Kinetic Hydrogen Isotope Effects in the Halogenation of 2-Oxocyclohexanecarboxylic Acid and its Methyl Ester

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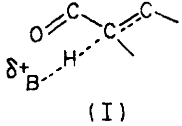
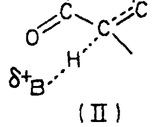
Measurements have been made on the rates of bromination of 2-oxocyclohexanecarboxylic acid and of bromination and iodination of methyl 2-oxocyclohexanecarboxylate. The observed rates are independent of the nature and concentration of the halogen involved and represent the rates of ionization or enolisation of the substrates. The reactions are base-catalysed and catalytic constants and kinetic hydrogen isotope effects for some carboxylate anions have been determined. Under comparable conditions, 2-oxocyclohexanecarboxylic acid is halogenated 500—1000 times more rapidly than is its methyl ester. Observed isotope effects (k_H/k_D) in the halogenation of the acid are high and relatively constant for the bases studied, varying between 7·2 for the uncatalysed reaction to 8·0 for acetate catalysis. Corresponding values for the ester vary between 4·2 (uncatalysed) and 7·5 (acetate catalysis) The results indicate a considerable degree of participation of the carboxylic acid group in the halogenation reaction.

RECENTLY Bell and Page[1] have reported rates of ionization or enolisation of a number of keto-acids in which the carboxylic acid group is suitably placed to assist the ionization, either by donating a proton to the oxygen atom of the ketone during the rate-determining step (I) or by the ionized carboxylate group stabilizing the protonated oxygen atom of the ketone (formed in a pre-equilibrium proton transfer) (II).



(I)



(II)

Rate enhancements of the keto-acids as compared with the corresponding alkyl esters were found to vary between 20-fold and over 200-fold, indicating a significant degree of participation by the carboxylate group.

Kirby and Meyer[2] have also found considerable enhancement of the rate of ketonization of 2-hydroxycyclohex-1-enecarboxylic acid, attributable to the catalytic effect of the neighbouring carboxylate group.

In this paper we report the rates and hydrogen isotope effects for the halogenation of 2-oxocyclohexanecarboxylate and of its methyl ester. For these reactions the rate is independent of the concentration or nature of the halogen involved (Br_2 or I_2), indicating that the rate-determining step is the transfer of a proton from the active C–H group to a base catalyst.

EXPERIMENTAL

Materials.—2-Oxocyclohexanecarboxylic acid, prepared and isolated according to the method reported by Corey,[3] was stable provided that it was stored at or below 0 °C. Corey[3] has shown that addition of 2 mol. equiv. of bromine to an aqueous solution of the acid in the presence of an acetate buffer results in the rapid uptake 1 mol. equiv. of Br_2 (presumably to give 1-bromo-2-oxocyclohexanecarboxylic acid), followed by a relatively slow uptake of a further mol. equiv., during which decarboxylation takes place, to give 2,2-dibromocyclohexanone. Methyl 2-oxocyclohexanecarboxylate was donated by Dr. R. L. Hafter. Inorganic materials were of AnalaR grade.

Kinetic Measurements.—The rate of disappearance of

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[1] R. P. Bell and M. I. Page, *J.C.S. Perkin II*, 1973, 1681.
[2] A. J. Kirby and G. Meyer, *J.C.S. Perkin II*, 1972, 1446.
[3] E. J. Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 3297.

bromine or iodine was followed spectrophotometrically by measurements at 398 or 353 nm, respectively with a Gilford 2400 instrument. Kinetic measurements were made at 10·0 ± 0·2 °C (keto-acid) and 25·0 ± 0·2 °C (keto-ester).

pK_a *Determinations.*—The pK_a value of the keto-acid was determined by studying the absorption at 400 nm of 2,4-dinitrophenol ($8{\cdot}5 \times 10^{-5}$M) in solutions containing various ratios of the neutral and anionic forms of the acid (*ca.* 9×10^{-3}M). Measurements were carried out at 23 and 10 °C.

RESULTS

pK_a *Value of* 2-*Oxocyclohexanecarboxylic Acid.*—From measurements of the absorption of 2,4-dinitrophenol (DNP), at 10 °C, $R = K_a(\text{keto-acid})/K_a(\text{DNP}) = 1{\cdot}81 \pm 0{\cdot}2$; at 23 °C, $R = 1{\cdot}40 \pm 0{\cdot}05$. The K_a value of 2,4-dinitrophenol has been given as $7{\cdot}76 \times 10^{-5}$ at 25 °C.[4] By measuring the absorption of 2,4-dinitrophenol in acetate buffers at 23 and 10 °C, we obtained values of $7{\cdot}61 \times 10^{-5}$ and $6{\cdot}26 \times 10^{-5}$, respectively. Combining these values with the foregoing values of R gave $K_a(\text{keto-acid}) = 1{\cdot}13 \times 10^{-4}$, *i.e.* $pK_a = 3{\cdot}95$ at 10 °C. The corresponding values at 23 °C were $1{\cdot}07 \times 10^{-4}$ and 3·90.

Bromination of 2-*Oxocyclohexanecarboxylic Acid.*—(i) *In acid solution.* Rates were measured in dilute aqueous perchloric acid. All solutions contained 0·05M-NaBr; initial bromine concentrations were *ca.* $1{\cdot}5 \times 10^{-3}$ mol l^{-1} and keto-acid concentrations *ca.* 10^{-3} mol l^{-1}. Ionic strength was maintained at 0·15 by addition of $NaClO_4$. Reactions were initiated by injection of *ca.* 30 µl of a stock solution of the keto-acid (*ca.* 0·1M) to the other reactants in a spectrophotometric cell. There was no instantaneous reaction with bromine, indicating the absence of any appreciable amount of enol.

The observed rate law was of the form shown in equation (1), where RCO_2H represents the keto-acid and $[Br_2^*]$ the total bromine concentration ($[Br_2^*] = [Br_2] + [Br_3^-]$).

$$d[Br_2^*]/dt = d[RCO_2H]/dt = k_0[RCO_2H] \qquad (1)$$

Values of the observed first order rate constant, k_0, are given in Table 1. These values give $k_0 = 1{\cdot}34 \pm 0{\cdot}04$ s^{-1} and show that the rate is independent of the acid concentration over the range studied.

TABLE 1

Rates of bromination of 2-oxocyclohexanecarboxylic acid in dilute $HClO_4$ solutions at 10 °C

[NaBr] = 0·05 mol dm^{-3}; ionic strength = 0·15.

$[HClO_4]$/mol dm^{-3}	0·0625	0·01	0·02	0·05	0·10	0·20 *
$10^2\,k$/s^{-1}	1·34	1·32	1·38	1·29	1·32	1·41

* Ionic strength = 0·25.

(ii) *In the presence of added base.* Reactions were carried out in chloroacetate, β-chloropropionate, and acetate buffers with varying buffer ratios. Concentrations of NaBr, Br_2, keto-acid were the same as for the reactions in acid solution. Ionic strength was maintained at 0·15 by the addition of $NaClO_4$. In all cases reactions were of the first order, with the observed rate law given by equation (2), in which RCO_2H and RCO_2^- represent the neutral and ionized forms of the keto-acid. The observed rate constants were consistent with the dominant reaction being that between RCO_2H and B (or the kinetically equivalent reaction between RCO_2^- and BH^+), where B represents the added base. Under these conditions the rate law will be given by equations (3) and (4). It can readily be shown that k_e and k' are related by equation (5). The fraction $[RCO_2H]/\{[RCO_2H] + [RCO_2^-]\}$, *i.e.* the fraction of un-ionized keto-acid can readily be calculated by using the known acidity constant of the various carboxylic acids at 10 °C.[5] The following values of the catalytic constants were found to fit the observed rate constants (k_e): $k_0 = 1{\cdot}34 \times 10^{-2}$ s^{-1}; k_B(chloroacetate) = $20{\cdot}9 \times 10^{-2}$; k_B(β-chloropropionate) = $78{\cdot}7 \times 10^{-2}$; k_B(acetate) = 121×10^{-2} dm^3 mol^{-1} s^{-1}. The observed rate constants in the various buffer solutions, together with those calculated from equation (4) and (5), are listed in Table 2.

$$-d[Br_2^*]/dt = -d\{[RCO_2H] + [RCO_2^-]\}/dt = k_e\{[RCO_2H] + RCO_2^-]\} \qquad (2)$$

$$-d\{[RCO_2H] + [RCO_2^-]\}/dt = k'[RCO_2H] \qquad (3)$$

$$k' = k_0 + k_B[B] \qquad (4)$$

$$k_e = k'[RCO_2H]/\{[RCO_2H] + [RCO_2^-]\} \qquad (5)$$

(iii) *Kinetic deuterium isotope effects.* A solution (0·1M) of 2-oxo[1-^{2}H]cyclohexanecarboxylic acid was prepared by dissolving 2-oxocyclohexanecarboxylic acid in D_2O and leaving the solution for at least 8 half lives. Bromination reactions were carried out by adding *ca.* 50 µl of this solution to *ca.* 2·5 ml of a solution containing appropriate amounts of Br_2, NaBr, and various buffers in a spectrophotometric cell. The observed rate constants were analysed in terms of equations (4) and (5) as for the corresponding [^{1}H]ketone. For the slowest brominations of the deuteriated ketones, a correction to the observed infinity value was required to allow for the effect of the subsequent bromination reaction (to give 2,2-dibromocyclohexanone). The rate of the first bromination step was always at least 10 times that of the subsequent step so that corrections were small.

Table 3 lists the observed rate constants for the bromination (k_e^D) in chloroacetate, β-chloropropionate, and acetate buffers. The resulting catalytic constants [equations (4) and (5)], together with the kinetic isotope effects, are listed in Table 4.

(iv) *Reactions in* D_2O *as solvent.* Rates of bromination in D_2O containing 0·06M-$DClO_4$ (prepared by dilution of 12M-$HClO_4$ with D_2O) were measured. Reaction solutions (after addition of *ca.* 50 µl of keto-acid in H_2O per 2·5 ml of reaction mixture) contained 97% D_2O. The results gave $k_0(D_2O) = 6{\cdot}30\ (\pm 0{\cdot}03) \times 10^{-3}$ s^{-1}, which corresponds to a solvent deuterium isotope effect $[k_0(H_2O)/k_0(D_2O)]$ of $2{\cdot}1_3$.

Halogenation of Methyl 2-*Oxocyclohexanecarboxylate.*—Rates and deuterium isotope effects for the bromination and iodination of the keto-ester were determined in chloroacetate and acetate buffers at 25 °C. The reactions are considerably slower than those of the keto-acid and for some reactions (particularly for the deuterio-compound) evaporation of Br_2 during the reaction was a problem. For this reason iodination rates only were obtained in some cases. For the bromination reactions, initial bromine concentrations were *ca.* 10^{-3} mol l^{-1}, sodium bromide concentrations 0·2 mol l^{-1}, and initial ketone concentrations

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[4] R. G. Bates and G. Schwarzenback, *Helv. Chim. Acta*, 1954, **37**, 1069.

[5] R. A. Robinson and R. H. Stokes, ' Electrolyte Solutions,' 2nd edn., Butterworths, London, 1959.

TABLE 2

Rates of bromination of 2-oxocyclohexanecarboxylic acid in various buffer solutions at 10 °C

[NaBr] = 0·05M; ionic strength = 0·15

Base (B)	10^2[B]/mol dm^{-3}	r [a]	% RCO_2H [b]	10^3k_e (obs.)/s^{-1}	10^3k_e (calc.) [c]/s^{-1}
(H_2O) [d]			100	13·4	13·4
$ClCH_2{\cdot}CO_2^-$	1·80	1·02	93·0	15·3	16·0
	3·00	1·02	93·0	17·0	18·2
	4·30	1·02	93·0	20·8	20·7
	5·40	1·02	93·0	22·6	23·0
	4·00	0·515	87·0	18·3	18·9
	5·00	0·212	72·0	16·3	17·2
$ClCH_2{\cdot}CH_2{\cdot}CO_2^-$	1·50	2·20	61·0	15·2	15·4
	2·50	2·20	61·0	21·0	20·2
	3·50	2·20	61·0	25·2	25·0
	4·50	2·20	61·0	30·4	29·8
$MeCO_2^-$	1·00	9·0	58·0	15·3	14·7
	2·00	4·0	38·0	14·9	14·3
	2·50	4·0	38·0	16·8	16·6
	3·50	4·0	38·0	21·1	21·2
	4·50	4·0	38·0	25·3	25·8
	3·00	2·33	26·4	12·7	13·1
	3·00	1·00	13·3	6·60	6·60
	4·00	0·50	7·1	5·20	4·40
	5·00	0·20	2·98	2·53	2·20

[a] r = [A]/[B] where A represents the acidic component of the buffer. [b] % Of un-ionized form of keto-acid. [c] Values calculated from equations (4) and (5). [d] See Table 1.

TABLE 3

Rates of bromination of 2-oxo[1-^{2}H]cyclohexane-carboxylic acid in various buffers at 10 °C

[NaBr] = 0·05M; ionic strength = 0·15

Base (B)	10^2[B]/mol dm^{-3}	r [a]	% RCO_2H [b]	$10^3k^D_e$ (obs.)/s^{-1}	$10^3k^D_e$ (calc.) [c]/s^{-1}
(H_2O)			100	1·85 (±0·05) [d]	1·85
$ClCH_2{\cdot}CO_2^-$	1·80	1·00	90	2·05	2·11
	3·00	1·00	90	2·33	2·40
	4·20	1·00	90	2·55	2·69
	5·40	1·00	90	2·95	2·98
$ClCH_2{\cdot}CH_2{\cdot}CO_2^-$	1·50	2·20	61·0	2·05	2·07
	2·50	2·20	61·0	2·65	2·70
	3·50	2·20	61·0	3·29	3·33
	4·50	2·20	61·0	3·95	3·96
$MeCO_2^-$	1·50	4·00	38·0	1·60	1·56
	2·50	4·00	38·0	2·12	2·13
	3·50	4·00	38·0	2·77	2·71
	4·50	4·00	38·0	3·27	3·28

[a] r = Buffer ratio = [A]/[B]. [b] % Un-ionized form of keto-acid. [c] Calculated from equations (4) and (5) by using catalytic constants listed in Table 4. [d] Average of 3 runs.

ca. 7 × 10^{-4} mol l^{-1}. There was no evidence of significant concentrations of enol in the aqueous solutions. The iodination of the corresponding ethyl ester is known to be reversible [6] under conditions where either [I^-] or [H^+] is high. Iodination reactions were carried out in solutions with [I^-] 4·6 × 10^{-3} mol l^{-1}, [ketone] *ca.* 8 × 10^{-4} mol l^{-1}, and initial [I_2] + [I_3^-] *ca.* 5 × 10^{-5} mol l^{-1}. Under these conditions, the reactions were of zero order in iodine concentration over at least 90% of the reaction. The effective extinction coefficient of iodine in the presence of 4·6 × 10^{-3}M iodide was taken to be 2·0 × 10^4 at 353 nm. This value was obtained from quoted values of $\varepsilon_{I_3^-}$ and the formation constant of I_3^-.[7] In all cases the observed rate law was of the form shown in equations (6) and (7), where B represents the added base, RCO_2Me represents the keto-ester, and X_2^* either $Br_2 + Br_3^-$ or $I_2 + I_3^-$.

TABLE 4

Catalytic constants for the bromination of 2-oxocyclohexanecarboxylic acid and kinetic deuterium isotope effects at 10 °C

Base (B)	$10^2k_B{}^H$ [a]/ dm^3 mol^{-1} s^{-1}	$10^2k_B{}^D$/ dm^3 mol^{-1} s^{-1}	$k_B{}^H/k^{BD}$
(H_2O) [b]	1·34	0·185	$7{\cdot}2_4$
$ClCH_2{\cdot}CO_2^-$	20·9	2·69	$7{\cdot}7_7$
$ClCH_2{\cdot}CH_2{\cdot}CO_2^-$	78·7	10·3	$7{\cdot}6_4$
$MeCO_2^-$	121	15·1	$8{\cdot}0_1$

[a] Catalytic constants for [^{1}H]ketone. [b] k_0 in s^{-1}.

$$-d[X_2^*]/dt = -d[RCO_2Me]/dt = k_e[RCO_2Me] \quad (6)$$

$$k_e = k_0 + k_B[B] \quad (7)$$

The observed rate constants in the buffers are listed in Table 5 and the resulting catalytic constants and deuterium isotope effects in Table 6.

The results in Table 5 show excellent agreement between rates of bromination and iodination for the [^{1}H]ketone. Rate constants for iodination of the [^{2}H]ketone are *ca.* 7% higher than those for bromination (in acetate buffers). This indicates that the ketone is only *ca.* 98·5% deuteriated, the remaining 1·5% [^{1}H]ketone being responsible for the slightly higher rate of iodination where the initial rate of consumption of the ketone was measured. For this reason the bromination rates were used in evaluating

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

[7] J. Awtrey and D. Connick, *J. Amer. Chem. Soc.*, 1951, **73**, 1842.

k^H_B/k^D_B for acetate catalysis. The quoted isotope effects for chloroacetate and the uncatalysed reaction may be *ca.* 6% too low for the same reason. Values of k^H_B in Table 5 may be compared with those obtained by Bell and Goldsmith[6] for the iodination of ethyl 2-oxocyclohexanecarboxylate. Their results were as follows: $k_0 = 0{\cdot}97 \times 10^{-5}$ s^{-1}; k_B(chloroacetate) = $31{\cdot}7 \times 10^{-5}$ dm^3 mol^{-1} s^{-1}; k_B(acetate) = 535×10^{-5} dm^3 mol^{-1} s^{-1}. As expected, values are very similar for the bases compared.

TABLE 5

Rates of bromination and iodination of methyl 2-oxocyclohexanecarboxylate (i) and its 1-deuterio-derivative (ii) in buffers at 25 °C

Base (B)	10^2[B]/ mol l^{-1}	$10^5k_{I_2}$/ s^{-1}	$10^5k_{Br_2}$/ s^{-1}	$10^5k_{calc.}$ [a]/ s^{-1}
(i)				
$ClCH_2{\cdot}CO_2^-$ [b]	3·60	5·44	5·90	5·30
	7·30	7·92	7·71	8·27
	10·9	10·5	11·6	11·0
	14·5	13·5	14·3	13·8
	18·2	16·5	16·3	16·6
$MeCO_2^-$ [c]	3·60	31·7	30·1	31·6
	7·30	59·1	58·6	61·4
	10·9	89·3	87·0	90·5
	14·5	121	126	120
	18·2	154	159	150
(ii)				
$ClCH_2{\cdot}CO_2^-$	3·60	1·06		1·04
	7·30	1·48		1·50
	10·9	1·92		1·95
	14·5	2·44		2·40
	18·2	2·88		2·87
$MeCO_2^-$	3·60	4·74	4·39	4·48
	7·30	9·17	8·61	8·47
	10·9	13·3	12·4	12·4
	14·5	16·8	15·1	16·3
	18·2	22·4	21·0	20·3

[a] Calculated from equations (6) and (7), by using catalytic constants from Table 6. [b] Buffer ratio ([A]/[B]) = 0·5. [c] Buffer ratio ([A]/[B]) = 1·5.

TABLE 6

Catalytic constants and kinetic deuterium isotope effects for the halogenation of methyl 2-oxocyclohexanecarboxylate at 25·0 °C

Base (B)	$10^5k_B^H$/ dm^3 mol^{-1} s^{-1}	$10^5k_B^D$/ dm^3 mol^{-1} s^{-1}	k_B^H/k_B^D
(H_2O)	2·50 [a]	0·59	$4{\cdot}2_3$
$ClCH_2{\cdot}CO_2^-$	77·5	12·5	$6{\cdot}2_0$
$MeCO_2^-$	807	108 [b]	$7{\cdot}4_7$

[a] k_0 in s^{-1}. [b] From bromination results.

DISCUSSION

The observed independence of the halogenation rates of halogen concentrations and the equivalence of the bromination and iodination rates confirm that the rate-determining step is enolisation or ionization of the active C–H group. The results summarised in Tables 4 and 6 show that the replacement of the ester group in methyl 2-oxocyclohexanecarboxylate with a carboxylic acid group results in considerable enhancement of the ionization rate. Allowing for the temperature difference, the rates are increased by *ca.* 500—1000-fold, depending on the catalysing base.

Although the range of bases studied is limited it is possible to estimate the Brönsted β coefficient for the two substrates by using the catalytic constants for the carboxylic acids. The results in Table 4 for 2-oxocyclohexanecarboxylic acid follow the Brönsted equation with a coefficient $\beta = 0{\cdot}42$; *cf.* 0·57 for the methyl ester and previously reported values for the ethyl ester of 0·63 (ref. 2) and 0·67 (ref. 6); the latter results were obtained for a much wider range of bases than in the present study. These reductions in β are consistent with the transition state occurring at an earlier stage in the reaction pathway for the keto-acid as expected if the carboxylic acid group is assisting the ionization to a greater extent than the ester group.

The observed isotope effect for the enolisation of the keto-acid is insensitive to the nature of the catalysing base, varying only from 7·2 to 8 for water and acetate catalysis and being approximately constant for the carboxylic acids. The values are also near the maximum expected on the basis of simple vibrational zero-point energy difference between the substrate C–H and C–D bonds. This contrasts sharply with the corresponding results for the keto-ester which show a variation from 4·2 to 7·5 over the same range of bases.

While all the above factors indicate a considerable degree of participation of the carboxylic acid group in the enolization reaction it is difficult to decide whether this involves the transition state (I), in which the carboxylic acid donates a proton during the ionization reaction, or the transition state (II) in which the carboxylate group stabilises the protonated oxygen atom of the ketone group. Indeed although the transition state (II) may be formally regarded as resulting from general acid catalysis of RCO_2^- by BH^+ and the transition state (I) from general base catalysis of RCO_2H by B, the only difference between the two is in the degree of proton transfer of the proton between the carboxylate group and the carbonyl oxygen atom. The observed solvent deuterium isotope effect ($k_{H_2O}/k_{D_2O} = 2{\cdot}1$) is quite high[8] and may indicate some motion of the carboxylate proton during the rate-determining step. However this result is not conclusive, as a similar value has been observed for the ionization of ethyl 2-oxocyclopentanecarboxylate.[9]

We thank Professor R. P. Bell (University of Stirling) for discussion.

[3/2286 *Received, 7th November*, 1973]

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[8] C. G. Swain and A. S. Rosenberg, *J. Amer. Chem. Soc.*, 1961, **83**, 2154.

[9] R. P. Bell, J. A. Fendley, and J. R. Hulett, *Proc. Roy. Soc.* 1956, *A*, **235**, 453.