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The Use of the RAFT-Technique for the Preparation of Temperature/pH Sensitive Polymers in Different Architectures

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Summary: In this contribution we report the use of the RAFT-technique for the preparation of three types of responsive polymeric materials with a high potential of application in the biomedical field: 1.-Diblock copolymers with reversible self-assembly capacity as a function of pH based on *N,N′*-diethylaminoethyl methacrylate (DEAEM) and 2-methacryloyloxy benzoic acid (MAOB); 2.-Diblock copolymers with reversible self-assembly capacity as a function of temperature, based *N*-isopropylacrylamide (NIPAAm) and n-hexyl acrylate (HA); and 3.-Polymeric stars with random number of arms consisting either in NIPAAm-arms or copolymeric NIPAAm-arms and hydrophobic core.

Keywords: block copolymers; RAFT; sensitive polymers; star polymers

Introduction

Reversible addition-fragmentation chain transfer polymerization (RAFT) is a relatively new controlled/''living'' free radical polymerization technique discovered by researchers at CSIRO in Australia.[1] It is probably the most versatile of such techniques being applicable to the widest range of monomers under a large number of experimental conditions. Unlike atom transfer radical polymerization (ATRP) or Nitroxide mediated free radical polymerization (NMRP), RAFT operates on the principle of degenerative chain transfer. The RAFT process involves conventional free radical polymerization of a vinyl type monomer in the presence of a suitable chain transfer agent (CTA). The CTA typically possesses a thiocarbonylthio group (S=C-S) with substituents R and Z that define the reaction kinetics and the degree of structural control. A wide range of CTA's has been reported including mainly dithioesters, trithiocarbonates, dithiocarbamates, and xanthates (dithiocarbonates).[2] While the major features of the RAFT polymerization mechanism are widely understood and accepted, there is still considerable debate over some fine aspects currently under special investigation by a IUPAC task group.[3] RAFT polymerization has become a powerful technique for the synthesis of well-defined polymers or copolymers with both low polydispersities and functionalized end groups as well as polymers with complex architectures.[4]

In this publication we present results of the use of the RAFT technique to produce responsive polymeric materials in architectures of linear homopolymers, random copolymers, blockcopolymers and polymeric stars with crosslinked core.

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Experimental Part

Materials

The free radical initiator 4,4-azobis(4-cyanovaleric acid) (ACVA, Aldrich) was re-crystalized from methanol. *N*-isopropylacrylamide (NIPAAm, Aldrich) was recryztallized from hexane. *N,N′*-diethylaminoethylmethacrylate (DEAEM, Aldrich), n-hexylacrylate (HA, Aldrich), 2-hydroxyethylmethacrylate (HEMA) and ethyleneglycol dimethacrylate (EGDMA, Aldrich) were purified by passing through a column filled with inhibitor remover for hydroquinone and hydroquinone monomethylether (Aldrich). Divinylbenzene (DVB) was purified by passing through a column filled with inhibitor remover for tert-butylcatechol (Aldrich). All other chemicals and solvents used were provided by Aldrich or Fermont and used as received.

Synthesis

All polymerizations were performed in ampoules. In all cases, 4-cyanopentanoic acid dithiobenzoate (prepared according to[5]) and ACVA were used as the CTA and initiator, respectively. The monomers, CTA and initiator (Figure 1) were dissolved in ethanol (for DEAEM), 1,4-dioxane (for NIPAAm), or 1,4-dioxane/water mixture (4:1) (for HEMA). Solutions were degassed by three freeze-pump-thaw cycles. After degassing, the ampoules were flame-sealed under positive argon pressure and heated in an oil bath at 70 °C. The polymerizations were terminated by rapid cooling and freezing. The homopolymers obtained were purified by repeated precipitations in petroleum ether (for polyDEAEM) and in ether (for polyNIPAAm and also for polyHEMA); and were dried in vacuum. Random copolymers of NIPAAm were also prepared using the same methodology as for pure NIPAAm polymerization in 1,4-dioxane adding different amounts of the comonomer 5-methacryloyloxy-penthanoic acid (MD4), prepared according to[6], in the recipe. Well characterized homopolymers synthesized in the first step were used as

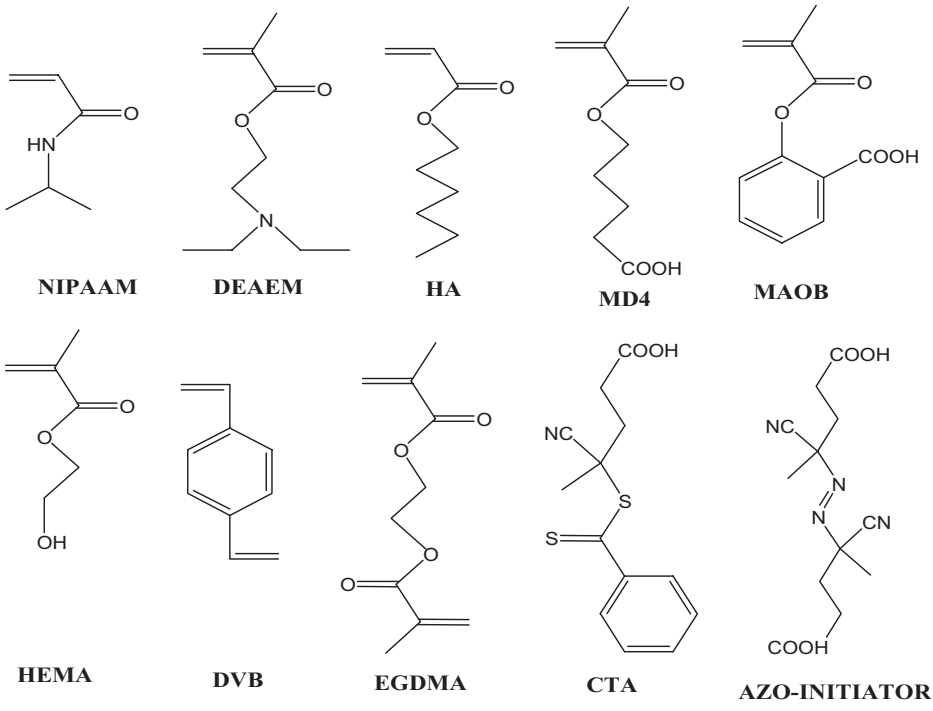

Figure 1.
Chemical structures of monomers, chain transfer agent (CTA) and azo-initiator used.

macro-CTA's for blockcopolymer and star synthesis. The macro-CTA (1 g) was dissolved in 40 mL of ethanol (for poly-DEAEM) or 1.5 g of macro-CTA in 30 mL of 1,4-dioxane (for polyNIPAAm) before adding the initiator and the second monomer in different amounts aiming different compositions. The monomers used to grow the second block were 2-methacryloyloxy benzoic acid (MAOB), prepared according to a published procedure,[7] and HA, respectively. In the case of polymeric stars, the second monomer was a crosslinker: ethylenglycol-dimethacrylate (EGDMA) or divinylbenzene (DVB) in the case of stars with polyNIPAAm arms, while mixtures of EGDMA with NIPAAm monomer were used for the preparation of stars with polyHEMA arms in different ratios. The purification of the products required several steps using different precipitants and solvents.

Characterization

The molecular weight's, polydispersity index (PDI) and radius of gyration (r_g) were determined by gel permeation chromatography (GPC) using a Varian 9002 chromatograph equipped with a refractive index (Varian RI-4) and a tri-angle light scattering detector (MINI-DAWN, Wyatt). Dynamic light scattering (DLS) measurements were carried out at room temperature (25 °C) using a Zeta-sizer "nano-ZS" from Malvern Instruments (ZEN3500) equipped with a green laser of 532 nm. The scattering intensity as a function of temperature was used also for measuring the lower critical solution temperature (LCST) of NIPAAm polymeric materials prepared. With the same equipment the Zeta-potential of polymer solutions was also measured. ^{1}H NMR spectra were obtained on a Varian, Mercury-200 MHz, or on a Varian Inova 500 MHz nuclear magnetic resonance instruments with $CDCl_3$, CD_3OD or DMSO-d_6 as solvents and tetramethylsilane (TMS) as internal reference.

Results and Discussion

Amphoteric Block Copolymers

Table 1 shows a selection of poly(DEAEM) polymers and their corresponding block-copolymers prepared by using the RAFT-technique. It is evident that the first block was prepared with very good polymer

Table 1.
Molecular characteristics of selected polymers and block copolymers prepared by RAFT.

Nr.	First Monomer	M:CTA:I	M_n(calc.)[a] [g/mol]	M_n[b] [g/mol]	M_w[b] [g/mol]	PDI	Mass Yield [%]
1	DEAEM	424:7.5:1	7,485	7,170	7,600	1.06	68.8
2	DEAEM	424:7.5:1	8,134	9,519	9,900	1.04	75.0
3	DEAEM	424:5.0:1	13,696	18,482	20,700	1.12	85.4
4	DEAEM	424:2.5:1	21,236	32,300	35,200	1.09	66.7
5	DEAEM	756:2.5:1	38,935	38,400	43,780	1.14	69.0

Nr.	First Monomer	M_w[b] [g/mol]	PDI	Second Monomer	$M_{w(total)}$[c] [g/mol]	Content 1st Mon[d]	Transition pH
1	DEAEM	9,900	1.04	MAOB	33,080	67%	8.0
2	DEAEM	17,100	1.01	MAOB	44,800	68%	8.0
3	DEAEM	35,700	1.06	MAOB	65,300	57%	8.0–9.0
4	DEAEM	43,780	1.14	MAOB	(54,000)[e]	–	6.0
5	DEAEM	43,780	1.14	MAOB	(64,000)[e]	81%	6.0

[a]Calculated according to $M_n(calc) = \{[M]/[CTA]\}\ M_o$ x yield + M_{CTA}.
[b]From GPC.
[c]From SLS.
[d]Calculated from ^{1}H-NMR.
[e]Estimated value.

characteristics and that the molecular weight can be fairly well predicted. Since the solubility characteristics of ampholytic block-copolymers depend on their composition and associate readily it was very difficult to measure adequately the molecular characteristics of the block copolymers.

Static light scattering (SLS) was used for some of them that were soluble in dimethylformamide to measure their molecular weight, however their polydispersities could not be determined by this method. These results proved the ''living'' character of the polymerization method used since the molecular weight increased as compared to that of the macro-CTA (rows 1–3 of second part in Table 1). The sensitive polymeric materials prepared show excellent characteristics in self-aggregation studies as a function of pH. Selected examples are shown in Figure 2. It is interesting to note that block copolymers self-aggregate into nano-sized particles corresponding roughly to micelle-like sizes (20–40 nm) at a given pH value. At higher pH values the ampholytic systems further aggregate into even larger structures that tend to precipitate with time. Lower pH-values resulted in molecularly dissolved block copolymers. Table 2 shows the results for the aggregation studies complemented with Z-potential measurements. From these results we can postulate that a rationale for understanding the observed behavior is that the polyDEAEM tertiary amine blocks are concentrated in the core of the aggregates at $pH > 7.4$ while the polyMAOB acid units are in the shell partially or fully ionized. Inversely, at $pH < 7$ the majority of the tertiary amine units are ionized yielding a molecular dissolution. At the pH-values between 7 and 10, the Z-potential shows negative or slightly positive (close to neutral) charge. This is an indication of intermolecular complexes formed during self-association. The self-association behavior of the block copolymer containing 81%molar of DEAEM units is very promising for drug delivery applications.

At physiological pH value of 7.4 this block copolymer forms micelle like structures of circa 30 nm diameter that are stable to changes in ionic strength as shown in Figure 2C while it dissociates by lowering the pH to 6 into 10 nm size macromolecules (see Figure 2B). If a drug can be loaded into that micelle-like structure formed, which is likely to be possible given the functional groups available, it can be transported at physiological conditions and may be delivered at sites with lower pH. Expected sites for this delivery are the gut and cancer tumors with lower pH than normal tissue.

Temperature Sensitive Random- and Block Copolymers

Table 3 shows in the first 6 rows a selection of polyNIPAAm polymers prepared for testing the RAFT polymerization conditions of this monomer using 4-cyanopentanoic acid dithiobenzoate as CTA. In all cases nearly monodisperse polymers with yields higher than 50% are obtained. The characteristic RAFT ''living'' behaviour is demonstrated in Figure 3. The expected linear increase of molecular weight with conversion is shown.

The GPC-traces show a shift to lower retention times (t_R) and also a slight band broadening with increasing polymerization time, although the polydispersity remains very low. Chain extension by using polyNIPAAm as macro chain transfer agent (macro-CTA) in RAFT block copolymerization is demonstrated in entries 7–10 in Table 3. The molecular weight increases while the polydispersity remains constant (entry 10) or increases slightly (entries 7–9). Entry 10 is a special case since the polymer used as macro-CTA is a random copolymer of NIPAAm with MD4. The preparation of random copolymers of NIPAAm with MD4 is shown in the entries 11-13 in Table 3. In all cases a molar ratio of monomers:CTA:initiator of 708:2.5:1 was used and the amount of MD4 in the monomer mixture was varied from 5 to 10% molar. The calculated composition by ^{1}H-NMR is very close to the monomer mixture in the feed. Furthermore, the obtained molecular

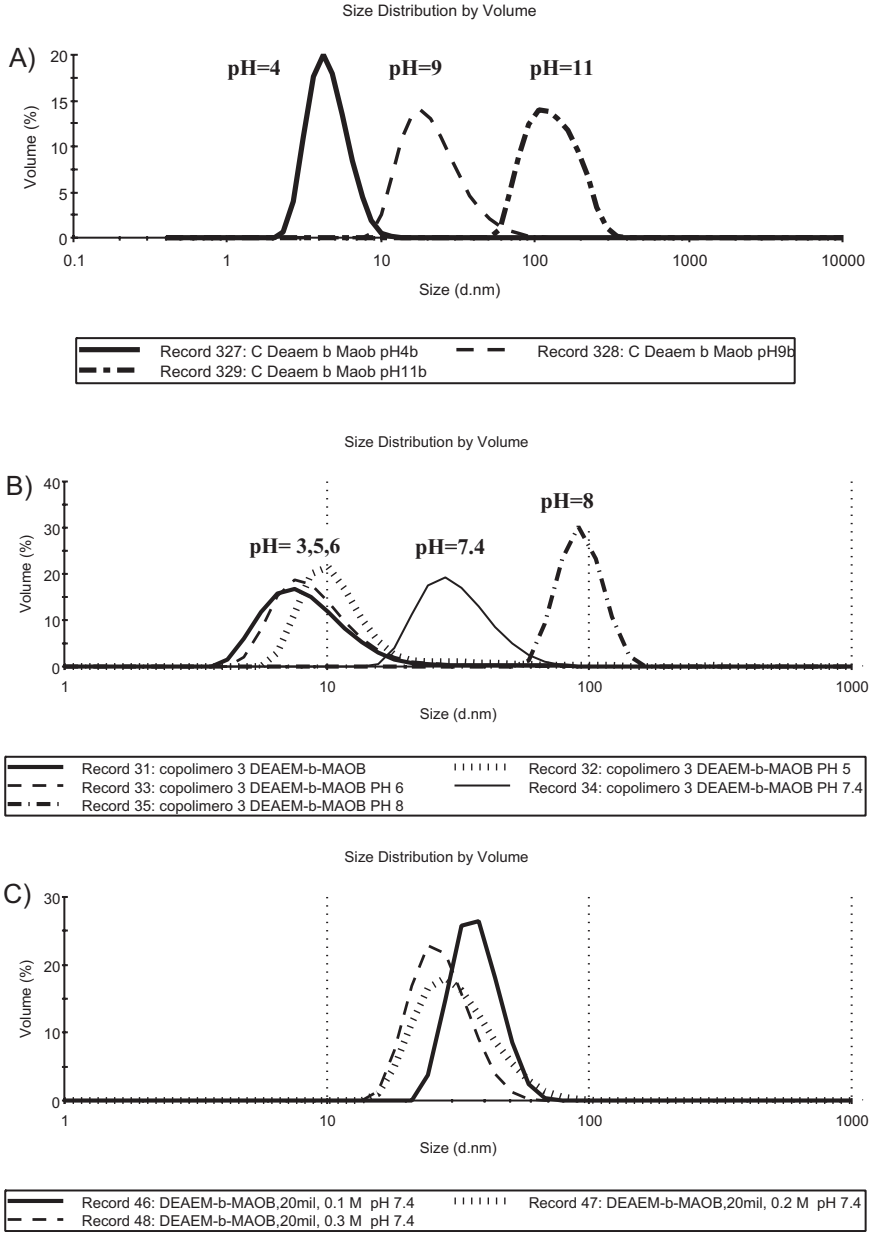

Figure 2.
Self aggregation behavior of selected poly(DEAEM-*b*-MAOB) blockcopolymers: A.-1 mg/mL solution of poly(DEAEM-*b*-MAOB) $M_w = 33{,}080$ g/mol, 67%DEAEM at different pH-values. B.-1 mg/mL solution of poly(DEAEM-*b*-MAOB) $M_w = 64{,}000$ g/mol, 81%DEAEM at different pH-values. C.-1 mg/mL solution in Buffer (pH 7.4) of poly(DEAEM-*b*-MAOB) $M_w = 64{,}000$ g/mol, 81%DEAEM at different salt concentration.

weights for copolymers containing 5 and 7% molar of MD4 are similar to the calculated value for pure polyNIPAAm (30,072 g/mol, entry 2 in Table 3) as expected for random copolymerization. The last column in Table 3 show results of the LCST determination by DLS. Two examples are shown also in Figure 4. It is

Table 2.
Selfaggregation studies on poli(DEAEM-*b*-MAOB) by changing pH (C = 1 mg/mL).

Diblock-copolymer	Molecularly dissolved	Micelle-like aggregates	Z-potential
Poly(DEAEM-*b*-MAOB)	pH = 3–8	pH = 9	pH = 6 (18.6mV)
26.1 Kg/mol	D_H = 4.6–6.6 nm	D_H = 23.5 nm	pH = 9 (−29.7 mV)
67% DEAEM			
Poly(DEAEM-*b*-MAOB)	pH = 3–7	pH = 9–11	pH = 3 (28.7 mV)
44.8 Kg/mol	D_H = 5.7–6.6 nm	D_H = 52–89 nm	pH = 10 (−29 mV)
68% DEAEM			
Poly(DEAEM-*b*-MAOB)	pH = 3,7	pH = 10	pH = 8 (−3.3 mV)
65.3 Kg/mol	D_H = 8.2–9.5 nm	D_H = 18.4 nm (78%)	pH = 9 (−26.1 mV)
57% DEAEM			
Poly(DEAEM-*b*-MAOB)	pH = 5–6	pH = 7.4	pH = 7.4 (10.5 mV)
54 Kg/mol	D_H = 9.5 nm	D_H = 45.8 nm	pH = 8 (0.2 mV)
Poly(DEAEM-*b*-MAOB)	pH = 3–6	pH = 7.4	pH = 6 (16.9 mV)
64 Kg/mol	D_H = 9.9–13.3 nm	D_H = 32.1 nm	pH = 7.4 (12.3 mV)
81% DEAEM			pH = 8 (−7.8 mV)

known that the LCST of polyNIPAAm in water is between 32 and 34 °C[8]; and it is expected that a NIPAAm block copolymer may show the same LCST than polyNIPAAm if there are no specific interactions between the two blocks. For two NIPAAm-HA block copolymers prepared, the measured LCST is similar to polyNIPAAm, i.e. 32 °C. The DLS results (Figure 4A) reflects that the average size increases above the LCST, due to aggregation produced by hydrophobic interactions, while the intensity of scattered light (turbidity) increases first and then drops due to aggregation followed by precipitation since the solution is not stirred during the measurement. Since the random copolymers of NIPAAm contain a monomer with a functional acid group (MD4, Figure 1) the determination of the LCST was performed in a buffer solution of pH 7.4. We have shown previously that the LCST of polyNIPAAm was modified widely by conventional free-radical copolymerization of NIPAAm with

Table 3.
Molecular characteristics of selected homo-, random- and block-copolymers prepared by RAFT.

Nr.	First Monomer	M:CTA:I[a]	Time [h]	M_n(calc.)[b] [g/mol]	M_n[c] [g/mol]	M_w[c] [g/mol]	PDI	Mass Yield [%]
1	NIPAAm	354:2.5:1	48	13,272	19,800	21,300	1.08	81.2
2	NIPAAm	708:2.5:1	48	30,072	37,000	39,300	1.06	93.1
3	NIPAAm	1416:2.5:1	48	57,498	57,000	71,400	1.25	89.4
4	NIPAAm	1415:5.0:1[d]	14	18,853	23,100	24,500	1.06	58.0
5	NIPAAm	1415:5.0:1[d]	15	21,736	25,100	26,900	1.07	67.0
6	NIPAAm	1415:5.0:1[d]	16	23,337	28,600	31,400	1.10	72.0

Nr.	NIPAAm	M_n[c] [g/mol]	PDI	Second Monomer	$M_{n(total)}$[c] [g/mol]	PDI	Content 1st Mon[e]	LCST in H_2O
7	NIPAAm	18,000	1.13	HA	24,500	1.33	67.5%	—
8	NIPAAm	19,000	1.04	HA	26,000	1.13	—	32 °C
9	NIPAAm	32,000	1.20	HA	39,300	1.25	—	32 °C
10	NIPAAm + 5% MD4	36,000	1.10	HA	50,000	1.10	88.3% + 4.3%	37 °C[f]
11	NIPAAm + 5% MD4	31,800	1.23	—	—	—	95.4% + 4.6%	40 °C[f]
12	NIPAAm + 7% MD4	30,700	1.25	—	—	—	93.3% + 6.7%	>45 °C[f]
13	NIPAAm + 10% MD4	25,000	1.28	—	—	—	93.3% + 10.5%	—

[a] $[M]_o$ = 0.70 M.
[b] Calculated according to $M_n(calc) = \{[M]/[CTA]\}\ M_o$ x yield + M_{CTA}.
[c] From GPC.
[d] $[M]_o$ = 1.41 M.
[e] Calculated from ^{1}H-NMR.
[f] in Buffer of pH 7.4.

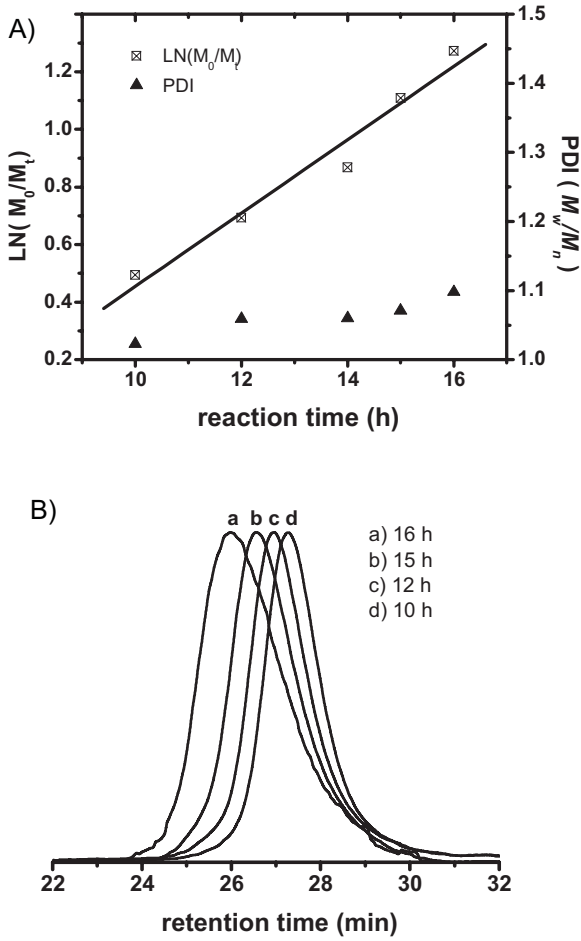

Figure 3.
Kinetics of RAFT polymerization of NIPAAm using 4-cyanopentanoic acid dithiobenzoate as CTA in *p*-Dioxane at 70 °C: A.- Evolution of molecular weight (M_n) and polydispersity (PDI) with conversion. B.-GPC traces from refractive index detector at different polymerization times.

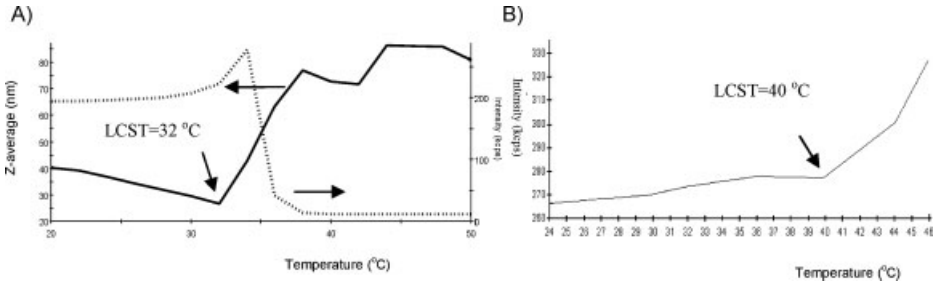

Figure 4.
Determination of the lower critical solution temperature (LCST) of NIPAAm copolymers by DLS: A.- Poly(NIPAAm-*b*-HA) of 26 Kg/mol in water. B.- Poly(NIPAAm-co-MD4) of 31.8 Kg/mol in buffer of pH 7.4

MD4 as a function of comonomer content and pH of the milieu.[6] In this study, random copolymers prepared by RAFT showed that the LCST increases with increasing MD4 content and a copolymer containing 4.6% of MD4 shows a LCST of 40 °C (Figure 4B). The corresponding block copolymer prepared using the random NIPAAm-MD4 copolymer as macro-CTA (entry 10 in Table 3) shows a LCST of 37 °C, which is a value very promising for thermoresponsive drug delivery applications.

Polymeric Stars with Temperature Sensitive Arms

The preparation of polymeric stars with crosslinked core by RAFT is a feasible alternative if a polymeric macro-CTA is chain extended with a DVB or EGDMA crosslinker. However, the macro-CTA to crosslinker ratio must be carefully tested to avoid a macro-gel formation. The star formation strategy by RAFT was adapted from the pioneering work by Zheng and Pan[9] and is outlined in Figure 5. Table 4 shows a selection of polymeric stars with polyNIPAAm arms and polyEGDMA or polyDVB core prepared by using the RAFT-technique prepared under optimized ratio of crosslinker to macro-CTA. It is worth to mention that a higher crosslinker to macro-CTA ratio as the described in Table 5, under the synthetic conditions used for each case, resulted in macroscopic gel formation in the reaction vessel. The reported molecular weights and polydispersities calculated by GPC were obtained using a dn/dc value reported for polyNIPAAm linear chains.[6] In the case of the polymeric star products using EGDMA as crosslinker the obtained molecular weights are only slightly higher than those of the macro-CTA's used, however the PDI increased. The GPC traces showed monomodal peaks and DLS measurements demonstrated increases in diameters (D_H) only compatible with the formation of star structures (Table 5). In the case of the polymeric star products prepared using

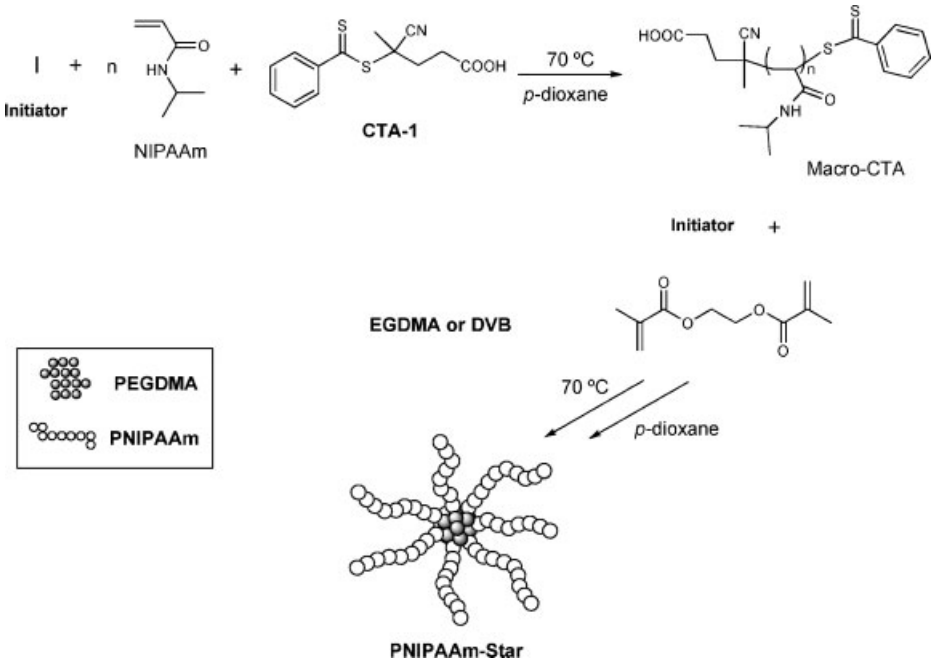

Figure 5.
Synthetic scheme for the preparation of polymeric stars with polyNIPAAm arms and crosslinked core by use of the RAFT-methodology.

Table 4.
Molecular characteristics of selected polymeric stars with polyNIPAAm arms and crosslinked core prepared by RAFT.

Nr.	Macro-CTA	Crosslinker	Crosslinker: macro-CTA	$M_{n(total)}$[a] g/mol	PDI[a]	Content NIPAAm[b]	LCST in H_2O
1	PolyNIPAAm 37 Kg/mol, PDI = 1.06	EGDMA	20:1	42,000	1.42	94.2%	32 °C
2	PolyNIPAAm 19.8 Kg/mol, PDI = 1.08	EGDMA	10:1	21,300	1.44	93.3%	34 °C
3	PolyNIPAAm 25.9 Kg/mol PDI = 1.09	DVB	30:1	136,800	1.94	88.9%	32 °C[d]
4	Poly(NIPAAm-co-MD4) 26.7 Kg/mol, PDI = 1.12	DVB	35:1	108,100	2.00	89.1% (6.8%)[c]	40 °C[d]

[a]From GPC.
[b]Calculated from ^{1}H-NMR.
MD4 Content.
[d]In Buffer of pH 7.4.

DVB as crosslinker the synthesis results were quite different. GPC traces of the polymeric products evidenced that the macro-CTA was not fully incorporated into the macromolecular star. Even if the content on star product was increased by varying preparation conditions, the reaction was never complete. A fractionation method was developed to purify the star products with crosslinked polyDVB core. A mixture of acetone/ether with a volume ratio equal to 0.5 was used to obtain two fractions, one star-rich and one arm rich fraction. The GPC results in Table 4 correspond to the star-rich fraction which has a relatively high molecular weight and large polydispersity. Despite the large polydispersity, the LCST behavior of poly-NIPAAm arms governed their overall temperature sensitivity.

It is noteworthy that a polymeric star product with poly(NIPAAm-co-MD4) arms and polyDVB core showed a LCST of 40 °C under physiological conditions which makes this star product an excellent candidate for testing in drug delivery applications. One step towards the potential application in drug delivery for the polymeric stars prepared is their aqueous behavior. Table 5 compares the hydrodynamic diameters (D_H) in THF, a good solvent for the polymeric stars arms and core and in water, which is only a good solvent for the star arms at room temperature. The diameter in water is between 30 to 40% higher than in THF for the polymeric arms; for the stars with crosslinked EGDMA core the size increases from 40 to 80% in water; while in the case of the products with crosslinked DVB core, this

Table 5.
Size analysis by DLS at room temperature for macro-CTA's (arms) and polymeric star products with crosslinked core prepared by RAFT (C = 1 mg/mL).

Nr.	Polymer	D_H in THF (nm)	D_H in Water (nm)
1	PolyNIPAAm "arm" (37,000 g/mol)	6.5	8.4
2	NIPAAm Star with EGDMA ratio 20:1 (from 37,000 g/mol polyNIPAAm)	140	193.6
3	PolyNIPAAm "arm" (12,000 g/mol)	3.0	3.9
4	NIPAAm Star with EGDMA ratio 10:1 (from 19,800 g/mol polyNIPAAm)	32.2	58.9
5	PolyNIPAAm "arm" (25,900 g/mol)	5.5	7.9*
6	NIPAAm Star with DVB ratio 30:1 (from 25,900 g/mol polyNIPAAm)	17.4	91.9*
7	Poly(NIPAAm-co-MD4) "arm" (26,700 g/mol)	6.4	7.3*
8	NIPAAm/MD4 Star with DVB ratio 35:1 (from 26,700 g/mol polyNIPAAm-MD4)	16.6	66.8*

*In Buffer of pH 7.4.

Table 6.
Reactions for star preparation consisting of polyHEMA arms and poly(NIPAAm-co-EGDMA) core with random number of arms.

EGDMA:PolyHEMA molar ratio	EGDMA content in NIPAAm/EGDMA mixture	t(h)	D_H Macro-CTA (nm)		D_H Star (nm)		Yield (%)
			DMF 25 °C	Water 10 °C	DMF 25 °C	Water 10 °C	
2.5:1[a]	10 mol%	24	4.4	3.2	13.5	8.2	54
5:1[a]	5 mol%	24	4.4	3.2	gel	gel	—
5:1[b]	5 mol%	24	7.4	4.5	25.9	8.6	70
10:1[b]	10 mol%	24	7.4	4.5	gel	gel	—
0:1[a]	0 mol%	24	4.4	3.2	6.2	—	63

[a]Poly(HEMA) macro-CTA of 7,000 g/mol.
[b]Poly(HEMA) macro-CTA of 24,000 g/mol.

increase is between 400 to 500% strongly suggesting star aggregation.

Polymeric Stars with Temperature Sensitive Core

The question arised if we could impart the temperature sensitive properties not only to the arms of the star but to the core. In order to test this possibility we prepare macro CTA's consisting of the hydrophillic not temperature sensitive biocompatible polymer: poly(HEMA) using the RAFT technique. For getting a star including NIPAAm units in the core, we modified the methodology described in Figure 5. A copolymerization of NIPAAm with EGDMA in the presence of poly(HEMA) arms was carried out to form the core. In doing so, the molar relations: NIPAAm:EGDMA and EGDMA/polyHEMA were adjusted. Results are reported in Table 6. Two different poly(HEMA) macro-CTA's were used for the star preparation with $M_n = 7{,}000$ g/mol and $M_n = 24{,}000$ g/mol. The poly(HEMA) with lower molar mass yielded a soluble star when a molar ratio EGDMA:Poly(HEMA) of 2.5 to 1 was used. Such material showed a three fold increase of D_H as compared with the initial macro-CTA both in DMF and in water, as measured by DLS (Table 6). Quite similar results were obtained with the poly(HEMA) having a $M_n = 24{,}000$ g/mol using a molar ratio of 5 to 1 (EGDMA:-Poly(HEMA)). The resulted material showed also a substantial increase of D_H as compared with the macro-CTA in DMF as well as in water. A blank probe of star formation under the same conditions but without any EGDMA resulted in a block-copolymer that shows an increase of D_H of only 60% in DMF. It is interesting to note that the polymeric star products formed expand better in DMF than in water. In fact the star products were not soluble in water at room temperature suggesting that the LCST of polyNIPAAm is lowered to values below room temperature as effect of the interactions with polyHEMA units, possibly through hydrogen bonding. For this reason, the size analysis in water was performed at 10 °C.

Conclusions

The RAFT technique allowed for preparation of ampholytic diblock copolymers using polyDEAEM as macro CTA and of temperature sensitive diblock copolymers using polyNIPAAm as macro CTA. The LCST of polyNIPAAm was adjusted by RAFT copolymerization with MD4. Self-aggregation conditions were determined for the obtention of nano-sized supramolecular structures with potential for drug delivery applications. RAFT crosslinking polymerization allowed the preparation of polymeric stars with polyNIPAAm or polyHEMA arms and crosslinked core. Some of these star products are promising also for drug delivery applications.

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