Well-defined thermoresponsive polyesteramides through one-pot multicomponent post-polymerization modification of poly(2-isopropenyl-2-oxazoline)

Florica Adriana Jerca[a,b], Valentin Victor Jerca[a,b]* and Richard Hoogenboom[a,]*

[a]Supramolecular Chemistry Group, Centre of Macromolecular Chemistry (CMaC), Department of Organic and Macromolecular Chemistry, Ghent University, Krijgslaan 281-S4, B-9000 Ghent, Belgium

[b]Centre of Organic Chemistry "Costin D. Nenitescu", Romanian Academy, 202B Spl. Independentei CP 35-108, 060023 Bucharest, Romania

Correspondence to: Richard Hoogenboom (E-mail: richard.hoogenboom@ugent.be), Valentin Victor Jerca (E-mail: victor_jerca@yahoo.com)

ABSTRACT

Thermoresponsive polymers that undergo a solubility phase in transition in water are an important as basis for the development for a wide variety of responsive and smart materials. In this study, the synthesis of thermoresponsive copolymers is demonstrated by the straightforward one-pot multicomponent post-polymerization modification of well-defined poly(2-isopropenyl-2-oxazoline) (PiPOx) by ring-opening reaction with multiple carboxylic acids. The reactions are carried out using dual, triple and quadruple mixtures of up to four different aliphatic carboxylic acids. The cloud point temperatures of the resulting polyesteramides can be finely tuned by adjusting the feed ratio and the hydrophilic-hydrophobic balance of the acids that are used for the ring-opening modification of PiPOx.

KEYWORDS: thermoresponsive; poly(2-isopropenyl-2-oxazoline); post-polymerization modification; one-pot modification; multicomponent modification

INTRODUCTION

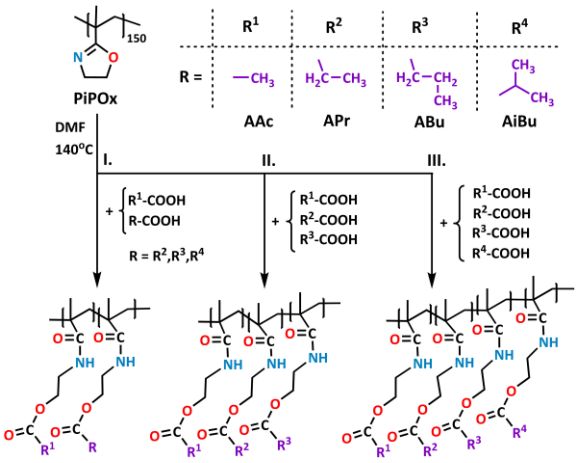
Tailored stimuli responsive polymers that can undergo a conformational or phase transitions in response to stimuli represent one of the most investigated topics in polymer and material science.[1-3] These polymers can be designed to respond to externally applied triggers (e.g. temperature, light, electric or magnetic fields), to internal stimuli such as chemical (e.g. pH or ionic strength) or biological stimuli (e.g. glucose, enzyme, antibodies).[4-8] The temperature responsive polymers are a class of stimuli-responsive materials that exhibit a discontinuous change of their physical properties with temperature.[9,10] Thermoresponsive polymers that exhibit an LCST behavior in aqueous media are attractive scaffolds as the temperature-response can play a key function in the development of sensing systems, and its interplay with other responses, such as pH or light gives rise to multiresponsive materials.[11-13] The majority of the thermoresponsive LCST polymers are obtained through (co)polymerization of functional monomers based on, e.g. poly(meth)acrylamides, poly[oligo(ethylene glycol) (meth)acrylate]s, poly(aminoethyl methacrylate)s, poly(2-alkyl-2-oxazoline)s and poly(vinyl methyl ether)s.[10,14,15] However, this strategy is not suitable when the functional groups present in the monomer interfere with the polymerization process, especially in the case of ionic and controlled radical polymerization. Additionally, the synthesis of

functional monomers often requires a laborious work involving several synthetic steps, low reaction yields and special storage conditions to prevent polymerization. Another drawback of this procedure is that tuning of the cloud point temperature (T_{CP}) is most straightforward for copolymerizations yielding a random distribution of the comonomers, which is often not the case.

Therefore, developing novel approaches to modulate the T_{CP} over a wide range of temperatures may provide easier access to polymer platforms with tunable T_{CP}. Post-polymerization modification, also known as polymer analogous reactions, of a reactive polymeric precursor into a new functional polymer can represent a simple and robust solution.[16,17] Obviously, a key advantage is that a series of copolymers with different modification degrees or functionalities can easily be obtained by adjusting the reaction conditions. Polymer modification reactions have emerged from early days of polymer chemistry with vulcanization[18] and hydrogenation[19] being the first examples. In recent years this approach has become a very attractive strategy in polymer synthesis due to the development of click-type reactions,[20] thiol-ene, thiol-yne[21-23] and activated esters chemistry,[24] which are tolerant towards a large number of functional groups. The copper-catalyzed azide–alkyne cycloaddition (CuAAC) is a very efficient method and has been successfully used to functionalize polymers, although for biomedical applications the presence of copper is not desired. Also, incorporation of azide or alkyne groups into polymers is sometimes hazardous and not straightforward. Radical mediated thiol click reactions are simple and efficient tools for modification of reactive polymers. However, the reactivity of the thiols is highly dependent on the electronic nature of the double or triple bond,[25] while the strong odor of thiols represents another drawback of this reaction. Polymers containing activated ester bonds have been thoroughly investigated by Theato's group during recent years.[16,24,26,27] The simple conversion with amines results in copolymers whose composition essentially depends on the feed ratio of the added amine. A drawback of this approach is that these polymers are vulnerable to hydrolysis by moisture and water traces, thus requiring appropriate dry storage conditions and preventing large scale synthesis.[28] The ideal reactive polymer precursor would have to meet the following conditions: i) readily available starting materials and reagents, ii) controlled molecular weight and dispersity, iii) the post-polymerization modification should be quantitative, iv) rapid reaction rates, v) simple reaction conditions (insensitive to water and oxygen), vi) tolerance to a variety of functional groups, vii) simple product isolation, viii) absence of catalyst and by-products and ix) minimized steric control.

2-Oxazolines are a class of monomers known for their ability to polymerize via cationic ring opening polymerization.[29-31] Comprehensive studies have been conducted also on the spontaneous zwitterionic copolymerization between 2-oxazolines and electrophiles to serve as a facile platform for the generation of sophisticated polyesteramides that have the ester and amide groups in the main chain.[32-35] However, the potential of these 2-oxazoline compounds to act as activating, directing or protecting groups has mostly been overlooked in polymer chemistry, while it has been thoroughly investigated in the field of organic synthesis.[36] 2-Oxazolines can react with a variety of nucleophilic agents such as: carboxylic acids, thiols, and phenols.[37,38] Under suitable conditions, the reaction of 2-oxazolines with carboxylic acids is quantitively yielding an esteramide structure.[1,39] 2-Isopropenyl-2-oxazoline (iPOx) is a commercial available monomer that has a vinyl moiety which can be used to prepare polymers that retain the oxazoline ring as a pendant group. iPOx was successfully polymerized via living anionic polymerization using commercially available n-butyllithium giving access to polymers with controlled molecular weight and narrow dispersity.[40,41] The post-polymerization modification reaction of PiPOx with carboxylic acids is a simple and robust method.[41,42] The reaction takes place at 140 °C yielding polyesteramide structures in the absence of catalyst and without generation of by-products. This reaction meets all the criteria mention above for an ideal post-polymerization modification reaction. In our recent previous study, we demonstrated the great potential of the PiPOx homopolymer to be used as a platform for the development of thermoresponsive PiPOx copolymers with LCST behavior.[41] We showed that different aliphatic carboxylic acids (acetic, propionic, butyric, and isobutyric acid) exhibit similar reactivity to PiPOx in DMF at 140 °C, and that the T_{CP} can be easily tuned in the range 5 to 97 °C by simply changing the hydrophobic character of the acid in combination

with controlling the PiPOx modification degree. However, such thermoresponsive PiPOx copolymers still retain a fraction of 2-oxazoline side groups which render the polymers instable under acidic conditions due to ring-opening reactions. So, even though we demonstrated the versatility of the quantitative and catalyst free PiPOx modification approach for the preparation of tunable thermoresponsive PiPOx copolymers in our previous report, the presence of the (mildly) reactive iPOx units may obstruct certain applications especially in acidic conditions.[41] Furthermore, the kinetic control over the partial modification of PiPOx is less robust than controlling the final composition of a fully modified PiPOx copolymer. Therefore, we aimed in this study to develop thermoresponsive polymers based on completely modified PiPOx using acetic acid to introduce hydrophilic ester amide side chains in combination with propionic, butyric or isobutyric ester amide side chains to regulate the hydrophobicity and control the T_{CP}'s. When modifying PiPOx with acetic acid, it was found that thermoresponsive copolymers were only obtained above 85% modification degree. This finding indicates that the resulting ester amide side chains are rather hydrophilic opening the path to the development of thermoresponsive polyesteramides based on full modification of PiPOx, using acetic acetic acid to introduce hydrophilic ester amide side chains in combination with modification with a more hydrophobic acid to induce thermoresponsivity of such copolymers as illustrated in Scheme 1. Importantly, the similar reactivity of the different carboxylic acids can be used to obtain thermoresponsive copolymers with approximate random distribution by one-pot multicomponent reaction. Thus, by systematically varying the molar compositions of acetic/propionic/butyric and isobutyric functionalities for the full modification of PiPOx, the effect of each dual, triple and quadruple combination of ester amide groups on the water solubility and tunable LCST behavior will be established, which will serve as basis to develop thermoresponsive polyesteramides with a T_{CP} between room and body temperature.



SCHEME 1 One-pot multicomponent post-polymerization modification reaction of PiPOx for the preparation of the thermoresponsive polyesteramides.

EXPERIMENTAL

Materials

Acetic acid (99.5%, AAc), propionic acid (99%, APr), butyric acid (99%, ABu), and isobutyric acid (99%, AiBu) purchased from TCI Europe were used as such. N, N'-dimethylformamide (Acros Organics, DMF) 99.8%, extra dry over molecular sieve was used for all chemical modifications. Poly(2-isopropenyl-2-oxazoline) (PiPOx) was prepared via living anionic polymerization using the optimized conditions reported in our previous paper.[41] The PiPOx used in this study has an average molar mass of 17100 Da and a molar mass distribution with a dispersity of 1.22.

Synthesis of the fully modified thermoresponsive polymers (AAc-co-Acids)

Individual solutions of 35 mg (0.315 mmol) PiPOx dissolved in approximately 0.63 mL DMF are prepared in advance. Then, the corresponding quantity of multiple intermixtures between the acids is added to each individual vial keeping constant the overall feed molar ratio to PiPOx:Acids = 1:2 and an overall molar concentration of the solution of 0.5 M. The molar ratios used between two acids are as follows AAc:APr = 90:10, 80:20, 70:30, 60:40, 50:50, 40:60, AAc:ABu/ AAc:AiBu = 95:5, 90:10, 85:15, 80:20, 75:25. The molar ratios used between three acids are AAc:APr:ABu = 95:2.5:2.5, 90:5:5, 80:10:10. The molar ratios between all four acids are AAc:APr:ABu:AiBu = 70:10:10:10, 70:10:5:15, 70:5:15:10, 70:15:5:10. The resulting vials are put to react for 6 h at 140 °C to ensure that fully modified structures are obtained. The cooled solutions are diluted with chloroform, precipitated two times in cold diethylether, and dried under vacuum at 55 °C. All samples are left to slowly dissolve in distilled water in an ice-bath (0-3 °C) followed by freeze-drying. The polymers are obtained with yields between 90-95%. The compositions for the double modified copolymers can be roughly estimated from ^{1}H-NMR spectroscopy (see Table 1), while the other mixed compositions are difficult to assess due to overlapping of the signals. The cloud points are measured by turbidimetry, using 10 mg polymer/ mL of distilled water and 0.5 °C/min heating rate.

TABLE 1 Characterization data for fully modified polyesteramides

Code	Molar feed ratio	[a]Copolymer comp.	[b]Mn (Da)	[b]Đ	[c]T_{CP} (°C)
AAc-APr	90 : 10	93 : 7	29300	1.24	53.8
AAc-APr	80 : 20	80.5 : 19.5	29900	1.23	45.3
AAc-APr	70 : 30	70.5 : 29.5	31400	1.23	40.6
AAc-APr	60 : 40	61 : 39	31800	1.23	35.2
AAc-APr	50 : 50	51 : 49	32100	1.24	29.3
AAc-APr	40 : 60	45 : 55	32300	1.25	26.7
AAc-ABu	95 : 5	97 : 3	32100	1.25	44.8
AAc-ABu	90 : 10	92 : 8	32400	1.26	39.2
AAc-ABu	85 : 15	88 : 12	32900	1.27	34.6
AAc-ABu	80 : 20	82 : 18	33400	1.24	30.1
AAc-ABu	75 : 25	77 : 23	33900	1.23	24.7
AAc-AiBu	95 : 5	96 : 4	31900	1.28	55.3
AAc-AiBu	90 : 10	92 : 8	32100	1.25	47.5
AAc-AiBu	85 : 15	88 : 12	32500	1.26	42.6
AAc-AiBu	80 : 20	82 : 18	32800	1.27	32.3
AAc-AiBu	75 : 25	77 : 23	33100	1.24	26.9
AAc-APr-ABu	95 : 2.5 : 2.5	-	32300	1.26	45.9
AAc-APr-ABu	90 : 5 : 5	-	32900	1.25	43.2
AAc-APr-ABu	80 : 10 : 10	-	33200	1.23	36.1
AAc-APr-ABu-AiBu	70 : 5 : 15 : 10	-	34300	1.24	21.7
AAc-APr-ABu-AiBu	70 : 10 : 5 : 15	-	34500	1.23	23.9
AAc-APr-ABu-AiBu	70 : 10 : 10 : 10	-	33900	1.25	22.2
AAc-APr-ABu-AiBu	70 : 15 : 5 : 10	-	33300	1.24	25.9

[a] The copolymer compositions were determined from ^{1}H NMR spectroscopy. [b] The molar mass of fully modified polyesteramides was determined by SEC in DMAc against PMMA standards. [c] The cloud point temperatures were measured in distilled water by turbidimetry at 10 mg/mL with a heating rate of 0.5 °C/min.

Characterization

^{1}H NMR spectra were recorded at 25 °C on a Bruker instrument operating at 400 MHz. Chemical shifts (δ) are referenced to $CDCl_3$ (δ 7.26 ppm). Size-exclusion chromatography (SEC) was performed on an Agilent 1260-series HPLC system equipped with a 1260 online degasser, a 1260 ISO-pump, a 1260 automatic liquid sampler (ALS), a

thermostatted column compartment (TCC) at 50°C equipped with two PL gel 5 µm mixed-D columns and a precolumn in series, a 1260 diode array detector (DAD) and a 1260 refractive index detector (RID). The used eluent is DMAc containing 50 mM of LiCl at a flow rate of 0.5 mL/min. The spectra are analyzed using the Agilent Chemstation software with the GPC add on. Molar mass values and Đ values are calculated against PMMA standards from PSS.

The cloud point temperatures (T_{CP}'s) were measured on a Crystal 16TM parallel crystallizer turbidimeter developed by Avantium Technologies connected to a recirculation chiller and dry compressed air. Polymer solutions (10 mg/mL) in distilled water are heated from 2 up to 5 °C above the cloud point with a heating rate of 0.5 °C/min followed by cooling to 2 °C at a cooling rate of 0.5 °C/min. This cycle was repeated two times. The T_{CP}'s are reported as the 50% transmittance temperature in the 2nd heating run.

RESULTS AND DISCUSSION

Three series of double modified polymers have been prepared by one pot multicomponent modification with mixtures of acetic acid and the three different more hydrophobic acids, namely propionic acid, isobutyric acid and butyric acid (Scheme 1. I), followed by a series of triple modified polymers (Scheme 1. II) and one quadruple modified polymers (Scheme 1. III). The full modification of PiPOx in these reactions was confirmed by ^{1}H NMR spectroscopy by complete disappearance of the iPOx signal at 3.72 ppm.

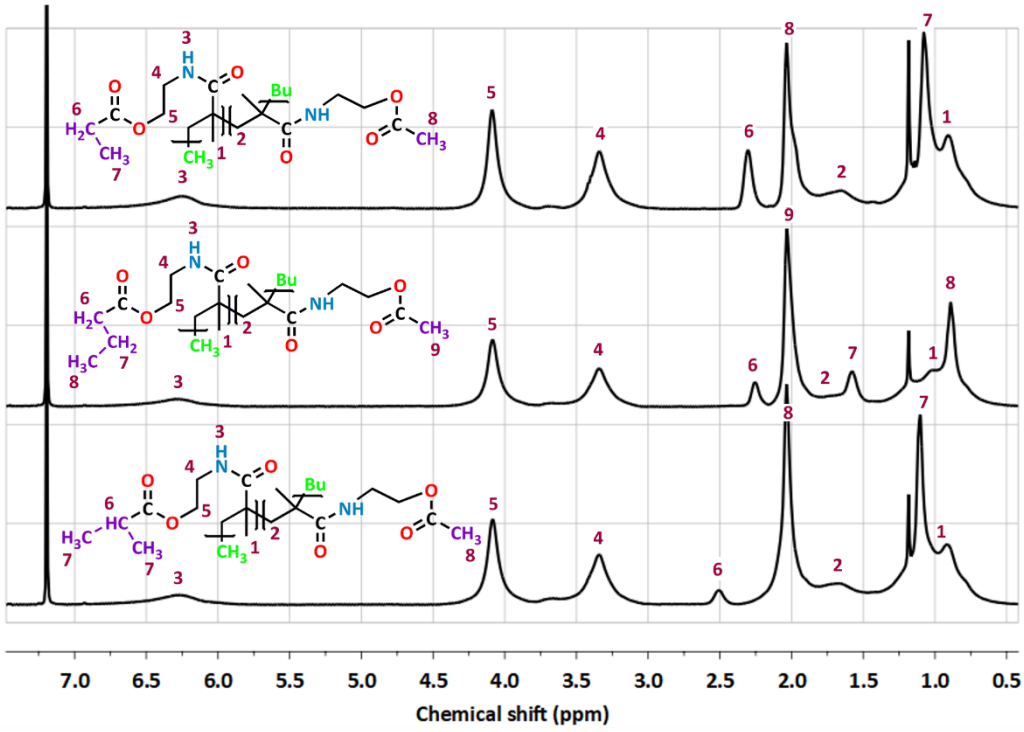


FIGURE 1 Selected ^{1}H NMR spectra in cholorform-d_1 for the fully modified copolymers AAc-co-APr (60:40) top, AAc-co-ABu (75:25) middle, and AAc-co-AiBu (75:25) bottom.

Selected ^{1}H NMR spectra of the double modified polymers are given in Figure 1 to highlight the combined modification with the two aliphatic functionalities. The molar ratio between the two acids in the dual modified copolymers was calculated from the ^{1}H-NMR spectra based on the proton area of the signal from 2.3 ppm (-*CH*$_2$-COO-) and the integral from the signal at 4.2 ppm (-CH$_2$-COO-*CH*$_2$-) and is given in Table 1. The thermoresponsive behavior of these fully modified copolymers was evaluated in distilled water by turbidimetry as previously

reported for the partially modified PiPOx copolymer series (see Table 1). The transmittance versus temperature profiles showed sharp transition curves for all double modified polymers, as shown in Figure 2. The transitions were fully reversible and revealed a small hysteresis. The resulting T_{CP} values for the double modified copolymer series are plotted versus the co-acid content in Figure 3A. Noteworthy is that the correlation between the T_{CP} and the co-acid content is best described using linear regression, see equations in Figure 3A, in contrast to the partially modified PiPOx copolymers that we reported earlier where the relation of T_{CP} versus acid modification degree was best described using exponential decay fits.[41] These different correlations may be ascribed to the size of the hydrophilic and hydrophobic repeat units in the copolymers. Within the partially modified PiPOx copolymer series, the hydrophilic iPOx units are significantly smaller than the hydrophobic ester amide side chains. Therefore, it may be hypothesized that the effect of the hydrophobic units on the solubility is stronger than the effect of the hydrophilic PiPOx units leading to a non-linear correlation. In contrast, the size of the acetic ester amide units and other acid modified ester amide units in the fully modified (co)polymers is similar leading to a more equal exposure to water and more equal contribution to solubility behavior.

The second notable difference between the partially modified PiPOx (PiPOx-Ax) copolymers and the fully modified (AAc-Ax) copolymers is that the T_{CP}'s of the fully modified copolymers are lower, e.g. 64.8 °C versus 45.3 °C for copolymers with 20 mol% APr, 58.5 °C versus 34.6 °C for copolymers with 15 mol% ABu and 77.6 °C versus 42.6 °C for copolymers with 12 mol% AiBu, respectively. This observation is in accordance with the more hydrophobic character of the acetyl ester amide functionality as compared to the 2-oxazoline ring as indicated by the LCST behavior of the PiPOx fully modified with acetic acid, which increases the overall hydrophobicity of the polymer and decreases the transition temperatures.

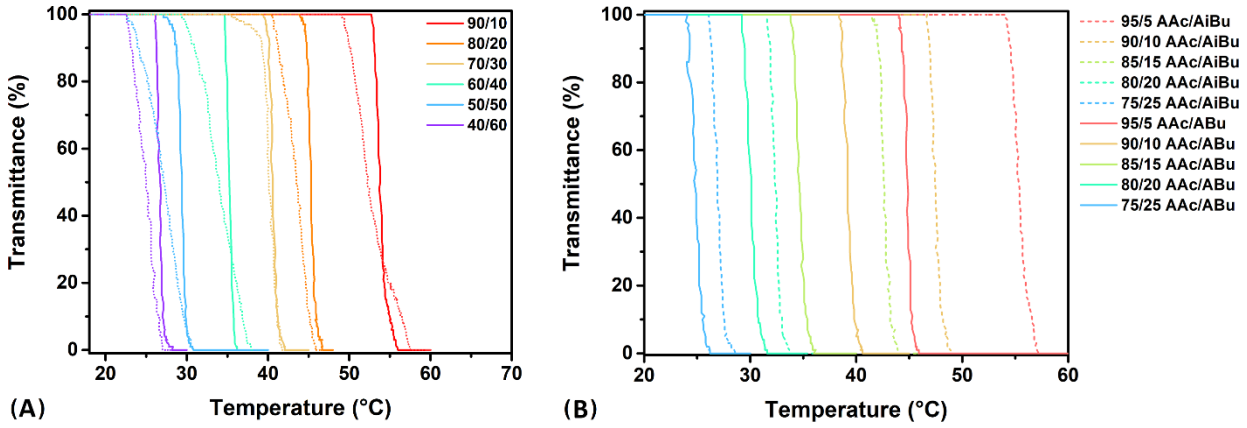


FIGURE 2 Transmittance versus temperature profiles for heating (solid lines) and cooling (dashed lines) cycles for AAc-co-APr series (A), and heating cycles for AAc-co-ABu (solid lines) and AAc-co-AiBu (dashed lines) series (B) in distilled water (10 mg/mL, 0.5 °C/min).

Interestingly, this difference between the partially and fully modified PiPOx copolymer series vanishes at higher contents of co-acid, especially for the AAc-co-APr series. Thus, at 55 mol% APr content, both the PiPOx-APr and the AAc-APr copolymers reached a similar value of the T_{CP} of 29.3 °C and 26.7 °C, respectively. This observation confirms our hypothesis that the exposure of the iPOx units to water is less efficient compared to acetic ester amide side chains. When the polymer is modified to a higher extend with propionic ester amide side chains, the iPOx units are more and more shielded eventually resulting in similar behavior of the partially and fully modified copolymer series.

Another intriguing observation is that the correlation of T_{CP} with co-acid content in the AAc-AiBu series is much steeper compared to the AAc-ABu and AAc-APr copolymer series. As the hydrophobicity of the ABu and AiBu ester amide side chains is believed to be rather similar, this difference between the T_{CP} values of the AAc-ABu and AAc-AiBu copolymers may be related to the higher rigidity and compactness of the latter. At low AiBu content the compactness leads to less shielding of the AAc amide side chains providing more hydrophilic copolymers compared to AAc-ABu while at higher AiBu content this effect becomes less and less important so that the overall similar hydrophobicity will determine the T_{CP} at higher (iso)butyric acid content leading to similar T_{CP} values for AAc-ABu and AAc-AiBu. Importantly, these three fully modified PiPOx copolymer series demonstrated that each reported combination of acids allows accurate tuning of the thermoresponsive properties of the copolymers, e.g. in between room temperature and body temperature.

To further demonstrate the level of control that we can achieve in regulating the thermoresponsiveness of fully modified PiPOx copolymers, we moved our attention to modification of PiPOx with more elaborated combinations of the aliphatic acids. The target thermoresponsive window for our triple and quadruple modified polymers based on AAc, APr and ABu or AAc, APr, ABu and AiBu, respectively, was between body and room temperature, being the relevant window for biomedical applications [43]. The turbidity curves from the second heating run of these copolymer series are displayed in (Figure 3B).

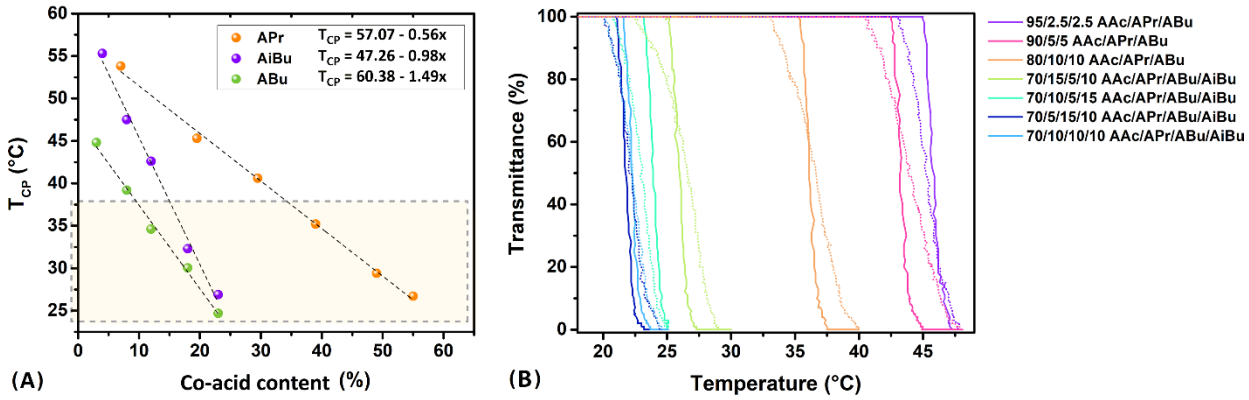


FIGURE 3 The correlation of co-acid content with the cloud point temperatures (T_{CP}) for the double modified AAc-co-Acid copolymer series (A); Transmittance versus temperature profiles for heating and cooling cycles of AAc-co-APr-ABu and AAc-co-APr-ABu-AiBu copolymer series in distilled water (10 mg/ml; 0.5 °C/min) (B).

If we look at the temperature profiles, we can observe that a copolymer modified with 80 mol% AAc and 10 mol% of both APr and ABu co-acids has a T_{CP} close to body temperature at 36.1 °C. This T_{CP} is nicely in between the T_{CP}'s of the AAc copolymers with 20 mol% of APr or ABu indicating that this triple modification strategy allows further fine-tuning of the thermoresponsive properties.

To further lower the T_{CP}s towards room temperature higher percentages of co-acids are required. Accordingly, a series of quadruple modified copolymers was prepared having 30 mol% of hydrophobic co-acids with different compositional mixtures of APr-ABu-AiBu, indeed resulting in T_{CP} values close to room temperature, namely 21.7 °C, 22.2 °C, 23.9 °C and 25.9 °C (Figure 3B). Thus, by mixing the acid-functionalities in a single modification step, the T_{CP}s of the resulting fully modified PiPOx copolymers can be accurately controlled in the range of room temperature to body temperature, demonstrating the feasibility of this approach.

CONCLUSIONS

In conclusion, we established a simple, robust and straightforward one-pot multi-component post-polymerization modification reaction for the synthesis of thermoresponsive copolymers. PiPOx was used as a reactive platform for full modification with two, three of four different carboxylic acids, yielding thermoresponsive polyesteramides. The T_{CP} could be easily tuned by simply changing the feed ratio of the acid components. Furthermore, an empirical model was established to predict the T_{CP} of the dual modified copolymers that followed a linear correlation between acid comonomers ratio and T_{CP}. The simplicity of the method, together with the large availability of commercially carboxylic acids provides a toolbox for the design of tailor made (multi) stimuli materials, which will be the focus of a future work.

ACKNOWLEDGEMENTS

F. A. Jerca acknowledges the Romanian National Authority for Scientific Research (UEFISCDI) for the financial support, mobility grant number PN-III-P1-1.1-MC-2017-1944 and grant PN-III-P1-1.2-PCCDI no.70/2018. R. Hoogenboom acknowledges Ghent University and the FWO Flanders for continuous support of his research.

REFERENCES AND NOTES

1. V. V. Jerca, F. A. Nicolescu, R. Trusca, E. Vasile, A. Baran, D. F. Anghel, D. S. Vasilescu, D. M. Vuluga. *React Funct Polym* **2011**, *71*, 373-379.
2. M. A. C. Stuart, W. T. S. Huck, J. Genzer, M. Müller, C. Ober, M. Stamm, G. B. Sukhorukov, I. Szleifer, V. V. Tsukruk, M. Urban, F. Winnik, S. Zauscher, I. Luzinov, S. Minko. *Nature Materials* **2010**, *9*, 101.
3. M. Wei, Y. Gao, X. Li, M. J. Serpe. *Polymer Chemistry* **2017**, *8*, 127-143.
4. V. R. de la Rosa, P. Woisel, R. Hoogenboom. *Materials Today* **2016**, *19*, 44-55.
5. C. Lu, M. W. Urban. *Progress in Polymer Science* **2018**, *78*, 24-46.
6. F. A. Nicolescu, V. V. Jerca, I. C. Stancu, D. S. Vasilescu, D. M. Vuluga. *Des Monomers Polym* **2010**, *13*, 437-444.
7. L. Xiaolin, Y. Ying, U. M. W. *Macromolecular Rapid Communications* **2017**, *38*, 1700030.
8. C. Zi-Quan, W. Guo-Jie. *The Chemical Record* **2016**, *16*, 1398-1435.
9. Y. Zhu, R. Batchelor, A. B. Lowe, P. J. Roth. *Macromolecules* **2016**, *49*, 672-680.
10. D. Roy, W. L. A. Brooks, B. S. Sumerlin. *Chemical Society Reviews* **2013**, *42*, 7214-7243.
11. C. Pietsch, R. Hoogenboom, U. S. Schubert. *Angewandte Chemie International Edition* **2009**, *48*, 5653-5656.
12. F. D. Jochum, L. zur Borg, P. J. Roth, P. Theato. *Macromolecules* **2009**, *42*, 7854-7862.
13. F. D. Jochum, P. Theato. *Polymer* **2009**, *50*, 3079-3085.
14. N. Vanparijs, L. Nuhn, B. G. De Geest. *Chemical Society Reviews* **2017**, *46*, 1193-1239.
15. G. Vancoillie, D. Frank, R. Hoogenboom. *Progress in Polymer Science* **2014**, *39*, 1074-1095.
16. P. Theato, H.-A. Klok. Functional polymers by post-polymerization modification: concepts, guidelines and applications; John Wiley & Sons, **2013**.
17. E. Blasco, M. B. Sims, A. S. Goldmann, B. S. Sumerlin, C. Barner-Kowollik. *Macromolecules* **2017**, *50*, 5215-5252.
18. W. A. Cunningham. *Journal of Chemical Education* **1935**, *12*, 120.
19. S. H., F. J. *Helvetica Chimica Acta* **1922**, *5*, 785-806.
20. G. M. A., G. M. I., K. Harm-Anton. *Angewandte Chemie International Edition* **2009**, *48*, 48-58.
21. K. M. J., B. D. J., H. C. J. *Journal of Polymer Science Part A: Polymer Chemistry* **2010**, *48*, 743-750.
22. A. B. Lowe. *Polymer Chemistry* **2014**, *5*, 4820-4870.
23. S. Reinicke, P. Espeel, M. M. Stamenović, F. E. Du Prez. *ACS Macro Letters* **2013**, *2*, 539-543.
24. A. Das, P. Theato. *Chemical Reviews* **2016**, *116*, 1434-1495.
25. H. C. E., B. C. N. *Angewandte Chemie International Edition* **2010**, *49*, 1540-1573.
26. T. Patrick. *Journal of Polymer Science Part A: Polymer Chemistry* **2008**, *46*, 6677-6687.
27. M. Eberhardt, R. Mruk, R. Zentel, P. Théato. *Eur Polym J* **2005**, *41*, 1569-1575.
28. C. P. Easterling, T. Kubo, Z. M. Orr, G. E. Fanucci, B. S. Sumerlin. *Chemical Science* **2017**, *8*, 7705-7709.
29. G. Mathias, V. Maarten, H. Richard. *Polymer International* **2018**, *67*, 32-45.

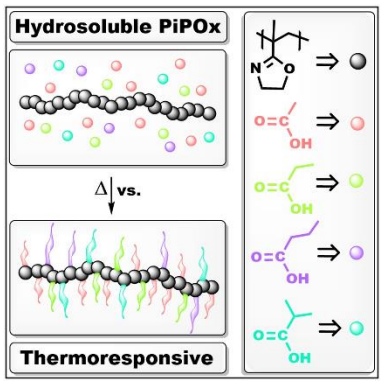
30. B. Verbraeken, B. D. Monnery, K. Lava, R. Hoogenboom. *Eur Polym J* **2017**, *88*, 451-469.
31. V. V. Jerca, F. A. Nicolescu, D. S. Vasilescu, D. M. Vuluga. *Polym Bull* **2011**, *66*, 785-796.
32. K. Kempe, P. A. J. M. de Jongh, A. Anastasaki, P. Wilson, D. M. Haddleton. *Chemical Communications* **2015**, *51*, 16213-16216.
33. P. A. J. M. de Jongh, A. Mortiboy, G. S. Sulley, M. R. Bennett, A. Anastasaki, P. Wilson, D. M. Haddleton, K. Kempe. *ACS Macro Letters* **2016**, *5*, 321-325.
34. K. Kristian. *Macromolecular Chemistry and Physics* **2017**, *218*, 1700021.
35. J. Steinkoenig, P. A. J. M. de Jongh, D. M. Haddleton, A. S. Goldmann, C. Barner-Kowollik, K. Kempe. *Macromolecules* **2018**, *51*, 318-327.
36. G. S. Wong, W. Wu, In Oxazoles: Synthesis, Reactions, and Spectroscopy; Taylor, E. C., Wipf, P., Weissberger, A., Palmer, D. C., Eds., **2004**.
37. B. M. Culbertson. *Progress in Polymer Science* **2002**, *27*, 579-626.
38. J. A. Frump. *Chemical Reviews* **1971**, *71*, 483-505.
39. M. C. Spiridon, F. A. Jerca, V. V. Jerca, D. S. Vasilescu, D. M. Vuluga. *Eur Polym J* **2013**, *49*, 452-463.
40. F. T. Reyes, E. L. Malins, C. R. Becer, M. A. Kelland. *Energy & Fuels* **2013**, *27*, 3154-3160.
41. F. A. Jerca, V. V. Jerca, A. M. Anghelache, D. M. Vuluga, R. Hoogenboom. *Polymer Chemistry* **2018,** doi:10.1039/C8PY00612A.
42. V. V. Jerca, F. A. Nicolescu, A. Baran, D. F. Anghel, D. S. Vasilescu, D. M. Vuluga. *Reactive and Functional Polymers* **2010**, *70*, 827-835.
43. M. A. Ward, T. K. Georgiou. *Polymers* **2011**, *3*, 1215.

GRAPHICAL ABSTRACT

Florica Adriana Jerca, Valentin Victor Jerca and Richard Hoogenboom

Well-defined thermoresponsive polyesteramides through one-pot multicomponent post-polymerization modification of poly(2-isopropenyl-2-oxazoline)

The preparation of polyesteramides by one-pot multicomponent post-polymerization modification of poly(2-isopropenyl-2-oxazoline) (PiPOx) allows access to a variety of tunable thermoresponsive structures which are of interest in the biomedical field. The ring-opening modification of PiPOx is highlighted as a versatile reaction platform for making polyesteramides based on: i) insensitivity to water and oxygen, ii) simple reaction conditions, iii) quantitative post-polymerization modification, iv) simple product isolation, and v) absence of catalyst and by-products.



GRAPHICAL ABSTRACT FIGURE