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Ring-opening polymerization of glycolide and *rac*-lactide, catalyzed by aryloxy magnesium complexes: DFT study of reaction profile and stereocontrol mechanism

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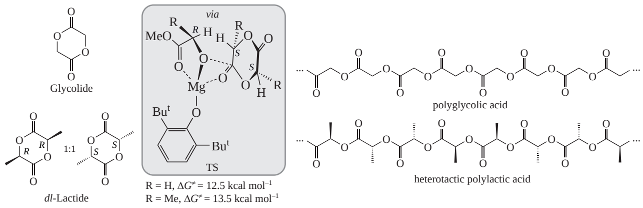
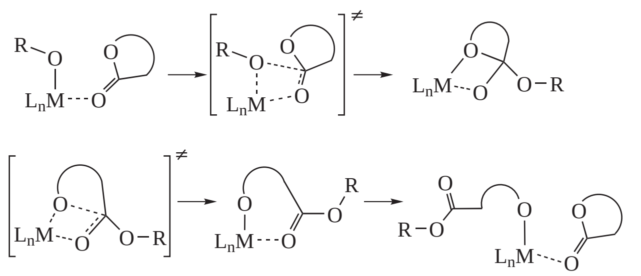
DFT modeling shows that the most likely route of *rac*-lactide ring-opening polymerization, catalyzed by mono-aryloxy magnesium complexes, includes the formation of lower energy polymer-Mg chelates, which makes the formation of heterotactic polylactide preferable.



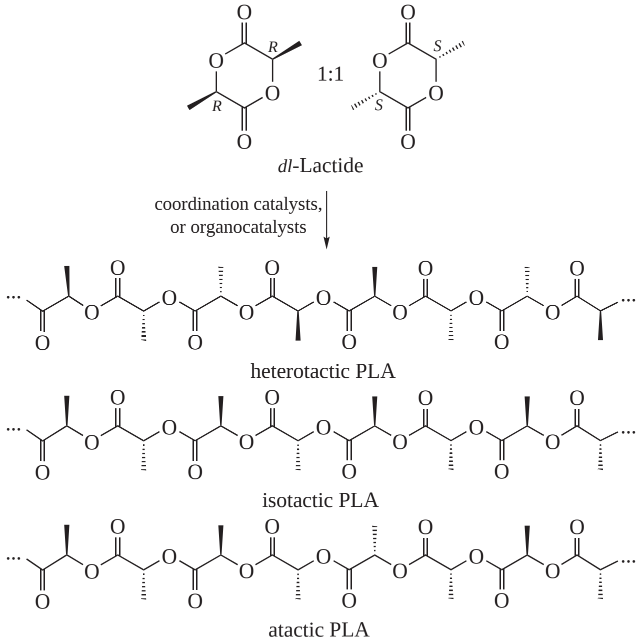
Ring-opening polymerization (ROP) of cyclic esters is a means of producing biodegradable and biocompatible materials with a potentially wide array of practical applications.[1–7] Complex metal alkoxides are effective ROP catalysts acting *via* a coordination–insertion mechanism (Scheme 1).



Scheme 1 Coordination–insertion ROP mechanism.

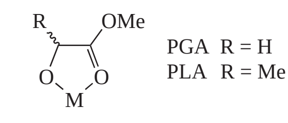
Among cyclic ROP substrates, glycolide (GL) and lactide (LA) can be especially noted. *dl*-Lactide is a racemic mixture of (*R*,*R*)- and (*S*,*S*)-lactides, and usually forms an atactic polymer.[8] However, in the presence of some catalysts, formation of isotactic[8] or heterotactic[8–15] polylactic acid (PLA) is observed (Scheme 2).

Magnesium aryloxy complexes are among the most prospective catalysts as they are non-toxic, highly active and can be used for obtaining various polymers for biomedical applications.[16–23] In our recent work[24] on new catalysts, 1:1 Mg complexes with biocompatible monodentate ligand 2,6-di-*tert*-butyl-4-methylphenol (butylated hydroxytoluene, BHT), we ascertained that $[(BHT)Mg(\mu\text{-}OEt)(THF)]_2$ at –5 °C initiated heterotactic *dl*-LA polymerization (P_r = 87%).[†] The purpose of this study was the development of a mechanistic model of GL and LA polymerization in the presence of mono-BHT Mg complexes, which would explain their high catalytic activity and stereoselectivity.



Scheme 2 PLA microstructures.

Most researchers[26–32] consider the coordinated ROP of GL and LA as a part of the general concept of coordination–insertion mechanism (see Scheme 1), without accounting for the ability of polyglycolic acid (PGA) or PLA to form stable chelate complexes between metal atoms and –OCH(R)C(O)– fragments. The



PGA/PLA–metal chelate intermediates

[†] *P*r is the probability of racemic placement between monomer units [*i.e.*, (*R*,*R*)-LA followed by (*S*,*S*)-LA or *vice versa*] and is determined from the methine region of the homonuclear decoupled ^{1}H NMR spectrum. The expressions for the tetrad concentrations in terms of P_r are:[10,25] $[mmm] = [2(1 - P_r)^2 + P_r(1 - P_r)]/2$; $[mrm] = [P_r^2 + P_r(1 - P_r)]/2$; $[mmr] = [rmm] = [P_r(1 - P_r)]/2$; $[rmr] = P_r^2/2$.

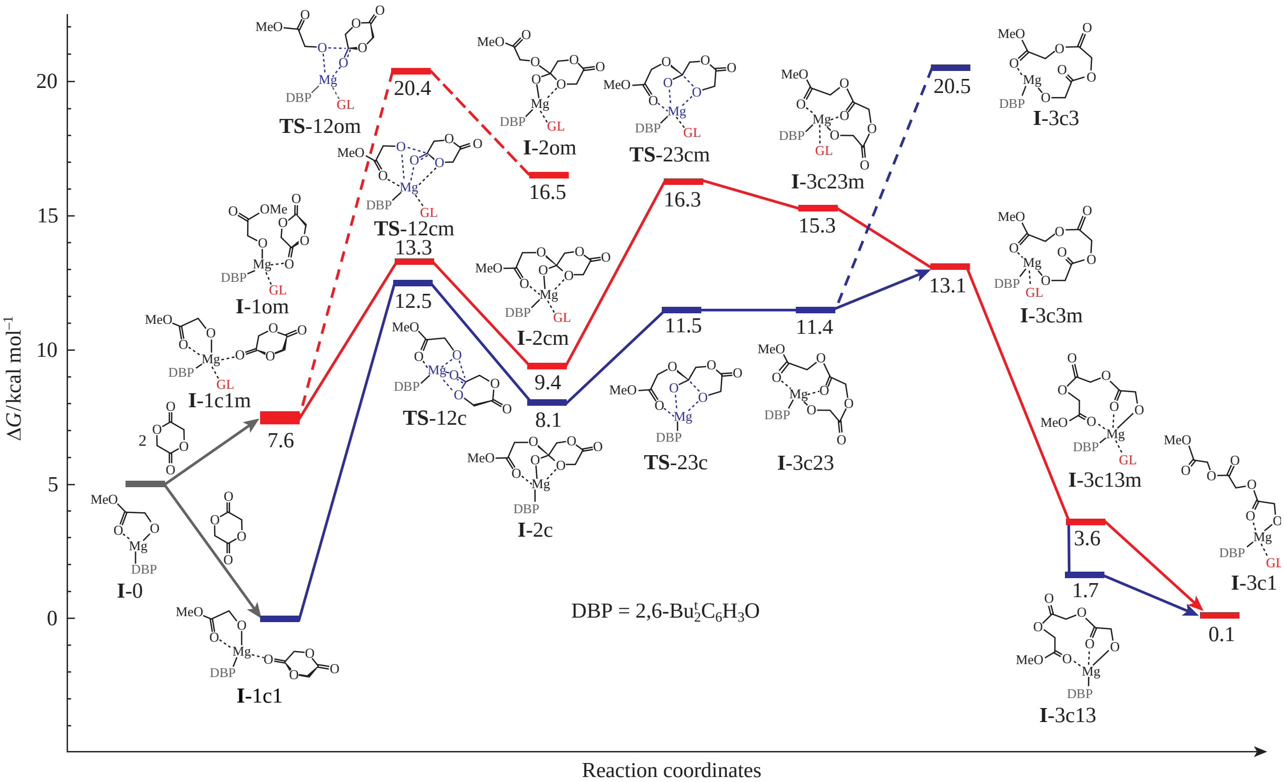


Figure 1 Energy profile of the ring-opening polymerization of glycolide catalyzed by DBP–Mg complex.

occurrence of such coordination has been experimentally verified by spectral and X-ray data.[33–36] Such a coordination was of notice in several works on DFT modeling of LA polymerization catalyzed by metal complexes with polydentate ligands.[36–39]

The question, which type of coordination is preferable during catalysis by aryloxy Mg complexes, was the key one in our study of reaction mechanism. We chose chelate 2,6-di-*tert*-butylphenoxymagnesium methyl glycolate complex, (DBP)Mg–$OCH_2C(O)OMe$ **I**-0 (Figure 1), as an initial compound for DFT modeling[‡] of GL ROP.

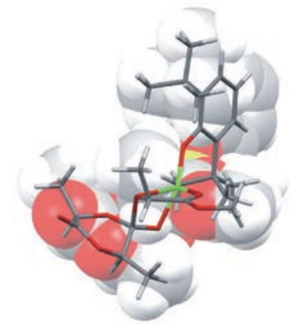
Calculations have shown that coordination of one molecule of GL by **I**-0 with a formation of intermediate **I**-1c is accompanied by a reduction in free energy by 4.9 kcal mol^{-1}. At the same time, coordination of a second molecule of GL with a formation of an 'open' tetragonal complex **I**-1om or a pentagonal chelate **I**-1cm is energetically unfavorable (ΔG = 2.7 kcal mol^{-1}). Intermediate **I**-1c was accepted as a ground state, the geometries and energies of possible intermediates and transition states were calculated, and energy profiles were constructed (Figure 1) for two alternative reaction pathways, one with an additional GL molecule coordination ('m'-series) and another without it. The most important transition state for GL ROP is the first one, **TS**-12c, between **I**-1c and **I**-2c (ΔG = 12.5 kcal mol^{-1}). The energy of **TS**-12cm for the transition between **I**-1cm and **I**-2cm is higher by just 0.8 kcal mol^{-1}, while the ΔG of the 'open' tetragonal transition state **TS**-12om is more than 20 kcal mol^{-1}. The energies of tetrahedral and pentagonal chelate transition states of the ring-opening stage, **TS**-23c and **TS**-23cm, differ by 4.8 kcal mol^{-1}. For intermediates of the **I**-3 group, products of the GL ring-opening, several types of structure are theoretically possible. These structures should differ by number and type of carbonyl oxygen atoms coordinated to Mg. Initially the tetragonal **I**-3c23 or pentagonal **I**-3c23m intermediates are formed. The pentagonal **I**-3c23m one is further stabilized by isomerization into **I**-3c3m and **I**-3c13m. A direct transition from **I**-3c23 to **I**-3c3 is energetically unfavourable, the formation of stable tetragonal **I**-3c13 requires an intermediate GL coordination. The catalytic cycle completes the replacement of a coordinated carbonyl group in **I**-3c13 with a GL molecule with the formation of **I**-3c1, isostructural to **I**-1c.

Therefore, in the case of mono-aryloxy Mg complexes, formation of chelates is a significant factor in lowering the energy of intermediates and transition states. The main pathway of the GL ROP cycle goes through tetragonal chelate transition states and intermediates. The activation energy of ROP is determined by the energy of **TS**-12c.

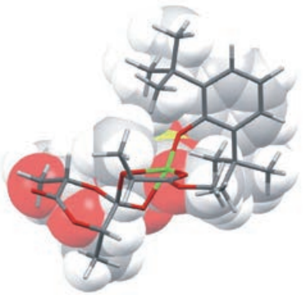
To explain the observed stereoselectivity of *dl*-lactide ROP leading to heterotactic polymer formation, we calculated the geometries and energies of transition sates **TS**-1 formed by methyl (*R*)- or (*S*)-lactates thus modeling the coordinated polymer chain, and (*S*,*S*)- or (*R*,*R*)-LA. The main factor in the TS destabilization is the van-der-Waals repulsion between methyl groups of methyl lactate and lactide. Thus, for the examined mechanism (*re*-attack by LA) transition states formed by (*R*)-lactate and LA enantiomers were characterized by lower energies (Figure 2). For transition sate formed by (*S*,*S*)-LA, the energy is minimal with a difference of 3.2 kcal mol^{-1} as compared to (*R*,*R*)-LA based transition state, which can be explained by conformational factors. The fact that insertion of (*S*,*S*)-LA is more favorable for methyl (*R*)-lactate complex shows that heterotactic PLA formation is the preferable pathway.

In conclusion, using DFT modeling we managed to construct an energy profile of glycolide ROP catalyzed by mono-aryloxy

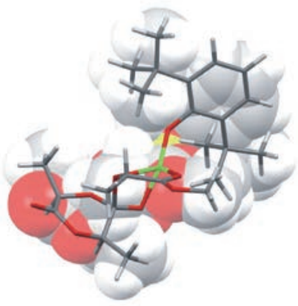
‡ Calculations were performed with the PRIRODA[40] program using Perdew–Burke–Ernzerhof (PBE) functional[41] and a 3ζ basis. The optimization of complex geometry, frequency analysis, and calculations of entropy corrections were made for gas phase at 298.15 K. Transition state ranges were found by energy scanning with sequential changing of key geometric parameters with a step of 0.01 Å. Intermediates (local minima) and transition states (first order saddle points) were found by optimizing the structures by energy and calculation of force constants matrices (Hessian) with a further analysis of resulting frequencies. The calculations were done for both monomer orientations, *si*- and *re*-; the more favorable *si*-orientation data are given and discussed in this article.



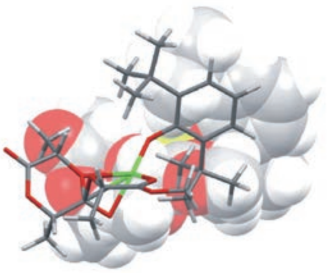
(*R*)-MeL-(*R*,*R*)-LA
15.7 kcal mol^{-1}



(*R*)-MeL-(*S*,*S*)-LA
13.5 kcal mol^{-1}



(*S*)-MeL-(*R*,*R*)-LA
22.8 kcal mol^{-1}



(*S*)-MeL-(*S*,*S*)-LA
18.1 kcal mol^{-1}

Figure 2 Van-der-Waals repulsion, LA conformations and Δ*G* (**I**-0) in key transition states **TS**-12c of *rac*-lactide polymerization.

Mg complexes. Minimum energies correspond to chelate intermediates and transition states, which include the –OCHRC(O)– fragment of the growing polymer chain. A comparative analysis of energies and geometries of key transition states at the coordination–insertion stage, including the stereochemistry of lactide and chelate fragment –OCHMeC(O)–, allowed us to establish (*S,S*)-LA insertion is more favorable for *R*-configuration of the –OCHMeC(O)– fragment, which explains the formation of heterotactic PLA by chain-end control of stereoselectivity.

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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.2017.05.020.

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