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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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, (H₂O)ₙ, n = 1–9, on the enol content of acetone has been 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 (ΔE_b) in the solution phase and greatly shifts the equilibrium in favor of the enol form. The results also show that under this condition, the enol content of acetone increased with decreasing polarity of the solvent. The practical conclusion of this study is that the enol content of carbonyl compounds can be maximized only by addition of a defined amount of water.

Keywords Enol content · DFT calculations · Water clusters · Hydrogen-bonded assembly · Water-clustered tautomer · Enolization reaction

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, Kₑ ([enol]/[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 values (pKₑ) of acetone which have been reported by other authors are given for comparison in Table 1.

The keto form is thermodynamically more stable than the enol form, but some factors, such as the 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, the more polar keto form in a polar solvent is the predominant tautomeric form due to the solvation effect [8, 15–21].

The 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 does not work well. In that case, spectroscopic methods, flash photolysis, and 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 the Kₑ of mono-carbonyl compounds. Recently, water was used as a catalyst to increase the rate of enolization reactions. It is found that the free energy of activation of the 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 the 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 a 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 these questions arise: does water change the reaction mechanism? Do water molecules alone 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, \((H_2O)_n, n = 2–9\), 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 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:

\[
K_e = e^{\left(\frac{-\Delta G}{RT}\right)}
\]

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.

Vibrational frequencies for characterizing stationary points were calculated at the same level. No imaginary frequency was observed. Thus, all optimized structures are true minima of the potential energy surface.

### Results and discussion

The water-clustered tautomers, including WCs, 1–5, 8, and 9, and the keto form (K) of acetone, \(K^n\), 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 (\(\alpha\)-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 \(\alpha\)-proton of acetone \(d_2\) are presented in Table 2.

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

According to Table 1, the K3 assembly is geometrically much more prone to being converted into the corresponding enol form, \(E^3\), in the solution phase because it has the

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

| Author       | \(K_e\)  | p\(K_e\) | Author       | \(K_e\)  | 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\(^e\) | 3.5 × 10^{-7} | 6.46 | Osuga\(^f\) | 4.0 × 10^{-2} | 1.4 |
| Kresse\(^e\) | 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]
shortest distance between the α-proton of acetone and the oxygen atom of water molecule (d2).

The enol contents 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, pKe, 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 pKe decreases with increase of the 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 behaves differently from most other WCs. But, in the polar solvents, WC with 3 water molecules shows 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, the cubic structure of which is disrupted by the formation of the 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 inser-

\[
\begin{array}{|c|c|c|c|}
\hline
\text{K}^n & \text{d}_1, \text{d}_2 (\text{Å}) & \text{Gas} & \text{Acetone} \\
\hline
\text{K}^1 & 1.90, 2.36 & 1.85, 2.76 & 1.84, 3.02 \\
\text{K}^2 & 1.82, 2.27 & 1.78, 2.86 & 1.78, 2.87 \\
\text{K}^3 & 1.77, 2.46 & 1.75, 2.40 & 1.75, 2.41 \\
\text{K}^4 & 1.89, 2.43 & 1.83, 2.69 & 1.83, 2.69 \\
\text{K}^5 & 1.94, 2.50 & 1.84, 2.57 & 1.84, 2.54 \\
\text{K}^6 & 1.93, 2.51 & 1.76, 3.33 & 1.75, 3.32 \\
\text{K}^7 & 1.86, 2.48 & 1.83, 2.62 & 1.82, 2.64 \\
\text{K}^8 & 2.00, 2.79 & 1.78, 3.02 & 1.77, 3.03 \\
\text{K}^9 & 1.85, 2.54 & 1.82, 3.01 & 1.82, 3.05 \\
\hline
\end{array}
\]

\[
\begin{array}{|c|c|c|c|}
\hline
\text{E}^n & \text{d}_3, \text{d}_4 (\text{Å}) & \text{Gas} & \text{Acetone} \\
\hline
\text{E}^1 & 1.87, - & 1.83- - & 1.84, - \\
\text{E}^2 & 1.82, 1.98 & 1.82, 2.03 & 1.83, 2.02 \\
\text{E}^3 & 1.76, 1.84 & 1.73, 1.84 & 1.74, 1.84 \\
\text{E}^4 & 1.72, 1.79 & 1.71, 1.82 & 1.73, 1.83 \\
\text{E}^5 & 1.75, 2.00 & 1.73, 1.98 & 1.74, 1.98 \\
\text{E}^6 & 1.72, 1.85 & 1.71, 1.87 & 1.72, 1.88 \\
\text{E}^7 & 1.66, 1.92 & 1.68, 1.93 & 1.70, 1.93 \\
\text{E}^8 & 1.68, 1.73 & 1.68, 1.76 & 1.69, 1.75 \\
\text{E}^9 & 1.65, 1.89 & 1.66, 1.90 & 1.67, 1.90 \\
\hline
\end{array}
\]

* The distance between the O atom of water molecule and the α-proton of K.
interaction between water molecules and the hydroxyl group of the enol form as a part of a stable WC [44]. For more details see the supporting information.

The orientation of orbitals and distance between the hydrogen atom of water and carbon–carbon double bond of the enol form in $E^5$ is such that H-π bonding can form quite easily (Fig. 4) [45]. Therefore, this extra interaction stabilizes more the assembly and increases $K_e$.

The energy difference ($\Delta E$) and the Gibbs free energy difference ($\Delta G$) of $K_n$ and $E_n$ assemblies in different solvents are plotted against the number of water molecules ($n$) in the WC (Fig. 5a, b). It is seen that the value of $\Delta E$ for acetone in the gas phase is 13 kcal/mol, which is in good agreement with experimental data, 13.9 kcal/mol [24, 46, 47]. The positive value of $\Delta E$ indicates that the keto form is more stable than the enol one. Decreasing $\Delta E$ values mean the enolization process is facilitated by the WC. In other words, the keto form of acetone is easier to convert to the enol form.

As shown in Fig. 5a, the $\Delta E$ 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 ($\Delta G$) graphs (Fig. 5b). 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:

$$E_b = \frac{\Delta E}{n}$$

The dipole moment of acetone and DMSO are 2.62 D and 3.96 D, respectively.
where \( n \) is the number of water molecules, \( E_{\text{H}_2\text{O}} \) is the energy of a water molecule, \( E_{\text{tautomeric form}} \) is the energy of the enol or keto form of acetone, and \( E_{\text{assembly}} \) is the energy of the assembly, \( K^n \) or \( E^n \). The binding energy \( (E_b) \) of each assembly \( (K^n \text{ and } E^n) \) is plotted against the number of involved water molecules \( (n) \) (Fig. 6a). From the graph, it is observed that the binding energy of each assembly increases with increasing \( n \). Except in some few special cases, the binding energy of \( E^n \) is a little higher than that of \( K^n \) both in the gas phase and in solution, but the \( K^n \) assemblies are still more stable than the \( E^n \) ones. The \( E_b \) values for the gas phase are higher than those for 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 (\( \Delta E_b \)) of water-clustered tautomers is calculated by subtracting \( E_b(K^n) \) from \( E_b(E^n) \). 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. 6b). 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 the enol form of acetone is approaching the keto form.
Conclusions

The results showed that the formation of mixed hydrogen-bonded assemblies between WC s and both tautomers of a carbonyl compound affect the equilibrium position of its enolization process. Also, it is seen that the enol content increased with decreasing 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 non-polar 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.

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Author contribution Both authors contributed equally to this work. N. Arshadi as a PhD thesis supervisor contributed to the study conception and design. All calculations and analysis were performed by Z. Tohidi Nafe as a PhD student. The first draft of the manuscript was written by Z. Tohidi Nafe, and N. Arshadi commented on previous versions of the manuscript. Both authors read and approved the final manuscript.

Availability of data and material The authors confirm that the data supporting the findings of this study are available within the article and its supplementary material.

Declarations

Conflict of interest The authors declare no competing interests.

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