

606. Ionisation Constants of the Synthetic Intermediates of Aucubin

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The apparent ionisation constants of mono- and di-carboxylic acids obtained as the synthetic intermediates of aucubin¹ have been determined at 20° in water. An empirical equation based on the inductive effect of the carbonyl group is presented for estimating ionisation constants of oxocarboxylic acids. It has again been found that in cyclopentane-1,2-dicarboxylic acids, the *cis*-isomer has a smaller K_1 and a larger K_1/K_2 .

A CARBONYL group naturally possesses acid-strengthening effects, which are expected to diminish exponentially as the distance between the carbonyl group and the carboxyl group increases. Appropriate analysis of the pK values measured for a series of monocarboxylic acids obtained as synthetic intermediates of aucubin (see Table 1) has led to the empirical relation (eqn. 3) which was derived as follows.

The inductive effect of a substituent on the acid strength of aliphatic carboxylic acids can be expressed^{2,3} by the general form

$$\Delta E = \epsilon^n D \quad (1)$$

where D is the effect of a substituent on an adjacent atom, n is the number of saturated carbon atoms between the carboxyl group and the substituent, and ϵ is a fraction fitting experimental data (usually² 1/2.8). If 4.88 is taken as the average pK constant for long-chain aliphatic acids, the pK for acids having substituents exerting an inductive effect can be expressed by

$$pK = 4.88 + D_1 \epsilon_1^m + D_2 \epsilon_2^n + \quad (2)$$

For oxocarboxylic acids belonging to type *A*, it has been found that the best fit between observed and calculated values (Table 1) is obtained when the electronegativity parameter, D , is taken as -1.83 and the fraction ϵ is taken as 1/3. Eqn. (2) thus leads to the empirical equation

$$pK = 4.88 - 1.83(3^{1-s} + 3^{1-t}) \quad (3)$$

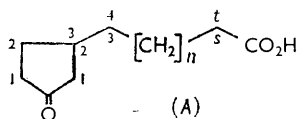
When a carboxyl group is attached directly to the five-membered ring, 0.09 pK unit should be added to those calculated from eqn. (3) since the mean difference in pK between *n*-paraffin monocarboxylic acids ($>C_6$) and cyclopentanecarboxylic acid is 0.09.

Where there is a significant discrepancy between the calculated and observed values of the pK , its extent may be taken as a qualitative measure of the effects which are not

¹ S. Fujise, H. Obara, and H. Uda, *Chem. and Ind.*, 1960, 289.

² G. E. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Englewood Cliffs, New Jersey, 1946, Sec. 25.

³ A. Streitwieser, jun., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York-London, 1961, p. 128.



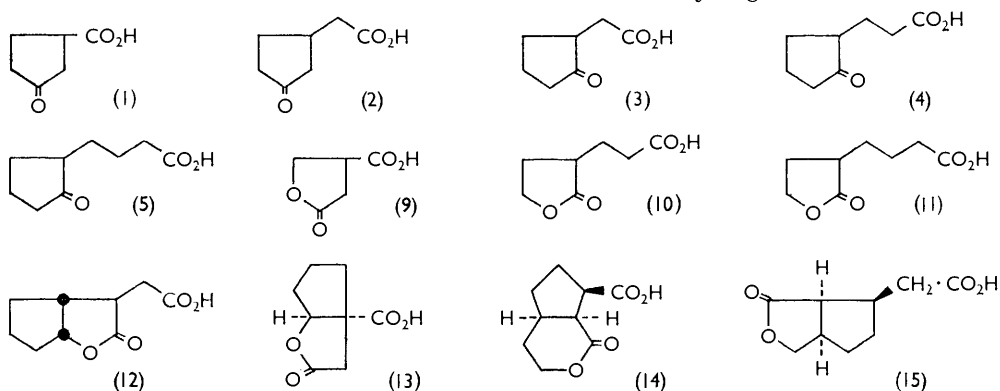
involved in the above equation, *viz.*, those transmitted through linkages by additional substituents introduced at positions not far from the carboxyl group and/or those transmitted directly through space or solvent to the carboxyl group. Equation (1) indicates that the carbonyl will have no detectable effect when both *s* and *t* are greater than 6. As

TABLE I
Ionisation constants of some oxocarboxylic acids

Compound	<i>s</i>	<i>t</i>	pK_{calc}	pK_{obs}	$ \Delta pK $
(1)	2	3	4.17	4.25	0.08
(2)	3	4	4.61	4.64	0.03
(3)	2	5	4.25	4.58	0.33
(4)	3	6	4.68	4.71	0.03
(5)	4	7	4.81	4.86	0.05
(6) $\text{H}_3\text{C}\cdot\text{CO}\cdot[\text{CH}_2]_2\cdot\text{CO}_2\text{H}$	2	∞	4.27	4.60 ^a	0.33
(7) $\text{H}_3\text{C}\cdot\text{CO}\cdot[\text{CH}_2]_3\cdot\text{CO}_2\text{H}$	3	∞	4.68	4.67 ^a	0.01
(8) $\text{H}_3\text{C}\cdot\text{CO}\cdot[\text{CH}_2]_4\cdot\text{CO}_2\text{H}$	4	∞	4.81	4.72 ^a	0.09

^a International Critical Tables, McGraw-Hill, New York, 1929, vol. 6, p. 259.

Table I shows, there is disagreement between the observed and calculated values of the pK in the case of the oxo-acids (3) and (6). Both (3) and (6) are γ -oxo-acids whose structures would favour the formation of an intramolecular hydrogen-bond between the



carbonyl and undissociated carboxyl group, and this would decrease the acid strength; in this case, by about 0.3 pK unit. A comparison of the n.m.r. spectra of the oxo-acids and their methyl esters did not provide any indication that these acids existed as pseudo-acids.

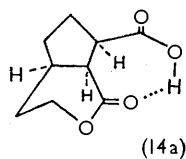
It is evident from a comparison of the pK values of (9), (10), and (11) (Table 2) with

TABLE 2
Ionisation constants of some lactone carboxylic acids

Compound	pK	Compound	pK	Compound	pK
(9)	3.75	(12)	4.27	(14)	4.76
(10)	4.55	(13)	3.99	(15)	4.88
(11)	4.76				

those of (1), (4), and (5), that an ester group has a more powerful acid-strengthening effect than a keto-group, and that the pK differences in going from (9) to (10) and from (10) to (11) are larger than those between (1) and (4) and (4) and (5), indicating that the inductive parameter may be larger than 1/3 (see eqn. 1). The fact that the pK values are the same

in (11) and (14) cannot be explained only by the inductive effect and is best attributed to the increased stabilisation of the undissociated acid by the strong intramolecular hydrogen bonding, as shown in (14a), which is facilitated by its steric environment resulting in a lowering of the acid strength of (14). In agreement with this conclusion, the infrared spectrum of the acid (14) in CHCl_3 showed the lactone carbonyl band at 1715 cm^{-1} which is notably lower than that of ordinary lactones.



The ionisation constants of a series of dibasic acids are summarised in Table 3. In general, the pK_1 of a *cis*-1,2-dicarboxylic acid is smaller than that of the corresponding *trans*-acid, but this is not the case with the cyclopentane-1,2-dicarboxylic acids and their analogues.⁴ This phenomenon is demonstrated by the following pairs of acids in Table 3: (16) and (17), (21) and (22), and (23) and (24). Although the difference is small, the same phenomenon is also observed with isocitric lactone (26) and alloisocitric lactone (27). Structures (26) and (27) have been confirmed by *X*-ray crystallography.⁵ The ratio K_1/K_2 is larger for the *cis*-acids, and this together with the smaller ionisation constants K_1 for the *cis*-acids provides a useful method of differentiating stereoisomeric cyclopentane-1,2-dicarboxylic acids and analogues, *e.g.*, γ -lactone-1,2-dicarboxylic acids.

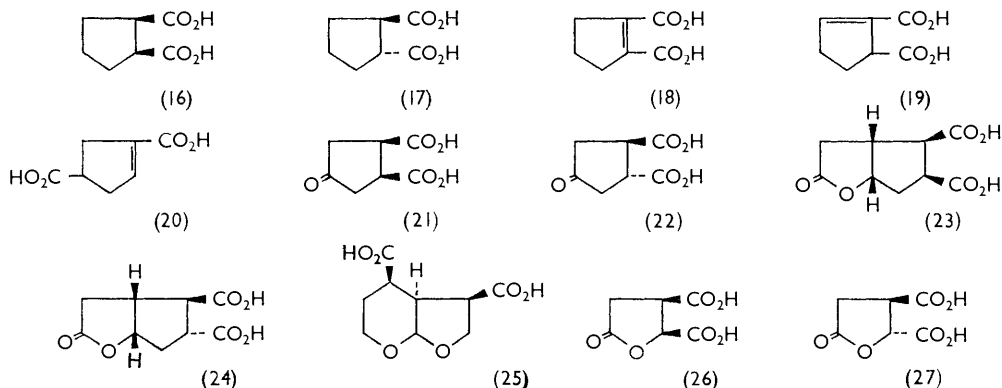
The large pK_2 value in (25) may be additional evidence for the *cis*-configuration of these substituents which was previously assigned on grounds of its formation from tetrahydroanhydroaucubin.¹

Sommer, Arya, and Simon recently deduced a simple equation⁶ that enables one to predict the pK value (in 80% MCS/water) of terpenoid carboxylic acids.⁷ This equation, in which only spacial interactions are taken into account, is indeed very useful in the conformational analysis of these compounds, but a rather large deviation has been noted where a nearby ketonic group is present. A better agreement between the observed and calculated values was obtained when corrections were made for the inductive effect calculated from eqn. (1).

TABLE 3
Ionisation constants of some dibasic acids

Compound	pK_1	pK_2	K_1/K_2	Compound	pK_1	pK_2	K_1/K_2
(16)	4.42	6.57	138	(22)	3.59	5.34	56
(17)	4.14	5.99	90	(23)	3.91	5.97	115
(18)	3.36	7.18	6600	(24)	3.34	5.51	148
(19)	4.03	5.92	78	(25)	4.28	6.74	288
(20)	4.27	5.10	6.8	(26)	2.26 ^a	4.50 ^a	171
(21)	3.90	5.60	150	(27)	2.13 ^a	3.95 ^a	66

^a O. Gawron and A. J. Glaid, *J. Amer. Chem. Soc.*, 1955, **77**, 6638.



EXPERIMENTAL

Materials (by K. K. and H. O.).—Details of preparations have been reported elsewhere. We thank Dr. H. Uda of this Department for a gift of (15) and (25).

pK Determinations. A pH meter model TTT1b Radiometer (Radiometer, Emdrupvej 72,

⁴ G. S. Hammond, in "Steric Effects in Organic Chemistry," ed. M. S. Newman, John Wiley and Sons, Inc., New York-London, 1956, ch. 9.

⁵ J. P. Glusker, A. L. Patterson, W. E. Love, and M. L. Dornberg, *J. Amer. Chem. Soc.*, 1958, **80**, 4426.

⁶ P. F. Sommer, V. P. Arya, and W. Simon, *Tetrahedron Letters*, 1960, No. 20, 18.

⁷ P. F. Sommer, C. Pascual, V. P. Arya, and W. Simon, *Helv. Chim. Acta*, 1963, **46**, 1734.

Copenhagen), fitted with an internally shielded glass electrode and a saturated calomel electrode was used for all potentiometric titrations. It was calibrated with 0.05M-potassium hydrogen phthalate solution. A 0.001M or 0.002M solution (25 ml.) in carbon dioxide-free, glass-distilled water was titrated with 0.100N-sodium hydroxide solution using an all-glass micrometer syringe. Temperature was maintained at 20°.

The p*K* values for monobasic acids were calculated by

$$pK = pH + \log \frac{[HA] - [H^+]}{[A^-] + [H^+]} \quad (4)$$

Calculations of p*K* values of dibasic acids from titration curves were made from eqns. (5) and (6) for sets of two points appropriately taken from the titration curves:⁸

$$pK_1 = \log |A_1B_2 - A_2B_1| - \log |B_1D_2 - B_2D_1| \quad (5)$$

$$pK_2 = \log |B_1D_2 - B_2D_1| - \log |A_1D_2 - A_2D_1| \quad (6)$$

where $A_j = a_j[H^+]_j + c[H^+]_j$, $B_j = 2c - a_j - [H^+]_j$, and $D_j = [H^+]_j^2(a_j + [H^+]_j)$, in which c , a_j , and $[H^+]_j$ are the total concentration of acid, total concentration of added alkali, and hydrogen ion concentration at two points chosen arbitrarily from the titration curves ($j = 1$ and 2). Spreads of p*K* values calculated in this way were within ± 0.10 .

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⁸ Cf. H. T. Britton, "Hydrogen Ions," Chapman and Hall, London, 1955, vol. 1, pp. 217, 218.