A DFT study on the mechanism for polymerization of δ-valerolactone initiated by N-heterocyclic carbene (NHC) catalysts

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Abstract

Polymerization reactions using renewable raw material as substrate (namely, δ-valerolactone) and N-heterocyclic carbenes (NHC) as organocatalysts to form polyesters were investigated by computational approaches. Two routes were investigated for the reaction, either with the NHC acting as a Brønsted base and activating an alcohol used as co-initiator or by direct nucleophilic attack of the NHC on the carbonyl carbon of the lactone, forming a zwitterionic intermediate. In agreement with previous studies, the lowest energy pathway leading to polymerization is that where the NHC activates the alcohol co-initiator, yielding a partially charged alkoxide that then performs a nucleophilic attack on the lactone. The proton affinity of the NHCs shows a high correlation with the activation enthalpy for the first reaction step. Thus, NHCs with high proton affinity stabilize the first intermediate and make the lactone ring-opening the rate-determining step for the reaction.

Introduction

Polylactones are aliphatic polyesters, that have attracted increased academic [1] and industrial [2] interest due to their high performance as biodegradable polymers obtained from renewable raw materials (lactones) [3,4]. Polylactones are also biocompatible and have attracted attention due to their applicability in packaging, agriculture, biomedical and pharmaceutical fields [5-8].

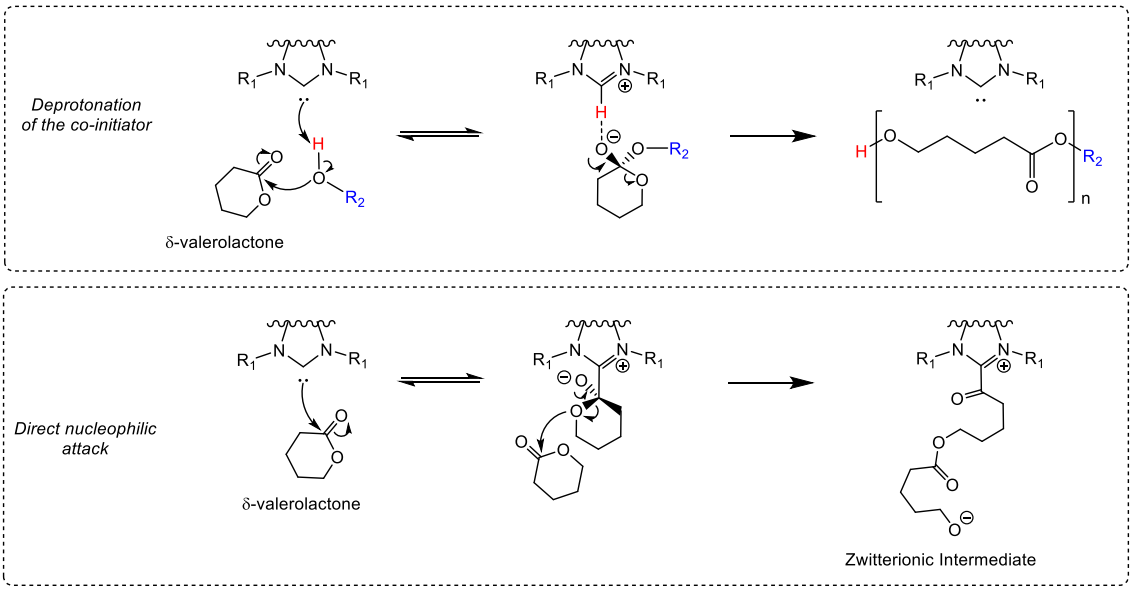
Poly(δ-valerolactone) is an aliphatic polyester produced by the polymerization of δ-valerolactone. A common synthetic route for poly(δ-valerolactone) and other aliphatic polyesters is the ring opening polymerization (ROP) of cyclic esters [9,10]. Four main mechanisms have been reported for the ROP of lactones, all of which depend on the catalyst: anionic or cationic ROP [11,12], monomer-activated ROP [13] and coordination-insertion ROP [11]. The preparation of aliphatic polyesters by polycondensation of hydroxycarboxylic acids has also been reported [12]. However, polymers with higher molecular weights and lower polydispersity are synthesized by ROP [10]; therefore, ROP is the preferred general route.

The use of catalysts in these reactions allows the formation of polymers with high molecular weights, in addition to the common catalyst role of decreasing the reaction activation energy and the reaction time. In recent years, there has been an attempt to replace classical methodologies for polymer synthesis by cheaper, less aggressive, and more efficient methods, e.g., employing metal-free organocatalysts in polymerization reactions [12,15-18]. In addition to being cheaper and environmentally friendly, the use of organocatalysts also reduces costs in the production of biocompatible polymers, as the additional step for the removal of metal contaminants is unnecessary [19]. In this context, N-heterocyclic carbenes (NHCs) have been suggested as promising organocatalysts for lactone polymerization reactions [20] due to their typical Brønsted basicity and nucleophilicity.

In this work, we employed density functional theory (DFT) calculations to investigate the reaction mechanism for polymerization of δ-valerolactone catalyzed by N-heterocyclic carbenes. The use of DFT modeling to describe the organocatalysis ROP of cyclic esters and other organocatalytic processes has been reviewed recently [21,22]. Our goal was to rationalize the reaction mechanism for polymerization, both in the absence and in the presence of an

alcohol as a co-initiator, as well as to quantify the effect of substituents on the NHC. Two routes are discussed for this reaction (**Scheme 1**). In the first route, alcohol is used as a co-initiator. In this case, the NHC acts as a Brønsted base activating the alcohol hydroxyl group by deprotonating it or forming a complex in a process that increases the electron density on the oxygen atom of the alcohol and aids the nucleophilic attack on the lactone. In the second route, direct nucleophilic attack of the NHC on the carbonyl carbon of the lactone occurs. In this case, the NHC acts as a nucleophile, attacking the lactone and forming a zwitterionic intermediate. Alternative mechanisms have been proposed for this polymerization reaction [23-25]. We revisit these mechanisms, especially regarding the possible formation of an adduct between the NHC, the alcohol and the lactone, considering a set of substituents on the NHC and their effects on thermodynamic and kinetic parameters. Our results provide additional information on this reaction mechanism, elucidating the main points on the potential energy surface and helping rationalize the factors controlling the efficiency of the catalyst, in particular the effect of substituents on the NHC.

Scheme 1. Two possible mechanisms for NHC catalyzed ring-opening polymerization of δ–valerolactone [24,25].



Methodology

All calculations were carried out at the quantum mechanical level, by means of density functional theory (DFT) using Gaussian09® software [26-29]. From the plethora of available density functionals we selected N12SX with range-separated hybrid NGA [30,31]. The N12SX functional has been evaluated in previous studies, presenting good precision for energetic properties and characteristics of solids and molecules, producing good results for thermochemistry [31]. The 6-311+G(d,p) basis set was used for all atoms [32,33].

The reaction mechanism with direct nucleophilic attack of the NHC on the lactone, forming a zwitterionic intermediate, and the mechanism passing through deprotonation of the co-initiator (alcohol) were simulated (**Scheme 1**). We first tried methanol and ethanol as co-initiator. Along the investigation, we identified that the results obtained with these two alcohols were similar; thus, we decided to report only the results obtained with ethanol as a co-initiator. Geometry optimizations of relevant points on the potential energy surface (PES) were performed. Each stationary point on the PES was characterized by analysis of the second-order Hessian matrix: points corresponding to a minimum energy on the PES have only positive values for their eigenvalues and points corresponding to transition structures have just one negative eigenvalue.

The thermodynamic data used to quantify the relative enthalpies were obtained from the vibrational frequency calculations, with T = 298 K and P = 1 atm. We report values (kcal mol^{-1}) for variation of enthalpy (ΔH) along the reaction pathway. Basis set superposition errors (BSSEs) were included using the counterpoise procedure [34]. In all calculations, the implicit solvation method was employed, using the polarizable continuum model through the differential equation formalism (IEFPCM) [35,36] and water as a solvent (ε = 78.35).

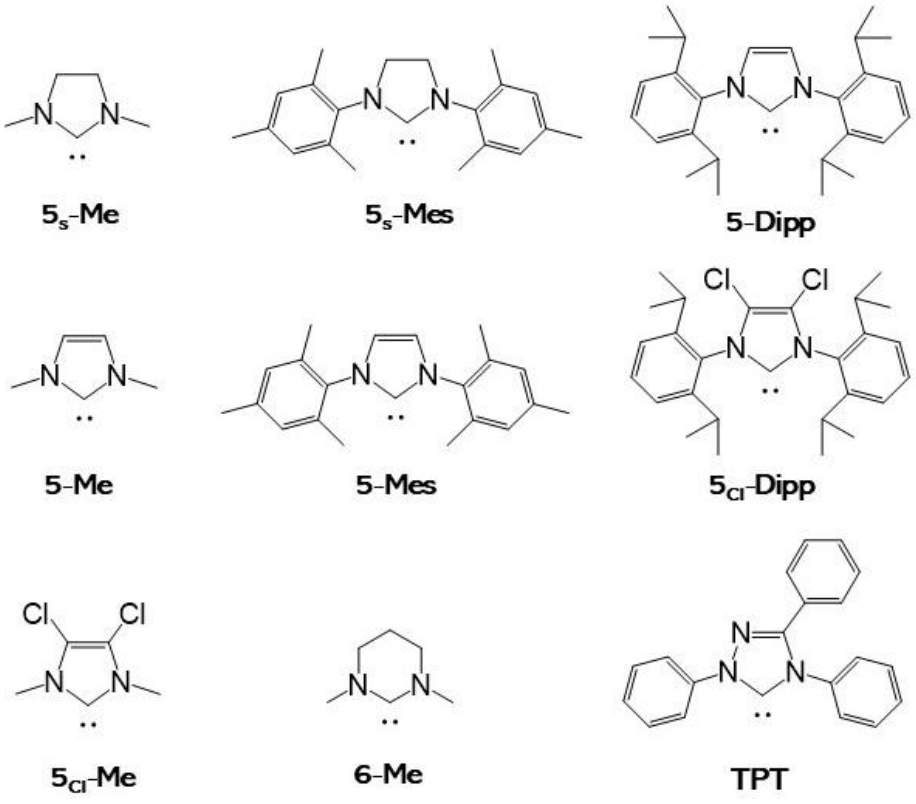
Results and Discussion

Molecular structure of the NHC catalysts

The investigated N-heterocyclic carbenes are represented in **Scheme 2**. These include a set of N-alkyl- and N-aryl-substituted derivatives that incorporate both electronic and steric effects. As expected, for the N-alkyl carbenes, geometry optimization leads to a final structure with a planar distribution of substituents around the nitrogen atoms [37]. Therefore, the central core formed

by the nitrogen atoms, the carbene carbon and the atoms connected to them are essentially in the same plane. For the N-aryl carbenes, geometry optimization revealed a preference for an orientation where the aromatic rings are orthogonal to the central ring (**Figure 1**). This is consistent with literature data [38-40]. X-ray diffraction analysis of crystalline structures similar to those studied in the present work also revealed an arrangement where the phenyl groups are orthogonal to the five-member ring. Arduengo and coworkers published crystallographic data for one of the derivatives we studied here (5_{Cl}-Dipp) [41]. In that study, the experimental angle between the central ring and the arene rings connected to the nitrogen atoms (represented by the C_{11}-C_{10}-N_{18}-C_{23} dihedral angle as shown in **Figure 1**) was 84.9º. This result compares to the corresponding calculated value of 89.3º. Considering the conjugation between the nitrogen lone electron pair and the conjugated aromatic ring, a coplanar orientation of these substituents in relation to the central ring could be expected, as seen, e.g., in N,N-dimethylaniline [42]. However, this is not the case. The orthogonal orientation observed for the N-aryl NHCs is probably due to steric crowding promoted by the bulky aryl substituents.

Scheme 2. Chemical structure of the NHC catalysts evaluated for ROP.



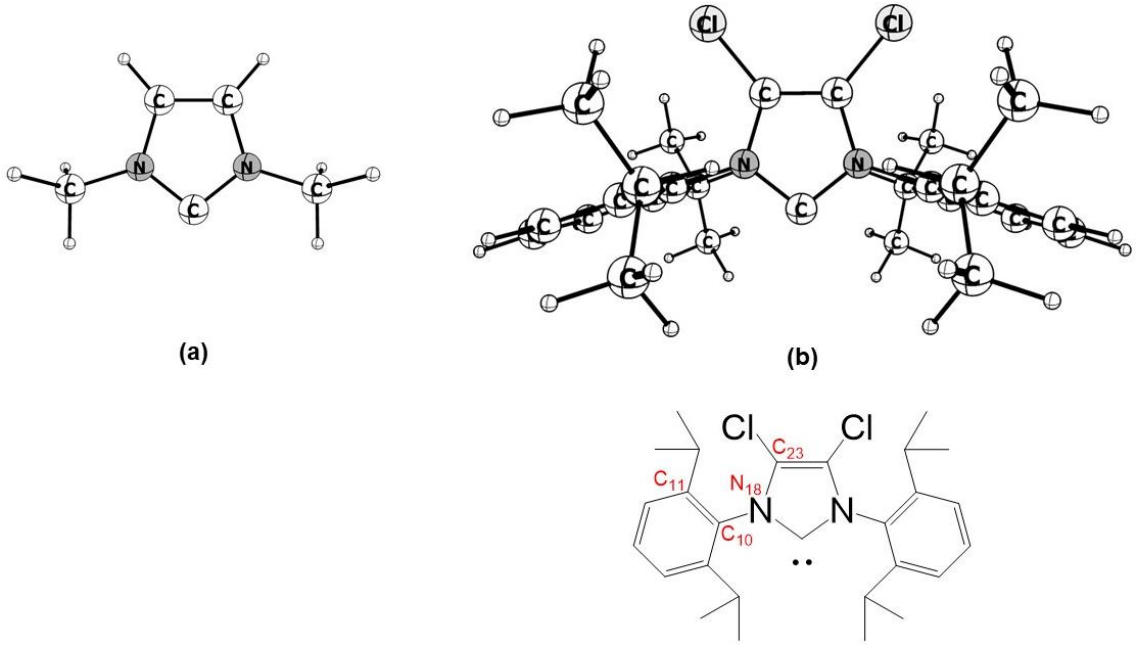


Figure 1. Representation of the optimized structures of (a) N,N-methyl (5_S-Me) and (b) N,N-2,6-di-isopropylphenyl (5_{Cl}-Dipp) NHCs using the N12SX functional with the 6-311+G(d,p) basis set and water as a solvent (IEFPCM, ε = 78.35), revealing the preference for an orientation where the aromatic rings are orthogonal to the central ring in the N-aryl carbene. In this example (5_{Cl}-Dipp), the calculated dihedral angle C_{23}-N_{18}-C_{10}-C_{11} is 89.3º.

Relative proton affinity of the NHCs

One possible role of the N-heterocyclic carbenes is to act as a proton acceptor in a concerted mechanism, where the deprotonated alcohol attacks the carbonyl group of the lactone. According to this hypothesis, the relative proton affinity of the N-heterocyclic carbenes can be used as an indicator of their catalytic activity.

The relative proton affinities of the NHCs were computed by means of a proton transfer equation between the NHCs and the alcohols methanol, ethanol, and glycerol (**Equation 1**, **Table 1**). A positive value for the relative proton affinity indicates a higher proton affinity of the alkoxide anion compared to the proton affinity of the NHC and *vice versa*.

$$R\text{-}OH + NHC \rightleftharpoons NHC\text{-}H^{+} + {}^{-}O\text{-}R \qquad (1)$$

ΔH ≡ proton transfer enthalpy

Table 1. Relative proton affinity of the NHCs, computed as the enthalpy change (ΔH, kcal mol^{-1}, 298 K, 1 atm) for **Equation 1**, and activation enthalpy ($\Delta H^{\neq}$, kcal mol^{-1}) for the first step (**TS1**) in the reaction depicted in **Figure 3** with ethanol as the co-initiator.

NHC Structure	Methanol	Ethanol	Glycerol	$\Delta H^{\neq}$
6-Me	3.16	3.36	-8.95	3.15
5$_S$-Me	9.71	9.91	-2.40	7.85
5-Me	10.54	10.74	-1.57	8.37
5$_S$-Mes	11.87	12.07	-0.24	10.32
5-Mes	12.35	12.55	0.24	10.24
5-Dipp	13.01	13.21	0.90	12.53
5$_{Cl}$-Me	17.55	17.74	5.44	12.23
5$_{Cl}$-Dipp	19.63	19.82	7.52	17.42
TPT	23.13	23.33	11.02	15.82

Calculations were performed using the N12SX functional with the 6-311+G(d,p) basis set and water as a solvent (IEFPCM, ε = 78.35). $\Delta H^{\neq}$ is the activation enthalpy for the reaction with ethanol and was corrected for basis set superposition error.

As shown in **Table 1**, the NHCs with the highest proton affinity are those with methyl groups attached to the nitrogen atoms (6-Me, 5$_S$-Me and 5-Me), particularly the NHC with a six-member central ring. The NHC with the lowest proton affinity is that with three aromatic rings attached to the central ring (TPT), followed by the NHCs containing the chlorine atoms and by those containing two aromatic rings connected to the central ring. When considering the ring size, data indicate that the NHC with a six-member ring has higher proton affinity than those containing a five-member ring. Unsaturation at position 4 of the five-member ring (5-Me x 5$_S$-Me and 5-Mes x 5$_S$-Mes) also decreases the proton affinity (by less than 1 kcal mol^{-1}).

Enthalpy changes for the proton transfer process represented in **Equation 1** are positive for methanol and ethanol, while for the most basic NHCs, we found a negative enthalpy change for proton transfer from the secondary hydroxyl group of glycerol to the NHCs. This is due to the high basicity of the alkoxide anion formed in the proton transfer process. Due to the intramolecular hydrogen bonds

that may be formed in the case of the glyceroxide anion, its formation is less endothermic than in the case of either the methoxide or the ethoxide anions. Another point shown in **Table 1** is that the enthalpy changes for the deprotonation of ethanol and methanol are similar, with enthalpy for proton transfer from ethanol being 0.2 kcal mol^{-1} (on average) higher than that for proton transfer from methanol. Based on this fact, we decided to continue the calculations using only ethanol, considering that this alcohol would also be a better representative for the sequence of the reaction. Glycerol gives enthalpy changes for proton transfer in **Equation 1** on average 12.3 kcal mol^{-1} more negative than that of ethanol (pKa = 16.0) [43], a consequence of the higher acidity of glycerol (pKa = 14.4) [44].

The basicity of NHCs and their importance on their catalytic role have been reported in previous studies [45]. In a recent publication, theoretical and experimental basicities of a large set of NHCs were reported, including most of the NHCs analyzed in the present work (**Figure 2**). **Figure 2** also gives the proton affinity relative to ethanol, as computed in the present work. There was a strong correlation between these two parameters (r^2 = 0.98), as expected.

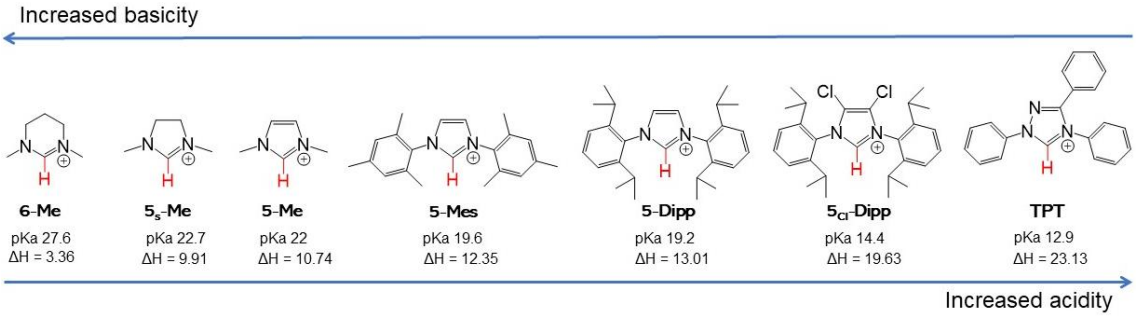


Figure 2. The pKa values in DMSO for protonated NHCs (from reference 45) and the corresponding calculated relative proton affinity in H_2O (ΔH, kcal mol^{-1}, computed according to equation 1, using ethanol).

Reaction mechanism

The general proposal for the mechanisms investigated in the present study is given in **Scheme 1**. We followed the two alternatives, either with an alcohol as a co-initiator or with the direct attack of the NHC on the lactone. The relevant stationary points in the mechanism involving an alcohol as a co-initiator in a two-step process are shown in **Figure 3**. In the first step there is a proton transfer from the alcohol to the NHC, concerted with the nucleophilic attack of the alcohol

on the lactone, passing through transition structure **TS1** (**Figure 3**) and forming **intermediate 1**. In the second step the carbon-oxygen bond in the lactone is broken while still interacting with the protonated NHC, via transition structure **TS2**, forming open lactone **intermediate 2**. The polymerization continues by a new attack of **intermediate 2** on a second lactone molecule, again with participation of the carbene as a proton acceptor. The chain reaction continues until the polymer is formed. The computed relative enthalpies for this process are depicted in **Figure 3**, considering the distinct NHC catalysts investigated here.

The results presented in **Figure 3** show that the first transition structure, the alcohol attack on the carbonyl carbon of the lactone concerted with proton transfer to the NHC, has a higher energy than the corresponding second transition structure, the opening of the lactone ring. However, for the more basic NHCs (e.g. 6-Me, 5s-Me and 5-Me), **intermediate 1** is more stable than the prereactive complex. For the most stable intermediate (6-Me), the activation enthalpy for the second reaction step is higher than that for the first step. Therefore, although the first reaction step is the rate-determining step for most NHCs, this may be reversed for highly basic NHCs, as in the case of 6-Me. In previous reports by Acharya et al [24] and Jones et al [25], the deprotonation of alcohol was also indicated as the step with the highest energy barrier. The second and following steps would occur with gradually lower energy barriers. Additionally, **Figure 3** shows a strong dependence of the activation energy for the first reaction step on the nature of the NHC, with computed values for TS1 ranging from 2.2 to 15.0 kcal mol^{-1}. However, the activation barrier for the second step is much less dependent on the nature of the NHCs, with activation enthalpies ranging from 5.9 to 7.7 kcal mol^{-1}.

There is an intimate correlation between the proton affinity of the NHCs computed according to **Equation 1** and the activation enthalpy for the attack of the alcohol on the lactone, concerted with proton transfer to the NHC (**Table 1**. The squared correlation coefficient (r^2) between the enthalpy for proton transfer in any of the three alcohols and $\Delta H^{\neq}$ is 0.90). The NHCs showing less positive enthalpies for the proton transfer process are also those showing the lowest activation enthalpies and *vice versa*.

For ethanol, the activation enthalpies are lower than the corresponding enthalpies for full proton transfer (even after correcting $\Delta H^{\neq}$ for BSSE), with the

difference increasing as the NHC proton affinity is reduced. Therefore, for ethanol as a co-initiator, the concerted reaction, with NHC acting as an ancillary species, is energetically more favorable than a reaction where full proton transfer occurs from the alcohol to the NHC. Computations for 5-Me using methanol as a co-initiator give essentially the same results as those for ethanol. However, due to the higher acidity of glycerol, full proton transfer is predicted when compared to the concerted process (ΔH = -1.6 kcal mol^{-1} for the reaction represented in **Equation 1** versus an activation enthalpy of $\Delta H^{\neq}$ = 8.7 kcal mol^{-1}). Therefore, at least for glycerol, a reaction involving full proton transfer would probably be the preferred reaction. This should also happen for similarly acidic alcohols.

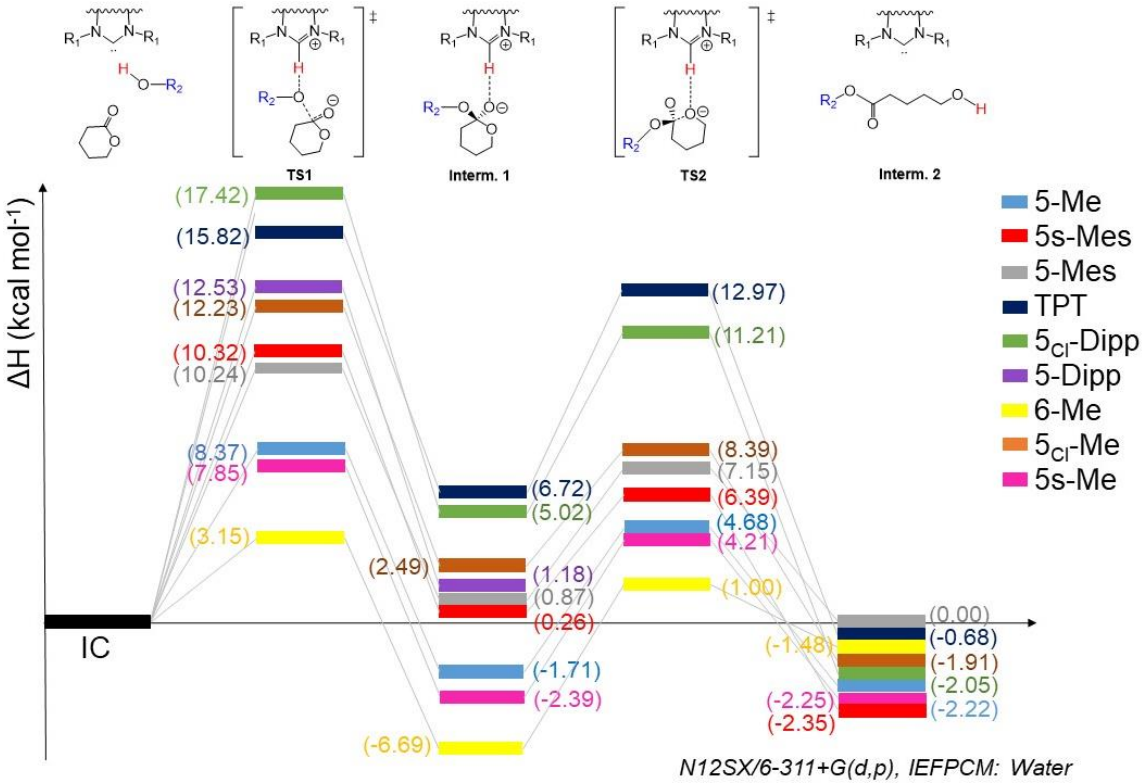


Figure 3. Enthalpy changes (kcal mol^{-1}) for formation of the relevant stationary points along the reaction pathway for the reaction mechanism involving deprotonation of the alcohol as co-initiator. The values are given relative to a prereactive complex (NHC, δ-valerolactone and ethanol). Values for **TS1** are corrected for BSSE.

The first intermediate (**Intermediate 1**) has a tetrahedral structure whose relative stability closely follows that of the preceding transition structure (**TS1**),

with some irrelevant inversions. This intermediate is stabilized by a hydrogen bond between the protonated NHC and the anion formed after attack of the alkoxide on the lactone, as represented in **Figure 3** [46,47]. Therefore, the ability of the NHCs to accept protons also extends to this stationary point. After attack of the alkoxide on the lactone, it may open to form the second intermediate (**Intermediate 2**), represented in **Figure 3** as an aliphatic alcohol, as it may capture the proton back from the NHC. As shown in **Figure 3**, the transition structure for opening the lactone ring (**TS2**) has lower energy than the corresponding transition structure for the first step (**TS1**), confirming the first step as the rate determining step, except, possibly, for highly basic NHCs, as discussed above. **Intermediate 2**, with a narrower energy range, also has lower energy than the corresponding **intermediate 1**. From **intermediate 2**, the reaction may continue in a similar way as from the starting alcohol, both from the geometry and energy points of view.

To verify whether the solvent has any significant effect on the relative energies for this mechanism, we computed the relative energies for all the stationary points (transition state TS1, the first intermediate, transition state TS2 and the second intermediate) using ethanol as the implicit solvent instead of water. For all stationary points, the average difference in the relative energies for the two cases is below 0.4 kcal mol^{-1}. There is no individual difference higher than 0.6 kcal mol^{-1}. This should not affect the profile given in **Figure 3**.

In the alternative mechanism for the polymerization reaction of lactones using N-heterocyclic carbenes [24,25], nucleophilic attack of NHC occurs directly on the carbonyl carbon of the lactone to form a zwitterionic intermediate. In the second stage, the zwitterionic intermediate attacks a second lactone molecule, resulting in ring opening of the first lactone, leading to a chain reaction that continues to form the polymer (**Figure 4**).

Figure 4 gives the relative enthalpies for intermediates and transition structures. Activation energies for the formation of the zwitterionic intermediate (**intermediate 3**) are also dependent on the NHC structure, ranging from 7.9 to 14.5 kcal mol^{-1}. The relative stability of zwitterion (**intermediate 3**) is, on average, 4.2 kcal mol^{-1} less stable than the corresponding **intermediate 1** of the first mechanism (**Figure 3**). However, when going to the second step in this mechanism, the opening of the lactone ring to form an alkoxide (**intermediate 4**),

we computed activation enthalpies (18.4 to 37.4 kcal mol^{-1}) that are considerably higher than the relative enthalpy for any of the transition structures or intermediates in the first mechanism. Additionally, the relative enthalpy of **intermediate 4** is also much higher than the corresponding enthalpy for any intermediate in the previous mechanism. These data clearly point to the conclusion that the mechanism where the NCHs act as a base, by accepting a proton from the alcohol, in contrast to a mechanism where it acts as a nucleophile by attacking the lactone, is the preferred pathway for this reaction in the presence of an alcohol as a co-initiator.

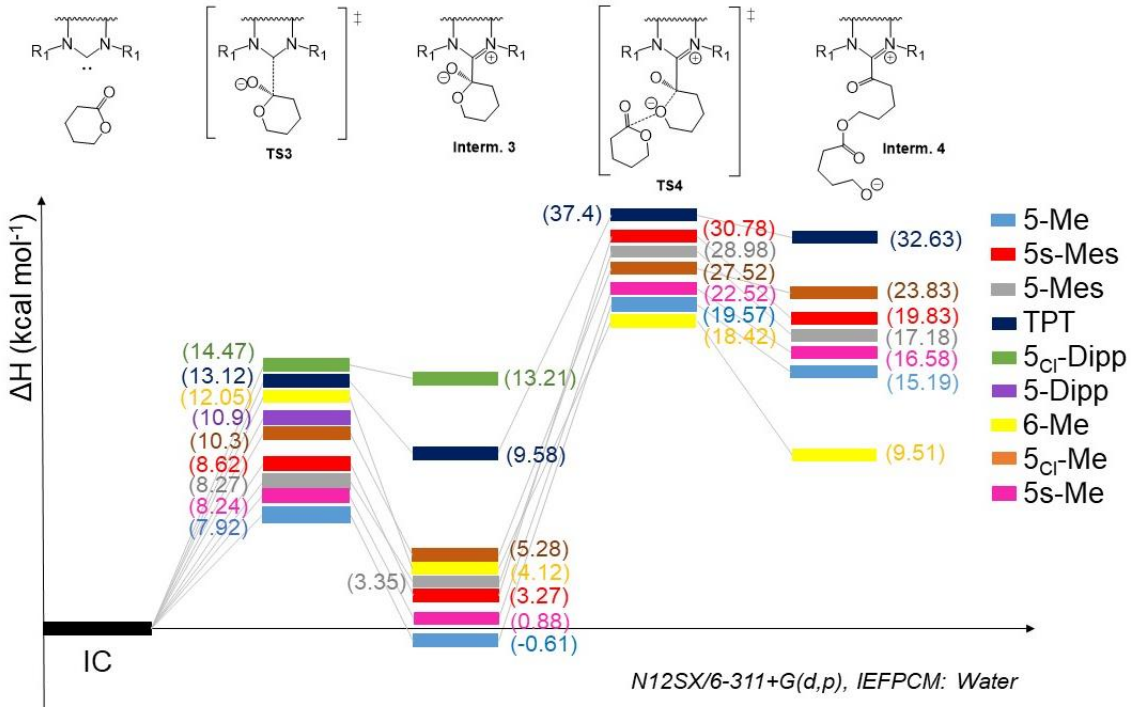


Figure 4. Enthalpy changes (kcal mol^{-1}) for the ROP of δ-valerolactone catalyzed by the NHCs via a direct nucleophilic attack of the NHC on the carbonyl carbon of the lactone forming a zwitterionic intermediate.

To rationalize the electronic effects of the NHCs, we also analyzed their HOMO, as these species act as a base in the most likely mechanism. One example of such an orbital is given in **Figure 5**, which shows the HOMO of 5-Me. The HOMO energies are given in **Table 2**. As expected, there is an intimate correlation between the HOMO energies (**Table 2**) and the proton affinities (**Table 1**) for the NHCs (the squared correlation coefficient r^2 is 0.91) [48]. Again, NHCs

having electronegative atoms or arene groups connected to the five-member ring are those with lower HOMO energies and NHCs with a six-member ring have the highest HOMO energy. Unsaturation also reduces the HOMO energy. Although the steric effect might also play some role in the relative energies of transition structures and intermediates [49,50], it seems that in the preferred mechanism, electronic effects are more relevant, as the NHCs do not have to come into close contact with the lactone.

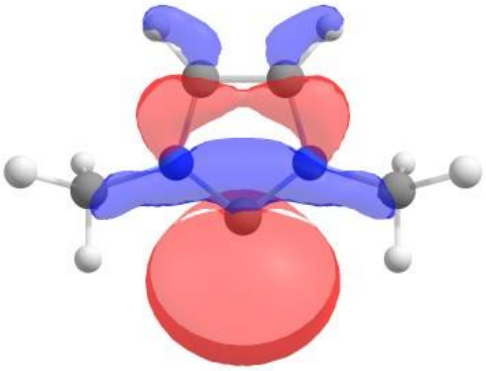


Figure 5. HOMO representation for 5-Me.

Table 2. HOMO energies (eV) for the NHCs.

NHC	HOMO Energy
5_{Cl}-Me	-6.08
5_{Cl}-Dipp	-6.06
TPT	-6.06
5-Dipp	-5.69
5-Mes	-5.60
5-Me	-5.57
5s-Mes	-5.44
5s-Me	-5.36
6-Me	-4.88

The results in the present work clearly indicate that in the presence of an alcohol as a co-initiator, the NHCs preferentially act as a base in the activation of the alcohol for the first step in the reaction mechanism to promote polymerization. As it acts as a base, the proton affinity of the NHCs and their HOMO energies both correlate with the activation enthalpies of the first, rate-determining step of the reaction. Although the activation enthalpies for the rate-determining step are

relatively low, they clearly depend on the structure of the NHC. For example, a six-member ring, compared to five-member rings, yields lower activation enthalpies. Unsaturation, as well as electron withdrawing groups bonded to the five-member ring, reduces the proton affinity and the HOMO energies, thereby increasing the activation enthalpies for the first step. These results confirm previous findings on similar systems [51-54]. The polymerization of δ-valerolactone [24] and Ɛ-caprolactone [25] catalyzed by NHC was studied by both computational and experimental methods. In both cases, it was concluded that the activation energy for polymerization in the presence of methanol is lower than in its absence, with the nucleophilic attack of the alcohol on the lactone being the rate-determining step. Although the zwitterionic mechanism has been proposed for ring-opening polymerization [53], other [54] and more recent computational and experimental studies [25] also concluded that NHCs act as ancillary bases promoting the nucleophilic attack of alcohol on lactone. Experimental studies showed that ring-opening polymerization in the presence of an alcohol as a co-initiator is much faster than in its absence [25].

Conclusions

The ring-opening polymerization reaction of δ-valerolactone was investigated in the presence and in the absence of an alcohol as a co-initiator, using N-heterocyclic carbenes as an organocatalyst. Our results show that a mechanism where the NHCs act as an ancillary base, promoting the nucleophilic attack of the alcohol on the lactone by abstracting a proton from the alcohol has lower activation enthalpies and leads to more stable intermediates than the alternative mechanism where the NHCs act as a nucleophilic species, attacking the carbonyl carbon of the lactone. The proton affinity and HOMO energies of the NHCs show a high correlation with the activation enthalpy of the first, rate-determining step of the reaction in the mechanism involving deprotonation of the alcohol as a co-initiator. Highly basic NHCs may reduce the activation enthalpy for the first step, thus making the second, lactone ring-opening step, the rate-determining step. Therefore, electronic effects on the NHCs, in contrast to steric effects, determine the activation enthalpy. Aryl or electronegative groups in the NHCs reduce their proton affinity and, consequently, increase the respective activation enthalpies. This agrees with recent experimental studies that show that

the reaction time, yield, and molecular weight distribution depend on the structure of the catalysts and the nature of the substituents. In general, the nature of the substituent has a pronounced effect on the stability and activity of the NHC catalyst.

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