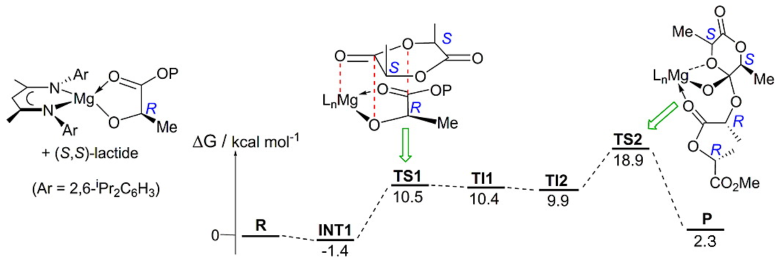
Article

A Computational Analysis of the Ring-Opening Polymerization of *rac*-Lactide Initiated by Single-Site β-Diketiminate Metal Complexes: Defining the Mechanistic Pathway and the Origin of Stereocontrol

Edward L. Marshall, Vernon C. Gibson, and Henry S. Rzepa

J. Am. Chem. Soc., **2005**, 127 (16), 6048-6051• DOI: 10.1021/ja043819b • Publication Date (Web): 29 March 2005



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
ARTICLES

A Computational Analysis of the Ring-Opening Polymerization of *rac*-Lactide Initiated by Single-Site β-Diketiminate Metal Complexes: Defining the Mechanistic Pathway and the Origin of Stereocontrol

Edward L. Marshall, Vernon C. Gibson, and Henry S. Rzepa*

Contribution from the Imperial College London, South Kensington Campus,
London SW7 2AY, United Kingdom

Received October 11, 2004; E-mail: h.rzepa@imperial.ac.uk

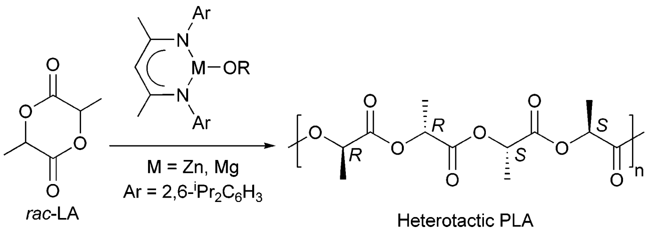
Abstract: The ring-opening polymerization of *rac*-lactide at a β-diketiminate magnesium center, [HC{CMeN-2,6-^{i}Pr$_2$C$_6$H$_3$}$_2$]Mg(OMe)(THF), has been investigated using a B3-LYP density functional procedure employing three different layers of basis set: 6-311G(3d) at the Mg center, 6-31G(d) for both the ligand skeleton and the monomer, and a STO-3G basis set at the bulky 2,6-diisopropylphenyl substituents. By studying the consecutive ring-opening of two lactide molecules, clear conclusions are drawn regarding both the mechanism of ring-opening and the origin of heterotactic stereocontrol observed with such initiators. Polymerization proceeds via two major transition states, an observation applicable to other coordinative initiator systems, with the highest energy transition state dictating the stereochemistry of monomer insertion. In the β-diketiminate magnesium system, a detailed examination of the rate-limiting second transition state geometries reveals that heterotactic poly(lactic acid) arises via the minimization of several steric interactions, possibly reinforced by an attractive CH$\cdots\pi$ interaction.

Introduction

Single-site metal catalysts have provided some of the most spectacular advances in controlled polymerization in recent years and have made available a plethora of new materials.[1] Most recently, there has been rapidly growing interest in the ring-opening polymerization (ROP) of lactide to afford poly(lactic acid) (PLA),[2] a new commodity polymer derivable from biorenewable resources such as corn starch, sugar, and dairy produce. To date, relatively little is understood about the intricacies of this ring-opening polymerization mechanism, a situation that needs to be addressed to enable catalyst design to advance on a rational basis, especially for the stereocontrolled polymerization of *rac*-lactide.

Among the most highly stereoselective initiators reported to date for the ROP of lactide, LA, are (BDI)M(OR) complexes (BDI = HC{CMeN-2,6-^{i}Pr$_2$C$_6$H$_3$}$_2$) based on Zn[3] and Mg,[3b,4] which exhibit high activity and good control for the conversion of *rac*-LA into heterotactic polylactide via the alternating incorporation of the two monomer enantiomers (Scheme 1). Studies by Coates and co-workers have underlined the importance of steric bulk in the *N*-aryl substituents, with a relatively small reduction in the size of the *N*-aryl ortho units resulting in significantly decreased stereocontrol[3b]. Further studies by Chisholm and co-workers indicate that the Mg and Zn systems both produce heterotactic PLA via mononuclear propagating species. Hence, in THF solvent, (BDI)MgOR initiators display high heteroselectivity, whereas in toluene or CH$_2$Cl$_2$, binuclear propagating species generate atactic material.[4b] Despite these advances, little is known about the origin of stereocontrol using these initiators. Here, we report a DFT study into the polymerization of *rac*-LA initiated by mononuclear (BDI)MgOMe(THF) with a view to obtaining a greater understanding of the intricacies associated with metal-alkoxide mediated ROP, as well as addressing the stereocontrol found in the β-diketiminate metal systems.

Scheme 1



---

[1] (a) Coates, G. W. *J. Chem. Soc., Dalton Trans.* **2002**, 467−475. (b) Gibson, V. C.; Marshall, E. L. In *Comprehensive Coordination Chemistry II*; McCleverty, J. A., Meyer, T. J., Eds.; Elsevier: London, 2003; Vol. 9, pp 1−74.

[2] (a) O'Keefe, B. J.; Hillmyer, M. A.; Tolman, W. B. *J. Chem. Soc., Dalton Trans.* **2001**, 2215−2224. (b) Drumright, R. E.; Gruber, P. R.; Henton, D. E. *Adv. Mater.* **2000**, *12*, 1841−1846.

[3] (a) Cheng, M.; Attygalle, A. B.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **1999**, *121*, 11583−11584. (b) Chamberlain, B. M.; Cheng, M.; Moore, D. R.; Ovitt, T. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2001**, *123*, 3229−3238. (c) Coates, G. W.; Cheng, M.; Chamberlain, B. M. WO 0134555.

[4] (a) Chisholm, M. H.; Huffman, J. C.; Phomphrai, K. *J. Chem. Soc., Dalton Trans.* **2001**, 222−224. (b) Chisholm, M. H.; Gallucci, J.; Phomphrai, K. *Inorg. Chem.* **2002**, *41*, 2785−2794. (c) Gibson, V. C.; Marshall, E. L.; Dove, A. P. WO 0238574, 2002.

10.1021/ja043819b CCC: $30.25

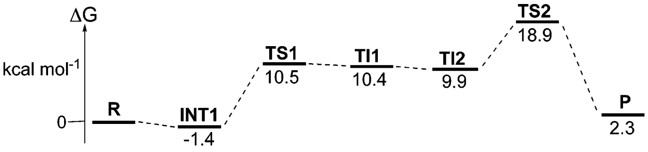
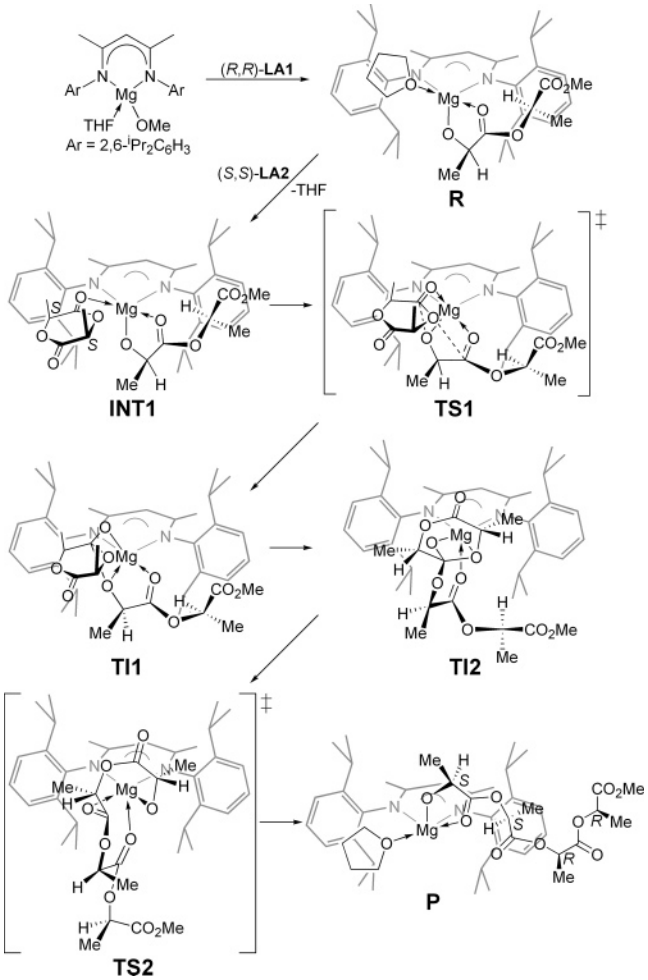


Figure 1. Calculated free energy values (kcal mol^{-1}) for the reaction coordinate corresponding to the *RR*,*SS* assembly mode.[6]

Scheme 2



Results and Discussion

The calculated reaction profile (Figure 1) for the polymerization of LA encapsulates key species proposed in the coordinative-insertion mechanism shown in Scheme 2. We have analyzed the heteroselectivity of the process by studying the addition of two successive LA units at the *β*-diketiminate supported magnesium center: the reaction coordinate depicted in Figure 1 and in Scheme 2 illustrates the ring-opening of an (*S*,*S*)-monomer at a previously ring-opened (*R*,*R*)-LA unit (an assembly hereafter termed *RR*,*SS*) at 298 K. The calculations were performed using a B3-LYP density functional procedure[5] and employ three different layers of basis set: 6-311G(3d) at the Mg center to achieve a realistic description of the metal coordination geometry, 6-31G(d) for both the BDI [HC-{C(Me)N}$_2$] skeleton and the two LA units to replicate stereoelectronics, and a minimal STO-3G basis set at the bulky aryl substituents to model steric effects. The ring-opening of the two LA molecules dictates the study of up to 127 atoms, with 728 associated basis functions. Electronic and thermal free energy corrections, and transition state characterization, were obtained via calculation of the Hessian (see Experimental Section). The calculated free energy values for the key species are summarized in Figure 1.

In the first phase of the study, we optimized the geometry of the first insertion product, **R**, arising from the ring-opening of a single lactide unit, (*R*,*R*)-**LA1**, at the (BDI)MgOMe(THF) center. The most favorable conformation was found to be a five-membered metal-lactate with THF bound to the magnesium.[3b,6,7] Coordination of a second monomer unit, (*S*,*S*)-**LA2**, to this complex via one of its carbonyl groups (Mg···O = 1.986 Å) results in displacement of the THF and affords the intermediate **INT1**. Polymerization then proceeds via two major transition states. The first of these, **TS1**, involves nucleophilic attack of the Mg-alkoxide at the coordinated C$_{\text{carbonyl}}$ of **LA2** (O−C = 1.737 Å, ν_{i} 101 cm^{-1}) with a weaker reciprocal interaction (2.745 Å) between the **LA2** O$_{\text{acyl}}$ and the C$_{\text{carbonyl}}$ of the **LA1** lactate ligand serving to determine the alignment of **LA2** relative to the ring-opened **LA1** fragment (Figure 2). This orientation is reinforced for this diastereoisomer by nucleophilic attack occurring in an antiperiplanar manner to the α-methyl of the bound carbonyl of **LA2**, thus allowing build up of charge at the carbonyl carbon to be delocalized into the C−C$_{\text{methyl}}$ σ^* orbital in accord with the Felkin/Anh/Eisenstein modification to Cram's rule.[8]

The complex then rearranges via a series of tetrahedral (at carbon) intermediates (**TI1**, **TI2**), resulting in close approach (2.371 Å) of the **LA2** O$_{\text{acyl}}$ atom to the Mg center. The new propagating alkoxide bond fully forms in **TS2** (1.877 Å), with concerted dissociation of the **LA2** O$_{\text{carbonyl}}$−Mg bond (2.679 Å) and cleavage of the original **LA2** C−O$_{\text{acyl}}$ bond (2.289 Å) to accomplish ring opening. This transition state ($\nu_{\text{i}} = 47$ cm^{-1}) has characteristics of a concerted [2+2] cycloreversion reaction. Further reorganization serves to extrude the polylactide chain from the coordination sphere of the metal, affording the THF adduct of a five-membered metallacyclic product, **P**. The calculated free energy barrier for the process is 18.9 kcal mol^{-1}, which shows good agreement with an experimentally determined value[9] of 16.9 ± 0.4 kcal mol^{-1} (an IEFPCM solvation correction[6,10] for THF further reduces the barrier to 18.2 kcal mol^{-1}). The solvent plays a key role in these calculations, serving to entropically balance the system with **R** + **LA2** ultimately generating **TS2** + THF (i.e., two molecules are converted into two other molecules). If THF is omitted from the calculations, the entropic disparity causes the computed barrier to rise to 26.8 kcal mol^{-1}, which is inconsistent with the relatively fast rate of propagation exhibited by this system.[3,4]

Overall, the free energy for the conversion of **R** into **P** is slightly endothermic, although the value of +2.3 kcal mol^{-1} is

---

(5) (a) *Gaussian 98*, revision A.11; Gaussian, Inc.: Pittsburgh, PA, 1998. (b) *Gaussian 03*, revision B.04; Gaussian, Inc.: Pittsburgh, PA, 2003. See the Supporting Information for the full list of authors.

(6) See the Supporting Information.

(7) Vanhoorne, P.; Dubois, Ph.; Jérôme, R.; Teyssié, Ph. *Macromolecules* **1992**, *25*, 37−44.

(8) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199−2204. (b) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205−2208. (c) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61−70.

(9) (a) Witzke, D. R.; Narayan, R.; Kolstad, J. J. *Macromolecules* **1997**, *30*, 7075−7085. (b) Duda, A.; Penczek, S. *Macromolecules* **1990**, *23*, 1636−1639.

(10) Cancès, M. T.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032−3041.

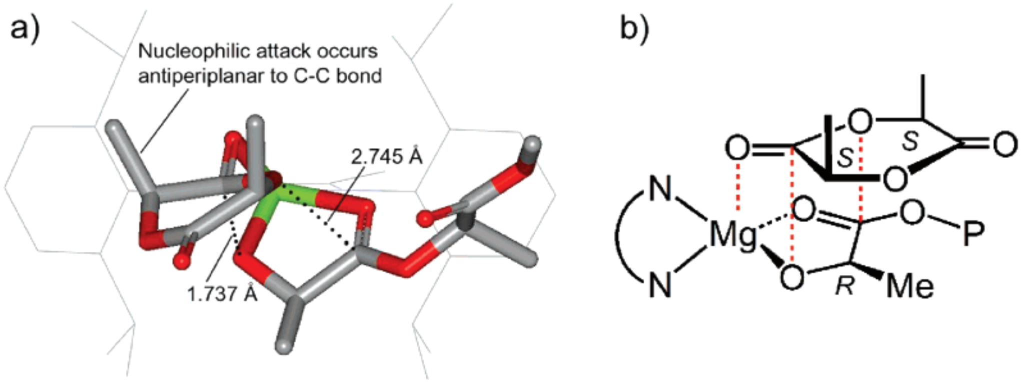


Figure 2. Calculated geometry for **TS1** for the *RR*,*SS* assembly mode (H atoms omitted for clarity: gray = C; red = O; green = Mg) as (a) a perspective view and (b) a schematic view.

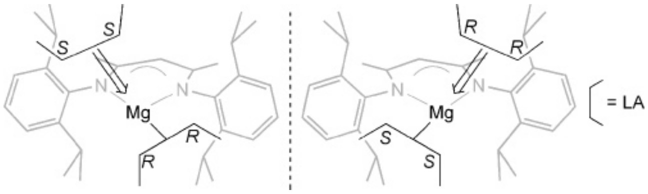


Figure 3. Schematic representation of the attack of (*S*,*S*)-**LA2** at ring-opened (*R*,*R*)-**LA1** (left) and its enantiomeric mirror image (right).

Table 1. Calculated Activation Free Energies (ΔG_{298}) for **TS1** and **TS2**

assembly mode	ΔG **TS1** /kcal mol^{-1}	ΔG **TS2** /kcal mol^{-1}
RR,*SS*	10.5	18.9
RR,*RR*	13.5	20.2
SS,*SS*	6.7	25.4
SS,*RR*	12.5	28.1

notably less than errors typically associated with nonisodesmic calculations (an experimental estimate[9b] is -2.5 kcal mol^{-1}). Our computed free energy values relate specifically to ring-opening of the second monomer unit, and hence this difference in free energy between **R** and **P** does not necessarily represent the limiting free energy of polymerization. With an increased number of repeat units, we would expect dispersion forces associated with the PLA chain to decrease, allowing the entropy of the system to become greater and the free energy to therefore become more favorable.

To analyze the stereoselectivity of this process, a total of eight assembly modes must be considered: **LA1** and **LA2** may both be either (*R*,*R*) or (*S*,*S*), and the approach of **LA2** may occur on either face of the **LA1** lactate-chelate. On closer inspection, it becomes apparent that the eight possibilities exist in enantiomeric pairs, and thus only four sets of calculations are required: an example of one such pair is represented in Figure 3. Accordingly, we have kept the direction of the **LA2** approach constant and calculated four **TS1** and their associated **TS2** geometries. In all four cases, **TS2** is higher in energy (Table 1) and therefore represents the rate-limiting step for the ring-opening event. The explanation for heterotactic polymer assembly is therefore contained within the four competing isodesmic **TS2** geometries shown in Figure 4.

The lowest free energy assembly mode found for **TS2** is *RR*,*SS*, for which ΔG is 1.3 kcal mol^{-1} lower than the next most favorable **TS2** geometry (*RR*,*RR*), and 6.5 and 9.2 kcal mol^{-1} lower in energy than for *SS*,*SS* and *SS*,*RR*, respectively.

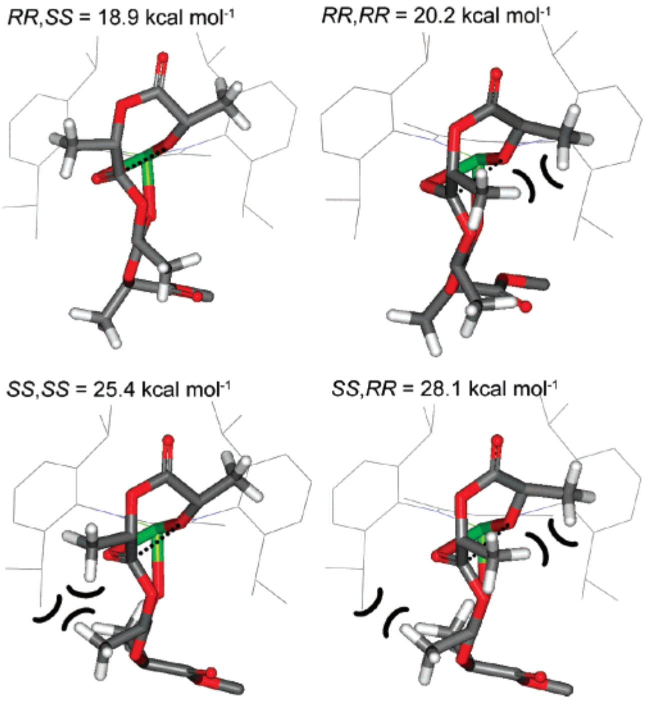


Figure 4. Calculated geometries and free energies (relative to **R** = 0) for **TS2** with areas of steric congestion highlighted (H atoms omitted except for the methyl groups of **LA1** and **LA2**: gray = C; red = O; green = Mg).

Heterotactic PLA is therefore generated by a pathway that alternates between the *RR*,*SS* mode illustrated and its enantiomeric partner, that is, addition of an (*R*,*R*)-monomer to the opposite face of an (*S*)-lactate chelate. The $\Delta(\Delta G)$ value of 1.3 kcal mol^{-1} corresponds to a probability of racemic enchainment, P_r, of 0.90. This compares well with experimentally obtained data for the Mg initiator in THF,[4b] which exhibits a level of heteroselectivity comparable to that of its zinc analogue (P_r = 0.90 at 298 K[3a]).

Close examination of the four competing **TS2** geometries shown in Figure 4 reveals that the favorable nature of the *RR*,*SS* isomer stems mainly from minimization of steric interactions between the methyl groups of **LA1** and **LA2** and the bulky aryl substituents, possibly reinforced by an attractive electronic interaction between a methyl C−H unit and the π-system of one of the N-aryl substituents. First, it should be noted that the splayed diequatorial conformation of the (*S*)-Me groups of **LA2** is preferred over the diaxial arrangement observed in *RR*,*RR* and *SS*,*RR*. In the *RR*,*SS* assembly mode, these alkyl substituents further nestle over the face of the aryl rings, thus avoiding the ^{i}Pr substituents. At least one Me group also appears to be positioned so as to engage in weak stabilizing C−H···π interactions[11] ($\mathrm{Ar_{centroid}}-\mathrm{C_{methyl}} = 3.2$ Å). In addition, when the **LA1** fragment of the propagating chain contains (*R*)-Me groups, they point away so as to minimize the steric conflict with the BDI ligand and the **LA2** unit. By contrast, the **LA1** Me groups of *SS*,*SS* and *SS*,*RR* are proximal to one of the BDI ^{i}Pr groups, and these geometries possess appreciably higher energies. The relatively large free energy differences between **TS2** for *RR*,*SS* and *SS*,*SS*, and for *RR*,*RR* and *SS*,*RR* (6.5 and 7.9 kcal mol^{-1}, respectively[12]), indicate that the clashes between the **LA1** methyls and the ancillary ligand represent the single most significant contribution to stereoselectivity, in accord with a ligand-assisted chain-end controlled mechanism. This observation explains the experimental finding that reducing the size of the ^{i}Pr groups in the zinc analogue results in a decrease in heteroselectivity.[3b]

We believe that several of the details described above may apply to other lactide polymerization initiators. However, we also note that the relative energies of **TS1** and **TS2** are likely to be influenced to a large extent by the size of the ancillary ligand and the nature of the metal. Hence, for other initiators it is possible that **TS1** will be the rate-limiting step,[13] and a brief discussion of the competing **TS1** geometries is therefore warranted here. Figure 5 shows the four minimized structures with potential destabilizing steric repulsions highlighted. The most favorable isomer is *SS*,*SS* as the two methyl groups on the approaching **LA2** are orientated on the face furthest away from the metal-lactate (**LA1**) chelate, the methyl group of which is also positioned so as to minimize interactions with the incoming monomer. Clearly, as the number of methyl groups inside the region of space between the **LA1** and **LA2** fragments increases, so does the free energy, with the *RR*,*RR* isomer particularly disfavored as all three methyl units now clash. Significantly, **TS1** favors isotactic PLA and therefore may be the more relevant transition state for isoselective lactide polymerization catalysts.

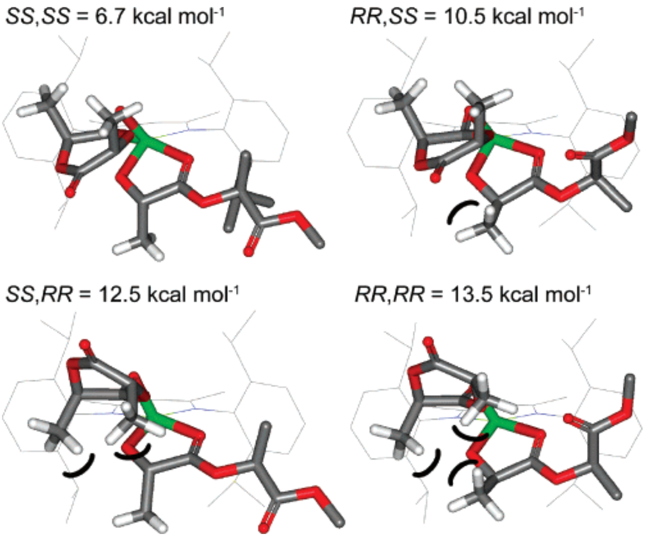


Figure 5. Calculated geometries and free energies (relative to **R** = 0) for **TS1** with areas of steric congestion highlighted (H atoms omitted except for one of the methyl groups of **LA1** and both methyl groups of **LA2**: gray = C; red = O; green = Mg).

Experimental Section

The potential surface was initially explored using the PM5 semiempirical method,[14] which is reported as describing Mg systems well.[15] Putative transition states were then reoptimized at the B3LYP level, using a general basis set involving use of 6-311G(3d) functions on the Mg center, 6-31(d) on the core metal ligand and the lactide units, and STO-3G on the metal ligand substituents. Characterization of located stationary points was via calculation of the Hessian matrix and establishing that one root of this matrix was negative, with the appropriate vectors for the required reaction. This calculation also provided zero-point and free energy corrections to the total energy. Continuum solvation corrections were estimated using the IEFPCM method.[10] Coordinates for stationary points, along with displacement vectors for the transition mode, are contained in the Supporting Information.

Conclusion

In summary, the detailed intricacies of the ring-opening polymerization of *rac*-lactide at a metal center have been delineated for the first time and the factors influencing stereoselectivity at a BDI-supported magnesium center are now reasonably well understood. We believe that many of the features described herein will apply to other lactide polymerization initiators. Of particular note, the approach of the monomer appears to be governed by both electrostatic and stereoelectronic interactions in **TS1**, and this may represent the rate-determining step for some catalysts. However, in the (BDI)Mg system, the stereoselectivity is determined by **TS2** and apparently arises from the minimization of several steric interactions and possibly from weak attractive C−H···π interactions. Related studies on other metal-based lactide polymerization systems will be reported later.

Supporting Information Available: Molecular coordinates (in CML format and viewed using the Jmol applet) with associated total energies, with corrections for zero-point and free energies, and normal mode vibrational coordinates (in XYZ format), annotated where appropriate with InChI (International Chemical Identifiers). This material is available free of charge via the Internet at http://pubs.acs.org.

JA043819B

---

(11) Umezawa, Y.; Tsuboyama, S.; Takahashi, H.; Uzawa, J.; Nishio, M. *Tetrahedron* **1999**, *55*, 10047−10056.

(12) The total energies of the four TS2 geometries are additive, demonstrating a self-consistency, that is, $(\Delta E_{RR,SS} - \Delta E_{RR,RR}) = (\Delta E_{SS,SS} - \Delta E_{SS,RR}) = 4.0$ and $(\Delta E_{RR,SS} - \Delta E_{SS,SS}) = (\Delta E_{RR,RR} - \Delta E_{SS,RR}) = 6.2$ kcal mol^{-1}. Differences in the Δ (ΔG) values arise due to nonadditivity in the rigid-rotor-harmonic-oscillator approximation in dealing with very low-frequency contributions to the entropy.

(13) Gibson, V. C.; Marshall, E. L.; Rzepa, H., manuscript in preparation.

(14) Stewart, J. J. P. *MOPAC2002*; CAChe Group: Portland, OR, 2002.

(15) Linnanto, J.; Korppi-Tommola, J. *J. Comput. Chem.* **2004**, *25*, 123 − 137.