Intramolecular General Acid Catalysis in the Halogenation of Ketones

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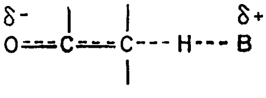
Measurements have been made of the rate of iodination in aqueous solution of 2-oxobicyclo[2.2.2]octane-1-carboxylic acid and its methyl ester. These reactions are of zero order with respect to iodine, the measured velocities representing the rate of ionization or enolization. In self-buffered or acid solutions the observed rate can be represented by $v = k_{\text{H}}[\text{RCO}_2\text{H}][\text{H}^+] + k_1[\text{RCO}_2^-][\text{H}^+] + k_3[\text{RCO}_2\text{H}][\text{RCO}_2^-]$. k_1 is *ca.* 200 times greater than the corresponding rate constant for the methyl ester, which we attribute either to intramolecular general acid catalysis, or to electrostatic stabilization of the transition state for the normal acid-catalysed mechanism of enolization. k_3 is probably attributable to bifunctional catalysis, since the rate of the iodination of the ionized form of the keto-acid, catalysed by acetic acid, is at least 16 times greater than for the corresponding methyl ester. Kinetic measurements on the halogenation of several other keto-carboxylic acids are also reported.

THE halogenation of ketones is catalysed by both acids and bases, and is believed to proceed through the enol or enolate ion. When the rate of these reactions is found to be independent of halogen concentration it is believed that enolization or ionization is the rate-determining step.[1] Thus in general base catalysis the reaction scheme is (1) and if $k_2[\text{X}_2] \gg k_{-1}[\text{BH}^+]$ the

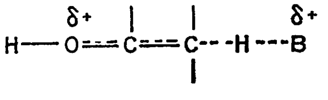
$$\text{SH} \underset{k_{-1}[\text{BH}^+]}{\overset{k_1[\text{B}]}{\rightleftharpoons}} \text{S}^- \xrightarrow{k_2[\text{X}_2]} \text{SX} \qquad (1)$$

observed rate constant is $k_1[\text{B}]$, and the transition state is represented by (I) (for an uncharged base).



$\overset{\delta-}{\text{O}}\mathrel{=\!=}\text{C}\mathrel{=\!=}\text{C}\cdots\text{H}\cdots\overset{\delta+}{\text{B}}$

(I)

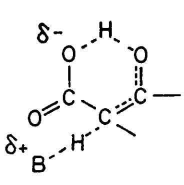


$\text{H}-\overset{\delta+}{\text{O}}\mathrel{=\!=}\text{C}\mathrel{=\!=}\text{C}\cdots\text{H}\cdots\overset{\delta+}{\text{B}}$

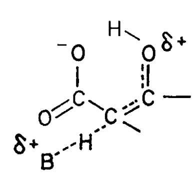
(II)

Intramolecular general base catalysis of this reaction has been demonstrated in several systems containing suitably disposed basic groups.[2] The mechanism for general acid catalysis is generally believed[3] to be its kinetic equivalent, specific acid–general base catalysis, with a transition state represented by (II) (for a positively charged acid). However, it is *a priori* possible[4] that these reactions could involve true general acid catalysis, *i.e.* a rate-determining proton transfer from the general acid to the oxygen atom of the ketone. Attempts to demonstrate bifunctional catalysis in the enolization of ketones have not been successful.[5] Intramolecular general acid catalysis has been observed in the halogenation of some keto-acids,[2] and has been invoked to account for the enhanced rate of enolization of acetoacetic acid compared with its ethyl ester,[6,7] but there are still mechanistic ambiguities.

In species containing both a keto and a carboxy-group intramolecular acid catalysis could formally arise either from the rate-determining proton transfer from the carboxylic acid group to the keto oxygen atom, or from a pre-equilibrium proton transfer with electrostatic or hydrogen-bonding stabilisation involving the ionized carboxy-group.[8] In presence of an uncharged base B (which might be a solvent molecule) the corresponding transition states are (III) and (IV): the latter might be regarded as an extreme case of (III).



(III)

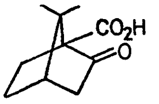


(IV)

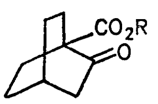
The present paper deals with the kinetics of halogenation of several keto-acids in which the disposition of the groups might favour neighbouring group participation in acid-catalysed enolization.

RESULTS AND DISCUSSION

7,7-Dimethyl-2-oxobicyclo[2.2.1]*heptane-*1*-carboxylic Acid* (V) *and* 2-*Oxobicyclo*[2.2.2]*octane-*1*-carboxylic Acid, or its Ester* (VI).—In order to detect intramolecular



(V)



(VI)

general acid catalysis compounds are required which normally exhibit acid catalysis but which do not readily undergo decarboxylation. Attention was therefore turned to certain β-keto-acids for which decarboxylation would require violation of Bredt's rule.[9]

The kinetics of iodination of 2-oxobicyclo[2.2.2]octane-1-carboxylic acid (VI; R = H) was investigated in hydrochloric acid and self-buffered solutions of varying

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[1] R. P. Bell, 'The Proton in Chemistry,' Cornell University Press, Ithaca, 1959, ch. IX.

[2] R. P. Bell and M. A. D. Fluendy, *Trans. Faraday Soc.*, 1963, **59**, 1623; E. T. Harper and M. L. Bender, *J. Amer. Chem. Soc.*, 1965, **87**, 5625; R. P. Bell, B. G. Cox, and J. B. Henshall, *J.C.S. Perkin II*, 1972, 1232.

[3] G. E. Lienhard and T.-C. Wang, *J. Amer. Chem. Soc.*, 1969, **91**, 1146.

[4] W. P. Jencks, *Chem. Rev.*, 1972, **72**, 705.

[5] G. E. Lienhard and F. H. Anderson, *J. Org. Chem.*, 1967, **32**, 2229; J. K. Coward and T. C. Bruice, *J. Amer. Chem. Soc.*, 1969, **91**, 5339.

[6] K. J. Pedersen, *J. Phys. Chem.*, 1934, **38**, 999.

[7] R. P. Bell and P. De Maria, *Trans. Faraday Soc.*, 1970, **66**, 930.

[8] (*a*) B. Capon, M. I. Page, and G. H. Sankey, *J.C.S. Perkin II*, 1972, 529; (*b*) P. J. Taylor, *ibid.*, p. 1077.

[9] R. Keese and E. P. Krebs, *Angew. Chem. Internat. Edn.*, 1971, **10**, 262.

pH, and at various concentrations of substrate and iodine. The first-order velocity constants k were calculated from the observed zero-order rate of decrease in tri-iodide absorbance at 353 nm by means of equation (2)

$$k = -\frac{K + [\mathrm{I}^-]}{\varepsilon[\mathrm{I}^-][\mathrm{ketone}]} \cdot \frac{\mathrm{d}A}{\mathrm{d}t} \qquad (2)$$

where K ($1{\cdot}40 \times 10^{-3}$ mol dm^{-3}) is the equilibrium constant for $\mathrm{I_3^-} \rightleftharpoons \mathrm{I_2} + \mathrm{I^-}$, ε is the molar absorption coefficient for tri-iodide, and $\mathrm{d}A/\mathrm{d}t$ is the slope of the linear plot of absorbance against time. Acidic solutions of potassium iodide undergo atmospheric oxidation to iodine,[10] and the observed slopes were corrected by simultaneously monitoring a potassium iodide solution of the same acidity. Provided that the distilled water used had been boiled and de-gassed this correction was significant only for $[\mathrm{H^+}] > 5 \times 10^{-3}$M. For $[\mathrm{H^+}] > 2 \times 10^{-2}$M the correction became as high as 30%, and these values were therefore omitted when calculating the parameters of the pH–rate profile. The rates were found to be independent of iodine concentration, and since this compound does not decarboxylate even when heated to 280 °C [11] and undergoes acid catalysed iodination it is clear that the observed rates of iodination are actually the rates of ionization or enolization of the ketone. The first-order rate constants at pH > 2 were found to depend upon the ketone concentration. These constants were measured at two or three ketone concentrations in the range 8×10^{-3}—3×10^{-2}M, and the values for each pH value plotted against the total substrate concentration. The intercept and slope give respectively k' and k'' in equation (3), and the values

$$\mathrm{Rate} = k'([\mathrm{RCO_2H}] + [\mathrm{RCO_2^-}]) + k''([\mathrm{RCO_2H}] + [\mathrm{RCO_2^-}])^2 \qquad (3)$$

of these constants are given in Table 1.

TABLE 1

Iodination of 2-oxobicyclo[2.2.2]octane-1-carboxylic acid at 25 °C (I = 0·2)

k'(calc.) from equation (5) with $k_\mathrm{H} = 7{\cdot}2 \times 10^{-7}$ dm^3 mol^{-1} s^{-1}, $k_0 = 1{\cdot}24 \times 10^{-8}$ s^{-1}, $K_\mathrm{a} = 8{\cdot}05 \times 10^{-5}$

k''(calc.) $= 1{\cdot}25 \times 10^{-6}$. $10^{-\mathrm{pH}}\, K_\mathrm{a}/(K_\mathrm{a} + 10^{-\mathrm{pH}})^2$

pH		1·08	1·30	1·37	1·70	2·01	2·32
$10^{10}k'/\mathrm{s^{-1}}$	Obs.	(824) *	(529) *	425	265	202	158
	Calc.	716	481	427	265	192	156
pH		2·74	2·97	3·16	3·42	3·69	3·80
$10^{10}k'/\mathrm{s^{-1}}$	Obs.	124	122	113	103	93	82
	Calc.	131	122	116	105	90	83
$10^{8}k''/\mathrm{dm^3\,mol^{-1}s^{-1}}$	Obs.	5	10	10	19	19	28
	Calc.	6	9	13	20	27	29
pH		3·98	4·28	4·71	4·93		
$10^{10}k'/\mathrm{s^{-1}}$	Obs.	69	45	36	18		
	Calc.	71	49	24	16		
$10^{8}k''/\mathrm{dm^3\,mol^{-1}s^{-1}}$	Obs.	49	34	24	15		
	Calc.	31	29	18	14		

* These rate constants were omitted when calculating the parameters of equation (5).

The pH profile for k' is shown in Figure 1. It can be represented by equation (4) which is equivalent to (5)

$$k'([\mathrm{RCO_2H}] + [\mathrm{RCO_2^-}]) = k_\mathrm{H}[\mathrm{RCO_2H}][\mathrm{H^+}] + k_0[\mathrm{RCO_2H}] \qquad (4)$$

$$k' = (10^{-2\mathrm{pH}}k_\mathrm{H} + 10^{-\mathrm{pH}}k_0)/(K_\mathrm{a} + 10^{-\mathrm{pH}}) \qquad (5)$$

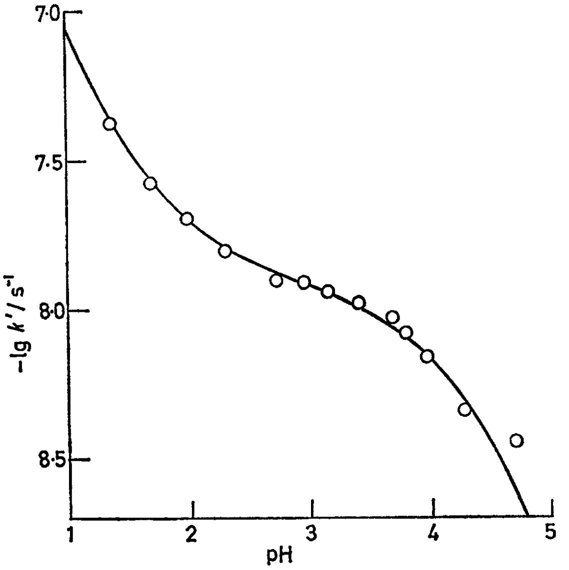

FIGURE 1 Iodination of 2-oxobicyclo[2.2.2]octane-1-carboxylic acid: comparison of equation (5) with experiment

TABLE 2

Iodination of 2-oxobicyclo[2.2.2]octane-1-carboxylic acid in acetate buffers at 25 °C (I = 0·2)

k(corr.) is the first-order constant due to acetate catalysis, obtained from the observed rate by subtracting the contributions represented by equation (3), the numerical values in Table 1 being used.

k(calc.) is obtained from equation (9), with $k_2' = k_4' = 0$, $k_3' + k_5'K_\mathrm{a}^\mathrm{K}/K_\mathrm{a}^\mathrm{A} = 2{\cdot}86 \times 10^{-6}$ dm^3 mol^{-1} s^{-1}, $\alpha = 10^{-\mathrm{pH}}/(K_\mathrm{a}^\mathrm{K} + 10^{-\mathrm{pH}})$, $\beta = 10^{-\mathrm{pH}}/(K_\mathrm{a}^\mathrm{A} + 10^{-\mathrm{pH}})$, $K_\mathrm{a}^\mathrm{K} = 9{\cdot}55 \times 10^{-5}$, $K_\mathrm{a}^\mathrm{A} = 2{\cdot}51 \times 10^{-5}$.

A = [AcOH] + [AcO$^-$]

10^3A/M		20	40	60	80
pH = 3·63, [AcOH] = 9·31[AcO$^-$], [RCO$_2$H] = 2·46[RCO$_2^-$]					
$10^{10}k/\mathrm{s^{-1}}$	Corr.	35	69	107	139
	Calc.	39	79	118	158
pH = 4·33, [AcOH] = 1·87[AcO$^-$], [RCO$_2$H] = 0·49[RCO$_2^-$]					
$10^{10}k/\mathrm{s^{-1}}$	Corr.	58	91	177	230
	Calc.	66	132	197	263
pH = 4·95, [AcOH] = 0·45[AcO$^-$], [RCO$_2$H] = 0·12[RCO$_2^-$]					
$10^{10}k/\mathrm{s^{-1}}$	Corr.	46	94	137	188
	Calc.	42	83	125	166

K_a^K and K_a^A are the dissociation constants of the keto-acid and of acetic acid respectively.

where K_a is the dissociation constant of RCO$_2$H. The line drawn in Figure 1 is calculated from equation (5) with $K_\mathrm{H} = 7{\cdot}12 \times 10^{-7}$ dm^3 mol^{-1} s^{-1}, $k_0 = 1{\cdot}24 \times 10^{-8}$ s^{-1}, and $K_\mathrm{a} = 8{\cdot}05 \times 10^{-5}$ mol dm^{-3}. The last value

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[10] L. Zucker and L. P. Hammett, *J. Amer. Chem. Soc.*, 1939, **61**, 2779.

[11] G. L. Buchanan, N. B. Kean, and R. Taylor, *J.C.S. Chem. Comm.*, 1972, 201; G. L. Buchanan, personal communication.

may be compared with $K_a = 9{\cdot}1\ (\pm 0{\cdot}5) \times 10^{-5}$ determined by pH titration under the same conditions.

The first term on the right hand side of equation (4) represents hydronium ion catalysis of the enolization of the undissociated keto-acid. The corresponding rate constant for the ester (VI; R = Me) was found to have the very similar value $5{\cdot}34 \times 10^{-7}$ dm^3 mol^{-1} s^{-1} (Table 3).

TABLE 3

Iodination of methyl 2-oxobicyclo[2.2.2]octane-1-carboxylate at 25 °C ($I = 0{\cdot}2$)

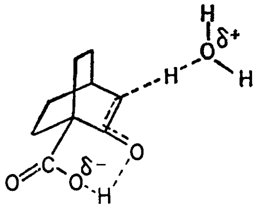
A = [AcOH] + [AcO$^-$]

k(calc.) = $5{\cdot}34 \times 10^{-7}$[H$^+$] + $5{\cdot}5 \times 10^{-8}$[AcOH] + $1{\cdot}3 \times 10^{-7}$[AcO$^-$]

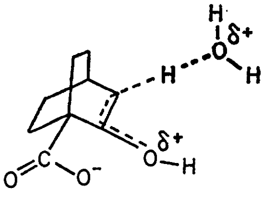
HCl solutions					
10^3[H$^+$]/M		5·0	10	20	50
$\frac{10^{10}k}{\text{s}^{-1}}$	Obs.	24	56	102	294
	Calc.	27	53	107	267
Acetate buffer solutions					
10^3A/M		20	40	60	80
		pH = 3·99, [AcOH] = 4·0[AcO$^-$]			
$\frac{10^{10}k}{\text{s}^{-1}}$	Obs.	20	25	34	60
	Calc.	14	28	41	55
		pH = 5·20, [AcOH] = 0·25[AcO$^-$]			
$\frac{10^{10}k}{\text{s}^{-1}}$	Obs.	26	39	61	96
	Calc.	22	45	67	90

The term in k_0 may represent either the ' spontaneous ' enolization of the undissociated keto-acid, or the kinetically equivalent hydronium ion catalysed enolization of the anion. In the latter event the second-order velocity constant k_1 is related to k_0 by $k_0 = k_1K_a$, giving $k_1 = 1{\cdot}25 \times 10^{-4}$ dm^3 mol^{-1} s^{-1}, which is 180 times greater than k_H, and 230 times greater than the corresponding value for the methyl ester. These facts clearly indicate some form of intramolecular stabilization of the transition state.

Inspection of a Dreiding model of the acid indicates a distance of *ca.* 210 pm between the oxygen atoms of the keto and carboxy-groups, which is favourable for electrostatic or hydrogen-bonding stabilization.[12] Two extreme forms of the transition state are shown as (VII) and (VIII), differing mainly in the position of protons. It is not possible at present to specify the transition state more closely.



(VII)



(VIII)

The term in k'' in equation (3) could alternatively be written as (6) where k'' depends upon pH, and hence upon the buffer ratio, while k_2, k_3, and k_4 do not. The plot of k'' against pH (Figure 2) indicates a bell-shaped profile between pH 2·7 and 5·0, suggesting that the term involving k_3 is dominant: this is consistent with the fact that there is no detectable dependence of rate upon substrate concentration below pH 2. The results are not accurate enough to warrant detailed analysis, but the solid line in Figure 2 is calculated from equation (6) with $k_3 = 1{\cdot}25 \times 10^{-6}$ dm^3 mol^{-1} s^{-1}, p$K = 4{\cdot}02$, and $k_2 = k_4 = 0$.

$$\begin{aligned}\text{Rate} &= k''([\text{RCO}_2\text{H}] + [\text{RCO}_2^-])^2 \\ &= k_2[\text{RCO}_2\text{H}]^2 + k_3[\text{RCO}_2\text{H}][\text{RCO}_2^-] + k_4[\text{RCO}_2^-]^2 \quad (6)\end{aligned}$$

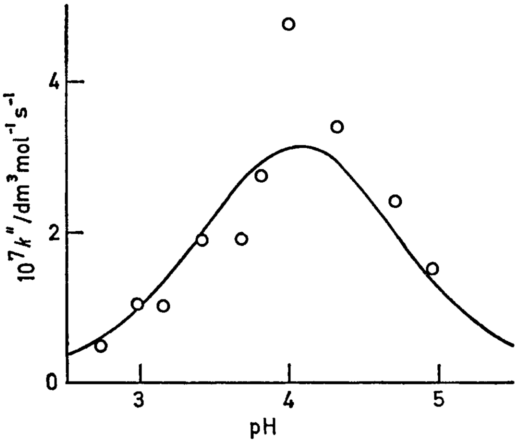


FIGURE 2 Iodination of 2-oxobicyclo[2.2.2]octane-1-carboxylic acid: comparison of equation (6) with experiment

The kinetics of the iodination of compound (VI; R = H) were also studied in acetate buffers. The results are given in Table 2, and plots of the observed first-order rate constants against the total buffer concentration are shown in Figure 3. The contribution of

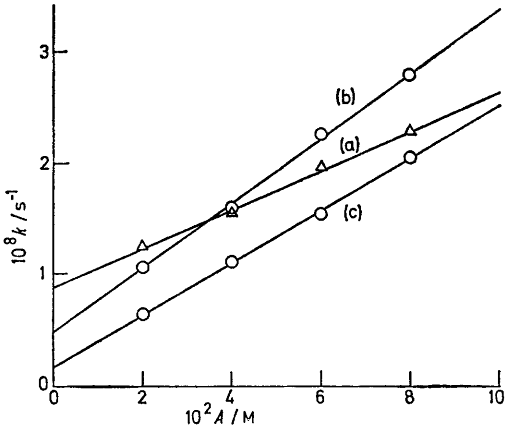


FIGURE 3 Iodination of 2-oxobicyclo[2.2.2]octane-1-carboxylic acid in acetate buffer solutions: plots of observed first-order rate constants against total buffer concentration at (a) pH 3·63, (b) pH 4·33, and (c) pH 4·95

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[12] G. C. Pimentel and A. L. McClellan, ' The Hydrogen Bond,' Freeman, San Francisco, 1960, p. 260.

catalysis by acetate species to the observed rate can be written formally as equation (7). The terms in k_3' and

$$k_2'[\mathrm{RCO_2H}][\mathrm{AcOH}] + k_3'[\mathrm{RCO_2H}][\mathrm{AcO^-}] + k_4'[\mathrm{RCO_2^-}][\mathrm{AcO^-}] + k_5'[\mathrm{RCO_2}][\mathrm{AcOH}] \quad (7)$$

k_5' are in fact kinetically indistinguishable, since expression (7) can be written alternatively as (8) where K_a^K

$$k_2'[\mathrm{RCO_2H}][\mathrm{AcOH}] + (k_3' + k_5'K_a^K/K_a^A)[\mathrm{RCO_2H}][\mathrm{AcO^-}] + k_4'[\mathrm{RCO_2^-}][\mathrm{AcO^-}] \quad (8)$$

and K_a^A are the dissociation constants of the keto-acid and acetic acid respectively. The slopes of the lines in Figure 3 thus represent compound catalytic constants k_c', given by equation (9) where α and β represent the

$$k_c' = k_2'\alpha\beta + (k_3' + k_5'K_a^K/K_a^A)\alpha(1 - \beta) + k_4'(1 - \alpha)(1 - \beta) \quad (9)$$

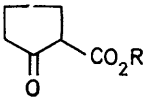
fractions of the keto-carboxylic and acetic acid respectively which are in the undissociated form, as calculated from the equations given in Table 2. A plot of k_c'/α against $1 - \beta$ is a straight line passing through the origin, indicating no detectable contribution from the terms in k_2' and k_4'. The slope of this line gives $k_3' + k_5'K_a^K/K_a^A = 2{\cdot}86 \times 10^{-6}$ dm^3 mol^{-1} s^{-1}: this is therefore the maximum possible value of k_3', while the maximum possible value of k_5' is $2{\cdot}86 \times 10^{-6}K_a^A/K_a^K = 7{\cdot}52 \times 10^{-7}$ dm^3 mol^{-1} s^{-1}. The value attributed to k_3' is somewhat greater than that found for the reaction $\mathrm{RCO_2H} + \mathrm{RCO_2^-}$ ($k_3 = 1{\cdot}25 \times 10^{-6}$ dm^3 mol^{-1} s^{-1}): this is as it should be, since $\mathrm{AcO^-}$ is a somewhat stronger base than $\mathrm{RCO_2^-}$.

It was not possible to obtain accurate results for catalysis by acetate species of the iodination of the corresponding keto-ester (VI; R = Me), since reaction is extremely slow even in saturated solutions of the ester. The results are given in Table 3, which also contains results for catalysis by hydrogen ions. The approximate values $k_{\mathrm{AcO}} \simeq 1{\cdot}3 \times 10^{-7}$ dm^3 mol^{-1} s^{-1}, and $k_{\mathrm{AcOH}} \simeq 5{\cdot}5 \times 10^{-8}$ dm^3 mol^{-1} s^{-1} may be compared with those found [13] for cyclopentanone ($k_{\mathrm{AcO}} = 7{\cdot}45 \times 10^{-7}$, $k_{\mathrm{AcOH}} = 1{\cdot}80 \times 10^{-7}$) and for cyclohexanone ($k_{\mathrm{AcO}} = 5{\cdot}88 \times 10^{-7}$, $k_{\mathrm{AcOH}} = 3{\cdot}26 \times 10^{-7}$).

In seeking evidence of intramolecular assistance in the keto-acid by comparing rate constants with those for the corresponding ester, an apparent difficulty arises because of the kinetic ambiguity of the second term of equations (8) and (9). However, the transition states arising from $\mathrm{RCO_2H} + \mathrm{AcO^-}$ and $\mathrm{RCO_2^-} + \mathrm{AcOH}$ are at least very similar (if we exclude the possibility of a rate-determining proton transfer from acetic acid to the keto oxygen atom) since their extreme forms are represented by (VII) and (VIII) with the water molecule replaced by an acetate ion: in fact they may well have an identical structure intermediate between these extremes. In this event the separation of the observed rate into two terms [k_3' and k_5' in (8) and (9)] is meaningless, and the best comparison is between the observed second-order constant for $\mathrm{RCO_2H} + \mathrm{AcO^-}$ ($2{\cdot}86 \times 10^{-6}$ dm^3 mol^{-1} s^{-1}) and the value given above for $\mathrm{RCO_2Me} + \mathrm{AcO^-}$ ($k_{\mathrm{AcO}} = 1{\cdot}3 \times 10^{-7}$ dm^3 mol^{-1} s^{-1}); this indicates an approximately 22-fold acceleration due to intramolecular catalysis by the carboxy-group. Alternatively, if the observed rate for the acid is interpreted in terms of the reaction $\mathrm{RCO_2^-} + \mathrm{AcOH}$ ($k_5 = 7{\cdot}5 \times 10^{-7}$ dm^3 mol^{-1} s^{-1}) this can be compared with $\mathrm{RCO_2Me} + \mathrm{AcOH}$ ($k_{\mathrm{AcOH}} = 5{\cdot}5 \times 10^{-8}$ dm^3 mol^{-1} s^{-1}), corresponding to a 14-fold acceleration: however, this is a somewhat less satisfactory comparison because of the different charges borne by the two substrates. In any event there is good evidence that bifunctional catalysis occurs in the iodination of 2-oxobicyclo[2.2.2]octane-1-carboxylic acid in acetate buffer solutions. The reaction is considerably facilitated by hydrogen bonding or electrostatic stabilization of the transition state, as shown in (VII) and (VIII) for the water-catalysed reaction.

The iodination of camphor and of compound (V) takes place too slowly at 25° for reliable kinetic measurements. The first-order constants are less than 10^{-9} s^{-1} for both compounds both in 0·1M-hydrochloric acid and in 0·2M-acetate buffer of pH 5·5.

2-Oxocyclopentanecarboxylic Acid (IX), *4,4,7-Trimethyl-3-oxobicyclo*[2.2.1]*heptane-2-carboxylic Acid* (X), *and their Esters*.—The reaction of iodine with several of these compounds does not go to completion, and bromine was therefore used as a scavenger, the reaction being monitored by observing the absorption of tribromide ion at 378 nm. More than one equivalent of bromine was added, and under these conditions the reaction followed a first-order course, and one equivalent of bromine was consumed, so that a first-order velocity constant can be derived without a knowledge of the exact concentrations of the reactants, or of the molar absorption coefficient of the bromine species present. In practice the absorbance continued to decrease slowly even after many half-lives, presumably because of a slow reaction with a second molecule of bromine. The velocity constants were therefore calculated from the observations over the first three half-lives by means of a computer program which treated the (hypothetical) absorbance at infinite time as an adjustable parameter. The velocity constants were independent of the concentrations of bromine and of hydrogen ion, showing that they represent rates of ionization or enolization of the ketone, catalysed only by solvent molecules.



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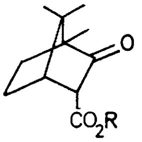
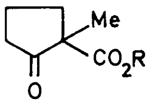


(X)



(XI)

The results are given in Table 4. For compound (IX; R = Et) the value obtained for velocity constant of the water catalysed reaction is in reasonable agreement with previous work,[13] which gave $k_0 = 2{\cdot}30 \times 10^{-3}$ s^{-1}.* Compound (X; R = H) was found to be a mixture of 30% *exo*- and 70% *endo*-isomers (see Experimental section), but the bromination reactions showed no departure from first-order kinetics, and since it is known [16] that an *exo*-proton is more readily removed than an *endo*-proton, we assume that our observed rate-constants refer to the 2-*endo*-isomer. The same applies to 2-*endo*-ethyl ester, for which the *endo* : *exo* ratio was 5 : 1.

TABLE 4

Bromination of 2-oxocyclopentanecarboxylic acid (IX), 4,4,7-trimethyl-3-oxobicyclo[2.2.1]heptane-2-carboxylic acid (X), and their esters in hydrochloric acid solutions at 25 °C

[H+] represents the initial value. Observed velocity constants are the mean of two determinations

$[H^+]$/M	1·0	10^{-1}	10^{-2}	10^{-3}	10^{-4}
(IX; R = H), $k_0 = 5{\cdot}2 \times 10^{-2}$ s^{-1}					
10^3k/s^{-1}	(48) *	53	51		
(IX; R = Et), $k_0 = 2{\cdot}14 \times 10^{-3}$ s^{-1}					
10^5k/s^{-1}	(291) *	219	213	214	212
(X; R = H), $k_0 = 6{\cdot}4 \times 10^{-4}$ s^{-1}					
10^5k/s^{-1}	(55) *	61	70	64	58
(X; R = Me), $k_0 = 6{\cdot}1 \times 10^{-5}$ s^{-1}					
10^6k/s^{-1}	(73) *	62	60	60	61

* These values were omitted when taking the mean.

Table 4 shows that for compounds (IX) and (X) conversion of the acid into the ester causes rate reductions by factors of 24 and 11 respectively. This may indicate that for the acids the transition state is stabilized by interaction between the carboxy-group and the keto oxygen atom, similar to that shown in structures (VII) and (VIII); the same type of explanation has been given [6] for the fact that the water-catalysed bromination of acetoacetic acid is 60 times faster than that of its ethyl ester.[7] Our results at different hydrogen ion concentrations do not reveal any catalysis by hydronium ions, though such catalysis might be obscured by the high rate of the water catalysed reaction.

1-*Methyl-2-oxocyclopentanecarboxylic Acid and its Ethyl Ester*.—In these compounds (XI; R = H or Et) there is no proton which can be activated by both the keto and the carboxy- (or ethoxycarbonyl) groups, and the only enolizable hydrogen atom should be similar in reactivity to those in cyclopentanone. The halogenation of these compounds should also be catalysed by acids, and it was hoped that a comparison between the acid and its ester would give further evidence for intramolecular assistance in the former.

The iodination of the ester (XI; R = Et) was studied at a number of hydrogen ion concentrations, and at various concentrations of substrate and iodine, the substrate being always present in large excess. The rate was found to be independent of the concentration of iodine and proportional to that of substrate. The correction for the atmospheric oxidation of iodide was negligible for $[H^+] < 5 \times 10^{-2}$M, and amounted to only 3% in 0·1M-hydrochloric acid. In the most acid solutions the iodine did not disappear completely, and the rate constants were obtained from the initial part of the reaction plot. The results are summarized in Table 5, in which each first-order rate constant represents the mean of at least two experiments. These rate-constants are well represented by $k = 3{\cdot}8 \times 10^{-8} + 9{\cdot}35 \times 10^{-6}[H^+]$. The first term refers to the water-catalysed reaction, and is not known with any certainty. On the other hand, a value of *ca.* 9×10^{-6} dm^3 mol^{-1} s^{-1} for the catalytic constant of hydronium ion is well established, and may be compared with $7{\cdot}0 \times 10^{-5}$ dm^3 mol^{-1} s^{-1} for the corresponding reaction of cyclopentanone.[17] Since the latter compound contains four equivalent hydrogens adjacent to the carbonyl group, compared with two in compound (XI), the ethoxycarbonyl group has only a small effect on the reactivity of the enolizable hydrogen.

TABLE 5

Iodination of ethyl 1-methyl-2-oxocyclopentanecarboxylate in hydrochloric acid solutions at 25 °C

$k(\text{calc.}) = 3{\cdot}8 \times 10^{-8} + 9{\cdot}35 \times 10^{-6}[H^+]$

$10^3[H^+]$/M		100	50	20	10
$\frac{10^9k}{s^{-1}}$	Obs.	964	520	234	119
	Calc.	973	506	225	135

The iodination of compound (XI; R = H) was studied under conditions similar to those used for the ester (zero-order reactions), and bromination was also studied in solutions containing more than one equivalent of bromine, when the reaction followed a first-order course. The observed first-order constants are collected in Table 6.

TABLE 6

Halogenation of 1-methyl-2-oxocyclopentanecarboxylic acid in hydrochloric acid solutions at 25 °C

(a) Bromination
(b) Iodine added initially
(c) Iodine added after 120 min
(d) Iodine added after 240 min

$[H^+]$/M		1·0	0·1	0·05	0·01	0·004	0·002
$\frac{10^6k}{s^{-1}}$	(a)		97		100		
	(b)	89	87	85	84	75	67
	(c)		46		41	43	30
	(d)		22			22	

Although the rate is independent of halogen concentration it cannot be attributed to an enolization process, since it is at least 2000 times greater than the water-

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* A similar study of ethyl 2-oxocyclohexanone carboxylate gave much higher rates than those previously reported.[14] However, an indirect confirmation of the earlier low value has recently been published,[15] and the reaction needs further investigation.

[13] R. P. Bell, R. D. Smith, and L. A. Woodward, *Proc. Roy. Soc.*, 1948, *A*, **192**, 479.

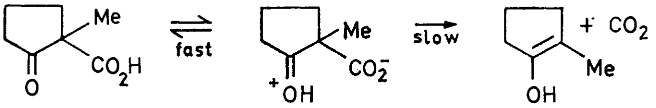
[14] R. P. Bell and H. L. Goldsmith, *Proc. Roy. Soc.*, 1951, *A*, **210**, 322.

[15] A. J. Kirby and G. Meyer, *J.C.S. Perkin II*, 1972, 1446.

[16] T. T. Tidewell, *J. Amer. Chem. Soc.*, 1970, **92**, 1448; F. G. Bordwell and K. C. Yee, *ibid.*, pp. 5933, 5939.

[17] M. I. Page, unpublished results.

catalysed rate for the ester, and shows little variation with hydrogen ion concentration over a wide range. It seems certain that the rate being measured is that of decarboxylation, according to the Scheme, the enol of cyclopentanone then reacting rapidly with halogen. The observed rate is similar to that reported[18] for the decarboxylation of α,α-dimethylacetoacetic acid ($3{\cdot}1 \times 10^{-5}$ s^{-1}), and further confirmation comes from experiments in which the solution of substrate was kept for 120 and 240 min before adding iodine: these times represent respectively one and two half-lives for the bromination reaction. Table 6 shows that the effect of this delay is to reduce the apparent first-order constants for iodination by factors of two and four respectively. This is readily explicable on the decarboxylation hypothesis, since in the absence of halogen the cyclopentanone enol will be converted to the keto form, which can only halogenate by slow enolization, while the amount of the original substrate remaining will be reduced to one half and one quarter after 120 and 240 min respectively. It is therefore not possible to make any comparison between rates of enolization for the acid and ester represented by (XI).



SCHEME

EXPERIMENTAL

Materials.—Compound (IX; R = Et) was a commercial product, which after distillation was >98% pure by g.l.c.

Compound (X; R = H) was prepared by the carbonation procedure of Normant,[19] m.p. 133—134·5 °C (lit.,[19] 128 °C) (Found: C, 67·55; H, 8·25. Calc. for $C_{11}H_{16}O_3$: C, 67·3; H, 8·2%); single spot on t.l.c., polyamide R_F 0·6 ($CHCl_3$), 0·8 (MeOH), silica R_F, 0·5 (4% acetic acid in 3 : 1 benzene–ethyl acetate); $\nu_{max.}$ ($1{\cdot}5 \times 10^{-3}$M in CCl_4) 1780, 1750, 1730, 1708, 3530, and broad peak at 3300 cm^{-1}. The ^1H n.m.r. spectrum shows the compound to be a mixture of 70% *endo*-carboxy-isomer and 30% *exo*-isomer; *exo*-isomer, τ ($CDCl_3$) 8·98, 9·05, 9·12(s), 7·08 (s, 2-*endo*-H), and 7·28 (d, $J_{1,6\,exo}$ 4 Hz, 1-H); *endo*-isomer, τ ($CDCl_3$) 6·60 (d, $J_{1,2\,exo}$ 5 Hz, 2-*exo*-H) and 7·50 (t, 1-H).

Compound (X; R = Me) was prepared by treating the acid with either diazomethane or acidified methanol. T.l.c. gave a single spot, and g.l.c. (Carbowax, Apiezon) only one peak, but the ^1H n.m.r. spectrum again revealed the presence of two isomers (20% *exo*-isomer); *exo*-isomer, τ ($CDCl_3$) 7·12 (s, 2-*endo*-H), 7·33 (d, $J_{1.6\,exo}$ 4 Hz, 1-H), 6·37(s), 9·01, 9·08, and 9·14(s); *endo*-isomer, τ ($CDCl_3$) 6·67 (dd, $J_{1,2\,exo}$ 4·8, $J_{2\,exo,6\,exo}$ 1·2 Hz, 2-*exo*-H) and 7·57 (t, 1-H), $\nu_{max.}$ (Nujol) 1760 and 1725 cm^{-1}. Equilibration of the isomers in 20% aqueous dioxan (pH 8), aqueous sodium hydroxide, or methanolic sodium methoxide gave about 25% *exo*- and 75% *endo*-isomer.

Compound (XI) was prepared as described by Nicole and Berlinguet.[20] The product was >99% pure by g.l.c. with traces of three impurities which were not ethyl adipate or (IX; R = Et). The u.v. spectrum in 0·1M-sodium hydroxide showed that <0·1% of unmethylated compound was present.

7,7-Dimethyl-2-oxobicyclo[2.2.1]heptane-1-carboxylic acid was prepared by a published method.[21]

2-Oxobicyclo[2.2.2]octane-1-carboxylic acid was prepared by the procedure of Buchanan,[22] m.p. 147—148 °C after three recrystallizations from benzene. Treatment of this acid with ethereal diazomethane gave the methyl ester, >98% pure by g.l.c. (5% QFI, 130 °C).

Other materials were of AnalaR grade.

Kinetic Measurements.—Self-buffered solutions of compound (VI; R = H) were prepared by adding sodium hydroxide solution to solutions of the acid.

Solutions of (IX; R = H) were prepared by dissolving a known weight of the ethyl ester in aqueous acetonitrile, adding an excess of alkali, leaving for a few hours, and then carefully acidifying the ice-cold solution to pH *ca*. 7. The solutions were then made up to a known volume with water and used immediately. The final solutions contained <1% acetonitrile.

The pH of all solutions was checked before and after a kinetic experiment, and if it had changed by more than 0·03 the experiment was rejected. Unless otherwise stated, the ionic strength was made up to $I = 0{\cdot}2$ by adding potassium chloride.

In iodination experiments the reaction solutions contained between 0·05 and 0·1M-iodide ions, and the initial iodine concentrations were in the range 2×10^{-5}—8×10^{-5}M. The concentration of substrate was between 4×10^{-3} and 3×10^{-2}M. In bromination experiments the initial concentration of bromine was between 1×10^{-3} and 3×10^{-3}M, and that of bromide ion between 0·05 and 0·1M.

The change of absorbance was followed on a Gilford 2400 recording spectrophotometer having a cell compartment controlled at 25 ± 0·05 °C. For reactions following a first-order course the output of the spectrophotometer was fed to a Digiac, and the data stored there subsequently punched onto tape. The first-order rate constants were determined from a generalized least-squares program, in which the rate constant and the initial and final values of the absorbance are all allowed to vary. The observed values of k' in Table 1 were fitted to equation (5) by a generalized least-squares method described previously.[8a]

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