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Original research article

Does Water Clustering Accelerate Acetylacetone Tautomerization Reaction?

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ABSTRACT

β-diketone tautomerization is a key reaction in synthetic chemistry that is known to be accelerated in polar protic solvents, such as water. However, the mechanism and number of water molecules for optimal catalytic effect remain unclear. To investigate this aspect, we employed a hybrid cluster-continuum approach using water clusters, $(H_2O)_n$, $n = 1 \sim 4$, to simulate tautomerization of acetylacetone (AA). We utilized CBS-Q energies, along with the geometries and solvation energies obtained from B3LYP/6-311+G(2d,2p), using the polarizable continuum model. The addition of one water molecule was shown to lower the activation energy (Ea) by 24 kcal/mol by actively participating in the proton transfer. Additional water molecules can further lower the Ea by 5 to 10 kcal/mol; however, the decrease in Ea saturates at n = 3 water molecules. Water molecules also help stabilize AA with a solvation energy of −6 kcal/mol per H_2O. These findings highlight the critical role of explicit water clusters in promoting the tautomerization reaction for AA.

Keywords: Computational chemistry; Hybrid cluster-continuum model; Keto-enol tautomerization; Proton relay

1. Introduction

β-diketone tautomerization is a fundamental proton transfer reaction essential for understanding various fields of chemistry, including biochemistry, organic chemistry, and drug design [1, 2]. This reaction is frequently observed in both reagent synthesis and biological processes, such as acetylacetone (AA) usage in metal chelation and malondialdehyde (MDA) production in lipid peroxidation [3, 4].

β-diketone tautomerization involves a hydrogen transfer from α-C to the carbonyl oxygen, leading to two competing enol conformers, E and Z isomers, as depicted in Fig. 1.

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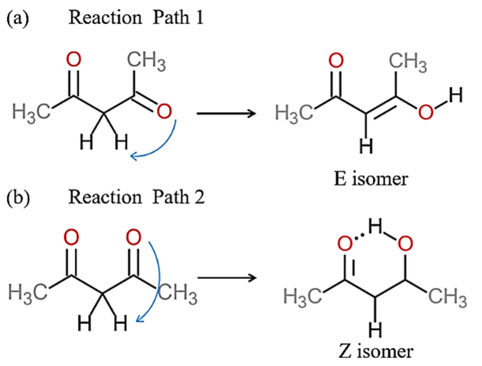

Fig. 1. Reaction pathways of acetylacetone tautomerization: (a) reaction path 1 forms the E isomer, (b) reaction path 2 leads to the Z isomer. (Curved arrow represents electron movement.).

In the presence of polar protic solvents, such as water or methanol, the rate of β-diketone tautomerization is significantly accelerated. This catalytic effect stems from the capability of polar protic solvents to behave as both hydrogen donors and acceptors. This allows solvents to form a proton-relay bridge to help facilitate tautomerization [1].

Solvent polarity also influences the tautomeric equilibrium. In the gas phase and non-polar solvent, Z isomers with intramolecular hydrogen bonding are favored over E isomers and keto forms, see Fig. 1b. However, in polar solvents, carbonyl and hydroxyl groups can form the hydrogen bonding network with solvent molecules, which stabilizes the keto tautomer and impedes the intramolecular hydrogen bond of Z isomer. As a result, the equilibrium shifts toward the keto tautomer [5-8].

Since both the number of solvent molecules and their interactions with β-diketone structures directly affect the tautomerization rate and equilibrium, understanding the roles of explicit solvents in the reaction mechanism is crucial for controlling the reactivity and selectivity of this process.

One common practice to theoretically study such solvation effects involves simulating a micro-solvated environment using a hybrid cluster-continuum model, in which a discrete solvent cluster (solvent)$_n$ is included alongside an implicit solvation model that only accounts for bulk solvent effects [9, 10].

Yamabe et al. and Freitag et al. [10, 11] studied β-diketone tautomerization utilizing this approach for of MDA in water clusters, (MDA—$(H_2O)_n, n = 1 \sim 6$). Both studies confirmed the significance of the water proton-relay bridge in facilitating the tautomerization reaction. However, the decrease in activation energies was found to saturate after four water molecules. These results demonstrated that the optimal catalytic effect can only be achieved from a particular cluster size.

Expanding on the studies by Yamabe et al. and Freitag et al., we investigated the tautomerization of AA, a widely used β-diketone reagent in chemical processes. Structurally, AA can be viewed as a methylated derivative of MDA, in which methyl groups replace the terminal hydrogen atoms. To examine the influence of water clustering in the aqueous phase reaction rate, we simulated AA tautomerization by varying the number of water clusters AA—$(H_2O)_n, n = 1 \sim 4$. In order to search for possible observables, we also evaluated the change in the UV spectra.

2. Materials and Methods

2.1 Energy calculation

We performed the calculation using density functional theory (DFT) with Becke's 3-parameter hybrid functional, B3LYP, with Pople's 6-311+G(2d,2p) basis set [14, 15], implemented in the Gaussian16 program. Up to 4 water molecules were treated explicitly in AA—$(H_2O)_n, n = 1 \sim 4$, while the remaining solvation environment was calculated using the polarizable continuum model (PCM) [17]. The optimized structures at the B3LYP/6-311+G(2d,2p) level were then used for single-point energy calculation at the CBS-Q level. Since direct CBS-Q calculations [18, 19] with PCM are not available, solvation effects were incorporated by combining gas-phase CBS-Q energies (E^{gas}_{CBS-Q}) with solvation corrections (ΔE^{B3LYP}_{solv}) obtained at the B3LYP/6-311+G(2d,2p) level using the PCM model. This approach is expressed as follows:

$$E^{solv}_{PCM/CBS-Q} = E^{gas}_{CBS-Q} + \Delta E^{B3LYP}_{solv}, \quad (2.1)$$

$$\Delta E^{B3LYP}_{solv} = E^{solv}_{PCM/B3LYP} - E^{gas}_{B3LYP}. \quad (2.2)$$

Energies in aqueous phase at the CBS-Q level ($E^{solv}_{PCM/CBS-Q}$) were used for all subsequent analyses due to their high accuracy in predicting thermochemical data from DFT-optimized structures. Previous studies for the CBS-Q energies also showed that it can reproduce energies of CCSD(T)/aug-cc-pVTZ. From $E^{solv}_{PCM/CBS-Q}$, we calculated activation energies (Ea), energy differences between E and Z enol isomers (ΔE_{enol}), and absolute solvent binding energies (E_{bind}) using the following equations.

$$Ea = E_{TS} - E_{diketone}, \quad (2.3)$$

$$\Delta E_{enol} = E_{E\ isomer} - E_{Z\ isomer}, \quad (2.4)$$

$$E_{bind} = \frac{E_{AA-(solvent)_n}}{n} - \frac{(E_{AA} + n \times E_{solvent})}{n}. \quad (2.5)$$

All energies in this study are corrected by harmonic zero-point energy at B3LYP/6-311+G(2d,2p) PCM level.

2.2 Transition state search

We explored AA-solvent clusters denoted as AA—$(H_2O)_n (n = 1 \sim 4)$. To systematically explore transition state (TS) geometries at each cluster size, solvent molecules were categorized into two types: proton-relay molecules, which form a hydrogen transfer bridge, and external solvent molecules, which do not directly engage in proton transfer. Various combinations of proton-relay and external solvent molecules were examined at each cluster size as depicted in Fig. 2.

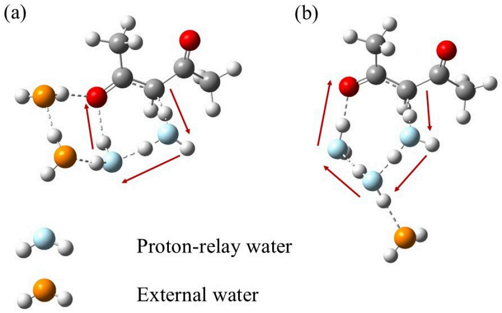

Fig. 2. TS of AA—$(H_2O)_4$ which forms E isomers (a) TS with two proton-relay and two external water molecules (2_2) (b) TS with three proton relay and one external water molecules (3_1) (Red arrows represent the proton transfer path from keto to enol tautomer. Oxygen of proton-relay water are colored in blue, and oxygen of external water are colored in yellow).

We initially prioritized locating the lowest energy TS geometry involving 1, 2, and 3 proton-relay water molecules. Then we added external solvent molecules to assess further stabilization.

2.3 UV-Vis simulation

UV-Vis spectra of the most stable keto and enol tautomers of each cluster size were simulated using Time-Dependent Density Functional Theory (TD-DFT) in the Gaussian 16 software package [20]. We focused on wavelengths longer than 200

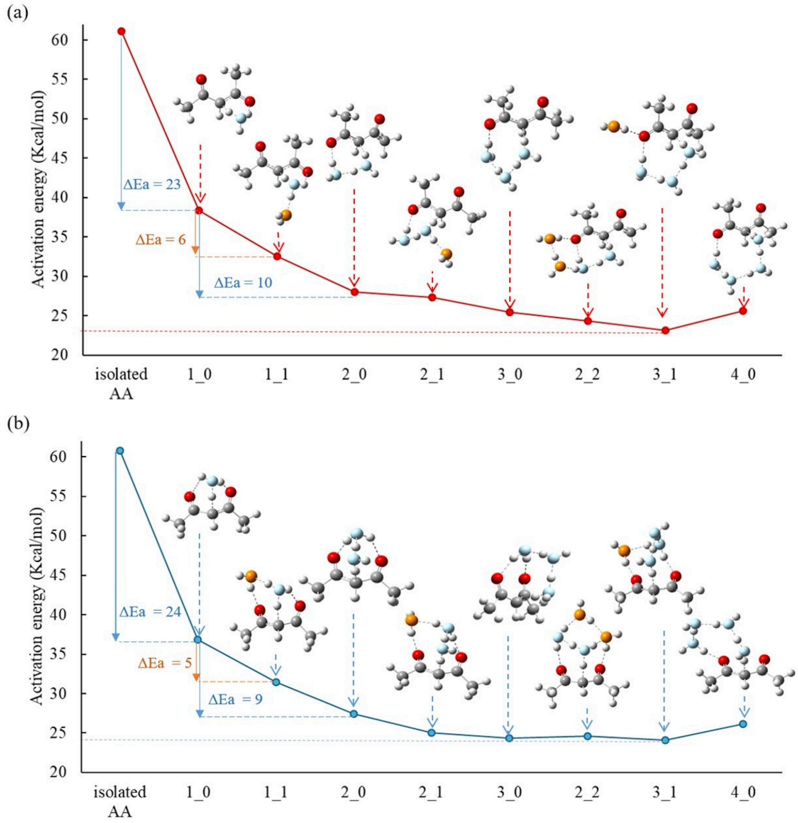

Fig. 3. Ea and TS of AA—$(H_2O)_n, n = 1 \sim 4$ at PCM/CBS-Q (a) reaction forming E enol isomers (b) reaction forming Z enol isomers (Oxygen of proton-relay water molecules are shown in blue, and oxygen of external water molecules are shown in yellow.).

Table 1. $Ea, \Delta E_{enol}$ and E_{bind} of AA—$(H_2O)_n$ tautomerization at PCM/CBS-QB3.

cluster size	Ea		ΔE_{enol}	E_{bind}
	path 1	path 2		
Isolated AA	61.16	60.79	8.18	
1_0	38.32	36.82	7.10	−5.01
1_1	32.57	31.47	6.39	−5.65
2_0	27.97	27.42	5.38	−5.19
2_1	27.31	25.01	5.72	−5.80
3_0	25.46	24.32	4.90	−5.36
2_2	24.33	24.59	6.56	−6.04
3_1	23.15	24.07	5.66	−5.78
4_0	25.63	26.14		−5.22

Note: Ea, ΔE_{enol} and E_{bind} were calculated based on Eqs. (2.3)-(2.5), respectively, in the unit of kcal/mol. Path 1 forms E-enol isomer, while path 2 forms Z-enol isomer. (Cluster size is expressed as (number of proton-relay water_number of external water)).

nm, as most standard UV-Vis spectrometers operate within this range.

3. Result and Discussion

3.1 Activation energy and tautomers' stability

Table 1 shows that water molecules significantly reduce the Ea of tautomerization, which was 61 kcal/mol in vacuum. As given in Fig. 3, the addition of one proton-relay H_2O molecule, AA(1_0), results in a reduction in Ea by 24 kcal/mol. The second proton-relay molecule, AA(2_0), further decreases the Ea by 10 kcal/mol. Notably, the addition of one external water molecule in AA(1_1) only lowers the Ea by 6 kcal/mol from the AA(1_0) cluster. Overall, both reactions forming E and Z isomers have comparable Ea values, with dif-

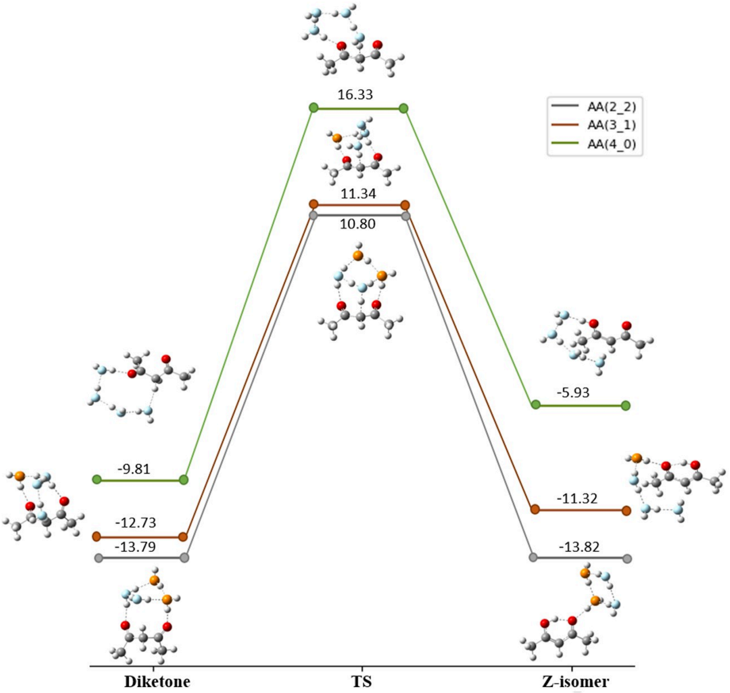

Fig. 4. Relative energy profiles of AA—$(H_2O)_4$ tautomerization path 2. Zero of energy is set to AA(2_0) + 2(H_2O).

ferences of less than 2 kcal/mol.

As shown in Fig. 3, the water cluster of AA(3_1) has the lowest Ea of 23.15 kcal/mol. However, one must also consider the stability of the starting AA—$(H_2O)_n$ cluster relative to the separated reactants to discuss the whole reaction process. In Fig. 4, we see that for the 4 water system, the TS of AA(2_2) possesses the lowest energy and also leads to the most stable keto and enol tautomers. These results suggest that AA(2_2) is the most favorable configuration in the water cluster system.

In Table 1, the absolute solvent binding energy lowers from −5 kcal/mol at AA(1_0) to −6 kcal/mol in AA(2_2) in water. These results support the increased stabilization of AA in the aqueous phase, where intermolecular hydrogen bonding between AA and water molecules stabilizes the diketone form compared to the enol form.

This explanation is also consistent with the decrease in the energy difference between the E and Z isomers (ΔE_{enol}) in Table 1. ΔE_{enol} was 8 kcal/mol for isolated AA in the PCM calculation. With additional explicit H_2O molecules, the ΔE_{enol} lowered to approximately 5 kcal/mol. These data indicate that the stability difference between the E and Z isomers decreases. The E isomer becomes increasingly stabilized while the intramolecular bond in the Z isomer is disrupted by competing intermolecular interactions with the solvent water molecules.

3.2 UV-Vis simulation

From the UV-Vis simulation, we found that the diketone absorption peaks

Table 2. Zero of energy of AA—$(H_2O)_n, n = 2 \sim 4$ tautomerization.

	reaction path 1			reaction path 2		
	diketone	TS	E isomer	diketone	TS	Z isomer
AA(2_0)+2(H_2O)	1.43	29.40	5.80	0.00	27.42	0.42
AA(2_1)+(H_2O)	-4.66	22.65	0.02	-6.33	18.68	-5.70
AA(3_0)+(H_2O)	-4.48	20.99	-1.05	-5.69	18.63	-5.95
AA(2_2)	-11.35	12.98	-7.26	-13.79	10.8	-13.82
AA(3_1)	-8.88	14.27	-5.30	-12.73	11.34	-11.32
AA(4_0)	-10.50	15.13	-6.38	-9.81	16.33	-5.93

[a] Zero of energy is set to AA(2_0)+2(H_2O)

fall below 200 nm; therefore, we focused on the E and Z isomers of the enol.

As summarized in Table 3, the computed UV-Vis absorption peaks of the isolated system using the PCM model exhibit consistent peak positions that are red-shifted compared to the vacuum calculation. We observe shifts of 9 and 6 nm for the E and Z isomers, respectively. Upon inclusion of explicit solvent molecules, we notice a further red shift.

Table 3. Wavelength of UV-Vis absorption peak of E and Z enol isomers (nm).

		E isomer	Z isomer
vacuum	isolated AA	232.93	243.73
H2O	isolated AA	241.57	249.85
	AA—(H_2O)	244.93	253.62
	AA—$(H_2O)_2$	245.00	253.83
	AA—$(H_2O)_3$	242.96	250.93
	AA—(H_2O)4	245.31	254.17

In the $n = 4$ water cluster system, the absorption peaks shift by 4 nm to 245 nm for the E isomer and 254 nm for the Z isomer, as illustrated in Fig. 5. This suggests enhanced solute–solvent interactions through hydrogen bonding, which stabilize the excited states and reduce the energy gap.

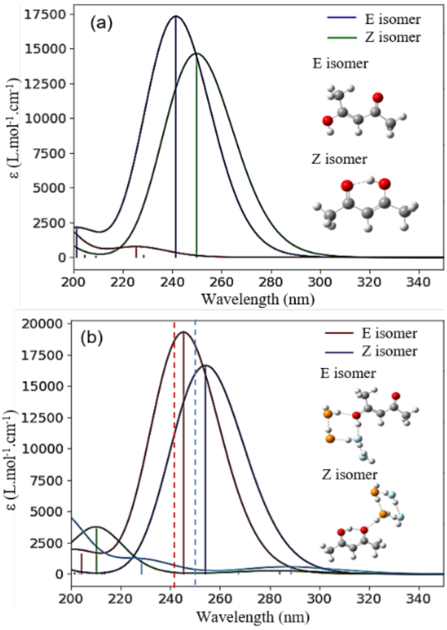

Fig. 5. UV-Vis spectra of enol tautomers (a) Isolated AA: E and Z isomers peak are 241.57 nm and 249.85 nm, respectively. (b) AA(2_2): E and Z isomer peak are 245.31 nm and 254.17 nm, respectively.

4. Conclusion

We calculated the acetylacetone tautomerization with explicit water clusters and demonstrated that the participation of H_2O in the proton transfer process significantly contributes to catalyzing the tautomerization reaction. One water molecule in the proton-relay can decrease the Ea by 24 kcal/mol, and a second water molecule in the proton relay further decreases the Ea by 10 kcal/mol. Such a decrease in Ea by 34 kcal/mol can result in an enhancement of reaction rate by 10^{25} times, showing that water clustering can greatly catalyze the tautomerization reaction. Interestingly, if the second water molecule is external, not participating in the proton relay, the Ea decrease is only 5 kcal/mol. This highlights the critical importance of proton relay water, and clustering with proper orientation is necessary.

The water system with two proton-relay molecules and two external molecules AA(2_2) was found to be most reactive for the 4-water complex. In addition to lowering the Ea, the addition of water molecules in the cluster also stabilizes the AA diketone conformer, thus explaining the tautomeric shift toward diketones in polar protic solvents.

The UV-Vis simulations showed that the inclusion of explicit water molecules results in measurable bathochromic shifts, which may help us extract possible solvation information from the experimental results. These results highlight the significant impact of H_2O clustering on both the energetics and spectroscopic signatures of β-diketone tautomerization.

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