The strength of a low-barrier hydrogen bond in water

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Abstract—There are large differences between the acidity of the enol of the acyclic diketone, 2,4-pentanedione and those of two cyclic diketones, 1,3-cyclopentanedione and 1,3-cyclohexanedione. Computational studies have demonstrated that these differences are largely due to the strength of the internal low-barrier hydrogen bond (LBHB) in the enol of 2,4-pentanedione. It is thus estimated that the lower limit of the additional free energy of formation in water for this LBHB over that of a conventional hydrogen bond is 4.1–5.3 kcal mol^{-1}. © 2002 Elsevier Science Ltd. All rights reserved.

Low-barrier hydrogen bonds (LBHBs) and the possible important role played by them in accelerating enzymatic reactions have drawn significant research effort in the past several years.[1–14] This special kind of hydrogen bond is characterized by a reduced distance between donor and acceptor atoms (≤ 2.6 Å) as compared to an ordinary hydrogen bond; the barrier against proton transfer thus falls to approximately the zero-point energy of the hydrogen atom.[15] Another characteristic of LBHBs is a markedly downfield NMR chemical shift for the shared proton, which is typically 16–20 ppm.

LBHBs have large gas phase free energies of formation. The gas phase strength for the hydrogen bond in FHF$^-$ has been estimated to be about 37 kcal mol^{-1}.[15,16] However, LBHBs are much weaker in solution, especially in water, which can compete for hydrogen bonding. The hydrogen bond in the monoanion of maleic acid has been estimated to be 4–5 kcal mol^{-1} in DMSO and 1 kcal mol^{-1} in water or methanol stronger than a conventional hydrogen bond in corresponding solvents.[17] The LBHBs in monoanions of dicarboxylic acids have been characterized and estimated to be up to 4 kcal mol^{-1} stronger than conventional hydrogen bonds in aqueous solution.[18] The results agree reasonably well with the value predicted by theoretical calculations.[19] On the other hand, LBHBs have been postulated as crucial features in enzymatic mechanisms where rate accelerations require stabilization of transition states by 10–20 kcal mol^{-1}.

We have noticed the large differences between the acidity of the enol of the acyclic diketone 2,4-pentanedione (acetylacetone) and those of two cyclic diketones, 1,3-cyclopentanedione and 1,3-cyclohexanedione. Enolone **1** has an internal hydrogen bond, which is not available in enolones **2** and **3**. This hydrogen bond can be classified as a LBHB due to its short internuclear distance of 2.38–2.60 Å[20,21] and the downfield NMR chemical shift at 16 ppm.[22] In this report, we estimate the strength of this LBHB in water by comparing the acidity of enolones **1**, **2**, and **3**.
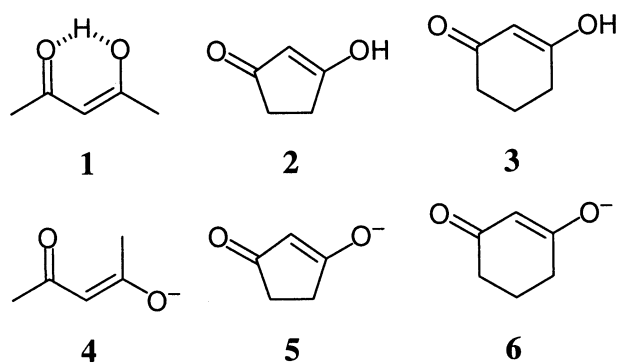
The differences in the acidities of the two types of enolones should be related to the strength of the hydrogen bond in enolone **1**, plus, perhaps, other factors. Other factors might include the distance between the negative oxygen atoms in the enolonate anions, departures from coplanarity in the conjugated π-electron systems of the enolones and enolonates, different changes in strain energy upon loss of the acidic proton, and, for reactions in solution, differential solvation of the conjugate acid and base forms.

Computational studies were carried out to determine the effects of some of these factors on the acidities of enolones **1**–**3**. Experimental gas phase data are available for the equilibrium between acetylacetone and its enol and for the acidity of the enol.[23] We find that at the MP2/6-31+G**//MP2/6-31+G* level the computed ΔH for the keto to enol conversion is −0.7 kcal mol^{−1}. Experimental values range from −2.4 to −4.7 kcal mol^{−1} and K_{eq} is reported to be 41, hence the enol is strongly favored in the gas phase. As found also by Dannenberg and Rios,[24] the use of diffuse functions on the hydrogens as well as the heavy atoms is necessary for computing the enolization reaction to be exothermic. At the same computational level we find the enthalpy of deprotonation, ΔH_{acid}, to be 343.2 kcal mol^{−1} for the enol, in agreement with the experimental value of 343.8±2.1 kcal mol^{−1}.[23] We conclude that this level is adequate for our purpose.[25]

Table 1 contains selected geometric features of compounds investigated in this study, optimized at MP2/6-31+G*. The short distance between the two oxygen atoms in enol **1** indicates a short, strong hydrogen bond involving the two oxygens and the intervening proton. The small dihedral between the two C–O bonds shows the overall planarity of the hydrogen-bonded enolone framework. These results as well as the C–C bonding distances (not shown) within the enolone moiety are in good agreement with the computational results of Dannenberg and Rios[24] and with experimental results of Iijima et al.[21] The C–O distances (not shown) are in excellent agreement with those of Dannenberg and Rios,[24] but slightly longer than those found by Iijima et al.[21,26]
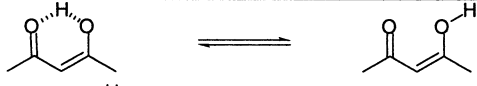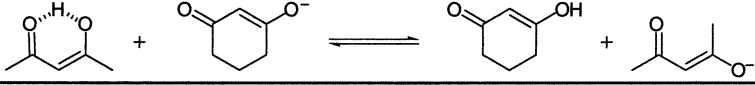
The O–O distances in structures listed in Table 1 are related to the presence or absence of repulsions between the two oxygens. The *syn*, planar conformer of enolate **4** has the oxygens much nearer one another than does the *anti* conformer (**4**) which is calculated to be 6.4 kcal mol^{−1} more stable at the MP2/6-31+G**//MP2/6-31+G* level. In both conformers the C2, C3, C4 angle is relatively large, perhaps to alleviate O–O repulsions. In enolone **2**, enolone **3**, and their enolonates **5** and **6** the O–O distances are longest of all with consequent minimization of electrostatic repulsion between the two oxygens.

The dihedral angles between the C–O moieties are very small in all enols and enolates. There appears to be no evidence that resonance stabilization of the enolone and enolonate species is compromised by lack of coplanarity, except in the transition state for interconversion of the enolate conformers of enol **1**.[28]

Table 2 shows three isomerizations taken from Dannenberg and Rios[24] and two homodesmotic reactions computed by us. Together they make the case that our level of computation is satisfactory for predicting the energetics of β-enolones and their enolates. Reaction (1) is Dannenberg and Rios' measure of the intramolecular hydrogen bonding strength for enol **1**, a conjugated enolone. Reaction (2) assays the stabilization contributed by resonance, but without hydrogen bonding. Reaction (3) provides a measure of intramolecular hydrogen bonding strength in an *unconjugated* enol. Dannenberg and Rios argue that the extra stabilization found for enol **1** is not simply due to conjugation but might be provided by a degree of aromaticity present in its cyclic six π-electron perimeter. Others have argued

Table 1. Selected geometric data of structures computed at MP2/6-31+G* (MP2/6-311+G**)

Structures	d, O···O (Å)	ω, O–C···C–O (°)
1	2.60 (2.55)	0.03 (0.01)
4	4.31 (4.31)	180.0 (180.0)
2	4.78	0.1
5	4.78	0.1
3	4.76	7.6
6	4.76	0.0

Table 2. Enthalpies of reaction for some isomerization and homodesmotic reactions relevant to the hydrogen-bonding strength in conjugated β-enolones

Number	Reaction	ΔH (kcal/mol)
1		12.0
2		5.0 (3.3)[a]
3		−6.0
4		14.5
5		11.5

[a] A computational correction for the different degree of substitution at the C=C unit lowers the resonance contribution to 3.3 kcal/mol.[21]

that this hydrogen bond is unusually strong because of 'resonance-assisted hydrogen bonding'.[29] Reactions (4) and (5) show that enolones **2** and **3** are more acidic than enolone **1** by an amount that is very close to the hydrogen bond strength in the latter as given by reaction (1). We conclude that it is therefore permissible to use the relative solution phase pK_a values of enolones **1–3** to estimate the strength of the internal hydrogen bond in a conjugated β-enolone.

However, it must be asked whether other factors contribute to the differences in the solution phase acidities of these enolones. Data in Table 1 show that there is no lack of planarity in the conjugated π-electron systems. Differential strain energy (increased angle strain) between the acid and base forms of enolone **1** could contribute to destabilization of the enolate, but similar (slightly smaller) increases in the C1, C2, C3 angle also occur upon deprotonation of enolones **2** and **3**. The O–O distances in the cyclic enolonates are larger than for enolate of enolone **1**. However simple electrostatic calculations show that this should not cause a significant difference, even in the gas phase.[30] Differences in the solvation of the conjugate acid and base forms could lead to differences in the acidities of internally H-bonded and non-H-bonded enolones. Enolone **1** is likely to be less well solvated, both in hydrogen-bonding donor and acceptor solvents, than enolones **2** and **3**.[31,32] This factor acts to stabilize the latter and *decrease* their acidities relative to that of enolone **1**. Since enolone **2** and enolone **3** are in fact *more* acidic than enolone **1**, the acidity differences provide a *lower limit* of the strength of the intramolecular LBHB in solution. Finally, it must be noted that the pK_a measurements in solution will lead to $\Delta\Delta G$ values, not $\Delta\Delta H$ values. Nevertheless, entropy contributions should not be critical since **1–3** *and* their enolates all have fixed, planar conformations.

We have determined the pK_a values of 2,4-pentanedione, 1,3-cyclopentanedione, and 1,3-cyclohexanedione in water to be 9.00, 5.23, and 4.34, respectively. The pK_a values were measured at 25°C via pH titration using a pH meter containing a glass electrode in an atmosphere of argon. The pK_a of 1,3-cyclopentanedione has not been measured previously and the pK_a values of the other two diketones are nearly identical with the values reported in the literature.[33] The two cyclic diketones exist in the enol form (enolones **2** and **3**) in water, however, 2,4-pentanedione exists mainly in the keto form with an equilibrium constant of 0.19.[27b,32] Therefore, the measured pK_a values for the cyclic ketones are those of enolones **2** and **3** while the pK_a for enolone **1** is calculated from the measured global pK_a and the equilibrium constant between the keto and enol forms to be 8.20, in excellent agreement with the reported value.[33]

The differences in the pK_a values of enolones **1** vs **2** or **1** vs **3** correspond to $\Delta\Delta G$ values of 4.1 and 5.3 kcal mol^{-1}, respectively. As discussed above, these values represent a conservative estimate of the additional free energy of formation in water for the LBHB in enolone

1 over that of a regular, external hydrogen bond. If the strengths of conventional hydrogen bonds are 4–8 kcal mol^{-1} in water, the overall strength of the LBHB in enolone **1** can be estimated to be at least 9–13 kcal mol^{-1}, in good agreement with the experimental and theoretical values of the LBHBs in the monoanions of dicarboxylic acids.[18,19] In a less polar environment, the strength of LBHB could be significantly higher than the values reported here and thus could be an important factor in enzymatic catalysis.

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26. The issue of the symmetric C_{2v} structure for enolone **1** was reconsidered by Dannenberg and Rios[24] who concluded that it probably does occupy the global minimum and that some stabilization (~ 6–8 kcal mol^{-1}) of the enol arises from aromaticity of its cyclic six π electron system. This interpretation receives support from the electron diffraction study of Lowrey et al. in which the two central C–C distances were found to be equal at 1.416 Å.[20] Other evidence, summarized in the review by Floris,[27] seems to favor the unsymmetrical structure. Our results show that at the MP2/6-311+G** level, with the inclusion of ZPVE corrections (calculated at the HF level), the symmetrical structure is 0.2 kcal mol^{-1} lower than the unsymmetrical structure, in agreement with the value reported by Dannenberg and Rios.[24] This structure is a proton transfer transition state having one imaginary frequency of 1688 cm^{-1}, calculated at HF/6-311+G**.

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28. The transition state for isomerization of the *anti* to the *syn* conformation of the enolate of **1** has one imaginary frequency (computed at HF/6-31+G*) of 165 cm^{-1}, corresponding to torsion about the C2–C3 bond. Its geometric parameters (computed at MP2/6-31+G*) are consistent with loss of resonance. For example, the torsional angle between the C–O moieties, ω, is 67.4° and the central C–C bonds have different lengths: 1.48 and 1.39 Å. The distance between the oxygens is closer to that of the less stable *syn* conformer in accord with Hammond's postulate. $\Delta H^{\ddagger}$ for this process (computed at MP2/6-31+G**// MP2/6-31+G*) is 19.1 kcal mol^{-1}. This value slightly overestimates the resonance stabilization energy of the *anti* enolate because the barrier occurs not at $\omega = 90°$ where the two halves of the π system are orthogonal, but closer to the *syn* state thus containing more than half of the destabilizing features of the latter. A crude estimate based on the percent progress of ω toward that of the *syn* conformer gives ca. 4 kcal mol^{-1} of *syn* destabilization, leaving about 15 kcal mol^{-1} for the resonance energy.

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30. For example: If we take 80% of the negative charge to be equally shared by the oxygens of the enolonate anions, and let the O–O interaction occur through a vacuum ($\varepsilon = 1$), the repulsion between the oxygens in enolate **4** is only 1.2 kcal mol^{-1} greater than in the cyclic enolonates using the O–O distances calculated by us (Table 1). Any reduction of charge, inequality in charge sharing, and (especially) solvation will reduce this difference.

31. It is well known that enolone **1** is less polar than 2,4-pentanedione itself, see: Emsley, J.; Freeman, N. J. *J. Mol. Struct.* **1987**, *161*, 193–204.

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