Rates and Equilibria of Keto–Enol and –Enolate Ion Interconversion in the 2,4,6-Trimethylacetophenone System. Reinvestigation of the Unusual Bromination Reaction

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The bromination of 2,4,6-trimethylacetophenone, whose unusual kinetics were once thought to be the result of slow, sterically hindered addition of bromine to the enol, was found to be a ring- rather than a side-chain-substitution reaction; kinetic and thermodynamic characteristics of this keto–enol system were determined by a combination of flash-photolytic and conventional kinetic techniques and were found to be little different from those of the parent (unsubstituted) acetophenone keto–enol system.

The conventional reaction mechanism for acid-catalysed halogenation of simple aldehydes and ketones consists of rate-determining formation of the enol isomer followed by rapid reaction of the latter with halogen (Scheme 1).[1] Such a mechanism requires the rate of reaction to be independent of halogen concentration, and this has in fact been found to be generally so, except at very low halogen concentrations. Quite recently, however, it was reported[2] that the bromination of 2,4,6-trimethylacetophenone in 50% aqueous acetic acid solution is first order in bromine at concentrations many orders of magnitude greater than those required to make the rate of bromination of acetophenone itself depend on bromine concentration,[3] and it was consequently proposed that steric hindrance by the *ortho* methyl groups of 2,4,6-trimethylacetophenone retards the normally very rapid addition of bromine to the carbon–carbon double bond of the enol sufficiently strongly to make that step rate-determining.[2] This is an interesting proposition, in as much as Fuson, in his classic studies of stable enols some 40 years ago, demonstrated that bulky substituents such as 2,4,6-trimethylphenyl (mesityl) can stabilize enols enough to permit their ready isolation,[4] and recent work has shown that mesityl groups confer thermodynamic stability on enols as well.[5] It would seem from this research on stable enols, however, that at least two bulky groups are required to produce much of an effect. In order to investigate this matter directly we have determined the kinetic and thermodynamic stability of 2,4,6-trimethylacetophenone enol and, in the course of doing so, have discovered that the original interpretation of the reaction of this ketone with bromine is incorrect.

We characterized the 2,4,6-trimethylacetophenone keto–enol system in wholly aqueous solution using methods we have employed for acetophenone[6] and other simple carbonyl compounds;[7] this involved measuring rates of ketonization of the enol and enolization of the ketone. Rates of ketonization were measured flash photolytically by generating the enol through photohydration of the corresponding acetylene, [equation (1)][8] or photosolvolysis of the vinyl chloride, [equation (2)];[9] the two methods gave identical kinetic results. Measurements in dilute perchloric acid solutions produced the rate constant $k^{\mathrm{K}}_{\mathrm{H^+}} = (1.09 \pm 0.01) \times 10^{2}\ \mathrm{mol^{-1}\ dm^{3}\ s^{-1}}$† for ketonization through reaction of the enol with hydronium ion, and measurements in dilute sodium hydroxide solutions gave $k'_0 = (5.36 \pm 0.15) \times 10^{3}\ \mathrm{s^{-1}}$† for ketonization through reaction of the enolate ion with water. The alkaline solution measurements also led to the acidity constant $\mathrm{p}K^{\mathrm{E}}_{\mathrm{a}} = 10.69 \pm 0.02$,†‡ for the enol ionizing as an oxygen acid.

We could not determine rates of enolization of 2,4,6-trimethylacetophenone in aqueous acid solution by bromine scavenging methods because here, just as in 50% aqueous acetic acid,[2] the bromination reaction was first order in bromine. It was also first order in ketone and zero order in acid and gave the bimolecular rate constant $k = 9.35 \pm 0.33\ \mathrm{mol^{-1}\ dm^{3}\ s^{-1}}$.† We could, however, use iodine as an enol scavenger, for the reaction of ketone with iodine was independent of iodine concentration and first order both in ketone and in acid. Measurements of iodination rates in dilute mineral acid gave $k^{\mathrm{E}}_{\mathrm{H^+}} = (1.30 \pm 0.06) \times 10^{-5}\ \mathrm{mol^{-1}\ dm^{3}\ s^{-1}}$,† which, when combined with the corresponding ketonization rate constant, provided the keto–enol equilibrium constant K^{E} $(= k^{\mathrm{E}}_{\mathrm{H^+}}/k^{\mathrm{K}}_{\mathrm{H^+}}) = (1.20 \pm 0.05) \times 10^{-7}, \mathrm{p}K^{\mathrm{E}} = 6.92 \pm 0.02$.†‡

In order to confirm that iodination was indeed occurring *via* rate-determining formation of the enol, we also determined rates of hydroxide-ion catalysed detritiation of 2,4,6-trimethylacetophenone isotopically labelled in the side-chain methyl group; this gave $k^{\mathrm{T}}_{\mathrm{HO^-}} = (2.65 \pm 0.06) \times 10^{-2}\ \mathrm{mol^{-1}\ dm^{3}\ s^{-1}}$.† This result, when combined with the hydroxide-ion catalysed enolization rate constant, $k^{\mathrm{E}}_{\mathrm{HO^-}} = (8.25 \pm 0.41) \times 10^{-1}\ \mathrm{mol^{-1}\ dm^{3}\ s^{-1}}$,† which can be calculated from the above keto–enol equilibrium constant and the rate data for ketonization in basic solution, gives the isotope effect $k_{\mathrm{H}}/k_{\mathrm{T}} = 10.4 \pm 0{\cdot}6$. This is similar to tritium isotope effects measured for hydroxide-ion catalysed enolization of other ring-substituted acetophenones,[10] and that reinforces our conclusion that measurements of the rate of iodination are in fact providing rates of enolization.

Iodine is larger than bromine, and any steric hindrance slowing the addition of bromine to the carbon–carbon double bond of 2,4,6-trimethylacetophenone enol should be present to an even greater extent in the addition of iodine. If this slowing is sufficient to make bromine addition rate-determining, it should certainly be sufficient to make iodine addition rate-determining as well. And yet, this is not the case. We resolved this apparent paradox by examining the product of the bromination reaction and found it to be entirely the ring-brominated material, 3-bromo-2,4,6-trimethylacetophenone,[11] for reaction in aqueous solution and 85% ring-brominated product plus 15% side-chain brominated material, ω-bromo-2,4,6-trimethylacetophenone,[12] for reaction in 50% aqueous acetic acid.§¶ This predominance of ring

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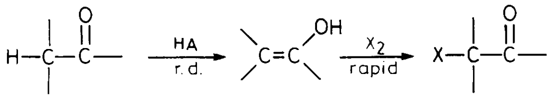
† Aqueous solution, 25 °C, ionic strength = 0.10 M.

‡ Concentration dissociation constant appropriate to ionic strength = 0.10 M.

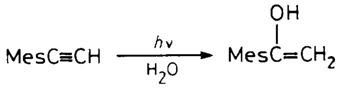
§ Initial concentrations were [ketone] = $[\mathrm{Br_2}]$ = 0.009 M for the reaction in water and [ketone] = 0.009 M and $[\mathrm{Br_2}]$ = 0.0005 M for the reaction in 50% aqueous acetic acid; 0.10 M HBr was also present in both reaction mixtures. Products were identified by comparison of proton n.m.r. spectra with those of authentic independently prepared samples, and quantitative analysis was performed by gas chromatography.

¶ Pinkus and Logaraj[13] now also find ring bromination to be the principal reaction in 50% aqueous acetic acid.

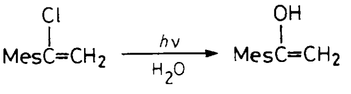


(r.d. = rate determining; X = halogen)

Scheme 1



$$\mathrm{MesC{\equiv}CH} \xrightarrow[\mathrm{H_2O}]{h\nu} \mathrm{MesC(OH){=}CH_2} \quad (1)$$



$$\mathrm{MesC(Cl){=}CH_2} \xrightarrow[\mathrm{H_2O}]{h\nu} \mathrm{MesC(OH){=}CH_2} \quad (2)$$

Table 1. Comparison of acetophenone and 2,4,6-trimethylacetophenone keto–enol systems

Parameter	Acetophenone[a]	2,4,6-Trimethyl-acetophenone
pK^{E}	7.96	6.92
pK_a^{E}	10.34	10.69
pK_a^{K}	18.31	17.61
$k_{H^+}^{E}/10^{-5}\,mol^{-1}\,dm^3\,s^{-1}$	1.21	1.30
$k_{H^+}^{K}/10^{3}\,mol^{-1}\,dm^3\,s^{-1}$	1.25	0.109

[a] Reference 6.

over side-chain bromination is consistent with the great accelerating effect of methyl groups on electrophilic aromatic bromination (mesitylene is 2 × 10^8 times more reactive than benzene),[14] and the lack of ring iodination is consistent with the known slowness and reversibility of aromatic iodination.[15]

Comparison of the results obtained here with those for acetophenone (Table 1) shows that introduction of *ortho* and *para* methyl groups does not change the characteristics of the keto–enol system very much. The largest differences are a factor of ten greater keto–enol equilibrium constant and a similar factor of ten slower rate of ketonization for 2,4,6-trimethylacetophenone. Rates of enolization of the two ketones are virtually the same, and enol acidity constants differ by only a factor of two and ketone acidity constants, by only a factor of five.

We are grateful to Professor A. G. Pinkus for communicating his recent results to us and to the Natural Sciences and Engineering Research Council of Canada and the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.

Received, 14th March 1989; Com. 9/01116A

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