The Decarboxylation of Some Heterocyclic Acetic Acids

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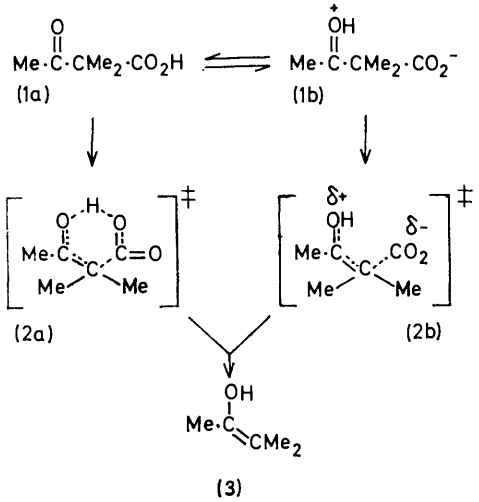
Decarboxylation rates are reported for 36 heterocyclic acetic acids. Reaction is due to the formally neutral species, *i.e.*, free acid or zwitterion. The question as to which of these is the actual reactant is critically discussed with respect to solvent and substituent effects, the nature of the heterocycle, trends in the activation parameters, and previous work on β-keto- and βγ-unsaturated acids. While no single piece of evidence is decisive, the zwitterionic mechanism is thought to be favoured by the facts taken together even for those compounds in which the proportion of zwitterion is probably very small. Some implications of this conclusion for the dearboxylation of the β-keto-acids are considered.

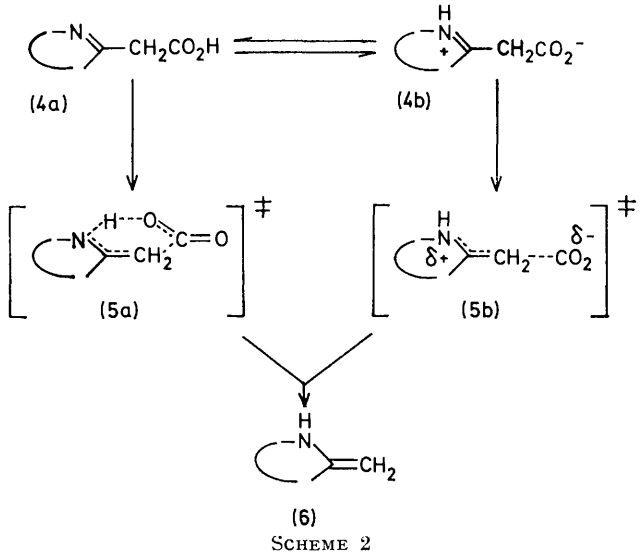
THE impossibility of identifying the true reactant out of a set of sub-species in mobile equilibrium by purely kinetic means is among the cardinal tenets of reaction mechanistic theory.[1a] The problem is particularly acute among reactions that involve ionic equilibria,[2-4] where even the study of salt effects will not resolve it.[5] The decarboxylation of the β-keto-acids provides a classical example of this mechanistic ambiguity. In that of αα-dimethylacetoacetic acid [6,7] both possible species react, the free acid (Scheme 1) about five times more rapidly



SCHEME 1

than its anion. Pedersen [7] demonstrated that the enol (3) is formed in the rate-determining step by showing that the adduct Me–CO–CMe_2Br results in the presence of bromine even though the product ketone itself is unreactive under these conditions. Two mechanisms are possible for the formation of (3): fission of the zwitterion (1b),[6-9] or the concerted pathway (1a) ⟶ (2a) ⟶ (3).[10-12] The latter was suggested since the influence of solvent is not great. However, Hine [13] has pointed out that solvent effects (like salt effects [5]) are ambiguous; any change in the reaction medium that operates to increase the proportion of zwitterion is likely at the same time to increase its stability, and it is only too probable that these opposing effects on the rate will cancel.

We became interested in this problem while investigating the decarboxylation rates of a wide range of heterocyclic acetic acids, many of which are potentially interesting as anti-arthritic agents.[14] Given that the reactant is the formally neutral species (see later), it is obvious that similar ambiguities arise (Scheme 2; *cf.* Scheme 1). Pasternak and van Doering [15] found the (+)-isomer of (10) to give the racemic 2-picoline, so proving the intermediacy of a species of type (6). They [15] and others [16] have demonstrated that 2- and 4-pyridylacetic acids



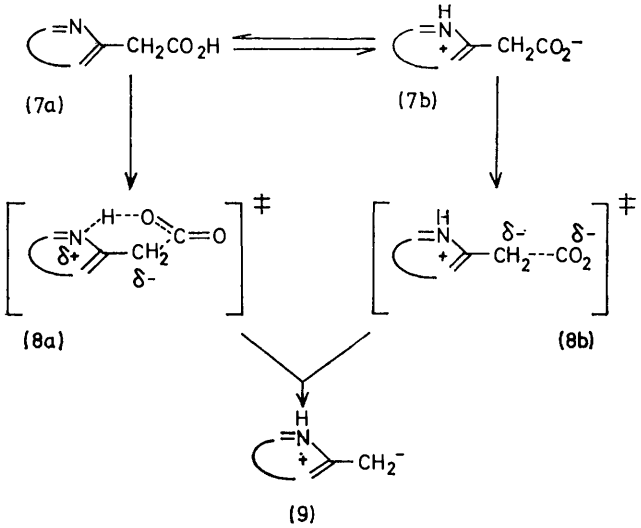
SCHEME 2

decarboxylate in water at comparable rates; since no such transition state as (5a) can be written for the latter,

[1] A. A. Frost and R. G. Pearson, 'Kinetics and Mechanism,' Wiley, New York, 1953, (*a*) p. 257; (*b*) p. 124.
[2] J. T. Edward and K. A. Terry, *J. Chem. Soc.*, 1957, 3527.
[3] J. Walker and F. J. Hambly, *J. Chem. Soc.*, 1895, **67**, 746.
[4] F. D. Chattaway, *J. Chem. Soc.*, 1912, **101**, 170.
[5] I. Weil and J. C. Morris, *J. Amer. Chem. Soc.*, 1949, **71**, 1664.
[6] K. J. Pedersen, *J. Amer. Chem. Soc.*, 1929, **51**, 2098.
[7] K. J. Pedersen, *J. Phys. Chem.*, 1934, **38**, 559.
[8] B. R. Brown, *Quart. Rev.*, 1951, **5**, 131.
[9] K. R. Brower, B. Gay, and T. L. Konkol, *J. Amer. Chem. Soc.*, 1966, **88**, 1681.
[10] F. H. Westheimer and W. A. Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 3283.
[11] C. G. Swain, R. F. W. Bader, R. M. Esteve, and R. N. Griffin, *J. Amer. Chem. Soc.*, 1961, **83**, 1951.
[12] F. H. Westheimer, *Proc. Chem. Soc.*, 1963, 253.
[13] J. Hine, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1956, p. 285.
[14] B.P.s 1,099,389, 1,121,922, 1,139,940, 1,147,068, and 1,164,510.
[15] V. Z. Pasternak and W. E. van Doering, *J. Amer. Chem. Soc.*, 1950, **72**, 143.
[16] F. R. Stermitz and W. H. Huang, *J. Amer. Chem. Soc.*, 1970, **92**, 1446; 1971, **93**, 3427.

they conclude that the zwitterionic mechanism (4b) ⟶ (5b) ⟶ (6) applies to both. It has also been shown[15,16] that, in both cases, cation and anion are comparatively unreactive.

Stermitz and Huang [16] note that the thermal decarboxylation rate of 3-pyridylacetic acid is immeasurably slower than that of its position isomers; similar differences are found among the thiazole-acetic [17] and -carboxylic [18] acids. In terms of substitution pattern this distinction between fast and slow rates corresponds to that between the so-called ' heterocyclic ' and ' aromatic ' positions in each ring; only the former can go by Scheme 2. We have investigated this point [19] and find, in comparable cases, an average difference of 10^5 in rate. The ' slow ' decarboxylations may go either according to Scheme 3, which is analogous to Scheme 2



SCHEME 3

except that the intermediate (9) is necessarily a zwitterion, or by the concerted pathway of Scheme 4 (for which see later discussion). We have no certain evidence on this point in the general case, but it may be significant that the decarboxylation of (39) under electron impact takes place equally by both routes.[20] Since this is a gas-phase reaction and our rate data relate to polar solvents which should heavily favour the more polar mechanism, it is reasonable to suppose that Scheme 3 applies in the present context. However, with the exception of (39) and (40), only ' fast ' decarboxylations are treated here.

EXPERIMENTAL

Materials.—2- and 4-Pyridylacetic acids were obtained commercially as their hydrochlorides and checked for purity before use. Other acetic acids and related compounds were supplied by those colleagues acknowledged at the end of this paper. Water was doubly deionised; other materials were of analytical reagent quality. The composition of mixed aqueous solvents is expressed as volume % non-aqueous component.

Kinetics.—All reactions were followed by measuring the amount of unchanged acid remaining. One of two methods was employed as appropriate:

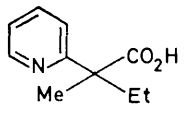
(a) *Potentiometry.* This was the method of choice, used for mixed aqueous and other neutral water-miscible solvents: it can also be used when the solvent is miscible in some proportion with aqueous acetone. It will be illustrated by the technique employed for 50% acetone. The acetic acid (*ca.* 10^{-3} mol) was dissolved in acetone (50 ml) already at the reaction temperature, and the solution was made up to 100 ml with water a little cooler than this; the starting time of the reaction was arbitrarily taken as that at which the correct temperature was attained, generally within 5 min. For rapid reactions ($t_{\frac{1}{2}} < 30$ min), the temperature differential was set empirically at a value to lead to the correct temperature straight away. Aliquot portions (10 ml) were removed at various intervals, diluted with chilled solvent, and titrated with 0·05M-potassium hydroxide solution on a Metrohm E336 Potentiograph after adding sufficient strong acid (*ca.* 0·5 ml of aqueous 0·1M-hydrochloric acid) to produce a sharp initial inflection. This prior addition of acid also served to stop the reaction. The amount of acetic acid remaining was then measured as the distance between inflections on the titration curve (maximum titre generally *ca.* 2 ml). While it is possible to remove most of the carbon dioxide generated or otherwise present by stirring the acidified solution for *ca.* 10 min, this precaution is unnecessary: at any solvent composition, the gap in pK_a between carbonic acid and any of these acetic acids is ample to avoid confusion. Tests have established that the presence of substantial amounts of carbon dioxide affects the reaction rate neither by distorting the point of inflection nor in any other way.

The above procedure is entirely satisfactory when, as for most of these compounds, the upper pK_a value in water (Table 1) is that of the acetic acid. For the pyridine- and quinoline-acetic acids, that is not so. In these cases, the aliquot portions were added to a sufficient volume of acetone to bring the final proportion of the latter to 80% or greater, when the above condition is satisfied. This technique was sometimes useful for the stronger acids generally, *e.g.*, for (41), whose decarboxylation rate in water (Table 2) was also followed in this way. In one case only, that of the imidazolylacetic acid (21), even this method proved inapplicable: the upper pK_a remains that of the base at any solvent composition. The method successfully employed in this case was to add 1·00 ml of 0·02N-hydrochloric acid to an aliquot portion containing 0·1 mequiv. of compound, and titrate to the *first* inflection; this amounts to back-titration of the amine liberated. In this case, prior stirring of the acidified solution to remove carbon dioxide was essential. Only the first 10% of the reaction was followed since some other, so far unidentified, type of decomposition supervened; consequently the results for (21) must be considered approximate.

The decarboxylation of (41) at 100 °C in water was likewise accompanied by some reaction which, again, has not been positively identified but, fortunately, did not interfere with the kinetic method. Since quaternised thiazoles are

[17] H. Schenkel and R. Mory, *Helv. Chim. Acta*, 1950, **33**, 16.
[18] H. Schenkel and M. Schenkel-Rudin, *Helv. Chim. Acta*, 1949, **31**, 924.
[19] P. J. Taylor, unpublished results.
[20] M. J. Rix and B. R. Webster, *Org. Mass Spectrometry*, 1971, **5**, 311.

known [21] to undergo hydrolysis of the ring, it is probable that the competing reaction is of this sort. Consistently, this reaction takes place in parallel with decarboxylation and leads to a carboxylic acid that does not decarboxylate.



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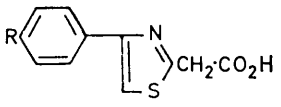

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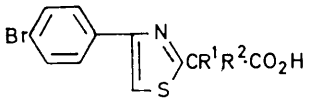
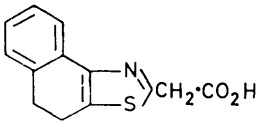


	R^1	R^2
(12)	H	H
(13)	H	Me
(14)	Me	Me
(15)	H	Et
(16)	H	Pr^i



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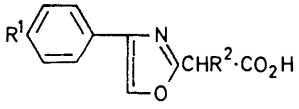
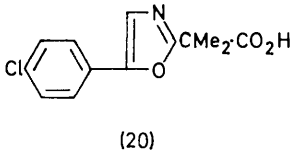


	R^1	R^2
(18)	Br	H
(19)	Cl	Me



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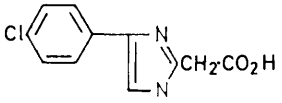

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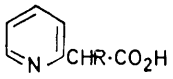
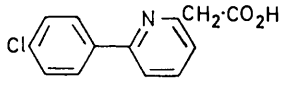


(22) R = H
(23) R = *p*-ClC_6H_4



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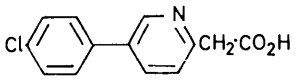

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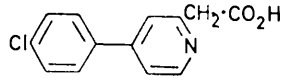

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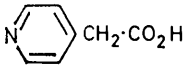

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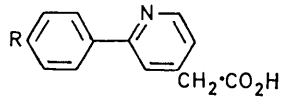
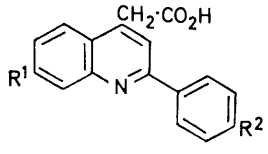
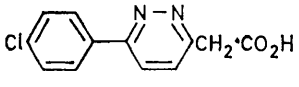


(28) R = H
(29) R = Cl



	R^1	R^2
(30)	H	Cl
(31)	Cl	H



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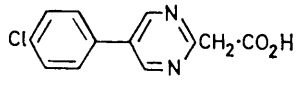

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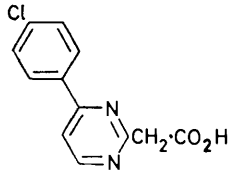

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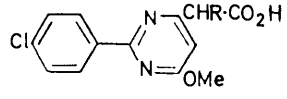
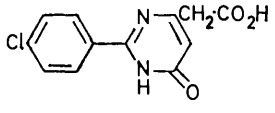


(35) R = H
(36) R = Me



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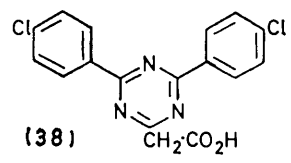

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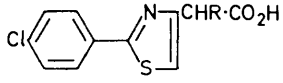
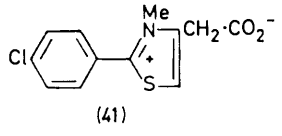


(39) R = H
(40) R = Me



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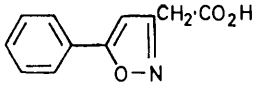

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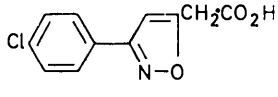


(43)

While so far as we can discover similar ring fissions have not been reported for quaternised imidazoles, a *consecutive* reaction of that sort taking place on the product would account for the observed behaviour of (21). These observations are also relevant in another context (see below).

When, as commonly, compounds were supplied as the ester, the above procedure was modified by dissolving *ca.* 10^{-3} mol of ester in a solution containing 2×10^{-3} mol of sodium hydroxide, and leaving it at the reaction temperature overnight; the reaction was then started by adding 2×10^{-3}

[21] R. R. Williams and A. E. Ruehle, *J. Amer. Chem. Soc.*, 1935, **57**, 1856.

mol of hydrochloric acid. This gives a solution of I = 0·02; elsewhere I was negligible. Since the pH plateau of maximum rate generally extends for some distance (see

TABLE 1

Decarboxylation rates and activation parameters for some heterocyclic acetic acids in 50% aqueous acetone at 50 °C, and pK_a values at I = 0·01 in water at 25 °C

Compd.	pK_a-(BH$^+$)	pK_a-(HA)	10^3k/min^{-1}	$\Delta H^\ddagger$ / cal mol^{-1}	$\Delta S^\ddagger$ / cal mol^{-1} K^{-1}
(12)	1·0	3·63	3·34	25,000	−0·5
(13)	0·8	3·84	9·98	24,100	−1·0
(14)			12·2	23·200	−4·0
(17)			6·0 [b]	26,400	4·9
(18)	0·2	3·43	0·75	27,900	5·1
(19)	−0·4	4·09	1·44	24,800	−3·2
(20)	0·18	3·91	9·60		
(21)	6·52	2·44	0·081 [b]	29,300	5·0
(22)	5·79	2·62 [a]	2·35	29,000	10·8
(23)			2140 [c]	24,600	10·8
(24)			1·47	27,700	5·8
(25)			9·60		
(26)			8·77		
(27)	5·88 [a]	3·00 [a]	7·02	27,000	6·9
(28)			4·84	22,300	−8·5
(29)			3·4 [b]	25,800	1·6
(30)			208	22,100	−1·6
(31)			35·8 [d]		
(32)	2·34	4·09	227	25,000	7·5
(33)	0·29	3·95	6·57	25,500	2·0
(34)	1·06	4·29	5·76	25,900	2·8
(35)	1·33	4·19	3·30	24,200	−3·4
(36)		4·45	4·26		
(37)	0·53	3·95	0·140	28,700	4·2
(38)	−1·6	4·07	47	21,300	−7·2

[a] J. H. Blanch, *J. Chem. Soc.* (*B*), 1966, 937. [b] Interpolated. [c] Extrapolated. [d] At 25 °C.

TABLE 2

Some decarboxylation rates in water at 100° (pK_a values at I = 0·01 and 25 °C)

Compound	pK(BH$^+$)	pK(HA)	10^3k/min^{-1}
(13)	0·8	3·84	555 [a]
(39)	1·24	4·23	0·0072
(40)	1·10	4·50	0·0113
(41)		2·86	2·45
(42)	−3·31	4·05	($\gtrsim 10^{-5}$)
(43)	−3·60	3·90	($\gtrsim 10^{-5}$)

[a] Extrapolated.

Figure 1), exact neutralisation was needed only in the case of the pyridyl- and quinolyl-acetic acids; elsewhere, it was only necessary to ensure that a slight excess of acid had been added. In the special case of compound (38), whose anion can decarboxylate, hydrolysis was stopped after 20 min at 60 °C in 50% acetone; this represents the best available compromise between hydrolysis of ester and loss of acid.

For good first-order kinetics, it is necessary that the solution pH shall remain between the upper and lower measured pK_a values (see below). This condition is automatically satisfied for the pure compound at the start of the reaction, and where pK(HA) > pK(BH$^+$), *i.e.*, in most cases, it continues to be satisfied as decarboxylation proceeds. However, the reverse holds for the pyridyl-, quinolyl-, and imidazolyl-acetic acids: decarboxylation here leads, not to an effectively neutral substance, but to a base. It is remarkable, at first sight, that decarboxylation should have given excellent first-order kinetics in at least the first two cases (in the third, for reasons sketched above, the reaction order has had to be assumed). We can only presume that, the reaction vessel being closed, the carbon dioxide produced in the reaction and trapped therein remained effectively as the product amine carbonate, so buffering the solution to about the right value. On addition of mineral acid to the aliquot portions, this carbonate is then rapidly destroyed.

(b) *U.v. spectrophotometry.* This method was used when (*a*) proved inapplicable. For the upper part of the pH profile at 84 °C in water shown on Figure 1, the sodium salt of (13) was dissolved in an aqueous buffer adjusted to I = 0·01 with sodium chloride (final concentration of

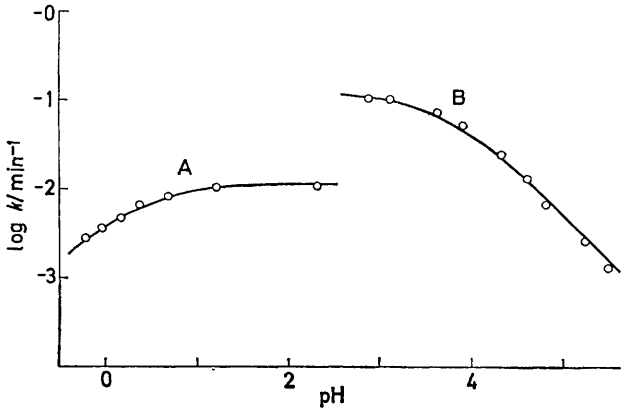


FIGURE 1 The pH profile for the decarboxylation of (13): (A) at I = 1·0 in 50% acetone at 50°, (B) at I = 0·1 in water at 84 °C

reactant *ca.* 10^{-5}M). Solution pH values were measured at 25 °C and corrected to 84 °C by using published [22] temperature coefficients. Aliquot portions (4 ml) were removed at various intervals, added to aqueous N-sodium hydroxide (1 ml), and rapidly cooled: this stops the reaction. This solution was then shaken with chloroform or cyclohexane (*ca.* 5 ml) and the u.v. absorbance of the aqueous layer was measured. Independent experiments established that, under these conditions, none of the acetic acid but all of the decarboxylated product was extracted into the non-aqueous layer. This fortunate circumstance applies equally to all other compounds studied in this way.

The reaction in water-immiscible solvents was studied by one variant or another on the method outlined above. Where possible, as with chloroform, the aliquot portion from the reaction mixture was itself used as the non-aqueous phase, aqueous alkali being used to extract the remaining acetic acid from it. The spectrophotometric technique also had to be used for the reactions in pyridine and acetic acid. Here the substrate was employed at much higher concentrations, so that a very small aliquot portion, *ca.* 0·1 ml, could be partitioned between chloroform and aqueous alkali as described above. The same technique was used, after suitable checks, in some other cases.

Reactions were followed for 3—4 half-lives, and all including (21) (but see above) gave excellent first-order rate plots. At least eight points were taken in each run and individual titres were reproducible to ±3%, from which rates determined by titration (all in Table 1 and most else-

[22] R. G. Bates, 'The Determination of pH,' Wiley, New York, 1964.

where) can be calculated [23] to possess a mean standard error of ±4·4%. Temperatures were measured using N.P.L.-calibrated thermometers accurate to ±0·2 °C and temperature coefficients were estimated from runs at three or four temperatures each separated by 10—15 °C. Activation parameters were calculated from the Eyring equation [24] and those obtained by titration possess [23] a mean standard error of ±5·8%; for $\Delta H^{\ddagger}$ *ca.* 25,000 cal mol^{-1} this amounts to limits of ±1400 cal mol^{-1} in $\Delta H^{\ddagger}$ and ±4·5 cal mol K^{-1} in $\Delta S^{\ddagger}$. No reliable estimate can be made for (21), but errors are presumably somewhat greater than this.

p*K* *Determinations.*—The lower pK_a in each pair (Table 1) was determined by u.v. spectrophotometry, the upper one potentiometrically with a Metrohm E 336 Potentiograph. Values were calculated in each case from several points on the titration curve and no determination was accepted unless the values calculated lay within a total range of 0·1 p*K* unit. (This does not apply to values of pK_a < 0·5, which are half-neutralisation points based on established H_0 scales). For the upper pK_a value [pK(BH$^+$)] of compound (21), titration in water was possible. For the remaining upper pK_a values [all pK(HA)] solubility considerations mostly precluded this, and the u.v. changes on ionisation were in general small. Since the pK_a values of acetic, benzoic, and such of these acids as can be determined in both solvents, are 1·0—1·2 p*K* units higher in 50% acetone than in water,[19] a mean value of pK_a = p$K_{(50\%\ \text{acetone})}$ − 1·1 has been used in compiling Table 1. We have found [19] this correction value valid for a wide range of carboxylic acids.

Products.—Since the decarboxylation of these compounds had already been studied qualitatively by those colleagues who made them, only spot checks were, in general, carried out. The decarboxylation of compound (13) was taken to completion in acetone and the whole material was analysed by n.m.r. spectrometry and by t.l.c. Only the expected product, 4-(*p*-chlorophenyl)-2-methylthiazole, could be detected. The same results were obtained in aqueous acetone, and other compounds in this solvent behaved similarly. Compound (21), which is only sparingly soluble in acetone, was converted quantitatively into 4-(*p*-chlorophenyl)-1,2-dimethylimidazole by evaporating a saturated solution under reduced pressure.

Attempted Quaternisations.—For reasons discussed below, it was of interest to attempt the preparation of zwitterions analogous to (41). The last compound had been obtained [25] by the quaternisation of (39) by use of methyl methanesulphonate under reasonably mild conditions. The attempt to quaternise (14) by similar means led to 4-(*p*-chlorophenyl)-2-isopropylthiazole as the only identifiable product. However, this amounted to only a part of the total reaction product; most of the rest was water-soluble, and its potentiometric behaviour, indicating the presence of basic material, suggests ring fission to have taken place as previously reported [21] in the alkaline hydrolysis of quaternised thiazoles. The absence of carboxylic acids from the products suggests that decarboxylation either preceded quaternisation, or immediately followed it; under certain at least of the conditions employed, the former reaction would not have been expected to go to completion. Qualitatively similar results were obtained in some other cases. In no case was any detectable amount of the hoped-for product obtained.

* The one contra-indication concerns a report by Gurch and Ramey [26] that the hydrochloride of 4-pyridylacetic acid decarboxylates in dimethyl sulphoxide solution. However, hydrochloric is known [27] to be a weak acid in this solvent, and pyridine is presumably a weak base, so extensive regeneration of the neutral species is probable. The authors themselves find no such reaction to take place in water. We believe their result to be an artefact.

RESULTS AND DISCUSSION

The pH Profile.—Figure 1 displays the pH profile for the decarboxylation of (13). As previously suspected [8,15,16] this is bell-shaped, reaction being mostly due to the formally neutral species. The apparent pK_a values derived from the calculated curves [pK(BH$^+$) 0·3 in $HClO_4$–$NaClO_4$, I = 1·0 in 50% acetone at 50 °C; pK(HA) 3·65 at I = 0·1 in water at 84 °C] agree closely enough with those measured at 25 °C in water (Table 1). Extension of this profile to its ultimate lower plateau at high pH reveals the anion also to decarboxylate but, at 84 °C, some 3000 times more slowly. The expected corresponding plateau at very low pH has not been sought. No other compound has been studied in such detail, but we have every reason to believe this situation to be general, and so far as it goes the literature [15-17] bears this out.*

The one partial exception is compound (38), whose anion decarboxylates only some ten times more slowly than the free acid. The relative instability of this anion is probably due to the very high electronegativity of the triazine ring, as reflected by pK(BH$^+$) (Table 1); as in the comparable decarboxylation of acetoacetate or nitroacetate anion,[6,7] the intermediate carbanion may well be relatively stable. It is not a simple consequence of easy decarboxylation generally: the anion of (23), itself extremely reactive, appears to be tolerably stable.

It has been noted above that acetic acid residues substituted in the ' aromatic ' positions of heterocyclic rings are not expected to decarboxylate readily. The thiazol-4-ylacetic acid (40) decarboxylates 5×10^4 times more slowly than its position isomer (13), and this difference is typical [19] (Table 2). It is noteworthy that the anions of (39) and (40) decarboxylate at a rate too low for reliable measurement.[19] No attempt has been made to trap either the methanols that might result from the attack of any of these anions on ketones (*cf.* the decarboxylation of quinoline-2-carboxylic acid [28]), or the methines (6) that are presumably the intermediates elsewhere.

Salt and Solvent Effects.—The effect of solvent on decarboxylation rate has been studied in detail only for the thiazolylacetic acids (12) and (13). Some rates, assembled in dielectric constant order, are shown in Table 3. Self-evidently, there is no correlation either with D or with any of the solvent parameters, *e.g.*,

[23] S. W. Benson, ' Foundations of Chemical Kinetics,' McGraw-Hill, New York, 1960.
[24] K. J. Laidler and H. Eyring, *Ann. New York Acad. Sci.*, 1940, **39**, 302.
[25] J. Hutton, personal communication.
[26] G. J. Gurch and K. C. Ramey, *Chem. Comm.*, 1968, 1211.
[27] A. J. Parker, *Quart. Rev.*, 1962, **16**, 163.
[28] P. Dyson and D. Ll. Hammick, *J. Chem. Soc.*, 1937, 1724.

TABLE 3

Decarboxylation rates (10^3k/min^{-1}) of compounds (12) and (13) at 50 °C in solvents of varying dielectric constant D

Solvent	D [a]	(12)	(13)
Dimethyl sulphoxide	48·9 [b]	8·65	
Dimethylformamide	37·6 [b]	11·3	
80% Acetone	32 [c]	6·84	22·6
90% Acetone	26 [c]	9·3	29·0
Acetone	20·7	11·8	38
n-Butanol	17·1	4·65	
Pyridine	12·3	*d*	
Acetic acid	6·15	2·54	
Ethyl acetate	6·02	7·72	
Chloroform	4·8	9·95	
Toluene	2·38	9·43	
Dioxan	2·21	4·25	

[a] Unless otherwise stated, from N.B.S. Circular 514, U.S. Government, Washington, 1951. [b] A. J. Parker, *Adv. Phys. Org. Chem.*, 1967, **5**, 173. [c] Interpolated. [d] Very low.

Brownstein's S-values,[29] Grunwald and Winstein's Y-values,[30a] or Kosower's Z-values,[31] that often prove relevant. The general similarity of these rates is equally compatible with reaction of the uncharged species by the cyclic mechanism (4a) ⟶ (5a) ⟶ (6) or, as Hine [13] has pointed out in a similar context, with the view that the proportion of zwitterion (4b), and its stability, cancel in their effects on the overall rate. The low rate in acetic acid, and the negligible reaction in pyridine, are presumably consequences of the pH profile.

The highly zwitterionic imidazolylacetic acid (21), which is relatively stable in water, decarboxylates in acetone to the extent that it dissolves at all. At first sight this might appear to support Hine's contention [13] that the decarboxylation of a zwitterion should depend sharply on the polarity of the solvent employed. Closer consideration shows that the *proportion* of neutral species will, in that event, equally so depend, so that this result is just as compatible with the 'no-mechanism' [32] hypothesis. We conclude that, as previously,[10] the influence of solvent provides little evidence as to mechanism.

Consistent with the slight effect of solvent, that of ionic strength is miniscule (*e.g.*, an acceleration of 10% in the presence of M-sodium perchlorate [19]).

The Effect of α-Alkylation.—The ready reaction of αα-dimethylacetoacetic acid was used by Pedersen [6,7] to demonstrate that the decarboxylation of β-keto-acids does not go through an enolic *initial* state (see Scheme 1). Pasternak and van Doering [15] made the same point with respect to compound (10); we now add the results for (14) and (20).

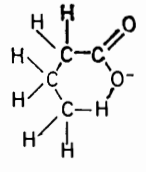
The effect of α-alkylation on reaction rate has been studied most comprehensively for the thiazolylacetic acids (12)—(16) (Table 4); other results are in Table 1. α-Methylation invariably increases reaction rate, in (13) by about three times, and here at least the effect seems independent of solvent (Table 3). Other alkyl groups have less effect, and a second α-methyl group has almost none. Four possible explanations suggest themselves: (*a*) relief of steric compression in the transition state; (*b*) inductive or (*c*) hyperconjugative stabilisation of a developing carbonium ion; (*d*) stabilisation of the incipient double bond (Scheme 2). Possibility (*a*) can be eliminated since αα-dimethylation should have led to an enormously increased reaction rate if this were so. The other possibilities can tentatively be discussed in

TABLE 4

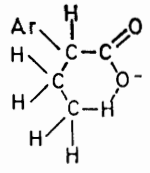
Decarboxylation rates (10^3k/min^{-1} at 50 °C) and activation parameters ($\Delta H^‡$ kcal mol^{-1}; $\Delta S^‡$ cal mol^{-1} K^{-1}) for some thiazoleacetic acids in various solvents and the solid state

		Water	50% Me_2CO	Me_2CO	Pr^iOH	1,2-Dichlorobenzene	Solid state
(12)	10^3k		3·34	11·8			
	$\Delta H^‡$		25·0	22·4			
	$\Delta S^‡$		−0·5	−6·3			
(13)	10^3k	1·92	9·98	38·0	10·5	81·6	0·086
	$\Delta H^‡$	26·6	24·1	21·6	21·6	17·3	
	$\Delta S^‡$	3·1	−1·0	−6·4	−9·1	−18·4	
(14)	10^3k		12·2	36·0			
	$\Delta H^‡$		23·2				
	$\Delta S^‡$		−4·0				
(15)	10^3k		5·06				0·38
	$\Delta H^‡$		25·0				
	$\Delta S^‡$		−0·1				
(16)	10^3k		4·67				0·21
	$\Delta H^‡$		23·7				
	$\Delta S^‡$		−4·3				

the light of variations in the activation parameters. Except in (15), alkylation lowers $\Delta H^‡$; however, in (14) and (16) this is opposed by a fall in $\Delta S^‡$. The latter effect is statistically barely significant, but it is tempting to regard it as genuine since electrostriction of these bulky alkyl groups in the highly polar transition state affords a ready explanation. If this is accepted, the observed Baker–Nathan reactivity order [33] results from the accidental near-cancellation of potential energy ($\Delta H^‡$) and solvation ($\Delta S^‡$) terms; [34] possibility (*c*) can



(44)



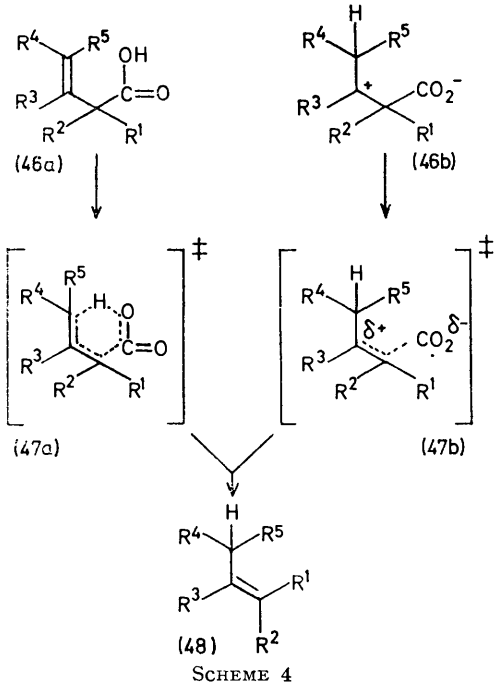
(45)

be eliminated. The anomalous $\Delta H^‡$ value of compound (15), if real, may relate to the unexpectedly high acidity of n-butyric acid, attributed by Ives and Marsden [35] to intramolecular C–H · · · O bonding in the anion. The cases compare as shown in (44) and (45); stabilisation

[29] S. Brownstein, *Canad. J. Chem.*, 1960, **38**, 1590.
[30] J. E. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions,' Wiley, New York, 1964, (*a*) p. 298; (*b*) p. 224.
[31] E. M. Kosower, *J. Amer. Chem. Soc.*, 1958, **80**, 3253.
[32] S. J. Rhoads, in 'Molecular Rearrangements,' ed. P. de Mayo, vol. I, Interscience, New York, 1963.
[33] J. W. Baker, 'Hyperconjugation,' Oxford, 1952; J. W. Baker and W. S. Nathan, *J. Chem. Soc.*, 1935, 1844.
[34] W. A. Sweeney and W. M. Schubert, *J. Amer. Chem. Soc.*, 1954, **76**, 1603; *ibid.*, *J. Org. Chem.*, 1956, **21**, 119; W. M. Schubert and R. G. Minton, *J. Amer. Chem. Soc.*, 1960, **82**, 6188.
[35] D. J. G. Ives and P. D. Marsden, *J. Chem. Soc.*, 1965, 649.

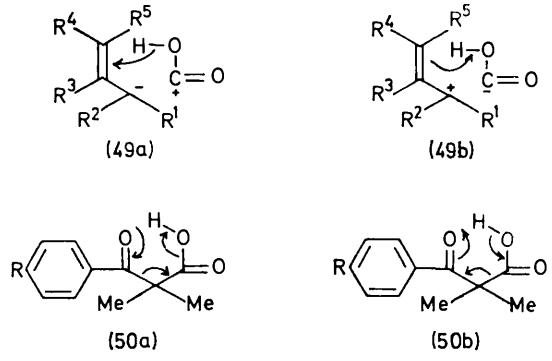
of the anion in this way should raise $\Delta H^{\ddagger}$. It may be significant that in the solid state, where a rigid molecular conformation is likely to eliminate differences in solvation, relative rates are much more nearly what might be expected on inductive grounds alone (Table 4).

Decision between possibilities (*b*) and (*d*) is more difficult. Alkylation stabilises carbonium ions [36] and destabilises carbanions,[37] but alkenes will isomerise to that form with the most heavily substituted carbon double bond even when the isomerisation process is carbanionic,[38] so the evidence from rates alone is equivocal. Bigley and his co-workers have recently made some important contributions to this subject. In the gas-phase decarboxylation of some βγ-unsaturated acids (46) they have shown that α-substitution (R^1, R^2) has a small effect in accelerating the reaction [39] and γ-substitution (R^4, R^5) a large effect in retarding it; [40] the latter is easily explained [40] as stabilisation of the ground state. Between reactant (46a) and product (48) they suggest [41]



SCHEME 4

the cyclic transition state (47a), analogously with (2a) and (5a). Bigley and Thurman draw attention [42] to the close qualitative resemblance between the accelerating effect of α-methylation on (46) in the gas phase,[39,42] and on the benzoylacetic acids (50) of Swain and his co-workers [11] in benzene solution; they argue from this to a close resemblance in mechanism. In both cases, about a five-fold rate acceleration is observed. Bigley



and Thurman argue [42,43] that this effect is far too slight to result from a fully developed carbonium ion, as (49b). However, it is considered [11] that proton transfer leads in the benzoylacetic acids; that is, the process, if cyclic, is better represented by (50b) than by (50a).* This view is based on the negative Hammett slope (ρ below −1, correlation with σ_p) shown when R is varied; Bigley and Thurman for (46; R^3 = substituted phenyl) find almost the same relation (ρ −1·1, correlation with σ^+) and argue similarly [42,43] against the direction of flow implied by (49a). Their final verdict [43] is for the 'no-mechanism' transition state (47a), but with proton transfer slightly in the lead as implied by the effect of α-methylation. In view of our results, even the last point is more equivocal than formerly it seemed: α-methylation of (39) also increases the rate, and here the α-carbon atom is probably carbanionic (Scheme 3). Nonetheless we retain the view that, elsewhere, carbonium-ion rather than carbanionic character is likely to be present. The α-(*p*-chlorophenyl) derivative (23) of (22) decarboxylates 10^3 times more rapidly than the parent compound, and the whole of this rate increase is contained in $\Delta H^{\ddagger}$. Similarly, Bigley and Thurman [44] find substitution of (46, R^3 = Ph) for (46, R^3 = H) to accelerate the reaction by 400 times and, again, a fall in $\Delta H^{\ddagger}$ is responsible. Both results fit better with a carbonium-ion than with a carbanionic mechanism [*cf.* (46b)], but better still with the stabilisation of an incipient double bond. We agree with Bigley and Thurman that, in all three cases, the last is probably the major factor.

Substitution in the Phenyl Ring.—*para*-Substitution in the phenyl ring of the thiazol-2-ylacetic acids (11) leads to a good Hammett plot with ρ *ca.* −0·4 (Figure 2). Results elsewhere are qualitatively similar [*cf.* the sequence (27), (28), (29)]. At first sight this agrees

* We are very conscious in discussing these points that, as Bigley and Thurman [43] have remarked, 'it is the fault of chemical symbolism that the partial electrical charges possible in [such formulae] cannot be shown properly.'

[36] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Bell, London, 1953, ch. 7.

[37] D. J. Cram, 'Fundamentals of Carbanion Chemistry,' Academic Press, New York, 1965, p. 21.

[38] A. Shriesheim, J. A. Hofmann, and C. A. Rowe, *J. Amer. Chem. Soc.*, 1961, **83**, 3731; H. O. House and V. Kramar, *J. Org. Chem.*, 1963, **28**, 3362.

[39] D. B. Bigley, *J. Chem. Soc.*, 1964, 3897.

[40] D. B. Bigley and R. W. May, *J. Chem. Soc.* (*B*), 1967, 557.

[41] R. T. Arnold, O. C. Elmer, and R. M. Dodson, *J. Amer. Chem. Soc.*, 1950, **72**, 4359.

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

[43] D. B. Bigley and J. C. Thurman, *J. Chem. Soc.* (*B*), 1968, 436.

[44] D. B. Bigley and J. C. Thurman, *J. Chem. Soc.*, 1965, 6202; *J. Chem. Soc.* (*B*), 1966, 1076.

quite well with the results of Bigley [42] and of Swain [11] and their co-workers discussed above, since the slope is in the same direction though its magnitude is somewhat less. However, the phenyl substituent lies further from

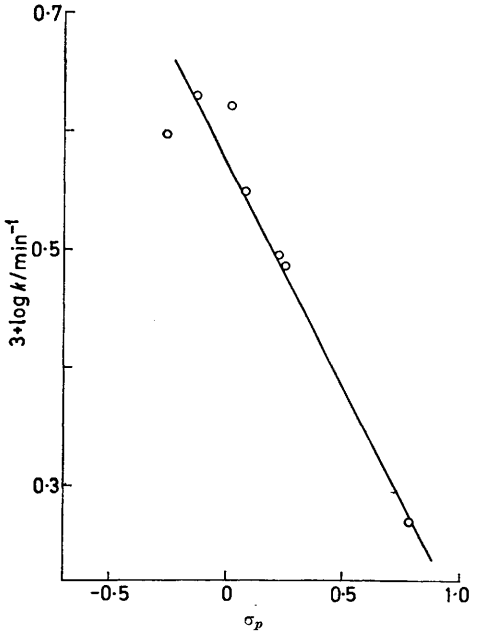


FIGURE 2 Hammett plot for the decarboxylation of series (11) at 50 °C in 50% acetone

the reaction centre (it is separated by the entire thiazole ring), and similar deductions as to the direction of electron flow may be illegitimate [*cf.* (50a) and (50b)]. It is unlikely that this relation, whatever its origin, is much affected by the angle which the phenyl group subtends towards the heterocyclic ring: the decarboxylation rate of (17), where this is constrained, differs little from that of (11, R = H) in which it is free (k = 6·0 and 4·21 × 10^{-3} min^{-1} respectively).

We suggest a quite different origin for this phenomenon: variation in the proportion of zwitterion x_Z. The inductive effect of the aryl group will affect both pK(BH$^+$) and pK(HA), but the latter much less since the carboxylic acid group is better shielded from its influence. While these pK_a values are mostly unknown and, in any case, this information in itself is insufficient for the purposes of calculation, it is reasonable to suppose that x_Z will fall as the gap between pK(BH$^+$) and pK(HA) widens, which is likely to happen as the substituent R becomes more electronegative. And while it would be possible for the varying stability of the zwitterion to exert a levelling effect, which to some extent it may, this is rather less likely than in the solvent case, since *ground-state* stability should be little affected by a remote substituent. The observed result is, at least, in the right direction to fit the zwitterionic hypothesis. The only reasonable explanation in terms of its alternative, namely a positive correlation between rate and ring-nitrogen electron density [*cf.* (50b)], is at once negatived by the total absence of any relation between rate and basicity discussed below.

The Heterocyclic Nucleus.—Almost the outstanding feature of these rates is their similarity. Leaving aside the special case of (23), the rates of Table 1 cover a total spread of 3000 : 1; out of 24 compounds, 17 have half-lives of between 1 and 10 hours at 50 °C in 50% acetone, and only three depart seriously from this. For a series of eight heterocyclic nuclei (10 distinct positions of substitution all told) which range from the very electron-rich imidazole to the equally electron-deficient 1,3,5-triazine, this is a remarkable result. We have somehow to explain it.

Intuitively, one might have expected some type of correlation with ring electron density: the more electronegative the heterocyclic ring, the more readily it can accept a negative charge from the departing carboxylate anion. We have direct evidence for this hypothesis in the case of (38), whose anion decarboxylates at a perceptible rate [even that of (23) does not]. However, an electron-deficient heterocycle is likely to be a poor base; (38) is the weakest base of those compounds listed in Table 1. Whether complete proton transfer is required as on the zwitterionic hypothesis, or whether the process is synchronous but proton transfer leads, the observed result is to be seen as the partial cancellation of factors that possess a common origin.

One possible clue comes from the relative ease with which anion and neutral species decarboxylate. There is no dispute concerning the mechanism of anionic decarboxylation: [6,8] it must go *via* (51) and (52). The stability of (52), and hence the ease of formation of the transition state (51), will be influenced, *inter alia*, by the

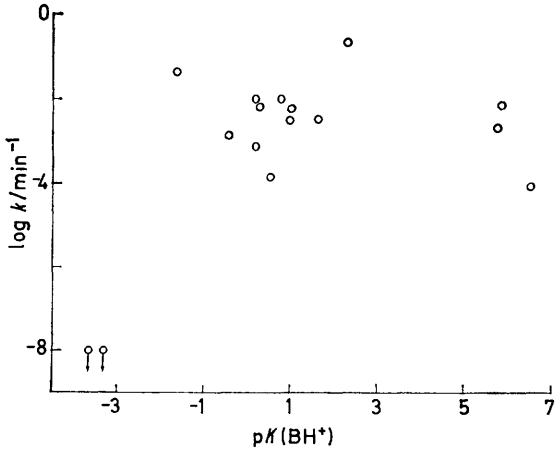
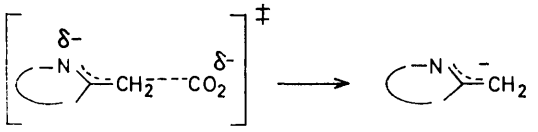


FIGURE 3 The relation between decarboxylation rate and pK(BH$^+$) for the compounds of Table 1

extent to which the heterocyclic nucleus can support a benzylic carbanion. This will be increased enormously if the ring is protonated, as in (5b). One might therefore expect a zwitterion to decarboxylate very much more rapidly than the corresponding anion, and it is at least a viable hypothesis that the degree of acceleration conferred by protonation should be tolerably constant from

one heterocyclic nucleus to another. Since we do not know the proportion of zwitterion that these compounds contain there is no direct way of testing this theory, but



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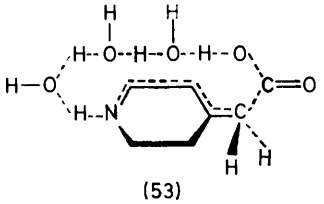

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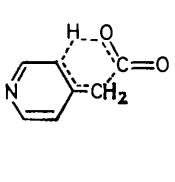

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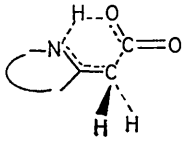

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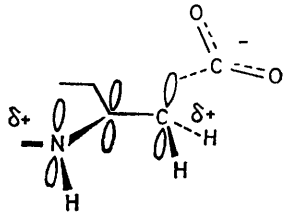

(56)

the following facts are suggestive. The thiazol-2-yl-acetic acid (13) decarboxylates 3×10^3 times more rapidly than its anion; for the triazinyl acid (38) there is barely a factor of 10. However little zwitterion (13) contains, it is evident, from the much reduced basicity of (38) (Table 1), that the latter must contain much less. By hypothesis, a smaller proportion of zwitterion means, not a smaller *actual* decarboxylation rate (which is controlled by other factors), but a smaller ratio between the decarboxylation rates of the formally neutral species and of the anion. This is found. Two examples can scarcely be said to prove the case, but at least the difference lies in the right direction, and it is difficult to think of any good rationalisation in terms of the ' no-mechanism ' hypothesis. The argument can be extended to predict that, should the proportion of zwitterion fall low enough, the *anion* will now decarboxylate the more rapidly. No example is known in the present series, but the experimental situation is approached by the β-keto-acids,[6,7] and the way in which this argument could be extended to them will be obvious.

Ring annelation, as in (30) and (31), causes a very large increase in rate. The implications of this extend beyond the present discussion, but it may be related to the loss in resonance energy, when compared with that for two isolated molecules, that always results from ring annelation.[45]

General Discussion.—The most comprehensive previous discussion of this subject is that by Bigley and Thurman.[42,43] In an elegant labelling experiment employing the carboxy-deuteriated derivative of (46), they have shown [42] that (46b) cannot be formed in a pre-equilibrium step since, while (48) as expected incorporates deuterium, there is none at any stage of the reaction in (46) itself. This proves beyond doubt the route involving the cyclic transition state (47a). From the close similarity of the effects of α-alkylation and of the aryl substituent (see above) on the decarboxylation of (46) and of Swain's benzoylacetic acids (50), they conclude that a common mechanism obtains. If the route (46a) ⟶ (47a) ⟶ (48) is proved, the sequence (1a) ⟶ (2a) ⟶ (3) follows. In the present case, α-alkylation has, if anything, even less effect than formerly, while change of solvent affects the rate to much the same extent as for the β-keto-acids. Extending Bigley's arguments, we should conclude that the heterocyclic acetic acids also decarboxylate *via* a neutral cyclic transition state (5a). Nevertheless, we cannot accept this conclusion.

There are, in the first place, a number of compounds in which evidence for the zwitterionic mechanism is unequivocal: the 4-pyridyl- and 4-quinolyl-acetic acids (27)—(31). It has previously been suggested [8] that the close similarity between 2- and 4-pyridylacetic acids in terms of decarboxylation rate argues strongly in favour of a similar mechanism for the former. Actually, it does not: if the pathways are in any case of nearly equal energy the evidence remains equivocal, a point explicitly recognised by Pasternak and van Doering.[15] However, we find that the close similarity in rate between (22) and (27) extends to $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, a circumstance scarcely conceivable without a common mechanism.* It would, no doubt, be possible in principle to write a cyclic transition state such as (53) with bridging water molecules, but in that case $\Delta S^{\ddagger}$ for (27) should be very much more negative than for (22) owing to the ' freezing ' of solvent involved in that structure.[1b] Similarly, one such as (54) might be written, but again $\Delta S^{\ddagger}$ should be much more negative (Bigley and Thurman [44] find values near -10 cal mol^{-1} K^{-1} in the gas phase) quite apart from any questions of relative rate. The zwitterionic mechanism for 4-pyridylacetic acid and its analogues may therefore be considered certain. That of the 2-acetic acid remains equivocal, but the argument from analogy is powerful.

A mechanism which applies to compounds that are largely zwitterionic may, of course, fail with those that are not, even though we may adapt Hine's point [13] concerning the effect of solvent (here structure †) on the opposing factors of zwitterionic proportion and stability to extend the argument in this direction. For one such compound, the evidence is decisive. From the pK_a values of (39) and (41) it is possible, by standard [46] methods, to calculate the proportion of zwitterion in the former as 2·2%, by using pK(HA) of (41) to ' stand in '

* This argument assumes, as a referee has pointed out, a similar ΔH and ΔS of solvation for the two zwitterions: a strong intramolecular hydrogen bond in the former might upset it.

† There are many contexts in which substituent and solvent operators commute; see ref. 30.

[45] G. W. Wheland, ' The Theory of Resonance.' Wiley, New York, 1955.

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

for the (inaccessible) acid pK_a of (39) cation. Hence the rate in terms of zwitterion, k_Z, for (39) is $3{\cdot}3 \times 10^{-4}$ min^{-1} [$k_Z = k_{obs}/x_Z$], which is amply covered by the actual decarboxylation rate of the anion (41). Since these rates were measured at 100 °C where the proportion of zwitterion is likely to be less, it is probable that, in fact, these 'actual' and 'theoretical' rates are nearly coincident. We can therefore prove the route (7b) ⟶ (8b) ⟶ (9) for (39). Since the compounds we are mostly considering go by a different mechanism (Scheme 2) this result is not directly relevant, but it is surely significant that this small amount of zwitterion is the preferred reactant despite the fuller separation of charge entailed in the transition state; which, in Scheme 2 as well, is what much of the argument is about. Also, the small proportion of zwitterion here found is probably echoed by most compounds in Table 1. It is also noteworthy that for both (13) and (39) the anion decarboxylates very much more slowly than the formally neutral species, a result easily understood on the zwitterionic hypothesis as the electron-withdrawing effect of the protonated ring (see above). Attempts to prepare analogues to (41) from compounds that react according to Scheme 2 have led only to decarboxylation, accompanied sometimes, we have reason to suspect, by the products of decarboxylation of *N*-methylated species of type (6). That fact alone is some indication that the zwitterionic theory may be correct.

It has been noted above that, here as elsewhere, the effect of solvent is equivocal. One piece of evidence, however, is highly suggestive. As the solvent is varied, a small change in the decarboxylation rate of (13) is accompanied by enormous changes in the activation parameters (Table 4). Such phenomena are not unusual,[30] but their existence here is surprising. The whole basis of Westheimer's argument [10,12] was the view that a solvent-insensitive reaction must mirror a solvent-insensitive transition state. Such is clearly not the case. The direction of the effect, that $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ both rise with solvent polarity, is consistent (as the reverse would not have been) with the zwitterionic hypothesis: the zwitterion is stabilised by a more polar environment, an effect that shows in $\Delta H^{\ddagger}$. Compensation by $\Delta S^{\ddagger}$ occurs for the usual [30,35,47] reasons. No parallel study of β-keto-acids appears to have been carried out. However, it is relevant that certain *anionic* decarboxylations have been reported [48,49] that show just the same effect, and while their mechanism as such is necessarily different, the important point is that the reactant is indubitably an ion and must demonstrate the trends that an ion should show. The latter series,[49] indeed, shows rates and activation parameters very similar to those found here.

Another point arises from a more careful consideration of the rival transition states, (5a) and (5b). The former can be represented as (55); the latter is shown in half-projection as (56). Maximum orbital overlap in (56) is achieved if, far from lying in the plane of the ring, the carboxylate group is displayed at right angles to it.* A similar rotation must take place in (55), but in this case can go no further than will permit the intramolecular N · · · H · · · O bond to be preserved, at least in aprotic solvents; hence (55) must be reached much earlier along the reaction co-ordinate than (56).† It follows that the transition states for the cyclic and zwitterionic mechanisms will tend to be reactant-like and product-like, respectively. It is for this reason that, contrary to previous opinion,[8,10] the species (4b) and (5a) are *not* equivalent (we have to agree with Bigley and Thurman [42] that previous writers have not been too careful to distinguish intermediates from transition states). While, as Bigley and Thurman have shown,[42,43] a species such as (56) is unlikely for a gas-phase reaction, in solution it will be a well solvated species, and should be favoured especially by dipolar aprotic solvents, which tend to break up intramolecular hydrogen bonds.[27] If one trend emerges from the solvent effects, it is that decarboxylation tends to be particularly easy in such solvents. For acetone as opposed to propan-2-ol (Table 4), two solvents of roughly equal dielectric constant, the effect is specifically on $\Delta S^{\ddagger}$, as it should be if the *initial state* already tends towards this conformation. This is scarcely evidence for the cyclic pathway.

Further consideration will show that the α-carbon atom of (56) should have carbonium-ion rather than carbanionic character (the effect will be slight; we are discussing only which movement of electrons leads). It has been seen that the balance of the evidence favours this; the steady fall in $\Delta H^{\ddagger}$ with α-substitution may probably be regarded as a simple electronic effect. We will also recapitulate the view that substitution in the phenyl ring affects the rate by affecting the proportion of zwitterion, and there is also the variable rate ratio of anion to free acid to consider. All these pointers favour the zwitterionic theory. The similar solvent and substituent effects found for the β-keto-acids might then be held to support a zwitterionic mechanism for the latter. No such conclusion is legitimate, since Bigley's contrary extrapolation is as good or better. For the β-keto-acids as for those we have examined, we believe the question of mechanism still to remain open.

None of these arguments, however compelling, amounts to proof. For that, some type of evidence not previously envisaged is required. We shall return to this subject on another occasion.

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† As a referee has noted, the equivalent of (55) for the βγ-unsaturated acids must certainly be buckled, since the carboxy-proton has to add from above or below the π-cloud.

[47] L. G. Hepler, *J. Amer. Chem. Soc.*, 1963, **85**, 3089.
[48] C. S. Tsai, *Canad. J. Chem.*, 1967, **45**, 873.
[49] A. Thomson, *J. Chem. Soc.* (*B*), 1970, 1198.