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THE ENOL OF ACETOACETIC ACID: A COMPUTATIONAL STUDY OF THE RELATIVE STABILITIES OF THE KETONE AND CARBOXYLIC ACID ISOMERS

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Ab initio **molecular orbital calculations at the MP2/6–311+G**//MP2/6–311+G** level show that the enol tautomer of acetoacetic acid in which the ketone group is enolized, 2, is more stable than its isomer in which the carboxylic acid group is enolized, 3, by 11·3 kcal mol^{-1}. This difference may be attributed to a difference in the strength of resonance interactions between the carbonyl and hydroxyl groups of the enols: the carbonyl group in both isomers is conjugated with two hydroxyl groups, but in the acid enol, 3, both interactions are vinylogous, whereas in the ketone enol, 2, one of the vinylogous effects is replaced by a stronger direct interaction. © 1997 by John Wiley & Sons, Ltd.**

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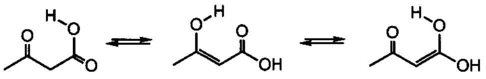
INTRODUCTION

Acetoacetic acid, **1**, has two different enolizable functional groups, and it therefore can, at least in principle, form two different kinds of enols, an enol of its ketone group, **2**, and an enol of its carboxylic acid group **3** [equation (1)]. The ketone enol (**2**) might, at first thought, be expected to be the much more stable isomer and the overwhelmingly predominant form in solution, inasmuch as keto–enol equilibrium constants for simple ketones, although small, are nevertheless very much greater than those for simple carboxylic acids, e.g. pK_E=8·33 for the enolization of acetone[1] [equation (2)] versus the estimate pK_E=20 for the enolization of acetic acid [equation (3)].[2]


(2)

Such an analogy, however, may not be entirely appropriate, because there is an important difference between the acetoacetic acid and acetic acid systems. The keto–enol equilibrium constant of acetic acid is as small as it is largely because the carboxylic acid group resonance interaction between its carbonyl and hydroxyl groups is lost upon enol formation, and the energy difference between its keto and enol forms is consequently correspondingly large. A similar effect is, of course, absent from the acetone system. Direct carboxylic acid group resonance is also lost upon formation of the carboxylic acid enol of acetoacetic acid, but that is now replaced by a vinylogous resonance interaction between carbonyl and hydroxyl groups through the newly formed enol double bond. The energy gained by this new interaction will offset that lost by removal of the carboxylic acid group, and the relative abundances of the two enols of acetoacetic acid may well be not as disparate as suggested by the difference between the keto–enol equilibrium constants for acetone and acetic acid.


1 **2** **3** (1)

It is difficult to address this issue experimentally because less than 1% of enol is in equilibrium with the keto form of


(3)

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acetoacetic acid in aqueous solution at 25 °C, and the lifetime of the enol is at best only a few seconds.[3] We have therefore turned to theory and have estimated the energies of the relevant species by *ab initio* molecular orbital calculation. In order to provide a comparison of acetoacetic acid with acetone and acetic acid, we have performed calculations on those systems as well.

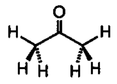
METHODS

Calculations were performed with the Gaussian-94 set of programs[4] using a 6–311 + G** basis set. Correlation effects were included at the second-order Møller–Plesset level and all geometries were fully optimized subject only to the restrictions indicated. Total and relative energies of the species calculated are summarized in Table 1, and geometrical parameters are available from the authors upon request. Energy minima for all non-constrained structures were confirmed by frequency analysis.

RESULTS AND DISCUSSION

Acetone and acetic acid

Our calculations indicate that the most stable structures of both acetone and acetic acid are the conformers shown as **4** and **5**, in which the carbonyl group is nearly eclipsed by adjacent C–H bonds; this is consistent with previous calculations and with experiment.[5] We also found the coplanar, *s-cis* orientation of the carbonyl and hydroxyl groups in acetic acid shown in **5** to be more stable than a coplanar, *s-trans* structure by 6·0 kcal mol^{-1} (1 kcal = 4·184 kJ), which agrees well with the 5·9 kcal mol^{-1} difference calculated before.[6] Rotating the hydroxyl group of acetic acid by 90° to give the perpendicular conformation, **6**, raised the energy by 14·3 kcal mol^{-1}, consistent with the 12·6 kcal mol^{-1} found before[6] and also with the 13–14 kcal mol^{-1} estimate of the resonance energy of acetic acid.[7]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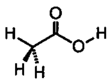
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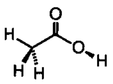
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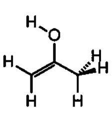
The most stable structure for the enol of acetone given by our calculations is that shown as **7** with an *s-cis* orientation about the C–O bond and a methyl group C–H bond eclipsing the double bond; this agrees with the results of calculations for this enol done before[8] and with the experimentally determined propensity of simple enols to adopt the *s-cis* conformation when there is no interference from groups at the other end of the double bond.[9] This enol lies 13·2 kcal mol^{-1} in energy above that of the keto form, which again is consistent with previous calculations[8a] and also with $\Delta H = 12 \pm 2$ kcal mol^{-1} for the keto–enol reaction in the gas phase that may be estimated[10] from two different determinations of the heat of formation of the enol.[11] This gas-phase value is also similar to $\Delta H = 10{\cdot}3 \pm 0{\cdot}4$ kcal mol^{-1} determined for this reaction in aqueous solution.[10] Rotating the hydroxyl group of acetone enol by 90° to give the perpendicular conformer, **8**, raised the energy by 5·3 kcal mol^{-1}; this is similar to the double bond stabilization energy of $D(=\Delta H) = 5{\cdot}4 \pm 0{\cdot}5$ kcal mol^{-1} estimated for the hydroxyl group,[12] which implies that this stabilization is largely conjugative in nature.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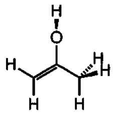
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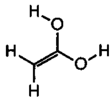
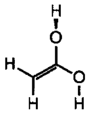

9

The most stable structure for the enol of acetic acid produced by our calculations is the completely planar conformer shown as **9**, with one *s-cis* and one *s-trans* orientation about its C–O bonds. Another planar conformer with both C–O bonds *s-cis* lies just 1·0 kcal mol^{-1} above **9** and the all *s-trans* conformer lies 0·9 kcal mol^{-1} above that; the latter, however, is no longer planar but has a dihedral angle of 135° between its O–H bonds. The energy difference between the keto form of acetic acid and its most stable enol isomer is 30·1 kcal mol^{-1}, which is not unlike the 27·3 kcal mol^{-1} that corresponds to the estimate $pK_E = 20$.[2] Rotating one hydroxyl group of the most stable enol conformer by 90° to give a perpendicular structure with the remaining in-plane C–O bond in an *s-cis* orientation, **10**, raises the energy by 4·3 kcal mol^{-1}, which is less than the effect produced by a similar rotation in the case of the enol of acetone. Rotating the remaining hydroxyl group by 90° can be done in two different ways, either to give a conformer with the hydroxyls pointing in opposite directions, **11**, that is 2·8 kcal mol^{-1} above **10**, or to give a conformer with the hydroxyls pointing in the same direction, **12**, that is 4·1 kcal mol^{-1} above **10**.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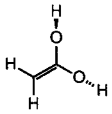
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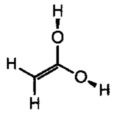
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Acetoacetic acid

The minimum energy structure of acetoacetic acid determined by our calculations is that shown as **13**, with the carbonyl group eclipsed by a C–H bond of the methyl group and an *s-trans* arrangement of the carbonyl and hydroxyl moieties of the carboxyl group. Such an *s-trans* arrangement is usually unfavorable, as is illustrated above for acetic acid, but here it is enforced by the formation of a stabilizing intramolecular hydrogen bond. The most stable structure of the ketone enol, **14**, also contains an intramolecular hydrogen bond, but now the carboxyl group is free to adopt the favorable *s-cis* arrangement; the *s-trans* structure is higher in energy by 5·2 kcal mol^{-1}, a difference similar to

Table 1. Calculated (MP2/6–311 + G**//MP2/6–311 + G**) energies of keto and enol species

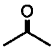
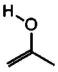
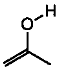
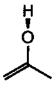
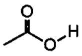
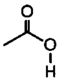
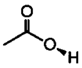
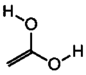
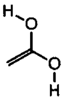
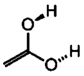
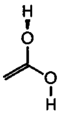
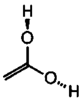
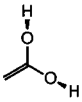
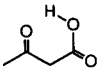
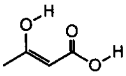
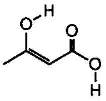
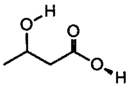
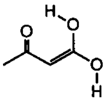
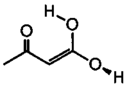
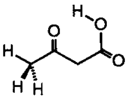
Species	Relative energy (kcal mol^{-1})	Total energy (au)
Acetone system		
	0·0	− 192·65530
	13·2	− 192·63426
	15·4	− 192·63073
	18·5	− 192·62584
Acetic acid system		
	0·0	− 228·56798
	6·0	− 228·55836
	14·3	− 228·54519
	30·1	− 228·51994
	31·1	− 228·51831
	32·0	− 228·51631
	34·4	− 228·51321
	37·2	− 228·50804
	38·5	− 228·50592

Table 1. Continued.

Acetoacetic acid system		
	0·0	− 380·84246
	− 2·2	− 380·84604
	3·0	− 380·83767
	9·8	− 380·82691
	9·0	− 380·82805
	14·9	− 380·81869

that found between the *s-cis* and *s-trans* structures of acetic acid. The only stable structure of the acid enol retaining an intramolecular hydrogen bond is that shown as **15** with an *s-cis* orientation of both its hydroxyl groups. The *s-cis*, *s-trans* structure, **16**, proved not to be an energy minimum: calculations beginning with this configuration resulted in a barrierless movement of the proton down the hydrogen bond, from the hydroxyl oxygen to the carbonyl oxygen, to give the ketone enol **14**.



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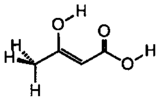

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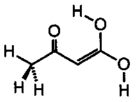

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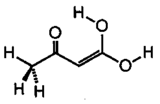

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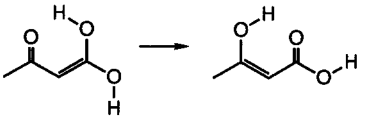
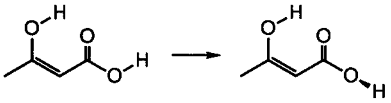


15 **14**

(4)

Our calculations show the ketone enol to be the decidedly more stable enol species: the energy change for the reaction converting the acid enol to the most stable ketone enol [equation (4)] is $\Delta E = -11{\cdot}3$ kcal mol^{-1}. This is a potential energy difference that applies to motionless molecules at 0 K, but it is likely that zero-point energies, heat capacities and entropies will be similar for species as alike as these two enols and that the free energy change at 25 °C will consequently be not very different from this value of ΔE. It seems safe to conclude, therefore, that the ketone enol will be the strongly dominant enol tautomer of acetoacetic acid.

Some insight into the source of this dominance may be gained by considering the interactions between the carbonyl and hydroxyl groups of the two enols involved in equation (4). The carbonyl group in both species is conjugated with two hydroxyl groups, but in the acid enol, **15**, both interactions are vinylogous through an intervening carbon–carbon double bond, whereas in the ketone enol, **14**, there is a direct interaction between adjacent carbonyl and hydroxyl groups in addition to a vinylogous interaction. The direct interaction appears to be stronger than a vinylogous one. This may be seen by comparing the energy change, $\Delta E = 12{\cdot}0$ kcal mol^{-1}, that accompanies 90° rotation of the non-hydrogen bonding hydroxyl group of the ketone enol



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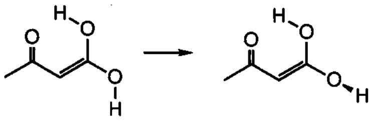

(6)

[equation (5)], which destroys the conjugative interaction, with the energy change, $\Delta E = 5{\cdot}9\ \text{kcal mol}^{-1}$, for the corresponding rotation in the acid enol [equation (6)].

Our calculations show the ketone enol, **14**, to be more stable than the keto form of acetoacetic acid by 2·2 kcal mol^{-1}. This may seem to be inconsistent with experiment, for a recent determination gives $pK_E = 2{\cdot}25$ for acetoacetic acid,[3] which corresponds to an energy difference of 3·1 kcal mol^{-1} in the opposite direction. Keto–enol equilibrium constants for β-dicarbonyl systems, however, are sensitive to the polarity of the medium, and values several orders of magnitude smaller in water than in the gas phase and non-polar solvents are not uncommon.[13] Since the experimental value $pK_E = 2{\cdot}25$ was determined in aqueous solution whereas the present calculations pertain to the gas phase, there would appear to be no great discrepancy between experiment and calculation. This conclusion is supported by the fact that our calculations show the dipole moment of the keto isomer, 5·98 D, to be considerably greater than that of the enol, 2·16 D, and the keto isomer would consequently be expected to be preferentially stabilized by transfer of the system from the gas phase to a polar solvent. In fact, an estimate of this effect made by the reaction field method with the Onsager model[14] using a dielectric constant of 78 does reverse the stability order, making the keto isomer favored by 2·0 kcal mol^{-1}.

ACKNOWLEDGEMENTS

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