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APPENDICES

APPENDIX A

KEY WORDS IN ROUTE SECTION OF GAUSSIAN03 PROGRAM USED IN THIS CALCULATION

Geometry optimization

For intermediate structure:

#P B3LYP/Gen Pseudo=read Opt=diis scf=direct nosymm Freq

For transition state structure: use only one option of *TS/QST2/QST3*

#P B3LYP/Gen Pseudo=read Opt=(*TS/QST2/QST3*,noeigentest,z-mat,calcfc, Maxcyc=500) scf=direct nosymm Freq

Frquency Calculation

#P B3LYP/Gen Pseudo=read Freq

IRC Calculation

Forward reaction coordinates:

#P B3LYP/Gen Pseudo=read IRC=(calcfc,forward,stepsize=20,maxpoints =10)

Reverse reaction coordinate:

#P B3LYP/Gen Pseudo=read IRC=(calcfc,reverse,stepsize=20,maxpoints=10)

NBO calculation

#P B3LYP/Gen Pseudo=read GFInput Pop=NPA

APPENDIX B

THE DETAILS OF GAUSSIAN BASIS SET ORDER FORM USED IN THIS CALCULATION

Two basis set, LANL2DZ and cc-pVTZ, were used in this calculation as a function of mixed basis set. We generated the basis set details from the website of EMSL gaussian basis set order form and added it in the end of input file (below the structure coordinate).

```
C H O 0
 cc-pVTZ
 ****
Sn     0
S   12   1.00
     38.4899420           0.0001220
     24.2856410          -0.0006380
     15.3232850           0.0025740
      9.6683900          -0.0108040
      6.1003740           0.0552060
      3.8490960          -0.2612420
      2.4286290           0.7008960
      1.5323690          -0.6044690
      0.9668650          -0.2359100
      0.6100540          -0.1507990
      0.3849200           0.2148350
      0.0444900           0.0956740
S   1   1.00
      0.1866400           1.0000000
S   1   1.00
      0.0920920           1.0000000
P   8   1.00
     60.2212000           0.0000420
     27.5393180          -0.0002100
     12.5938050           0.0009210
      5.7591810          -0.0056980
      2.6336890           0.0451000
      1.2043930          -0.1728060
      0.5507720           0.0285410
      0.0396340           0.2073430
P   1   1.00
      0.2244350           1.0000000
P   1   1.00
      0.0951810           1.0000000
D   1   1.00
      0.2699130           1.0000000
D   1   1.00
      0.1140290           1.0000000
F   1   1.00
      0.2846360           1.0000000
****

SN    0
SN-ECP    4    46
g-ul potential
  1
  2     1.000000000          0.000000000
s-ul potential
  2
  2     1.969725000         67.925347000
  2     0.972375000         -7.478546000
p-ul potential
  2
  2     1.999210000         56.602880000
  2     0.999042000         -2.161776000
d-ul potential
  1
  2     0.500361000          2.576336000
f-ul potential
  1
  2     1.230880000        -10.109253000
```

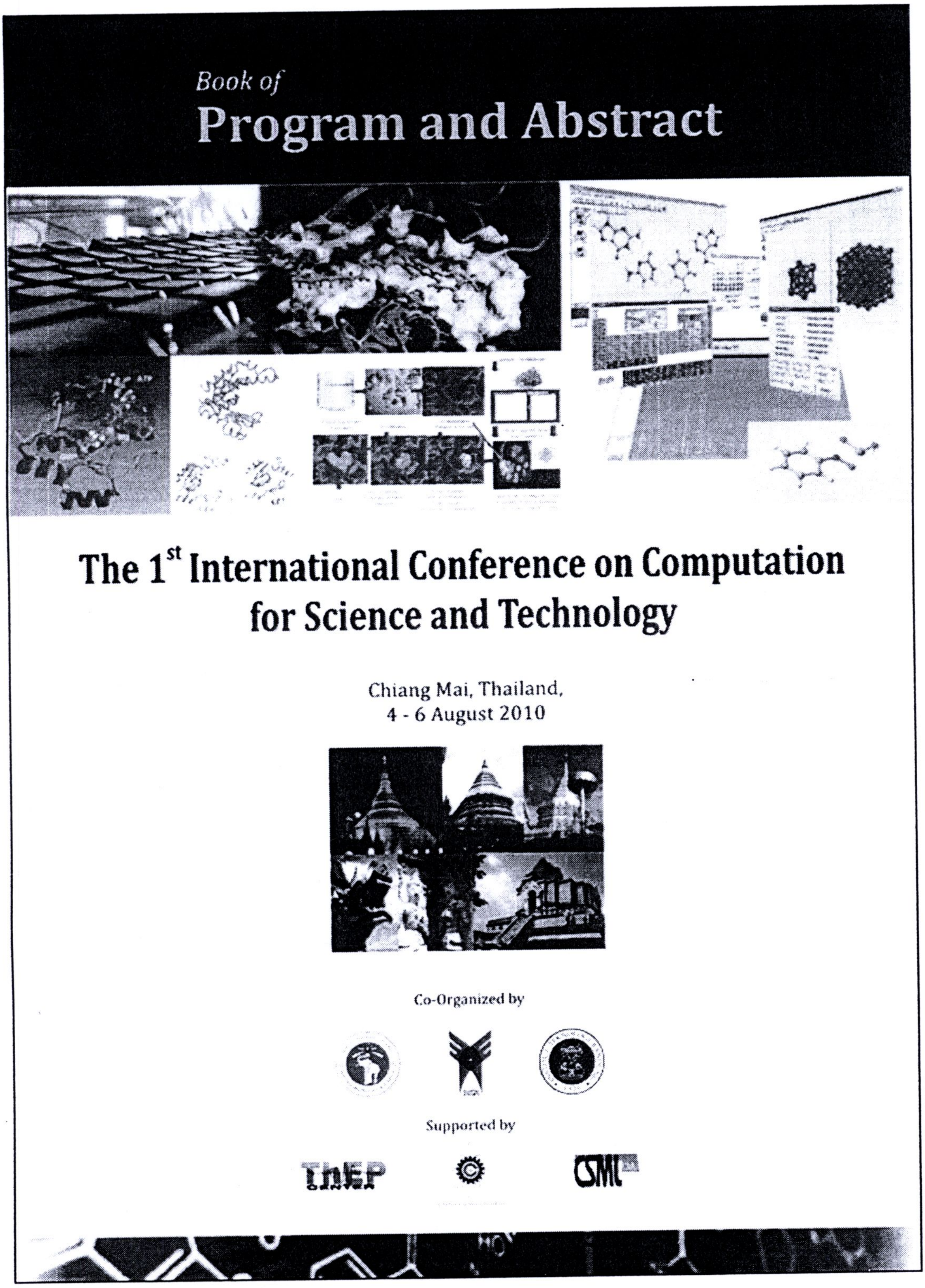
APPENDIX C

PRESENTATIONS IN INTERNATIONAL CONFERENCES CONCERNED WITH THIS THESIS

1) Theoretical Study of the Ring-Opening Polymerization of ε-Caprolactone Initiated by Novel Tin(II) Alkoxides" at *"The 1st International Conference on Computation for Science and Technology (ICCST-I)"*, 4-6 August 2010, Centara Duangtawan Hotel, Chiang Mai. (**Oral presentation**)

2) Theoretical Study of Ring-opening Polymerization of ε–Caprolactone Initiated by Tin(II) Methoxide: Mechanism and Kinetics at *"Pure and Applied Chemistry International Conference 2011 (PACCON 2011)*", 5-7 January 2011, Miracle Grand Hotel, Bangkok. (**Oral presentation and Proceeding publication**)

3) Theoretical Study of Ring-Opening Polymerization of ε–Caprolactone Initiated by Tin(II) Alkoxides at "*International Congress for Innovation in Chemistry (PERCH-CIC Congress VII)*", 4-7 May 2011, Jomtien Palm Beach Hotel & Resort, Chonburi, Thailand. (**Poster presentation**)



Book of

Program and Abstract

The 1st International Conference on Computation for Science and Technology

Chiang Mai, Thailand,
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Theoretical Study of the Ring-Opening Polymerization of ε-Caprolactone Initiated by Novel Tin(II) Alkoxides

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The ring-opening polymerization (ROP) mechanisms of ε-Caprolactone (CL) with novel Tin(II) alkoxide, $Sn(OR)_2$ initiators (R = n-C_4H_9, n-C_6H_{13}, n-C_8H_{17}) were investigated using density functional theory (DFT) calculations. The optimized geometries and corresponding energies of stationary along reaction pathway confirmed a four-step coordination-insertion mechanism. The coordination of CL onto Tin(II) metal center led to a nucleophilic addition of the carbonyl group of CL, followed by an intramolecular alkoxide ligand exchange. A monomer insertion was completed by the CL ring opening via acyl-oxygen bond cleavage. The formation of the four-membered ring Tin(II) transition state was found to be the rate-determining step. Furthermore, kinetic rate constants for each reaction of CL with $Sn(OR)_2$ were calculated using the transition state theory. The calculated rate constants were in good agreement with available experimental data. The $Sn(OR)_2$ initiator as R being n-C_4H_9 was found to give the faster rate due to the least steric hindrance effect and the short ligand compared to other R groups. This study could be useful to ROP of CL initiated by Tin(II) alkoxide.

***Keywords**: ring-opening polymerization, ε-caprolactone, novel tin(II) alkoxides*

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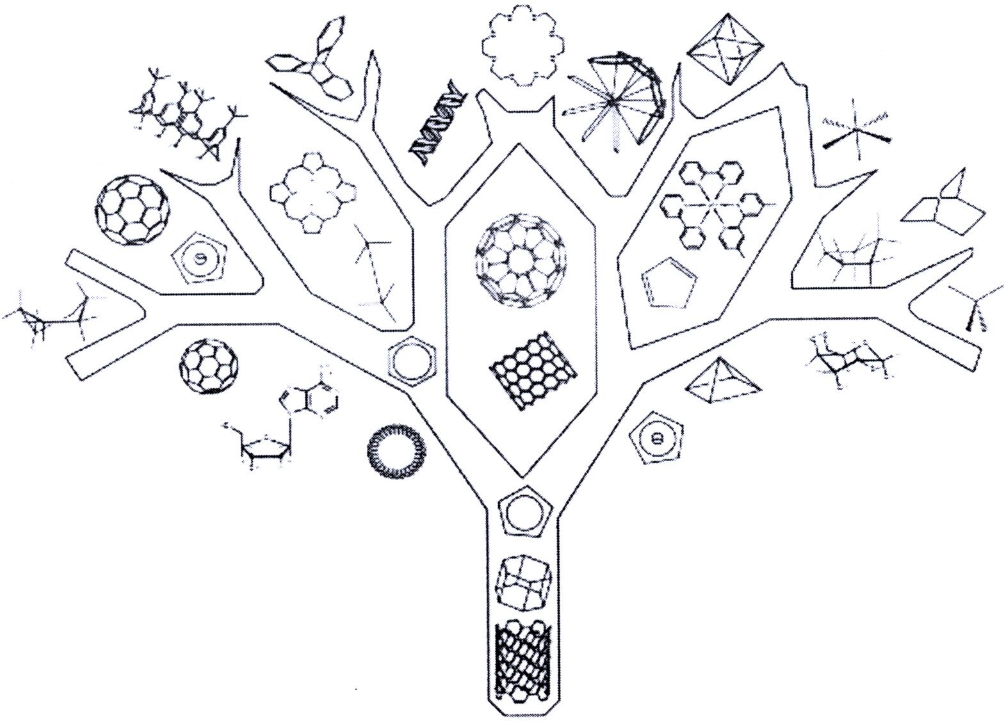

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Theoretical Study of Ring-Opening Polymerization of ε-Caprolactone Initiated by Tin(II) Methoxide: Mechanism and Kinetics

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Abstract: The ring-opening polymerization (ROP) mechanism of ε-caprolactone (CL) with tin(II) methoxide initiator, $Sn(OMe)_2$, was investigated using quantum chemical calculation. Geometry optimization was calculated using density functional theory (DFT) at B3LYP level with mixed basis set. Our calculation results support a coordination-insertion mechanism initiated by tin(II) methoxide with two transition states prior to the ROP. The relative energies of all investigated stationary points along the reaction profile were calculated from potential energy surface. From the energy profile, tin(II) methoxide initiator demonstrated exothermic reaction and the rate determining step was the nucleophilic attack of the methoxide on the carbonyl carbon of the CL monomer at the first transition state (TS1). The electronic and structural information of transition state structures along the reaction pathway was employed to obtain the thermal rate constant using the transition state theory with TheRATE program.

Introduction

Currently, there has been increasing interest in materials derived from bio-renewable resources as environmentally sustainable alternatives to petrochemical-derived products. Among the most prominent examples are poly(lactic acid) (PLA) and poly(ε-caprolactone) (PCL) have been studied intensively due to their biodegradability, biocompatibility and permeable properties and have shown their potential applications in a variety of field such as biomedical and pharmaceutical industries as a resorbable implant material and a vehicle for controlled drug delivery [1-3]. A convenient synthetic route to PLA and PCL is ring-opening polymerization (ROP) of corresponding cyclic ester monomers [1,4, 5].

ROP has been widely studied and many efficient initiators have been developed. Three methods of ROP mechanism are cationic, anionic and coordination-insertion [6]. The coordination-insertion is the best method due to its advantages such as easy control of the molecular weight (MW), the lower risk of side reactions and the higher molecular weight obtained [7].

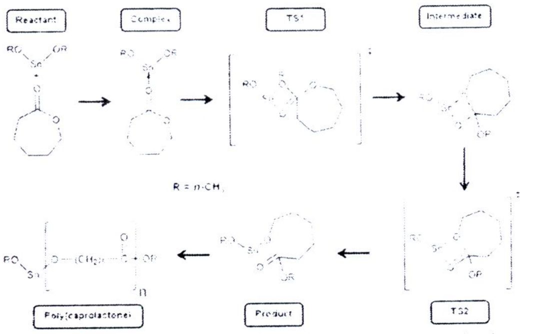
The most common catalyst used in coordination-insertion is metal alkoxides, such as tin, aluminium, trivalent lanthanide, magnesium, zinc derivatives, group IV metals and iron [8-11]. These metal alkoxides have been reported to be effective initiators that initiate ROP of cyclic esters. Among them, tin alkoxide is suitable for the ROP catalyst because of its solubility and ease of handling. In particular, tin(II) 2-ethylhexanoate, commonly known as stannous octoate ($SnOct_2$), is the most widely used in both scientific research and industrial production. It is the catalyst that has been accepted by the U.S. Food and Drug Administration (FDA) [12]. The polymerization mechanism with this initiator is rather complex and several mechanisms have been proposed in the past [13-16]. In the polymerization process, $SnOct_2$ acts as an initiator in the presence of an alcohol (ROH) coinitiator before carrying to actual initiating species. So, $SnOct_2$ is not the true initiator. For this reason, true initiators were developed by Winita *et al.* [17] and the new mechanism was also proposed as shown in Scheme 1. From their experiment, the synthesis was achieved on several tin(II) alkoxides initiators. These new initiators can completely control the ROP polymerization of CL and give the high MW polymers. Their kinetic study from dilatometry method at 120 °C of ROP polymerization showed very interesting results. All initiators performed high reactivity and fast reaction as a first order rate respected to monomer concentration. However, a clear description of this ROP mechanism is still ambiguous.

For more understanding of this mechanism, the theoretical calculations by means of quantum chemical calculation and transition state theory (TST) [18] will be used to investigate the reaction mechanism and reaction rate constant [2, 19-23]. Furthermore, the calculated rate constant will be compared with experimental data [18].

Computational Details

Theoretical study by means of quantum chemical calculation was used to investigate the ROP mechanism of CL initiated by tin(II) methoxide, $Sn(OCH_3)_2$ initiator. Geometries, energies and vibrational frequencies of all stationary points (reactant, complex, transition state, intermediate and product) along with reaction profiles were computed using the hybrid density functional theory (DFT) at

B3LYP level [24]. For metal atom, a doublet-ζ-valence quality basis set LANLD2Z was assigned for Sn atom. A relativistic electron core potential (ECP) developed by Hay and Wadt replaced the Sn core electron [25, 26]. For non-metal atom, a valence triple zeta with polarization function (VTZ2P) at cc-pVTZ was assigned for C, H, and O atoms. This popular and computationally cheap method predicted reliable geometries and energetic as reported in previous works [21, 18]. The character of intermediates and transition states was confirmed by performing frequency calculations [19, 21]. The energy barrier heights of all reactions were corrected by including the zero-point energy corrections [27]. All calculations were performed with the Gaussian03 software package [28]. The information obtained from quantum chemical calculation was employed to determine the thermal rate constant of the reaction. The thermal rate constant at temperature 120 °C was calculated using the conventional transition state theory (TST) [18] method implemented in TheRATE program by University of Utah's web-based kinetics module within the Computational Science and Engineering Online suite (CSEOnline) [29]. Finally, the calculated rate constants will be compared with the available experimental data.



Scheme 1. Proposed mechanism for ring-opening polymerization of ε-caprolactone initiated by tin(II) alkoxide

Results and Discussion

The tin(II) methoxide assisted ROP coordination-insertion mechanism for monomer of CL was investigated by DFT(B3LYP) with mix basis set method. The corresponding DFT based optimized structures and energies of each step followed Scheme 1 are depicted in Figure 1. The exo-carbonyl group of CL coordinates the Sn metal (**Complex**) with O^1 in the *cis* position, resulting in a Sn-O^2 distance of 2.58 Å. The energy of **Complex** formation is -7.03 kcal mol^{-1}. The transformation of **Complex** into **TS1** involves addition of the Sn-O^3 onto the C^1-O^2 double bond and a corresponding rotation of the O^1-C^1-O^2 plane 90° forming a planar four-membered ring (**TS1**) having sp^2-sp^3 hybridized C^1 which is located above that O^2-C^1-O^1 plane. This process lengthens the Sn-O^3 and shortens the Sn-O^2 (Figure 1). This process requires moderate energy (14.01 kcal mol^{-1}) and the supported DFT with only one negative imaginary frequency is confirmed. The nature bond orbital (NBO) charges along the reaction pathway on Sn and C^1 slightly increase and on O^3 also increase but those on O^1 and O^2 decrease (Figure 2).

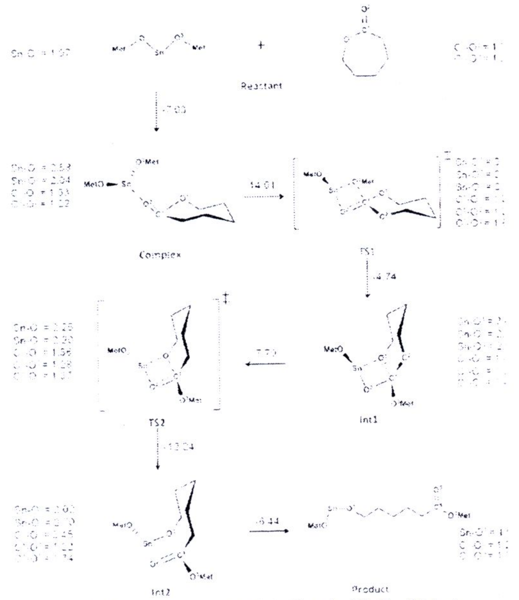


Figure 1. ROP mechanism of CL initiated with $Sn(OMet)_2$. Bond lengths are in Å and energies are in kcal mol^{-1}

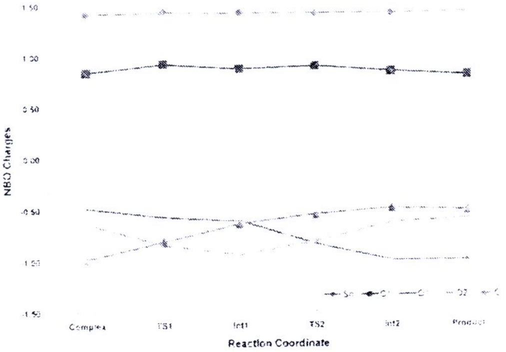


Figure 2. Natural bond orbital charges of several atoms involved in the reaction intermediates in the polymerization of CL initiated by $Sn(OMe)_2$

The conversion of **TS1** to intermediate1 (**Int1**) involves rotation of CL ring around the C^1-O^2 bond resulting in a decrease and increase in the Sn-O^3 and Sn-O^1 distances respectively (Figure 1). The Sn-O^1 distance is about 3.40 Å which is not a bond between but only attractive force between the two atoms. The energy of **Int1** formation is -4.73 kcal mol^{-1} above the **Complex**. The optimized transition state 2, **TS2**, shows a four-membered ring with nearly equal Sn-O^1 and Sn-O^2 distance and a sp^3 hybridized C^1 atom with C^1-O^1, C^1-O^2 and C^1-O^3 bond lengths between 1.28 and 1.86 Å. This step is completely attained when the bond of Sn-O^1 is created. The **TS2** structure is confirmed by an imaginary frequency and intrinsic reaction coordination (IRC) calculation indicating that saddle point along the reaction pathway is exists. This **TS2** eventually ruptures to intermediate2 (**Int2**) and then form **Product** with increasing bond length of C^1-O^1. Our DFT based calculation gave two transition state formation steps with the **TS1** being as the rate-determining step. Our calculated results based on proposed mechanism in Scheme 1 of tin(II) methoxide with CL is found similar to the proposed ROP mechanism of SnMe$_3$OMe with 1,5-dioxepan-2-one (DXO) reported by von Schenck and co-workers [21]. This may be due to the similarity of coordinate stability for Sn both in tetravalent and divalent forms. The overall reaction is exothermic.

The relative energies of all investigated stationary points (**Reactant**, **Complex**, **TS1**, **Int1**, **TS2**, **Int2** and **Product**) along the reaction profile for ROP mechanism of CL initiated by tin(II) methoxide are showed in Figure 3. From energy profile, the **Reactant** energy is assigned to be 0.00 kcal mol^{-1}. The **Complex** energy is lower than the **Reactant** energy about -7.03 kcal mol^{-1}. For **TS1**, the barrier height energy of this step is 14.01 kcal mol^{-1} and the **TS1** energy is 6.98 kcal mol^{-1} above **Reactant** energy. For the intermediate 1 (**Int1**), the energy is found to be 2.24 kcal mol^{-1} above the **Reactant** energy. The apparent barrier height of **TS2** step is 7.78 kcal mol^{-1} when compared with **Int1**. From the energy profile, the first transition state formation (**TS1**) is a rate determining step of this reaction.

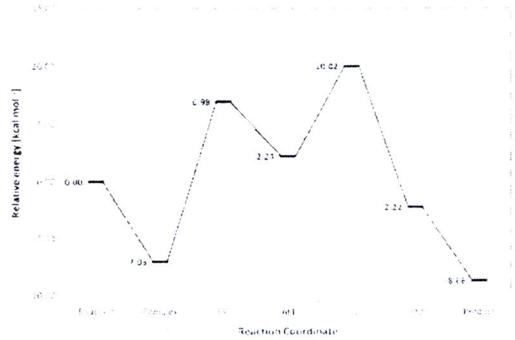


Figure 3. Relative energy profile for ROP mechanism of CL initiated by tin(II)-methoxide, calculated at B3LYP method

The thermal rate constant at 120 °C was calculated to be 357.4 L mol^{-1} min^{-1} (shown in Table 1) using information from the quantum calculation with TST implemented in TheRATE program. The calculated value is in a good agreement within a factor of two compared with experimental data.

Table 1 The theoretical and experimental rate coefficient of tin(II) methoxide initiator

Sn(OR)$_2$	Temperature (°C)	Rate coefficient (L mol^{-1} min^{-1})	
		Experiment^a	Theory^b
Met	120	712.2	357.4

^{a}Calculated by dilatometry's measurement of Winita's group [17].
^{b}Calculated by TheRATE program of university of Utah [29].

Conclusions

The ring-opening polymerization of ε-caprolactone with tin(II) methoxide initiator has been carried out using density functional method. The reaction proceeds via coordination-insertion mechanism initiated by tin(II) methoxide. The relative energy profile of tin(II) methoxide is calculated and showed in the Figure 3. The overall reaction is exothermic. The barrier heights are 14.01 kcal mol^{-1} and 7.8 kcal mol^{-1} for TS1 and TS2, respectively. The rate-determining step is the nucleophilic attack (TS1 formation step) of the tin(II) methoxide on the exo-ring carbonyl carbon of ε-caprolactone. The rate constant obtained from TST is a factor of two compared with available experimental data indicating that TST can be further used to predict the rate constant of other tin(II) alkoxide initiators.

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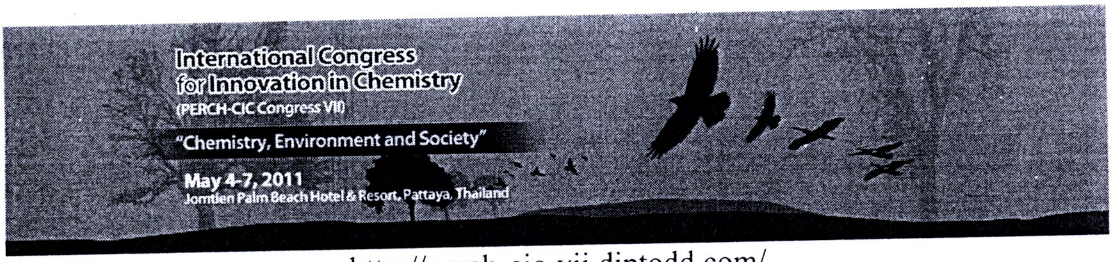

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Theoretical Study of Ring-Opening Polymerization of ε–Caprolactone Initiated by Tin(II) Alkoxides

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Abstract

The ring-opening polymerization (ROP) mechanisms of ε-caprolactone (CL) with tin(II) alkoxide, $Sn(OR)_2$ initiators ($R = n\text{-}C_4H_9$, $i\text{-}C_4H_9$, $t\text{-}C_4H_9$, $n\text{-}C_6H_{13}$, $n\text{-}C_8H_{17}$, $n\text{-}C_{10}H_{21}$) were investigated using density functional theory (DFT) at B3LYP level. Our calculation results support coordination-insertion mechanism with two transition states (TS1, TS2) prior to completion of ROP via acyl-oxygen bond cleavage. The relative energies along the reaction profile of all initiators demonstrated exothermic reaction and the rate determining step was the nucleophilic attack of the alkoxide on the carbonyl carbon of the CL monomer at TS1. Furthermore, kinetics rate constants of all ROP reactions were calculated using the transition state theory with TheRATE program. The calculated rate constants were in good agreement with available experimental data. The $Sn(OR)_2$ initiator as R being $n\text{-}C_4H_9$ was found to give the faster rate constant due to the least steric hindrance effect and the short ligand compared to other R groups.

Introduction

Poly(ε-caprolactone) (PCL) has been studied intensively due to its biodegradability, biocompatibility, and also in biomedical such as drug delivery. A convenient synthetic route to PCL is a ring-opening polymerization (ROP) of ε-caprolactone (CL) monomers via coordination-insertion mechanism with metal initiator. In particular, tin(II) alkoxides is the most widely use of metal catalyst in coordination-insertion. For this reason, true initiators were developed by Dumklang *et al.* and the new mechanism was also proposed as shown in figure 1.

From their experimental results, tin(II) alkoxides can completely control the ROP of CL and gave the high molecular weight polymers. And, their kinetic studies showed very interesting results. However, a clear description of their ROP mechanisms is still ambiguous. So that, the quantum chemistry calculation and transition state theory (TST) will be used to investigate the reaction mechanism and reaction rate constant.

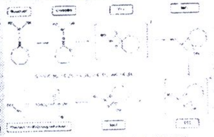
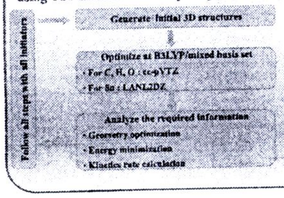


Figure 1: Scheme of new purpose mechanism for ROP of CL initiated by tin(II) alkoxide

Computational method

Quantum chemical calculation was used to investigate the ROP mechanism of CL initiated by tin(II) alkoxides, $Sn(OR)_2$ when $R = n\text{-}C_4H_9$, $i\text{-}C_4H_9$, $t\text{-}C_4H_9$, $n\text{-}C_6H_{13}$ and $n\text{-}C_8H_{17}$ (figure 2). The thermal rate constants of the reactions were calculated using TST method. The computing step was shown in diagram below.



Follow all steps with all initiators

Generate initial 3D structures

Optimize at B3LYP/mixed basis set
- For C, H, O : cc-pVTZ
- For Sn : LANL2DZ

Analyze the required information
- Geometry optimization
- Energy minimization
- Kinetics rate calculation

Figure 2: The structures of five target initiators used in this study

Results and Discussion

According to the geometry information, our results support a coordination-insertion mechanism initiated by tin(II) alkoxides with two transition states and seven states of reaction prior to the ROP (**Reactant**, **Complex**, **TS1**, **Int1**, **TS2**, **Int2**, **Product**). The detailed information on the ROP mechanism is described in the following six steps and all initiators show the similar results following figure 3 as an example of $Sn(On\text{-}C_4H_9)$. The relative energy profile is plotted and compared in figure 4. The apparent energy barriers at **TS1** of initiation step of $Sn(On\text{-}But)_2$, $Sn(On\text{-}Hex)_2$, $Sn(On\text{-}Oct)_2$, $Sn(Oi\text{-}But)_2$ and $Sn(Ot\text{-}But)_2$ are 14.58, 14.61, 14.59, 15.04 and 20.04 kcal mol^{-1}, respectively. For **TS2**, the energy barrier heights of all initiators are 9.62, 9.61, 9.7, 8.94 and 9.18 kcal mol^{-1}, respectively.

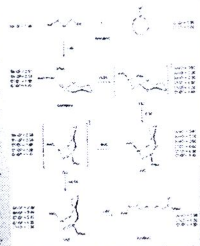


Figure 3: Structures of target tin(II) alkoxide initiators used in ROP of CL

Results and Discussion

From figure 4, it indicates that the TS1 energy barrier is rate determining step of this ROP reaction. And overall reaction of all initiators is exothermic. The thermal rate constants in the range of 100-120 °C (table 1) were calculated in which the higher temperature, the faster rate constants become. And the calculated values are in good agreement within a factor of two compared with experimental data. Especially, $Sn(On\text{-}C_4H_9)_2$ shows the highest rate constants compared with the other initiators. These rate constant results are also related to the energy barrier (**TS1**) of $Sn(On\text{-}C_4H_9)_2$ which is the lowest compared to the other initiators. So, $Sn(On\text{-}C_4H_9)_2$ gives the highest reaction rate among the other initiators.

There are two main effects on the initiators. First, the effect of long chain on R group in $Sn(OR)_2$ initiators starting from C_4 (*n*-But) to C_6 (*n*-Hex) and C_8 (*n*-Oct) shows slightly energy change on the **TS1** relative energy and the rate constant decreases as the number of carbon atom (C_4, C_6 and C_8) on R group of initiator increases. The longer chain on R group slightly destabilizes the **TS1** formation stability. Therefore the shorter R group is more favorable to make the rate of reaction go faster within the same condition. Second, the effect of branching group on alkyl group in $Sn(OR)_2$ initiators from C_4(*n*-But) to *iso*-C_4 (*i*-But) and *tert*-C_4 (*t*-But) reveals significantly change on energy of **TS1** formation. Obviously the more steric hindrance of branching, the less stable of **TS1** is observed resulting in decrease of rate constants.

Figure 4: Relative energy profile for ROP of CL initiated by five tin(II) alkoxide, calculated at B3LYP method

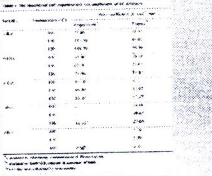


Table 1: The theoretical and experimental rate coefficient of all initiators

Conclusion

DFT at B3LYP level calculations of stationary points along the reaction pathway in the ROP of CL initiated by tin(II) alkoxides give insight into the addition detailed mechanisms of initiation and propagation processes. The reaction proceeds via coordination-insertion mechanism and the rate determining step is the nucleophilic attack (**TS1** formation). The overall reaction is exothermic. Both transition states (**TS1**, **TS2**) having four-membered ring are found in all cases. The $Sn(OR)_2$ with R having $n\text{-}C_4H_9$ has the lowest apparent energy barriers resulting in the fastest rate constant under the same condition among all five initiators. The calculated rate constants of all initiators by TST are in good agreement with experimental results in which a factor of two.

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Publications

- **C. Sattayanon**, W. Punyodom, P. Meepowpan and N. Kungwan, Theoretical Study of Ring-opening Polymerization of ε–Caprolactone Initiated by Tin(II) Methoxide: Mechanism and Kinetics, *Proceeding of Pure and Applied Chemistry International Conference 2011 (PACCON 2011)*, 2011.