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Computational Investigation of Mechanisms for Ring-Opening Polymerization of ϵ-Caprolactone: Evidence for Bifunctional Catalysis by Alcohols

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Abstract: Stepwise addition/elimination and concerted mechanisms for the methanolysis of ϵ-caprolactone, as a model for the initiation and propagation of ring-opening polymerization (ROP), have been investigated computationally using the B3LYP/6-31G* density functional method, with assistance from one or two ancillary methanol molecules. The effects of specific solvation by these extra methanols in cyclic hydrogen-bonded clusters are very significant, with barrier height reductions of about 50 kJ mol^{-1}. However, the effects of bulk solvation as treated by the polarized continuum model are almost negligible. Increasing the ring size lowers the barriers for both the addition and elimination steps of the stepwise mechanism but does not do so for the concerted mechanism; a stepwise mechanism is preferred for methanol-assisted ROP. The essential catalytic role of solvent molecules in this reaction is to avoid the unfavorable accumulation or separation of charges.

Introduction

The ring-opening polymerization (ROP) of a variety of cyclic esters, including ϵ-caprolactone (ϵ-CL) to form biocompatible, biodegradable polymers has generated great interest in recent years. This is due to the potential application of these materials in areas of medicine such as drug delivery, implants, and tissue engineering.[1] New polymers are continually being developed, creating a great demand for new materials and for improved syntheses. ROP is the most commonly used synthetic strategy for preparing these macromolecules and can be carried out with overall high efficiency using transition-metal (TM) initiating compounds.[2]

Despite controversy regarding some initiators, ROP has been shown to proceed by a coordination-insertion mechanism with acyl−oxygen cleavage of the monomer and insertion into the metal−oxygen bond of the initiator. Much work has been focused on the synthesis of new tin, aluminum, and TM initiators,[3] with the goal of increasing reactivity and the production of novel polymer structures.[4] Reaction mechanisms involving TMs have been investigated by kinetic, spectroscopic,[5,6] or chromatographic methods.[7] Commercial catalysts for these important processes are currently based on complexes of tin,[8] but with growing environmental concerns, there is a need to develop more benign catalysts.

As the first part of an extensive computational modeling study of ROP mechanisms catalyzed by TM complexes,[9] we wish to report now upon alternative mechanisms for the reference reaction of ϵ-CL initiated by alcohol with a view to determining what factors govern the reactivity of these systems.

The first step of lactone ROP requires an initiator ROH, as shown in the initiation step of Scheme 1; subsequent chain-propagation steps involve the ring-opened intermediate

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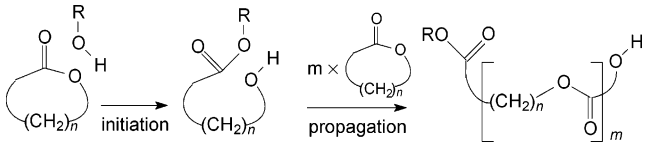
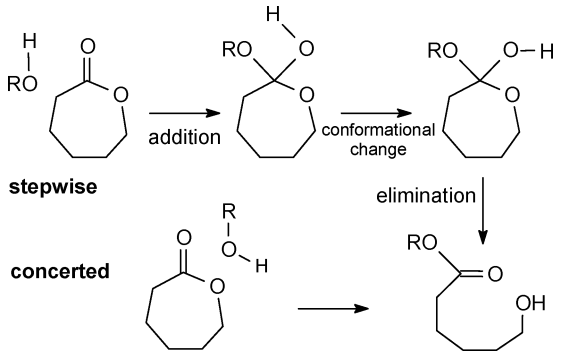
Scheme 1



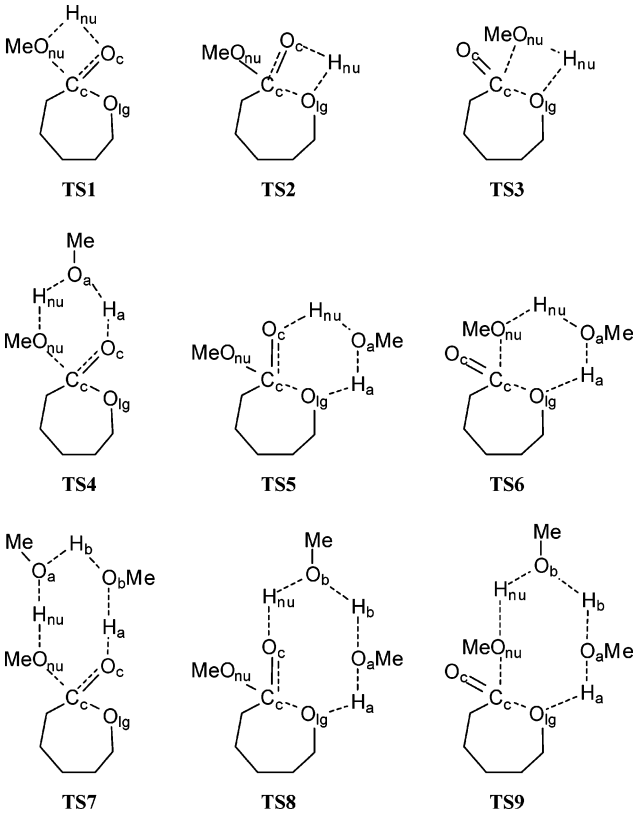
Scheme 2



reacting with further lactone monomers to yield polymers. Both initiation and propagation steps may be subject to catalysis. We have employed density functional theory to perform a computational study of mechanisms (Scheme 2) for the initiation step with ϵ-CL and R═Me (methanol). This serves also as a model for the propagation steps, where ROH is ring-opened ω-hydroxyester. We have considered two overall mechanisms: (a) the stepwise addition−elimination of MeOH across the acyl C═O bond and (b) a concerted addition of MeOH across the acyl C−O bond (metathesis). For each alternative, we have also considered the possibility of either one, two, or three MeOH molecules in cyclic hydrogen-bonded complexes (Chart 1 shows transition structures **TS1**−**TS9** for these complexes), analogous to those found in many other related processes.[10] Analogous mechanisms for the neutral and water-assisted hydrolysis of acyclic esters, methyl formate[11] and ethyl acetate,[12] have been the subjects of previous computational studies, but the present work is the first such study of lactone alcoholysis.

A cyclic transition state involving three molecules of methanol has been proposed by Venkatasubban et al.[13a] for the neutral methanolysis of *p*-nitrophenyl trifluoroacetate in acetonitrile, for which the apparent kinetic order with respect to MeOH is 2.87. Hydrolysis of the same ester in acetonitrile shows a similar apparent kinetic order of 3.22 with respect to both H_2O and D_2O, and proton inventory studies with H_2O/D_2O mixtures suggest a transition state involving the transfer of three protons. These authors recognized that similar cyclic transition states could exist for both the formation and breakdown of a hemiorthoester intermediate. Similar results have been obtained for the hydrolysis of *p*-methylphenyl trichloroacetate in acetonitrile.[13b] The cyclic transition states for reactions in acetonitrile/water mixtures are in contrast to the acyclic three-proton model proposed for ester hydrolysis in water. It is thought that this difference is due to the stabilization of the developing charges on the oxygens by hydrogen bonds to bulk water in aqueous solution; this kind of stabilization is difficult to achieve in a predominantly nonaqueous medium, which forces a cyclic transition state with minimal development of the charges.[13a]

Chart 1. Cyclic Transition Structures for Stepwise and Concerted Mechanisms of ϵ-CL ROP Initiation Involving One, Two, or Three CH_3OH Molecules[a]



[a] Subscripts denote the following: nu, nucleophile; lg, leaving group; c, carbonyl; a, first ancillary molecule; b, second ancillary molecule.

Methods

The calculations of density functional theory using the B3LYP exchange-correlation functional[14,15] were carried out with the GAMESS-UK[16] and Gaussian 03 packages of programs,[17] using the 6-31G* basis set.[18] The geometries and energies of each structure were fully optimized and its nature confirmed by frequency analysis. Transition structures (TSs) were located by means of the EF algorithm[19] and characterized by frequency calculations, both in vacuo and in solution. Intrinsic reaction co-ordinate (IRC) calculations were used to verify the adjacent local minima. Charge distributions were obtained by natural population analysis.[20] Solvent effects were examined by means of the polarized continuum method (PCM),[21] whereby the solvent was characterized by its dielectric constant (ϵ = 32.6 for methanol and ϵ = 78.4 water) around a cavity shaped by a superposition of spherical solute atoms; frequencies and zero-point energies were computed for each stationary structure in PCM methanol and water. Computed bond lengths are given in angströms, bond angles in degrees, total energies in hartrees, and unless otherwise stated zero-point energies and relative energies in kJ mol^{-1}.

Results and Discussion

Table 1 contains relative energies in a vacuum, methanol, and water for each B3LYP/6-31G*-optimized geometry with respect to the reactant complex for the methanolysis of ϵ-CL.

Table 1. B3LYP/6-31G* Relative Energies (kJ mol^{-1}) in a Vacuum (Potential Energy ΔE_{tot}, Zero-Point-Corrected Energy ΔE_0, and Free Energy ΔG_{298} at 298 K and 1 atm) and in PCM Methanol and Water for the Methanolysis of ϵ-Caprolactone

	vacuum			MeOH	H_2O
species	ΔE_{tot}	ΔE_0	ΔG_{298}	ΔE_0	ΔE_0
One Methanol					
ϵ-CL + CH_3OH **(3)**	31	27			
ϵ-CL·CH_3OH **(4)**	0	0	0	0	0
addition TS **(TS1)**	173	163	179	173	176
intermediate **(5a)**	28	33	50	43	47
conformational TS **(5a → 5b)**	42	48	66		
intermediate **(5b)**	18	23	41	32	43
elimination TS **(TS2)**	155	145	162	166	166
product **(6)**	−10	−8	2	8	3
concerted TS **(TS3)**	172	160	176	176	176
Two Methanols					
ϵ-CL + $2CH_3OH$ **(7)**	91	77			
ϵ-CL·$2CH_3OH$ **(8)**	0	0	0		
addition TS **(TS4)**	138	124	138	126	127
intermediate + CH_3OH **(9a)**	42	48	60	59	61
intermediate + CH_3OH **(9b)**	30	35	45	34	39
elimination TS **(TS5)**	119	104	118	114	120
product·CH_3OH **(10)**	−14	−14	−15	−21	−16
concerted TS **(TS6)**	178	160	172	169	167
Three Methanols					
e-CL + $3CH_3OH$ **(11)**	146	126			
e-CL·$3CH_3OH$ **(12)**	0	0	0		
addition TS **(TS7)**	125	101	113	95	100
intermediate + $2CH_3OH$ **(13a)**	33	38	45	61	60
intermediate + $2CH_3OH$ **(13b)**	33	37	44	33	38
elimination TS **(TS8)**	129	110	124	106	109
product·$2CH_3OH$ **(14)**	−9	−10	−14	−15	−15
concerted TS **(TS9)**	174	161	177	165	166

Potential energy differences ΔE_{tot}, zero-point-corrected 0 K energy differences ΔE_0, and free energy differences ΔG_{298} at 298 K and 1 atm are shown for calculation in a vacuum, whereas only the ΔE_0 results are shown for solvated species. The relative free energies for species along the reaction coordinates within the cyclic complexes are independent of the choice of standard state. The discussion below is based on the 0 K energies unless otherwise noted. Figures 1−3 respectively show structures and relative energies for reactions involving one, two, and three methanol molecules. The atom-labeling scheme used throughout is shown in Chart 1.

ϵ-CL ROP with One CH_3OH Molecule. The formation of reactant complex **4** from ϵ-CL **1** and a single methanol **2** (the combined energy of which is denoted by **3**) is energetically favorable by 27 kJ mol^{-1} in a vacuum at 0 K. The addition of $MeO_{nu}H_{nu}$ to the C_c═O_c double bond, the first step of the stepwise mechanism, involves a four-membered-ring **TS1** in which formation of the new O_{nuc}−C_c bond and breaking of the carbonyl π bond are coupled to proton transfer from the nucleophile to the carbonyl oxygen atom O_c, yielding a hemiacetal intermediate **5a** that is 33 kJ mol^{-1} above the reactant complex (Scheme 2). This tetrahedral adduct must undergo a favorable conformational change (−10 kJ mol^{-1}) to **5b** in order to facilitate the elimination step stereoelectronically. The transition structure **5a → 5b** for this conformational change involves an energy barrier of only 15 kJ mol^{-1}. The second step of the stepwise mechanism also involves a four-membered-ring **TS2**, in which cleavage of the C_c−O_{lg} bond and reformation of the carbonyl π bond are coupled to proton transfer from the hemiacetal O_c−H to the ring oxygen atom O_{lg}, giving the ring-opened methyl 6-hydroxyhexanoate product **6**, which lies 8 kJ mol^{-1} in energy below **4**. The energies of **TS1** and **TS2** relative to **4** are, respectively, 163 and 145 kJ mol^{-1}, indicating that the first step (addition) would be rate-determining. The calculated barrier height for the addition of methanol to ϵ-CL is very similar in magnitude to those calculated previously for the addition of one molecule of water or methanol to aldehydes by means of a four-membered-ring TS.[22]

Along the concerted reaction path, the methanol nucleophile attacks the carbonyl C_c but transfers its proton directly to the leaving-group O_{lg} atom of the lactone. This mechanism is comparable to intermolecular concerted S_N2 acyl transfer, but its quasi-intramolecular nature imposes a severe geometrical constraint such that it would be considered as front-side nucleophilic attack. Alternatively, the mechanism may be regarded as a metathesis, with two new σ bonds (O_{nuc}−C_c and H−O_{lg}) being formed simultaneously with breaking of the methanol O−H and lactone C_c−O_{lg} σ bonds, leading directly to the hydroxyester product **6**. The four-membered-ring **TS3** (Figure 1) lies 160 kJ mol^{-1} above the energy of the reactant complex **4**, suggesting that both stepwise and concerted mechanisms might be competitive for ROP involving only one molecule of methanol. However, **TS1**, **TS2**, and **TS3** are each highly strained, and it is unlikely that any significant fraction of the actual gas-phase alcoholysis of ϵ-CL proceeds by means of either of these one-methanol mechanisms since both involve a very high energy barrier. The unfavorable strain energy could be relieved by the incorporation of one or two additional methanol molecules into a cyclic hydrogen-bonded supermolecule, as discussed below.

ϵ-CL ROP with Two CH_3OH Molecules. An additional methanol molecule may be incorporated into a cyclic hydrogen-bonded complex such that it acts both as a proton donor to the ϵ-CL and as a proton acceptor to the original (nucleophilic) methanol. Thus, the ancillary methanol (MeO_a-H_a in Chart 1) may serve as a bifunctional catalyst.[10a,c,23]

The formation of reactant complex **8** from ϵ-CL **1** and 2× MeOH **2** is energetically favorable by 77 kJ mol^{-1} in a vacuum; note that cooperativity among the interactions between the component species in **8** causes the association energy to be greater than twice that in **4**. The methanol-assisted addition of methanol to the C_c═O_c double bond, the first (addition) step of the stepwise mechanism, involves a six-membered-ring **TS4** in which formation of the new O_{nu}−C_c bond and breaking of the carbonyl π bond are coupled to a double proton transfer from the nucleophile via the ancillary MeOH to O_c, yielding a complex **9a** of methanol with a hemiacetal intermediate that is 48 kJ mol^{-1} above **8** (Figure 2). This tetrahedral adduct must undergo a favorable

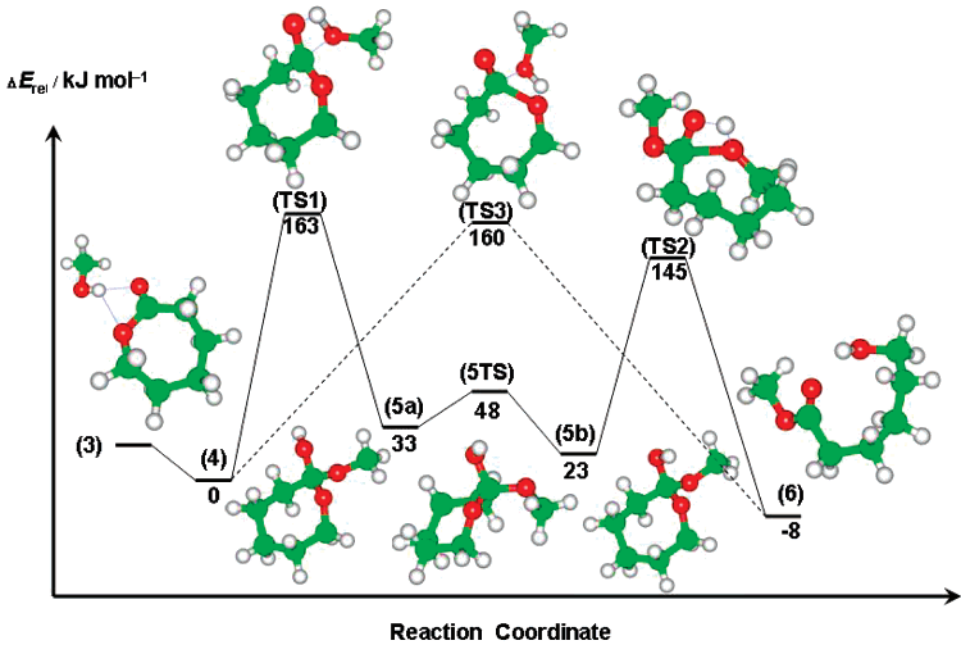


Figure 1. Zero-point-corrected B3LYP/6-31G* energy profile in a vacuum for the stepwise (solid line) and concerted (dashed line) mechanisms of ϵ-CL ROP with one CH_3OH molecule.

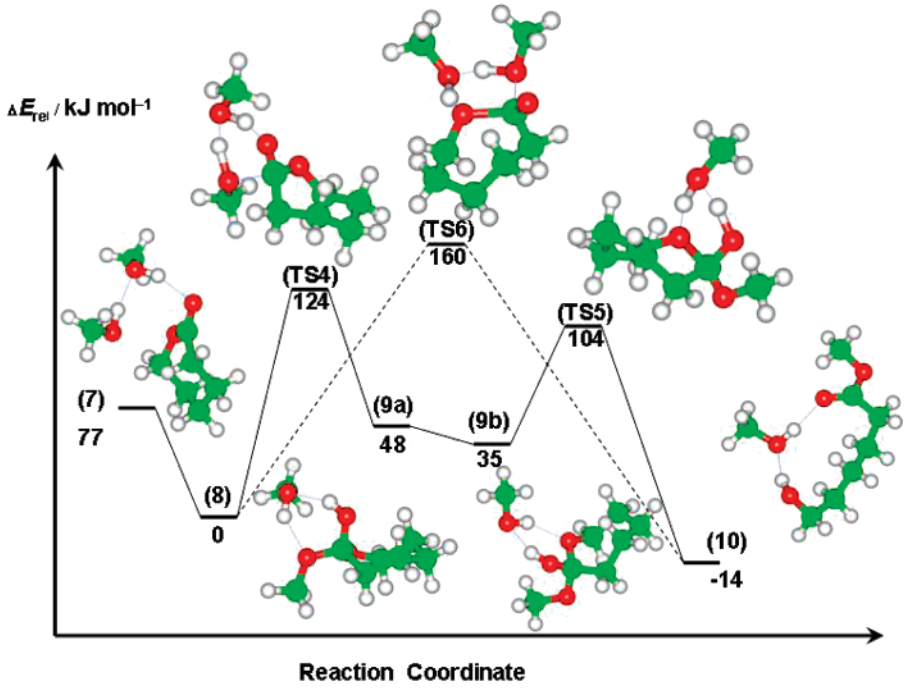


Figure 2. Zero-point-corrected B3LYP/6-31G* energy profile in a vacuum for the stepwise (solid line) and concerted (dashed line) mechanisms of ϵ-CL ROP with two CH_3OH molecules.

conformational change (-13 kJ mol^{-1}) to **9b** in order to facilitate the elimination step stereoelectronically. This change involves not only internal rotation of the hydroxyl group but also a repositioning of the ancillary MeOH; however, as for TS **5a** → **5b**, the energy barrier is not expected to be large, and the transition structure for this conformational rearrangement has not been characterized in this study. The second (elimination) step of this mechanism also involves a six-membered-ring **TS5**, in which cleavage of the C_c-O_{lg} bond and reformation of the carbonyl π bond are coupled to proton transfer from the hemiacetal O_c-H via the ancillary MeOH to O_{lg}, giving the ring-opened product complex **10** of methanol with methyl 6-hydroxyhexanoate, which lies 14 kJ mol^{-1} in energy below **8**. The energies of **TS4** and **TS5** relative to **8** are, respectively, 124 and 104 kJ mol^{-1}, indicating that the addition step would be rate-determining.

Along the reaction path for the concerted mechanism, the nucleophilic methanol attacks C_c with a transfer of its proton via the ancillary MeOH directly to O_{lg}, which is the leaving group. Again, this mechanism resembles concerted S_N2 acyl transfer, but still its quasi-intramolecular nature involves a

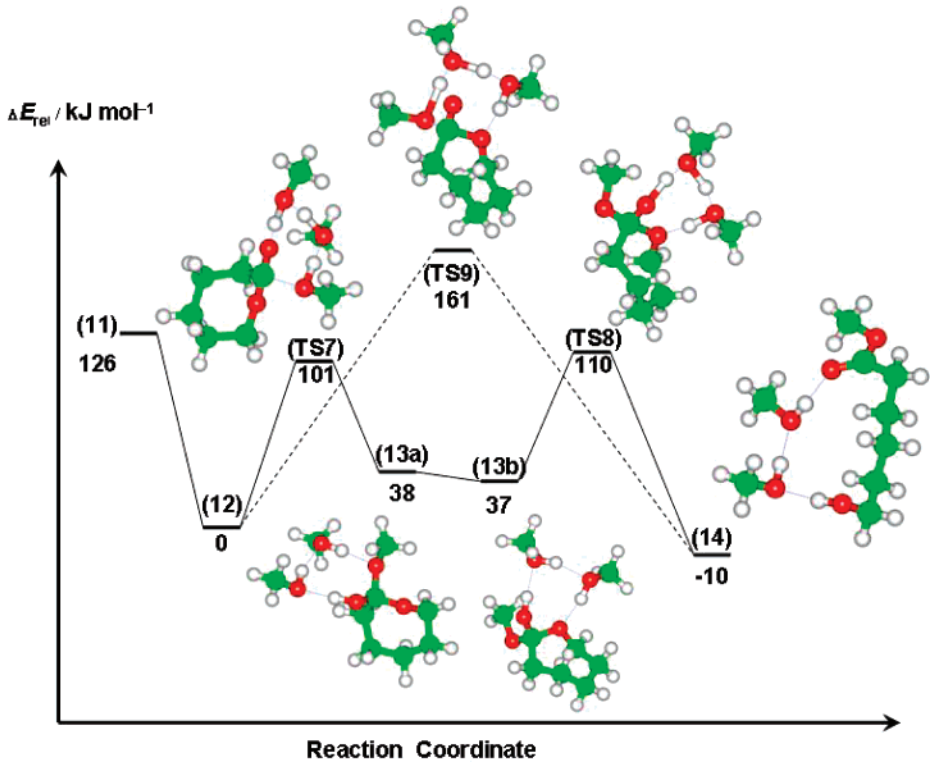


Figure 3. Zero-point-corrected B3LYP/6-31G* energy profile in a vacuum for the stepwise (solid line) and concerted (dashed line) mechanisms of ϵ-CL ROP with three CH_3OH molecules.

very severe geometrical constraint ($O_{nu}C_cO_{lg}$ angle = 93°) despite the expanded size of the cyclic TS. The six-membered-ring **TS6** (Figure 2) once again lies 160 kJ mol^{-1} above the energy of the reactant complex **8**, indicating that expansion from a four-membered ring to a six-membered ring is not accompanied by reduction of the energy barrier for the concerted mechanism. Whereas the reaction involving only one molecule of methanol showed that both the stepwise and concerted mechanisms might be competitive for ROP, it is clear that the methanol-assisted reaction favors the stepwise addition/elimination, for which the rate-determining step is 36 kJ mol^{-1} lower than the barrier for the concerted mechanism.

ϵ-CL ROP with Three CH_3OH Molecules. The formation of reactant complex **12** from ϵ-CL **1** and 3× MeOH **2** is energetically favorable by 126 kJ mol^{-1} in a vacuum; again, cooperativity among the interactions between the component species in **12** causes the association energy to be greater than thrice that in **4**. Incorporation of the third methanol molecule further expands the cyclic hydrogen-bonded complex to an eight-membered ring. Addition to the $C_c{=}O_c$ double bond is coupled to a triple proton transfer: from the nucleophile to the first ancillary methanol, from this to the second ancillary methanol, and from that to O_c. Inspection of the transition vector and the IRC path confirms that **TS7** is the only stationary point between **12** and the tetrahedral intermediate **13a**, which lies 38 kJ mol^{-1} above the reactant complex (Figure 3). Following a conformational change and repositioning of the two ancillary methanols, the elimination phase of the stepwise mechanism proceeds from intermediate **13b** by means of another eight-membered cyclic **TS8**, again involving a triple proton transfer from O_c to O_{lg} via the two ancillary methanols. The energies of **TS7** and **TS8** relative to **12** are, respectively, 101 and 110 kJ mol^{-1}, now indicating that the elimination step would be rate-determining. The barrier for the addition step via **TS7** is 23 kJ mol^{-1} lower than that via **TS4** with one fewer methanol, whereas the barrier for the elimination step via **TS8** is a little higher than that via **TS5** with the smaller ring. Note that **TS8** (as shown in Figure 3) is the lowest of three conformations considered with differing relative orientations of the methyl groups of the ancillary methanols: the other conformations were 6 and 9 kJ mol^{-1} higher in energy.

Along the concerted reaction path, **TS9** again involves a triple proton transfer from O_{nu} to O_{lg} via the two ancillary methanols in an eight-membered ring. At 161 kJ mol^{-1}, the barrier for this mechanism is remarkably similar to those for the concerted mechanisms via **TS3** and **TS6** with the smaller rings. Inclusion of the third methanol favors the stepwise over the concerted mechanism by 51 kJ mol^{-1}. Note that these (relative) energies are zero-Kelvin enthalpy changes; consideration of temperature-dependent entropy contributions within the cyclic complexes does not materially alter any of the conclusions in the above discussion: the relative free energies at 298 K (Table 1) for the various TSs of interest are all raised by a small amount in the range 12−17 kJ mol^{-1} but do not show any changes of mechanistic significance.

Continuum Solvent Effects. The reoptimization of all stationary structures with PCM methanol and PCM water, and the inclusion of zero-point energies obtained from vibrational frequencies computed with these continuum models, leads to very similar energetic trends to those discussed above for the reactions in a vacuum (Table 1).

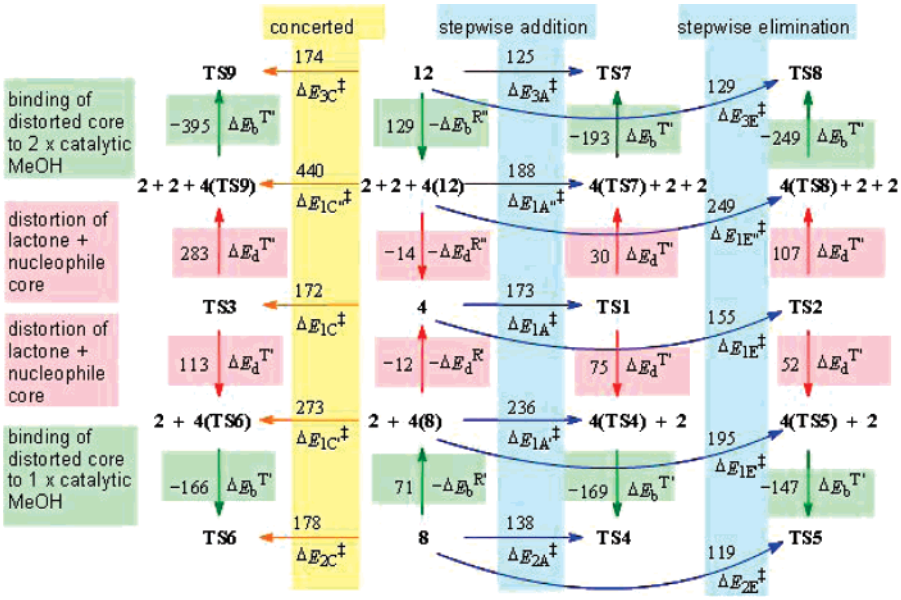


Figure 4. Energetics of ϵ-CL methanolysis analyzed in terms of contributions from the binding (green) of one (lower half) or two (upper half) ancillary methanol molecules and distortion (pink) of the lactone + nucleophilic methanol reacting core for the concerted (yellow, left half) and stepwise addition and elimination (blue, right half) mechanisms.

Although the concerted mechanism is competitive with the stepwise addition/elimination mechanism for the unassisted reaction, the stepwise mechanism is favored for reactions assisted by either one or two ancillary methanols. The addition step is rate-determining for reactions involving four- or six-membered rings, and the barrier height decreases with increasing ring size in both solvents, with the consequence that the elimination step becomes rate-determining for the largest (eight-membered) ring. Most of the barrier heights are slightly larger in solution than in a vacuum. However, the overall effect of PCM solvation, in which methanol or water is treated as a continuum characterized by the dielectric constant of the bulk solvent, upon the reaction energetics is rather small and uninteresting by comparison with the specific effects of the ancillary methanols considered in the next section.

Specific Solvation by Ancillary Methanol Molecules: Analysis of Distortion and Binding Energy Contributions. The purpose of this section is to consider how the barrier-height reductions reported above are achieved. The analysis presented assumes a "fundamentalist" view of catalysis, which focuses upon the differential stabilization of the transition state relative to the reactant state. The source of the catalytic effect of the ancillary methanol molecule(s) may be analyzed most directly in terms of potential energies (i.e., not including zero-point energies). It is convenient to consider the interaction energy of either a reactant complex or a transition structure with a catalyst as the sum of two components. The first is a distortion energy required to alter the geometries of the "core" fragments (lactone + nucleophile) of the uncatalyzed reaction to the structures they possess in the catalyzed reaction. The second is an intrinsic binding energy for bringing the distorted core together with the catalyst, which is either a single ancillary methanol (1× catalytic MeOH) or two ancillary methanols (2× catalytic MeOH). These components are color-coded in Figure 4 (pink for distortion and green for binding) and applied to both concerted (yellow) and stepwise (blue) mechanisms.

The potential energy barrier $\Delta E_{2A}^{\ddagger}$ for the addition step of the two-methanol stepwise mechanism (**8** → **TS4**, lower-right of Figure 4) may be expressed by eq 1.

$$\Delta E_{2A}^{\ddagger} = \Delta E_{1A}^{\ddagger} - \Delta E_b^{R'} - \Delta E_d^{R'} + \Delta E_b^{T'} + \Delta E_d^{T'} \quad (1)$$

$\Delta E_{1A}^{\ddagger}$ is the barrier height (173 kJ mol^{-1}) for the addition step of the one-methanol stepwise mechanism (**4** → **TS1**, middle right of Figure 4). $\Delta E_b^{R'}$ and $\Delta E_b^{T'}$ are the respective binding energies (−71 and −169 kJ mol^{-1}) of one additional methanol **2** with species **4(8)** and **4(TS4)**, which are the distorted "core" (ϵ-CL + nucleophilic methanol) fragments **4** as found in reactant complex **8** and transition structure **TS4**. $\Delta E_d^{R'}$ and $\Delta E_d^{T'}$ are the corresponding respective distortion energies (12 and 75 kJ mol^{-1}) of those core fragments relative to **4** and **TS1**. The ancillary methanol, which acts as both a hydrogen-bond acceptor and a hydrogen-bond donor, has a much stronger interaction with the distorted core in **TS4** than in **8** because of the greater dipolar character that develops as the nucleophilic addition proceeds;[25] the dipole moment of the core fragment increases from 3.44 d in **4(8)** to 4.77 d in **4(TS4).** The distortion energy of the ϵ-CL + nucleophile core from **TS1** to **TS4** is greater than that from **4** to **4(8)**. The difference $\Delta E_b^{T'} - \Delta E_b^{R'} = -98$ kJ mol^{-1} is the contribution to catalysis from the interaction of the reacting core with one ancillary methanol serving as a bifunctional catalyst. This amount is offset by the difference $\Delta E_d^{T'} - \Delta E_d^{R'} = +63$ kJ mol^{-1}, which is the net distortion energy that must be paid in order for the core to attain the necessary geometry to realize its increased interaction with the catalyst. The net catalytic effect $\Delta E_{1A}^{\ddagger} - \Delta E_{2A}^{\ddagger}$ is 35 kJ mol^{-1} (Table 2) for a single ancillary methanol on the addition step of the stepwise mechanism.

A similar analysis follows for catalysis of the stepwise mechanism by two ancillary methanols. The potential energy

Table 2. Analysis of the Effect of the Number *N* of Ancillary Methanol Molecules upon the Relative Energy Barriers (kJ mol^{-1}) for the Stepwise and Concerted Mechanisms

	addition			concerted			elimination		
$N=$	0	1	2	0	1	2	0	1	2
$\Delta E_{core}^{\ddagger}$	173	173	173	172	172	172	155	155	155
$\Delta E_{distortion}^{\ddagger}$	0	63	16	0	101	268	0	40	93
$\Delta E_{binding}^{\ddagger}$	0	−98	−64	0	−95	−266	0	−76	−120
$\Delta E_{total}^{\ddagger}$	173	138	125	172	178	174	155	119	129
$\Delta E_{catalysis}^{\ddagger}$		−35	−48		+6	+2		−36	−26

barrier $\Delta E_{3A}^{\ddagger}$ for the addition step involving a total of three methanols (**12** → **TS7**, upper right of Figure 4) may be expressed by eq 2.

$$\Delta E_{3A}^{\ddagger} = \Delta E_{1A}^{\ddagger} - \Delta E_b^{R''} - \Delta E_d^{R''} + \Delta E_b^{T''} + \Delta E_d^{T''} \quad (2)$$

$\Delta E_b^{R''}$ and $\Delta E_b^{T''}$ are the respective binding energies (−129 and −193 kJ mol^{-1}) of two additional methanols (**2** + **2**) with species **4(12)** and **4(TS7)**, which are the distorted core fragments **4** as found in reactant complex **12** and transition structure **TS7**. $\Delta E_d^{R''}$ and $\Delta E_d^{T''}$ are the corresponding respective distortion energies (14 and 30 kJ mol^{-1}) of those core fragments relative to **4** and **TS1**. The ancillary methanol dimer fragment, which again acts as both a hydrogen-bond acceptor and a hydrogen-bond donor, also has a much stronger interaction with the distorted core in **TS7** than in **12** because of the greater dipolar character that develops as the nucleophilic addition proceeds; the dipole moment of the core fragment increases from 3.33 d in **4(12)** to 4.50 d in **4(TS7)**. The distortion energy of the core from **TS1** to **TS4** is greater than that from **4** to **4(12)**. The difference $\Delta E_b^{T''} - \Delta E_b^{R''} = -64$ kJ mol^{-1} is the contribution to catalysis from the interaction of the reacting core with two ancillary methanols serving bifunctionally as a catalytic dimer. This amount is offset by the difference $\Delta E_d^{T''} - \Delta E_d^{R''} = +16$ kJ mol^{-1}, the net distortion energy for the core to attain the necessary geometry to realize its increased interaction with the catalyst. The net catalytic effect $\Delta E_{1A}^{\ddagger} - \Delta E_{3A}^{\ddagger}$ is 48 kJ mol^{-1} (Table 2) for two ancillary methanols on the addition step of the stepwise mechanism.

In like manner, the effects of either one (lower left) or two (upper left of Figure 4) ancillary methanols on the concerted mechanism may be analyzed in terms of the potential energies of distortion of the core and of binding to it. Now $\Delta E_b^{T'}$ is the binding energy (−166 kJ mol^{-1}) of one additional methanol **2** with species **4(TS6)**, which is the distorted core **4** as found in **TS6**, and $\Delta E_d^{T'}$ is the distortion energy (113 kJ mol^{-1}) of the core relative to **TS3**. The difference $\Delta E_b^{T'} - \Delta E_b^{R'} = -95$ kJ mol^{-1} is the apparent contribution to catalysis from the interaction of the reacting core with one ancillary methanol. However, this amount is more than offset by the difference $\Delta E_d^{T'} - \Delta E_d^{R'} = +101$ kJ mol^{-1}, the net distortion energy. The difference $\Delta E_{1C}^{\ddagger} - \Delta E_{2C}^{\ddagger} = +6$ kJ mol^{-1} shows that a single ancillary methanol actually increases the barrier for the concerted mechanism.

The binding energy $\Delta E_b^{T''}$ (−395 kJ mol^{-1}) of two methanols with **4(TS9)** is clearly very large but so also is the distortion energy $\Delta E_d^{T''}$ (283 kJ mol^{-1}) of the core relative to **TS3**. The apparent contribution to catalysis is the difference $\Delta E_b^{T''} - \Delta E_b^{R''} = -266$ kJ mol^{-1}, which is almost exactly balanced by the net distortion energy $\Delta E_d^{T''} - \Delta E_d^{R''} = +268$ kJ mol^{-1}; the difference $\Delta E_{1C}^{\ddagger} - \Delta E_{3C}^{\ddagger} = +2$ kJ mol^{-1} shows that two ancillary methanols do not serve to catalyze the concerted mechanism. Two extra methanols stabilize the reacting core for the concerted mechanism much more than one extra methanol stabilizes it because the dipole moment in **4(TS9)** is much larger than that in **4(TS6)** (4.70 d vs 3.82 d). In contrast, for the addition step, two extra methanols stabilize the reacting core less well than one extra methanol because the dipole moment in **4(TS7)** is smaller than that in **4(TS4)** (4.50 d vs 4.77 d). However, the distortion energy incurred by the reacting core in order to benefit from the favorable energy of binding to one or two extra methanols is dramatically larger for the concerted mechanism than for the addition step of the stepwise mechanism.

The far right of Figure 4 shows the distortion and binding energies for the elimination step of the stepwise mechanism, which may be instructively compared with those for the concerted mechanism. It is evident from Figure 1 that **TS2** and **TS3** differ only in respect to which oxygen atom (O_c or O_{nu}) is partially bonded to H_{nu}; **TS5** and **TS6** are similarly related, and so also are **TS8** and **TS9**. The binding energy (−147 kJ mol^{-1}) of one additional methanol **2** with species **4(TS5)** is a little less than with **4(TS6)**, but the distortion energy (52 kJ mol^{-1}) to reach **4(TS5)** from **TS2** for the elimination step is markedly lower than that to reach **4(TS6)** from **TS3** for the concerted mechanism (113 kJ mol^{-1}). Similarly, while the binding energy (−249 kJ mol^{-1}) of two additional methanols with **4(TS8)** (dipole moment 1.57 d) is smaller than with **4(TS9)** (dipole moment 4.70 d), the distortion energy (107 kJ mol^{-1}) to obtain **4(TS8)** from **TS2** is much lower than the 283 kJ mol^{-1} required to obtain **4-(TS9)** from **TS3**. Consequently, the net catalytic effects $\Delta E_{1E}^{\ddagger} - \Delta E_{2E}^{\ddagger} = 36$ kJ mol^{-1} for one ancillary methanol and $\Delta E_{1E}^{\ddagger} - \Delta E_{3E}^{\ddagger} = 26$ kJ mol^{-1} for two ancillary methanols cause significant reductions in the barrier heights for the elimination step of the stepwise mechanism.

The bottom line of this analysis is that for the stepwise mechanism the binding energy of the transition state (relative to reactants) is always greater than the distortion energy of the transition state (relative to reactants) for interaction with either one or two ancillary methanols. In contrast, for the concerted mechanism, the binding energy of the transition state (relative to the reactants) is cancelled out by the distortion energy of the transition state (relative to the reactants) for interaction with either one or two ancillary methanols. Thus, the ancillary methanols generate catalysis for the stepwise mechanism but not for the concerted mechanism.

TS Geometries and Charge Changes. Just as in the previous section interactions between the reacting core and the catalyst were analyzed in terms of distortion and binding, so also may the barrier for the uncatalyzed reaction be decomposed. Thus, the 173 kJ mol^{-1} potential energy barrier for the addition step may be broken down into three

Table 3. Selected B3LYP/6-31G*-Optimized TS Bond Lengths (Å) and Bond Angles (Degrees) for Methanolysis of ϵ-Caprolactone in a Vacuum

# MeOH	species	$O_{nu}-C_c$	C_c-O_{lg}	$C_c=O_c$	$O_{nu}-H_{nu}$	O_c-H_{nu}	$O_{lg}-H_{nu}$/ $O_{lg}-H_a$[a]
	ϵ-CL **1**		1.361	1.208			
	CH_3OH **2**				0.969		
1	addition **TS1**	1.883	1.343	1.308	1.291		1.183
	elimination **TS2**	1.336	1.887	1.312		1.173	1.290
	concerted **TS3**	1.802	1.804	1.189	1.201		1.216
2	addition **TS4**	1.819	1.350	1.288	1.266		1.243
	elimination **TS5**	1.355	1.814	1.297		1.208	1.234
	concerted **TS6**	1.733	1.723	1.201	1.230		1.218
3	addition **TS7**	1.853	1.355	1.287	1.241		1.183
	elimination **TS8**	1.385	1.738	1.283		1.325	1.300
	concerted **TS9**	1.598	1.572	1.239	1.576		1.400

[a] $O_{lg}-H_{nu}$ for # MEOH = 1; $O_{lg}-H_a$ for # MeOH = 2 and 3.

components: 32 kJ mol^{-1} to dissociate the ϵ-CL and nucleophilic methanol fragments as found in the reactant complex **4**, 198 kJ mol^{-1} to distort these fragments to the geometry they have in **TS1**, and -58 kJ mol^{-1} to reassociate these fragments to form **TS1**. The distortion energy is the sum of 61 kJ mol^{-1} for ϵ-CL and 137 kJ mol^{-1} for the methanol. The primary cause for the large distortion energy of the nucleophile is the significant stretching of the $O_{nu}-H_{nu}$ bond from 0.969 to 1.291 Å (Table 3). The C_c-O_{lg} bond is shorter, and the $C_c=O_c$ bond longer, in **TS1** than in ϵ-CL, and the sum of the three angles CC_cO_{lg}, $O_{lg}C_cO_c$, and CC_cO_c around the carbonyl C_c atom decreases from 360° in the trigonal planar lactone to 353° in the partly pyramidalized TS for the addition step. In contrast, the ϵ-CL distortion required to reach **TS3** for the concerted mechanism is much larger (178 kJ mol^{-1}): this is due to the very considerable lengthening of the C_c-O_{lg} bond (from 1.361 to 1.804 Å) and a greater degree of pyramidalization (to 349°) in **TS3**. The distortion energy of the methanol in the concerted mechanism is only 86 kJ mol^{-1} since the $O_{nu}-H_{nu}$ bond is stretched much less in **TS3** than in **TS1**. The association energy between the distorted ϵ-CL and methanol fragments to form **TS3** for the concerted mechanism is more favorable (-125 kJ mol^{-1}) than for the addition step of the stepwise mechanism, because the distorted ϵ-CL involves greater charge separation in the highly stretched C_c-O_{lg} bond.

The $O_{nuc}C_cO_c$ angle in the four-membered ring of **TS1** is 86°, and the $O_{nu}H_{nu}O_c$ angle is 128° (Table 4). Correspondingly, the $O_{nuc}C_cO_{lg}$ angle is more acute (78°) in TS3, whereas the $O_{nu}H_{nu}O_{lg}$ angle is more obtuse (137°). These elements of angle strain are subsumed into the association energy of the distorted ϵ-CL and methanol fragments to form the respective TSs: less strain in these interfragment angles is reflected in a more favorable association energy.

Expansion from the four-membered **TS1** to the six-membered **TS4** for the addition step leads to an increase in the $O_{nu}C_cO_c$ angle from 86° to 101°, and the $C_c=O_c$ and $O_{nu}H_{nu}$ bonds are less stretched. These geometrical changes, which one might think would reduce strain in the TS, are nevertheless part of the *unfavorable* distortion energy from **TS1** to **4(TS4)** (Table 2). However this distortion involves not only geometrical factors but also changes in the charge distribution (Table 5). The $O_{nu}H_{nu}O_a$ and $O_aH_aO_c$ hydrogen-bond angles are relaxed from 128° to an average value of 157°, a change that should also reduce strain; this contribution is subsumed into the interaction energy (Table 2) between the distorted core and an (undistorted) ancillary methanol. Further expansion of the hydrogen-bonded cyclic system to an eight-membered ring by inclusion of the second ancillary methanol in **TS7** causes an additional reduction in $O_{nu}H_{nu}$ bond stretching and further relaxation of the $O_{nu}C_cO_c$ angle (to 106°) and the average OHO hydrogen-bond angle (to 171°).

Adding the ancillary methanols to the concerted mechanism expands the four-membered ring in **TS3** first to a six-membered ring in **TS6** and then to an eight-membered ring in **TS9**. The trends in the bond angles are very similar to those described for the addition step and, therefore, do not provide an explanation for the lack of catalysis by the additional methanol molecules. However, although there is a marked decrease in the C_c-O_{lg} bond length, there are also very significant increases in the $C_c=O_c$ and $O_{nu}H_{nu}$ bond lengths as the hydrogen-bonded connection between O_{nu} and O_c expands. The $C_c=O_c$ stretching is accompanied by an increase in electronic charge upon O_c (Table 5), even though

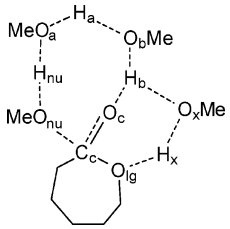
Table 4. Selected B3LYP/6-31G*-Optimized TS Bond Angles (Degrees) for the Methanolysis of ϵ-Caprolactone in a Vacuum

# MeOH	species	$O_{nu}C_cO_c$	$O_{nu}C_cO_{lg}$	$O_cC_cO_{lg}$	<OHO>	ΣC_c
	ϵ-CL **(1)**			118		360
1	addition **TS1**	86	110	114	128	353
	elimination **TS2**	120	106	85	126	
	concerted **TS3**	115	78	111	137	349
2	addition **TS4**	102	102	114	157	348
	elimination **TS5**	117	102	101	158	
	concerted **TS6**	113	93	111	156	344
3	addition **TS7**	106	101	111	171	349
	elimination **TS8**	119	103	104	168	
	concerted **TS9**	112	97	110	170	338

Table 5. Selected B3LYP/6-31G* Natural Population Analysis (NBO) TS Atomic Charges for the Methanolysis of ϵ-Caprolactone in a Vacuum

# MeOH	species	O_{nu}	O_{lg}	O_c	C_c	H_{nu}	H_{lg}	H_c
				reactive complex				
1	**4**	−0.644	−0.431	−0.470	0.611	0.429		
2	**8**	−0.675	−0.457	−0.539	0.641	0.434	0.438	
3	**12**	−0.675	−0.452	−0.507	0.649	0.443	0.446	
				addition				
1	**TS1**	−0.720	−0.542	−0.784	0.886	0.527		
2	**TS4**	−0.706	−0.587	−0.767	0.862	0.521		0.527
3	**TS7**	−−0.722	−0.556	−0.733	0.881	0.527		0.521
				concerted				
1	**TS3**	−0.706	−0.716	−0.563	0.805	0.541		
2	**TS6**	−0.697	−0.702	−0.622	0.829	0.536	0.530	
3	**TS9**	−0.680	−0.687	−0.765	0.845	0.531	0.546	
				elimination				
1	**TS2**	−0.437	−0.648	−0.653	0.712		0.457	
2	**TS5**	−0.457	−0.657	−0.673	0.739		0.475	0.480
3	**TS8**	−0.469	−0.658	−0.686	0.766		0.487	0.480

Chart 2



this degree of freedom does not contribute to the reaction coordinate. The extra methanol molecules are unable to stabilize this negative charge buildup on O_c since they are hydrogen-bonded to the "wrong" atom, O_{nu}.

In contrast, ring expansion in **TS2**, **TS5**, and **TS8** for the elimination step leads to decreases in the C_c-O_{lg} and $C_c=O_c$ bond lengths and increases in the $O_cC_cO_{lg}$ and average OHO angles, with consequent reductions in strain. There is a slight increase in negative charge on O_c, but this is directly involved in the hydrogen-bonding interactions linking this atom with O_{lg}.

One might speculate as to the possible catalytic effect of a third ancillary methanol. In the light of the results discussed above for one and two methanols, to extend the size of a hydrogen-bonded ring system further from 6 to 8 to 10 would probably not be the most effective strategy. Instead, it might be preferable to deploy the extra methanol in a second hydrogen-bonded ring, as shown in Chart 2. This arrangement would ensure that any negative charge increase on O_c would be stabilized by bonding interactions with H_b, either covalently in the intermediate of a stepwise mechanism or noncovalently in a concerted mechanism.

Orbital Interactions. Nucleophilic addition to the carbonyl group of ϵ-CL requires overlap between a lone-pair orbital n_O on O_{nu} and the antibonding $\pi^*(C_c=O_c)$ orbital, with a consequent preference for approach along the Bürgi−Dunitz trajectory, roughly perpendicular to the plane of the lactone, and ideally close to the tetrahedral angle for $O_{nu}C_cO_c$. Expansion of the cyclic TS by the inclusion of two ancillary methanol molecules allows this geometry to be adopted, with $O_{nu}C_cO_c$ increasing from 86° in **TS1** to 106° in **TS7**, while keeping O_{nu} away from O_{lg} at a respectable angle of 101°. On the other hand, nucleophilic substitution at C_c requires overlap between n_O on O_{nu} and the antibonding $\sigma^*(C_c-O_{lg})$ orbital, with a strong preference for a collinear alignment of O_{nu} with the C_c-O_{lg} bond. In practice, steric constraints and the necessity of transferring a proton from O_{nu} to O_{lg} together do not permit the $O_{nu}C_cO_{lg}$ angle to adopt a value anyway close to 180°: the best that can be achieved is 78° in **TS3**, increasing to 97° in **TS9**. In a planar lactone, the $\pi^*(C_c=O_c)$ and $\sigma^*(C_c-O_{lg})$ orbitals are orthogonal, but any distortion away from planarity allows the two orbitals to mix. Thus, any development of overlap between n_O and $\sigma^*(C_c-O_{lg})$ is inevitably accompanied by overlap between n_O and $\pi^*(C_c=O_c)$ with consequent lengthening of the $C_c=O_c$ bond and an accumulation of electron density on O_c. This might possibly be avoided if the nucleophilic attack could be decoupled from the proton transfer, but this would require a different type of catalyst.

Conclusions

Stepwise addition/elimination and concerted mechanisms for methanolysis of ϵ-caprolactone have been investigated computationally as a model for ROP, with assistance from one or two ancillary methanol molecules. The effects of specific solvation by these extra methanols in cyclic hydrogen-bonded clusters are very significant, whereas the effects of bulk solvation as treated by the PCM method are almost negligible. Increasing the ring size lowers the barriers for both the addition and elimination steps of the stepwise mechanism but does not do so for the concerted mechanism; a stepwise mechanism is therefore preferred for methanol-assisted ROP. This is because for the stepwise mechanism the intrinsic binding-energy of the reacting core with the catalyst in the transition state (relative to reactants) is always greater than the distortion energy of those core fragments in the transition state (relative to reactants) for interaction with either one or two ancillary methanols. In contrast, for the concerted mechanism, the intrinsic binding-energy term is cancelled out by the distortion energy term for interaction with either one or two ancillary methanols. The distortion energies are large in the transition states for the concerted mechanism because the geometry required in order for nucleophilic addition to occur simultaneously with proton transfer to the leaving group forces electronic charge onto the carbonyl oxygen, even though this is not part of the reaction coordinate. Thus, the ancillary methanols generate catalysis for the stepwise mechanism but not for the concerted mechanism. The essential role of a catalyst is to avoid unfavorable accumulation or separation of charges. The key requirement for catalyst design is to avoid an unfavorable buildup of charge. It may be noted that the oxyanion hole of serine proteases fulfills this requirement for the enzymic catalysis of biological acyl transfer reactions.

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Supporting Information Available: Coordinates, total energies, zero-point energies for all optimized structures, transition frequencies for transition structures, and full Gaussian citation. This material is available free of charge via the Internet at http://pubs.acs.org.

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