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Efficient synthetic approach to copolymers of glycolic and lactic acids for biomedical applications

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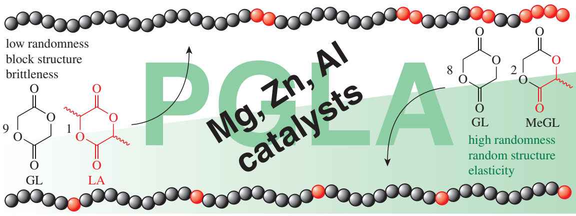
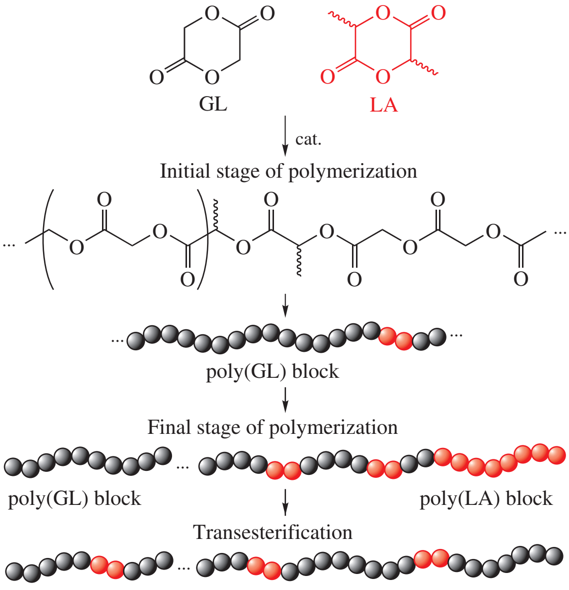
An efficient approach to copolymers of glycolic and lactic acids applied in biomedical materials was developed using ring-opening polymerization catalysts based on alkoxy complexes of 'biometals' (Mg, Al, and Zn) and 3-methyl-1,4-dioxane-2,5-dione and glycolide as comonomers.



Copolymers of glycolic and lactic acids (PGLA) are widely used in surgical sutures, in tissue engineering, and in the development of drug delivery systems.[1–6] Modern methods for their synthesis are based on a ring-opening copolymerization (co-ROP) of glycolide (GL) and lactide (LA),[7,8] which requires harsh conditions because of the high melting point (225–230 °C) and low solubility of poly(GL).[7] Since GL is significantly more reactive than LA, long polyglycolate blocks are always formed at the initial step of copolymerization, which leads to a decreased elasticity of the polymer (Scheme 1).[9–11] To increase PGLA randomness, the catalysts that remain active at temperatures exceeding 100 °C are used,[12] *e.g.* a mildly toxic tin(II) octanoate.[13,14] The replacement of this catalyst with non-toxic 'biometal' (Mg, Al, Zn) analogues is an actual problem.[8,15–20]

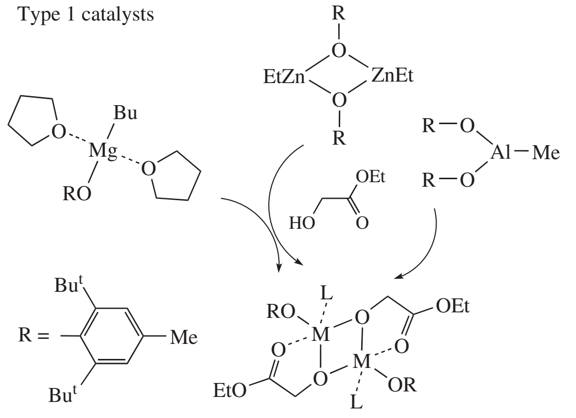


Scheme 1

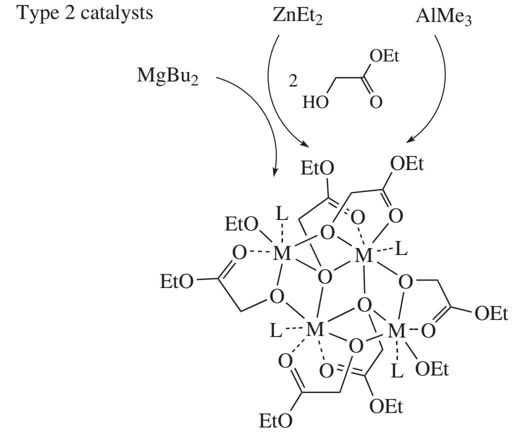
We have recently demonstrated that alkoxy complexes of Mg, Al, and Zn with 2,6-di-*tert*-butyl-4-methylphenolate (BHT) are active catalysts for ROP in a solution under mild conditions for essential cyclic monomers (lactones, lactides, and phosphates).[10,21–24] This work is the first comparative study of 'biometal' BHT–alkoxides under harsh conditions. Complexes **Mg1**, **Zn1**, and **Al1** were obtained by a reaction of the corresponding BHT–alkyl derivatives[21,25,26] with ethyl glycolate at a ratio of 1 : 1 and used in ROP *in situ* (Scheme 2). Previously we have also shown that BHT–Mg–Bu alcoholysis products are heteroleptic dimers.[24] Complexes **Mg2**, **Zn2** and **Al2** were obtained by reaction of Bu_2Mg, Et_2Zn, and Me_3Al, respectively, with two equivalents of ethyl glycolate (see Scheme 2). Unlike BHT derivatives, these complexes are presumably oligomeric.[24]

Most of the copolymerization experiments with both types of catalysts were carried out in a minimal amount of toluene (*ca.* 30 vol%) at a temperature that ensures the initial homogeneity (~110 °C). The first series of reactions was performed to synthesize a copolymer with LA : GL ratio of 75 : 25 (Table S1, see Online Supplementary Materials, entries 1–6). In these experiments, soluble copolymers were obtained with LA : GL ratios and M_n of the products corresponding to the calculated values. When the fraction of GL was increased up to 50%, partially insoluble copolymers containing extended poly(GL) blocks were formed in the presence of **Mg1** (see Table S1, entry 7). The modest decrease in the conversion of monomers in the presence Mg and Zn complexes (see Table S1, entries 8–10) can also be explained by the formation of poly(GL) blocks, which reduce the copolymer solubility in the reaction medium. **Al1** and **Al2** complexes demonstrated the maximal productivity resulting in copolymers with a substantially broadened molecular weight distribution (MWD) (see Table S1, entries 11 and 12). At the LA : GL ratio of 25 : 75, the difference in productivity between the Mg and Zn complexes and the Al derivatives became more noticeable (see Table S1, entries 13–18), while BHT complex **Al1** demonstrated the best catalytic performance.

The final series of experiments was carried out with the LA : GL ratio of 10 : 90 corresponding to the composition of suture materials widely used in surgery.[2,3] The use of size-exclusion chromatography to analyze copolymers with a high



Mg1, **Zn1**, **Al1**
dimeric presumable structure

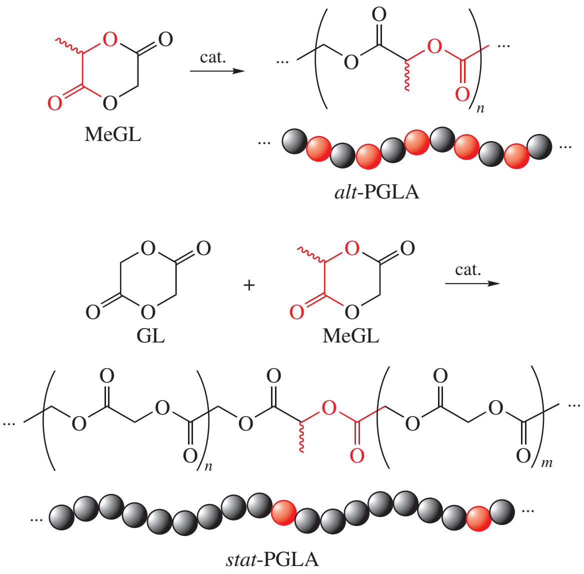


Mg2, Zn2, Al2
oligomeric presumable structure
L is the additional ligand (alkyl, alkoxy) or solvent

Scheme 2

GL content is limited by their low solubility. PGLA melting point determined by DSC correlated with the length of GL blocks in the copolymer and its mechanical properties (Figure S14, see Online Supplementary Materials). Low-soluble copolymers with high melting points were formed in the presence of Mg and Zn complexes at 110 °C [Figure S14(*a*)] while the complete conversion of comonomers was not achieved after 4 h of the reaction (Table S1, entries 19–22). In the case of Al complexes (Table S1, entries 23 and 24), the conversion was higher and the product had a lower melting point. To synthesize copolymers with high randomness, the reaction temperature was increased up to 150 °C. Using **Al2** and **Zn2** complexes at this temperature (Table S1, entries 25 and 26), we obtained the copolymers with phase characteristics close to the high-quality ‘suture’ PGLA Vicryl [Figure S14(*c*,*d*) *vs.* S14(*e*)]. In the presence of tin(II) octanoate under the same conditions (Table S1, entry 27), a partially soluble product with a high melting point was obtained [Figure S14(*f*)].

In this work, we proposed a fundamentally new approach to solve the problem of statistical PGLA synthesis based on the use of 3-methyl-1,4-dioxane-2,5-dione (methyl glycolide, MeGL), the cyclic ester including both glycolate and lactate fragments.[27–29] It was previously reported that MeGL readily forms a homopolymer consisting of alternating glycolate and lactate units (Scheme 3),[9,11] while copolymerization of MeGL with other cyclic esters has not been investigated. The presence of the glycolate fragment allowed us to hypothesize that MeGL should take an intermediate position in the reactivity between GL and LA, providing an opportunity to synthesize the statistical PGLA *via* controlled ROP (see Scheme 3).



Scheme 3

MeGL was copolymerized with GL in the presence of BHT complexes **Mg1**, **Zn1**, and **Al1** (Table S1, entries 28–33) and the products were investigated using both spectral methods and DSC. The copolymerization of MeGL and GL at the ratio of 20 : 80 (this ratio of comonomers provides a polymer composition similar to that of polymer with LA : GL ratio of 10 : 90) and at moderately elevated temperatures (110 °C) resulted in highly statistical PGLA with promising physical characteristics [Figure S14(*g*–*i*)].

Therefore, we have revealed the high catalytic productivity of alkoxy complexes of ‘biometals’ (Mg, Zn, and Al) in the copolymerization of glycolide and lactide. In the presence of BHT-alkoxy complexes, copolymerization was complicated by the formation of polyglycolate blocks, producing partially soluble polymer products with high melting points. The Mg, Zn and Al complexes with ethyl glycolate could effectively catalyze transesterification with the formation of statistical PGLA, while the reactions were accompanied by fragmentation and cyclization with decreasing the molecular weight of the products and broadening of the MWD.

These problems were solved by replacing the relatively low reactive lactide with methyl glycolide, the cyclic ester with an intermediate reactivity between GL and LA. The copolymerization of GL and MeGL in the presence of Mg, Zn and Al BHT-alkoxy complexes under relatively mild reaction conditions produced high molecular weight PGLA with advanced physical characteristics.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.07.024.

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