Intra- and Inter-molecular Catalysis and Hydrogen Isotope Effects in the Iodination of *o*- and *p*-Carboxyacetophenone

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Measurements have been made of the rate of iodination of *o*- and *p*-carboxyacetophenone and their deuteriated analogues. These reactions are of zero order with respect to iodine, the measured rate representing the rate of ionization of the acetyl group. In self-buffered solutions of the *ortho*-compound the rate can be attributed solely to intramolecular proton transfer from the acetyl to the carboxylate group. In acetate and pyridine buffers there is also a contribution from intermolecular proton transfer to acetate ion or pyridine, and this is the only type of process detectable for the *para*-compound. The kinetic hydrogen isotope effect for the intramolecular process (k^H/k^D = 5·4) is considerably greater than that for any of the intermolecular processes (k^H/k^D = 4·0). A study was also made of the catalytic effect of the anions of the carboxyacetophenones in the decomposition of nitramide and the mutarotation of glucose. This leads to an estimate of the ' true ' acid–base properties of the carboxy-group in *o*-carboxyacetophenone, and hence to a quantitative comparison between intra- and inter-molecular catalysis; it also shows that in aqueous solution 81% of the undissociated acid exists as the cyclic tautomer.

THE action of bases in abstracting a proton from a CH group adjacent to a carbonyl group is responsible for basic catalysis in many organic reactions proceeding through carbanion intermediates, notably the halogenation of ketones and similar substances. If an active CH group and a basic group are suitably situated in the same molecule the possibility arises of intramolecular basic catalysis. This has been demonstrated [1] in the iodination of the species $CH_3CO[CH_2]_nCO_2^-$ with $n = 2$—5 and 11. The rate of zero-order iodination (equivalent to the rate of ionization of the ketone) passes through a maximum when $n = 3$. For more rigid systems, Harper and Bender [2] obtained good evidence for intramolecular catalysis in the iodination

[1] R. P. Bell and M. A. D. Fluendy, *Trans. Faraday Soc.*, 1963, **9**, 1623.

[2] E. T. Harper and M. L. Bender, *J. Amer. Chem. Soc.*, 1965, **87**, 5625.

of the anions of *o*-carboxy-acetophenone and -isobutyrophenone, most of the work relating to the latter substance. The present paper reports a direct comparison of intra- and inter-molecular catalysis in the iodination of *o*- and *p*-carboxyacetophenone, together with measurements of deuterium isotope effects. Since the *ortho*-compound exists partly as a cyclic tautomer, the directly measured pK value does not give a correct measure of the acid–base properties of the carboxy-group, and we have therefore measured the catalytic effect of the anions of *o*- and *p*-carboxyacetophenone in the mutarotation of glucose and the decomposition of nitramide. These measurements also yield the equilibrium ratio for the tautomers of the *ortho*-compound in aqueous solution. This procedure has already been described for the analogous *o*-carboxybenzaldehyde.[3]

EXPERIMENTAL

Materials.—*o*-Carboxyacetophenone was prepared from malonic acid and phthalic anhydride in pyridine solution.[4] After successive recrystallization from water and benzene it had m.p. 116 °C. *p*-Carboxyacetophenone was obtained by permanganate oxidation of *p*-methylacetophenone.[5] The product contained some benzene-1,4-dicarboxylic acid, which was difficult to remove by recrystallization. Final purification was by vacuum sublimation at *ca.* 180 °C. The product had m.p. 200 °C, and titration with sodium hydroxide indicated a purity of 101%, possibly showing the presence of *ca.* 1% benzene-1,4-dicarboxylic acid.

Both *o*- and *p*-carboxyacetophenone were deuteriated (in the methyl and carboxy-groups) by the same procedure. The solid was dissolved in 40 mol/mol of deuterium oxide (>99·5% deuterium) containing sodium carbonate. After refluxing for 1 h the solution was cooled and acidified, and the precipitated solid was filtered off. This procedure was repeated with 80 mol/mol deuterium oxide, and the product was recrystallized from benzene. ^{1}H N.m.r. examination of the resulting *o*-carboxyacetophenone showed >99% deuteriation in the methyl group. For the *para*-compound no suitable solvent could be found for n.m.r. examination, but completeness of deuteriation was demonstrated by the fact that a third repetition of the deuteriation procedure produced no change in the rate of iodination.

Other materials were of AnalaR grade. For iodination experiments with *o*-carboxyacetophenone without an added buffer system self-buffered solutions were prepared by adding sodium hydroxide solution to solutions of the acid form (HA). In the most acidic solution the true value of [A$^-$] was obtained by correcting the stoicheiometric value by adding [H$^+$]. The latter quantity was calculated from the thermodynamic dissociation constant together with activity coefficients calculated from the Davies equation (1), where I is the ionic strength. In a few

$$-\lg f_{\pm} = [0{\cdot}50I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}})] - 0{\cdot}2I \qquad (1)$$

instances the iodination of *o*-carboxyacetophenone was studied in solutions made by adding sufficient sodium hydroxide solution to a solution of the acid to bring the pH to 6·0 (glass electrode). This procedure was used for all the experiments with *p*-carboxyacetophenone and the two deuteriated compounds in which no other buffer system was added. In these solutions virtually the whole of the carboxyacetophenone is present as the anion.

Other buffer solutions were made by mixing solutions of acetic acid and sodium hydroxide or of pyridine and hydrochloric acid. For iodination experiments the carboxyacetophenones were added to these buffer solutions as solutions of the sodium salt, prepared by neutralizing the acid with sodium hydroxide solution. When deuteriated compounds were used the acid form of the substrate was added to the acetate or pyridine buffer solution before adding the appropriate amount of sodium hydroxide, so as to avoid exchange of deuterium in alkaline solution. In the pyridine buffers (pH > 6) the carboxyacetophenones may be assumed to be completely ionized, and in the less acid acetate buffers ([HOAc]/[AcO$^-$] < 0·5) the concentration of the anion A$^-$ is given by [A$^-$] = K_{HA}[S]/(K_{HA} + rK_{HOAc}), where [S] is the total concentration of substrate, r is the stoicheiometric buffer ratio (which is virtually unchanged by the addition of the substrate) and K_{HA} and K_{HOAc} are the thermodynamic dissociation constants. We have used the values pK_{HA} = 4·13 and 3·83 for *o*- and *p*-carboxyacetophenone respectively.[6]

In the more acid acetate buffers (r = 0·5, 1·0, and 10·0) this simple procedure cannot be used, since the acetate buffer ratio is somewhat displaced by the addition of the substrate, and the hydrogen ion concentration, h, is no longer negligible compared with the concentrations of the other acidic and basic species. A complete treatment, neglecting only [OH$^-$], gives equation (2) where K_1 and

$$h^3 + (K_1 + K_2 + \beta_1 + \beta_2)h^2 + (K_1K_2 + \beta_1K_2 + \beta_2K_1 - \alpha_1K_1)h - \alpha_1K_1K_2 = 0 \qquad (2)$$

K_2 are the concentration dissociation constants of acetic acid and carboxyacetophenone respectively, and α_1, β_1, and β_2 are the stoicheiometric concentrations of acetic acid, acetate ion, and carboxyacetophenone (added as the sodium salt). The values of K_1 and K_2 at the appropriate ionic strength were calculated from the thermodynamic values by using activity coefficients calculated from equation (1). For almost all the solutions studied the first term of equation (2) is negligible. The true concentrations of acetate ion and carboxyacetophenone anion are then calculated from h, K_1, K_2, $\alpha_1 + \beta_1$, and β_2. The maximum correction to the stoicheiometric concentrations was 17%, and it was usually much smaller.

Iodination Kinetics.—The rate of disappearance of iodine was followed by the decrease in absorption due to triiodide ion, either a Gilford 2400 or a Unicam SP 700 recording spectrophotometer being used. All reaction solutions contained 0·1M-iodide ion, and the initial iodine concentration was in the range 1—3 × 10^{-5}M. The effective molar absorbance of iodine under these conditions is 2·52 × 10^4 at 360 and 2·49 × 10^4 at 353 nm. The cell compartments of the spectrophotometers were controlled at 25 ± 0·05 °C. In most series of experiments the ionic strength was made up to a fixed value by the addition of sodium perchlorate. The concentration of carboxyacetophenone was in the range 1—3 × 10^{-2}M,

[3] R. P. Bell, B. G. Cox, and B. A. Timimi, *J. Chem. Soc.* (*B*), 1971, 2247. The principles of this method were first stated clearly by J. N. Brönsted and K. J. Pedersen, *Z. phys. Chem.* (*Leipzig*), 1924, **108**, 185.

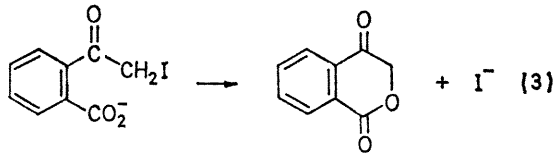
[4] H. L. Yale, *J. Amer. Chem. Soc.*, 1947, **69**, 1547.

[5] E. Bergman and J. Blum, *J. Org. Chem.*, 1959, **24**, 549.

[6] L. G. Bray, J. F. J. Dippy, and S. R. C. Hughes, *J. Chem. Soc.*, 1957, 265.

so that it remained effectively constant during the iodination. In experiments with *o*-carboxyacetophenone the optical density decreased linearly with time over at least 90% of the reaction, demonstrating that the reaction is truly zero order with respect to iodine, and hence that the rate of ionization (or enolization) of the acetyl group is being measured. Several successive additions of iodine were made to each mixture, and the rate of iodination was found to decrease by a few % after the first addition, after which it remained constant. This was probably due to a small quantity of a more reactive impurity, and the first addition was ignored in calculating the reaction velocity. A falling off in velocity at the extreme end of each experiment is attributable to ineffective scavenging by the very low concentrations of iodine ($<10^{-6}$M), rather than to a slight reversibility of the iodination, since the optical density fell to zero eventually.

Under basic conditions the carboxymonoiodoacetophenones would be expected to iodinate at least 100 times more rapidly than the parent compounds, and although the iodine concentrations were $<0{\cdot}3\%$ of the substrate concentrations this should lead to an acceleration of iodine uptake as the reaction proceeds. The fact that no such acceleration was observed with *o*-carboxyacetophenone can be attributed to the rapid conversion of the mono-



iodo-compound into a lactone by reaction (3). This lactone offers no possibilities for intramolecular catalysis, and its iodination in presence of acetate ion or pyridine should be relatively slow. The rapid formation of an analogous lactone in the bromination and iodination of *o*-carboxyisobutyrophenone was firmly established by Harper and Bender,[2] and can be safely assumed in our system.

In the iodination of *p*-carboxyacetophenone there is no possibility of either intramolecular catalysis or lactonization, and iodination should accelerate as the reaction proceeds. Some acceleration was in fact observed in acetate and pyridine buffers, and the rates quoted refer to the earlier part of the reaction.

The observed iodination rates can therefore be equated throughout to the rate of ionization of the acetyl group, but could in principle involve either the carboxylic acid or the carboxylate anion. As will be shown later, no reaction of the acidic form of *o*-carboxyacetophenone can be detected, and the first-order velocity constants in Table 1 have therefore been obtained by dividing the rate of consumption of iodine (in mol l^{-1} s^{-1}) by the concentration of the anion. No evidence was obtained for the relative reactivities of the acid and the anion of *p*-carboxyacetophenone, but experiments were designed so that the substrate was present almost exclusively as anion, since their main purpose was a comparison with the *ortho*-compound.

Tautomeric Equilibrium and 'True' Dissociation Constant of o-Carboxyacetophenone.—The procedure and treatment of the results followed exactly that of Bell and Cox [3] on *o*-carboxybenzaldehyde. As in the earlier work, the measurements on the mutarotation of glucose served only as a rough confirmation of the conclusions drawn from the decomposition of nitramide. For the former reaction

TABLE 1

Rates of ionization of carboxyacetophenones at 25 °C; [A⁻] = concentration of substrate anion and r = stoicheiometric buffer ratio, [acid]/[base]

(a) *o*-Carboxyacetophenone, self-buffered.

* Solution brought to pH 6·0 by adding sodium hydroxide.

I	r	10^4[H⁺]/M	10^4[A⁻]/M	10^5k/s⁻¹
0·20	*	0·01	100	203
0·20	*	0·01	200	204
0·20	*	0·01	250	203
0·20	*	0·01	300	205
0·20	*	0·01	400	205
0·13	0·0265	0·033	300	211
0·13	0·110	0·14	300	212
0·13	0·133	0·17	300	210
0·13	0·204	0·28	300	214
0·125	0·224	0·30	250	186
0·12	0·525	0·65	201	204
0·115	1·08	1·36	151	197
0·11	2·12	2·56	103	179
0·11	5·16	5·69	55·7	174
0·20	20·6	13·2	28·2	186
0·20	31·0	14·6	24·6	191
0·20	40·5	16·3	23·8	179

Mean $k = 1{\cdot}98 \times 10^{-6}$ s⁻¹. Mean k (excluding last five entries) $= 2{\cdot}05 \times 10^{-6}$ s⁻¹.

(b) [ω-$^2H_3$]-*o*-Carboxyacetophenone. Sodium salt at pH 6. Five experiments with [A⁻] ≃ 0·03M, I = 0·13, gave 10^5k = 385, 381, 381, 375, and 385 s⁻¹; mean 381 s⁻¹.

(c) *o*-Carboxyacetophenone in acetate buffers. I = 0·3 throughout. k(cal)/s⁻¹ $= 2{\cdot}05 \times 10^{-6} + 4{\cdot}0 \times 10^{-6}$[AcO⁻].

10^4[A⁻]/M	10^3[AcO⁻]/M	10^6[H⁺]/s⁻¹	10^5k(obs)/s⁻¹	10^5k(calc)/s⁻¹
r = 0·1				
98	40	3·0	237	221
293	40	3·0	235	221
98	80	3·0	254	238
305	80	3·0	258	238
98	120	3·0	266	253
293	120	3·0	274	253
98	160	3·0	284	269
317	160	3·0	273	269
98	200	3·0	296	285
285	200	3·0	285	285
r = 0·2				
96	200	5·9	298	285
r = 0·25				
94	201	7·4	303	285
r = 0·5				
90	201	14·8	296	286
r = 1·0				
82	42	27·4	209	222
82	82	28·7	227	238
81	122	29·1	243	254
81	162	29·3	257	271
81	202	29·5	271	286
r = 10·0				
33·6	47	252	194	221
31·8	87	274	212	240
31·1	127	282	243	256
30·8	167	286	260	272
30·6	207	289	276	288

(d) [ω-$^2H_3$]-*o*-Carboxyacetophenone in acetate buffers. r = 0·1, I = 0·3. [A⁻] ≃ 0·04M throughout. k(calc)/s⁻¹ $= 3{\cdot}81 \times 10^{-7} + 1{\cdot}04 \times 10^{-6}$[AcO⁻].

10^3[AcO⁻]/M		40	80	120	160	200
10^5k/s⁻¹	(obs)	43	47	51	55	59
	(calc)	42	46	51	55	59

TABLE 1 (*continued*)

(e) *o*-Carboxyacetophenone in pyridine buffers. $r = 0{\cdot}1$, $I = 0{\cdot}15$. $[A^-] \simeq 0{\cdot}02$M throughout. $k(\text{calc})/s^{-1} = 2{\cdot}15 \times 10^{-6} + 2{\cdot}33 \times 10^{-5}$[pyridine]

10^3[Pyridine]/M		24	48	73	97	120
$10^6k/s^{-1}$	(obs)	300	335	381	437	484
	(calc)	271	327	385	431	495

(f) [ω-$^2H_3$]-*o*-Carboxyacetophenone in pyridine buffers. $r = 0{\cdot}1$, $I = 0{\cdot}15$. $[A^-] \simeq 0{\cdot}02$M throughout. The sodium salt of this sample gave $k = 4{\cdot}15 \times 10^{-7}$ s^{-1} at pH 6, compared with $3{\cdot}81 \times 10^{-7}$ s^{-1} in Table 1(b); it was therefore assumed to contain only 98% deuterium. $k(\text{calc})/s^{-1} = 4{\cdot}18 \times 10^{-7} + 6{\cdot}1 \times 10^{-6}$[pyridine]

10^3[Pyridine]/M		24	48	73	97	120
$10^6k/s^{-1}$	(obs)	57	71	86	99	117
	(calc)	57	71	90	101	115

(g) *p*-Carboxyacetophenone. Sodium salt at pH 6. $I = 0{\cdot}10$. $[A^-] \simeq 0{\cdot}02$M, $k = 7{\cdot}6 \times 10^{-9}$ s^{-1}.

(h) *p*-Carboxyacetophenone in acetate buffers, $r = 0{\cdot}1$, $I = 0{\cdot}3$. $[A^-] \simeq 0{\cdot}01$M throughout. $k(\text{calc})/s^{-1} = 9 \times 10^{-9} + 1{\cdot}7 \times 10^{-6}$[AcO$^-$].

10^3[AcO$^-$]/M		20	40	60	80	100
$10^9k/s^{-1}$	(obs)	44	77	104	141	182
	(calc)	43	77	111	145	179

(i) *p*-Carboxyacetophenone in pyridine buffers, $r = 0{\cdot}1$, $I = 0{\cdot}15$. $[A^-] \simeq 0{\cdot}02$M throughout. $k(\text{calc})/s^{-1} = 15 \times 10^{-7} + 3{\cdot}7 \times 10^{-5}$[pyridine].

10^3[Pyridine]/M		25	50	75	100	125
$10^8k/s^{-1}$	(obs)	110	202	297	387	472
	(calc)	107	200	293	385	478

(j) [ω-$^2H_3$]-*p*-Carboxyacetophenone in pyridine buffers, $r = 0{\cdot}1$, $I = 0{\cdot}15$. $[A^-] \simeq 0{\cdot}02$M throughout. $k(\text{calc})/s^{-1} = 3 \times 10^{-8} + 9{\cdot}3 \times 10^{-6}$[pyridine].

10^3[Pyridine]/M		25	50	75	100	125
$10^8k/s^{-1}$	(obs)	29	52	72	92	118
	(calc)	26	50	73	96	119

TABLE 2

Rate constants and isotope effects in the ionization of carboxyacetophenones at 25 °C; k_1/s^{-1} = intramolecular rate constant, and k_B/l mol s^{-1} = intermolecular rate constant

Base	$10^8k_1^H$	$10^8k_1^D$	$10^8k_B^H$	$10^8k_B^D$	k^H/k^D
o-Carboxyacetophenone					
	205 *	38·1			5·4
Acetate			400	104	3·9
Pyridine			2330	570 *	4·1 *
p-Carboxyacetophenone					
Acetate			170		
Pyridine			3700	930	4·0

* Mean value, omitting the last 5 entries in Table 1(a).
† Corrected for incomplete deuteriation: see Table 1(f).

TABLE 3

Catalysis of nitramide decomposition at 25 °C by the anions of carboxyacetophenones; k/s^{-1} = first-order rate constant

o-Carboxyacetophenone, buffer solutions with $r = 0{\cdot}1$, $I = 0{\cdot}10$ $k(\text{calc})/s^{-1} = 4{\cdot}7 \times 10^{-5} + 6{\cdot}27 \times 10^{-3}[A^-]$.

$10^3[A^-]$/M		20	40	60	80	100
$10^6k/s^{-1}$	(obs)	175	309	431	538	667
	(calc)	172	298	423	549	674

$K_{HX} = 3{\cdot}09 \times 10^{-4}$, [HY]/[HX] = 4·3.

p-Carboxyacetophenone, buffer solutions made by saturating 0·1M-NaOH solution with solid acid, pH ≃ 6, $I = 0{\cdot}10$ $k(\text{calc})/s^{-1} = 4{\cdot}7 \times 10^{-5} + 1{\cdot}07 \times 10^{-2}$ [A$^-$].

$10^3[A^-]$/M		20	40	60	80	100
$10^6k/s^{-1}$	(obs)	274	469	650	860	1154
	(calc)	261	475	659	903	1117

TABLE 4

Catalysis of glucose mutarotation at 18 °C by the anions of carboxyacetophenones; k/s^{-1} = first-order rate constant; $I = 0{\cdot}20$, buffer solutions as in Table 3

o-Carboxyacetophenone, $k(\text{calc})/s^{-1} = 1{\cdot}90 \times 10^{-4} + 4{\cdot}6 \times 10^{-4}$ [A$^-$]

$10^3[A^-]$/M		40	80	120	160	200
$10^6k/s^{-1}$	(obs)	208	225	246	259	276
	(calc)	208	227	245	264	282

p-Carboxyacetophenone, $k(\text{calc})/s^{-1} = 1{\cdot}90 \times 10^{-4} \times 4{\cdot}1 \times 10^{-4}$ [A$^-$]

$10^3[A^-]$/M		38	75	113	151	188
$10^6k/s^{-1}$	(obs)	204	219	242	246	273
	(calc)	206	221	236	252	267

the observed catalytic constant of the anion of *p*-carboxyacetophenone (for which no ring–chain tautomerism is possible) deviates from the Brönsted relation derived from the rather scattered plot for other carboxylate ions: moreover, the small slope of this plot ($\beta = 0{\cdot}4$) implies a low accuracy in deriving the ' true ' dissociation constant for the *ortho*-compound. On the other hand, for the decomposition of nitramide, catalysis by the anion of *p*-carboxyacetophenone accords well with the Brönsted relation ($\beta = 0{\cdot}8$) and the derived quantities for the *ortho*-compound should be reasonably accurate.

The experimental results are given in Tables 3 and 4, in which HX and HY denote respectively the open-chain and ring forms of *o*-carboxyacetophenone.

DISCUSSION

The results for iodination of *o*-carboxyacetophenone in self-buffered solutions [Table 1(a)] show clearly that the ionization of the methyl group is largely by intramolecular proton-transfer to the carboxylate group. The value of the first-order rate constant k, which is the observed zero-order rate constant divided by the concentration of the anion, is independent of anion concentration and of the hydrogen ion concentration over a wide range, even when a large proportion of the substrate is in the protonated form. The magnitude of k, *ca.* 2×10^{-6} s^{-1}, is much too great to be attributed to intermolecular catalysis by water molecules, since for ketones not containing strongly electronegative substituents the latter process has rate constants of *ca.* 10^{-10} s^{-1}.[7] A kinetically equivalent process would be the transfer of methyl protons from the undissociated acid to hydroxide ions, but calculation shows that the observed rate corresponds to a rate constant of $1{\cdot}4 \times 10^4$ l mol^{-1} s^{-1} for this process: this seems improbably high, and in fact measurements by Jones and his collaborators[8] on proton transfer to hydroxide ions from a number of substituted acetophenones give velocity constants of around 1 l mol^{-1} s^{-1}. It therefore seems certain that the observed rate is primarily due to the abstraction of protons from the acetyl by the *ortho*-carboxylate group.

[7] See *e.g.*, R. P. Bell, and O. M. Lidwell, *Proc. Roy. Soc.*, 1940, *A*, **176**, 88.
[8] J. R. Jones, R. E. Marks, and S. C. Subba Rao, *Trans. Faraday Soc.*, 1967, **63**, 111, 993; J. R. Jones, *ibid.*, 1969, **65**, 2138.

The values of k in Table 1(a) show some tendency to decrease in the most acid buffers, but it is doubtful whether this is a real effect, since in these solutions the calculated anion concentration depends considerably on the values assumed for the activity coefficients, and the discrepancy is no greater than the uncertainty in using equation (1) up to $I = 0{\cdot}2$. In subsequent calculations we have used $k_i^H = 2{\cdot}05 \times 10^{-6}$ s^{-1}, *i.e.* the mean value excluding the five most acid buffers. The results fail to show any intramolecular acid catalysis by the carboxy-group in carboxyacetophenones, which would of course produce larger values of k in the more acid solutions. Intramolecular acid catalysis has been detected in the analogous enolization of aliphatic keto-acids,[1] and its absence in the present instance may be attributed to the fact that about 80% of the acid exists in solution as its cyclic tautomer, or to stabilization of the keto-form by hydrogen bonding to the carboxy-group. The latter explanation has been suggested for the absence of detectable intermolecular catalysis by strong acids or metal ions in the enolization of *o*-carboxy- and *o*-hydroxy-acetophenone.[9]

The results for iodination in acetate buffers [Table 1(c)] show clearly a contribution due to proton abstraction by acetate ion, and can be accounted for over a wide range of buffer ratios by the addition of a term $k_{AcO}[AcO^-][A^-]$ to the rate of disappearance of iodine. There are some small systematic discrepancies between the observed and calculated rate constants, but they cannot be rationalized by including in the rate equation extra terms involving [AcOH] or [OH$^-$]. They are probably again due to incorrect assumptions about activity coefficients: in particular, for $r = 10{\cdot}0$ the concentration of acetic acid reached 2M, which constitutes a considerable change of medium.

Our value of $k_{AcO} = 4{\cdot}0 \times 10^{-6}$ l mol^{-1} s^{-1} is similar to that of $2{\cdot}3 \times 10^{-6}$ l mol^{-1} s^{-1} obtained by extrapolating to 25 °C the results of Evans and Gordon [10] for the acetate-catalysed bromination of acetophenone in 75% aqueous acetic acid at 45, 55, and 65 °C. It is also consistent with our failure to observe any intermolecular catalysis involving two *o*-carboxyacetophenone anions, as shown by the absence of any trend with [A$^-$] in the values of k in Tables 1(a) and 1(c). The 'true' acid-base properties of the carboxy-group are represented by $K_{HX} = 3{\cdot}1 \times 10^{-4}$ (Table 3), so that the anion of the substrate might be expected to have an intermolecular catalytic constant of k_{A^-} $4{\cdot}0 \times 10^{-6} \times (1{\cdot}75 \times 10^{-5}/3{\cdot}1 \times 10^{-4})^{0{\cdot}8} = 4 \times 10^{-7}$ l mol^{-1} s^{-1}. Since the maximum value of [A$^-$] in our experiments was 0·04M, the maximum contribution of this type of intermolecular catalysis to the observed value of k would be $4 \times 10^{-7} \times 0{\cdot}04 = 1{\cdot}6 \times 10^{-8}$ s^{-1}, which would escape detection.

The importance of intermolecular catalysis can be conveniently expressed as an 'effective concentration' c_i, equal to the ratio of the first-order constant k_i to the second-order constant k_{A^-}. The calculation in the last paragraph gives $c_i = 2{\cdot}05 \times 10^{-6}/4 \times 10^{-7} = 5$ mol l^{-1}. This is considerably less than $c_i = 56$ mol l^{-1} given by Harper and Bender [2] for carboxyisobutyrophenone, though the values are not strictly comparable, since Harper and Bender made their comparison with the iodination of isobutyrophenone catalysed by benzoate ion, rather than with any intermolecular process involving *o*-carboxyisobutyrophenone itself. As recently shown clearly by Page and Jencks,[11] even very high values of c_i can be accounted for in terms of loss of translational and rotational entropy, without introducing any special concepts. Operationally, c_i may be regarded as the concentration (often hypothetical) at which the inter- and intra-molecular processes would make equal contributions to the reaction rate. This formulation embraces not only entropy effects, but also any differences in activation energy which might favour one or other of the two processes.

The results in pyridine buffers [Table 1(e)] similarly demonstrate intermolecular basic catalysis by pyridine molecules. The constant term in the equation for k(calc) is slightly greater than the value already given for k_i, but the difference can be reasonably attributed to intermolecular catalysis by hydroxide ions. The ratio $k_{py} : k_{AcO}$ is 5·8, which is greater than the ratio of the acid dissociation constants of acetic acid and pyridinium ion (3·0): this is presumably because the reaction with acetate ion is retarded by repulsion by the negative charge on the substrate anion.

The measurements with *p*-carboxyacetophenone [Tables 1(g)—(i)] for which intramolecular proton transfer can be excluded, served mainly for comparison with the *ortho*-compound. The observed rate for the sodium salt at pH 6 might contain contributions from the processes $A^- + H_2O$, $A^- + OH^-$, $HA + OH^-$, and $A^- + A^-$, but the reaction is so slow that no attempt was made to separate these contributions. (If the rate constant for $A^- + A^-$ is assigned the value 4×10^{-7} l mol^{-1} s^{-1}, as estimated for the *ortho*-compound, this would account for the whole of the observed rate.) In any case, the rate is about 300 times less than that observed for *o*-carboxyacetophenone, thus confirming the importance of intramolecular catalysis for the latter compound. The values of k_{AcO} and k_{py} for *p*-carboxyacetophenone are similar to those for the *ortho*-compound, being respectively somewhat smaller and somewhat greater. Since the repulsion between the two negative charges should be less important in the *para*-compound, this suggests that the reaction of the *ortho*-compound with pyridine involves appreciable steric hindrance.

The measurements with deuteriated compounds [Tables 1(b), (d), (f), and (j)] are interpreted along

[9] A. Schellenberger, G. Oehme, and G. Hübner, *Chem. Ber.*, 1965, **98**, 3578.

[10] D. P. Evans and J. J. Gordon, *J. Chem. Soc.*, 1938, 1434. A conversion of units is also involved, since the 'velocity constants' quoted by these authors appear to be expressed as ml 0·02N-thiosulphate per min per 20 ml sample of 0·1M-ketone containing 20 g l^{-1} of sodium acetate!

[11] M. I. Page and W. P. Jencks, *Proc. Nat. Acad. Sci. U.S.A.*, 1971, **68**, 1678.

similar lines. The observed isotope effects are collected in Table (2), which shows that k^H/k^D for the intramolecular process (5·4) is considerably greater than the values found for the intermolecular reactions (3·9, 4·1, and 4·0). The differences in the basic strengths of the groups involved are small, and in any case would be expected to influence k^H/k^D in the opposite direction,[12] so that some other explanation is needed. It may be significant that model calculations [13] predict a strong dependence of the isotope effect upon internuclear distance, so that the higher value for the intramolecular process may depend upon a more favourable distance between the carbon and oxygen atoms between which the proton is transferred.

[12] D. J. Barnes and R. P. Bell, *Proc. Roy. Soc.*, 1970, *A*, **318**, 421.

The measurements on catalysis of the decomposition of nitramide and the mutarotation of glucose (Tables 3 and 4) are of value here chiefly in providing a value for the 'true' basic strength of the anion of *o*-carboxyacetophenone, but our finding that in aqueous solution 81% of the acid exists as the cyclic tautomer may be compared with values of 71 to 84% derived from i.r. and n.m.r. data relating to various non-aqueous solvents.[14]

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[13] R. P. Bell, W. H. Sachs, and R. L. Tranter, *Trans. Faraday Soc.*, 1971, **67**, 1995.

[14] K. Bowden and G. R. Taylor, *J. Chem. Soc.* (*B*), 1971, 1390.