Association and Tautomeric Equilibrium in β-Keto Acids

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Examination of the concentration dependence of n.m.r. spectra of 3-oxo-3-phenylpropanoic acid and related compounds demonstrates that the tautomeric equilibrium constant in β-keto acids is dependent upon the state of association.

β-Keto acids are important synthetic and biochemical intermediates and yet there is little available information regarding their solution phase structure.[1] Examination of the effects of structure,[2] solvent,[3,4] and concentration on the keto–enol tautomeric equilibrium has only recently begun and the literature is still devoid of a detailed description of their state of association in solution.† We now report preliminary results, bearing on the state of association of β-keto acids and on the relationship between association and tautomeric equilibrium, that demonstrate that these compounds are unusual tautomeric systems for which adequate models do not exist.

The % enol (by ^{1}H n.m.r. spectroscopy) in solutions of benzoylacetic (3-oxo-3-phenylpropanoic) acid (**1**)‡ follows a solvent dependence completely analogous to that observed for acetoacetic (3-oxobutanoic) acid.[4] Specifically, the % enol decreases with increasing solvent polarity [C_6D_6, 36.9 ± 0.5%; $CDCl_3$, 23.6 ± 1.4%; $(CD_3)_2SO$, 14.3 ± 1.4%]§ as expected if the keto form is the more polar of the two tautomers. Substitution of a methyl or ethyl group at the 2-position¶ of (**1**) lowered the % enol beyond our limits of detection even in C_6D_6. For concentrations from 0.03 to 0.37 M in $(CD_3)_2SO$, the tautomeric equilibrium constant of (**1**) is invariant within experimental error. Surprisingly, the equilibrium in $CDCl_3$ shows a striking concentration dependence (Figure 1) with % enol *increasing* at higher concentrations despite expectations that the polarity of the medium rises as more of the polar substrate is added.

Examination of ^{1}H n.m.r. chemical shifts provides some insight. The enol hydroxy proton in (**1**) has a chemical shift consistent with the existence of a strong intramolecular hydrogen bond[4] over the entire range of concentrations studied.‖ This resonance exhibits a small but highly reproducible concentration dependent shift change (Figure 1) consistent with weakening of the intramolecular hydrogen bond[8] with increasing substrate concentration. Acetoacetic and *p*-fluorobenzoylacetic acid behave in an analogous fashion. This concentration dependence closely parallels that for the % enol, suggesting a similar origin for both phenomena. The % enol is also enhanced by addition of acetic acid to 0.02 M solutions of (**1**) in $CDCl_3$ which produces a smooth increase in % enol up to a maximum of *ca.* 30% at a total acid concentration of 1.0 M. We ascribe all of the above observations to an increase in association with increasing substrate (or total acid) concentration. Curve shapes in Figure 1 suggest that the amount of association approaches zero at *ca.* 0.01 M and 100% at *ca.* 0.12 M concentrations.

Proton decoupled 75 MHz ^{13}C n.m.r. spectra of $CDCl_3$ solutions of (**1**) show individual peaks for every carbon of each tautomer. Peaks at δ 176.3 and 169.8 (0.03 M solution), assigned by shift analogy[4,9] to the enol and keto carboxy carbons respectively, are shifted downfield with increasing substrate concentration (Table 1), consistent with an increase in association at higher concentration. A peak (δ 173.8) assigned to the hydroxy-bearing vinyl carbon of the enol exhibits a smaller downfield shift with increasing concentration while the carbonyl carbon of the keto tautomer is shifted upfield. The shift variation for the carboxy carbons is fully consistent in both direction and magnitude with the analogous changes due to dimeric association of acetic acid in $CDCl_3$ solutions, which occurs in a similar range of concentrations.[10] The behaviour of the carbonyl carbon of the keto tautomer is strongly suggestive of hydrogen-bonding at the carbonyl at low concentrations and this is almost certainly caused by intramolecular hydrogen-bonding which becomes important at concentrations where dimeric association is unimportant. This latter point is particularly interesting with regard to the intramolecular catalysis of enolization in β-keto acids,[11,12] suggesting a possible solvent and concentration dependence for that pathway.

$PhCOCH_2CO_2H$
(**1**)

Finally, ^{1}H n.m.r. spectra of (**1**) in $CDCl_3$ at −50 °C, using fresh samples prepared (less than three minutes prior to observation) at this temperature, show greatly enhanced enol populations (maximum observed 77% enol). Since the observed % enol under these conditions is much higher than it is at equilibrium at this temperature, this apparently represents a pre-equilibrium condition and suggests that (**1**) exists as its enol tautomer in the solid state. In this regard i.r. spectra (KBr

Table 1. ^{13}C chemical shifts (δ values) for benzoylacetic acid in $CDCl_3$ *vs.* Me_4Si.

Shift		Assignment
0.03 M	0.12 M	
169.8	171.5	keto carboxy
173.8	173.9	enol vinyl
176.3	177.0	enol carboxy
194.6	193.7	keto carbonyl

† For previous evidence of association see note 15 of ref. 3.

‡ Ethyl benzoylacetate (Aldrich) was hydrolysed according to the procedure of Swain *et al.*[5] and the product was recrystallized from benzene and dried under vacuum before use: m.p. 99.5—100.5 °C (lit.[5] 99.5—100 °C).

§ These values represent the average of determinations on eight to twelve samples (0.030 M), with error limits calculated at a 95% confidence interval. All % enol values in this communication were established by integration of appropriate n.m.r. peaks.

¶ 2-Methylbenzoylacetic acid (m.p. 79—80 °C) and 2-ethylbenzoylacetic acid (m.p. 82—83 °C) were prepared *via* the known esters[6] and gave i.r., n.m.r., and high resolution mass spectral data fully consistent with expectations.

‖ The enol hydroxy proton in (**1**) appears as a sharp peak indicating that chemical exchange is slow on the n.m.r. time scale under the experimental conditions. In contrast, the carboxy proton resonance is severely broadened and could not be located unambiguously except at very high substrate concentrations. It is not surprising that enol hydroxy and carboxy proton resonances appear as separate peaks since Reeves[7] has reported similar results for solutions of β-diketones and acetic acid.

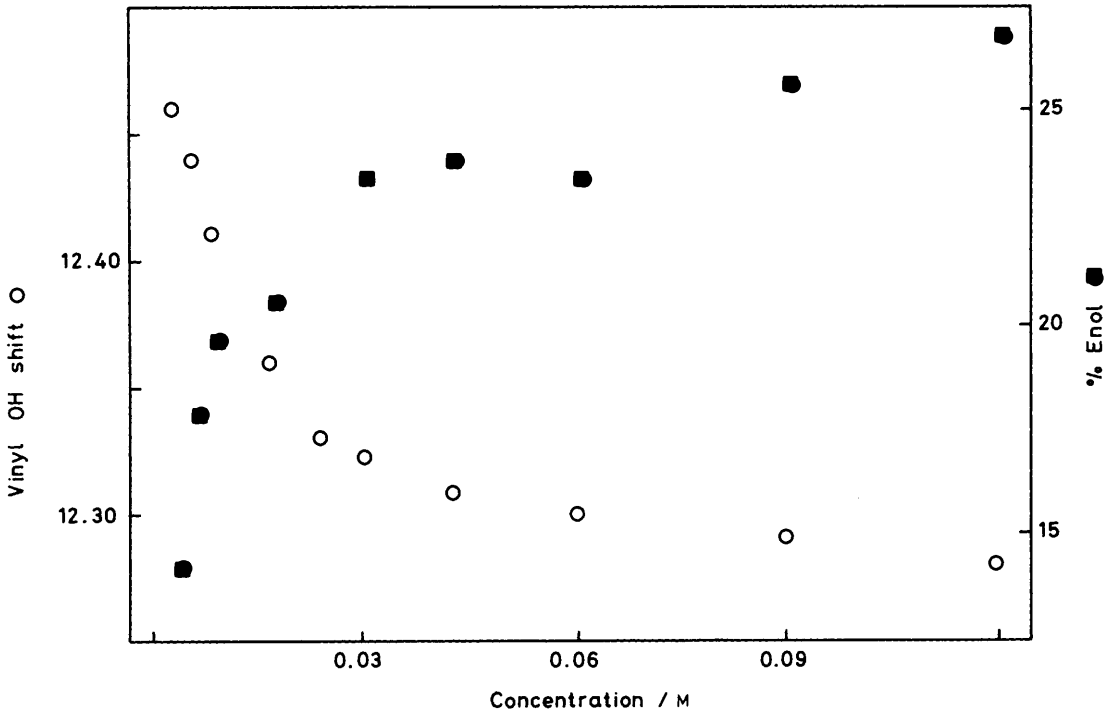

Figure 1. Enol vinyl hydroxy proton shift (open circles) and % enol *vs.* concentration of benzoylacetic acid in $CDCl_3$.

pellet) demonstrate that (**1**) and *p*-fluorobenzoylacetic acid are enolic in the solid state while benzoylacetic acids with methyl or ethyl groups at the 2-position are ketonic.

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