Synthesis of New Glycine-based Polymers and their Thermoresponsive Behavior in Water

Florent Mohimont, Jutta Rieger, François Stoffelbach

Synthesis of new glycine-based polymers and their thermoresponsive behavior in water

Florent Mohimont, Jutta Rieger*, François Stoffelbach*

Sorbonne Université, CNRS, UMR 8232, Institut Parisien de Chimie Moléculaire (IPCM), Polymer Chemistry Team, 4 Place Jussieu, 75252 Paris Cedex 05, France

E-mail: jutta.rieger@sorbonne-universite.fr; francois.stoffelbach@sorbonne-universite.fr

Keywords:

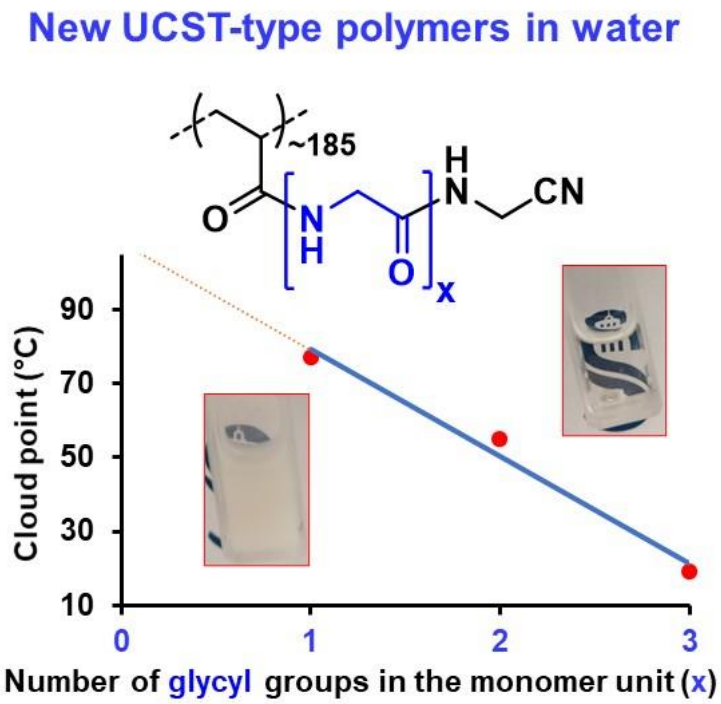
water-soluble thermosensitive polymers, UCST, LCST, RAFT polymerization

Abstract

In this work, we develop new glycine-derived polymers that exhibit thermoresponsive properties in water. Therefore, a series of monomers containing one, two or three amide functional groups and one terminal cyanomethyl group is synthesized. The resulting homopolymers, obtained by free radical polymerization (FRP) and reversible addition fragmentation chain transfer (RAFT) polymerization, display a sharp and reversible upper critical solution temperature (UCST)-type phase transition in water. Additionally, we show that the cloud point (T_{CP}) can be adjusted over more than 60 °C by the number of glycyl groups present in the monomer structure and by the polymer's molar mass. These novel thermoresponsive polymers based on cyanomethylglycinamide enrich the range of non-ionic UCST polymers and are promising to find applications in various fields.

For Table of Contents use only

Cyanomethylglycinamide-derived polymers exhibit an upper critical solution temperature-type thermal transition in water. Their cloud point can be adjusted over a large temperature range (from approximately 20 to 85 °C), by tuning the polymer's molar mass and/or the number of amide functional groups in the monomer structure.



1. Introduction

Thermosensitive polymers that have an upper or a lower critical solution temperature, namely UCST and LCST respectively, have been extensively studied in the field of polymer science in recent decades. This is mainly due to their potential applications, for example as sensors or in the biomedical field.[1,2,3,4,5,6] In the case of UCST polymers, a temperature increase leads to a transition of the polymer chains from a globule to a coil conformation in solution. There are only a few non-ionic homopolymers that have an UCST in pure water. These include poly(*N*-acryloylglycinamide) (PNAGA)[7] and its derivatives, such as poly(*N*-acryloyl-

asparaginamide)[8], poly(6-acryloyloxymethyluracil)[9], poly(*N*-acryloylnipecotamide)[10] and poly(methacrylamide)[11]. We have recently discovered that poly(*N*-cyanomethylacrylamide) (PCMAm), which combines the two functional groups of poly(acrylamide-*co*-acrylonitrile) (P(Am-*co*-AN))[11,12,13], namely an amide and a carbonitrile, can also exhibit a UCST-type temperature transition in water, provided that the molar mass is sufficiently low.[14] However, the relatively high cloud point (T_{CP}) of PCMAm, which is generally above 50 °C, may limit its application in the biomedical field. To address this limitation, hydrophilic comonomers, such as acrylamide (Am) or acrylic acid, were introduced into the polymer to reduce and fine-tune the transition temperature. Interestingly, P(CMAm-*co*-Am) copolymers with a degree of polymerization (DP_n) close to 50 exhibit a transition temperature, which can be decreased from 80 °C to 20 °C by increasing the Am content. In the literature, it is well-establish that the T_{CP} of LCST-type thermoresponsive poly(meth)acrylamides is closely correlated to the structure of the *N*-substituents.[15,16,17,18] Furthermore, we have recently shown that the thermoresponsive properties of poly(*N*-cyanoalkylacrylamide)s strongly depend on the alkyl spacer between the amide and carbonitrile groups. Unlike PCMAm, homopolymers of *N*-cyanoethylacrylamide (CEAm)[19] possessing an ethylene instead of a methylene spacer exhibit either a LCST or both a LCST and an UCST in pure water.

In this study, we designed new monomers combining the functional groups of P(CMAm-*co*-Am), namely cyano and amide functional groups. We hypothesized that the addition of supplementary amide functional group(s) in the monomer unit should result in polymers, which conserve a UCST-type transition with T_{CP} below those of PCMAm homopolymers. Furthermore, to establish relationships between structure and properties, we investigated the impact of various structural parameters on the thermosensitivity of the resulting homopolymers in water: the impact of the molar mass, the number of amide functional groups, the type of alkyl spacer, and the presence/absence of the cyano group in the monomer unit.

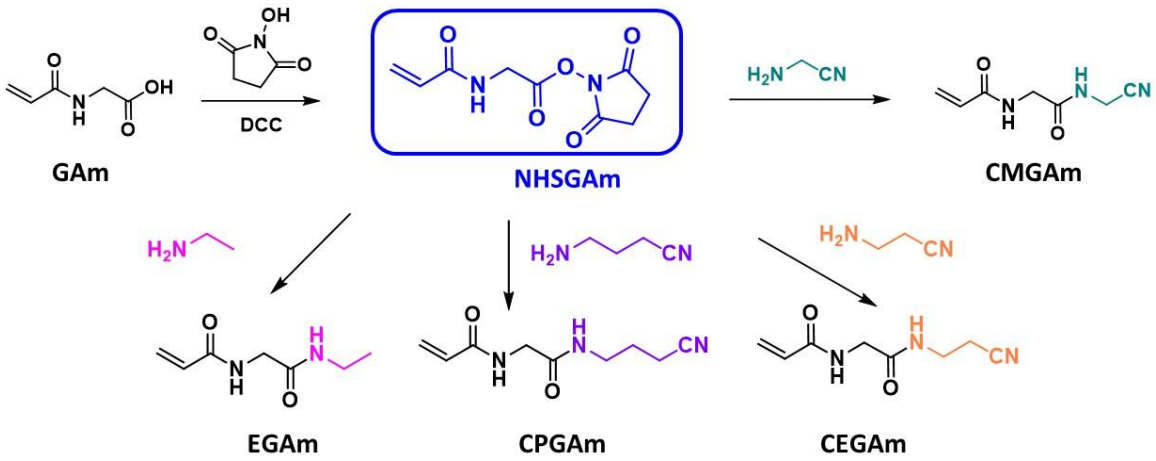
2. Results and Discussion

2.1. Preparation and polymerization of glycine-based monomers possessing various terminal groups

Synthesis of monomers based on glycine

To the best of our knowledge, there is only one mention of *N*-acryloyl-*N'*-cyanomethylglycinamide (CMGAm) (**Scheme 1**) in the literature (in 1968), a study on efficient hepatic agents, in which CMGAm was part of the screening among other aminoacetonitrile derivatives.[20] Its polymerization has however never been reported. In the study, CMGAm was obtained by reaction of acryloyl chloride with 2-amino-*N*-(cyanomethyl)acetamide, in 51% yield. In contrast, we based our synthesis strategy on an activated ester, namely *N*-succinimidyl *N*-acryloylglycinate (NHSGAm), used as a versatile platform to obtain different monomers in good yield (**Scheme 1**). Although NHSGAm should be a useful platform to straightforwardly access a large range of functional monomers, only one publication mentions its use for the preparation of hydroxamic acid polymers.[21] We synthesized NHSGAm from *N*-acryloylglycine (GAm) following a previously described protocol[21] that we adapted to increase the reaction yield from 53% to 89% (see Supporting Information and **Figure S1**). By reaction of NHSGAm with aminoacetonitrile, CMGAm could be obtained in 81% yield (see Experimental Section). ^{1}H and ^{13}C NMR spectra of CMGAm recorded in DMSO-d_6 display all characteristic signals of the monomer's vinyl, amide and methylene groups (**Figure S3**). Using the same synthetic strategy, we prepared *N*-acryloyl-*N'*-cyanoethylglycinamide (CEGAm), *N*-acryloyl-*N'*-cyanopropylglycinamide (CPGAm) and *N*-acryloyl-*N'*-ethylglycinamide (EGAm) monomers by reacting NHSGAm with 3-aminopropionitrile, 4-aminobutyronitrile and ethylamine respectively (**Scheme 1**, see Experimental Section). To the best of our knowledge, CEGAm and CPGAm have never been described in the literature, and only one patent[22] from 1968 mentions the use of EGAm for the preparation of new photographic materials. In this patent, EGAm was obtained by reacting acryloyl chloride with 2-amino-*N*-ethylacetamide.

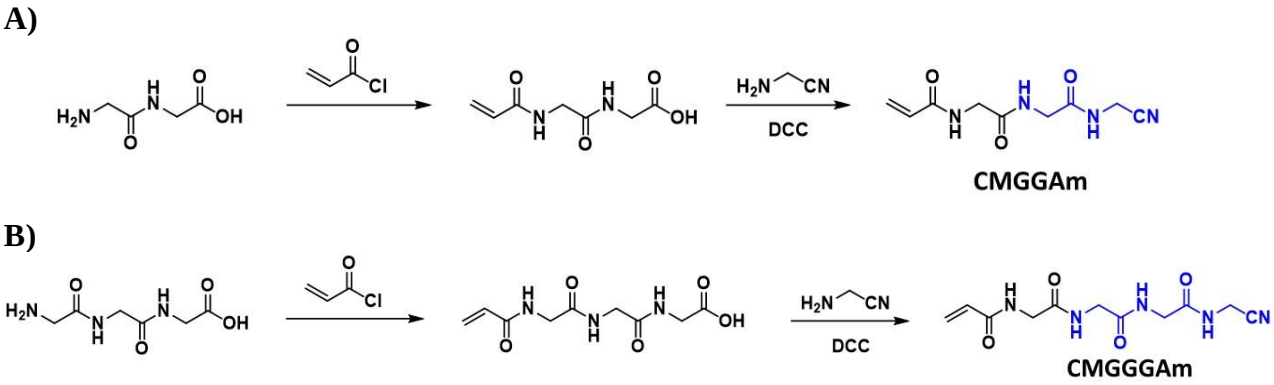
Using our synthesis strategy, we successfully obtained CEGAm, CPGAm, and EGAm as assessed by NMR (See **Figures S4 to S6** and Experimental Section).



Scheme 1. Synthetic routes of monomers based on glycine.

Synthesis of monomers based on diglycine and triglycine

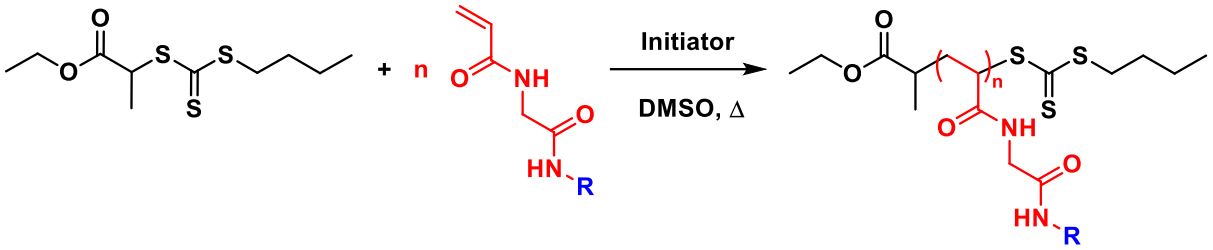
In order to establish structure-properties relationships, the number of amide functions was increased by introducing two or three additional glycyl units into the monomer structure. Therefore, *N*-acryloylglycylglycine cyanomethyl amide (CMGGAm) and *N*-acryloylglycylglycylglycine cyanomethyl amide (CMGGGAm) (**Scheme 2**) were synthesized in two steps: In a first step, diglycine or triglycine is reacted with acryloyl chloride according to reported conditions.[23] The second step consists in the amidation of the intermediates (*N*-acryloylglycylglycine (GGAm) and *N*-acryloylglycylglycylglycine (GGGAm)) with aminoacetonitrile in the presence of *N,N′*-dicyclohexylcarbodiimide (DCC) (see Experimental Section).



Scheme 2. Synthetic route of *N*-acryloylglycylglycine cyanomethyl amide (CMGGAm) (A) and *N*-acryloylglycylglycylglycine cyanomethyl amide (CMGGGAm) (B).

Polymerization of glycine-based monomers

We firstly investigated the ability of CMGAm to be homopolymerized by free radical polymerization (FRP) using 2,2'-azobis(2-methylproprionitrile) (AIBN) as the initiator (**P6**, **Table 1**). After 1 hour of reaction in DMSO at 70 °C, the polymer was recovered by precipitation in acetone and analyzed by size exclusion chromatography (SEC) in DMF. As shown in Table 1, the polymer displayed a high dispersity ($Đ$ = 3.0) and a number-average molar mass (M_n) of 150 kg mol^{-1} was determined by SEC (with a PMMA calibration). The ability of CMGAm to be radically homopolymerized in a controlled fashion by RAFT was then investigated in DMSO solution, using ethyl 2-(butylthiocarbonothioylthio)propanoate, a trithiocarbonate-type chain transfer agent (CTA) well-known to control the polymerization of acrylamides (**Scheme 3**). Not only the transfer agent but also the initiator (AIBN) were chosen nonionic in order to avoid any possible effect of the chain end on the thermoresponsive behavior.[7,10]



Scheme 3. General synthesis pathway of the new homopolymers *via* RAFT polymerization.

As shown in **Figure S15** and summarized in **Table 1**, the thermally-initiated RAFT polymerization of CMGAm was well controlled in DMSO with dispersities ($Đ = M_w/M_n$) below 1.4 and SEC chromatograms that evolved consistently toward higher molar masses by targeting higher DP_n (between 20 and 350).

Next, the ability of CMGGAm and CMGGGAm - which contain one and two additional glycyl groups compared to CMGAm - to be radically homopolymerized by FRP and RAFT polymerization in DMSO solution was investigated. As shown in **Figure S16** and summarized in **Table 1**, the thermally-initiated RAFT polymerization of CMGGAm conducted in DMSO remained quite well controlled with dispersities below 1.6 and SEC chromatograms that evolved toward higher molar masses with increasing theoretical DP_n (between 60 and 180). However, for similar degrees of polymerization, the molar mass dispersity significantly increases with the number of glycyl groups. For instance, for a DP_n about 185, $Đ$ increased from 1.28 to 1.57 to 2.06 for PCMGAm, PCMGGAm and PCMGGGAm respectively (**Table 1** and **Figure S17**). We can thus assume that the glycyl groups give rise to side reactions during radical polymerization.

Table 1. Experimental conditions and results for the RAFT-mediated polymerizations of glycine-based monomers performed at 20 wt% in DMSO[#]

Monomer	Entry	$[M]_0$ / $[CTA]_0$	Time (min)	Conv[a] (%)	$DP_{n,th}$[b]	$M_{n,th}$[b] (kg mol^{-1})	$M_{n,SEC}$[c] (kg mol^{-1})	$Đ$[c]	$T_{CP,\ UCST}$[d] (°C)
CMGAm	P1	29	56	75	21	3.8	5.5	1.16	48
	P2	68	164	73	50	8.6	12.0	1.21	59
	P3	150	55	71	106	18.0	22.2	1.26	72
	P4	283	304	65	184	31.0	40.3	1.28	77
	P4bis	286	135	68	194	32.3	37.3	1.34	81
	P5	420	295	83	349	58.6	64.8	1.33	85
	P6*	-	63	95	-	-	149.9	3.01	> 85
CEGAm[e]	P7	221	206	81	179	32.7	42.7	1.15	soluble
	P8	310	92	79	245	44.7	53.1	1.22	soluble
CPGAm	P9	243	467	68	166	32.7	38.8	1.48	insoluble
	P10*	-	47	97	-	-	166	3.34	insoluble
EGAm	P11	271	167	67	147	23.2	25.0	1.29	60 (LCST)
	P12*	-	77	96	-	-	107.3	2.76	49 (LCST)
CMGGAm	P13	73	69	80	58	13.3	13.2	1.22	38
	P14	132	210	73	96	21.8	16.9	1.53	46
	P15	251	155	71	179	40.4	30.8	1.57	55
	P16*	-	53	93	-	-	56.9	3.99	73
CMGGGAm[f]	P17	154	510	69	106	30.1	17.3	1.55	19
	P18	247	452	77	190	53.7	20.7	2.06	19
	P19**	-	412	64	-	-	26.0	1.82	19

[#] Polymerizations were performed at 70 °C in presence of a RAFT agent (CTA) using AIBN as a radical initiator at an initial molar ratio of CTA/AIBN: 1/0.1-0.5. *Free radical polymerization (without RAFT agent) at an initial molar ratio of monomer/AIBN: 200/1. **Free radical polymerization at an initial molar ratio of CMGGGAm/AIBN: 690/1. [a] Determined by ^{1}H NMR analysis. [b] Theoretical number-average degree of polymerization, $DP_{n,th}$, and number-average molar mass, $M_{n,th}$, calculated using the experimental conversion. [c] Number-average molar mass, M_n, and dispersity, $Đ$, determined by SEC in DMF (+ LiBr 1g L^{-1}) with a PMMA calibration. [d] Determined by turbidimetry in water at 1 wt%, measured on the 1st cooling ramp at 1 °C min^{-1}. [e] Polymerizations were performed at 40 °C using V70 as a radical initiator. [f] Polymerizations were performed at 5 wt%.

2.2. Study of the thermoresponsive behavior of the homopolymers in water

2.2.1. PCMGAm

Firstly, the thermoresponsive properties of 1 wt% aqueous solutions of PCMGAm were studied by turbidimetry. A typical UCST-type thermoresponsive behavior with a sharp transition was observed for all PCMGAm prepared by RAFT polymerization: the polymers were insoluble in

water at low temperatures, whereas they became soluble at high temperatures. **Figure 1** shows that the UCST-type transition temperature is strongly DP_n-dependent: T_{CP} increases from 48 to 85 °C when the DP_n is increased from 21 to 349. The PCMGAm obtained by FRP (**P6**, **Table 1**) with the highest molar mass, stayed turbid up to 85 °C, but demonstrated the beginning of a transition at around 90 °C. This decrease in solubility with increasing chain length is thermodynamically expected and was previously described for other UCST-type homopolymers such as poly(*N*-acryloylasparaginamide)[8]. Interestingly, two consecutive turbidity measurements revealed a sharp and reversible UCST-type transition with a very small hysteresis, similar to PCMAm homopolymers (**Figure S21**). Compared with PCMAm of similar DP_n, the introduction of a glycyl group into the monomer structure significantly decreases the T_{CP} : Whereas a PCMAm of DP_n = 183 is insoluble in water at 1 wt% (at least up to 90 °C, **Table S1**), for a PCMGAm of similar length (**P4**, **Table 1**) the T_{CP} is reduced to 77 °C, and a T_{CP} of 85 °C is only reached at a much higher DP_n of 349 (**P5**, **Table 1**) (**Figure 2**). We also investigated the impact of polymer concentration on the phase transition behavior of PCMGAm. The turbidity curves of sample P3bis (See **Table S2**) at 2.0, 0.5 and 0.25 wt% in **Figure S22** show that the T_{CP} of PCMGAm decreases from 73 °C to 62 °C as the polymer concentration decreases.

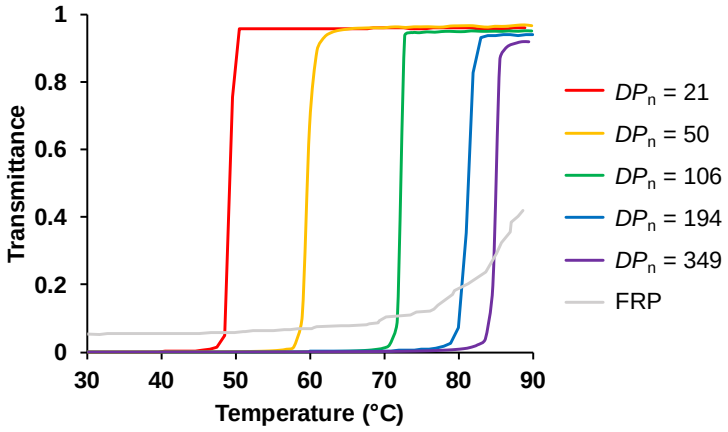


Figure 1. Influence of the DP_n on turbidity curves (first cooling at 1 °C min^{-1}) of PCMGAm recorded at 1 wt% in water (Experiments P1 to P3 and P4bis to P6 in Table 1).

2.2.2. Influence of the number of glycyl units in the monomer structure

We also examined how the introduction of two and three glycyl units into the monomer structure (CMGGAm and CMGGGAm) affects the thermoresponsive behavior of homopolymers in water. To this end, we compared the thermoresponsiveness of 1 wt% aqueous solutions of PCMGAm, PCMGGAm, and PCMGGGAm homopolymers of different chain lengths by turbidimetry (**Table 1**, entries P1 to P6, P13 to P16 and P17 to P19). Generally, like PCMGAm, PCMGGAm and PCMGGGAm homopolymers exhibit a UCST behavior (see **Figures S23** and **S24**). However, the transition temperature and its sensitivity to DP_n clearly depend on the number of glycyl units, *i.e.* the number of amide functions. The comparison of three homopolymers prepared by FRP (**P6**, **P16**, **P19**) shows large differences in T_{CP}, indicating that the solubility of the polymers increases significantly with the addition of amide functions in the order of PCMGAm < PCMGGAm < PCMGGGAm. However, the M_n of these three polymers are different so that an impact of the molar mass cannot be excluded. **Figure 2A** shows the comparison of the three homopolymers obtained by RAFT radical polymerization with similar $DP_n \sim 185$. The UCST transition decreases linearly from 81 °C to 19 °C as the number of glycyl groups increases from 1 to 3 (**Figure 2B**). By incorporating amide functional groups into the monomer unit, the solubility of the polymer in water can be enhanced, thereby reducing the UCST-type temperature transition.

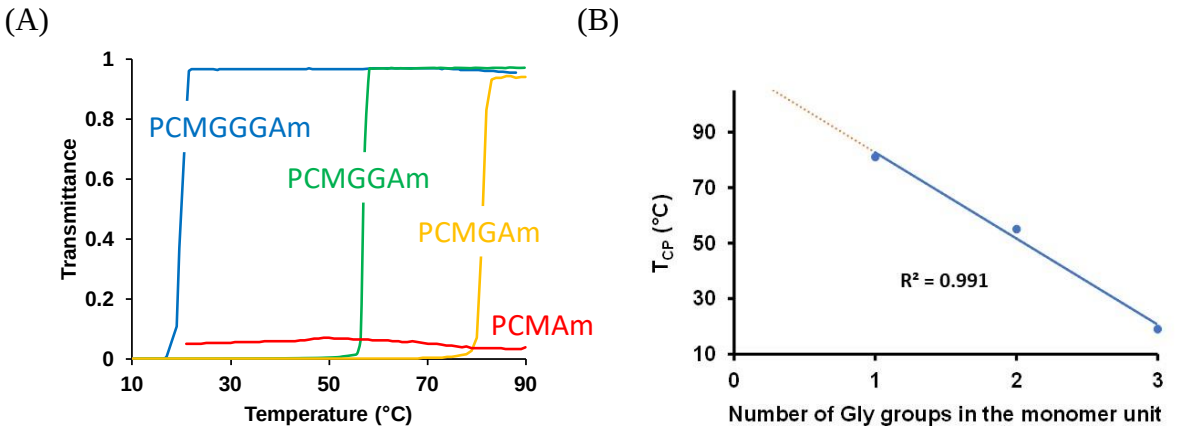


Figure 2. Turbidity curves (first cooling) of PCMG$_x$Am polymers with x = 0, 1, 2 and 3 (with similar DP_n ~ 185) at 1 wt% in water (A) (Table 1 and Table S1). T_{CP} of the same homopolymers as a function of the number of glycyl groups in the monomer unit (B).

Maruyama *et al.*[24] have shown that log P (the log10 of the octanol−water partition coefficient) which quantifies the hydrophobicity of small molecules[25], is a useful indicator that can guide tuning the T_{CP} of UCST-type polymers. We therefore calculated the log P values of CMAm (-0.33), CMGAm (-1.47), CMGGAm (-2.62) and CMGGGAm (-3.77) monomer units and plotted them with the T_{CP} of the corresponding homopolymers. As shown in **Figure S25**, a linear relationship was observed between the log P and T_{CP}. This comparison and additional results reported in Table 1 confirm that the T_{CP} of the homopolymer decreases when the number of glycyl groups in the monomer structure increases. The DP_n dependency of the T_{CP} was studied for the three homopolymers and the results are summarized in **Figure 3**. While the T_{CP} of PCMAm, PCMGAm, and PCMGGAm is strongly influenced by the DP_n, the T_{CP} of PCMGGGAm is around 20 °C for all three samples, indicating a poor dependency on DP_n.

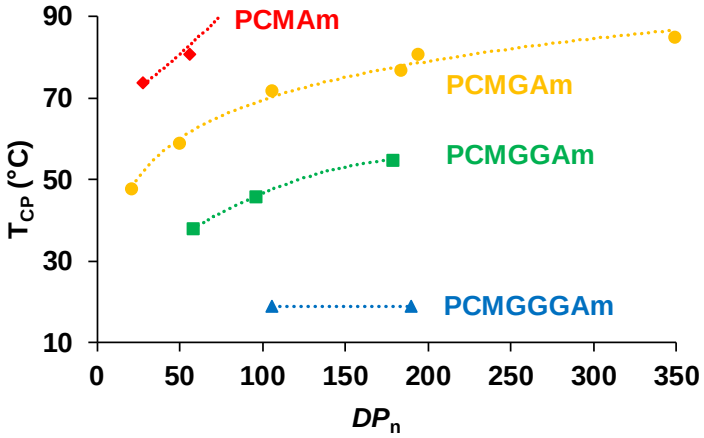


Figure 3. Comparison of T_{CP} (first cooling) versus DP_n for PCMG$_x$Am (with x = 0 to 3) at 1 wt% in water (Table 1 and Table S1).

2.2.3. Impact of the alkyl spacer

As mentioned in the introduction, we have recently shown that the spacer between the amide and cyano group has a great impact on the thermoresponsive properties of poly(*N*-cyanoalkyacrylamide)s. Changing the spacer from methylene to ethylene switched the typical UCST-type properties of PCMAm towards a LCST-type (or a dual LCST/UCST-type) behavior for poly(*N*-cyanoethylacrylamide) (PCEAm).[19] Specifically, PCEAm with DP > 300 demonstrated solely a LCST-type transition, while polymers with intermediate DP (100-300) displayed a dual temperature response, with LCST < UCST. Shorter polymers were found to be water-soluble at 1 wt% in water. Therefore, we studied the thermoresponsiveness of poly(*N*-acryloyl-*N'*-cyanoethylglycinamide (PCEGAm), which distinguishes itself from PCMGAm by the presence of an extra methylene group between the amide and cyano functional groups in the monomer units. Surprisingly, the PCEGAm homopolymer with a DP_n of around 180 (**P7 in Table 1**, **Figure S26**) is soluble in water at 1 wt% over the whole temperature range studied, while the corresponding PCMGAm (**P4 in Table 1**) has a relatively high UCST-type T_{CP} close to 80 °C. Even when the DP_n of PCEGAm was increased to 245 the polymer remained water-soluble with no notable thermoresponsiveness (see **Figure S26**). Consequently, the addition of

an extra methylene group in the monomer structure increases greatly the water solubility of the resulting polymer, while the UCST properties are lost. We can hypothesize that the presence of an additional methylene group in CEGAm units should favor side-chain mobility/flexibility reducing polymer-polymer interactions induced by amide and cyano functions. We next investigated homopolymers of CPGAm, which differs from CMGAm by the presence of two additional methylene groups (**Scheme 1**). This additional methylene group should reduce the hydrophilicity of the polymer compared to PCEGAm, which could lead to the recovery of a thermoresponsiveness. We therefore studied a PCPGAm homopolymer with a DP_n of around 170 (**P9**, **Table 1**) and compared it with PCMGAm (**P4**, **Table 1)**. The turbidimetry measurements at 1 wt% in water (**Figure S27**) showed that the polymer was insoluble in water over the whole temperature range studied, no thermal transition was observed. The presence of an extra methylene group in CPGAm units significantly enhances the hydrophobic nature of the polymer in comparison to PCEGAm, resulting in its complete insolubility in water at least up to 90 °C at 1 wt%. In summary, the solubility of poly(*N*-acryloyl-*N*'-cyanoalkylglycinamide) varies significantly with the alkyl group located between the second amide function and the cyano functional group, and decreased in the following order $-CH_2-CH_2- > -CH_2- >> -(CH_2)_3-$.

2.2.4. Impact of the absence of the CN group

In addition to H-bond donating and/or accepting functional groups, such as amides, ureas etc., the cyano group has been identified as a relevant functional group to generate UCST behavior of polymers.[4,26] For instance, Uchiyama and Otsuka *et al.*[27] reported that dipole−dipole interactions between the cyano groups of the AN units play a crucial role in the UCST behavior of P(Am-*co*-AN). We therefore studied a PEGAm homopolymer, which has the same structure as PCMGAm except that the cyano functional group is replaced by a methyl group assumed to be "inert" in the monomer structure. Unexpectedly, the substitution of the CN groups induced a LCST behavior, with a T_{CP} of 60 °C for $PEGAm_{147}$ (**P11** in **Table 1** and **Figure S28**). A

LCST behavior has already been observed for structurally similar polymers, namely poly(*N*-acryloylglycine ethyl ester),[17] for which a significantly lower $T_{CP,\ LCST}$ around 20 °C has been reported (DP_n ~ 180, turbidimetry at 1 wt% in water). Thus, the presence of a second amide group in the monomer units of PEGAm results in a higher $T_{CP,\ LCST}$ showing again that the presence of this functional group enhances the overall polymer solubility in water.

3. Conclusion

New UCST-type thermosensitive homopolymers were successfully synthesized using cyanomethylglycinamide-based monomers through RAFT polymerization in a controlled manner. An example of these homopolymers is PCMGAm, which displays a sharp and reversible UCST-type thermal transition in pure water. The transition temperature depends on the degree of polymerization, and varies from 48 °C to 85 °C for a DP_n range of 20 to 350. In comparison to PCMAm, the incorporation of a glycyl group into the monomer structure significantly reduces the T_{CP} of the homopolymer. In addition, we showed that the transition temperature can be fine-tuned by modifying the number of glycyl groups within the monomer structure. For instance, by adding two supplementary glycyl groups to CMGAm, for similar DP_n around 185 the T_{CP} is reduced from 77 to 19 °C. We have also demonstrated that the alkyl group positioned between the last amide function and the terminal cyano functional group has a great effect on the solubility of poly(*N*-acryloyl-*N*'-cyanoalkylglycinamide)s: the water-solubility decreases in the following order: $-CH_2-CH_2- > -CH_2- >> -(CH_2)_3-$. Furthermore, the presence of the CN group in the monomer structure has a significant impact on the thermoresponsive properties of the homopolymers in water. When the CN group is substituted by a methyl group, the resulting polymer exhibits characteristics similar to those of a polymer with a LCST. Thereby, the UCST-type transition of the cyanomethylglycinamide-based polymer is mainly caused by dipole-dipole interactions between the cyano groups of the monomer units in addition to hydrogen bonds between the amide groups. These innovative

polymers are paving the way for a new category of responsive materials. Their distinct and reversible transition temperatures, which can be adjusted to match physiological temperature, make them highly promising options for biomedical applications.

4. Experimental Section

***Materials*:** Aminoacetonitrile sulfate (97%, ABCR), acryloyl chloride (97%, Aldrich), *N*-hydroxysuccinimide (98%, Aldrich), *N,N'*-dicyclohexylcarbodiimide (99%, Acros Organics), 3-aminopropionitrile (98%, ABCR), glycylglycylglycine (≥ 98%, ABCR), ethylamine 2.0 M solution in THF (Aldrich), 2,2′-azobis(isobutyronitrile) (AIBN, ≥ 98%, Aldrich), acetonitrile (≥ 99.9%, Aldrich), acetone (≥ 99%, Aldrich), dimethyl sulfoxide (DMSO, ≥ 99.9%, Aldrich), ethyl acetate ((≥ 99.5%, Aldrich), dichloromethane (DCM, ≥ 99%, Aldrich), *N*,*N*-dimethylformamide extra dry over Molecular Sieve (DMF, 99.8%, Thermo Scientific) were used as received. *N*-acryloylglycine (GAm)[28], *N*-acryloylglycylglycine (GGAm)[23], 4-aminobutanenitrile[29] and ethyl 2-(butylthiocarbonothioylthio)propanoate[14] were synthesized according to protocols previously described. Anhydrous dichloromethane (DCM) and tetrahydrofuran (THF) were obtained from a MBraun solvent purification system (MB SPS-800).

***Characterization*:** ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 300 K on a Bruker 300 MHz or 400 MHz spectrometer in 5 mm diameter tubes. SEC measurements were carried out at 60 °C in DMF (+LiBr, 1 g L^{-1}) as mobile phase at a flow rate of 0.8 mL min^{-1} using toluene as a flow rate marker. Polymer solutions were prepared at a concentration of 5 mg mL^{-1} and filtered through a 0.2 μm PTFE membrane. 100 μL of solution was injected for each measurement for analysis. The separation system was composed of two PSS GRAM 1000 Å columns (8 × 300 mm; separation limits: 1 to 1000 kg mol^{-1}) and one PSS GRAM 30 Å (8 × 300 mm; separation limits: 0.1 to 10 kg mol^{-1}) coupled with a modular differential refractive index (RI) detector Viscotek 3580. Molar masses (M_n, M_w, respectively the number-average

molar mass and the weight-average molar mass) and dispersities ($Đ = M_w/M_n$) were calculated using OmniSEC 5.12 software with a calibration curve based on narrow PMMA standards (from Polymer Standard Services). Turbidimetry measurements of homopolymers in water were performed on an Agilent spectrophotometer Cary 100 UV-Vis equipped with a Peltier-type temperature control system by measuring the transmittance at a wavelength of 670 nm. The heating/cooling rate was maintained constant at 1 °C min^{-1}. Samples were prepared at a concentration of 1 wt% by diluting the polymer in ultra-pure water. The cloud point (T_{CP}) was determined at the inflection point. Log P of monomer units were calculated by Chemdraw Prime 22.0.0.22 (PerkinElmer, Inc.).

Synthesis of monomers:

Synthesis of CMGAm

Aminoacetonitrile sulfate (6.50 g; 61.8 mmol) was dissolved in 25 mL of distilled water, and NaOH was added progressively to obtain a pH of 11. The mixture was extracted with dichloromethane (DCM, 3x50 mL), the organic phases were collected, dried with $MgSO_4$ and filtered. The solution of aminoacetonitrile in DCM was added to a 250 mL round-bottomed flask containing 6.85 g of *N*-succinimidyl *N*-acryloylglycinate (30.3 mmol). The mixture was stirred for 1 h at room temperature, then the reaction medium was cooled down at -18 °C in a freezer for 1 h. The mixture was filtered and the obtained solid was dissolved in 150 mL of acetone at 60 °C prior to being crystallized at -18 °C in a freezer overnight. The mixture was filtered to obtain a grey solid, which was dried under vacuum at 40 °C (4.09 g; yield = 81%). ^{1}H NMR (**Figure S3**) (300 MHz, DMSO-d_6): δ (ppm) 8.61 (broad, 1H, N**H**), 8.44 (broad, 1H, N**H**), 6.29 (dd, 1H, C**H**=CH_2), 6.14 (dd, 1H, C**H**$_2$=CH), 5.66 (dd, 1H, C**H**$_2$=CH), 4.15 (d, 2H, C**H**$_2$CN), 3.84 (d, 2H, C**H**$_2$CO). ^{13}C NMR (**Figure S3**) (100 MHz, DMSO-d_6): δ (ppm) 170.1 (**C**=O), 165.5 (**C**=O), 131.9 (**C**H=CH_2), 126.1 (**C**H_2=CH), 118.0 (**C**N), 42.2 (**C**H_2CO), 27.5 (**C**H_2CN).

Synthesis of CEGAm

N-Succinimidyl *N*-acryloylglycinate (2.0 g; 8.8 mmol) and 3-aminopropionitrile (0.75 mL; 10.2 mmol) were dissolved in 50 mL of acetonitrile. The mixture was stirred for 2 h at room temperature, and afterwards cooled down to -18 °C in a freezer for 1 h. The mixture was filtered to obtain the product as a white solid. To increase the yield, the filtrate was evaporated under reduced pressure at 40 °C to yield a solid, which was dissolved in 30 mL of acetone and crystallized at -18 °C in a freezer. A white solid was obtained by filtration of the mixture and was dried under vacuum at 40 °C (1.11 g; yield = 69%). ^{1}H NMR (**Figure S4**) (300 MHz, DMSO-d_6): δ (ppm) 8.37 (broad, 1H, N**H**), 8.26 (broad, 1H, N**H**), 6.30 (dd, 1H, C**H**=CH_2), 6.13 (dd, 1H, C**H**$_2$=CH), 5.64 (dd, 1H, C**H**$_2$=CH), 3.80 (d, 2H, C**H**$_2$CO), 3.3 (t, 2H, C**H**$_2$$CH_2$CN), 2.64 (t, 2H, C**H**$_2$CN). ^{13}C NMR (**Figure S4**) (100 MHz, DMSO-d_6): δ (ppm) 169.2 (**C**=O), 164.9 (**C**=O), 131.5 (**C**H=CH_2), 125.4 (**C**H_2=CH), 119.2 (**C**N), 41.9 (**C**H_2CO), 34.8 (**C**$H_2$$CH_2$CN), 17.5 (**C**$H_2$CN).

Synthesis of CPGAm

N-Succinimidyl *N*-acryloylglycinate (0.98 g; 4.3 mmol) and 4-aminobutanenitrile (0.40 g; 4.8 mmol) were dissolved in 100 mL of ethyl acetate. The mixture was stirred for 2 h at room temperature, then the reaction medium was cooled down at -18 °C in a freezer for 2 h. The mixture was filtered and the solvent was evaporated under reduced pressure at 40 °C. The obtained solid was dissolved in 30 mL of acetone at 40 °C and crystallized at -18 °C in a freezer. A white solid was obtained by filtration and was dried under vacuum (0.48 g; yield = 57%). ^{1}H NMR (**Figure S5**) (300 MHz, DMSO-d_6): δ (ppm) 8.34 (broad, 1H, N**H**), 8.00 (broad, 1H, N**H**), 6.30 (dd, 1H, C**H**=CH_2), 6.12 (dd, 1H, C**H**$_2$=CH), 5.63 (dd, 1H, C**H**$_2$=CH), 3.76 (d, 2H, C**H**$_2$CO), 3.16 (q, 2H, C**H**$_2$$CH_2$$CH_2$CN), 2.5 (m, 2H, C**H**$_2$CN), 1.70 (quint, 2H, C**H**$_2$$CH_2$CN). ^{13}C NMR (**Figure S5**) (100 MHz, DMSO-d_6): δ 169.3 (**C**=O), 165.4 (**C**=O), 132.0 (**C**H=CH_2), 125.8 (**C**H_2=CH), 120.9 (**C**N), 42.6 (**C**H_2CO), 37.8 (**C**$H_2$$CH_2$$CH_2$CN), 25.6 (**C**$H_2$$CH_2$CN), 14.3 (**C**$H_2$CN).

Synthesis of EGAm

N-Succinimidyl *N*-acryloylglycinate (1.01 g; 4.47 mmol) was dissolved in 70 mL of anhydrous THF. 2.5 mL of a 2.0 M solution of ethylamine in THF (5.1 mmol) was added to the flask. The mixture was stirred for 3 h at room temperature. The solvent was evaporated under reduced pressure at 40 °C. The obtained solid was dissolved in 50 mL of acetone at 40 °C and crystallized at -18 °C in a freezer. The mixture was filtered to obtain a white solid (0.205 g; yield = 29%). ^{1}H NMR (**Figure S6**) (300 MHz, DMSO-d_6): δ (ppm) 8.29 (broad, 1H, N**H**), 7.88 (broad, 1H, N**H**), 6.31 (dd, 1H, C**H**=CH_2), 6.12 (dd, 1H, C**H**$_2$=CH), 5.63 (dd, 1H, C**H**$_2$=CH), 3.75 (d, 2H, C**H**$_2$CO), 3.09 (quint, 2H, C**H**$_2$$CH_3$), 1.02 (t, 3H, C**H**$_3$). ^{13}C NMR (**Figure S6**) (100 MHz, DMSO-d_6): δ 168.7 (**C**=O), 165.3 (**C**=O), 132.1 (**C**H=CH_2), 125.7 (**C**H_2=CH), 42.5 (**C**H_2CO), 33.8 (**C**$H_2$$CH_3$), 15.2 (**C**$H_3$).

Synthesis of CMGGAm

Aminoacetonitrile sulfate (5.02 g; 47.8 mmol) was dissolved in 20 mL of distilled water, and NaOH was added progressively to obtain a pH of 11. The mixture was extracted with DCM (3x40 mL), the organic phases were collected, dried with $MgSO_4$ and filtered. 183.4 g of this DCM solution was added to a 500 mL round-bottomed flask containing 3.98 g of *N*-acryloylglycylglycine (21.36 mmol) and 6.00 g of *N,N'*-dicyclohexylcarbodiimide (29.07 mmol) dissolved in 125 mL of anhydrous DMF in an ice bath. The reaction medium was stirred for 2 h at 0 °C, then left in the fridge at 4 °C overnight without stirring. The mixture was thereafter filtered at room temperature. The obtained solid was dissolved in 100 mL of distilled water at 80 °C and immediately filtered, the solid was washed with 100 mL of water at 80 °C. The aqueous solution was cooled down to 0 °C in an ice bath and filtered to yield the product as a white solid, which was dried under vacuum at 40 °C. The filtrate was freeze-dried to recover additional product (3.59 g; yield = 74.9%). ^{1}H NMR (**Figure S7**) (300 MHz, DMSO-d_6): δ (ppm) 8.54 (broad, 1H, N**H**), 8.40 (broad, 1H, N**H**), 8.29 (broad, 1H, N**H**), 6.32 (dd, 1H, C**H**=CH_2), 6.14 (dd, 1H, C**H**$_2$=CH), 5.64 (dd, 1H, C**H**$_2$=CH), 4.15 (d, 2H, C**H**$_2$CN), 3.85 (d,

2H, C**H**$_2$CO), 3.77 (d, 2H, C**H**$_2$CO). ^{13}C NMR (**Figure S7**) (100 MHz, DMSO-d$_6$): δ 170.1 (**C**=O), 169.8 (**C**=O), 165.5 (**C**=O), 131.9 (**C**H=CH$_2$), 126.0 (**C**H$_2$=CH), 118.0 (**C**N), 42.6 (**C**H$_2$CO), 42.2 (**C**H$_2$CO), 27.5 (**C**H$_2$CN).

Synthesis of CMGGGAm:

Aminoacetonitrile sulfate (7.55 g; 71.8 mmol) was dissolved in 20 mL of distilled water, and NaOH was added progressively to obtain a pH of 11. The mixture was extracted with DCM (3x50 mL), the organic phases were collected, dried with $MgSO_4$ and filtered. 98 mL of this solution were added to a 500 mL round-bottomed flask containing 5.96 g of *N*-acryloylglycylglycylglycine (24.5 mmol) and 7.08 g of *N,N'*-dicyclohexylcarbodiimide (34.3 mmol) dissolved in 150 mL of anhydrous DMF in an ice bath. The mixture was stirred overnight in an ice bath. The mixture was filtered and the obtained solid was washed with 300 mL of DCM. The solid was added in 300 mL of distilled water and heated at 80 °C in an oil bath for 1 h then filtered immediately, the solid was washed with 50 mL of water at 80 °C. The filtrate was cooled down at 4 °C in a fridge for 2 h then filtered, the obtained solid was washed with 50 mL of cold water. The white solid was dried under vacuum at 40 °C (1.54 g; yield = 22%). ^{1}H NMR (**Figure S8**) (400 MHz, DMSO-d$_6$): δ (ppm) 8.51 (broad, 1H, N**H**), 8.39 (broad, 1H, N**H**), 8.23 (broad, 1H, N**H**), 8.20 (broad, 1H, N**H**), 6.31 (dd, 1H, C**H**=CH$_2$), 6.13 (dd, 1H, C**H**$_2$=CH), 5.64 (dd, 1H, C**H**$_2$=CH), 4.15 (d, 2H, C**H**$_2$CN), 3.85 (d, 2H, C**H**$_2$CO), 3.76 (m, 4H, C**H**$_2$CO). ^{13}C NMR (**Figure S8**) (100 MHz, DMSO-d$_6$): δ 170.1 (**C**=O), 169.8 (**C**=O), 165.5 (**C**=O), 131.9 (**C**H=CH$_2$), 126.0 (**C**H$_2$=CH), 118.0 (**C**N), 42.6 (**C**H$_2$CO), 42.5 (**C**H$_2$CO), 42.2 (**C**H$_2$CO), 27.5 (**C**H$_2$CN).

Supporting Information

The monomers' ^{1}H and ^{13}C NMR spectra, as well as the synthesis of monomer intermediates, are provided. Furthermore, experimental details regarding polymerizations and supplementary data are included.

Acknowledgements

The authors thank the Sorbonne Université Doctoral School ED397 for funding.

References

[1] Q. Zhang, Y. Zhang, Y. Wan, W. Carvalho, L. Hu, M. J. Serpe, *Prog. Polym. Sci.* **2021**, 101386.

[2] W.-M. Wan, F. Cheng, F. Jäkle, *Angew. Chem. Int. Ed*. **2014**, *53*, 8934.

[3] W.-M. Wan, P. Zhou, F. Cheng, X.-L. Sun, X.-H. Lv, K.-K. Li, H. Xu, M. Sund, F. Jäkle, *Soft Matter* **2015**, *11*, 7159.

[4] J. Seuring, S. Agarwal, *Macromol. Rapid Commun*. **2012**, *33*, 1898.

[5] J. Seuring, S. Agarwal, *ACS Macro Lett*. **2013**, *2*, 597.

[6] G. Shao, Y. Liu, R. Cao, G. Han, B. Yuan, W. Zhang, *Polym. Chem*. **2023**, *14*, 1863.

[7] J. Seuring, F. M. Bayer, K. Huber, S. Agarwal, *Macromolecules* **2012**, *45*, 374.

[8] S. Glatzel, A. Laschewsky, J. Lutz, *Macromolecules* **2011**, *44*, 413.

[9] T. Aoki, K. Nakamura, K. Sanui, A. Kikuchi, T. Okano, Y. Sakurai, N. Ogata, *Polym. J*. **1999**, *31*, 1185.

[10] Y. Akiyama, *Macromol. Rapid Commun.* **2021**, 2100208.

[11] J. Seuring, S. Agarwal, *Macromolecules* **2012**, *45*, 3910.

[12] C. Zhao, Z. Ma and X. X. Zhu, *Prog. Polym. Sci.* **2019**, *90*, 269.

[13] N. Audureau, C. Coumes, J.-M. Guigner, T. P. T. Nguyen, C. Ménager, F. Stoffelbach, J. Rieger, *Polym. Chem*. **2020**, *11*, 5998

[14] N. Audureau, C. Veith, F. Coumes, T. P. T. Nguyen, J. Rieger, F. Stoffelbach, *Macromol. Rapid Commun.* **2021**, 2100556.

[15] Y. Hou, Y. Guo, S. Qian, H. Khan, G. Han, W. Zhang, *Polymer* **2019**, *167*, 159.

[16] Y. Cao, X.X. Zhu, J. Luo, H. Liu, *Macromolecules* **2007**, *40*, 6481.

[17] S. Chen, Y. Zhang, K. Wang, H. Zhou, W. Zhang, *Polym. Chem*. **2016**, *7*, 3509.

[18] D. Yu, C. Luo, W. Fu, Z. Li, *Polym. Chem*. **2014**, *5*, 4561.

[19] N. Audureau, F. Coumes, J. Rieger, F. Stoffelbach, *Polym. Chem*. **2022**, *13*, 1075.

[20] S. Suzur, T. Irikura, *Chem. Pharm. Bull*. **1968**, *16*, 1417.

[21] A. Winston, D. V. P. R. Varaprasad, J. J. Metterville, H. Rosenkrantz, *J. Pharmacol. Exp. Ther*. **1985**, *232*, 644.

[22] H. M Wagner, W. M. Przezdziecki (Kodak) *GB1108383A*, **1968**.

[23] S. Heise, G. Manecke, C. Schroeter-Kermani, H. Kleinkauf, *Biotechnology and Bioengineering* **1988**, *32*, 400.

[24] N. Shimada, T. Sasaki, T. Kawano, A. Maruyama, *Biomacromolecules* **2018**, *19*, 4133.

[25] C. C. Bannan, G. Calabró, D. Y. Kyu, D. L. Mobley, *J. Chem. Theory Comput*. **2016**, *12*, 4015.

[26] Y. Nan, C. Zhao, G. Beaudoin, X. X. Zhu, *Macromol. Rapid Commun*. **2023**, *44*, 2300261.

[27] C. Otsuka, Y. Wakahara, K. Okabe, J. Sakata, M. Okuyama, A. Hayashi, H. Tokuyama, S. Uchiyama, *Macromolecules* **2019**, *52*, 7646.

[28] N. Higashi, R. Sonoda, T. Koga, *RSC Adv*. **2015**, *5*, 67652.

[29] T. Y.-H. Wu (Apros Therapeutics, Inc.) *US20190314372A1*, **2019**.