Obvious complexity of the anionic polymerization of malolactonic acid esters

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Summary

The anionic polymerization and copolymerization of butyl and benzyl malolactonates initiated with potassium acetate/dibenzo-18-crown-6 or [222] complex have been studied at 40°C in bulk and in dichloromethane and tetrahydrofuran solutions. Kinetics and polymer molecular weights were followed by SEC. In bulk and for conversion below 30%, molecular weights are close to those calculated for a living process then the conversion increase leads to a significant discrepancy between theoretical and measured molecular weights. In solution, side reactions take place significantly and no evident relationship between molecular weight and initiator concentration can be established, even at low conversion. Same situation was observed in the case of block copolymers synthesis. At last, evidence for transfer reactions has been shown by using model reactions.

Introduction

The variety of β-substituted β-lactones is very important because great attention is being paid to high molecular weights polyesters aimed at biodegradable or hydrolyzable poly-esters for temporary applications (1). The adjustement of the properties can be obtained by the tailor-making of polymers owning a degradable chiral backbone and side functional groups. Thus, suitable polymer properties such as hydrophilic/hydrophobic balance, morphology, degradation rate, or bioactive molecules attaching can be achieved by copolymerization, cross-linking and chemical modification.
The poly(β-malic acid), a polyester with pendant carboxyl groups and a stereogenic center in the monomer unit, is a very good candidate for building such multimeric and polyvalent derivatives (2). A large family of functional polymers, copolymers and stereocopolymers of poly (β-malic acid) have been prepared (3–5). These compounds contain different types of specific side ester groups (neutral, chiral, reactive) (5–8) and hydrophilic sites arranged in variable proportions and distributions in the macromolecular chain for modulating solubility and rate degradation. At last, polymer drug carriers have been exemplified by linking 5-fluorouracil and chloramphenicol through the side carboxyl group of the malic acid unit (9,10). The possibility for building such tailor-made macromolecules with a strictly controlled composition has been used for preparing biomimetic hydrophilic polymers of malic acid interacting with heparin binding fibroplast growth factor (11).

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The anionic ring opening polymerization of these β-substituted β-lactones initiated with weak bases such as tetraalkylammonium benzoates or amines is well established, the alkyl oxygen bonds of the monomer molecules being cleaved by carboxylate anions as propagating species (12). But, in most cases, discrepancies appear between theoretical and measured molecular weights.

In this paper, we wish to report kinetic results on the anionic polymerization of benzyl and butyl malolactonates as model monomers and to discuss on mechanistic aspect of both lactones polymerization for concluding to the complexity and to the non living character of the process.

Experimental

Materials and methods

All chemicals were purchased from Sigma or Janssen Chemicals.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker ATC-300 spectrometer.

Samples were analysed by size-exclusion chromatography (SEC) with a 10^5, 10^4, 10^3, 500 and 2 x 100 Å set of styragel columns using toluene or THF as eluent (flow-rate 1 ml . min^{-1}) and connected to a Waters Model 410 Differential Refractometer and a Viscotek Differential Refractometer/Viscometer.

Osmometry measurements were carried out with a Mechrolab High Speed Membrane Osmometer Model 501 in toluene at 37°C.

Initiators

Stoichiometric mixtures of potassium acetate and of the complexing agent (2,3,11,12-dibenzo-1,4,7,10,13,16-hexaoxaclyclooctadeca-2,11-diene (DB$_{18}$C$_6$) or cryptand [222]), tetraethyl or tetramethylammonium benzoate were dried under vacuum during several hours.

Monomer syntheses

The syntheses of lactones **1** and **2** have been previously described in details (13,14). For detailed formulas of **1** and **2**, see scheme 1 in the text.

lactone **1** : (4 RS)-4-benzyloxycarbonyl-2-oxetanone.

^{1}H NMR (CD$_3$COCD$_3$): 3.69–4.09 (2dd, H$_a$ and H$_b$), 5.09–5.13 (dd, Hc), 5.27 (s, 2H), 7.34–7.46 (m, C$_6$H$_5$).

^{13}C NMR (CD$_3$COCD$_3$): 43.3 (C$_3$), 65.62 (C$_4$), 67.34 (CH$_2$C$_6$H$_5$) 128.65 et 135.72 (C$_6$H$_5$), 166.76 (C$_5$), 168.53 (C$_2$).

lactone **2** : (4RS)-4-butyloxycarbonyl-2-oxetanone.

^{1}H NMR (CD$_3$COCD$_3$): 0.9 (t, 3H), 1.36–1.44 (m, 2H), 1.61–1.7 (m, 2H), 3.64–4.00 (2dd, H$_a$ and H$_b$), 4.19–4.23 (t, 2H), 5.01–5.05 (dd, H$_c$).

^{13}C NMR (CD$_3$COCD$_3$): 13.26 (CH$_3$), 18.47 (CH$_3$CH$_2$), 30.52 (OCH$_2$CH$_2$), 43.24 (C$_3$) 65.53 (C$_4$), 65.62 (OCH$_2$), 166.84 (CO), 168.2 (C$_2$).

Polymer synthesis

Polymerizations were carried out under nitrogen at several temperatures. The kinetic of the reaction was followed by the periodical removal of aliquots at different times and the polymerization reaction was stopped by addition of HCl solution.

The polymers were studied after dissolution in acetone and precipitation in methanol.

Characterization

The variation of molecular weight has been monitored by SEC measurements. M$_n$ of reprecipitated samples have been compared with the values obtained by osmometry and by differential refractometry/viscosity (universal calibration) in order to determine a corrective factor.

Results and discussion

General Features of Polymerization.
The lactone **1** and **2** were anionically polymerized in bulk and in solution in the presence of a stoichiometric mixture of potassium acetate and dibenzo-18-crown-6 complex (**A**) or [222] (**B**) as initiator. All experiments were carried out with a ratio monomer/initiator close to 10^3 in order to synthesize polyesters with M_n in the range 1.5–2 x 10^5.

Size exclusion chromatography and IR spectroscopy analysis of samples taken during the reaction were used to follow both monomer consumption and formation of polymer. No cyclic oligomers are formed during the polymerization reaction. Similar results have been observed for polymerizations initiated by tetraethyl or tetramethylammonium benzoate or by (B). All results are summarized in table 1.

Table 1 - Anionic polymerization of (4RS)-4-benzyloxycarbonyl-2-oxetanone **1** and (4RS)- 4-butyloxycarbonyl-2-oxetanone **2** in bulk and in solution.
a) Initiator : *: (**A**) - **: (**B**)
b) M_n th = (Monomer)/(Initiator) $\times$ Conversion $\times$ Molar mass of the monomer.

Initiator[a) $\times 10^6$ mol	Monomer $\times 10^3$ mol	Experimental conditions	%HP	M_n th[b)	M_n
Lactone 1					
2.0*	1.95	20°C mass	30	60250	66200
			44	88350	81400
			71	142200	93600
2.0*	1.95	60°C mass	33	66200	56000
			67	134500	130000
			92	184750	108500
2.0*	2.0	40°C CH_2Cl_2	44	96000	64100
Lactone 2					
1.4*	1.7	40°C mass	32	66800	76000
			46	95200	84700
			55	115850	93150
1.8 **	1.6	40°C mass	19	29900	30000
			31	48800	50000
			44	69300	76850
			96	151500	58800
5.8*	5.0	40°C CH_2Cl_2	19	39200	15350
1.5*	1.3	35°C THF	5	7450	3350

In these conditions, the rates of polymerization are very low compared to those generally observed for β-lactones. For example with **1** = 1.95×10^{-3} mol and (**A**) = 2×10^{-6} mol, 100% conversion are reached after 26 hours reaction at 60°C. Moreover, under the same conditions, the rates of polymerization of **2** initiated by (**A**) or by (**B**) are close (100% after 28 hours), but significantly faster than in the case of tetramethyl or tetraethylammonium benzoates (100% after 72 hours).
For two experiments in bulk with (**A**) as initiator, Figure 1a displays the consumption of lactone **1** in bulk.
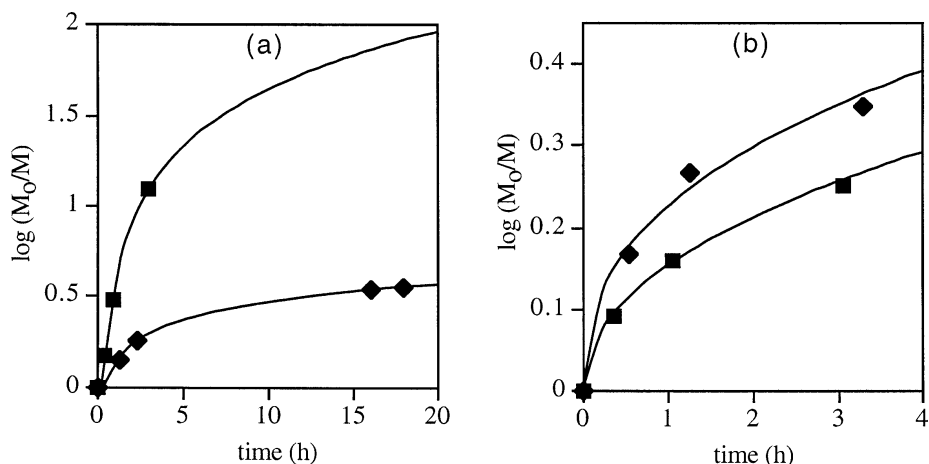
Figure 1 - Conversion-time plot for the polymerization of lactones **1** and **2** in bulk.
a) **1** : (**A**) : ◆ 20°C ■ 60°C   b) **2** : 40°C : ◆ (**A**) ■ (**B**)

Up to 40% of conversion, the monomer consumption is very fast and seems to follow a classical first order, the active sites concentration remaining approximatively constant. For higher yields, a discrepancy from the linearity is observed showing a pronounced slowing down of the rate at 20°C.

A similar phenomenon takes place for lactone **2** in bulk at 40°C (Figure 1b) for the polymerizations initiated by (**A**) and (**B**).

The variation of the molecular weight of the polymer with conversion has been followed using the SEC curves. At the beginning of the reaction, for both lactones, in the linear part of the conversion curve, experimental molecular weights are close to those calculated in agreement with a living process (table 1), and the polydispersity index M_w/M_n remains lower than 1.2. Plot of M_n with monomer conversion leads to a linear relationship from the origin up to 50% and 40% yield for **1** and **2** respectively (Figures 2a, 2b).
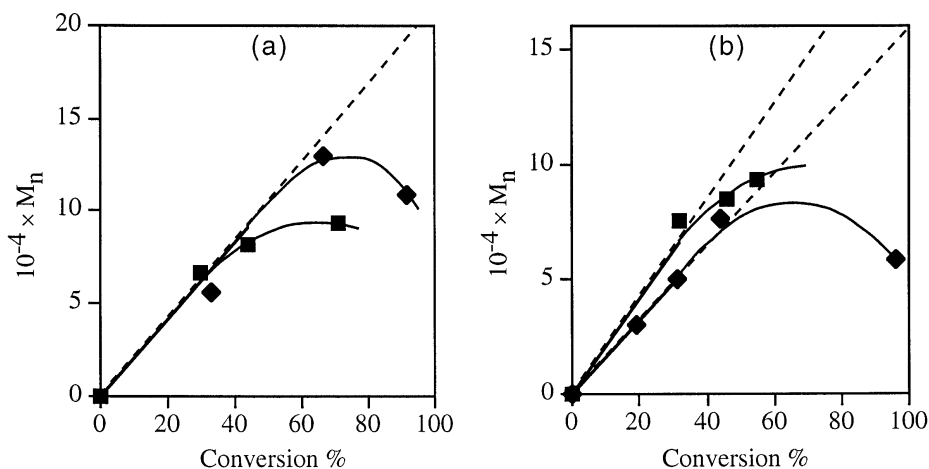

Figure 2 - M_n as a function of conversion for the polymerization of **1** and **2** in bulk.
---- theoretical curve   a) **1** : (**A**) : ◆ 60°C ■ 20°C   b) **2** : 40°C : ◆ (**A**) ■ (**B**)

For higher conversion, a significant reduction of the experimental molecular weight is observed and the maximum value of M_n calculated for a "living" polymerization process at 100% conversion is never obtained.

The ratio M_w/M_n rapidly increases with a simultaneous increase of the number of polymeric chains. The continuous increase of the macromolecules concentration is in agreement with the existence of transfer reaction and/or of degradation reaction.

This effect seems to be more pronounced for the polymerization of both lactones **1** or **2** in methylene chloride or THF as solvent at 40°C, the experimental M_n beeing lower (by a factor 0.8 for **1** and 0.5 for **2**) than the theoretical M_n even at low conversion (Table 1).

Copolymers

In order to prepare block copolymers, a "living" prepolymer of lactone **2** M_{SEC} = 93000) was first synthesized and used to initiate the polymerization of lactone **1** after dissolution in CH_2Cl_2. At the end of the reaction, SEC trace displays two peaks clearly identified at M_{SEC} = 110000 and 31000. Both peaks have been respectively assigned to the copolymer **2-b-1** and to the homopolymer of **1**. A similar result was obtained with a prepolymer of lactone **1** (M_{SEC} = 74000) as initiator. In this case, two peaks corresponding respectively to M_{SEC} = 86000 and 11000 were observed after addition of **2**.

These results are in good agreement which those obtained during the homopolymerization of these lactones and suggest a significant presence of transfer reactions. Due to the particular chemical structure of these lactones, a monomer transfer reaction can be considered.

Model reactions

In the anionic polymerization of β-lactones owning an hydrogen atom in the α-position initiated by carboxylate anion, chain transfer can occur by proton abstraction on a monomer molecule by the initiator or by the active chain end. (scheme 1)
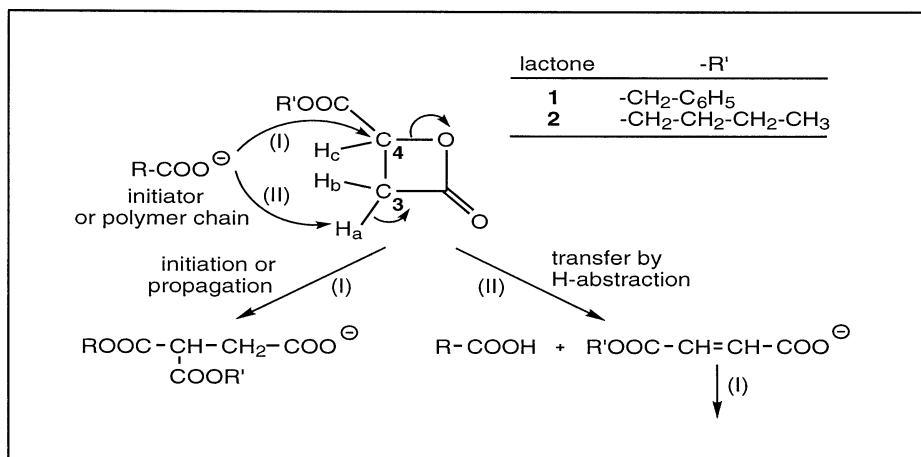
Scheme 1 - Different pathways for the reaction of carboxylate and malolactonate.

This scheme shows the different reactions that can occur between carboxylate anion and the monomer. The initiation and propagation reactions result of the ring-opening via a S_N2 at the C_4-O bond (path I). According to path II, the monomer transfer reaction leads to the formation of a carboxylic acid function and of an unsaturated carboxylate which

can also react giving either propagation (path I) or transfer reaction (path II) leading to a chain with an insaturated end group.

However, ^{1}H NMR analysis of high molecular weight homopolymer does not display any signal corresponding to the presence of a double bond.

As a model, experiments involving reactions of benzylmalolactonate **1** with (**A**) or $C_6H_5CO_2^-,^+NMe_4$ with various ratios (lactone / initiator = 1, 2 and 3) were carried out in CH_2O_2, at 40°C. In each case, the ^{1}H NMR spectrum of the reaction product displays one signal corresponding to OH end group at δ = 10.5 ppm and two doublets at δ = 6.59 and 7.01 ppm assigned to a trans HC=CH (J = 16 Hz).

According to this experimental evidence, the formation of unsatured compounds seems to confirm the presence of transfer reactions to the monomer in agreement with the results reported by Duda (15), Jedlinski (16) and Kricheldorf (17). Such a reaction involving a proton transfer reaction has already been considered in previous papers reporting the synthesis of block copolymers containing ε-caprolactone (18,19).

In the case of α-methyl-α-propyl-β-propiolactone, the polymerization reaction initiated by (**B**) leads to a "living polymer" with controlled molecular weight up to Mn = 130000 with a narrow molecular weight distribution. No monomer transfer reaction is observed, probably on account of the absence of an hydrogen atom in the α-position (20).

A last attempt at transesterification has been made through reaction on a model molecule owning the side ester group of monomer **1**. Several experiments have been carried out using benzyl butyrate in bulk and in solution in the presence of potassium acetate/$DB_{18}C_6$ complex and tetramethylammonium benzoate. G.C. analysis of the mixtures after one week reaction did not display any peaks corresponding to benzyl acetate or benzoate. One can conclude that side ester groups do not give rise to any side reaction during polymerization.

An increase of the polydispersity index can also be due to degradation reactions by the carboxylate anion of the initiator and/or of the growing polymeric chain.

In order to examplify this type of reaction, 7.2×10^{-6} mol of (**A**) was added to 0.26g of a deactivated poly(benzyl-β-malate) (M_n = 99000) and the mixture kept at 40°C for one month. A strong decrease of the molecular weight (M_n = 32500) was observed without any change in the ^{1}H NMR spectrum of the mixture.

Moreover, it was also observed that the polymeric chains of a non deactivated polymer (M_n = 66000) obtained for quantitative yield and kept for a month in the reaction medium under nitogen are relatively stable.

During the anionic polymerization of lactones **1** or **2**, besides monomer transfer reaction which lowers the molecular weight of the polymers, secondary chain degradation reactions can take place by reaction of the remaining initiator on the growing polymeric chains.

Conclusion

This study confirms the non-living process of the anionic polymerization of malolactonic acid esters initiated by various carboxylates in bulk or in solution, and the difficulty to synthesize polymers with controlled high molecular weight and narrow molecular weight distribution.

The synthesis of such homopolymers or copolymers aimed at the preparation of polymeric devices for drug delivery systems with a specific hydrophilic/ hydrophobic balance needs another route involving the polymerization of α,α′-substituted-β-lactones derivated from malic acid in order to minimize side reactions.

References

1. Jérome R, Teyssié Ph (1989) Anionic Ring-Opening Polymerization: Lactones. In: Allen G (ed) Comprehensive Polymer Science. Pergamon Press, Oxford, (vol.3, pp 501–510)
2. Vert M, Lenz RW, (1979) Polym Prep 20:608
3. Caron A, Braud C, Bunel C, Vert M (1990) Polymer 31:1797
4. Guérin Ph, Francillette J, Braud C, Vert M (1986) Makromol Chem Macromol Symp 6:305
5. Boutault K, Cammas S, Huet F, Guérin Ph (1995) Macromolecules 28:3516
6. Renard E, Boutault K, Langlois V, Guérin Ph (1996) Polym Bull 36:585
7. Ramiandrasoa P, Guérin Ph, Girault JP, Bascou Ph, Hammouda A, Cammas S, Vert M (1993) Polym Bull 30:501
8. Cammas S, Boutault K, Huet F, Guérin Ph (1994) Tetrahedron Asymmetry 5:1989
9. Ouchi T, Fujimo A, Tanaka K, Banba T (1990) J Controlled Release 12:143
10. Leboucher-Durand MA, Langlois V, Guérin Ph (1996) Polym Bull 36:35.
11. Dubois MC, Baltaze JP, Langlois V, Guérin Ph (1996) IUPAC Meeting on Macromolecules, Biodegradable Polymers, Prague
12. Hofman A, Slomkowski S, Penczek S (1984) Makromol Chem 185:91
13. Guérin Ph, Vert M, Braud C, Lenz RW (1985) Polym Bull 14:187
14. Guérin Ph, Vert M (1987) Polym Commun 28:11
15. Duda A (1992) J Polym Sci 30:21.
16. Kurcok P, Kowalczuck M, Hennek K, Jedlinski Z (1992) Macromolecules 25:2017
17. Kricheldorf HR, Scharnagl N (1989) J Macromol Sci A26(7):951
18. Hsieh HL (1978) J Appl Polym Sci 22: 1119
19. Keul H, Höcker H (1986) Makromol Chem 187: 2833
20. Haggiage J, Hémery P, Boileau S, Lenz RW (1983) Polymer 24: 578