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Controlled Synthesis of Block Copolymers containing *N*-isopropylacrylamide by Reversible Addition-Fragmentation Chain-Transfer (RAFT) Polymerization

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Abstract. Synthesis of diblock copolymers of *N*-isopropylacrylamide with n-hexyl acrylate, styrene, methyl methacrylate and 2-hydroxyethyl methacrylate, were carried out by using a sequential "living" polymerization method in the presence of chain transfer agent (CTA) 4-Cyano-4-(phenylcarbonothioylthio)pentanoic acid. The block copolymer composition and molecular weight could be well controlled while maintaining a narrow molecular weight distribution. The block copolymers were characterized by ^{1}H NMR, GPC with MALLS detection and DSC. The molar ratio CTA/Initiator rather than the sequence of monomer addition is the key parameter for achieving the desired materials. We report the first synthesis of poly(HEMA)-*b*-poly(NIPAAm) with a polydispersity index (IPD) of 1.20 by RAFT.
Keywords: Block Copolymer, RAFT, poly(NIPAAm), poly(MMA), poly(HEMA), poly(St).

Resumen. La síntesis de copolímeros en dibloques de *N*-isopropilacrilamida con acrilato de n-hexilo, estireno metacrilato de metilo y metacrilato de 2-hidroxietilo, se llevó a cabo mediante polimerización viviente secuencial en presencia del agente de transferencia de cadena (CTA) ácido 4-ciano-4-[fenilcarbonotioiltio] pentanoico. La composición y peso molecular de los copolímeros en bloques se pudo controlar manteniendo un índice de polidispersidad bajo. Los copolímeros en bloque se caracterizaron por ^{1}H RMN, GPC con MALLS y por DSC. La relación CTA/Iniciador resultó ser más relevante que la secuencia de adición de monómeros para lograr los materiales deseados. Se reporta por primera vez la síntesis de poli(HEMA)-*b*-poli(NIPAAm) con un índice de polidispersidad de 1.20 por RAFT.
Palabras clave: Copolímeros en bloques, RAFT, poli(NIPAAm), poli(MMA), poli(HEMA), poli(St).

Introduction

Controlled/living free radical polymerization has attracted much attention of polymer chemists in recent years because it is a powerful tool to synthesize polymers with well-defined structures, and a wide range of monomers can undergo radical polymerization under relatively simple conditions [1]. The term living polymerization originally described a polymerization in which the chain could only propagate and not undergo chain transfer or irreversible termination [2]. Thus, in an ideal living polymerization system, each chain should maintain its ability to further propagate in the presence of the monomer. The last 15 to 20 years has been witness to unprecedented advances in controlled polymer synthesis. This has been due, in part, to the discovery and development of controlled/living free radical polymerization (CRP) techniques [3]. Among all techniques, reversible addition fragmentation chain transfer (RAFT) polymerization, first reported by the Australian CSIRO group in 1998 [4], is a versatile method capable of inducing living behavior for various monomers via a range of initiation methods, solvents and reaction temperatures [5]. The reversible addition fragmentation chain transfer (RAFT) polymerization process has been shown to be a highly versatile and widely applicable living radical polymerization method that lends itself to complex architectural design [6]. Therefore the use of RAFT polymerization in research groups worldwide has grown in the last years and is predicted to grow more rapidly after a world known supplier of chemicals (Aldrich) started to sell a series of different RAFT chain transfer agents (CTA´s) [7].

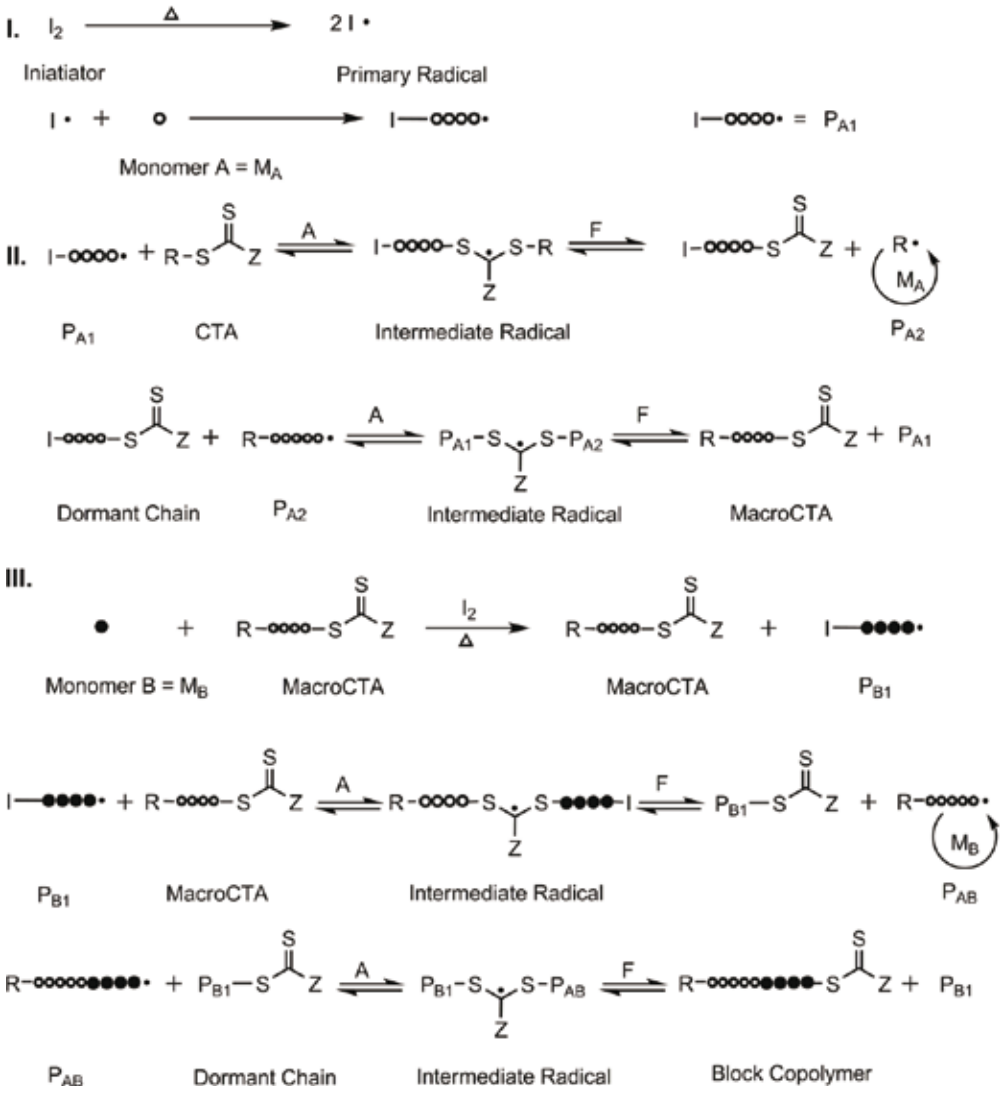
The generally accepted mechanism of RAFT polymerization is shown in Scheme 1. The molecular weight of the obtained polymer is controlled by the monomer to CTA ratio and can be roughly predicted using the following idealized equation:

$$M_n = \frac{[M]_0 \times M_{mon} \times \rho}{[CTA]_0} + M_{CTA} \quad (1)$$

Where $[M]_0$ is the initial monomer concentration, M_{mon} is the molecular weight of the monomer, ρ is the conversion, M_{CTA} is the molecular weight of the CTA, and $[CTA]_0$ is the initial concentration of the CTA [4, 8]. The polymer product of a RAFT polymerization contains in very high percentage the CTA-moiety in its structure. Therefore it is also called macro-CTA and can be activated again for further grow as expected in any living polymerization process. This property of the macro-CTA´s obtained by RAFT can be exploited for chain extension with a different monomer opening the door for block copolymer synthesis. However pursuing block copolymers by using any living polymerization method sequentially requires adjustment of polymerization conditions in each step. It is easy to predict that this will not work for any desired combination of monomers; especially if reactive functional groups are present and also if the polymerization rate of both monomers is very different.

In the case of the RAFT polymerization method, one requirement for forming a narrow polydisperse AB diblock copolymer in a sequential copolymerization is that the first-formed polymeric thiocarbonylthio compound (macro-CTA) should have a high transfer constant in the subsequent polymerization

step to allow the grow of the B block (Scheme 1, Step III) [9]. In the absence of chain transfer to solvent, initiator, or monomer, the total number of chains formed will be equal to (or less than) the moles of dithio compound employed plus the moles of initiator-derived radicals generated during the course of the polymerization. These additional initiator-derived chains are a source of homopolymer impurity in block copolymer synthesis. The level of impurities can be controlled by appropriate selection of the reaction conditions. For maximum purity, it is desirable to use a concentration of initiator as low as practicable and to choose solvents and initiators which give minimal chain transfer. However this is not enough. The sequence of monomer addition may have a great impact in the outcome of a block copolymer synthesis by RAFT. The RAFT addition-fragmentation equilibrium in block copolymerization goes through an intermediate dithio radical containing two polymer chains, one of the first monomer (A) and the second one of the second added monomer in the sequence (B); see fore last reaction in Scheme 1, Step III. This intermediate radical may fragment in two ways; to yield an active A-polymer chain and a dormant B-polymer macro-CTA (desired forward fragmentation), or two yield an active B-polymer chain and a dormant A-polymer macro-CTA (undesired back fragmentation). The forward fragmentation would result finally in the desired product: a dormant block copolymer (last reaction of Scheme 1); while the back fragmentation would favor the formation of more homopolymer B. In extreme case a mixture of homopolymer A and homopolymer B could be obtained rather than the desired block copolymer. To favor the block copolymer formation and to diminish the homopolymer impurity, it has been suggested to chose as A monomer (the first in the RAFT sequence) one yielding a good leaving group under the reaction conditions used and as B monomer (the second in the RAFT sequence) one that yields a worse leaving group under the same reaction conditions. For instance the A monomer could be a methacrylate while the B monomer could be an acrylate. Following this



Scheme 1. RAFT mechanism for homopolymerization (I) and (II) and chain extension of a macro CTA (III). A = addition, F = Fragmentation.

strategy it is usually not difficult to achieve block copolymers with no detectable homopolymer impurity (<5%) while still achieving an acceptable rate of polymerization [10].

The aim of this investigation was to find an easy to follow strategy for the well controlled synthesis of temperature sensitive diblock copolymers containing poly(*N*-isopropylacrylamide) (PNIPAAm) as one of the blocks, a well known and worldwide investigated sensitive polymer [11, 12], and representative types of polymers as the second block of different families: styrenics, acrylates and methacrylates. Well defined blockcopolymers containing polyNIPAAm sequences are goal materials for several biotechnology applications including drug delivery [12, 13], among others. One of these block copolymers is reported as prepared by RAFT for the first time, while for the others low polydispersity indices and wide composition range, was a goal.

Results and Discussion

RAFT homo-polymerizations: Preparation of macro-CTA's

The overall conditions for the RAFT polymerization of macro-CTA's as applied in this paper and their results are shown in Table 1. The molecular weight of the homo-polymers is well controlled by the monomer to CTA concentration ratio as predicted by the idealized equation (1) as can be seen comparing the theoretical with the molecular weights measured by gel permeation chromatography (GPC) with multiangle laser light scattering detection (MALLS). The key to the RAFT process and subsequently control over molecular weight is the thiocarbonylthio moiety of the CTA. However the CTA to initiator ratio needed to obtain the theoretical molecular weight depends on the monomer type and the desired molecular weight. The comparison between MMA and HA is lesson telling. For MMA a 1.25 to 1 ratio of CTA to initiator is enough to control the molecular weight and PDI, while for HA at least a 12 to 1 ratio of CTA initiator is needed to yield the desired molecular weight maintaining a low PDI. This may result from the fact that MMA is reported to show a high transfer constant to CTA's of the dithiobenzoate type, while acrylic esters do not show a high transfer constant [10]. The kinetic constant of propagation (k_p) reflects the polymerization rate of a given monomer under given conditions of concentration, solvent and temperature. The reported values for MMA and n-butyl acrylate (BA) under the same polymerization conditions: 833 and 33,700 $Lmol^{-1}s^{-1}$ show that BA polymerizes 40-times faster than MMA [14]; it can be assumed that HA polymerizes at a similar rate than BA since dodecyl acrylate has a k_p value very similar to BA (36,400 $Lmol^{-1}s^{-1}$) [14]. The chain transfer constant (C_{tr}) is the ratio of the kinetic constant of chain transfer (k_{tr}) to the kinetic constant of propagation ($C_{tr} = k_{tr}/k_p$), therefore a high value of propagation kinetics (k_p) results in a lower constant of chain transfer. If a high rate of transfer to the CTA is needed for a controlled RAFT process, then a higher concentration of CTA

Table 1. RAFT polymerizations of macro-CTA´s.

Macro-CTA	Time (h)	$[CTA]_0:[I]_0$	$[M]_0:[CTA]_0:[I]_0$	Yield[b] (%)	$M_n$theo[c] (g/mol)	M_n GPC[d] (g/mol)	PDI[f]
Poly(NIPAAm)	48	25 : 1	105 : 1 : 0.04	64	7639	10,780	1.18
Poly(NIPAAm)	48	5 : 1	256 : 1 : 0.20	59	17,000	21,500	1.11
Poly(NIPAAm)	48	7.7 : 1	373 : 1 : 0.13	70	29,495	31,590	1.19
Poly(NIPAAm)	48	4 : 1	540 : 1 : 0.25	64	39,000	43,000	1.21
Poly(MMA)	24	1.25 : 1	520 : 1 : 0.80	71	37,600	37,020	1.15
Poly(MMA)	24	1.25 : 1	600 : 1 : 0.80	75	43,100	43,930	1.09
Poly(MMA)	24	8.3 : 1	348 : 1 : 0.12	60	20,900	20,760	1.09
Poly(MMA)	24	16.7 : 1	280 : 1 : 0.06	55	15,400	16,000	1.05
Poly(HA)	24	33.3 : 1	88 : 1 : 0.03	62	8840	9909	1.09
Poly(HA)	24	25 : 1	133 : 1 : 0.04	71	14,990	16,510	1.18
Poly(HA)	18	12.5 : 1	198 : 1 : 0.08	50	15,700	16,580	1.19
Poly(HA)	24	14.3 : 1	190 : 1 : 0.07	63	19,026	20,500	1.22
Poly(HEMA)	8	50 : 1	307 : 1 : 0.02	30	11,990	13,650[e]	1.26
Poly(HEMA)	16	25 : 1	263 : 1 : 0.04	75	25,680	26,180[e]	1.50
Poly(HEMA)	16	14.3 : 1	412 : 1 : 0.07	60	32,100	37,800[e]	1.55
Poly(St)[a]	24	9.1 : 1	2500 : 1 : 0.11	22	68,000	69,970	1.10
Poly(St)[a]	24	8.3 : 1	1500 : 1 : 0.12	22	34,320	36,900	1.15
Poly(St)[a]	24	10 : 1	1500 : 1 : 0.10	21	31,500	32,100	1.20

[a] Initiator AIBN; [b] As determined gravimetrically; [c] Calculated using equation 1; [d] GPC in THF; [e] GPC in DMF; [f] PDI = M_w/M_n.

is needed when the k_p is also high. In the case of NIPAAm the CTA's initiator ratio used to control molecular weight and polydispersity is 4 to 1, an intermediate value as compared with MMA and HA. A fast lecture of this result is that NIPAAm transfer ability to the CTA used is intermediate, also. Unfortunately there are no reliable values of k_p reported for NIPAAm. The only report we found using pulsed laser polymerization in water at room temperature gave values varying significantly depending on monomer concentration, initiator type and its concentration, etc.; the average value is around 20,000 $Lmol^{-1}s^{-1}$ [15]. In another report the kinetics of NIPAAm polymerization in dioxane are reported to show a value for $k_p/[k_t]^{1/2}$ of 0.58 [16]. Using as an approximation the reported termination constant for acrylamide (no value reported for NIPAAm) in a water/Dioxane mixture of 2.3×10^8 $Lmol^{-1}s^{-1}$ [17] we calculate an approximate $k_p = 8800$ $Lmol^{-1}s^{-1}$ for NIPAAm. Both values of propagation constant are lower than for HA. From results in Table 1 follows also that for a given monomer a low molecular weight macro CTA may be prepared not only by increasing the CTA concentration as expected (lowering the monomer to CTA ratio in accordance with equation 1); it is also important to lower the initiator concentration in order to maintain a monomer to initiator concentration ratio ($[M]_o$:$[I]_o$) resulting in a similar polymerization rate than for a higher molecular weight macro-CTA. In the case of NIPAAm this ratio was 2600 for a 10.8 Kg mol^{-1} macro-CTA, while for HA this ratio was 2700 for a 9.9 Kg mol^{-1} macro-CTA.

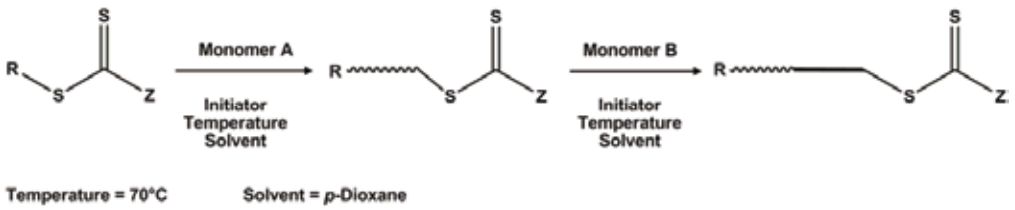
For the RAFT polymerization of HEMA the situation is very different from the parent monomer MMA; even if both monomers are from the same family, their properties (MMA, hydrophobic and HEMA, hydrophilic) and polymerization behavior are quite different. The kinetic constant of propagation (k_p) of HEMA is 3270 $Lmol^{-1}s^{-1}$ [14], 4 times greater than that of MMA and from the results obtained is evident that the transfer ability to the CTA used in this study is not very efficient for HEMA. The result is that for controlling the molecular weight and polydispersity of poly(HEMA) by RAFT polymerization it was necessary to increase the CTA to initiator ratio to values between 25 and 50, more than ten times that needed for controlling MMA homopolymerization. More CTA means higher transfer rate to the CTA and lower polymerization rate. By doing this a 75% yield of poly(HEMA) was obtained in 16 h, while for the same 75% yield of poly(MMA) 24 h of polymerization were needed. Even if the goal molecular weights in both cases were achieved (compare values of theoretical and GPC measured molecular weights in Table 1 for poly(MMA) and poly(HEMA) at 75% yield), the polydispersity is quite different 1.09 for poly(MMA) while 1.50 for poly(HEMA) was measured. A further increase in CTA concentration in RAFT polymerization of HEMA showed that only up to 8 h of polymerization (30% yield) resulted in a relatively low PDI of 1.26. In the case of HEMA is evident that a controlled radical polymerization is only achieved at low polymerization yield, while at higher yields the polydispersity grows to reach values close to non controlled radical polymerization. This result indicates that side reactions and possibly polymer chain termination through polymer to polymer addition widens the PDI. In summary it is evident that the CTA chosen for this study works well for the RAFT polymerization of MMA, NIPAAm and HA; while for HEMA another CTA type is needed. In any case limiting the polymerization yield of HEMA a macro-CTA with good characteristics for further use can be obtained.

In the case of Styrene this monomer is known to readily polymerize but at a slow rate. The reported k_p is 341 L $mol^{-1}s^{-1}$ [14], the smallest of all monomers used in this study. Styrene transfer ability is high since styryl radicals are stabilized by resonance. The results in Table 1 show clearly that poly(St) can be prepared by RAFT at a high molecular weight with a narrow polydispersity, however at a low polymerization rate resulting in lower yields than for the other monomers at the synthetic conditions chosen in our studies. For a faster polymerization of styrene by RAFT, a higher monomer and initiator concentration and temperature can be used while adjusting the CTA to initiator ratio. Polymerization of styrene in bulk adding a certain amount of CTA at high temperature is also possible [10].

Block copolymers

The synthetic procedure to prepare diblock copolymers is presented in Scheme 2, while the RAFT mechanism was described in Scheme 1. Since from the RAFT methodology it is expected that a certain small amount of initiator derived polymers (terminated) are included in the macro-CTA used in this step of synthesis, and because the RAFT copolymerization mechanism goes through the formation of homopolymers of the second monomer; it is advisable to limit the monomer conversion in this second step of block copolymer formation to values between 50-70%.

In this way, the purification of the block copolymer product includes in first step the precipitation of the polymer product, eliminating residual monomer (mayor contaminant) and initiator derived subproducts; and in the second step separation of homopolymer(s) (minor contaminants) from the block copolymer.



Scheme 2. Outline of general methodology for the synthesis of block copolymers.

Theoretical molecular weight of the block copolymers can be calculated by using the following idealized equation:

$$M_n\ (\text{Block}) = \frac{[M]_0 \times M_{mon} \times \rho_{mon}}{[\text{macro}-\text{CTA}]_0} + M_n\ (\text{macro}-\text{CTA}) \quad (2)$$

where $[M]_0$ is the initial concentration of monomer in the second step, M_{mon} is the molecular weight of this monomer, ρ_{mon} is the conversion of this monomer, $[\text{macro-CTA}]_0$ is the initial concentration of the macro-CTA and M_n (macro-CTA) is the molecular weight of the macro-CTA (first block).

The specific results obtained are discussed below for each type of block copolymer.

Synthesis of and poly(MMA)-*b*-poly(NIPAAm) and poly(NIPAAm)-*b*-poly(MMA)

As quoted before, for a block copolymerization using RAFT it is advisable to start with the monomer that shows higher transfer ability for the CTA selected. In this case is advisable to start with MMA in the first step and follow with NIPAAm monomer. Table 2 show the results obtained by this suggested strategy. Since NIPAAm will grow in the second block, CTA to initiator ratios from 3 to 1 to 7 to 1 were tested. A relatively small second block of poly(NIPAAm) was grown in a controlled fashion. By comparing the theoretical molecular weight with the one measured by GPC maintaining a PDI close to 1.1 demonstrates the RAFT control. Figure 1, section A) shows GPC traces from a macro-CTA of poly(MMA) as compared with the resulting chain extended block copolymer; the GPC traces show a similar shape with no shoulders indicating that the grow was the same for all macro-CTA chains.

The reverse strategy of starting with a poly(NIPAAm) macro-CTA and growing a poly(MMA) second block, was tested trying to adjust the RAFT polymerization conditions to those appropriate for the RAFT polymerization of the second monomer. Results are presented in Table 3. As expected the block copolymers were grown to satisfactory molecular weights (compare calculated with measured molecular weights), however the PDI increased from 1.1 to 1.4 values. This is a clear indication of a loss of RAFT control. Even if the CTA to initiator ratio was increased from 1.25 to 1, used for homopolymerization of MMA, to 1.7 to 1 ratio, no substantial improvement in PDI was obtained. However the GPC traces, as shown in Figure 1 section B), shows that the GPC chromathograms have a similar shape with no shoulders indicating no termination and no homopolymer suggesting that the chain extension was effective and relatively ordered.

Another fact that needs to be highlighted is that the calculated molecular weight of the second block is relatively large, up to the same size of the starting macro-CTA. Growing a small block is expected to impact less the polydispersity of a polymer than growing a big block. The relative size of each

Table 2. Preparation of poly(MMA)-*b*-poly(NIPAAm) starting with a polyMMA macro-CTA.

First Block				Second Block					
Macro-CTA	M_n g/mol	PDI	$[PMMA]_0:[I]_0$	$[NIPAAm]_0:[PMMA]_0$	M_n theo[a] g/mol	M_n GPC g/mol	PDI[b]	NIPAAm content[c] Mol%	Yield[d] %
Poly(MMA)	43,930	1.09	3.22 : 1	160 : 1	54,500	47,800	1.15	10	58.0
Poly(MMA)	37,020	1.15	7.14 : 1	226 : 1	52,200	50,690	1.14	20	59.5
Poly(MMA)	50,650	1.07	5.55 : 1	149 : 1	64,200	58,550	1.04	17	81.0

[a] Using the idealized equation 2; [b] PDI = M_w/M_n; [c] By ^{1}H-NMR; [d] by mass of recovered polymer.

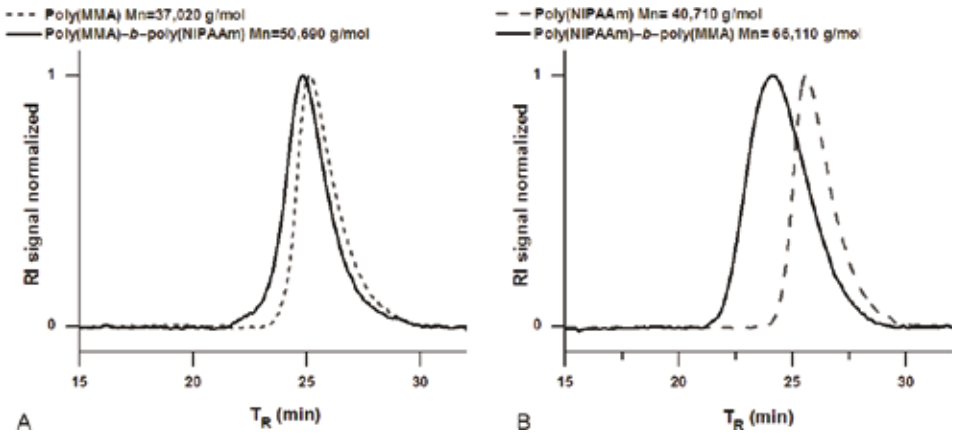


Fig. 1. GPC chromatograms of the sequential synthesis of poly(NIPAAm)-*b*-poly(MMA) block copolymers: A) Starting with a poly(MMA) macro-CTA; B) Starting with a poly(NIPAAm) macro-CTA.

Table 3. Preparation of poly(NIPAAm)-*b*-poly(MMA) starting with a polyNIPAAm macro-CTA.

First Block				Second Block					
Macro-CTA	Mn g/mol	PDI	$[PNIPAAm]_0:[I]_0$	$[MMA]_0:[PNIPAAm]_0$	M_n theo[a] g/mol	M_n GPC g/mol	PDI[b]	NIPAAm content[c] Mol%	Yield[d] %
Poly(NIPAAm)	40,710	1.10	1.47 : 1	547 : 1	69,200	66,110	1.49	25	52.0
Poly(NIPAAm)	33,670	1.10	1.73 : 1	590 : 1	71,500	77,800	1.34	27	63.7
Poly(NIPAAm)	30,890	1.11	1.66 : 1	638 : 1	72,000	75,700	1.45	30	64.0
Poly(NIPAAm)	45,190	1.15	1.38 : 1	743 : 1	89,200	83,910	1.47	35	59.1

[a] Using the idealized equation 2; [b] PDI = M_w/M_n; [c] By ^{1}H-NMR; [d] by mass of recovered polymer.

block in the block copolymer can be estimated by assuming that all macro-CTA chains are active and therefore calculating the number of units dividing the molecular weight (M_n) by the monomer molecular weight before chain extension (first block) and after chain extension, taking the by GPC measured M_n, substracting the macro-CTA M_n value and calculating the number of units of this second block. Another form is by determining the molar ratio of each type of units in a good solvent for both blocks using ^{1}H-NMR. Figure 2 shows a ^{1}H-NMR spectra of a poly(MMA)-*b*-poly(NIPAAm) in deuterated chloroform (200 MHz). Selecting the areas of the signals at 4 ppm (for methine proton of NIPAAm) in relation to the area of the signal at 3.8 ppm (for methyl protons (3) of MMA), the content of NIPAAm in the block copolymer was calculated to be 20%. On the other side the ratio as calculated based on measured molecular weight by GPC (M_n) is 24.6% for NIPAAm giving the general formula $poly(MMA)_{370}$-*b*-$poly(NIPAAm)_{121}$. The difference by both methods may reflect the inaccuracy in determining the true molecular weight, since the dn/dc value used was calculated and perhaps also a 200 MHz spectrum is not enough for an accurate content determination by NMR.

In conclusion for a block copolymer formation for which the two monomers show very different polymerization ability for a selected CTA, it is important to follow the strategy of starting with the methacrylate type monomer and chain extending with the acrylamide type of monomer. The increase of PDI by not observing this suggestion may be reduced by adjusting the CTA to initiator ratio for the second monomer; however the loss of control cannot be neglected. In the literature there is only one report on the preparation of NIPAAm/MMA block copolymers by RAFT [18]. A total of three block copolymers were prepared using *S*-methoxycarbonylphenylmethyl dithiobenzoate as CTA. Only one of the block copolymers prepared has a polydispersity lower than 1.4. That copolymer contains only 8 mol% of MMA and was tested with success for temperature sensitive micellization. In that report the authors do not pay attention to the sequence of monomer addition and use a similar macro-CTA to initiator ratio for both types of monomers.

Synthesis of poly(NIPAAm)-*b*-poly(HA) and poly(HA)-*b*-poly(NIPAAm)

Starting with the fact that a CTA to initiator ratio for well controlled NIPAAm RAFT polymerization was a third of that required for HA under our experimental conditions, we concluded that NIPAAm could be a better transferring monomer to the CTA used than HA. Therefore we decide to test first the synthesis of block copolymers of poly(NIPAAm)-*b*-poly(HA), starting with poly(NIPAAm) macro-CTA´s. Table 4 summarize the results of this strategy. As can be seen, when using a ratio of $[CTA]_0/[I]_0$ of 2.5 to 2.85 block copolymers with high polydispersity were obtained, no matter if the size of the second block, relative to the first block, was small or big PDI values from 1.53 (small) to 1.99 (big) were obtained. When the CTA to initiator ratio was raised to 12.5 to 1, a value for which HA homopoly-

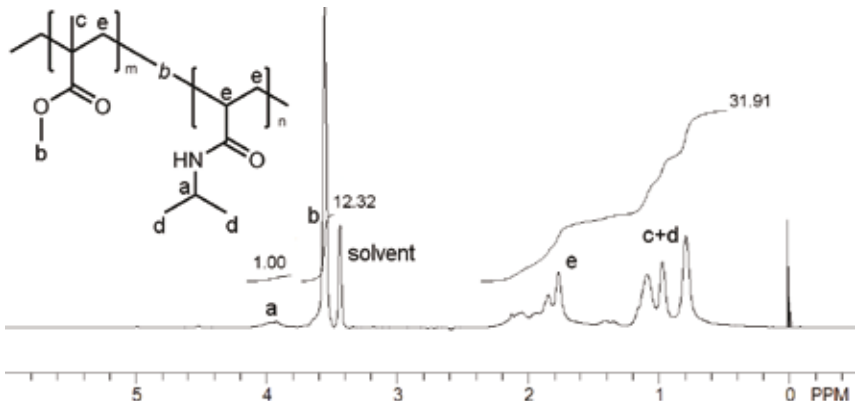


Fig. 2. ^{1}H-NMR Spectrum of $poly(MMA)_{370}$-*b*-$poly(NIPAAm)_{121}$, M_n = 50,690 g/mol.

Table 4. Preparation of poly(NIPAAm)-*b*-poly(HA) starting with a polyNIPAAm macro-CTA.

First Block			Second Block						
Macro-CTA	Mn g/mol	PDI	$[PNIPAAm]_0:[I]_0$	$[HA]_0:[PNIPAAm]_0$	M_n theo[a] g/mol	M_n GPC g/mol	PDI[b]	NIPAAm content[c] Mol%	Yield[d] %
Poly(NIPAAm)	17,090	1.15	2.50 : 1	260 : 1	35,300	27,600	1.84	42.5	45
Poly(NIPAAm)	15,300	1.08	2.63 : 1	184 : 1	34,000	29,660	1.99	39	65
Poly(NIPAAm)	24,830	1.01	2.85 : 1	283 : 1	49,000	30,980	1.53	53	55
Poly(NIPAAm)	10,780	1.16	12.5 : 1	183 : 1	24,600	31,000	1.23	40	49

[a] Using the idealized equation 2; [b] PDI = M_w/M_n; [c] By ^{1}H-NMR; [d] by mass of recovered polymer.

Table 5. Preparation of poly(HA)-*b*-poly(NIPAAm) starting with a polyHA macro-CTA.

First Block			Second Block						
Macro-CTA	Mn g/mol	PDI	$[PHA]_0:[I]_0$	$[NIPAAm]_0:[PHA]_0$	M_n theo[a] g/mol	M_n GPC g/mol	PDI[b]	NIPAAm content[c] Mol%	Yield[d] %
Poly(HA)	16,500	1.21	6.5 : 1	150 : 1	30,000	29,400	1.19	49	80
Poly(HA)	9,900	1.19	12.5 : 1	276 : 1	34,900	40,100	1.20	68	79

[a] Using the idealized equation 2; [b] PDI = M_w/M_n; [c] By ^{1}H-NMR; [d] by mass of recovered polymer.

merizes by RAFT in a controlled way, the result is dramatically better (last row in table 4): the PDI droped to 1.23 no matter that the size of the grown second block is higher than the first block. This result demonstrated that not only the sequence of monomer addition but also the CTA to initiator ratio are important for the success of RAFT block copolymerization.

The reverse strategy, starting with poly(HA) macro-CTA´s and growing a poly(NIPAAm) second block, showed unexpectedly very good results. Meeting the CTA to initiator conditions for RAFT of NIPAAm homopolymerization (a 6.5 to 1 ratio) resulted in essentially the same PDI for the first block and for the resulting block copolymer (Table 5), even if the size of the second block was very similar to that of the first block. The last row of Table 5 shows an experiment for which we adjusted the CTA to initiator ratio for growing a 3 times longer second blocks than the first block. Using a 12.5 to 1 ratio we succeded in maintaining the same PDI while growing a 3 times larger second block, even if it was advisable to grow an acrylic second block rather than a NIPAAm block. Either we are wrong with the assumption that NIPAAm has an intermediate growing ability in RAFT processes between methacrylates and acrylates; or the CTA to initiator ratio has an even more profound impact than the monomer addition sequence in the outcome of RAFT block copolymerization. Figure 3 compares GPC chromatograms for examples of the two strategies used based on macro-CTA´s with similar molecular weights and the same ratio of $[Macro\text{-}CTA]_0:[I]_0$, one starting with a poly(NIPAAm) macro-CTA (section A) and the second one starting with a poly(HA) macro-CTA (section B). The results show essentially the same polydispersity index. The differences

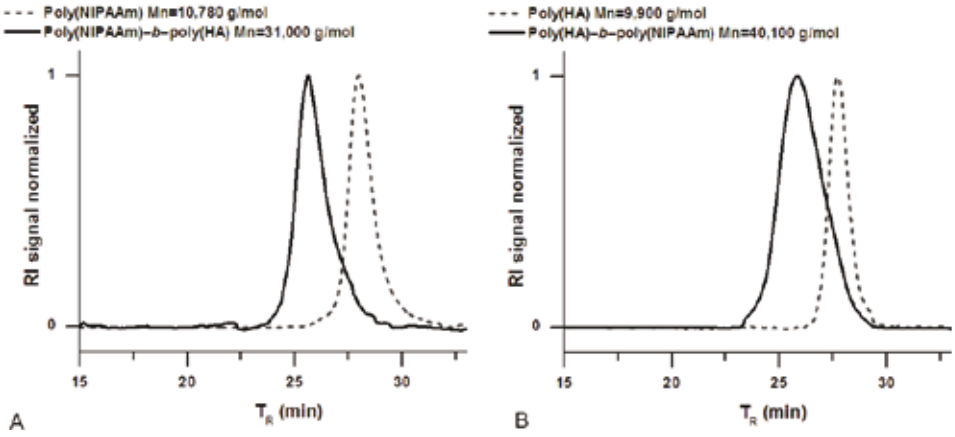


Fig. 3. GPC chromatograms of the sequential synthesis of poly(NIPAAm)-*b*-poly(HA) block copolymers: A) Starting with a poly(NIPAAm) macro-CTA; B) Starting with a poly(HA) macro-CTA.

in molecular weights of the block copolymers is due to the different ratio $[MacroCTA]_0$:$[Monomer]_0$. The chromatograms show a shift in retention time, as expected for chain extension, and no shoulders in the chromatograms indicating absence of chain termination and no unreacted macro-CTA.

Synthesis of poly(HEMA)-*b*-poly(NIPAAm)

From the RAFT homopolymerization experiments we learned that HEMA polymerizes faster than NIPAAm at the same CTA to initiator ratio of 25 to 1 (Table 1). On the other side the CTA used for our studies is evidently not very appropriate for controlling HEMA polymerization at high polymerization yields. Therefore it was advisable to try the block copolymer formation starting with a poly(NIPAAm) macro-CTA and growing a second block of poly(HEMA). These experiments were all unsuccessful; a polymer product with a PDI of 4.5 and in some cases a gel product was formed. When we tried the reverse strategy, using a poly(HEMA) macro-CTA and growing a poly(NIPAAm), block in the second step, we have success (Table 6). We were able to grow a relatively small poly(NIPAAm) second block but with an overall PDI of 1.20. Since the polydispersity of the macro-CTA was larger and the block copolymerization yield is 59% it is a strong indication that in the homopolymerization of HEMA an appreciable amount of terminated (non-living) chains are produced through the not well controlled methodology. However the CTA-functionalized poly(HEMA) chains were able to act as very good macro-CTA for NIPAAm polymerization yielding a well defined block copolymer in acceptable yield.

Since the macro-CTA used for the preparation of the well defined block copolymer had a not so good polydispersity of 1.5, we tested in how far the composition of the block copolymer as calculated from the GPC molecular weight determination, described before for poly(MMA)-*b*-poly(NIPAAm), could be compared to the composition measured using ^{1}H-NMR in deuterated methanol, a good solvent for both blocks. Figure 4 shows the ^{1}H-NMR spectrum of the block copolymer (200 MHz). The composition was calculated using the signals at 3.77 ppm for a methylene (two b Protons of HEMA units in the block copolymer) and the signal at 4 ppm where two proton types are superimposed: the methine (a´) proton of NIPAAm units and the other methylene (two "a" protons) of HEMA units. The NMR calculation yielded a 30% content on NIPAAm units, while the GPC calculation results in a general formula of $poly(HEMA)_{201}$-*b*-$poly(NIPAAm)_{99}$, representing a 33% NIPAAm content, a very good match.

For some applications of block copolymers and also for stability purposes it is desired to remove the thiocarbonylthio group from the polymer product. There are several methods for performing this [7, 19]. Since poly(HEMA)-*b*-poly(NIPAAm) is water soluble, we decided to test a simple procedure reported in a conference [20]: radical exchange using hydrogen peroxide aqueous solution.

Table 6. Preparation of poly(HEMA)-*b*-poly(NIPAAm).

First Block				Second Block					
Macro-CTA	Mn g/mol	PDI	$[PNIPAAm]_0$:$[I]_0$	$[HEMA]_0$:$[PNIPAAm]_0$	M_n theo[a] g/mol	M_n GPC g/mol	PDI[b]	NIPAAm content[c] Mol%	Yield[d] %
Poly(NIPAAm)	21,500	1.10	10 : 1	1126 : 1	57,000	73,570	4.51	40	24
Poly(HEMA)	26,180	1.50	$[PHEMA]_0$:$[I]_0$ 3 : 1	$[NIPAAm]_0$:$[PHEMA]_0$ 200 : 1	39,500	37,400	1.20	30	59

[a] Using the idealized equation 2; [b] PDI = M_w/M_n; [c] By ^{1}H-NMR; [d] by mass of recovered polymer.

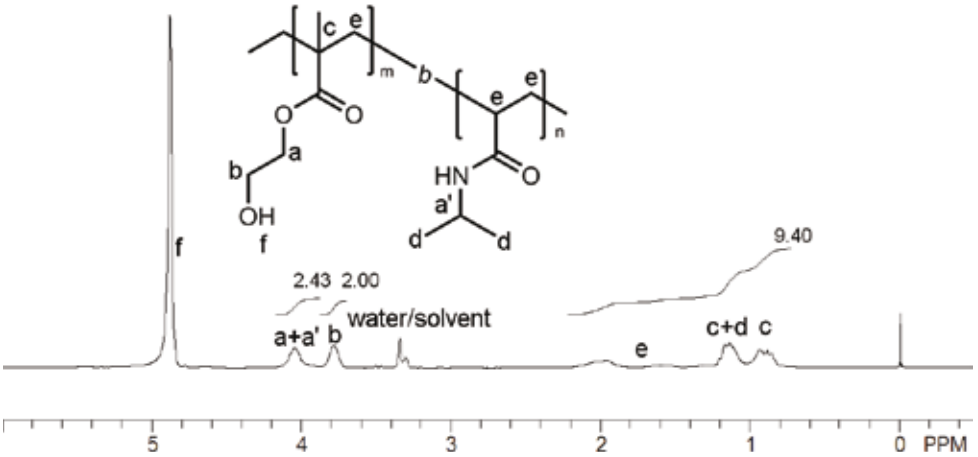


Fig. 4. ^{1}H-NMR Spectrum $poly(HEMA)_{201}$-*b*-$poly(NIPAAm)_{99}$, M_n = 37,400 g/mol.

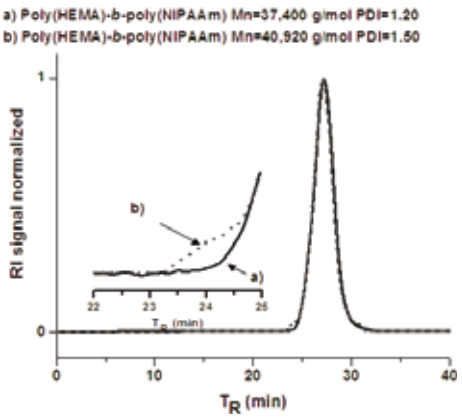


Fig. 5. GPC chromatograms of poly(HEMA)-*b*-poly(NIPAAm): a) as synthesized and b) after removal of thiocarbonylthio-group.

Figure 5 show GPC chromatograms of the block copolymer as synthesized (M_n = 37,400 g/mol; PDI 1.2), and after reaction with hydrogen peroxide to remove the thiocarbonylthio group (M_n = 40,920 g/mol; PDI 1.5). Even if the desired group removal was evident by a change in color from pink to white (dithiobenzoates are red) the process resulted also in increase of polydispersity. The insert in Figure 5 shows that a higher molecular weight shoulder is produced; this is an indication of termination of chains by polymer to polymer addition. Using hydrogen peroxide for this removal was not very successful; we recommend using instead the improved radical exchange method with azo-compounds reported recently [19].

Poly(NIPAAm)-*b*-poly(St) and poly(St)-*b*-poly(NIPAAm)

The first synthesis of poly(NIPAAm)-*b*-poly(St) block copolymers by RAFT was reported by Nuopponen et al. [21]. The authors used the same CTA as we are using in this study, so our results can be well compared to those. From our results in the homopolymerizations studies follows that the best promising strategy would be to start with polystyrene macro-CTA´s and to grow a poly(NIPAAm) block in the second step. That was the strategy followed in reference [21] with success. Giving the fact that we showed for other systems that changing the CTA to initiator ratio we succeeded in preparing block copolymers in the opposite sequence, we wanted to test here if this was possible.

Table 7 shows the results on block copolymers synthesized, it appears that when a poly(NIPAAm) macro-CTA is used to grow a second block of poly(St), the polydispersity decreases with increasing ratio of $[\text{Macro-CTA}]_0$:$[I]_0$. A ratio of macro-CTA to initiator greater than 7 is needed to control the block copolymerization while for block copolymers prepared starting with a poly(St) macro-CTA a ratio of 3.5 to 1 is enough to yield good polydispersity, see Table 8.

Figure 6 shows chromatograms from the two strategies for the synthesis of poly(NIPAAm)-*b*-poly(St) block copolymers; section A compares chromatograms of the synthetic strategy starting with a poly(NIPAAm) macro-CTA and section B compares chromatograms of the synthetic strategy starting with a poly(St) macro-CTA. Note the large displacement of block copolymer retention time in section A and also note that no shoulders or additional peaks are observed demonstrating a clean block copolymer product. In the case of section B a small shift in retention time is observed because the difference in molecular weight between macro-CTA and block copolymer is not as big as for the other case (section A).

DSC measurements

The glass transition temperature (T_g) of selected block copolymers was determined by calorimetry (DSC) and are shown in Table 9. In general terms, the results show that different blocks are phase separated since two separate Tg´s with values similar

Table 7. Preparation of poly(NIPAAm)-*b*-poly(St) starting with a poly(NIPAAm) macro-CTA.

First Block			Second Block						
Macro-CTA	Mn g/mol	PDI	$[\text{PNIPAAm}]_0$:$[I]_0$	$[St]_0$:$[\text{PNIPAAm}]_0$	M_n theo[a] g/mol	M_n GPC g/mol	PDI[b]	NIPAAm content[c] Mol%	Yield[d] %
Poly(NIPAAm)	33,360	1.282	7.4 : 1	1620 : 1	135,500	142,800	1.32	33	60
Poly(NIPAAm)	56,380	1.109	3.5 : 1	400 : 1	81,500	87,500	1.46	49	60

[a] Using the idealized equation 2; [b] PDI = M_w/M_n; [c] By ^{1}H-NMR; [d] by mass of recovered polymer.

Table 8. Preparation of poly(St)-*b*-poly(NIPAAm) starting with a poly(St) macro-CTA.

First Block			Second Block						
Macro-CTA	Mn g/mol	PDI	$[\text{PSt}]_0$:$[I]_0$	$[\text{NIPAAm}]_0$:$[\text{PSt}]_0$	M_n theo[a] g/mol	M_n GPC g/mol	PDI[b]	NIPAAm content[c] Mol%	Yield[d] %
Poly(St)	66,410	1.08	3.5 : 1	685 : 1	112,800	91,380	1.21	29	55
Poly(St)	32,100	1.20	3.6 : 1	220 : 1	47,000	48,240	1.22	35	40

[a] Using the idealized equation 2; [b] PDI = M_w/M_n; [c] By ^{1}H-NMR; [d] by mass of recovered polymer.

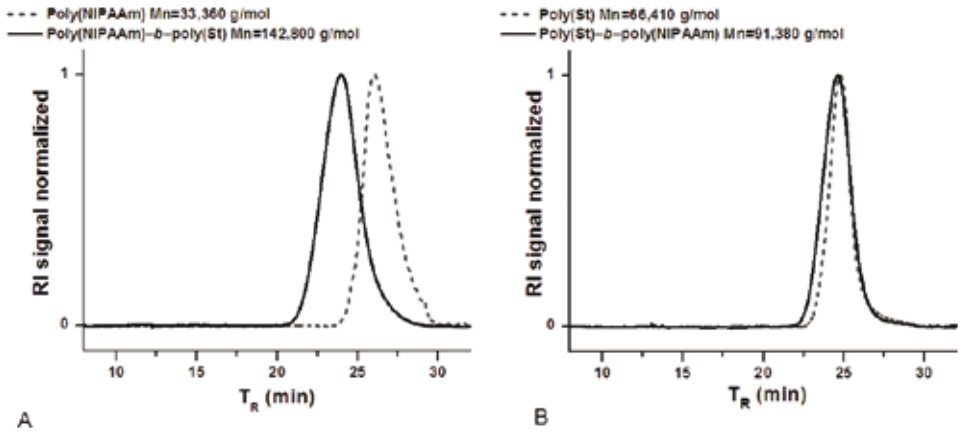


Fig. 6. GPC chromatograms of the sequential synthesis of poly(NIPAAm)-*b*-poly(St) block copolymers: A) Starting with a poly(NIPAAm) macro-CTA; B) Starting with a poly(St) macro-CTA.

Table 9. Glass transition temperatures of blockcopolymers by DSC.

Copolymer	M_n g/mol	PDI	T_g 1st Block (°C)	T_g Homopolymer 1st Block (°C)[a]	T_g PNIPAAm Block (°C)[b]
Poly(MMA)-*b*-poly(NIPAAm)	66,410	1.08	125	105	135
Poly(St)-*b*-poly(NIPAAm)	91,380	1.21	107	100	138
Poly(HEMA)-*b*-poly(NIPAAm)	37,400	1.20	120	85	145
Poly(HA)-*b*-poly(NIPAAm)	40,100	1.20	—	−57	136

[a] From reference [22], atactic polymers; [b] Reported T_g of 130 °C [22].

to those reported for the pure homopolymer segments in Polymer Handbook [22] are found. However, a detailed analysis of these T_g-values shows that in all cases, the measured values are higher than the reported ones. This finding may result from the method used in the DSC analysis (temperature modulation of 0.5 K with a heating rate of 5 K/min). In the case of polyNIPAAm block (130 °C reported) and polySt block (100 °C reported) the measured T_g-values are only 5 to 8 °C higher; however in the case of the polyMMA block (105 °C reported) and polyHEMA block (85 °C reported), the measured values are significantly higher: 125 °C and 120 °C respectively. One possible explanation for the high T_g of polyMMA block could be an increased tacticity, since it is reported that the T_g value for syndiotactic PMMA is 126 °C [22]. In the case of the polyHEMA block, we can postulate that hydrogen bonding to the polyNIPAAm block in the blockcopolymer could be responsible for the increased T_g of the polyHEMA block. This argument is supported by the fact that the polyNIPAAm block in the same blockcopolymer shows also an abnormal high T_g value of 145 °C. It is worth to mention that the T_g of the polyHA block (−57 °C reported) could not be determined in our experimental setup working in the temperature range from −50 to 220 °C.

Conclusions

It was demonstrated that a series of diblock copolymers containing poly(NIPAAm) as one of the blocks can be prepared by sequential "living" radical polymerization by using the RAFT methodology. Only one chain transfer agent was used, however it was possible to prepare macro-CTA´s with controlled molecular weight and low polydispersity of different type of monomers: acrylics (HA), methacrylics (MMA), acrylamides (NIPAAm) and styrenics (St) by adjusting the CTA to Initiator ratio. In the synthesis of block copolymers the good choice of the first block (monomer showing best transfer ability to the CTA) results in a better controlled block copolymer in terms of relative size of blocks, predicted molecular weight and low polydispersity; however the reverse strategy: starting with the monomer showing worst transfer ability, may result also in block copolymers with controlled molecular weight and polydispersity if the CTA to Initiator ratio is adjusted accordingly. The RAFT homopolymerization of HEMA using the chosen CTA for this study resulted in a non controlled process, however by adjusting the CTA to Initiator ratio and limiting the monomer conversion, good working macro-CTA´s can be prepared that showed ability to grow a poly(NIPAAm) second block with controlled molecular weight and polydispersity.

Experimental Section

Materials

N-isopropylacrylamide (NIPAAM) was purified by recrystallization in hexane. Methyl methacrylate (MMA) and styrene (St) were distilled adding 1,3,5,trimethyl-2,4,6-tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)benzene (ETHANOX-330) as polymerization inhibitor during distillation. The monomers n-hexyl

acrylate (HA) and 2-hydroxyethyl methacrylate (HEMA) were purified by passing through a column containing an inhibitor remover for methyl ether hydroquinone (MEHQ). The following solvents were used in the RAFT polymerization: 1,4 dioxane (99%) for RAFT polymerization; and tetrahydrofurane (THF, HPLC Grade, >99%) and N,N´-dimethylformamide (DMF, HPLC Grade, >99%) for GPC characterization. All monomers and solvents were bought from Sigma-Aldrich, Mexico.

Synthesis and polymerizations

Synthesis of CTA and Polymerizations

The synthesis of 4-Cyano-4-(phenylcarbonothioylthio)pentanoic acid was conducted according to the literature [23, 24].

All polymerizations were performed in ampoules. In all cases, 4-Cyano-4-(phenylcarbonothioylthio)pentanoic acid and 4,4'-azo-bis(4-cyanopentanoic acid) (Aldrich) were used as the CTA and initiator, respectively. One exception was that for the synthesis of poly(St) macro-CTA and its block copolymer with poly(NIPAAm), 4,4'-azobis(Isobutironitrile) (AIBN, Aldrich) as initiator was used. Calculated amounts of monomers, CTA and initiator were dissolved in 1,4-dioxane (20 mL) under stirring at room temperature. Solutions were degassed by three freeze-pump-thaw cycles. After degassing, the ampoules were flame-sealed under vacuum and heated in an oil bath at 70 °C while stirring. The polymerizations were terminated by rapid cooling and freezing. The homopolymers obtained, also named macro-CTA´s since they include the CTA-moiety, were purified by repeated precipitations using appropriate non-solvents: ethyl ether for poly(NIPAAm) and poly(HEMA), petroleum ether for poly(MMA), methanol for poly(St) and poly(HA). Products were dried in vacuum overnight, characterized and stored in a cool dry place until further use. An example of the synthesis of poly(NIPAAm) is described in detail: *N*-isopropylacrylamide (4 g, 0.035 mol), 4,4'-azobis(4-cyanopentanoic acid) (0.012 g, 0.042 mmol) and 4-Cyano-4-(phenylcarbonothioylthio)pentanoic acid (0.0569 g, 0.204 mmol) were dissolved in 1,4 dioxane (30 mL) and poured in a glass ampoule (50 mL) containing a magnetic stir bar. Oxygen was removed using 3 freeze-thaw evacuation cycles, and the ampoule was sealed with flame under vacuum. The ampoule containing polymerization solution was submerged in an oil bath with magnetic stirring at 70 °C. The polymerization was stopped by rapid cooling at a given time. The polymerization yield was obtained gravimetrically by adding a 5 fold excess of cold ethyl ether. The polymer product was purified by dissolution in the minimum amount of acetone followed by adding a 5 fold excess of cold ether and filtering. This procedure was repeated three times to remove residual monomer followed by drying under vacuum to constant weight.

Block Copolymerizations

Well characterized homopolymers synthesized in the first step were used as macro-CTA´s. The calculated amount of macro-CTA was dissolved in 1,4-dioxane (20 mL) before adding the second monomer in different amounts aiming different compositions, and the initiator. The copolymerization procedure was the same as for polymerization. For means of purification the following combination of solvent/non-solvent was establish for each type of block copolymer: acetone/ethyl ether followed by acetone/petroleum ether for poly(NIPAAm)-*b*-poly(MMA); methanol/ethyl ether for poly(NIPAAm)-*b*-poly(HEMA), THF/ethyl ether followed by THF/methanol for poly(NIPAAm)-*b*-poly(St) and acetone/methanol for poly(NIPAAm)-*b*-poly(HA). As an example, the detailed synthesis of a poly(NIPAAm)-*b*-poly(MMA) block copolymer starting with a macro-CTA of poly(NIPAAm) is described next: poly(NIPAAm) (1.0 g, 0.03455 mmol) M_n = 30,890 g/mol, 4,4'-azobis(4-cyanopentanoic acid) (11.1 mg, 0.042 mmol) and (2.2 g, 22 mmol) of MMA were dissolved in 1,4 dioxane (40 mL) as solvent, and poured in a glass ampoule (50 mL) containing a magnetic stir bar. Oxygen was removed using 3 freeze-thaw evacuation cycles, and the ampoule was sealed with flame under vacuum. The ampoule containing copolymerization solution was submerged in an oil bath with magnetic stirring at 70 °C. The polymerization was stopped by rapid cooling at a given time. The copolymerization yield was obtained gravimetrically by adding a 5 fold excess of ethyl ether, filtering, dissolving the filtrate in acetone, precipitating again using petroleum ether, and filtering again. This procedure was repeated three times to remove residual monomer and homopolymers, it was followed by drying under vacuum to constant weight.

Characterization Methods

Nuclear Magnetic Resonanz Spectroscopy (NMR)

^{1}H NMR measurements were carried out on a Varian Mercury (200 MHz) NMR instrument using chloroform-*d* and methanol-d_4 as solvents and tetramethylsilane as reference. The main signals of NMR spectra for one example of each macro-CTA are described below. The multiplicity of signal is abbreviated as follows: s = singlet, d = doublet, t = triplet, br = prefix for broad signal.

Macro-CTA of poly(NIPAAm): GPC(THF) M_n = 21,500 g/mol, PDI = 1.11. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.45 (1H, brs, NH), 4.05 (1H, brs, CH), 2.06 (1H, brs, CH), 1.69 (2H, brm, CH_2), 1.12 (6H, brs, 2(CH_3)).

Macro-CTA of poly(MMA)**:** GPC(THF) M_n = 39,120 g/mol, PDI = 1.09. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.60 (3H, brs, OCH_3), 2.00 (2H, m, CH_2), 0.90 (3H, m, C-CH_3).

Macro-CTA of poly(HA): GPC(THF) M_n = 20,500, PDI = 1.22. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.0 (2H, m, CH_2), 2.34 (2H, m, CH_2), 1.88 (1H, brs, CH), 1.63 (2H, m, CH_2), 1.28 (6H, m, $(CH_2)_3$), 0.83 (3H, m, CH_3).

Macro-CTA of poly(HEMA): GPC(DMF) M_n=13,650 g/mol, PDI = 1.26. ^{1}H-NMR (CD_3OD, 200 MHz) δ 4.15 (2H, m, CH_2), 3.77 (2H, m, CH_2), 1.93 (2H, m, CH_2), 1.02 (3H, m, CH_3).

Macro-CTA of poly(St): GPC(THF) M_n = 69,970 g/mol, PDI = 1.10. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.37 (3H, m, (Arom. 3CH)), 6.44 (2H, m, (Arom. 2CH)), 1.99 (1H, m, CH), 1.29 (2H, m, CH_2).

Gel Permeation Chromatography (GPC) with multiangle laser light scattering detection (MALLS)

The number-average molecular weights (M_n) and polydispersity of the molecular weight distribution (M_w/M_n) of the polymers were determined with two sets of GPC equipment. (1) For all homopolymers (macro-CTA´s) and block copolymers (excepting polyHEMA and its block copolymers), a Varian 9002 chromatograph equipped with two mixed-bead columns in series (Phenogel 5 linear and Phenogel 10 linear) and two detectors: refractive index (Varian RI-4) and a tri-angle light scattering detector (MINI-DAWN, Wyatt Technology), was used. The measurements were performed in THF at 35 °C and at a flow rate of 0.5 mL/min. Reported dn/dc values poly(MMA) [25], poly(St) [25] and poly(NIPAAm) [26] were used for the molecular weight evaluations of poly(MMA), poly(St) and poly(NIPAAm) macro-CTA´s, respectively. The dn/dc of poly(HA) was determined using a differential refractometer IR OptiLab DSP (Wyatt Technology) at a wavelength $\lambda = 633$ nm, 40 °C, using six solutions with concentrations of 1.2 mg/mL to 3.5 mg/mL in THF, obtaining a value of 0.066 mL/g. (2) For poly(HEMA) macro CTA´s and its block copolymers, the second, gel permeation chromatography (GPC) equipment is a Waters 510 HPLC with three Asahipak columns (Shodex) in series (GF-1G7B, GF-510HQ, GF-310HQ) in a column oven (40 °C) and two detectors: refractive index (Optilab DSP, Wyatt Technology) and a multiangle light scattering detector (Dawn DSP, Wyatt Technology), was used. The measurements were performed in DMF at 40 °C as the mobile phase at a flow rate of 0.4 mL/min. Reported dn/dc values in DMF for poly(HEMA) [25] and poly(NIPAAm) [27] were used for the molecular weight evaluations of poly(HEMA) and poly(NIPAAm), respectively. For the molecular weight calculation of block copolymers the average dn/dc was calculated from the dn/dc values for the corresponding homopolymers in the blocks.

Differential scanning calorimetry

The glass transition temperature (T_g) of polymers were obtained on a TA Instrument modulated DSC 2920. Analyses were carried out under nitrogen. Samples of 5-10 mg were heated in aluminum pans at a heating rate of 5 K/min in the temperature range from –25 ºC to 220 ºC using a temperature modulation of ±0.5 K every 60 sec.

Acknowledgements

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