# Inter- and Intra-molecular Catalysis in the Enolization of Derivatives of 2′-Carboxyacetophenone

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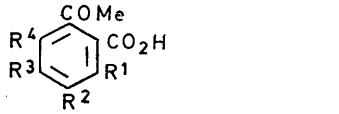
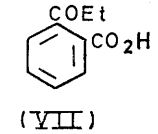
Kinetic results are reported for the rates of enolization of ten derivatives of 2′-carboxyacetophenone, as measured by their rates of iodination or detritiation. Rates of intramolecular proton transfer in the anions of these compounds can be measured throughout, as well as transfer to hydroxide ions, and in some instances intermolecular catalysis by added pyridine or acetate ions can also be detected. The efficiency of the intramolecular process is considerably affected by substituents, and the major effects appear to be steric ones. The equilibrium proportion of cyclic lactol isomer in aqueous solutions of these compounds was determined by combining conventional p*K* values with the catalytic effect of their anions in the decomposition of nitramide, and there is an inverse relation between the proportion of cyclic isomer and the efficiency of the intramolecular proton transfer. Kinetic isotope effects are reported for several intra- and inter-molecular processes, and these also are sensitive to geometrical factors.

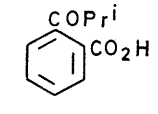
It has been previously shown[1] that the iodination of 2′-carboxyacetophenone in aqueous solution is of zero order with respect to iodine, showing that the rate-determining step involves the ionization or enolization of the ketone, followed by rapid reaction with iodine. The reaction is catalysed by added bases, but there is also a considerable 'spontaneous' rate, which is proportional to the concentration of the ketocarboxylate anion, and which was attributed to intramolecular proton abstraction by the basic carboxylate group. The present paper reports a similar study of the iodination of nine derivatives of 2′-carboxyacetophenone, mostly with ring substituents, and rates of detritiation were measured for seven of these. Detritiation experiments were also carried out with four related acetophenones not containing carboxy-groups.



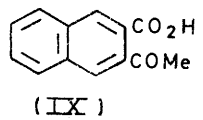
(I) $R^1$-$R^4$ = H
(II) $R^1$ = Me, $R^2$-$R^4$ = H
(III) $R^1$-$R^3$ = H, $R^4$ = Me
(IV) $R^1$ = $R^4$ = H, $R^2$ = $R^3$ = Me
(V) $R^1$ = $R^4$ = H, $R^2$ = $R^3$ = OMe
(VI) $R^1$-$R^4$ = Cl



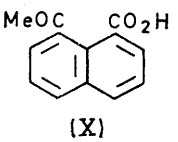
(VII)



(VIII)



(IX)



(X)

The work also included measurements of the dissociation constants of the keto-acids and of the catalytic effect of their anions in the decomposition of nitramide and the mutarotation of glucose. As demonstrated previously [1-3] the results of these last measurements can be used to determine the equilibrium proportion of the cyclic tautomers present in solution.

## EXPERIMENTAL AND RESULTS

*Materials.*—The keto-acids (I)—(X) were investigated. 2′-Carboxyacetophenone (I) was a pure commercial specimen. The remaining compounds were prepared from the appropriately substituted phthalic anhydride, usually by reaction with alkylcadmium, though for (III) the anhydride was heated with malonic acid and pyridine: for (IX) both procedures were used.

For the preparation of (II), 3-methyl-1,2,3,6-tetrahydrophthalic anhydride was prepared as described by Newman and McCleary [4] and dehydrogenated by heating with sulphur. The final product (II) had m.p. 127.5—128.5° (lit. 122—124; [5] 126—127° [6]) after recrystallizing twice from benzene–pentane and twice from water. 3-Nitrophthalic anhydride was converted to (III) by the procedure described by Yale.[7] The final product had m.p. 163—164° (lit. 159—161; [7] 159—160; [8] 164—165° [9]) after recrystallizing from benzene and water.

Compounds (IV) and (V) have not been previously reported. For (IV), 2,3-dimethylbuta-1,3-diene was prepared from pinacol, and converted to 4,5-dimethyl-*cis*-1,2,3,6-tetrahydrophthalic anhydride by a Diels–Alder reaction with maleic anhydride.[8,9] The Diels–Alder adduct was dehydrogenated by heating with sulphur to 250—260° for 30 min, and the resulting 4,5-dimethylphthalic anhydride recrystallized from benzene and sublimed (yield 66% based on the adduct). The anhydride was converted to (IV) by reaction with methylcadmium (6 h reflux in benzene solution). After recrystallizing twice from benzene, once from ethanol–water, and once from benzene it had m.p. 148—148.5° (Found: C, 68.95; H, 6.4. $C_{11}H_{12}O_3$ requires C, 68.75; H, 6.25%), (yield 37% based on 4,5-dimethylphthalic anhydride).

Compound (V) was obtained by the reaction of methylcadmium with 4,5-dimethoxyphthalic anhydride. The latter compound was prepared by published methods,[10,11] m.p. 181—185° (lit.,[11] 175—177°), and used without further

[1] R. P. Bell, B. G. Cox, and J. B. Henshall, *J.C.S. Perkin II*, 1972, 1232.
[2] R. P. Bell, B. G. Cox, and B. A. Timimi, *J. Chem. Soc.* (*B*), 1971, 2247.
[3] R. P. Bell and A. D. Covington, *J.C.S. Perkin II*, 1975, 1343.
[4] M. S. Newman and C. D. McCleary, *J. Amer. Chem. Soc.*, 1941, **63**, 1542.
[5] P. R. Jones and P. J. Desio, *J. Org. Chem.*, 1965, **30**, 4293.
[6] M. S. Newman and A. L. Leegwater, *J. Amer. Chem. Soc.*, 1968, **90**, 4410.
[7] H. L. Yale, *J. Amer. Chem. Soc.*, 1947, **69**, 1547.
[8] C. F. H. Allen and A. Bell, 'Organic Syntheses,' Wiley, New York, 1955, Coll. Vol. 3, p. 312.
[9] E. H. Farmer and F. L. Warren, *J. Chem. Soc.*, 1929, 897.
[10] G. A. Edwards, W. H. Perkin, jun., and F. W. Stoyle, *J. Chem. Soc.*, 1925, 195.
[11] T. Ikeda, S. Kanahara, and T. Ujiie, *Kanazawa Daigaku Yakagakubu Kenkyu Nempô*, 1958, **8**, 1 (*Chem. Abs.*, 1959, **53**, 4287i).

purification. When working up the product from the reaction with methylcadmium, no precipitate was obtained on final acidification, but the ether extract of the acid solution yielded a yellow oil, which solidified to an impure white solid when the last traces of solvent were removed *in vacuo*. This was purified *via* the methyl ester, prepared by refluxing with methanol (catalyst sulphuric acid). After removal of most of the methanol an ethereal solution of the product was washed with aqueous sodium carbonate to remove acidic material, and the oil which remained after removing the ether was refluxed with aqueous sodium hydroxide. The solution was cooled, acidified, and extracted with ether. Removal of ether from the dried extract gave the final product (V), m.p. 139—140°, equivalent wt. 225 (calc. for $C_{11}H_{12}O_5$; 224), (yield 12% based on the anhydride).

Compound (VI) had m.p. 185—187° (lit.,[5] 184—186°); its preparation followed the procedure given by Jones and Desio.[5] Compounds (VII) and (VIII) were prepared by the method of de Benneville [12] and purified by dissolving in aqueous alkali, precipitating by adding hydrochloric acid to pH 6, and recrystallizing three times from water. Compound (VII) had m.p. 92—94° (lit. 85—88; [12] 96—97° [13]), and compound (VIII) m.p. 122.5—123.5° (lit. 120—121°; [14] 121.5—122.5; [15] 121.8—122.4° [16]). Compound (IX) had m.p. 169—170°C (lit.,[17] 170—171°) after three recrystallizations from benzene, and compound (X) m.p. 171—172° (lit.,[18] 173—174°) after three recrystallizations from aqueous ethanol.

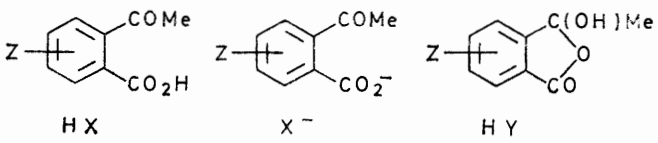
4′,5′-Dimethylacetophenone, isobutyrophenone, and 3-acetylnaphthalene [analogues of (IV), (VIII), and (IX) respectively] were pure commercial products. Pyridine was dried over potassium hydroxide pellets and then distilled from fresh potassium hydroxide on to a molecular sieve. Solutions were made up with deionized water which had been distilled from potassium permanganate.

2′,3′,4′,5′-Tetrachloroacetophenone was prepared as described by Pearson *et al.*[19] The mixture of the 2′,3′,4′,5′- and 2′,3′,5′,6′-isomers obtained by distilling the crude product was fractionally sublimed to remove the bulk of the predominant 2′,3′,5′,6′-compound, and the residue recrystallized from pentane. This yielded a mixture of the two isomers which could not be completely separated even by high-pressure liquid chromatography. However, when the tritiated product was detritiated in alkaline solution, the first-order reaction plots were linear over at least four half-lives, suggesting that, as might be expected, the two isomers differ little in reactivity.

*Determination of* p$K_a$ *Values.*—Values not recorded in the literature were determined spectrophotometrically by measuring the absorbance of a small quantity of keto-acid added to a formate or acetate buffer system. This method involves equilibria between two acid–base systems of the same charge type, so that activity coefficients cancel to a good approximation at the ionic strength $I$ = 0.01M employed. The molecule and anion of (IX) do not differ sufficiently in absorption spectra for this method to be applicable, and instead the absorbance of an indicator (Bromophenol Blue) was measured in buffer solutions of the keto-acid. In this system the two acid-base systems are of different charge types, but since the ionic strength was kept at 0.001M, activity coefficients will be sufficiently close to unity to be omitted.

For each compound 6—8 solutions were investigated, with buffer ratios varying by at least a factor of ten, and the stoicheiometric buffer ratios were corrected by using approximate values for the hydrogen ion concentrations. No trends were observed in the derived values of p$K_a$, and their mean values, given in Table 1, are estimated to be accurate to within ±0.02 p$K$ units.

*'True' p$K_a$ Values and Tautomeric Equilibria.*—In aqueous solutions of derivatives of 2′-carboxyacetophenone the species in Scheme 1 are present and the 'true' p$K_a$,




SCHEME 1

p$K_a$′, is defined as that referring to the equilibrium between HX and X⁻, while the p$K_a$ determined by conventional means will of course involve the sum of the concentrations of HX and HY. It is then obvious that $K_a'/K_a = 1 + K$, where $K$ = [HY]/[HX] is the tautomeric equilibrium constant. As previously demonstrated,[1-3,20,21] the values of $K_a$′ can be derived by measuring the catalytic effect of the anions X⁻ in the decomposition of nitramide. For each compound five solutions were studied with [X⁻] in the range 0.01—0.1M; pH was *ca.* 6, and the ionic strength was made up to 0.1M. The experimental method was as previously described.[2] The values of p$K_a$′, estimated to be accurate to ±0.01 p$K$ units, are given in Table 1. For compounds (III)—(V) analogous measurements were made on the anion-catalysed mutarotation of glucose. For reasons given previously [1,2] this reaction is less suitable than the decomposition of nitramide for determining $K_a$′, and served only to give a rough confirmation of the values obtained by the latter method. Compound (X) is insufficiently soluble to be studied as a catalyst for the nitramide reaction, and the approximate value of $K$ given in Table 1 is calculated on the assumption that p$K_a$′ = 3.6.

Jones and Desio [5] have used $^1$H n.m.r. measurements to study the tautomeric equilibria of (I)—(III) and (VI) in chloroform solution. Their findings correspond roughly with our own, but exact agreement would not be expected in view of the difference of solvent. We found that the i.r. spectra (Nujol or halogenocarbon mull) of most of the compounds show typical OH stretching absorption bands at 3 265—3 400 cm$^{-1}$, indicating that the solids consist of the cyclic form HY; on the other hand (III) and (IX) give instead a broad band covering the range 2 400—3 200 cm$^{-1}$, attributable to a dimer of the carboxylic acid form HX. It is of interest that (III) is the only compound studied whose aqueous solution was found to contain more than 50% of

[12] P. L. de Benneville, *J. Org. Chem.*, 1941, **6**, 462.
[13] R. L. Frank, H. Eklund, J. W. Richter, C. R. Vanneman, and A. N. Wennerberg, *J. Amer. Chem. Soc.*, 1944, **66**, 1.
[14] W. Roser, *Ber.*, 1884, **17**, 2777.
[15] R. L. Letsinger and W. J. Vullo, *J. Org. Chem.*, 1960, **25**, 1844.
[16] E. T. Harper and M. L. Bender, *J. Amer. Chem. Soc.*, 1965, **87**, 5625.
[17] W. Ried and K. H. Bonninghausen, *Annalen*, 1961, **639**, 56.
[18] P. R. Jones and A. A. Lavigne, *J. Org. Chem.*, 1960, **25**, 2020.
[19] D. E. Pearson, H. W. Pope, W. W. Hargrove, and W. E. Stamper, *J. Org. Chem.*, 1958, **23**, 1412.
[20] J. N. Brönsted and K. J. Pedersen, *Z. phys. Chem.*, 1924, **108**, 185.
[21] R. P. Bell, 'The Proton in Chemistry,' Chapman and Hall, London, 1973, 2nd edn., pp. 221—223.

HX (Table 1), though no close parallelism with the solid state need be expected.

TABLE 1

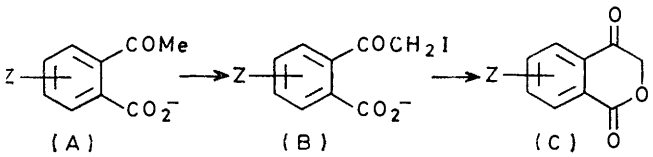
$pK_a$ Values and tautomeric equilibria in water at 25°

| Compound | Buffer | λ/nm | $pK_a$ | $pK_a'$ | $K$ |
|---|---|---|---|---|---|
| (I) | | | 4.13 [a] | 3.51 [a] | 3.2 [a] |
| (II) | Acetate | 252 | 4.68 | 3.45 | 16 |
| (III) | | | 3.26 [b] | 3.08 | 0.52 |
| (IV) | Formate | 265 | 4.24 | 3.65 | 2.9 |
| (V) | Acetate | 278 | 4.43 | 3.63 | 5.1 |
| (VI) | Formate | 255 | 4.10 | 3.00 | 12 |
| (VIII) | | | 4.55 [c] | 3.68 | 5.6 |
| (IX) | Keto-acid + indicator | 435, 590 | 4.47 | 3.64 | 6.3 |
| (X) | Acetate | 328 | 5.52 | | (≈100) * |

[a] Ref. 1. [b] J. Tirouflet, *Compt. rend.*, 1953, 1426: value at 20°. [c] Ref. 16. * Calculated assuming $pK_a' = 3.6$.

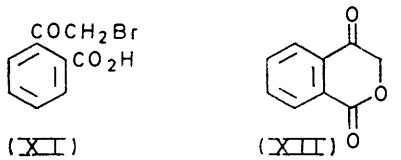
*Measurement of Rates of Halogenation.*—With the exception of the experiments with compound (III), the disappearance of iodine was followed by recording the absorbance at 353 nm due to the tri-iodide ion. Measurements were made with a Gilford 2400 or Unicam SP 700A or 500 spectrophotometer, the temperature of the cell compartment being controlled at 25 ± 0.05°. After allowing for the slight dissociation of the tri-iodide ion according to $I_3^- \rightleftharpoons I_2 + I^-$, its effective molar absorption coefficient in presence of 0.1M-iodide was taken as $2.49 \times 10^4$ dm$^3$ mol$^{-1}$ cm$^{-1}$. Since the iodination product of (III) absorbs in the same range as tri-iodide ion, halogenation of this compound was followed by titrating 1 cm$^3$ samples with $10^{-3}$M-sodium thiosulphate solution from a micrometer syringe, the end-point being detected by the ' dead-stop ' method.[22]

The detailed study of the iodination of 2′-carboxyacetophenone [1] has shown that in self-buffered solutions the rate is proportional to the concentration of the anion and independent of pH: this rate was attributed to intramolecular abstraction of the COMe protons by the carboxylate group. In the present study this intramolecular rate was measured in solutions of the keto-acids brought to pH 6.0 by adding sodium hydroxide. Typical initial concentrations were [anion] = $10^{-3}$M, [$I_3^-$] = $10^{-5}$M, [$I^-$] = $10^{-1}$M. The tri-iodide concentration decreased linearly with time over at least 80% of each reaction, but the rate ultimately fell off, presumably owing to insufficiently rapid halogenation of the enol or enolate ion at the very low iodine concentrations involved. Compound (VI) was exceptional, in that the rate of halogen consumption decreased steadily throughout each reaction, and no rates of iodination are reported for this substance.




SCHEME 2

It was assumed that the 2-iodo-2′-carboxyacetophenone first formed cyclizes rapidly to an isochroman-1,4-dione, as in Scheme 2. This will render the iodination irreversible, and in the absence of added basic catalysts will also effectively prevent the consumption of more than one molecule of iodine, since there are no possibilities for intramolecular catalysis in (C). Rapid cyclization of the 2-bromo- and 2-iodo-compounds was demonstrated by Harper and Bender [16] for 2′-carboxyisobutyrophenone, and has been assumed by analogy for 2′-carboxyacetophenone.[1] Further evidence has now been obtained by observations on 2-bromo-2′-carboxyacetophenone (XI) and isochroman-1,4-dione (XII), prepared as described by Gabriel.[23]* Both compounds were purified by vacuum sublimation: their m.p.s agreed with those given by Gabriel, and their structures were confirmed by their $^1$H n.m.r. spectra. (XI) shows u.v. absorption maxima at 212 and 235 nm, and (XII) at 222, 257, and *ca.* 300br nm. In acetate buffers the conversion (XI) ⟶ (XII) could be conveniently followed at 258 or 307




nm, isosbestic points being observed at 232 and 241 nm. The rate increases with increasing pH in the range 3.6—4.8, corresponding to increasing dissociation of (XI) to its anion, but shows no dependence on buffer concentration. The velocity constants obtained were of low accuracy, since (XII) undergoes a slower subsequent reaction (probably opening of the lactone ring), but an approximate value for the cyclization of the anion of (XI) is $2 \times 10^{-2}$ s$^{-1}$. The observed velocity constant for the iodination of the anion of 2′-carboxyacetophenone in self-buffered solutions is $2 \times 10^{-6}$ s$^{-1}$, and although this will be increased by a factor of *ca.* 100 by halogen substitution it is clear that cyclization will be faster than the introduction of a second halogen atom. The rates of iodination can therefore be equated to the rate of intramolecular proton transfer in the anion of the original compound, and the values of $k_i^H$ in Table 3 have been obtained by dividing the zero-order rate of iodination (in mol dm$^{-3}$ s$^{-1}$) by the anion concentration.

For nearly all the substrates investigated the rate of iodine consumption is increased by the addition of acetate or pyridine buffers. The increase usually amounts to less than a factor of two in a 0.2M-buffer solution, and extrapolation to zero buffer concentration gives rates equal to those in self-buffered solutions of the same pH. In the earlier work on 2′-carboxyacetophenone [1] this increase was attributed to intermolecular basic catalysis of the initial enolization by acetate ions or pyridine, but this interpretation now appears to be incorrect, at least in a quantitative sense. In the presence of these added buffer systems the plots of [$I_3^-$] against time show several abnormal features. The initial portion of the plot often shows acceleration, and although the central section may be approximately linear, its slope increases somewhat with increasing iodine concentration, and is reduced by increasing [$I^-$]: these abnormalities are accentuated if a second quantity of iodine is added to a solution which has reacted.

All these observations are consistent with the assumption that the formation of the cyclic product (C) is followed by the reversible reaction (Scheme 3), which is base-catalysed and zero-order with respect to halogen. In fact, in acetate buffers at pH 4.75 compound (XII) was found to react

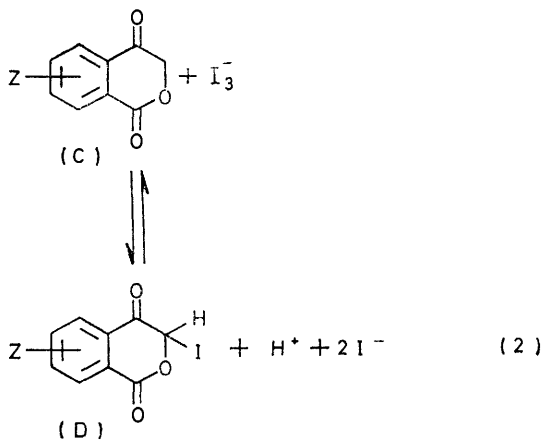
* Gabriel supposed the cyclized product to be hydroxymethylenephthalide, but this structure is inconsistent with its $^1$H n.m.r. spectrum.

[22] C. W. Foulk and A. T. Bawden, *J. Amer. Chem. Soc.*, 1926, **48**, 2045.

[23] S. Gabriel, *Ber.*, 1907, **40**, 4227.

rapidly with halogens. With iodine the reaction is partially reversible even with $[I^-]$ as low as 0.004M. With bromine the reaction goes to completion, but the initial rates are closely similar for the two halogens, and the observed first-order constants for the reaction (C) ⟶ (D) are given approximately by $k = 10^{-2}[AcO^-]\ s^{-1}$. Calculation then shows that the extra iodine consumption due to this reaction can account for most, if not all, of the increase of velocity observed in acetate buffers, and it will certainly contribute substantially in pyridine buffers also: for this reason no details of iodination experiments in buffer solutions are given in this paper.

The above interpretation is supported by the fact that the addition of buffers was found to cause no detectable rate increase for compounds (VIII) and (X). For the former the analogue of (C) will contain no replaceable hydrogen, while for the latter it is unlikely to be formed since it would contain a seven-membered ring in which five of the ring atoms are constrained to a planar configuration with three angles




SCHEME 3

of 120°.* Finally, the strongest confirmation of this view comes from the results of the detritiation experiments described in the next two sections.

In the absence of added buffers, complications due to reaction (2) will be minimal. The anions of the keto-acids are weaker bases than acetate ion, and their concentration did not exceed 0.02M, so that no appreciable base catalysis of the reaction (C) ⟶ (D) is to be anticipated. Values of $k_i^H$ obtained from iodination measurements in self-buffered solutions or by extrapolation to zero concentration of added buffers should therefore provide reliable estimates of the rate of intramolecular proton transfer.

In order to derive kinetic isotope effects, by comparison with rates of detritiation, rates of bromination in alkaline solution were measured for compounds (I), (IV), and (VIII), and also for isobutyrophenone. The procedure was essentially that described by Jones *et al.*[24] and involved following the decrease in absorption by hypobromite ion at 330 nm. Typical initial concentrations were [substrate] = $4 \times 10^{-4}$M, $[BrO^-] = 2 \times 10^{-3}$M, $[OH^-] = 0.1$M. With compounds (I) and (IV) three moles of $BrO^-$ disappeared per mole of substrate, but with the two isopropyl ketones only one mole was consumed.

The rates of ionization derived from halogenation experiments are recorded in Table 3 as $k_i^H$ (first-order constant for intramolecular proton transfer) and $k^H_{OH}$ (second-order constant for proton transfer to hydroxide ions).

*Tritiation Procedures.*—Tritiated specimens of the keto-acids were prepared as follows. To the potassium salt of the substrate (0.2 g )were added tritiated water (20 mm³; 5 Ci cm⁻³), 5M-potassium hydroxide (10 mm³), and enough dioxan (0.3—1.0 cm³) to form a homogeneous solution, which was left at room temperature for 24 h and then acidified with 0.1M-hydrochloric acid. The solvent was removed by freeze-drying and the residue washed with aqueous dioxan, which was similarly removed. Less than 1% of the tritium in the resulting substrate was labile, being presumably present as $CO_2T$.

Tritiated samples of 4′,5′-dimethylacetophenone 2′,3′,4′,5′-tetrachloroacetophenone, isobutyrophenone, and 2-acetylnaphthalene were prepared by the following procedure. To ketone (0.5 g) were added tritiated water (5 mm³; 5 Ci cm⁻³), one pellet of sodium hydroxide, and enough dioxan to give a homogeneous solution above the excess of solid sodium hydroxide. The whole was left for 24 h at room temperature, the solution decanted off and then dried ($Na_2SO_4$). Portions of this dioxan solution were used directly in the kinetic experiments.

*Measurement of Rates of Detritiation.*—For keto-acids in acetate or pyridine buffers detritiation was followed to <3% completion by counting samples of water removed by freeze-drying. Enough tritiated substrate was added to buffer solution (20 cm³) at 25° to give between $2 \times 10^5$ and $4 \times 10^5$ counts min⁻¹ cm⁻³. Samples (1 cm³) were taken periodically and the water removed by freeze-drying. Distillate (0.5 cm³) was counted in N.E. 250 scintillator (5 cm³; Nuclear Enterprises Ltd.) on an Intertechnique SL30PR liquid scintillation counter. Plots of counts min⁻¹ against the time of sampling were linear, and the first-order velocity constants $k_{obs}$ were obtained by dividing the slopes of these lines by the number of counts per minute given by 0.5 cm³ of unseparated reaction mixture.

The measurement of detritiation rates in presence of hydroxide ions, a much faster reaction, resembled the procedure of Jones *et al.*[24] Detritiation was followed to completion, so that each reaction followed a first-order course, which was monitored by counting samples of the substrate extracted with toluene. The tritiated substrate, or its dioxan solution, was added to 0.1M-potassium hydroxide solution (20 cm³) at 25°. Samples (1 cm³) were removed periodically and added to tubes containing a solution of diphenyloxazole in sulphur-free toluene (10 cm³) together with either water (for ketones) or 0.1M-hydrochloric acid (for keto-carboxylic acids) (10 cm³). The tube was shaken vigorously, the toluene layer separated and dried ($Na_2SO_4$), and the dried toluene solution (5 cm³) counted on the liquid scintillation counter. Plots of lg(counts min⁻¹) against time of sampling were straight lines, the slopes of which gave the first-order rate constants $k$; the second-order constant for detritiation is then given by $k^T_{OH} = k/[OH^-]$, values of which are given in Table 3.

As a check on the validity of these procedures the rate of detritiation of compound (IV) in 0.1M-potassium hydroxide was measured by three different methods. Method (a)

* If the monoiodo-derivative of (X) does not readily cyclize, then even in the absence of added buffers the initial intramolecular proton transfer may lead to the consumption of more than one molecule of iodine, though there is no direct evidence for this.

[24] J. R. Jones, R. E. Marks, and S. C. Subba Rao, *Trans. Faraday Soc.*, 1967, **63**, 111, 993; and earlier papers.

was that described in the last paragraph. Method (b) employed the increase of tritium content in the water: samples (1 cm³) of acidified reaction mixture were freed from substrate by washing three times with toluene (10 cm³) * and the water layer (0.5 cm³) counted in N.E. 250 scintillator (3 cm³), giving a count $C_t$. The value of $C_\infty$ was determined from three samples taken after >10 half-lives, and the first-order rate constant obtained from a plot of $\lg(C_\infty - C_t)$ against time. Method (c) employed the same procedure, except that <4% of the total reaction was followed, and the first-order constant was calculated by dividing the slope of the linear $C_t$–$t$ plot by $C_\infty$, which in this method was obtained by counting a sample of unseparated reaction solution. The three methods gave velocity constants $10^6 k_1 = 89$, 91, and 93 $s^{-1}$ respectively, which are effectively identical.

proportional increase was only about half that observed in iodination experiments. This suggests once more that the latter is not a reliable method for measuring rates of intermolecular proton transfer to added bases, though part of the difference may be due to a difference in isotope effects for inter- and intra-molecular reactions, as mentioned in the Discussion section. The rate of detritiation extrapolated to zero pyridine concentration gives a value of $k_i^T$ in agreement with that derived from the measurements in acetate buffers. For intramolecular tritium transfer to pyridine molecules, the velocity constant given in Table 2 is calculated on the assumption that the rate law is $v = [X^-](k_i^T + k_{Py}^T[Py])$, and the same applies to the measurements for compound (X) in pyridine buffers. Compound(s) (VI) [and (II)] in acetate buffers gave a linear increase of detritiation rate with acetate concentration, and for the first of these

TABLE 2

Rates of detritiation in buffer solutions ($10^9 k_{obs}/s^{-1}$) (ionic strength made up to 0.3M with KCl throughout)

Acetate buffers $r$ = [AcOH]/[AcO⁻]

| $10^2$[AcO⁻]/M | Compound | (I) | (II) | (IV) | (VI) | | (VIII) |
|---|---|---|---|---|---|---|---|
| | $r$ | 1.00 | 1.00 | 1.00 | 1.00 | 5.00 | 1.00 |
| 200 | | 47 | 3.8 | 59 | 150 | | 149 |
| 100 | | 45 | 1.9 | 62 | 84 | 47 | 151 |
| 70 | | | | | | 36 | |
| 50 | | 48 | 1.2 | 61 | 52 | | 156 |
| 40 | | | | | | 25 | |
| 0 | | 47 | | 61 | 19 | 11 | 152 |
| | $10^9 k_i^T$ | 58 | 0.7 | 79 | 23 | 23 | 248 |
| | $10^8 k_{AcO}^T$ | | 3.1 | | 81 | 76 | |

Pyridine buffers [PyH⁺] = [Py] throughout

| $10^2$[Py]/M | Compound | (IV) | (X) |
|---|---|---|---|
| 200 | | 104 | 4.63 |
| 100 | | 84 | 2.65 |
| 50 | | 77 | 1.92 |
| 0 | | 66 | 0.87 |
| | $10^9 k_i^T$ | 76 | 2.7 |
| | $10^7 k_{Py}^T$ | 22 | 0.57 |

TABLE 3

Summary of intra- and inter-molecular velocity constants

| Compound | $10^8 k_i^H$ | $10^9 k_i^T$ | $10^3 k_{OH}^H$ | $10^5 k_{OH}^T$ | $10^4 (k_{OH}^T)_a$ * | $10^8 k_{AcO}^T$ | $10^7 k_{Py}^T$ |
|---|---|---|---|---|---|---|---|
| (I) | 205 | 58 | 89 | 149 | 54 ‡ | <2 | |
| (II) | 3.3 | 0.7 | | 75 | 45 ‡ | 0.31 | |
| (III) | 56 | | | 74 | 589 ‡ | | |
| (IV) | 265 | 79 | 48 | 91 | 33 | <3 | 22 |
| (V) | 336 | | | | | | |
| (VI) | 83 † | 23 | | 4 900 | 326 | 76 | |
| (VII) | 710 | | | | | | |
| (VIII) | 502 | 248 | 36 | 20 | 1.1 | <8 | |
| (IX) | 105 | | | 123 | 54 | | |
| (X) | 1.0 † | 2.7 | | | | | 0.57 |

* These values refer to the corresponding ketone. † Obtained from $k_i^T$ assuming that $k_i^H/3k_i^T = 12$. ‡ Values from ref. 24. In this Table $k_i$ is in $s^{-1}$, and all other constants in $dm^3\ mol^{-1}\ s^{-1}$.

The results for detritiation in buffer solutions are collected in Table 2. Compounds (I), (IV), and (VIII) show no increase of rate with increasing acetate concentration, thus confirming the conclusion reached in the last section that the increase observed in the iodination experiments is largely due to complications which arise for halogenation but not for detritiation. The observed rates of detritiation can therefore be attributed to intramolecular transfer to the carboxylate group, and since the fraction of substrate present as the anion is $K_a(K_a + K_{AcOH})^{-1}$, where $K_a$ is the conventional dissociation constant of the substrate, the intramolecular rate constant is given by $k_i^T = k_{obs} K_a^{-1}(K_a + K_{AcOH})$.

An increase of detritiation rate with buffer concentration was observed for compound (IV) in pyridine buffers, but the consistent velocity constants were obtained for two different buffer ratios on the assumption that the rate law is $v = [X^-](k_i^T + k_{AcO}^T[AcO^-])$: this confirms the view that under our experimental conditions tritium transfer to the basic buffer components takes place mainly from the anion of the substrate, which is the predominant species present.

## DISCUSSION

The kinetic results are summarised in Table 3. The most complete set of values is that for $k_i^H$, representing

* Most of the substrates used could not be efficiently removed by toluene extraction, and separation was therefore effected by freeze-drying in the experiments on buffer solutions.

the rates of intramolecular proton transfer in the anions of ten 2′-carboxyacetophenones. There are three main ways in which a substituent might affect these rates. (a) Through the basic strength of the carboxylate group. This should lead to a parallelism between $k_i^H$ and $pK_a'$, the 'true' $pK$ of the keto-carboxylic acid (Table 1). (b) Through the reactivity of the group COMe. This suggests a comparison with the values of $k_{OH}^T$ or $(k_{OH}^T)_a$. (c) By steric effects influencing the ease with which the cyclic transition state is formed. Such effects would be most marked for ring substituents adjacent to the carboxy or acetyl groups, and also might be reflected in variations of the constant $K$ (Table 1) expressing the equilibrium proportion of the cyclic tautomer in solution.

Examination shows that the variations in $k_i^H$ or $k_i^T$ cannot be wholly accounted for by any one of these factors, nor by any simple combination of them. There are, however, qualitative indications that steric effects constitute the most important single factor determining the rate of the intramolecular process. Thus in the series derived from benzene particularly low values of $k_i$ are observed for compounds (II) and (VI), which are the only ones having substituents *ortho* to the carboxy or acetyl groups.* Similarly, $k_i$ is very low for the naphthalene derivative (X), for which the cyclic transition state would contain six atoms, in addition to the proton. Examination shows that it would be sterically impossible for the system C · · · H · · · O to attain the approximately linear configuration which is believed to favour proton transfer. It is also noteworthy that the above three compounds are just those for which the equilibrium proportion of lactol isomer in solution is particularly high (see Table 1). This means that steric effects which favour the lactol isomer of the undissociated acid have a retarding effect on intramolecular proton transfer in the anion. A similar inverse relation has been observed in a series of aliphatic γ-ketocarboxylic acids,[3] and is not unreasonable, since quite different types of cyclic structure are involved in the two processes.

The efficiency of the intramolecular process is conveniently expressed as an effective concentration $c_i$, defined by $c_i = k_i/k^*$, where $k^*$ is the second-order constant for intermolecular catalysis by a hypothetical carboxylate ion having the same basic strength as the carboxylate group in the substrate. When values for $k_{AcO}$ are available $k^*$ can be estimated from equation (1), where

$$k^* = k_{AcO}(K_{AcOH}/K_a')^{0.8} \quad (1)$$

$K_a'$ is the 'true' dissociation constant of the keto-acid, and 0.8 is the value commonly found for the Brönsted exponent in this class of reaction. Values of $k_{AcO}^T$ are available only for compounds (II) and (VI), leading to $c_i^T = 2.6$ and 0.75M respectively. These two substrates are of low efficiency as regards intramolecular enolization, and it is in fact for this reason that the intermolecular reaction with acetate ions is detectable. For the remaining compounds only an upper limit can be given for $k_{AcO}^T$ and $k^*$, and the limits given in Table 3 lead to a lower limit of $c_i^T > 20$M for compounds (I), (IV), and (VIII).

Another type of estimate gives results which are consistent with this lower limit. For the enolization of acetone the ratio $k_{OH}^H/k_{AcO}^H$ is *ca.* $10^6$, while for the ketone $SO_3^-CH_2COMe$ this ratio is $1.5 \times 10^5$.[25] In our experiments the corresponding ratios $k_{OH}^T/k_{AcO}^T$ are $2.4 \times 10^5$ and $6.4 \times 10^4$ for compounds (II) and (IV) respectively. If it is assumed that $k_{OH}^T/k_{AcO}^T = 10^5$ for compounds (I), (IV), and (VIII), then the above arguments lead to $c_i^T = 39$, 66, and 890M respectively. Not much quantitative significance can be attached to these values, but it is clear that, with the exception of the sterically hindered compounds (II) and (VI), intramolecular proton transfer in these relatively rigid systems is 10—100 times more effective than in the more flexible aliphatic keto-acids.[3]

The values in Table 3 give some information about kinetic isotope effects, summarised in Table 4. For most

TABLE 4

Tritium isotope effects

| Compound | (I) | (II) | (IV) | (VIII) |
|---|---|---|---|---|
| $k_i^H/3k_i^T$ | 12 | 15 | 11 | 20 ($k^H/k^T$) |
| $k_{OH}^H/3k_{OH}^T$ | 20 | | 18 | 18 ($k^H/k^T$) |

of the compounds the comparison is between the ionisation of $CH_3$ and of $CH_2T$, so that the true isotope effect is given by $k^H/3k^T$, but for compound (VIII) there is only one ionisable hydrogen, and no statistical correction is needed. The isotope effects are similar in magnitude to those obtained by Jones *et al.*[24] for substituted acetophenones. For compounds (I) and (IV) the isotope effect is much smaller for the intramolecular than for the intermolecular process: this may be because the cyclic transition state compels the system C · · · H · · · O to adopt a non-linear configuration, for which lower isotope effects have been predicted on theoretical grounds.[26] This difference is not apparent for compound (VIII), for which the steric situation will be affected by the presence of the two methyl groups. It would be of interest to make further comparative studies of isotope effects for intra- and inter-molecular processes.

If the value of $k_i^H/3k_i^T$ for compound (I) is combined with the Swain–Schaad relation,[27] a value of $k_i^H/k_i^D = 5.4$ is predicted, which is close to the value of 5.6 previously measured.[1]

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* For compound (VI) the absolute values of $k_i$ are not markedly low, but the high values of $k_{OH}^T$ and $k_{AcO}^T$ show that the four chlorine substituents have a strongly activating effect on the COMe group, so that much higher values of $k_i$ would have been expected.

[25] R. P. Bell, G. R. Hillier, J. W. Mansfield, and D. G. Street, *J. Chem. Soc.* (*B*), 1967, 827.
[26] R. A. More O'Ferrall, *J. Chem. Soc.* (*B*), 1970, 785.
[27] C. G. Swain, E. C. Stivers, J. F. Reuwer, and L. J. Schaad, *J. Amer. Chem. Soc.*, 1958, **80**, 5885.