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Alternating Copolymerization of Bio-based *N*-acetylhomocysteine Thiolactone and Epoxides

Nicolas Illy,* Valentin Puchelle, Simon Le Luyer and Philippe Guégan

Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire, Equipe Chimie des Polymères, 4 place Jussieu, F-75005 Paris, France.

Corresponding Author

* Nicolas Illy: Phone 33 (0)1 44275513 E-mail: nicolas.illy@sorbonne-universite.fr

KEYWORDS: alternating copolymerization, anionic ring-opening polymerization, bio-based γ -thiolactone, epoxide, polythioether.

Abstract

The anionic ring-opening polymerizations (AROP) of bio-based *N*-acetyl homocysteine thiolactone (NHTL) and different epoxides were carried out using benzyl alcohol and 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) as initiating system. This polymerization is a rare example of AROP in the presence of an acidic moiety (acetamido group). Well-defined alternating poly(ester-*alt*-sulfide)s are obtained with number-average molar masses M_n ranging from 1.7 to 13.0 kg mol⁻¹ and dispersities as low as 1.14. The presence of one acetamido function in the lateral group on each repeating unit of the copolymers derived from NHTL results in very significant increases (up to 94°C) of the glass transition temperature T_g compared to similar poly(ester-*alt*-sulfide) derived from petro-based

γ -butyrolactone (BTL). These functional poly(NHTL-*alt*-epoxide)s are valuable structures with numerous potential applications due to the presence in each repeating unit of one cleavable ester group and one redox-sensitive thioether group.

Introduction

In recent years, various sulfur-containing polymers including poly(thioether)s, poly(thiourethane)s, poly(thiocarbonate)s and poly(thioester)s, have been synthesized by alternating or multi-component polymerization.[1] These copolymers display a wide range of applications in various fields. The copolymerization of carbon disulfide (CS₂) with episulfides afforded sulfur-rich poly(trithiocarbonate)s with high refractive indexes,[2, 3] while its copolymerization with diamines led to poly(thiourea)s with promising self-healing and heavy metal absorption properties.[4] The alternating copolymerization of carbonyl sulfide (COS) with epoxides has provided a variety of colorless and highly transparent poly(thiocarbonate)s with high refractive index and Abbe number, which favor their applications as optical materials.[5-7] COS can also be copolymerized with aziridine leading to polythiourethanes with potential applications in optical materials, coatings, heavy-metal recognition and medical technology.[8] The ring-opening polymerization of cyclic thioanhydrides and episulfides or epoxides allowed the syntheses of well-defined poly(thioester)s with alternating sequences.[9, 10] Selenium-containing poly(thioester) with high refractive index were prepared by alternating copolymerization of episulfides with gamma-selenobutyrolactone.[11]

The synthesis of poly(thioether)s by anionic ring-opening polymerization of episulfides is known since decades. Poly(thioether)s have also been recently synthesized by one-pot reactions of epoxides with carbonyl sulfide[12] or with carbon disulfide[13] according to an addition mechanism followed by a de(thio)carboxylative ring-opening polymerization of the generated cyclic (di)thiocarbonates. Polythioethers are industrially used as adhesives, sealants,[14] and coatings[15] (e.g. Thioplast® M from Nouryon) and have a high potential for biomedical applications. However in comparison with their polyether counterparts, the range of polythioether repeating units and architectures that can be prepared by controlled chain polymerization remains rather limited. Therefore, the development of easy-to-implement synthetic routes for the preparation of well-defined functional polythioethers (e.g. biodegradable polythioethers) is a key challenge in macromolecular engineering.

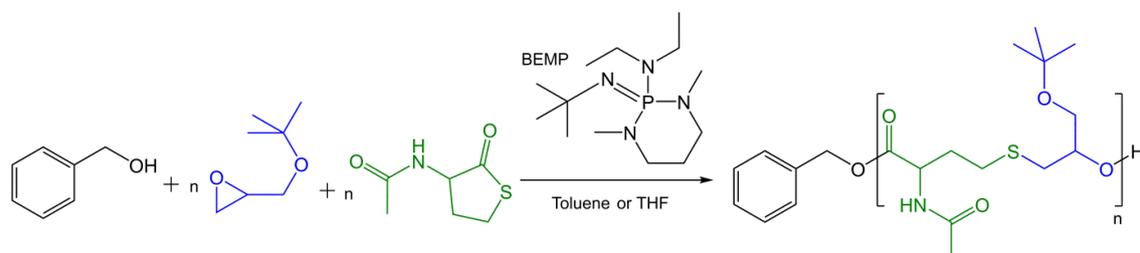
γ -Thiolactone chemistry has already been well reported as a highly useful tool for polymer functionalization and postmodification.[16] Since 1956, thiolactones are used for the introduction of thiol groups in proteins.[17] In contrast, thiolactones have been scarcely employed as monomers in macromolecular chemistry until the recent papers of Du Prez and co-workers.[18-21] They showed that γ -thiolactones bearing allyl or acrylate groups can be ring-opened by primary amines releasing a thiol-containing AB monomer, that can be subsequently polymerized by stepwise thiol-ene polymerization paving the way to the syntheses of numerous functionalized polymers with polythioether/polyurethane or polyamide/polythioether backbones. Interestingly, the amine-thiol-ene protocol has been successfully applied to a bio-based thiolactone derived from 10-undecenoic acid and DL-homocysteine thiolactone.[21] Multifunctional sequence-defined oligomers have been synthesized using the inherent double modification properties of the thiolactone moiety of α -isocyanato- γ -thiolactone and the high reactivity of isocyanates with alcohols.[22, 23] Martens *et al.* demonstrated that these multifunctional sequence-defined macromolecules can be used

for chemical data storage.[24] To the best of our knowledge, the homopolymerization of monocyclic γ -thiolactones have never been reported. However, Yuan *et al.* succeeded to homopolymerized a 4-hydroxyproline-derived γ -thiolactone to produce a fully recyclable polythioester.[25] The polymerization is made possible by the increase of the ring strain due to the bridged bicyclic nature of the monomer.[26] Destarac and co-workers reported the copolymerization of substituted γ -thiolactones with trimethylene carbonate.[27] In 1998, the alternating ring-opening copolymerization of γ -thiobutyrolactone with epoxides catalyzed by quaternary onium salts was reported by Nishikubo and co-workers.[28] Perfectly alternating poly(ester-*alt*-sulfide)s were obtained with high dispersities (\bar{M}_w/\bar{M}_n) and low molar-mass control. A better control of the alternating ring-opening copolymerization and an extension of the epoxy monomer scope was recently achieved using alcohol-phosphazene bases as initiating systems.[29] The generated poly(thioether-*alt*-ester)s are attractive functional materials due to the presence of both biodegradable ester groups and oxydable (reactive oxygen species-sensitive) thioether groups in each repeating unit of the main backbone. The use of two distinct monomer sets could advantageously enabled the facile tuning of the properties of the resultant copolymers. But, if epoxides with various structures have been copolymerized with γ -butyrothiolactone, the latter is up-to-now the only γ -thiolactone that has been efficiently used in such copolymerization. In particular, *N*-acetylhomocysteine thiolactone (NHTL), also called citiolone, is commercially-available at relatively low cost and can be synthesized from renewable resources, acetic acid and D,L-homocysteine thiolactone hydrochloride.[21, 30]

In this work, the alternating ring-opening copolymerization of NHTL with different epoxides is examined. Despite the presence of an acidic amide group on NHTL making anionic polymerization challenging, well-defined poly(thioether-*alt*-ester)s bearing a lateral amide group in each repeating unit have been synthesized using benzyl alcohol and a phosphazene base (BEMP) as initiating system. A drastic increase of the glass transition

temperatures has been evidenced compared to alternating copolymers from the same epoxides but using γ -thiolactone instead of NHTL.

DISCUSSION



Scheme 1. Synthesis of poly(NHTL-*alt*-*t*BuGE) using benzyl alcohol-BEMP as initiating system.

Table 1. Experimental conditions and molecular characteristics of poly(NHTL-*alt*-epoxide)s synthesized using benzyl alcohol and BEMP as initiating system.

| Run | ROH ^a :Base:Epoxide:NHTL | Epoxide ^b | Solvent | T° [°C] | Time [h] | Cv ^c [%] | M _{n,th} [g mol ⁻¹] | M _n (NMR) [g mol ⁻¹] | M _n (SEC) ^d [g mol ⁻¹] | Đ (SEC) |
|-----|-------------------------------------|----------------------|---------|------------|-------------|------------------------|---|--|---|---------|
| 1 | 1:1:0:25 | - | Toluene | 90 | 24 | 0 | - | - | - | - |
| 2 | 1:1:25:0 | <i>t</i> BuGE | Toluene | 90 | 24 | 0 | - | - | - | - |
| 3 | 1:1:25:25 | <i>t</i> BuGE | Toluene | 90 | 4,5 | 90 | 6570 | 6500 | 5300 | 1.29 |
| 4 | 1:1:25:25 | <i>t</i> BuGE | Toluene | 90 | 24 | 100 | 7300 | 6200 | 4100 | 1,51 |
| 5 | 1:2:25:25 | <i>t</i> BuGE | Toluene | 90 | 24 | 100 | 7300 | 3000 | 1700 | 1.62 |
| 6 | 1:1:25:25 | <i>t</i> BuGE | - | 90 | 3.25 | 91 | 6600 | 5800 | 5400 | 1.98 |
| 7 | 1:1:25:25 | <i>t</i> BuGE | Toluene | 60 | 4,5 | 85 | 6205 | 6700 | 5600 | 1.23 |
| 8 | 1:1:25:25 | <i>t</i> BuGE | Toluene | 30 | 55 | 90 | 6570 | 5400 | 5000 | 1.27 |
| 9 | 1:1:40:40 | <i>t</i> BuGE | Toluene | 60 | 7 | 82 | 9600 | 8100 | 6900 | 1.31 |
| 10 | 1:1:25:25 | <i>t</i> BuGE | THF | 60 | 19 | 100 | 7300 | 5900 | 6320 | 1.29 |
| 11 | 1:1:25:25 | <i>t</i> BuGE | THF | 55 | 4.5 | 95 | 6950 | 6750 | 5500 | 1.23 |
| 12 | 1:1:50:50 | <i>t</i> BuGE | THF | 55 | 5 | 85 | 12500 | 14000 | 12950 | 1.14 |
| 13 | 1:1:25:25 | BO | THF | 55 | 6 | 92 | 5400 | 5800 | 3880 | 1.37 |
| 14 | 1:1:25:25 | PhGE | THF | 55 | 21 | 99 | 6800 | 6250 | 2500 | 1.71 |
| 15 | 1:1:25:25 | BnGE | THF | 55 | 6 | 80 | 6600 | - | 5600 | 1.50 |

^a ROH = benzyl alcohol

^b *Tert*-butyl glycidyl ether (*t*BuGE), butylene oxide (BO), phenyl glycidyl ether (PhGE) and benzyl glycidyl ether (BnGE).

^c Conversion was determined by ¹H NMR in CDCl₃ of the reaction mixture by comparing the signals corresponding to the -CHR- group in α position of the repeating unit ester group to the -CHR- group next to the acetamido group of both monomer and polymer (Figure S4).

^d Determined by SEC (THF, 40 °C, poly(methyl methacrylate) standards).

First, the homopolymerization of NHTL (Table 1, run 1) and *t*BuGE (Table 1, run 2) were tried in toluene at 90°C using benzyl alcohol - BEMP as initiating system. No homopolymerization occurred for both experiments. These results are not surprising as the ring-opening homopolymerization of monocyclic γ -thiobutyrolactone has never been reported. Similarly, to the best of our knowledge, BEMP was never successfully used as single catalyst for epoxide polymerization. As reported in Table 1 runs 3-5 and 7-9, *tert*-butyl glycidyl ether (*t*BuGE) and NHTL were successfully copolymerized in toluene using benzyl alcohol and BEMP as initiating system. Considering that no homopolymerization of both monomers occurred using the same initiating system at 90°C and by analogy with the recently reported alternating AROP of γ -thiolactone with epoxides, perfectly alternating structures are postulated (Scheme 1).[29] Three experiments were performed at 90, 60 and 30°C (Table 1, runs 3, 7-8). An increase of the viscosity followed by a phase separation took place. At 60 and 90°C, high conversions were obtained after 4.5 hours, while the propagation rate was significantly lower and 55 hours were necessary to achieve a similar conversion at 30°C. Good agreements are observed between the theoretical M_n and the experimental M_n measured by ^1H NMR and size exclusion chromatography (SEC). In addition, all copolymers display spectroscopic data consistent with the postulated alternating structure initiated by a benzyloxy group. All the signals observed in ^1H and ^{13}C NMR could be assigned on the spectra (Figures 1 and S5).

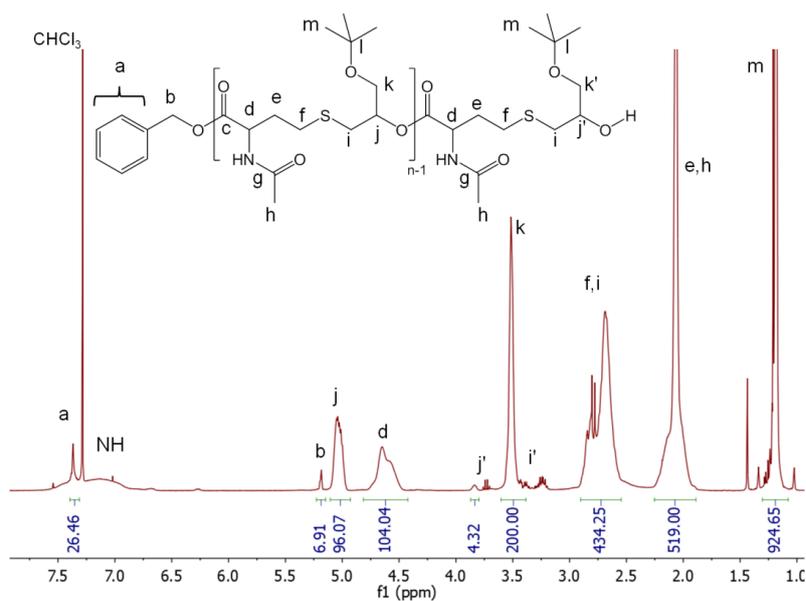


Figure 1. ^1H NMR spectrum of poly(NHTL-*alt*-*t*BuGE) in CDCl_3 at 25°C (Table 1, run 9).

The Fourier-transform infrared (FT-IR) spectrum of poly(NHTL-*alt*-*t*BuGE) (Figure S6) also confirmed the alternating character of the polymerization showing the complete disappearance of the absorbance peak corresponding to thioester carbonyl at 1693 cm^{-1} , and the formation of a new peak at 1739 cm^{-1} , associated with the carbonyl of the generated ester group in each repeating unit. Interestingly, NHTL monomer possesses an acidic amide-NH hydrogen and a conjugated carbonyl moiety, which were likely to react with the anionic propagating centers.[31-33] However, no interferences with the mechanism of the alternating polymerization have been evidenced. With the help of a ^1H - ^{15}N *heteronuclear single quantum correlation* (HSQC) NMR spectrum, the large ^1H NMR signal between 6.8 and 7.6 ppm could be attributed to NH of the unmodified acetamido groups (Figure 2).

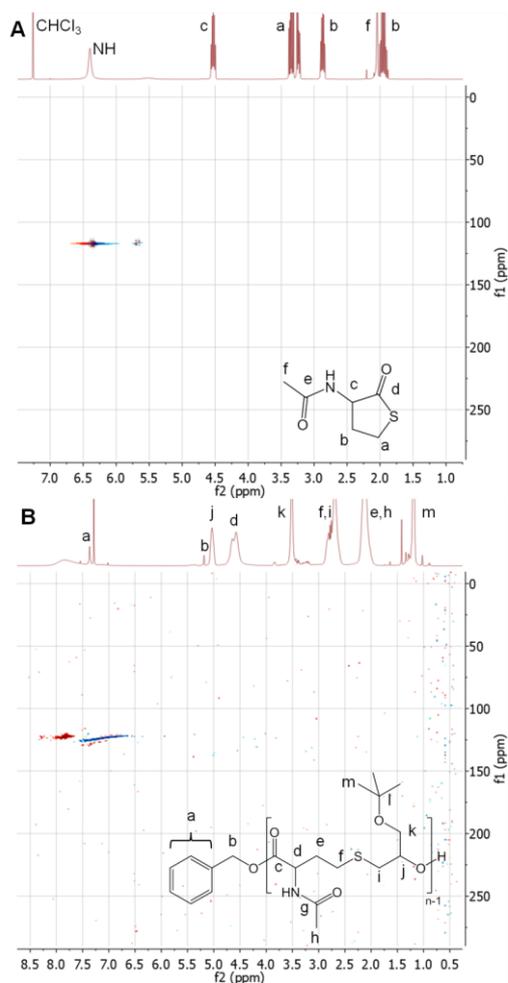


Figure 2. 2D ^1H - ^{15}N HSQC NMR spectra in CD_2Cl_2 at room temperature: A) N-acetyl homocysteine thiolactone; B) poly(NHTL-*alt*-tBuGE) (Table 1, run 5).

Longer reaction time (Table 1, run 4) resulted in reduced M_n , higher Đ and low-molar-mass tailing in the SEC trace. We assume that the latter result is due to the occurrence of transesterification reactions between propagating alcoholates and ester groups of the macromolecular chains. A similar behavior was previously described for the alternating copolymerization of γ -butyrolactone with epoxides.[29] A higher amount of BEMP (2 eq., Table 1, run 5) resulted in even more reduced M_n and higher Đ (Table 1, run 5). It was previously demonstrated that higher amount of phosphazene base favor the occurrence of side-reaction due to an increase the propagating center reactivities.[32-33] A polymerization in the bulk at 90°C resulted in high dispersity polymer (Table 1, run 6). In order to increase

the M_n , a reaction was performed at 60°C by increasing the $([\text{NHTL}]_0 + [\text{tBuGE}]_0) / [\text{ROH}]_0$ ratio (Table 1 run 9, $X_{n,\text{targeted}} = 80$). However, the phase separation occurring during the chain growth is detrimental to monomer conversions and limits the achievable M_n .

Non-polar toluene was replaced by THF, a solvent of moderate polarity, in order to avoid phase segregation by simultaneously increasing the solvation of the propagating anions and the polymer chain solubility (Table 1, runs 10-11). High monomer conversions were achieved and the reaction mixtures remained homogeneous throughout all the conversion range. Even for a targeted degree of polymerization of 100, a well-defined poly(NHTL-*alt*-tBuGE) with the expected M_n and a low dispersity (Figure S7) was obtained (Table 1, run 12). The scope of this alternating copolymerization has been extended to other epoxide monomers (Table 1, runs 13-15): butylene oxide (BO), phenyl glycidyl ether (PhGE) and benzyl glycidyl ether (BnGE), resulting in the expected alternating structures: poly(NHTL-*alt*-BO), poly(NHTL-*alt*-PhGE) and poly(NHTL-*alt*-BnGE), respectively (Figures S8-S12).

Table 2. Thermal properties of the alternating copolymers.

| Entry | Run | Chemical nature | $T_{d,10\%}$ [°C] ^a | T_{dm} [°C] ^b | T_g [°C] |
|-------|-----------------|---|--------------------------------|----------------------------|------------|
| 1 | Table 1, run 5 | poly(NHTL- <i>alt</i> -tBuGE) | 288 | 307 | 44 |
| 2 | Table 1, run 5 | poly(NHTL- <i>alt</i> -BO) | 282 | 303 | 37 |
| 3 | Tables 1, run 6 | poly(NHTL- <i>alt</i> -PhGE) | 286 | 313 | 35 |
| 4 | Table 1, run 7 | poly(NHTL- <i>alt</i> -BnGE) | 282 | 313 | 5 |
| 5 | Table S1, run 1 | poly(BTL- <i>alt</i> -tBUGE) ^c | 318 | 349 | -33 |
| 6 | Table S1, run 2 | poly(BTL- <i>alt</i> -BO) ^c | 296 | 318 | -57 |

^a Decomposition temperature after 10% weight loss.

^b Decomposition temperature at maximum degradation rate (derivative thermogravimetry).

^c Prepared according to Puchelle et al.[29]

Lastly, four poly(NHTL-*alt*-epoxide)s and two poly(BTL-*alt*-epoxide)s were characterized by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). Their

thermal stabilities and characteristics are summarized in Table 2. A one-step degradation profile was observed for poly(NHTL-*alt*-*t*BuGE) as shown in Figure 3. The decomposition after 10% weight loss occurred at 288 °C and is followed by a rapid weight loss. Identical one-step degradation profile were observed for all the alternating copolymers with the decomposition after 10% weight loss ranging from 282 to 318 °C (Figures S13-S17). Similar degradation temperatures have been observed for polythioethers in the literature, suggesting that carbon-sulfur bond is the weakest linkage in the polymer structure.[21]

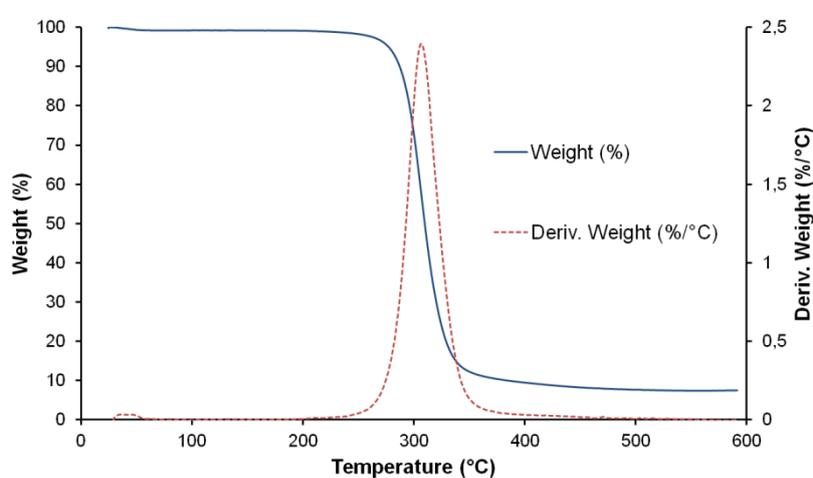


Figure 3. TGA curve and its first derivative measured under a stream of nitrogen between 20 and 600 °C with a heating rate of 20 °C min⁻¹ for a poly(NHTL-*alt*-*t*BuGE) (Table 2, entry 1).

All copolymers are amorphous, only displaying glass transition temperatures (T_g) (Figure 4). Poly(BTL-*alt*-*t*BuGE) and poly(BTL-*alt*-BO) exhibited T_g values equal to -33 and -57°C, reflecting the flexible nature of thioether bonds. Interestingly, the T_g of poly(NHTL-*alt*-*t*BuGE) is +77 °C higher than the one of poly(BTL-*alt*-*t*BuGE). This difference strongly suggests that the additional acetamido groups in each repeating unit allow the formation of intermolecular hydrogen bonds. This H-bound effect is confirmed with poly(NHTL-*alt*-BO) and poly(BTL-*alt*-BO) for which the gap of the T_g values is equal to 94 °C. Examples of such hydrogen-bonding side groups that modify glass transition temperatures have been previously reported in the literature.[35] Intermolecular hydrogen bonds act as temporary cross-links

which restrict motion, decrease free volume and increase T_g. In most cases, the extent of T_g increase depends on the density of hydrogen-bonding side-groups.[36] In addition to hydrogen bonding, the side group chemical structure is believed to play an important role in T_g values. The higher T_g value of poly(BTL-*alt-t*BuGE) compared to the one of poly(BTL-*alt-t*BuGE) can be explained by the increase of the steric hindrance due to the introduction of bulky *tert*-butoxy groups. Curiously, the T_g of poly(NHTL-*alt*-BnGE) is 30 °C lower than the one of poly(NHTL-*alt*-PhGE), which could be explained by a slightly longer and flexible spacer containing one additional methylene group. In the latter case, the aromatic group separated from the backbone by a quite flexible spacer could interfere with the formation of the hydrogen bonds.

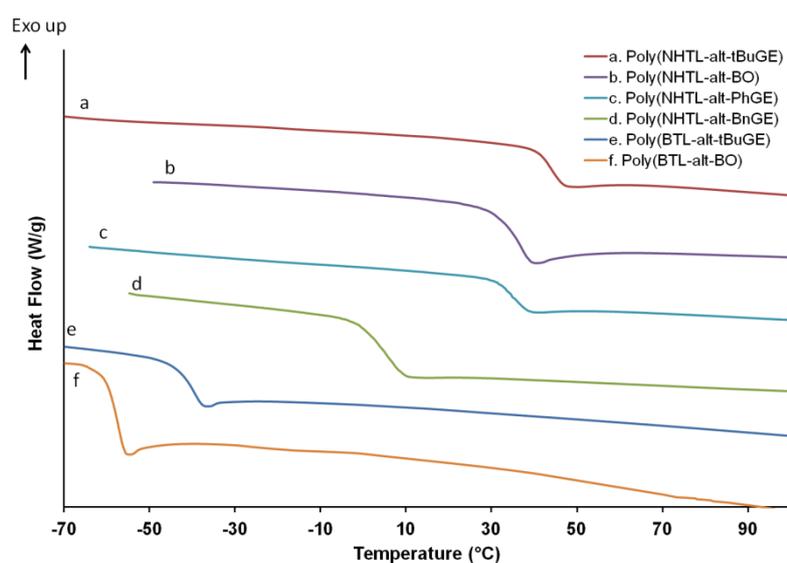


Figure 4. DSC curves of second heating scans at 10°C/min: a) poly(NHTL-*alt-t*BuGE); b) poly(NHTL-*alt*-BO); c) poly(NHTL-*alt*-PhGE); d) poly(NHTL-*alt*-BnGE); e) poly(BTL-*alt-t*BuGE) and f) poly(BTL-*alt*-BO).

CONCLUSION

The scope of the alternating AROP of γ -thiolactone with epoxides has been extended to sustainable NHTL despite the presence of the weakly acidic amide group. Well-defined poly(ester-*alt*-thioether)s have been synthesized in THF using benzyl alcohol-BEMP as initiating system. These NHTL-based copolymers have much higher T_g compared to similar BTL-based copolymers, due to the presence of acetamido lateral substituents in each repeating unit and their ability to establish intermolecular H-bonding. Our results indicates that N-functionalized thiolactones are promising building block for synthesizing sulfur-containing alternating copolymers and pave the way to the valorization in AROP of monomers derived from the bio-based and commercially-available homocysteine thiolactone.[21] The alternating copolymerization of NHTL with sterically-hindered bio-based epoxides is currently under investigation, allowing for a one-pot preparation of renewable copolymers with tunable properties.

EXPERIMENTAL SECTION

Materials. Phosphazene base 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) solution (1.0 mol.L^{-1} in hexane, Sigma-Aldrich), CaH_2 (93%, 0-2 mm grain size, Acros Organics), benzyl alcohol (99.8% anhydrous, Sigma-Aldrich), and DL-*N*-Acetylhomocysteine thiolactone (98%, Sigma-Aldrich) were used as received. 1,2-epoxybutane (BO) (>99%, Sigma-Aldrich), *tert*-butyl glycidyl ether (*t*BuGE) (99%, Sigma-Aldrich), phenyl glycidyl ether (99%, Sigma-Aldrich), benzyl glycidyl ether (99%, Sigma-Aldrich), and γ -thiobutyrolactone (TBL) (98%, Sigma-Aldrich) were distilled over CaH_2 twice prior use. Toluene and THF were dried with an MBRAUN MB SPS-800 solvent purification system under nitrogen.

Instruments. ^1H , ^{13}C NMR and ^1H - ^{15}N HSQC spectra were recorded in CDCl_3 or CD_3COCD_3 using a Bruker 400 MHz NMR spectrometer. IR spectra were collected using a Perkin-Elmer Spectrum1000 FTIR infrared spectrometer with a diamond ATR probe. Size Exclusion Chromatography Experiment (SEC) were carried out on three PL gel Mixed-C $5\mu\text{m}$ columns ($7,5 \times 300$ mm; separation limits: 0,2 to $2000 \text{ kg}\cdot\text{mol}^{-1}$) maintained at 40°C and sample Viscotek GPCmax delivery module and 2 modular detectors: a Viscotek 3580 differential refractive index (RI) detector and a Shimadzu SPD20-AV diode array UV detector. THF was used as the mobile phase at a flow rate of $1 \text{ mL}\cdot\text{min}^{-1}$, toluene was used as a flow rate marker. All polymers were injected ($50 \mu\text{L}$) at a concentration of $5 \text{ mg}\cdot\text{mL}^{-1}$ after filtration through a $0.45 \mu\text{m}$ pore-size membrane. The OmniSEC 4.6.2 software was used for data acquisition and analysis. Number-average molar masses (M_n), weight-average molar masses (M_w) and dispersities were determined by SEC with a calibration curve based on poly(methyl methacrylate) standard, using the RI detector. The thermal decomposition was evaluated by thermogravimetric analysis (TGA) using a TA Q50 apparatus. Data were collected using a $20^\circ\text{C}/\text{min}$ ramp to 600°C . The experiment was run under a stream of nitrogen. DSC measurements were carried out using a TA DSC Q2000 calibrated with indium standard. Sample (ca 15 mg) was placed in an aluminum cell and initially cooled at -70°C . Two heating ($10 \text{ K}\cdot\text{min}^{-1}$) - cooling ($10 \text{ K}\cdot\text{min}^{-1}$) cycles were then applied in the -70 to 200°C temperature range.

General copolymerization procedure. The copolymerization was carried out according to the following typical procedure. In a glove-box, 2.0 mL of THF, $12 \mu\text{L}$ of benzyl alcohol (0.1160 mmol), 0.43 mL of tert-butyl glycidyl ether (3.0290 mmol), and 0.49 g of N-acetylhomocysteine thiolactone (3.0149 mmol) were introduced under nitrogen into a polymerization tube. Then, $120 \mu\text{L}$ of BEMP solution (0.120 mmol) were added using a microsyringe. After closure of the flask, the reaction mixture was stirred at 60°C and left to

react for the required period of time. After removing residual monomers and solvent by rotary evaporation, the polymer was dissolved in methanol and dialyzed in cellulose ester membrane (Repligen Spectra/Por 6 dialysis tubing, flat width = 45 mm, molecular cutoff = 1 kDa) against methanol for 24 hours. After removing the solvent under vacuum at 50 °C a white solid was obtained. Yield: 87 %. Deviations from this general procedure are summarized in Table 1.

Notes

The authors declare no competing financial interest.

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Supporting Information

^1H ^{13}C COSY ^1H - ^{15}N HSQC NMR spectra, ATR FT-IR spectra and SEC trace. This material is available free of charge via the Internet at

Data availability

The data that support the findings of this study are available from the corresponding author, NI, upon reasonable request.

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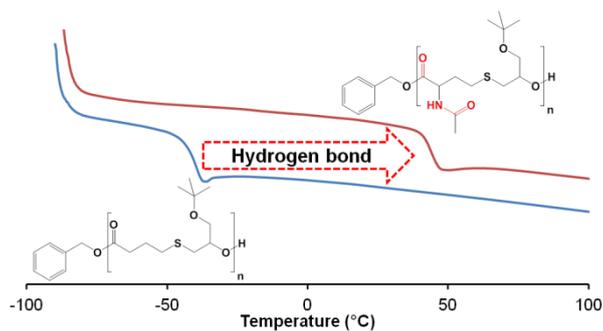
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Alternating Copolymerization of Bio-based N-acetylhomocysteine Thiolactone and Epoxides

Nicolas Illy,* Valentin Puchelle, Simon Le Luyer and Philippe Guégan



Highlights

- * Bio-based N-acetylhomocysteine thiolactone was used in anionic copolymerization.
- * Well-defined alternating poly(ester-*alt*-thioether)s are synthesized.
- * Lateral acetamido groups induced large increase of glass transition temperatures.