925. *Kinetics of the Decarboxylation of Oxaloacetic Acid.*

By E. Gelles.

The kinetics of decarboxylation of oxaloacetic acid in aqueous solution have been studied at 25°, 30°, and 37° over a range of pH. Arrhenius parameters are obtained for the first-order decomposition of oxaloacetic acid and of its univalent anion. The kinetics of decarboxylation of other β-keto-carboxylic acids are discussed.

The relative rates of decarboxylation of acids and their anions are now known for a number of β-keto-carboxylic acids. The considerable variation in these relative reactivities is produced by an interplay of energy and entropy factors, an analysis of which could throw further light on the reaction mechanism. Kinetic data for an acid and its anion have been reported at more than one temperature only for malonic acid.[1, 2] The kinetics of the decarboxylation of oxaloacetic acid have been studied in detail at 37°.[3] This reaction is of interest for several reasons, *e.g.*, catalysis by paramagnetic ions [4] and carbon-isotope effects.[5] Arrhenius parameters have now been obtained for the first-order decarboxylation of oxaloacetic acid and of its univalent anion.

Experimental

Weighed samples of oxaloacetic acid (Found, by titration against alkali: *M*, 132·5. Calc. for $C_4H_4O_5$: *M*, 132·1) were dissolved in the requisite amounts of water, standard hydrochloric acid, and potassium chloride solutions. The apparatus and experimental procedure have been described previously.[4] Kinetic measurements were made in a water thermostat controlled to ±0·01°. " AnalaR " materials and " grade A " volumetric glassware were used.

Results

Pedersen has shown that oxaloacetic acid and its two anions separately undergo first-order decarboxylation to pyruvic acid.[3] The observed first-order rate coefficient for the total reaction, $k_{\text{obs.}}$, is related to the separate rate constants for the acid, k_0, for the univalent anion, k_1, and for the bivalent anion, k_2:

$$k_{\text{obs.}} = k_0 + (k_1 - k_0)\,\alpha_1 + (k_2 - k_0)\,\alpha_2 \qquad \ldots\ldots \quad (1)$$

where α_1 and α_2 are the degrees of ionisation to univalent and bivalent ions, respectively. Pedersen has determined the ionisation constants of oxaloacetic acid, K_1 and K_2, (and of the decomposition product, pyruvic acid) as a function of ionic strength at 25° and 37°.[6] The required ionisation constants for 30° have been calculated from these data:

$$\begin{aligned}
\text{at } 25^\circ: \quad & -\log K_1 = 2{\cdot}555 - 1{\cdot}013I^{\frac{1}{2}} + 0{\cdot}75I; \\
& -\log K_2 = 4{\cdot}370 - 2{\cdot}026I^{\frac{1}{2}} + 1{\cdot}57I \\
\text{at } 30^\circ: \quad & -\log K_1 = 2{\cdot}511 - 1{\cdot}023I^{\frac{1}{2}} + 0{\cdot}80I; \\
& -\log K_2 = 4{\cdot}365 - 2{\cdot}047I^{\frac{1}{2}} + 1{\cdot}60I \\
\text{at } 37^\circ: \quad & -\log K_1 = 2{\cdot}450 - 1{\cdot}038I^{\frac{1}{2}} + 0{\cdot}86I; \\
& -\log K_2 = 4{\cdot}359 - 2{\cdot}076I^{\frac{1}{2}} + 1{\cdot}65I \qquad \ldots\ldots \quad (2)
\end{aligned}$$

For a given mixture the degrees of ionisation, α_1 and α_2, and the ionic strength, I, are calculated from equations (2)—(5), where HA^- and A^{2-} represent the univalent and bivalent anions of oxaloacetic acid, respectively:

$$\alpha_1/(1 - \alpha_1 - \alpha_2) = K_1/[H^+]; \quad \alpha_2/(1 - \alpha_1 - \alpha_2) = K_1K_2/[H^+]^2 \qquad . \quad (3), (4)$$

$$I = \tfrac{1}{2}([H^+] + [K^+] + [Cl^-] + [HA^-] + 4[A^{2-}]) \qquad \ldots . \quad (5)$$

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[1] Hall, *J. Amer. Chem. Soc.*, 1949, **71**, 2691.

[2] Fairclough, *J.*, 1938, 1186.

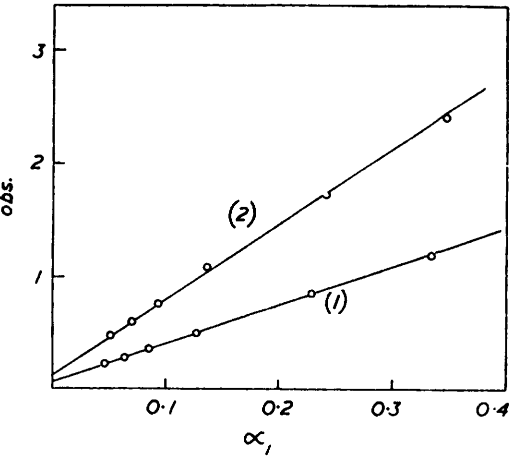
[3] Pedersen, *Acta Chem. Scand.*, 1952, **6**, 285.

[4] Gelles and Clayton, *Trans. Faraday Soc.*, 1956, **52**, 353.

[5] Gelles and Reed, *Nature*, 1955, **176**, 1262.

[6] Pedersen, *Acta Chem. Scand.*, 1952, **6**, 243.

Kinetic measurements have now been made at three temperatures. For a given oxaloacetic acid concentration, experiments were carried out at a number of hydrochloric acid concentrations, so that the sum of the hydrochloric acid and potassium chloride concentrations was 0·100. At the concentrations of mineral acid used the bivalent anion made a very small contribution to the total rate of reaction. The experiments at 37° gave values of k_0 and k_1 slightly higher than those generally found by Pedersen, but in excellent agreement with his data for similar oxaloacetic acid concentrations.[3] The results of typical experiments at 25° and 30° for one oxaloacetic acid concentration are summarised in Table 1. Concentrations are quoted in moles/l. and first-order rate coefficients in min.$^{-1}$ units. The oxaloacetic acid concentration is 0·0294. It is seen that agreement between observed and calculated rate coefficients would not be adversely affected by neglecting the very small contribution to the rate of the bivalent anion. Preliminary values of k_0 and k_1 were obtained graphically on this basis. Neglecting the term due to the bivalent anion in equation (1), we have



Variation of first-order rate coefficients with degree of ionisation of oxaloacetic acid. Plots of $10^3k_{obs.}$ *against* α_1, (1) *at* 25°, (2) *at* 30°.

$$k_{obs.} = k_0 + (k_1 - k_0)\,\alpha_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The Figure shows plots of $k_{obs.}$ against α_1. The observed rate coefficients are obtained from first-order Guggenheim plots covering four half-times of reaction, and are accurate to ±1—2%. The first-order rate law is obeyed for the total reaction to a very good approximation essentially because the ionisation constants of oxaloacetic acid and the decomposition product, pyruvic acid, are nearly equal.[3] The values of α_1 and α_2 given in Table 1 are calculated for the beginning of the reaction : their variation during the course of the reaction is inappreciable. The values

TABLE 1. *Decarboxylation of acid and anion.*

Temp.	[HCl]	[KCl]	I	α_1	α_2	$10^3k_{obs.}$	$10^3k_{calc.}$
25°	0·000	0·100	0·1098	0·3342	0·0046	1·17	1·19
,,	0·010	0·090	0·1067	0·2284	0·0018	0·84	0·829
,,	0·030	0·070	0·1037	0·1275	0·0005	0·490	0·490
,,	0·050	0·050	0·1025	0·0855	0·0002	0·350	0·350
,,	0·070	0·030	0·1019	0·0640	0·0001	0·273	0·278
,,	0·100	0·000	0·1014	0·0463	0·00006	0·221	0·219
		$10^3k_0 = 0{\cdot}064$, $10^3k_1 = 3{\cdot}40$ $(10^3k_2 \sim 1)$					
30°	0·000	0·100	0·1102	0·3473	0·0047	2·40	2·41
,,	0·010	0·090	0·1071	0·2417	0·0019	1·71	1·72
,,	0·030	0·070	0·1040	0·1377	0·0005	1·06	1·04
,,	0·050	0·050	0·1027	0·0933	0·0002	0·745	0·745
,,	0·070	0·030	0·1020	0·0700	0·0001	0·591	0·592
,,	0·100	0·000	0·1015	0·0507	0·00007	0·472	0·466
		$10^3k_0 = 0{\cdot}134$, $10^3k_1 = 6{\cdot}67$ $(10^3k_2 \sim 2)$					
37°		$10^3k_0 = 0{\cdot}345$, $10^3k_1 = 15{\cdot}4$, $10^3k_2 = 4{\cdot}2$					

of k_0 are accurate to ±3—4%, those of k_1 to ±1—2%. The values of $k_{\text{calc.}}$ listed in Table 1 are calculated from the final values of k_0, k_1, and k_2.

TABLE 2. *Observed and calculated rate constants.*

$k_0 = 5{\cdot}13 \times 10^{14} \exp(-25{,}800/RT)$, $k_1 = 2{\cdot}87 \times 10^{14}$. $\exp(-23{,}100/RT)$ min.$^{-1}$.

		25°		30°		37°	
		obs.	calc.	obs.	calc.	obs.	calc.
Acid	10^3k_0	0·064	0·065	0·134	0·132	0·345	0·347
Anion	10^3k_1	3·40	3·44	6·67	6·57	15·4	15·4

Arrhenius activation energies and *A* factors derived from the experimental results are used to calculate rate constants, which are compared with the observed rate constants in Table 2. The agreement is satisfactory. The activation energies for the acid and anion are considered to be accurate to ±500 and ±300 cal./mole, respectively, and there is a corresponding uncertainty in the *A* factors.

DISCUSSION

The Arrhenius parameters for oxaloacetic and malonic acids are compared in Table 3. The values for malonic acid and anion have been evaluated from Hall's data [1] (80—90°) on malonic acid over a range of pH, and Fairclough's data [2] (76—120°) on sodium hydrogen malonate.

TABLE 3. *Arrhenius parameters for oxaloacetic and malonic acids.*

	Oxaloacetic		Malonic	
	Acid	Anion	Acid	Anion
E (kcal./mole)	25·8	23·1	30·8	27·9
$10^{-13}A$ (sec.$^{-1}$)	0·85	0·48	5·5	0·0098

For both compounds the anion has a lower activation energy for decarboxylation than has the acid. The pre-exponential *A* factors are around 10^{13} sec.$^{-1}$, except for the malonate ion. For malonic acid and the malonate ion the ratio of *A* factors is about 600. Malonic acid reacts 10 times faster than its anion at 90° (~4 times faster at 30°), as the entropy factor outweighs the energy factor. In oxaloacetic acid, where this entropy effect is absent, the anion is 50 times more reactive than the undissociated acid at 30°.

Oxaloacetic acid can form two univalent ions (I) and (II).

(I) $H_2OC{\cdot}CO{\cdot}CH_2{\cdot}CO_2^-$ $\quad$ $^-O_2C{\cdot}CO{\cdot}CH_2{\cdot}CO_2H$ (II)

A comparison of the ionisation constants of pyruvic, oxaloacetic, and acetoacetic acid confirms that the univalent oxaloacetate ion is predominantly (II). However, evidence is available that (I) is very much more reactive than (II).[7] Structure (II) would indeed be expected to be less reactive than the un-ionised acid; the major contribution to the rate of decarboxylation of the anion may be taken to come from structure (I). In that case, the *A* factor for structure (I) will be greater than the experimental value given in Table 3 by a factor depending on the equilibrium concentrations of (I) and (II).

The most probable conformations of malonic acid and anion are the hydrogen-bonded forms (III) and (IV). In malonic acid (III) a proton must be transferred from one carboxyl group to another for decarboxylation to occur. Malonic acid will therefore react in its most probable conformation and show a normal *A* factor of about 10^{13} sec.$^{-1}$. In the malonate ion (IV) decarboxylation is possible without proton transfer if the carboxyl group (*b*) is eliminated preferentially, as might be expected by analogy with the oxaloacetate ion. The malonate ion might then react by way of an energetically easier path with the carboxyl groups twisted out of the plane of the carbon skeleton. The observed low *A* factor may be associated with this less probable conformation.

The differences in the activation energies of acid and anion for oxaloacetic and malonic acid, and for other β-keto-carboxylic acids are most easily interpreted in terms of the electronic effect of substituent groups on the stability of the activated complex, to which

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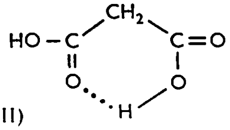
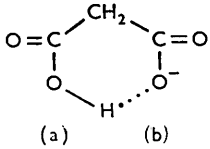
[7] Steinberger and Westheimer, *J. Amer. Chem. Soc.*, 1951, **73**, 429.

the enol $HO{\cdot}CX{:}CY_2$ or ion $^-O{\cdot}CX{:}CY_2$ is a contributing structure. Electrophilic groups will stabilise the ion more than the enol, and electron-releasing groups are expected to act in the reverse manner.



(III)



(IV)

In Table 4 relative rates of decarboxylation of acid and anion are collected for a number of β-keto-acids.[8, 9] The relative rate for malonic acid is given for 30°, and the other data are for temperatures in the range 18—45°

TABLE 4. *Relative rates of decarboxylation of acid and anion.*

Compound	X	Y	Acid	Anion
αα-Dimethylacetoacetic acid	Me	Me, Me	200	1
Acetoacetic acid	Me	H, H	50	1
Malonic acid	OH	H, H	4	1
Phenylmalonic acid	OH	H, Ph	1	3
Dibromomalonic acid	OH	Br, Br	1	$\gg 1$
Acetonedicarboxylic acid	$CH_2{\cdot}CO_2H$	H, H	1	3
Oxaloacetic acid	CO_2H	H, H	1	50

As substituent groups become more electrophilic the relative stability of the activated complex of the anion increases and the activation energy is lowered more than that of the acid, so that the relative rate of the anion increases. In malonic acid the anion would then be expected to have a lower activation energy, as is indeed the case, but the entropy effect causes the acid to react more rapidly. Increasing electrophilic substitution increases the difference in activation energies of acid and anion until this effect overcomes the entropy effect, and leads to the anion's reacting faster than the acid.[9]

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[8] Brown, *Quart. Reviews*, 1951, **5**, 131.
[9] Gelles, *J. Amer. Chem. Soc.*, 1953, **75**, 6199.