# The Decarboxylation of Some Heterocyclic Acetic Acids. Part II.[1] Direct and Indirect Evidence for the Zwitterionic Mechanism

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Macroscopic and model $pK_a$ values for the 2- and 4-pyridylacetic acids in aqueous propan-2-ol have been measured and used to evaluate the microscopic $pK_a$ values as a function of solvent composition. From these are calculated the mole fractions of neutral form and zwitterion present, which in conjunction with the observed decarboxylation rate allows this to be re-expressed in terms of these sub-species (as $k_N$ and $k_Z$ respectively). The smoothness of the relation between $k_Z$ and solvent composition, and the contrast in this respect with $k_N$, are used as evidence that decarboxylation goes through the zwitterion. Similar calculations applied to some of the heterocyclic acetic acids previously examined show that $k_Z$, but not $k_N$, is a linear or slightly curved function of Perrin's nuclear σ constants; this and other evidence is interpreted in favour of the zwitterionic route for the whole range of heterocycles examined. A refinement of the theory implicates tautomeric ratio, which has been measured for some heterocyclic acetates, as a further influence on decarboxylation rate. The β-keto-acids are discussed in the light of these results: it is concluded that they also are probably decarboxylated by the zwitterionic mechanism.

THE mechanism of decarboxylation of the β-keto-acids has long been the subject of dispute. Two rival routes have been proposed: that going through the zwitterion (1b),[2,3] or that involving the cyclic transition state (2a)[4-6] (Scheme 1; X = O). Despite the fact that, as



(1a)   (2a)

(3)

(1b)   (2b)

SCHEME 1
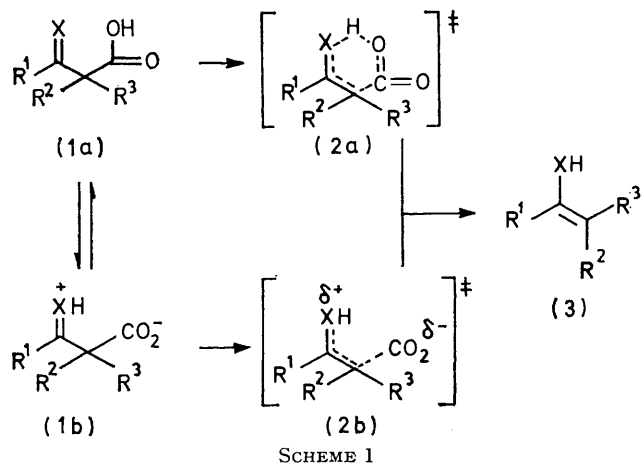
we[1] have pointed out, the transition states (2a) and (2b) are stereochemically quite distinct, decision between these mechanisms is peculiarly difficult. As first pointed out by Hine,[7] most arguments that support one theory can be used, with suitable modification, equally to support the other. The dispute is bedevilled by the fact, long known,[8] that sub-species in equilibrium will always mimic the thermodynamic behaviour of the dominant, and no argument so far used has turned the flank of this position.

Recently, Bigley and Thurman[6] have demonstrated that the gas-phase decarboxylation of the β,γ-unsaturated acids (Scheme 1; X = CR₂) goes by the cyclic pathway (1a) ⟶ (2a) ⟶ (3). From this, and from the close similarity of the solvent and substituent

effects between these and the β-keto-acids studied by Swain et al.,[5] they deduce a common mechanism to obtain. Precisely similar effects are shown by the heterocyclic acids (Scheme 1; X = nitrogen atom of heterocyclic ring) whose decarboxylation rates we have recently reported,[1] and it would be natural on this evidence alone to draw similar conclusions. However, for certain of these compounds the cyclic mechanism is sterically impossible, and from the evidence taken together we believe it to be unlikely for the remainder.[1] This evidence nevertheless is circumstantial, and despite much that is suggestive, nothing so far can be proved.

We now return to the subject with evidence which we believe to be decisive in one disputed case, and overwhelmingly compelling elsewhere. We conclude with some comments on mechanisms of decarboxylation generally.

*Direct Evidence: the Pyridylacetic Acids.*—The decarboxylation rate of most heterocyclic acetic acids in 50% acetone can be followed by titration of the acid remaining.[1] This is possible because the upper $pK_a$ value ($pK_B$ of Scheme 2) is essentially that of the



$$K_A = K_1 + K_2 \qquad K_B^{-1} = K_3^{-1} + K_4^{-1}$$
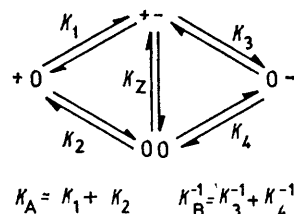
SCHEME 2   The convention used here is that of ref. 10

carboxy-group. For the highly zwitterionic pyridylacetic acids, this is not so; $pK_B$ is that of the cation (*i.e.* $pK_3$ not $pK_4$), and in consequence its titre does not change as the reaction proceeds ($pK_A$ is too low for reliable potentiometric estimation). We discovered in

[1] Part I, P. J. Taylor, *J.C.S. Perkin II*, 1972, 1077.

[2] K. J. Pedersen, *J. Amer. Chem. Soc.*, 1929, **51**, 2098; *J. Phys. Chem.*, 1934, **38**, 559.

[3] K. R. Brower, B. Gay, and T. L. Konkol, *J. Amer. Chem. Soc.*, 1966, **88**, 1681.

[4] F. H. Westheimer and W. A. Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 3283; F. H. Westheimer, *Proc. Chem. Soc.*, 1963, 253.

[5] C. G. Swain, R. F. W. Bader, R. M. Esteve, and R. N. Griffin, *J. Amer. Chem. Soc.*, 1961, **83**, 1951.

[6] D. B. Bigley and J. C. Thurman, *J. Chem. Soc. (B)*, 1967, 941; 1968, 436; *Tetrahedron Letters*, 1967, **25**, 2377.

[7] J. Hine, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1956, p. 285.

[8] A. A. Frost and R. G. Pearson, 'Kinetics and Mechanism,' Wiley, New York, 1953, p. 264.

the course of that work that this situation could be remedied by conducting titrations in 80% acetone, where $pK_B$ is that of the *acid* (*i.e.* $pK_4$). Further experimentation showed this reversal to be extraordinarily sudden: it probably takes place between 50 and 60% acetone. In seeking an explanation for this remarkable observation, we were led to the reasoning behind the experiments here to be described.

As mixed aqueous solvents become less aqueous, basic $pK_a$ values generally fall whereas acid $pK_a$ values rise.[9] A weak base–weak acid salt may, therefore, become essentially a neutral species as this proceeds. However, both $pK_a$ values will change gradually. In the present case, however, there is an extra complication. There are not two $pK_a$ values, but four (Scheme 2); a stronger base and stronger acid associated with the zwitterion, a weaker base and weaker acid associated with the neutral species. The overall change in $pK_a$, therefore, should be very much greater than is normal, and the transition from one dominant species to the other could, by a kind of 'positive feedback,' give rise to a discontinuity. The possibility of that discontinuity provides the rationale for what follows.

From any three ionisation constants, the relative amounts of zwitterion and of neutral species may in principle be calculated.[9,10] Given this information, the observed rate constant $k_{obs}$ may be re-expressed in terms of zwitterion or neutral species as $k_Z = k_{obs}/x_Z$ or as $k_N = k_{obs}/x_N$ respectively. By hypothesis, one only of $k_Z$ and $k_N$ is 'real'; the other is bogus. In deciding which is which, we make one simple, fundamental postulate. We suppose that the 'real' rate constant will be some monotonic function of solvent composition: a straight line or a smooth continuous curve. It can be shown that, in the idealised case, the expected relationship for the 'bogus' rate constant will then be a switchback *i.e.*, two such lines (or curves) separated by another of different slope.* The necessity for this follows from the mathematical circumstance that, if $y = f(x)$, the relation $y = f(1 - x)$ cannot simultaneously hold. If the observed discontinuity is sudden enough, it should therefore be possible to resolve this point.

Before this theory could be put to the test, however, there were some practical difficulties to overcome. The first concerns the calculation of the microscopic ionisation constants $K_1$—$K_4$. This is normally accomplished [9,10] from the macroscopic constants $K_A$ and $K_B$, and any one of the remainder. For the α-amino-acids it is conventionally accepted [9,13] that $K_2$ is closely approximated by $K_a$ for the corresponding ester ($K_{OMe}$ in the Tables) since electron withdrawal due to $CO_2H$ and $CO_2R$ is virtually identical.[14] That convention has

been adopted here. However, it is useful only so long as $K_1 > K_2$, *i.e.* the zwitterion remains the dominant species. Once the neutral species predominates $K_2$ and $K_A$ converge, and the attempt to estimate $K_1$ this way involves the measurement of a small difference between large quantities. So far as we can ascertain, how to calculate $K_Z$ (Scheme 2) for a compound largely in the neutral form is a question that has never been considered.

We have attempted a solution in the following way. The various σ values for carboxylate anion [14] all lie close to zero; that is, the best approximation to $CO_2^-$ is probably H. If that is so the solution is very convenient, since the appropriate compounds, here 2- and 4-methylpyridine, are available as decarboxylation products. Data are presented in Table 3 which show that, in water, this $pK_a$ value (tabulated as $pK_{Me}$) indeed lies close to $pK_3$ in four such cases. However, this approximation may not continue to hold in mixed aqueous solution. We have examined this question over the range of composition for which the normal convention can be used (the first seven points in Tables 1 and 2), and in fact ($pK_{Me} - pK_3$) falls with increasing propan-2-ol content, eventually becoming negative. However, this difference shows some tendency to stabilise (it may even start to reverse), so the last available value has been used to compute $pK_3$ for the last four points. In these, we have assumed the relations $pK_3 - pK_{Me} = 0.1$ and $0.4$ for 2- and 4-pyridylacetic acids respectively. The microscopic values of Tables 1 and 2 follow from these twin assumptions. Close inspection of the data will reveal that these assumptions are to some extent mutually incompatible, presumably because both are distorted by solvent dependence. One might reasonably expect this to be more severe for that concerning $pK_3$, as we have assumed, since the solvation properties of $RCH_3$ and $RCH_2CO_2^-$ are likely to differ more than those of $RCO_2H$ and $RCO_2R'$. Despite these caveats this treatment is here adopted as the best approximation currently available, and detailed justification must depend on the final result for 4-pyridylacetic acid (see below). In any case, the second assumption is not introduced till the critical crossover region is past.

The other hiatus concerns the calculation of $x_Z$ and $x_N$. There is a well known formula, due to Ebert,[9,13] for the calculation of the zwitterionic ratio $K_Z$, but when even at the isoelectric point substantial amounts of cation and anion may still be present, this formula is inadequate. So far as we can ascertain the appropriate equations, though simple, do not appear in the literature, so they have been derived and are given as an Appendix

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* It may be objected that extremum phenomena, now known [11] to be common in mixed aqueous solution, might vitiate this conclusion. However, these generally appear to result from solvent–solvent interactions, so that while they show in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, they cancel in $\Delta G^{\ddagger}$ (log $k$). There may be exceptions to this in cases where the transition state is structurally very dissimilar from the reactant,[12] but that is not so here. In any case, extremum effects lead normally to a single change in slope, not to two as predicted here.

[9] A. Albert and E. P. Serjeant, 'Ionisation Constants of Acids and Bases,' Methuen, London, 1962.

[10] J. T. Edsall, R. B. Martin, and B. R. Hollingworth, *Proc. Nat. Acad. Sci. U.S.A.*, 1958, **44**, 505.

[11] See *e.g.* E. M. Arnett, in 'Physico-Chemical Processes in Mixed Aqueous Solvents,' ed. F. Franks, Heinemann, London, 1967.

[12] P. J. Taylor, *J. Chem. Soc.* (B), 1968, 1554.

[13] L. Ebert, *Z. Phys. Chem.*, 1926, **121**, 385.

[14] C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 1964, **2**, 323.

to this paper. As it turns out, the proportion of cation plus anion present in these solutions ranges from 7 to 15%, so the correction is not negligible. It becomes so when ($pK_B - pK_A$) exceeds four p$K$ units, at which point the above proportion has fallen to *ca.* 2%; it is effects on potentiometrically accessible acid and base $pK_a$ values, a fact consistent with the nearly equal dielectric constants of these co-solvents. All rate and $pK_a$ determinations were therefore performed in aqueous propan-2-ol. Results are assembled in Tables 1 and 2,

TABLE 1

Microscopic $pK_a$ values [a] and mole fractions zwitterion ($x_Z$) and neutral species ($x_N$) at 25°, and rate constants at 60° for 2-pyridylacetic acid in aqueous propan-2-ol

| Pr$^i$OH (%) [b] | p$K_{OMe}$ [c] | p$K_{Me}$ | p$K_A$ | p$K_B$ | p$K_1$ | p$K_2$ | p$K_3$ | p$K_4$ | $x_Z$ | $x_N$ | $10^3 k_{obs}$/min$^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 20 | 3·87 | 5·60 | 2·79 | 5·57 | *2·81* | (3·87) | *5·53* | *4·49* | 0·85 | 0·077 | 0·45 |
| 30 | 3·66 | 5·47 | 2·80 | 5·54 | *2·87* | (3·66) | *5·47* | *4·68* | 0·79 | 0·13 | 1·26 |
| 40 | 3·43 | 5·23 | 2·85 | 5·50 | *2·98* | (3·43) | *5·37* | *4·92* | 0·67 | 0·24 | 3·00 |
| 45 | 3·39 | 5·10 | 2·90 | 5·46 | *3·07* | (3·39) | *5·29* | *4·97* | 0·61 | 0·29$_5$ | 4·60 |
| 50 | 3·35 | 5·00 | 2·97 | 5·42 | *3·18* | (3·35) | *5·21* | *5·04* | 0·52 | 0·37 | 6·88 |
| 55 | 3·32 | 4·91 | 3·04 | 5·37 | *3·36* | (3·32) | *5·05* | *5·09* | 0·41$_5$ | 0·46$_5$ | 9·24 |
| 60 | 3·26 | 4·82 | 3·11 | 5·48 | *3·65* | (3·26) | *4·92* | *5·31* | 0·26 | 0·63 | 12·8 |
| 65 | 3·10 | 4·71 | 3·09 | 5·67 | *3·95* | *3·15* | (4·81) | *5·61* | 0·12$_5$ | 0·78 | 15·2 |
| 70 | 3·02 | 4·58 | 3·13 | 5·81 | *4·26* | *3·16* | (4·68) | *5·78* | 0·068 | 0·85 | 19·7 |
| 75 | 2·90 | 4·41 | 3·18 | 5·92 | *4·59* | *3·20* | (4·51) | *5·90* | 0·036 | 0·89 | 25·2 |
| 80 | 2·85 | 4·22 | 3·27 | 6·00 | *4·95* | *3·28* | (4·32) | *5·99* | 0·018 | 0·90 | 31·5 |

[a] Values in parentheses are assigned on assumptions discussed in the text, italicised ones are calculated from these. [b] Pr$^i$OH $x$-vol to water (100 − $x$) vol. [c] p$K_a$ Value of methyl ester.

TABLE 2 [a]

Microscopic $pK_a$ values and mole fractions zwitterion ($x_Z$) and neutral species ($x_N$) at 25°, and rate constants at 55° for 4-pyridylacetic acid in aqueous propan-2-ol

| Pr$^i$OH (%) | p$K_{OMe}$ | p$K_{Me}$ | p$K_A$ | p$K_B$ | p$K_1$ | p$K_2$ | p$K_3$ | p$K_4$ | $x_Z$ | $x_N$ | $10^3 k_{obs}$/min$^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 20 | 4·53 | 5·84 | 3·14 | 5·78 | *3·16* | (4·53) | *5·76* | *4·32* | 0·88 | 0·037 | 0·241 |
| 30 | 4·38 | 5·62 | 3·22 | 5·76 | *3·25* | (4·38) | *5·73* | *4·60* | 0·84 | 0·063 | 0·677 |
| 40 | 4·23 | 5·21 | 3·30 | 5·73 | *3·35* | (4·23) | *5·68* | *4·80* | 0·78 | 0·105 | 1·58 |
| 45 | 4·14 | 5·12 | 3·35 | 5·71 | *3·43* | (4·14) | *5·63* | *4·92* | 0·74 | 0·14$_5$ | 2·71 |
| 50 | 4·04 | 5·08 | 3·44 | 5·69 | *3·57* | (4·04) | *5·56* | *5·09* | 0·65 | 0·22 | 3·84 |
| 55 | 3·93 | 5·02 | 3·54 | 5·67 | *3·77* | (3·93) | *5·44* | *5·28* | 0·50 | 0·35 | 5·80 |
| 60 | 3·85 | 4·94 | 3·60 | 5·71 | *3·96* | (3·85) | *5·35* | *5·46* | 0·36$_5$ | 0·48 | 7·09 |
| 65 | 3·82 | 4·84 | 3·54 | 5·84 | *4·14* | *3·66* | (5·24) | *5·72* | 0·22 | 0·66$_5$ | 9·19 |
| 70 | 3·72 | 4·75 | 3·52 | 5·94 | *4·31* | *3·59* | (5·15) | *5·87* | 0·14$_5$ | 0·74$_5$ | 12·2 |
| 75 | 3·66 | 4·65 | 3·52 | 6·01 | *4·48* | *3·57* | (5·05) | *5·96* | 0·098 | 0·80 | 16·5 |
| 80 | 3·55 | 4·51 | 3·57 | 6·05 | *4·71* | *3·60* | (4·91) | *6·02* | 0·064 | 0·83 | 21·1 |

[a] For key see notes to Table 1.

therefore unimportant for the α-amino-acids that have mostly been considered.
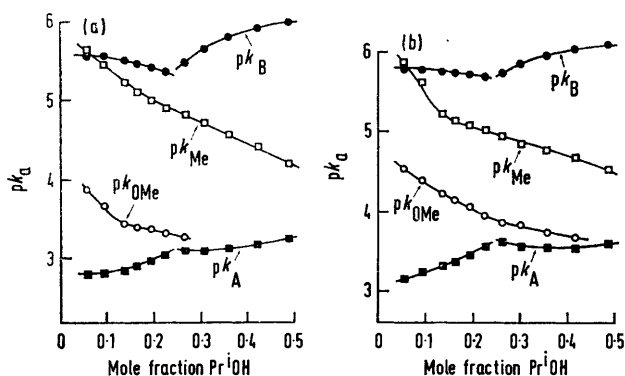


FIGURE 1 Measured $pK_a$ values in aqueous propan-2-ol at 25° for (a) 2-pyridylacetic acid, (b) 4-pyridylacetic acid, and related compounds (for key to nomenclature see Tables 1 and 2)

Our final problem concerned the choice of solvent. Aqueous acetone as previously [1] used is u.v.-opaque, so does not allow the determination of $pK_A$ and $pK_B$ by u.v. methods. Preliminary tests showed that aqueous propan-2-ol and aqueous acetone have very similar

and those that benefit from visible display appear further on Figures 1—4.

Figure 1(a) displays the $pK_A$, $pK_B$, $pK_{OMe}$, and $pK_{Me}$ values for 2-pyridylacetic acid as a function of mole
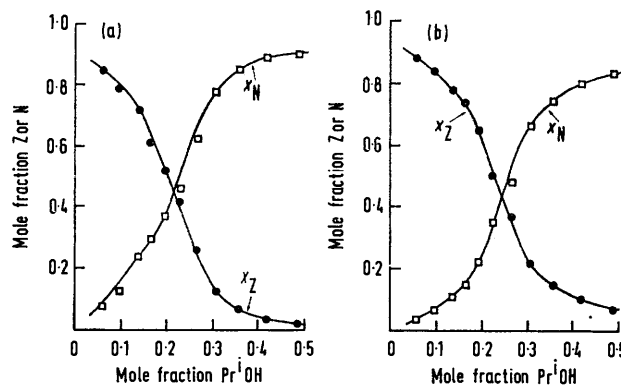


FIGURE 2 Calculated mole fractions of zwitterion $x_Z$ and neutral species $x_N$ in aqueous propan-2-ol for (a) 2-pyridylacetic acid, (b) 4-pyridylacetic acid

fraction of propan-2-ol. The discontinuity in $pK_A$ and $pK_B$ is clearly apparent; it probably occurs at almost

the same point as in aqueous acetone. The resulting values of $x_Z$ and $x_N$ appear, similarly, on Figure 2(a). Their relative proportions do not depend on solvent composition quite so steeply as Figure 1(a) would
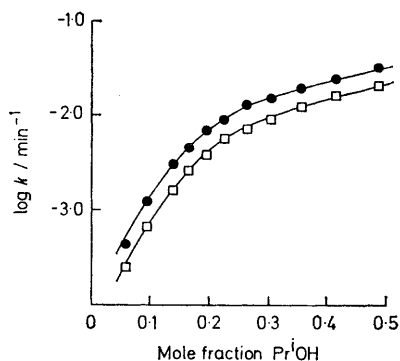


FIGURE 3 Observed rate as a function of solvent composition in aqueous propan-2-ol for 2-pyridylacetic acid at 60° (circles) and 4-pyridylacetic acid at 55° (squares)

suggest, but the effect is certainly far more pronounced than would be expected for a simple weak base–weak acid salt. The overall rate $k_{obs}$ is shown on Figure 3. There may be a change of slope near the crossover point, a possibility deliberately emphasised by the way the lines are drawn, but the effect is not pronounced and in itself, as sufficiently discussed,[1] this fact alone conveys no information. However, the evidence of Figure 4(a) is decisive. Here $k_Z$ is a smooth, almost linear function of solvent composition; $k_N$ shows the ' switchback ' effect predicted. The first is therefore the ' real,' the second the ' bogus,' rate coefficient.

It may reasonably be objected that, while the effect is there, its magnitude is small and the assumptions involved are open to question. To settle this matter we

assumptions for the last four points appear to introduce one. We conclude that the zwitterionic mechanism applies to both.

The solvent scale used in Figure 4 is that of mole fraction, since this function most generally leads to linearity with such thermodynamic quantities as log $k$ and $pK_a$ in mixed aqueous solvents.[15] It is true that the use of other scales, e.g. % composition, causes appreciable extra curvature in the lines for $k_Z$. However, there is no solvent scale that can straighten $k_N$, and no plausibility in the proposition that, when these compounds behave so similarly, the mechanism remains ambiguous for the one though certain for the other.
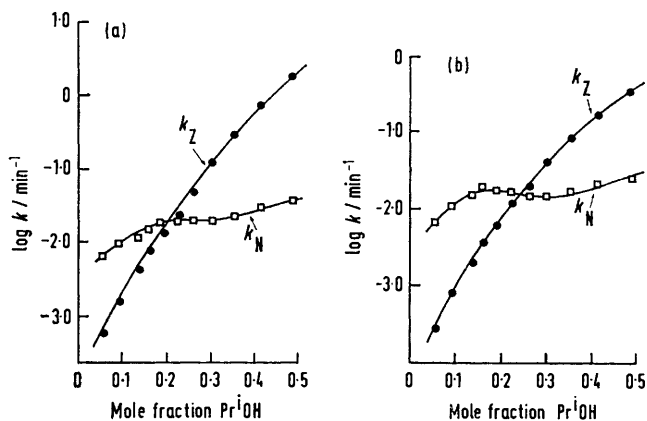


FIGURE 4 $k_Z$ (circles) and $k_N$ (squares) as a function of solvent composition in aqueous propan-2-ol for (a) 2-pyridylacetic acid, (b) 4-pyridylacetic acid

We believe we have come as close as is ever likely to be possible to a kinetic proof of mechanism in a case such as this.

TABLE 3

Microscopic $pK_a$ values [a] for some heterocyclic acetic acids in water at 25°

| Acid | $pK_{OMe}$ | $pK_{Me}$ | $pK_A$ | $pK_B$ | $pK_1$ | $pK_2$ | $pK_3$ | $pK_4$ | $(pK_{Me} - pK_3)$ | $x_Z$ | $x_N$ |
|------|-----------|-----------|--------|--------|--------|--------|--------|--------|-----------|--------|--------|
| (4) [b] | 5·12 | 6·55 | 2·26 | 6·52 | 2·26 | (5·12) | 6·52 | 3·66 | 0·03 | 0·98₅ | 0·0013 |
| (5) [b] | 4·15 | 5·94 | 2·62 | 5·79 | 2·63 | (4·15) | 5·78 | 4·26 | 0·16 | 0·92₅ | 0·028 |
| (6) [b] | 5·00 | 6·03 | 3·00 | 5·88 | 3·00 | (5·00) | 5·87 | 3·87 | 0·16 | 0·92 | 0·0093 |
| (13) | | 2·46 | 1·24 | 4·23 | (2·86) [c] | 1·25 | 2·61 | 4·22 | −0·15 | 0·022 | 0·91₅ |

[a] For key see notes to Table 1.    [b] $pK_a$ Values from J. H. Blanch, *J. Chem. Soc. (B)*, 1966, 937, except for $pK_{Me}$, from A. Gero and J. J. Markham, *J. Org. Chem.*, 1951, 16, 1835.    [c] See ref. 1.

have repeated the entire cycle with 4-pyridylacetic acid, for which the zwitterionic mechanism is unambiguous.[1] The results are displayed on Figures 1(b), 2(b), 3, and 4(b). All closely resemble their companions and the final plot of $k_Z$ and $k_N$ [Figure 4(b)] shows an effect which, while more pronounced than that of Figure 4(a), is not spectacularly so. Probably the reason lies in the somewhat sharper crossover shown by $x_Z$ and $x_N$ [Figure 2(b)], itself plausibly the result of this compound's greater separation of charge. In neither case is any discontinuity in $k_Z$ evident, nor does the switch in

[15] N. M. Ballash, E. B. Robertson, and M. D. Sokolowski, *Trans. Faraday Soc.*, 1970, 66, 2622.

*Indirect Evidence: the Remainder.*—*The zwitterionic ratio.* A conclusion reached for compounds that are highly zwitterionic cannot necessarily be generalised to those that are not. The pyridylacetic acids are unique in that the transition from one predominant species to the other can be achieved in mixed aqueous solvents. The imidazolylacetic acid (4) is too strong a base to exhibit this effect, whereas the remaining compounds we have investigated [1] are all too weak. For these, therefore, a different approach has had to be employed.

As Bigley and Thurman [6] have remarked, the zwitterionic theory effectively subsumes the decarboxylation of the β-keto-acids (and of those here discussed)

TABLE 4

Microscopic $pK_a$ values [a] and mole fractions zwitterion $(x_Z)$ and neutral species $(x_N)$ for various heterocyclic acetic acids in 46% propan-2-ol at 25°, and decarboxylation rate constants [b] in 50% acetone at 50°

| Compound | $pK_{OMe}$ | $pK_{Me}$ | $pK_A$ | $pK_B$ | $pK_1$ | $pK_2$ | $pK_3$ | $pK_4$ | $x_Z$ | $x_N$ | $10^3 k_{obs}/$ min$^{-1}$ | $\Sigma\sigma$ [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (4) | 4·48 | 5·78 | 2·76 | 6·44 | 2·77 | (4·48) | 6·43 | 4·72 | 0·95 | 0·018₅ | 0·081 | 0·57 |
| (5) | 3·39 | 5·10 | 2·90 | 5·46 | 3·07 | (3·39) | 5·29 | 4·97 | 0·61 | 0·29₅ | 2·35 | 0·75 |
| (6) | 4·14 | 5·12 | 3·35 | 5·71 | 3·43 | (4·14) | 5·63 | 4·92 | 0·74 | 0·14₅ | 7·02 | 0·96 |
| (7) | −0·29 | 1·07 | −0·29 | 5·05 [d] | 3·29 | (−0·29) | (1·47) | 5·05 | 2·6 × 10⁻⁴ | 0·99₅ | 3·29 [e] | 1·51 |
| (8) | 1·03 | 2·31 | 1·03 | 5·19 [d] | 3·51 | (1·03) | (2·71) | 5·19 | 3·3 × 10⁻³ | 0·98 | 227 | 1·41 |
| (9) | 0·0 | 0·99 | 0·0 | 4·73 [d] | 3·34 | (0·0) | (1·39) | 4·73 | 4·5 × 10⁻⁴ | 0·99 | 3·34 | 1·53 |
| (10) | 0·41 | 0·73 | 0·41 | 5·29 [d] | 4·57 | (0·41) | (1·13) | 5·29 | 6·9 × 10⁻⁴ | 0·99 | 3·30 | 1·85 |
| (11) | −1·1 | −0·92 | −1·1 | 4·53 [d] | 3·95 | (−1·1) | (−0·52) | 4·53 | 8·9 × 10⁻⁶ | 0·99₅ | 0·75 | 1·89 |
| (12) | −1·6 | −0·63 | −1·6 | 5·17 [d] | 3·80 | (−1·6) | (−0·23) | 5·17 | 3·9 × 10⁻⁶ | 1·00 | 23·5 [e] | 2·58 |

[a] For key to these see notes to Table 1. [b] Ref. 1. [c] For origin and meaning see text. The following $\sigma$ values are used: =N−, $\alpha$, 0·75; $\beta$, 0·65; $\gamma$, 0·96; −NH−, $\alpha$, −0·24; −O−, $\alpha$, 1·08; $\beta$, 0·25; −S−, $\alpha$, 0·72; $m$-OMe, 0·08; $m$-Ph, 0·06; $p$-Ph, 0·01. [d] In 50% acetone (see ref. 1). [e] Statistically corrected for two equivalent nitrogen atoms.

under Brown's [16] general heading of anionic decarboxylation. The unprotonated and protonated forms of the intermediate anion may be schematically represented as
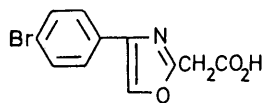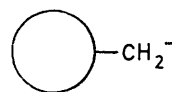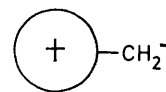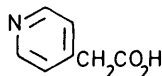


(4)



(5)



(6)



(7)



(8)



(9)



(10)



(11)
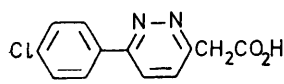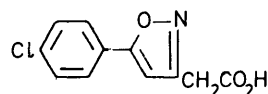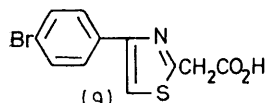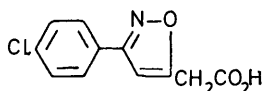


(12)



(13)



(14)
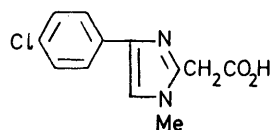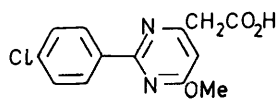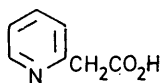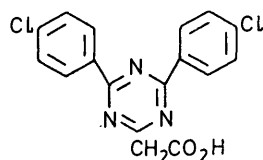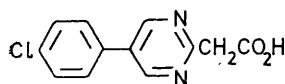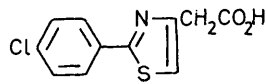


(15)

(16) and (17) where the latter, as we [1] have observed, is simply a resonance form of (3); the increased electron-withdrawing effect of the positive charge in (17) should make the decarboxylation rate faster. Intuitively, one might therefore suspect some correlation between rate and ring electronegativity. The difficulty lies in finding an accessible physical quantity that may plausibly relate to the latter. As a start, one might consider resonance energies. Unfortunately, those for heterocycles that appear in the literature [17-19] are mutually contradictory, and while Dewar's most recent values [19]



(16)          (17)

are probably to be preferred, such key structures as thiazole and oxazole are absent, and the validity of even the best data is reduced by factors to which Dewar himself [19,20] has drawn attention. More relevant perhaps might be ring electron density at the carboxymethyl substituent position, but once again published data are fragmentary, subject to the same qualifications as above,[20] and in addition possess the crippling disadvantage that their method of calculation relates them to a relative not an absolute scale, so that they cannot be transferred from one heterocycle to another. We have had to fall back, therefore, on empirical criteria.

In preliminary attempts at a correlation with our previous [1] values of $k_{obs}$, the following candidate parameters were tested: chemical shift of the $\alpha$-methylene protons; $\Delta\lambda_{max.}$ on protonation; basic $pK_a$ of the compound itself or its parent heterocycle; acid $pK_a$; basic $pK_a$ of the compound in which $CH_2CO_2R$ is replaced by $NH_2$; $\nu_{C=O}$ of that in which $OH$ replaces $CH_2CO_2R$; and the nuclear $\sigma$ constants of Jaffé and

[16] B. R. Brown, Quart. Rev., 1951, 5, 131.
[17] D. W. Davies, Trans. Faraday Soc., 1955, 51, 449.
[18] G. W. Wheland, ' Resonance in Organic Chemistry,' Wiley, New York, 1955, p. 80ff.
[19] M. J. S. Dewar and G. J. Gleicher, J. Chem. Phys., 1966, 44, 759.
[20] M. J. S. Dewar, ' The Molecular Orbital Theory of Organic Chemistry,' McGraw-Hill, New York, 1969, ch. 9.

Perrin.[21,22] All had to be rejected. However, one significant correlation did emerge. If the data are restricted to those acids (in Table 1 of ref. 1) which contain a p-chloro- or a p-bromo-group and no α-substituent, there is a good linear relation between the summation of these nuclear and other σ constants ('Σσ' of Table 4 *) for the carboxyalkyl substituent position and *enthalpy* of reaction $\Delta H^{\ddagger}$ (Figure 5). The
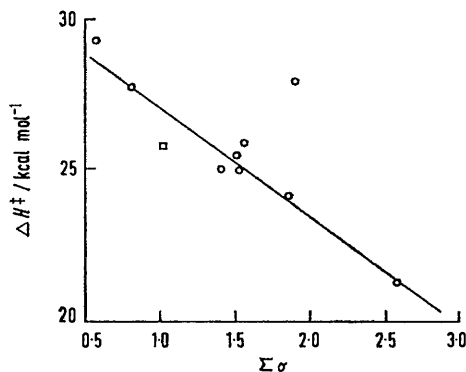


FIGURE 5    Relation between $\Delta H^{\ddagger}$ and $\Sigma\sigma$ for the decarboxylation rates of some heterocyclic acetic acids from ref. 1 (see text)

attempt at a correlation has been confined in the above manner since the data [1] make it clear that $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, but not $\Delta G^{\ddagger}$, are very sensitive to substituent, behaviour typical of self-compensating changes in solvation.[23] The one seriously deviant point, that for the oxazolyl-acetic acid (11), may originate this way, since this compound, alone in the series, possesses a site alternative to (and perhaps better than) nitrogen for an intra-molecular hydrogen bond. It may be significant that $\Delta H^{\ddagger}$ for this compound is abnormally affected by α-methylation.[1] Consistently, the only other deviant point, and this in the opposite direction, is for a 4-pyridylacetic acid derivative incapable of any intra-molecular bonding at all.

There is a particular reason why, in this case, the appropriate reactivity index might well be correlated better with enthalpy than with free energy (rate) as such. If we are right that the zwitterion is the true reactant, then the observed rate is the product of two quantities: a pre-equilibrium ionisation and a subsequent reaction step. It follows that the observed enthalpies and entropies will each be composite in character. Consider the ionisation step first. It is now well established [24] that ionisation processes tend to be largely entropy-controlled: enthalpies are generally small and, within a given series (phenols,[24] carboxylic acids [25,26]), nearly a constant. Data for appropriate bases are more difficult

* These summed σ values are calculated from the compilation by Barlin and Perrin [22a] except that, for nitrogen, the recent values of Deady et al.[22b] based on diazinecarboxylate hydrolysis have been preferred. It is also assumed that the value for p-chlorophenyl equals that for phenyl [14] itself.

[21] H. H. Jaffé, Chem. Rev., 1953, 53, 191; J. Chem. Phys., 1952, 20, 1554; D. D. Perrin, J. Chem. Soc., 1965, 5590.
[22] (a) G. B. Barlin and D. D. Perrin, Quart. Rev., 1966, 20, 75; (b) L. W. Deady, D. J. Foskey, and R. A. Shanks, J. Chem. Soc. (B), 1971, 1962.

to find, but while enthalpies for these are greater, reflecting that for the ionisation of water, there is, again, some evidence [26-28] for near-constancy inside a given class. Accepting this, the overall $\Delta H^{\circ}$ of ionisation may well be very similar for all the compounds in Figure 5; it follows that the 'true' or zwitterionic enthalpy of reaction $\Delta H_{\mathrm{Z}}^{\ddagger}$ will probably show much the same order. Now it has been observed [24,29] that the success of the Hammett correlation depends on an implicit parallelism between enthalpy and free energy: it succeeds, in general, only when $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are related in some non-random manner. Provided that *solvation* terms are factored out, a condition here sought, if not certainly achieved, by standardising all structural features save only the heterocyclic nucleus itself, it follows that $\Delta H_{\mathrm{Z}}^{\ddagger}$ and $\Delta G_{\mathrm{Z}}^{\ddagger}$ should run parallel (when this condition fails the more sophisticated treatment of Hepler [24] must be used). We postulate, in short, that $\Delta H^{\ddagger}$ in Figure 5 'stands in' for the missing, unknown, zwitterionic rate constant $k_{\mathrm{Z}}$. It follows from this treatment that the failure of $k_{\mathrm{obs}}$ to correlate with $\Delta H^{\ddagger}$ is mainly the fault of large compensating changes in the entropy terms, especially in the entropy of ionisation $\Delta S^{\circ}$.

It therefore became relevant to measure $k_{\mathrm{Z}}$ and $k_{\mathrm{N}}$ for as many of these compounds as possible. This requires knowledge of $x_{\mathrm{Z}}$ and $x_{\mathrm{N}}$, which can in principle be obtained as described above. As already observed, aqueous acetone turns out in this respect to have been an unfortunate choice of solvent, and insufficient material remained to repeat the entire investigation. We have compromised by comparing rates in 50% acetone with mole fractions in 46% propan-2-ol, which last appears from our data [30] to be the closest possible equivalent to the former in its effect on potentiometrically accessible acid and basic p$K_{\mathrm{a}}$ values [n.b. that p$K_{\mathrm{B}}$ values derive from 50% acetone where known, and that 45% propan-2-ol values are quoted and used for (5) and (6)]. We have also adopted the convention, based on compounds (4)—(6), that p$K_3$ = p$K_{\mathrm{Me}}$ + 0.4 under these conditions. Data are assembled in Table 4, and the resulting relations between $k_{\mathrm{Z}}$ or $k_{\mathrm{N}}$ and $\Sigma\sigma$ are shown on Figure 6.

The relation between $k_{\mathrm{Z}}$ and $\Sigma\sigma$ appears on Figure 6(a). It takes the form of a line [equation (1), $r = 0.96$] or a gentle curve [equation (2), $r = 0.98$]. The latter as well as the former is shown although the extra term is only significant at the 5.9% level. Despite

$$\log k_{\mathrm{Z}} = 3.96 \pm 0.46\Sigma\sigma - 5.41 \pm 0.72 \qquad (1)$$

$$\log k_{\mathrm{Z}} = 7.77 \pm 1.68\Sigma\sigma - 1.25 \pm 0.54(\Sigma\sigma)^2 - 7.86 \pm 1.20 \qquad (2)$$

[23] D. J. G. Ives and P. D. Marsden, J. Chem. Soc., 1965, 649.
[24] L. G. Hepler, J. Amer. Chem. Soc., 1963, 85, 3089.
[25] J. J. Christensen, R. M. Izatt, and L. D. Hansen, J. Amer. Chem. Soc., 1967, 89, 213.
[26] R. P. Bell, 'The Proton in Chemistry,' Methuen, London, 1959, ch. 5.
[27] J. M. Essery and K. Schofield, J. Chem. Soc., 1961, 3939.
[28] J. J. Christensen, J. H. Rytting, and R. M. Izatt, J. Chem. Soc. (B), 1970, 1643.
[29] L. P. Hammett, 'Physical Organic Chemistry,' 2nd edn., McGraw-Hill, New York, 1970, p. 404.
[30] R. G. Button and P. J. Taylor, unpublished data.

this we consider it intuitively reasonable; there is no fundamental reason why the relation should be linear, and indeed its curvature, if real, could well result from a slow drift of the transition state along the reaction co-ordinate with increasing electronegativity of the hetero-cyclic ring. A rather similar phenomenon is thought [31] to explain the curvature that has recently been detected [32] in some Brönsted plots which Figure 6(a) superficially resembles. Approximations apart, either correlation is probably as good as can be expected for nuclear $\sigma$ constants at this stage in their development. The significance of this relation, whichever form may be preferred, is that it is derived from compounds based on seven heterocyclic nuclei and ranging in nature from the wholly zwitterionic to some containing only parts per million of zwitterion. Over the whole of this range,
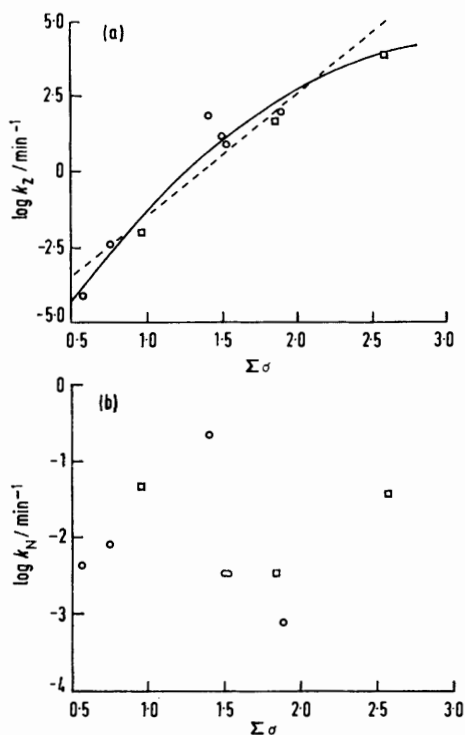


FIGURE 6 Relation between $\Sigma\sigma$ and (a) $k_Z$, (b) $k_N$, for the compounds of Table 4 (the squares are those points not used on Figure 7)

there seems no need to postulate the intervention of any competing mechanism.

By contrast, the relation between $\Sigma\sigma$ and $k_N$ [Figure 6(b)] is no more than a scatter diagram. These equally result from the attempt to find correlations between $k_Z$ or $k_N$ and any of the alternative empirical parameters already tried for $k_{obs}$ (see above). The one partial exception is a rather poor correlation between $k_Z$ and $pK_2$ which presumably reflects, in imperfect form, the derivation of '$\Sigma\sigma$.' No correlation between $k_N$ and any

[31] M. Eigen, *Angew. Chem.*, 1963, **75**, 489.
[32] M. E. Langmuir, L. Dogliotti, E. D. Black, and G. Wetter-mark, *J. Amer. Chem. Soc.*, 1969, **91**, 2204; W. P. Jencks and M. Gilchrist, *ibid.*, 1968, **90**, 2622.

sort of structural parameter, separately or in combin-ation, has been found.

One other way in which these data can be used is worth mentioning. It has been seen [1] that the acid related to (9) by $\alpha$-methylation decarboxylates $3 \times 10^3$ times faster than its anion, whereas the anion of (12) is only about ten times less reactive than the formally neutral species. This gap in reactivity ratio is surprising since, as argued previously,[1] something like constancy might have been expected: apart from the negative charge, all factors are virtually the same. This applies equally whether the cyclic or the zwitterionic route is considered [*i.e.*, the transition states (18a) or (18b) with



( 18a )　　　　( 18 b )
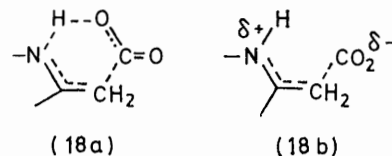
or without a proton on nitrogen]. Given $x_Z$, it is possible in the latter eventuality to make an approximate calculation of the 'true' rate ratio, *i.e.* $k_Z/k_{anion}$ (the former eventuality leaves the superficial facts un-changed). If compound (9) and its $\alpha$-methyl derivative contain about the same mole fraction of zwitterion, this rate ratio is *ca.* $7 \times 10^5$. For compound (12), it is *ca.* $2\cdot5 \times 10^6$. This is near enough a constant for present purposes and, in addition to providing striking circum-stantial confirmation of the zwitterionic theory, it suggests that the anion may well become the more reactive species once the proportion of zwitterion falls low enough.

*The tautomeric ratio.* Another way of looking at this reaction starts from a further consideration of the rival transition states (18a) and (18b).

Decarboxylation, by either mechanism, eventually involves the formation of an intermediate whose tauto-meric form is highly unfavourable.[33] In so far as the transition state resembles this intermediate, the same must be true of that. This suggests the possibility that some part of these differences in rate, and perhaps some of the scatter on Figure 6(a), may be due to the inter-vention of this additional factor. To check on this possibility, we require the tautomeric ratio of some close model for the transition state.

In the nature of things, no model can be exact. How-ever, a possible approximation involves the equilibrium (19) $\rightleftharpoons$ (20), where the nature of R is to be decided. Species of type (20; R = H) are commonly somewhat



( 19 )　　　　( 20 )
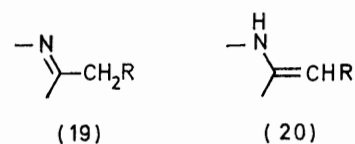
unstable, and in addition lack the conjugation with carbonyl present in (18). This last feature is prominent,

[33] A. R. Katritzky and J. M. Lagowski, *Adv. Heterocyclic Chem.*, 1963, **1**, 341.

perhaps too prominent, in compounds for which $R = CO_2R'$, and which can be made by $N$-methylation of the heterocyclic acetates. Their accessibility helped to dictate the choice of these compounds for study.

Compound availability and preparative difficulties have drastically curtailed the number of examples even so, but the six that have been prepared at least all represent a different heterocyclic nucleus. Their $pK_a$ values ($pK_{NMe}$) and resultant tautomeric ratios [$K_T = (20)/(19)$] are given in Table 5 for 46% propan-2-ol

TABLE 5

Tautomeric ratio for the equilibrium (19) $\rightleftharpoons$ (20) for some compounds in 46% propan-2-ol

| Compound | $pK_{NMe}$ | $-pK_T$ [a] |
|---|---|---|
| (21) | ca. 15 | ca. 10 |
| (22) | 9·00 | 5·61 |
| (23) | 5·91 | 6·20 |
| (24) | 4·01 | 2·98 [b] |
| (25) | 3·64 | 3·64 |
| (26) | 5·16 | 6·26 [b] |

[a] For definition see text. [b] It is assumed that minor substitutions such as methyl for ethyl ester in (24) or $p$-chloro for $p$-bromo in (26) do not affect $K_T$ appreciably.

[the $pK_a$ of (19) is that given for the appropriate ester ($pK_{OMe}$) in Table 4]. Data for (22) in water have been reported by Jones and Katritzky.[34] Tautomeric ratios for the whole set have also been measured in water.[30] The $pK_{NMe}$ of (21) * is so high, and the compound itself so sensitive to alkali, that the value quoted can be considered accurate only to the nearest unit. All these $pK_{NMe}$ values are sensitive to solvent, the value in 46%



(21)  (24)  (22)  (25)  (23)  (26)
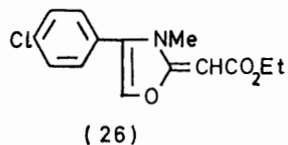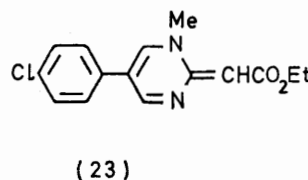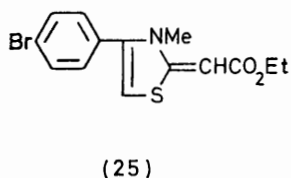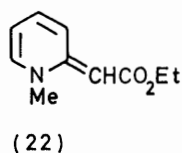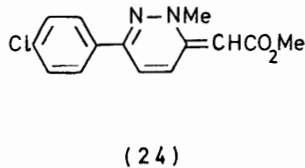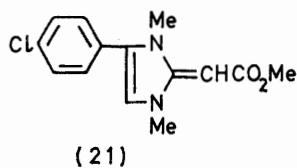
propan-2-ol lying 1·5—2 units below that in water. The value for (21) in 46% propan-2-ol has been obtained by assuming a difference at the top end of this range, there

* This compound, with $pK_a$ ca. 17 in water, is one of the strongest organic bases yet to be reported (see M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *Chem. Comm.*, 1971, 510, for another recent example).

being evidence (see Tables 3 and 4) that the $pK_a$ values of (4) and related compounds are unusually solvent-sensitive. Even so, the very large tautomeric ratio is probably a minimum. The alkali-sensitivity of these compounds has been previously discussed [34] with respect
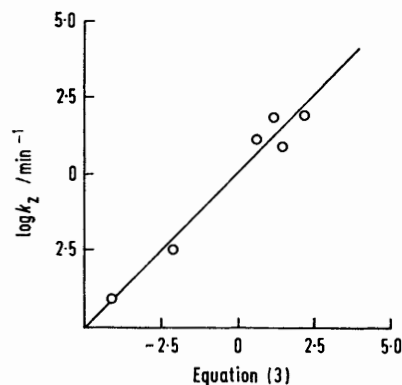


FIGURE 7 Relation between $k_Z$ and a mixed function of $\Sigma\sigma$ and $K_T$ according to equation (3)

to (22) and attributed to covalent hydration. Their time-dependent u.v. changes are all similar (disappearance of the strong band at >300 nm), and so probably is the explanation for them. Except for (21), however, it has proved possible to measure these $pK_{NMe}$ values without appreciable interference from alkaline attack.

Inspection of Table 5 reveals some very suggestive features, notably the relatively favourable tautomeric ratio for the pyridazine (24) and the exceedingly unfavourable one for the imidazole (21). Consistently with this the corresponding acetic acids (8) and (4) are notably reactive and unreactive, respectively (Table 4). Nevertheless, statistical analysis reveals no significant correlation between $k_Z$ or $k_N$ and $K_T$ as such. If however $k_Z$ is analysed as a mixed function of $\Sigma\sigma$ and $K_T$, equation (3) results. Though the presence of the term

$$\log k_Z = 3.88 \pm 0.65\Sigma\sigma - 0.298 \pm 0.133 \, pK_T - 3.37 \pm 1.43 \quad (3)$$

in $K_T$ improves the fit only at the 11·2% level of significance despite the slightly better correlation coefficient (from $r$ 0·96 to 0·985), to the eye at least there is some improvement [Figure 7; *cf.* Figure 6(a)], and we think it likely that this correlation is genuine. In view of the imperfections of the model, this result is probably as good as could have been hoped.

The intervention of tautomeric ratio as a factor in decarboxylation rate may explain one result already noted [1] as a puzzle. The isoxazolylacetic acids (14) and (15) decarboxylate in water at a rate which, even at 100°, is extremely low. Their very low basicity ($pK_A$ −3·31 and −3·60 respectively), leading as it will to a proportion of zwitterion far less even than for (12), must furnish part of the explanation. Tautomeric ratio may supply the remainder. 3-Hydroxyisoxazoles

34 R. A. Jones and A. R. Katritzky, *Austral. J. Chem.*, 1964, 17, 455.

are among the few known heteroaromatic compounds that exist as such when the ketone alternative is available,[35] and the tautomeric ratio even for the 5-isomer [36] is probably close to unity. Both, therefore, exhibit an unusual reluctance to support an exocyclic double bond, and if that applies in a favourable case, it must be even more pronounced in this one. For these compounds, $K_T$ could be still more negative than the $10^{-10}$ for (21). Using that value, and assuming one of $10^{-8}$ for $x_Z$, equation (3) may be used to predict a value of $k_{obs}$ for (14) and (15) in the region of $10^{-6}$—$10^{-10}$ min$^{-1}$. To fit the facts a value at the bottom end of this range is required, but at least this very rough calculation does not give obviously ridiculous results.

Another problem left over from the previous investigation[1] concerns the much enhanced decarboxylation rate of the quinolylacetic acids as compared to their pyridyl analogues, for which enhanced electronegativity seems an improbable explanation. However, it is well established[33] that ring annulation reduces resistance to exocyclic double bond formation, no doubt by reducing the loss in resonance energy, and that factor could be operative here. We conclude, on qualitative as much as on quantitative grounds, that tautomeric ratio probably does have some bearing on decarboxylation rate.

*Conclusions.*—The decarboxylation of the β,γ-unsaturated acids has been shown, by Bigley and Thurman,[6] to go through the cyclic transition state (2a). We believe that we have demonstrated, in terms hardly less unambiguous, that decarboxylation even of the least basic heterocyclic acetic acid goes *via* the zwitterionic intermediate (1b). In between lies the disputed territory of the β-keto-acids, for which zwitterionic structures can neither be proved nor excluded. We conclude by advancing an argument that, so far as we are aware, has never been used in this context before.

From the published thermochemical data[37] it is possible to deduce that, in the gas or liquid phase, acetic acid is endergonic with respect to methane and carbon dioxide by a margin of about 10 kcal mol$^{-1}$. Such a margin does not necessarily apply in other cases, and in any case the acid is likely to be stabilised relative to its breakdown products in aqueous or partly aqueous solution, but it still seems probable that decarboxylation tends to be a mildly exergonic process. We do not know how these three classes of compound compare in that respect, but there is no reason to suppose that they are very dissimilar. Also we know from the evidence presented above that the tautomeric equilibrium [(19) ⇌ (20); R = $CO_2R'$] lies very much against double bond formation, and for [(19) ⇌ (20); R = H] it is likely to be still less favourable; such data as exist[33] bear this out. Consequently (3) in these cases must be

highly endergonic with respect to the final rearranged product, perhaps by 10—15 kcal mol$^{-1}$ or more. These features are shown on the schematic free energy diagram, Figure 8(a). With $\Delta G^{\ddagger}$ *ca.* 25 kcal mol$^{-1}$ (ref. 1), the methine (20; R = H) therefore cannot lie too far below the transition state. It follows on Hammond's principle[38] that the transition state is well advanced along the reaction co-ordinate; there is plenty of room between this and the reactant to accommodate some such intermediate as a zwitterion. Incidentally, the slow drift in position of the transition state with electronegativity, postulated above, is only too likely on this argument.

For the β,γ-unsaturated acids, a wholly different situation obtains. Here the intermediate *is* the final product; there may be some energetic difference between the isomeric alkenes, but surely not much. Hence species (3) is of very much lower energy than formerly [Figure 8(b)]. It follows[38] that the transition state must be much more reactant-like: there is little room here for an intermediate, and Bigley's conclusion[6] necessarily holds.

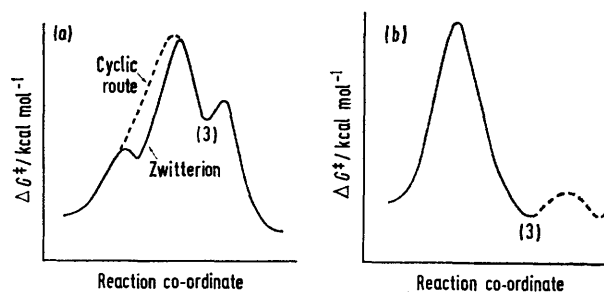It will at once be evident that the β-keto-acids fit the first case much more closely than the second. Once



FIGURE 8 Simulated free energy diagrams for the decarboxylation of (a) the heterocyclic acetic acids, (b) the β,γ-unsaturated acids (see text)

again (3) is a metastable species, for acetone[39] by a factor *ca.* $10^6$ (which should be still less in more polar media[40]), *i.e.* by much the same margin as for the heterocyclic acetic acids. Concurrently, $\Delta G^{\ddagger}$ is of the same order.[2,5] There is, therefore, ample room for a zwitterion. While mere adumbration of this possibility does not prove its truth, we feel this point of difference between the β,γ-unsaturated and the β-keto-acids to be stronger than any point of resemblance so far claimed. Direct evidence of the type adduced above is scarcely conceivable in this case, but the acceleration of β-keto-acid decarboxylation specifically by primary amines[41] is much more readily understood in terms of the zwitterion (27) than in any other way. Incidentally, one related decarboxylation in solution quite certainly goes by the zwitterionic route. While formally the same alternatives as elsewhere (Scheme 3) exist for the

[35] A. J. Boulton, A. R. Katritzky, A. M. Hamid, and S. Øksne, *Tetrahedron*, 1964, **20**, 2835.
[36] A. J. Boulton and A. R. Katritzky, *Tetrahedron*, 1961, **12**, 41.
[37] From N.B.S. Circular 500, U.S. Govt. Printing Office, Washington, 25, D.C., 1952.

[38] G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.
[39] G. Schwarzenbach and Ch. Wittwer, *Helv. Chim. Acta*, 1947, **30**, 669.
[40] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' 2nd edn., Bell and Sons, London, 1969, p. 799.
[41] K. J. Pedersen, *J. Amer. Chem. Soc.*, 1938, **60**, 595.

β-hydroxy-acids studied by Noyce and his co-workers,[42] the cyclic transition state (29a) would involve the



(27)
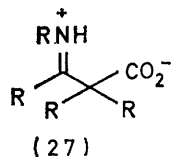
concerted making and breaking of *three* bonds of which only one concerns proton transfer, which surely rules
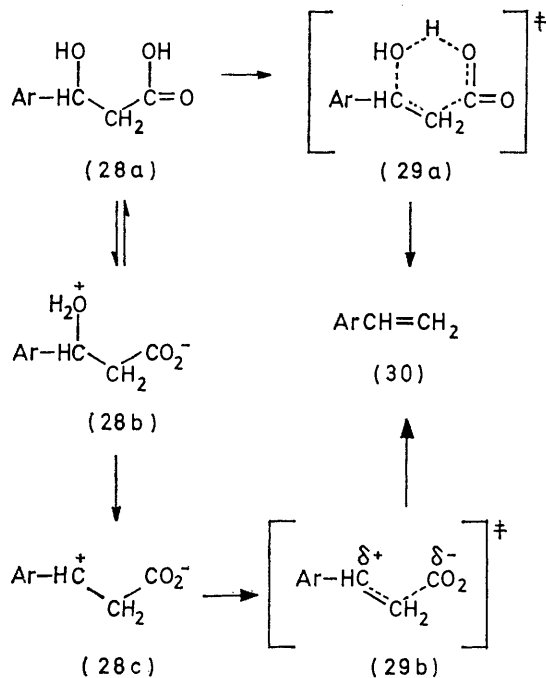


SCHEME 3

this mechanism out of court. If the zwitterionic pathway is certain here, it is at least perfectly reasonable for the equally non-basic β-keto-acids.

ation this way in highly polar solvents not impossible even when a carbonium ion would have to be formed [*cf.* (28c)]. We believe, in conclusion, that the heterocyclic acetic acids decarboxylate by the zwitterionic mechanism under all conditions studied, and that β-keto-acids probably do; but the last cannot be proved either way at present, and much more evidence will be needed before firm conclusions can be drawn.

EXPERIMENTAL

The following procedure for compound (26) illustrates the general method for the preparation of the anhydro-bases described in Tables 5 and 6.

4-(p-*Chlorophenyl*)-2-*ethoxycarbonylmethylene*-3-*methyl-oxazoline* (26).—To a mixture of dimethyl sulphate (0·16 ml) and nitrobenzene (3 ml), both previously dried over anhydrous potassium carbonate, 4-(*p*-chlorophenyl)-2-ethoxycarbonylmethyloxazole (0·295 g) was added and the solution was heated 3·5 h at 100—110°, left overnight, and stirred for 24 h in contact with saturated aqueous potassium iodide solution. The nitrobenzene layer after separation was freeze-dried and the resulting solid was triturated with ether (2 × 10 ml) to yield the *hydriodide* (Table 6). The latter was dissolved in aqueous sodium carbonate and filtered, the filtrate was extracted with chloroform, and the chloroform layer, after drying over anhydrous potassium carbonate, was evaporated under reduced pressure to yield the crystalline *anhydro-base* (26).

The pyridazine (24) and thiazole (25) anhydro-bases appeared in the nitrobenzene layer after digestion with aqueous potassium iodide without the need for treatment with alkali. By contrast, alkali will not liberate the imidazole anhydro-base (21). Elemental analyses (Table 6) are reported for these anhydro-bases when they could be isolated sufficiently free of inorganic material; otherwise they are given for the hydriodides. The latter were in any case used for the p$K_a$ determinations. The pyridine anhydro-base (22) has been described.[34] Attempts to make a triazine anhydro-base by similar methods failed; only unchanged starting material was recovered.

*Kinetics and Equilibria.*—Materials and methods were

TABLE 6

Analytical and other data for anhydro-bases

| | | | | Found (%) | | | | Required (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Compound | M.p. (°C) | $\lambda_{max.}$/nm [a] | Formula | C | H | N | I | C | H | N | I |
| (21), HI | 137—139 | *ca.* 320 | $C_{14}H_{16}ClIN_2O_2$ | 41·1 | 4·1 | 7·1 | 30·6 | 41·3 | 3·9 | 6·9 | 31·2 |
| (22) | 52 [b] | 375 [c] | $C_{10}H_{13}NO_2$ | 66·7 | 7·1 | 8·3 | | 67·0 | 7·3 | 7·8 | |
| (23), HI | | 333 | $C_{15}H_{18}ClIN_2O_2$ | 42·4 | 3·7 | 6·5 | | 43·0 | 3·8 | 6·7 | 30·3 |
| (24) | 194—195 | 341 | $C_{14}H_{13}ClN_2O_2$ | 61·1 | 5·0 | 9·9 | | 60·7 | 4·7 | 10·1 | |
| (25) | 131—132·5 | 331 | $C_{14}H_{14}BrNO_2S$ | 49·7 | 4·2 | 4·0 | | 49·4 | 4·1 | 4·1 | |
| (26), HI | 130—132 | 331 | $C_{14}H_{15}ClINO_3$ | 40·4 | 3·6 | 3·5 | | 41·2 | 3·7 | 3·4 | 31·1 |

[a] Long-wavelength peak of anhydro-base. [b] Lit.,[34] 52—54 °C. [c] Ref. 34.

In the absence of direct methods much might be accomplished by a more careful study of solvent effects, especially as regards variations in the activation parameters and possible specific effects due to dipolar aprotic solvents (*cf.* ref. 1). There is also the interesting question as to where in this sequence, as the medium is changed, one mechanism shades into the other; gasphase decarboxylation by the zwitterionic route is improbable even for the pyridylacetic acids, decarboxyl-

as previously [1] described. Aqueous p$K_a$ values were mostly measured by u.v. spectrophotometry; that for (21) assumes the $H_-$ scale of Rochester [43] and was approximated from a number of solutions made in strong alkali and at once examined (the half-neutralisation point is reached in *ca.* 13·5M-sodium hydroxide solution). The p$K_A$ and p$K_B$

[42] D. S. Noyce and S. K. Brauman, *J. Amer. Chem. Soc.*, 1968, **90**, 5218; D. S. Noyce, L. Gortler, M. J. Jorgensen, F. B. Kirby, and E. C. McGoran, *ibid.*, 1965, **87**, 4329.

[43] C. H. Rochester, *Quart. Rev.*, 1966, **20**, 511.

values for the 2- and 4-pyridylacetic acids were also measured by u.v. methods; some $pK_B$ values were double-checked by potentiometry. Otherwise values in aqueous propan-2-ol, including all those of Table 5, were mostly obtained by potentiometric titration. Since aqueous buffers were used to calibrate the glass electrode and no attempt was made to correct for liquid junction errors, the values for aqueous propan-2-ol cannot be considered ' true ' $pK_a$s but at any given solvent composition they will be internally self-consistent, so the calculation of $K_T$ and mole fraction is unaffected by this. Published information [44] suggests the liquid junction potential correction to be small for aqueous alcoholic solvents over this mole fraction range.

There are individual features of some interest. Those anhydro-bases examined (Table 6) show strong u.v. absorption beyond 300 nm, as previously noted [34] for one of them. Their $pK_a$ values are exceptionally sensitive to solvent composition, presumably because the base and its cation are so markedly different in structure. Consequently, $K_T$ also varies; it is appreciably less negative in water. As the pH scale is ascended, the u.v. spectra of the 2- and 4-pyridylacetic acids show changes which differ markedly according as to whether zwitterion or neutral species is the intermediate form: the first of these has the stronger spectrum, and for the latter acid this is the strongest in the set. U.v. changes at more than one wavelength, in general near 230 and 275 nm, were used in deriving the $pK_a$ values, and results were rejected unless there was good agreement.

For rates and $pK_a$ determinations, means of 2—4 results were taken. Calculated values of $\pm 5\%$ for the standard deviation of $k_{obs}$ and of $\pm 0.04$ for that of $pK_a$ lead to e.s.d. values of $\pm 5\%$ in $x_Z$ or $x_N$ in the centre of the mole fraction scale and $\pm 2\%$ at its extremes. The resulting values of $k_Z$ and $k_N$ have e.s.d. values of $\pm 12\%$ across the mole fraction scale, i.e. $\pm 0.05$ in $\log k$, or about twice the vertical spread represented by each point on Figure 4.

## APPENDIX

In terms of Scheme 2 we have the definitions (4)—(6).[10,13]

$$K_A = K_1 + K_2 \tag{4}$$

$$1/K_B = 1/K_3 + 1/K_4 \tag{5}$$

$$K_Z = K_1/K_2 = K_4/K_3 = x_Z/x_N \tag{6}$$

It is readily shown [10,13] that equation (7) obtains. The

$$(x_Z + x_N) = 1/([H^+]/K_A + 1 + K_B/[H^+]) \tag{7}$$

isoelectric point is defined by (8). Substituting (8) in (7)

$$[H^+] = (K_A K_B)^{\frac{1}{2}} \tag{8}$$

and making use of (4)—(6) to define $x_Z$ and $x_N$ separately, we have equations (9) and (10) at the isoelectric point.

$$x_Z = \left(\frac{K_1}{K_A}\right)\left[\frac{(K_A/K_B)^{\frac{1}{2}}}{2 + (K_A/K_B)^{\frac{1}{2}}}\right] = \left(\frac{K_B}{K_3}\right)\left[\frac{(K_A/K_B)^{\frac{1}{2}}}{2 + (K_A/K_B)^{\frac{1}{2}}}\right] \tag{9}$$

$$x_N = \left(\frac{K_2}{K_A}\right)\left[\frac{(K_A/K_B)^{\frac{1}{2}}}{2 + (K_A/K_B)^{\frac{1}{2}}}\right] = \left(\frac{K_B}{K_4}\right)\left[\frac{(K_A/K_B)^{\frac{1}{2}}}{2 + (K_A/K_B)^{\frac{1}{2}}}\right] \tag{10}$$

Equations (9) and (10) have been used to derive the $x_Z$ and $x_N$ values of Tables 1—4; they reduce to Ebert's formula [9,13] as the ratio $K_A/K_B$ approaches infinity.

[44] C. L. de Ligny and M. Rehbach, *Rec. Trav. chim.*, 1960, **79**, 727.