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COMMUNICATION

Lactide-derived monomers for radical thiocarbonyl addition-ring-opening copolymerisation

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The six-membered DL-thionolactide and DL-dithionolactide are reactive in radical ring-opening copolymerisation with a series of vinyl monomers to yield chemically degradable polymers. Bleach is an excellent degrading agent for both thioester and thioacetal linkages compared to classical nucleophilic treatment with amines.

Introduction

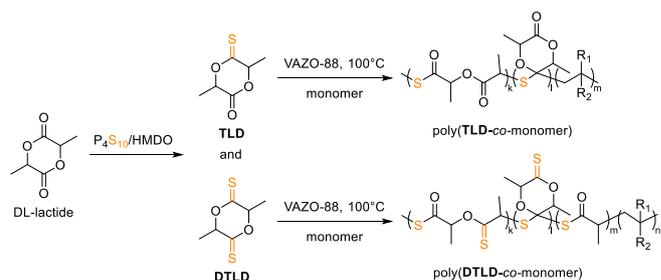
In today's chemical industry, nearly 50% of the worldwide production volume of synthetic polymers are produced by radical polymerization of vinyl monomers. Although much appreciated for the excellent reproducibility and scalability of their manufacturing processes, together with high structural and functional diversity, free radical polymers suffer from a lack of degradability due to their all-carbon backbone. The critical environmental concern of plastic pollution partly originates from this feature. Moreover, the long-term chemical stability of vinyl polymers is a major obstacle to their implementation in biomedical applications.

The use of radical polymerization to introduce chemical diversity and degradability to the polymer backbone was pioneered by the Bailey^{1,2} group in the 80s with formation of in-chain ester groups by radical ring-opening polymerization (rROP) of cyclic ketene acetals (CKAs). This topic has recently been rejuvenated by several groups^{3–7} to serve the growing demand for biodegradable vectors for nanomedicine.^{4,7}

A few years ago, the groups of Gutekunst⁸ and Roth⁹ independently reported the thionolactone dibenzo[c,e]-oxepane-5-thione (DOT) as a means to produce degradable polythioesters by so-called thiocarbonyl addition-ring opening (TARO) polymerization. In this process, growing radicals add to C=S bonds¹⁰ followed by fragmentation and ring-opening to form a new propagating radical,

by analogy with reversible addition-fragmentation chain transfer (RAFT) polymerization.¹¹ DOT monomer was shown to exclusively introduce ring-opened thioester backbone units in acrylate,^{8,9} acrylamide,^{9,12} and maleimide-based polymers.¹³ Earlier this year, d'Agosto and co-workers reported the synthesis of degradable DOT-based styrene (St) and acrylate copolymers by aqueous emulsion polymerization.¹⁴ In contrast, DOT is inert in methyl methacrylate (MMA) polymerization and it acts as an inhibitor when copolymerized with vinyl acetate and N-vinylpyrrolidone.

Last year, we¹⁵ and the Guillaneuf group¹⁶ independently reported a TARO polymerization process for making degradable copolymers of vinyl monomers with the structurally simple and easy-to-make ϵ -thionocaprolactone (TCL). TCL exhibits excellent reactivity in copolymerization with vinyl esters, but is unreactive in copolymerization with St, acrylates and methacrylates. Therefore, there is a strong need for diversification of TARO monomers in order to make them reactive with the broadest range of comonomers possible.



Scheme 1 Lactide-derived approach for synthesis of thioester/ester-containing copolymers

We hypothesised that the six-membered ring thionolactide (TLD, Scheme 1) could undergo rROP polymerisation, with the low ring strain of TLD being compensated by the stability of the acrylate nature of the ring-opened radical (Scheme 2a), which may facilitate TLD copolymerisation with more activated monomers (MAMs) like acrylates or styrene.

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Electronic Supplementary Information (ESI) available: [more info about material and methods used, NMR spectra of monomers and polymers, additional tables giving more details on polymerisation results, as well as detailed info about SEC results of copolymers before and after degradation]. See DOI: 10.1039/x0xx00000x

COMMUNICATION

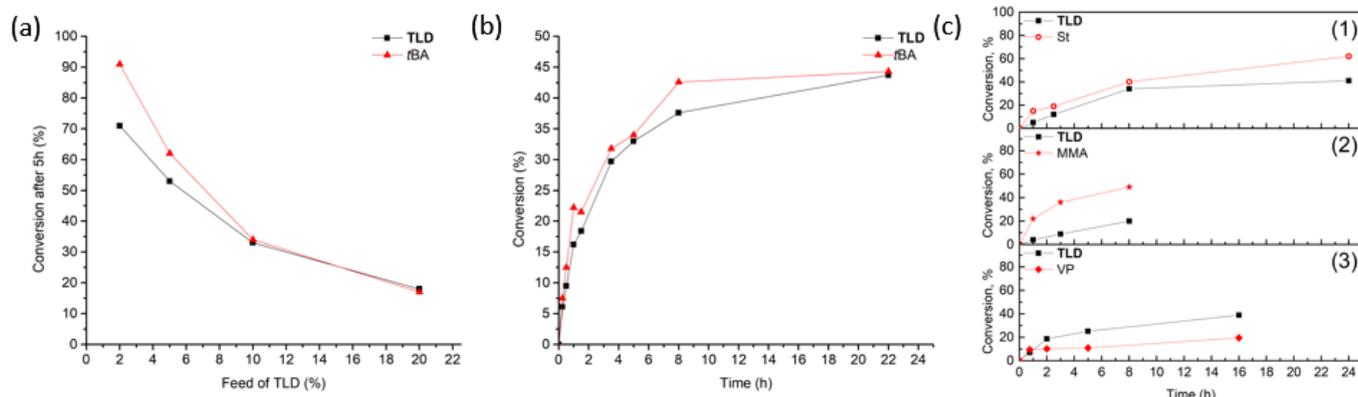


Fig. 1. Copolymerisation of **TLD** with various comonomers at 100°C [VAZO-88]₀/[Monomers]₀ = 0.5%. (a) Influence of **TLD** feed composition on **TLD** and **tBA** conversions after 5 h, (b) **TLD** and **tBA** conversions with time for $f_{\text{TLD}}=0.1$ (c) **TLD** and comonomer ((1) St, (2) MMA and (3) VP) conversions with $f_{\text{TLD}}=0.1$.

Therefore, the aim of this work was to study the TARO copolymerization of **TLD** and its dithionated derivative **DTLD** (Scheme 1) with a range of monomers of disparate reactivities, and evaluate the degradability of the resulting copolymers with a series of degrading agents.

Results and discussion

Thionolactide **TLD** was previously reported by Mangalum et al.¹⁷ for use in hetero Diels-Alder reactions and to our knowledge has never been tried as a monomer in radical polymerisation. To investigate its reactivity in rROP polymerisation, we repeated the authors' synthesis and isolated analytically pure **TLD**. High temperature polymerisation conditions (100°C, 0.5 mol. % VAZO-88) were selected to favour ring-opening over ring-retained propagation as we assumed similar behaviour in polymerisation as cyclic ketene acetals (CKAs) which have shown to ring open more readily at higher temperature.¹⁸

Our attempts to homopolymerize **TLD** were unsuccessful and resulted in recovery of unreacted monomer. This result was not surprising considering the 6-membered ring nature of **TLD** and the fact that other thionolactone-derived monomers like **TCL**¹² and **DOT**¹⁶ only homopolymerize in very specific conditions.

To estimate the reactivity profile of **TLD**, we carried out its copolymerisation with less activated monomer (LAM) vinyl pivalate (VP) and several more activated monomers (MAM): *tert*-butyl acrylate (*t*BA), styrene (St) and methyl methacrylate (MMA). Firstly, the effect of **TLD** feed on the copolymerisation with MAMs was studied in the case of *t*BA (Fig. 1a). We varied **TLD** feed from 2 mol % to 20 mol % and followed the conversion of both monomers after a fixed polymerisation time of 5h. We observed a strong retardation of the copolymerisation with

increasing feed of **TLD** with similar conversions for both monomers in all cases. In order to study the copolymerization kinetics, 10 mol. % feed of **TLD** was selected for all subsequent copolymerisations as a compromise between the incorporation of a sufficient amount of **TLD** in copolymer and acceptable conversions with sufficiently high molar mass of the formed copolymers.

Copolymerization kinetics were investigated for **TLD-tBA**, **TLD-St**, **TLD-MMA** and **TLD-VP** pairs of monomers (Figs. 1b and 1c). A selection of results is presented in Table 1.

Table 1. Copolymerisation of **TLD** with different monomers. Reaction conditions: bulk, 10 mol % feed of **TLD** with 0.5 mol. % of VAZO-88 at 100°C.

Comonomer (M)	Time h	X_{TLD}^a %	X_{M}^a %	F_{TLD} %	M_n^b kg mol ⁻¹	\bar{D}^b
VP	16	39	19	18	1.0	1.2
St	24	41	62	7	5.7	1.9
<i>t</i> BA	8	38	43	9	7.0	1.9
MMA	8	20	49	4	5.4	1.9

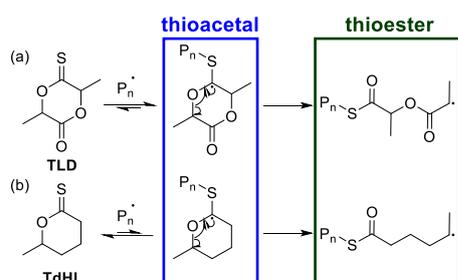
^a Determined by ¹H NMR

^b Determined by SEC in THF with PMMA calibration

The copolymerisation of **TLD** with vinyl pivalate proceeded in a different fashion than with MAM monomers: for the VP-**TLD** system, only low molar mass polymer ($M_n=1000$ g mol⁻¹) was obtained with significantly higher consumption of **TLD** relative to VP. Also, when comparing total conversion for **TLD-MAMs** and **TLD-VP**, a plateau value of 50% is reached for **TLD-MAMs** in over 24 hours (Fig. S11). On the other hand, for **TLD-VP** system total conversion hardly reaches 20% after 20 hours. These results suggest that vinyl ester growing radicals add readily to **TLD**, with the newly formed radical poorly propagating by addition to another monomer unit, leading to chain termination.

Copolymerisation of **TLD** with St and *t*BA exhibited similar reactivity profiles, with both cyclic and non-cyclic monomers converting at similar rates (Figs. 1b and 1c). The molar fraction of incorporated **TLD** in copolymers as well as M_n of both copolymers are in the same range (Table 1).

Copolymerisation of **TLD** with MMA was less successful. MMA was consumed at a much faster rate than **TLD** (Fig. 1c) allowing only maximum of $F_{\text{TLD}} = 4$ mol. % (Table 1) with M_n values in the same range as for other MAMs tested in copolymerisation.



Scheme 2 TARO polymerisation mechanism for **TLD** (a) and **TdHL** (b)

To better understand the structure-reactivity relationship of **TLD**, a structurally similar 6-membered ring without a second ester function inside the ring, namely δ -thionohexalactone **TdHL** (Scheme 2b), was synthesised and tested in copolymerisation with *t*BA at various feeds of **TdHL** between 5 and 50 mol. %. Contrary to **TLD**, the presence of **TdHL** had little effect on the rate of polymerisation of *t*BA (Fig. S12). A significant fraction of **TdHL** was incorporated only when thionolactone was fed in large quantities ($F_{\text{TdHL}} = 0.064$ for $f_{\text{TdHL}} = 0.5$, see more details in Table S3). The marked difference of reactivity between **TdHL** and **TLD** with *t*BA can be assigned to the enhanced activation of the C=S bond of **TLD** for addition of propagating radical and formation of a long-lived thioacetal intermediate radical causing retardation (Scheme 2). This formed radical can either cross-propagate in its ring-retained form or ring-open and release a methyl propionyl-type radical. Additionally, chain terminating behaviour was observed for both **TLD** and **TdHL**. It could be revealed by plotting M_n vs $1/(\text{monomer feed})$ (Fig. S13). This chain terminating property is probably related to the 6-membered ring nature of monomers, which makes the thioacetal radical inherently stable and long-lived, increasing the probability of chain termination over propagation to another monomer.

The random incorporation of **TLD** in the obtained copolymers was confirmed by studying their chemical degradation. We tested several different degrading systems with varying durations of treatment: Isopropylamine (IPA), KOH in THF/H₂O and NaOCl in THF/H₂O (bleaching).

IPA is a weak nucleophile that is known to cleave the thioester links of TARO polymers^{8,9,15,16} but is not expected to degrade thioacetal groups. Hence, KOH and bleach were tested as stronger degrading agents with potential to cleave both types of **TLD** units. Treatment with excess of IPA for 1 day at room temperature, the classical conditions for degrading thioester

links in copolymers of DOT⁹ and TCL¹⁵, was ineffective for poly(*t*BA-*co*-**TLD**) and poly(St-*co*-**TLD**). Only when treatment was extended up to one month was partial degradation of the copolymers observed (Fig. 2). Treatment with KOH for 1 month led to more degradation than in the case of IPA but still not complete (Fig. 2). We then tried to accelerate degradation and ensure efficient cleavage of both thioester and thioacetal links¹⁹ by choosing bleach solution as degrading agent. Significant shifts from high molar mass copolymer to low molar mass fragments were observed for both poly(*t*BA-*co*-**TLD**) (Fig. 2 and Table S4) and poly(St-*co*-**TLD**) (Fig. 2 and Table S5). The multiple-fold decrease in M_w values suggest random insertion of **TLD** within the copolymer backbone.

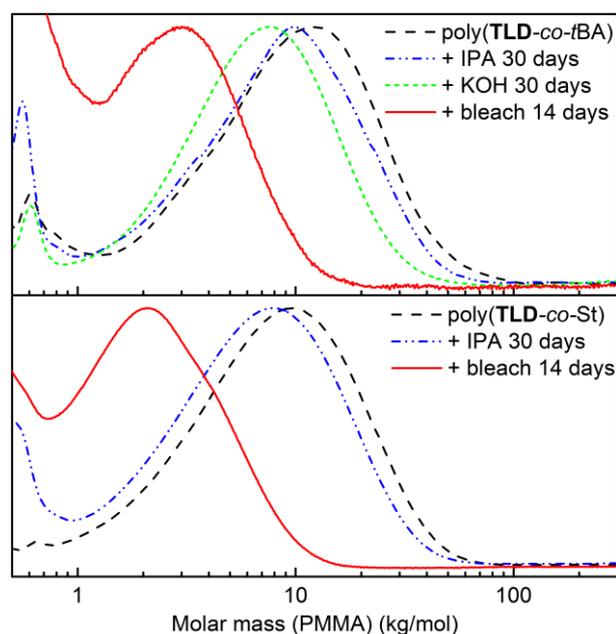


Fig. 2 Degradation of poly(*t*BA-*co*-**TLD**) and poly(St-*co*-**TLD**) using different agents (for more info see Tables S4 and S5 respectively).

For comparison, PSt, PtBA and PMMA homopolymers showed no significant change in molecular weight after treatment with isopropylamine (IPA), KOH or bleach as degrading agents.

We were not able to degrade poly(MMA-*co*-**TLD**) to low molar mass fragments with any of the degrading agents. After 14 days treatment with bleach we could decrease M_w by 10% (see table S6). Such particular resilience to degradation can be partly explained by the drift of composition and low **TLD** content for a large proportion of the copolymer. Indeed, based on the cumulative molar fraction of **TLD** in copolymer after 1, 3 and 8h of reaction (Table S1), it was estimated that ~70 wt% of the poly(MMA-*co*-**TLD**) sample contained only 2-3 mol% **TLD**. Moreover, sterically hindered thioester links in the MMA copolymer make it hard for the degrading agent to access - (C=O)S- carbonyl for nucleophilic attack. If **TLD** is incorporated in the ring-closed form, thioacetal links are most likely shielded by the hydrophobic environment of PMMA backbone from oxidation by hypochlorite anion.

Finally, we analysed the microstructure of purified poly(St-co-TLD) copolymer using 1D and 2D-NMR experiments.¹⁵ For all copolymers studied, a significant fractionation of TLD-rich chains occurred in typical precipitation media, making the signal intensity of TLD units very weak in the recovered copolymer. We could not give accurate ratios between the different microstructures in formed polymer because of the combination of broad weak signals with low TLD content, and were only able to identify the presence of different species in poly(St-co-TLD).

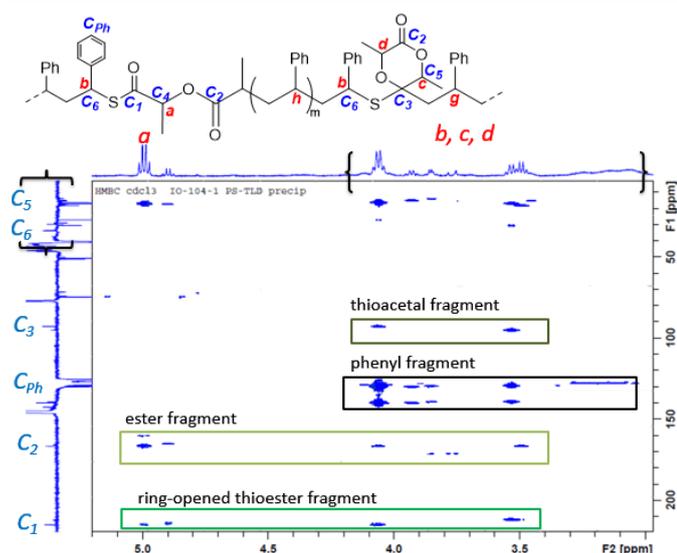


Figure 4 HMBC of poly(St-co-TLD) from Table 1. Different microstructures present in the copolymer are shown, from ring-opened thioester to ring-closed thioacetal.

From microstructure analysis of TCL/vinyl ester copolymers,¹⁵ we know that $-(\text{C}=\text{O})\text{S}$ - thioester of ring-opened units has a characteristic signal in ^{13}C NMR $\delta = 199$ ppm, while thioacetal derived from propagation in ring-closed form has a signal at $\delta = 90$ -95 ppm.

For poly(St-co-TLD) in ^{13}C -Jmod NMR (Fig. S15) we observed a pronounced group of signals at $\delta = 212$ -215 ppm which can only be attributed to C_1 thioester fragments incorporated in the copolymer. Also, we assigned a group of signals at around $\delta = 95$ ppm to quaternary C_3 from ring-closed thioacetal units incorporated in the copolymer. HSQC NMR of poly(St-co-TLD) (Fig. S17) confirms C_3 as quaternary carbon as there is no single bond correlation between any proton and the signal of C_3 at δ around 95 ppm. From HMBC NMR (Fig. 4) we could identify that signal **a** at $\delta = 4.98$ ppm comes from ring-opened units of TLD by J^2 correlation with C_1 and J^3 correlation with C_2 (Fig. S16). In the range from 4.2 ppm to 3 ppm on ^1H NMR we have superposition of signals which should come from different species identified by HMBC cross-referenced with HSQC and COSY (see Fig. S17, S18 and S19). The group of proton signals **c**, **d** corresponding to C-H comes from ring-closed units of TLD in the copolymer which is evidenced by correlation J^3 or J^2 with. Also, C-H proton **b** which comes from styrene propagating radical added to sulphur of TLD (ring-opened or closed) is present in the range from 4.2 ppm to 3 ppm as evidenced by HMBC correlation J^2 and J^3 with C_{Ph} and J^3 with C_1 or C_3 .

Finally, the bifunctional thionated version of DL-lactide **DTLD** was synthesised as reported by Mangalum et al.¹⁷ We performed preliminary tests in copolymerisation with tBA and MMA (Table 2). We used $f_{\text{DTLD}} = 0.05$ in both copolymerisations, considering a doubled amount of thionocarbonyl groups in the monomer, which makes it reasonable to compare with copolymerisations of TLD where $f_{\text{TLD}} = 0.1$. **DTLD** was more reactive than TLD in copolymerisation with tBA (Table 2), proceeding to full conversion of both monomers after 5h with much higher M_n than with TLD. In contrast, only 33% of TLD ($f_{\text{TLD}} = 0.1$, Table S1, entry 6) and 53% ($f_{\text{TLD}} = 0.05$, Table S2, entry 3) reacted under the same conditions. The copolymerisation of **DTLD** with MMA (Table 2) showed less retardation and much higher $M_n = 15$ kg mol $^{-1}$ compared to TLD-MMA system, but with a similarly low level of **DTLD** incorporation to that of TLD.

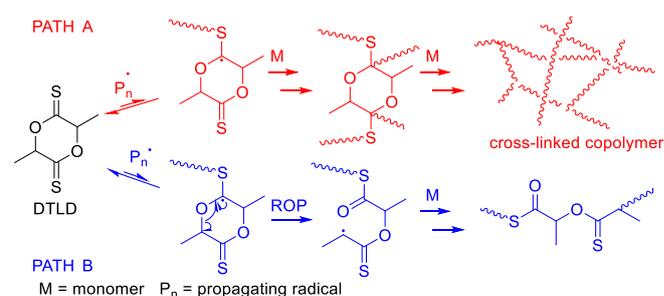
Table 2. Copolymerisation of **DTLD** with different monomers. Reaction conditions: bulk with 0.5 mol. % of VAZO-88 for 5h at 100°C.

Comonomer (M)	f_{DTLD} %	X_{DTLD}^a %	X_M^a %	F_{DTLD} %	M_n^b kg mol $^{-1}$	D^b
tBA	5	100	98	5	28.3	2.5
MMA	5	20	80	2	15	2.7

^a Determined by ^1H NMR

^b Determined by SEC in THF with PMMA calibration

DTLD-based copolymers were dissolved readily in organic solvents such as CHCl_3 and THF, with relatively well-defined molar mass distributions (see Fig. S14 for SEC chromatogram of poly(**DTLD**-co-tBA)). Due to the presence of two polymerizable groups in the **DTLD** monomer, 1,2-polymerization via a ring-closed thioacetal would be expected to lead to cross-linked polymer (Scheme 3). The absence of both higher molar mass and gel fractions suggests a negligible proportion of 1,2-polymerization and favours a ring-opening mechanism.



Scheme 3 Alternative propagation routes for copolymerization of DTLD via ring-retained structure (thioacetal form) - path A; or via TARO mechanism - path B

Finally, poly(tBA-co-**DTLD**) was degraded by IPA for 30 days and by bleach for 14 days (Fig. S14, Table S7) to yield similar polymer fragments with M_w values roughly divided by 3 after degradation. This confirmed the presence of **DTLD** as thioester links in the copolymer backbone. If present, thioacetal units would have led to marked differences in M_w depending on the degrading agent, as observed with TLD.

Conclusions

We have described the radical ring-opening copolymerisation of DL-thionolactide (**TLD**), a new TARO monomer available after simple thionation of cheap and abundant DL-lactide. Although reactive in copolymerisation with vinyl pivalate and methyl methacrylate, **TLD** is better adapted for statistical copolymerisations with styrene and acrylates. Using δ -thionohexalactone **TdHL** as a model 6-membered ring monomer, we could evidence the crucial role played by the ester group and methyl in beta position to C=S in **TLD** activation. The presence of both ring-opened thioester and ring-retained thioacetal units was revealed through complementary ^1H NMR, COSY, HSQC and HMBC experiments. The copolymerisation of difunctional **DTLD** with *t*-butyl acrylate gave less retardation and produced higher molar mass polymers than with **TLD**, with apparent selective formation of thioester units. The degradation of **TLD**- and **DTLD**-containing polymers by isopropylamine was less efficient than for polymers based on DOT and TCL. Bleach was identified as an excellent degrading agent for copolymers comprising both thioester and thioacetal linkages. The synthesis of copolymers with degradable **TLD**-based segments by RAFT polymerisation is currently being investigated.

Author Contributions

Conceptualization: M. D., S. H.; experimentation: O. I.; supervision: S. M., M. D., S. H.; writing: O. I., S. M., S. H., M. D.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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