

SYNTHESIS AND PROPERTIES OF BIORESORBABLE AND HIGHLY FLEXIBLE 1,3-TRIMETHYLENE CARBONATE/ ϵ -CAPROLACTONE COPOLYMERS

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Abstract

Ethyl ethoxy zinc (II) has been prepared and emerged as very effective initiators for ring-opening polymerization of 1,3-trimethylene carbonate (TMC) and its copolymerization with ϵ -caprolactone (CL) to produce high molar mass polymers. The copolymerization of TMC and CL was performed in bulk at 120°C. The obtained copolymers were characterized by multiblock microstructure. The highest reactivity rate was demonstrated by trimethylene carbonate in comparison with ϵ -caprolactone monomer. The thermal and mechanical properties of the copolymers were strongly dependent on the monomer composition. Preliminary tests of monomers copolymerization using reactive extrusion yielded positive result.

Keywords: copolymerization, caprolactone, trimethylene carbonate, bioresorbable polymers

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Introduction

The recent rapid progress of many medical disciplines creates the need numerous new bioresorbable materials with physical and biological properties tailored strictly to a particular purpose. In many cases, for manufacturing bioresorbable implants such as nerve guides, stents, or scaffolds for culturing fibroblasts, very flexible, biocompatible and biodegradable materials with good tensile strength are required. For such applications, aliphatic polyester copolymers or poly (ester-co-carbonates) containing flexible carbonate and caproyl units in chain composition seem to be very useful. Introduction of carbonate linkages into a rigid polymer chain not only improves the elasticity of final copolymers, but also influences the hydrolytic degradation profiles and decreases total acidity of the degradation products. Copolymers of ϵ -caprolactone (CL) and trimethylene carbonate (TMC) due to its high permeability to drugs, and very good mechanical properties and flexibility seem to be very interesting, especially for many applications as carriers in controlled drug release systems or as a material for forming different kinds of scaffolds and membranes used in tissue engineering.

Copolymers of CL and TMC were mostly prepared according to ring opening polymerization (ROP) using different metal complexes as insertion-coordination initiators, as well as; stannous octoate [1,2], lanthanide or yttrium tripropoxide [3], lanthanide phenoxide complexes [4] or acetylacetonate zirconium (IV) [5]. The A-B-A triblock copolymers of TMC/CL were prepared with 2,2-dibutyl-2-stanna-1,3-dioxepane (DSDOP) [6].

In this publication we are presenting studies on the ROP of cyclic TMC with CL in the presence of simple, practically nontoxic ethoxy ethyl zinc (II) complex as an initiator. This compound has proven to be very active and effective initiator of the copolymerization and allowed to obtain copolymers with yield of nearly 100% within several minutes. The high reaction rate, high efficiency and not specially demanding conditions for its conducting, led us to attempt the synthesis of TMC/CL copolymers directly with extruder, thus combining the synthesis of these copolymers with processing.

Materials and Methods

Monomers and initiators

The used cyclic 1,3-trimethylene carbonate (TMC) was obtained from Boehringer (Ingelheim, Germany) and purified by recrystallization from dried ethyl acetate. The second monomer; ϵ -caprolactone (ϵ -CL) (Fluka) was distilled in vacuum over freshly powdered calcium hydride before use. Ethyl ethoxy zinc (II) was synthesized in our laboratory. This compound was obtained after reaction of diethylzinc (1,1 M solution in toluene -Aldrich) with absolute ethyl alcohol 99.8% pure p.a. (POCH Gliwice) conducted in anhydrous tetrahydrofuran (THF) 99.9 % (Aldrich) solution at 60°C.

Synthesis of poly(trimethylenecarbonate) and trimethylene/ ϵ -caprolactone copolymers

TMC model polymerization reaction was carried out within one hour in THF solution and with the presence of ethyl ethoxy zinc (II) as the initiator and initiator to monomer molar ratio (I/M) as 1: 10, at 90°C. The resulting oligomer TMC solution was hydrolyzed, to separate the zinc compounds by mixing with a small amount of hydrochloric acid solution in THF. The volume of evolved gas which was obtained during this reaction was measured using a burette filled with anhydrous ethanol, connected directly to the reaction vessel.

The process of trimethylene carbonate with ϵ -caprolactone copolymerization was conducted in bulk. The produced copolymers were purified from residual monomer by dissolving in chloroform and then precipitation in cold methanol. The final product was dried at 45°C in vacuum.

Preliminary tests of 1,3-trimethylene carbonate with ϵ -caprolactone copolymerization and processing by reactive extrusion were conducted with the use of Haake MiniLab IIs micro-extruder. The monomers with a proper amount of initiator (M/I rate as 1000/1) were placed in a dry, cooled glass ampoule (approximately at 7-10°C) in argon atmosphere. Then, the premixed whole content of this ampoule was introduced by specially designed dispenser to the extruder, previously heated to temperature of 120°C and mixing with bypass cycle was started. The conical screws' rotation of the device was set up at the maximum - 300 rpm. During stirring of the mixture, temperature and torque was continuously monitored. After 4 minutes, we observed rapid growth of torque to a virtually constant value, which indicated a strong increase of mixture viscosity due to its high conversion. At this moment, we switched the mode cycle of device and extruded samples in the form of a wire with diameter of 5 mm.

Measurements

The conversion of the reaction was determined with ¹H NMR spectroscopy. The ¹H NMR spectra were recorded at 600 MHz with Avance II Bruker TM at 25°C. Dried chloroform-d₆ was used as solvent and tetramethylsilane was applied as the internal standard.

The number-average and weight-average molar masses (M_n and M_w , respectively) as well as dispersity indexes (M_w/M_n) of the copolymers were determined by gel permeation chromatography with a Viscotek RImax chromatograph. Chloroform was used as the eluent; the temperature and the flow rate were 35°C and 1 mL/min, respectively. Two PL Mixed E columns with a Viscotek model 3580 refractive index detector and injection volume equal to 100 μ L were used. The molar masses of copolymers were calibrated with polystyrene standards but the correct M_n value for PTMC was determined by appropriate conversion, according to the method described by Kricheldorf et al. [7].

Thermal properties, such as glass transition temperatures and enthalpies of crystallization or melting, were studied by differential scanning calorimeter using a DSC Du Pont 1090B apparatus calibrated with gallium and indium.

Results and Discussions

Proposed mechanism of TMC polymerization initiated with ethyl ethoxy zinc (II)

To know the TMC polymerization mechanism, the model reaction with using ethyl ethoxy zinc (II) as an initiator and with I/M ratio as 1:10 was carried out. Then, we hydrolyzed the products by reaction with solution of hydrochloric acid, in order to separate the metal in the form of zinc chloride (II) from the organic part. During this reaction strong emission of ethane was observed (SCHEME 1).

The measured amount of evolved gas and maintained reaction stoichiometry indicates that polymer chain growth occurred only on the ethoxy groups of the initiator, as shown in diagram (FIG. 1). The obtained average molar mass of the final product proved the proposed mechanism too. The number average molar mass of the final TMC oligomer, calculated both on the basis of the number of formed oligomers end groups (^1H NMR measurements) and with GPC measurements (after appropriate conversion due to the applied calibration styrene standards [7]) was close to the theoretical, calculated value, taking into account the possibility of chain propagation on only one ligand of started initiating complex. Analysis of the NMR spectra revealed that the coordination of TMC monomer to the central metal atom, and then ring opening of this cyclic monomer and its insertion between the central zinc and the ethoxy group (metal – oxygen bond) was the first initiation stage of observed polymerization. The growth of polycarbonate chain on the ligand formed this way was the next main stage of this reaction according to the well-known coordination – insertion mechanism.

If during the initiation of the tested reaction, the insertion reaction was followed also by the opening of the ethyl ligand's metal-carbon bond, we would observe propagation of two polymer chains on one initiation complex, which means that after the hydrolysis of the resulting polycarbonate the average molar mass of final products would be about twice lower than this calculated theoretically with our previous assumption. If the investigated reaction proceeded according to this hypothetical mechanism with insertion on both ligands we would not observe the gas evolution during hydrolysis of polymerization product because of lack of metal-carbon bindings in this case too.

SCHEME 1. Proposed mechanism of TMC initiated with ethyl ethoxy zinc (II).

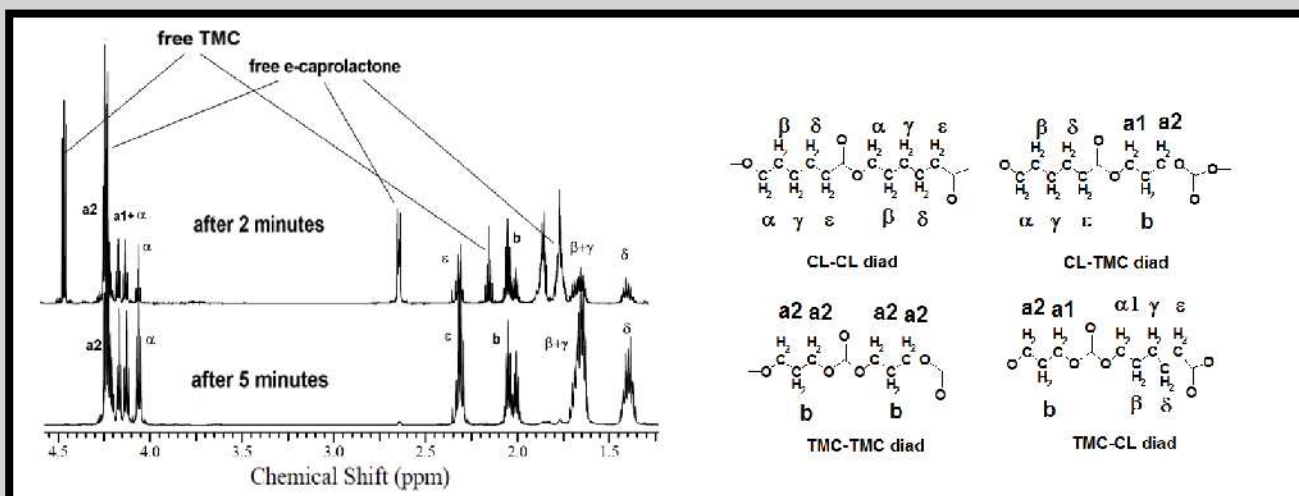
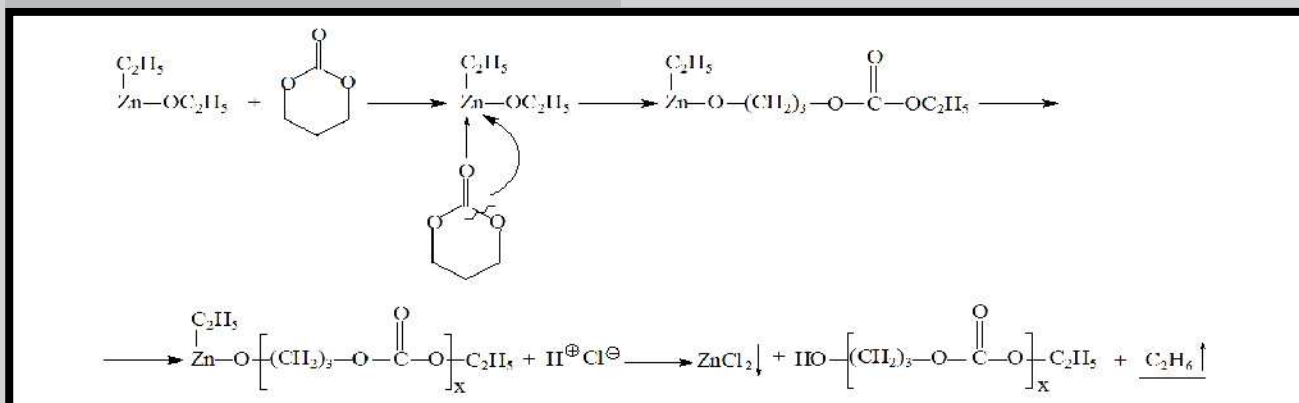


FIG. 1. ^1H NMR spectra (in CDCl_3) of equimolar ϵ -caprolactone/TMC copolymer obtained with $\text{Zn}(\text{OC}_2\text{H}_5)_2(\text{C}_2\text{H}_5)$ at different conversion after 2 minutes or 5 minutes of reaction.

TABLE 1. Results of TMC with CL copolymerization.

No.	TMC ⁰ [mol %]	TMC ^N [mol %]	Time [min]	C [%]	M _n [kDa]	D	L _{CL}	L _T
1	15	17	18	98	78.2	1.7	6.6	1.6
2	30	31	15	~100	92.1	2.1	3.7	1.6
3	40	40	10	~100	110.2	2.0	2.8	1.9
4	70	70	10	~100	140.2	2.0	3.1	7.2
5	85	86	8	99	150.2	2.1	2.0	11.5
6	100	100	5	~100	128.0	2.1	-	-

Where: TMC⁰ - initial feed molar fraction of TMC, TMC^N - feed molar fraction of TMC in the product, C - total conversion of copolymerization, M_n - number average molar mass, calibration with polystyrene standards, D - molar mass dispersion, L_{CL}, L_{TMC} - average length of caproyl and carbonate microblock calculated with NMR. Copolymerization in bulk, at 120°C with M/I ratio as 800/1.

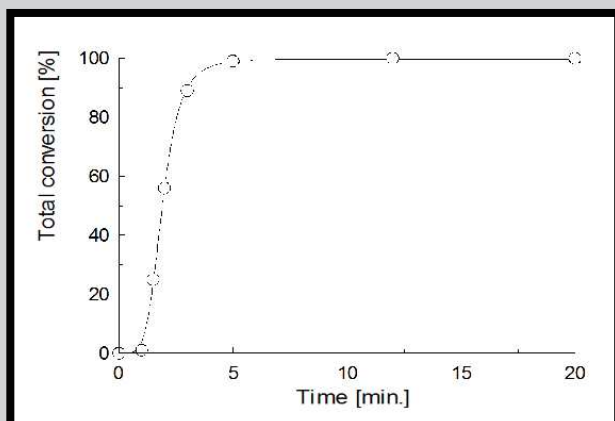


FIG. 2. Total conversion of monomers in copolymerization with M/I ratio as 800:1 of equimolar mixture of TMC with CL, initiated with $\text{Zn}(\text{OC}_2\text{H}_5)_2(\text{C}_2\text{H}_5)$ and carried out in bulk at 120°C.

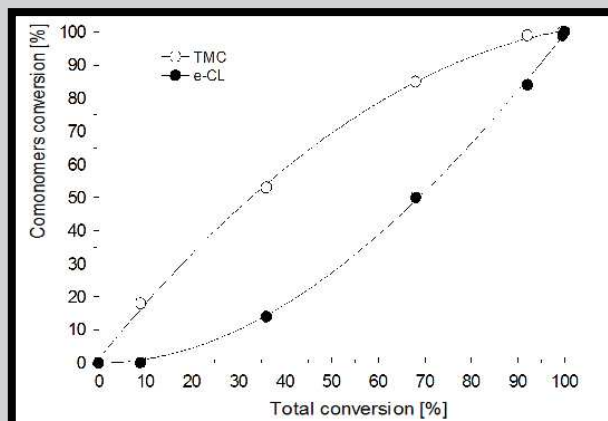


FIG. 3. Dependence of the CL and TMC conversion on the total conversion of the copolymerization. The starting CL/TMC molar ratio was of 1:1, initiated with $\text{Zn}(\text{OC}_2\text{H}_5)_2(\text{C}_2\text{H}_5)$, with M/I ratio as 800:1 and carried out in bulk at 120°C.

Synthesis and characterization of copolymers

A series of TMC/CL copolymers with different composition, using ethyl etoxy zinc (II) as an initiator was obtained. The results are presented in TABLE 1 and FIG. 1.

The conducted copolymerization yielded rather surprising results. At a relatively short period, after several minutes (FIG. 2), regardless of the composition of the reaction mixture, we obtained almost total conversion of both comonomers. The resulting copolymers were characterized with high molar masses, close to the expected values. The copolymer chain propagation proceeded only on one ethanolic ligand, similar to the previously investigated TMC homopolymerization. During the investigated copolymerization, TMC comonomer presented higher reactivity than CL (FIG. 3), in contrast to the case of TMC/CL copolymerization conducted with the use of $\text{Zr}(\text{acac})_4$ [5] or $\text{Sn}(\text{oct})_2$ [4]. The obtained copolymers presented multiblock chain structure, significantly different from those obtained using aforementioned initiators. The reason for this phenomenon was mainly a low rate of intermolecular transesterification, significantly lower than during the copolymerization initiated by zirconium or tin compounds.

Copolymerization of TMC with CL using reactive extrusion

During our investigations, we tried to carry out continuous production of TMC/CL bioresorbable products by reactive extrusion, according to the method presented above. For this purpose, copolymerization of TMC (about 85 mol.%) with CL and processing of obtaining TMC/CL copolymers in properly equipped laboratory extruder was conducted (FIG. 4). We obtained samples of high molar mass copolymers with good yield and composition practically this same as started reaction mixture, in form of extruded homogenous rods. The obtained results are presented in TABLE 2.

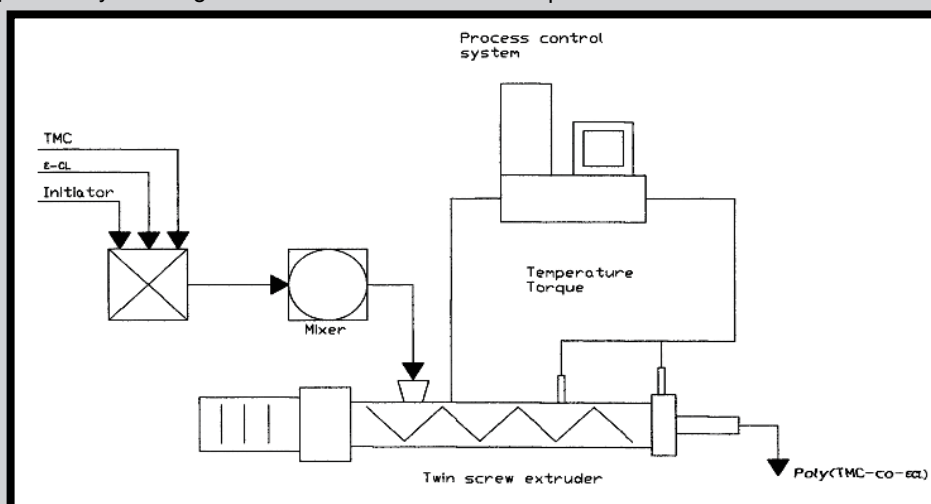


FIG. 4. Scheme of the TMC/CL copolymerization with extruder use.

TABLE 2. Results of TMC/CL copolymers obtained with extruder.

No.	TMC:CL copolymer [mol %]	Time [min]	C [%]	M_n [kDa]	D
1	87 : 13	5	98	201.1	2.2
2	88 : 12	4	92	195.5	2.2

Where: C – total conversion of monomers, Time – time of reaction and extrusion cycle, M_n – average number molar mass of obtained copolymer, D – molar mass dispersity

TABLE 3. Thermal and mechanical properties of TMC/CL copolymers.

No.	TMC:CL copolymer [mol %]	T_g [°C]	ΔH_m [J/g]	T_m [°C]	E [MPa]	σ_{max} [MPa]	ϵ_{max} [%]	σ_{break} [MPa]
1	19:81	-46.6	36.5	56.3	112.7	12.6	1500	12.6
2	50:50	-37.5	-	-	12.9	1.5	1500	1.46
3	82:18	-14.7	-	-	3.2	0.8	105	0.43

Where: T_g – glass transition temperature, ΔH_m – heat of melting, T_m – melting temperature, E- Young's modulus; $\sigma_{max, break}$ – maximal stress, stress at break; ϵ_{max} – maximal elongation,

Thermal and mechanical characteristics of copolymers

In TABLE 3 we summarized the thermal and mechanical investigation results obtained for TMC/CL copolymer with selected composition. The results proved that the thermal and mechanical properties of synthesized copolymers were strongly dependent on the monomer composition. The semi-crystalline copolymer with the highest caprolyl content presents the best parameters. With decreasing of CL microblocks average length, deterioration of the mechanical strength of copolymers was observed.

Conclusions

Ethyl etoxy zinc (II) proved to be very active initiator for the homopolymerization of TMC and its copolymerization with ϵ -caprolactone. TMC/CL copolymers obtained this way, with caprolyl units content of more than 70%, showed semi-crystallinity. Other synthesized copolymers were amorphous because of the impossibility to create separate ordered crystalline phase when the average length of caprolyl microblocks was less than 5-6 units. This phenomenon resulted in Young module decrease of copolymers which proceeds with increase of TMC content in the started copolymerization mixture. Received copolymers, especially those containing caprolyl units in amount more than 50% mol., are the most promising materials for the manufacturing of porous nerve guides or drug loading coating materials because of their good mechanical properties and demonstrated high flexibility. What seems to be important, these TMC/CL copolymers using the proposed simple and non-toxic zinc initiator, due to their high rate of reaction, are possible to synthesize and simultaneously to process using conventional extruder for plastics.

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References

- [1] Lemmouchi Y., Schacht E., Kageruka P., De Deken R., Diarra B., Diall O., Geerts S.: Biodegradable polyesters for controlled release of trypanocidal drugs: In vitro and in vivo studies. *Biomaterials* 19 (1998) 1827-1837.
- [2] Pêgo A.P., Zhong Z., Dijkstra P.J., Grijpma D.W., Feijen J.: Influence of catalyst and polymerization conditions on the properties of 1,3-trimethylene carbonate and ϵ -caprolactone copolymers. *Macromol. Chem. Phys.* 204 (2003) 747-754.
- [3] Schappacher M., Fabre T., Mingotaud A.F., Soum A.: Study of a (trimethylenecarbonate-co- ϵ -caprolactone) polymer - Part 1: preparation of a new nerve guide through controlled random copolymerization using rare earth catalysts *Biomaterials* 22 (2001) 2849-2855.
- [4] Sheng H., Zhou L., Zhang Y., et al.: Anionic lanthanide phenoxide complexes as novel single-component initiators for the polymerization of ϵ -caprolactone and trimethylene carbonate. *J. Polym. Sci.: Part A: Polym. Chem.* 45 (2007) 1210-1218.
- [5] Dobrzynski P.: Mechanism of ϵ -caprolactone polymerization and ϵ -caprolactone/trimethylene carbonate copolymerization carried out with $Zr(Acac)_4$. *Polymer* 48 (2007) 2263-2279.
- [6] Kricheldorf H.R., Stricker A.: Poly(lactones), 47 A-B-A triblock copolyesters and random copolyesters of trimethylene carbonate and various lactones via macrocyclic polymerization. *Macromol. Chem. Phys.* 200 (1999) 1726-1733.
- [7] Kricheldorf H. R., Stricker A., Gomurashvili Z.: Polymers of carbonic acid, 30. Ring-expansion polymerization of trimethylene carbonate (TMC, 1,3-dioxanone-2) with dibutyltin succinate or adipate. *Macromol. Chem. Phys.* 202 (2001) 413-420.