

NEW FUNCTIONAL ALIPHATIC POLYCARBONATES – MATERIALS FOR ADVANCED BIOMEDICAL APPLICATIONS

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Abstract

The aim of this study is to develop a new method of synthesis of functional (co)polycarbonates by ring-opening polymerization of ethyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (MTC-Et), benzyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (MTC-Bz) and their copolymerization with 1,3-trimethylene carbonate (TMC) with potential application in the formation of bioresorbable scaffolds for living cells and drug delivery, systems for achieving controlled drug release. (Co)polymerizations were conducted in bulk, in the presence of low toxic lanthanum acetylacetonate - La(acac)₃·xH₂O as catalyst. All synthesized materials were obtained at 120°C.

The results are very promising. A series of (co) polymers were obtained with high conversion and relatively high molecular weights. The composition of the comonomers and their sequence lengths were determined by means ¹H NMR and ¹³C NMR measurements. Higher reactivity during the investigated copolymerizations presented carbonates with pending ethyl or benzyl group than 1,3-trimethylene carbonate. The thermal properties obtained (co)polymers were characterized by differential scanning calorimetry.

Keywords: bioresorbable polymers, cyclic carbonates (co)polymerization, 1,3-trimethylene carbonate, functional polymers

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Introduction

Copolymers based on 1,3-trimethylene carbonate are promising materials for medical and pharmaceutical applications due their high elasticity, biocompatibility and susceptibility to biodegradation. Copolymers of TMC with glycolide [1-2], lactide [3-4] and ε-caprolactone [5-6] have been described in numerous publications. However, in other applications, polymer materials with specific functionalities are desirable. Functional synthetic polymers are significant, for example, as components for injectable gels [7], systems for targeted drug delivery [8] and materials for specific interactions with biological systems [9]. Therefore, the need for suitable methods for the preparation of a wide variety of functional biomaterials, seem to be pressing problem.

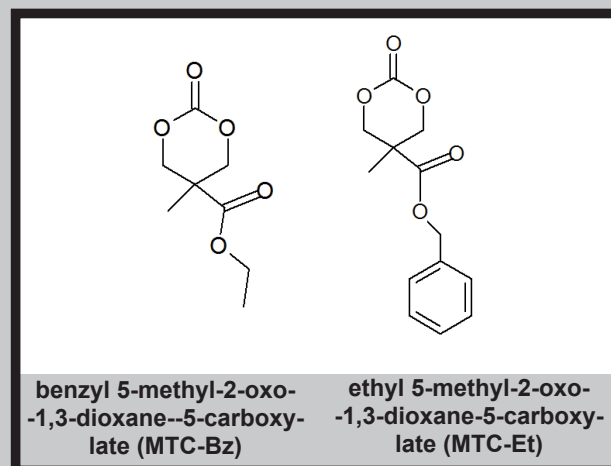
In this work, we present a new method of synthesis of functional (co)polycarbonates by ring-opening polymerization of ethyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (MTC-Et), benzyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (MTC-Bz) and their copolymerization with 1,3-trimethylene carbonate (TMC). Lanthanum acetylacetonate, compound simple in structure, stable and low toxicity, was used as catalyst.

Develop of a new methods of synthesis of functional (co) polycarbonates allows to obtain biomaterials with potential application in the formation of drug delivery systems for achieving controlled drug release and in tissue engineering as materials for forming bioresorbable scaffolds with novel properties such as hydrophilicity control, flexibility, as well as with bioactivity and possibility to curing of proteins or peptides on the surface.

Materials and methods

Monomers and initiators

Monomer: 1,3-trimethylene carbonate (TMC) was obtained from FORUSORB (Huizhou Foryou Medical Devices Co., Ltd, China). It was purified by re-crystallization from dried ethyl acetate and then dried in a vacuum oven at room temperature. Both: benzyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (MTC-Bz) and ethyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (MTC-Et) were synthesized in our laboratory according to the previously published procedure [10]. The commercially available catalyst: Lanthanum (III) acetylacetonate hydrate, La(acac)₃·xH₂O (Sigma-Aldrich) was used as received.



Polymerization and copolymerization procedure

The ring-opening (co)polymerization was carried out in a glass flask equipped a magnetic stirrer, using La(acac)₃·xH₂O as catalyst. Selected amounts monomer(s) and catalyst were introduced in argon atmosphere into a flask. The flask was immersed in an oil bath at 120°C. After the selected reaction time, the flask was quenched to room temperature. The resulting (co)polymers were purified by dissolving in chloroform and dropwise to cold methanol. Finally, the purified material was dried in a vacuum at room temperature.

Measurements

The conversion of the monomers and the microstructure of the obtained copolymers were determined by ¹H and ¹³C NMR spectroscopy. The ¹H NMR spectra were recorded at 600 MHz using a Avance II Bruker TM at 25°C. Dried dimethyl sulfoxide-d₆ (DMSO-d₆) was used as the solvent, and tetramethylsilane (TMS) was applied as the internal standard. The ¹H NMR spectra were obtained with 64 scans, 2.65s acquisition time, and 11 μs pulse width.

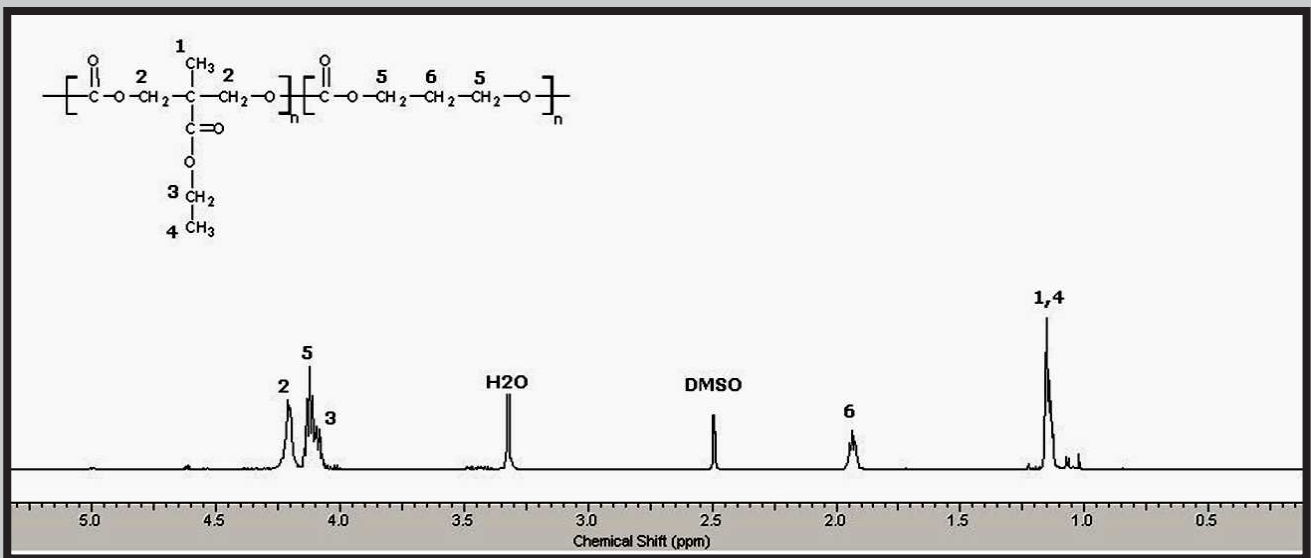


FIG. 1. ^1H NMR spectrum (in DMSO-d_6) of equimolar TMC/ MTC-Et copolymer obtained with $\text{La}(\text{acac})_3 \cdot x\text{H}_2\text{O}$.

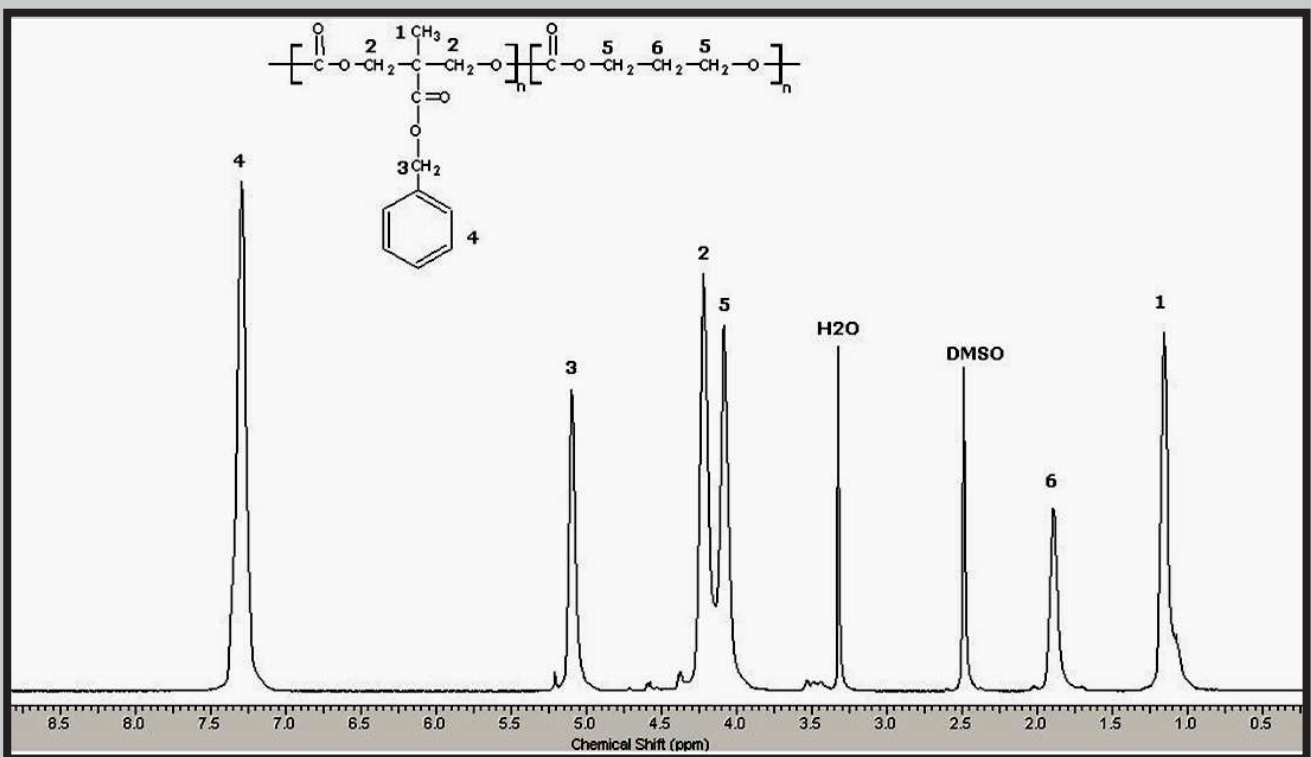


FIG. 2. ^1H NMR spectrum (in DMSO-d_6) of equimolar TMC/ MTC-Bz copolymer obtained with $\text{La}(\text{acac})_3 \cdot x\text{H}_2\text{O}$.

The ^{13}C NMR spectra were recorded at 150 MHz with 19500 scans, 0.91s acquisition time, and 9.1 μs pulse width.

The weight-average molar masses and dispersity indexes of the homopolymers and copolymers were determined by gel permeation chromatography (GPC) with a Viscotek RImax chromatograph. Chloroform was used as the eluent, and the temperature and the flow rate were 35°C and 1mL/min, respectively. Two PL Mixed C columns with a Viscotek model 3580 refractive index detector were used. The molecular weights were calibrated with polystyrene standards.

Thermal properties (T_g , T_m and ΔH_m) were examined by differential scanning calorimeter with a DuPont 1090B apparatus, calibrated with gallium and indium (heating and cooling rate of 20°C/min in the range from -100°C to 220°C).

Results and discussions

Ring-opening polymerization of ethyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (MTC-Et) and benzyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (MTC-Bz) and their copolymerization with 1,3-trimethylene carbonate (TMC) were conducted in bulk in the presence of $\text{La}(\text{acac})_3 \cdot x\text{H}_2\text{O}$ as catalyst. The results are summarized in TABLE 1 and 2.

A series of copolymers 1,3-trimethylene carbonate with MTC-Et were obtained with high conversion 99% (TABLE 1, run 1-4). The time required to obtain a full conversion ranged from 24 to 28 hours in case of copolymerization of equimolar mixture of TMC with MTC-Et (FIG. 3). The composition of the copolymers were determined by ^1H NMR spectrum (FIG. 1). The area of the signal of $[\text{CH}_2\text{-CH}_2\text{-CH}_2]$ group of TMC unit at ($\delta=1.84\text{-}1.98$ ppm) and the signals of $[\text{CH}_2\text{O}]$ group of MTC-Et unit at ($\delta=4.16\text{-}4.28$ ppm) were employed to calculate the composition of the copolymers.

TABLE 1. Properties of 1,3-trimethylene carbonate/ MTC-Et copolymers with various composition^a.

No.	(TMC: MTC-Et) ⁰ [% mol]	Time [h]	Conv. [%]	(TMC: MTC-Et) ^N [% mol.]	M _w [kDa]	D	L _{TMC}	L _{MTC-Et}	T _g [°C]	T _m [°C]	H _m [J/g]
1.	100 : 0	2	100	100 : 0	56,6	2,1	-	-	-13,4	-	-
2.	80 : 20	24	99	80 : 20	60,9	15	7,4	1,8	-7,6	41	5,4
3.	50 : 50	28	99	49 : 51	27,1	3,3	4,2	4,4	-12,3	30	8,2
4.	20 : 80	24	99	21 : 79	75,7	15	2,3	5,9	-3,2	42,4	9,5
5.	0 : 100	3	97	100 : 0	143	13	-	-	-0,5	29,7	7,5

^a (Co)polymerizations were performed at 120 °C with the La(acac)₃ x H₂O to monomer ratio (I/ M) averaged 1 : 1000
Where: (TMC:MTC-Et)⁰ – initial feed molar fraction TMC and MTC-Et, **Conv.** - total conversion of copolymerization, (TMC: MTC-Et)^N – feed molar fraction of TMC and MTC-Et, **M_w** – weight-average molecular weight were determined by GPC and calibrated with polystyrene standards, **D=M_w/M_n** – dispersity, **L_{TMC}**, **L_{MTC-Et}** - average length of carbonates microblock, calculated with NMR, **T_g** – glass-transition temperature, **T_m** – melting temperature of the crystalline phase, **ΔH_m** - heat of melting of the crystalline phase

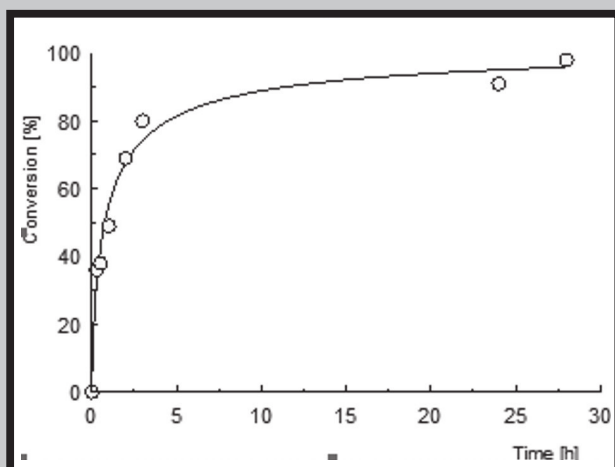


FIG. 3. The rate of conversion of monomers as a function of copolymerization time (copolymerization of equimolar mixture of TMC with MTC-Et).

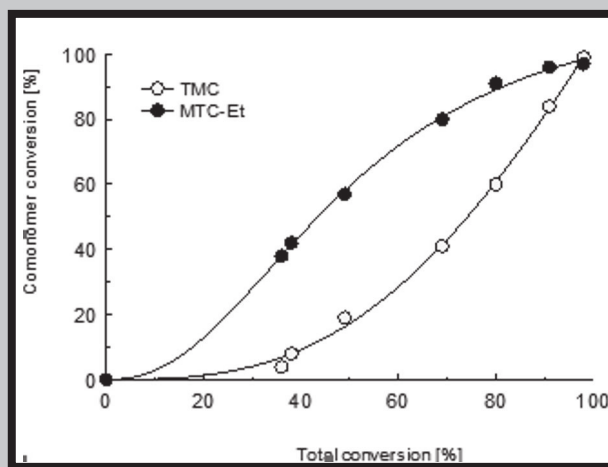


FIG. 4. Dependence of the TMC and MTC-Et conversion on the total conversion of the copolymerization (TMC/ MTC-Et molar ratio was of 1:1)

TABLE 2. Properties of 1,3-trimethylene carbonate/ MTC-Bz copolymers with various composition^a.

No.	(TMC: MTC-Bz) ⁰ [% mol]	Time [h]	Conv. [%]	(TMC: MTC-Bz) ^N [% mol.]	M _w [kDa]	D	L _{TMC}	L _{MTC-Bz}	T _g [°C]	T _m [°C]	H _m [J/g]
1.	100 : 0	2	100	100 : 0	56,6	2,1	-	-	-13,4	-	-
2.	80 : 20	2	~100	80 : 20	33,7	10,5	8,5	2,2	16,2	-	-
3.	50 : 50	2	~100	43 : 57	23,6	14,7	8,0	10,7	21,2	-	-
4.	20 : 80	2	~100	15 : 85	31,1	9,6	2,0	11,2	17	-	-
5.	0 : 100	3	97	0 : 100	36	7,6	-	-	4,1	42	15,2

Where: (TMC: MTC-Bz)⁰ – initial feed molar fraction TMC and MTC-Bz, **Conv.** - total conversion of copolymerization, (TMC: MTC-Bz)^N – feed molar fraction of TMC and MTC-Bz, **M_w** – weight-average molecular weight were determined by GPC and calibrated with polystyrene standards, **D=M_w/M_n** – dispersity, **L_{TMC}**, **L_{MTC-Bz}** - average length of carbonates microblock, calculated with ¹³C NMR, **T_g** – glass-transition temperature, **T_m** – melting temperature of the crystalline phase, **ΔH_m** - heat of melting of the crystalline phase

^a (Co)polymerization was performed at 120 °C with the La(acac)₃ x H₂O to monomer ratio (I/ M) averaged 1 : 1000

The mole compositions of copolymers were in accordance with the monomers feed ratio. The resulting copolymers were characterized by relatively high molar masses M_w. High dispersion of copolymers containing 20 and 79 mole% MTC-Et (TABLE 1, row 2,4), indicates relatively strong intermolecular transesterification of functional carbonate (MTC-Et) ester bonds.

During the investigated copolymerization, MTC-Et comonomer presented higher reactivity than 1,3-trimethylene carbonate (FIG. 4), contrary to the case of TMC/ 2,2-dimethyltrimethylene carbonate copolymerization conducted with the use of Zn(acac)₂xH₂O, described in a previous publication [11].

The thermal properties of the copolymers of 1,3-trimethylene carbonate with MTC-Et were verified by DSC analysis. All obtained copolymers are semi-crystalline. We observed that the glass-transition temperature (T_g) and melting temperature decreases with increasing content of TMC in copolymer.

Other hand, the copolymerization of 1,3 trimethylene carbonate/ MTC-Bz has proceeded faster and the time required to achieve complete conversion was only 2 hours (FIG. 5).

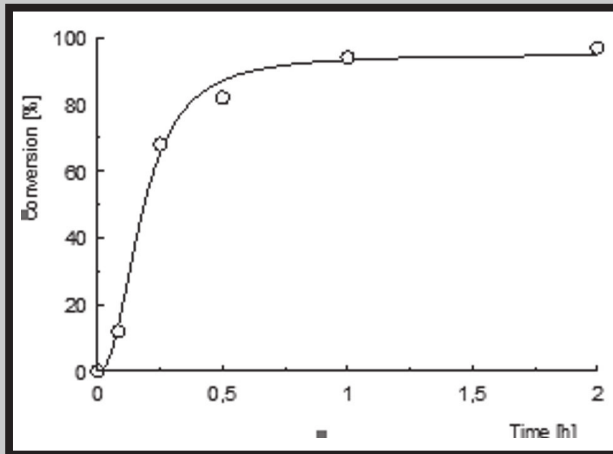


FIG. 5. The rate of conversion of monomers as a function of copolymerization time (copolymerization of equimolar mixture of TMC with MTC-Bz).

The copolymer composition was characterized by ^1H NMR spectrum (FIG. 2). The area of the signal of $[\text{CH}_2\text{-CH}_2\text{-CH}_2]$ group of TMC unit at $\delta=1.79\text{-}1.97$ ppm and the signals of $[\text{CH}_2\text{O}]$ group of MTC-Bz unit at ($\delta=4.96\text{-}5.16$ ppm) were employed to calculate the composition of the copolymers. The molar masses (M_w s) were determined for soluble fraction only since gel fraction was present in the products. High dispersion indicates relatively strong intermolecular transesterification of functional carbonate (MTC-Bz) ester bonds, also in the case of 1,3-trimethylene carbonate/ MTC-Bz copolymers (TABLE 2, row 2, 3, 4),

For the copolymerization of 1,3-trimethylene carbonate / MTC-Bz the higher reactivity observed for the carbonate with benzyl group (MTC-Bz) relative to TMC (FIG.6).

The thermal analysis showed that copolymers of 1,3-trimethylene carbonate with MTC-Bz, irrespective of the composition, are completely amorphous whereas poly(MTC-Bz) is semi-crystalline.

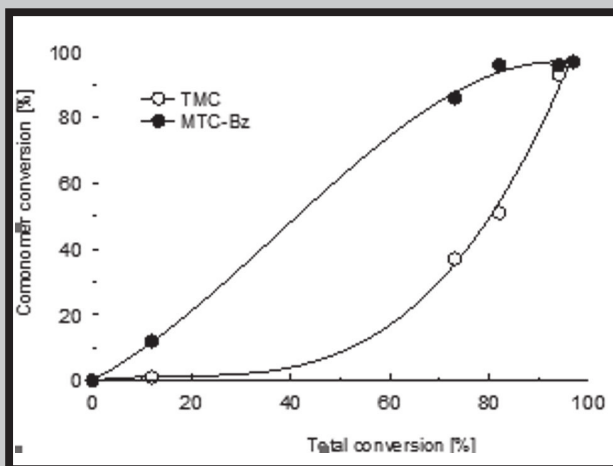


FIG. 6. Dependence of the TMC and MTC-Bz conversion on the total conversion of the copolymerization (TMC/ MTC-Bz molar ratio was of 1:1).

Conclusions

Lanthanum (III) acetylacetonate was shown to be effective catalyst for homopolymerization both functional carbonates and their copolymerization with 1,3-trimethylene carbonate. The preliminary results are very promising. We obtained of a new (co)polymers with high conversion and relatively high molecular weights.

Received copolymers, especially semi-crystalline 1,3-trimethylene carbonate/ MTC-Et copolymers, are promising materials for forming scaffolds used in tissue engineering or carriers in controlled drug release systems.

Acknowledgements

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