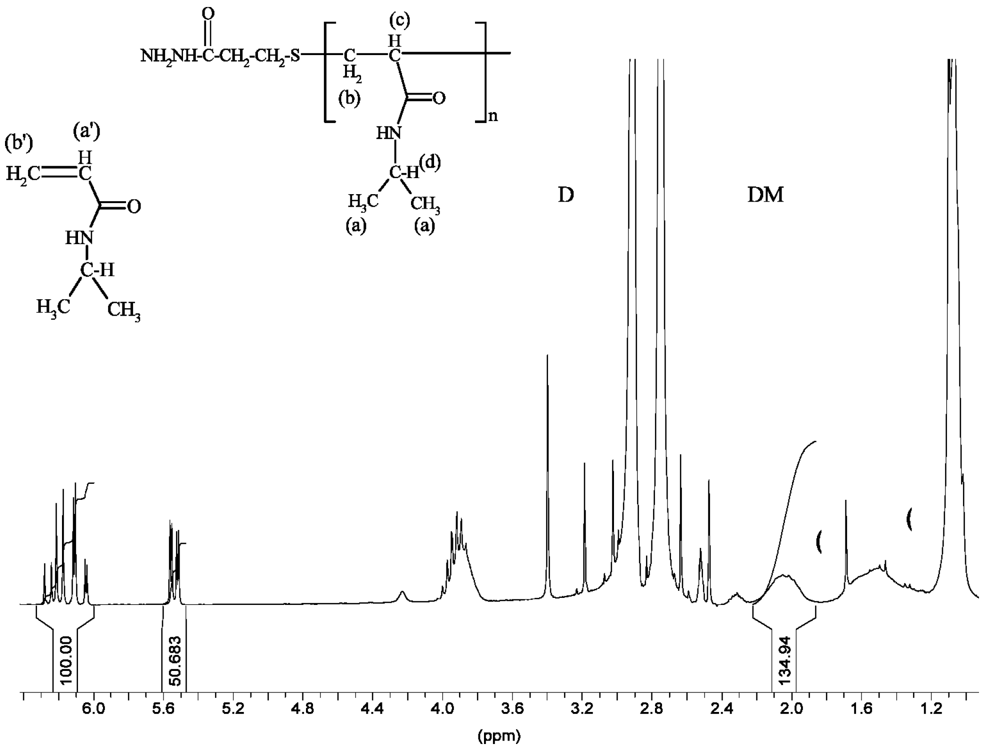


Figure 2. ^{1}H NMR spectrum of the PNIPAAm obtained through telomerization at 65 °C in DMF in the presence of the 3′-mercaptopropionic hydrazide as transfer agent.

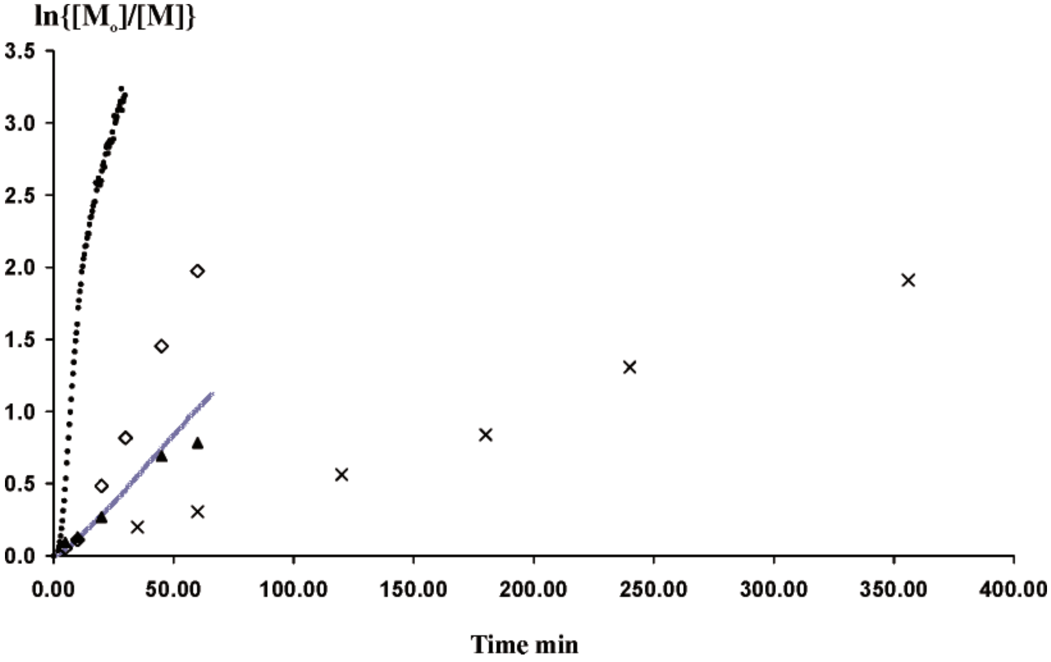


Figure 3. Monomer consumption (followed by FT-NIR) as a function of time for the telomerization of NIPAAm at 65 °C in different solvents in the presence of 3′-mercaptopropionic hydrazide as chain transfer agent (telogen). Key: (—) dioxane; (▲) methanol; (◇) methanol/water (4:6, v/v); (×) DMF; (●) dioxane/water (1:1, v/v); [M] monomer concentration at the given time; [M_o] initial monomer concentration.

telomerization in DMF. The consumption of the chain transfer agent was followed by titrating aliquots of the samples taken during the reaction with Ellman's reagent.[26] This colorimetric essay allows the detection of primary thiols by a reaction with 5,5′-dithiobis[2-nitrobenzoic acid] (DTNB). Under mildly alkaline conditions, the displaced nitrobenzoate anion shows a characteristic absorbance at 410 nm, which can be correlated to the sulfudryl group of the transfer agent.

The influence of the solvent on the monomer and telogen consumption can be seen in Figures 3 and 4. Differences can be observed for the monomer consumption rate, cf. Figure 3. Propagation is most rapid in the dioxane/water mixture. In contrast, only small changes are observed for the telogen consumption, except for the dioxane/water mixture. The chain transfer constant, $C_T = k_{tr}/k_p$, should vary accordingly. In fact, as summarized in Table 1, the C_T values vary between a value of about

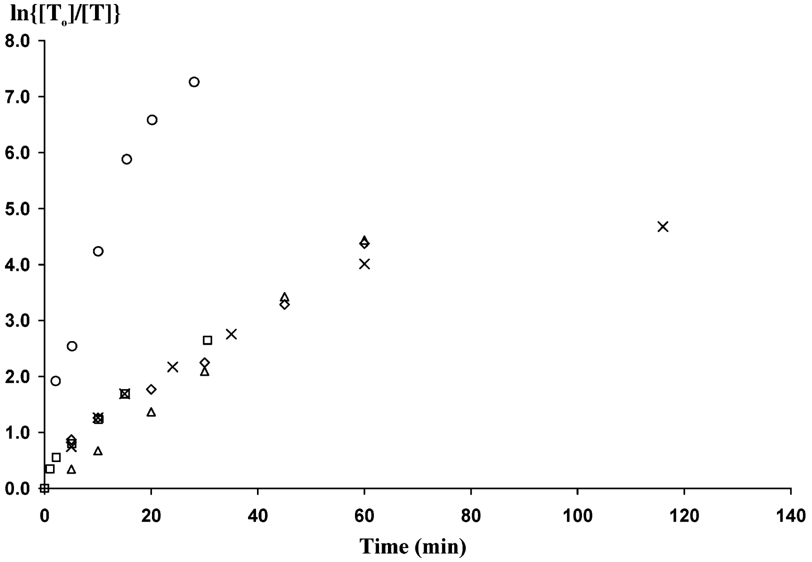


Figure 4. Telogen consumption as a function of time for the telomerization of NIPAAm at 65 °C in different solvents in the presence of 3′-mercaptopropionic hydrazide as chain transfer agent (telogen). Key: (□) dioxane; (▲) methanol; (◇) methanol/water (4:6, v/v); (×) DMF; (○) dioxane/water (1:1, v/v); [T] telogen concentration at a given time; [T$_o$] initial telogen concentration.

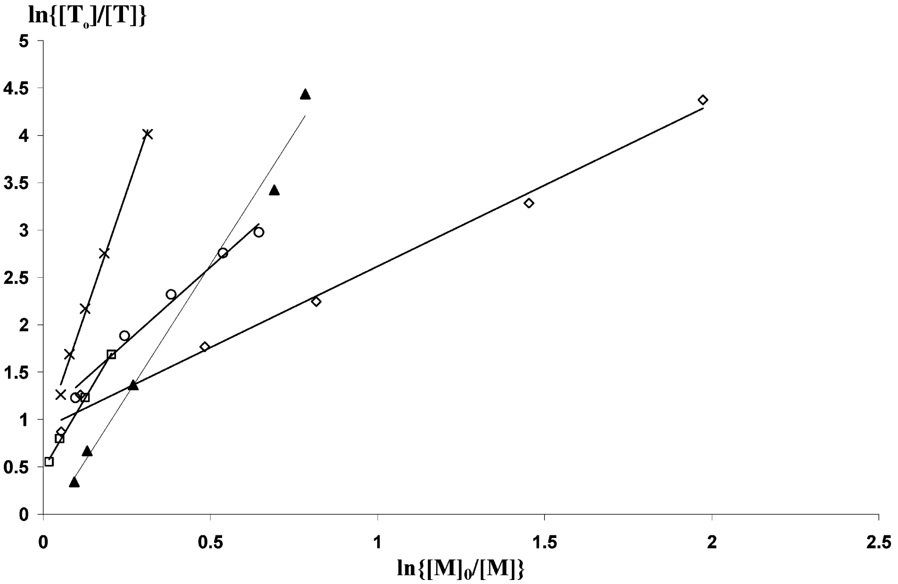


Figure 5. Relationship between the telogen and the monomer consumption in the telomerization of NIPAAm (monomer) at 65 °C in different solvents in the presence of 3′-mercaptopropionic hydrazide as chain transfer agent (telogen). Key: (□) dioxane; (▲) methanol; (◇) methanol/ water (4:6, v/v); (×) DMF; (○) dioxane/water (1:1, v/v). Straight lines represent linear regressions. According to the relationship proposed in ref 25 (O'Brien and Gornick) the slopes of the plots give the C_T value of the reaction.

10 found for DMF and a value of 1.7 found for the mixture of methanol and water. Values were calculated from 4 to 7 data points in each case. The correlation coefficient of the linear relationship (R^2) was 0.99 or higher in all cases as shown in Figure 5.

Discussion

Chain transfer constants vary with the type of monomer and telogen.[31] It is therefore difficult to compare our results with the C_T values found in the literature. However, the values measured for a range of solvents in these experiments are in the same order of magnitude as those found by Desponds and Freitag (ref 32, Table 1), who observed a $C_T = 4.1$ for the telomerization of NIPAAm in pure ethanol using methyl 3-mercaptopropionate as chain transfer agent; a telomerization system which is similar to the one used in this study. The value found by Tekei et al.[33] for the telomerization of NIPAAm in DMF using 3-mercaptopropionic acid as chain transfer agent, on the other hand, is several orders of magnitude lower. The observed divergence of the C_T value could be partially explained by differences in the telogen reactivity. It has been reported that the acidic character of the thiol group, which corresponds to its telogen activity, is increased by electron-drawing groups.[14,19,31,33] Lu et al.[31] showed, e.g., that for a series of telogens ($HSCH_2CH_2R$) the reactivity increased for R = $-NH_2 < -COOCH_3 <$ COOH < -$CONHNH_2$. We can therefore expect the 3-mercaptopropionic hydrazide used by us to have a higher C_T then methyl-3-mercaptopropionate used in ref 31.

In systems with $C_T \gg 1$, "telomerization" will result in a complex mixture of telomers and polymers.[19] For the production of compounds with a controlled molecular mass and well-defined end groups such systems are unsuitable. In the case considered here, DMF ($C_T = 10.3$) hence constitutes an unsuitable solvent, while a 6:4 mixture of methanol and water ($C_T = 1.7$) could most likely be used. A similar effect was observed by Loubat et al.[14] for the telomerization of acrylic acid in the presence of thioglycolic acid as transfer agent. They found that the C_T value for any telomerization can be lowered by increasing the molar fraction of water in the mixture. In fact, they could reach a $C_T = 1$ by increasing the fraction of water in THF to 80%. In our study a similar investigation of the effect of increasing amounts of water was not possible, since we produced PNIPAAm, which, other than acrylic acid, precipitates from hydroorganic mixtures when the proportion of water reaches a certain critical value (cononsolvency effect).[37,38] A study of the PNIPAAm solubility in different mixtures of methanol and water (data not shown) showed that the maximum content of water in such a solution was 40%, at higher contents the PNIPAAm precipitated. However, such a mixture gave the above-mentioned C_T value of 1.7, which allows the construction of a satisfactory telomer carrying a reactive hydrazide moiety in good proportion.

Several approaches to explain the solvent effect in polymerizations can be found in the pertinent literature. Gromov et al.[34,35] also reported that changing the solvent in a polymerization reaction may cause a change in the overall rate of polymerization by several orders of magnitude. This effect was most pronounced when changing from an organic solvent to an aqueous solution. This solvent dependence was explained by a decrease in the activation energy of the chain propagation reaction, which determines the rate constant, k_p.[24,25,28] Acrylamide monomers can exist in a self-associated form (dimers, trimers) due to their ability to form intermolecular hydrogen bonds.[35,36] Gromov et al.[35] proposed that only the individual monomer is able to participate in the chain propagation reaction. Solvents, which destabilize the monomer associates by interaction with the monomer via hydrogen bridges or by a dipole−dipole interaction, will therefore increase the propagating rate of the polymerization. Chapiro et al.,[36] on the other hand, proposed that the growing radical chains react preferentially with the monomer aggregates rather than with a free monomer. However, according to their theory solvents, which form hydrogen bridges or dipole−dipole interactions stabilize rather than break the associates. In both cases we can thus expect a faster polymerization reaction in solvents that are able to interact with the monomer/monomer associate structures.

Such an effect can serve as a basis for the explanation of some of our results. The highest C_T value (10.3) is found for DMF, i.e., a solvent that is unable to form strong hydrogen bonds or dipole−dipole interactions with the monomer. Similar and intermediate C_T values are found for dioxane ($C_T = 6.0$, dipole−dipole interaction) and methanol ($C_T = 5.5$, hydrogen bonds). The value dropped to 3.2 when the reaction was carried out in a 1:1 mixture of dioxane/water and—as already stated—to a value as low as 1.7 when a 6:4 methanol/water mixture was used. The strong decrease in the C_T value observed upon the addition of water may in addition be due to the influence water has on certain acrylamide monomers. It has been claimed[28,35] that the ability of water to form strong hydrogen bonds can favor the enol form of the acrylamide monomer and therefore increase its reactivity as well as stabilize the growing radical.[36,39] This effect was demonstrated by Saini et al.,[39] who observed that the solvent effect on the copolymerization of styrene or methyl methacrylate with acrylamide disappeared once the acrylamide was replaced by *N,N*-dimethylacrylamide, i.e., a monomer that cannot exist in the enolform.

Among the solvents used in this study, the 1:1 mixture of dioxane and water presents a special case. When the telomerization was carried out in this mixture compared to pure dioxane, the rate of monomer consumption was increased as expected, and full monomer conversion was reached in a few minutes, Figure 3. Only in this case among all investigated, however, did we also observe a change (increase) of the telogen consumption rate, Figure 4. As a consequence, the C_T value calculated for this system was still comparatively high (3.2). Gromov et al.[28,34,40] have observed an abrupt increase of the rate of polymerization of acrylamide in aqueous solvents when the molar fraction of water surpassed a certain value. They explained this phenomenon by a hydrophobic effect. Even below the phase transition temperature PNIPAAm is known to form associates/microaggregates in water.[41] These microaggregates may solubilize residual monomer molecules thereby altering their local concentration, but may also exert a favorable influence on the spatial arrangement of groups involved in the chain propagation reaction.[34,40] The influence of a similar phenomenon can perhaps explain the increase of the transfer reaction rate observed for the dioxane/water system compared to all other investigated solvents and solvent mixtures, especially if we assume that the PNIPAAm microaggregates would preferentially solubilize the chain transfer agent, which after all contains a large hydrophobic group. The increase of the local telogen concentration would conceivably increase the transfer rate by a kind of “micellar catalysis” .

Conclusions

The telomerization kinetics of NIPAAm show the expected general behavior. The solvent is crucial for creating a well-behaved system and exerts its effect via the monomer consumption rate. Solvents, such as hydroorganic mixtures, that interact well with the monomer (hydrogen bridge formation) result in chain transfer constants close to 1 (e.g., $C_T = 1.7$ for a 6:4 mixture of methanol/water) and hence should be suitable for the intended telomerization. Organic solvents and in particular solvents lacking the ability to interact with the monomer, e.g., DMF, resulted in much higher C_T values ($C_T = 10.7$ for DMF). In such systems the desired chain transfer effect on the polymer size (distribution) is much less pronounced. A further decrease of the C_T value by adding more water to the reaction mixture is not feasible in the case of NIPAAm due to the possible manifestation of cononsolvency effects. Even in the case of a comparatively predictable monomer like NIPAAm, the characterization of the reaction kinetics is advised for any new reaction system, as we observed at least one case in our study, where not only the monomer consumption rate, but also that of the telomer and consequently the polymerization rate changed (dioxane/water, 1:1), presumably due to a hydrophobic effect. An—in view of the high water content—surprisingly high chain transfer constant of $C_T = 3.2$ was observed in this case.

Acknowledgment. This work was financed by the Swiss National Science Foundation (SNF, Grant No. 2100-049276.96 to R.F.), by the Commission for Technology and Innovation (CTI, Grant No 4731.2 to R.F.), and by polyTag Technology SA, Männedorf, Switzerland.

References and Notes

(1) Odian, G. *Principles of Polymerisation*, 3rd ed.; John Wiley & Sons: New York, 1991.
(2) Mayo, F. R.; Gregg, R. A.; Matheson, M. S. *J. Am. Chem. Soc.* **1951**, *73*, 1691.
(3) Handford, W. E.; Joyce, R. M. (*du Pont*), U.S.: Patent 2,440,800, 1948.
(4) Starks, C. M. *Free radical Polymerisation*; Academic Press Inc.: New York, 1974, 267 pp.
(5) Boutevin, B.; Pietrasanta, Y. Telomerisation. In *Comprehensive polymer science*; Eastmond, G. C. L. A., Russo, S., Sigwalt, P., Eds.; Pergamon: New York, 1989; Vol. 3, pp 185–194.
(6) Gordon, B.; Loftus, J. E. *Telomerisation*. In *Encyclopedia of polymer science*; Kirk, D.F. Ed.; Wiley: New York; 1989; pp 533–554.
(7) Boutevin, B. *J. Polym. Sci., Polym. Chem.* **2000**, *38*, 3235–3243.
(8) Ding, Z.; Fong, R. B.; Long, C. L.; Stayton, P. S.; Hoffman, A. S. *Nature* **2001**, *411*, 59–62.
(9) Hoffman, A. S.; Stayton, P. S.; Bulmus, V.; Chen, G.; Chen, J.; Cheung, C.; Chilkoti, A.; Ding, Z.; Dong, L.; Fong, R.; Lackey, C. A.; Long, C. J.; Miura, M.; Morris, J. E.; Murthy, N.; Nabeshima, Y.; Park, T. G.; Press, O. W.; Shimoboji, T.; Shoemaker, S.; Yang, H. J.; Monji, N.; Nowinski, R. C.; Cole, C. A.; Priest, J. H.; Harris, J. M.; Nakamae, K.; Nishino, T.; Miyata, T. *J. Biomed. Mater. Res.* **2000**, *52*, 577–586.
(10) Garret-Flaudy, F.; Freitag, R. *Biotechnol. Bioeng.* **2000**, *71*, 223–234.
(11) Costioli, M. D.; Fisch, I.; Garret-Flaudy, F.; Hilbrig, F.; Freitag, R. *Biotechnol. Bioeng.* **2003**, *81*, 535–545.
(12) Takei, Y. G.; Matsukata, M.; Aoki, T.; Sanui, K.; Ogata, N.; Kikuchi, A.; Sakurai, Y.; Okano, T. *Bioconjug. Chem.* **1994**, *5*, 577–582.
(13) Loubat, C.; Boutevin, B. *Macromol. Chem. Phys.* **2000**, *201*, 2853–2860.
(14) Loubat, C.; Javidan, A.; Boutevin, B. *Macromol. Chem. Phys.* **2000**, *201*, 2845–2852.
(15) Boutevin, B.; Mouanda, J.; Pietrasanta, Y. *J. Polym. Sci., Polym. Chem.* **1986**, *24*, 2891–2902.
(16) Boutevin, B.; Parisi, J. P.; Vaneeckhoutte, P. *Eur. Polym. J.* **1990**, *26*, 1027–1033.
(17) Boutevin, B.; Parisi, J. P.; Vaneeckhoutte, P. *Eur. Polym. J.* **1991**, *27*, 159–163.
(18) Boutevin, B.; Parisi, J. P.; Vaneeckhoutte, P. *Eur. Polym. J.* **1991**, *27*, 1029–1034.
(19) Bechkok, A.; Belbachir, M.; Guyot, B.; Boutevin, B. *Eur. Polym. J.* **1999**, *35*, 413–421.
(20) Baudin, G.; Boutevin, B. *Makromol. Chem.* **1987**, *188*, 2339–2352.
(21) Boutevin, B.; Pietrasanta, Y.; Baudin, G. *Makromol. Chem.* **1985**, *186*, 283–295.
(22) Boutevin, B.; Maubert, C.; Pietrasanta, Y.; Sierra, P. *J. Polym. Sci., Polym. Chem.* **1981**, *19*, 511–522.
(23) Barson, C. A.; Mather, R. R.; Robb, J. C. *Trans. Faraday Soc.* **1970**, *66*, 2585–2589.
(24) Barson, C. A.; Luxton, A. R.; Robb, J. C. *Trans. Faraday Soc.* **1972**, *68*, 1666.
(25) O'Brien, J. L.; Gornick, F. *J. Am. Chem. Soc.* **1955**, *77*, 4757–4763.
(26) Ellman, G. L. *Arch. Biochem. Biophys.* **1959**, *82*, 70–77.
(27) Costioli, M. D.; Hilbrig, F.; Freitag, R. *React. Funct. Polym.* **2004**, submitted.
(28) Gromov, V. F.; Bogachev, Y. S.; Bune, Y. V.; Zhuravleva, I. L.; Teleshov, E. N. *Eur. Polym. J.* **1991**, *27*, 505–508.
(29) Lanzendörfer, M. G.; Schmalz, H.; Abetz, V.; Müller, A. H. E. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **2001**, *42* (1), 329–330.
(30) Schilli, C.; Lanzendoerfer, M. G.; Mueller, A. H. E. *Macromolecules* **2002**, *35*, 6819–6827.
(31) Lu, Z. R.; Kopeckova, P.; Wu, Z.; Kopecek, *J. Bioconjug. Chem.* **1999**, *9*, 793–804.
(32) Desponds, A.; Freitag, R. *Langmuir* **2003**, *19*, 6261–6270.
(33) Takei, Y. G.; Aoki, T.; Sanui, K.; Ogata, N.; Okano, T.; Sakurai, Y. *Bioconjugate Chem.* **1993**, *4*, 42–46.
(34) Gromov, V. F.; Bune, E. V.; Teleshov, E. N. *Russ. Chem. Rev.* **1994**, *63*, 507–517.
(35) Gromov, A. V.; Galperina, T. O.; Osmanov, O.; Khominkoviski, P. M.; Abkin, A. D. *Eur. Polym. J.* **1980**, *16*, 529–535.
(36) Chapiro, A.; Perec-Spritzer, L. *Eur. Polym. J.* **1975**, *11*, 59–69.
(37) Papayiotou, M.; Garret-Flaudy, F.; Freitag, R. *Polymer* **2004**, *45*, 3055–3061.
(38) Schild, H. G.; Muthukumar, M.; Tirrell, D. A. *Macromolecules* **1991**, *24*, 948–952.
(39) Saini, G.; Leoni, A.; Franco, S. *Makromol. Chem.* **1971**, *146*, 165–171.
(40) Barabanova, A. I.; Bune, E. V.; Gromov, A. V.; Gromov, V. F. *Eur. Polym. J.* **2000**, *36*, 479–483.
(41) Eggert, M.; Freitag, R. *J. Polym. Sci., Part A: Polym. Chem.* **1994**, *32*, 803–813.
(42) Boutevin, B.; Rigal, G.; El Asri, M.; Lakhlifi, T. *Makromol. Chem.* **1996**, *197*, 2273–2287.
(43) Baudin, G.; Boutevin, B.; Mistral, JP.; Parisi, J. P.; Pietrasanta, Y. *Makromol. Chem.* **1987**, *188*, 1055–1066.
(44) Pichot, C.; Pellicier, R.; Grossetete, P.; Guillot, J. *Makromol. Chem.* **1984**, *185*, 113–127.
(45) Pucci, B.; Maurizis, J. C.; Pavia, A. A. *Eur. Polym. J.* **1991**, *27*, 1101–1106.
(46) Boutevin, B.; Pietrasanta, Y. *Makromol. Chem.* **1986**, *187*, 1657–1668.
(47) Leydet, A.; Barragan, V.; Boyer, B.; Roque, J. P.; Pucci, B.; Pavia, A. A. *Macromol. Chem. Phys.* **1995**, *196*, 3877–3890.

MA0484882