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Density Functional Theory Study of Selective Deacylation of Aromatic Acetate in the Presence of Aliphatic Acetate under Ammonium Acetate Mediated Conditions

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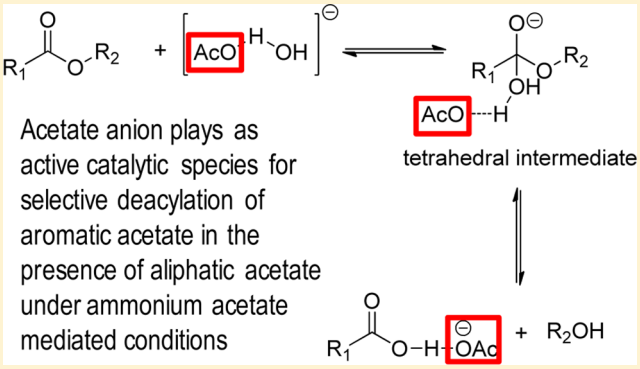
Supporting Information

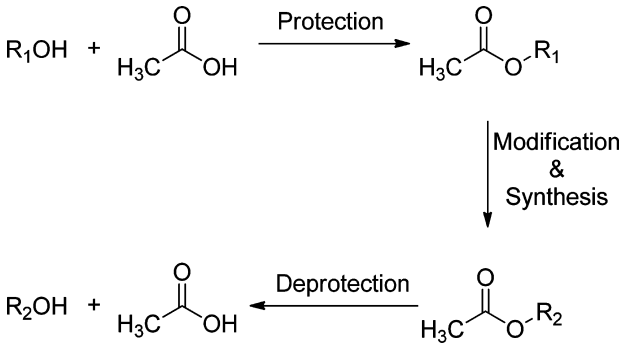
ABSTRACT: Aromatic acetates can be selectively deprotected in the presence of aliphatic acetates under ammonium acetate mediated condition. B3LYP/6-31++G** level of theory was demonstrated to be successfully used to model the relative reaction rates for deacylation reactions for aliphatic and aromatic ester systems. On the basis of the mechanistic studies, acetate anion is most likely to be the active catalyst for the ester deacylation reactions under ammonium acetate mediated condition.



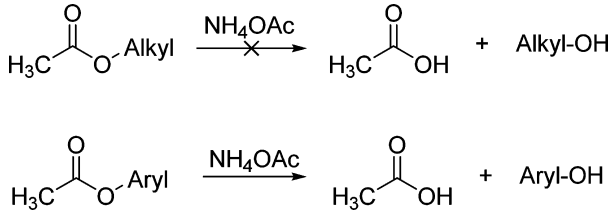
1. INTRODUCTION

The protection of hydroxyl groups is generally required prior to modification and syntheses of bioactive natural products. The most popular protection method is to make the acetates of the compounds because of their ease of formation and cleavage (Scheme 1). Deprotection of these acetates can be achieved by acidic or basic deacylation or by hydrogenolysis. However, these deprotection methods cannot selectively deprotect aromatic acetates, which is very useful in synthetic organic chemistry. Ramesh et al. reported that aromatic acetates can be selectively deacylated at room temperature in the presence of aliphatic acetates under ammonium acetate mediated condition (Scheme 2).[1] However, the mechanism for this selective deacylation reaction was not understood. Here, computational modeling was performed to investigate the mechanism and kinetics of this type of reactions to provide further insight into the role of ammonium acetate.

Scheme 1. Protection (Acylation) and Deprotection (Deacylation) of Hydroxyl-Containing Compounds Using Acetic Acid (AcOH)



Scheme 2. Selective Deprotection of Aromatic Acetate in the Presence of Aliphatic Acetate under Ammonium Acetate Mediated Conditions



2. COMPUTATIONAL METHODS

2.1. Molecular Modeling. B3LYP[2−4] (Becke three-parameter hybrid exchange functional combined with the Lee−Yang−Parr correlation functional) is the most popular and tested method. The B3LYP level of theory is speedy and accurate enough to obtain results with reasonable accuracy for the molecules in question. All density functional theory (DFT)[5] calculations were performed with the

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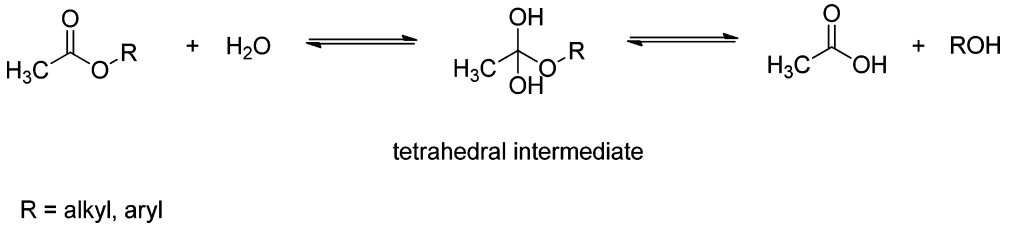
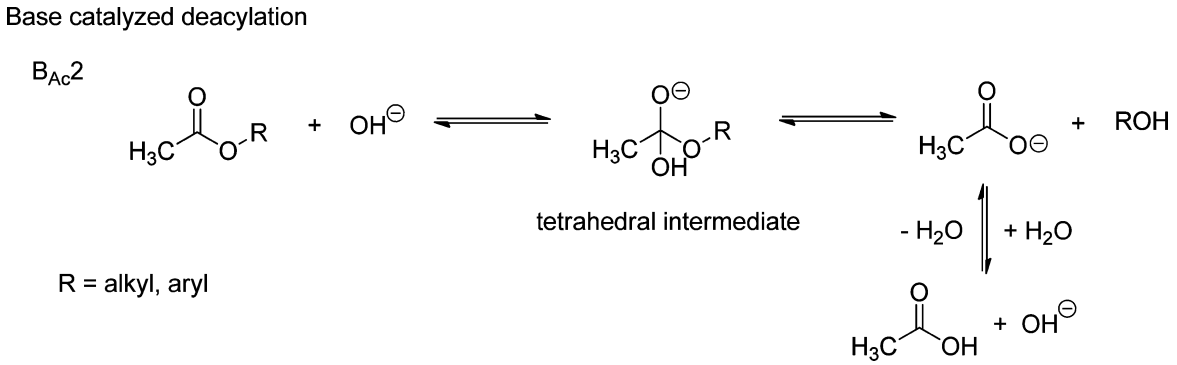
Scheme 3. Proposed Mechanism for Deacylation of Acetates under Neutral Condition



Scheme 4. Proposed Mechanism for Base-Catalyzed Deacylation of Acetates



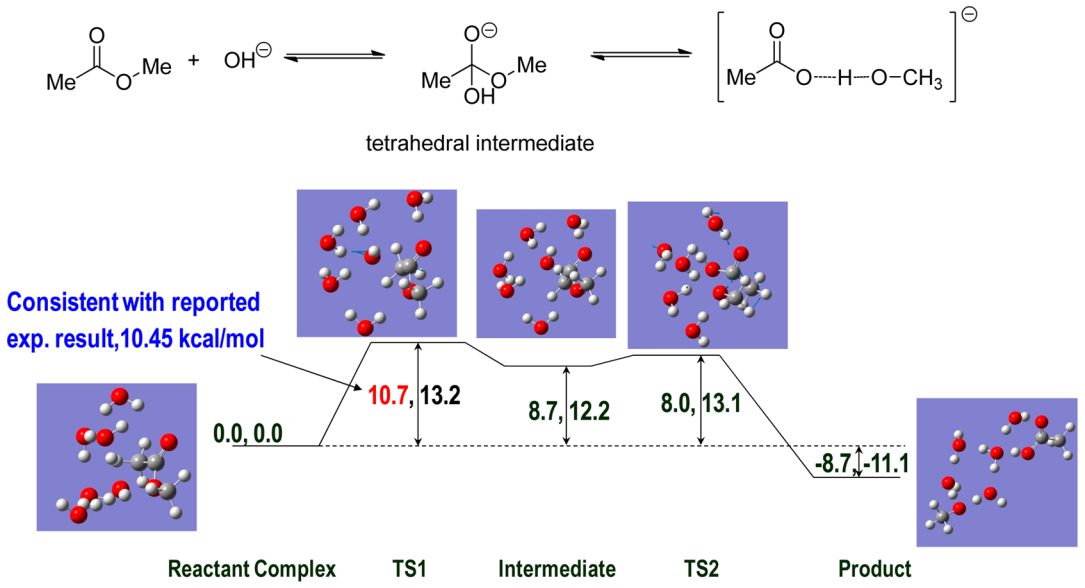


Figure 1. Energetics, ΔH, ΔG (kcal/mol) at 25 °C, for methyl acetate deacylation under hydroxyl-catalyzed mechanism ($B_{AC}2$), calculated at the B3LYP/6-31++G** level of theory.

Gaussian09[6] program package at Dow's High Performance Computing facilities. All geometry optimizations and vibrational frequency calculations were carried out at the B3LYP level of theory with the 6-31++G** basis set (B3LYP/6-31++G**). Zero-point vibrational energy corrections were scaled[7] by a factor of 0.9899. Transition states for each reaction were located at the B3LYP/6-31++G** level of theory. Calculation of the vibrational frequencies confirmed these optimized structures to be transition states. To locate the reactants and products connected by these transition states, the transition-state geometries were displaced by 10% along the normal coordinate for the imaginary vibrational frequency and then optimized with the analytical second derivatives (opt = calcall or calcfc).

Because the hydrogen-bonding interaction can play an important role in these reactions, the effect of solvation was investigated by an explicit method instead of an implicit method. This explicit method involves introducing a specific number of water molecules to the calculated system to hopefully account for all of the hydrogen bonding and some specific intermolecular interactions. In general, two water molecules were included to coordinate with two oxygen atoms on one acetate reactant, methyl acetate or phenyl acetate or acetate anion, and 3 water molecules were introduced to coordinate with hydroxyl anion.

Rate constants were calculated for these reactions according to the Transition State Theory (TST):

$$k = \kappa(T)\frac{k_B T}{h}\exp\left(\frac{-\Delta^{\ddagger}G^{o}(T)}{RT}\right) \quad (1)$$

A Wigner tunneling correction[8] was applied to these rates according to the equation

$$\kappa(T) = 1 + \left(\frac{1}{24}\right)\left(\frac{h\omega}{2\pi k_B T}\right)^2 \quad (2)$$

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in which ω is the imaginary vibrational frequency for the transition state.

2.2. OLI Calculation. The concentration of acetate anion (C_{AcO^-}) at 25 °C was calculated by OLI Stream Analyzer.[9] The calculated parameters are listed below.

Automatic Chemistry Model	Aqueous (H+ ion) Databanks
Isothermal Calculation	Temperature: 25.0 °C
	Pressure: 1.000 atm
Stream Inflows	H_2O: 55.5087 mol
	$NH_4[C_2H_3O_2]$: 0.800 mol
	Total Inflow: 56.3087 mol
Stream Parameters	Row Filter Applied: Only Non Zero Values

3. RESULTS AND DISCUSSION

Because the experimental studies for deacylation under neutral and basic conditions have been reported for methyl acetate[10−12] and phenyl acetate,[10,11,13] these two systems were chosen to validate our computational method.

Acetates containing aliphatic and aromatic functional groups can go through a deacylation reaction to form acetic acid and alcohol products under neutral, acidic, and basic condition. In general, this deacylation reaction for most acetates is extremely slow under neutral condition even at elevated temperatures.[10,11] The proposed mechanism is shown in Scheme 3. Base is usually used to catalyze the reaction, and the proposed mechanism is listed in Scheme 4. For aliphatic and aromatic acetates, generally $B_{Ac}2$ (Scheme 4) is the widely accepted mechanism for base-catalyzed deacylation reaction.[14]

3.1. Studies on Methyl Acetate and Phenyl Acetate Systems under Neutral and Basic Conditions. *3.1.1. Methyl Acetate Deacylation under Base-Catalyzed Mechanism ($B_{AC}2$).* As shown in Figure 1, the transition state models predict stepwise mechanisms for the hydroxyl-catalyzed methyl acetate deacylation reaction involving two TSs (Figure 2) and one tetrahedral intermediate. Three water molecules mainly coordinate with an oxygen atom on hydroxyl and two water molecules with those on methyl acetate to account for the hydrogen bonding. The calculated activation enthalpy and activation free energy are 10.7 and 13.2 kcal/mol, respectively, for the first step which is the rate-determining step (RDS) for this reaction (Figure 1). The calculated activation enthalpy, 10.7 kcal mol, is consistent with the reported experimental result,[12] 10.45 kcal/mol. This consistency indicates that our computational method can provide reasonable kinetics for the hydroxyl-catalyzed deacylation reaction of methyl acetate.

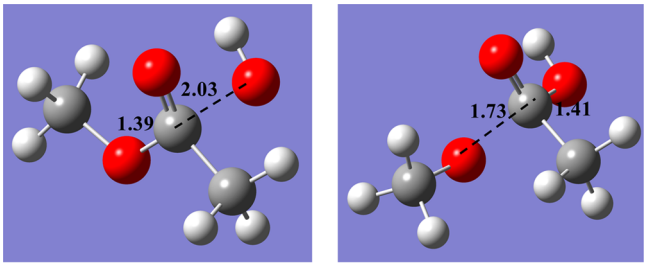

Figure 2. Geometries for transition states for methyl acetate deacylation (water molecules are excluded for clarity) under hydroxyl-catalyzed mechanism ($B_{AC}2$), calculated at the B3LYP/6-31++G** level of theory. Units for lengths are Å.

3.2.2. Phenyl Acetate Deacylation under Base-Catalyzed Mechanism ($B_{AC}2$). As shown in Figure 3, similar to the methyl acetate deacylation reaction, the transition state models predict stepwise mechanisms for the hydroxyl-catalyzed phenyl acetate deacylation reaction involving two TSs (Figure 4) and one tetrahedral intermediate. Three water molecules mainly coordinate with an oxygen atom on hydroxyl and two water molecules with those on phenyl acetate to account for the hydrogen bonding. The calculated activation enthalpy and activation free energy are 11.7 and 12.8 kcal/mol, respectively, for the first step, which is the RDS of this reaction (Figure 3). The calculated activation enthalpy, 11.7 kcal/mol, matches the reported experimental result,[13] 11.9 kcal/mol, reasonably well. The consistency indicates that our computational method can provide reasonable kinetics for the hydroxyl-catalyzed deacylation reaction of phenyl acetate.

3.2.3. Methyl Acetate and Phenyl acetate Deacylation under Neutral Conditions. As shown in Figures 5 and 7, under neutral conditions, the transition state models predict stepwise mechanisms (2 TSs as shown in Figure 6) for methyl acetate deacylation while predicting a concerted mechanism (1 TS as shown in Figure 8) for phenyl acetate deacylation. Two water molecules coordinate with oxygen atoms on methyl acetate/phenyl acetate to account for the hydrogen bonding. Isotope effects and other kinetic studies[15−17] have supported the feasibility of concerted acyl transfer and indicated that concerted mechanism is more likely to happen for esters with weakly basic leaving groups. The phenoxy group is a weaker basic leaving group than methoxyl, which may explain why they have different mechanism under neutral conditions. Under neutral conditions, the calculated activation enthalpies and activation free energies for both methyl acetate and phenyl acetate deacylation are much higher than the corresponding energies under hydroxyl-catalyzed condition: in the case of methyl acetate deacylation, 18.1 kcal/mol higher for activation enthalpy and 21.5 kcal/mol higher for activation free energy; and in the case of phenyl acetate deacylation, 16.1 kcal/mol higher for activation enthalpy and 21.9 kcal/mol higher for activation free energy. These are consistent with the experimental results that the deacylation reaction for most esters is extremely slow (longer than days) under neutral conditions even at elevated temperature, and that the deacylation reaction can be catalyzed under basic condition.[10,11]

As discussed above, the B3LYP/6-31++G** level of theory was validated by experimental results for model systems, methyl acetate and phenyl acetate, and proven to be a suitable computational method to study relative rates of deacylation reactions for the acetate system. Therefore, this computational method was used to study the ammonium acetate mediated deacylation.

3.2. Studies on Methyl Acetate and Phenyl Acetate Systems under Ammonium Acetate Mediated Conditions. Even though the ammonium acetate mediated deacylation reaction shown in Scheme 1 has been reported since 2003,[2] no known theoretical study has been performed to investigate why ammonium acetate can provide a highly selective deacylation for aromatic acetates in the presence of aliphatic acetates. Understanding the mechanism for this selectively catalytic reaction can provide useful information to optimize the reaction condition and possibly to design better reactants and final products.

Two possible mechanisms are listed in Scheme 5 for this ammonium acetate mediated deacylation reactions. One is

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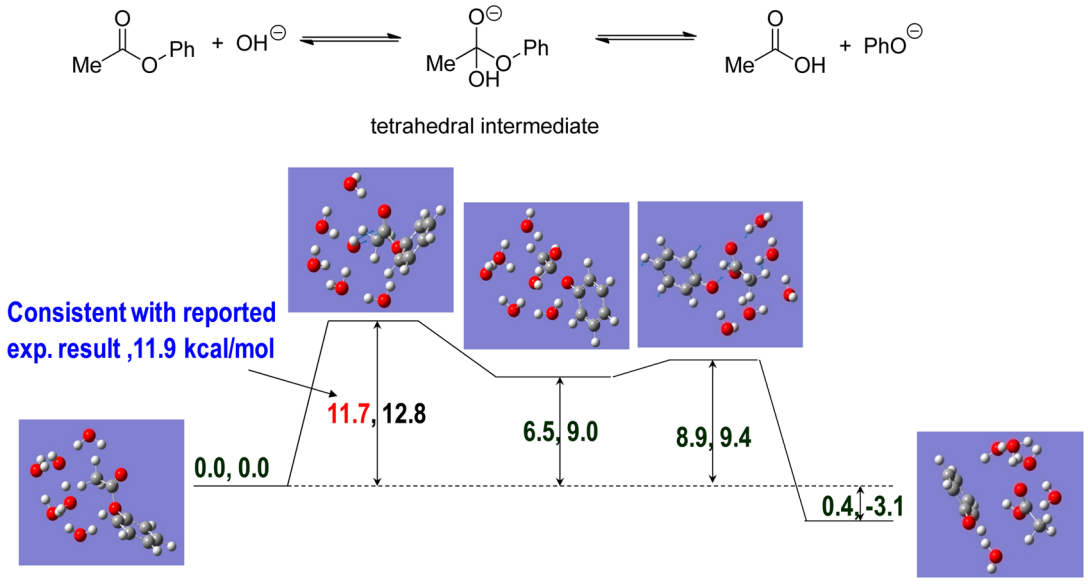

Figure 3. Energetics, ΔH, ΔG (kcal/mol) at 25 °C, for phenyl acetate deacylation under hydroxyl-catalyzed mechanism ($B_{AC}2$), calculated at the B3LYP/6-31++G** level of theory.

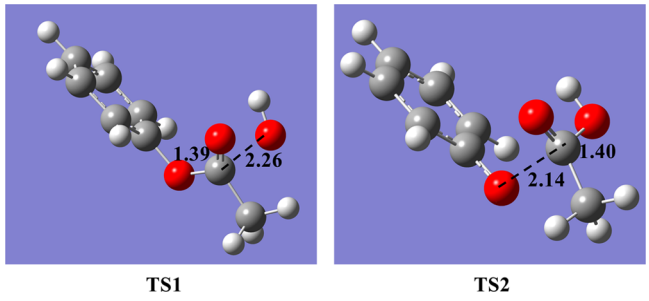

Figure 4. Geometries for transition states for phenyl acetate deacylation (water molecules are excluded for clarity) under hydroxyl-catalyzed mechanism ($B_{AC}2$), calculated at the B3LYP/6-31++G** level of theory. Units for lengths are Å.

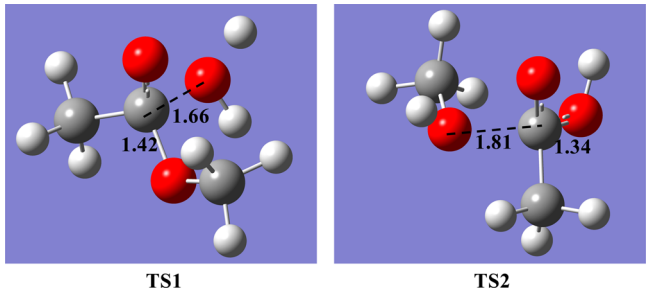

Figure 6. Geometries for transition states for methyl acetate deacylation (water molecules are excluded for clarity) under neutral conditions, calculated at the B3LYP/6-31++G** level of theory. Units for lengths are Å.

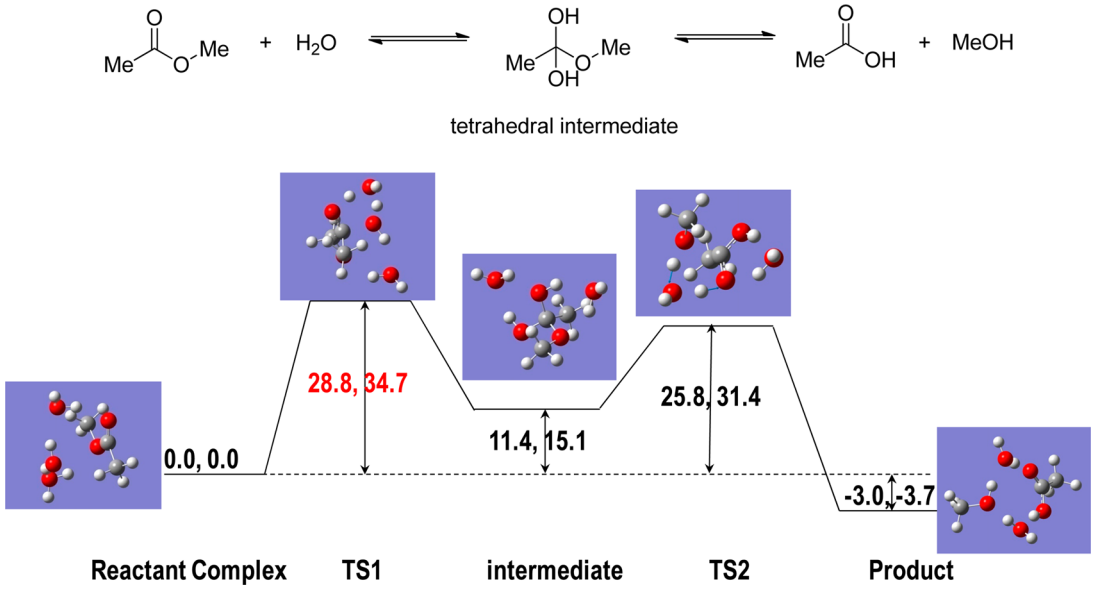

Figure 5. Energetics, ΔH, ΔG (kcal/mol) at 25 °C, for methyl acetate deacylation under neutral conditions, calculated at the B3LYP/6-31++G** level of theory.

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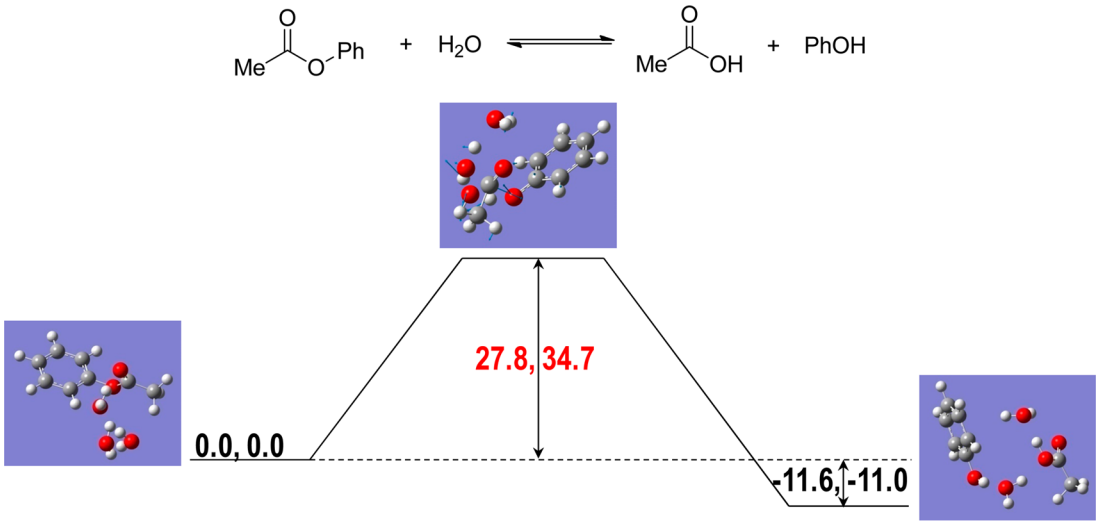

Figure 7. Energetics, ΔH, ΔG (kcal/mol) at 25 °C, for phenyl acetate deacylation under neutral conditions, calculated at the B3LYP/6-31++G** level of theory.

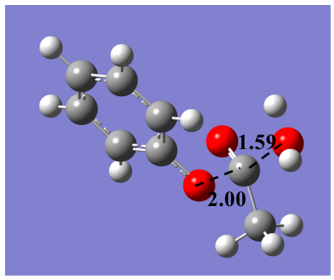

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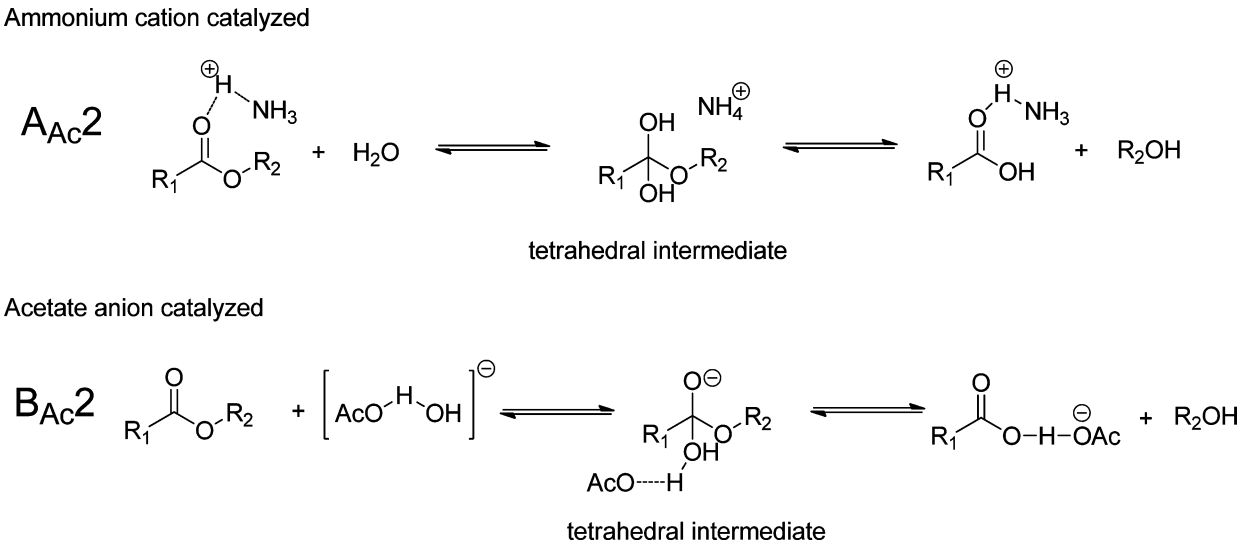
Figure 8. Geometry for the transition state for phenyl acetate deacylation (water molecules are excluded for clarity) under neutral conditions, calculated at the B3LYP/6-31++G** level of theory. Units for lengths are Å.

through an ammonium cation catalyzed mechanism, and the other through an acetate anion catalyzed mechanism. Both mechanisms were explored using our verified computational method.

3.2.1. Ammonium Cation Catalyzed Mechanism. Figure 9 shows the activation energies for the first step, tetrahedral intermediate formation, of methyl acetate and phenyl acetate deacylation through ammonium cation associated mechanism. One water molecule mainly coordinate swith ammonium cation and two water molecules with methyl acetate or phenyl acetate to account for the hydrogen bonding. As shown in Figure 9, the activation energies, both the activation enthalpies and activation free energies, for deacylation through the ammonium associated mechanism are close to those under neutral conditions (Figure 5 and 7), in the cases of methyl acetate and phenyl acetate. Also, the activation energies are very similar between the methyl acetate and phenyl acetate deacylation reactions, for activation enthalpy, only 0.9 kcal/mol difference, and for activation free energy, only 0.6 kcal/mol. This small difference indicates that the ammonium cation associated pathway is unlikely to be a real mechanism for ammonium acetate catalyzed deacylation. This conclusion is consistent with the experimental results from Narender et al.[18] which demonstrated that sodium acetate could work in a similar role as

Scheme 5. Possible Mechanisms for Ammonium Acetate Mediated Deacylation Reactions



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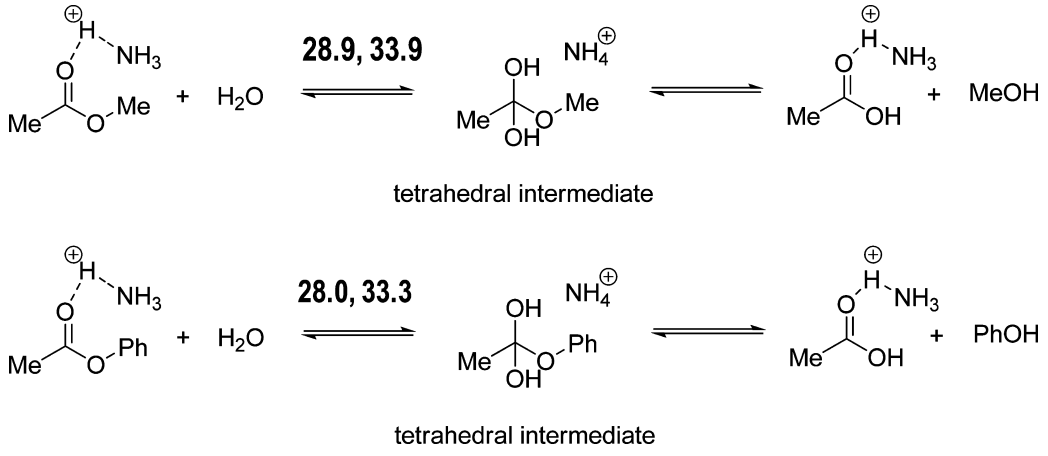

Figure 9. Activation energies, $\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$ (kcal/mol) at 25 °C, for methyl acetate and phenyl acetate deacylation through ammonium cation associated mechanism, calculated at the B3LYP/6-31++G** level of theory.

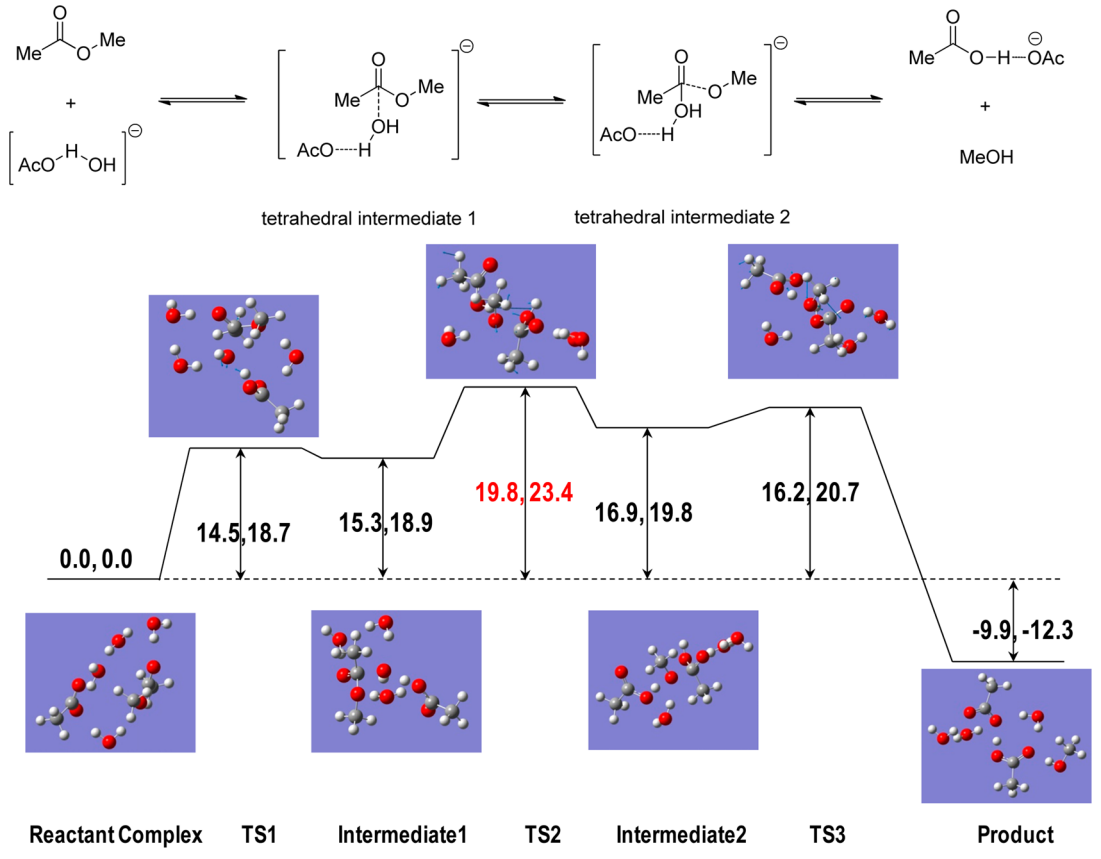

Figure 10. Energetics, ΔH, ΔG (kcal/mol) at 25 °C, for methyl acetate deacylation through acetate anion associated mechanism, calculated at the B3LYP/6-31++G** level of theory.

ammonium acetate to selectively deacylate aromatic acetates in the presence of aliphatic acetates.

3.2.2. Acetate Anion Catalyzed Mechanism. Figures 10 and 11 show energetics for methyl acetate and phenyl acetate deacylation through an acetate anion associated mechanism. Two water molecules mainly coordinate with acetate anion, and two water molecules with methyl acetate or phenyl acetate to account for the hydrogen bonding. The transition state models predict stepwise mechanisms for both methyl acetate (3 TSs as shown in Figure 12) and phenyl acetate (2 TSs as shown in Figure 13) deacylation reactions. Even though the relative total energy of the first TS for methyl acetate reaction, 16.5 kcal/mol, is slightly higher than that of the first intermediate, 16.2 kcal/mol, after the thermal correction for enthalpy and free energy, the relative enthalpy and free energy of the first TS for methyl acetate reaction, 14.5 and 18.7 kcal/mol, are lower than the corresponding energies of the first intermediate, 15.3 and 18.9 kcal/mol (Figure 10). For the methyl acetate reaction, the second step has the highest activation free energy (Figure 10). For the phenyl acetate reaction, the first step has higher activation free energy (Figure 11). This indicates that the second step is the RDS for the methyl acetate deacylation reaction and the first step for the phenyl acetate one. In order to generate kinetic results from calculated activation energies,

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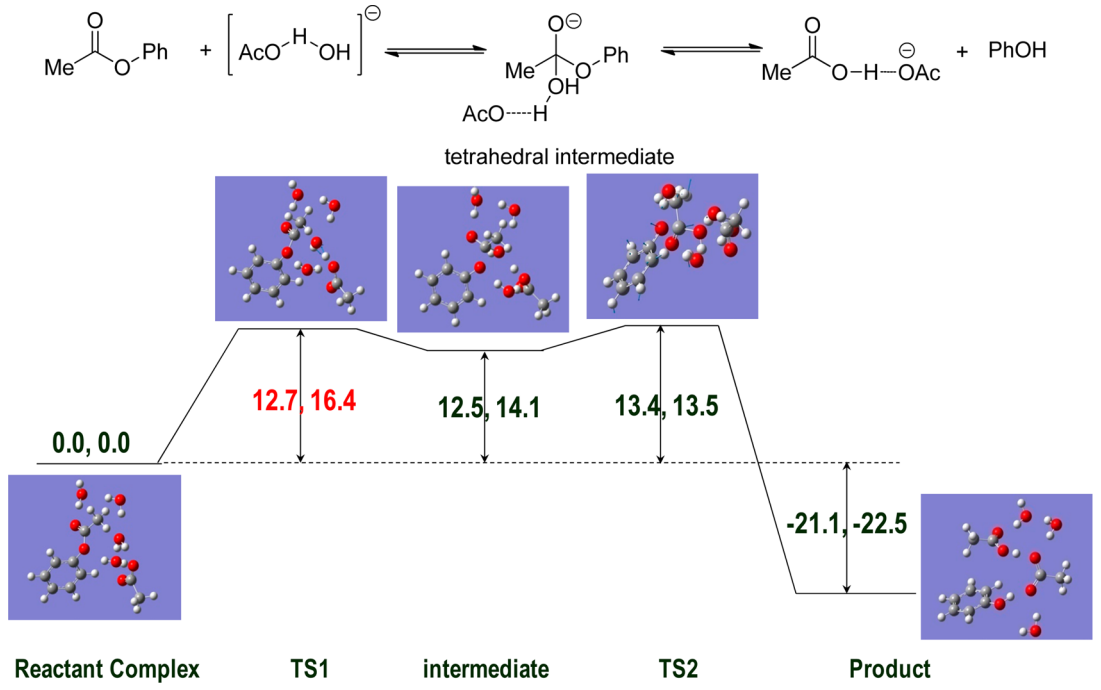

Figure 11. Energetics, ΔH, ΔG (kcal/mol) at 25 °C, for phenyl acetate deacylation through acetate anion associated mechanism, calculated at the B3LYP/6-31++G** level of theory.

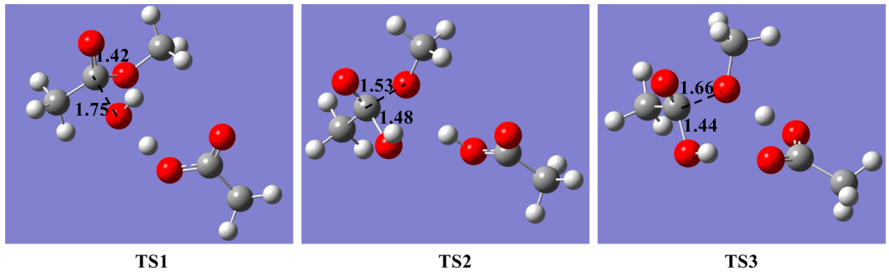

Figure 12. Geometries for transition states for methyl acetate deacylation (water molecules are excluded for clarity) through acetate anion associated mechanism, calculated at the B3LYP/6-31++G** level of theory. Units for lengths are Å.

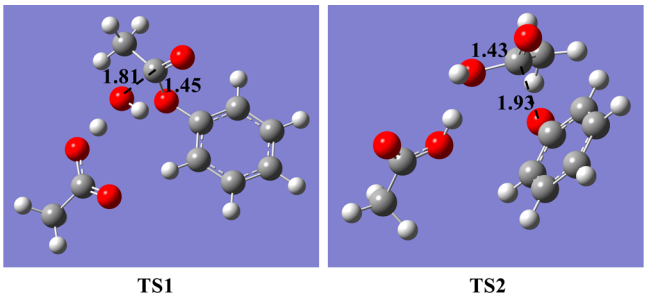

Figure 13. Geometries for transition states for phenyl acetate deacylation (water molecules are excluded for clarity) through acetate anion associated mechanism, calculated at the B3LYP/6-31++G** level of theory. Units for lengths are Å.

Transition State Theory (TST) was employed. Because activation free energies were used in TST, the activation free energies for RDS were chosen in each reaction to calculate its rate constant, e.g., 23.4 kcal/mol was used for methyl acetate deacylation, and 16.4 kcal/mol for phenyl acetate. The activation free energy for methyl acetate deacylation is 7.0 kcal/mol higher than that for phenyl acetate. Is this activation energy difference significant enough to explain the selective deacylation of aromatic acetate in the presence of aliphatic acetates under ammonium acetate mediated condition?

Table 1 lists calculated kinetic results and reported experimental results for methyl acetate and phenyl acetate deacylation under ammonium acetate mediated conditions ($B_{Ac}2$ in Scheme 5). The experimental conditions were room temperature, 0.8 mol/L ammonium acetate, and 1:4 v/v water/MeOH as cosolvent. To mimic the experimental conditions, calculations were performed under the condition of 25 °C, 0.8 mol/L ammonium acetate, and explicit water added. The reason to apply water molecules instead of water/MeOH is that the explicit (hydrogen bonding phenomena) solvent effects for water can fairly well represent that of water and MeOH cosolvent system, and that using one solvent system can simplify the calculation significantly. Based on the OLI calculation for 0.8 mol/L NH_4OAc in water (typical loading for reaction), the concentration of acetate anion, $C_{acetate^-}$, is 0.56 mol/L at 25 °C. Because the starting ester (methyl acetate or phenyl acetate) concentration for the standard operation is less than 0.4 mol/L and acetate anion acts as a catalyst, and to simplify the calculation, we assume that it is a pseudo-first order reaction for ester. The rate coefficients can be calculated from eq 5.

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Table 1. Calculated and Experimental Kinetic Results for Methyl Acetate and Phenyl Acetate Deacylation under Ammonium Acetate Mediated Conditions

	calculated results[a]					
				[ester]$_t$/[ester]$_0$[f]		
	$\Delta G^{\ddagger}_{25\ ^\circ C}$[c]	k′[d]	k'_{rel}[e]	after 1 h	after 4 h	exptl results[b]
methyl acetate	23.4	$2.5 \times 10^{-5}K$	1.0	100.0%	100.0%	no reaction in 4 h
phenyl acetate	16.4	$3.41K$	1.3×10^{5}	29.3%	0.7%	complete reaction in 4 h

[a]Calculated results through acetate anion associated mechanism using B3LYP/6-31++G** level of theory (at 25 °C, 0.8 mol/L NH_4OAc, water as solvent). [b]Experimental results from literature work (at rt, 0.8 mol/L NH_4OAc, 1:4 v/v water/MeOH as solvent).[1] [c]Calculated activation free energies, kcal/mol. [d]Calculated rate constants, s^{-1}. [e]Calculated relative rate constants when methyl acetate is arbitrarily set to 1, equilibrium is assumed to be constant, and K is the same for both methyl acetate and phenyl acetate systems, no unit. [f]Assume K = 0.0001.

$$K = \frac{C_{\text{reactant complex}}}{C_{\text{acetate}^-} \times C_{\text{ester}}} \tag{3}$$

$$k' = kKC_{\text{acetate}^-} \tag{4}$$

$$\begin{aligned} -r_{\text{ester}} &= \frac{dC_{\text{ester}}}{dt} \\ &= kC_{\text{reactant complex}} \\ &= k'C_{\text{ester}} \\ &= kKC_{\text{acetate}^-}C_{\text{ester}} \\ &= \kappa(T)\frac{k_B T}{h}\exp\left(\frac{-\Delta^{\ddagger}G^{\circ}(T)}{RT}\right)KC_{\text{acetate}^-}C_{\text{ester}} \end{aligned} \tag{5}$$

Assuming the equilibrium constant, K, is constant for all of the ester NH_4OAc systems, as shown in Table 1, the deacylation rate for phenyl acetate is ~1.3×10^5 faster than that for methyl acetate at 25 °C. By arbitrarily setting K to 0.0001, based on our calculated results, after 4 h reaction at 25 °C, phenyl acetate reacts completely, while methyl acetate remains intact (Table 1). Our calculated relative reaction rates for methyl acetate and phenyl acetate systems shows that the deacylation rate for phenyl acetate is much faster, which is consistent with the reported experimental data.[1] It is highly possible that the acetate anion associated pathway is the mechanism for this selective deacylation reaction for aromatic acetate.

4. CONCLUSIONS

In this study, the B3LYP/6-31++G** level of theory was demonstrated to be successfully used to model the relative reaction rates for deacylation reactions for aliphatic and aromatic ester systems. On the basis of the mechanistic studies, acetate anion is most likely to be the active catalyst for the ester deacylation reactions under ammonium acetate mediated condition.

■ ASSOCIATED CONTENT

Supporting Information

Bottom-of-well energies, enthalpies, and free energies for all optimized structures, and Cartesian coordinates of these structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Ramesh, C.; Mahender, G.; Ravindranath, N.; Das, B. *Tetrahedron* **2003**, *59*, 1049.
(2) Parr, R. G.; Yang, W. *Density Functional Theory in Atoms and Molecules*; Oxford University Press: New York, 1989.
(3) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(4) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(5) Labanowski, J. W.; Andzelm, J. *Density Functional Methods in Chemistry*; Springer: New York, 1991.
(6) Frisch, M. J. et al. *Gaussian 09*, Revision A.02; Gaussian, Inc.: Wallingford, CT, 2009.
(7) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.
(8) Wigner, E. P. *Phys. Rev.* **1955**, *98*, 145.
(9) *OLI Stream Analyzer 2.0*; OLI System, Inc.: Morris Plains, NJ, 2011.
(10) Lowry, T. H.; Richarson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987.
(11) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structures*, 6th ed.; Wiley-Interscience: New York, 2007.
(12) Fairclough, R. A.; Hinshelwood, C. N. *J. Chem. Soc.* **1937**, 538.
(13) Bunton, C. A.; O'Connor, C.; Turney, T. A. *Chem. Ind. (London)* **1967**, 1835.
(14) Zhan, C.; Landry, D. W.; Ornstein, R. L. *J. Phys. Chem. A* **2000**, *104*, 7672.
(15) Hengge, A. C.; Hess, R. A. *J. Am. Chem. Soc.* **1994**, *116*, 11256.
(16) Hess, R. A.; Hengge, A. C.; Cleland, W. W. *J. Am. Chem. Soc.* **1998**, *120*, 2703.
(17) Colthurst, M. J.; William, A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1493.
(18) Narender, T.; Papi Reddy, K.; Madhur, G. *Synth. Commun.* **2009**, *39*, 1949.