Polymer Bulletin 9, 276–283 (1983)

Polymer Bulletin

New Polymer Syntheses

8. Synthesis and Polymerization of L-Lactic Acid O-Carboxyanhydride (5-Methyl-Dioxolan-2,4-dione)

Hans R. Kricheldorf and J. Michael Jonté

Institut für Angewandte Chemie der Universität, Martin-Luther-King-Platz 6, D-2000 Hamburg 13, Federal Republic of Germany

SUMMARY

L-Lactic acid O-carboxyanhydride (L-Lac-OCA) was prepared by phosgenation of L-lactic acid lithium salt. Its polymerization was conducted using a variety of initiators, and the resulting poly(L-lactides) were characterized by ^{1}H- and ^{13}C-NMR spectra, by vapor pressure osmometry (VPO) and by optical rotation. Number average molecular weights > 3 000 were never obtained. Also polymerizations of D,L-Lac-OCA did not give higher Mn's. The formation of isotactic triads was favored under all conditions. Furthermore, copolymerizations of L-Lac-OCA and various α-amino acid N-carboxyanhydrides (NCAs) only yielded low molecular weight poly(depsipeptides). The polymerization mechanism is discussed.

INTRODUCTION

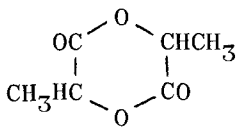
Poly(L-lactide) and copolymers of L-lactic acid and glycolic acid are interesting biodegradable plastics, because the degradation products do not exhibit any toxicity. They were commercialized as fibers for medical purposes, such as surgery. The synthesis of these polyesters is based exclusively on the ring opening polymerization of L,L-lactide (1). Such polymerizations require transesterification catalysts along with higher temperatures, reaction conditions that are not suited for the preparation of block copolyesters. Furthermore, copolymers of L-lactic acid and α-amino acids (so called poly(depsipeptides)) are not obtainable in this way. Hence, a novel approach to the preparation of homo- and copolymers of lactic acid should be investigated, namely synthesis and polymerization of L-Lac-OCA (2). This monomer was expected to be reactive enough to allow polymerizations under mild conditions and copolymerizations with α-amino acid NCAs (3).

Table 1 Reaction conditions and results of various polymerizations of L-Lac-OCA and D,L-Lac-OCA

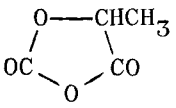
No.	OCA	Initiator	Mon / Init.	Solvent	Temp. (°C)	Yield (%)	Tm (°C)	$[\alpha]_D^{20}$ in $CHCl_3$	$\overline{Mn}$ (VPO)
1	L-Lac	Pyridine	1:10	Pyridine	20	88[a]	124[a]	-140.0	1 800
2	L-Lac	Triethylamine	50: 1	Dioxane	20	40	--	- 75.4	--
3	L-Lac	K-O-t.-Bu	300: 1	Dioxane	100	67	--	- 60.8	--
4	L-Lac	K-O-t.-Bu	300: 1	DMF	100	60	--	- 31.2	--
5	L-Lac	---	--	---	100	90	--	-100.5	--
6	L-Lac+ Gly-NCA	Pyridine	1:10	Pyridine	20	45	100-110	---	--
7	L-Lac+ Glu-NCA[b]	Pyridine	1:10	Pyridine	20	7	70-80	---	--
8	D,L-Lac	Pyridine	1:10	Pyridine	20	75[a]	64[a]	- 0.8	3 000
9	D,L-Lac	$Ti(O\text{-}Bu)_4$	1: 100	CH_2Cl_2	20	74[a]	42[a]	- 0.8	--
10	D,L-Lac	---	--		100	87[a]	25[a]	- 0.6	1 500

a) isolated by filtration from cold methanol

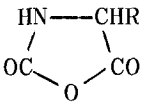
b) γ-O-Benzyl-L-glutamate-NCA



1



2



3

RESULTS and DISCUSSION

The synthesis of D,L-Lac-OCA by direct phosgenation of D,L-lactic acid has been described[1]; yet this method was not satisfactory in the case of L-lactic acid for two reasons. First, pure,water-free L-lactic acid is difficult to prepare because a removal of water causes formation of L-lactide (1) which is difficult to separate from both the lactic acid and its OCA 2. Second, the formation of large amounts of HCl during phosgenation causes formation of byproducts. Therefore, the best results were obtained, when the non-hygroscopic (and commercially available) lithium salt of L-lactic acid was phosgenated using N-methylmorpholine as an additional HCl acceptor. This amine is advantageous for three reasons: 1) it is less basic than most trialkylamines, so that racemization of L-Lac-OCA is less probable; 2) it is less nucleophilic than pyridine, so that initiation of the polymerization is less probable; 3) its hydrochloride is less soluble than that of most other tertiary amines.

The polymerizations conducted with L-Lac-OCA are summarized in Table I (Nos. 1-5). Because theoretical considerations along with experimental results obtained by Tighe et al.[1] from polymerizations of mandelic acid OCA indicate that protic nucleophiles are not useful as initiators,exclusively aprotic bases and thermal initiation were investigated. All results were disappointing. In the case of strong bases (Nos. 1-4) the optical rotations demonstrate that the polymerization were accompanied by partial racemization. The optical rotation decreases with increasing basicity of the initiator,suggesting that reversible deprotonation of the α-C-proton (Eq.(1)) took

place. This mechanism is supported,first by the mechanism of the alkoxide initiated polymerization of L-proline-NCA[2] which is also accompanied by racemization. Second, we have previously shown[3] that N-(-o-nitrophenylsulfenyl)-NCAs undergo racemization in a 1 % solution of triethylamine in 1,4-dioxane at 20°C. The deprotonation of the monomers (2) is also of interest with respect to the polymerization mechanism, because it may lead to the initiation reaction (2), if impurities that are more acidic than the OCA are absent. In the case of the less basic, but more nucleophilic pyridine the heterolytic cleavage of the anhydride group (Eq.(3)) might be an alternative initiation. An analogous mechanism has been reported for pyridine-initiated polymerization of N-substituted NCAs[4].

Whatever the initiation step,the propagation most likely results from the reaction between monomer and carbonate chain end (4) + (5). A similar propagation, "the carbamate mechanism" has been proposed for the polymerization of NCAs[5]. Regardless of the initiation the kinetics should be first order with respect to both monomer and initiator. Hence, the pseudo first order kinetics found by Tighe et a [1] for the pyridine-initiated polymerization of mandelic acid OCA, does not prove the intermediate formation of α-lactones (8) which is highly unlikely. Despite different polymerization mechanism we agree with Tighe et al. that acidic protons may be responsible for the termination step. In our mechanistic scheme, protonation and decarboxylation (5) + (6) yield relatively unreactive OH groups. A further termination might result from the disproportionation of the intermediately formed mixed anhydride group (Eq.(7)). Such "disproportionations" are wellknown, e.g. from the reactions of carboxylic acids or thiol acids with isocyanates and isothiocyanates [6-8]. These two termination steps would explain why both base- and heat-initiated polymerizations of OCAs cannot yield high molecular weight polyesters.

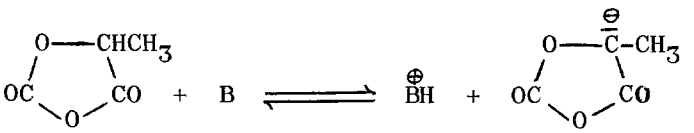
In this connection, it is noteworthy that 100.5 MHz ^{13}C NMR spectra show that the polylactides Nos. 2-4 are heavily contaminated with side products. In contrast, products Nos. 1 and 5

(Table 1) show clean NMR spectra. However, even in the optimum case (No.1) vapor pressure osmometry measurements gives a number molecular weight of merely 1 800 ($\overline{DP}$ 25). Since the α-amino acid NCAs possess acidic N-protons, it is ovbious on the basis of our mechanistic scheme that copolymerization of L-Lac-OCA and amino acid NCAs cannot yield higher average degrees of polymerization ($\overline{DP}$s). Indeed the copolymerizations Nos.6 and 7 gave mainly sirupy reaction products. In the case of D,L-Lac-OCA, a monomer first prepared by Davies[9], $\overline{DP}$s in the range of 20-40 were found (Nos. 8,9). These results agree well with those of Tighe[1] who found $\overline{DP}$s between 2.5 and 25 for pyridine initiated polymerization of L- and D,L-mandelic acid OCA. Hence, we must conclude that OCAs are not suitable for the preparation of high molecular weight polyester or polydepsipeptides.

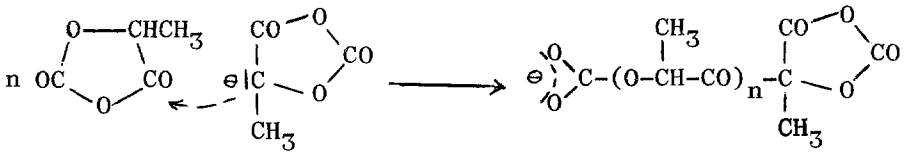
Nonetheless, the polymerization of D,L-Lac-OCA was interesting with respect to the stereospecificity.Lillie and Schulz have demonstrated[10] that it is feasible to analyze the tacticity of poly(D,L-lactide) by means of ^{13}C NMR spectra. Our 100.5 MHz ^{13}C NMR spectra exhibit a clear triad pattern of the α-C signal (Fig. 1 A), and the isotactic triad was assigned by addition of poly(L-lactide) (Fig. 1 B). From the peak intensities we may conclude that in all three polymerizations (Nos. 8-10) isotactic sequences were preferentially formed. This result is interesting because most polymerizations of D,L-amino acid NCAs behave likewise [11-13]. Finally, it is to be mentioned that our chemical shifts (69.0, 69.2, 69.3, 69.4 ppm) and our triad assignment do not agree with those of Lillie and Schulz[7]. Because the signal-to-noise ratio of their spectra is poor, the 67.06 ppm peak they have listed, probably does not belong to the triad pattern. More detailed ^{1}H NMR studies of the tacticity of poly-(D,L-lactides) prepared from D,L-L,L lactide have been published by other authors [14,15].

Experimental

L-Lac-OCA: A quantity of 2.5 - 3.0 mol phosgene was condensed and diluted with ca. 1.5 l cold, dry tetrahydrofuran. Then 1.0 mol lithium L-lactate (Sigma Chemicals) was added portionwise

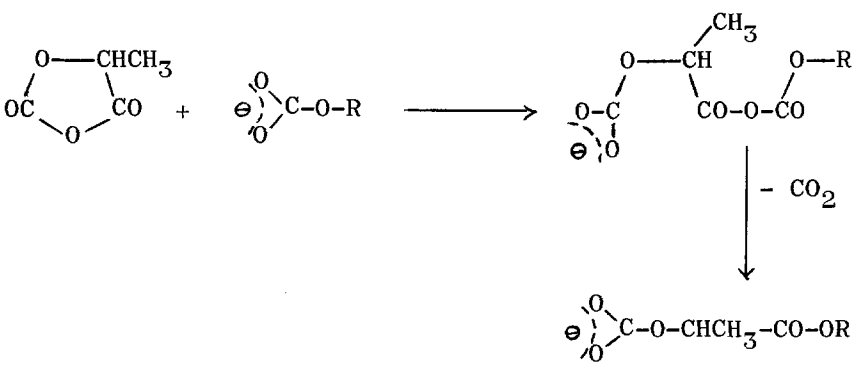


(1)



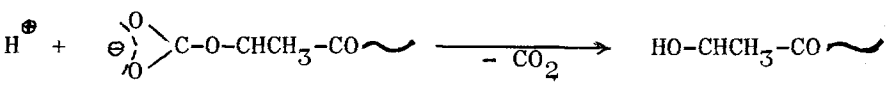
(2)

(3)

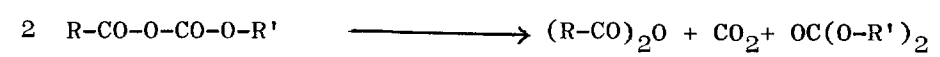


(4)

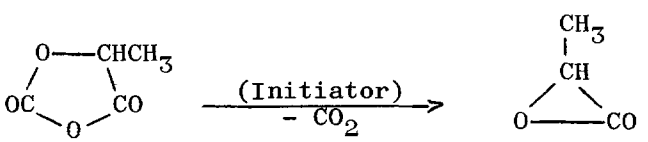
(5)



(6)



(7)



(8)

under cooling, so that a reaction temperature of 0 ∓ 5°C was maintained. When a clear solution was obtained, a solution of 1.0 mol N-methyl morpholine in 500 ml dry tetrahydrofuran was added slowly under cooling. Afterwards, the excess phosgene was removed overnight by a slow stream of nitrogen, the reaction mixture was filtered under exclusion of moisture and the filtrate concentrated in vacuo. The L-Lac-OCA was crystallized by portionwise addition of carbon tetrachloride under dooling with ice. It was treated with dry charcoal in ethyl acetate and twice recrystallized from ethyl acetate/carbon tetrachloride.
Yield: 61 %; m.p. 54-56°C;
Analyses calcd. for $C_4H_4O_4$ (116.05) : C 41.4, H 3.5
Found: C 41.2, H 3.5; $[\alpha]_D^{20}$ = -19.2 (c=10g/l in chloroform)

D,L-Lac-OCA was prepared analogously: mp. 24-26°C (mp.26°C in ref.9).

Polymerizations: The initiator was added to the solution of 25 mmol Lac-OCA in 25 ml of a dry solvent and the glass flask was closed with a freshly prepared calcium chloride drying tube. The polymers were precipitated into ice-cold methanol and isolated by filtration (Nos. 1,8-10), or the methanol solutions were brought to dryness in a vacuum of 12 mbar.

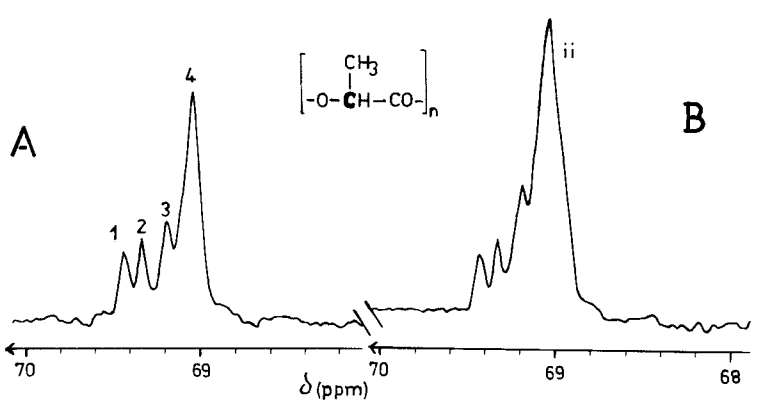


Fig.1 100.5 MHz ^{13}C NMR spectra measured in $CDCl_3$ (int. TMS): A) poly(D,L-lactide) No.8 (Table 1); B) the same sample after addition of ca. 25 mol % poly(L-lactide).

References:

1) J.Smith and J.Tighe; Makromol.Chem. 182, 313 (1981)
2) M.Goodman and U.Arnon; Biopolymers 1, 500 (1963)
3) H.R.Kricheldorf and M.Fehrle; Chem.Ber. 107, 3533 (1974)
4) H.R.Kricheldorf and K.Bösinger; Makromol.Chem. 177, 1243 (1976)
5) R.Idelson and E.R.Blout; J.Ann.Chem.Soc. 79,39,48 (1957)
6) C.Naegeli; Helv.Chim.Acta 18, 142 (1935)
7) St.Goldschmidt and M.Wick; Liebigs Ann.Chem.575,217 (1952)
8) H.R.Kricheldorf and E.Leppert; Makromol.Chem.167,47 (1973)
9) W.H.Davies; J.Chem.Soc. (London) 1357 (1951)
10) E.Lillie and R.C.Schulz; Makromol.Chem.176, 1901 (1975)
11) H.R.Kricheldorf and T.Mang; Makromol.Chem.182, 3077 (1981)
12) H.R.Kricheldorf and T.Mang; Makromol.Chem.183, 2113 (1982)
13) H.R.Kricheldorf and W.E.Hull; Biopolymers 21,1635 (1982)
14) A.Schindler and D.Harper; J.Polym.Sci.Polym.Letters Ed.14 729 (1976)
15) F.Chabot and M.Vert; Polymers (1983) in press

We thank the Deutsche Forschungsgemeinschaft for financial support.

Received December 13, accepted December 21, 1982