# Intra- and Inter-molecular Catalysis in the Halogenation of some Oxo-carboxylic Acids

By **Ronald P. Bell** * and **Anthony D. Covington**, Department of Chemistry, University of Stirling, Scotland

The dissociation constants of twelve oxo-carboxylic acids have been measured, and also the catalytic effect of the anions of eight of them in the decomposition of nitramide. The results are used to deduce the equilibrium fraction of the cyclic lactol isomers in aqueous solution: this fraction is considerable only for 2,2-dimethyl- (50% lactol) and 2,2,3-trimethyl-levulinic acid (87% lactol).

The rates of iodination of the twelve acids were measured in self-buffered solutions and in acetate buffers. The reaction is of zero order with respect to iodine, and the observed rates are interpreted in terms of ionization or enolization: both intra- and inter-molecular acid–base catalysis could be evaluated. For four acids the relative rates of reaction at different sites were measured by a $^1H$ n.m.r. study of exchange in deuterium oxide.

In the two series $MeCO\cdot[CH_2]_n\cdot CO_2H$ and $PhCO\cdot[CH_2]_n\cdot CO_2H$ the intramolecular rate has its maximum value when $n = 3$, corresponding to a cyclic transition state containing six atoms including the proton. For two acids it was shown that analogous inter- and intra-molecular processes have indistinguishable activation energies, thus confirming the view that the efficiency of the latter depends upon entropic factors. The detailed results for seven alkyl-levulinic acids were difficult to interpret, but abnormally low intramolecular rates were found for the two acids which have appreciable lactol contents in solution.

PREVIOUS work [1] on the iodination of a series of acids $MeCO\cdot[CH_2]_n\cdot CO_2H$ ($n = 2, 3, 4, 5,$ or $11$) showed that the groups $-CO_2^-$ and $-CO_2H$ can act as effective intramolecular catalysts for the ionization or enolization of the system $-CH_2\cdot CO\cdot CH_2-$, this effect being most marked for $n = 3$. Similar behaviour was subsequently observed in the iodination of nitro-carboxylic acids [2] and of diethylamino-ketones.[3] The present paper deals with the effect of alkyl substitution in 4-oxopentanoic (levulinic) acid and of chain length in the series $PhCO\cdot[CH_2]_n\cdot CO_2H$. Measurements of activation energies are also reported, and n.m.r. investigation of hydrogen–deuterium exchange was used to obtain information about the site of substitution in the alkyl-levulinic acids. Conventional acid dissociation constants were measured for the twelve acids studied, and for eight of them the 'true' constant was determined by measuring the catalytic effect of the anion in the decomposition of nitramide, whence the proportion of acid existing as cyclic lactol tautomer in aqueous solution was estimated.[4]

## EXPERIMENTAL

*Materials.*—Levulinic and 5-oxohexanoic acids were fractionally distilled commercial products. 6-Oxoheptanoic acid was prepared as described by Ruzicka *et al.*[5] and recrystallized four times from diethyl ether. 2-Methyl-levulinic acid was prepared by standard acetoacetic ester synthesis from ethyl 2-bromopropionate with subsequent alkaline hydrolysis: [6] the product was distilled three times.

2,2-Dimethyl-levulinic (mesitonic) acid was prepared by Lapworth's method,[7] with some modification. The amount of nitrile extracted by ether was very small, but the aqueous solution gave a good yield of the required acid on acidifying with concentrated hydrochloric acid and extraction with ether. The residue left after evaporating off the ether was crystallized six times from hexane–ethyl bromide.

Methyl 2-bromoethyl ketone was prepared as described by Catch *et al.*[8] and converted into 3-methyl-levulinic acid by the method of Adams and Long.[9] The product was distilled twice, crystallized twice from hexane–ethyl bromide, and redistilled to give colourless crystals on condensing.

Ethyl 3,3-dimethylsuccinate was prepared by the method of Baumgarten and Gleason [10] and converted by treatment with thionyl chloride into the acyl chloride of the half-ester, which on reaction with methylzinc iodide gave ethyl 3,3-dimethyl-levulinate. The free acid was obtained by alkaline hydrolysis and recrystallized three times from hexane–methylene chloride.

2,2,3-Trimethyl-levulinic acid was prepared as described by Bardhan [11] and recrystallized four times from ethyl bromide–light petroleum.

The method of Jackman *et al.*[12] was used to prepare 1-bromo-3,3-dimethylbutan-2-one, which was then condensed with diethyl malonate. The resulting ester gave on refluxing with concentrated hydrochloric acid 5,5-dimethyl-4-oxohexanoic acid (5,5,5-trimethyl-levulinic acid), which was recrystallized four times from petroleum (b.p. 60—80°) and twice from diethyl ether.

3-Benzoylpropionic acid was prepared as described by Somerville and Allen [13] and recrystallized three times from water. 4-Benzoylbutyric acid was prepared by the same method, glutaric anhydride being used instead of succinic anhydride, and was recrystallized four times from water. 5-Benzoylpentanoic acid was prepared by the analogous

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[1] R. P. Bell and M. A. D. Fluendy, *Trans. Faraday Soc.*, 1963, **59**, 1623.

[2] H. S. Wilson and E. S. Lewis, *J. Amer. Chem. Soc.*, 1972, **94**, 2283.

[3] R. P. Bell and B. A. Timimi, *J.C.S. Perkin II*, 1973, 1518.

[4] R. P. Bell, B. G. Cox, and B. A. Timimi, *J. Chem. Soc.* (*B*), 1971, 2247.

[5] L. Ruzicka, C. F. Seidel, H. Schinz, and H. Pfeiffer, *Helv. Chim. Acta*, 1948, **31**, 422.

[6] C. Pascual, D. Wegmann, V. Graf, R. Scheffold, P. F. Sommer, and W. Simon, *Helv. Chim. Acta*, 1964, **47**, 213.

[7] A. Lapworth, *J. Chem. Soc.*, 1904, 1218.

[8] J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 1948, 272.

[9] R. Adams and R. S. Long, *J. Amer. Chem. Soc.*, 1940, **62**, 2292.

[10] H. E. Baumgarten and D. C. Gleason, *J. Org. Chem.*, 1951, **16**, 1658.

[11] J. C. Bardhan, *J. Chem. Soc.*, 1928, 2604.

[12] M. Jackman, M. Klenk, B. Fishburn, B. F. Tullar, and J. Archer, *J. Amer. Chem. Soc.*, 1948, **70**, 2886.

[13] L. F. Somerville and C. F. H. Allen, *Org. Synth.*, Coll. Vol. II, 1966, p. 81.

procedure described by Hill[14] and was recrystallized three times from water and once from benzene–hexane.

' Acetyl-levulinic acid ' was prepared as described by Bredt[15] and recrystallized four times from methylene chloride–light petroleum. Its $^1$H n.m.r. spectrum showed τ ($CCl_4$) 7.40 (4 H, m), 7.95 (3 H, s), and 8.25 (3 H, s) [*cf.* 7.35 (4 H, m) 7.95 (3 H, s), and 7.85 (3 H, s) for levulinic acid], demonstrating that it has the cyclic structure $MeC(OAc)\cdot CH_2\cdot CH_2\cdot CO\cdot O$ as proposed by Bredt[15] on the basis of chemical evidence, and excluding the possibility that it is the enol acetate, $CH_2{:}C(OAc)\cdot CH_2\cdot CH_2\cdot CO_2H$ or $MeC(OAc){:}CH\cdot CH_2\cdot CO_2H$.

The physical properties of the oxo-acids are listed in Table 1. Their equivalent weights were determined with an estimated accuracy of ±0.2% by titration with standard sodium hydroxide solution. In addition $^1$H n.m.r. spectra were consistent with the structures allotted. The spectrum of compound (VIII) showed an additional peak at low τ value, indicating a considerable proportion of the lactol form, in agreement with Table 4.

TABLE 1

Oxo-acids investigated

| | | Formula | M.p. (°C) | B.p. (°C) [mmHg] | Equiv. wt. | |
|---|---|---|---|---|---|---|
| | | | | | Obs. | Calc. |
| (I) | Levulinic | $MeCO\cdot[CH_2]_2\cdot CO_2H$ | | 112—115 [0.7] | 116.3 | 116.1 |
| (II) | 5-Oxohexanoic | $MeCO\cdot[CH_2]_3\cdot CO_2H$ | | 109—111 [0.6] | 129.9 | 130.1 |
| (III) | 6-Oxoheptanoic | $MeCO\cdot[CH_2]_4\cdot CO_2H$ | 36—38 | | 144.6 | 144.1 |
| (IV) | 2-Methyl-levulinic | $MeCO\cdot CH_2\cdot CHMe\cdot CO_2H$ | | 94—96 [0.5] | 129.2 | 130.1 |
| (V) | 2,2-Dimethyl-levulinic | $MeCO\cdot CH_2\cdot CMe_2\cdot CO_2H$ | 74—76 | | 143.9 | 144.1 |
| (VI) | 3-Methyl-levulinic | $MeCO\cdot CHMe\cdot CH_2\cdot CO_2H$ | 30—32 | 95—97 [0.1] | 130.2 | 130.1 |
| (VII) | 3,3-Dimethyl-levulinic | $MeCO\cdot CMe_2\cdot CH_2\cdot CO_2H$ | 42—44 | | 130.0 | 130.1 |
| (VIII) | 2,2,3-Trimethyl-levulinic | $MeCO\cdot CHMe\cdot CMe_2\cdot CO_2H$ | 77—78 | | 158.0 | 158.1 |
| (IX) | 5,5,5-Trimethyl-levulinic | $Me_3C\cdot CO\cdot[CH_2]_2\cdot CO_2H$ | 64—66 | | 157.1 | 158.1 |
| (X) | 4-Oxo-4-phenylbutyric | $PhCO[CH_2]_2\cdot CO_2H$ | 115—116 | | 178.3 | 178.1 |
| (XI) | 5-Oxo-5-phenylpentanoic | $PhCO\cdot[CH_2]_3\cdot CO_2H$ | 127—128 | | 192.0 | 192.1 |
| (XII) | 6-Oxo-6-phenylhexanoic | $PhCO\cdot[CH_2]_4\cdot CO_2H$ | 77—78 | | 207.0 | 206.1 |
| (XIII) | ' Acetyl-levulinic ' | $MeC(OAc)\cdot[CH_2]_2\cdot CO\cdot O$ | 75—76 | | | |

All inorganic materials were of AnalaR grade, and solutions were prepared with de-ionized water which had been distilled from alkaline potassium permanganate.

*Measurements of Conventional and ' True ' Dissociation Constants.*—Conventional acid dissociation constants were determined at 25 °C from pH measurements on self-buffered solutions by means of a glass electrode, calibrated between each pair of readings at pH 4.008 (potassium hydrogen phthalate) and 6.48 (phosphate buffer). For each acid between six and nine solutions were prepared in duplicate with buffer ratios ($r$ = [HX]/[X$^-$]) between 0.1 and 10 and ionic strengths adjusted to a fixed value (between 0.004 and 0.02) by adding potassium chloride. The true buffer ratio $r$ was calculated from the expression $r = ([HX]^* - [H^+])/([X^-]^* + [H^+])$, where the asterisk denotes stoicheiometric value. The thermodynamic dissociation constant, $K_a$, was then obtained from equation (1), with $f_\pm$

$$pK_a = pH + \lg r - \lg f_\pm \qquad (1)$$

given by equation (2).[16] The values of $G_a$ showed no trend with buffer ratio, and their mean values are given in Table 4.

$$-\lg f_\pm = 0.50\, I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}) - 0.2I \qquad (2)$$

As explained in the Discussion section, the ' true ' dissociation constants of the chain forms of the acids were derived from the catalytic effect of their anions on the decomposition of nitramide. This decomposition was followed kinetically at 25.0 ± 0.1 °C by measuring the pressure of the nitrous oxide evolved in the apparatus previously described.[17] Measurements were made in self-buffered solutions of the oxo-acids at about pH 5, so that catalysis by hydroxide ions could be ignored.[18] For acids (I), (II), (IV), and (VIII) in Table 1 duplicate experiments were made with six different anion concentrations in the range 0.01—0.1M at a constant ionic strength of 0.1. Less extensive measurements were made with acids (V), (VII), (IX), and (X), and acids (III), (VI), (XI), and (XII) were not studied with nitramide owing to low solubility or lack of time. Individual reactions followed a strictly first-order course, and the first-order velocity constants satisfied the equation $k = k_0 + k_b[X^-]$, where $k_0$ is the ' spontaneous ' first-order constant observed by Baughan and Bell[19] at 25 °C, equal to $4.70 \times 10^{-5}$ s$^{-1}$. A typical set of results for one acid is shown in Table 2. The ' true ' dissociation constant $K_A'$ of the chain form of the acid was then calculated from equation (3), which was found by Baughan and

$$\lg k_b = -4.849 - 0.758 \lg K_a' \qquad (3)$$

Bell to represent accurately the catalytic constants of the anions of eight carboxylic acids not offering any possibilities for tautomerism. The values obtained for $K_a'$ are included in Table 4.

*Measurement of Rates of Halogenation.*—Rates of iodination were measured by following the absorption at 353 nm due to tri-iodide ion, which was assumed to have a molar absorptivity $\varepsilon = 2.528 \times 10^4$ mol$^{-1}$ dm$^3$ cm$^{-1}$.[1,20] Allowance was made for the slight dissociation in the presence of 0.1M-iodide ion by using the equilibrium constants given by

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[14] J. W. Hill, *J. Amer. Chem. Soc.*, 1932, **54**, 4105.

[15] J. Bredt, *Annalen*, 1886, **236**, 225.

[16] C. W. Davies, *J. Chem. Soc.*, 1938, 2093.

[17] R. P. Bell and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1949, 1288.

[18] L. K. J. Tong and A. R. Olsen, *J. Amer. Chem. Soc.*, 1941, **63**, 3406.

[19] E. C. Baughan and R. P. Bell, *Proc. Roy. Soc.* (*A*), 1937, **158**, 464.

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

Awtrey and Connick.[21] Bromination (used only for 3-methyl-levulinic acid) was followed at 400 nm, the molar absorptivity $\varepsilon = 187$ mol$^{-1}$ dm$^3$ cm$^{-1}$ reported by Bell and Pring [22] being used. The fall in optical density was recorded on a Gilford 2400 spectrometer with 1 cm cells thermostatted to ±0.1 °C. Self-buffered solutions were prepared from standard sodium hydroxide solution and solutions of oxo-acid which had been titrated against the standard. For experiments in acetate buffers reaction mixtures were prepared by adding to the acetate buffer an oxo-acid buffer having the same pH: this was achieved by choosing the two buffer ratios in the inverse ratio of the two dissociation constants, and was checked by pH measurements. All reaction solutions were made up to an ionic strength $I = 0.2$ by adding potassium chloride or sodium perchlorate for iodination and bromination respectively, and 0.1M-iodide ion was present in all iodination experiments. Reaction solutions were prepared in duplicate, and two successive additions of iodine solution made to each, so that each kinetic result is the mean of four values, which normally agreed to within ±2%.

TABLE 2

Rate of nitramide decomposition at 25 °C in 2-methyl-levulinate buffers

| $10^5[X^-]$ / mol dm$^{-3}$ | $10^6k$ / s$^{-1}$ | $10^4k_B$ / dm$^3$ mol$^{-1}$ s$^{-1}$ | $10^7K_a'$ / mol dm$^{-3}$ |
|---|---|---|---|
| 201 | 130 | 406 | 275 |
| 201 | 132 | 417 | 266 |
| 403 | 216 | 417 | 265 |
| 403 | 230 | 452 | 239 |
| 604 | 299 | 415 | 267 |
| 604 | 291 | 401 | 279 |
| 806 | 354 | 379 | 300 |
| 806 | 380 | 412 | 269 |
| 1 007 | 476 | 425 | 259 |
| 1 007 | 474 | 423 | 260 |
| 1 007 | 458 | 407 | 274 |

Mean $K_a' = (2.68 \pm 0.03) \times 10^{-5}$

With two exceptions mentioned below, the spectrophotometer traces for iodination were invariably linear over at least 90% of their course, indicating that the reactions are of zero order with respect to tri-iodide ion, which therefore acts as an efficient scavenger for the enol or enolate ion formed initially. The traces show some deceleration during the last few per cent of the reaction, attributable to incomplete scavenging or slight reversibility at very low iodine concentrations. Since the concentration of substrate was at least 1 000 times that of iodine, it can be assumed that only mono-iodination takes place.

3-Methyl-levulinic acid gave abnormal iodination traces, showing deceleration over the whole of their course. For bromination, accelerating traces were obtained (owing to multiple halogenation at the higher halogen concentrations employed), and the rates recorded represent initial rates of bromination: they are less accurate than those for the remaining substrates.

*Measurement of Hydrogen–Deuterium Exchange*.—For four of the oxo-acids [(I), (IV), (V), and (VIII)] the relative rates of exchange at different positions were determined by observing the decrease with time of the integrated $^1$H n.m.r. signals (Perkin-Elmer R10 spectrometer) in 1 : 1 buffer solutions in deuterium oxide. For compounds (IV), (V), and (VIII) the signals from the unreactive methyl substituents acted as internal standards, and for (I) a small amount of added 1,4-dioxan served the same purpose. The results, which are not of high accuracy, are given in Table 3. They are, however, borne out for (I) and (VIII) by the qualitative appearance of the spectra after longer periods of exchange. In the case of (I), where the main product is $CH_3\cdot CO\cdot CD_2\cdot CH_2\cdot CO_2D$, the original multiplet at $\tau$ *ca.* 7.5 (two adjacent $CH_2$ groups) has shrunk to a small broad singlet, while the singlet at $\tau$ *ca.* 8 ($CH_3$) is little affected. For (VIII), where the main products will be $CD_3\cdot CO\cdot CHMe\cdot CMe_2\cdot CO_2H$ and $CHD_2\cdot CO\cdot CHMe\cdot CMe_2\cdot CO_2H$, the original singlet at $\tau$ *ca.* 8.5 (terminal $CH_3$) is reduced to a small, broad singlet, while the quartet at $\tau$ *ca.* 8 (single proton in the 3-position coupled with methyl substituent) and the multiplet at $\tau$ *ca.* 9 (three unreactive methyl substituents) are little changed.

TABLE 3

Rates of hydrogen–deuterium exchange at 25 °C

$v_3$, $v_5$ = rates of deuterium incorporation at carbon atoms 3 and 5
$v_5/v_3$ (corr.) has been corrected for the different numbers of hydrogen atoms at the two sites.

| | Compound: | (I) | (IV) | (V) | (VIII) |
|---|---|---|---|---|---|
| $v_5/v_3$ | obs. | $0.11 \pm 0.03$ | $0.20 \pm 0.03$ | $1.6 \pm 0.1$ | $32 \pm 13$ |
| | corr. | $0.07 \pm 0.02$ | $0.13 \pm 0.02$ | $1.0 \pm 0.1$ | $10 \pm 4$ |

## RESULTS

*Acid Dissociation Constants and Tautomeric Equilibria*.—The values of the overall dissociation constants, $K_a$, and the ' true ' values, $K_a'$, derived from catalysis of the nitramide decomposition are collected in Table 4. It has been shown previously [3] that $K_a$ and $K_a'$ are related by equation (4),

$$K_a = K_a'(1 + K_X)^{-1} \qquad (4)$$

where $K_X$ is the equilibrium constant [lactol]/[oxo-acid]. For most of the acids studied, $K_a$ and $K_a'$ are virtually identical and vary little with alkyl substitution, indicating inappreciable amounts of lactol isomer, but for compounds (VII) and (VIII) $K_a$ was abnormally low, and equation (4) can be used to calculate the equilibrium proportion of lactol in aqueous solution: these results are given in Table 4. Similar calculations were made for compounds (VII) and (IX), but here the differences between $K_a$ and $K_a'$ are smaller, and the result is correspondingly less certain. Our results for the proportion of the cyclic tautomer show general agreement with those of Pascual *et al.*,[6] who measured the dissociation constants of six of the acids in aqueous methylcellosolve and compared them with ' true ' values obtained by making arbitrary assumptions about the effects of methyl substitution. These assumptions are not borne out by our measurements on the nitramide decomposition, and since further the solvents are different in the two investigations no quantitative agreement would be expected. Our values for the overall dissociation constants of (I) and (II) in water at 25 °C are close to those previously reported for 18 °C: $2.30 \times 10^{-5}$ and $2.18 \times 10^{-5}$, respectively.[23,24]

[21] A. D. Awtrey and R. E. Connick, *J. Amer. Chem. Soc.*, 1951, **73**, 1842.

[22] R. P. Bell and M. Pring, *J. Chem. Soc.* (*A*), 1966, 1607.

[23] E. Larson and B. Adell, *Z. phys. Chem.*, 1931, **A157**, 342.

[24] E. Larson, *Z. phys. Chem.*, 1932, **A166**, 241.

TABLE 4

Dissociation constants and tautomeric equilibria at 25 °C

Error limits represent standard deviations of the mean

| Acid | $10^7K_a$ / mol dm$^{-3}$ | $10^7K_a'$ / mol dm$^{-3}$ | % Lactol * (a) | % Lactol * (b) |
|---|---|---|---|---|
| (I) | 245 ± 2 | 251 ± 4 | 0 | 0 |
| (II) | 219 ± 2 | 187 ± 3 | 0 | |
| (III) | 185 ± 2 | | | |
| (IV) | 273 ± 3 | 268 ± 3 | 0 | 0 |
| (V) | 103 ± 1 | 206 ± 9 | 50 ± 8 | 41 |
| (VI) | 307 ± 3 | | | 0 |
| (VII) | 223 ± 2 | 264 ± 3 | 16 ± 2 | 0 |
| (VIII) | 18.4 ± 0.2 | 142 ± 3 | 87 ± 1 | 88 |
| (IX) | 157 ± 2 | 191 ± 11 | 18 ± 6 | |
| (X) | 198 ± 6 | 216 ± 12 | 0 | |
| (XI) | 168 ± 5 | | | |
| (XII) | 149 ± 5 | | | |

* (a) Present investigation; (b) ref. 23.

*Iodination Kinetics.*—The observed rate of disappearance of iodine, $v$, might in principle involve contributions from twelve different reactions, reducible to seven kinetically distinguishable terms. As shown for levulinic acid [1] several of these are often negligible, and under our conditions the rate in acetate buffers was always expressible in the form of equation (5), where $[HX]^*$ is the total concentration of

$$v = k_1[X^-] + k_2[HX]^* + k_3[X^-][HX]^* + k_4[HX]^*[AcO^-] + k_5[X^-][AcO^-] \quad (5)$$

both forms of the undissociated oxo-acid. The last term could not always be detected with certainty, and the last two are of course absent for self-buffered solutions. In determining $k_1$ — $k_5$ from the experimental results equation (5) can be conveniently rewritten in various ways involving the stoicheiometric acid concentration $a = [X^-] + [HX]^*$ and either of the buffer ratios $r = [HX]^*/[X^-]$ or $r' = [AcOH]/[AcO^-]$, remembering that $r/r' = K_a(HX)/K_a(AcOH)$.

TABLE 5

Detailed results for the iodination of levulinic acid at 25 °C

Calculated values from equation (5) and the velocity constants in Table 6

(a) Self-buffered solutions, $r = 2.078$

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| $10^3a$/mol dm$^{-3}$ | | 31 | 61 | 92 | 123 | 154 | 184 | 215 | 246 |
| $10^{10}v$/mol dm$^{-3}$ s$^{-1}$ | Obs. | 36 | 75 | 122 | 175 | 231 | 303 | 366 | 453 |
| | Calc. | 34 | 75 | 122 | 175 | 234 | 300 | 372 | 450 |

(b) Self-buffered solutions, $a = 0.1228$M

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| $r$ | | 0.230 | 0.366 | 0.537 | 0.757 | 1.050 | 1.461 | 2.078 |
| $10^{10}v$/mol dm$^{-3}$ s$^{-1}$ | Obs. | 316 | 302 | 288 | 260 | 239 | 205 | 170 |
| | Calc. | 319 | 303 | 284 | 261 | 235 | 207 | 175 |

(c) Acetate buffers, $a = 0.0282$M

| $r'$ | $10^4[AcO^-]$ | $10^{10}v$/mol dm$^3$ s$^{-1}$ Obs. | $10^{10}v$/mol dm$^3$ s$^{-1}$ Calc. |
|---|---|---|---|
| 0.60 | 0 | 59 | 59 |
| | 267 | 63 | 64 |
| | 533 | 69 | 69 |
| | 800 | 74 | 74 |
| 1.00 | 0 | 51 | 50 |
| | 267 | 56 | 57 |
| | 533 | 63 | 63 |
| | 800 | 70 | 70 |
| 2.75 | 0 | 32 | 32 |
| | 267 | 40 | 41 |
| | 533 | 49 | 50 |
| | 800 | 60 | 59 |
| 5.67 | 0 | 21 | 21 |
| | 280 | 32 | 32 |
| | 560 | 44 | 44 |
| | 840 | 56 | 55 |

Kinetic experiments were planned in the following series:

(a) self-buffered solutions with constant $r$ and varying $a$;
(b) self-buffered solutions with constant $a$ and varying $r$;
(c) acetate buffer solutions with constant $a$: four different buffer ratios were employed, for each of which four acetate concentrations between zero and 0.08M were investigated.

The best values of the velocity constants, together with their standard deviations, were determined by a non-linear least-squares computer program, and the agreement between the observed and calculated velocities is illustrated by Table 5, which gives the detailed results for levulinic acid. Similar series of experiments were carried out with compounds (V), (VII), and (VIII). The remaining acids were investigated in less detail. Only series of type (c) were carried out with (II), (III), (IX), and (X), only (a) and (b) for (VI), and only (a) for (IV). Measurements with (XI) and (XII) were restricted to series (b), and because of the low solubility of the acids only buffer ratios in the range $r = 0.005$—$0.05$ could be used: hence $k_1$ was the only velocity constant which could be determined for these two compounds. Since the pH of these last solutions could be as high as 7, some contribution from proton abstraction by hydroxide ions might be suspected, but comparison with rates of this process for other ketonic substances [25] suggests that this could not exceed 1% of the observed rates, and this is confirmed by the internal consistency of the values of $k_1$.

The velocity constants at 25 °C are collected in Table 6. For compounds (I)—(III) the values of $k_1$ and $k_2$ in Table 6 agree satisfactorily with those previously reported,[1] and the same is true for $k_4$ for compound (I).

For compounds (I) and (III) measurements of type (c) were also carried out at 35, 45, and 55 °C. Although the relative contributions of intra- and inter-molecular processes (involving mainly $k_1$ and $k_4$, respectively) varied considerably within each series, no systematic variations in tempera-

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[25] R. P. Bell, G. R. Hillier, J. W. Mansfield, and D. G. Street, *J. Chem. Soc.* (*B*), 1967, 827.

ture coefficient were detected, the observed activation energies being 102 and 88 kJ mol$^{-1}$ for (I) and (III), respectively. For this reason the results of these experiments (ninety-six in all) are not reported in detail.

## DISCUSSION

Table 4 shows that the only acids which contain a considerable equilibrium proportion of the lactol form in aqueous solution are (V) and (VIII), *i.e.* 2,2-dimethyl- and 2,2,3-trimethyl-levulinic acids. This accords with the well-known fact that *gem*-dialkyl substitution favours ring formation, though the reasons for this are still incompletely understood. It is possible that appreciable amounts of lactol are present also in solutions of compounds (VII) and (IX), though such low lactol contents cannot be established with certainty by the method used.

TABLE 6

Collected velocity constants at 25 °C

| Compound | $10^8k_1$ | $10^9k_2$ | $10^8k_3$ | $10^8k_4$ | $10^8k_5$ |
|---|---|---|---|---|---|
| (I) | 28.1 ± 0.2 | 15 ± 1 | 151 ± 2 | 165 ± 9 | 27 ± 5 |
| (II) | 180 ± 11 | 201 ± 72 | | 169 ± 42 | |
| (III) | 8.3 ± 0.3 | 60 ± 3 | | 65 ± 2 | 16 ± 2 |
| (IV) | 31 ± 1 | 22 ± 7 | 275 ± 5 | 198 ± 4 | 35 ± 5 |
| (V) | 12 ± 1 | 26 ± 6 (52) * | 60 ± 14 | 350 ± 32 | 26 ± 18 |
| (VI) | 15 ± 1 | 15 ± 5 | 180 ± 50 | | |
| (VII) | 18.7 ± 0.3 | 22 ± 3 | 64 ± 2 | 69 ± 5 | 17 ± 4 |
| (VIII) | 3.5 ± 0.2 | 7 ± 1 (54) * | 240 ± 20 | 142 ± 10 | |
| (IX) | 10.5 ± 0.4 | 3 ± 1 | 120 ± 5 | 66 ± 2 | 20 ± 10 |
| (X) | 84 ± 2 | | | 36 ± 13 | |
| (XI) | 1 300 ± 10 | | | | |
| (XII) | 90 ± 1 | | | | |

* Corrected for the proportion of lactol isomer present.

With regard to the rates of iodination, evidence has already been given that these correspond to the introduction of one iodine atom, and can be equated to rates of ionization or enolization. For those terms in equation (5) which involve undissociated acid ($k_2$, $k_3$, and $k_4$) allowance should be made for the existence of appreciable proportions of (V) and (VIII) in the lactol form. An estimate of the reactivity of this form was obtained by studying the iodination kinetics of acetyl-levulinic acid (XIII), shown in the Experimental section to have an analogous cyclic structure. The reaction in acetate buffers was of zero order with respect to iodine, the rate of iodination being given by equation (6) where [S] is

$$v/\text{mol dm}^3\ \text{s}^{-1} = [\text{S}]\ (7.8 \times 10^{-10} + 2.6 \times 10^{-9}[\text{AcO}^-]) \quad (6)$$

the concentration of substrate. The probable mechanism of this base-catalysed reaction is

$$\mathrm{Me}\overline{\mathrm{C(OAc)\cdot CH_2\cdot CH_2\cdot CO\cdot O}} + \mathrm{B} \longrightarrow \mathrm{MeC(OAc)}{:}\mathrm{CH\cdot} + \mathrm{CH_2\cdot CO_2^-} + \mathrm{BH^+},$$

though by analogy with the findings of Kirby and Meyer [26] for the ketonization of 2-acetoxycyclohex-1-enecarboxylate this may be followed by the rapid rearrangement $\mathrm{MeC(OAc){:}CH\cdot CH_2\cdot CO_2^-} \longrightarrow \mathrm{MeC\text{-}(O^-){:}CH\cdot CH_2\cdot CO\cdot OAc}$. Either of these products should react rapidly with iodine, thus accounting for the zero-order behaviour. In any event, the rates represented by equation (6) are much smaller than the total observed rates, and the values of $k_2$ can therefore be corrected on the assumption that the lactol isomer is unreactive. These corrected values are given in parentheses in Table 6.*

In the aliphatic series $\mathrm{MeCO\cdot[CH_2]_{\mathit{n}}\cdot CO_2H}$ [compounds (I)—(III)] the intramolecular rate constants $k_1$ and $k_2$ both show a marked maximum when $n = 3$, in agreement with previous findings,[1] while the intermolecular constant $k_4$ varies only slightly. If we assume that the greater part of the reaction involves the methylene group of $\mathrm{CH_3\cdot CO\cdot CH_2}$– [as shown by Table 3 for compound (I)], this indicates that the cyclic transition state is most readily formed when it contains six atoms including the proton. In the aromatic series $\mathrm{PhCO\cdot[CH_2]_{\mathit{n}}\cdot CO_2H}$ [compounds (X)—(XII)] the maximum in $k_1$ at $n = 3$ is even more marked, and here there is no ambiguity about the site of reaction. The finding that the analogous inter- and intra-molecular processes for compounds (I) and (III) have indistinguishable activation energies indicates that the efficiency of the latter is due to entropic factors. This is of course the generally accepted view, but has rarely been confirmed experimentally.

The standard entropies of activation calculated from our results are (in J K$^{-1}$ mol$^{-1}$): compound (I) $\Delta S_1^\ddagger$ −37, $\Delta S_4^\ddagger$ −22; compound (III) $\Delta S_1$ −94, $\Delta S_4^\ddagger$ −77. No significance can of course be attached to an absolute comparison of $\Delta S_1^\ddagger$ and $\Delta S_4^\ddagger$, since the latter is dependent upon the choice of concentration units, while the former is not. It is however of interest that $\Delta S_1^\ddagger$ for compound (I) is smaller than the value of −60 J K$^{-1}$ mol$^{-1}$ which can be derived from the results of Bell and Cox [27] on the equilibrium isomerisation of 2,2,3-trimethyl-levulinic acid: similar values are obtained for the isomerisation equilibria of straight-chain hydrocarbons to give five- and six-membered rings.[28] As anticipated, the intramolecular process for compound (III) involves a considerably more negative entropy of activation.

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* Corresponding corrections have not been applied to $k_3$ and $k_4$, since their values are less accurately known, and each of them may include two possible mechanisms; see ref. 1.

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

[27] R. P. Bell and B. G. Cox, following paper.

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

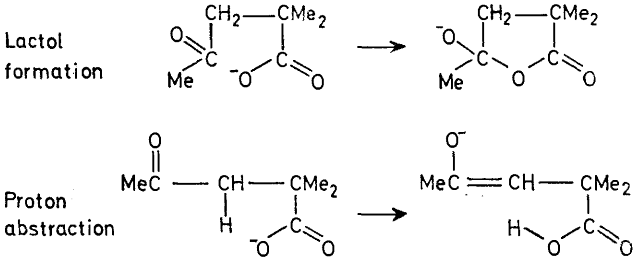
The 'effective concentration' of the carboxylate group in the intramolecular reaction of the anion may be defined as $k_1/k_5$, since the acidic strengths of the oxo-carboxylic acids are close to that of acetic acid, and is close to 1 mol $dm^{-3}$ throughout. For the same reason $k_3$ and $k_4$ are always of similar magnitudes, while $k_5$ is considerably smaller because of the retarding effect of the negative charge.

TABLE 7

Intramolecular catalysis at positions 3 and 5

| Compound: | | (I) | (IV) | (V) | (VII) | (VIII) | (IX) |
|---|---|---|---|---|---|---|---|
| $10^3k_1/s^{-1}$ | position 3 | 25 | 26 | 5 | | 0.1 | 10 |
| | position 5 | 3 | 5 | 7 | 19 | 3 | |

It is difficult to rationalize the results for the six methyl-substituted levulinic acids [(IV)—(IX)]. Although substantial steric effects might have been anticipated, both the intra- and inter-molecular velocity constants vary within a small range, though not in parallel with one another. Any quantitative interpretation must allow for the fact that with the exception of compounds (VII) and (IX) two reaction sites are possible. The results in Table 3, which refer to conditions under which the term in $k_1$ is dominant, can be used to separate out the contributions to $k_1$ from positions 3 and 5. The results, which are of low accuracy, are given in Table 7. The only striking feature is the very low rate at position 3 for compound (VIII), and, to a lesser degree, for compound (V). These are the only two acids with two methyl groups in the 2-position, and are also the only two which form a considerable proportion of the lactol isomer in aqueous solution (Table 4). The cyclic configurations leading to lactol formation and proton abstraction are of course different, as shown in the Scheme for compound (V), and it appears that the substitution of two methyl groups in the 2-position favours the first configuration but disfavours the second. A similar inverse relationship between ring–chain tautomerism and intramolecular proton abstraction has been found to hold for nine derivatives of 2-carboxyacetophenone.[29]



SCHEME

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[29] R. P. Bell, D. W. Earls, and J. B. Henshall, submitted to *J.C.S. Perkin II.*