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ARTICLE

ϵ -Thionocaprolactone: an accessible monomer for preparation of degradable poly(vinyl esters) by radical ring-opening polymerization

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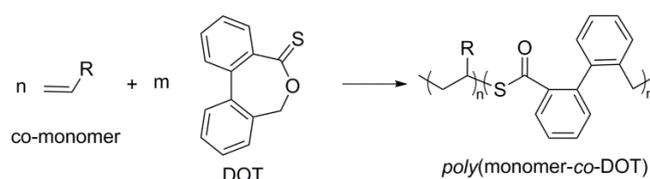
The 7-membered cyclic thionolactone, ϵ -thionocaprolactone (TCL), undergoes radical copolymerization with vinyl esters to form degradable copolymers. While most radical ring-opening monomers require laborious and low-yielding syntheses, TCL can be prepared in one step from caprolactone (75% yield). TCL copolymerizes readily with vinyl esters, but is unreactive towards more activated monomers and does not homopolymerize under radical conditions. The molecular weight and to some extent the dispersity of the TCL/vinyl ester copolymers can be controlled via xanthate-mediated RAFT polymerization in the range of 5–20 kg.mol⁻¹. Analysis of the copolymer structure shows a high level of TCL–TCL dyads, suggesting that the terminal copolymerization model does not accurately describe TCL copolymerization.

INTRODUCTION

While polymers derived from radical polymerization are ubiquitous in today's society, their indestructibility has caused increasing concern. Plastic microparticles are now found all over the globe, from the ocean depths¹ to the high mountain peaks of the Pyrenees.² In biomedical applications, controlled degradability is important to allow controlled drug release, reduce complications associated with the long term presence of a foreign material, and ensure renal clearance of high molecular weight polymers.³

Many strategies have been developed to introduce degradable functionalities into the backbone of vinyl polymers. Of these, the best known involve the use of radically polymerizable cyclic monomers⁴ such as cyclic ketene acetals⁵ or cyclic allylic sulfide lactones^{6,7} that isomerize on polymerization to form degradable in-chain esters. Cyclic ketene acetals such as 2-methylene-1,3-dioxepane (MDO),^{8,9} 5,6-benzo-2-methylene-1,3-dioxepane^{5,9–10} and 2-methyl-4-phenyl-1,3-dioxolane^{9,11–13} copolymerize well with less-activated monomers such as vinyl esters,^{14–16} vinyl ethers¹⁷ and ethylene,^{18,19} but are only weakly reactive in copolymerization with more activated monomers such as styrene,⁸ acrylates²⁰ and methacrylates.^{9,11–13} Cyclic allylic sulfides, which propagate through a sulfur-centered radical, show greater reactivity towards more activated monomers such

as methyl methacrylate and methyl acrylate.²¹ In 2019, two groups^{22,23} independently reported a new class of cyclic monomer, the thionolactone dibenzo[*c,e*]oxepane-5-thione (DOT). DOT was shown to homopolymerize,²⁴ albeit slowly, and copolymerize with monomers including acrylates^{22,23}, acrylamides,^{22,25} acrylonitrile²² and maleimides²⁴ via an addition-fragmentation mechanism, similar to that of a RAFT agent, isomerizing in the process to form a degradable thioester (Scheme 1). DOT inhibits the polymerization of vinyl acetate and *N*-vinyl carbazole, and retards the polymerization of styrene without being incorporated.²² The linear thionoester, benzyl thionobenzoate, had previously been shown to be an effective chain transfer agent ($C_s = 1.0$) in the polymerization of styrene.^{26,27}



Scheme 1. Copolymerization of DOT.

Access to radically polymerizable cyclic monomers has generally been limited due to problems of synthesis and stability. Seven-membered cyclic ketene acetals such as MDO are produced via low-yielding multistep syntheses,[†] often requiring large quantities of solvent, and are very sensitive to hydrolysis. Cyclic allylic sulfide lactones are similarly difficult to synthesize.⁷ DOT can be prepared in two steps from diphenic anhydride in 32% overall yield: first a reduction with sodium borohydride followed by thionation with Lawesson's reagent.²²

In addition to DOT, Bingham and Roth made a number of unsuccessful attempts to copolymerize several thionolactones

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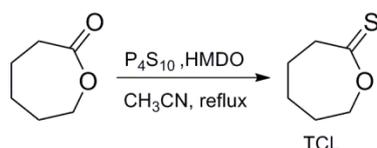
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derived from commercially available lactones including γ -phenyl- γ -butyrolactone.²² Their attempts focused on lactones with aromatic substituents that could stabilize the ring-opened radical, with structures reminiscent of MDPO or BMDO.

Such radical-stabilizing substituents are not always necessary, however. Radical ring-opening of MDO takes place even though it leads to a primary radical without stabilizing groups. The polymerization is driven partly by relief of ring strain, and partly by the change in energy associated with the replacement of the ketene acetal group by an ester. Similarly, reversible addition fragmentation reactions take place in the xanthate-mediated polymerization of ethylene, forming primary radicals.²⁸ We hypothesized that the presence of a radical stabilizing group such as phenyl may not be necessary if the thionolactone ring was sufficiently strained. This led us to consider ϵ -thionocaprolactone (TCL) as a potential radical ring-opening monomer, due to its structural similarities with MDO (scheme 2).

TCL is a yellow liquid that can be synthesized in a single step from ϵ -caprolactone,²⁹ a substrate that is available in industrial quantities (Scheme 2). Under anionic polymerization conditions, it undergoes ring-opening with partial isomerization to form a polymer containing a mixture of thioester and thionoester groups,³⁰ while under organocatalysed ring-opening polymerization conditions it polymerizes with conservation of the thionocarbonyl group to form a poly(thionoester).³¹ In the following article we report the first study of the reactivity of TCL in radical (co)polymerization.



Scheme 2. Synthesis of thionocaprolactone (TCL)

MATERIALS AND METHODS

2-mercaptopropionic acid methyl ester *O*-ethyl dithiocarbonate (XA1) was synthesized according to a literature procedure.³² The following chemicals were used as received, ϵ -caprolactone (97%, Sigma-Aldrich), hexamethyldisiloxane (HMDO, $\geq 98\%$, Sigma-Aldrich), phosphorus pentasulfide (P_4S_{10} , 97% grade, Acros Organics) and di-*tert*-butyl peroxide (DTBP, 98%, Sigma-Aldrich). The following chemicals were purified before use: 2,2'-azobis(2-methylproprionitrile) (AIBN, 98%, Sigma-Aldrich) was recrystallized from methanol and dried under vacuum. 1-vinyl-2-pyrrolidinone (NVP, $>99\%$, Sigma-Aldrich) was distilled under reduced pressure. *n*-Butyl acrylate (nBA, $\geq 99\%$, Sigma-Aldrich), vinyl acetate (VAc, $>99\%$, Sigma-Aldrich) and vinyl pivalate (VPiv, $>99\%$, Sigma-Aldrich) were purified by passing through neutral Al_2O_3 .

The following solvents were used as received: toluene (Sigma-Aldrich, HPLC grade), petroleum ether (Sigma-Aldrich, HPLC grade), cyclohexane (Sigma-Aldrich, HPLC grade) and *N,N*-dimethylformamide (DMF, Sigma-Aldrich, HPLC grade). Ethyl

acetate (EtOAc, Sigma-Aldrich, HPLC grade), Acetonitrile (MeCN, Acros, HPLC grade) was further dried using a solvent purifier (MBRAUN SP5).

Nuclear magnetic resonance (NMR) spectra (1H , ^{13}C) were recorded at 25 °C on a Bruker Avance 300 MHz instrument and all 2D NMR experiments were recorded at Bruker Avance 500 MHz equipped with 5 mm TCI cryoprobe. 1H NMR spectra were recorded at 300.13 MHz (500.13 MHz for 2D experiments) is reported to ± 0.5 Hz. The resonance multiplicities are described as s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). ^{13}C NMR spectra were recorded at 75.47 MHz (125.75 MHz for 2D). Chemical shifts δ are reported in parts per million (ppm) and are referenced to the residual solvent peak ($CDCl_3$: H = 7.26 ppm and C = 77.16 ppm).

Size-exclusion chromatography (SEC) analyses in THF was performed on a system composed of an Agilent technologies guard column (PLGel20 μm , 50 \times 7.5 mm) and a set of two Waters columns (1 \times Styragel[®] HR 3, 7.8 \times 300 mm and 1 \times Styragel[®] HR 4, 7.8 \times 300 mm). Detections were conducted using a Wyatt Optilab[®] rEX refractive index detector and a Varian ProStar 325 UV detector (dual wavelength analysis). Analyses were performed at 35°C and a flow rate of 1.0 mL min^{-1} . Poly(methyl methacrylate) (PMMA) standards (960 – 1.37 $\times 10^5$ g mol^{-1}) were used for calibration. Poly(NVP-*co*-TCL) and VAc/TCL copolymers prepared by RAFT polymerization were analyzed in DMF + LiBr (10mM) and performed on a system composed of an Agilent technologies guard column (PLGel20 μm , 50 \times 7.5 mm) and a set of two Waters columns (1 \times Styragel[®] HR 3, 7.8 \times 300 mm and 1 \times Styragel[®] HR 4, 7.8 \times 300 mm) and calibrated using polystyrene (PSt) standards (580 - 7.5 $\times 10^5$ g mol^{-1}). Detections were conducted using a Wyatt Optilab[®] rEX refractive index detector, a Varian ProStar 325 UV detector (dual wavelength analysis) and a Wyatt MiniDawn TREOS multi-angle light scattering detector. Analyses were performed at 55 °C with a flow rate of 1.0 mL min^{-1} .

EXPERIMENTAL PROCEDURE

Preparation of thionocaprolactone (TCL)

Following Curphey's protocol,²⁹ P_4S_{10} (21.9 mmol), ϵ -caprolactone (87.91 mmol) and hexamethyldisiloxane (146.31 mmol) were mixed in 90 mL of dried acetonitrile. Then the reaction mixture was stirred under argon for 15 min at room temperature and then refluxed at 82°C for 2 h. The dark mixture was then cooled down to 0°C, 22.5 mL of a K_2CO_3 solution (5M) were added and the mixture was stirred for 30 min at 0°C. The product was mixed with water (200 mL), extracted with ethyl acetate (3 \times 100 mL) and the combined organic layers were washed with water and brine. The organic solution was dried with $MgSO_4$ and evaporated under reduced pressure. The product was purified by column chromatography with cyclohexane/ethyl acetate (7:3) eluent. Yield: 75%.

NMR: 1H ($CDCl_3$; 300 MHz): δ (ppm) 1.79 (m, 2H); 1.91 (m, 4H); 3.20 (m, 2H); 4.50 (m, 2H). Spectrum shown in Fig. S1.

^{13}C ($CDCl_3$; 76 MHz): δ (ppm) 25.9; 28.5; 28.6; 46.2; 74.4; 227.5

90% Vinyl acetate/ 10% TCL copolymerization procedure

AIBN (16mg, 0.1 mmol), TCL (0.24 g, 1.8 mmol) and VAc (1.54 g, 17.9 mmol) were mixed. The solution was transferred into a Carius tube which was sealed under vacuum after degassing by three freeze-pump-thaw cycles. Then the tube was put in an oil bath at 70°C for 6h. The polymerization was stopped by rapid cooling. After opening the tube, part of the solution was immediately transferred to the NMR tube for conversion analysis. The polymer for SEC analysis was used after evaporation of residual monomer. Polymer was purified by precipitation in 1/10 v/v toluene/petroleum ether. VAc conversion = 85%, TCL conversion = 100%, F_{TCL} = 0.12. M_n = 22.8 kg mol⁻¹, \bar{D} = 2.84.

¹H NMR (300 MHz, CDCl₃) δ (ppm): 6.42 (m, 1H) 4.89 (s, 1H), 3.2 – 4.15 (m, CH₂), 2.87 (t, CH₂), 2.53 (t, CH₂), 2.25 – 1.2 ppm (m).

RAFT copolymerization of VAc and TCL

A typical procedure, similar to that used for VPiv/TCL copolymerization, is given as follows: a stock solution of AIBN (63 mg, 0.38 mmol) TCL (1 g, 7.68 mmol), XA1 (144 mg, 0.69 mmol) and VAc (5.95 g, 69.1 mmol) was prepared. Aliquots of 1 ml were transferred into 7 Carius tubes which were sealed under vacuum after degassing by three freeze-pump-thaw cycles. Then the tubes were put in an oil bath at 70°C and withdrawn at hourly intervals. The polymerization was stopped by rapid cooling. After opening the tube, part of the solution was immediately transferred to a NMR tube for conversion analysis. The polymer for SEC analysis was recovered after evaporation of residual monomer. After 7 h reaction: VAc conversion = 69%, TCL conversion = 98%, F_{TCL} = 0.14, M_n = 6 kg mol⁻¹, \bar{D} = 1.54.

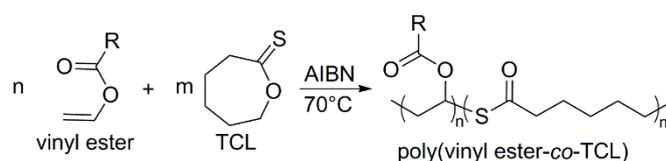
Chemical degradation

We adapted a protocol reported by Roth and co-workers.²² 20 mg of the copolymer was diluted in 1 mL of dichloromethane before isopropyl amine (1mL) was added. The mixture was stirred in a sealed vial overnight at room temperature. Solvent and excess of amine were evaporated under reduced pressure, and then the residue was dissolved in 4 ml of THF and analyzed by SEC.

RESULTS AND DISCUSSION

We synthesized TCL from ϵ -caprolactone in 70% yield, following Curphey's procedure.²⁹ In an initial series of copolymerization tests under conventional radical conditions (f_{TCL} = 0.1, 70°C, 0.5 mol% AIBN, Table 1), TCL readily formed copolymers with vinyl esters such as vinyl acetate (VAc) and vinyl pivalate (VPiv). Consumption of the TCL was accompanied by disappearance of the yellow color of the thionolactone, suggesting its isomerization to the colorless thiolactone (Scheme 3). Attempts to copolymerize TCL with N-vinyl pyrrolidinone resulted in retardation of the polymerization forming low molar mass, highly disperse copolymer with little incorporation of TCL. TCL was inert in the polymerization of butyl acrylate (nBA), neither affecting the polymerization kinetics nor being incorporated into the copolymer. Our attempts to homopolymerize TCL were

unsuccessful, even in the presence of tert-butyl peroxide at 130°C.



Scheme 3. Radical ring-opening copolymerization of TCL with isomerization to a thioester.

Table 1. Radical copolymerization of TCL with a series of comonomers.^a

<i>M</i>	f_{TCL}	<i>t</i> (h)	X_{TCL}^b	X_M^b	F_{TCL}^b	M_n^c (kg.mol ⁻¹)	\bar{D}^c
VPiv	0.1	8	1.00	0.77	0.13	35.5	2.6
VAc	0.1	6	1.00	0.85	0.12	22.8	2.7
VAc	0.3	8.5	0.29	0.10	0.53	13.0	2.7
NVP	0.2	7	0.07	0.33	0.05	0.4	3.3
nBA	0.1	6	0.00	0.96	0.00	N. D.	N. D.

^a bulk, 0.5 mol.% AIBN relative to comonomers, T=70°C; ^b Conversion (X) and copolymer composition (F) determined by ¹H NMR; ^c Determined by SEC. See Materials and Methods for details.

As our best results were obtained with vinyl esters, these were investigated in greater detail. Kinetic studies showed that TCL was consumed more rapidly in copolymerization than VAc (Figure 1) or VPiv (Figure S2). At f_{TCL} = 0.1, the copolymerization could be carried out to high conversion, producing poly(VAc-co-TCL) with number-average molar mass (M_n) of 35.1 kg mol⁻¹. At higher proportions of TCL, the reaction was much slower, with only 10% conversion of TCL and 29% conversion of VAc after 8.5 h in mixtures containing 30% TCL (Table 1).

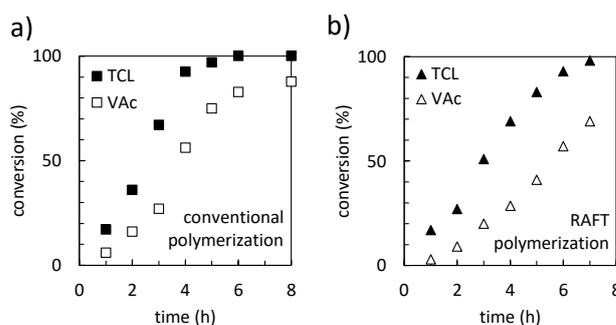


Fig. 1. Copolymerization kinetics of vinyl acetate and TCL (f_{TCL} = 0.1) under conventional radical polymerization conditions (a) and in the presence of RAFT agent XA1 (b). See Fig. S3 for details on calculation of comonomer conversion by ¹H NMR.

Polymerization in the presence of a RAFT agent

RAFT copolymerizations of VAc with 10 mol.% TCL were conducted in bulk at 70°C with AIBN initiation and 2-mercaptopropionic acid methyl ester *O*-ethyl dithiocarbonate (XA1) as chain transfer agent (Table S1). This xanthate RAFT agent was selected due to its ability to control the polymerization of less-activated monomers such as vinyl

esters³³ and ethylene,²⁸ the latter exhibiting primary propagating radicals similar in nature to those of TCL.

A VAc/TCL copolymerization was followed over time with a [comonomer]/[XA1] ratio corresponding to a theoretical M_n of 10 kg mol⁻¹ at full conversion. As for the conventional polymerization, TCL was converted faster than VAc during polymerization to reach 95% conversion after 7 h, with only 69% VAc reacted at this stage (Fig. 1b and Table S1). While the overall rate of polymerization was slower in the presence of XA1, there was no effect on the relative rates of incorporation of each monomer into the copolymer (Figs. 1 and S4). M_n increased gradually with conversion of the monomers, with values which were slightly lower than theoretical expectations (Fig 2b). This may be explained by the lower hydrodynamic volume of P(TCL-co-VAc) relative to the PS standards used to calibrate the SEC columns, as evidenced by comparing M_n values determined by calibration and SEC-RI-MALS for one P(TCL-co-VAc) sample (Table S1, entry 1). The molar mass distributions obtained at high monomer conversion are shown in Figure 2a. Dispersities are initially high but decrease during polymerization, with values of 2.1-2.7 during most of the polymerization (Fig. 2b and Table S1, entries 2-7), decreasing to 1.5-1.6 in the final stages of the polymerization (Table S1, entries 8 - 9).

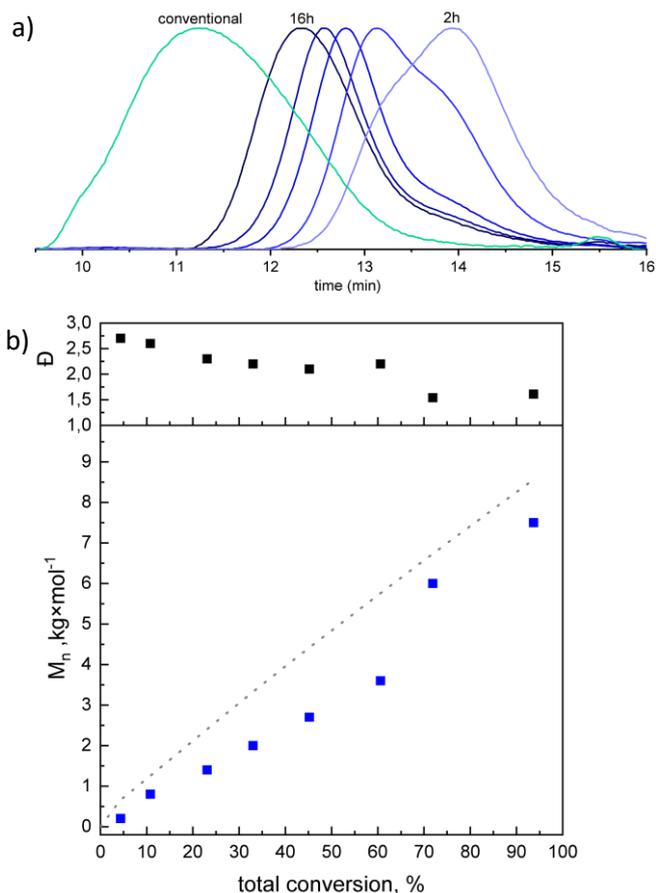


Fig. 2. (a) Size exclusion chromatograms (DRI detection, DMF + LiBr eluent) of poly(TCL-co-VAc) obtained via RAFT polymerization at f_{TCL} of 0.1 (blue) at 2 h, 3 h, 5 h, 6 h and 16 h of reaction. Polymer obtained via conventional polymerization (green) shown for comparison. (b) Evolution of M_n and dispersity as a function of total monomer

conversion in RAFT copolymerization of VAc and TCL ($f_{TCL} = 0.1$) Dashed line represents theoretical M_n .

The high dispersities may be due to the co-existence of two types of xanthate-capped chain during polymerization, namely VAc-XA1 and TCL-XA1, which exhibit very different reactivities towards VAc and ethylene growing radicals. While reversible chain transfer is fast in RAFT homopolymerization of VAc with XA1 ($C_{ex} \sim 25$),³⁴ it appears to be slower in the RAFT homopolymerization of ethylene, a model for the TCL-derived primary radical, producing polymers with dispersities ranging from 1.4-2.0.²⁸ Additionally, the TCL-XA1 species may be expected to be poorly reactive as a RAFT agent for radicals derived from VAc, due to the lack of stabilization of the leaving group. A similar situation is obtained in the RAFT polymerization of vinylidene difluoride (VDF), in which a small but significant fraction of head-to-head addition leads to the formation of primary radicals which react with RAFT agent to form $-CF_2CH_2$ -xanthate species, which are poor chain transfer agents for the $-CH_2CF_2^*$ propagating radical that results from head-to-tail addition.³⁵ A similar process, involving radicals of disparate reactivities derived from TCL and VAc, may be responsible for the low molecular weight tailing observed in Fig. 2a.

Vinyl pivalate (VPiv) was copolymerized with 10 mol% TCL (Table S2). XA1 concentration was varied in order to target M_n values of 5, 10 and 20 Kg mol⁻¹. Similarly to VAc, VPiv was converted slower than TCL, with conversions >90% for both monomers after 6-7 h. As expected for a controlled RAFT process, the molar masses obtained at high monomer conversions were inversely proportional to the initial XA1 concentration (Fig. 3), with values very close to theory (Table S2). Dispersities tended to increase with decreasing XA1 concentration (Table S2).

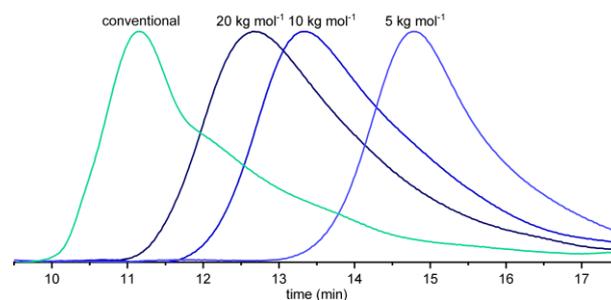


Fig. 3. Size exclusion chromatograms (DRI detection, THF) of poly(TCL-co-VPiv) obtained via RAFT polymerization (blue) at $M_{n,theo}$ of 20, 10 and 5 kg.mol⁻¹. Poly(VPiv-co-TCL) obtained through conventional radical polymerization (green) is shown for comparison.

Copolymerization kinetics, copolymer microstructure and sequence distribution. Analysis of the copolymerization kinetics was performed by fitting the mole fraction of TCL in the comonomer feed (f_{TCL}) to the total conversion using the integrated form of the terminal copolymer composition equation. Point estimates for reactivity ratios and joint confidence regions (JCR) were obtained using the visualization of the sum of squared residuals space (VSSRS) technique developed by Van den Brink et al.^{36,37} This procedure gave apparent reactivity ratios of 0.3 for r_{VAc} and 3 for r_{TCL} , indicating a strong tendency towards cross-propagation for VAc, and a

tendency towards homopropagation for TCL. The 95% joint confidence interval for the reactivity ratios is roughly elliptical (Figure S5), ranging from 0.2-0.5 for r_{VAc} and 0.8 - 8 for r_{TCL} . The lack of precision in the result for TCL is due to the difficulty of carrying out reactions at high TCL concentration. Similar results were obtained for vinyl pivalate, with estimated reactivity ratios of 10 (r_{TCL}) and 0.3 (r_{VPiv}) (see Fig. S5 for JCR). These results suggest that both radicals derived from addition to vinyl ester and those resulting from ring-opening of TCL preferentially add to the thiocarbonyl group of TCL.

These reactivity ratios may be compared to those recently reported^{38,39} for the MDO-VAc copolymerization: $r_{\text{MDO}} = 0.95$, $r_{\text{VAc}} = 1.7$. While the values of r_{TCL} and r_{MDO} are broadly similar (at least within the limits of the uncertainty, which is significant in both cases), there is a clear difference between the values of r_{VAc} in the two copolymerizations. In the limit of low TCL or VAc concentration and low overall conversion, copolymers of VAc with MDO will be slightly enriched in VAc relative to the feed composition, while copolymers of VAc with TCL will be enriched in TCL. As the polymerization proceeds, TCL will be depleted in the monomer mixture, leading to the potential formation of PVAc homopolymer at higher conversions. In practice, this problem could be mitigated by the continual addition of TCL in a semicontinuous process.

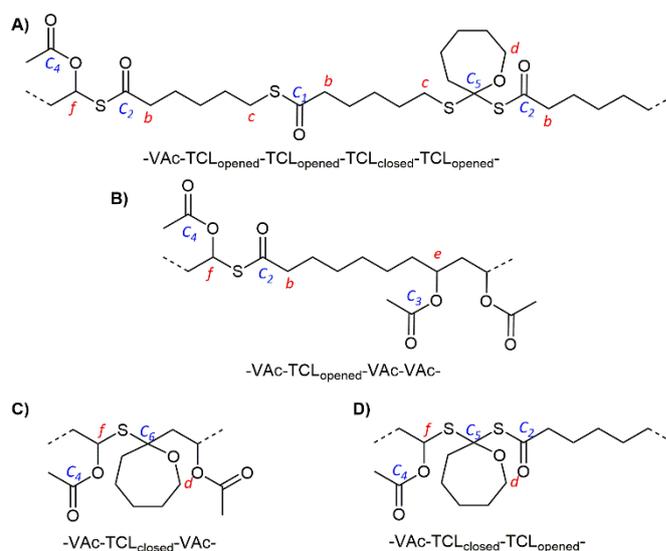
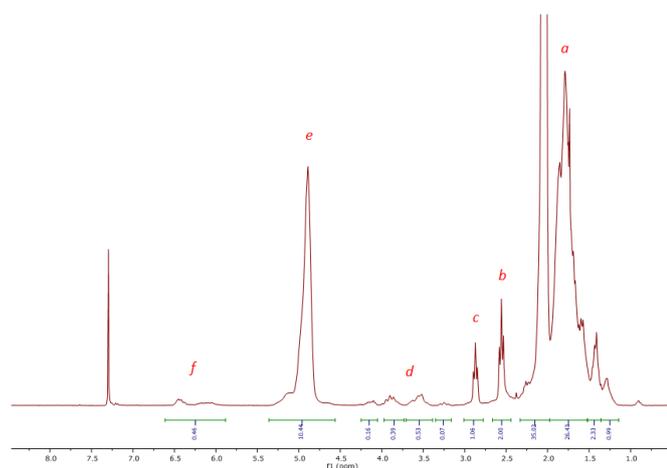


Fig. 4. ^1H NMR spectrum of a P(VAc-co-TCL) copolymer (top) and proposed peak assignments (below)

More detailed analysis of the structure of the copolymer was carried out using ^1H (Fig. 4), ^{13}C (Figs. S6-S8) and 2D NMR (Figs S9-S15) spectroscopy. Fig. 4 shows the ^1H NMR of a VAc/TCL (7.6/1)(table S1, entry 1) copolymer. Signals *a* in the region 1.20-2.25 ppm are attributed to methylene of TCL and VAc chains and methyl group of VAc. The pseudo-triplet *b* at 2.56 ppm corresponds to the methylene group in the α -position of the carbonyl ($-\text{S}(\text{C}1=\text{O})\text{-CH}_2-$) in the TCL unit (Fig. 4, structures A and B), while the pseudo-triplet *c* at 2.87 ppm corresponds to the TCL methylene directly connected to the sulfur of a second TCL unit ($-\text{CH}_2\text{-S}(\text{C}_2=\text{O})-$), when two or more TCL units are following each other (Fig. 4, structure A). These attributions were confirmed by 1D/2D NMR experiments ($^1\text{H}/^{13}\text{C}$ NMR HMBC, see Figs. S10-S11) and by comparison with proton NMR spectra of TCL homopolymer.³⁰ Multiplet signals *d* which appear in the 3.20-4.15 ppm region are related to methylene groups ($-\text{CH}_2\text{-O}-$) of cyclic thionolactone units included in the polymer chain (Fig. 4, structures C and D), however their concentration is too low to give definitive structures. $^1\text{H}/^{13}\text{C}$ NMR HMBC/HSQC experiments (Figs. S12-S15) confirmed that the $\text{CH}_2\text{-O}$ groups which appear as diastereotopic protons are close to an asymmetric carbon, such as the carbons C_5 at $\delta = 90.9$ ppm and C_6 at $\delta = 67.0$ ppm. The singlet signal at 4.89 ppm belongs to methine groups *e* of VAc units, as in conventional PVAc. The multiplet signal *f* at 6.42 ppm corresponds to methine groups which belong to VAc units connected to a sulfur atom from a TCL unit (opened or closed) (Figs. S11-S13). This signal confirms that the VAc and TCL units in the polymer are connected to each other. Based on Fig. 4, the relative integrations

of b , which corresponds to the open form of TCL (TCL_{open}), and d , for the cyclic form of TCL ($\text{TCL}_{\text{closed}}$), to those of e/f (methine groups of VAc) indicate a TCL/VAc molar ratio of 1/6.7, which is consistent with theoretical expectations ($\text{TCL}/\text{VAc}=1/7.6$ based on data of Table S1, entry 1).

While the majority of incorporated TCL was present as the ring-opened thioester, comparing the integration of d to that of b shows that 36.5% of TCL was incorporated in ring-closed form as a cyclic thioacetal or orthodithioester (Fig. 4, respectively structures C and D). It should be noted that these structures are also hydrolytically unstable and will contribute to the degradability of the copolymer.⁴⁰ Comparison of integrations of f and e shows that 4.2% of the VAc units are connected to TCL, which means that copolymer chains are composed of VAc sequences of an average length of 24 units between each TCL segment. Meanwhile, the b/c ratio of 2/1.06 shows that there nearly two opened TCL units on average in a sequence, far greater than would be expected for a purely random copolymerization containing only 10% TCL.

This unexpectedly high proportion of TCL-TCL dyads led us to further investigate the microstructure of VAc/TCL copolymers with samples prepared with initial TCL monomer fractions ranging from 0.01 to 0.5 (Table 2). Regardless of the initial fraction of TCL in the copolymerization, the average TCL sequence length remained close to 2 (Table 2). Similarly, the average VAc sequence length was roughly twice that expected for a purely random copolymer. We note that, while highly interesting from a mechanistic point of view, this is disadvantageous in so far as chain degradation is concerned as degradable units are most efficiently used when they are evenly distributed along the chain.

Table 2. Variation of average TCL and VAc sequence lengths as a function of f_{TCL} in copolymerization of TCL with VAc.^a

f_{TCL}	X_{TCL}	X_{VAc}	$\text{TCL}_{\text{closed}},\%$	N_{TCL}^a	N_{VAc}^b
0.01	100	97	~50 ^b	1.7	>200 ^{b,d}
0.05	100	91	61	1.6	46.5 ^d
0.10	100	85	36	2.1	24
0.20	52	27	43	2.1	7.5
0.29	40	10	34	2.3	4.7
0.39	16	4.7	39	2.4	2.4
0.50	11	12	43	2.4	2.5

^a average sequence length of TCL units, calculated from ratio of ¹H NMR peak areas at 2.9 and 2.5 ppm ($N_{\text{TCL}} = (1-r_{2.9/2.5})^{-1}$). ^b average sequence length of VAc units, calculated from ratio of ¹H NMR peak areas at 6.0-6.5 and 5.0 ppm ($N_{\text{VAc}} = (1-r_{6.0-6.5/5.0})^{-1}$). ^c approximate values due to low signal intensity. ^d Average sequence length of VAc units includes contributions from VAc homopolymer formed once TCL had fully reacted.

This is a strong indication that the simplistic terminal model of copolymerization does not adequately describe the copolymerization of TCL. The mechanism for incorporation of TCL-TCL dyads into the polymer remains unknown but may involve a dimeric TCL complex. The retardation observed in copolymerization and the failure of TCL to homopolymerize may be a result of a slow ring-opening step. While ring-closed

structures are incorporated into the copolymer, indicating that this radical is capable of propagation, it may be expected to propagate slowly, resulting in significant termination of the initially-formed cyclic radical.

Degradation. TCL/VPIV copolymers were degraded via aminolysis using isopropylamine in dichloromethane, following the protocol reported by Bingham and Roth.²² VPPIV, rather than PVAc, was used for these studies as the bulky pivalate group is more resistant to hydrolysis than the acetate group. To control for the possible aminolysis of the pendant ester groups, which would also lead to a decrease in molar mass, a VPPIV homopolymer (Table S3) was subjected to the same treatment. Copolymers of VPPIV and TCL showed a significant decrease in molecular weight after aminolysis (Figs. 5 and S16, Tables S3 and S4), further confirming the incorporation of the thioester group into the polymer backbone. In contrast, no decrease in molecular weight was observed for P(VPIV) under the same conditions (Fig. 5 and Table S4). In the absence of incorporated TCL, P(VPIV) showed only a slight broadening of the molar mass distribution, accompanied by the appearance of a high molecular weight shoulder, which can be attributed to aminolysis of the xanthate end-group followed by partial oxidative coupling via disulfide linkages.^{41,42} A small amount of residual polymer can be observed in Figure 5a, which may indicate the presence of some VPPIV homopolymer formed as a result of composition drift (depletion of TCL) during the copolymerization.

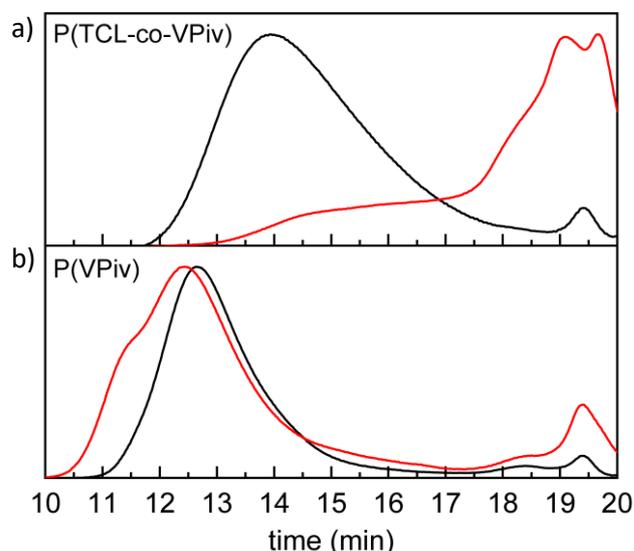


Fig. 5. Comparison of SEC chromatograms of polymers before (black) and after (red) treatment with excess isopropylamine and (a) P(VPIV-co-TCL), (b) P(VPIV).

Conclusions

TCL can be copolymerized with vinyl esters under radical polymerization conditions to produce copolymers containing degradable thioester and thioacetal linkages. While less versatile than many ring-opening monomers, its reactivity is complementary to that of DOT. A thorough NMR investigation of the VAc / TCL system revealed the presence of a significant proportion of TCL ring-closed units with, quite unexpectedly,

TCL units mostly present as dyads. Xanthate-mediated RAFT copolymerization of VAc/TCL and VPiv/TCL led to degradable copolymers of controlled molar masses and moderately high dispersities. Advantageously, TCL can be synthesized in good yield from ϵ -caprolactone in a single step, using inexpensive reagents.

Author Contributions

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Conflicts of interest

There are no conflicts to declare.

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Notes and references

‡ MPDL, a five-membered CKA, can be synthesized in two steps and 65% overall yield from bromoacetaldehyde dimethyl acetal and 1-phenyl-1,2-ethanediol.¹²

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