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N-Heterocyclic Carbene-Catalyzed Ring Opening Polymerization of ε-Caprolactone with and without Alcohol Initiators: Insights from Theory and Experiment

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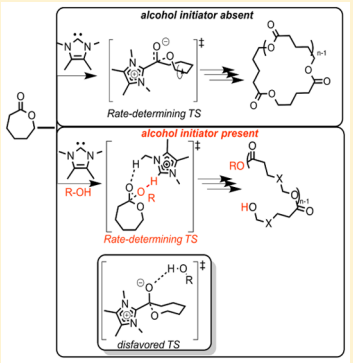
Supporting Information

ABSTRACT: Computational investigations with density functional theory (DFT) have been performed on the N-heterocyclic carbene (NHC) catalyzed ring-opening polymerization of ε-caprolactone in the presence and in the absence of a methanol initiator. Much like the zwitterionic ring opening (ZROP) of δ-valerolactone which was previously reported, calculations predict that the mechanism of the ZROP of caprolactone that occurs without an alcohol present involves a high-barrier step involving ring opening of the zwitterionic tetrahedral intermediate formed after the initial nucleophilic attack of NHC on caprolactone. However, the operative mechanism by which caprolactone is polymerized in the presence of an alcohol initiator does not involve the analogous mechanism involving initial nucleophilic attack by the organocatalytic NHC. Instead, the NHC activates the alcohol through hydrogen bonding and promotes nucleophilic attack and the subsequent ring-opening steps that occur during polymerization. The largest free energy barrier for the hydrogen-bonding mechanism in alcohol involves nucleophilic attack, while that for both ZROP processes involves ring opening of the initially formed zwitterionic tetrahedral intermediate. The DFT calculations predict that the rate of polymerization in the presence of alcohol is faster than the reaction performed without an alcohol initiator; this prediction has been validated by experimental kinetic studies.



INTRODUCTION

Organocatalyzed ring-opening polymerization (ROP) has become a versatile strategy for polymer synthesis during the past decade.[1−4] Cyclic monomers such as lactones, lactides, and carbonate esters have been successfully polymerized with alcohol initiators to form a variety of linear polymers. A number of research groups have demonstrated that a wide variety of organocatalysts may be used to promote the ring opening of cyclic monomers[5] including nucleophilic bases such as DMAP,[6] N-heterocyclic carbenes (NHCs),[7−21] TBD,[22−30] DBU,[14,23,31,32] phosphazenes,[33,34] and hydrogen-bond donors such as fluorinated diols,[35] thioureas, and sulfonamides,[36,37] as well as catalysts formed by acid/base conjugates such as benzoic acid/DBU.[31,38,39] Recent reports have also demonstrated that bifunctional organic acids catalyze ring-opening polymerizations.[40−49,39,50−52]

One of the more noteworthy developments in recent years has been the discovery that cyclic polymers may be formed by the exclusion of the alcohol reagent from the reaction in a process known as zwitterionic ring-opening polymerization (ZROP).[53−55] Nucleophiles such as TBD, DBU,[32] and NHCs[16,56−58] have been used to catalyze the ZROP of lactones,[21,56,57] lactides[16,58] and other cyclic monomers[59,60] to form cyclic polymers. Cyclic polymers are desirable targets since the cyclic architecture may bestow physical properties that are different from their linear analogues.[61−64]

Two types of mechanisms have customarily been invoked for the ring opening of cyclic monomers with alcohol initiators catalyzed by organic nucleophiles/bases.[3,65] A nucleophilic mechanism involves attack of the nucleophile on the carbonyl group of the lactone to form a zwitterionic tetrahedral intermediate (Scheme 1b(i)). This tetrahedral species then ring opens to form a zwitterionic intermediate. These initial steps are common to reactions initiated by alcohol as well as those in which the initiator is absent (i.e., ZROP, Scheme 1a). Propagation follows initiation in both cases, but the reactions differ in their chain-termination step. If present, the alcohol attacks the base-bound ring-opened zwitterionic oligomer followed by catalyst release (Scheme 1b(i)). However, in the absence of an alcohol, the ring-opened zwitterionic oligomer can cyclize to liberate the nucleophilic catalyst and a cyclic polymer (Scheme 1a).

Alternatively, for reactions carried out in the presence of an alcohol initiator, the nucleophile can act as a general base by

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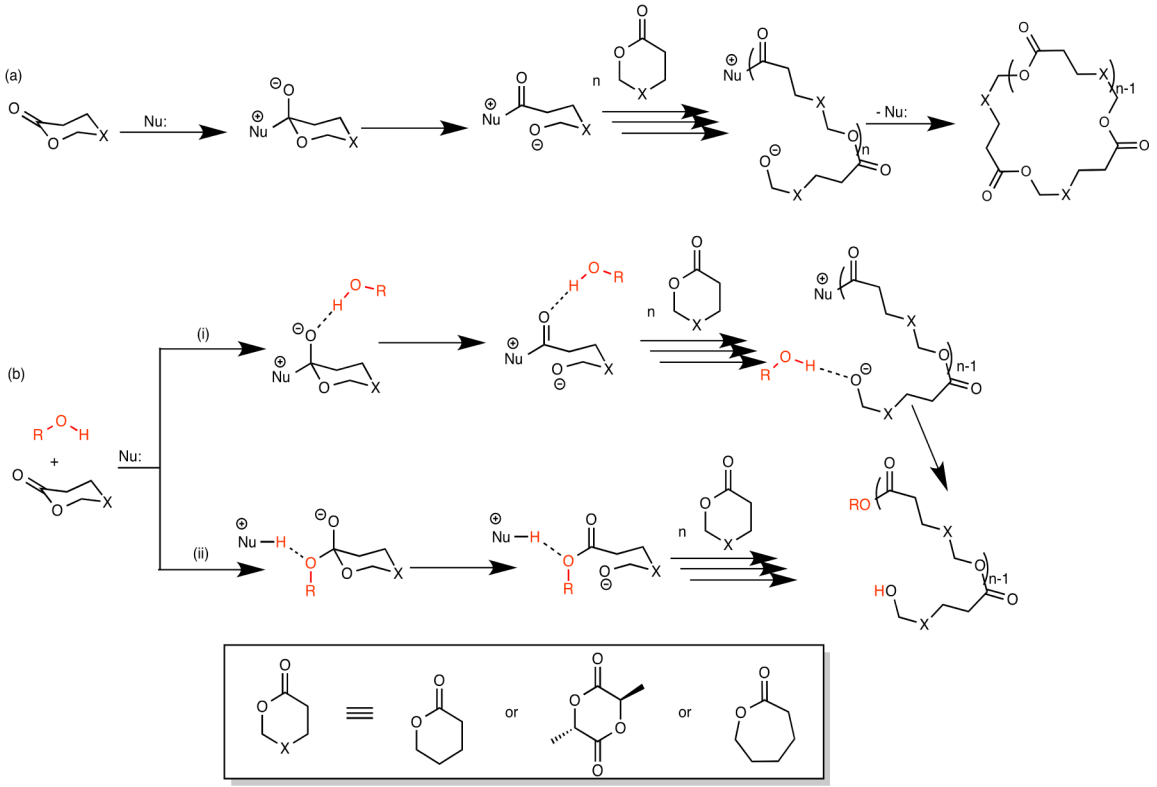
J. Phys. Chem. B XXXX, XXX, XXX−XXX

Scheme 1. Base-Catalyzed (a) Zwitterionic Ring-Opening Polymerization (ZROP) of Lactones and (b(i)) Nucleophilic and (b(ii)) Hydrogen-Bonding Mechanisms for the Ring-Opening Polymerization of Lactones in the Presence of Alcohol Initiator



hydrogen bonding to the alcohol and activating it for nucleophilic attack on the carbonyl group of the lactone (Scheme 1b(ii)). Bifunctional bases such as the guanidine TBD activate both the alcohol and the carbonyl group at the same time through hydrogen bonding.[65,66] In addition, these bifunctional organocatalytic bases facilitate ring opening and product formation by forming hydrogen bonds with the tetrahedral intermediate.

Computational studies performed on the mechanisms of TBD-catalyzed ROPs indicate that the hydrogen-bonding mechanism is favored over that in which the base acts as a nucleophile.[65,66] Pyridine-catalyzed ROPs of cyclic monomers have also been investigated computationally by several groups. Bonduelle and co-workers have determined that the hydrogen-bonding mechanism is operative in the DMAP-catalyzed ROP of lactides.[67] Interestingly, the Zipse group has concluded that the related DMAP-catalyzed esterification reactions of alcohols by acyclic anhydrides follow a nucleophilic mechanism.[68−70]

NHCs have been extensively used in both ROP with alcohol initiators and in ZROP in which alcohols are not present. Whether NHCs activate through the hydrogen-bonding mechanism or whether initial nucleophilic attack on the cyclic monomer is more favored has not been systematically addressed. Both mechanisms have been proposed for reactions involving NHCs, as they are potent hydrogen-bond acceptors and stronger bases than TBD, MTBD, or DBU.[71] Experiments have shown that NHCs form hydrogen-bonded adducts with alcohols[72] that may play a key role in ROP.[20] To illustrate, NHCs have been shown to be effective catalysts for the polymerization of ethylene oxide with ethylene glycol,[73,74] presumably via formation of hydrogen-bonded NHC−alcohol adducts.

Computational studies have not been performed on the NHC-catalyzed ROP of cyclic monomers in alcohol, but Lai and co-workers have performed a limited theoretical investigation of NHC-catalyzed transesterification reactions of acyclic esters with alcohols.[75] Transition states were found for the nucleophilic attack of NHC-bound alcohols on esters, but the barriers for these transformations were only compared to energies of the tetrahedral intermediates formed by the nucleophilic attack of the NHC on the ester. The authors concluded that the hydrogen-bonding mechanism is more favorable than the nucleophilic mechanism due to the fact that the barriers are lower than the energies of the computed tetrahedral intermediates.

For the ZROP of cyclic monomers without an alcohol initiator, nucleophilic attack by the NHC on the lactone and by subsequent nucleophilic attack of the ring-opened alkoxides on cyclic monomers is a plausible mechanism.[16,32,55−60] We have published a computational study on the ring opening and subsequent oligomerization of valerolactone with the NHC, Me_4IMC, and showed that the step possessing the largest barrier involves the ring opening of the zwitterionic tetrahedral complex formed by the nucleophilic attack of Me_4IMC on δ-valerolactone.[76] This is due to the fact that ring opening causes a partial positive charge to develop on the carbon attached to the imidazolium ring (previously belonging to the NHC organocatalyst) which already bears a delocalized positive charge. All of the barriers thereafter, even those involving ring opening of valerolactone rings that are attached to oxygen atoms, are much smaller and almost equal. These computed results were consistent with kinetic studies.

While a number of computational studies have been performed on reactions catalyzed by TBD[65,66] and

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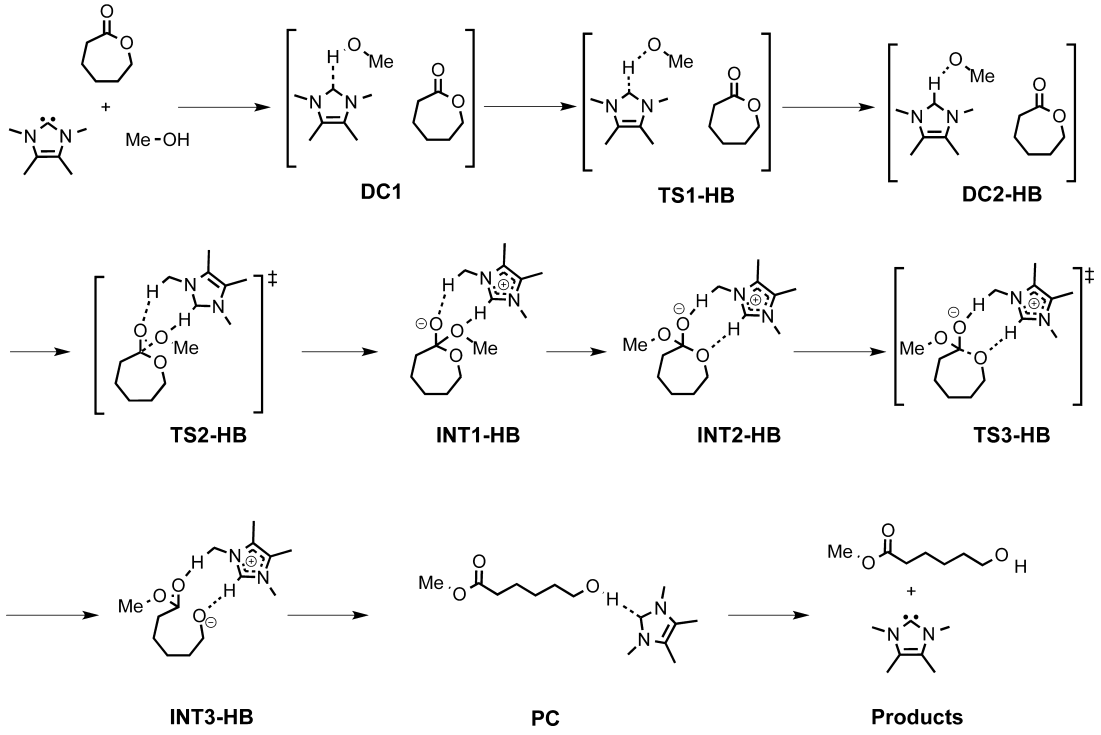
J. Phys. Chem. B XXXX, XXX, XXX−XXX

Scheme 2. Computed Stationary Points for the Hydrogen-Bonding Mechanism in the Me_4IMC-Catalyzed Ring Opening of Caprolactone in the Presence of Methanol



DMAP,[67−70] reactions catalyzed by NHCs have not been subjected to a rigorous theoretical treatment. Herein we report detailed computational studies on two types of ring-opening polymerizations of caprolactone catalyzed by Me_4IMC: the first done in the presence of methanol and the second involving ZROP in the absence of an alcohol initiator. Through these investigations we have determined the mechanism involved in the ROP of caprolactone with an alcohol. The mechanism of the ZROP of caprolactone in the absence of alcohol has also been compared with the earlier study involving valerolactone. Finally, reactions done in the presence and absence of an alcohol initiator have been validated experimentally.

COMPUTATIONAL METHODS

All calculations were performed with the dispersion-corrected[77] B3LYP[78−81] (B3LYP-D3) density functional theory (DFT) method as implemented in the GAMESS-US suite of computational packages. Geometry optimizations were performed with the 6-311+G(2d,p)[82] basis set followed by single point energy calculations with the aug-cc-pVTZ[83,84] basis set. A continuum dielectric with the IEF-cPCM[85−87] method was utilized to represent reaction conditions in implicit THF solvent (ε = 7.58 at 298 K). Reported energies are free energies (kcal/mol). Neither translational nor rotational corrections to the free energy at 298 K were used, and instead only vibrational free energy corrections to the electronic energy at 298 K were included following recommendations for molecules optimized in implicit solvent.[88] The rigid rotor harmonic oscillator approximation approach (RRHO) developed by Grimme was used to replace the vibrational entropies for modes of stationary points with frequencies below 100 cm^{-1} to correct for the breakdown of the harmonic oscillator model for free energies of low-frequency vibrational modes.[89] Normal modes of all structures were examined to verify that equilibrium structures possess no imaginary frequencies and that one imaginary frequency corresponding to bond formation or bond breaking was obtained for transition state structures. Intrinsic reaction coordinate (IRC) calculations were also performed to verify that transition states are connected to reactant complexes and intermediates on the potential energy surfaces of reactions. Partial charges were determined from a fit to the electrostatic potential calculated on four Connolly surfaces at 1.4, 1.6, 1.8, and 2.0 times the van der Waals radii with the B3LYP-D3/aug-cc-pVTZ//6-311G+(2d,p) method. These charges were constrained to reproduce the dipole moment of the molecule.[90]

RESULTS AND DISCUSSION

Hydrogen-Bonding vs Nucleophilic Mechanism with an Alcohol Initiator. Structures arising from hydrogen-bonding and nucleophilic mechanisms for the ROP of caprolactone with methanol organocatalyzed by 1,3,4,5-tetramethylimidazol-2-ylidene (Me_4IMC) are shown in Schemes 2 and 3, respectively. The free energy reaction profiles of both mechanisms are shown in Figure 1.

The hydrogen-bonding mechanism begins with the formation of a dipole complex, DC1, between caprolactone and the hydrogen-bonded Me_4IMC-methanol complex (see Scheme 2 and Figure 1). This complex, DC1, is the global minimum on the free energy surface for the reaction prior to formation of the product complex, PC. Partial transfer of the proton from the alcohol to the NHC in DC1 occurs in TS1-HB ($C-H_{DC1}$ = 1.8 Å; $C-H_{TS1\text{-}HB}$ = 1.3 Å), leading to the formation of a new dipole complex, DC2-HB ($C-H_{DC2\text{-}HB}$ = 1.6 Å). The free energy barrier for proton transfer is small, only 2 kcal/mol, and the second dipole complex is only about 1 kcal/mol less stable than the first. Thereafter three transformations are responsible for nucleophilic attack by methanol and ring opening of caprolactone. The first involves the NHC-

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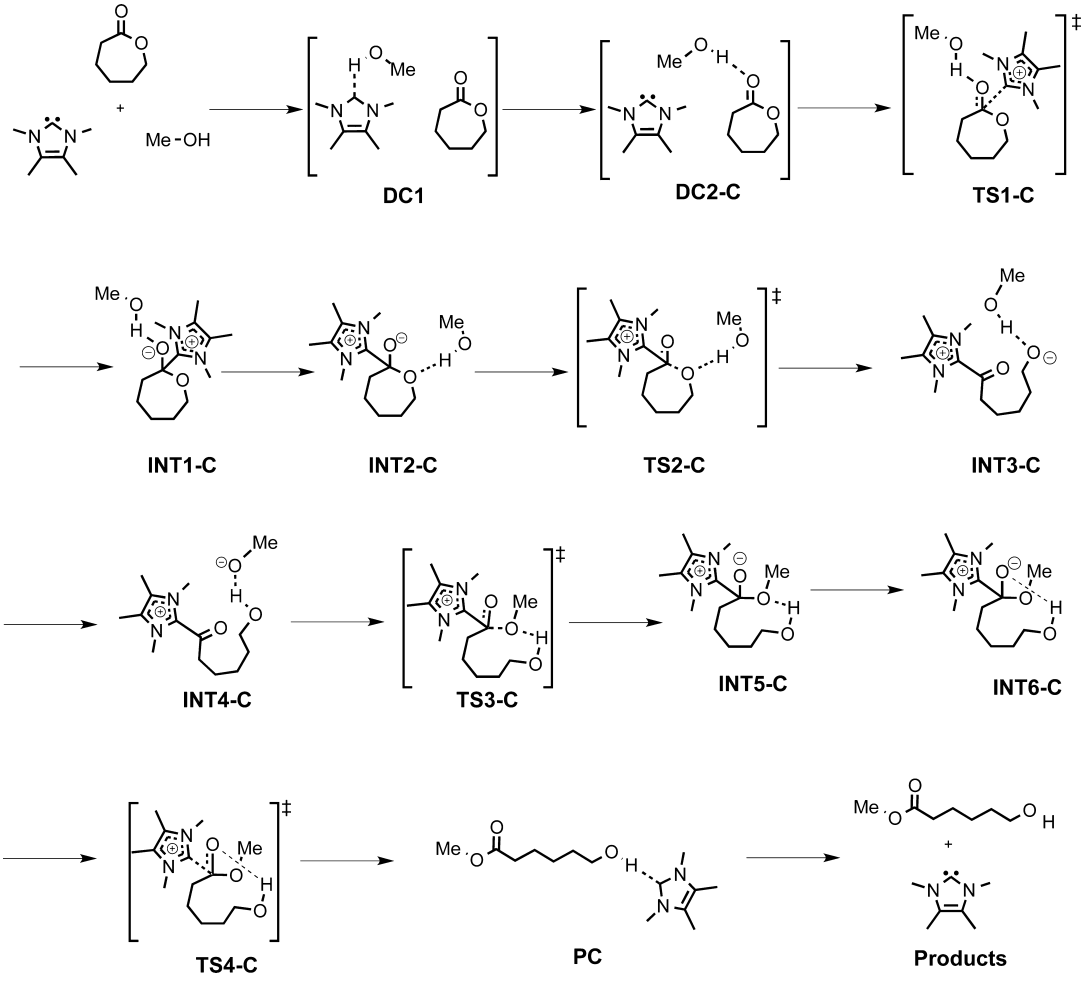
Scheme 3. Computed Stationary Points for the Nucleophilic Mechanism of the Me_4IMC-Catalyzed Ring Opening of Caprolactone in the Presence of Methanol



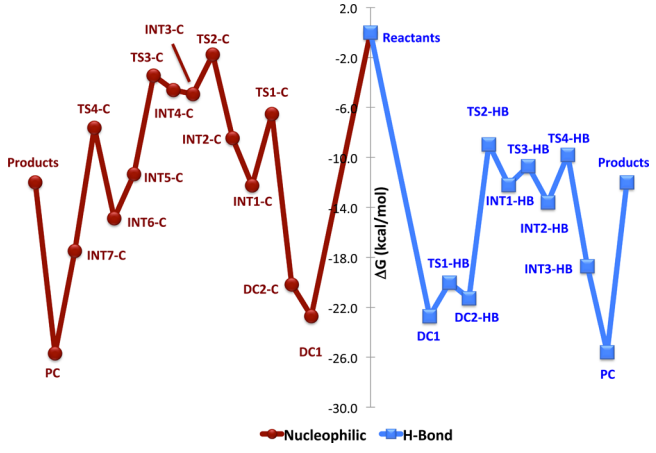


Figure 1. Reaction pathways and free energies (kcal/mol) for the Me_4IMC-catalyzed ring opening of caprolactone in the presence of methanol by the nucleophilic (red) and hydrogen-bonding (blue) mechanisms.

facilitated nucleophilic attack of the methanol on caprolactone in TS2-HB to form INT1-HB. The hydroxylic proton has been fully transferred from methanol to the base during this process. During the second transformation, TS3-HB, the protonated NHC base shifts from being hydrogen-bonded to what was formerly the carbonyl oxygen in INT1-HB to being hydrogen-bonded to the ring oxygen in INT2-HB. Finally, ring opening occurs in TS4-HB during which the NHC catalyst is hydrogen-bonded to the ring oxygen. The free energy barriers for all of these transformations are very similar, ranging from 12 to 14 kcal/mol; the largest barrier corresponds to initial nucleophilic attack by methanol. INT3-HB and PC are formed prior to liberation of the NHC catalyst to form the product. Product formation is predicted to be overall exergonic with respect to separated reactants.

The reactant complex, DC1, is common to both the hydrogen-bonding and nucleophilic pathways (see Scheme 3 and Figure 1). DC2-C, which is 3 kcal/mol less stable than DC1, is formed by the rearrangement of methanol from being hydrogen-bonded to the NHC in DC1, to being hydrogen-bonded to caprolactone. The nucleophilic attack of the NHC on caprolactone occurs in TS1-C forming the tetrahedral zwitterionic intermediate, INT1-C, in which methanol is hydrogen-bonded to an alkoxide which was formerly the carbonyl oxygen. The free energy barrier of this transformation is 16 kcal/mol and the energy of the resulting intermediate is +11 kcal/mol with respect to DC1. Rearrangement of the methanol molecule from being bonded to the alkoxide to being bonded to the ring oxygen results in the formation of INT2-C and is endothermic by about 4 kcal/mol since the alkoxide is no longer stabilized by hydrogen bonding. This rearrangement

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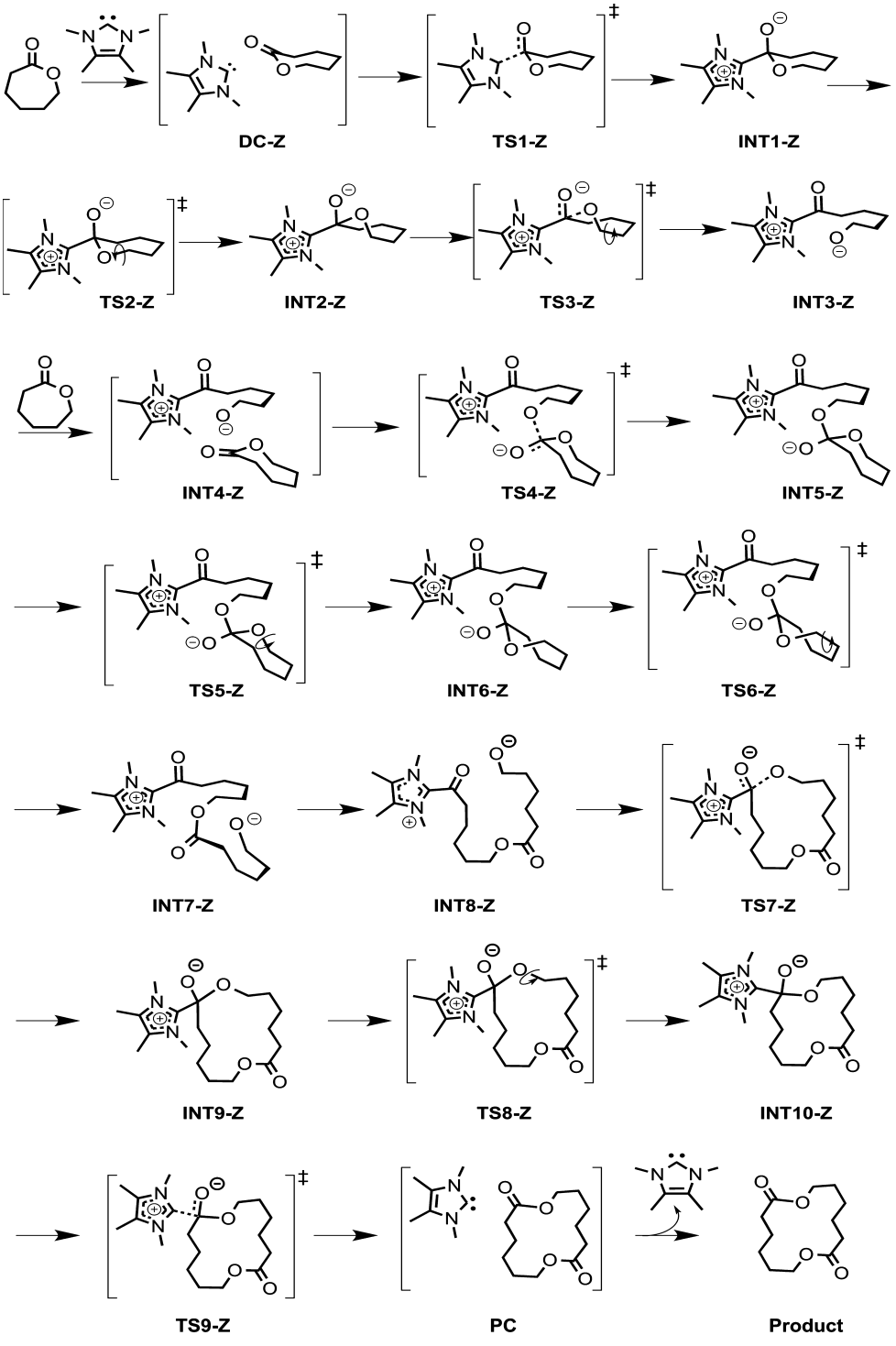
Scheme 4. Computed Stationary Points for the Zwitterionic Ring-Opening Dimerization of Caprolactone by Me_4IMC



facilitates ring opening in TS2-C since methanol forms a hydrogen bond with the ring oxygen and stabilizes the developing negative charge. The predicted free energy barrier for ring opening is 21 kcal/mol. The zwitterionic intermediate formed by ring opening, INT3-C, has a free energy of 18 kcal/mol with respect to DC1.

The formation of ring-opened caprolactone is facilitated by the generation of the H-bond adduct INT4-C formed from methanol and the alkoxide terminus of the zwitterionic intermediate. The resulting transition state for nucleophilic attack of the methoxide on the imidazolium-bound hydroxyl ketone, TS3-C, possesses a free energy barrier of 19 kcal/mol. A hydrogen bond between the terminal hydroxyl group of the imidazolium-bound ketone and the methoxide anion is present in the transition structure for this transformation. Also notable is the fact that the partial bond formed between the oxygen atom belonging to methoxide and the carbonyl carbon is very long at 3.25 Å, presumably due to the Coulombic attraction between the partially positively charged carbonyl carbon, which is adjacent to the imidazolium group, and the negatively charged oxide. The zwitterionic tetrahedral intermediate formed after nucleophilic attack, INT5-C, has a free energy

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J. Phys. Chem. B XXXX, XXX, XXX−XXX

of 11 kcal/mol relative to the energy of DC1. Rearrangement of the hydrocarbon chain in INT5-C results in the formation of INT6-C, which is about 4 kcal/mol more stable than INT5-C due to hydrogen bonding between the terminal hydroxyl group and the alkoxide. The NHC catalyst is then expelled in TS4-C, which possesses a barrier of 15 kcal/mol. INT7-C is directly formed from this transition state, followed by the product complex, PC, in which the NHC catalyst is hydrogen-bonded to the terminal hydroxyl group and then the product.

The highest energy transition state for the nucleophilic mechanism is predicted to be the ring opening of the imidazolium-bound caprolactone ring in TS2-C. The free energy barrier for this transformation is only slightly larger than the transition state for the attack of methoxide on the imidazolium-bound hydroxyl ketone. Overall, these calculations predict that hydrogen-bond activation of the alcohol by the NHC is favored by about 6 kcal/mol over nucleophilic attack by the NHC on the lactone for ROP in the presence of alcohol. This result is similar to previous computational research demonstrating that bases such as TBD catalyze the ROP of cyclic monomers with alcohols via a hydrogen-bonding mechanism.[65,66]

ZROP in the Absence of an Alcohol Initiator. Structures for the NHC-catalyzed ZROP of caprolactone are shown in Scheme 4, and the computed free energies of these structures are shown in Figure 2. The reaction has been modeled from the

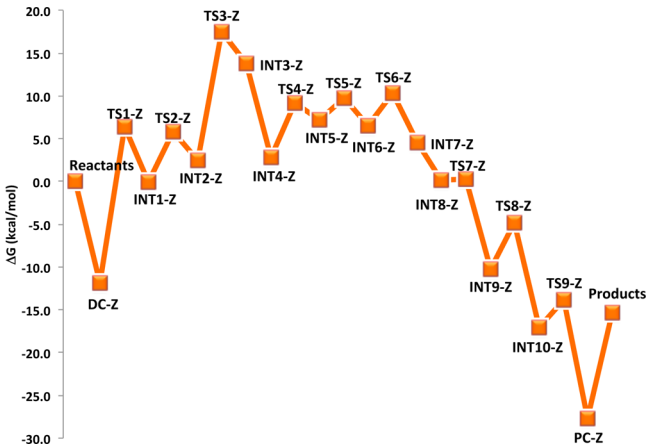

Figure 2. Reaction pathway and free energies (kcal/mol) for the Me_4IMC-catalyzed zwitterionic ring-opening dimerization of caprolactone in the absence of methanol.

completely separated reactants to the formation of the cyclic dimer in order to capture all of the chemical processes involved in the formation of higher order oligomers. These results are largely in agreement with previous findings on the ZROP of valerolactone, which was reported in great detail elsewhere.[76] As such, only the main features of the current study as well as the main differences between the current study involving caprolactone and the previous study involving valerolactone will be highlighted here.

The reactant complex, DC-Z, formed by the interaction of caprolactone with the NHC is stabilized by about 12 kcal/mol in comparison with the completely separated reactants. DC-Z is the local minimum formed prior to the key transition structures. The barrier for initial nucleophilic attack by the NHC on caprolactone in TS1-Z is 18 kcal/mol.

Unexpectedly, a transition structure could not be located for the opening of the caprolactone ring from INT1-Z, the intermediate formed after initial nucleophilic attack. However, a transition structure could be found after conversion of INT1-Z, a Z-ester into INT2-Z, the E-ester, via the transition state TS2-Z. As previously noted in the computational study of the ZROP of valerolactone,[76] the transition structure for the ring opening of a zwitterionic tetrahedral intermediate such as this involves rotation around the dihedral angle formed by O−C−C−C (Figure 3). The reason that the Z-ester does not ring-open can be explained by close examination of the Newman projections of both intermediates. Rotation around the dihedral angle formed by O−C−C−C in the E-ester, INT2-Z, results in the transition structure, TS2-Z, the maximum point on the free energy surface in which the C−O bond is nearly eclipsed with the C−H bond. In contrast, for the C−O bond to eclipse the C−H bond in the transition structure for the Z-ester, INT1-Z, the bond distance between the oxygen atom and the carbonyl carbon at this dihedral angle would have to be >3 Å, too far away for these atoms to interact. So the Z-ester has to be converted into the E-ester before ring opening can occur. The barrier for conversion of the Z-ester to the E-ester is only 6 kcal/mol with respect to INT1-Z (18 kcal/mol with respect to DC-Z).

The predicted barrier for ring opening in TS3-Z is 29 kcal/mol with respect to DC-Z. The ring opens to form INT3-Z, which then forms a complex with another molecule of caprolactone in INT4-Z. Transformations proceeding from INT4-Z to INT8-Z involving the second molecule of caprolactone all have free energy barriers that are lower than those for analogous processes involving the first caprolactone molecule. Ring closure and formation of the NHC-bound cyclic dimer occurs in TS7-Z. An E-ester, INT9-Z, is formed from this transformation, which is converted into the Z-ester, INT10-Z, in TS8-Z. The product complex, PC, is formed by release of the NHC catalyst from this ester in TS9-Z, prior to formation of the product

Overall, these calculations predict that, except for a few key differences, the mechanism for the NHC-catalyzed ZROP of caprolactone is very similar to that of valerolactone,[76] as is the free energy profile. The rate-determining step of the reaction is the ring opening of the first caprolactone molecule occurring after initial nucleophilic attack by the NHC catalyst. All of the subsequent steps possess much lower barriers, and the reaction becomes increasingly exergonic as it progresses. The key difference is that for the reaction involving valerolactone, ring opening proceeds directly from the zwitterionic tetrahedral intermediate to formation of the zwitterionic imidazolium-bound alkoxide ketone, whereas in the reaction involving caprolactone, the E-ester must rearrange to form the Z-ester before ring opening can proceed.

It is instructive to compare mechanisms involving nucleophilic catalysis by the NHC catalyst with the alcohol initiator and in its absence, even though calculations have predicted that the ROP of caprolactone in the presence of an alcohol initiator follows a hydrogen-bonding mechanism in preference to the covalent mechanism. The step possessing the largest barrier is similar in both cases and involves ring opening of the tetrahedral zwitterionic intermediate formed after nucleophilic attack of the NHC on caprolactone. The free energy barrier for ROP with an alcohol present via the nucleophilic mechanism is 21 kcal/mol, which is 8 kcal/mol lower than the corresponding ZROP process in the absence of

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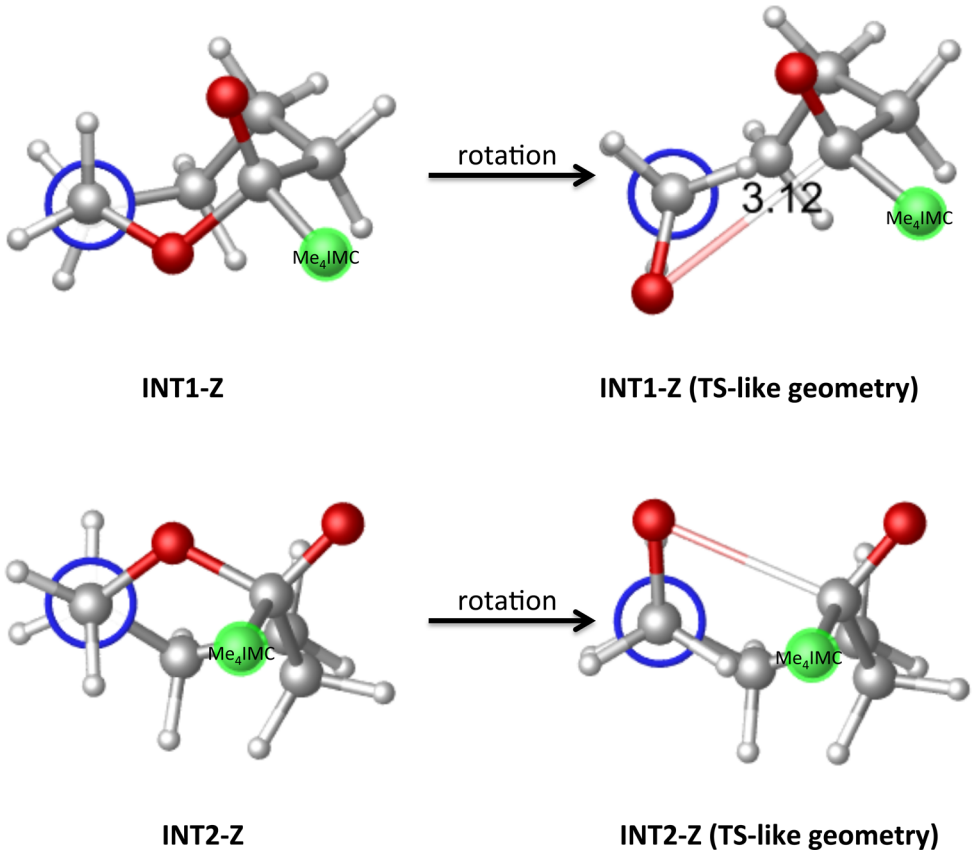

Figure 3. Newman projections for intermediates INT1-Z and INT2-Z and the respective geometries into which each intermediate must be deformed to achieve their ring-opened transition state structures. Distances are shown in angstroms. Atoms belonging to Me_4IMC have been omitted for clarity.

alcohol. Evidently the presence of the alcohol lowers the barrier for ring opening by stabilizing the partial negative charge that develops on the ring oxygen during the transition state. Moreover, while a ring flip is required to convert the Z-ester present in the ring into an E-ester before ring opening during the ZROP process, no such transformation is needed when the alcohol is present. In addition, for the latter case, the ring opens via lengthening of the C−O bond whereas torsional rotation is required to open the ring during ZROP.

Experimental Studies. The computations predict that ring-opening polymerizations of lactones conducted in the presence of alcohol are faster than the ZROP process when alcohol is absent. To corroborate this prediction, we carried out the polymerization of caprolactone in THF under identical conditions with and without added alcohol initiator. The experimental studies were carried out with the isopropyl-substituted carbene 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene rather than the tetramethyl carbene (Me_4IMC); nevertheless these data should provide a reasonable comparison. Conversion was monitored by removing aliquots from the polymerization (Figure 4). ROP in the presence of alcohol was found to be several times faster than in the absence, as predicted from the computational studies (Figure 1 vs Figure 2) consistent with the lower calculated free energy barrier associated with the hydrogen-bonding pathway.

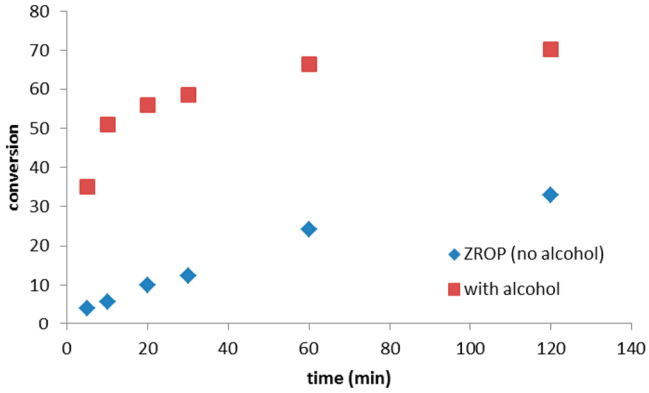

Figure 4. Experimental kinetic data of caprolactone polymerization in the presence and absence of alcohol initiator.

CONCLUSION

The N-heterocyclic carbene-catalyzed ring-opening polymerization of caprolactone in the presence and absence of alcohol initiators has been studied experimentally and computationally. Computational investigations with the B3LYP-D3 density functional theory method have been performed on the Me_4IMC-catalyzed ring opening of caprolactone in the presence of methanol and the Me_4IMC-catalyzed zwitterionic ring-opening dimerization of caprolactone. Two mechanisms have been compared for the reaction performed in the presence of methanol: a mechanism involving initial hydrogen-bonding activation of alcohol by the NHC prior to nucleophilic attack on caprolactone and that involving initial nucleophilic attack by the organocatalytic base. Calculations predict that the hydrogen-bonding mechanism is preferred to the mechanism involving basic nucleophilic attack by about 6 kcal/mol. The

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rate-determining step for the hydrogen-bonding mechanism involves nucleophilic attack by alcohol.

The rate-determining step in the Me_4IMC-catalyzed zwitterionic ring-opening dimerization of caprolactone is the ring opening of the first caprolactone molecule after initial nucleophilic attack by the NHC catalyst. This process has a free energy barrier of 28 kcal/mol, which is larger than the free energy for the rate-determining step in the Me_4IMC-catalyzed ring opening of caprolactone by methanol. These predicted free energy differences have been validated by experiments showing that the rate for ROP in the presence of alcohol is faster than the reaction in the absence of alcohol.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, energies, and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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