

# Reaction Paths of Keto–Enol Tautomerization of $\beta$ -Diketones

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Density functional theory calculations were conducted on the title reactions with water molecules. Malonaldehyde, acetylacetone, and malonic acid were adopted as reactants. A reaction of malonaldehyde and (2 + 2) water molecules was found to proceed by a small (ca. 7 kcal/mol) activation energy. Two are reactant and two are catalyst molecules, respectively. The intramolecular hydrogen bond in the enol form is disrupted by the intermolecular one. Tautomerization transition-state geometries for acetylacetone and malonic acid are similar to that of malonaldehyde. Without the enhanced reactivity of water hydrogen-bond networks, tautomerization reactions undergo large activation energies. Various reaction models of (malonaldehyde)<sub>n</sub> (*n* = 2, 3, and 4) have given the energetic result. The keto–enol tautomerization has an analogy with the bimolecular nucleophilic elimination (E2) mechanism.

## Introduction

Keto–enol tautomerization of  $\beta$ -diketones has been investigated extensively.<sup>1</sup> In Scheme 1, the parent  $\beta$ -diketone is malonaldehyde (MDA, R = H), and the representative one is acetylacetone (AA, R = CH<sub>3</sub>).<sup>2</sup> Malonic acid (MA, R = OH) is a dicarboxylic acid.

The enol form is more stable than the keto form in the gas phase, and the equilibrium shifts toward the keto one as the solvent polarity increases.<sup>2</sup> Gas-phase geometries of keto and enol forms of AA were determined by electron-diffraction measurements.<sup>3</sup> O···O distances in keto and enol forms are 2.767 and 2.381 Å, respectively.<sup>3b</sup>

For three  $\beta$ -diketones, MDA,<sup>4</sup> AA,<sup>5</sup> and MA,<sup>6</sup> many ab initio calculations were made. In those studies, equilibrium constants of the keto–enol tautomerism and energy differences of two tautomers were examined.<sup>4d,e,i,j,n,5b,c,6c</sup> In particular, proton-transfer reactions within enol forms (C=O···H–O–C) → (C–O–H···O=C) were examined very extensively with interest in tunneling effect of the double-well potentials.<sup>4a–c,f,h,l,m,r,s,5a,6a</sup>

Despite those experimental and theoretical studies, reaction paths of the keto–enol tautomerization of the  $\beta$ -diketones have not been investigated. Direct proton shift from keto to enol form seems to be unlikely. The C–H bond energies of keto-form MDA, AA, and MA (R–CO–CH<sub>2</sub>–CO–R → R–CO–CH\*–CO–R + H\*) are 84.5, 87.6, and 93.0 kcal/mol, respectively.<sup>7</sup> Some condition is needed to cleave the tight C–H bond in keto form. Proton relays via auxiliary molecules would be required to attain the tautomerization with small activation energies. Water clusters are known to enhance proton relays when they are bound appropriately to substrate molecules.<sup>8</sup> Since the tautomeric equilibria in water were examined experimentally,<sup>2a–c</sup> reaction models of  $\beta$ -diketones (H<sub>2</sub>O)<sub>n</sub> are adopted in this work. The suffix *n* is the number of water molecules. It is of mechanistic interest to investigate how the C–H bond in the keto form is cleaved to cause the tautomerization (Scheme 2).

Solvent-assisted tautomerizations of simple carbonyl derivatives<sup>9a</sup> and 2(1H)-pyridone<sup>9b</sup> were studied theoretically. Proton-

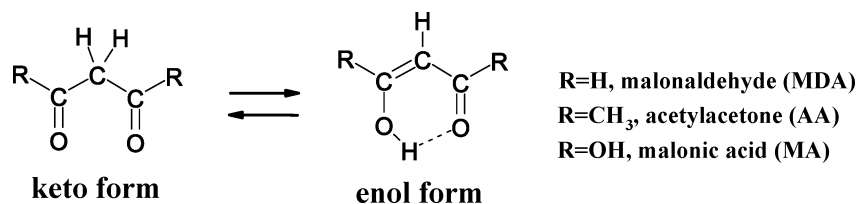
relay paths were traced, and the water dimer (H<sub>2</sub>O)<sub>2</sub> was found to give relatively small activation energies. At those transition state geometries, hydrogen-bond directionality was attained.

First, a systematic and computational analysis of participation of water clusters in the tautomerization will be made by the use of MDA. Second, the obtained reaction path for MDA will be applied to those for AA and MA. Third, the proton-relay pattern in the  $\beta$ -diketone(H<sub>2</sub>O)<sub>n</sub> reaction model will be extended to the ( $\beta$ -diketone)<sub>n</sub> system. Finally, the tautomerization will be assigned to a mechanism of organic chemical reactions.

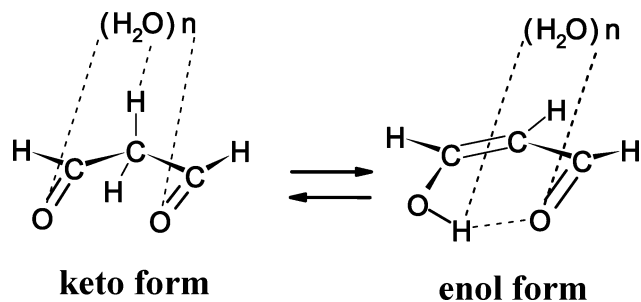
## II. Calculation Method

The geometries malonaldehyde, malonaldehyde(H<sub>2</sub>O)<sub>n</sub> (*n* = 1–6), (malonaldehyde)<sub>n</sub> (*n* = 2–4), acetylacetone(H<sub>2</sub>O)<sub>4</sub>, and malonic acid(H<sub>2</sub>O)<sub>6</sub> were determined by density functional theory calculations. B3LYP/6-31G\* methods<sup>10</sup> were used for geometry optimizations. The solvent effect was taken into account by Onsager's self-consistent field with the dielectric constant = 78.39 (water).<sup>11</sup> B3LYP seems to be a suitable method because it includes the electron-correlation effect to some extent. B3LYP/6-311+G(2d,p) calculations were also performed for the key species, namely, keto form, transition state (TS), and enol form in Figures 1 and 4. Energies of the keto form, TS, and enol form in Figure 4 and TS in Figure 5 were refined by B3LYP/6-311+G(2d,p) self-consistent reaction field (SCRFF)=PCM<sup>12</sup> single-point calculations, which are free from the dipole-moment approximation of the SCRFF dipole.

TSs were characterized by vibrational analyses, which checked whether the obtained geometries have single imaginary frequencies ( $\nu^\ddagger$ s). From TSs, reaction paths were traced by the IRC (intrinsic reaction coordinate) method<sup>13</sup> to confirm that the reactants and products are keto and enol forms, respectively. All the calculations were carried out using the Gaussian 98<sup>14</sup> program package installed on Compaq ES 40 at the Information Processing Center (Nara University of Education).

SCHEME 1. Tautomerism of  $\beta$ -Diketones.

## SCHEME 2. Tautomerization of Malonaldehyde Aided by Water Molecules



## III. Computational Results and Discussions

Figure 1 shows a direct proton-transfer route, keto  $\rightarrow$  enol, of malonaldehyde. The TS has a highly strained four-membered ring, which leads to a very large activation energy (59.99 kcal/mol). At the TS, a C–H bond is elongated (1.515 Å) substantially. The cis enol form cannot be arrived at because the cis form undergoes a large exchange repulsion at TS. The direct tautomerization is improbable.

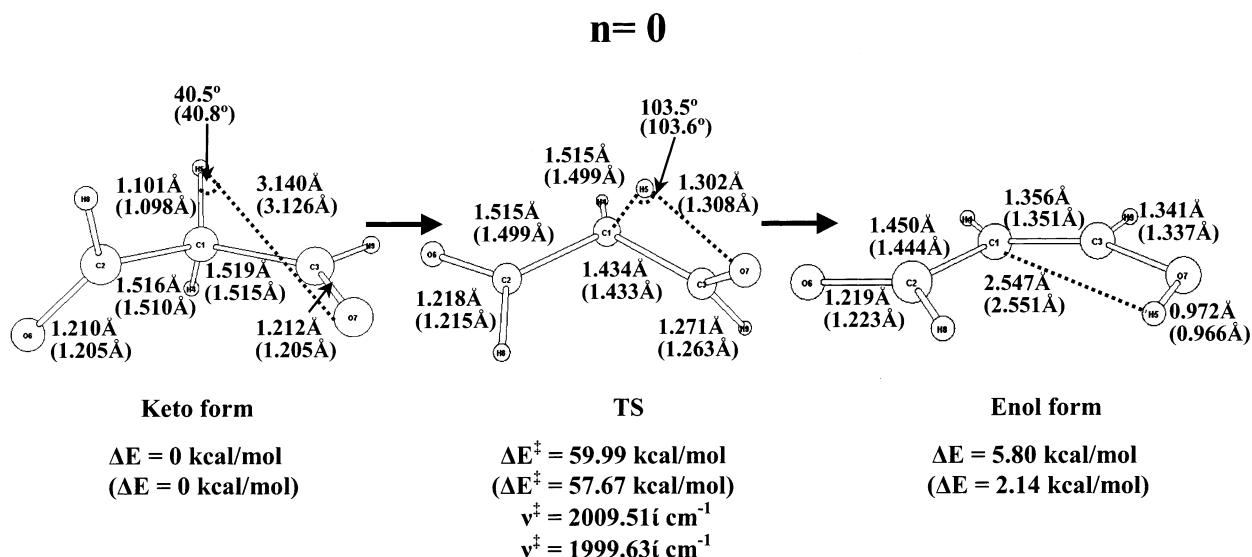
Figure 2 shows transition-state geometries of the tautomerization of malonaldehyde( $\text{H}_2\text{O}$ ) $_n$ . When water molecules are involved in proton relays, the strain of the relay network may be relaxed. As  $n = 1 \rightarrow 2 \rightarrow 3$ , the activation energies ( $\Delta E^\ddagger$ ) decrease (31.10  $\rightarrow$  20.43  $\rightarrow$  13.14 kcal/mol). At  $n = 4$ , the size of the relay network is too large to afford the cis enol form of an intramolecular hydrogen bond. Also, the activation energy  $\Delta E^\ddagger$  ( $n = 4$ ) = 18.00 kcal/mol is larger than  $\Delta E^\ddagger$  ( $n = 3$ ) = 13.14 kcal/mol. The  $n = 3$  model appears to be best for ready

proton transfer (i.e., tautomerization). However, it has a nearly symmetric structure with respect to the relay network plane. Solvent effect by catalytic water molecules would be small. On the other hand, the  $n = 2$  model has a vacant space at the right side. Catalytic water molecules may be coordinated at the space.

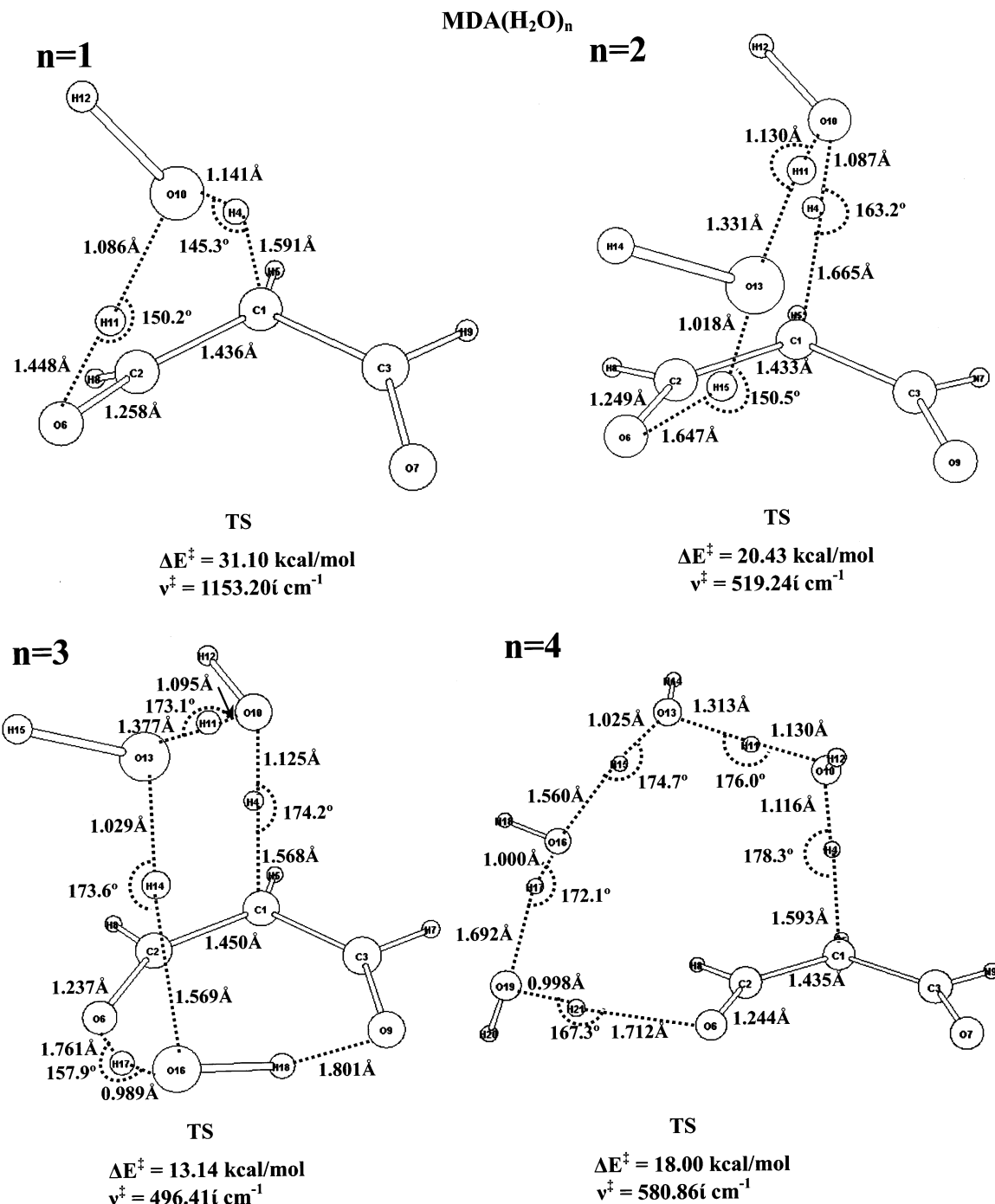
As for geometric parameters, the distances of the C–H bond that is cleaved (C1–H4) are  $\sim 1.6$  Å and those of the C–C bond (C1–C2) are  $\sim 1.4$  Å. The O $\cdots$ H lengths at proton relays depend on the number of water molecules ( $n$ ).

Figure 3 exhibits TS geometries of malonaldehyde ( $\text{H}_2\text{O}$ ) $_2$  and catalytic water molecules. For the  $n = 2 + 1$  model, a right-sided water molecule (H17–O16–H18) connects one reactant O–H bond (O13–H14) with the free aldehyde oxygen (O6). Through the connection, the activation energy ( $\Delta E^\ddagger = 13.64$  kcal/mol) is as small as  $\Delta E^\ddagger$  ( $n = 3$ ) = 13.14 kcal/mol. A larger catalytic bridge is expected to lower activation energies. As expected, the  $n = 2 + 2$  model has a substantially small activation energy,  $\Delta E^\ddagger = 7.39$  kcal/mol. Further coordination of catalytic water molecules ( $n = 2 + 3$  and  $n = 2 + 4$ ) was examined. Activation energies,  $\Delta E^\ddagger$  ( $n = 2 + 3$ ) = 7.07 kcal/mol and  $\Delta E^\ddagger$  ( $n = 2 + 4$ ) = 7.16 kcal/mol, are very similar to  $\Delta E^\ddagger$  ( $n = 2 + 2$ ) = 7.39 kcal/mol. Since excessive association of water molecules is entropically unfavorable, the  $n = 2 + 2$  reaction model is thought to be most likely. Cooperation of two reactant and two catalytic water molecules has brought about a ready tautomerization path.

As for geometric parameters, the distances of the C–H bond that is cleaved (C1–H4) are  $\sim 1.4$  Å. They are smaller than those in Figure 2, which indicates that the reactions in Figure



**Figure 1.** A keto–enol tautomerization reaction of malonaldehyde via the direct proton transfer.  $\Delta E^\ddagger$  and  $\Delta E$  are energies relative to that of the keto form.  $\nu^\ddagger$  stands for the sole imaginary frequency, which verifies that the obtained geometry is correctly at a saddle point. Values without and with parentheses are those of B3LYP/6-31G(d) SCRF=dipole and B3LYP/6-311+G(2d,p) SCRF=dipole geometry optimizations. In the enol form, an intramolecular hydrogen bond is not formed, because the strained TS geometry gives O7–O6 exchange repulsion in two C–O bonds cis.



**Figure 2.** Transition-state geometries of the keto–enol tautomerization of malonaldehyde with  $n$  water molecules. All of them are concerned with proton relays for the tautomerization.

3 are *earlier* than those in Figure 2 according to the Hammond's postulate.<sup>15</sup>

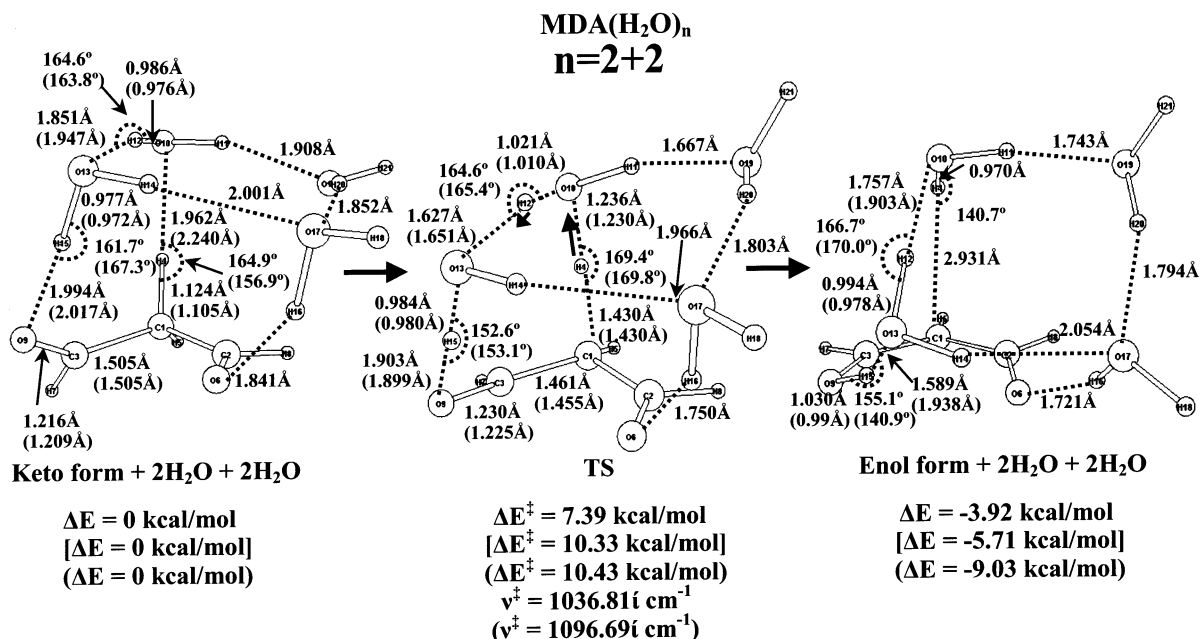
In TS geometries of Figures 2 and 3, the model of MDA(H<sub>2</sub>O)<sub>2+2</sub> has been found to be the best one for tautomerization. Figure 4 shows a reaction course of the model. To the keto form, water tetramer is coordinated so that an oxygen atom, O10, becomes significantly nucleophilic (Scheme 3). The HOMO shape demonstrates that the nucleophilic center is perfectly localized at O10 despite the delocalization character. The HOMO energy is  $-0.42$  au, which is much higher (the smaller ionization potential) than  $-0.50$  au of the free water molecule.

By high nucleophilicity of O10, the C1–H4 bond is elongated (1.124 Å) in the keto form + 2H<sub>2</sub>O + 2H<sub>2</sub>O. The cis enol form

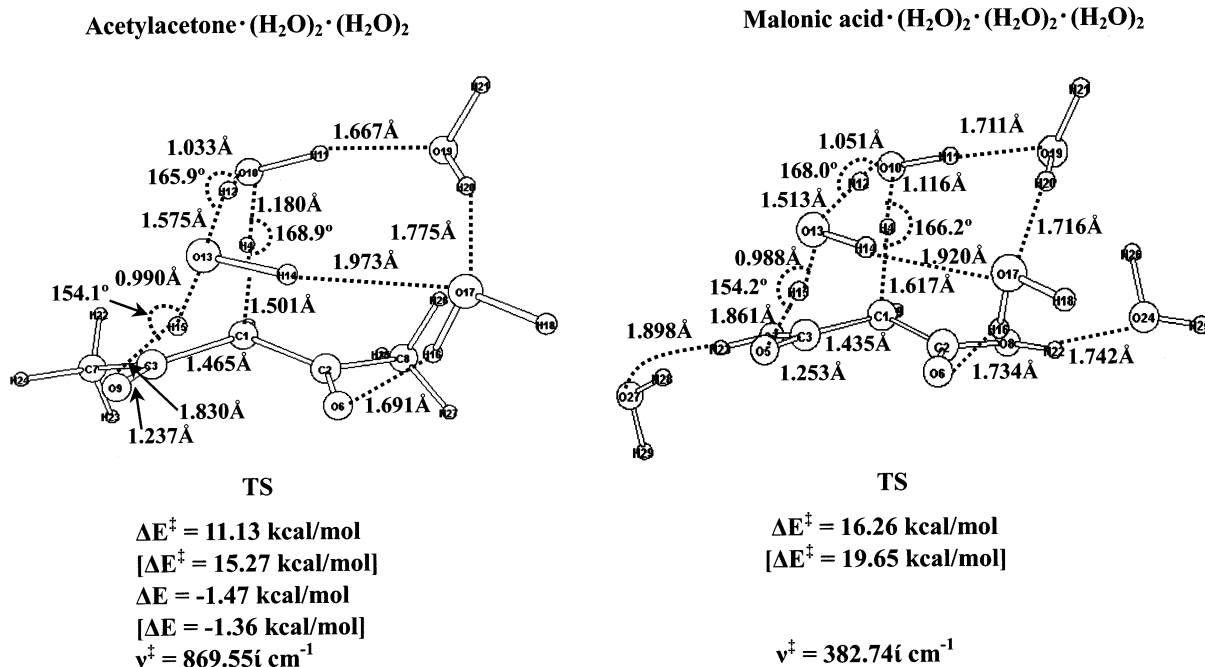
is needed to support the tetramer ring network. At enol form + 2H<sub>2</sub>O + 2H<sub>2</sub>O, the tetramer is retained and interrupts formation of the cis enol intramolecular hydrogen bond (H15...O6). On account of the great hydrogen-bond capability of the water cluster, its formation is blocked (Scheme 4).

Disruption of the cis enol intramolecular hydrogen bond in water was suggested by calorimetric and NMR spectroscopic experiments.<sup>2b</sup> The enol intramolecular bond of acetylacetone was reported to be disrupted by solvents, water, and methanol. Thus, Figure 4 has demonstrated that cooperation of two reactant and two catalytic water molecules causes the ready C–H (C1–H4) bond scission of the keto form and that the newly formed enol O–H bond participates in the intermolecular hydrogen bond rather than in the intramolecular one. As for geometric





**Figure 4.** The most likely reaction composed of malonaldehyde and (2 + 2) water molecules. Values without and with square brackets are of RB3LYP/6-311+G(2d,p) SCRF=PCM calculations. For TS, reaction-coordinate vectors corresponding to the sole imaginary frequency ( $\nu^\ddagger = 1036.81i$  cm<sup>-1</sup>) are sketched.



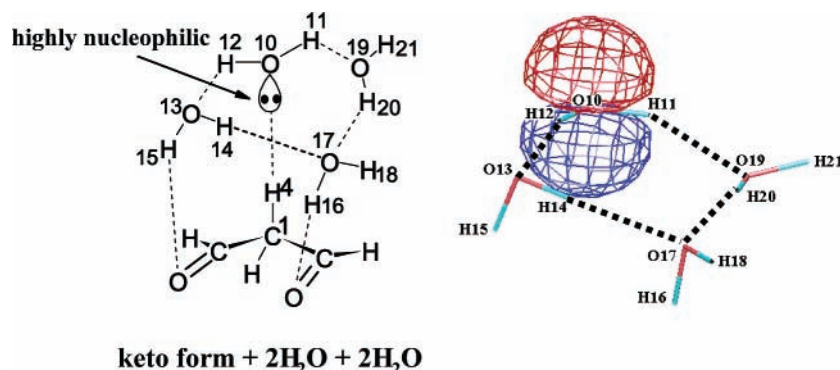
**Figure 5.** Transition-state geometries of the tautomerization of acetylacetonone and malonic acid with water molecules. For malonic acid, two water molecules (H29O27H28 and H25O24H26) are attached to two carboxyl groups, respectively.

To simulate the keto–enol tautomerization in water-free, e.g., chloroform solvent, various reaction models were considered. Figure 7 shows a reaction model of (malonaldehyde)<sub>2</sub>. One keto and one enol MDAs are involved, where the enol form gets a proton (H4) and releases one (H10) at TS. Although the proton-exchange path does not involve ring strain (163.5° and 170.3° at TS), the activation energy is large (28.86 kcal/mol). Other TS geometries of (MDA)<sub>n</sub> ( $n = 2, 3,$  and  $4$ ) with larger activation energies are shown in the Supporting Information. The result suggests that the tautomerization without the highly activated proton relays of water hydrogen bonds is difficult.

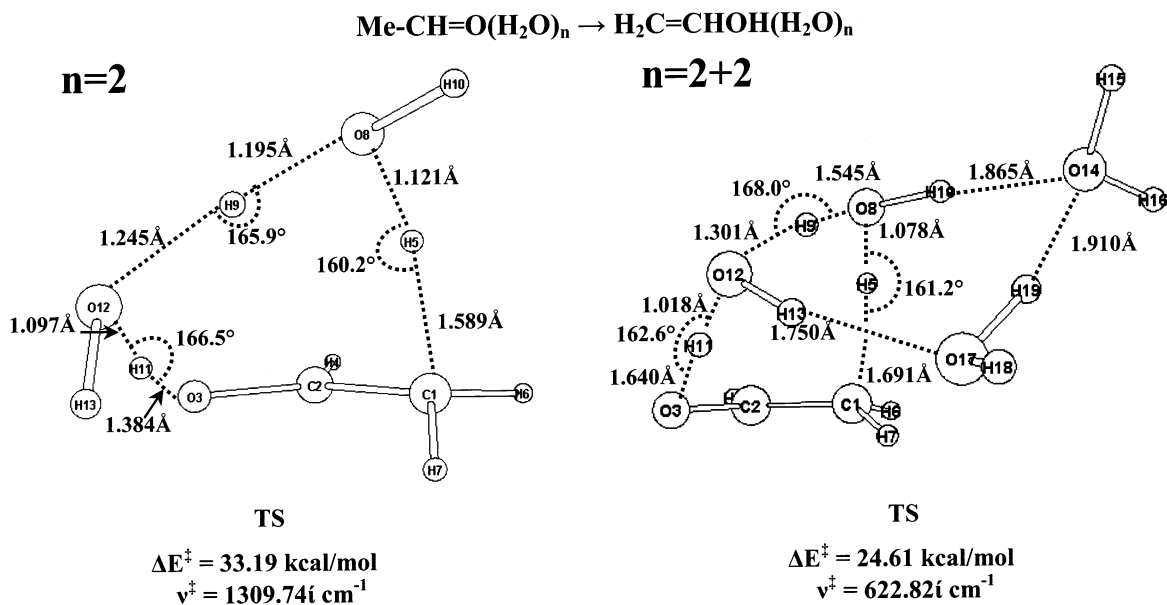
The methylene C–H bond in the keto form cannot be cleaved readily by the other nucleophilic sources than a water molecule connected by hydrogen-bond networks (Scheme 3).

#### IV. Concluding Remarks

In this work, reaction paths of the keto–enol tautomerization via water molecules have been investigated systematically. There has been a mechanistic question; why is a tight C–H covalent bond cleaved in the course of the tautomerization? A combination of two reactant and two catalytic water molecules ( $n = 2 + 2$ ) has given a significantly nucleophilic oxygen atom (O10

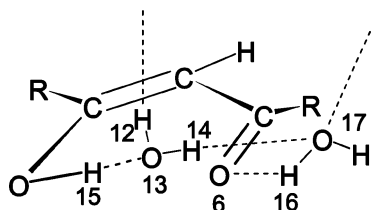
SCHEME 3. A Water Tetramer Makes an Oxygen O10 Highly Nucleophilic<sup>a</sup>

<sup>a</sup> The spatial extension of the HOMO of the (H<sub>2</sub>O)<sub>4</sub> fragment is shown at the right side.



**Figure 6.** TS geometries of the tautomerization, acetaldehyde(H<sub>2</sub>O)<sub>n</sub> → vinyl alcohol(H<sub>2</sub>O)<sub>n</sub> with  $n = 2$  and 4.

## SCHEME 4. The H15...O6 Intramolecular Hydrogen Bond Is Not Completed by Intermolecular Bonds

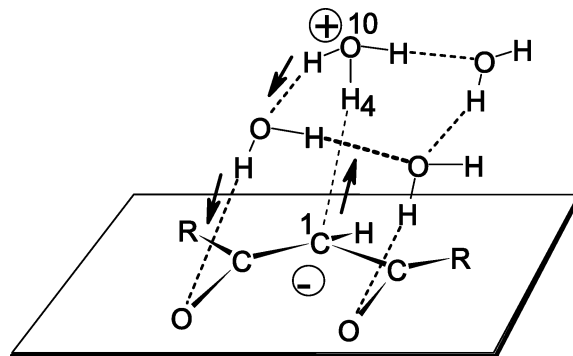


in Figures 3–5). Ready C–H (C1–H4) bond cleavage has been attained (Scheme 5).

The cis enol form is the consequence of proton relays along the hydrogen-bond network. The cis enol form can hardly contain the intramolecular hydrogen bond owing to them. Without the enhanced reactivity of those networks, large activation energies have been calculated (Figure 7). This result suggests that the water content is needed for ready tautomerization. In view of TS geometries in Figures 4 and 5, the keto–enol tautomerization may have analogy to the E2 mechanism (Scheme 6).<sup>17</sup>

A C–H bond is cleaved by a nucleophile (here, O10 in Scheme 3). A C–C single bond is converted to a C=C double bond. The C–L heterolytic scission corresponds to conversion of the C=O bond to the C–O bond. The ion-pair product (Nu–

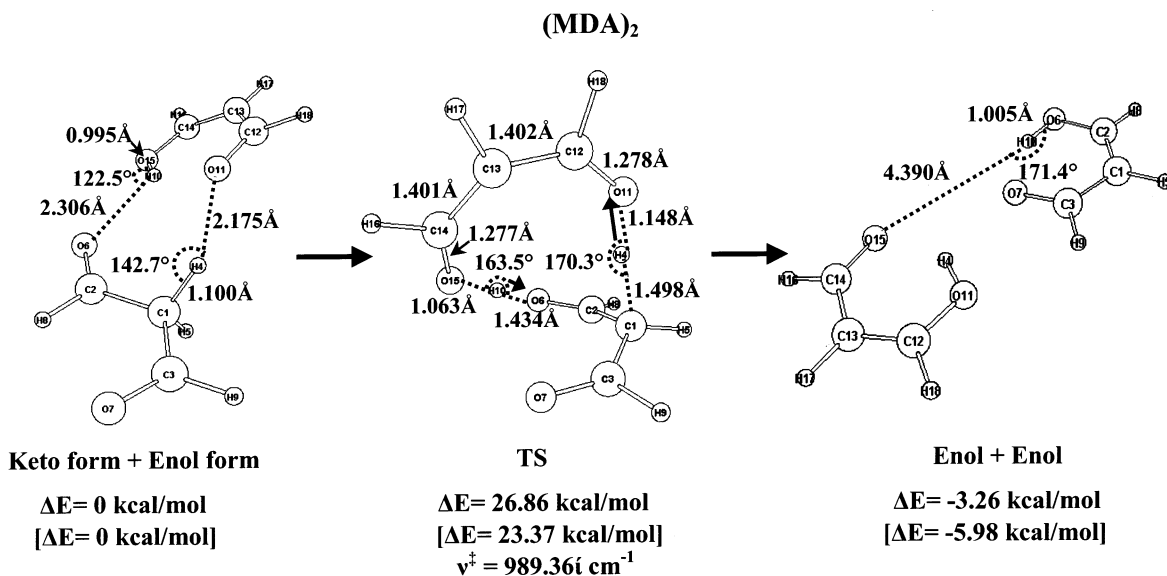
## SCHEME 5. A Proton Relay via a Water Dimer Promoted by the Ion-Pair-Like Electronic Charge Distribution and a Catalytic Water Dimer



H<sup>+</sup> and L<sup>-</sup>) in E2 is absent in the present reaction via neutralization by proton relays.

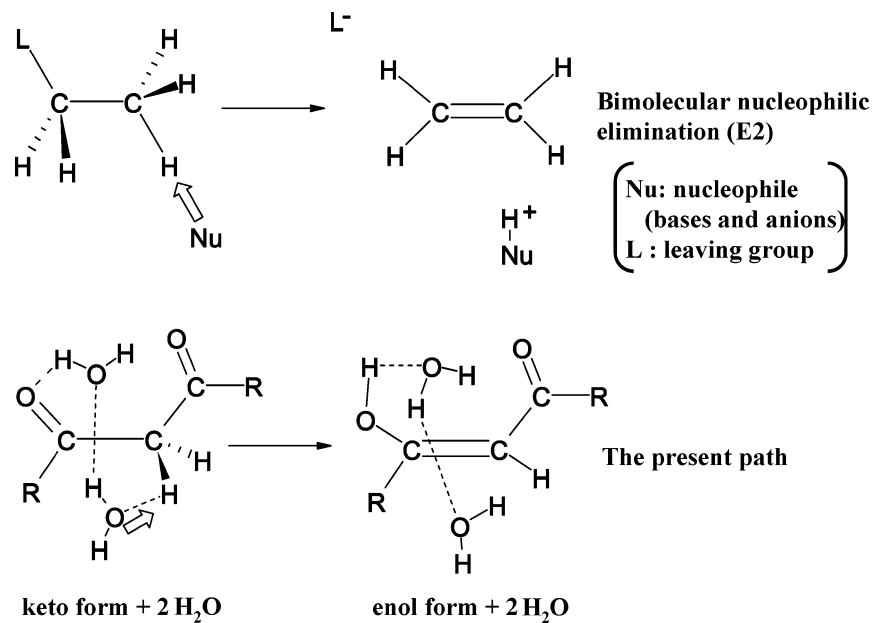
Formation of the intramolecular hydrogen bond in the enol form would not be a prime factor of the tautomerization.

The hydrogen-bond energy of HO–H...OH<sub>2</sub> is only 5 kcal/mol. The methylene group of  $\beta$ -diketones is apparently hydrophobic. Indeed the water-assisted tautomerization seems to be an unlikely process, but the (2 + 2)H<sub>2</sub>O cluster can be a highly reactive reagent. Water clusters may accommodate substrates



**Figure 7.** A reaction of malonaldehyde dimer. Values without and with square brackets are of RB3LYP/6-31G(d) SCRF=dipole and single-point RB3LYP/6-311+G(2d,p) SCRF=PCM calculations.

### SCHEME 6. Analogy between E2 and the Present Path for Tautomerization



flexibly with the low-energy reaction paths, when the hydrogen bond directionality is assured. The reaction mechanism of hydrolyses, condensation, and others in aqueous media would be discussed generally in terms of the directionality criterion.

**Supporting Information Available:** Figures showing various transition states of (malonaldehyde)<sub>n</sub> tautomerization. This material is available via the Internet at <http://pubs.acs.org>.

### References and Notes

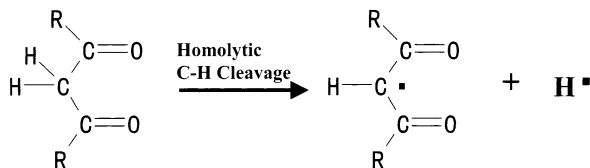
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(7) Present results of (U)B3LYP/6-311+G(2d,p) calculations.



Compound	R	kcal/mol
malonaldehyde	H	84.45
acetylacetone	CH <sub>3</sub>	87.62
malonic acid	OH	93.04

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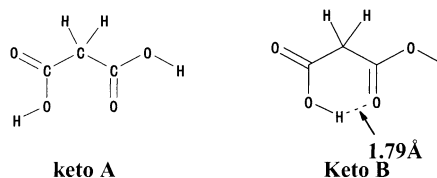
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(16) In the gas phase, the keto B form is 0.79 kcal/mol (B3LYP/6-311+G(2d,p)) more stable than the keto A form. On the other hand, when two water molecules are coordinated to the malonic acid molecule, keto A is 3.93 kcal/mol more stable. In order to show that the keto A is a reactant, two water molecules (O24H25H26 and O27H28H29) were added.

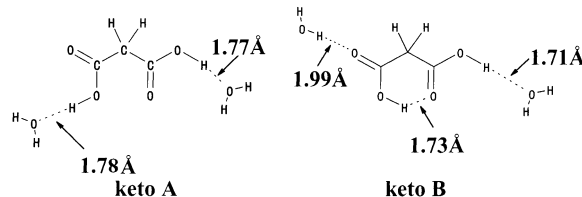
#### Gas-phase



keto A

keto B

#### Two water molecules added



keto A

keto B

(17) Banthorpe, D. V. *Reaction Mechanism in Organic Chemistry*, Vol. 2: *Elimination Reactions*; Hughes, E. D., Ed.; Elsevier: London, 1963.