Detritiation of Diethyl [2-$^3H_1$]Malonate

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Rate constants for the base-catalysed detritiation of diethyl malonate have been determined in aqueous solution. Various indicators of transition state structure, such as primary hydrogen isotope effects, Brönsted β exponent, rates of ion recombination, and solvent isotope effects all give a consistent picture. The results are compared with those obtained for carbon acids activated by cyano and disulphonyl groups.

THE recent development of ^{3}H n.m.r. spectroscopy [1] has greatly increased the attractions of tritium as a tracer.[2] However in contrast to ^{14}C-labelled compounds many ^{3}H-labelled compounds can not safely be used as tracers because the label may be lost in a hydrogen exchange process. It becomes necessary therefore to determine the stability of the label in the compound under conditions which are closely similar to those experienced during the compound's use as a tracer.

Diethyl [2-$^3H_1$]malonate is only one of several malonates that have found wide use as precursors in biogenetic studies of fungal metabolites.[3] These and other studies [4] have established the importance of malonate as a C_2 biosynthetic unit. In our own studies [5] we have shown that the biosynthesis of penicillic acid involves the condensation of a single acetate unit with three malonate units. As part of this work we have measured the rates of detritiation of diethyl malonate under various conditions. Although previous studies [6-8] on the rates of ionisation of this compound have been carried out the data are not readily convertible into detritiation rates because of the variability of primary hydrogen isotope effects.

EXPERIMENTAL

Materials.—Diethyl malonate (5 ml; distilled) was treated with tritiated water (0.01 ml; 5 Ci ml^{-1}) and sodium carbonate (10 mg) in dioxan (1 ml) at room temperature for 2 days. Anhydrous sodium sulphate was then added. Distillation of the supernatant liquid afforded tritiated diethyl malonate, b.p. 42° at 0.5 mmHg.

Buffer solutions were prepared by partially neutralising solutions of the carboxylic acids with standardised sodium hydroxide or by using corresponding amounts of the sodium salt of the acids. Sodium chloride was used to maintain the ionic strength of the medium at 0.1M.

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[8] R. P. Bell and J. E. Crooks, *Proc. Roy. Soc.*, 1965, *A*, **286**, 285.

Kinetics.—(a) A trace amount of labelled substrate was added to the reaction medium (75 ml) in a thermostat and samples (5 ml) were withdrawn at different time intervals and injected into tubes containing scintillator (10 ml; 3.4 g l^{-1} 2,5-diphenyloxazole in toluene) and water (10 ml). The mixture was shaken, the toluene layer was separated and dried (Na_2SO_4), and the tritium content of a portion (5 ml) determined. The first-order detritiation rate constants (k^T) were calculated from the slopes ($-k^T/2.303$) of the plots of log (counts min^{-1}) against time.

TABLE 1

Rates of detritiation of $CHT(CO_2Et)_2$ in water at various temperatures

T/K	[HCl]/M	10^6k^T/s^{-1}
298.2		3.59 ± 0.07
	0.01	3.55
	0.10	6.86
308.2		9.18 ± 0.05
318.2		22.8 ± 0.30
328.2		54.7 ± 0.40

TABLE 2

Activation parameters for detritiation of $CHT(CO_2Et)_2$ in water at 298.2 K; data for $CHT(CN)_2$ and $CHT(SO_2Ph)_2$ given for comparison

	$CHT(CO_2Et)_2$	$CHT(CN)_2$ [11]	$CHT(SO_2Ph)_2$ [20]
10^6k^T/s^{-1}	3.59	8 370	36 500
$\Delta G_1^\ddagger$/kJ mol^{-1}	114	95.0	81.5
$\Delta H_1^\ddagger$/kJ mol^{-1}	71.7	67.8	48.1
E_a/kJ mol^{-1}	74.2	70.3	50.6
$\Delta S_1^\ddagger$/J K^{-1} mol^{-1}	−142	−91	−112

TABLE 3

Rate constants for the base-catalysed bromination and detritiation of diethyl malonate at 298.2 K

Base	pK^0	$10^4k_B^H$[6,8]/ dm^3 mol^{-1} s^{-1}	$10^4k_B^T$/ dm^3 mol^{-1} s^{-1}	k^H/k^T [a]	k_{-1}
(1) Water	−1.74	44.1×10^{-4}	6.47×10^{-4}	3.4	4.9×10^8
(2) Chloroacetate	2.86	7.29	0.88	4.2	2.0×10^7
(3) Glycolate	3.82	35.7			
(4) Benzoate	4.19		6.04		
(5) Acetate	4.75	226	15.3	7.4	8.0×10^6
(6) Isobutyrate	4.86		17.6		
(7) Pivalate	5.03	372	20.7	9.0	6.9×10^6

[a] Statistical factor of 2 included so that comparison is between CH_2 and CT_2 groups and not CH_2 and CHT.

TABLE 4

Indicators of transition state structure for the ionisation of some carbon acids $RCH + H_2O \longrightarrow RC^- + H_3O^+$

	$CH_2(CO_2Et)_2$	$CH_2(CN)_2$ [11,19]	$CHMe(SO_2Et)_2$ [12,20]
pK^0	13.3	11.19	14.56
k_1/s^{-1}	2.45×10^{-5}	2.86×10^{-2}	3.5×10^{-5}
k_{-1}/dm^3 mol^{-1} s^{-1}	4.9×10^8	1.8×10^9	1.3×10^{10}
$\beta(RCO_2^-)$	0.79 (0.66)	0.98 *	~0.8 (1.0)
$k^H/k^T(H_2O,OAc^-)$	3.4, 7.4		
$k^H/k^D(H_2O,OAc^-)$	1.9_7	1.49, 1.47 *	1.8, 2.1
$k^T_{H_2O}/k^T_{D_2O}$	2.1	3.67	3.5 †

* Refers to the very similar t-butylmalononitrile. † Refers to the very similar $CH_2(SO_2Et)_2$.

(b) In the initial rate method [9] the samples (5 ml) withdrawn from the reaction medium were injected into tubes containing toluene (10 ml) and water (10 ml). The toluene layer was separated off and the aqueous layer shaken with further toluene to ensure complete extraction of the labelled substrate. The radioactivity of the aqueous layer was determined by counting a portion (1 ml) in an NE-250 liquid scintillator. The radioactivity at infinite time (C_∞) could be obtained by counting a similar quantity of the reaction mixture, because the low concentration of diethyl malonate employed did not introduce any quenching problems. Plots of C_t against time were strictly linear, providing k^T values from the slopes ($C_\infty k^T$). In those cases where both methods were used, good agreement was obtained.

RESULTS AND DISCUSSION

The rate of detritiation of diethyl malonate in water at 298.2 K (Table 1) is the same as in dilute hydrochloric acid (0.01M) showing that the reaction is not catalysed by hydronium ions. However, a further 10-fold increase in acid concentration brings about a two-fold acceleration in the rate of detritiation. Similar effects have been reported in the base-catalysed bromination of the same compound.[6] Both probably reflect the fact that hydrolysis of the ester is a competing reaction under these conditions.

The replacement of one of the hydrogen atoms in methane by activating groups such as CO_2Et, CN, or SO_2CH_3 has approximately the same effect on acidity. Thus Pearson and Dillon [10] estimate the pK_a values of CH_3CO_2Et, CH_3CN, and $CH_3SO_2CH_3$ to be 25, 24.5, and 23 respectively. The insertion of a second, similar activating group brings the pK_a values down still further, to 13.3 for $CH_2(CO_2Et)_2$,[10] 11.19 for $CH_2(CN)_2$,[11] and 12.55 for $CH_2(SO_2CH_3)_2$.[12] The only other reported

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[9] J. A. Elvidge, J. R. Jones, C. O'Brien, E. A. Evans, and H. C. Sheppard, *J.C.S. Perkin II*, 1973, 1889.

[10] R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, 1953, **75**, 2439.

[11] F. Hibbert, F. A. Long, and E. A. Walters, *J. Amer. Chem. Soc.*, 1971, **93**, 2829.

[12] R. P. Bell and B. G. Cox, *J. Chem. Soc. (B)*, 1971, 652.

value for diethyl malonate (15.75) refers to a mixed aqueous solvent.[13]

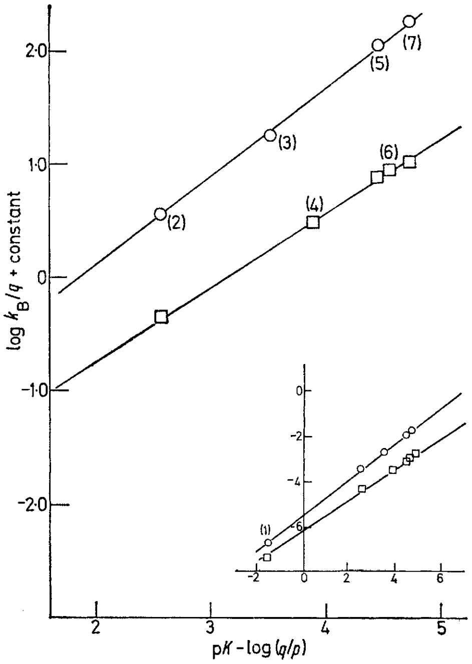
Although the thermodynamic functions ΔH° and ΔS° for the overall ionisation process are available only for malononitrile, values of $\Delta H_1^{\ddagger}$ and $\Delta S_1^{\ddagger}$, the enthalpy and entropy of activation, respectively, for the ionisation reaction are available (Table 2) for both diethyl malonate and malononitrile and also for $CH_2(SO_2Ph)_2$ which is a good model for $CH_2(SO_2CH_3)_2$. These show that the much slower rate of detritiation of diethyl malonate is due to a higher enthalpy of activation and a much more negative entropy of activation. This would seem to suggest considerable interaction of the solvent and the CO_2Et groups and it seems significant that the value of $\Delta S_1^{\ddagger}$ is close to that found for benzoylacetone and ethyl 2-oxocyclopentanecarboxylate,[14] compounds which show structural features similar to diethyl malonate. It is also consistent with a reaction mechanism which involves proton transfer between two neutral substrates and formation of a transition state that resembles an ion pair ($RC^- \cdots H^+H_2O$) and which is considerably more solvated than the substrate.

For the detritiation studies in the presence of buffers five or six different concentrations were employed for a single buffer ratio. The plots of k^{T} against anion concentration $[B^-]$ were strictly linear, the intercept in all cases corresponding to the water-catalysed rate and the slope to the catalytic rate coefficient ($k^{\mathrm{T}}_{\mathrm{B}^-}$). Values were obtained for five carboxylate anions and these together with the water-catalysed rate coefficient are given in Table 3. The earlier results of Bell and his co-workers [6,8] on the bromination of diethyl malonate are also included.

Information concerning the structure of the transition state can be obtained in a variety of ways, (i) from primary isotope effects, (ii) the Brönsted relationship, (iii) solvent isotope effects, and (iv) the rates of ion-recombination.

(i) *Primary Isotope Effects*.—There is now a good deal of evidence,[15] both theoretical and experimental, to show that $k^{\mathrm{H}}/k^{\mathrm{D}}$ (or $k^{\mathrm{H}}/k^{\mathrm{T}}$) varies with the symmetry of the transition state, with reactant-like and product-like transition states having low isotope effects and a symmetrical transition state giving a maximum value. Combination of Bell's data [6,8] with our own detritiation results provides (after making allowance for a statistical factor of two) values of $k^{\mathrm{H}}/k^{\mathrm{T}}$. For water the value is very low but for the carboxylate anions higher values are obtained, with $k^{\mathrm{H}}/k^{\mathrm{T}}$ increasing with the base strength of the catalyst. This trend is to be expected for a compound having a pK_a of 13.3; the anion of diethyl malonate is a much more powerful base than any of the catalysts used so that an increase in the base strength of the latter will render the transition state more symmetrical, leading to an increase in $k^{\mathrm{H}}/k^{\mathrm{T}}$.

(ii) *The Brönsted Relationship*.—Bell and his co-workers found that if log $k^{\mathrm{H}}_{\mathrm{B}}/q$ was plotted against pK − log (q/p), where p and q are the customary statistical factors that take into account the number of acidic and basic sites in a particular catalyst, a good linear relationship was obtained with a slope β of 0.79. A similar treatment of the tritium results (Figure) gives an equally good plot with a somewhat lower slope (0.66). This difference results from the observed variation in hydrogen isotope effects, amounting to a factor of *ca.* 3 as the catalyst basicity changes by 7 pK units. In other studies [16,17] the variation in isotope effect has been less pronounced so that the two values of β are closer or even identical. Strictly speaking the detritiation rates should be plotted against the pK^0 values of the tritiated acids. If this were possible the slopes should be identical as it has usually been assumed that the potential energy changes for the proton transfer reaction describe the same curvature as do the deuteron (or triton) transfer reactions.



Brönsted plot for the ionisation of diethyl malonate: ○, bromination results; □, detritiation results. Inset figure contains results for water catalysis. Numbers refer to those in Table 3

In the past the magnitude of the exponent β has been taken to signify the degree of proton transfer in the transition state. Although there are indications that such an interpretation may need modification for some nitro-compounds [18] the value for diethyl malonate is

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[13] P. Rumpf, E. d'Incan, and R. Schaal, *Bull. Soc. chim. France*, 1955, 122; R. Schaal, *J. chim. Phys.*, 1955, **52**, 784, 796.

[14] J. A. Elvidge, J. R. Jones, C. O'Brien, E. A. Evans, and H. C. Sheppard, *J.C.S. Perkin II*, 1973, 2138.

[15] See *e.g.* R. P. Bell, 'The Proton in Chemistry,' Chapman and Hall, London, 1973, 2nd edn., ch. 11; J. R. Jones, 'The Ionisation of Carbon Acids,' Academic Press, London, 1973, ch. 9.

[16] D. J. Barnes and R. P. Bell, *Proc. Roy. Soc.*, 1970, *A*, **318**, 421.

[17] D. W. Earls, J. R. Jones, and T. G. Rumney, *J.C.S. Faraday I*, 1972, 925.

[18] F. G. Bordwell, W. J. Boyle, jun., J. A. Hautala, and K. C. Yee, *J. Amer. Chem. Soc.*, 1969, **91**, 4002.

entirely normal and there seems to be no reason to believe that it represents anything but a correct, although somewhat insensitive, measure of transition state structure.

(iii) *Rates of Ion Recombination.*—Taking the value of 13.3 for the pK_a of diethyl malonate and the bromination results of Bell and his co-workers it is possible to calculate the rates of the reverse reaction (Table 3). The data show that for the hydronium-catalysed reaction the rate is *ca.* 25-fold faster than for the next strongest acid (chloroacetic) and somewhat below the value expected for a diffusion controlled process. The dependence of rate on the strength of the carboxylic acids is as expected for a reaction exhibiting an α exponent of 0.34.

(iv) *Solvent Isotope Effects.*—Hibbert and Long[19] have recently shown how studies of solvent isotope effects, can supplement information obtained by other means, and in particular have proposed a useful generalisation for proton transfer reactions in which the solvent water acts as the base catalyst. When the primary isotope effect is low because of a high degree of proton transfer the solvent isotope effect is likely to be large and when the primary isotope effect is small because of a reactant-like transition state the solvent isotope effect will be low. These proposals are in agreement with the results of model calculations. Our findings (Table 4) show that $k^T(H_2O)/k^T(D_2O)$ is large but not as high as the values reported for malononitrile[19] and 1,1-bisphenylsulphonylethane.[20]

Apart from diethyl malonate the two other types of carbon acids that have been most extensively studied are the cyano-compounds by Long and his co-workers[11,19] and the disulphones by Bell and Cox[12] and more recently Hibbert.[20] It is of interest to compare the different findings (Table 4). Although $CHMe(SO_2Et)_2$ is over 2 pK units weaker than diethyl malonate its rate of ionisation is somewhat faster. The values for the rate constants for ion recombination increase in the order keto-ester < cyano < disulphone, indicating that the degree of asymmetry of the transition state also increases in this order. The values of the exponent β for carboxylate anion catalysis are also consistent with this viewpoint especially if one takes into account Hibbert's comment[20] that the value for the disulphone is close to unity if the point for water catalysis is neglected. This interpretation is supported by the finding that the value of the exponent obtained by changing the substrate, rather than the catalyst, is unity.

For all three compounds the primary isotope effects for water catalysis are low. The values for acetate catalysis remain virtually the same as for water in the case of the disulphone and cyano-compounds but are considerably higher for diethyl malonate, again indicating a less asymmetric transition state for this compound. In fact all these indicators of transition state structure, including the solvent isotope effects, are consistent with one another and lend support to the belief that for the compounds investigated each is a correct measure of transition state structure.

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[19] F. Hibbert and F. A. Long, *J. Amer. Chem. Soc.*, 1971, **93**, 2836.

[20] F. Hibbert, *J.C.S. Perkin II*, 1973, 1289.