6296 *J. Phys. Chem. A* **2007,** *111,* 6296−6303

Reaction Paths of the Water-Assisted Solvolysis of *N*,*N*-Dimethylformamide

Noriko Tsuchida, Harumi Satou, and Shinichi Yamabe*

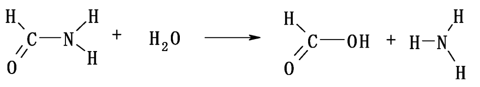
Department of Chemistry, Nara University of Education; Takabakake-cho, Nara 630-8528, Japan

Received: April 13, 2006

Density functional theory calculations were conducted on the title reactions with explicit inclusion of a variety of water molecules, $\mathrm{H{-}CO{-}NMe_2 + MeOH + (H_2O)_n \rightarrow H{-}CO{-}OMe + HNMe_2 + (H_2O)_n}$. Geometries of transition states, reactant-like complexes and product-like ones were determined by the use of RB3LYP/6-31G(d) SCRF=dipole. Concerted paths were examined with $n = 0-3$. Their Gibbs activation energies are larger than the experimental value. Stepwise paths were also investigated with $n = 2-4$. The $n = 4$ model has the energy close to the experimental value. However, when the catalytic water molecules were added to the $n = 4$ one, the stepwise path was switched to the concerted one. A systematic comparison of the concerted path with $n = 2 + 1$, $2 + 2$, $2 + 3$, $2 + 4$, $2 + 5$, $2 + 4 + 4$, and $2 + 5 + 5$ models was made, and the water-dimer based reaction path was found to be most favorable. The contrast between the concerted path of the amide solvolysis (and hydrolysis) and the stepwise one of the ester hydrolysis was discussed in terms of the frontier-orbital theory.

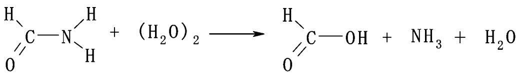
I. Introduction

The hydrolysis or solvolysis of amides is a reaction of great importance, because it is a model of the cleavage of peptide bonds in living system.[1] In the hydrolysis, formally, a nucleophilic water molecule attacks the carbonyl carbon atom to form a C−O bond and to cleave the C−N bond (eq 1). The first



$$\mathrm{HC(=O){-}NH_2 + H_2O \longrightarrow HC(=O){-}OH + H{-}NH_2} \qquad (1)$$

theoretical study on eq 1 was made in 1982. A concerted path was traced along with the stepwise one including the tetrahedral intermediate.[2] The activation free energy calculated by MP3/6-31G*//RHF/3-21G is 58.6 kcal/mol for the concerted path. They are 51.5 and 41.3 kcal/mol for the stepwise one. Because the model (one molecule of formamide and that of water) is too small, those energies are too large for the reaction to take place. In 1994, a reaction of eq 2 was studied computationally.[3a]

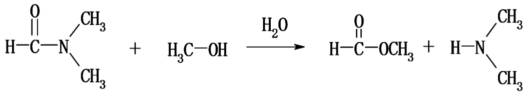


$$\mathrm{HC(=O){-}NH_2 + (H_2O)_2 \longrightarrow HC(=O){-}OH + NH_3 + H_2O} \qquad (2)$$

Only the concerted path was investigated with the activation free energy, 45.40 kcal/mol (relative to the weakly bound complex, MP3/6-31G*//RHF/3-21G). Although the energy is lowered by the water-dimer participating model, still it is too large. In addition, the stepwise path was not examined by the dimer model.[3] Thus, the noncatalytic and neutral hydrolysis of amides has not been investigated precisely.

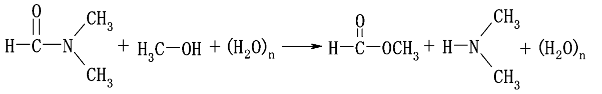
Recently, we reported calculated results on the hydrolysis of ethyl acetate.[4] A reaction model, $\mathrm{Me{-}CO{-}OEt + (H_2O)_l \rightarrow R{-}CO{-}OH + HOEt + (H_2O)_{l-1}}$, was investigated systematically with various l values ($l = 1-5$, 9, 12, and 16). The stepwise path with $\Delta G^{\ddagger}(\mathrm{TS1}) \approx 30$ kcal/mol was much more favorable than the concerted one with $\Delta G^{\ddagger}$ (TS1) ≈ 43 kcal/mol (Scheme 1). The transition state (TS) geometry involving the water tetramer as the reactant was insensitive to the addition of catalytic water molecules.

The free energies of the solvolysis of eq 3 was determined calorimetrically in the aqueous media.[5] A stepwise path was



$$\mathrm{H{-}C(=O){-}N(CH_3)_2 + H_3C{-}OH \xrightarrow{H_2O} H{-}C(=O){-}OCH_3 + H{-}N(CH_3)_2} \qquad (3)$$

assumed with an unstable tetrahedral intermediate, and the activation free energy of the rate-determing step was estimated to be +30.2 kcal/mol. The water molecules would work to promote the bond interchange in eq 3 through hydrogen bonds. In this work, the reaction of eq 3 was investigated computationally. Various concerted and stepwise reaction paths were employed in eq 4, and their reactivities were examined in terms of the calculated activation free energies. It was found that the



$$\mathrm{H{-}C(=O){-}N(CH_3)_2 + H_3C{-}OH + (H_2O)_n \longrightarrow H{-}C(=O){-}OCH_3 + H{-}N(CH_3)_2 + (H_2O)_n} \qquad (4)$$

stepwise path is transformed to the concerted one, as n grows large. That is, the superiority or inferiority, between the concerted and stepwise paths of eq 4 is not so distinct as that in the ester hydrolysis. The concerted path with $n = 2 + 5$ was calculated to be the most likely one, where +5 stands for the outer catalytic water molecules.

II. Calculation Method

The geometries of $\mathrm{DMF{\cdot}MeOH{\cdot}(H_2O)_n}$ were determined by density functional theory calculations. The B3LYP/6-31G* method[6] was used for geometry optimizations. B3LYP seems to be a suitable method, because it includes the electron correlation effect to some extent. At the optimizations the solvent effect was taken into account by Onsager's self-consistent field with the dielectric constant equal to 78.39 (water).[7] The solvent

---

* Corresponding author. E-mail: yamabes@nara-edu.ac.jp.

10.1021/jp068051r CCC: $37.00

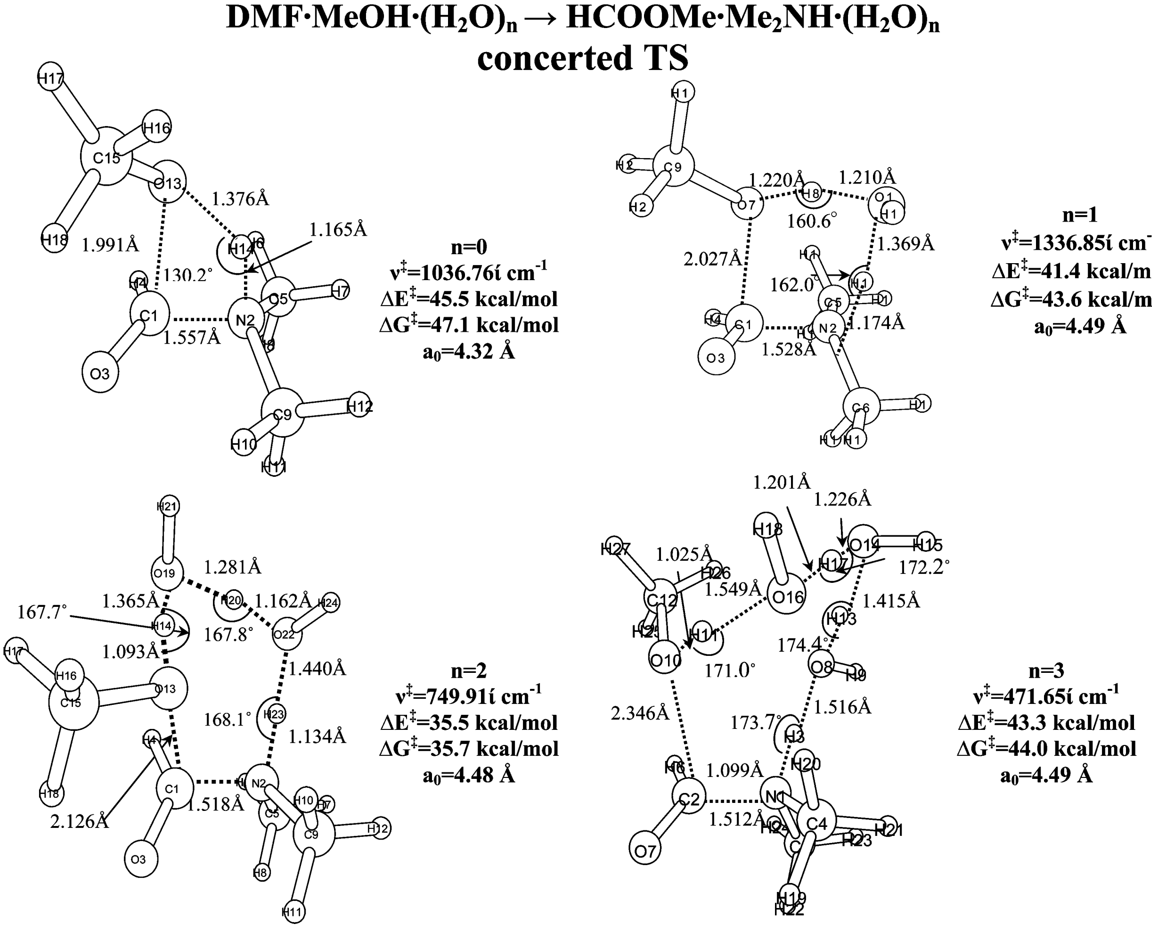
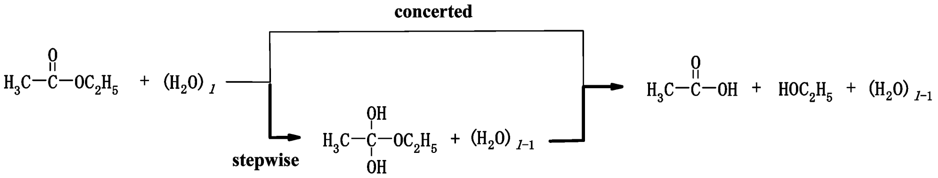


Figure 1. Transition state (TS) geometries of the concerted reactions. To each geometry, the sole imaginary frequency ($\nu^{\ddagger}$) is shown. DMF is dimethylformamide.

SCHEME 1: Two Paths of the Ester Hydrolysis[a]



[a] The stepwise path is much more favorable than the concerted one, which has been reported recently.[4]

is viewed as a continuous medium of uniform dielectric constant (ϵ), and the solute occupies a spherical cavity of radius a_0 within it.

Transition states (TSs) were characterized by vibrational analyses, which checked whether the obtained geometries have single imaginary frequencies ($\nu^{\ddagger}$). From TSs, reaction paths were traced by the IRC (intrinsic reaction coordinate) method[8] to obtain the energy-minimum geometries. The Gibbs free energy was estimated by the use of the equations of molecular thermodynamics.[9] That is, the free energy was calculated by the RB3LYP/6-31G* SCRF=dipole electronic energy, the Cartesian coordinates of the optimized geometries and the harmonic frequencies. The temperature T = 298.15 K was adopted, because the experiments were carried out at that temperature.[5] To check the reliability of the RB3LYP/6-31G* SCRF=dipole calculations, RB3LYP/6-31G* gas phase and RB3LYP/6-31(+)G* SCRF=dipole ones were also carried out. On the key reacting systems, $n = 4 + 4$ (stepwise) or $n = 2 + 4 + 2$ (concerted) in Figure 4 and $n = 2 + 5$ in Figure 6. In the 6-31(+)G basis set, diffuse functions were added to five oxygen atoms, O6, O12, O15, O19, and O22, and the nitrogen atom, N2. Further, geometries of TSs in Figures 4 and 6 were optimized by B3LYP/6-311++G** SCRF=dipole. By the three ways of calculations, it was judged whether TSs are for stepwise or concerted paths. Single-point energy calculations, B3LYP/6-311++G** SCRF=dipole and B3LYP/6-311++G** SCRF=PCM,[10] were conducted, and their energies are also shown in Figures 4 and 6. All the calculations were carried out using the GAUSSIAN 03[11] program package at the Information Processing Center (Nara University of Education). It seems now to be established that B3LYP calculations may give reliable results of proton transfers and bond interchanges along hydrogen bond.[12]

III. Results and Discussions

Figure 1 and Figures S1 and S7 (Supporting Information) show concerted paths of $HCO-NMe_2 + MeOH + (H_2O)_n \rightarrow HCOOMe + HNMe_2 + (H_2O)_n$. Except $n = 0$, water molecules

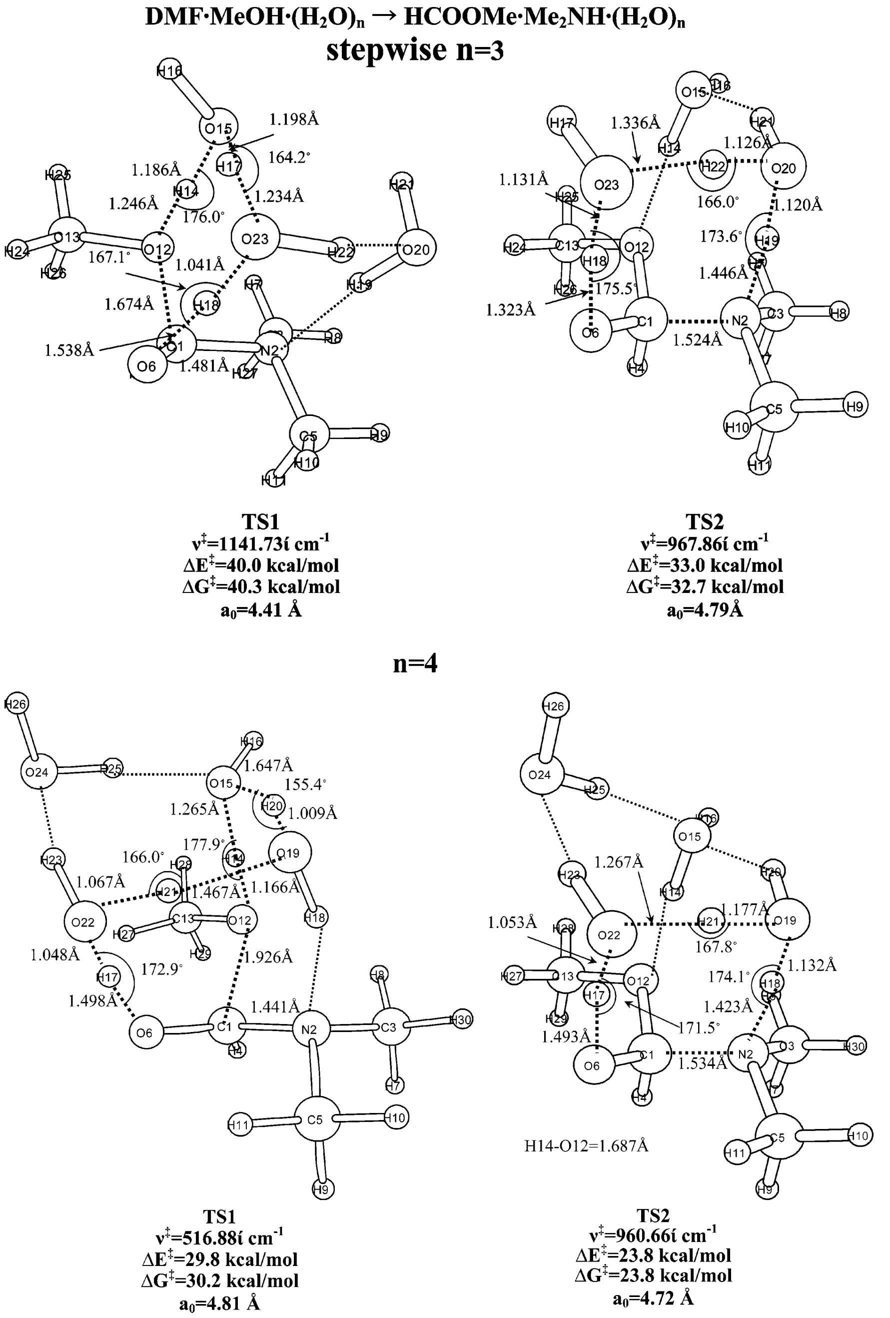


Figure 2. Two transition state (TS1 and TS2) geometries of the stepwise reaction path of DMF·MeOH·$(H_2O)_n$ → TS1 → Int → TS2 → HCOOMe·Me_2NH·$(H_2O)_n$ ($n = 3$ and 4). Purple broken lines show routes of the proton relay.

are concerned with the proton relays to support the hydrogen-bond linearity. Bond cleavage and formation occur simultaneously. Figure 1 exhibits the calculated activation free energies ($\Delta G^{\ddagger}$) as well, which are relative to those of the reactant-like complex ("precursor" called here). Among the four, the $n = 2$ energy ($\Delta G^{\ddagger}$=35.69 kcal/mol) is smallest but is larger than the experimental one ($\Delta G^{\ddagger}$=30.2 kcal/mol).[5] The energetic result demonstrates either that the concerted path is unfavorable or that catalytic H_2O molecules are needed to lower the energy of the path.

The upper illustrations in Figure 2 show two TS geometries of a stepwise path ($n = 3$). In the first step (TS1), two water molecules (H16O15H17 and H22O23H18) work for the bond interchange up to the tetrahedral intermediate (Int of $n = 3$ in Figure S2-3 of the Supporting Information). In the second step

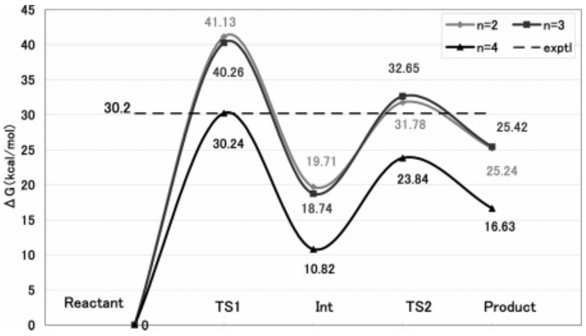
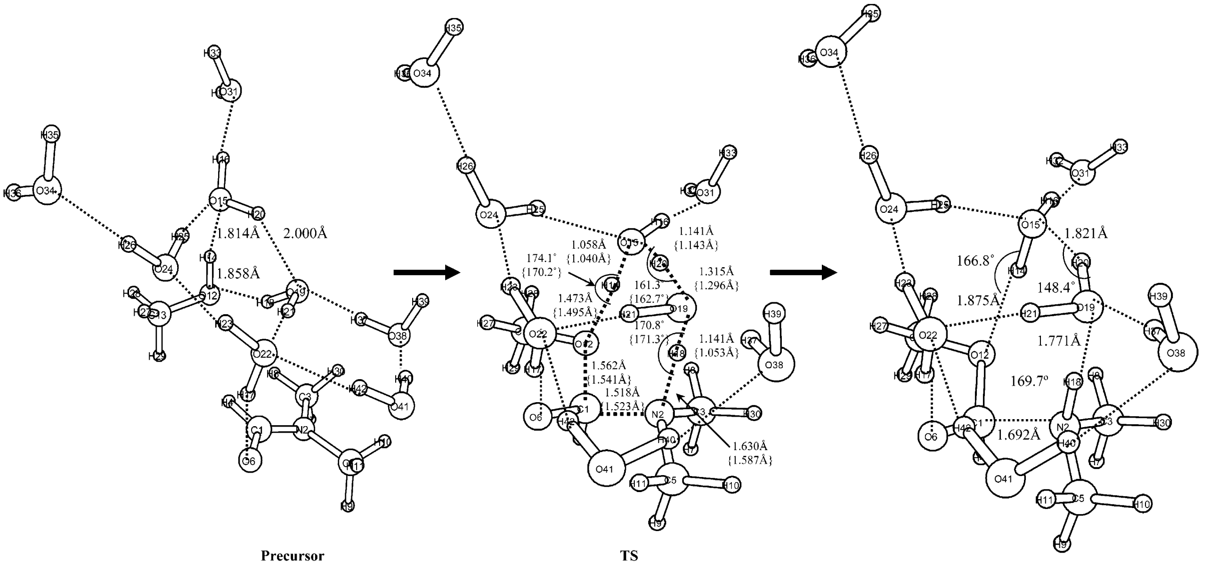


Figure 3. Gibbs energy diagrams (T = 298.15 K, P = 1 atm) of the stepwise reactions, DMF·MeOH·$(H_2O)_n$ → TS1 → Int → TS2 → HCOOMe·Me_2NH·$(H_2O)_n$. The experimental $\Delta G^{\ddagger}$ value is 30.2 kcal/mol from ref 5. The TS geometries of $n = 3$ and $n = 4$ are shown in Figure 2.

$DMF{\cdot}MeOH{\cdot}(H_2O)_4{\cdot}(H_2O)_4 \rightarrow HCOOMe{\cdot}Me_2NH{\cdot}(H_2O)_8$
n=4+4 (stepwise) ⇒ n=2+4+2 (concerted)



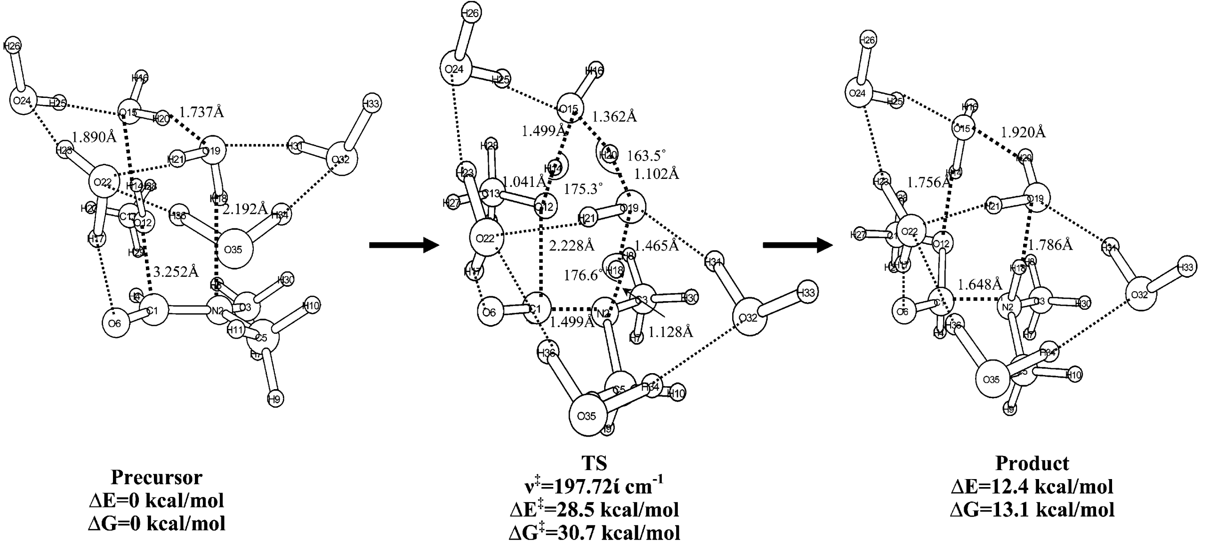
Precursor
ΔE=0 kcal/mol
(ΔE=0 kcal/mol)
[ΔE=0 kcal/mol]
{ΔE=0 kcal/mo}
<ΔE=0 kcal/mol>
ΔG=0 kcal/mol
(ΔG=0 kcal/mol)
[ΔG=0 kcal/mol]
{ΔG=0 kcal/mol}
<ΔG=0 kcal/mol>

TS
$\nu^{\ddagger}$=475.81*i* cm^{-1}
$\Delta E^{\ddagger}$=32.9 kcal/mol
($\Delta E^{\ddagger}$=31.8 kcal/mol)
[$\Delta E^{\ddagger}$=36.9 kcal/mol]
{$\Delta E^{\ddagger}$=37.2 kcal/mo}
$\Delta G^{\ddagger}$=33.3 kcal/mol
($\Delta G^{\ddagger}$=31.3 kcal/mol)
[$\Delta G^{\ddagger}$=38.6 kcal/mol]
{$\Delta G^{\ddagger}$=37.6 kcal/mol}
a_0=5.25 Å

Product
ΔE=13.8 kcal/mol
(ΔE=12.7 kcal/mol)
[ΔE=11.4 kcal/mol]
{ΔE=11.0 kcal/mol}
<ΔE=12.2 kcal/mol>
ΔG=17.0 kcal/mol
(ΔG=16.6 kcal/mol)
[ΔG=19.6 kcal/mol]
{ΔG=14.2 kcal/mol}
<ΔG=15.3 kcal/mol>

Figure 4. Concerted reaction of $DMF{\cdot}MeOH{\cdot}(H_2O)_4{\cdot}(H_2O)_4 \rightarrow$ TS $\rightarrow HCOOMe{\cdot}Me_2NH{\cdot}(H_2O)_8$. Bold broken lines of TS show routes of the proton relay. "$n = 4 + 4$ (stepwise) $\Rightarrow n = 2 + 4 + 2$ (concerted)" means that the extended model of the stepwise $n = 4$ path (Figure 2), $n = 4 + 4$, turns to a concerted one during the geometry optimizations. The values in parentheses are by RB3LYP/6-31G* gas phase, and those in square brackets are by RB3LYP/6-31(+)G* SCRF=dipole. {ΔE} and {ΔG} are single-point energy differences obtained by RB3LYP/6-311++G** SCRF=dipole//RB3LYP/6-31G* SCRF=dipole. $\langle\Delta E\rangle$ and $\langle\Delta G\rangle$ are those by RB3LYP/6-311++G** SCRF=PCM//RB3LYP/6-31G* SCRF=dipole. Distances and angles in braces were obtained by RB3LYP/6-311++G** SCRF=dipole geometry optimizations.

$DMF{\cdot}MeOH{\cdot}(H_2O)_2{\cdot}(H_2O)_4 \rightarrow HCOOMe{\cdot}Me_2NH{\cdot}(H_2O)_6$
concerted n=2+m
=2+4



Precursor
ΔE=0 kcal/mol
ΔG=0 kcal/mol

TS
$\nu^{\ddagger}$=197.72*i* cm^{-1}
$\Delta E^{\ddagger}$=28.5 kcal/mol
$\Delta G^{\ddagger}$=30.7 kcal/mol
a_0=5.27 Å

Product
ΔE=12.4 kcal/mol
ΔG=13.1 kcal/mol

Figure 5. Concerted reaction of $DMF{\cdot}MeOH{\cdot}(H_2O)_2{\cdot}(H_2O)_4 \rightarrow$ TS $\rightarrow HCOOMe{\cdot}Me_2NH{\cdot}(H_2O)_6$. Four water molecules, O22H17H23, O24H25H26, O32H33H34, and O35H34H36, work as catalysts. Bold broken lines show routes of the proton relay. The a_0 value of TS is 5.27 Å.

(TS2), H17O23H22 and H24O20H19 are concerned with the different interchange. The lower illustrations in Figure 2 exhibit TS1 and TS2 of $n = 4$. Although the relay route of TS2 along the bold broken lines is practically the same as that of $n = 3$, that of TS1 is very different. TS1 of $n = 4$ has a twisted relay route of the bold line, O6...H17...O22...H21...O19...H20...O15...H14...O12...C1. The detailed paths of $n = 3$ and 4 along with those of $n = 2$ are shown in Figure S2 (Supporting Information). The $n > 4$ models contain outer H_2O molecules and will be shown later. Figure 3

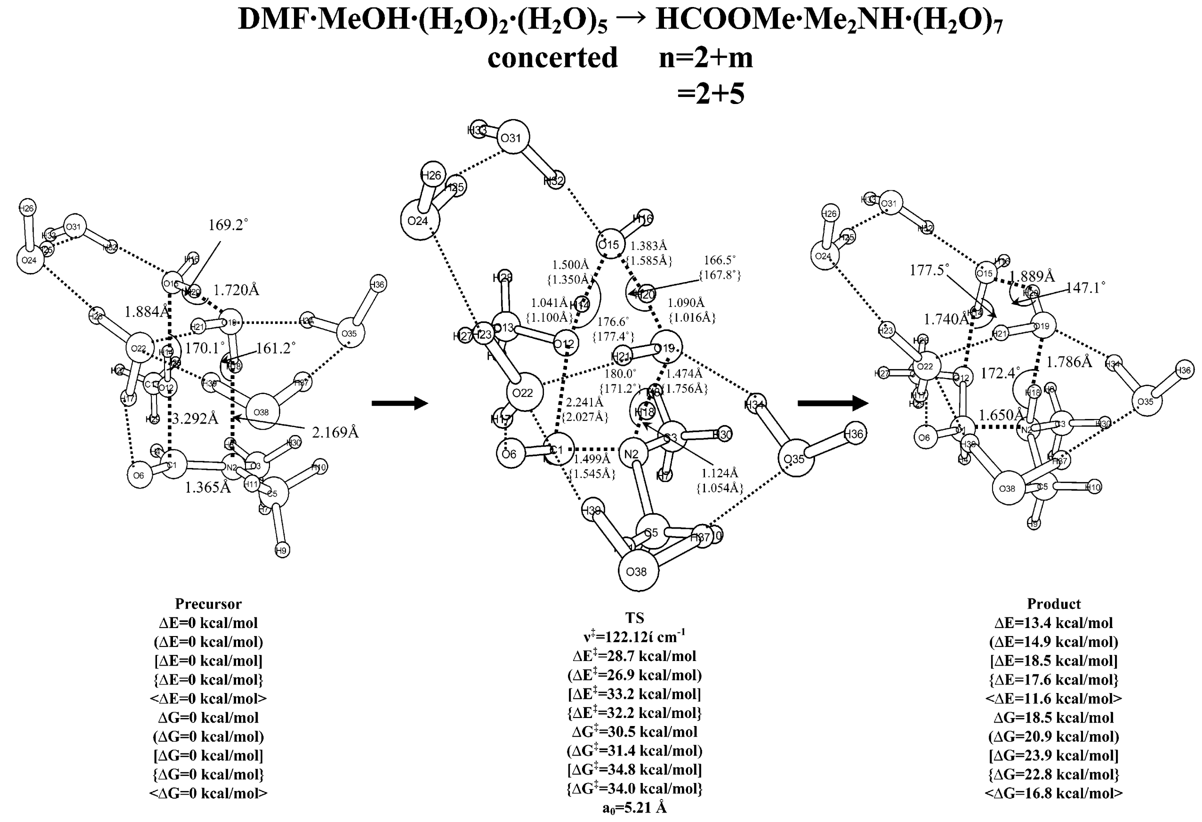


Figure 6. Concerted reaction of DMF·MeOH·$(H_2O)_2$·$(H_2O)_5$ → TS → HCOOMe·Me_2NH·$(H_2O)_7$. Five water molecules of the outside connected by dotted lines are catalysts. Bold broken lines show routes of the proton relay. Use of parentheses, braces, and other enclosures is the same as in Figure 4.

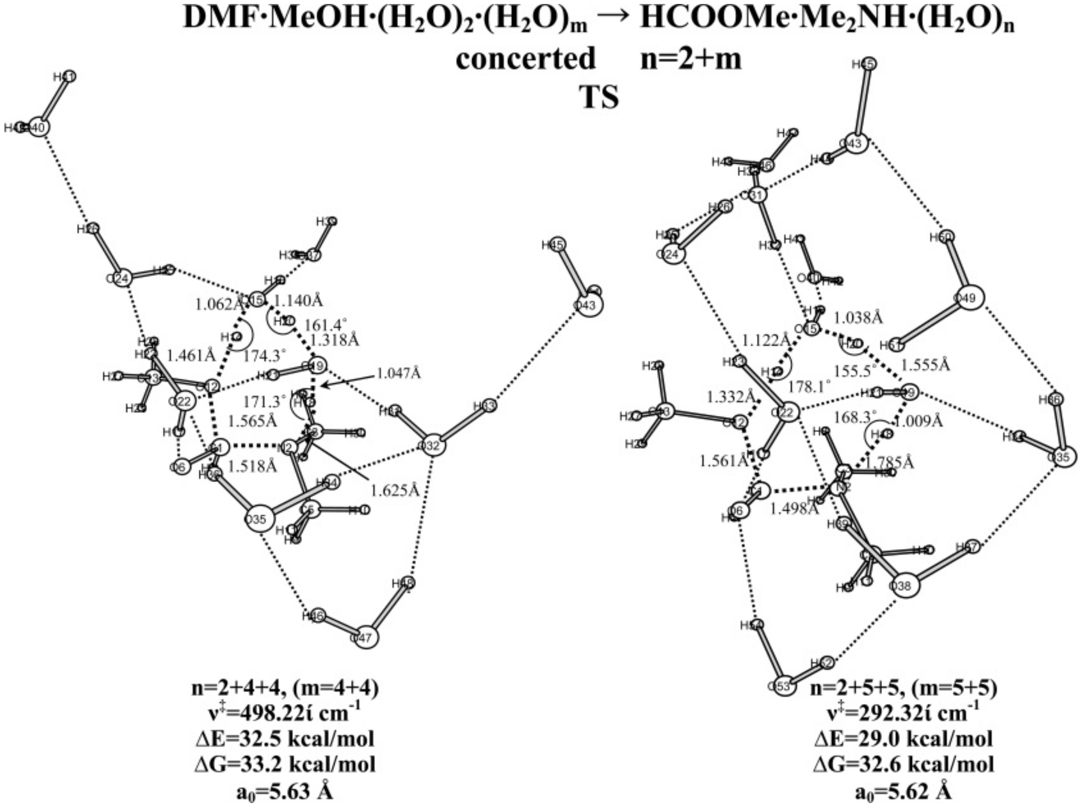


Figure 7. TS geometries of the concerted reaction, DMF·MeOH·$(H_2O)_2$·$(H_2O)_m$ → TS → HCOOMe·Me_2NH·$(H_2O)_n$ ($n = 2 + 4 + 4$ and $2 + 5 + 5$, i.e., $m = 4 + 4$ and $5 + 5$).

shows the energy changes. The $n = 4$ stepwise path has the smallest energy, and $\Delta G^{\ddagger}$(TS1) = 30.24 kcal/mol is apparently in excellent agreement with the experimental one, 30.2 kcal/mol.[5] However, the agreement might be fortuitous, and larger ($n > 4$) models need to be examined to ensure that the $n = 4$ based stepwise one is meaningful regardless of their sizes.

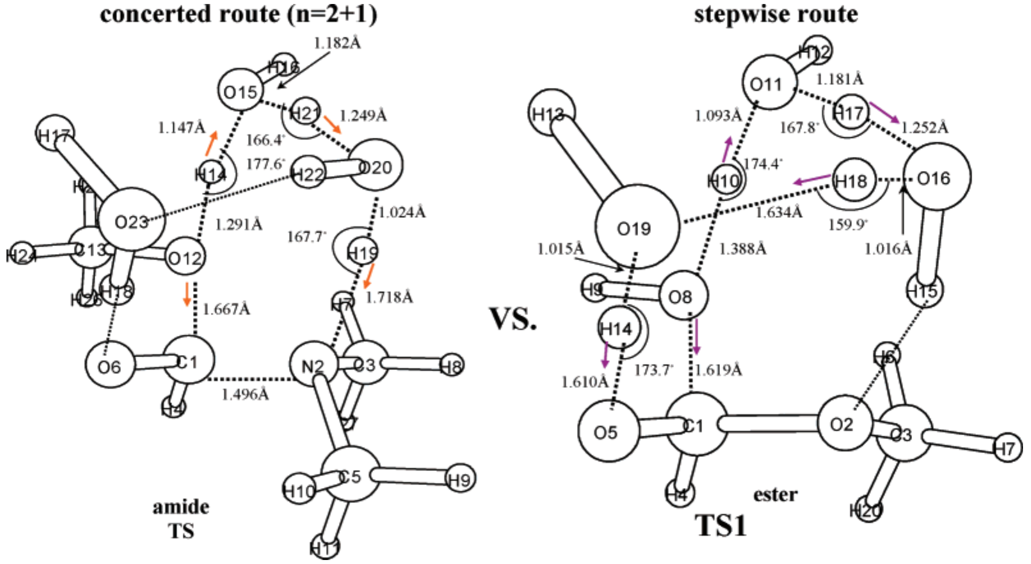


Figure 8. Comparison of TS structures of amide and ester. Bold broken lines and orange arrows for the amide TS show a concerted proton relay. Bold broken lines and purple arrows for the ester TS1 show proton relay of the first step up to the tetrahedral intermediate.

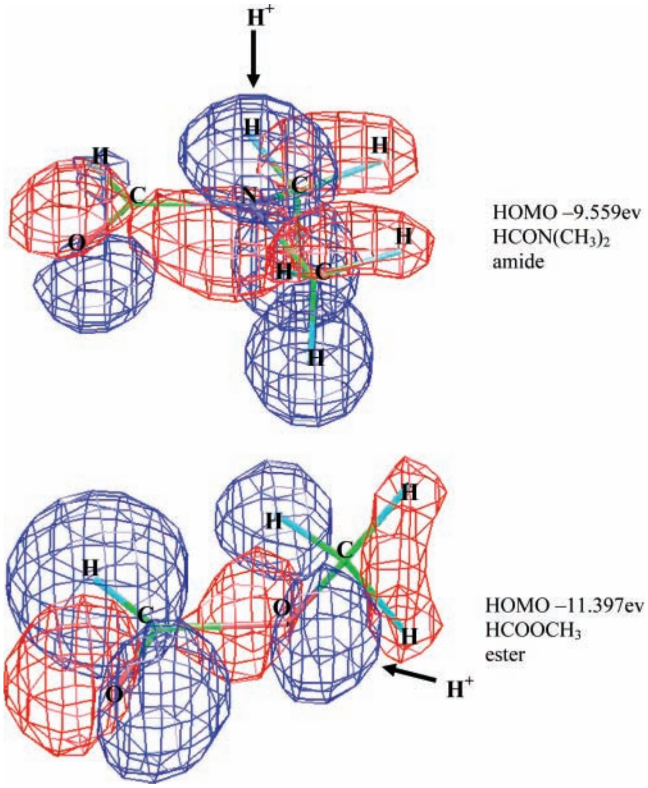
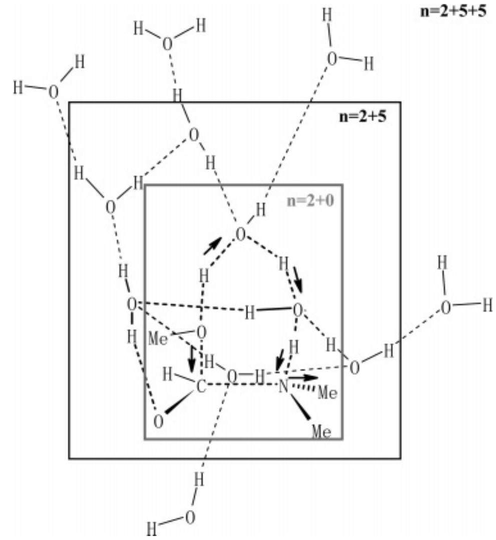


Figure 9. Shapes of HOMO for the *N*,*N*-dimethylformamide and methyl formate. Arrows stand for directions of the attack by electrophiles.

Figure 4 shows the reaction path of $n = 4 + 4$. The outer four water molecules are coordinated to H26, H16, O19, and O22, respectively. We attempted to determine the geometry of TS1 of the stepwise path by the $n = 4 + 4$ model. But, after the geometry optimization, TS1 was converted to TS of the concerted path! The catalytic four water molecules switched the reaction mechanism, stepwise → concerted. Thus, the $n = 4$ model in Figure 2 was found to be a mere artifact in the limited size and meaningless. At this stage, it was realized that the effect of addition of outer molecules on the concerted paths needs to be re-examined. In Figure 2, the $n = 2$ model is best, and in Figure 4 it is involved as the bond interchange circuit. The $n = 2$ based concerted paths were investigated by $n = 2 + m$. Figure S3 (Supporting Information) exhibits geometries of $m = 1-3$. Figure S4 (Supporting Information) shows the path of a different $n = 2 + 3$ model. The TS geometries in Figure S3 involve the common $n = 2$ reaction circuits. Although the $n = 2$ based concerted path was confirmed to be size independent, the corresponding $\Delta G^{\ddagger}$ values, $\Delta G^{\ddagger} = 33.60$ kcal/mol ($m = 1$), $\Delta G^{\ddagger} = 34.99$ kcal/mol ($m = 2$), and $\Delta G^{\ddagger} = 39.66$ kcal/mol ($m = 3$), are larger than the experimental one, 30.2 kcal/mol.[5] Addition of outer water molecules to the $n = 2$ reacting system (Figure S3, $m = 1-3$) seems still insufficient to reproduce the energy. Figure 5 shows the reaction path of $n = 2 + 4$. Its TS contains two catalytic circuits connected by black dotted lines. The calculated value, $\Delta G^{\ddagger} = 30.71$ kcal/mol, is in good agreement with the experimental one. The four catalytic water molecules ($m = 4$) work effectively to lower the energy. The dual-circuit pattern is involved also in the TS geometry of Figure 4. Then, it is not the stepwise $n = 4 + 4$ but the concerted $n = 2 + 4 + 2$. Figure 6 shows another concerted path, i.e., $n = 2 + 5$. Its TS has the Gibbs free activation energy, $\Delta G^{\ddagger} = 30.54$ kcal/mol. According to the $\Delta G^{\ddagger}$ values, the superiority or inferiority between $n = 2 + 4$ (Figure 5) and $n = 2 + 5$ (Figure 6) cannot be judged. Further addition of water molecules to $n = 2 + 4$ and $n = 2 + 5$ was made. TS geometries of $n = 2 + 4 + 4$ and $n = 2 + 5 + 5$ are shown in Figure 7. The detailed two paths are shown in Figure S5 (Supporting Information). The extended models in Figure 7 indicate that $n = 2 + 5 + 5$ is slightly more favorable than $n = 2 + 4 + 4$. Noteworthy is that the bond-interchange circuit (bold broken lines) is nearly invariant in $n = 2 + 1$, $n = 2 + 2$, $n = 2 + 3$, $n = 2 + 4$, $n = 2 + 5$, $n = 2 + 4 + 2$, $n = 2 + 4 + 4$, and $n = 2 + 5 + 5$. The $n = 2$ based concerted path has been confirmed.

The concerted paths of Figures 4 and 8 were obtained by B3LYP/6-31G* SCRF=dipole calculations. The results were examined by RB3LYP/6-31G* gas-phase and B3LYP/6-31(+)-G* SCRF=dipole geometry optimizations. These values are shown in the two figures with parentheses and square brackets, respectively. TS geometries of RB3LYP/6-31G* gas phase and RB3LYP/6-31(+)G* SCRF=dipole were determined by the use of the Hesian force constants of RB3LYP/6-31G* SCRF=dipole. They were confirmed to be for the concerted paths and are

SCHEME 2: Best Concerted Reacting System of the Solvolysis of H−CO−NMe$_2$ + Me−OH + (H$_2$O)$_n$ → H−CO−OMe + HNMe$_2$ + (H$_2$O)$_n$ in Eq 4



similar to the TS geometry of RB3LYP/6-31G* SCRF=dipole. Thus, the present results of the superiority of the concerted path over the stepwise one would be insensitive to the computational methods adopted.

A contrast between the present amide solvolysis and the ester hydrolysis has been found, which is shown in Figure 8. The left-side “amide TS” is taken from $n = 2 + 1$ in Figure S3. The right-side “ester TS1” denotes the transition-state geometry in a reaction, H−CO−OMe + (H$_2$O)$_4$ → H−CO−OH + HOMe + (H$_2$O)$_3$.[13] Although the TS geometry optimizations were conducted by the use of similar initial conditions, concerted and stepwise routes were obtained, respectively. The contrast was examined in terms of HOMOs of *N*,*N*-dimethylformide and methyl formate (Figure 9). The ability of the proton acceptanc of the amide was compared with that of the ester. The amide HOMO expands its lobe perpendicularly to the molecular plane and has a high-lying energy (−9.559 eV). On the other hand, the ester HOMO does it along the sp^3-inclined direction and has a low-lying energy (−11.397 eV). Because the nucleophilic attack to LUMO ($\pi^*_{C=O}$) of the two substrates commonly occurs out of the plane, the amide substrate may be subject to both nucleophilic and electrophilic attacks out of plane. Thus, the concerted path in the compact out-of-plane space is likely with aid of the large proton affinity of the nitrogen lone-pair orbital (i.e., the high-lying HOMO). On the other hand, the ester substrate does not allow the concerted path owing to the poor ability of the proton acceptance of the ether oxygen atom. The tetrahedral intermediate needs to intervene to make cleavage of the C−O single bond ready.

The potential energy surfaces in the adopted reaction models are very complicated. Then, although we have obtained the likely ones, there would be more surfaces by changing the location of outer water molecules. Determination of every such configuration is beyond the scope of this work. However, proton-relay patterns in the reaction-center obtained here would be insensitive to the location of those molecules.

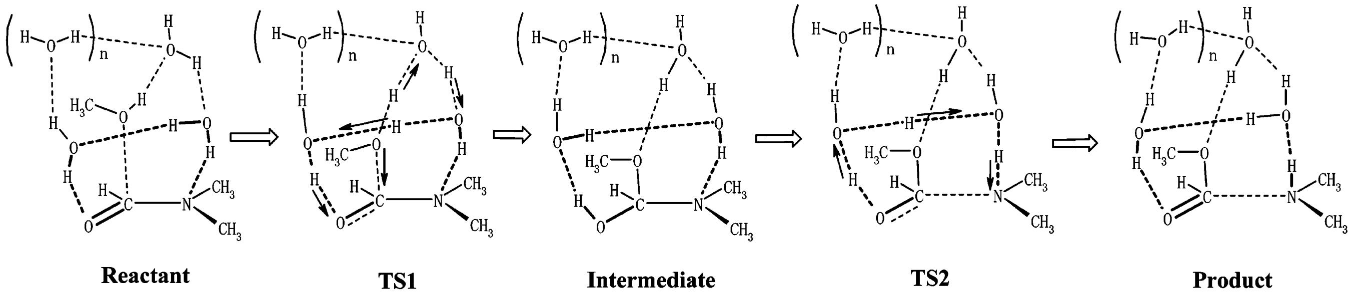
IV. Concluding Remarks

In this work, a solvolytic reaction of eq 4 has been investigated systematically. Water molecules work as both reactants and catalysts. The water-dimer ($n = 2$) based concerted path is most favorable energetically. The catalytic water molecules do not distort the $n = 2$ circuit and lower the activation free energy. The reaction pattern obtained here is illustrated in Scheme 2.

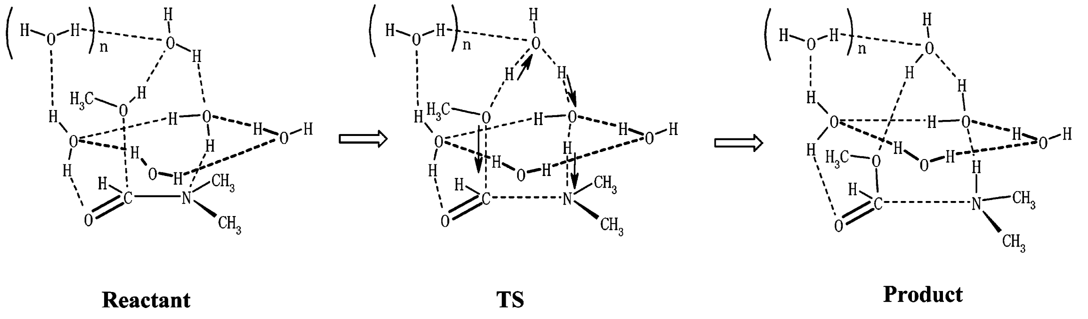
The present result that the water dimer and a MeOH molecule are reactants should correspond to the water-trimer participation in the hydrolysis of amides. In fact, the $l = 3$ participation was confirmed to be best in HCO−NH$_2$ + (H$_2$O)$_l$ → HCO−OH + NH$_3$ + (H$_2$O)$_{l-1}$ (Figure S6 in Supporting Information). Thus,

SCHEME 3: Summary of the Water-Assisted Solvolysis of *N*,*N*-dimethylformamide

Stepwise reaction



Concerted reaction



the treatment of only the dimer model was insufficient.[3] On the amide C−N bond, the water trimer (or MeOH plus water dimer) may form a strainless hydrogen-bond circuit for the ready proton transfer. The trimer participation in hydrolyses and isomerizations is thought to be likely generally. One water molecule acts as a proton donor, and the other does as a nucleophile (base). To connect them spatially, an auxiliary one is needed. In fact, the trimer is also necessary to stabilize the zwitterionic form of glycine, forming a bridge.[14]

In summary, the contrast of the stepwise and concerted paths may be represented by a slight difference in proton-relay patterns (Scheme 3).

Supporting Information Available: Figures S1−S9. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Breslow, R.; Wernick, D. L. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 1303. (b) Christianson, D. W.; Lipscomb, W. N. *Acc. Chem. Res.* **1989**, *22*, 62. (c) Matthews, B. W. *Acc. Chem. Res.* **1988**, *21*, 333. (d) Williams, A. J. *Am. Chem. Soc.* **1976**, *98*, 5645. (e) Ślebocka-Tilk, H.; Bennet, A. J.; Hogg, H. J.; Brown, R. S. *J. Am. Chem. Soc.* **1991**, *113*, 1288.

(2) Oie, T.; Loew, G. H.; Burt, S. K.; Binkley, J. S.; MacElroy, R. D. *J. Am. Chem. Soc.* **1982**, *104*, 6169.

(3) (a) Antonczak, S.; Ruiz-Lopez, M. F.; Rivail, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 3912. (b) Antonczak, S.; Ruiz-Lopez, M. F.; Rivail, J. L. *J. Mol. Model.* **1997**, *3*, 434.

(4) Yamabe, S.; Tsuchida, N.; Hayashida, Y. *J. Phys. Chem A* **2005**, *109*, 7216.

(5) Guthrie, J. P. J. *Am. Chem. Soc.* **1972**, *96*, 3608.

(6) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1998**, *37*, 785.

(7) Onsager, L. *J. Am. Chem. Soc.* **1938**, *58*, 1486.

(8) (a) Fukui, K. *J. Phys. Chem.* **1970**, *74*, 4161. (b) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1987**, *90*, 2154.

(9) Knox, J. H. *Molecular thermodynamics: An introduction to statistical mechanics for chemists*; Wiley: Chichester, U.K., 1978.

(10) (a) Cancès, M. T.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032. (b) Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253. (c) Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *106*, 5151.

(11) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Pittsburgh, PA, 2003.

(12) (a) Schiott, B. *J. Chem. Soc., Chem. Commun*. **2004**, 498. (b) Lee, J. Y. *Chem. Phys.* **2004**, *299*, 123. (c) Bouchy, A.; Rinaldi, D.; Rivail, J.-L. *Int. J. Quantum Chem*. **2004**, *96*, 273. (d) Grabowski, S. J.; Dubis, A. T.; Martynowski, D.; Glowka, M.; Palusiak, M.; Leszczynski, J. *J. Phys. Chem. A* **2004**, *108*, 5815. (e) Li, Y.; Farrar, J. M. *J. Phys. Chem. A* **2004**, *108*, 9876. (f) Scott, J. R.; Wright, J. B. *J. Phys. Chem. A* **2004**, *108*, 10578. (g) Khoroshun, D. V.; Warnke, K.; Ke, S. C.; Musaev, D. G.; Morokuma, K. *J. Amer. Chem. Soc.* **2003**, *125*, 570. (h) Fernandes, P. A.; Ramos, M. J. *J. Amer. Chem. Soc.* **2003**, *125*, 6311.

(13) The stepwise route is slightly less stable than that obtained previously[4] in the hydrolysis of ethyl acetate.

(14) Yamabe, S.; Ono, A.; Tsuchida, N. *J. Phys. Chem. A* **2003**, *107*, 7915.