Studies in Decarboxylation. Part VI.[1] A Comparison of the Transition States for the Decarboxylation of β-Keto- and βγ-Unsaturated Acids[2]

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The effect of substituents on the rate of thermal decarboxylation of βγ-unsaturated acids is compared to their effect on the decarboxylation of β-keto-acids. From the close similarity observed, it is argued that the reactions have nearly identical transition states. It is demonstrated that the transition state for the olefinic acids is largely non-polar; by analogy, the keto-acids are concluded to decarboxylate through a largely non-polar mechanism. The earlier arguments concerning β-keto-acid decarboxylation are critically reviewed.

THE gas-phase decarboxylation of βγ-unsaturated acids has been shown[1] to proceed through a fully concerted mechanism. The transition state involves synchronous making or breaking of all the bonds in a six-membered ring. On the other hand, the transition state for the decarboxylation of β-keto-acids has been the object of speculation. Pedersen[3] suggested that αα-dimethylacetoacetic acid decomposes as a zwitterion (I). Westheimer and Jones[4] found that the rate of decarboxylation of this acid was virtually independent of the dielectric constant of the solvent. Since the formation of the polar intermediate should be facilitated by solvents of high dielectric constant, it was concluded that the reactive intermediate must be a neutral species (II). The same conclusion was reached by Swain *et al.*[5] who extended the method to other acids. However, Hine[6]

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[1] Part V, D. B. Bigley and J. C. Thurman, *J. Chem. Soc.* (*B*), 1967, 941.

[2] Preliminary account of part of this work, D. B. Bigley and J. C. Thurman, *Tetrahedron Letters*, 1967, 2377.

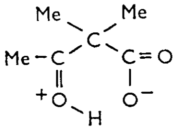
[3] K. J. Pedersen, *J. Phys. Chem.*, 1934, **38**, 559.

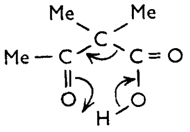
[4] F. H. Westheimer and W. A. Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 3283.

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

[6] J. Hine, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1952.

pointed out that, although (I) should be less readily formed in solvents of low dielectric constant, it should be more reactive owing to charge destruction in the reaction. The evidence of solvent effects cannot therefore be taken as conclusive. The extreme similarity of structures (I) and (II) has been commented upon,[6,7] and it is the fault of chemical symbolism that the partial electrical charges possible in (II) cannot be shown properly. The existence of a significant deuterium isotope effect in the decarboxylation favours formulation (II), since a full covalent bond is being broken in the transition state. Indeed, Swain *et al.*[5] suggested that the variation of deuterium isotope effect with substituent in a series of substituted benzoylacetic acids can be used to show that the hydrogen migrates as a proton and not as a hydride ion [*i.e.*, arrows representing electron displacements in (II) are drawn in an anticlockwise direction]. Brower, Gray, and Konkol[8] used measurements of the volume of activation in support of structure (I), and so re-opened the whole question.


(I)


(II)

We now describe the decarboxylation of the olefinic analogues of the benzolacetic acids used by Swain *et al.*, as a comparison of the transition states of the two reactions and to test their criterion concerning the nature of the transferred hydrogen.

EXPERIMENTAL

2,2-Dimethyl-3-phenylbut-3-enoic acid was prepared by methods described previously.[9]

2,2-Dimethyl-3-(p-methoxyphenyl)but-3-enoic Acid.—An attempted Reformatsky reaction performed by adding a mixture of ethyl 2-bromoisobutyrate and *p*-methoxyacetophenone to zinc in benzene solution led exclusively to 4,4′-dimethoxy-β-methylchalcone, m.p. 94·5° (lit.,[10] 96°, cf. ref. 11), by condensation between two molecules of the ketone. The procedure was then as follows. *p*-Methoxyacetophenone (0·8 mole) was added in 1 : 1 ether–benzene (300 ml.) to a stirred solution of Reformatsky reagent prepared[12] from ethyl 2-bromoisobutyrate (0·8 mole). The mixture was refluxed for 45 min. after the initial vigorous reaction, and work-up gave ethyl 3-hydroxy-2,2-dimethyl-3-(*p*-methoxyphenyl)butanoate which was dehydrated over P_2O_5 in benzene solution (reflux; 1 hr.) without further purification. The resulting unsaturated ester was refluxed for 15 hr. in aqueous alcoholic potassium hydroxide, alcohol removed by distillation, the solution acidified, and the required *acid* extracted with ether. It formed crystals, m.p. 42—43° (36 g.) (Found: C, 71·5; H, 7·6%; Equiv., 219·5. $C_{13}H_{16}O_3$ requires C, 70·8; H, 7·25%; Equiv., 220).

2,2-Dimethyl-3-(p-tolyl)but-3-enoic Acid.—Ethyl 3-hydroxy-2,2-dimethyl-3-(*p*-tolyl)butanoate (b.p. 142—160°/5 mm.) was prepared from *p*-methylacetophenone (0·8 mole) by the Reformatsky reaction described above. Dehydration and hydrolysis gave an oil (55 g.), b.p. 159—163°/0·7 mm. (some decomp.). Redistillation gave the *acid* as an oil, b.p. 140—142°/0·2 mm., n_D^{22} 1·5254 (Found: C, 76·85; H, 7·85%; Equiv., 204·5. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·85%; Equiv., 204).

2,2-Dimethyl-3-(p-chlorophenyl)but-3-enoic Acid.—Ethyl 3-hydroxy-2,2-dimethyl-3-(*p*-chlorophenyl)butanoate, was prepared from *p*-chloroacetophenone (55 g.) by the Reformatsky reaction described above; dehydration and hydrolysis as before gave the required *acid*, needles (3·5 g.), m.p. 93·5—94·5° (Found: C, 63·85; H, 5·65; Cl, 15·9%; Equiv., 223. $C_{12}H_{13}ClO_2$ requires C, 64·15; H, 5·8; Cl, 15·8%; Equiv., 224·5).

2,2-Dimethyl-3-(m-nitrophenyl)but-3-enoic Acid.—Reformatsky reagent,[12] prepared from ethyl 2-bromoisobutyrate (83 g.) in benzene, was filtered free from zinc and added dropwise under nitrogen to a stirred solution of *m*-nitroacetophenone (70 g.) in benzene (1 l.), while the mixture was kept at 17—21° with an ice-bath. After work-up, ethyl 3-hydroxy-2,2-dimethyl-3-(*m*-nitrophenyl)butanoate was dehydrated without further purification and the product refluxed for 3 hr. with 7% aqueous-alcoholic potassium hydroxide. The *acid*, isolated from much tar, was twice recrystallised (animal charcoal), to give pale yellow needles (10 g.), m.p. 90—91° (Found: C, 61·3; H, 5·5; N, 5·9%; Equiv., 234·5. $C_{12}H_{13}NO_4$ requires C, 61·25; H, 5·55; N, 5·95%; Equiv., 235).

TABLE 1

Physical constants and yields of $X{\cdot}C_6H_4{\cdot}CMe{:}CMe_2$

X	B. p./mm.	n_D (temp.)	$\lambda_{max.}$ (mμ) (ε)	Yield (%)
m-NO_2	*ca.* 115°/2	—	240sh, 252 (10,800)	53·5
p-Cl	*ca.* 75/5	1·5386 (21°)	242 (6500)	98
H *	189—190/760	1·5208 (22)	240 (6000)	99
p-Me	68—69/0·5	1·5213 (20)	238 (7500)	97
p-MeO †	88—93/10	1·5311 (24)	238 (8900)	100

* C. G. Overberger and H. Gainer, *J. Amer. Chem. Soc.*, 1958, **80**, 4561, b. p. 189—190·5°, n_D^{24} 1·5191. † G. G. S. Dutton, M. E. D. Hillman, and J. G. Moffat, *Canad. J. Chem.*, 1964, **42**, 480, b. p. 65°/0·1 mm., n_D^{25} 1·5310.

TABLE 2

Substituent effects and isotope effects in decarboxylation of $X{\cdot}C_6H_4{\cdot}C({:}CH_2){\cdot}CMe_2{\cdot}CO_2H$

X	10^{-5} Mean k_H (sec.$^{-1}$)	10^{-5} Mean k_D (sec.$^{-1}$)	k_H/k_D	Temp.
m-NO_2	1·53 ± 0·05	0·51 ± 0·025	3·00 ± 0·3	187·3°
p-Cl	3·36 ± 0·10	1·72 ± 0·07	1·95 ± 0·14	187·3
H	5·06 ± 0·05	2·39 ± 0·10	2·12 ± 0·09	187·3
	9·53			196·4
	9·84 *			196·4
p-Me	9·98 ± 0·35	4·89 ± 0·15	2·04 ± 0·13	187·3
p-MeO	39·3 ± 1·0	21·4 ± 0·50	1·84 ± 0·09	187·3

* Run in the presence of *ca.* 5 moles % of water.

Olefins from the Decarboxylation of Substituted 2,2-Dimethyl-3-phenylbut-3-enoic Acids.—These were isolated by heating the corresponding acids at *ca.* 220° for ten reaction half-lives in an open flask fitted with a reflux condenser,

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[7] B. R. Brown, *Quart. Rev.*, 1952, **5**, 131.

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

[9] D. B. Bigley and J. C. Thurman, *J. Chem. Soc.* (*B*), 1966, 1076.

[10] E. C. Dodds, R. L. Huang, W. Lawson, and R. Robinson, *Proc. Roy. Soc.*, 1953 (*B*), **140**, 470.

[11] E. Blaise and A. P. Courtot, *Bull. Soc. chim. France*, 1906, **35**, 357.

[12] W. R. Vaughan, S. C. Bernstein, and M. E. Lorber, *J. Org. Chem.*, 1965, **30**, 1790.

and identified by u.v. and n.m.r. spectroscopy. Yields (Table 1) were estimated as described previously.[9]

Kinetics.—Kinetic runs were performed in break-seal tubes as described previously.[9,13] Rate constants were derived from a least-squares treatment of the data. Deuterium labelling was effected as described before.[1] The results (Table 2) show that traces of water (and presumably D$_2$O) in the sample have no significant effect on the rate.

Deuterium Exchange Experiments.—Samples of the labelled acids (Table 3) were heated in sealed tubes under the conditions shown. There is clearly no exchange.

DISCUSSION

Table **4** shows a comparison of the rates of decomposition of substituted benzoylacetic acids X·C$_6$H$_4$·C(:Y)·CR$_2$·CO$_2$H (R = H; Y = O)[5] and the corresponding βγ-unsaturated acids (R = Me; Y = CH$_2$). It was necessary to introduce a *gem*-dimethyl group in the βγ-unsaturated acid at the α-carbon atom to prevent isomerisation to the corresponding α-methylcinnamic acid. Both reactions are accelerated by electron-donating substituents; the overall changes in rate were only 25-fold for the olefinic acids and 8-fold for the keto-acids. The keto-acids fit a σ plot [Figure (a)] while the olefinic acids fit better with a σ$^+$ plot [Figure (b)]. We shall return to this point later. Even the best-fitting plots are curved, although the exclusion of the nitro-compound from each series would give a good correlation. Non-linear Hammett plots were previously obtained for ' no mechanism ' reactions, and are thought to be due to the delicate balance between bond making and breaking processes in the transition state.[14] The degree of concertedness in such a reaction would depend on the substituents present, in which case ρ need not be constant, but could be a function of σ. According to this interpretation the first four acids of each series exhibit (within the series) the same degree of bond making and breaking in the transition state. The powerful electron-withdrawing *m*-nitro-group upsets this balance and moves the transition state to a different position on the reaction co-ordinate. The Claisen rearrangement gives a plot similar to Figures (a) and (b) and has ρ ~ −0·4 to −0·6.[14] For the linear portion of the olefinic acid curve, ρ is *ca.* −**1·1**, indicating that, at least in this region, the present reaction is slightly more electron-demanding.

TABLE 3

N.m.r. data in deuterium exchange experiments

N.m.r. bands (τ-values) Origin	Quartet 2·8—3·3 ar.C–H	Doublet 4·65—4·9 =CH$_2$	Singlet 6·25 CH$_3$O–	Singlet 8·65 $>$CMe$_2$	Ratio of integrals of methylene to other protons
p-MeO·C$_6$H$_4$·C(:CH$_2$)·CMe$_2$·CO$_2$D	3·94	1·92	2·81	6·34	0·147
p-MeO·C$_6$H$_4$·C(:CH$_2$)·CMe$_2$·CO$_2$D, 14 hr. at 100°	3·95	1·88	2·89	6·12	0·145
p-MeO·C$_6$H$_4$·C(:CH$_2$)·CMe$_2$·CO$_2$D, recovered after 40 min. at 185°	5·4	2·65	4·2	9·5	0·139

N.m.r. bands (τ-values) Origin	Multiplet 1·7—2·5 ar·C–H	Doublet 4·4—4·7 =CH$_2$	Singlet 8·5 $>$CMe$_2$	Ratio of integrals of methylene to other protons
m-NO$_2$·C$_6$H$_4$·C(:CH$_2$)·CMe$_2$·CO$_2$D	9·8	4·9	15·0	0·197
m-NO$_2$·C$_6$H$_4$·C(:CH$_2$)·CMe$_2$·CO$_2$D, recovered after 24 hr. at 185°	9·7	4·8	15·7	0·189

The changes in synchronism discussed above should be reflected in changes in the deuterium isotope effect. Those unsaturated acids which fit the linear portion of the Hammett plot exhibit nearly identical isotope effects (the mean experimental error is ±**0·15**), but the *m*-nitro-acid, which falls off the Hammett plot, exhibits a markedly enhanced isotope effect.

The situation with the keto-acids used by Swain *et al.* is less clear. These workers noted that the *p*-methoxy-acid was out of order in terms of isotope effect. With the new data on the olefinic acids, we prefer to describe the *p*-methyl acid as having an unusually low deuterium isotope effect. The cause of this low effect is not clear, but this single value is out of line with the regularities of the rest of the Table. Swain *et al.* concluded, from the variation of their deuterium isotope effect with substituent, that proton transfer occurs in the transition state, and not hydride transfer. Our data do not permit such a conclusion, since there is an overall change of only one unit in the isotope effect, and for four of the substituents virtually no change. The relative rates for the two series of acids point to a close similarity of mechanism, and we conclude that the variation of isotope effect with substituent is not a reliable guide to the electronic nature of the migrating hydrogen.

TABLE 4

Relative rates and deuterium isotope effects in decarboxylation

	Benzoylacetic acids[5]		2,2-Dimethyl-3-phenylbut-3-enoic acids	
X	Rel. rate	k_H/k_D	Rel. rate	k_H/k_D
m-NO$_2$	0·29	2·85	0·30	3·00
p-Cl	0·40	1·67	0·67	1·95
H	1·00	1·40	1·00	2·13
p-Me	1·52	0·85	1·97	2·04
p-MeO	2·25	1·20	7·75	1·84

In Part III[9] the rates of decarboxylation of 2,2-dimethyl-3-phenylbut-3-enoic acid and of the 4-phenyl isomer are compared. The former acid, being an α-substituted styrene with the large isobutyryl group

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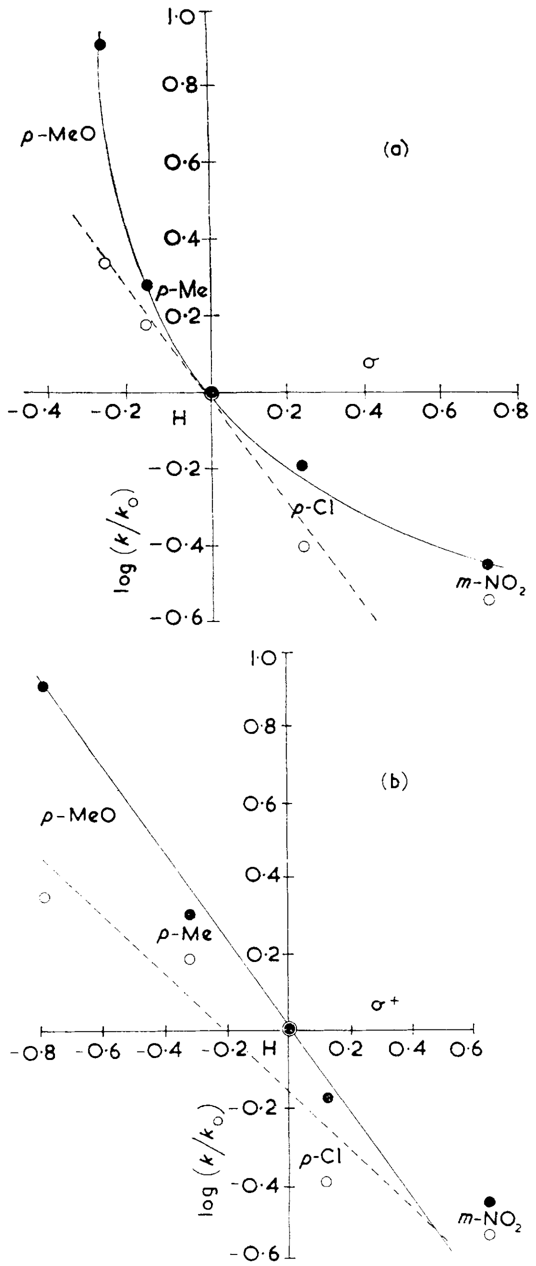
[13] D. B. Bigley, *J. Chem. Soc.*, 1964, 3897.

[14] S. J. Rhoads, in ' Molecular Rearrangements,' ed. P. de Mayo, part I, ch. 11, Interscience, New York, 1963.

forcing the double bond out of the plane of the benzene ring, was expected to show little conjugation. On the other hand, the product of decarboxylation, having only an α-methyl group, was described as more highly conjugated although it now has a *cis*-β-methyl group. The acids and olefins of the present paper support this thesis.

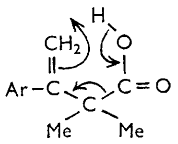


Hammett σ and σ^+ plots

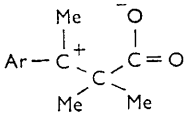
○ Benzoylpropionic acids
● 2,2-Dimethyl-3-phenylbut-3-enoic acids

The *K*-bands in the ultraviolet spectra of the acids all appear as either shoulders or maxima at about 225 mμ. The effect of substituents on the absorption wavelength is much smaller than for fully conjugated double bonds[15] ($\Delta\lambda_{max.} \sim 2$ mμ on changing from a *p*-methoxy- to a *m*-nitro-substituent, cf. $\Delta\lambda_{max.}$ 37 mμ for the corresponding cinnamic acids[15b]). The product styrenes have absorptions in the region of 240 mμ, and $\Delta\lambda_{max.}$ 4 mμ, indicating enhanced, though by no means full, conjugation. In the present series, changes in rate must be due to electric rather than strain[16] effects, because substituents are remote from the reaction centre. The transition complex for decarboxylation will presumably have an intermediate degree of conjugation.

The observation of deuterium isotope effects in the decarboxylation of βγ-unsaturated acids (Table 2) favours formulation (III) for the transition state, since the O–H bond is completely broken in the intermediate (IV). However, it was previously pointed out[17] that an X–H bond may be broken prior to the transition state



(III)



(IV)

but still result in an isotope effect if there is a rapid pre-equilibrium.

We previously eliminated this possibility for 2,2-dimethyl-4-phenylbut-3-enoic acid by exchange experiments;[1] similar experiments described in the Experimental section rule out the pre-equilibrium for the present series of acids. The isotope effect is thus consistent with transition state (III) and precludes (IV).

Formulation (III) implies strict synchronism of bond changes with no development of charge. It is now of interest to enquire how much charge development does occur. A strong indication may be extracted from Part IV.[16] The effect of methylating the β-carbon atom of 2,2-dimethylbut-3-enoic acid is to enhance its rate of decarboxylation by a factor of 45 (gas-phase reaction). It was shown in Part IV that at least part of this rate enhancement is due to a strain factor; electrically, therefore, the rate enhancement is less than a factor of 45. (IV) represents the extreme of charge production. The unmethylated acid (IV; Ar = H) contains a secondary carbonium ion, while the methylated acid (IV; Ar = Me) has a tertiary carbonium ion. It has been estimated[18] that the latter is more stable by 16 kcal./mole in the gas phase. Even in solution, where the carbonium ions are stabilised by solvation, t-butyl bromide undergoes an S_N1 reaction up to 10^6 times faster (depending on solvent) than does isopropyl bromide.[19] The modest rate enhancement observed in

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[15] O. M. Wheeler and C. B. Covarrubias, (*a*) *Canad. J. Chem.*, 1962, **40**, 1224; (*b*) *J. Org. Chem.*, 1963, **28**, 2015.

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

[17] K. J. Laidler, ' Chemical Kinetics,' McGraw-Hill, New York, 1965, p. 494.

[18] A. Streitwieser, ' Solvolytic Displacement Reactions,' McGraw-Hill, New York, 1962, p. 181.

[19] C. K. Ingold, ' Structure and Mechanism in Organic Chemistry,' Bell, London, 1963, p. 316.

[20] H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191.

the present decarboxylation reaction is suggestive therefore of only a small degree of charge production in the transition state. The most negative ρ-values in the literature are of the order -5 (*e.g.*, for the solvolysis of phenyldimethylcarbinyl chlorides, ρ is $-4{\cdot}62$).[20] The present value of $-1{\cdot}2$ might correspond therefore to *ca.* 20% production of a positive charge on C-3.

The nature of the deuterium isotope effect in β-keto-acid decarboxylation cannot be probed in the same direct way. While rates measured at a single temperature should be treated with some caution, it is significant that, where other comparisons can be made, the similarity is maintained. For example, Pedersen[3] showed that αα-dimethylacetoacetic acid decarboxylates at 4·5 times the rate of the parent acid; we have shown that αα-dimethylbut-3-enoic acid decarboxylates at 5·6 times the rate of its parent acid.[16] These comparisons suggest that the transition states for the two series must be very similar. According to these arguments, the decarboxylation of β-keto-acids is better described by (II) than by (I).

The fact that the keto-acids of Table 1 fit a σ plot while the unsaturated acids fit a σ^+ plot (in both cases with the exception of the nitro-acids) need not invalidate the comparison. A partial positive charge set up in transition state (IV) must reside on the carbon atom adjacent to the benzene ring. It will then be able to conjugate with the benzene ring and should fit a σ^+ correlation. In the keto-acid series, the carbonyl oxygen may accept the positive charge, when a correlation with σ is expected.

There remains the claim by Brower *et al.*,[8] supported by evidence from the volumes of activation, that the decarboxylation of β-keto-acids proceeds through the zwitterionic form (I). We consider these conclusions to be insecure for the following reasons. The changes in $\Delta V^\ddagger$ are compared for the decomposition of malonic acid in solvents ranging in polarity from water to tetrahydrofuran, in which $\Delta V^\ddagger$ was $+5$ and -10 ml./mole respectively. This change of 15 ml./mole was compared with a similar change (16 ml./mole) for the reaction between n-butyl bromide and pyridine, and it was argued that, since this reaction forms ionic products from neutral reactants, the decarboxylation reaction must also involve an ionic 'product' (the transition state). However, the absolute magnitudes of the two series of $\Delta V^\ddagger$'s are quite different, the Menschutkin reaction having $\Delta V^\ddagger$ in the range -26 to -42 ml./mole. The significance of this large difference is uncertain, and we consider that the conclusion about malonic acid must be treated with caution. Indeed, in the absence of solvent effects, a $\Delta V^\ddagger$ near to zero is normally associated with a neutral transition state.

Extending their conclusion about malonic acid to the decarboxylation of other acids, Brower *et al.* found that $\Delta V^\ddagger$ for acetoacetic acid was $+4$ and for picolinic acid $+17$ ml./mole, both in aqueous solution. Since the values for malonic and acetoacetic acid were almost the same in water, it was concluded that the latter acid also decarboxylates through the zwitterion. This conclusion, based as it is on a measurement in only one solvent, is clearly not secure. Many factors can influence $\Delta V^\ddagger$ in a given reaction,[21] and the similar values obtained for malonic and acetoacetic acid might be fortuitous. The observed $\Delta V^\ddagger$ for the decarboxylation of picolinic acid is considerably greater, but there is good independent evidence that this acid does decarboxylate through a zwitterion.[22] Finally, the trihalogenoacetic acids are known[7] to decarboxylate through the anion, giving rise to a small change of charge in comparison to zwitterion formation, yet they have small positive values for $\Delta V^\ddagger$ similar to those of β-keto acids.

We believe, therefore, that the data of Brower *et al.* do not lead to a single interpretation of the decarboxylation of β-keto-acids, and that our arguments do not at present require revision.

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[21] E. Whalley, *Adv. Phys. Org. Chem.*, 1964, **2**, 93.

[22] B. R. Brown and D. Ll. Hammick, *J. Chem. Soc.*, 1949, 659.