

Experimental and Computational Studies on the Mechanism of Zwitterionic Ring-Opening Polymerization of δ -Valerolactone with N-Heterocyclic Carbenes

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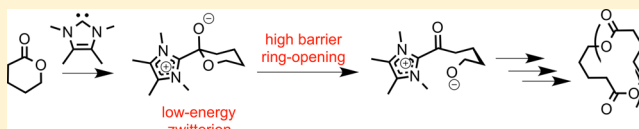
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S Supporting Information

ABSTRACT: Experimental and computational investigations of the zwitterionic ring-opening polymerization (ZROP) of δ -valerolactone (VL) catalyzed by the N-heterocyclic carbenes (NHC) 1,3-diisopropyl-4,5-dimethyl-imidazol-2-ylidene (**1**) and 1,3,4,5-tetramethyl-imidazol-2-ylidene (**2**) were carried out. The ZROP of δ -valerolactone generates cyclic poly-(valerolactone)s whose molecular weights are higher than predicted from $[\text{VL}]_0/[\text{NHC}]_0$. Kinetic studies reveal the rate of polymerization is first order in $[\text{VL}]$ and first order in $[\text{NHC}]$. Density functional theory (DFT) calculations were carried out to elucidate the key steps involved in the ring-opening of δ -valerolactone and its subsequent oligomerization. These studies have established that the initial steps of the mechanism involve nucleophilic attack of the NHC on δ -valerolactone to form a zwitterionic tetrahedral intermediate. DFT calculations indicate that the highest activation barrier of the entire mechanism is associated with the ring-opening of the tetrahedral intermediate formed from the NHC and δ -valerolactone, a result consistent with inefficient initiation to generate reactive zwitterions. The large barrier in this step is due to the fact that ring-opening requires a partial positive charge to develop next to the directly attached NHC moiety which already bears a delocalized positive charge.



INTRODUCTION

Cyclic polymers exhibit intriguing properties^{1–4} but are challenging synthetic targets due to the entropic constraints of coupling the chain ends of large linear molecules. Zwitterionic^{5,6} ring-opening polymerization (ZROP)⁷ of lactones and other strained cyclic monomers^{8,9} with N-heterocyclic carbenes (NHC),^{10–13} amidine¹⁴ (DBU = 1,8-diazabicyclo[5.4.0] undecen-7-ene), or pyridines^{4,15} such as DMAP (4-dimethylaminopyridine) is a versatile strategy for generating cyclic macromolecules. The ZROP of lactide with the aryl-substituted NHC IMes (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) occurs within minutes at room temperature in tetrahydrofuran (THF) or toluene to generate cyclic poly(lactides).^{12,13} In contrast, the ring-opening polymerization of ϵ -caprolactone (CL) or δ -valerolactone (VL) requires the more nucleophilic alkyl-substituted carbenes **1** and **2**.¹⁰ Kinetic and mechanistic studies of the ZROP of lactide with the NHC IMes suggested a nucleophilic monomer-activated mechanism where ring-opening of the lactone generates a zwitterionic intermediate Z_1 which reacts with the lactone monomer to generate larger zwitterions (see Scheme 1). Cyclization of the zwitterions at either the acyl-imidazolium terminus or internal esters of the zwitterion liberates the cyclic polyesters. Kinetic studies of the ZROP of lactide with IMes demonstrated that the formation of the initial zwitterion Z_1 (initiation) was slower than addition of monomer

to growing zwitterions Z_n . Experimental studies indicated that the rate of polymerization as well as the molecular weights and molecular weight distributions of the resulting cyclic polyesters are a complicated function of the rates of initiation, propagation, and cyclization,¹² but the influence of the nucleophile or electrophile on these relative rates is not yet clear.

Theoretical studies have illuminated many of the pathways for acylation reactions catalyzed by nucleophiles; for many of these reactions, acylated nucleophiles analogous to Z_1 have been identified as intermediates.^{16–18} Computational studies of the NHC-catalyzed transesterification reactions¹⁹ or DMAP-catalyzed ring-opening polymerization reactions²⁰ indicated that, in the presence of alcohols, a hydrogen-bonding mechanism was preferred to a nucleophilic mechanism involving zwitterionic intermediates. In the absence of alcohols, a hydrogen-bonding mechanism is precluded, but few theoretical studies have been carried out on ZROP reactions.^{8,14}

Herein we describe the ZROP of δ -valerolactone (VL) with the N-heterocyclic carbene 1,3-diisopropyl-4,5-dimethyl-imida-

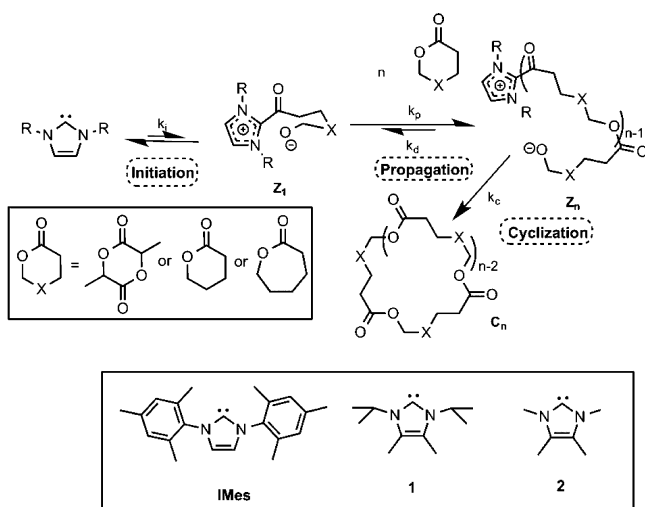
Special Issue: William C. Swope Festschrift

Received: January 7, 2014

Revised: March 24, 2014

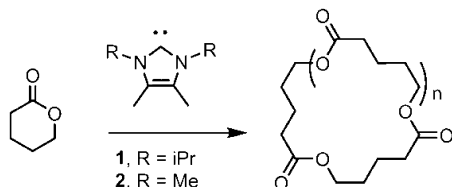
Published: April 4, 2014

Scheme 1. Previously Proposed Mechanism for the Zwitterionic Ring-Opening Polymerization (ZROP) of Lactones¹²



zol-2-ylidene (**1**) and a computational analysis of the initiation, dimerization, and cyclization pathways for the polymerization of δ -valerolactone using the related carbene 1,3,4,5-tetramethylimidazol-2-ylidene (**2**) (Scheme 2).

Scheme 2. Zwitterionic Ring-Opening Polymerization of δ -Valerolactone



RESULTS AND DISCUSSION

The ring-opening polymerization of δ -valerolactone occurs readily in THF at room temperature in the presence of the isopropyl-substituted carbene **1** or the methyl-substituted carbene **2**. With the methyl-substituted carbene **2**, the rates are too fast to monitor conveniently, so a series of kinetic runs were carried out with carbene **1** at a variety of concentrations (Table 1). Aliquots were removed at various time points in the polymerization and analyzed via ¹H NMR and gel permeation

chromatography (GPC) to determine conversion and molecular weight.

In the absence of alcohol initiators, the ring-opening polymerization of VL with carbene **1** is rapid, reaching 70% conversion within 3 min ($[\text{VL}]_0 = 1.0 \text{ M}$, $[\text{NHC}]_0 = 0.01 \text{ M}$). The resulting poly(valerolactone)s (pVL's) are predominantly cyclic,¹⁰ as evidenced by their intrinsic viscosities and the lack of end groups detected by ¹H NMR spectroscopy. The intrinsic viscosities of the pVL's as a function of M_w were analyzed by gel-permeation chromatography with an in-line viscometer and light-scattering detector. The intrinsic viscosities of the pVL's generated by NHC **1** relative to an independently prepared linear pVL were lower ($[\eta]_{\text{cyclic}}/[\eta]_{\text{linear}} = 0.66$), consistent with a cyclic topology.⁶

As observed previously for the ZROP of lactide with NHC IMes,¹² the kinetics and evolution of molecular weight with time for the polymerization of VL with carbene **1** are consistent with a chain-growth polymerization that deviates significantly from living behavior. The molecular weights of the cyclic pVL increase with increasing conversion but are higher than predicted and exhibit no obvious correlation to the ratio of $[\text{VL}]_0/[\text{NHC}]_0$. Under the conditions employed (THF, 25 °C), the molecular weights obtained range between $M_n = 19\,000$ – $39\,000 \text{ Da}$ with polydispersities from $1.23 < M_w/M_n < 1.43$.

The kinetics for the polymerization of VL with **1** differ from that previously observed for the polymerization of lactide with IMes.¹² The dependence of the initial rates on $[\text{NHC}]_0$ and $[\text{VL}]_0$ indicates that the rate is first-order in $[\text{NHC}]$ and $[\text{VL}]$ (see Figures S2–S5, Supporting Information). Nevertheless, the observation that the molecular weights are higher than that predicted on the basis of $[\text{VL}]_0/[\text{NHC}]_0$ suggests that initiation to generate reactive propagating zwitterions is inefficient and slower than propagation. To provide insight on the origin of this behavior, density functional theory (DFT) calculations were carried out to illuminate some of the key intermediates and the barriers for different steps in the ring-opening of δ -valerolactone by carbene **2** and subsequent cyclization to the cyclic dimer.

Shown in Scheme 3 are a series of intermediates and transition states identified by DFT calculations for the ZROP of δ -valerolactone with the tetramethyl-substituted NHC **2**. Calculations were performed on the ring-opening of two equivalents of δ -valerolactone by carbene **2** and cyclization to form the cyclic dimer in order to capture the fundamental steps involved in the initial stages of the ZROP process. The reaction profile and free energies for this process are shown in Scheme 3 and Figure 1.

The calculations reveal the initial formation of a dipole-stabilized reactant complex, DC. Initial C–C bond formation

Table 1. Zwitterionic Ring-Opening Polymerization of VL with NHC **1** at 25 °C in THF

entry	$[\text{VL}]_0 \text{ (M)}$	$[\text{NHC}]_0 \text{ (M)}$	M/I	time (min)	conversion (%)	$M_n^a \text{ (Da)}$	$M_n \text{ (predicted)}$	M_w/M_n^a
1	1.25	0.0025	500	10	29	23 000	14 420	1.27
2	1.00	0.0025	400	10	29	23 000	11 600	1.31
3	0.75	0.0025	300	10	22	19 000	6717	1.28
4	1.25	0.005	250	5	52	22 000	12 998	1.43
5	1.00	0.005	200	5	45	20 000	8984	1.31
6	0.75	0.005	150	5	34	22 000	5123	1.23
7	1.25	0.01	125	3	71	39 000	8875	1.29
8	1.00	0.01	100	3	62	34 000	6218	1.32
9	0.75	0.01	75	3	55	28 000	4110	1.41
10	0.50	0.01	50	3	43	25 000	2169	1.32

^aDetermined by GPC using polystyrene standards.

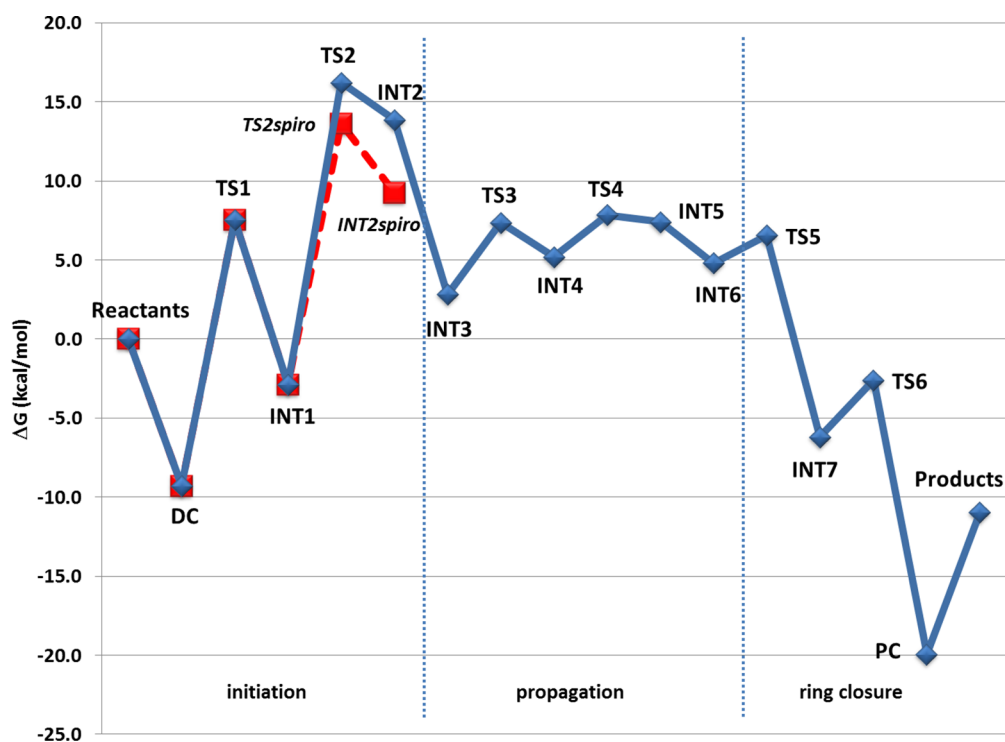
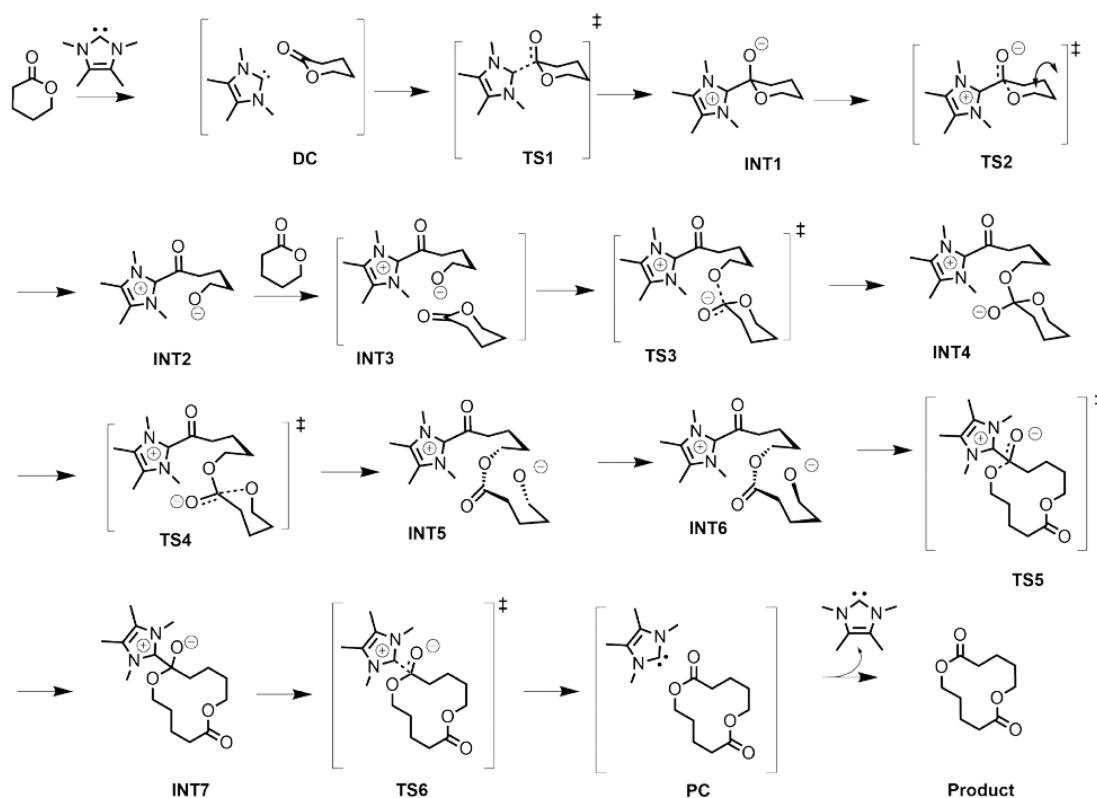
Scheme 3. Computed Mechanism for the Nucleophilic Ring-Opening of δ -Valerolactone with NHC 2 to Generate the Cyclic Dimer

Figure 1. Reaction pathway and free energies, in kcal/mol, for the catalytic dimerization of δ -valerolactone with NHC 2. All energies relative to isolated reactants (2 molecules of δ -valerolactone + NHC 2).²¹

occurs by nucleophilic attack of the carbene 2 on δ -valerolactone to afford INT1, a zwitterionic tetrahedral intermediate. The DFT calculations reveal that tetrahedral intermediate INT1 is significantly lower in energy than INT2, the previously proposed

zwitterionic intermediate Z_1 (Scheme 1). The formation of INT1 from DC proceeds through transition state TS1 with a free energy barrier of 17 kcal/mol. Examination of the geometry for TS1 reveals that a weak hydrogen bond ($d_{H-O} = 2.31$ Å) develops

between a hydrogen atom belonging to one of the methyl groups on the NHC and the carbonyl oxygen of δ -valerolactone (Figure 2a). In transition state TS1, a partial positive charge ($+0.22e$) is

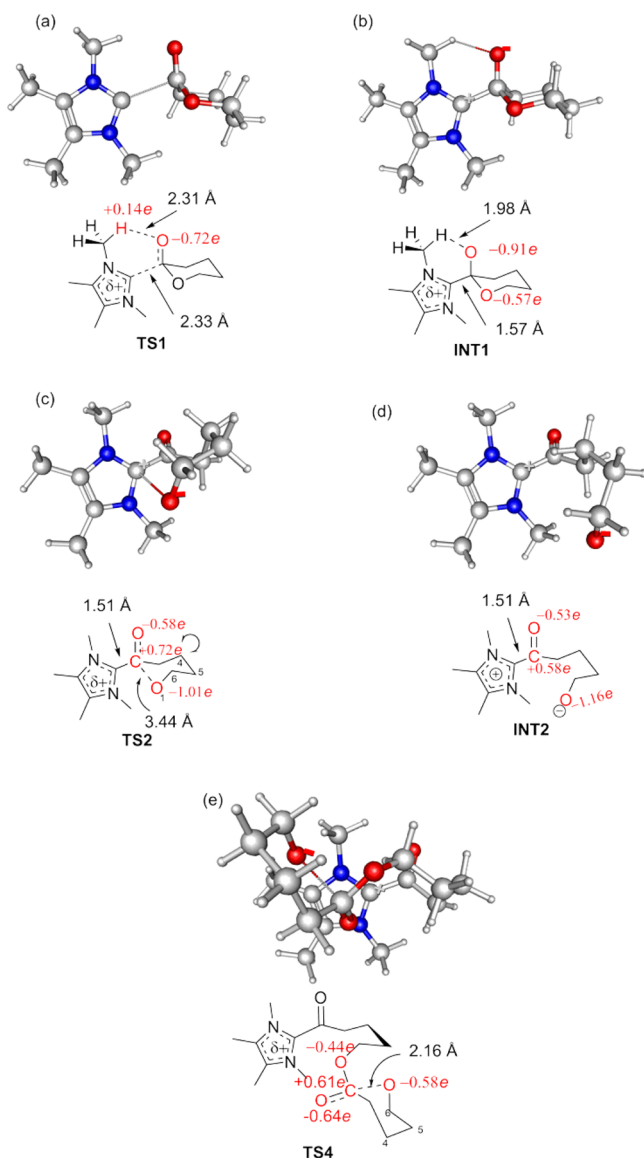


Figure 2. Structures for the (a) transition state for nucleophilic attack by carbene 2 on δ -valerolactone (TS1), (b) resulting intermediate (INT1), (c) transition state for ring-opening of NHC-bound δ -valerolactone (TS2), (d) intermediate (INT2) formed from TS2, and (e) transition state (TS4) for ring-opening of the second δ -valerolactone ring on the path to formation of the cyclic dimer.

delocalized throughout the imidazolium heterocycle with the protons of the *N*-methyl groups also bearing partial positive charges ($+0.14e$). The zwitterionic nature of the tetrahedral intermediate INT1 is evident from the calculated partial charge of $+0.51e$ on the imidazolium ring, $-0.91e$ on the carbonyl oxygen, and $-0.57e$ on the ester oxygen.

Ring-opening of the tetrahedral intermediate INT1 in TS2 is associated with a relatively high activation barrier of 19 kcal/mol (or 26 kcal/mol relative to DC) to afford the zwitterion INT2. In TS2, a partial charge of $+0.71e$ is calculated for the imidazolium ion and $-1.01e$ for the terminal oxygen of the alkoxide leaving group. The transition state for ring-opening in TS2 does not just

involve bond stretching, which is typical for transition states in which bonds are made or broken; instead, as shown in Figure 2c, C–O bond stretching is concomitant with puckering of the δ -valerolactone ring at C-4.

In addition to the zwitterionic intermediate INT2, a neutral spirocyclic intermediate INT2spiro (charge on imidazole is $+0.05e$) was identified in the ring-opening of the tetrahedral intermediate INT1 (Figure 3). Similar spirocyclic intermediates

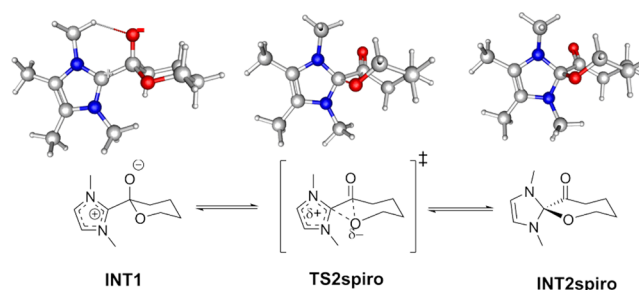


Figure 3. Formation of spirocycle INT2spiro from zwitterionic tetrahedral intermediate INT1.

were previously observed from lactones and saturated NHC¹² and proposed as intermediates in the ZROP of *N*-carboxyanhydrides.⁹ Although the spirocycle INT2spiro is a neutral compound and INT1 is a zwitterionic compound, INT2spiro is predicted to be about 10 kcal/mol less stable than INT1. The larger relative stability of INT1 in comparison to INT2spiro is due to the fact that the imidazolium ring in INT1 is aromatic but this aromaticity is absent in INT2spiro. The formation of INT2spiro from INT1 is calculated to be more facile than formation of the zwitterion INT2, with a barrier (INT1 \rightarrow TS2spiro \rightarrow INT2spiro) of 17 kcal/mol. However, we could identify no low energy pathway for the direct conversion of INT2spiro to the zwitterion INT2; all pathways investigated from INT2spiro resulted in the reformation of INT1. Overall, these calculations predict that INT2spiro forms more quickly than INT2 but this spirocyclic intermediate is predicted to be a dormant species that reverts to INT1 before conversion into INT2. Despite several attempts, we have to date been unsuccessful in attempts to prepare or characterize INT1 spectroscopically.

The zwitterionic intermediate INT2 associates readily with another molecule of δ -valerolactone to generate the dipole-stabilized complex INT3. Nucleophilic attack of the alkoxide of INT3 on the carbon of the carbonyl group of δ -valerolactone in TS3 produces the zwitterionic tetrahedral intermediate INT4.

The ring-opening of the tetrahedral INT4 to the zwitterion INT5 is facile and requires only an additional 2.6 kcal/mol in free energy. This transition state has a much lower barrier than that of the ring-opening of tetrahedral intermediate INT1 to give INT2 (19 kcal/mol). These results indicate that the barrier to ring-opening of these tetrahedral intermediates to open zwitterions depends sensitively on whether a cationic imidazolium heterocycle in TS2 or a neutral open δ -valerolactone moiety in TS4 ($-\text{O}(\text{CH}_2)_4\text{CO}-$, charge is $+0.01e$) is attached to the tetrahedral intermediate. The difference between these transition states is illustrated by a comparison of the charges that develop during the transition state for ring-opening (see Figure 2c and d). Figure 2c shows that, as the first δ -valerolactone ring opens, a partial positive charge of $+0.72e$ needs to develop on the carbonyl carbon atom bound to the imidazolium heterocycle. The barrier

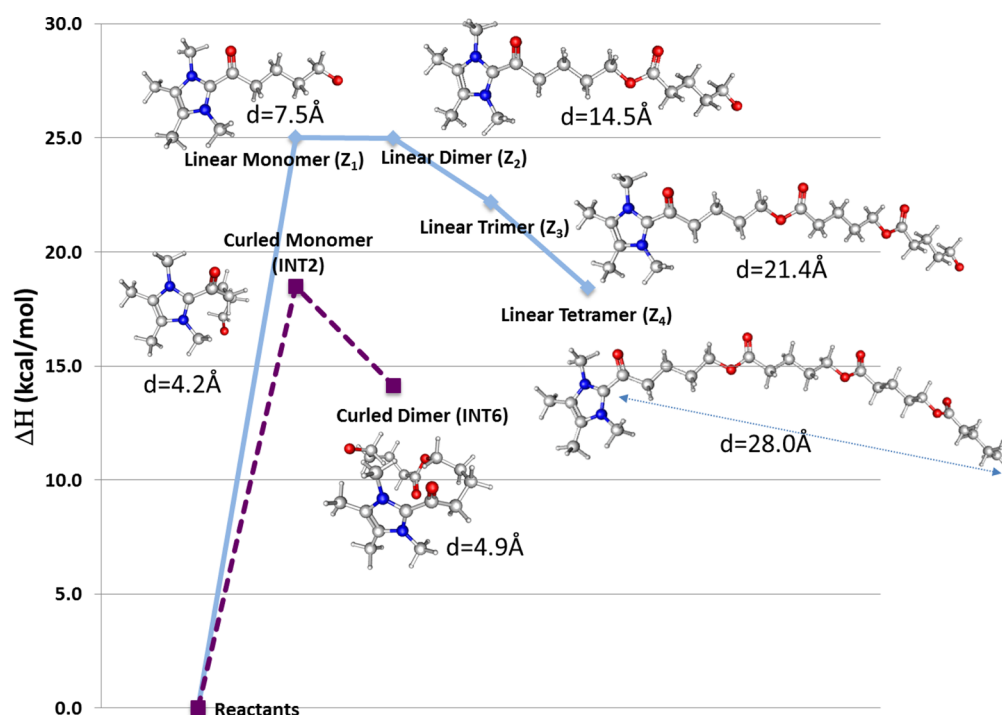


Figure 4. Enthalpies, in kcal/mol, for formation of four linear extended and two curled NHC-bound zwitterions formed from successive ring-opening of δ -valerolactone molecules. Distances, between the carbon atoms of the imidazolium rings and the terminal alkoxide oxygen atoms, d , are shown in Å; enthalpies are with respect to four δ -valerolactone molecules and carbene **2** at infinite separation.

for this process is expected to be high, since the imidazolium heterocycle also bears a partial positive charge (+0.71e). In contrast, in transition state TS4 (Figure 2d), the carbon of the carbonyl group in this tetrahedral intermediate is bound to oxygen and is far (4.0 Å, charge on carbonyl C is +0.61e) from the positively charged imidazolium ion. Note that ring-opening in TS4 involves only C–O bond stretching and not ring-puckering, in contrast with TS2 for which both motions are present.

A number of conformations are accessible for zwitterions incorporating two δ -valerolactones: three that were identified include²² INT6, INT5 (+2.5 kcal/mol relative to INT6), and an extended linear zwitterion (linear Z_2 , +9.0 kcal/mol relative to INT6). The varying energies of these conformations are largely a result of the Coulombic energies associated with the different distances between the imidazolium ion and the terminal alkoxides. For the lowest energy conformer INT6, we could identify a nearby transition state TS5 (less than 2 kcal/mol) for formation of a new tetrahedral intermediate INT7 resulting from nucleophilic attack of the terminal alkoxide at the acyl-imidazolium terminus. This process leads to the formation of the cyclic dimer of δ -valerolactone with release of carbene **2**. TS6, in which the carbene **2** dissociates from INT7 is the transition state for the formation of the product complex, PC, and this process possesses a barrier of ~ 3 kcal/mol.

A significant result derived from the calculated reaction pathway shown in Figure 1 is that the ring-opening of tetrahedral intermediate INT1 in TS2 to form the ring-opened zwitterionic monomer INT2 is calculated to be the step with the highest barrier for the polymerization of δ -valerolactone. This provides important insight on the mechanism of zwitterionic polymerization, particularly for the initial steps leading up to the proposed reactive zwitterionic species INT3 to INT6. As the calculations were carried out only for the catalytic ring-opening of two δ -valerolactones to the cyclic dimer, and do not explicitly

account for the entropic contributions of all of the conformational isomers associated with each of the calculated intermediates,²³ we did not attempt to correlate the calculated barriers directly to the experimental rate of polymerization.²⁴ Nevertheless, the high barrier for the unimolecular ring-opening of INT1 provides one rationale for the low rate of initiation to generate the reactive zwitterions (INT1–INT6). The low barriers associated with the subsequent additions of δ -valerolactone and cyclization to liberate cyclic polyactones would lead to a polymerization mechanism characterized by slow initiation (formation and opening of INT1), rapid propagation, and facile cyclization to liberate cyclic oligomers and polymers. In this situation, the molecular weights would not be expected to correlate with the ratio of $[\text{VL}]_0/[\text{NHC}]_0$, since the concentration of productive zwitterions would depend on the rate of ring-opening of INT1 to INT2.

Another intriguing outcome of the calculations is the prediction that the zwitterionic tetrahedral intermediate INT1 is calculated to be more stable than the ring-opened zwitterion INT2. Tetrahedral zwitterionic intermediates had not been considered as stable resting states in zwitterionic polymerization reactions,⁷ as these species typically break down readily in nucleophilic acylation reactions.^{25,26}

In this study, we have calculated only the initial stages in the ring-opening polymerization of two equivalents of δ -valerolactone and cyclization to the cyclic dimer. These results indicate that the formation of the cyclic dimer is enthalpically favorable from carbene **2** and two δ -valerolactones (see Figure S7 in the Supporting Information) but that the initial stages of the zwitterionic polymerization are associated with a high kinetic barrier in the opening of INT1. The initial stages of the reaction are also thermodynamically unfavorable due to the generation of charged zwitterionic intermediate INT2. Nevertheless, release of the ring-strain of δ -valerolactone results in an enthalpy of

polymerization of ΔH_p of approximately -2.0 to -6.5 kcal/mol,^{23,27} so subsequent additions of VL monomer to zwitterions INT6 and higher would be driven by the progressive release of ring strain energy with each successive addition of δ -valerolactone. The loss of translational entropy of the monomer upon enchainment will incur an entropic penalty; for ring-opening of lactones, this is partially compensated by the increase in conformational degrees of freedom upon ring-opening.²⁶ Estimates for the standard entropy of polymerization of δ -valerolactone range from $\Delta S^\circ = -33^{23}$ to -15 cal/(mol K),²⁷ which at 298 K would correspond to a thermodynamic entropy penalty ($-T\Delta S$) between $+9.9$ and $+4.5$ kcal/mol.

Moreover, the barriers for these subsequent additions of monomers would be expected to be comparable to that of the conversion of INT3 to INT6 (free energy difference of 5 kcal/mol), resulting in a rapid polymerization once a significant concentration of INT3 builds up. Thus, the thermodynamics of the polymerization are likely to become favorable once three or more δ -valerolactones are enchainment.

The degree to which ring-opening and the generation and separation of charge contribute to the thermodynamics is illustrated in a "worst-case scenario" in Figure 4, where the enthalpies of a series of linear zwitterionic intermediates²⁸ are compared to that of the reactants (four VL and carbene **2** at infinite separation). These calculations reveal that generation of a linear zwitterion from carbene **2** and VL is unfavorable by 25 kcal/mol. Addition of successive δ -valerolactones to the extended linear zwitterion Z_1 leads to an additional stabilization as a consequence of the release of strain in the monomer.

The structures in Figure 4 were artificially chosen to be the linear extended zwitterions simply to provide an estimate of the degree to which the separation of charge would influence the thermodynamics of enchainment. The Coulombic attraction of the zwitterionic chain ends will favor conformations in which the charged ends of the zwitterionic intermediates will be closely adjacent to each other. This was assessed by a comparison of the enthalpies of the low energy zwitterions INT2 and INT6 to those of the linear extended zwitterions Z_1 and Z_2 (Figure 4). The fact that the zwitterions INT2 and INT6 are 6.5 and 10.8 kcal/mol more stable than the extended zwitterions Z_1 and Z_2 is a consequence of the shorter distance between the terminal alkoxide anion and the imidazolium cation (4.38 Å vs 7.50 Å for INT2 and Z_1 , respectively, and 4.90 Å vs 14.49 Å for INT6 and Z_2 , respectively).

CONCLUSIONS

Zwitterionic ring-opening polymerization (ZROP) of δ -valerolactone with N-heterocyclic carbenes (NHC) 1,3-diisopropyl-4,5-dimethyl-imidazol-2-ylidene (**1**) and 1,3,4,5-tetramethyl-imidazol-2-ylidene (**2**) occurs readily at room temperature in THF to generate cyclic poly(valerolactone)s. Theoretical studies indicate that nucleophilic attack by the NHC on δ -valerolactone initially produces a zwitterionic tetrahedral intermediate INT1 whose ring-opening to an acyl-imidazolium intermediate INT2 is the critical step for generating reactive zwitterions. Subsequent nucleophilic addition of a δ -valerolactone molecule to the alkoxide of the acyl-imidazolium zwitterion and cyclization of the zwitterion INT6 to the cyclic dimer are calculated to have low barriers.

The ring-opening of the imidazolium tetrahedral intermediate INT1 possesses the largest barrier for the reaction, whereas ring-opening of subsequent alkoxy tetrahedral intermediates possesses low barriers. Calculations indicate that a positively

charged imidazolium group stabilizes the tetrahedral intermediate and leads to a high barrier for elimination of the alkoxide in the formation of the acyl-imidazolium zwitterion. The calculations provide a rationale for the low initiation efficiency and are consistent with a polymerization mechanism that involves slow initiation, fast propagation, and cyclization to liberate cyclic lactones.

The zwitterionic tetrahedral intermediate INT1 also rearranges to a neutral spirocyclic intermediate, but calculations indicated that this intermediate does not lie on the pathway for ring-opening but instead reverts to the tetrahedral intermediate INT1.

EXPERIMENTAL AND COMPUTATIONAL DETAILS

Materials and Methods. All reactions and polymerizations were performed in a drybox or with Schlenk techniques under nitrogen. ^1H nuclear magnetic resonance (NMR) spectra were recorded at room temperature on a 400 MHz spectrometer, with shifts reported in parts per million downfield from tetramethylsilane and referenced to the residual solvent peak. Gel permeation chromatography (GPC) was performed in tetrahydrofuran (THF) at a flow rate of 1.0 mL/min on a Waters chromatograph equipped with four 5 μm Waters columns (300 mm \times 7.7 mm) connected in series. The Viscotek S3580 refractive index detector and Viscotek GPCmax autosampler were employed. The system with a triple detection system (Viscotek, Houston, TX) including a light scattering detector and viscometer was calibrated using monodisperse polystyrene standards (Polymer Laboratories). The right-angle light scattering (RALS) method was used to determine absolute molecular weights of polymers. Correction for any angular dissymmetry factor in the RALS data was performed in the TriSEC software using the viscometer signal. The angular dissymmetry correction is negligible because the polymers studied are relatively small compared to the laser wavelength (610 nm). The polymer solution (ca. 10 mg/mL) was prepared by dissolving the polymer in THF.

δ -Valerolactone was purchased from Sigma-Aldrich and distilled twice over calcium hydride. THF and toluene were distilled from sodium/benzophenone and degassed by three freeze–pump–thaw cycles. 4-Nitrophenol was purchased from Sigma-Aldrich and purified by recrystallization from toluene and followed by sublimation. 1,3-Diisopropyl-4,5-dimethylimidazol-2-ylidene (**1**) was prepared according to the literature procedure.^{29,30}

Representative Procedure for the Preparation of Cyclic δ -Valerolactone with 1,3-Diisopropyl-4,5-dimethylimidazol-2-ylidene. Liquid δ -valerolactone (312 mg, 3.12 mmol) was weighed into a vial in the glovebox and dissolved in THF (2.85 mL). To this solution was added carbene **1** (5.62 mg, 0.031 mmol) dissolved in THF (0.26 mL, from a 0.12 M stock solution) and allowed to stir at room temperature. After 7 min, the reaction was quenched via addition of solid 4-nitrophenol (20 mg, 0.14 mol) and allowed to stir for 30 min. Conversion (65%) was determined by ^1H NMR of the crude sample. The polymer was purified by precipitating twice from methanol and analyzed by GPC. $M_w = 32\,500$ g/mol, PDI = 1.28, $dn/dc = 0.0722$ (RALS).

Computational Methodology. All calculations were performed with the GAMESS-US^{31–33} suite of packages using the dispersion-corrected³⁴ B3LYP^{35–38} (B3LYP-D3) density functional theory (DFT) method. Geometry optimizations were performed with the 6-311+G(2d,p)³⁹ basis set followed by single

point energy calculations with the aug-cc-pVTZ^{40,41} basis set. A continuum dielectric with the IEF-cPCM^{42–44} method was utilized to represent reaction conditions, and all reported stationary points were optimized in implicit THF solvent ($\epsilon = 7.58$ at 298 K). Reported energies are free energies in kcal/mol. Thermal and vibrational free energy corrections to the electronic energy at 298 K were used in accordance with recommendations for molecules optimized in implicit solvent.⁴⁵ It should be noted that the proper treatment of the translational and rotational partition functions in PCM calculations is not well understood,^{46,47} particularly when the number of molecules changes, for example, when going from reactants at infinite separation to the reactant complex (DC); current choices of approximation lead to widely varying results (see ref 45, p 14561), neither of which seems correct. Thus, in the text, we have not compared the free energies of species with differing numbers of molecules (i.e., reactants \rightarrow DC, INT2 \rightarrow INT3, and PC \rightarrow products). 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 coordinate⁴⁸ (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//B3LYP-D3/6-311G+(2d,p) method. These charges were constrained to reproduce the dipole moment of the molecule.⁴⁹

■ 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.

■ ACKNOWLEDGMENTS

This material is based on work supported by the National Science Foundation (DMR-1001903 and CHE-1306730).

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