CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200800346

Monomer versus Alcohol Activation in the 4-Dimethylaminopyridine-Catalyzed Ring-Opening Polymerization of Lactide and Lactic *O*-Carboxylic Anhydride

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Abstract: Model reactions for the 4-dimethylaminopyridine (DMAP)-catalyzed ring-opening polymerization of lactide and the corresponding lactic *O*-carboxylic anhydride (lacOCA) have been studied computationally at the B3LYP/6–31G(d) level of theory. The solvent effect of dichloromethane was taken into account through PCM/SCRF single-point calculations at the B3LYP/6–31G(d) level of theory. In marked contrast with that predicted for the reaction of alcohols with acetic anhydride, the mechanism in which nucleophilic activation of the monomer involving acylpyridinium intermediates was found to be energetically less favorable than the base activation of the alcohol through hydrogen bonding. The concerted pathway for the ring-opening of lactide and lacOCA was shown to compete with the traditional stepwise mechanism involving tetrahedral intermediates. Furthermore, DMAP is proposed to act as a bifunctional catalyst through its basic nitrogen center and an acidic *ortho*-hydrogen atom.

Keywords: density functional calculations · dimethylaminopyridine · hydrogen bonds · organocatalysis · ring-opening polymerization

Introduction

Aliphatic polyesters, and especially polylactides (PLAs), are attracting increasing attention as resorbable biomaterials and commodity thermoplastics.[1] Spectacular progress has been achieved over the last ten years regarding the preparation of PLAs under mild conditions with a high level of control in terms of molecular weight, polydispersity, end-group fidelity, and even tacticity. In this respect, the organocatalyzed ring-opening polymerization (ROP) of lactide,[2] which gives access to polymers free of metallic contaminants, is particularly promising. This approach was pioneered in 2001 by Hedrick and co-workers[3] using 4-dimethylaminopyridine (DMAP), a well-known catalyst for acylation and transesterification reactions.[4] A broad range of organocatalysts were then developed, including *N*-heterocyclic carbenes (NHCs),[5] trifluoromethanesulfonic acid (HOTf),[6] thiourea/amine combinations,[7] guadinines,[8] and phosphazenes[9] (Scheme 1).

The organocatalyzed ROP of lactide clearly proceeds very differently to ROP promoted by metal complexes (so-called coordination–insertion ROP),[10,11] but the precise mode of action of the organocatalysts remains superficially understood. Monomer activation has been frequently postulated, except for phosphazenes, for which alcohol activation has been proposed.[9] The competition between these two pathways has been recently investigated theoretically for the NHC-catalyzed ROP of lactide[12] and the guanidine-catalyzed ROP of δ-valerolactone.[13] In addition, a comprehensive DFT study by Zipse and co-workers demonstrated that the nucleophilic pathway is far more favorable energetically

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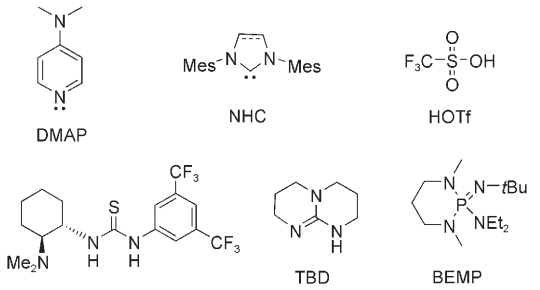
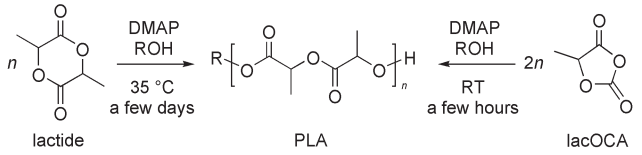


Scheme 1. Representative organocatalysts developed for the ROP of lactide.

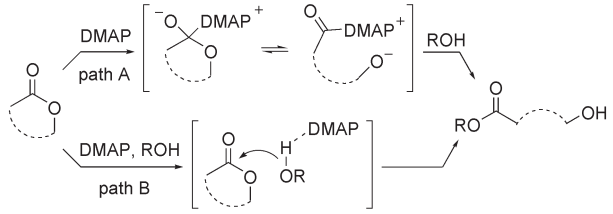
than the basic route in the DMAP-catalyzed esterification of alcohols with acetic anhydride.[14]

In this context, we report herein a detailed computational study of the DMAP-catalyzed ROP of lactide (Scheme 2)



Scheme 2. DMAP-catalyzed ROP of lactide and lacOCA.

and lactic *O*-carboxylic anhydride (lacOCA), an activated equivalent.[15,16] In both cases, the base activation of the initiating/propagating alcohol (Scheme 3, path B) was much



Scheme 3. Schematic representation of the nucleophilic/monomer (path A) and basic/alcohol (path B) activation mechanisms for the DMAP-catalyzed ROP of lactide and lacOCA (ROH refers to the initiating/propagating alcohol).

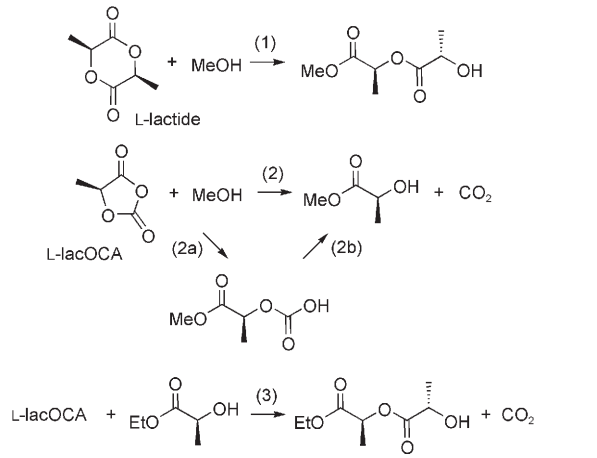
more energetically favorable than the nucleophilic activation of the monomer (Scheme 3, path A). The key role of multiple hydrogen bonding is evidenced, as well as the possibility of DMAP acting as a bifunctional catalyst.

Results and Discussion

All stationary points were optimized at the B3LYP/6–31G(d) level of theory. The solvent effect of dichloromethane was taken into account through PCM/SCRF single-point calculations at the B3LYP/6–31G(d) level of theory.[17] Unless otherwise stated, the various reaction profiles are discussed in electronic energies.

Ring-opening of L-lactide: The ROP of L-lactide was calculated by modeling the initiating/propagating alcohol as methanol. As anticipated, reaction (1) was predicted to be favored enthalpically but disfavored entropically (Table 1).[18] The resulting free enthalpy of reaction ΔG_{298K} is fairly small ($\Delta G = -6.1$ and $+1.2$ kcal mol^{-1} in the gas phase and dichloromethane, respectively).

Table 1. Energetic data of the model ring-opening reactions (1)—(3) of lactide and lacOCA.



Reaction	ΔE_{int}[a] [kcal mol^{-1}]	ΔH_{298K} [kcal mol^{-1}]	ΔS_{298K} [cal mol^{-1} K^{-1}]	ΔG_{298K} [kcal mol^{-1}]
(1) gas	−17.6	−15.7	−32.2	−6.1
(1) dichloromethane	−10.2	−8.3	−31.8	+1.2
(2) gas	−19.2	−19.4	−4.3	−18.1
(2) dichloromethane	−15.2	−15.4	−4.7	−14.0
(2a) gas	−16.2	−14.0	−34.9	-3.6
(2a) dichloromethane	−12.1	−9.9	−34.9	+0.5
(2b) gas	−3.0	−5.4	+30.5	−14.5
(2b) dichloromethane	−3.1	−5.5	+30.2	−14.5
(3) gas	−14.1	−14.5	−6.7	−12.5
(3) dichloromethane	−10.6	−11.0	−6.7	−9.0

[a] At the B3LYP/6–31G(d) level of theory.

The nucleophilic route for the ROP of lactide was investigated first, and the acylpyridinium intermediate **I** was located on the potential-energy surface (PES). The optimized geometry of **I** displays typical N–CO and C=O bond lengths (1.47 and 1.20 Å, respectively) and slight torsion between the pyridinium ring and C=O skeleton (C_{ortho}NCO torsion angle: 14°; Figure 1).[19] The alkoxide terminus liberated by the ring-opening of lactide is strongly engaged in hydrogen bonding with methanol (O···H–O 1.64 Å). Extra stabilization occurs through one of the *ortho*-hydrogen atoms of the pyridinium ring (O···H–C 1.72 Å).[20,21] Acylpyridinium species **I** is located about $\Delta E = 25$ kcal mol^{-1} higher in energy than the separated reactants, thus suggesting a fairly large activation barrier for such a monomer activation pathway.

As a first evaluation of the concurrent basic route, the tetrahedral intermediates that result from the addition of methanol to lactide were searched for on the PES. The local minimum **II1** corresponds to an ion-pair structure, with the proton of methanol virtually transferred to the basic nitro-

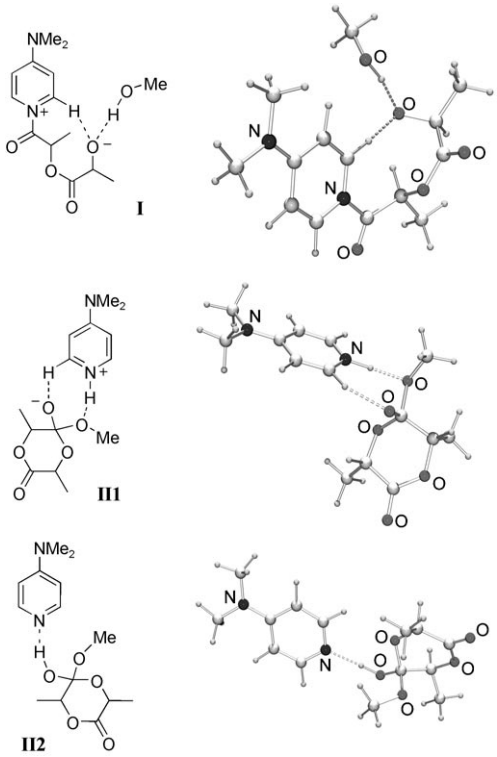


Figure 1. Optimized structures for the acylpyridinium **I** and tetrahedral **II1** and **II2** intermediates that derive from lactide.

gen atom of DMAP (N–H 1.07 Å), and with the negatively charged exocyclic oxygen atom engaged in weak nonclassical hydrogen bonding[20] with one of the *ortho*-hydrogen atoms of the pyridinium ring (O···H–C 1.97 Å). The neutral form **II2** was also optimized. As a result of the proton transfer, the shortest hydrogen bond involves, in this case, the exocyclic OH group and basic nitrogen atom from DMAP (N···H–O 1.78 Å). From an energetic viewpoint, the ion-pair intermediate **II1** is located on a very flat region of the PES, namely, about $\Delta E = 10$ kcal mol^{-1} higher in energy than the separated reactants. The neutral form **II2** is more stable than **II1** by about $\Delta E = 20$ kcal mol^{-1} in the gas phase. This energy separation decreases to $\Delta E = 10$ kcal mol^{-1} in dichloromethane, probably because of the superior stabilization of the more polar structure **II1**.

Given the higher stability of the tetrahedral versus acylpyridinium intermediates, the whole reaction profile of the basic route[22] was studied (Figure 2). The transition states **TS1** and **TS2**, which connect the ion-pair intermediate **II1** to the ternary complex of reactants **R** and the neutral intermediate **II2**, respectively, were located. Both **TS1** and **TS2** are very close in energy to **II1**, with barrier heights of only a few kcal mol^{-1} (Table 2). In addition, **II2** connected with **P** via **TS3**, with a barrier height of about $\Delta E = 10$ kcal mol^{-1} in dichloromethane ($\Delta E = 20$ kcal mol^{-1} in the gas phase).

The possibility of a concerted ring-opening reaction of lactide with methanol was then investigated. Nucleophiles normally react with carboxylic acid derivatives through an addition/elimination sequence, but recent studies on the hydrolysis, alcoholysis, and aminolysis of carboxylic esters[23–25] revealed that the concerted pathway may be much more accessible than anticipated and compete with the stepwise mechanism. The transition state **TS4** was indeed found to directly connect **R** with **P**. The corresponding barrier height is comparable to the barrier predicted for the stepwise pathway, thus suggesting that the ring-opening process may occur indifferently in a stepwise or concerted manner.

Ring-opening of L-lacOCA with methanol: As already noted,[15] reaction (2), which models the ROP of L-lacOCA, is significantly more favorable thermodynamically than reaction (1) (Table 1). The decomposition that occurs in reaction (2) over two stages allowed us to estimate the driving force of the reaction better; namely, the ring-opening step [reaction (2a)] provides the major part of the enthalpic term, whereas the decarboxylation step [reaction (2b)] definitely plays a key role entropically.

The structures of the ensuing acylpyridinium compounds were optimized to gain greater insight into the nucleophilic activation of lacOCA with DMAP. Two local minima **I′1** and **I′2** could be located before and after decarboxylation, respectively (Figure 3). The N–C=O skeleton in **I′1** (N–C 1.48, C=O: 1.20 Å; C_{ortho}NCO torsion angle 23.4°) has a very similar geometry relative to **I**, and the two terminal oxygen atoms of the carbonate moiety are engaged in hydrogen bonding with methanol (O···H–O 1.77 Å) and one *ortho*-hydrogen atom of the pyridinium ring (O···H–C: 2.05 Å). The geometric data of **I′2** only differ from **I′1** in the almost coplanar arrangement of the pyridinium ring and C=O skeleton (C_{ortho}NCO torsion angle 1.4°). This feature most probably results from the hydrogen bonding of the alkoxide terminus of **I′2** with both the methanol (O···H–O 1.58 Å) and one *ortho*-hydrogen atom of the pyridinium ring (O···H–C 1.81 Å). In addition to these acylpyridinium structures, the DMAP/α-lactone[26] adduct **I′3**, which formally results from the ring closure of **I′2**, was located as a minimum on the PES.

In marked contrast with that observed for lactide, acylpyridinium species **I′1** is only a few kcal mol^{-1} higher in energy than the separated reactants (Table 3). The charge separation induced by the nucleophilic ring-opening process is significantly less disfavorable with lacOCA as a result of the enhanced reactivity of the carboxylic anhydride moiety and the delocalized character of the liberated carbonate group. The entropic effect associated with the loss of carbon dioxide had to be taken into account to reliably compare the pyridinium structures before and after decarboxylation; therefore, the free enthalpies were calculated at 25 °C. Accordingly, all **I′1**, **I′2**, and **I′3** were predicted to be very close in energy.

All attempts to localize the transition states that lead to acylpyridinium compounds **I′1** and **I′2** from lacOCA failed, but transition states that correspond to the subsequent reaction of methanol with **I′1** and **I′2** were found (**TS′0a** and **TS′0b**, respectively). In both cases, the nucleophilic attack of methanol on the activated carbonyl group is assisted intra-

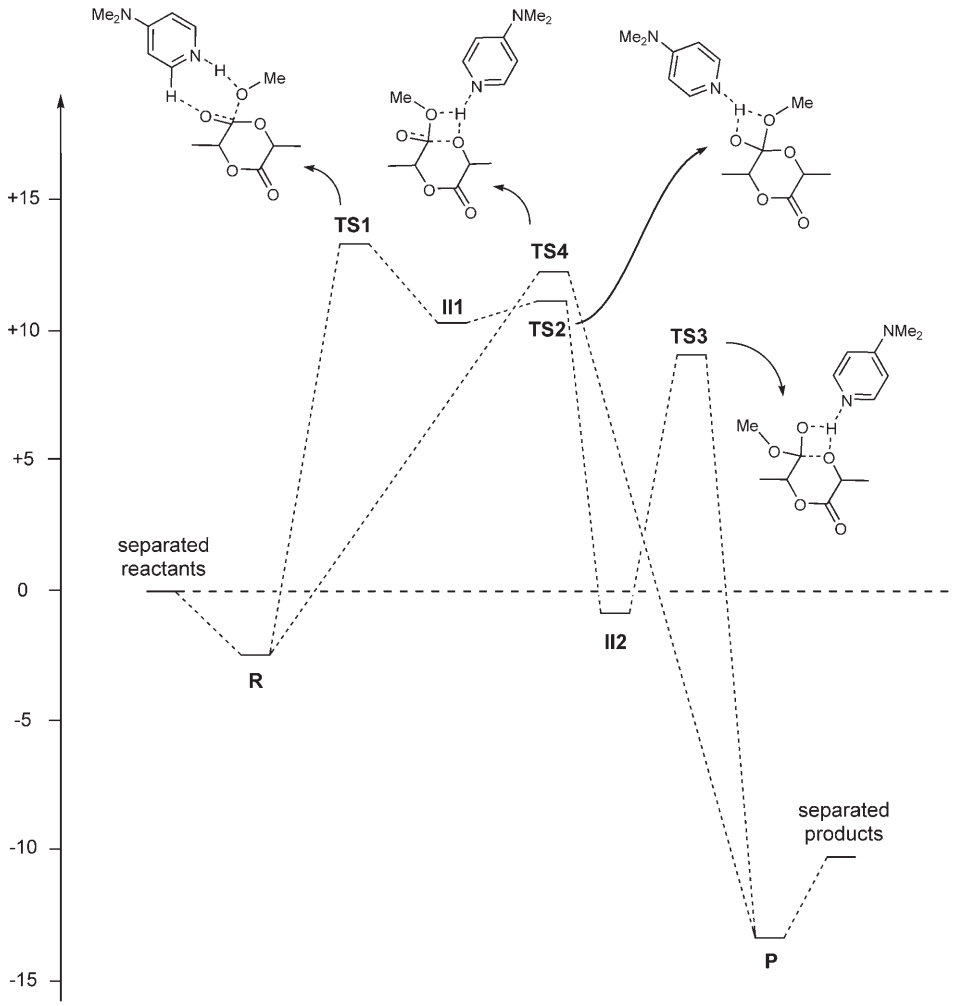


Figure 2. Energy profile of the base-catalyzed mechanism of the DMAP-catalyzed ring-opening of L-lactide with methanol, as calculated at the B3LYP/6–31G(d) level of theory (PCM/SCRF single-point calculations, including zero-point vibrational energy (ZPVE) correction).

Table 2. Energetic data (relative to the separated reactants) for the model ring-opening reaction (1) of lactide.

	E_{int}[a] [kcal mol^{-1}]	E_{int}[b] [kcal mol^{-1}]
ternary complex of reactants **R**	−15.1	−2.5
I	+22.1	+23.7
TS1 (R→II1)	+8.0	+13.4
II1	+6.9	+10.2
TS2 (II1→II2)	+9.2	+10.9
II2	−15.7	−0.7
TS3 (II2→P)	+5.1	+8.9
TS4 (R→P)	+13.9	+12.3
binary complex of products **P**	−26.4	−13.2

[a] At the B3LYP/6–31G(d) level of theory. [b] PCM/SCRF single-point calculations at the B3LYP/6–31G(d) level of theory, including ZPVE correction.

molecularly by the carbonate or alkoxide terminus. At all levels of the calculations, **TS′0b** was slightly favored energetically over **TS′0a**.

As far as the competitive base-catalyzed mechanism is concerned, local minima were found for the ion-pair and neutral tetrahedral intermediates **II′1** and **II′2** (Figure 4). The optimized geometries of these intermediates very much resemble the geometries of **II1** and **II2** derived from lactide: 1) the proton of methanol is transferred to the basic nitrogen atom of DMAP (N−H 1.07, O···H 1.60 Å) in the ion-pair structure **II′1**; 2) **II′1** is stabilized by a nonclassical hydrogen bond[20] involving one *ortho*-hydrogen atom of DMAP (O···H−C 2.07 Å); and 3) the neutral form **II′2** results from proton transfer to an exocyclic oxygen atom of lacOCA. Both tetrahedral intermediates **II′1** and **II′2** were readily energetically accessible (Table 4), and their formation from lacOCA was predicted to be more favorable by about $\Delta E =$ 10 kcal mol^{-1} relative to the formation of **II1** and **II2** from lactide. This difference most likely results from the nature of the functional group (*O*-carboxylic anhydride/ester) rather than the ring size of the monomer. Indeed, the tetrahedral intermediate is also computed to be about $\Delta E = 10$ kcal mol^{-1} higher in energy than the separated reactants for the related five-membered lactone, namely, α-methyl-γ-butyrolactone (see the Supporting Information). The ring-opened intermediate **III′**,[27] which derives from **II′1**/**II′2** and precedes the final decarboxylation step, was optimized. A strong hydrogen bond appears between the liberated hemi-carbonic acid terminus and DMAP (N···H 1.66 Å), and the formation of **III′** from **II′1**/**II′2** was predicted to be energetically favorable by about $\Delta E =$ 15 kcal mol^{-1}.

The whole reaction profile of the basic pathway was determined. Transition state **TS′1** connects the ternary complex of reactants **R′** with the ion-pair tetrahedral intermediate **II′1**, with barrier heights of about $\Delta E = 15$ and 7 kcal mol^{-1} in the gas phase and dichloromethane, respectively, which are about half of the barrier heights predicted for lactide (Figure 5). The ring-opening of **II′1** into **III′** proceeds in a concerted or stepwise fashion, with both routes requiring only small activation barriers. In addition, two closely related transition states, **TS′4a** and **TS′4b**, were found for the

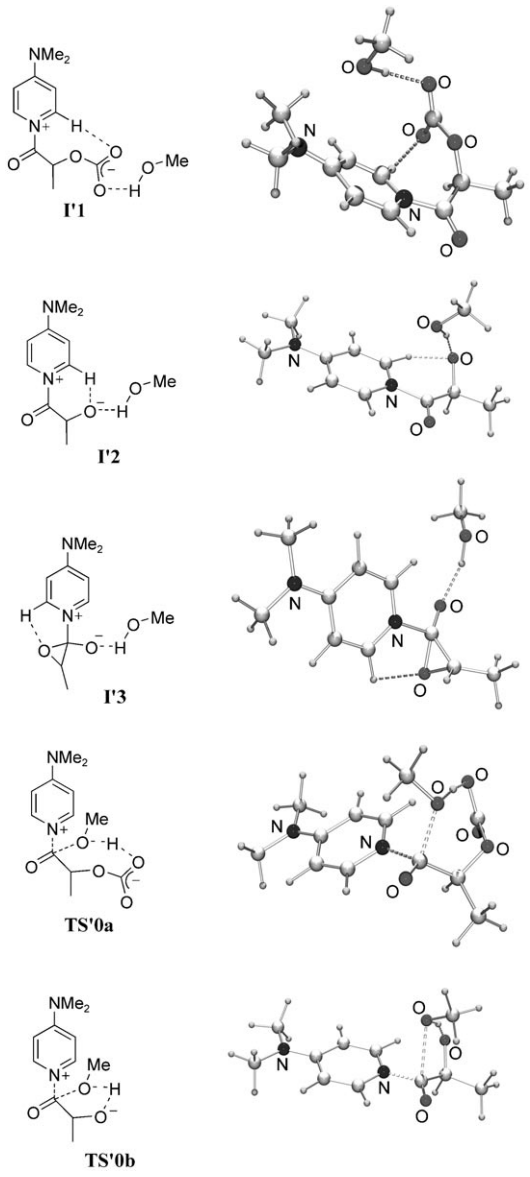


Figure 3. Optimized structures for the pyridinium intermediates **I′1–3** derived from lacOCA and transition states **TS′0a** and **TS′0b** associated with the subsequent reaction of methanol.

Table 3. Energetic data (relative to the separated reactants) for the nucleophilic mechanism of the model ring-opening reaction (2) of lacOCA.

	E_{int}[a] [kcal mol^{-1}]	E_{int}[b] [kcal mol^{-1}]	G_{298}[c] [kcal mol^{-1}]
I′1	+2.8	+2.0	+27.1
I′2 + CO_2	+17.5	+12.3	+29.5
I′3 + CO_2	+17.3	+16.4	+29.8
TS′0a	+21.7	+22.5	+47.5
TS′0b + CO_2	+18.2	+13.2	+31.4

[a] At the B3LYP/6–31G(d) level of theory. [b] PCM/SCRF single-point calculations at the B3LYP/6–31G(d) level of theory, including ZPVE correction. [c] Gibbs free energy computed at 25 °C.

concerted ring-opening of **R′** into **III′** (Figure 6). In both transition states, DMAP activates methanol through its

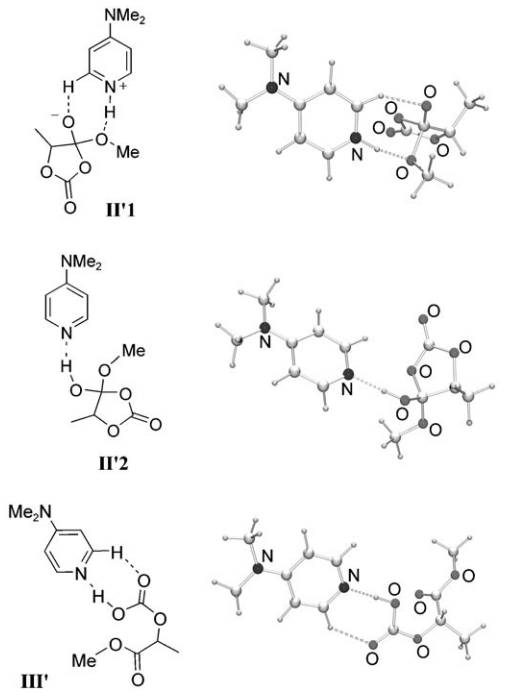


Figure 4. Optimized structures for the tetrahedral **II′1** and **II′2** and ring-opened **III′** intermediates derived from lacOCA.

Table 4. Energetic data (relative to the separated reactants) for the base-catalyzed mechanism of the model ring-opening reaction (2) of lacOCA.

	E_{int}[a] [kcal mol^{-1}]	E_{int}[b] [kcal mol^{-1}]	G_{298}[c] [kcal mol^{-1}]
ternary complex of reactant **R′**	−18.5	−5.7	+1.2
TS′1 (R′→II′1)	−3.2	+0.7	+21.8
II′1	−3.7	−2.1	+22.9
TS′2a (II′1→III′)	−1.5	−2.2	+25.1
TS′2b (II′1→II′2)	−1.1	−0.6	+25.9
II′2	−21.4	−7.0	+4.2
III′	−31.0	−19.4	−7.2
TS′3 (II′2→III′)	−14.4	−10.8	+12.2
TS′4a (R′→III′)	−1.7	+1.2	+22.7
TS′4b (R′→III′)	−2.4	+1.0	+22.5
TS′5 (III′→P′)	−19.0	−12.2	+1.9
ternary complex of products **P′**	−32.8	−19.9	−13.0

[a] At the B3LYP/6–31G(d) level of theory. [b] PCM/SCRF single-point calculations at the B3LYP/6–31G(d) level of theory, including ZPVE correction. [c] Gibbs free energy computed at 25 °C.

basic nitrogen atom and concomitantly interacts with the oxygen atoms developing negative charges (endocyclic in **TS′4a** and exocyclic in **TS′4b**) through one *ortho*-hydrogen atom. The corresponding barrier heights are very similar to those predicted for the stepwise pathway, thus suggesting that both routes may also intervene at this stage.

Finally, the ring-opened intermediate **III′** connects with the ternary complex of products **P′** via transition state **TS′5**. The proton transfer that accompanies this decarboxylation is promoted by double hydrogen bonding to DMAP, and the

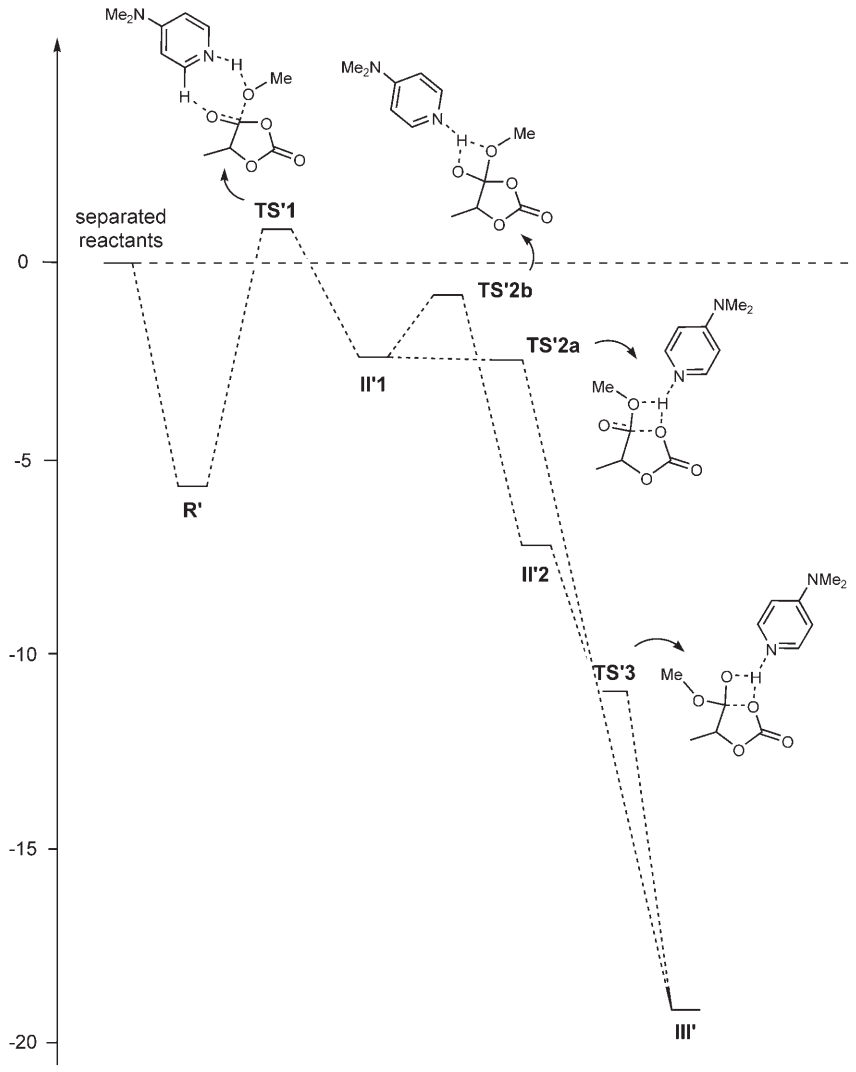


Figure 5. Energy profile of the base-catalyzed mechanism of the DMAP-catalyzed ring-opening of lacOCA with methanol (stepwise route to **III′**), as calculated at the B3LYP/6–31G(d) level of theory (PCM/SCRF single-point calculations, including ZPVE correction).[28]

corresponding energy barrier amounts to $\Delta E = 12$ kcal mol^{-1} in the gas phase ($\Delta E = 7$ kcal mol^{-1} in dichloromethane).

From these results, it is most likely that the DMAP-catalyzed ROP of lacOCA occurs by the activation of the initiating/propagating alcohol through hydrogen bonding, rather than nucleophilic activation of the monomer. Indeed, the highest transition state throughout the base-catalyzed mechanism lies significantly lower in energy than the most favorable transition state for the addition of methanol along the nucleophilic pathway (**TS′0b**). Accordingly, the difference in the activation barriers of the two pathways exceeds $\Delta E =$ 15 kcal mol^{-1} in electronic energies and $\Delta G = 9$ kcal mol^{-1} in Gibbs free energies. The ring-opening of lacOCA is predicted to proceed indifferently through a stepwise or concerted pathway. In addition, the possibility of DMAP acting both as a hydrogen-bond acceptor (through its basic nitrogen center) and a weak hydrogen-bond donor (through one *ortho*-hydrogen atom) is pointed out. This situation is reminiscent of that reported recently for the 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD)-catalyzed ROP of δ-valerolactone,[13] in which guanidine simultaneously activated the alcohol and monomer through hydrogen-bonding interactions to the basic nitrogen atom and acidic NH moiety. To the best of our knowledge, such a bifunctional role has not yet been proposed for DMAP.

Ring-opening of L-lacOCA with L-ethyl lactate: The pivotal role played by the alcohol in the base-catalyzed pathway prompted us to investigate the ring-opening of lacOCA with ethyl lactate as a more realistic model for the propagating alcohol. Reaction (3) was about $\Delta E = 5$ kcal mol^{-1} less favorable than reaction (2) (Table 1), but a very similar reaction profile was found along the basic pathway. Indeed, the replacement of methanol by the more sterically hindered and less-nucleophilic ethyl lactate did not noticeably modify the structures and energies of the various intermediates and transition states (Table 5; see the Supporting Information). These results further confirm the base activation of the alcohol as the preferred pathway in the DMAP-catalyzed ROP of lacOCA.

Comparison of carboxylic anhydrides and *O*-carboxylic anhydrides in the DMAP-catalyzed reactions of alcohols: The mechanism of base catalysis predicted herein for the DMAP-promoted reactions of alcohols with lacOCA markedly contrasts with the nucleophilic pathway substantiated by Zipse and co-workers for the esterification of alcohols with acetic anhydride.[14] To shed light on this discrepancy, we examined the influence of the primary/tertiary class of the alcohol engaged. Indeed, this aspect may explain at least in part the different behavior predicted for the lacOCA/MeOH and Ac_2O/*t*BuOH systems. Key points along the nucleophile- and base-catalyzed reactions of acetic anhydride were, thus, reoptimized with both *tert*-butyl alcohol and methanol (see the Supporting Information). With acetic anhydride, the acylpyridinium intermediate was predicted to be more stable than the separated reactants by $\Delta E = 4$ kcal

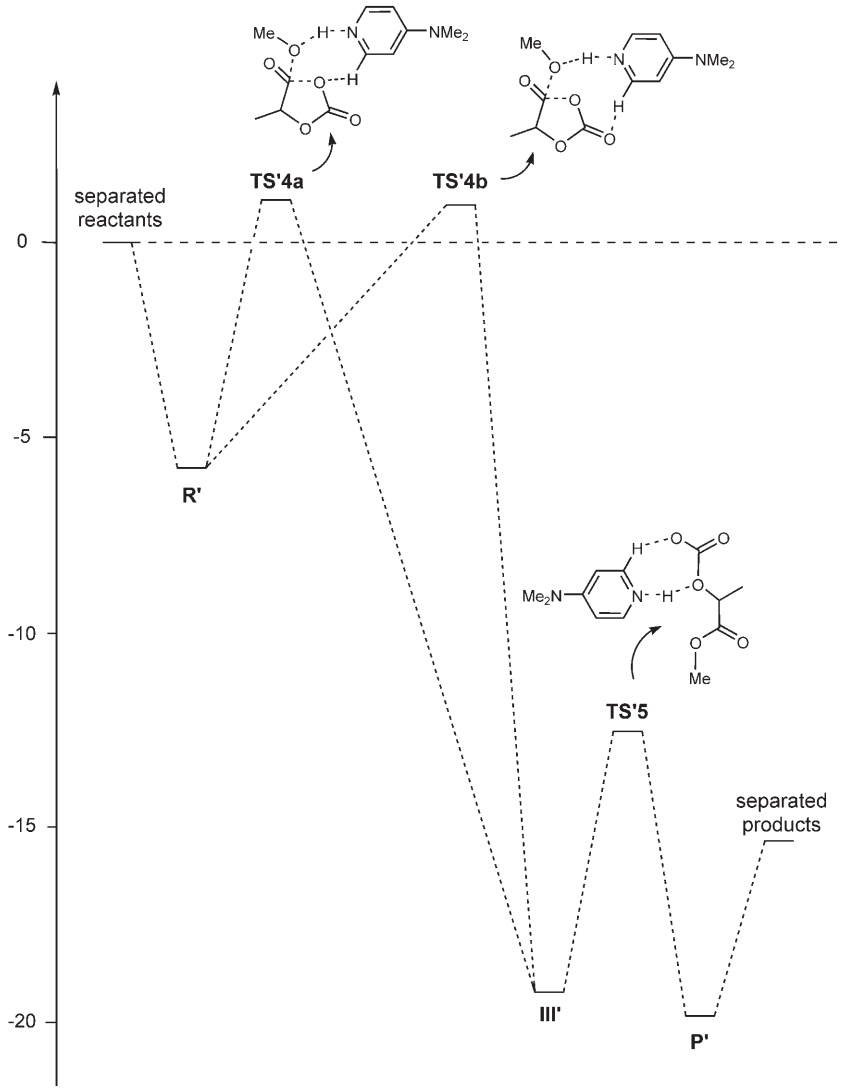


Figure 6. Energy profile of the base-catalyzed mechanism of the DMAP-catalyzed ring-opening of lacOCA with methanol (concerted route to **III′**) and subsequent decarboxylation, as calculated at the B3LYP/6–31G(d) level of theory (E_{int}; PCM/SCRF single-point calculations, including ZPVE correction).

Table 5. Energetic data (relative to the separated reactants) for the base-catalyzed mechanism of the model ring-opening reaction (3) of lacOCA.

	E_{int}[a] [kcal mol^{-1}]	E_{int}[b] [kcal mol^{-1}]
ternary complex of reactant **R″**	−16.6	−3.8
TS″1 (R″→II″1)	−0.6	+4.7
II″1	−1.0	+2.3
TS″2a (II″1→III″)	+3.0	+2.6
TS″2b (II″1→II″2)	+1.3	+3.3
II″2	−12.8	+1.0
III″	−24.3	−12.9
TS″3 (II″2→III″)	−9.0	−3.2
TS″4a (R″→III″)	−2.3	+3.7
TS″4b (R″→III″)	+0.3	+8.3
TS″5 (III″→P″)	−14.1	−15.8
ternary complex of products **P″**	−27.9	−16.1

[a] At the B3LYP/6–31G(d) level of theory. [b] PCM/SCRF single-point calculations at the B3LYP/6–31G(d) level of theory, including ZPVE correction.

mol^{-1}. The transition states for its formation, **pyr-TS$_{tBuOH}$** and **pyr-TS$_{MeOH}$**, were readily accessible in energy (only $\Delta E =$ 3 kcal mol^{-1} higher than the pyridinium compound), and, as expected, the influence of the alcohol was negligible. The transition states **nuc-TS$_{tBuOH}$** and **nuc-TS$_{MeOH}$** associated with the subsequent reaction of the alcohol were also located. In agreement with Zipse and co-workers,[14] the rate-determining step is the acyl transfer with *tert*-butyl alcohol (**nuc-TS$_{tBuOH}$** is located $\Delta E =$ 3.7 kcal mol^{-1} above **pyr-TS$_{tBuOH}$**). With methanol, the activation barriers for the two steps are very similar, the transition state for the acyl transfer **nuc-TS$_{MeOH}$** is located $\Delta E =$ 1 kcal mol^{-1} below **pyr-TS$_{MeOH}$**.

We studied the transition states **bas-TS$_{tBuOH}$** and **bas-TS$_{MeOH}$** that correspond to the reaction of acetic anhydride with *tert*-butyl alcohol and methanol promoted by hydrogen bonding with DMAP to compare the nucleophilic and basic pathways. Accordingly, **bas-TS$_{tBuOH}$** was $\Delta E =$ 8.6 kcal mol^{-1} above **nuc-TS$_{tBuOH}$**, thus suggesting that the base-catalyzed mechanism can hardly compete with the nucleophilic route for tertiary alcohols, in accord with Zipse and co-workers.[14] The nucleophilic mechanism was also more favorable than the basic route with methanol, but the difference between the energy barriers decreases to only $\Delta E = 2.1$ kcal mol^{-1} (between **pyr-TS$_{MeOH}$** and **bas-TS$_{MeOH}$**), thus suggesting that the two pathways may become competitive for primary alcohols.

The influence of the cyclic/acyclic nature of the substrate was briefly investigated by using methylsuccinic anhydride as a model cyclic carboxylic anhydride (see the Supporting Information). In marked contrast with acetic anhydride, the corresponding acylpyridinium intermediate was about $\Delta E =$ 5 kcal mol^{-1} above the separated reactants. This finding suggests that the nucleophilic pathway is somewhat disfavored for cyclic substrates and that the basic route may become more favorable, at least with primary alcohols. The transition state for the base-catalyzed reaction of methanol, predicted to be $\Delta E = 3$ kcal mol^{-1} below the pyridinium inter-

mediate, confirmed this hypothesis. From this comparison of carboxylic anhydrides and *O*-carboxylic anhydrides, it is clear that the competition between the nucleophilic and basic pathways is governed by subtle effects, such as the tertiary/primary class of the alcohol and the cyclic/acyclic nature of the substrate.

Conclusion

This computational investigation supports the base-catalyzed mechanism for the DMAP-promoted ROP of lactide and lacOCA. The DMAP-catalyzed acylation of alcohols with acetic anhydride had been shown to proceed preferentially through a nucleophilically activated mechanism that involves acylpyridinium intermediates. In marked contrast, the ring-opening reactions of lactide and lacOCA with alcohols are predicted herein to occur through the activation of the alcohol and with both the traditional stepwise mechanisms, which involve tetrahedral intermediates and the concerted pathway, being conceivable. The critical role of the tertiary/primary class of the alcohol and the cyclic/acyclic nature of the substrate in the competition between the nucleophilic and basic mechanisms is highlighted.

In addition, the optimized intermediates and transition states in the base-catalyzed ring-opening of lactide and lacOCA substantiate the central role of multiple hydrogen bonding and evidence the possibility of DMAP acting as a bifunctional catalyst through its basic nitrogen center and an acidic *ortho*-hydrogen atom. These results further emphasize the potential of bifunctional systems in efficiently promoting ring-opening polymerization and should stimulate the investigation of new organic systems susceptible to cooperative activation of the monomer and propagating moiety.

Experimental Section

Computational studies: The theoretical treatment of the systems included herein was performed by using the density-functional approach[29] with the B3LYP hybrid functional. Calculations were carried out with the Gaussian 03 series of programs.[30] All stationary points were optimized at the B3LYP/6–31G(d) level of theory. Only the most stable conformational isomer was considered in the discussion for all intermediates and transition states. The nature of all the stationary points was verified by calculations of the vibrational frequency spectrum, and intrinsic reaction coordinate (IRC) computations[31] were carried out to ascertain the connectivity of the transition states. The solvent effect of dichloromethane ($\varepsilon = 8.93$) was taken into account through PCM/SCRF single-point calculations for the B3LYP/6–31G(d) gas-phase structures.[32] The reliability of the B3LYP method was assessed by using single-point calculations at the MP2/6–31G(d) level of theory for the reaction of lacOCA with methanol.

Acknowledgements

We are grateful to the CNRS, UPS, UPV/EHU, MEC (Ingenio-Consolider 2010), and RDR2 cluster "Aller vers une Chimie Eco-compatible" for financial support and to CalMip (CNRS, Toulouse, France) and SGI/IZO-SGIker UPV/EHU for generous allocation of computational resources. C.B. acknowledges the French Ministry "Education Nationale, Enseignement Supérieur, Recherche" for a PhD grant. Helpful discussions with Dr. L. Maron (Toulouse) and Dr. K. Miqueu (Pau) are especially appreciated.

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Received: February 25, 2008
Published online: April 30, 2008

