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Synthesis and self-assembly of carbamoylmethylphosphonate acrylamide-based diblock copolymers: new valuable thermosensitive materials

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We report the synthesis by RAFT polymerization of well-defined diblock copolymers bearing carbamoylmethylphosphonate moieties which proved to sorb gadolinium. These poly(diethyl-6-(acrylamido)hexylcarbamoylmethylphosphonate-*b*-acrylic acid) (P(CPAAm6C-*b*-AA)) copolymers were able to self-assemble as a function of the temperature, above their cloud point value.

Phosphorus containing compounds have gained considerable attention in recent years as phosphorus moieties enabled a wide range of interesting properties.¹⁻³ In particular, phosphonated-based materials were already successfully used for their metal sorption abilities,⁴⁻⁶ making them notably suitable for applications in the biomedical field^{7, 8} or for water treatment.⁹⁻¹¹ For this latter purpose, we recently reported an innovative approach with the use of valuable copolymers combining both thermosensitive and chelating properties. These materials allowed combining advantages of water soluble polymeric sorbents and insoluble polymeric resins as both complexation and filtration steps below and above the CP, respectively, were easy to perform. Synthesis of thermosensitive copolymers bearing phosphonic acid groups, namely the poly(*N-n*-propylacrylamide-*stat*-2-(methacryloyl oxy)methylphosphonic acid) (P(NnPAAm-*stat*-hMAPC1)), was achieved by free radical polymerization. Resulting statistical copolymers still efficiently sorbed di- or trivalent cations (Ni²⁺, Ca²⁺, Cd²⁺, Al³⁺) just above the cloud point (CP), thus leading to the development of an original sorption-separation process targeting the removal and the recovery of metal elements from industrial wastewater.^{10, 12} More recently, the synthesis of homopolymers combining both chelating groups and thermosensitivity from a single original monomer, the diethyl-6-(acrylamido)hexylcarbamoylmethylphosphonate (CPAAm6C), was described.¹³ Carbamoylmethylphosphonate moiety was of

interest as it was proved that this functional group efficiently sorbed lanthanides,¹⁴ especially gadolinium (Gd).¹³ Polymerization of CPAAm6C was achieved by free radical process. As a consequence, it was impossible to control the molecular weight and build complex architectures for the produced polymers.

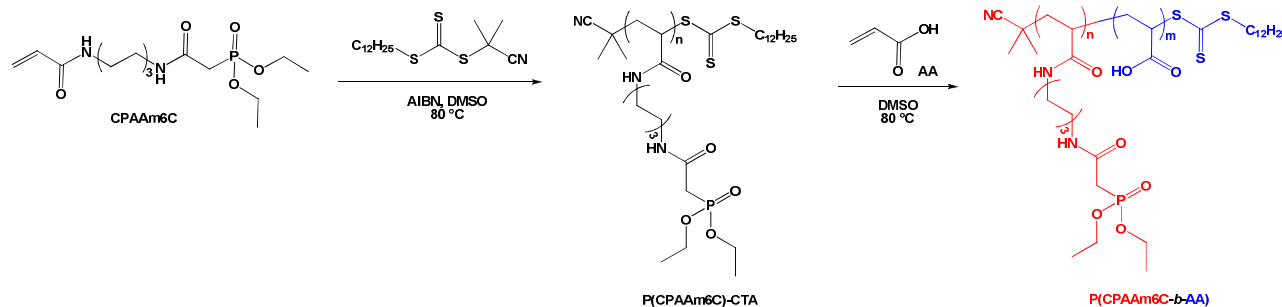
Side to free radical process, living radical polymerization^{15, 16} (LRP) of functional monomers enabling the design of very specific materials with controlled architecture, predictable molecular weight and possible chain-end functionalization¹⁷⁻²⁰ was successfully performed. Among the different controlled radical polymerization strategies, Reversible Addition-Fragmentation Transfer (RAFT) polymerization^{21, 22} was successfully used for the controlled polymerization of a limited number of phosphorus-containing monomers such as vinylphosphonic acid,²³ dimethyl-*p*-vinylbenzyl phosphonate,²⁴ or 3-[2(acryloyloxy)ethoxy-3-oxopropyl] (phenyl) phosphinic acid.²⁵ RAFT polymerization of phosphonated-based acrylamide and methacrylate was also carried out allowing the synthesis of well-defined poly(diethyl-2-(acrylamido)ethylphosphonate) and poly(dimethyl(methacryloyloxy)methylphosphonate), respectively.^{26, 27}

In the present contribution, we report the RAFT polymerization of another phosphorus-based acrylamide which then permitted the original one-pot synthesis of well-defined thermosensitive poly(diethyl-6-(acrylamido)hexylcarbamoylmethylphosphonate-*b*-acrylic acid) (P(CPAAm6C-*b*-AA)) diblock copolymers. Different molecular weights were targeted for each block. These water soluble copolymers self-assembled above the cloud point when the thermoresponsive complexing P(CPAAm6C) block became insoluble, leading to amphiphilic copolymers. Such materials could be useful due to both thermosensitivity property^{28, 29} and ability to complex gadolinium (Gd(III)).¹³

We first determined the experimental conditions allowing the control of the RAFT polymerization of the diethyl-6-(acrylamido)hexylcarbamoyl methylphosphonate (CPAAm6C)

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Scheme 1. Reactional pathway of the one-pot synthesis of poly(diethyl-6-(acrylamido)hexylcarbamoylmethylphosphonate-*b*-acrylic acid) (P(CPAAm6C-*b*-AA)) diblock copolymers.

Table 1. Characteristics of the different (co)polymers prepared by RAFT polymerization using 2-cyano-2-propyl dodecyl trithiocarbonate as chain transfer agent (CTA).

Type	Polymer name	$M_{n,theo}$ ($g \cdot mol^{-1}$) ^a	CPAAm6C conv. (%) ^b	AA conv. (%) ^b	$M_{n,exp}^{NMR}$ ($g \cdot mol^{-1}$) ^b	$M_{n,exp}^{SEC}$ ($g \cdot mol^{-1}$) ^c	\bar{D} ^c	CP ^d (°C)
<i>Homo</i>	P(CPAAm6C)-CTA_1	2100	84	-	1950	3800	1.19	35
<i>poly</i>	P(CPAAm6C)-CTA_2	7000	80	-	6700	5900	1.25	40.1
<i>mers</i>	P(CPAAm6C)-CTA_3	12800	73	-	11700	8100	1.28	40.9
<i>Copo</i> <i>lymers</i>	P(CPAAm6C- <i>b</i> -AA)_1	2100-2050	84	82	1950-2050	-	-	39.6
	P(CPAAm6C- <i>b</i> -AA)_2	12800-1900	73	75	11700-1800	-	-	36.2
	P(CPAAm6C- <i>b</i> -AA)_3	7000-2000	80	80	6700-1950	-	-	46.2
	P(CPAAm6C- <i>b</i> -AA)_4	7400-16600	85	95	6600-14300	-	-	> 50

^a Determined for each block in the case of the copolymers, $M_{n,theo} = ([M]_0/[CTA] \times M_w \text{ of the monomer} \times \text{conv})/100$; ^b determined for each block by ¹H NMR in DMSO-*d*₆; ^c Estimated by PMMA-calibrated SEC at 60 °C in DMF (+ LiCl 0.1% weight); ^d determined by UV-Visible spectroscopy at a 500 nm wavelength with a polymer concentration equal to 5 g.L⁻¹, with a 0.1 °C per minute temperature ramp. For copolymers, pH was adjusted at 8 using small quantity of a 0.1N sodium hydroxide solution.

monomer. The reaction was carried out at 80 °C in DMSO using 2-cyano-2-propyl dodecyl trithiocarbonate and AIBN as chain transfer agent (CTA) and initiator, respectively (Scheme 1). The [CTA]/[AIBN] ratio was equal to 2. The theoretical molecular weight ranged from 2000 to 14000 g.mol⁻¹. We can notice that a short induction period equal to 15 minutes was observed in all cases. Conversion was determined by ¹H NMR in deuterated DMSO comparing the integration of the acrylic protons between 5.5 and 6.3 ppm of the CPAAm6C monomer with the one of the methylene of the ethoxy group at 4 ppm in both monomer and polymer. Results obtained are gathered in Table 1. Conversion varied from 73 to 83 % as a function of the theoretical molecular weight targeted. The number-average molecular weights were determined by size exclusion chromatography (SEC) at 60 °C using DMF as eluent (+ LiCl 0.1 %wt) and PMMA standards. Their evolution *versus* conversion was linear (see ESI, Fig. S1 left), indicating that polymer chains grew simultaneously. Additionally, monomodal SEC traces were obtained (see ESI, Fig. S1 right) and dispersities were quite narrow as \bar{D} was comprised between 1.19 and 1.25. At the end of the polymerization reaction, DMSO was removed by cryodistillation and resulting P(CPAAm6C)-CTA were purified by dialysis against water allowing the elimination of low quantity of residual monomer. The molecular weight of the purified polymers was also determined by ¹H NMR by comparison of the integrations of the methyl of the CTA and the methylene of the ethoxy group of the phosphonated moiety, at 0.86 and around 4 ppm, respectively. The M_n found

by ¹H NMR were close from theoretical ones, and were in general higher than those calculated by size exclusion chromatography using PMMA standards. To conclude, RAFT polymerization of CPAAm6C was controlled for molecular weights ranging from 2000 to 14000 g.mol⁻¹. We can also mention that it was impossible to prepare well-defined P(CPAAm6C) with higher molecular weight due to the relatively low reactivity of the P(CPAAm6C) monomer. ¹H NMR proved the presence of the trithiocarbonate function at the polymer chain end, notably with the signal at 0.86 ppm for the methyl group of the dodecyl segment of the CTA, thus allowing the synthesis of block copolymers.

The synthesis of diblock copolymers with P(CPAAm6C) and poly(acrylic acid) (P(AA)) segments was achieved. P(CPAAm6C-*b*-AA) diblock copolymers were prepared in an one-step synthesis as we noticed that the conversion of the CPAAm6C monomer did not increase after 240 minutes of polymerization, this reaction parameter being perfectly reproducible. So, the same experimental procedure was used for the synthesis of the P(CPAAm6C) block also leading to the comparable conversion than for the synthesis of the homopolymers. Then, after 240 minutes, an appropriate quantity of acrylic acid was added according to the P(AA) molecular weight targeted. We checked by ¹H NMR in DMSO-*d*₆ that the carbamoylmethylphosphonated acrylamide monomer did not react anymore after the addition of AA. Integrations at 4 and 5.5 ppm corresponding to the methylene

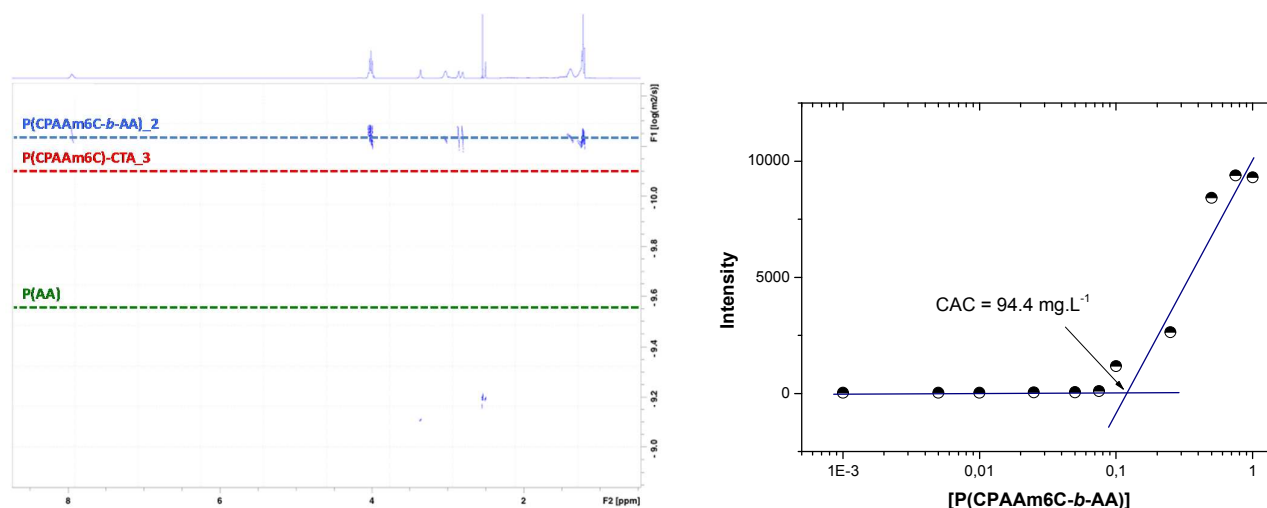


Fig. 1 left: 2D DOSY NMR in DMSO- d_6 at room temperature of the poly(acrylic acid) (P(AA)), the P(CPAAm6C)-CTA_3 homopolymer, and the P(CPAAm6C-*b*-AA)_2 copolymer. F1 represents the logarithm of the diffusion coefficient; right: Determination of the critical aggregation concentration (CAC) of P(CPAAm6C-*b*-AA)_3 by static light scattering.

of the ethoxy group and to the acrylic system, respectively, were compared (see ESI, Fig. S2). After acrylic acid addition, the relative intensities corresponding to the residual CPAAm6C monomer showed no variation. Only the relative intensities of acrylic acid protons decreased. This was explained by the very low reactivity of CPAAm6C in comparison with the one of acrylic acid. Conversion of the AA monomer was also determined by ^1H NMR comparing the acrylic protons of the AA to the signal at 4 ppm of the CPAAm6C used as internal probe. Molecular weight was measured using the experimental conversion as it was not possible to determine it by SEC as the P(CPAAm6C-*b*-AA) were not soluble in common solvents such as DMF. Experimental M_n were close from theoretical ones for all P(CPAAm6C-*b*-AA) diblock copolymers synthesized (Table 1). The latter were purified by cryodistillation to remove acrylic acid traces and DMSO. Then a dialysis was carried out against water to eliminate residual CPAAm6C monomer. Finally, in order to confirm the formation of diblock copolymer, the product obtained was analyzed by 2D DOSY NMR³⁰⁻³² and was compared with P(CPAAm6C)-CTA and P(AA) homopolymers (Fig. 1 left). The diffusion coefficient values of P(CPAAm6C)-CTA_3 and P(AA)₂₆ homopolymers were 7.94×10^{-11} and $2.82 \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$, respectively. In the case of the P(CPAAm6C-*b*-AA)_2 diblock copolymer, only one diffusion coefficient value was obtained ($5.75 \times 10^{-11} \text{ m}^2 \cdot \text{s}^{-1}$), indicating that both blocks belonged to the same macromolecule thus proving the formation of the diblock copolymers. Additionally, 2D DOSY NMR also demonstrated that acrylic acid did not homopolymerize as there was no signal at $2.82 \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$ for the copolymer. Same results were obtained for other materials. So we managed to prepare well-defined P(CPAAm6C-*b*-AA) diblock copolymers varying and controlling the length of either the P(CPAAm6C) or P(AA) block.

Thermosensitivity properties of all polymers were then determined (Table 1). For this purpose, solutions at a concentration equal to $5 \text{ g} \cdot \text{L}^{-1}$ were prepared in milli Q water

as turbidity appeared in all cases for a concentration higher than $1 \text{ g} \cdot \text{L}^{-1}$. In the case of the copolymers, pH was adjusted at 8 using a very small quantity of a 0.1N sodium hydroxide aqueous solution, which favored the solubility of the P(AA) block. The addition of NaOH did not have a noticeable influence on the cloud point values. It is important to specify that the cloud point of P(CPAAm6C) prepared by free radical polymerization was $42.5 \text{ }^\circ\text{C}$ ($M_n = 31000 \text{ g} \cdot \text{mol}^{-1}$ determined by SEC in DMF + LiCl 0.1 %wt).¹³ Comparable CP values were found for P(CPAAm6C)-CTA synthesized by RAFT polymerization except for the shortest polymer ($M_n = 3800 \text{ g} \cdot \text{mol}^{-1}$ determined by SEC in DMF + LiCl 0.1 %wt) with a CP equal to $35 \text{ }^\circ\text{C}$. This difference was attributed to the lauryl hydrophobic polymer chain end which had a non negligible influence in the case of this very low molecular weight polymer, lowering the CP value. Concerning the copolymers, CP logically increased with the hydrophilic poly(acrylic acid) proportion except for P(CPAAm6C-*b*-AA)_2. In this particular case, CP was surprisingly lower and no logical explanation was found. Further investigations are necessary to better understand such behavior. Finally, when comparing turbidity of P(CPAAm6C) and P(CPAAm6C-*b*-AA) at low concentration in water ($1 \text{ g} \cdot \text{L}^{-1}$), turbidity was logically weaker for the copolymers, due to the formation of aggregates.

To conclude, original P(CPAAm6C-*b*-AA) thermosensitive diblock copolymers were prepared with CP varying from 36 to $46 \text{ }^\circ\text{C}$ as a function of each block relative proportion. These copolymers were fully soluble in water below the CP whereas a different behavior was expected above the CP. Indeed, as the P(CPAAm6C) becomes insoluble at higher temperature than the CP, diblock copolymers will be amphiphilic which will lead to the formation of aggregates above the critical aggregation concentration (CAC).

So, light scattering measurements were conducted at $50 \text{ }^\circ\text{C}$ varying the P(CPAAm6C-*b*-AA)_3 copolymer concentration from $1 \cdot 10^{-3}$ to $1 \text{ g} \cdot \text{L}^{-1}$. The evolution of the intensity as a

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function of the concentration led to the CAC as the intensity dramatically increased when the objects were formed in the solution (Fig. 1 right). CAC was measured at 94.4 mg.L⁻¹, proving that the P(CPAAm6C-*b*-AA) self-organized. These copolymers could possibly be able to complex gadolinium, and could represent an interesting opportunity for medical diagnostic imaging for instance, P(AA) being known as biocompatible.³³

Conclusions

RAFT polymerization of CPAAm6C was first performed, allowing the synthesis of P(CPAAm6C)-CTA with controlled molecular weight and low dispersities. Then, different P(CPAAm6C-*b*-AA) diblock copolymers were prepared by RAFT polymerization varying the chain length of each block. Thermosensitivity properties of P(CPAAm6C) and P(CPAAm6C-*b*-AA) polymers were determined and as expected, cloud point increased with P(AA) content. As P(CPAAm6C) is thermosensitive, amphiphilic diblock copolymers were obtained above the cloud point when associated with poly(acrylic acid). These copolymers were able to self-organize in water at appropriate temperature, leading to the formation of aggregates. As carbamoylmethylphosphonate moiety of P(CPAAm6C) is able to complex gadolinium, such materials are of great interest. The evaluation of the complexation of gadolinium by these original P(CPAAm6C-*b*-AA) copolymers will be the subject of a forthcoming publication.

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Graphical abstract

Synthesis and self-assembly of carbamoylmethylphosphonate acrylamide-based diblock copolymers: new valuable thermosensitive materialsFabrice Azemar,^a Donatien Gomes-Rodrigues,^a Jean-Jacques Robin,^a and Sophie Monge^{a*}