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Ring-Opening Polymerization of ε-Caprolactone Catalyzed by Sulfonic Acids: Computational Evidence for Bifunctional Activation

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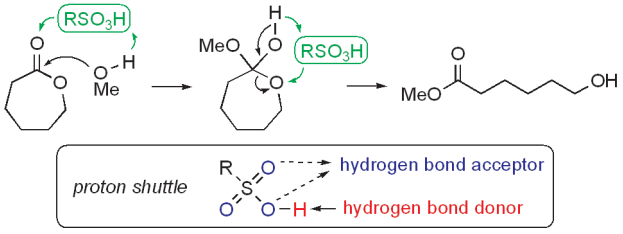
Received July 8, 2010

Bifunctional activation of the nucleophilic addition and ring-opening



The mechanism of ring-opening of ε-caprolactone by methanol catalyzed by trifluoromethane and methane sulfonic acids has been studied computationally at the DFT level of theory. For both elementary steps, the sulfonic acid was predicted to behave as a bifunctional catalyst. The nucleophilic addition proceeds via activation of both the monomer and the alcohol. The ring-opening involves the cleavage of the *endo* C−O bond of the tetrahedral intermediate with concomitant proton transfer. In both cases, the sulfonic acid acts as a proton shuttle via its acidic hydrogen atom and basic oxygen atoms. The computed activation barriers are consistent with the relatively fast polymerizations observed experimentally at room temperature with both catalysts.

Introduction

The past decade has witnessed spectacular progress in organocatalyzed ring-opening polymerization (ROP).[1] Following the pioneering contribution of Hedrick and Waymouth using DMAP (4-dimethylaminopyridine),[2] a broad range of organocatalysts have been developed, including N-heterocyclic carbenes,[3] sulfonic acids,[4] guanidines,[5] phosphazenes,[6] etc. The combination of tertiary amines with various types of hydrogen-bond donors such as thioureas,[7] amides,[8]

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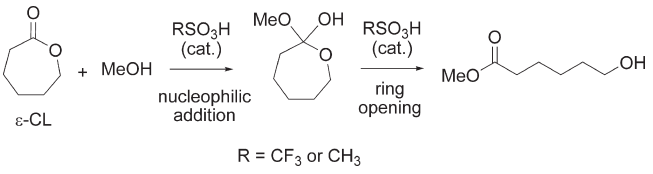
DOI: 10.1021/jo101346t Published on Web 08/27/2010

sulfonamides,[9] and fluorinated alcohols[10] also proved efficient in promoting controlled ROP.[11] In addition to catalytic performance and polymerization control, increasing efforts have been devoted to better understand the precise mode of action of the various organo-catalysts in order to determine the key factors in terms of activity and selectivity. In contrast with metal alkoxides that invariably promote ROP via a coordination−insertion mechanism,[12] various pathways can be distinguished with organo-catalysts: (i) electrophilic or nucleophilic activation of the monomer, (ii) basic activation of the initiating/propagating alcohol, and (iii) concomitant activation of the monomer and initiating/propagating alcohol, that is, bifunctional activation.[1c]

Recently, more insight into the precise role of the catalyst as well as the true nature of the key intermediates has been gained experimentally by spectroscopic studies as well as X-ray diffraction studies.[1c] Computational studies have also attracted increasing interest to shed light on the mechanism of organo-catalyzed ROP.[13−16] Accordingly, the concomitant activation of the monomer and alcohol has been substantiated for the bicyclic guanidine TBD (1,5,7-triazabicyclo-[4.4.0]dec-5-ene)[14] and for a thiourea/sparteine derivative.[15] Surprisingly, such a cooperativity has also been pointed out recently for DMAP-catalyzed ROP.[16,17] In addition to the basic activation of the alcohol, the acidic *ortho*-hydrogen atoms were predicted to activate the monomer by nonclassical hydrogen bonding.

Significant progress has been achieved over the past few years in the ROP catalyzed by sulfonic acids.[4] Trifluoromethane and methane sulfonic acids were found to be simple, robust, and efficient catalysts to promote the controlled ROP of lactide, ε-caprolactone, and β-butyrolactone under mild conditions in the presence of an alcohol as the initiator.[4] Interestingly, these two acids display similar activities toward ε-caprolactone, despite a significant difference in acidity. This prompted us to investigate theoretically the mechanism of the ROP catalyzed by sulfonic acids in order to shed light on the precise mode of action of these acid catalysts. A detailed DFT (density functional theory) study has been performed on the model reaction of ring-opening of ε-caprolactone (ε-CL) by methanol catalyzed by trifluoromethane sulfonic acid (HOTf) and methane sulfonic acid (MSA).[18] The results of this study are reported here.

SCHEME 1. Two-Step Reaction between ε-Caprolactone and Methanol Used As a Model to Study the Role of Sulfonic Acid Catalysts



Computational Details

Trimolecular reactions involving a sulfonic acid (either MSA or HOTf), ε-caprolactone, and an alcohol (methanol) have been investigated, and their free energy profiles have been determined (Scheme 1). For both elementary steps, namely, nucleophilic addition and ring-opening, different pathways have been considered. The nucleophilic addition and ring-opening of ε-caprolactone can also be envisaged to occur concertedly, but this reaction pathway was found to require a prohibitive activation energy (~40 kcal·mol^{-1}).[18] Due to the fact that the reactions involve three molecules, the reference energy has been set to the most stable adduct involving the three molecules. Indeed, it is now well established that classical DFT methods have a problem in computing the entropy within the harmonic approximation. Moreover, this error is increased when the molecularity is strongly reduced from the separated molecules to the ternary adduct. Thus, to reduce this problem, it has been decided in this study to set the reference energy to zero for the most stable ternary adduct of reactants.

Calculations were carried out with the Gaussian 03[19] suite of programs at the DFT level of theory using the hybrid functional B3PW91.[20] Sulfur, carbon, oxygen, and hydrogen atoms were described with a 6-31G(d,p) double-ζ basis set.[21] Fluorine atom was treated with a Stuttgart−Dresden pseudopotential in combination with its adapted basis set,[22] augmented by a set of polarization function d.[23] Geometry optimizations were carried out without any symmetry restrictions, and the nature of the *extrema* was verified with analytical frequency calculations. The intrinsic reaction coordinate was followed using the IRC technique for all located transition states. Solvent effects (toluene and dichloromethane) were estimated by single-point CPCM calculations[24] on the optimized gas phase structures.

Results and Discussion

Reaction of ε-Caprolactone with Methanol Catalyzed by HOTf. For clarity, the two steps of the reaction, namely, nucleophilic addition and ring-opening, will be discussed separately.

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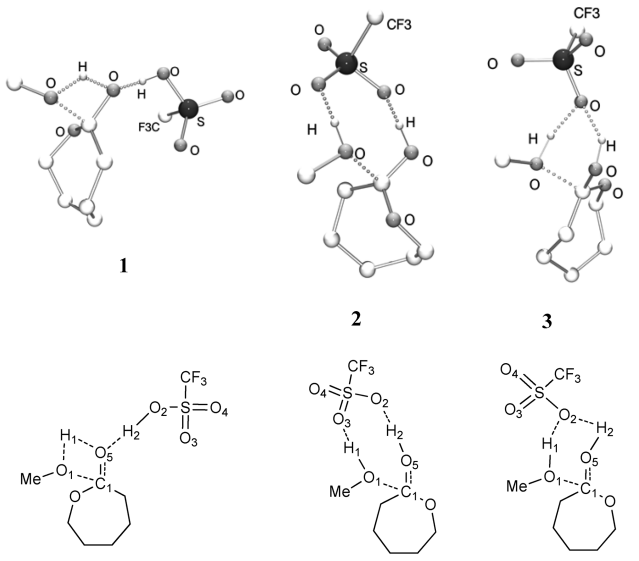

	O_1C_1	C_1O_5	O_1H_1	O_5H_1	O_5H_2	O_2H_2
1	1.73	1.35	1.22	1.22	1.44	1.05
1'	1.77	1.34	1.23	1.20	1.58	1.01
	O_1C_1	C_1O_5	O_1H_1	O_3H_1	O_5H_2	O_2H_2
2	2.02	1.27	0.99	1.66	1.07	1.38
2'	1.95	1.27	1.01	1.58	1.11	1.32
	O_1C_1	C_1O_5	O_1H_1	O_2H_1	O_5H_2	O_2H_2
3	1.83	1.32	1.03	1.52	1.00	1.77
3'	1.86	1.31	1.04	1.50	1.02	1.62

FIGURE 1. Optimized geometries of the transition states **1**−**3** associated with the nucleophilic addition of methanol on ε-caprolactone catalyzed by trifluoromethanesulfonic acid. Selected bond distances are given in Å.

First Step: Nucleophilic Addition (NA) of Methanol on ε-Caprolactone. Three different transition states connecting the ternary adduct of reactants **R** and the tetrahedral intermediate **TI** were located on the potential energy surface (PES) (Figure 1). The first transition state, **1**, corresponds to the nucleophilic attack of methanol on the carbonyl group of ε-CL with electrophilic assistance of the acid. The hydrogen of the acid is engaged in a weak hydrogen bond with the *exo*-oxygen of ε-CL ($O_{exo}\cdots H$ distance is 1.44 Å vs 1.05 Å for the $H\cdots O_{acid}$ distance). The proton of methanol is partially transferred to the *exo*-oxygen of ε-CL (the two $O\cdots H$ distances are 1.22 Å), leading to a four-membered ring.

In addition to the electrophilic assistance of ε-CL by the acid, the second transition state, **2**, involves activation of methanol by the acid through hydrogen bonding. The transfer of the proton of the acid to the *exo*-oxygen of ε-caprolactone is enforced ($O_{exo}\cdots H$ distance of 1.07 Å vs $O_{acid}\cdots H$ distance of 1.38 Å). Moreover, the hydrogen of methanol is engaged in a weak interaction with one basic oxygen (different from the one carrying the hydrogen) of the acid ($O_{acid}\cdots H$ distance of 1.66 Å vs 0.99 Å for the $O\cdots H$ bond in methanol). This leads to an eight-membered ring structure. Even though the activation of ε-CL predominates over that of methanol, the geometry of transition state **2** indicates the ability of the acid to activate simultaneously the two partners. The sulfonic acid can thus be considered to act in this case as a "proton shuttle". The NA of methanol on ε-CL is less advanced in **2** than in transition state **1**: the oxygen atom of methanol is only loosely bonded to the carbonyl group ($O\cdots C$ distance of 2.02 Å in **2** vs 1.73 Å in **1**), while the C═O bond of ε-CL retains marked double-bond character ($C\cdots O$ distance of 1.27 Å in **2** vs 1.35 Å in **1**).

The third located transition state, **3**, also involves a cooperative activation of ε-CL and methanol by the sulfonic acid. Here, only one oxygen of the acid is involved. The proton transfer from the acid to ε-CL is further enhanced with respect to **2** ($O_{exo}\cdots H$ distance of 1.00 Å vs $O_{acid}\cdots H$ distance of 1.77 Å). The hydrogen of the methanol is engaged in a weak hydrogen bond with the oxygen atom of the acid carrying the proton ($O_{acid}\cdots H$ distance of 1.52 Å vs 1.03 Å for the $O\cdots H$ bond in methanol). Here also, the sulfonic acid formally acts as a "proton shuttle" but via a six-membered-ring structure. The NA of methanol on ε-CL is more advanced than in **2**, but less than in **1**, as apparent from the intermediate values of the forming C−O and disrupting C═O bonds.

From an energetic viewpoint (Figure 2), the activation barrier for the monofunctional mechanism (via transition state **1**) is high (38 kcal·mol^{-1}) and hardly compatible with the mild conditions of polymerization.[4b,c] The experimental observations are in better agreement with the barriers predicted for the two bifunctional pathways (via transition states **2** and **3**). Indeed, the two respective barriers are almost identical (∼16.5 kcal·mol^{-1}) and much lower than the one found for the monofunctional pathway. The large differences found between transition state **1** on one hand and transition states **2** and **3** on the other hand strongly support a bifunctional activation for the NA step. Although the main role of the sulfonic acid is, as expected, the activation of ε-CL, these results underline the important influence of the concomitant activation of the alcohol (methanol here) by the acid. These secondary interactions allow reducing the ring strain associated with the proton transfer from the alcohol to the ε-CL (four-membered ring for **1** vs eight- and six-membered rings for **2** and **3**, respectively). The three pathways lead to the formation of three adducts between the acid and tetrahedral intermediate that differ by the nature of the hydrogen bonds involved. The difference in energy between these three adducts is small (less than 3.5 kcal·mol^{-1}), and the formation of this intermediate is predicted to be endothermic by about 10 kcal·mol^{-1}.

Second Step: Ring-Opening (RO) of the Tetrahedral Intermediate. This step involves the cleavage of the *endo* C−O bond of the tetrahedral intermediate **TI** with concomitant proton transfer. Two different TSs were located on the PES (Figure 3). The first one, **4**, is a direct ring-opening without active participation of the acid that remains in the interaction through a hydrogen bond with the OMe group. The *endo* C−O bond is almost broken (1.79 Å vs 1.38 Å in the tetrahedral intermediate), and the proton bridges almost symmetrically the two oxygen atoms (1.20 and 1.24 Å).

In the second transition state, **5**, the sulfonic acid bridges the hydroxyl group and *endo* oxygen involved in the ring-opening. The proton transfer from the acid to the *endo* oxygen is highly advanced ($O_{endo}\cdots H$ distance of 1.05 Å vs 1.44 Å for the $O_{acid}\cdots H$ one) and is concomitant with the breaking of the *endo* C−O bond (1.65 Å vs 1.38 Å in the tetrahedral intermediate). Moreover, a weak hydrogen bond is formed between the hydroxyl group and the dicoordinate oxygen atom of the acid ($O_{acid}\cdots H$ distance of 1.85 Å vs 0.98 Å in the hydroxyl group). Accordingly, the sulfonic acid can be considered to act here also as a "proton shuttle" via a six-membered-ring transition state (similar to **3** for the NA step). A related eight-membered-ring structure (similar to that

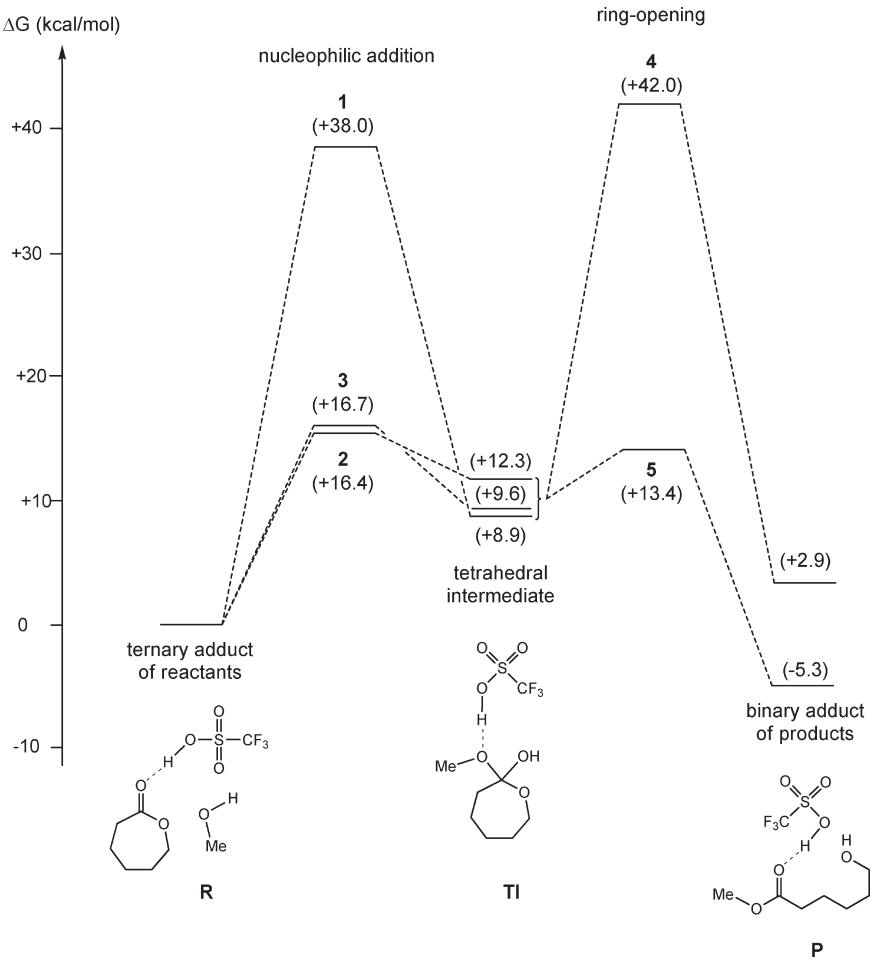

FIGURE 2. Computed free energy profiles for the reaction of ε-caprolactone with methanol catalyzed by trifluoromethanesulfonic acid (calculations in the gas phase at the B3PW91/SDDALL(F),6-31G(d,p)(C,H,O,S) level of theory).

encountered in **2** for the NA) can also be envisioned, but no respective transition state could be located on the PES. Compared to transition state **4**, the ring-opening is less advanced in **5**, as apparent from the values of the disrupting C−O and re-forming C═O bonds.

From an energetic point of view (Figure 2), the uncatalyzed pathway for the ring-opening step (via transition state **4**) requires an energy barrier of about 32 kcal·mol^{-1} from the tetrahedral intermediate. Assistance by the sulfonic acid (transition state **5**) reduces drastically the barrier (to about 3−4 kcal·mol^{-1}), so that the ring-opening becomes an easy process. The products **P** arising from transition states **4** and **5** are monoadducts between methanol and ε-CL in interaction with the acid through hydrogen bonding. The energetic difference of 8 kcal·mol^{-1} between these two products results from the nature of the hydrogen bonds involved: either with the methoxy group (for the product coming from **4**) or with the carbonyl group (for the most stable product coming from **5**). Overall, the reaction of ε-caprolactone with methanol is predicted to be slightly exothermic, in agreement with the free enthalpy of polymerization determined experimentally ($\Delta G°_p \approx -3$ kcal·mol^{-1} at 25 °C).[25]

Analyzing the whole reaction profile, it is clear that the sulfonic acid plays a major role in both steps, acting as a "proton shuttle" via its acidic hydrogen atom and basic oxygen atoms. Such a bifunctional behavior has been recently pointed out computationally for the *p*-toluenesulfonic acid-catalyzed nucleophilic substitution of phenolic hydroxyl groups with sulfur nucleophiles[26a] and for the trifluoromethanesulfonic acid-catalyzed addition of phenols to simple olefins.[26b] The most favorable TS (**2** and **3** for NA, and **5** for RO) are close in energy, and since the tetrahedral intermediate is destabilized by about 10 kcal·mol^{-1} with respect to the ternary adduct of reactants, the rate-determining step appears to be the initial nucleophilic attack.

Reaction of ε-Caprolactone and Methanol Catalyzed by MSA. A similar study has then been carried out with methanesulfonic acid as the catalyst. The free energy profile computed at room temperature is given in Figure 4. The two steps, nucleophilic addition and ring-opening, will be discussed successively, and special attention will be devoted to the differences observed between the two acids.

First Step: Nucleophilic Addition of Methanol on ε-Caprolactone. As for HOTf, three transition states were found to

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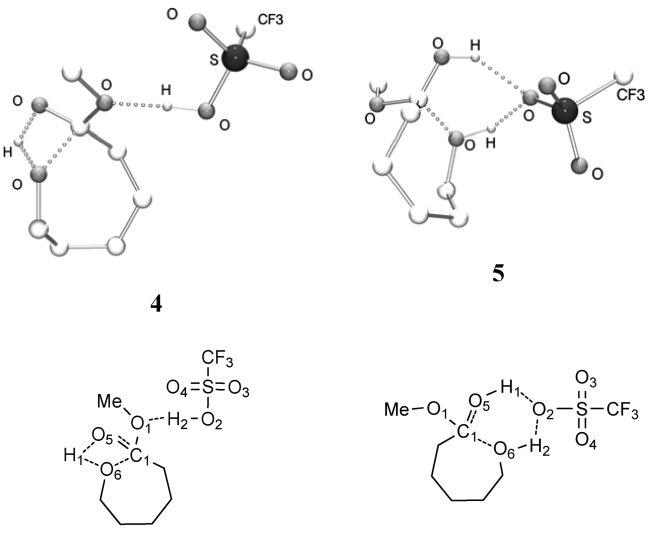

	O_6C_1	O_5H_1	O_6H_1	O_1H_2	O_2H_2
4	1.79	1.20	1.24	1.62	1.00
4'	1.79	1.20	1.23	1.71	0.99
	O_6C_1	O_5H_1	O_2H_1	O_6H_2	O_2H_2
5	1.65	0.98	1.85	1.05	1.44
5'	1.75	1.00	1.65	1.04	1.49

FIGURE 3. Optimized geometries of the transition states **4** and **5** associated with the ring-opening of the tetrahedral intermediate. Selected bond distances are given in Å.

connect the ternary adduct of reactants **R′** and the tetrahedral intermediate **TI′**. They relate to **1**, **2**, and **3** and are thus referred to as **1′**, **2′**, and **3′**, respectively (see Figure 1 for key geometric data). Transition state **1′** corresponds to the nucleophilic attack of methanol assisted by hydrogen bonding of the carbonyl group of ε-CL to the acid. The $O_{exo}\cdots H$ distance in **1′** (1.58 Å) is noticeably longer than that of **1** (1.44 Å), in agreement with the lower acidity of MSA compared to HOTf.[27] Consistently, the NA of methanol is slightly less advanced with MSA than with HOTf, as apparent from the distance of the forming CO bond (1.77 Å for **1′** vs 1.73 Å for **1**). Concomitantly, the proton of methanol is partially transferred to the *exo* oxygen of the ε-CL with quasi-identical $O\cdots H$ distances (1.23 and 1.20 Å).

The second transition state, **2′**, adopts an eight-membered-ring structure. The sulfonic acid acts as a proton donor toward ε-CL and as a proton acceptor toward methanol. The proton transfer from the acid to the *exo* oxygen of ε-CL is less advanced with MSA than with HOTf ($O_{exo}\cdots H$ distance of 1.11 Å for **2′** vs 1.07 Å for **2**), in line with the relative acidity of the two catalysts. Reciprocally, the proton of methanol forms a stronger hydrogen bond with the oxygen atom of MSA than that of HOTf ($O_{acid}\cdots H$ distance of 1.58 Å for **2′** vs 1.66 Å for **2**). Thus, the sulfonic acid acts as a "proton shuttle" in both cases, but the magnitude of the two hydrogen bonds is influenced to some extent by the CH_3/CF_3 groups. Note also that the formation of the OC bond between methanol and ε-CL is slightly more advanced in **2′** than in **2** (1.95 Å for **2′** vs 2.02 Å for **2**).

The third located transition state, **3′**, corresponds to a cooperative activation of ε-CL and methanol by the O−H group of the sulfonic acid. Compared with **3**, the major difference is the lower degree of proton transfer toward the *exo* oxygen of ε-CL ($O_{acid}\cdots H$ distance of 1.62 Å for **3′** vs 1.77 Å for **3**), again in agreement with the lower acidity of MSA compared with HOTf. The additional hydrogen bond toward the proton of methanol is only marginally shorter with MSA (1.50 Å) than with HOTf (1.52 Å).

The energy barriers associated with the three pathways also deserve comment. Transition state **1′**, corresponding to the sole electrophilic activation of ε-CL, lies high in energy (41.9 kcal·mol^{-1}). Much lower barriers were predicted for the two bifunctional pathways. Transition states **2′** and **3′** were found only 20.0 and 22.7 kcal·mol^{-1} above the ternary adduct of reactants, in agreement with the relatively fast polymerization observed experimentally at room temperature.[4b] The difference in energy between **2′** and **3′** falls within the precision of the computational method,[28] so that none of the pathway can be discarded and eventually they both intervene. MSA most likely behaves as HOTf, acting concomitantly as a proton donor toward ε-CL and as a proton acceptor toward methanol. Transition states **1′**, **2′**, and **3′** lead to three forms of the tetrahedral intermediate **TI′** that lie close in energy ($\Delta G < 4.2$ kcal·mol^{-1}), about 10 kcal·mol^{-1} above the ternary adducts of reactants **R′**.

Second Step: Ring-Opening of the Tetrahedral Intermediate. As for HOTf, two pathways were located for this step. Transition state **4′** corresponds to direct ring-opening, the sulfonic acid simply interacting with the OMe group. In line with the lower acidity of MSA, the corresponding $O_{alcohol}\cdots H$ distance is noticeably longer in **4′** (1.71 Å) than in **4** (1.62 Å), but all the other geometric features are very similar. The other transition state, **5′**, adopts a six-membered-ring structure. Here, the cleavage of the *endo* C−O bond of ε-CL and the proton transfer are assisted by the O−H group of the sulfonic acid. Compared with that encountered with HOTf, the proton transfer from the acid to the *endo* oxygen is about as advanced, but the hydrogen bond between the hydroxyl group of the tetrahedral intermediate and the dicoordinate oxygen atom of the acid is significantly enforced ($O_{acid}\cdots H$ distance of 1.65 Å in **5′** vs 1.85 Å in **5**). The cleavage of the *endo* C−O bond proceeds concomitantly with the proton transfer and is further advanced with MSA compared to HOTf (1.75 Å vs 1.65 Å). Again, the acid is found here to behave as a "proton shuttle" between the hydroxyl group and the disrupting C−O bond of the tetrahedral intermediate.

Transition state **4′** is prohibitively high in energy (about 32 kcal·mol^{-1} above the tetrahedral intermediate), while ring-opening via transition state **5′** requires only ca. 8 kcal·mol^{-1}. This emphasizes the critical role of MSA in this step as well. The sulfonic acid is predicted to act as a bifunctional catalyst for both the nucleophilic addition and the ring-opening. The respective transition states (**2′** and **3′** for NA, and **5′** for RO) are strongly stabilized by hydrogen bonding with both the acidic hydrogen atom and the basic oxygen atoms. Overall, the reaction is slightly exothermic (the most stable form of the ring-opened product lies 6.3 kcal/mol below the ternary

(27) Hammett acidities are as follows: HOTf ($H_0 \approx -14$) and MSA ($H_0 \approx -1$): (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463. (b) Pataï, S.; Rappoport, Z. In *The Chemistry of Sulphonic Acids, Esters and their Derivatives*; John Wiley and Sons: New York, 1991; p 251.

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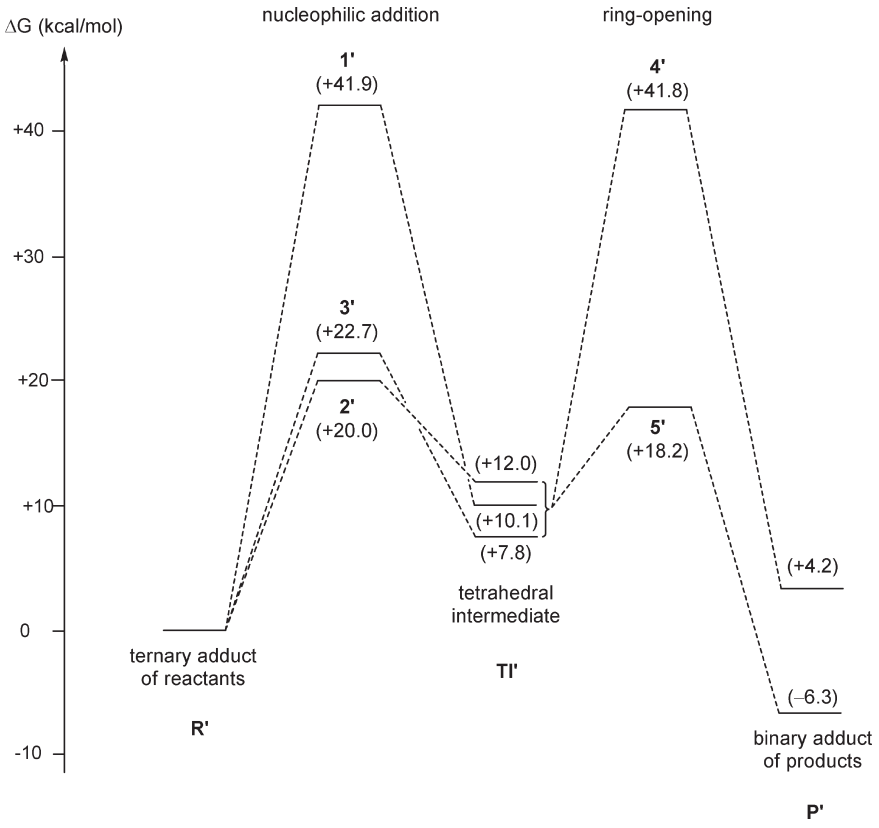

FIGURE 4. Computed free energy profiles for the reaction of ε-caprolactone with methanol catalyzed by methanesulfonic acid (calculations in the gas phase at the B3PW91/6-31G(d,p)(C,H,O,S) level of theory).

adducts of reactants), and the rate of the reaction is likely to be determined by the initial NA.

The detailed analysis of the reaction profiles with HOTf and MSA revealed strong analogies between the two sulfonic acids, despite their large difference in acidity. The structures of the key transition states are overall similar and substantiate the bifunctional role of the acid in the two elementary steps. The presence of an acidic hydrogen atom as well as basic oxygen atoms makes sulfonic acids efficient proton shuttles. This view is further supported by the variations observed in the magnitude of the hydrogen bonds arising from HOTf and MSA. Indeed, the electron-withdrawing character of the CF_3 group compared with CH_3 increases the acidity of the hydrogen atom, but decreases the basicity of the oxygen atoms.

The activation barriers predicted for MSA and HOTf are in the same range, despite a significant difference in acidity. The slightly higher values found for MSA over HOTf suggest that ring-opening polymerization of ε-CL should proceed faster when catalyzed by HOTf, whereas experimentally, MSA was found to be slightly more active.[4b] Given the precision of the method used and the approximations made, the computed reaction profiles match reasonably well with the experimental results. At this stage, it is certainly not possible to account quantitatively for the slight difference in activity observed experimentally, but the two sulfonic acids can be reasonably considered to behave as proton shuttles and thus to act as bifunctional catalysts.

In order to check the validity of the conclusions drawn from the gas phase calculations, solvents were included by means of single-point CPCM calculations on the gas phase optimized structures. The effects of toluene and dichloromethane (DCM) on the energies of the transition states (**1**−**5**, **1**′−**5**′) were considered (see Table S1 in the Supporting Information). Accordingly, transition states $\mathbf{1}^{(\prime)}$ and $\mathbf{4}^{(\prime)}$ were found to be only slightly affected by the inclusion of solvation effects and remain around 40 kcal·mol^{-1} above the ternary adducts of reactants $\mathbf{R}^{(\prime)}$. In contrast, the energies of the bifunctional transition states ($\mathbf{2}^{(\prime)}$, $\mathbf{3}^{(\prime)}$, and $\mathbf{5}^{(\prime)}$) are lowered by 5 to 10 kcal·mol^{-1}, leading to a substantial decrease of the activation barriers compared to the gas phase. This further supports the fact that the bifunctional routes are the preferred pathways for the ROP of ε-caprolactone, with the sulfonic acids acting simultaneously as donor and acceptor of hydrogen bonds.

Conclusion

In conclusion, the mechanism of ring-opening polymerization of lactones catalyzed by sulfonic acids has been studied computationally. The model reaction between ε-caprolactone and methanol was predicted to involve bifunctional activation in both elementary steps. The initial nucleophilic addition proceeds by concomitant activation of the monomer and alcohol, and during the ring-opening step, the sulfonic acid acts as a proton shuttle between the hydroxyl group and the disrupting C−O bond of the tetrahedral intermediate. Such a bifunctional behavior has been only rarely pointed out for sulfonic acids to date,[26] but draws some parallel with that commonly encountered with

phosphoric acids.[29] These results are consistent with the experimental observations and further emphasize the importance of secondary interactions and bifunctional activation in hydrogen-bonding catalysis.[30]

Acknowledgment. We are grateful to the CNRS, the ANR (ANR-08-CP2D-01-BIOPOLYCAT), and the University Paul Sabatier (France) for financial support of this work. C. Navarro (Arkema) is also warmly acknowledged for fruitful discussions. CINES and CALMIP are acknowledged for a grant of computing time. L.M. thanks the Institut Universitaire de France.

Supporting Information Available: Complete ref 19 citation; coordinates of all stationary point structures in *xyz* format; computed energies for the transition states **1**−**5** and **1′**−**5′** taking into account solvent effects. This material is available free of charge via the Internet at http://pubs.acs.org.

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