Theoretical study of efficiency comparison of Ti (IV) alkoxides as initiators for ring-opening polymerization of ε-caprolactone

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ABSTRACT
The initiators used in the ring-opening polymerization (ROP) were theoretically studied. The ROP of ε-caprolactone initiated by Ti (IV) alkoxides were investigated using high level adiabatic mapping B3LYP/LANL2DZ calculations. The initiators were modeled to be four types; Ti (IV) n-propoxide, Ti (IV) n-butoxide, Ti (IV) 2-ethylhexoxide and Ti (IV) t-butoxide, in order to investigate the efficiency of Ti (IV) alkoxides as initiators. The reactivity of modeled initiators was compared with the experimental results and other theoretical work. The calculated results showed that the first step of reaction is the rate limiting step of the ROP. The efficiency of initiators can be ranked as Ti (IV) n-propoxide > Ti (IV) n-butoxide > Ti (IV) 2-ethylhexoxide > Ti (IV) t-butoxide. The calculated results are in good agreement with experimental results.

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1. Introduction
Poly (ε-caprolactone) (PCL), a synthetic and aliphatic polyester from ε-caprolactone monomer, is a biodegradable and biocompatible plastic. Because of its biodegradability and good compatibility with the human body [1,2], it has been used in wide range of applications, for example, drug controlled release, tissue engineering and disposable packaging [3]. Normally, PCL with controllable molecular weight is obtained from ring-opening polymerization (ROP) of ε-caprolactone monomer initiated with catalysts. It is well-known that ROP of ε-caprolactone occurs via coordination-insertion mechanism with metal alkoxide initiators. A variety of metal alkoxides [4–15] such Al, Sn, Ti, Zn, Sc and Y have been reported for ROP ε-caprolactone. Among them, Ti (IV) alkoxides are considered as one of the most effective initiators capable of producing PCL with both a high and controlled molecular weight, due to its vacant d orbitals that can react as coordination initiators [16]. The ROP of PCL with Ti (IV) alkoxides was described by a coordination-insertion mechanism with two important steps of reaction as illustrated in Fig. 1. Initially, the Ti (IV) alkoxide coordinates with the ε-caprolactone monomer and then the oxygen of the alkoxide group attacks the initiator at the carbonyl carbon of the monomer leading to the cleave of ε-caprolactone ring by acyloxyxid bond breaking.

Experimental studies [7,10,17–20] on ROP of ε-caprolactone initiated with Ti (IV) alkoxides have been reported. Cayuela and co-workers [7] studied the ROP of ε-caprolactone using titanium n-propoxide (Ti(O-n-Pr)_4) and titanium phenoxide (Ti(OPh)_4). The kinetic of polymerization with Ti(O-n-Pr)_4 was found to be faster than Ti(OPh)_4. The PCL produced with co-initiator between 2-allyloxyxethanol and titanium tetraisopropoxide was reported by Xia and co-workers [17] as new catalysts, however its performance was limited, with high transesterification reaction during the polymerization process. Li and team [18] studied the Ti[O(CH_2)_4COCH_3](O-n-Pr)_4 initiated polymerization of ε-caprolactone and they reported that the four alkoxide arms in Ti[O(CH_2)_4COCH_3](O-n-Pr)_4 shared a similar activity in the initiation of ROP. The activation energy of polymerization was 106 kJ/mol. Zeng and co-workers [19] studied three types of the titanium alkoxide catalysts, titanium dichlorodiisoproproxide (TiCl_2(OiPr)_2), titanium chlorotriisopropoxide (TiCl(OiPr)_3) and titanium tetraisoproproxide (Ti(OiPr)_4). They found that the polymerization rate increased with

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the number of OiPr in the initiators. The initiating sites of TiCl₂(OiPr)₂, TiCl(OiPr)₃, and Ti(OiPr)₄ measured by nuclear magnetic resonance was 1.9, 2.6 and 3.8, respectively. From the value of determined activation titanium alkoxides are the most highly efficient and active in the polymerization.

Recently, Meelua and co-workers [10] studied the isoconver-sional kinetic analysis of ROP of ε-caprolactone with Ti (IV) alkox-ides as initiators. Efficiency sequence of these initiators was Ti (IV) n-propoxide > Ti (IV) n-butoxide ≈ Ti (IV) 2-ethylhexoxide > Ti (IV) t-butoxide. The ROP of ε-caprolactone initiated with Ti (IV) n-propoxide had the lowest activation energy. Furthermore, they compared four metal t-butoxide such as Al, Sn, Li and Ti t-butoxides. In results, the Ti (IV) t-butoxide exhibited more covalent bonding and more solubility than Sn (IV) t-butoxide. Its effectiveness as a coordination–insertion initiator was related to the interatomic distance of the metal–oxygen bond [13].

From literature review above on ROP of ε-caprolactone with different Ti (IV) alkoxides, the effectiveness of initiator was experimentally investigated. However, these experimental studies could not provide sufficiently information for the short-life chemical species such as intermediates and transition state, the details of which form a very important criterion for evaluating the performance of initiators. The theoretical simulations can serve as a powerful tool to clarify the information mechanisms of the ROP processes of cyclic esters [8,9,14,21]. Understanding of this type of reaction mechanism is very important for designing more effective initiators for the ROP of ε-caprolactone or other cyclic esters. In this study, the ROP of ε-caprolactone using Ti (IV) alkoxides with different alkoxyl groups was investigated using DFT calculations. The effect of alkyl groups on the reactivity of initiators was studied using the information obtained the calculations. The computed parameters such as activation energies were compared with available experimental data.

2. Computational details

The ROP mechanism of ε-caprolactone using four types of Ti (IV) alkoxide as initiators was modeled. The DFT calculations [22,23] at B3LYP hybrid functional [24,25] with LANL2DZ basis set [24,25] were applied. The high level adiabatic mapping calculation of B3LYP/LANL2DZ was performed by QoMMMa program [26]. This program is a code linking between Gaussian03 [27] as for quantum mechanics (QM) and Tinker [28] as for molecular mechanics (MM) calculations. The atoms of ε-caprolactone and initiators were treated as the QM part. A methane molecule was incorporated as the MM part and accounted into the system to run the QoMMMa code. The MM part was assigned and treated based on the CHARMM27 parameter set [29]. However, the MM part has very weak interaction with the other part, only the QM part was considered [11] for overall energy comparison. The coordination–insertion mechanism of ε-caprolactone with Ti (IV) alkoxide is depicted in Fig. 1. The first step of ROP involves bond forming between Ti20 of the initiator and O17 carbonyl of the ε-caprolactone, bond forming between O23 of the initiator and C6 carbonyl of the ε-caprolactone, and bond breaking of the O23 A Ti20 bond. The second step describes bond breaking [(Ti20 A O17) + (C6 A O18)] – bond forming (Ti20 A O18). The calculation begins with reactant at RC1 = 3.9 Å and decreases the value until reaching 0.7 Å. Next,
the RC2 was calculated from $-0.7$ Å to 3.1 Å. A full optimization at B3LYP/LANL2DZ level was applied at each point along the reaction coordinates of RC1 and RC2. In order to constrain these reaction coordinates, a harmonic force constant for adiabatic mapping of 1000 kcal mol$^{-1}$ Å$^{-2}$ was applied.

Four of the different Ti (IV) alkoxide initiators used in this study are Ti (IV) n-propoxide, Ti (IV) n-butoxide, Ti (IV) 2-ethylhexoxide and Ti (IV) t-butoxide as displayed in Fig. 2.

3. Result and discussion

3.1. Energetic aspects of the ROP mechanism

There are two main steps and five species in ROP mechanism of $\varepsilon$-caprolactone with Ti (IV) alkoxides namely reactant, the first transition state (TS1), intermediate (INT), the second transition state (TS2) and product which are shown in Fig. 1. TS1 and TS2 demonstrate five-coordinated structures at Ti (IV) alkoxide center corresponding to tin (IV) coordination [30]. The chemical structure for each initiator has different steric hindrance as a result of the different R group. Ti (IV) n-propoxide has a three carbon linear chain which is the shortest chain length, Ti (IV) n-butoxide has a four carbon linear chain and Ti (IV) 2-ethylhexoxide has ethyl group on the six carbon linear chain, which is the longest chain length in this initiator set. The long chain length of Ti (IV) 2-ethylhexoxide would make it more difficult to interact with the monomer. The Ti (IV) t-butoxide has the same number of carbon atom as Ti (IV) n-butoxide but a different isomer (tertiary) with the highest steric hindrance in this initiator set.

The summarized potential energy profiles of two reaction steps are given in Table 1 and plotted in Fig. 3. The first step is found to be the rate-determining step in all initiators. As clearly seen in Fig. 3 (left), Ti (IV) n-propoxide has the lowest steric hindrance. The potential energy barrier of this initiator in TS1 is 14.22 kcal/mol at RC1 = 1.89 Å. INT is observed at RC1 = $-0.70$ Å, the potential energy is 0.79 kcal/mol. For TS2 in Fig. 3 (right), the ring of $\varepsilon$-caprolactone is open with the potential energy barrier of 8.24 kcal/mol at RC2 = 1.89 Å. For Ti (IV) n-butoxide, the first step at RC1 = 1.90 Å has 15.58 kcal/mol of the potential energy barrier. The potential energy of INT is 2.12 kcal/mol. For the second step at RC2 = 2.10 Å, the potential energy barrier is 8.68 kcal/mol. For the reaction of Ti (IV) 2-ethylhexoxide, the potential energy required for TS1 and INT formations are 22.82 and 14.89 kcal/mol, respectively. The steric hindrance of this longest chain of R-group in this initiator causes a high energy requirement for TS2 formation of 22.53 kcal/mol at RC2 = 0.69 Å. The last initiator, Ti (IV) t-butoxide with highest steric hindrances, has potential energies for TS1 (at RC1 = 1.11 Å), INT (at RC1 = $-0.70$ Å) and TS2 (RC2 = 2.29 Å) of 28.47, 19.48 and 22.93 kcal/mol, respectively.

3.2. Comparison of initiators

In order to compare the steric hindrance of the R-group of Ti (IV) alkoxide initiators on the ROP of $\varepsilon$-caprolactone, the potential energy of each reaction state as shown in Table 1 is considered separately. The potential energies of TS1s for Ti (IV) n-propoxide, Ti (IV) n-butoxide, Ti (IV) 2-ethylhexoxide and Ti (IV) t-butoxide are 14.22, 15.58, 22.82 and 28.47 kcal/mol, respectively. From the results of TS1 formation, the potential energy barrier significantly increases with steric hindrance both from the long chain length and bulky group. The Ti (IV) n-propoxide has the lowest potential energy barrier and Ti (IV) t-butoxide has the highest potential energy barrier in this set of initiators. Therefore the longer chain length and more bulky group of the initiators have a strong effect on TS1 formation in terms of blocking the initiator to approach the $\varepsilon$-caprolactone resulting in the lower reactivity.
For INTs, the energy of Ti (IV) \(n\)-propoxide, Ti (IV) \(n\)-butoxide, Ti (IV) 2-ethylhexoxide and Ti (IV) \(t\)-butoxide are 0.79, 2.12, 14.89 and 19.48 kcal/mol, respectively. The Ti (IV) \(n\)-propoxide has the lowest potential energy which is most stable intermediate than the others while Ti (IV) 2-ethylhexoxide and Ti (IV) \(t\)-butoxide have unstable INTs.

The potential energy barrier of TS2s, for Ti (IV) \(n\)-propoxide, Ti (IV) \(n\)-butoxide, Ti (IV) 2-ethylhexoxide and Ti (IV) \(t\)-butoxide are 8.24, 8.68, 22.53, 22.93 kcal/mol, respectively. It is obviously seen that the longer linear chain length of R-groups (Ti (IV) \(n\)-propoxide and Ti (IV) 2-ethylhexoxide) has a strong effect on potential energy barriers (8.44 and 22.53 kcal/mol). Also the branches R-groups (Ti (IV) \(n\)-butoxide and Ti (IV) \(t\)-butoxide) have significantly role on the potential energy barrier (8.68 and 22.93 kcal/mol). The longer chain and more bulky group clearly reduce the ability of ring-cleavage prior to forming the polymer product.

### 3.3. Charge analysis

The change of Mulliken charge during reaction was analyzed for the first and the second steps of \(e\)-caprolactone in the ROP. The result for Ti (IV) \(n\)-propoxide is shown in Fig. 4 as a representative of this set of initiators and the results for the other initiators are given in Figs. S1–S3 of the Electronic Supplementary Material.

As seen in Fig. 4, the Mulliken charges of C6 and Ti20 atoms change slightly in both steps of the reaction. The first step of the Mulliken charge of the O23 atom increases from 0.59 to 0.29 e, while the Mulliken charge of the O17 atom decreases from 0.11 to 1.39 e.
−0.27 to −0.63 e. For the second step, the Mulliken charge of the O17 increases from −0.61 to −0.34 e, while the Mulliken charge of the O18 atom decreases from −0.32 to −0.62 e. The Mulliken charge of this result indicates that the oxygen atom has bonded to titanium atom by a more negative charge than the others in the system. The Ti20 atom has Mulliken charge about 1.20 e. This positive charge is an electrophilic atom which is good for nucleophilic oxygen attacking at the first step of the reaction. The C6 atom has Mulliken positive charge about 0.45 e which is also good for negative O23 atom attacking. From the Mulliken charge analysis, the electrons are delocalized from the O23 atom to the O17 atom in the first step of the reaction. In the second step, the electrons are delocalized from the O17 atom to the O18 atom. This charge analysis result of Ti (IV) alkoxide is corresponds to tin (IV) alkoxide which was also reported in other work [11].

A comparison between the calculated potential energy barriers and the activation energy from experimental work [10] is given in Table 2. The trend of energies of the calculation results agrees nicely with the experimental results. Ti (IV) n-propoxide has the lowest energy barrier and Ti (IV) t-butoxide has the highest energy barrier for both results. The activation energy of Ti (IV) n-butoxide and Ti (IV) 2-ethylhexoxide in the experimental results are within the same range, but the potential energy barrier from calculated results of Ti (IV) n-butoxide is slightly lower than the potential energy barrier of Ti (IV) 2-ethylhexoxide due to the steric hindrance of the molecules which increases the potential energy barrier of the system. These make the calculated results slightly different to experimental results. The computed potential energy barrier in the Ti (IV) n-butoxide is in the experimental range while such energy for the remaining initiators is higher than the experimental activation energy. This could be due to the computed potential energy barrier was calculated in gas phase while the experimental activation energy was evaluated in solution or condensed phase which has other properties such as solubility of the initiator in solution affecting the activation energy barrier. That is an initiator with higher solubility in solution will give lower activation energy barrier due to the fact that the monomer can easily access reaction site on the initiator. However, the calculated results and the experimental results are comparable and in good agreement.

4. Conclusions

The ROP mechanism of ε-caprolactone using Ti (IV) alkoxide initiators was simulated using DFT calculations. Four initiators were tested; Ti (IV) n-propoxide, Ti (IV) n-butoxide, Ti (IV) 2-ethylhexoxide and Ti (IV) t-butoxide. The mechanism consists of two main steps (two transition states formation) and five species along the reaction coordinates. The rate limiting step is attributed to the first transition state formation. Two transition states have five-coordinate structures which are found in all reactions of the initiators. The calculated results show that the Ti (IV) n-propoxide has the lowest potential energy barrier in this set of initiator because it has the lowest steric hindrance and Ti (IV) t-butoxide has the highest potential energy due to the most bulky group. The potential energy barrier of the reaction using Ti (IV) n-butoxide is close to that of Ti (IV) n-propoxide. The potential energy barrier of Ti (IV) 2-ethylhexoxide is lower than that using Ti (IV) t-butoxide. The longer chain length and bulkier group of the initiators have a strong effect on TS1 and TS2 formations in terms of blocking the initiator to approach the ε-caprolactone and the cleavage of ε-caprolactone ring, respectively resulting in the lower reactivity in the initiator. According to the results, Ti (IV) n-propoxide is the best initiator in this set. Moreover, the energy of calculated results are in good agreement with the energy of experimental results.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.comptc.2016.05.017.

References


Table 2

<table>
<thead>
<tr>
<th>Initiators</th>
<th>Calculated potential energy barrier (kcal/mol)</th>
<th>Experimental activation energy (kcal/mol) [10]</th>
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<tr>
<td>Ti (IV) n-propoxide</td>
<td>14.22</td>
<td>9.55–11.22</td>
</tr>
<tr>
<td>Ti (IV) n-butoxide</td>
<td>15.58</td>
<td>12.18–16.00</td>
</tr>
<tr>
<td>Ti (IV) 2-ethylhexoxide</td>
<td>22.82</td>
<td>12.18–16.00</td>
</tr>
<tr>
<td>Ti (IV) t-butoxide</td>
<td>28.47</td>
<td>20.06–25.55</td>
</tr>
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