

The use of the RAFT-technique for the preparation of temperature/pH sensitive polymers in different architectures

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1. Abstract

Reversible addition-fragmentation chain transfer (RAFT) polymerization is a polymerization technique that has emerged in the last ten years as may be the most versatile and simple method for the preparation of polymers using a wide range of monomers and controlling their size, architecture and functionality. 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.

2. Introduction

Reversible addition-fragmentation chain transfer polymerization (RAFT) is a relatively new, so called, 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 impact 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] Despite the fact that the details on

the RAFT mechanism are 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]

3. Experimental

3.1 Synthesis

All polymerizations were performed in ampoules. In all cases, 4-cyanopentanoic acid dithiobenzoate (prepared according to [5]) and 4,4-azobis(4-cyanopentanoic acid) were used as the CTA and initiator, respectively. The monomers, CTA and initiator (Figure 1) were dissolved in ethanol (DEAEM) or 1,4-dioxane (NIPAAm). 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 and 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 acid comonomer 5-methacryloyloxy-pentanoic acid (MD4 [6]) in the recipe. Well characterized homopolymers synthesized in the first step were used as macro-CTA's for blockcopolymer and star synthesis. The macro-CTA was dissolved in ethanol or 1,4-dioxane (20 ml) before adding the initiator and the second monomer in different amounts aiming different compositions (MAOB/MAPB [7] and HA).

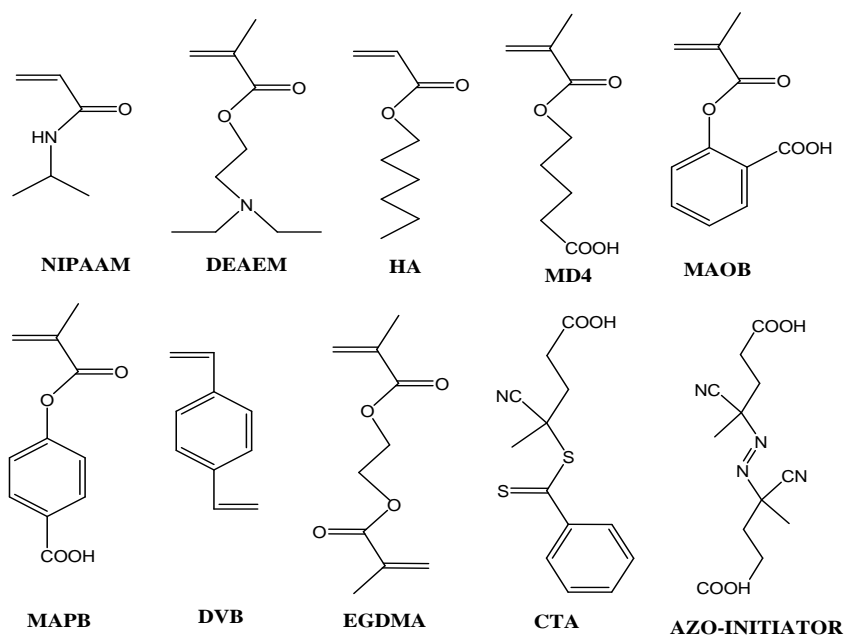


Figure 1. Chemical structures of monomers, chain transfer agent (CTA) and initiator.

In the case of polymeric stars, the second monomer was a crosslinker: ethyleneglycol-dimethacrylate (EGDMA) or divinylbenzene (DVB). The purification of the products required several steps using different precipitants and solvents.

3.2 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. ^1H 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.

4. Results and Discussion.

Table 1 shows a selection of block-copolymers and polymeric stars prepared by using the RAFT-technique. It is evident that the first block (arm of star) was prepared with very good polymer characteristics while the RAFT control is partially lost in the second step. Nevertheless the sensitive polymeric materials prepared show excellent characteristics in self-aggregation studies as a function of pH (rows 1-3 in Table 1) or as a function of temperature (rows 4-10 in Table 1).

5. Conclusions

Using the RAFT technique it was possible to prepare ampholytic diblock copolymers using polyDEAEM as macro CTA, temperature sensitive diblock copolymers and polymeric stars 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.

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

Nr.	First Monomer	M _w ^a	PDI	Second Monomer	M _{w(total)} ^b	PDI	Content 1 st Mon ^c	Transition pH
1	DEAEM	9,900	1.04	MAOB	33,080	-	67%	8.0
2	DEAEM	35,700	1.06	MAOB	65,300	-	57%	8.0-9.0
3	DEAEM	43,780	1.14	MAOB	64,000	-	81%	6.0
	First Monomer	M _n ^a	PDI	Second Monomer	M _{n(total)} ^a	PDI	Content 1 st Mon ^c	LCST (H ₂ O)
4	NIPAAm	18,000	1.13	HA	24,500	1.33	67.5%	32 °C
5	NIPAAm	32,000	1.20	HA	39,300	1.25	--	32 °C
6	NIPAAm + MD4	36,000	1.10	HA	50,000	1.10	88.3%+ 4.3%	37 °C*
7	NIPAAm + MD4	31,800	1.23	---	---	---	95.4%+ 4.6%	40 °C*
	First Monomer	M _n ^a	PDI	Second Monomer	M _{n(total)} ^a	PDI	Content 1 st Mon ^c	LCST (H ₂ O)
8	NIPAAm	37,000	1.062	EGDMA	72,000	1.026	--	32 °C
9	NIPAAm	25,930	1.093	DVB	136,800	1.947	88.9%	32 °C
10	NIPAAm + MD4	26,720	1.125	DVB	108,100	2.005	89.1% + 6.8%	40 °C*

Molecular weights in g mol⁻¹ ^a From GPC. ^b From SLS. ^c Calculated from ¹H-NMR. * In Buffer pH 7.4

Acknowledgements

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