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Radical Copolymerization of Thionoglycolide and Derivatives for Preparation of Degradable Vinyl Polymers

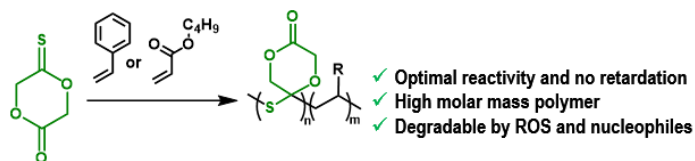
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For Table of Contents use only



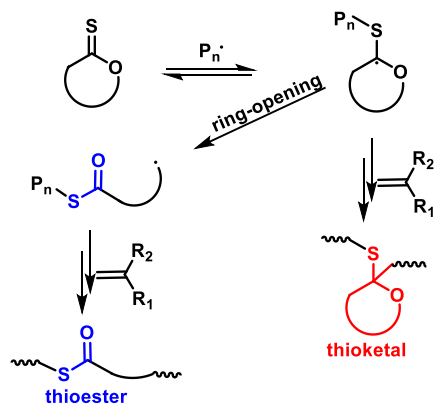
ABSTRACT: This study explores the copolymerization behavior of thionated glycolide derivatives, with a focus on thionoglycolide (TGD). It was found that TGD exhibits a nuanced reactivity profile, showing the highest compatibility with styrene and *tert*-butyl acrylate (*t*BA). Kinetic analysis of the TGD/*t*BA system conducted at 100°C in bulk demonstrated comparable incorporation rates for both monomers. Furthermore, RAFT copolymerization mediated by a trithiocarbonate RAFT agent resulted in well-defined copolymer with $M_n = 13.4 \text{ kg mol}^{-1}$ and $D = 1.2$. 2D-NMR Microstructural analysis revealed that TGD was exclusively incorporated in its ring-closed S,O-thioketal form, suggesting a selective 1,2-vinyl propagation mechanism. The degradability of the resulting copolymers was also investigated, with NaOCl, NaOMe, and benzoyl peroxide effectively cleaving S,O-thioketal linkages.

INTRODUCTION

Vinyl polymers produced by radical polymerization are among the most challenging plastics to render degradable,¹ as their backbones consist of hard-to-cleave C-C bonds. This challenge can be addressed by incorporating a comonomer that is designed to introduce degradable groups into the backbone.² The most common comonomers used for this purpose, such as cyclic ketene acetals (CKA),³ sulfide cyclic methacrylates,⁴ and macrocyclic allylic sulfides,⁵ to name a few, contain an exo-methylene double bond. This double bond allows the addition of propagating radicals onto the cyclic structure, followed by ring-opening enabled by weak sigma bond in beta position to exomethylene group, thereby introducing degradable ester moieties in the polymer backbone.⁶

In recent years, there has been a growing interest in radical copolymerization of thionolactones for preparation of degradable⁷⁻⁹ and recyclable polymers.⁹ Thionolactones have several advantages over previous generations of ring-opening monomers, such as

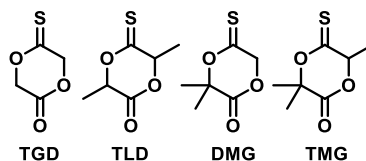
enhanced stability compared to cyclic ketene acetals and streamlined synthesis.¹⁰ Their radical polymerization is feasible if the C=S double bond allows for their propagation either in ring-closed or ring-opened form, and leads to the incorporation of thioketal or thioester linkages, respectively (Scheme 1).¹¹



Scheme 1 Competing mechanisms of ring-opening and 1,2 propagation for thionolactones.

We have previously shown that the proportion of thionolactone incorporated as thioester or thioketal depends on the ring-size.¹¹ For instance, for copolymerization of vinyl pivalate (VPi) with unsubstituted thionolactones of different ring sizes at 100°C in bulk, the highest fraction of incorporation (>80%) in the thioester form was obtained with 7-membered ϵ -thionocaprolactone (TCL), while the lowest amount (<20%) was found for 6-membered δ -thionovalerolactone (TVL). Importantly, both types of incorporated linkage in the vinyl polymer are readily and selectively degraded under accelerated chemical conditions. Thioesters can be cleaved by nucleophiles, while thioketals can be broken down by peroxides.¹² Alternatively, a reagent such as bleach¹³ that combines nucleophilic and oxidizing properties, or a reagent with high affinity to sulfur atoms such as silver nitrate¹⁴ can be employed for simultaneous degradation of both types of linkages.

In 2022 Satoh et al.¹⁴ and our group¹³ independently reported the free radical copolymerization of the thionated lactide, 3,6-dimethyl-5-thioxo-1,4-dioxan-2-one (TLD, Scheme 2) with more activated monomers (MAMs) including acrylates and styrene (St). Unlike other thionolactones suitable for copolymerization with MAMs such as dibenzo[*c,e*]oxepin-5(7*H*)-thione (DOT),^{7,8} TLD can be prepared in one step from a biosourced and readily available starting material, L-lactide.¹⁴ However, TLD copolymerization is limited by significant retardation, relatively low molar masses of the produced polymers and slow degradation.¹³ We hypothesized that both the retardation of polymerization and the slow degradation of the polymer may be due to steric hindrance from the methyl group α to the thiocarbonyl.¹³ The use of unsubstituted thionoglycolide TGD (Scheme 2) might decrease the retardation of polymerization while maintaining good reactivity with acrylates and styrene and also facilitate the degradation of obtained copolymers due to lower steric hindrance of the degradation site. In this paper, we investigate the reactivity of TGD in radical copolymerization with a series of vinyl monomers and study the degradability of the produced copolymers. Additionally, we synthesized original 3,3-dimethyl-5-thioxo-1,4-dioxan-2-one (DMG, Scheme 2) and 3,3,6-trimethyl-5-thioxo-1,4-dioxan-2-one (TMG, Scheme 2) in order to study the effect of methyl substituents in various positions on the reactivity of thionoglycolide and its derivatives in radical polymerization.



Scheme 2 Thionoglycolide and racemic derivatives used in this study

EXPERIMENTAL SECTION

Materials and methods. The following chemicals were used as received: phosphorus pentasulfide (P_4S_{10} , 97% grade, Acros Organics), chloroacetyl chloride (98%, Sigma-Aldrich), 2-chloropropionyl chloride (97%, Sigma-Aldrich), glycolide (99%, Sigma-Aldrich), hexamethyldisiloxane (HMDSO, $\geq 98\%$, Sigma-Aldrich), α -hydroxyisobutyric acid (99%, Sigma-Aldrich), glycolide (99%, Alfa Aesar), magnesium sulfate (99.5%, Sigma-Aldrich), potassium carbonate (K_2CO_3 , 99%, Sigma-Aldrich), 1,1'-azobis(cyanocyclohexane) (V-88, 98%, Sigma-Aldrich) and naphthalene (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. Vinyl acetate (VAc, $>99\%$, Sigma-Aldrich), *tert*-butyl acrylate (*t*BA, $>99\%$, Sigma-Aldrich), styrene (St, $>99\%$, Sigma-Aldrich) and *N,N*-dimethyl acrylamide (DMA, $>99\%$, Sigma-Aldrich), were purified by passing through neutral Al_2O_3 prior to use.

The following solvents were used as received: cyclohexane (Sigma-Aldrich, HPLC grade), dichloromethane (Sigma-Aldrich, HPLC grade), diethyl ether (VWR, HPLC grade), ethyl acetate (EtOAc, Sigma-Aldrich, HPLC grade), ethanol (anhydrous, Sigma-Aldrich), petroleum ether (Sigma-Aldrich, HPLC grade). Acetonitrile (MeCN, Acros, HPLC grade), and toluene (Acros, HPLC grade) were further dried using a solvent purifier (MBRAUN SP5).

NMR spectra (1H , ^{13}C) were recorded at 25 °C on a Bruker Avance 300 MHz instrument and all 2D NMR experiments were recorded on a Bruker Avance 500 MHz spectrometer equipped with 5 mm TCI cryoprobe. 1H NMR spectra were recorded at 300.13 MHz (500.13 MHz for 2D experiments) \pm 0.5 Hz. ^{13}C NMR spectra were recorded at 75.47 MHz (125.75 MHz for 2D).

Size-exclusion chromatography (SEC) analyses in THF was performed on a system of an Agilent technologies guard column (PLGel20 μm , 50 \times 7.5 mm) and a set of three Shodex columns (KF-805 + KF-804 + KF-802.5). Analyses were performed at 35°C and a flow rate of 1.0 mL min^{-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 (MALS) detector. Poly(methyl methacrylate) (PMMA) standards ($960 - 1.37 \times 10^5$ g mol^{-1}) were used for calibration. Number-average (M_n) and weight-average (M_w) molar masses were evaluated using Waters Empower software. All SEC chromatograms have been normalised to polymer peaks.

Synthesis of 5-thioxo-1,4-dioxan-2-one TGD. Glycolide (4 g, 34.5 mmol), P_4S_{10} (3.8 g, 8.6 mmol) and hexamethyldisiloxane (9.4 g, 58 mmol) were dissolved in 30 mL of anhydrous toluene. Then the reaction mixture was purged with argon for 15 minutes at room

temperature and then refluxed for 5 hours. The dark mixture was then cooled down to room temperature and half of the solvent removed under reduced pressure. The residue was taken up in DCM and passed through a silica column ($R_f = 1.0$) to remove sulfur impurities. The crude product was then passed through a second silica column using a diethyl ether/petroleum ether solvent mixture (25/75) as the eluent ($R_f = 0.3$). After removal of the solvent, the yellow solid was analysed by NMR, yield 33% (1.5 g). TGD was sublimized 2 times before polymerization.

TGD NMR. ^1H (CDCl_3 ; 300 MHz) δ (ppm): 5.01 (s, 2H, $\text{O}(\underline{\text{CH}}_2)(\text{C}=\text{O})$); 5.19 (s, 2H, $\text{O}(\underline{\text{CH}}_2)(\text{C}=\text{S})$). ^{13}C (CDCl_3 ; 76 MHz) δ (ppm): 73.1 ($\text{O}\underline{\text{C}}\text{H}_2(\text{C}=\text{S})$); 75.1 ($\text{O}\underline{\text{C}}\text{H}_2(\text{C}=\text{O})$); 167.5 ($\text{OCH}_2(\underline{\text{C}}=\text{O})$); 210 ($\text{CH}_2(\underline{\text{C}}=\text{S})$).

Synthesis of 3,3-dimethyl-5-thioxo-1,4-dioxan-2-one DMG and 3,3,6-trimethyl-5-thioxo-1,4-dioxan-2-one TMG. 1) Chloroacetyl chloride or 2-chloropropionyl chloride (88.5 mmol) and α -hydroxyisobutyric acid (9.2 g, 88.5 mmol) were dissolved in 20 mL of anhydrous acetonitrile in a round bottom flask. The reaction mixture was kept at 80°C overnight until HCl was no longer released. After the reaction mixture was cooled down to room temperature and was diluted with 200 mL of anhydrous acetonitrile. Triethylamine (17.9 g, 177 mmol) was added slowly under vigorous stirring and then the reaction mixture was heated at 80°C for another 6 hours. At the end of the reaction the white crystals of precipitated triethylammonium chloride were filtered off and the solvent evaporated under reduced pressure. The crude mixture was mixed with 250 mL of diethyl ether and the rest of triethylammonium chloride was removed by filtration. The diethyl ether was then removed by evaporation under reduced pressure. 3,3-dimethylglycolide **1** or 3,3,6-trimethylmethylglycolide **2** respectively were obtained and were further purified by sublimation under reduced pressure. Yield **1** and **2** 40%.

1 NMR. ^1H (CDCl_3 ; 300 MHz) δ (ppm): 1.67 (s, 6H, $\text{OC}(\underline{\text{CH}}_3)_2(\text{C}=\text{O})$); 5.01 (s, 2H, $\text{OCH}(\underline{\text{CH}}_2)(\text{C}=\text{O})$). ^{13}C (CDCl_3 ; 76 MHz) δ (ppm): 15.5 ($\text{OC}(\underline{\text{C}}\text{H}_3)_2(\text{C}=\text{O})$); 19.3 ($\text{OC}(\underline{\text{C}}\text{H}_3)_2(\text{C}=\text{O})$); 75.1 ($\text{O}\underline{\text{C}}\text{H}_2(\text{C}=\text{O})$); 78.4 ($\text{O}\underline{\text{C}}(\text{CH}_3)_2(\text{C}=\text{O})$); 167.5 ($\text{OC}(\text{CH}_3)_2(\underline{\text{C}}=\text{O})$); 175.4 ($\text{OCH}_2(\underline{\text{C}}=\text{O})$).

2 NMR. ^1H (CDCl_3 ; 300 MHz) δ (ppm): 1.68 (m, 9H, $\text{OCH}(\underline{\text{C}}\text{H}_3)(\text{C}=\text{O})$ and $\text{OC}(\underline{\text{C}}\text{H}_3)_2(\text{C}=\text{O})$); 5.09 (q, 1H, 7.2 Hz, $\text{OCH}(\underline{\text{C}}\text{H}_3)(\text{C}=\text{O})$). ^{13}C (CDCl_3 ; 76 MHz) δ (ppm): 17.56 ($\text{OCH}(\underline{\text{C}}\text{H}_3)(\text{C}=\text{O})$); 25.41 ($\text{OC}(\underline{\text{C}}\text{H}_3)_2(\text{C}=\text{O})$); 26.37 ($\text{OC}(\underline{\text{C}}\text{H}_3)_2(\text{C}=\text{O})$); 73.05 ($\text{O}\underline{\text{C}}\text{H}(\text{CH}_3)(\text{C}=\text{O})$); 80.69 ($\text{O}\underline{\text{C}}(\text{CH}_3)_2(\text{C}=\text{O})$); 166.82 ($\text{CH}(\text{CH}_3)(\underline{\text{C}}=\text{O})\text{O}$); 168.75 ($\text{C}(\text{CH}_3)_2(\underline{\text{C}}=\text{O})\text{O}$).

2 **1** or **2** (34.7 mmol), P_4S_{10} (3.9 g, 8.7 mmol) and hexamethyldisiloxane (9.4 g, 58.0 mmol) were dissolved in 50 mL of anhydrous toluene. Then the reaction mixture was stirred under argon for 15 minutes at room temperature and then refluxed for 24 hours. The dark mixture was then cooled down to room temperature and half of the solvent removed under reduced pressure. The residue was taken up in DCM and passed through a silica column ($R_f = 1.0$) to remove sulfur impurities. The crude product was then passed through a second silica column using a diethyl ether/ petroleum ether solvent mixture (30/70) and (20/80 respectively) as the eluent ($R_f = 0.3$). Collected from the column DMG or TMG respectively were further sublimed to obtain pure product (60°C, 10^{-2} mbar). The collected sublimated crystals of DMG were recrystallized before their use in polymerization. Yield of DMG 20% and TMG 25%.

DMG NMR. ^1H (CDCl_3 ; 300 MHz) δ (ppm): 1.73 (s, 6H, $\text{OC}(\underline{\text{C}}\text{H}_3)_2(\text{C}=\text{O})$); 5.22 (s, 2H, $\text{OCH}_2(\text{C}=\text{S})$). ^{13}C (CDCl_3 ; 76 MHz) δ (ppm): 25.18 ($\text{OC}(\underline{\text{C}}\text{H}_3)_2(\text{C}=\text{O})$); 73.81 ($\text{O}\underline{\text{C}}\text{H}_2(\text{C}=\text{S})$); 82.45 ($\text{O}\underline{\text{C}}(\text{CH}_3)_2(\text{C}=\text{O})$); 167.66 ($\text{OCH}_2(\underline{\text{C}}=\text{O})$); 206.19 ($\text{C}(\text{CH}_3)_2(\underline{\text{C}}=\text{S})$).

TMG NMR. ^1H (CDCl_3 ; 300 MHz) δ (ppm): 1.79 (m, 6H, $\text{OC}(\underline{\text{CH}_3})_2(\text{C}=\text{O})$); 1.87 (d, 3H, $^3\text{J}=6.6$ Hz, $\text{OCH}(\underline{\text{CH}_3})(\text{C}=\text{S})$); 5.19 (q, 1H, $^3\text{J}=6.6$ Hz, $\text{OCH}(\underline{\text{CH}_3})(\text{C}=\text{S})$). ^{13}C (CDCl_3 ; 76 MHz) δ (ppm): 21.52 ($\text{OCH}(\underline{\text{CH}_3})(\text{C}=\text{S})$); 24.74 ($\text{OC}(\underline{\text{CH}_3})_2(\text{C}=\text{O})$); 26.28 ($\text{OC}(\underline{\text{CH}_3})_2(\text{C}=\text{O})$); 79.58 ($\text{OCH}(\underline{\text{CH}_3})(\text{C}=\text{S})$); 83.24 ($\text{OC}(\underline{\text{CH}_3})_2(\text{C}=\text{O})$); 168.98 ($\text{CH}(\underline{\text{CH}_3})(\underline{\text{C}}=\text{O})$); 211.35 ($\text{C}(\underline{\text{CH}_3})_2(\underline{\text{C}}=\text{S})$).

Typical copolymerization protocol. AIBN or V-88, thionolactone, *t*BA and naphthalene as internal standard (10 mg) 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 60°C or 100°C for a given time. 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 (for more information on conversion determination refer to ESI). The polymer was analysed by SEC and used after evaporation of residual monomer. Polymer was usually precipitated in a mixture of 70% MeOH/ 30% Water.

Chemical degradation in accelerated conditions. 10 mg of copolymer was diluted in 1 mL of THF. The degradation agent (isopropylamine or ethylene diamine (1 mL) for aminolysis; bleach solution (1 mL) for bleaching; 40 mg of benzoyl peroxide in 1 mL of THF for peroxidation; 30 mg of MeONa in methanol for methanolysis was added. The mixture was stirred in a sealed vial at room temperature for 3 days. All volatiles were evaporated under reduced pressure. For SEC analysis the residue was dissolved in 1 mL of THF and filtered through PTFE 40 μm filter. For GC-MS-ES or NMR analysis, the residue was dissolved in DCM or in CDCl_3 , respectively.

RESULTS AND DISCUSSION

Synthesis of thionoglycolide and derivatives. The thionation of glycolide derivatives has not been studied in the literature. Only one article¹⁵ reports the thionation of L-lactide and racemic DL-lactide using P_4S_{10} /hexamethyldisiloxane as an adaptation of Curphey's protocol.¹⁶ In this work, the thionation of the starting glycolides involve 1,4-dioxane-2,5-dione (glycolide) which is commercially available, and the previously reported 3,3-dimethyl-1,4-dioxane-2,5-dione¹⁷ and 3,3,6-trimethyl-1,4-dioxane-2,5-dione¹⁸ which were synthesized using an adaptation of the procedure reported by Trimaille et al.,¹⁸ starting from commercially available hydroxyisobutyric acid and chloroacetyl chloride or 2-chloropropionyl chloride in a one-pot process.

Thionoglycolide (TGD), 3,3-dimethyl-5-thioxo-1,4-dioxan-2-one (DMG) and 3,3,6-trimethyl-5-thioxo-1,4-dioxan-2-one (TMG) were synthesized in yields of 33%, 20% and 25% respectively (^1H NMR, Fig. S1), with X-Ray crystal structures characterized (Fig S14, S16 and S18 respectively). The obtained yield of TGD was higher than that of TLD,¹⁵ DMG and TMG which can be attributed to the less hindered carbonyl group of TGD.

Radical copolymerization of thionoglycolide TGD. Results of radical copolymerization of TGD with vinyl monomers at 60°C with 0.1% of AIBN as initiator are shown in Table 1. Similarly to TLD,^{13,14} TGD did not homopolymerize (Table 1, entry 1). In copolymerization with vinyl acetate (VAc), TGD is consumed more rapidly than VAc with significant retardation of polymerization,

resulting in low conversion and low molar mass polymers (Table 1, entry 2). This result is similar to those obtained for copolymerization of TLD with VPI.¹³ We assume that in both cases, the vinyl ester propagating radical readily adds onto the thiocarbonyl C=S of the comonomer, forming a radical that is less reactive towards propagation and more prone to termination.

Table 1. Copolymerization of TGD with different comonomers (M) in bulk with 0.1 mol. % of AIBN at 60°C.

Entry	Comonomer (M)	f_{TGD}	Time, h	$X_{\text{TGD}}^{\text{a}}$, %	X_{M}^{a} , %	F_{TGD}	M_{n}^{b} kg mol ⁻¹	D^{b}
1 ^c	-	1	24	0	-	-	-	-
2	VAc	0.1	22	48	26	0.17	4.7	2.9
3	DMA	0.05	22	100 ^d	13	n.d.	n.d.	n.d.
4	St	0.05	24	42	49	0.043	7.9	2.2
5	St ^e	0.1	5	85	96	0.092	4.3	2.8
6	<i>t</i> BA	0.05	24	93	100	0.047	111.1	2.1

^a Conversion (X) and copolymer composition (F) determined by ¹H NMR

^b Determined by SEC in THF with PMMA calibration

^c Homopolymerization attempt has been conducted in CD₃CN (10 wt.% monomers)

^d TGD decomposed in the presence of DMA

^e in bulk, at 100°C with 0.5 mol. % of V-88.

Our attempts to polymerize TGD with dimethyl acrylamide (DMA) led to complete inhibition of polymerization (Table 1, entry 3) and change in color of the reaction medium from bright yellow to dark red. We assume that a side reaction between TGD and DMA resulted in the formation of side products responsible for the observed inhibition.

TGD readily copolymerized with St (Table 1, entry 4), exhibiting similar consumption rates for both monomers and resulting in the formation of a moderate molar mass polymer ($M_{\text{n}} = 7.9 \text{ kg mol}^{-1}$). In contrast to the copolymerization of TLD with St at 100°C,¹³ high monomer conversion with no retardation of polymerization of St was observed in the presence of TGD in the same conditions (Table 1, entry 5).

The copolymerization of TGD with *tert*-butyl acrylate (*t*BA) was the most successful, resulting in high conversion of both monomers and the formation of a high molecular weight polymer with an M_{n} of 111.1 kg mol⁻¹ (see Table 1, entry 6). These results suggest that TGD has a better suited reactivity with *t*BA than TLD,¹³ which can be attributed to a disfavoring effect of methyl substitution in the case of TLD. Based on these encouraging results of copolymerization of TGD with *t*BA at 60°C, we conducted a kinetic investigation of their copolymerization in bulk with $f_{\text{TGD}} = 0.1$ at 100°C with V-88 as initiator (Figure 1), in reaction conditions identical to those of our previous study on TLD.¹³ TGD and *t*BA copolymerized at similar rates without signs of retardation and similar to random copolymerization profile. After 90 min the conversion plateaued at 72% for TGD and 92% for *t*BA, which corresponded to a TGD content in the copolymer (F_{TGD}) of 0.08. This plateauing of the conversions is attributed to the high viscosity of the *Pt*BA-rich polymerization medium. Based on SEC results, high molar mass polymer was obtained ($M_{\text{n}} = 35 \text{ kg mol}^{-1}$ and $D = 1.9$). These findings are a significant improvement on the TLD / *t*BA system, where after 90 min of reaction the conversions of TLD and *t*BA were only 18% and 21%, respectively, and polymer of much lower molar mass was obtained ($M_{\text{n}} = 7 \text{ kg mol}^{-1}$ and $D = 1.9$).

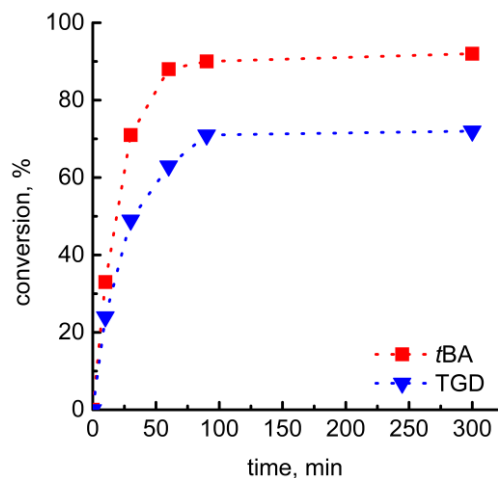


Figure 1 Evolution of conversions over time for the copolymerization of *t*BA with TGD ($f_{\text{TGD}} = 0.1$) in bulk at 100°C with 0.5% of V-88 initiator.

Microstructure of P(*t*BA-*co*-TGD). A P(*t*BA_{0.92}-*co*-TGD_{0.08}) sample obtained from our kinetic study was purified through precipitation in MeOH/H₂O and its microstructure was further investigated using ¹H, ¹³C, and 2D NMR techniques. On Figure 2, the ¹H NMR spectrum of the copolymer is shown with all characteristic signals assigned. Firstly, signals **a** and **b** at 4.0-4.7 ppm correspond to methylene protons of ring-closed thioketal TGD units. This was confirmed by the correlation of these signals in 2D NMR with quaternary thioketal carbon **f** at 85 ppm on ¹H-¹³C HMBC (Figure S11). No ring-opened thioester units were detected in the copolymer, as evidenced by the absence of a characteristic thiocarbonyl signal in the ¹³C NMR spectrum within the 200-230 ppm region (Figure S12). These results suggest the copolymerization of TGD leads to exclusive 1,2 propagation.

In addition, a distinctive methine -CH-S signal **c**₁ in the range of 3.0-3.7 ppm (Figure 2) indicates the incorporation of TLD units in the copolymer backbone. This signal originates from the *t*BA unit connected to the sulfur of the thioketal, which is distinct from signal **c**₂ at 2.5 ppm corresponding to the methine signal of *t*BA homosequences.

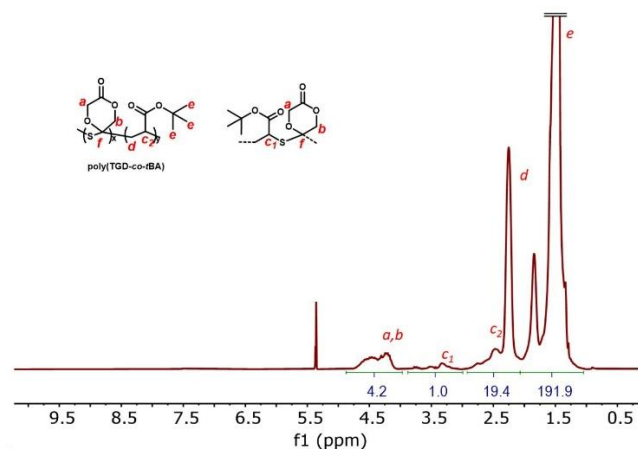


Figure 2 ¹H NMR (300 Hz in CD₂Cl₂) of purified P(*t*BA_{0.92}-*co*-TGD_{0.08}) from Table S2 entry 1.

Degradation kinetics in P(*t*BA-*co*-TGD). After confirming through NMR investigation that TGD is incorporated in the copolymer exclusively in its ring-closed form, we examined the degradability profile of S,O-thioether links within the copolymer. We prepared a P(*t*BA_{0.82}-*co*-TGD_{0.18}) copolymer in bulk with $f_{\text{TGD}}=0.2$, at 60°C for 16h with 0.3% of AIBN relative to monomers. TGD and *t*BA conversions were respectively 71% and 78%, with $F_{\text{TGD}} = 0.18$.

In Figure 3, we present the degradation kinetics of a copolymer dissolved in CH₂Cl₂ (10 mg mL⁻¹), as measured by SEC, across different degradation systems: aminolysis with isopropylamine (IPA) or diethylamine (Et₂NH), peroxidation using benzoyl peroxide (BPO), bleaching with NaOCl, and nucleophilic degradation with sodium methoxide MeONa. We also subjected the homopolymer of *Pt*BA to similar degradation tests, and it showed no significant change in SEC chromatograms after treatment with NaOCl, MeONa and IPA for one month (Fig S2). M_w was used instead of M_n to follow the polymer evolution under degrading conditions as more reliable indicator of polymer degradation, due to a disproportionate influence on M_n of low molecular weight oligomers and molecules which skews the assessment of the polymer's overall molecular weight distribution.

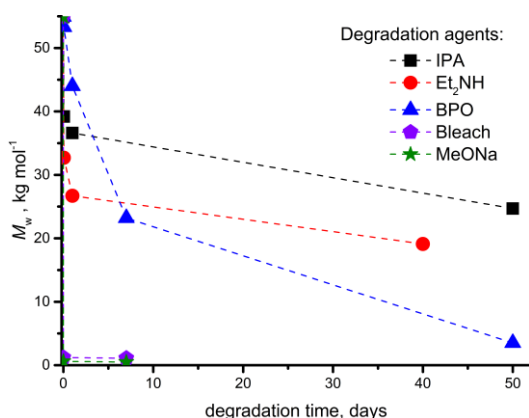


Figure 3 Decrease in M_w of P(*t*BA_{0.82}-*co*-TGD_{0.18}) over time after treatment with different degrading agents, determined by SEC with PMMA calibration. Lines between points are included to guide the reader's eye.

The most efficient degrading agents for the copolymer P(*t*BA_{0.82}-*co*-TGD_{0.18}) were bleach and MeONa (Fig. 3), resulting in complete degradation of thioether linkages with a 98% and 99% decrease of M_w , respectively, occurring in just 20 minutes of stirring at room temperature. There was no further change in the oligomer size after prolonged treatment. While the efficiency of bleach in degrading thioether links was expected, the efficiency of MeONa was intriguing.

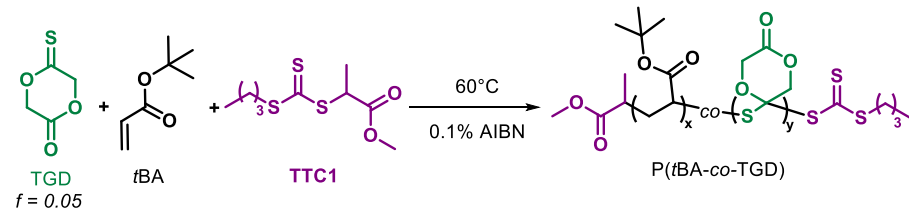
To gain further insight, we purified the oligomers after degradation with MeONa through extraction and analyzed the fragments using ¹H NMR (Fig. S3), as Gas Chromatography–Mass Spectrometry with Electrospray Ionization (GC-MS-EI) analysis was unsuccessful. ¹H NMR spectrum has shown the change in the shape of signals *a* and *b*, which indicates minor structural changes in the TGD moiety. A near complete disappearance and change in shape of signal *c*₁ indicates cleavage of the methylene CH-S, characteristic to TGD-*t*BA diads. Moreover, the signal *c*₂ from *t*BA-*t*BA diads remained intact. We assume that nucleophilic degradation in this case proceeds through a cascade process that commences with the cleavage of the exo-ester fragment of the incorporated TGD.

Subsequently, the ring-opening of glycolide fragment changes the reactivity of the thioketal bond, making it more susceptible to nucleophilic cleavage. A similar nucleophilic degradation mechanism, starting with the cleavage of an ester fragment in the ketal cycle, has been reported for copolymers of 4,4-disubstituted five-membered cyclic ketene hemiacetal esters with vinyl monomers.¹⁹

A milder nucleophilic degradation with primary and secondary amines proved to be less efficient than that of MeONa. A M_w decrease of only 65% was achieved with the use of Et₂NH over 40 days, and a 55% M_w loss was reached with IPA over 50 days (Fig 3). The significant change in M_w in the first day of degradation, followed by an incremental decrease over 40-50 days, can be attributed to the nucleophilic degradation of an extremely small fraction of thionoglycolide (<2 % of incorporated TGD), incorporated in the ring-opened thioester form.

Finally, the peroxidation with BPO was slower than bleaching but led to a steady decrease in M_w of the polymer reaching 94% loss of M_w of P(*t*BA-co-TGD) in 50 days. The oxidation of cyclic thioketals should proceed through oxidation of S⁻² to S⁰, followed by rearrangement of sulfine to sulfenic derivative and consequent hydrolytic cleavage of S-O bond with formation of hemi-acetal which is then slowly converted into corresponding alcohol and ketone.¹²

RAFT copolymerization of TGD with *t*BA. RAFT copolymerizations of *t*BA with 5 mol.% of TGD were conducted in bulk at 60°C with 0.1% AIBN initiator and methyl 2-(butylthiocarbonothioylthio)propanoate (TTC1) as chain transfer agent (Scheme 3). This trithiocarbonate RAFT agent was selected due to its ability to control the polymerization of more-activated monomers such as *t*BA, and since trithiocarbonates have been shown to be suitable for controlling polymerization of TLD.¹⁴



Scheme 3 RAFT copolymerization of *t*BA and TGD with TTC1 as a chain transfer agent.

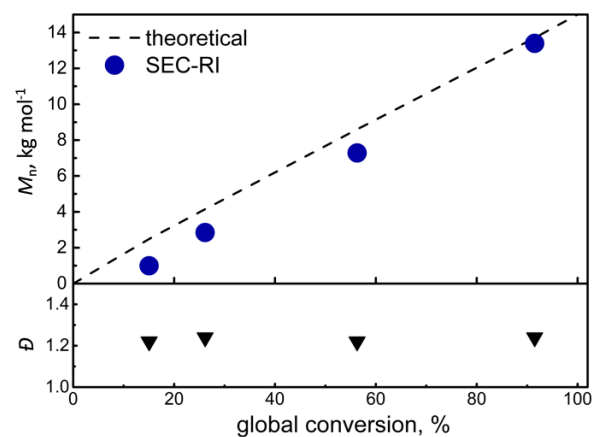


Figure 4 Evolution of M_n and dispersity as a function of global monomer conversion in RAFT copolymerization of *t*BA and TGD ($f_{TGD} = 0.05$) with TTC1. Conditions: bulk, 0.1% AIBN relative to monomers, 60°C.

A *t*BA/TGD copolymerization was monitored over time with a targeted theoretical M_n of 15.4 kg mol⁻¹ at full conversion (see Figure 4). Both monomers reacted at similar rates, enabling the establishment of a random distribution of TGD along the polymer chains (Table S1, entries 1-4). M_n gradually increased as monomer conversion progressed, initially slightly lower than the theoretical expectations, and matching the theoretical expectation during the final stage of polymerization. Furthermore, SEC chromatograms revealed monomodal populations (Figure S4), with dispersities maintained at 1.2 throughout the polymerization.

Finally, in order to demonstrate the chain-end fidelity of trithiocarbonate chain end in P(*t*BA-*co*-TGD)-TTC1 copolymer, we conducted a chain extension of P(*t*BA-*co*-TGD)-TTC1 macro-RAFT agent with St (Fig 5, [St]₀/[macro RAFT]₀/[AIBN]₀ = 840/1/0.3, $X_{St} = 55\%$). After chain extension, the SEC chromatogram of the P(*t*BA-*co*-TGD)-*b*-PSt diblock copolymer was monomodal, with M_n of 47.3 kg mol⁻¹ estimated using PMMA calibration which is slightly lower than the theoretical expectation of 62.3 kg mol⁻¹, and a moderate dispersity of 1.5.

The random incorporation of TGD in the initial RAFT-controlled acrylic block is clearly demonstrated by degradation experiments involving bleach on both the macro-RAFT agent and the resultant diblock copolymer (Table 2, SEC chromatograms are available in the ESI, Figure S6, S7 and S8). Specifically, bleaching of P(*t*BA-*co*-TGD)-TTC1 resulted in decrease in M_n of the copolymer to 2.4 kg mol⁻¹, which is close to the expected molar mass of 2.6 kg mol⁻¹ for these degraded oligomers. Additionally, the M_n of the diblock copolymer decreased from 47.3 kg mol⁻¹ to 35.2 kg mol⁻¹ following degradation, aligning with theoretical predictions.

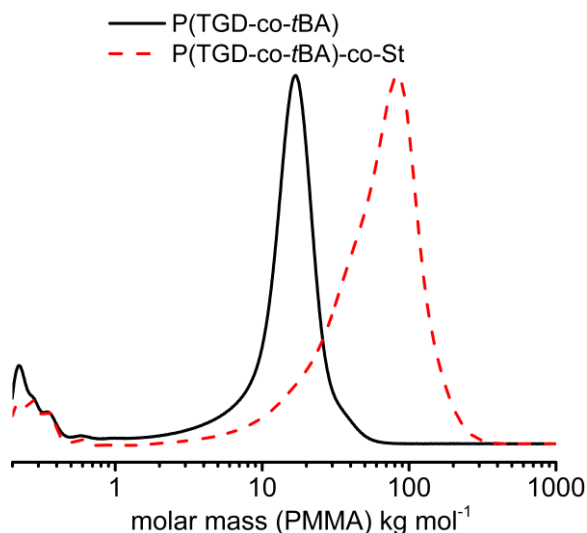


Figure 5 Molar mass distributions obtained from SEC for P(*t*BA_{0.951-*co*}-TGD_{0.049})-TTC1 macro-RAFT agent prepared using TTC1 (as described in Table S1, entry 4) and chain extended with polystyrene.

Table 2 Degradation treatments for *t*BA copolymers of different compositions.

Entry	Sample ^a	Before bleach		After bleach		
		M_n^b kg mol ⁻¹	\bar{D}^b	M_{calc}^c kg mol ⁻¹	M_n^b kg mol ⁻¹	\bar{D}^b
1	P(<i>t</i> BA _{0.951-<i>co</i>} -TGD _{0.049})-TTC1	13.4	1.2	2.5	2.4	1.5
2	P(<i>t</i> BA _{0.951-<i>co</i>} -TGD _{0.049})- <i>b</i> -PSt-TTC1	47.3	1.5	36.4 ^d	35.2	1.6

^a Samples prepared following protocols as described in the Table S1 for entries 1, 3 and as described in Table 1 for entry 2.

^b Determined by SEC in THF with PMMA calibrations.

^c Theoretical fragment size after bleaching is calculated as follows $M_{\text{calc}} = M_{t\text{BA}} * (1 - F_{\text{TGD}}) / (F_{\text{TGD}})$

^d Theoretical fragment size after bleaching of the diblock copolymer is calculated as follows:

$$M_{\text{calc}} = M_n(\text{P}(t\text{BA-co-TGD})\text{-}b\text{-PSt-TTC1}) - M_n(\text{P}(t\text{BA-co-TGD})\text{-TTC1}) + M_{t\text{BA}} * (1 - F_{\text{TGD}}) / (F_{\text{TGD}})$$

Structure-reactivity investigation for substituted thionoglycolides. The copolymerizations of DMG and TMG with *t*BA were conducted under identical experimental conditions to those of TGD and TLD with *t*BA. All copolymerizations strongly slowed down after 100 min and completely stopped after ~5 h due to total decay of the initiator ($t_{1/2} = 1.5$ h at 102°C),²⁰ leading to incomplete monomer conversions. *t*BA was always consumed faster than thionoglycolides. The overall polymerization rate increased in the order TLD < TMG < DMG < TGD (Figure 6a), which reflects the highest reactivity of TGD in copolymerization with *t*BA over its methyl substituted counterparts. No correlation was found between the degree of substitution in thionoglycolides and their reactivity profiles. For instance, dimethyl substitution on the α -carbon to the carbonyl group of DMG resulted in a slower polymerization rate compared to the unsubstituted TGD. Conversely, dimethyl substitution on the alpha carbon to the carbonyl in TMG led to a faster polymerization rate compared to the monomethyl substitution in symmetrical TLD.

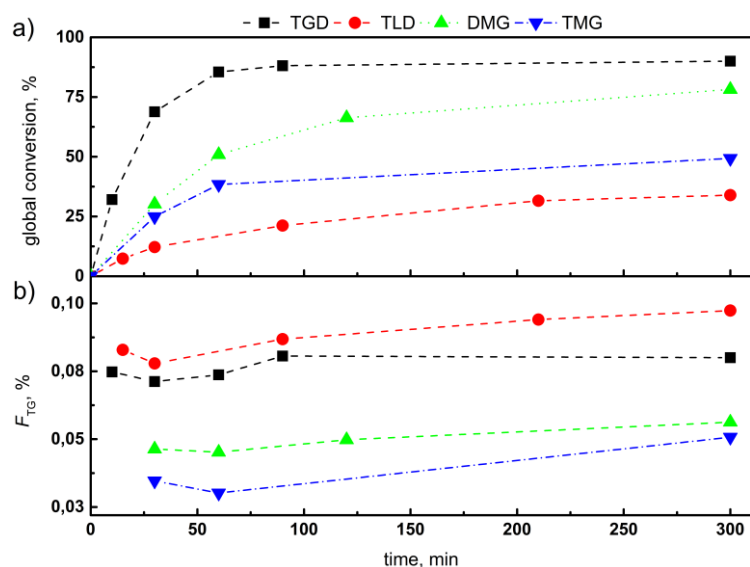


Figure 6 Evolution of global conversion (a) and fraction of incorporated thionoglycolide (F_{TG}) (b) in the copolymerization of thionoglycolides ($f_{\text{TG}} = 0.1$) with *t*BA at 100°C with 0.5% of V-88. Lines between points are included to guide the reader's eye. Data for TLD taken from ref ¹³.

In contrast, the fraction of incorporated thionoglycolide derivatives in the copolymer follows a different trend with the increase of F_{TG} in the order: TMG \approx DMG \ll TGD \approx TLD (Figure 6b). Both symmetrical thionoglycolides TLD and TGD were largely incorporated in copolymers, with respectively 9.7 and 8.0 % after 5 h (Table S2). These values are close to the initial feed while unsymmetrical TMG and DMG reacted almost 2 times less than the initial feed ($F_{\text{TG}} = 0.053$ - 0.056, see Table S2). The stabilization of the ring-opened radical (primary for TGD, secondary for TLD, and tertiary for DMG and TMG) does not appear to directly influence the fraction of incorporated thionolactone in the copolymer. This observation might be rationalized by the polymerization predominantly

occurring via a 1,2-propagation mechanism rather than through radical ring-opening. This mechanism was confirmed for TGD (*vide supra*) and played a significant role in the polymerization of TLD in previous literature.¹⁴ However, in the cases of DMG and TMG, it was not possible to determine the ratio between incorporated ring-opened and ring-closed signals from ¹H NMR due to broad, overlapping signals (Fig. S13). These observations suggest that the driving force of the radical propagation of thionoglycolide-like monomers lies in both stabilization of the intermediate acetal radical and accessibility for subsequent 1,2 propagation reactions.

Similarly, SEC results of the copolymers obtained after 5 hours of reaction have confirmed that the highest molar mass polymer was obtained in the copolymerization with TGD, where the M_n increases in the following order: TLD<TMG≈DMG<TGD (M_n =8.0, 13.4, 13.6 and 35 kg mol⁻¹ respectively, see Table S2 and Figure S10 for more details). These trends, derived from both conversion and SEC results, validate our initial hypothesis that methyl substitution of the thionoglycolide monomer induces deactivation of propagating radicals in copolymerization with *t*BA.

Finally, copolymers obtained with *t*BA from different thionoglycolides were subjected to degradation by bleach and analyzed by SEC (Table S3). All copolymers exhibited signs of near-complete degradation, with M_n after degradation slightly higher than the molar mass of calculated oligomer fragments. It is noteworthy that the copolymer containing TGD degraded to the lowest oligomer fragments compared to the substituted TLD, DMG, or TMG (2.4, 2.9,3.3, 5.6 kg mol⁻¹ respectively), despite the fraction of incorporated TLD in the copolymer being slightly higher than in the case of TGD (0.097 and 0.08 respectively).

Conclusions. Among the tested thionoglycolides, TGD has shown to be the most effective thionoglycolide for preparation of degradable thioketal-containing polymers with *tert*-butyl acrylate and styrene, showcasing high conversion rates of both monomers and the formation of polymers with substantially high molar masses, surpassing the performance of its methyl substituted counterparts. Moreover, good RAFT control of the TGD / *t*BA copolymerization opens the access to complex well-defined polymers with degradable segments for potential applications in various fields.

Additionally, the degradation process for TGD-containing copolymers, achieved through the cleavage of S,O-thioketal links with agents such as bleach, MeONa, and benzoyl peroxide, presents a viable alternative to the ester or (thio)ester-based routes for creating degradable vinyl polymers.

ASSOCIATED CONTENT

Supporting Information includes reaction conditions and polymer characterization tables, SEC results for degradation of all polymer samples, NMR spectra of model compounds and polymers, ESI-MS spectra of degradation products as well as characterization of degradation products and possible reaction mechanisms. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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