

# Theoretical study on the reaction mechanism for the hydrolysis of esters and amides under acidic conditions

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**Abstract**—The mechanisms underlying the hydrolysis of methyl acetate and acetamide under acidic conditions were investigated using the MP2/6-311+G(d,p)//MP2/6-31+G(d,p) level of theory. It was necessary to include two water molecules as reactants to obtain a tetrahedral (TD) intermediate for the  $A_{AC}2$  mechanism that Ingold classified for the hydrolysis of methyl acetate. This mechanism includes two TS structures, one for the formation of the TD intermediate and the other for its decomposition. Since the activation energies were calculated to be 15.7 and 18.3 kcal mol<sup>-1</sup>, the second step determines the rate of hydrolysis. The calculated value was close to that observed at ~16 kcal mol<sup>-1</sup>. It was confirmed that the  $A_{AC}2$  mechanism had a barrier lower by 9.9 kcal mol<sup>-1</sup> than the  $A_{AL}2$  mechanism. The  $A_{AC}2$  mechanism is also applicable to the acid-catalyzed hydrolysis of acetamide. It is not the TD intermediate with which the NH<sub>3</sub><sup>+</sup> moiety forms, but one further step is required to produce the final products, acetic acid and ammonium ion.

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## 1. Introduction

A lot of chemical compounds are used to maintain our comfortable life even though some of them are environmentally harmful. Biochemical oxygen demand (BOD) degradation is used as the index to determine whether or not chemical compounds easily degrade under the natural conditions. The index written in the OECD 301C guideline has also been adopted as an index of environmental loads of chemical compounds in the Chemical Substances Control Law of Japan. The law requires prior evaluation of certain hazardous properties of new chemical substances intended for industrial use. Although the existing chemical substances (ca. 20,000 substances) in 1973 were decided to be examined by the Japanese Government, only one tenth of them have been examined in 2005. It is, therefore, necessary to introduce other techniques without experiments such as the Quantitative Structure–Activity Relationship (QSAR) method to quickly finish the examination of the existing chemical substances.

The guideline presumes that microorganisms degrade all the compounds although esters, acid anhydrides, acyl halides, etc. are easily hydrolyzed. Therefore, there should be serious problems if we use data based on the guideline in order to make QSAR models<sup>1</sup> for the BOD degradation.

Experimental data of easily decomposing compounds should be excluded for the QSAR analysis. However, it is impossible to experimentally examine rates of hydrolysis for all the compounds.

It is common knowledge that the rates of chemical reactions are dependent on their activation energies. We can use the energies for hydrolysis as an index of easy decomposition under natural conditions. Theoretical calculations such as the Density Functional theory (DFT) and molecular orbital (MO) calculations can compute such values, which can be compared with the experimental ones if solvent effects were included in the calculations. Therefore, theoretical methods are one of the feasible solutions to avoid experimental difficulties.

Carbon dioxide is saturated in the natural conditions of water in rivers and lakes. Therefore, hydrolysis of compounds proceeds under these acidic conditions. We have to understand the mechanism of the reaction in detail in order to calculate the activation energies of hydrolysis under these conditions. Although the mechanisms responsible for the alkaline hydrolysis of esters and amides have been theoretically investigated,<sup>2</sup> there are few theoretical studies on the acid-catalyzed hydrolysis of esters and amides. In the present study, our attention was focused on the mechanisms responsible for the acid-catalyzed hydrolysis of methyl acetate and acetamide.

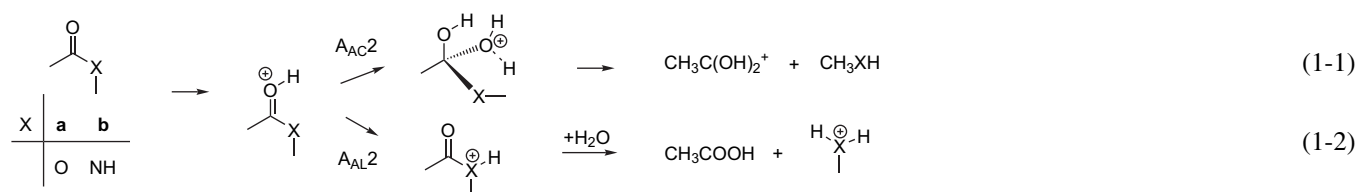
Textbooks of organic chemistry state that the reaction under acidic conditions proceeds under the mechanism shown in Eq. 1-1, the  $A_{AC}2$  (acid-catalyzed acyl cleavage second

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order reaction) mechanism.<sup>3</sup> In this mechanism, the ester first accepts a proton at the carbonyl oxygen and this change enhances the positive charge on the carbonyl carbon. This protonation facilitates the successive addition of water at that position to form a tetrahedral (TD) intermediate, consisting of the protonated ester and water. We tried to optimize the TD intermediate at the B3LYP/6-31G(d) level of theory and found that the TD geometry is not a minimum for the energy surface. Experimental studies also suggested that one or two more water molecules are related to the formation of the intermediate.<sup>4</sup>

It is also possible to consider the A<sub>AL</sub>2 (acid-catalyzed alkyl cleavage second order reaction) mechanism, where the reactant is a species with a proton at the ether oxygen as described in Eq. 1-2.<sup>5</sup> In this case, the products are acetic acid and protonated alcohol or amine.

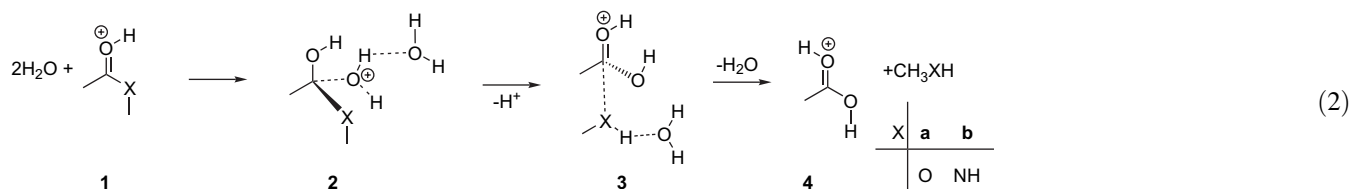


Both the mechanisms are applicable to the hydrolysis of an amide, although  $\text{RNH}_2$  is a worse leaving group than  $\text{ROH}$ . In the present study, we investigated these mechanisms using a model with two or three water molecules. As discussed later, the inclusion of solvent water molecules as the reactant is critical to express both the A<sub>AC</sub>2 and the A<sub>AL</sub>2 mechanisms correctly and obtain activation energies close to those observed.

## 2. Method of calculations

All of the geometry optimizations were performed using the Gaussian03 program<sup>6</sup> at the MP2/6-31+G(d,p) level of theory. The relative stability of structures related to the hydrolysis was refined at the MP2/6-311+G(d,p)/MP2/6-31+G(d,p) level of theory.<sup>7</sup> The intrinsic reaction coordinates (IRCs)<sup>8</sup> were also calculated to analyze the mechanisms in detail at the B3LYP/6-31G(d) level of theory. Vibration frequencies were calculated to confirm that the obtained geometries were stable or transition (TS) structures. We used Jmol for the molecular modeling.<sup>9</sup>

In the present study, two or three water molecules are included as the reactants to partially include a solvent effect. One is required to form the TD intermediate **2** and the other plays an important role in the decomposition of the TD intermediate shown in Eq. 2. This is a similar technique that we used for analyzing the oxygen exchange during the alkaline hydrolysis of methyl acetate.<sup>10</sup>



## 3. Results and discussions

### 3.1. Hydrolysis of methyl acetate under acidic conditions

Although no stable structures for the TD intermediate with one water molecule as the reactant were obtained as discussed above, an optimization with one additional water molecule produced such an intermediate **2a** (see Fig. 1). The C(1)–O(2) length was calculated to be 1.535 Å, a rather long C–O bond length. The second water interacts with a hydrogen atom from the other water molecule, making a C–O bond with the carbonyl carbon C(1). This interaction enhances the nucleophilicity of the oxygen atom O(2). In **2a(TS)**, the C(1)–O(2) and H(3)–O(4) lengths are longer by 0.127 and 0.160 Å, respectively, than those of **2a**. The TS has only one imaginary frequency of 137.7i  $\text{cm}^{-1}$ .

As the TD intermediate **2a** was optimized, the hydrolysis via the A<sub>AC</sub>2 mechanism proceeds in two steps: the formation of the TD intermediate and its decomposition. A TS of the second step **3a(TS)** was determined and shown in Figure 1. Although the H(3)–O(4) and O(4)–H(5) lengths were calculated to be 1.054 and 1.005 Å, the O(2)–H(3) and H(5)–O(6) lengths turned out to be 1.451 and 1.749 Å. This suggests that an oxonium ion was interacting with two oxygen atoms, O(2) and O(6) in **3a(TS)**, with one imaginary frequency of 271.7i  $\text{cm}^{-1}$ . This geometry is suitable for decomposing the TD intermediate into the final products, i.e., water as a reactant accepts a proton connecting with O(2), and simultaneously donates its own proton to O(6). Therefore, it is not necessary to consider an internal proton transfer in the A<sub>AC</sub>2 mechanism as Ingold suggested.<sup>5</sup> A cyclic TS was proposed from the observation that the carbonyl oxygen-18 is exchanged in  $\text{D}_2\text{O}$  during the acid-catalyzed hydrolysis of esters.<sup>11</sup> The calculated TS geometry is consistent with the experimentally proposed one.

It is a rather difficult problem to consider what geometry should be used for the reactant in the present model for calculating the activation energies. For example, the most stable ‘reactant’ of the present model was calculated to have the geometry shown as **1a'**. This is more stable by 10.2 kcal  $\text{mol}^{-1}$  than **1a**. However, there is no similarity for the geometry of **1a** to the TD intermediate **2a**. Solvent water molecules are believed to be present over and/or under the protonated methyl acetate, like **1a** in aqueous solution; the water molecules related to the hydrolysis are not those

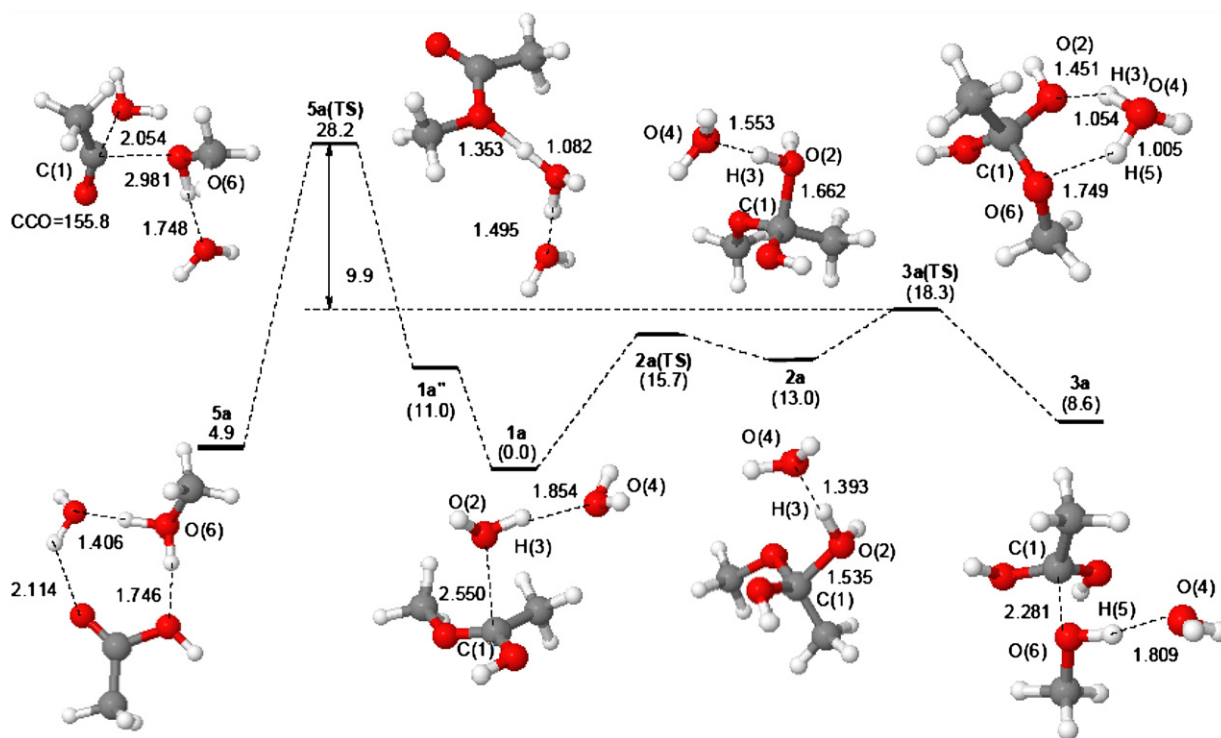
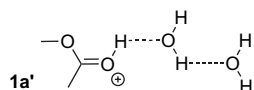
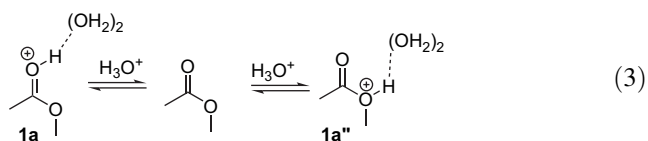


Figure 1. Energy diagram among structures of hydrolysis for methyl acetate. Units for lengths and energies are Å and kcal mol<sup>-1</sup>.

bonded to the proton on the carbonyl oxygen in **1a'** but positioned over the carbonyl carbon in **1a**. Therefore, we adopted **1a** as the reactant for the A<sub>AC</sub>2 mechanism, although it is not the global minimum on the potential surface of the present model. Since we adopted **1a** as the reactant, the activation energy was calculated to be 15.7 kcal mol<sup>-1</sup> for the first step. The **3a(TS)** is higher in energy by 4.6 kcal mol<sup>-1</sup> than **2a** and by 18.3 kcal mol<sup>-1</sup> than **1a**. According to the magnitude of the activation energies, the second step is the rate-determining step for the A<sub>AC</sub>2 mechanism. The latter barrier magnitude is close to that observed for methyl acetate under acidic conditions, ~16 kcal mol<sup>-1</sup>.<sup>12</sup>



The geometry with the protonated ether oxygen such as **1a''** in Figure 1 is the key to understanding the A<sub>AL</sub>2 mechanism described in Eq. 3. The **1a''** intermediate was calculated to be less stable by 11.0 kcal mol<sup>-1</sup> than **1a**. Potential energy surface scans were performed to find the TS of the mechanism. The obtained structure **5a(TS)** was also displayed in Figure 1.



The lengths of C(1)–O(4) and C(1)–O(6) were calculated to be 2.054 and 2.981 Å, and the C(7)–C(1)–O(8) angle was to be 155.8°. Since the C(1)–O(6) length is rather long,

a CH<sub>3</sub>C<sup>+</sup>(=O) fragment was almost formed in the TS. This feature of the geometry destabilizes the TS by 9.9 kcal mol<sup>-1</sup> in comparison with the **3a(TS)**. Thus, the TS is less stable by 28.2 kcal mol<sup>-1</sup> than **1a**. An IRC calculation confirmed that the **5a(TS)** is bonded with **5a**, in which acetic acid interacts with H<sub>2</sub>O and CH<sub>3</sub>OH<sub>2</sub><sup>+</sup> since the O(6) is connected with two hydrogen atoms. Therefore, the hydrolysis of methyl acetate proceeds under the A<sub>AC</sub>2 mechanism rather than the A<sub>AL</sub>2 one.

It was experimentally determined that two water molecules are involved in the hydrolysis, and act as a proton donor and a nucleophile.<sup>13</sup> Lane and co-workers pointed out the assistance of another water molecule to form the TD intermediate.<sup>11</sup> The present results are consistent with these hypotheses.

### 3.2. Hydrolysis of acetamide under acidic conditions

Protonation of the carbonyl oxygen is also the first event of the hydrolysis of acetamide, although its mechanism is less clear than that for esters.<sup>3</sup> An A<sub>AC</sub>2 mechanism similar to the ester hydrolysis should also be applicable to the amide hydrolysis as represented in Eq. 1-1. The rate of amide hydrolysis has been observed to be rather slow in comparison to that of the ester hydrolysis.

Two water molecules are not enough to optimize both the structures corresponding to **1a** and the TD intermediate. Moreover, no TD intermediates with three water molecules were obtained even though we conducted geometry searches. Therefore, the B3LYP/6-31G(d) level of theory was used to analyze the potential surface of the acetamide in detail. A TS structure similar to **3a(TS)** was obtained

with an imaginary frequency  $502.4i \text{ cm}^{-1}$ . Since the TS geometry was similar to that of **3a(TS)**, it was designated, **3b'(TS)**.

An IRC calculation using **3b'(TS)** was performed to elucidate this reaction mechanism in detail, and the results are displayed in Figure 2. The geometry with  $s=-1.0 \text{ amu}^{1/2} \text{ Bohr}$  looks like the TD intermediate, such as **2a(TS)**. The C(1)–O(2) length is longer by  $0.062 \text{ \AA}$  than in the TS ( $s=0.0$ ). It is very clear from the geometry at the TS and  $s=1.4 \text{ amu}^{1/2} \text{ Bohr}$  that the O(4) accepts a proton from the O(2), and donates another proton to N(5) in the reaction.

A proton relay occurs by the help of O(4) during  $s=0.0$  and  $1.4 \text{ amu}^{1/2} \text{ Bohr}$  on the IRC. With respect to the geometry at  $s=3.0 \text{ amu}^{1/2} \text{ Bohr}$ , the  $\text{NH}_3^+$  moiety has already formed. This feature in the geometry is different from that of **3a**, in which there is no C(1)–O(6) bond ( $2.281 \text{ \AA}$ ) corresponding to the C(1)–N(5) bond. Although the TD intermediate such as **2a** is not a minimum on the potential surface, two water solvent molecules play a critical role in transforming the molecular geometry from **1b'** to **3b'** (Fig. 3).

The geometry shown in Figure 3 was optimized at the MP2/6-31+G(d,p) level of theory using that previously obtained

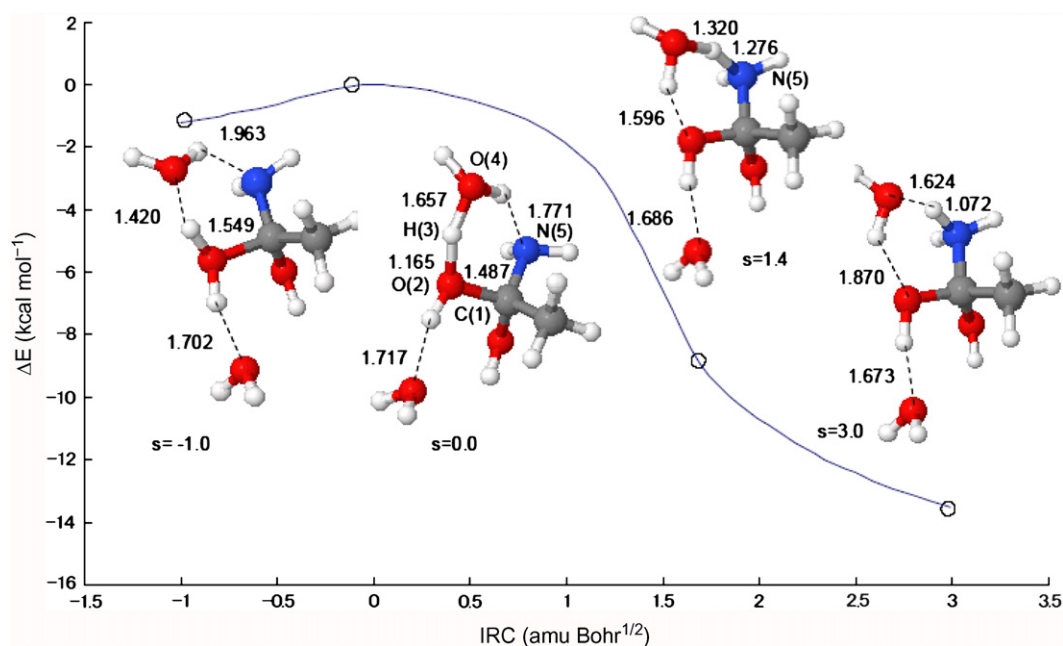


Figure 2. Change in the potential energy and geometry transformation along the IRC.

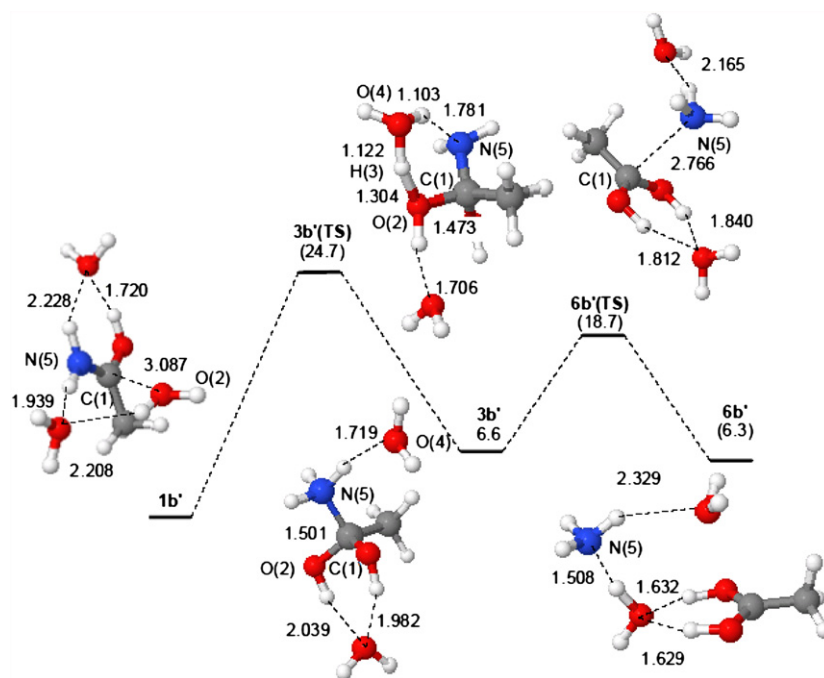


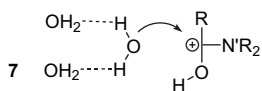
Figure 3. Energy diagram among structures of hydrolysis for acetamide. Units of energies and lengths are  $\text{kcal mol}^{-1}$  and  $\text{\AA}$ .



on the IRC at  $s = -1.0 \text{ amu}^{1/2} \text{ Bohr}$  as shown in Figure 3. Since it is similar to **1a** except for the additional water molecule, we designated it as **1b'** and adopted it as the reactant for the mechanism for acetamide. Furthermore, this is not the global minimum of the potential surface of the model as well. The C(1)–O(2) length was calculated to be 3.087 Å. A hydrogen bonding network lets the O(2) of the water stay over the carbonyl carbon C(1). Similar optimizations using the geometry at  $s = 0.0 \text{ amu}^{1/2} \text{ Bohr}$  were performed to obtain **3b'**(TS). Since the two O(4)–H lengths were calculated to be 1.122 and 1.103 Å, an oxonium ion must be interacting with the protonated acetamide in **3b'**(TS). Another optimization using the geometry at  $s = 3.0 \text{ amu}^{1/2} \text{ Bohr}$  produced the structure of **3b'** with an  $\text{NH}_3^+$  moiety. The C(1)–N(5) bond (1.501 Å) is not weakened very much. The geometrical features are similar to that for  $s = 3.0$  but is different from that in **3a** for methyl acetate.

It is necessary to point out that one more step is required to produce the final products,  $\text{CH}_3\text{C}(\text{OH})_2^+$  **4** and  $\text{NH}_3$  because a C(1)–N(5) bond still exists in the intermediate **3b'**. **6b'**(TS) inherits the geometric features of **3b'** except for the rather long C(1)–N(5) length (2.766 Å).

Kinetic data<sup>4,15</sup> showed that three water molecules are involved in the rate-determining step of amide hydrolysis, as that shown in 7.



Although the experimental expectation is consistent with the present calculated results,<sup>4,15</sup> it is not necessary to consider the TD intermediate such as **2a** on the IRC.

The intermediate decomposed to  $\text{NH}_3$  and **6b'** with the activation energy of  $12.1 \text{ kcal mol}^{-1}$  from **3b'** or  $18.7 \text{ kcal mol}^{-1}$  from **1b'**. Since the activation barrier from **1b'** was calculated to be  $24.7 \text{ kcal mol}^{-1}$ , the rate-determining step is the formation of **3b'** from **1b'**. The activation energies for simple glycine peptides were observed to be  $\sim 20 \text{ kcal mol}^{-1}$ , which are smaller by 4–5  $\text{kcal mol}^{-1}$  than that from the calculations.<sup>16</sup>

#### 4. Concluding remarks

In the present study, we studied the hydrolysis mechanism of methyl acetate and acetamide under acidic conditions by use of MO calculations at the MP2/6-311+G(d,p)//MP2/6-31+G(d,p) level of theory. We came to the following conclusions from the theoretical results.

- (1) It was confirmed that the rate-determining step is the decomposition of the TD intermediate using the  $A_{AC}2$  mechanism for methyl acetate. The calculated activation energy ( $18.3 \text{ kcal mol}^{-1}$ ) is close to that observed.
- (2) Since the activation energy of the  $A_{AL}2$  mechanism was calculated to be  $28.2 \text{ kcal mol}^{-1}$ , which is larger by  $9.9 \text{ kcal mol}^{-1}$  than the  $A_{AC}2$  mechanism, the acid-catalyzed hydrolysis of methyl acetate proceeds under the  $A_{AC}2$  mechanism.

- (3) It was confirmed that three water molecules are related to the  $A_{AC}2$  mechanism. Although the mechanism is applied to the hydrolysis of acetamide, the TD intermediate does not exist on the IRC. The reaction proceeds through one step from **1b'** to **3b'**. The activation energy was calculated to be  $24.7 \text{ kcal mol}^{-1}$ .
- (4) The intermediate **3b'** still includes the  $\text{NH}_3^+$  moiety, which is easily released to form the final products in the additional step.

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#### Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.11.039.

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