Kinetics and mechanism of glycolide and ethylenoxalate copolymerization. Characteristics of the copolymers formed and mechanism of the biodegradation

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SUMMARY. The study of glycolide (GL) and ethylenoxalate (EO) copolymerization with the use of $SnCl_2$ 2 H_2O as a catalyst was carried out by ^1H NMR spectroscopy. Monomer reactivities are found to be close and equal to 1,1 and 1,11 for GL and 0,71 and 0,85 for EO at 150 and 170 °C, respectively. Kinetic data obtained show that the reaction proceeds without induction period up to entire consumption of every monomer. The detailed identification of ^1H spectra enables to follow the polymer microstructure in the course of copolymerization. Thermal properties of copolymers and their biodegradation abilities have been studied. The biodegradation rate is shown to increase with growing EO proportion in the copolymer. The lactone biodegradation mechanism where the electrophility of carbon and nucleophility of OH group are playing the most important role, is suggested. The correlation between the biodegradation rate and the chemical shift in ^{13}C NMR spectra of the carbon atom of the carbonyl group has been established.

Introduction

Polyglycolide (PGL) and its copolymers with lactide (LA) and other lactones are well-known [1-4] and widely applied in medicine. Copolymers of glycolide (GL) and ethylenoxalate (EO) (the latter is an isomer of GL) are practically unstudied though they may be interesting as biodegradable materials. Much is known in the literature about the copolymerization of GL with LA. However, the ability of GL and EO to polymerize has been studied much less, though it is apparently interesting to copolymerize dilactone (GL) with diester (EO). This work is dedicated to the investigation of GL and EO copolymerization , study of properties of polymers obtained, and their biodegradation ability. For this system, we developed the NMR spectroscopy method which makes it possibly not only to monitor rates of incorporation of every monomer into polymer but also to elucidate the structures of copolymers formed.

Results and Discussion

Polymerization was carried out in bulk at 130, 150 and 170 °C with $SnCl_2.2H_2O$ as a catalyst. Five systems containing 12.4, 39.4, 46, 75.8 and 91.5 mol-%. GL were investigated. The mixture of monomers and the catalyst was poured into fragile bulbs without moisture and oxygen access at the temperature above the melting point, sealed off the vacuum line and kept in the thermostat for definite time. The content of each bulb was dissolved in DMSO-d_6 and its ^1H NMR spectra were registered (Figs. 1 and 2).

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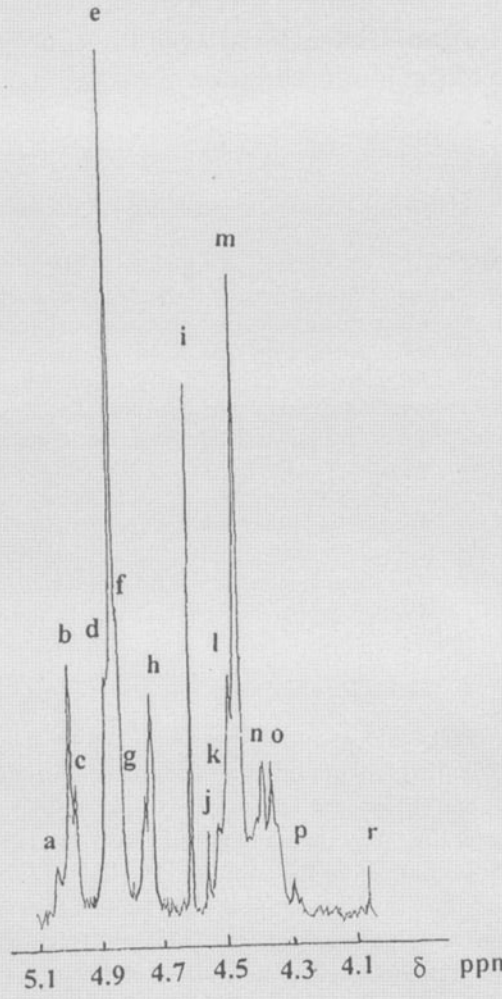

Fig.1: ^{1}H NMR spectrum of the GL (46 mol-%) -EO copolymerization product. The spectrum was measured on Bruker-250 MHz device at 293 °C. Monomers were polymerized at 170 °C for 90 min.
Chemical shifts:

a	b	c	d	e	f	g	h	i
5.05	5.01	4.99	4.89	4.87	4.85	4.8	4.75	4.62

j	k	l	m	n	o	p	r
4.55	4.52	4.48	4.46	4.38	4.36	4.32	4.05

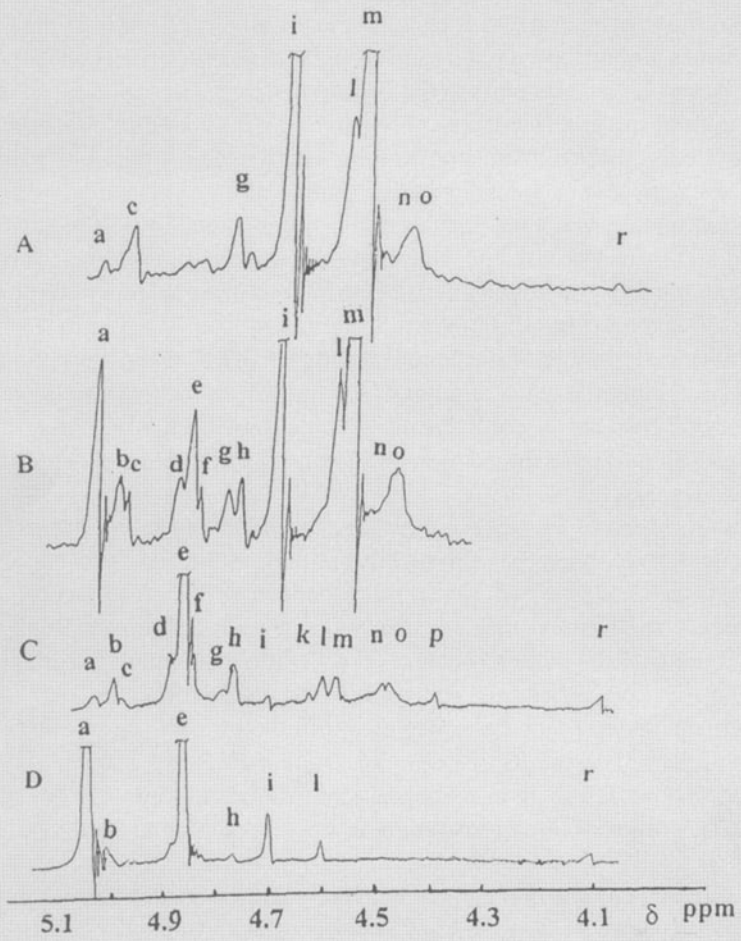

Fig. 2. HNMR spectrum of the GL and EO copolymerization product . The spectrum is measured on Tesla 100 MHz device at 120-130 °C. Polymerization was carried out with $SnCl_2 2H_2O$ at 150(A), 170 °C (B,C,D) for 60, 80, 330, 60 min, respectively. The concentration of GL in the initial mixture, mol- % : A = 12.4, B = 39.4, C = 75.8, D = 91.5.

Chemical shifts:

a	b	c	d	e	f	g	h
5.05	5.01	4.99	4.89	4.87	4.85	4.80	4.77

i	l	m	n	o	p	r
4.70	4.59	4.56	4.49	4.47	4.36	4.14

For the interpretation of NMR spectra (Tab. 1), integral intensities of both signal groups and separate resonances were compared [5].

Calculations of integral intensities showed the following.
1. The ratio of the integral intensity of resonances a-h/i-p does not change in the course of polymerization and is equal to the initial GL/EO ratio in the mixture. a-h resonances are attributed to GL and its units in the copolymer and i-p resonances to EO and its units in the copolymer.
2. The ratio of integral intensities of resonance sums b,c,g,h/n,o remain constant for all systems studied at any conversion, which makes it possible to assign b,c,g,h resonances to cross units of GL , and n,o - to EO ones.
3. The domination of c,g resonances in the systems with low GL concentration (Fig.2a) and their decrease and simultaneous growing b,n resonances with increasing the GL content enables the attribution of c,i to dimer GL units, and b,h ones to end units of GL tetramers and n-mers.
4. The discrete structure of the central resonance of GL is most pronounced in spectra containing the equal amount of EO and GL in the mixture as well as the presence of 7 resonances confirms the pentade sensitivity of GL. So, d, f resonances should be assigned to central units of tetramers and penultimate groups of n-mers.
Thus, in GL spectra CH_2 cross-groups are tetrade sensitive, and the rest are pentade sensitive. In general, the spectrum of GL in the copolymer is to some extent symmetrical as regads to central resonance of PGL. Therefore, assignments of different group resonances to its right or left part (high or low fields) is done on the basis of general considerations on inductive effects.
The identification of EO units spectra is based on the following.
1. Data presented in point 2 allow to the attribution resonances n,o to two CH_2 groups of one of cross units of EO.
2. Spectrum C in Fig. 2 gives evidence that resonances l, m may be attributed to two CH_2 groups of other cross units or the corresponding border units of n-mer.
3. The dynamics of spectral change with increasing EO unit content in the copolymer (spectra A, B in the Fig.2) corroborates the above conclusions. At the same time, it indicates that one of the CH_2 groups of EO cross-units is not distinguished from the CH_2 groups of the central units of the trimer or n-mers.
4. Spectrum D in Fig. 2 shows that only one i resonance relates to the EO units in the copolymer.
Other resonances:
Chemical shifts of resonances j, r correspond exactly to two CH_2 groups of hydrolyzed GL. In the absence of resonance j , r relates to alcohol CH_2 end group of the GL unit.
Resonance p is, apparently, one of resonances of hydroxyl end groups of EO since it corresponds practically entirely to one of hydrolyzed EO groups.
Resonance k may be attributed either to one of variants of the monomer unit of EO in the copolymer, or the end OH group. The more exact attribution is not possible yet.

Tab. 1. The identification of resonances of ^{1}H NMR spectra of GL and EO copolymers and the model compounds [#)]

Compound	Group	Chemical shift, ppm	State
a	$(OCH_2CO)_2$ (monomer)	5.05	s
b, h	OC(O)C(O)-OCH$_2$C(O)OCH$_2$C(O)-OCH$_2$CH$_2$	5.01; 4.77	s
c, g	OC(O)C(O)-OCH$_2$C(O)OCH$_2$C(O)-OCH$_2$CH$_2$	4.99; 4.80	s
d, e, f	OC(O)C(O)-OCH$_2$C(O)OCH$_2$C(O)-[OCH$_2$C(O)]$_{2n}$- OCH$_2$C(O)OCH$_2$C(O)-OCH$_2$CH$_2$	4.89; 4.87; 4.85	
i	[OCH$_2$CH$_2$OC(O)C(O)] (monomer)	4.70	s
l, m, n, o	OCH$_2$C(O)-OCH$_2$CH$_2$OC(O)C(O)-[OCH$_2$CH$_2$OC(O)C(O)]$_n$-OCH$_2$CH$_2$OC(O)C(O)-CH$_2$C(O)	4.59, 4.56, 4.49 4.47	
j, r	HOC(O)CH$_2$OC(O)CH$_2$OH^x	4.58, 4.08	s
j, r	HOC(O)CH$_2$OC(O)CH$_2$-[OC(O)CH$_2$]$_{2n}$-OC(O)CH$_2$OC(O)CH$_2$Oh^{xx}	4.58 (4.55); 4.08, (4.12) 4.79, 4.73	
p	HOC(O)C(O)CH$_2$CH$_2$OH^x	4.31, 3.71	t

[#)] The data were obtained in the study of the monomer hydrolysis and olygomer synthesis.

Kinetics. On the basis of the data on ^{1}H NMR spectra, kinetic copolymerization curves were obtained for four EO-GL mixtures with different relationships of the monomer content (Fig.3).

As can be seen, the kinetic curves of GL and EO consumption have no induction period, and the copolymerization proceeds up to the completion. The copolymerization constants determined graphically by Fineman-Ross method are close to each other. They are equal to 1.1 and 0.71 at 150 °C, 1.17 and 0.85 at 170 °C for GL and EO, respectively.

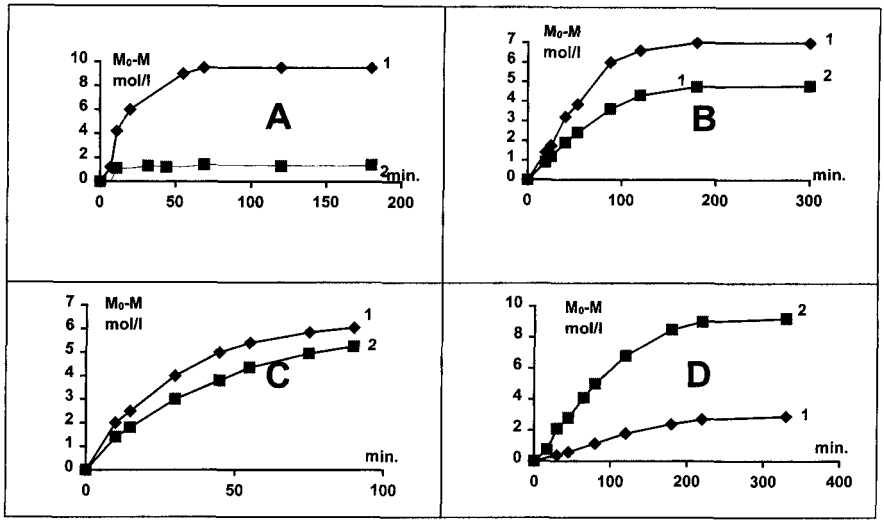

Fig .3. Kinetic curves of EO (1) and GL (2) consumption in their copolymerization in melt (170 °C). The initial content of the monomer mixture (GL, mol-%) and concentration of catalyst (mol/l): A) 12.4, B) 39.4, $1.5.10^{-3}$, C) 46,0, $6.8.10^{-4}$, D) 75.8, $2.8.10^{-4}$

Thermal properties of GL/EO copolymers were obtained from DSK analysis and are shown in Table 2.

Tab. 2.

GL/EO	T_g/°C	T_m/°C	(H_m)/(J/g)	Ratio of lengths of the GL and EO units
91/9	52	197	18.73	36 : 1
76/24	57	-	-	9 : 2
39/61	62	-	-	4 : 3
12/88	57	157	9.88	3 : 9
0/100	44	189	62	

To characterize the copolymer microstructure, we determined the average length of GL and EO units using formulas shown below.

For GL $\dfrac{\text{Sum of intensities of b,c,....n resonances}}{\text{Sum of intensities of b and c (or q +n) resonances}}$

For EO $\dfrac{\text{Sum of intensities of l, m and o resonances}}{\text{}}$

Sum of intensities of n and o resonances

The results are shown in Table 3.

Tab.3. The average length of GL and EO units in the copolymer

Composition of the original mixture (mol-% GL)	Length of GL units	Length of EO units	Temperature, ^{0}C
12.4	2.8	8.9	170
	2.9	9.1	150
	2.8	9.3	130
39.4	4.3	3.2	170
	3.85	3.35	150
	4.1	3.25	130
46	5.0	2.6	170
76	8.9	1.6	170
	12.2	2.0	150
91.5	36	1	170

As can be seen from the data given in Tables 2 and 3, the crystallinity is observed at the block length not shorter than 9 or 36 monomer units of EO and GL, respectively. It corresponds to the copolymer containing not more than 10 mol-% one comonomer.

Biodegradation . Copolymer biodegradation was estimated by a decrease in the weight of copolymer tablets, which were implanted into rats.

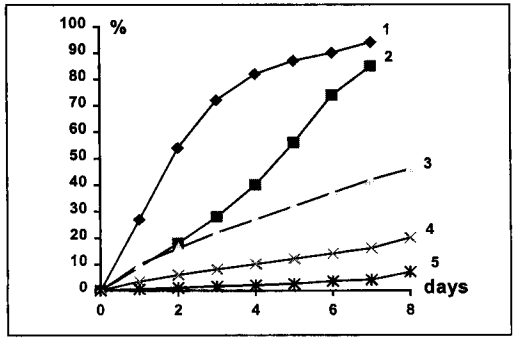

Fig. 4. Kinetic curves of degradation of tablets of GL-EO copolymers of various composition. Content of EO (mol-%) in copolymer: 1 = 75, 2 = 50, 3 = 22, 4 = 10, 5 = 0

As can be seen from Fig. 4, the biodegradation rate increases with the increasing content of EO in the copolymer. We suggest that the process of biodegradation and degradation *in vitro* of GL and EO copolymers are caused by hydrolysis of the ester bond at the nucleophilic attack of carbonyl carbon by OH groups of water or hydoxyl end groups both being present in the system originally and formed during the monomer hydrolysis.
The degradation rate depends on the electrophility of carbonyl carbon and on the nucleophility of the hydroxyl end groups of the copolymer. The electrophility of the carbonyl carbon and the nucleophility of the hydroxyl end group are determined by both the inductive effect of neighboring groups (for example, CH_2 and CO groups have an opposite action) and the possibility of the formation of complexes with the solvent as well as metal ions present in the organism or added with the catalyst. So, everything that increases the positive charge on carbon must accelerate copolymer degradation.
The value of the chemical shift of the CO group in ^{13}C NMR spectra may serve as an index of the positive charge on the carbon atom of the CO group. Actually, the good correlation between the biodegradability and values of chemical shifts of CO groups in various polymers and monomers is observed.

Biodegradability:	EO >	GL >	LA >	*p*-dioxanon >	ε- caprolactone
Chemical shift of CO-signals (in DMSO-d_6)					
of the polymer	156.24,	167.99,	169.49,	170.94	173.8
of the monomer	154.10,	165.41,	168.67,	168.96	-

The value of the chemical shifts of monomers is lower than that of polymers which accounts for the fact that the monomers degrades faster than polymers and residual amounts of monomers in the polymer may accelerate degradation.
In the case of copolymers of GL and EO, the effect of EO is pronounced in the following way. Chemical shifts of the CO-signals of PGL and polyethyleneoxalate are equal to 168 and 156, respectively. But the nucleophylicity of hydroxyl ethylenoxalate end group ($HO\text{-}CH_2\text{-}CH_2\text{-}O(CO)$) is higher than one of the hydroxyl glycolyl end group ($HO\text{-}CH_2\text{-}C(O)$). All this accelerates degradation of polyglycolide modified by
EO. The sample crystallinity also effects the degradation rate. In our opinion, association of CO and CH_2 group in the crystal increases the electron density on the carbon and makes the polymer more stable.

Conclusion

The data obtained make it possible to perform the controlled synthesis of GL-EO copolymers of the necessary microstructure and biodegradability and to produce

materials for medicine with short periods of biodegradation. The theoretical consideration of the biodegradability permit the forecast of possible periods of biodegradation of various polymers. It also explains the peculiarities of autocatalytical processes in biodegradation as well as the effect of impurities, additives, enzymes and etc.on the biodegradation processes.

References

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