Theoretical Study of the Effect of Water Clusters on the Enol Content of Acetone as a Model for Understanding the Effect of Water on Enolization Reaction

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Research Article

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Abstract

The enolization of simple carbonyl compounds is a key reaction for many chemical and biochemical processes. Numerous theoretical and experimental studies have been done to probe aspects of the mechanism of this reaction. In this work, the effect of small water clusters, $(\text{H}_2\text{O})_n$; $n=1-9$, on the enol content of acetone is investigated by using density functional theory calculations at the M06 level of theory in the gas and solution phases. The calculations indicated that the formation of hydrogen-bonded assemblies between water clusters and both tautomers of acetone affect the enolization reaction. Among them, the trimeric water cluster has the highest binding energy difference (DE_b) in the solution phase and greatly shift the equilibrium in the favor of the enol form. The results also shown that under this condition, the enol content of acetone increased by decreasing the polarity of the solvent. The practical conclusion of this study is that the enol content of carbonyl compounds can be maximized only by addition a defined amount of water.

Introduction

The study of enolization or keto-enol tautomerism of ketones from experimental and theoretical aspects is an active area of research due to its essential role in the chemical and biochemical processes [1–4]. Experimental data reveal that the enol content, K_e ($[\text{enol}]/[\text{ketone}]$), of simple ketones, is low even in pure form and in their aqueous solutions. It is not over 1–2 % [5, 6]. The enol content value ($\text{p}K_e$) of acetone were reported by other authors are given for comparison, Table 1.

Table 1
Some reported values for enol content value of acetone at 25°C

Author	K_e	$\text{p}K_e$	Author	K_e	$\text{p}K_e$
Schwarzenbach ^a	2.5×10^{-4}	3.6	Gero ^b	1.5×10^{-4}	3.82
Bell ^a	$< 10^{-4}$	4	Hine ^c	2.4×10^{-7}	6.62
Chiang ^a	6×10^{-9}	8.22	Sunner ^d	1.6×10^{-4}	3.8
Dubois ^a	3.5×10^{-7}	6.46	Osugi ^e	4.0×10^{-2}	1.4
Kresge ^a	4.6×10^{-9}	8.34	Msiedeen ^f	3.5×10^{-11}	10.5
a) In aqueous solution [7–10]. b) In 75% methanol-water [5]. c) Idealized gas state[11]. d) In 60% ethanol-water[12]. e) In toluene/high pressure [13]. f) DFT study in gas phase [14].					

The keto form is thermodynamically more stable than the enol form, but some factors, such as dielectric constant and hydrogen bond-forming ability of solvent, temperature, concentration, catalyst, and substituent groups, shift the equilibrium in favor of the enol form. For instance, more polar keto form in a polar solvent is the predominant tautomeric form due to the solvation effect [8, 15–21].

Enol content of carbonyl compounds has been traditionally determined by the Kurt-Meyer titration method but when the amount of enol form is less than 1 ppm this technique doesn't work well. In that case, spectroscopic methods, flash photolysis, thermochemical and kinetic methods can be used [6, 7, 14, 22–26]. Also, some theoretical studies have been carried out as well [27–32].

Researchers are interested in designing systems that improve K_e of mono-carbonyl compounds. Recently, water was used as a catalyst to increase the rate of enolization reactions. It is found that free energy of activation of keto-enol tautomerization process decreases in the presence of one or two water molecules [16, 17, 21, 28, 31]. It also seems that water molecules control the pathway of aldol reaction by decreasing or increasing the formation rate of enol intermediate, in other words, the enol content of the carbonyl compound. In our previous work, we theoretically found that the aldol reaction in the presence of L-proline as a catalyst can proceed concurrently through enamine-based and enol-based pathways in DMSO as solvent at room temperature. But, the formation of the enol intermediate predominates upon the addition of water [33]. Also, the product of L-proline-catalyzed aldol reaction between acetone and 4-nitrobenzaldehyde in the presence of water shows good yield and weak stereoselectivity but in the absence of water, the results reversed [34, 35].

Now the question arises, does water change the reaction mechanism? Do water molecules lonely or together affect the reaction rate? To answer these questions, we calculated the enol content of acetone in the presence of one molecule of water and some small water clusters (**WCs**) using DFT calculations.

Computational Method

All the calculations were performed using the Spartan '16 software package [36]. The enol content of acetone was examined in the presence of one molecule of water and some small **WCs**, $(\text{H}_2\text{O})_n$, $n = 2-9$, in the gas phase and acetone and DMSO as a solvent at room temperature, Fig. 1 [37–39].

The key idea of the work is based-on the formation of a hydrogen-bonded assembly between a **WC** and both tautomeric forms of acetone - *water-clustered tautomers* - and thus, hydrogen bonding plays an important role in the stability and behavior of the assemblies. The computations were done using the M06, the hybrid functional of Truhlar, which can account for dispersion interactions and describe some weak non-covalent interactions such as hydrogen bonding [40–42]. So, all calculations were carried out at the M06/6–31 + G** level of theory in the gas phase and acetone and DMSO as a solvent at room temperature. Solvent effects were included using the SM8 solvation model.

The enol content (K_e) was calculated based on the thermodynamic properties of the assembly of both tautomeric forms of acetone with the same water cluster by the following equation:

$$K_e = e^{(-\frac{\Delta G}{RT})}$$

, where K_e is the equilibrium constant between the tautomers, the gas constant R is 8.314 J/mol and the temperature T is 298.15 K.

Frequency calculation for characterizing stationary point was calculated at the same level. No imaginary frequency reveals that all of the structures are in ground states.

Results And Discussion

The water-clustered tautomers including **WCs**, **1–5**, **8** and **9**, and the keto form (**K**) of acetone, **Kⁿ**, show one hydrogen bond between its oxygen atom and the **WCs**. But, in two other assemblies including **6** and **7**, the acetone molecule enters into the structure of **WC** and forms a new mixed cluster. In all assemblies, the oxygen atom of one water molecule is slightly pointed to the hydrogen atom of the methyl group (α -proton) of the acetone. This interaction may facilitate the formation of enol through proton abstraction by the nearby water molecule, Fig. 2. The length of the hydrogen bond between **K** and **WC** (d_1) and the distance between the water molecule and the α -proton of acetone (d_2) are presented in Table 2.

In the water-clustered tautomers including enol form (**E**) of acetone, **Eⁿ**, the hydroxyl group actively participate, mainly through two hydrogen bonds, to merge two structures into a new **WC**-like structure, Fig. 3. The length of two hydrogen bonds between **E** and **WC** (d_3 , d_4) are presented in Table 2.

Table 2

The length of hydrogen bonds between **K** or **E** and **WCs** in **Kⁿ** or **Eⁿ** assemblies in the gas phase and solution at the M06/6-31 + G** level of theory

K ⁿ				E ⁿ
	d ₁ -d ₂ [*] (Å)				d ₃ -d ₄ (Å)		
	Gas	Acetone	DMSO		Gas	Acetone	DMSO
K ¹	1.90–2.36	1.85–2.76	1.84–3.02	E ¹	1.87--	1.83--	1.84--
K ²	1.82–2.27	1.78–2.86	1.78–2.87	E ²	1.82–1.98	1.82–2.03	1.83–2.02
K ³	1.77–2.46	1.75–2.40	1.75–2.41	E ³	1.76–1.84	1.73–1.84	1.74–1.84
K ⁴	1.89–2.43	1.83–2.69	1.83–2.69	E ⁴	1.72–1.79	1.71–1.82	1.73–1.83
K ⁵	1.94–2.50	1.84–2.57	1.84–2.54	E ⁵	1.75-2.00	1.73–1.98	1.74–1.98
K ⁶	1.93–2.51	1.76–3.33	1.75–3.32	E ⁶	1.72–1.85	1.71–1.87	1.72–1.88
K ⁷	1.86–2.48	1.83–2.62	1.82–2.64	E ⁷	1.66–1.92	1.68–1.93	1.70–1.93
K ⁸	2.00-2.79	1.78–3.02	1.77–3.03	E ⁸	1.68–1.73	1.68–1.76	1.69–1.75
K ⁹	1.85–2.54	1.82–3.01	1.82–3.05	E ⁹	1.65–1.89	1.66–1.90	1.67–1.90
* Distance between the water molecule and the α-proton of K							

According to Table 1, the **K³** assembly is geometrically much more prone to convert into the corresponding enol form, **E³**, in the solution phase. Because, it has the shortest distance between the α-proton of acetone and the oxygen atom of water molecule (d₂).

The enol content of acetone in the presence of different **WCs** and in the gas phase or polar solvents were calculated based-on the Gibbs free energy of both assemblies, **Kⁿ** and **Eⁿ**, Table 3. It is expected that the increase in the water content leads to the rise of the enol content, pK_{e} of acetone because of the formation of hydrogen-bonded assemblies, **Kⁿ** and **Eⁿ**, that stabilize both tautomeric forms of acetone. But the results showed that the number of water molecules of **WCs** and the solvent polarity have different effects on the enol content of acetone. The pK_{e} decreases with the increasing of solvent polarity. Therefore, the gas phase and non-polar solvents are more suitable condition for the enolization of acetone.

In the gas phase, the **WC** including **5** water molecules behave differently from most other **WCs**. But, in the polar solvents, **WC** with **3** water molecules show such a behavior. For both cases the enolization of acetone is maximum. It seems that the **WCs** can stabilize the enol form more than the keto form by the formation of an assembly that includes a more stable **WC**-like segment, **E³** and **E⁵**, Fig. 3. The significant decrease of enol content in **8** can be attributed to the high stability of its **WC**, which the cubic structure of it is disrupted by the formation of **E⁸** assembly, Table 3, Fig. 3. (H₂O)₄ and (H₂O)₈ among the other small cyclic **WCs** have distinct stability. Therefore, as is seen in Fig. 2, **K⁴** and **K⁸** show the resistance of the **WC** against insertion of carbonyl group [43]. Also, the relatively high enol content of **9** can be explained based-on the stabilizing interaction between water molecules and the hydroxyl group of enol form as a part of a stable **WC** [44].

Table 3
The enol content of acetone, pK_e in the presence of **WCs** in the gas phase and in acetone and DMSO as a solvent at M06/6–31 + G** levels of theory

pK_e			
n	Gas	Acetone	DMSO
0	10.30	12.20	12.20
1	10.20	10.80	11.50
2	9.38	11.80	12.30
3	9.06	9.08	9.24
4	9.39	10.40	10.10
5	8.00	9.48	10.30
6	8.30	10.60	10.70
7	8.34	10.40	10.60
8	10.00	12.30	11.93
9	8.69	9.43	9.35
The dipole moment of acetone and DMSO			

are 2.62 D and 3.96 D, respectively.

The orientation of orbitals and distance between the hydrogen atom of water and carbon-carbon double bond of the enol form in **E⁵** is such that H- π bonding can form quite easily, Fig. 5 [45]. Therefore, this extra interaction stabilizes more the assembly and increases the K_e .

The energy difference (ΔE) and the Gibbs free energy difference (ΔG) of $\mathbf{K}^n$ and $\mathbf{E}^n$ assemblies in different solvents are plotted against the number of water molecules (n) in the **WCs**, Fig. 6a and b. It is seen that the value of ΔE for acetone in the gas phase is 13 kcal/mol, which is in good agreement with experimental data, 13.9 kcal/mol [46–48]. The positive value of ΔE indicates that the keto form is more stable than the enol one. Decreasing the ΔE values mean the enolization process is facilitated by the **WCs**. In other words, the keto form of acetone is easier to convert to the enol form.

As shown in Fig. 6a, the ΔE values for **3**, **5** and **9** assemblies in the polar solvents and for **5** and **9** assemblies in the gas phase are all minimum values. The above results are also confirmed by the Gibbs free energy difference (ΔG) graphs, Fig. 6b. It is seen that **3** for the solution phase and **5** for the gas phase are global minimum.

To confirm these results, the binding energy for the assemblies was calculated. The binding energy of an assembly (E_b) is defined as:

$$E_b = \left(n \times E_{H_2O} + E_{tautomericform} \right) - E_{assembly}$$

, where n is the number of water molecules, E_{H_2O} is the energy of a water molecule, $E_{tautomericform}$ is the energy of enol or keto form of acetone and $E_{assembly}$ is the energy of assembly, $\mathbf{K}^n$ or $\mathbf{E}^n$. The binding energy (E_b) of each assembly ($\mathbf{K}^n$ and $\mathbf{E}^n$) was plotted against the number of involved water molecules (n), Fig. 8a. From the graph, it is observed that the binding energy of each assembly is increased by increasing n . Except in some few special cases, the binding energy of $\mathbf{E}^n$ is a little higher than $\mathbf{K}^n$ in both the gas phase and in solution, but the $\mathbf{K}^n$ assemblies are still more stable than the $\mathbf{E}^n$ ones. The E_b values for the gas phase are higher than the solution phases. This is due to the interaction of water molecules with the solvent, which leads to weakening of the hydrogen bonds in the solution phase and, therefore, decreasing the stability of assemblies.

The binding energy difference (ΔE_b) of water-clustered tautomers is calculated by subtracting $E_b(\mathbf{K}^n)$ from $E_b(\mathbf{E}^n)$. This quantity is a good and reliable estimate of the overall energy for the enolization reaction of acetone. An energy diagram is created by plotting the $-\Delta E_b$ values as a function of n , Fig. 8b. The pK_e values are also plotted for comparison. As is seen, the enolization reaction of acetone is very favorable in the presence of 5 and 3 water molecules in the gas and solution phases, respectively. As mentioned before, in these cases, the binding energy of enol form of acetone is approaching to the keto form.

Conclusions

The results showed that the formation of mixed hydrogen-bonded assemblies between **WCs** and both tautomers of a carbonyl compound affect the rate of the enolization process, but may changes the mechanism of its self-aldol reaction in the presence of L-proline as a catalyst. Also, it is seen that the enol

content increased by decreasing the polarity of the solvent, so the trend is gas > acetone > DMSO. It indicated that the shift of the keto-enol equilibrium toward the enol tautomer was highest in nonpolar solvents.

As reported earlier, the L-proline-catalyzed aldol reaction in organic solvents may proceed through two parallel competing reaction pathways ($\Delta E_a \sim 2$ kcal/mol), the formation of enamine or the formation of enol as an intermediate, based on the amount of water. The enamine formation is a favorable pathway in the absence of water, but the addition of a small amount of water preferred the formation of enol [33].

According to our results, the enol content (K_e) of acetone improved by adding a defined amount of water. Any changes in this defined amount of water cause a decrease in the enol formation. Thus, the enol formation pathway preferred the enamine one in the presence of an optimized amount of water. If this conclusion is correct, then the addition of a non-optimized amount of water to the proline-catalyzed aldol reaction solvent can have unpleasant effects on the yield and stereoselectivity of the reaction [34, 35]. This topic is currently under investigation in our group for more confirmation and development.

Declarations

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Code availability 'Not applicable'

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Figures

Figure 1

The most stable structure of used small WCs, $(\text{H}_2\text{O})_n$, $n=2-9$.

Figure 2

The structures of K-WC assemblies in the gas phase, K_n , n : number of water molecules of WC; $n = 0-9$.

Figure 3

The structures of E-WC assemblies in the gas phase, E_n , n : number of water molecules of WC; $n = 0-9$.

Figure 4

The HOMO orbital of E_5

(a)

(b)

Figure 5

a) Energy difference (ΔE) and b) Gibbs free energy difference (ΔG) of Kn and En vs. the number of water molecules (n) in the assembly, at the M06/6-31+G** level of theory

Figure 6

(a) The binding energy of water-clustered tautomers (E_b) and (b) the binding energy difference of them ($-\Delta E_b$) and pK_e values in the gas and solution phases as a function of the number of water molecules (n) in the assembly, calculated at the M06/6-31+G** level of theory

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