DFT Study To Explore the Importance of Ring Size and Effect of Solvents on the Keto–Enol Tautomerization Process of α- and β-Cyclodiones

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ABSTRACT: We have explored the effect of ring size on keto–enol tautomerization of α- and β-cyclodiones using the M062X-SMD\_aq/6-31+G(d,p) level of theory. The calculated results show that the activation free energy barrier for the keto–enol tautomerization process of α-cyclopropanedione (1) is 54.9 kcal/mol, which is lower compared to that of the other cyclic diketo systems studied here. The four-membered β- and α-cyclobutanedione (2 and 6) do not favor keto–enol tautomerization unlike other studied cyclic systems because of the ring strain developed in the transition-state geometries and their corresponding products. Water-assisted keto–enol tautomerization with one molecule reveals that the free energy activation barriers reduce almost half compared to those for the uncatalyzed systems. The two-water-assisted process is favorable as the activation free energy barriers lowered by ~10 kcal/mol compared to those of the one-water-assisted process. The ion-pair formation seems to govern the lowering of activation barriers of α- and β-cyclodiones with two water molecules during the keto–enol tautomerization process, which however also overcomes the favorable aromatization in the three-membered ring system. The free energy activation barriers calculated with the M062X-SMD\_aq/6-31+G(d,p) level predicted that the keto–enol tautomerization process for the α-cyclodiones follows the following trend: 2 > 3 > 4 > 5 > 1. Water-assisted tautomerization of α-cyclodiones also predicted 1-W and 1-2W as the most favored processes; however, 5-W and 5-2W were found to be disfavored in this case. The β-cyclodione systems also showed similar trends as obtained with α-diketone systems. The influence of bulk solvent on the keto–enol tautomerization process favors the formation of the enol form in a more polar solvent medium even under mixed solvent conditions in acetonitrile and hexane at M062X-SMD\_acetonitrile/6-31+G(d,p) and M062X-SMD\_hexane/6-31+G(d,p) levels of theory.

INTRODUCTION

Tautomerization is known to be one of the essential processes in chemistry and biology, more specifically, keto–enol and amino–imino tautomerizations. The mechanistic pathways of keto–enol tautomerization, the influence of solvent molecules, and the role of different substituents have been investigated. It has been reported that the enols derived from unhindered, unconjugated ketones are present in a minuscule amount at equilibrium. Research efforts have been put forward to design systems to improve the enol content. Keto–enol tautomerization has been observed in many biological processes that directly or indirectly proceed through keto–enol or amino–imino tautomerism, e.g., pyranose to furanose ring conversion of cyclic carbohydrate, glucose to fructose conversion, etc. Keto–enol tautomerism also plays an important role in the formation of kynurenic acid, an antiepileptic and anticonvulsant compound, which is generated during the metabolism of L-tryptophan. In the keto–enol tautomerization equilibrium process, one proton transfers from the α-carbon center to carboxyl oxygen through space via bond formation. This proton transfer process is accelerated in the presence of solvent molecules or by suitable substituents. In the case of acyclic ketone, reports reveal that the keto form is more stable in a polar solvent compared with the enol form.

The proton transfer in the keto–enol tautomerization process can be acid- or base-catalyzed in different solvent media. In this regard, water-assisted keto–enol tautomerization processes have been investigated. The water-assisted keto–enol tautomerization process was called the “bifunctional water-catalyzed proton transfer” process because in such keto–enol tautomerization a water molecule acts as both a proton donor and a proton acceptor. The keto–enol tautomerization of α-cyclopropanedione (cyclopropane-1,2-dione, 1), an enolizable α(α) diketone, has been studied experimentally and theoretically. The keto–enol form is more stable compared with the diketone form because of the aromatic character of the keto–enol form having two π-

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electrons. Furthermore, $\alpha$-cyclodiones and $\beta$-cyclodiones have been extensively studied because of their use in organic chemistry and also because they are well studied by crystallographers.\textsuperscript{7,10,13,49-60} The presence of cyclic-$\alpha$-diketones and cyclic-$\beta$-diketones in various crystals results in significant optical, electrical, and magnetic properties of the respective crystals. Not only these compounds exhibit substantial applications in the optical probe and laser material, but also their keto−enol tautomerization process has a significant role in various chemical reactions.\textsuperscript{17,61,62} The aerobic oxidation of cyclopentane-1,2-dione, \(\text{(cyclopropane-1,2-dione, 1)}\), \(\text{(cyclohexane-1,3-dione, 6)}\), \(\text{(cyclopentane-1,3-dione, 7)}\), \(\text{(cyclohexane-1,3-dione, 8)}\), and \(\text{(cycloheptane-1,3-dione, 9)}\), to examine the keto−enol tautomerism mechanism at the same level of theory. The solvent effect on such keto−enol tautomerism has been examined in the presence of the explicit water molecules and implicit SMD solvation model where water (\(\epsilon = 78.8\)), acetonitrile (\(\epsilon = 35.7\)), and \(n\)-hexane (\(\epsilon = 1.9\)) have been used as solvents.\textsuperscript{13}

### RESULTS AND DISCUSSION

**$\alpha$-Cyclodiones.** The keto−enol tautomerized form of cyclopropane-1,2-dione (1) is of considerable interest and is known as a photochemical precursor to hydroxyacetylene.\textsuperscript{46} It is reported in the literature that the keto−enol form of 1 is more stable compared with the diketo form because of aromatization in the keto−enol form.\textsuperscript{22} The activation free energy barrier for the keto−enol tautomerization process of cyclopropane-1,2-dione is 54.9 kcal/mol, and the keto−enol form, hydroxycyclopropenone, is stable by 18.2 kcal/mol compared with the diketo form in the aqueous phase at the M062X-SMD\(_{aq}\)/6-31+G(d,p)//M062X/6-31+G(d,p) level of theory. The enol form could exist in two different conformations, i.e., the cis conformation, the hydroxyl group orientated toward the keto group to form a hydrogen bond, and the trans orientation (Figure S1). It is worth mentioning here that the cis conformers are generally more stable compared with the trans conformers because of the O−H···O hydrogen bonding interaction. In an earlier report, the calculations performed with the PCM-B3LYP/6-31++G(d,p) and PCM-MP2/6-31++G(d,p) levels of theory also suggest that the keto−enol form is stable by \(\sim 20\) kcal/mol.\textsuperscript{46}

The cyclobutane ring is a strained system and prefers to adopt a puckered conformation. The presence of two carbonyl groups in the cyclobutanedione ring forces it to be planar than the preferred puckered structure (Figure 1). The geometries optimized using M062X/6-31+G(d,p) reveal that the diketo form (2) and the keto−enol form are planar in their ground-state geometries (Figure 1). The M062X-SMD\(_{aq}\)/6-31+G(d,p)-calculated free energy of activation is 75.5 kcal/mol, and the diketo form is energetically favored compared with the keto−enol form by 6.0 kcal/mol. The presence of three sp\(^2\)-hybridized carbon atoms in the keto−enol form of the four-membered ring causes more strain compared to that in the diketo form with two sp\(^2\)-hybridized carbon atoms. There are a

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**Scheme 1. Water-Unassisted and Assisted Keto−Enol Tautomerization Process for 1,2- and 1,3-Cyclic Diketo Systems**

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**Figure 1.** Keto−enol tautomerization process of cyclic-1,2- and cyclic-1,3-diones of three-to-seven-membered rings. Key: yellow, C; red, O; and white, H.
few reports on cyclobutane derivatives to stabilize the enol forms using fluoro substituents. The thermodynamic stability achieved for the enol forms than for the corresponding keto forms is due to the greater destabilization of the later form. The free energy activation barrier calculated with the higher homologue, i.e., cyclopentane-1,2-dione (3), is 70.1 kcal/mol, and the keto–enol form is stable by 2.1 kcal/mol compared with the diketo form. The cyclohexane ring always prefers the chair conformation, and we have observed that the diketo form also preferred the chair conformation; however, the keto–enol form exists in an envelope-like conformation and is energetically favored by ~1 kcal/mol (Table 1). The experimental results corroborate keto–enol formation in cyclohexane-1,2-dione. The M062X-SMDaq/6-31+G-(d,p)-calculated activation free energy barrier for cyclohexane-1,2-dione (4) is 67.3 kcal/mol. An alkyl substitution in the ring system can improve the enol formation in cyclohexene-1,2-diketone. The experimental report reveals that the appropriate substituents at the proper position can influence the keto–enol tautomerization process in cyclohexene ring systems. The cycloheptane ring is one of the larger ring systems, and the angle strain does not allow it to exist in a planar conformation. The diketo (5, Figure 1) form always exists in a puckered conformation, and two carbonyl groups orient opposite to each other. The keto–enol form, however, adopts an envelope-like structure, which suffers from more ring strain compared to that in the diketo form. The calculated activation free energy barrier for cycloheptane-1,2-dione (5) is 64.0 kcal/mol, whereas the keto–enol form is energetically unstable by 0.9 kcal/mol compared with the diketo form. The activation free energy barriers and the reaction energies calculated at the MP2-SMDaq/6-311++G+(d,p)//M062X/6-31+G(d,p) levels of theory are in good agreement with those calculated at M062X-SMDaq/6-31+G-(d,p)//M062X/6-31+G(d,p) levels of theory (Table S1).

The mechanism of keto–enol tautomerism studied computationally and experimentally suggests that the proton of the α carbon center transfers through space via bond formation in the transition state (Figure 2). We have examined this process while running the intrinsic reaction coordinate (IRC) calculations of keto–enol tautomerism of three-to-seven-membered rings in the gas phase. The IRC calculations suggest that hydrogen (α-carbon) is transferred to the oxygen of the carbonyl group following three steps: (i) C–H bond breaking, (ii) movement of the proton toward the carbonyl group through space, and (iii) O–H bond formation. The transition-state (TS) geometry analyses for the cyclic-1,2-diones (1–5) suggests that the distance between the proton of α-carbon (H4, atom number 4, see Figure 1) and the carbonyl group of oxygen (O1, atom number 1, see Figure 1) decreases with the increasing ring size (Figure 2). The observed longest distance is 1.39 Å for the three-membered ring (1-TS), and the shortest one is 1.29 Å for the seven-membered ring (5-TS, Figure 2). The calculated dihedral angle O1–C2–C3–H4 is −56.9 for the three-membered ring, −62.0 for the four-membered ring, −34.91 for the five-membered ring, 12.59 for the six-membered ring, and −4.25 for the seven-membered ring (Figure 1). The dihedral angle analyses suggest that proton transfer through space is easier for larger ring systems compared with the smaller rings. In the case of the seven-membered ring system, the oxygen (O1) of the carbonyl group and the hydrogen (H4) of the α-carbon lie almost in the same plane, which facilitates through the space proton transfer process.

β-Cyclodiones. The keto–enol tautomerization process for the β-cyclodiones is very similar to that of the corresponding cyclic-1,2-diketo systems. The M062X-SMDaq/6-31+G(d,p)//M062X/6-31+G(d,p)-calculated activation free energy barrier is 70.3 kcal/mol for cyclobutane-1,3-dione (6); and the keto–enol form is unstable by 4.6 kcal/mol. There are two possible enolizable CH2 sites available in the five, six, and seven-membered β-cyclodiones. However, H4 is more acidic compared with H5, and subsequently, H4 is enolized (Figure 1). The density functional theory (DFT)-calculated activation

Table 1. Free Energy Differences Calculated at M062X-SMDaq/6-31+G(d,p)//M062X/6-31+G(d,p) Levels of Theory, Given in kcal/mol

| 1,2-diketo systems | 1,3-diketo systems | 1,3-diketo systems |
|-------------------|-------------------|-------------------|
| ΔG° | ΔG | NICS(1)zz | ΔG° | ΔG | NICS(1)zz |
| 1 | 54.9 | −18.2 | −7.6 | 6 | 70.3 | 4.6 | 0.6 |
| 2 | 75.7 | 6.1 | −1.1 | 7 | 64.0 | 0.3 | 0.0 |
| 3 | 70.1 | −2.1 | −0.8 | 8 | 58.4 | 1.4 | 0.9 |
| 4 | 67.3 | −0.8 | 0.1 | 9 | 55.3 | 4.6 | 1.0 |
| 5 | 64.0 | 0.9 | −0.8 | 2 > 3 > 4 > 5 > 1 | 6 > 7 > 8 > 9 |

The NICS(1)zz indices for the transition-state (TS) structures are given in ppm.

Figure 2. All of the transition-state structures and corresponding distances are given in angstrom. The distance between the proton of α-carbon center and carbonyl oxygen is decreasing with the increasing ring size. Key: yellow, C; red, O; and white, H.
free energy barrier for the enolization of H4 in cyclopentane-1,3-dione (7) is 64.4 kcal/mol, and the corresponding keto-enol form is unstable by 0.3 kcal/mol in the aqueous phase. On the other hand, the activation free energy barrier for the enolization of H5 is 71.6, and the corresponding keto-enol form is unstable by 11.2 kcal/mol (Table S3). Similar trends were also observed for six- and seven-membered rings (Table S3). The previously reported result also shows that the activation energy barrier for 7 is 64.4 kcal/mol; however, the keto-enol form was found to be marginally stable, ~2.0 kcal/mol, at the CPCM-B3LYP/6-31+G(d,p) level with the SMD chemical shift (NICS) calculations for each transition-state form.

We have further performed the nucleus-independent chemical shift (NICS) calculations and observed that the TS of the three-membered (1-TS) ring has the higher negative NICS value compared to that of the other rings (Table 1). The NICS(1)zz values revealed that 1-TS has the higher aromaticity compared to that of the other ring systems. On the other hand, the keto-enol form of the three-membered ring has higher aromaticity (~9.8) compared to that of the other ring systems (Table S2). This is to note here that the calculated NICS(1)zz values for aromaticity of nonplanar and nonconjugate systems may not be the exact aromaticity values as the program is designed for the planar and conjugate systems.

Water-Assisted Tautomerization. We have extended DFT calculations with one water molecule to examine the catalytic effect on the keto-enol tautomerization process. It is reported in the literature that the presence of a single water molecule can affect the activation free energy barrier, and it becomes almost half of the uncatalyzed activation free energy barrier. The calculated results show that the water molecule initially interacts with the carbonyl group through H-bonding interactions (Figure S2). In the case of 1,2-diketo systems, there is a possibility that the water molecule can also interact with the two carbonyl groups via hydrogen bonding interactions. However, such geometries were not obtained for 1-W, 2-W, and 4-W. Nevertheless, hydrogen-bonded 3-W and 5-W have been located at the same level of theory, but these geometries are energetically less stable than those where the water molecule interacts with a carbonyl group and the adjacent CH2 group (Figure S2). The distance between the carbonyl groups in the cyclic systems governs the formation of hydrogen-bonded structures with the water molecule. The geometry in the water-assisted tautomerization process has been observed as described in the literature. The water-assisted proton transfer process to carbonyl oxygen in keto-enol tautomerization occurs through the water molecule. The water-mediated proton transfer process facilitates the tautomerization process, and the activation free energy barrier is almost half of the water uncatalyzed barrier (Tables 1 and 2). The calculated activation free energy barriers for cyclopropane-1,2-dione in the presence of one water molecule (1-W, Figure S2) are 15.2 and 37.9 kcal/mol for cyclobutane-1,2-dione (2-W), cyclopentane-1,2-dione (3-W), and cyclohexane-1,3-dione (4-W).

| 1,2-diketo systems | 1,3-diketo systems |
|-------------------|-------------------|
| ΔG (kcal/mol)     | ΔG (kcal/mol)     |
| NICS(1)zz (ppm)   | NICS(1)zz (ppm)   |
| 1-W 15.2 -22.3 -7.6 30.2 0.8 -1.2 |
| 2-W 37.9 2.5 -0.9 6-W 30.2 0.8 -1.2 |
| 3-W 34.3 -4.8 -1.1 7-W 28.6 -1.9 -2.4 |
| 4-W 34.7 -3.6 -1.0 8-W 29.7 -0.4 -0.4 |
| 5-W 48.2 1.4 -4.4 9-W 30.5 1.4 -0.3 |
| 5-W>2-W>4-W>3-W>1-W 9-W>6-W>8-W>7-W |

*Free energies are given in kcal/mol. The NICS(1)zz values for the TS structures are given in ppm.*
34.3 kcal/mol for cyclopentane-1,2-dione (3-W), 34.7 kcal/mol for cyclohexane-1,2-dione (4-W), and 48.2 kcal/mol for cycloheptane-1,2-dione (5-W) at the M062X-SMDaq/6-31+G(d,p)//M062X/6-31+G(d,p) level of theory. On the other hand, the activation free energy barriers with one water molecule for cyclic-1,3-diketo systems are 30.2, 28.6, 29.7, and 30.5 kcal/mol for four- (6-W), five- (7-W), six- (8-W), and seven-membered (9-W) rings, respectively. The results reveal that water-catalyzed keto-enol tautomerization in the aqueous phase affects the smaller ring system more compared with the larger ring systems. The computed results show that the activation free energy barrier for the four-membered ring (2-W) is higher compared to that for the five- (3-W) and six-membered (4-W) rings. Importantly, the free energy activation barrier calculated for cycloheptane-1,2-dione (5-W) is highest in this series, which shows the opposite trend to that of the results obtained without the water molecule. The water molecule in TS geometry (5-W-TS) induces ring strain that causes the ring to be highly distorted and subsequently increases the activation free energy barrier for keto-enol tautomerization compared to that for the other cyclic-1,2-diketo systems (Figure 3). The observed trend for the activation free energy barrier for the cyclic-1,2-diketo system is 5-W > 2-W > 4-W > 3-W > 1-W, and cyclic-1,3-diketo systems also showed a similar trend in the aqueous medium. The keto-enol form of the water-assisted tautomerization process is more stable compared to that of the water-unassisted tautomerization process. However, the trans conformer of the keto-enol form is marginally stable than that of the cis conformer in the presence of water molecule unlike in the absence of water molecule. The water molecule facilitates the formation of hydrogen bond in the trans conformer. Furthermore, activation free energy barriers and the reaction energies calculated at MP2-SMDaq/6-311++G(d,p) levels of theory corroborate the results calculated at M062X-SMDaq/6-31+G(d,p) levels of theory (Table S1).

The one-water-assisted keto-enol tautomerization process for α- and β-cyclodiones is energetically favored as observed in this study. Therefore, it is important to examine the role of the additional water molecule in these keto-enol tautomerization processes. This is to note that the process involving a proton transfer assisted with two water molecules is even biologically significant.76 Tautomerization assisted with two water molecules has been examined in two possible orientations. In the first case, the additional water molecule is not directly participating in the keto-enol process. In the second case, the two water molecules facilitate the proton transfer process, and similar processes have also been reported.38 We have determined the stability of keto-enol tautomers and the activation barriers with two water molecules at the M062X-SMDaq/6-31+G(d,p) level of theory. The proton transfer process mediated by two water molecules in
Table 3. Free Energy Differences at the M062X/6-31+G(d,p) Level of Theory in the Aqueous Phase

| 1,2-diketo systems | 1,3-diketo systems |
|---------------------|---------------------|
| \( \Delta G^\ddagger \) | \( \Delta G \) | NICS(1)zz | \( \Delta G^\ddagger \) | \( \Delta G \) | NICS(1)zz |
| 1-2W | -24.7 | -8.1 | 6-2W | 16.5 | 0.8 | 9.1 |
| 2-2W | 25.4 | 2.8 | 1-1 | 15.6 | 0.8 | 3.2 |
| 3-2W | 22.8 | -3.9 | 7-2W | 16.0 | -0.1 | 3.1 |
| 4-2W | 24.2 | -3.3 | 8-2W | 20.3 | -0.9 | 2.4 |
| 5-2W | 39.1 | -1.0 | 9-2W | 9-2W > 6-2W > 8-2W > 7-2W |

**Table 4. Free Energy Calculated in the Acetonitrile Solvent at the M062X/6-31+G(d,p) Level of Theory and the Free Energy Values in n-Hexane, a Nonpolar Solvent, Are Given in Parentheses**

| 1,2-diketo systems | 1,3-diketo systems |
|---------------------|---------------------|
| \( \Delta G^\ddagger \) | \( \Delta G \) | \( \Delta G \) | \( \Delta G \) |
| 1 | 57.8 (60.5) | -13.7 (11.3) | 6-W | 32.1 (32.7) | 1.3 (2.1) |
| 2 | 77.5 (78.2) | 8.6 (9.1) | 6-W | 30.0 (30.2) | -1.5 (-1.0) |
| 3 | 70.6 (70.2) | -0.7 (-2.8) | 7-W | 31.2 (30.8) | 0.1 (-0.2) |
| 4 | 67.1 (66.1) | 0.0 (-2.3) | 8-W | 31.6 (32.8) | 2.5 (4.1) |
| 5 | 67.7 (63.0) | 1.5 (-0.6) | 9-W | 31.6 (32.8) | 2.5 (4.1) |

"Free energies are given in kcal/mol. The NICS(1)zz values for the TS structures are given in ppm.

"Free energies are given in kcal/mol.

keto–enol tautomerization is energetically favored compared with the first case (Figures 4, S3, Tables 3, and S4). The incorporation of second water molecule facilitates the transfer of proton and hence affects the activation barriers significantly. The activation free energy barrier calculated for 1 with two water molecules is 4.3 kcal/mol, and the tautomeric form is stable by -24.7 kcal/mol (Table 3 and Figure 4). The activation free energy barrier of the proton transfer processes assisted by two water molecules for the other systems examined with the M062X-SMD\(_{aq}\)/6-31+G(d,p) level is reduced by ~10 kcal/mol compared to that of the one-water-assisted process (Tables 2 and 3). The significant lowering of the activation free energy barriers by two water molecules makes the keto–enol tautomerization process more favorable compared with the water-unassisted and one-water-assisted tautomerization processes. The activation free energies follow similar trends as obtained with one water molecule, where 1-2W has the lowest barrier and 5-2W has a barrier higher than that for other ring systems studied here.

Interestingly, the NICS(1)zz index value (−8.1) for 1-2W-TS has not been significantly changed compared to that of 1-W-TS (−7.6). This result suggests that aromatization does not influence the two-water-assisted tautomerization process. However, the activation barrier calculated at the same level of theory is much lower for 2W-TS compared to that for 1W-TS. The geometrical analyses reveal that while transferring the hydrogen from the α-carbon center with two water molecules a significant negative charge develops on this carbon center, which stabilizes the positive charge developed on the H\(_2\)O’ fragment of 1-2W-TS (Figure S4). The ion-pair formation seems to be responsible for the lowering of the activation barrier with two water molecules compared to that with the case of one water molecule. Earlier reports on the water-assisted keto–enol tautomerization process of malonaldehyde also demonstrated the ion-pair formation in the transition-state structure.

**Effect of Solvent Polarity.** There are reports that the dominance of the keto form in polar solvents is observed experimentally due to the strong solvation effect, whereas in nonpolar solvents, the tautomeric equilibrium is usually shifted toward the formation of enol forms.\(^{11,24,77,78}\) Acyclic β-diketones and β-ketoesters follow Meyer’s rule of a shift in the tautomeric equilibrium toward the keto tautomer with increasing solvent polarity because the keto form is more polar than the enol form and hence is more stable in polar solvents.\(^{78}\) However, a report on keto–enol tautomerization of some specific Schiff bases demonstrated an opposite solvent-dependent effect.\(^{79}\) We have extended our computational effort to examine the impact of solvent polarity on the keto–enol tautomerization process of the cyclic diketo systems using the SMD solvation model with acetonitrile (35.7) at M062X-SMD\(_{acetonitrile}\)/6-31+G(d,p) and n-hexane (1.9) at M062X-SMD\(_{hexane}\)/6-31+G(d,p)/M062X/6-31+G(d,p). The DFT calculations performed for α- and β-cyclodiones reveal that the activation free energy barriers increase with the decreasing solvent polarity. The activation free energy barrier predicted for cyclopropane-1,2-dione is 54.9 kcal/mol in water, 57.9 kcal/mol in acetonitrile, and 60.5 kcal/mol in n-hexane. Furthermore, the stability of the keto–enol form of the three-membered ring decreases with the decreasing solvent polarity, i.e., the keto–enol form is more stable in water than in acetonitrile and n-hexane (Table 4). The keto–enol form of cyclopropane-1,2-dione is stable by 17.9 kcal/mol in water, and the stability decreases to 13.7 kcal/mol in the acetonitrile solvent and 11.3 kcal/mol in hexane. Furthermore, the study has been carried out with larger ring systems, and
DFT calculations revealed that the activation energy barrier increases in the less polar solvent compared to that in the polar solvent (Table 4). Quantum chemical calculations at the M062X/6-31+G(d,p) level of theory show that the polar solvent stabilizes the enol form of cyclic systems to a greater extent compared with the less polar solvents. These results suggest that the keto—enol tautomeric equilibrium can be altered with cyclic diketones compared with the acyclic systems using different solvent media.  

The importance of dipole moments of keto and enol forms can govern their stability in different solvent media.  Therefore, we have also examined the dipole moment of the studied systems in the gas phase at the M062X/6-31+G(d,p) level of theory (Table S5). The dipole moment calculations in the gas phase suggest that the keto—enol forms are more polar than the corresponding diketo forms and hence the propensity to obtain the former form would be likely with cyclic systems in a polar solvent system. Nonetheless, the computational results presented here for the cyclic systems warrant experimental verification.

There are reports available in the literature where water-catalyzed reactions have been studied in the acetonitrile or a nonpolar solvent or a mixed interface of two immiscible solvents.  Therefore, it is interesting to examine the role of the bulk solvent in water-assisted keto—enol reactions along with that in the unassisted reaction. The activation free energy barrier of cyclic-1,2-dione in the presence of one and two water molecules increases in a nonpolar solvent, and the keto—enol forms are relatively more stabilized than the diketo forms (Tables 1, 2, and 4). 1,3-Diketo systems also showed very similar behavior in solvents as observed with 1,2-diketo systems (Table 4). It is important to note that the keto—enol tautomerization process largely follows a similar trend in aqueous, acetonitrile, and n-hexane media and even in the mixed solvent conditions.

In this article, we have examined the effect of ring size on the keto—enol tautomerization process in cyclic-1,2 and 1,3-diketo systems at the M062X/6-31+G(d,p) level of theory in aqueous medium. The water-assisted keto—enolization process with one and two water molecules at the same level of theory was also studied. The computational studies revealed the following results:

Aromaticity plays an essential role in the equilibrium process for the cyclopropane-1,2-dione ring, where the keto—enol form was favored by 18.2 kcal/mol over the diketo form. The computational results suggest that the activation free energy is the lowest for the three-membered ring in the series and hence this ring can be preferred for the keto—enol tautomerization process. The geometrical analyses suggest that proton transfer in the larger ring systems is more facile compared to that in the smaller ring systems.

The activation free energy barriers calculated for β-cyclodiones systems follow similar trends; however, the activation free energy barriers are lower compared to those for the corresponding α-cyclodione systems. The adjacent carbonyl groups in α-cyclodione systems experience severe electronic repulsion in the transition states and hence raise the activation barrier for keto—enol processes compared to that for the β-cyclodiones. The activation free energy barriers for the keto—enol tautomerization process for the α-cyclodiones systems follow the following trend: 2 > 3 > 4 > 5 > 1, and a similar trend was also noticed for the β-cyclodione systems. The results of MP2-SMD_aq/6-311++G(d,p)//M062X/6-31+G(d,p) levels of theory further corroborate those calculated at M062X-SMD_aq/6-31+G(d,p)//M062X/6-31+G(d,p) levels of theory.

Water-assisted keto—enol processes for α- and β-cyclodiones systems showed a remarkable reduction in the activation free energies in each case. The activation free energy barrier reduced to 15.2 kcal/mol for 1-W in the water-assisted process from 54.9 kcal/mol in the water-unassisted process and 4.3 kcal/mol for 1-2W. The activation free energy barriers for the tautomerization processes assisted with two water molecules are decreased by ~10 kcal/mol due to ion-pair formation in 2W-TSs. Importantly, the keto—enol process is relatively unfavored for 5-W and 5-2W with the water-assisted processes compared to that of the water-uncatalyzed system. The water molecules in TS geometry of 5-W-TS and 5-2W-TS induce ring strain that caused the ring to be highly distorted and hence increased the activation free energy barrier. The trend observed for the activation free energy barrier for the α-cyclodione system is 5-W > 2-2W > 4-W > 3-W > 1-W, and β-cyclodione systems also followed a similar trend in aqueous medium. The activation free energy barrier for the two-water-assisted process follows a trend very similar to that observed for the one-water-assisted process.

The influence of bulk solvent on the keto—enol tautomerization process was also examined for cyclic diketo systems in acetonitrile and hexane solvents. The calculated results suggest the formation of an enol form in a more polar solvent medium even under mixed solvent conditions. The dipole moment values govern the stability of cyclic diketones in different solvent media, and the extent of formation of keto—enol would be higher with cyclic systems compared to that with the acyclic ones in a polar solvent. This study sheds light on the influence of ring size and the solvent polarity on the keto—enol tautomerization processes that can contribute to design many systems of biological and chemical interests.

All of the geometries were optimized using the M062X/6-31+G(d,p) level of theory in gas phase.  M062X is a hybrid meta exchange-correlation functional and one of the best functionals to study the organic and biological small molecules.  Harmonic frequency calculations have also been carried to examine the minima of the optimized geometries with no imaginary frequency. We located the TS structures on the potential energy surface, and the TSs have been confirmed with one imaginary frequency.roll

Further intrinsic reaction coordinate (IRC) calculation was performed to connect the reactants, TSs, and products at the same level of theory. We also performed single-point energy calculation using the same level of theory in three different solvents, i.e., water (ε = 78.8), acetonitrile (ε = 35.7), and n-hexane (ε = 1.9), using the SMD solvation model with the self-consistent reaction field method. The Gibbs free energy in the solvent phase has been calculated as

\[
G_{aq} = G_{gas} + (E_{aq} - E_{gas}) + \Delta G^\text{i atm} \cdot \text{M}^{-1}
\]
where $G_{aq}$ and $E_{aq}$ are the Gibbs free energy and electronic energy in the aqueous phase, $G_{gas}$ and $E_{gas}$ are the Gibbs free energy and electronic energy in the gas phase, $\Delta G = G_{aq} - G_{gas}$ is the correction associated with the change in the standard state from the gas phase (1 atm) to solution (1 mol/L), and its value at 298.15 K is 0.003012 hartree.\textsuperscript{93–97} The free energy differences were calculated as
\[
\Delta G = G_k - G_{diketo}
\]
where $\Delta G$ is the free energy difference, $G_k$ is the energy of the transition-state geometry or the keto--enol form, and $G_{diketo}$ is the free energy of the cyclic diketo form.

The aqueous phase results calculated using the M062X/6-31+G(d,p) level of theory have been carefully compared with those calculated from the MP2/6-311++G(d,p), MP2/aug-cc-pVDZ, MP2/aug-cc-pVTZ, and MP2/aug-cc-pVQZ methods in the aqueous phase,\textsuperscript{101,102} All of the above density functional calculations were performed using the Gaussian 09 (G09) software package.\textsuperscript{103}

Furthermore, we carried out NICS calculations with the GIAO\textsuperscript{100} method for all of the studied structures at M062X/6-31+G(d,p) in the aqueous phase.\textsuperscript{101,102} All of the above calculations have been carried out with the Gaussian 09 (G09) software package.\textsuperscript{103}

To explore keto--enol tautomerization of cyclic diketones, the computational methods and basis sets have been examined. The DFT M062X functional and MP2 with Pople-type basis sets and Dunning’s correlation-consistent basis sets were employed using the M062X/6-31+G(d,p) optimized geometry. In this work, we have chosen 6-31+G(d,p) and 6-311++G(d,p) as Pople basis sets, whereas aug-cc-pVDZ, aug-cc-pVTZ, and aug-cc-pVQZ as the correlation-consistent basis sets. We have carried out single-point energy calculations in the aqueous medium using the SMD solvation model for cyclopropane-1,2-dione (1) as a representative case to examine the method adopted in this study. The 6-31+G(d,p) Pople basis set employs 105 basis functions for 1, 134 basis functions for 1-W, and 163 basis functions for 1-W, whereas 6-311++G(d,p) uses 124 basis functions for 1, 160 basis functions for 1-W, and 196 basis functions for 1-W. On the other hand, aug-cc-pVDZ employs 133 basis functions for 1 and aug-cc-pVTZ employs 276 basis functions for 1. The aug-cc-pVQZ uses 492 basis functions for 1, 836 basis functions for 1-W, and 1524 basis functions for 1-W. The Dunning correlation-consistent basis sets have the advantage that they provide a consistent set of basis sets for extrapolating to the basis set limit; however, the number of basis functions increases rapidly from double $\zeta$ to quadruple $\zeta$ and hence the computational cost. The free energies calculated for cyclopropane-1,2-dione (1) with M062X-SMD$\textsubscript{aq}$/6-31+G(d,p) and MP2-SMD$\textsubscript{aq}$/6-31++G(d,p) in the aqueous phase are similar to those calculated with MP2-SMD$\textsubscript{aq}$/aug-cc-pVDZ, MP2-SMD$\textsubscript{aq}$/aug-cc-pVTZ, and MP2-SMD$\textsubscript{aq}$/aug-cc-pVQZ in the aqueous phase using the geometries optimized using the M062X/6-31+G(d,p) level of theory (Table S5).

The free energies in MP2-SMD$\textsubscript{aq}$/6-31++G(d,p), MP2-SMD$\textsubscript{aq}$/aug-cc-pVDZ, MP2-SMD$\textsubscript{aq}$/aug-cc-pVTZ, and MP2-SMD$\textsubscript{aq}$/aug-cc-pVQZ methods have been calculated using the following equation
\[
G_{aq} = E_{aq} + G_{\text{correction, gas}}
\]

where $G_{aq}$ is the aqueous phase free energy, $E_{aq}$ is the aqueous phase energy, and $G_{\text{correction, gas}}$ is the free energy correction value of the gas phase obtained at the M062X/6-31+G(d,p). The activation free energy barrier and reaction free energies have been calculated using eq 2.

To examine the influence of solvent on the geometry and energy, we have further performed the optimization of three-membered ring systems (1, 1-W, and 1-W) at the M062X-SMD$\textsubscript{aq}$/6-31+G(d,p) level of theory and compared the results with the those obtained from single-point aqueous phase calculations. The free energy values calculated from aqueous phase optimization are not significantly different (Table S5). The results of the M062X-SMD$\textsubscript{aq}$/6-31+G(d,p) level of theory show a similar trend as that calculated with the M062X-SMD$\textsubscript{aq}$/6-31+G(d,p) level of theory. The geometries obtained with M062X-SMD$\textsubscript{aq}$/6-31+G(d,p) for systems 1, 1-W, and 1-W are slightly varied from the gas phase optimized geometries (Figure S5). Furthermore, we have also extended the optimization of the four-membered ring in the aqueous phase with the M062X-SMD$\textsubscript{aq}$/6-31+G(d,p) level of theory, and the results are in line with the single-point calculated results (Figure S5 and Table S7). In this study, the free energies for the computed systems were reported with M062X-SMD$\textsubscript{aq}$/6-31+G(d,p)/M062X/6-31+G(d,p) and MP2-SMD$\textsubscript{aq}$/6-31++G(d,p)/M062X/6-31+G(d,p) levels of theory in the solvent phase (Table S1).

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.omega.8b01008

Cartesian coordinates optimized using the M062X/6-31+G(d,p) level of theory, the keto--enol tautomerization process assisted by two water molecules and corresponding free energy values, free energies calculated using MP2-SMD$\textsubscript{aq}$/6-31++G(d,p)//M062X/6-31+G(d,p) levels of theory, and NICS(1)zz values calculated using the M062X-SMD$\textsubscript{aq}$/6-31+G(d,p) level of theory (PDF)

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**Table S5.** Activation Free Energy Barriers and Reaction Free Energies Calculated at the Different Levels of Theory Using Geometries Optimized Using the M062X/6-31+G(d,p) Level of Theory Given in kcal/mol

| Method                          | $\Delta G^a$ | $\Delta G$ |
|--------------------------------|-------------|------------|
| M062X-SMD$\textsubscript{aq}$/6-31+G(d,p) | 1           | 54.9       |
| M062X-SMD$\textsubscript{aq}$/6-31+G(d,p) | 1-W         | 53.8       |
| M062X-SMD$\textsubscript{aq}$/6-31+G(d,p) | 2-W         | 53.6       |
| MP2-SMD$\textsubscript{aq}$/6-31++G(d,p) | 1           | 56.5       |
| MP2-SMD$\textsubscript{aq}$/6-31++G(d,p) | 1-W         | 54.6       |
| MP2-SMD$\textsubscript{aq}$/6-31++G(d,p) | 2-W         | 56.2       |
| MP2-SMD$\textsubscript{aq}$/aug-cc-pVTZ | 1           | 14.5       |
| MP2-SMD$\textsubscript{aq}$/aug-cc-pVTZ | 1-W         | 14.1       |
| MP2-SMD$\textsubscript{aq}$/aug-cc-pVTZ | 2-W         | 12.9       |
| MP2-SMD$\textsubscript{aq}$/aug-cc-pVQZ | 1           | 21.9       |
| MP2-SMD$\textsubscript{aq}$/aug-cc-pVQZ | 1-W         | 20.6       |
| MP2-SMD$\textsubscript{aq}$/aug-cc-pVQZ | 2-W         | 20.1       |

\textsuperscript{a}Free energy differences have been calculated using eqs 1 and 2, \textsuperscript{b}Optimization of 1, 1-W and 1-W has been carried out at the M062X-SMD$\textsubscript{aq}$/6-31+G(d,p) level of theory.
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