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Reaction Paths of the Water-Assisted Neutral Hydrolysis of Ethyl Acetate

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Density functional theory calculations were conducted on the title reactions with explicit inclusion of a variety of water molecules. Concerted reaction paths were examined first in the reaction model, ester$(H_2O)_n$ → $MeCOOH(H_2O)_{n-1}EtOH$, with $n = 1-4$. Their Gibbs activation energies are much larger than the experimental value, and the concerted paths are unfavorable. Various stepwise paths were investigated, and the ester$(H_2O)_4$ reactant gives a likely stepwise path. The $n = 4$ based reaction models, $n = 4 + 5$ and $n = 4 + 12$, were found to have similar proton-relay shapes with good hydrogen-bond directionality. The distinction of either the concerted or the stepwise path is described by the position of only one proton in the "junction" water molecule.

I. Introduction

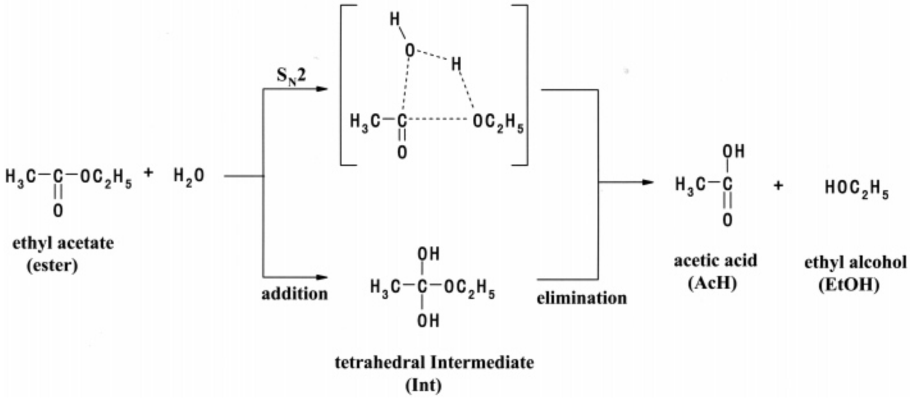
The hydrolyses of esters are fundamental reactions. In the acyl transfer processes, the ^{18}O labeling experiments by Bender provided evidence for tetrahedral intermediates of carboxylic esters.[1] Since then, those reactions are thought to proceed not through the concerted S_N2 mechanism but through the addition−elimination one.[2] Two mechanisms are illustrated formally in Scheme 1 by the use of the most typical substrate, ethyl acetate. Generally, acyl transfer reactions with strong nucleophilies and poor leaving groups proceed via the tetrahedral intermediates,[3] to which the reaction in Scheme 1 belongs. Despite the established stepwise mechanism in Scheme 1, its understanding at molecular level is not yet satisfactory; how many water molecules are concerned with the addition and the elimination? There are only two quantum chemical approaches to the water assisted neutral hydrolysis of formyl ester[4] and ethyl acetate.[5] However, the number of water molecules is limited to two or three, and the reaction models are not necessarily relevant to the behavior in aqueous media.

In our previous work, it was demonstrated that the size exension of water clusters enhances their electrophilicity and nucleophilicity.[6] On the other hand, the hydrogen-bond directionality imposes clusters of limited size on reaction systems.[7] There should be an optimal number of water molecules in the addition or the elimination of Scheme 1. In this work, we attempted to trace both mechanisms in Scheme 1 systematically by the use of a variety of water molecules. Particular interest is in the borderline of the two mechanisms in Scheme 1. The concerted and stepwise paths are thought to be close to each other in the hydrogen bond network around the substrate, ester. DFT calculations were carried out on the possible paths so as to shed light on the borderline.

II. Calculation Method

The geometries of ester$(H_2O)_n$ ($n = 2, 3, 4, 5, 9, 12$, and 16) were determined by density functional theory calculations. The B3LYP/6-31G* method[8] was used for geometry optimizations. At the optimizations the solvent effect was taken into account by Onsager's self-consistenet field with the dielectric constant = 78.39 (water).[9] B3LYP seems to be a suitable method because it includes the electron correlation effect to some extent.

SCHEME 1: Formal Presentation of the Neutral Hydrolysis of Ethyl Acetate[a]



[a] Abbreviations used in this work are shown in parentheses.

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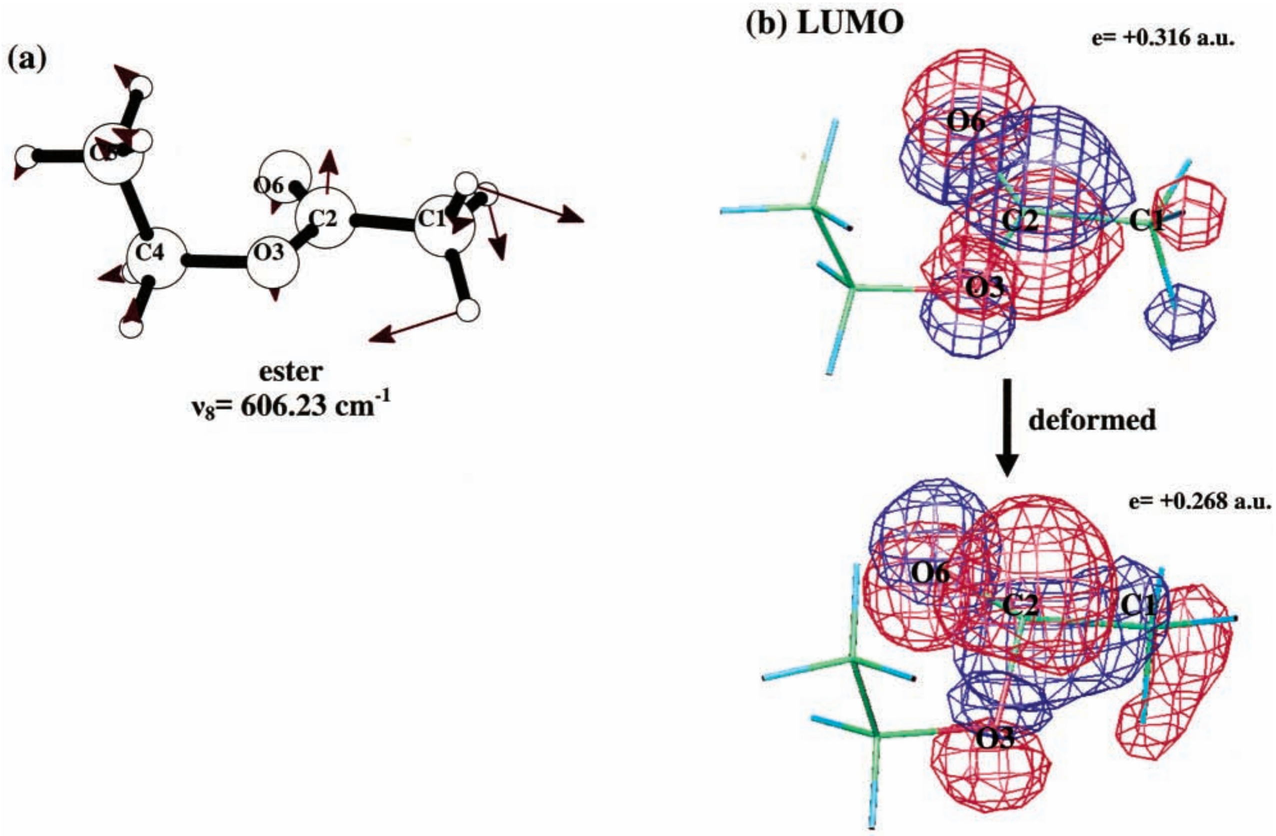
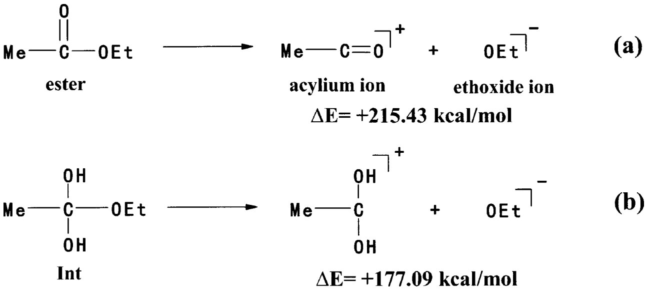


Figure 1. (a) The geometry of ethyl acetate, and the vibrational mode of the eighth lowest harmonic frequency, $\nu_8 = 606.23$ cm^{-1}. Empty small circles stand for hydrogen atoms. (b) The shapes and orbital energies of LUMO for the equilibrium and deformed geometries. The deformation is made along the 8-th vibrational mode.

SCHEME 2: Destabilizing Energies for Heterolytic C−O Bond Scissions



Transition states (TSs) were characterized by vibrational analysis, which checked whether the obtained geometries have single imaginary frequencies ($\nu^{\ddagger}$s). Form TSs, reaction paths were traced by the IRC (intrinsic reaction coordinate) method[10] to obtain the energy-minium geometries. All the calculations were carried out using the GAUSSIAN 98[11] program package installed on Compaq ES 40 at the Information Processing Center (Nara University of Education).

III. Results and Discussions

Figure 1(a) shows the geometry of ethyl acetate (called here ester). As a substrate, the $\Pi^*_{c=0}$ MO of the ester is subject to nucleophilic attacks along the out-of-plane direction. The reactivity of $\Pi^*_{c=0}$ is enhanced by the out-of-plane deformation. The eighth normal-mode vibration shown in Figure 1a gives the deformation. Through the deformation, the orbital lobe of LUMO is enlarged at the carbonyl carbon as Figure 1b shows. At LUMO of the deformed geometry, the antibonding character of C2−O3 is small, which means that the nucleophilic attack on the carboxyl carbon invokes hardly the C2−O3 bond scission.

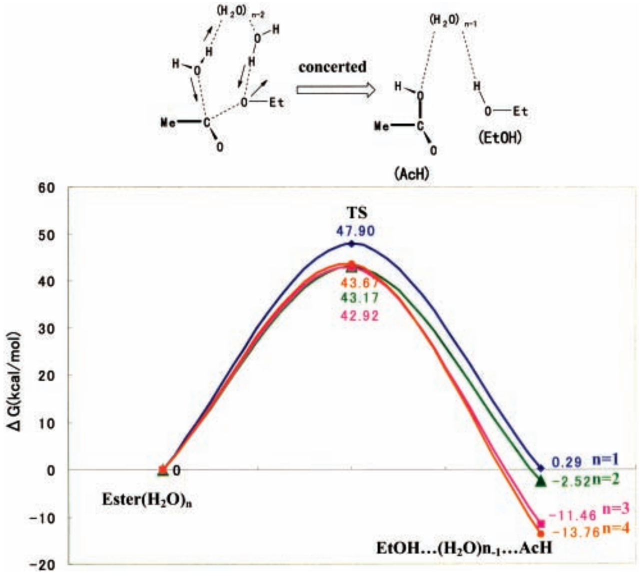


Figure 2. Gibbs energy diagrams ($T = 298.15$ K, P = 1 atm) of the concerted reactions, ester$(H_2O)_n$ → TS → AcH$(H_2O)_{n-1}$EtOH. The experimental $\Delta G^{\ddagger}$ value is 28.43 kcal/mol from ref 12. The corresponding TS geometries are in Figure 3, and the detailed reaction paths are shown in Figures S1 ($n = 1$), S2 ($n = 2$), S3 ($n = 3$), and S4 ($n = 4$) of Supporting Information.

Destabilizing energies (ΔEs) for the heterolytic dissociations of the ester and the intermediate (Int) according to Scheme 1

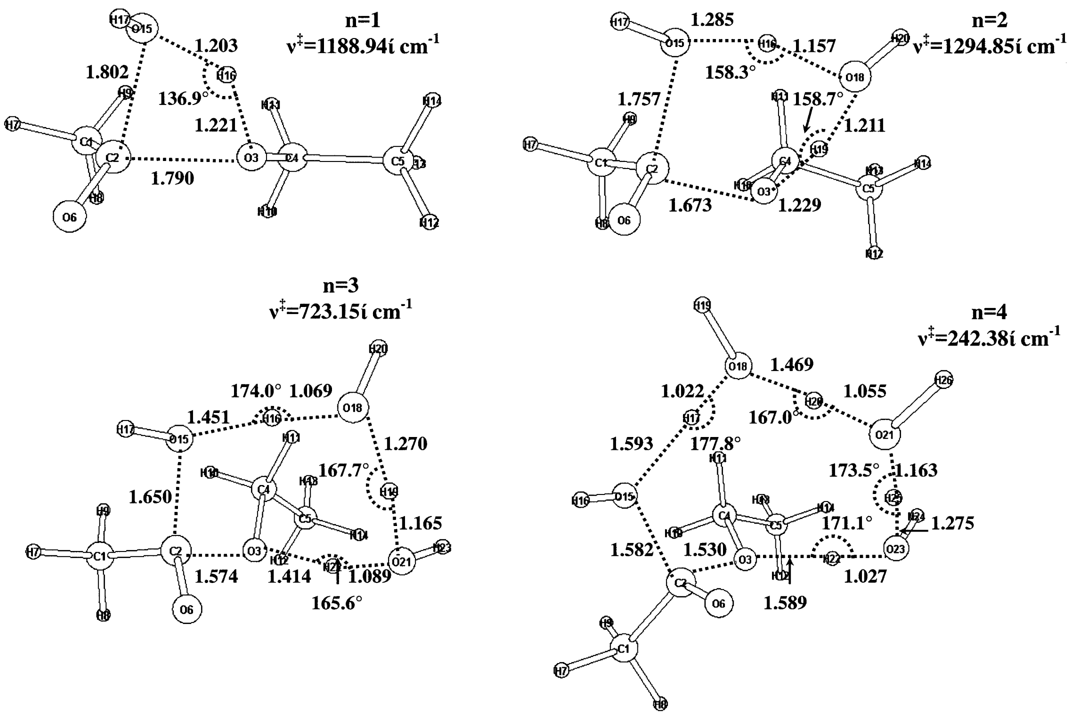


Figure 3. Transition state (TS) geometries of the concerted reactions. To each geometry, the sole imaginary frequency ($\nu^{\ddagger}$) is shown. Distances are in Angstrom.

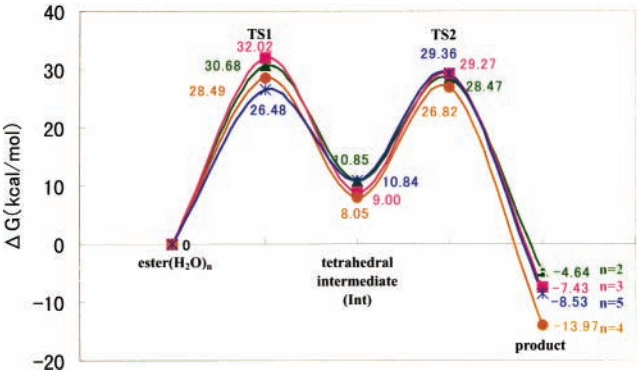
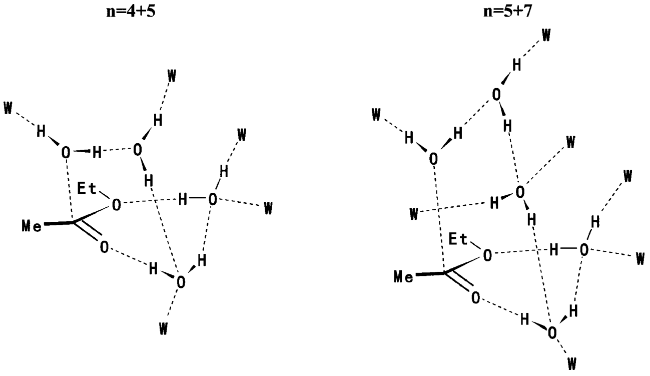


Figure 4. Diagrams of Gibbs free energies for stepwise paths of the water assisted neutral hydrolysis. The experimental $\Delta G^{\ddagger}$ value is 28.43 kcal/mol from ref 12. The detailed reaction paths corresponding to respective energy changes are shown in Figures S5 (n = 2), S6 (n = 3), 5 (n = 4), and 6 (n = 5). Figure S's are in Supporting Information.

SCHEME 3: Reaction Models to Judge Which Is More Favorable, the n = 4 or 5 Based System[a]



[a] W stands for an outer water molecule.

were computed by (U)RB3LYP/6-311+G(2d,p) ZPE and are shown in Scheme 2. There is a large difference of the ΔE values. In reaction b, the fragment ion $MeC(OH)_2^+$ is a tertiary carbonium ion, of which the stability makes ΔE of reaction b much smaller. Thus, intervention of Int would be needed to cleave the C−OEt bond readily. The concerted (S_N2) reaction in Scheme 1 is expected to be unlikely. However, this expectation must be examined numerically in concerted proton-relay paths. As an electrophilic substrate, the ester will react with water clusters.

Figure 2 exhibits changes in Gibbs free energies for the concerted reaction, ester$(H_2O)_n$ → (TS) → EtOH$(H_2O)_{n-1}$ AcH, to which the experimental value of $\Delta G^{\ddagger}$ = 28.43 kcal/ mol is attached.[12] The four calculated $\Delta G^{\ddagger}$ values are more than 40 kcal/mol and are much larger than $\Delta G^{\ddagger}$(exptl) = 28.43 kcal/ mol. It is interesting that while the exotherimicity is improved as $n = 1 \rightarrow 4$ (0.29 → −2.52 → −11.46 → −13.76 kcal/ mol), the activation energy is not improved. The corresponding four TS geometries are shown in Figure 3. Proton relays via water molecules lead to the concerted processes. As n becomes larger, distances of the newly formed C···O and the cleaved C···O bonds are shortened. A water molecule attacks the carbonyl carbon as nucleophile, and a proton is transmitted to the ether oxygen. In accordance with the prediction by LUMO energies (Figure 1), the ester substrates get electronic charge densities from the water clusters(e.g., for n = 2, the water dimer is +0.19 cationic). Although apparently reasonable concerted paths of Figure 3 are present, they are unfavorable as shown in Figure 2. Next, stepwise paths in Scheme 1 need to be considered.

Figure 4 presents energy diagrams for stepwise paths. Experimentally, the neutral ester hydrolyses were suggested to be caused by two or more water molecules.[13] In fact, at least two ones are necessary for the stepwise paths. The n = 2 reaction was already examined.[5] However, the present system-

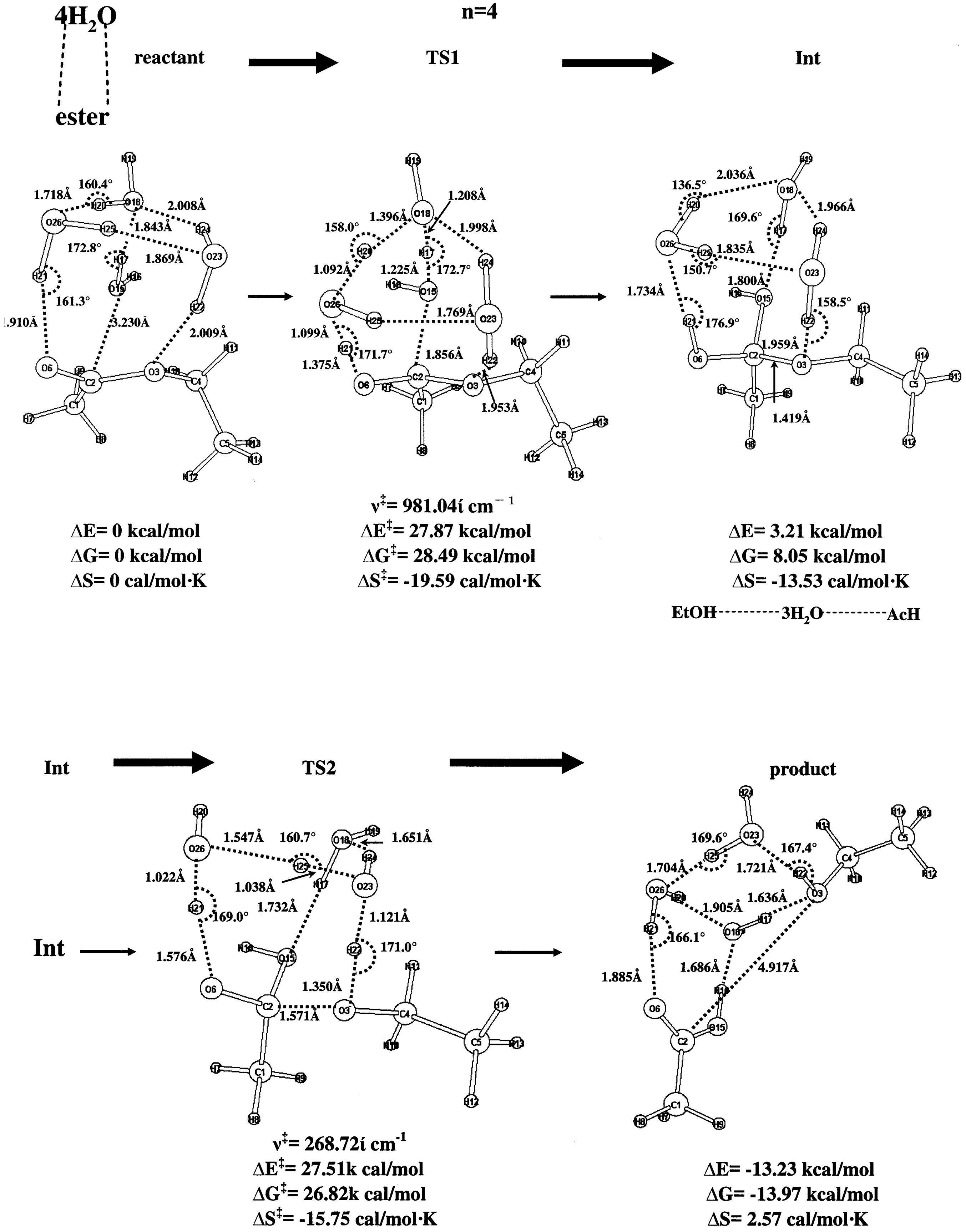


Figure 5. The stepwise reaction path of ester$(H_2O)_4$ → Int → $EtOH(H_2O)_3AcH$. Distances are Angstrom, and empty small circles stand for hydrogen atoms. Δ*E* and Δ*G* are relative electronic and Gibbs free energies, respectively, where positive values mean less stable states. Δ*S* is the entropy change. Δ*G* values are also shown in Figure 3. The reaction-coordinate vectors corresponding to the sole imaginary frequency ($\nu^{\ddagger}$) are attached to TS geometries.

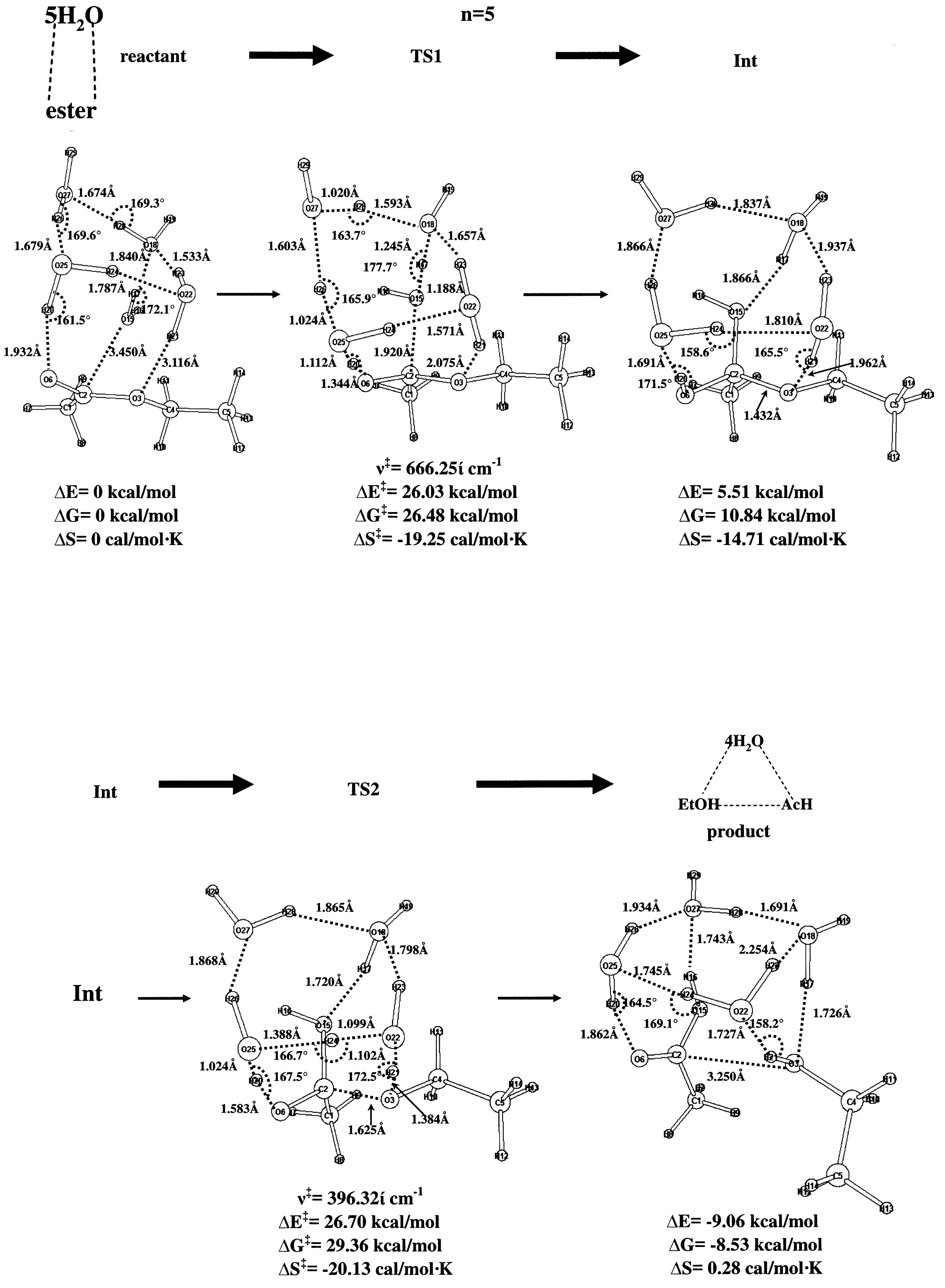


Figure 6. The stepwise path of ester$(H_2O)_5$ → Int → EtOH$(H_2O)_4$AcH. Δ*G* values are also shown in Figure 3.

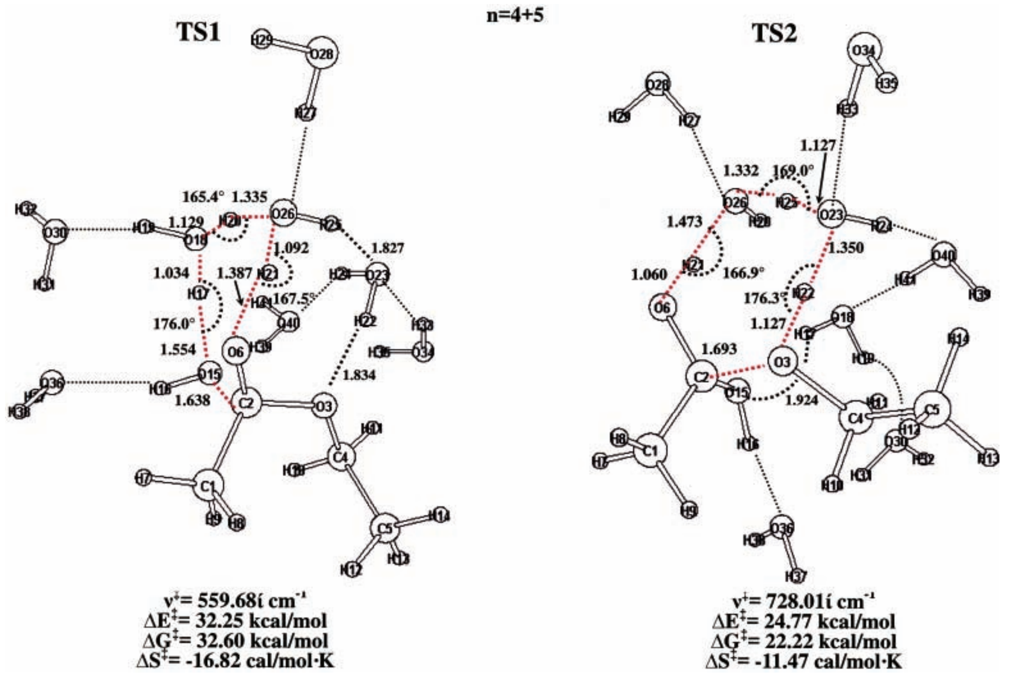


Figure 7. Two TS geometries (TS1 and TS2) of the reaction, ester$(H_2O)_{4+5}$ → TS1 → Int → TS2 → AcH$(H_2O)_8$EtOH. Red broken lines show routes of the proton relay.

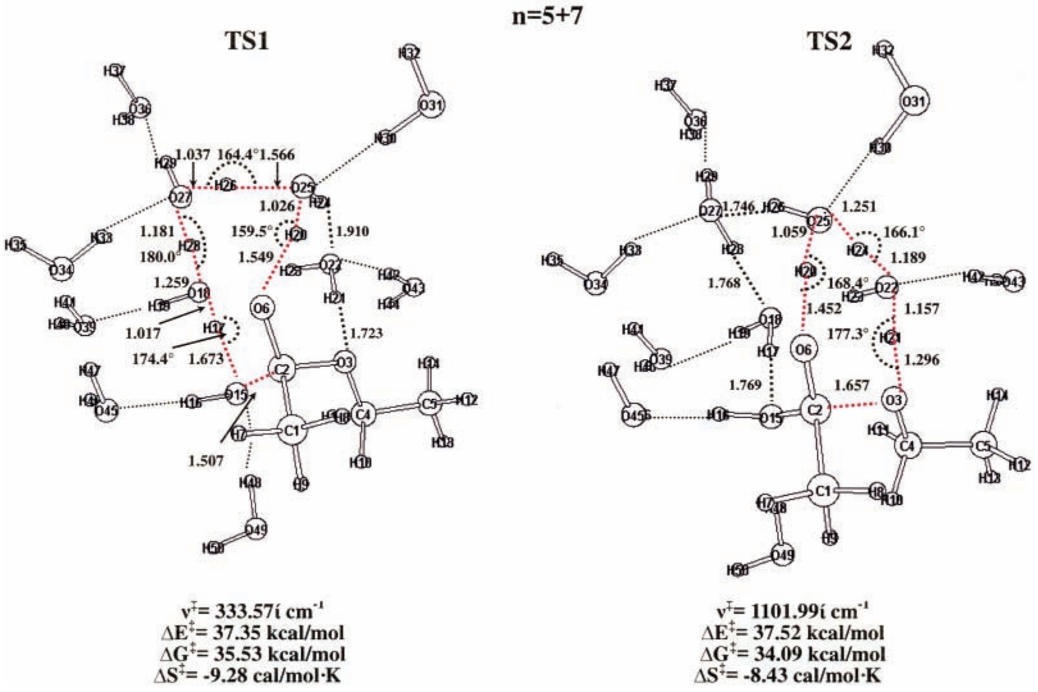
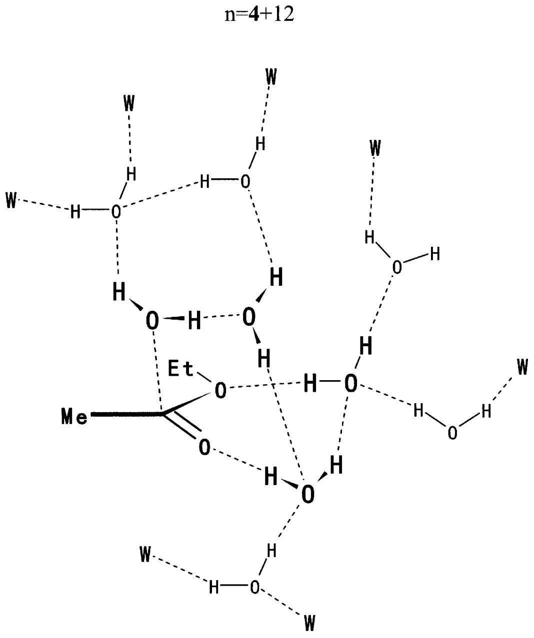


Figure 8. Two TS geometries (TS1 and TS2) of the reaction, ester$(H_2O)_{5+9}$ → TS1 → Int → TS2 → AcH$(H_2O)_{13}$EtOH.

atic analyses have shown that $n = 4$ and 5 have smaller $\Delta G^{\ddagger}$ values than $n = 2$ and 3. The $n = 2$ and 3 reaction paths are shown in Figures S5 and S6 in Supporting Information. At TS1, water dimers are reactants to afford tetrahedral intermediates (Ints) for both $n = 2$ and 3. Proton relay patterns are similar between $n = 2$ and 3. The $n = 2$ and 3 stepwise reaction models have been found to have insufficient hydrogen bond directionality (O···H−O hydrogen bond angles <160°). Accordingly, their $\Delta G^{\ddagger}$ values of TS1 are larger than those of $n = 4$ and 5.

The reaction models of ester$(H_2O)_n$ ($n = 4$ and 5) are investigated here for the first time, and they have only slightly different energy changes in Figure 4. Figure 5 exhibits the stepwise reaction path of $n = 4$. At TS1, a water trimer is involved in the proton relay toward Int ($n = 4$ is $n = 3 + 1$). The relay path has good hydrogen bond directionality. By the electronic densities, the substrate ester works as an electron acceptor at TS1. At TS2, a water dimer is involved in the relay. Again, the directionality is good. At TS2, a water trimer is not fit for the proton relay. The size of the trimer is too large between two

SCHEME 4: The $n = 4 + 5$ Centered Expansion Model



geminal oxygen atoms in Int. Figure 6 shows the stepwise path of $n = 5$. At TS1, $n = 5$ is equal to $n = 4 + 1$, and tetramer is involved in the proton relay to afford Int. The proton-relay pattern of TS2 of $n = 5$ is similar to that of $n = 4$. While $\Delta G(n = 4) = 28.49$ kcal/mol $>$ $\Delta G(n = 5) = 26.48$ kcal/mol for TS1, $\Delta G(n = 4) = 26.82$ kcal/mol $<$ $\Delta G(n = 5) = 29.36$ kcal/mol for TS2. The superiority or inferiority between $n = 4$ and $n = 5$ cannot be judged in the present comparison. Models more than 5 water molecules were also traced. However, they were transformed to $n = 4$ and 5 plus outer water molecules.

To judge which is more favorable, the $n = 4$ or 5 based model, large reacting systems were made. They are shown in Scheme 3. Figure 7 shows two TS geometries of $n = 4 + 5$. Their reaction-center shapes (hydrogen-bond circuits) are similar to those of $n = 4$ (Figure 5). The outer H_2O molecules (Ws in Scheme 3) do not invade the proton relay regions. Figure 8 exhibits two TS geometries of $n = 5 + 7$ which reveal that the shapes of the $n = 5$ reactions centers are involved therein. The comparison of the $\Delta G^{\ddagger}$ values in Figures 7 and 8 shows that both energies of TS1 and TS2 of $n = 4 + 5$ are smaller than those of $n = 5 + 7$, respectively, indicating that the $n = 4$ based model is more favorable than the $n = 5$ one.

The $n = 4$ based model is further checked by a $n = 4 + 12$ one in Scheme 4 and Figure 9. TS searches of $n = 4 + 12$ were very difficult; however, TS1 and TS2 were successfully determined. Even in this large reaction system, the features (proton relays along hydrogen bonds with good directionality) of the central $n = 4$ moiety are maintained.

IV. Concluding Remarks

In this work, the neutral ester hydrolysis reaction has been investigated computationally. Reaction systems with a variety of water molecules have been considered. Although strainless and reasonable reaction paths are present, the concerted mechanism is unfavorable regardless of the number of water molecules. The acyl OC−OEt bond is too rigid to cleave concertedly. To transform the bond to the standard ether C−O bond, intervention of a tetrahedral intermediate (Int) is needed. In the stepwise path, $n = 4$ based reaction models have been found to be favorable both structurally and energetically. The favorable model is depicted in Scheme 5.

TS1 is the addition path and TS2 is the elimination one in Scheme 1, respectively. In TS1, the reactant is a water trimer whereas it is a dimer in TS2. In TS1, a water molecule works as a junction either for the concerted path or for the stepwise one. The role of the junction is explicitly presented in Figure 10. In the left side of the Figure, TS of the $n = 4$ concerted path is shown. A blue-color proton is situated outside of the

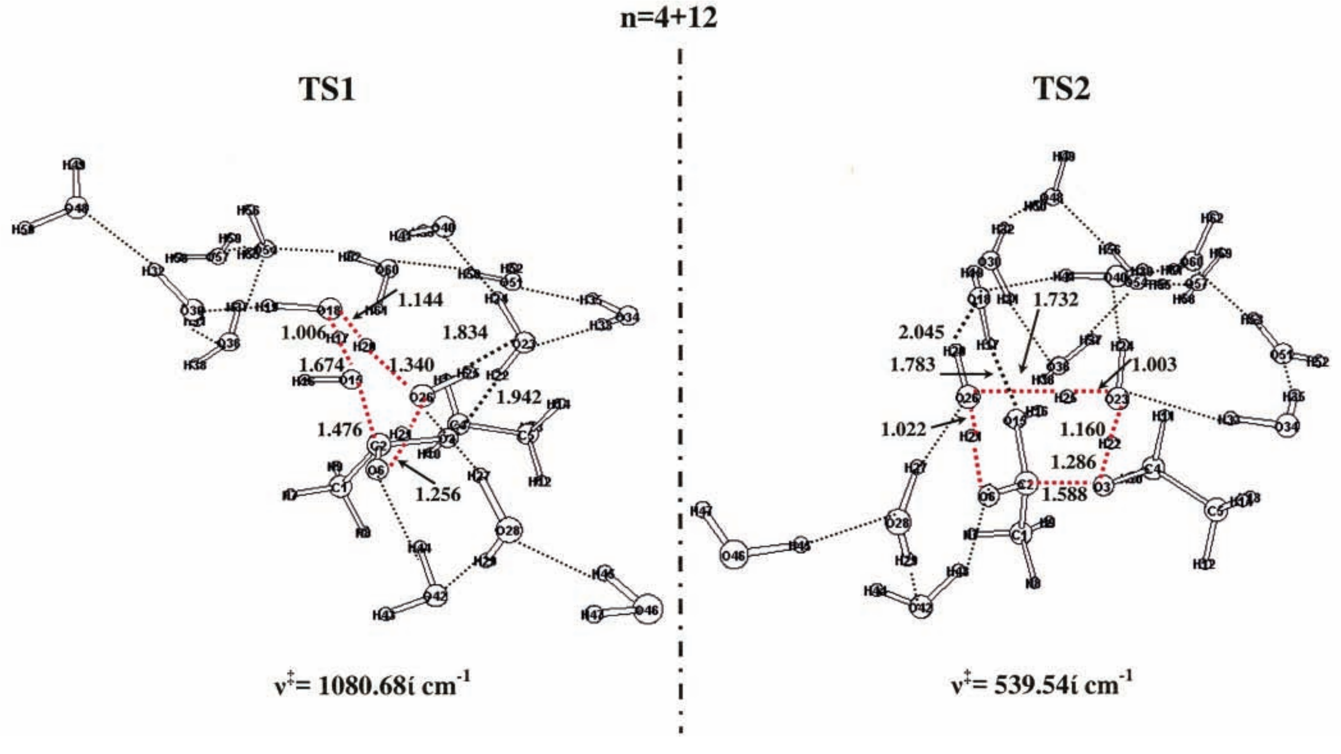
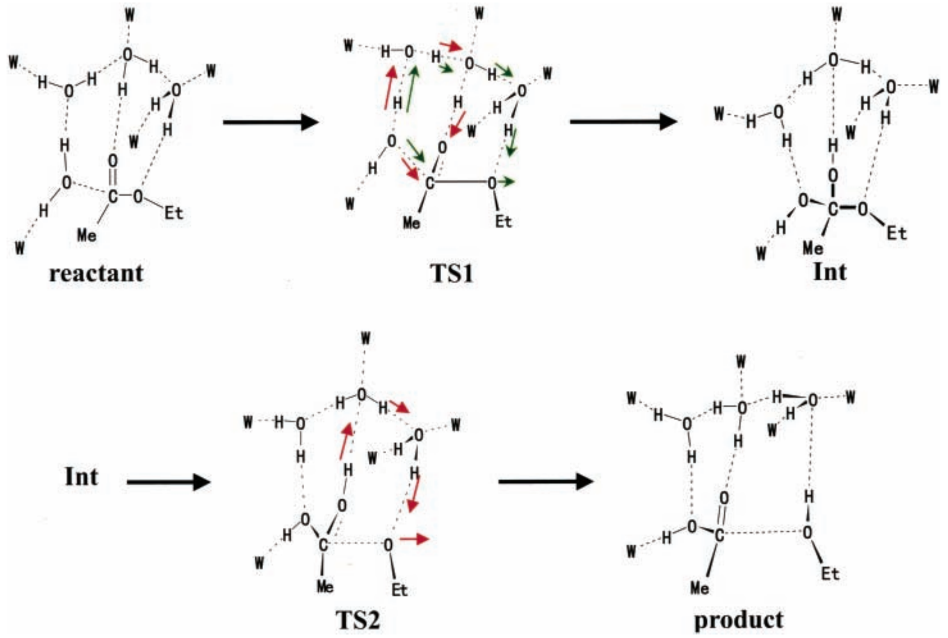


Figure 9. Two TS geometries (TS1 and TS2) of the stepwise reaction path of ester$(H_2O)_{16}$ → TS1 → Int → TS2 → $AcH(H_2O)_{15}EtOH$.

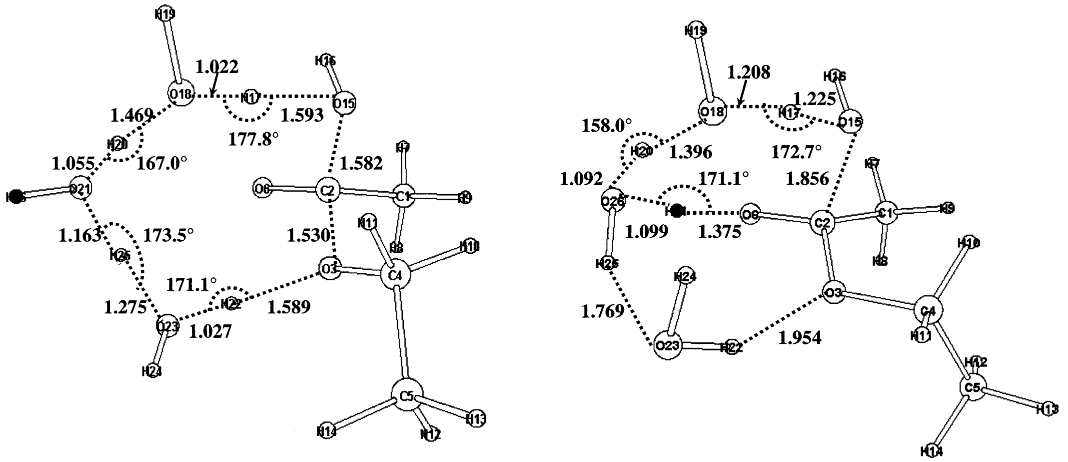
SCHEME 5: Summary of This Work on the Water-Assisted Neutral Hydrolysis of Ethyl Acetate[a]



[a] W stands for outer-sphere water molecules. At TS1, green arrows indicate the concerted and unfavorable path. At TS1 and TS2, red-arrow proton relays afford the stepwise path with a tetrahedral intermediate (Int). Four water molecules are concerned with those relays.

n=4

TS of the concerted reaction in Figure 3 **TS1 of the stepwise reaction in Figure 5**



$\nu^{\ddagger}$= 242.38*i* cm^{-1}
$\Delta E^{\ddagger}$= 43.72 kcal/mol
$\Delta G^{\ddagger}$= 43.67 kcal/mol

$\nu^{\ddagger}$= 981.04*i* cm^{-1}
$\Delta E^{\ddagger}$= 27.87 kcal/mol
$\Delta G^{\ddagger}$= 28.49 kcal/mol

Figure 10. A distinction between the concerted ($n = 4$) and the stepwise ($n = 3 + 1$) paths. When a blue-colored proton is outside the hydrogen bond network, the concerted path was obtained. When the proton is inside the network, the stepwise path was obtained.

hydrogen bond circuit. A large circuit affords the concerted path. In the right of the Figure, the proton is inside the large circuit, and a smaller circuit is generated as a shortcut. The latter circuit leads to Int via TS1. Thus, the distinction of either the concerted or the stepwise path in Scheme 1 is endowed with the position of only one proton, which has been obtained within framework of the structures and the hyper surface of the electronic energy.

Supporting Information Available: Figures of concerted reaction paths and stepwise reaction paths of esters. This information is available free of charge via the Internet at http://pubs.acs.org.

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