Brönsted Exponents in the Proton Abstraction from Derivatives of Ethyl α-Benzylacetoacetate, 3-Benzylpentane-2,4-dione, and Benzylmalononitrile

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Measurements are reported of the rates of proton transfer from ring-substituted ethyl α-benzylacetoacetates, 3-benzylpentane-2,4-diones, and benzylmalononitriles to a series of carboxylate ions. For the first two series the Brönsted exponents for substitution in the carbon acid are considerably greater than those for substitution in the carboxylate ion, and this behaviour is compared with the more extreme differences previously reported for reactions of the nitro-alkanes. For the benzylmalononitriles both exponents are equal to unity. Velocity constants are also given for the reactions of 3-benzylpentane-2,4-diones with water and with pyridine, and of benzylmalononitriles with water.

In an acid–base reaction (1) the necessary equilibrium conditions are satisfied if the forward and reverse reactions obey Brönsted relations of the form (2), where K_1 and K_2 are the acid strengths of A_1 and A_2 expressed on the same scale. Although a simple molecular basis

$$A_1 + B_2 \underset{k_-}{\overset{k_+}{\rightleftharpoons}} B_1 + A_2 \qquad (1)$$

$$k_+ = GK_1^{\beta_1}K_2^{-\beta_2}; \quad k_- = GK_1^{-(1-\beta_1)}K_2^{1-\beta_2} \qquad (2)$$

for the Brönsted relation in terms of intersecting potential energy curves suggests that β_1 and β_2 should be equal, there is no thermodynamic necessity for this to be the case. Numerous investigations have been made in which A_1 is a carbon acid and B_2 is varied through a series of similar bases such as carboxylate ions, but systematic variations in A_1 have rarely been carried out, partly because many carbon acids are too weak for a reliable determination of their strength to be made. Recently, however, Bordwell and his collaborators[1-4] have studied several series of nitro-alkanes, and found that not only did β_1 and β_2 differ greatly, but that β_1 was frequently greater than unity, implying a negative exponent for the reverse reactions. It is of interest to investigate how far this behaviour extends to other series of carbon acids, and the present paper deals with three such series, chosen to contain a single reactive hydrogen atom and to have measurable dissociation

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constants in water. The reactions of a single compound of each class with a series of carboxylate ions gave β_2, and β_1 was determined by introducing ring substituents into the benzyl group. Reaction rates were measured either by using halogen scavengers for the carbanions formed, or by tritium exchange.

EXPERIMENTAL

Materials.—Most of the benzyl derivatives were prepared by one of two general methods: (*a*) reaction of the active methylene compound with 1 equiv. of potassium hydroxide and 1 equiv. of substituted benzyl chloride or bromide 1,1-diethoxyethane, as described by Weizmann *et al.*;[5] (*b*) preparation of the sodium salt of the active methylene compound by treatment with 1 equiv. of sodium ethoxide, and refluxing with the substituted benzyl halide (usually the bromide) in dry ether or benzene. In both methods the reaction mixture was acidified and extracted with ether and the products were purified as described below. All had ^{1}H n.m.r. spectra in accord with their structures.

Ethyl α-benzylacetoacetate [method (*a*)] was distilled at 156—158 °C and 12 mmHg (lit.,[5] 156—160 °C and 13 mmHg). Ethyl α-(4-nitrobenzyl)acetoacetate [method (*b*)] was purified by t.l.c. on silica with 80% ether–petroleum. The pale yellow solid was recrystallised from 50% benzene–petroleum; m.p. 43 °C (lit.,[6] 43—45 °C). Ethyl α-(3-methylbenzyl)acetoacetate [method (*b*)] was distilled at 116—117 °C and 0.8 mmHg (lit.,[7] 110—112 °C and 0.25 mmHg). Ethyl α-(4-chlorobenzyl)acetoacetate [method (*b*)] was distilled at 123 °C and 4 mmHg (lit.,[8] 190—197 °C and 18 mmHg). Ethyl α-(4-methoxybenzyl)acetoacetate [method (*b*) from 4-methoxybenzyl bromide, b.p. 130 °C at 16 mmHg (lit.,[9] 130 °C at 16 mmHg), itself prepared from the corresponding alcohol[10]] was distilled at 145 °C and 0.05 mmHg (lit.,[11] 172 °C and 0.25 mmHg).

Ethyl α-(4-cyanobenzyl)acetoacetate has not been described previously. 4-Cyanobenzyl bromide was prepared by bromination of *p*-toluonitrile.[12] The product of method (*b*) was purified by column chromatography on silica with 50% ether–petroleum, giving an oil which solidified, $\nu_{\text{max.}}$ (liquid) 2220 ($C\equiv N$) and 1720 and 1740 cm^{-1} ($C=O$).

3-Benzylpentane-2,4-dione [method (*b*)] was distilled at 125 °C and 3.25 mmHg (lit.,[13] 110—112 °C and 2 mmHg). 3-(4-Nitrobenzyl)pentane-2,4-dione [method (*b*)] was purified by t.l.c. on silica with 80% ether–petroleum. The oil obtained solidified; m.p. 82 °C (from ethanol). 3-(4-Methoxybenzyl)pentane-2,4-dione [method (*b*)] was distilled at 166 °C and 0.7 mmHg (lit.,[14] 174—176 °C and 1 mmHg).

3-(4-Cyanobenzyl)pentane-2,4-dione [method (*b*)], not described previously, was purified by column chromatography on silica with 50% ether–petroleum and recrystallised from 70% ethanol–water; m.p. 38—40 °C, $\nu_{\text{max.}}$ 2215 cm^{-1} ($C\equiv N$). 3-(4-Chlorobenzyl)pentane-2,4-dione [method (*b*)] was distilled at 164 °C and 1.5 mmHg.

Methods (*a*) and (*b*) give poor yields in the benzylmalononitrile series, so benzylmalononitrile was prepared by the sequence diethyl benzylmalonate * $\longrightarrow$ benzylmalonoamide[15] $\longrightarrow$ benzylmalononitrile,[16] m.p. 90 °C (from aqueous methanol) (lit.,[16] 79 °C; lit.,[17] 91 °C). 4-Cyanobenzylmalononitrile, not described previously, was prepared by the same method as benzylmalononitrile. Diethyl 4-cyanobenzylmalonate was distilled at 219 °C and 1 mmHg. The final product could not be distilled and was extracted with ether; m.p. 118 °C (from aqueous methanol), $\nu_{\text{max.}}$ 2 260w and 2 240s cm^{-1} ($C\equiv N$).

4-Chlorobenzylmalononitrile [method (*a*)] was purified by sublimation at 150 °C and 3 mmHg; m.p. 86—89 °C (lit.,[16] 89 °C). 4-Nitrobenzylmalononitrile [method (*b*)], not described previously, was recrystallised from 90% methanol–water, but still contained some 4-nitrobenzyl bromide, which was removed by t.l.c. (silica; ether); m.p. 150 °C (from 90% methanol–water), $\nu_{\text{max.}}$ 2 260 ($C\equiv N$) and 1 350 and 1 520 cm^{-1} (NO_2).

Deionised water was distilled from potassium permanganate. It was then boiled for 30 min and cooled under nitrogen. Propionic acid was distilled at 140 °C and 760 mmHg and 2-chloropropionic acid at 83 °C and 12 mmHg. 3-Chloropropionic acid was recrystallised from cyclohexane. All other materials were of AnalaR grade. Buffer solutions were prepared by adding sodium hydroxide solution to a solution of the acid, and their concentrations were varied by diluting this solution. All reaction mixtures were made up to an ionic strength of 0.2 mol dm^{-3} by adding potassium chloride: their pH values were checked (glass electrode), and were adjusted in the diluted solutions by adding hydrochloric acid when necessary. For buffer solutions containing monochloroacetic and 2-chloropropionic acids the concentration of the basic buffer component was corrected by adding to it the hydrogen ion concentration, calculated on the assumption that $f_\pm = 0.72$.

Determination of Acidity Constants.—The pK values of the substrates were determined at 25 °C by measuring absorbances in standard buffer solutions,[18] 0.1M- and 1M-potassium hydroxide, and 0.1M-hydrochloric acid, the last two serving to obtain the molar absorptivities of the anion and the uncharged molecule. In the potassium hydroxide solutions the absorbance decreased slowly with time, and a short extrapolation was made to zero time. Thermodynamic values of pK were obtained by inserting activity coefficients calculated from equation (3), where the ionic strength I

$$-\lg f_\pm = 0.51\, I^{\frac{1}{2}}/(1 + 1.65\, I^{\frac{1}{2}}) \qquad (3)$$

varied from 0.09 to 0.13 mol dm^{-3}. Aqueous solutions of derivatives of pentane-2,4-dione contain an appreciable proportion of enol, and a correction is necessary to obtain the pK value of the keto-form. The proportion of enol was determined by two concordant methods. In the first substrate was added to a bromine–bromide solution

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* Prepared by method (*b*).

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of known concentration, and the absorbance–time curve extrapolated back to zero time, thus giving the amount of bromine which reacted instantaneously with enol. In the second method bromine was added to a solution of substrate, followed immediately by an excess of allyl alcohol to remove the unchanged bromine. The resulting solution was treated with potassium iodide, which reacts with the bromo-compound to produce an equivalent quantity of iodine: this iodine was then estimated spectrophotometrically as I_3^- at 353 nm. In this way solutions of 3-(4-methoxybenzyl)pentane-2,3-dione were found to contain 18% of enol, and the corresponding figure for the other four derivatives was 15%. No enol was detected in solutions of the other substances investigated. The final pK values are given in Table 1.

Kinetic Measurements.—Most of the reaction velocities were measured by using bromine as a scavenger for the carbanion. In a typical experiment a buffer solution (2 cm^3) 0.1M in potassium bromide and 5×10^{-5}M in bromine was brought to 25 ± 0.1 °C in the cell compartment of a Gilford 2400 spectrophotometer. The reaction was initiated by adding sufficient of a 0.02M-solution of substrate in acetonitrile to give a concentration of 3×10^{-5}M, and the decrease in tribromide absorption at 300 nm was followed. The observed fall in absorbance was from about 0.24 to 0.15, and the rate was independent of bromine concentration.

Under the above conditions bromine does not act as an efficient scavenger for the anions of malononitrile derivatives, and for this series the concentrations of bromine and substrate used were respectively about 5×10^{-3} and 6×10^{-4}M, giving a fall in absorbance at 380 nm from 1.8 to 1.6. Even at this concentration scavenging is effective only at pH > 5, which limits the range of bases which can be studied. At pH > 5 the rate of disappearance of bromine is independent of bromine concentration.

The course of the reactions is strictly first order for benzylmalononitrile, but shows evidence of a slow subsequent decrease in bromine concentration for the other two series. This has been observed previously [19] for diketones, and was attributed to decomposition of the bromo-compound and reaction of the products with bromine, but it could also be due to bromination of other parts of the molecule or to loss of bromine by evaporation from the cell. The present results were analysed by the LETAGROP VRID computer program of Sillén [20] for a first-order process plus a linear decrease in absorbance. When the linear decrease is subtracted the consumption of bromine has the calculated value in all cases.

Because of the problems of scavenging the anion of benzylmalononitrile with bromine, the effect of substituents in this series was studied by measuring rates of tritium exchange, and the same method was used for the reaction of substituted pentane-2,4-diones with water and with pyridine. The substance was tritiated by dissolving 0.1 g in dry dioxan (1 cm^3) containing tritiated water (1 mm^3; 5 Ci cm^{-3}). This solution was kept for at least 24 h at room temperature for the malononitriles and for several days at 50 °C for the pentane-2,4-diones. After adding anhydrous sodium sulphate *ca.* 2 mm^3 of the dioxan solution was added to 20 cm^3 of thermostatted buffer or acid solution. Portions (1 cm^3) were removed at suitable intervals and added to a mixture of water (10 cm^3) and sulphur-free toluene (10 cm^3) containing 2,5-diphenyloxazole (7 g dm^{-3}). After shaking, the toluene layer was separated and dried, and a sample (5 cm^3) was counted in an Intertechnique SL30 liquid scintillation counter. In several instances the count after more than 8 half-lives was checked and found to be effectively zero. First-order rate constants were therefore obtained from linear plots of ln(counts min^{-1}) against time. This technique is practicable only for rather slow reactions, and the malononitriles were therefore studied in monochloroacetate buffers at 5 °C, rather than in acetate buffers at 25 °C.

Each carboxylate buffer solution was studied at five concentrations with [RCO_2^-] in the range 0.01—0.2M, and the second-order velocity constants were obtained from the slopes of linear plots of the observed first-order constants against [RCO_2^-]. Detritiation of the benzylpentane-2,4-diones in pyridine buffers was studied at only a single pyridine concentration (0.1M), and the rate due to pyridine was obtained by subtracting the water rate, which for both benzylpentane-2,4-dione and benzylmalononitrile was the same in 10^{-3}M- and 10^{-2}M-hydrochloric acid. The velocity constants for all the reactions are collected in Table 1.

RESULTS AND DISCUSSION

The velocity constants in each series obey Brönsted type relations, and this is true both when a given carbon acid reacts with a series of carboxylate ions, and when a given carboxylate ion reacts with a series of carbon acids. The best values of the coefficients in these relations are given in Table 1, which also compares the observed and calculated velocity constants. The value of β given for the reaction of benzylmalononitriles with monochloroacetate ion needs correcting for the fact that pK_1 was measured at 25 °C and k at 5 °C. This correction was estimated by measuring the absorbance of solutions of benzylmalononitrile and 4-nitrobenzylmalononitrile at both temperatures in 0.1M-hydrochloric acid, 1M-sodium hydroxide, and also two phosphate buffers having pH values at 25 °C of 11.40 and 11.80. These measurements yield the ratio of the dissociation constants of the two compounds at each temperature, without any assumptions about the temperature dependence of the pH values of the buffer solutions. It was found that ΔpK_1 was 0.85 at 5 °C and 0.93 at 25 °C. Combination of the former value with the kinetic results at 5 °C has the effect of raising β from 0.90 to 0.98: the last value is included in the collected values of β in Table 2.

In the reactions of the two series of carbonyl compounds with carboxylate ions, β_1 (for substitution in the carbonyl compound) is considerably greater than β_2 (for substitution in the carboxylate ion). This is qualitatively the same difference as has been found for reactions of the nitro-alkanes.[1-4] though in the present study β_1 does not rise above unity. The differences between β_1 and β_2 can therefore be accounted for by any of the effects previously suggested for the nitro-alkanes: distribution of the negative charge in the transition state,[21] existence of a real or virtual intermediate,[4] or solvation of the

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transition state.[22] At present it is difficult to decide amongst these explanations, but it is of interest that such differences occur in carbon acids other than the nitroalkanes.

TABLE 1

Collected velocity constants

Values at 25 °C unless otherwise stated; k in l mol^{-1}s^{-1}, k_0 in s^{-1}. In deriving the Brönsted exponents the following values of pK_2 were used: monochloroacetic 2.86, 2-chloropropionic 2.96, 3-chloropropionic 4.00, benzoic 4.21, acetic 4.75, propionic 4.87

$PhCH_2{\cdot}CH(COMe){\cdot}CO_2Et + RCO_2^-$
$k = 1.17 \times 10^{-4}\, K_2^{-0.44}$

R =	CH_2Cl	MeCHCl	$CH_2Cl{\cdot}CH_2$	Ph	Me	Et
10^4k obs.	21	24	70	85	144	157
calc.	21	24	68	84	145	163

$XC_6H_4{\cdot}CH_2{\cdot}CH(COMe){\cdot}CO_2Et + MeCO_2^-$
$k = 1.31 \times 10^7\, K_1^{0.76}$

X =	4-OMe	4-Me	3-Me	H	4-Cl	4-CN	4-NO_2
pK_1	11.89	11.88	11.87	11.81	11.57	11.23	11.06
10^4k obs.	118	124	139	144	198	370	500
calc.	121	123	125	139	211	380	520

$PhCH_2{\cdot}CH(COMe)_2 + RCO_2^-$ $k = 2.48 \times 10^{-4}\, K_2^{-0.44}$

R =	CH_2Cl	MeCHCl	Ph	Me	Et
10^4k obs.	45	49	190	290	350
calc.	45	50	177	300	350

$XC_6H_4{\cdot}CH_2{\cdot}CH(COMe)_2 + MeCO_2^-$ $k = 3.49 \times 10^4\, K_1^{0.58}$

X =	4-OMe	H	4-Cl	4-CN	4-NO_2
pK_1	10.57	10.49	10.25	9.69	9.54
10^3k obs.	29	36	40	86	99
calc.	29	36	40	84	103

$XC_6H_4{\cdot}CH_2{\cdot}CT(COMe)_2 + H_2O$ $k_0 = 1.48\, K_1^{0.48}$

(K_1 relates to untritiated compound)

X =	4-OMe	H	4-Cl	4-CN	4-NO_2
pK_1	10.57	10.49	10.25	9.69	9.54
$10^7\, k_0$ obs.	119	147	179	330	390
calc.	133	137	178	330	390

$XC_6H_4{\cdot}CH_2{\cdot}CT(COMe)_2$ + pyridine $k = 1.62 \times 10^2\, K_1^{0.44}$

(K_1 relates to untritiated compound)

X =	4-OMe	H	4-Cl	4-CN	4-NO_2
pK_1	10.57	10.49	10.25	9.69	9.54
10^5k obs.	34	43	52	90	97
calc.	37	39	50	88	103

$PhCH_2{\cdot}CH(CN)_2 + RCO_2^-$ $k = 1.23\, K_2^{-1.00}$

R =	$CH_2Cl{\cdot}CH_2$	Ph	Me	Et
10 k obs.	12.6	19	73	87
calc.	12.3	20	69	91

$XC_6H_4{\cdot}CH_2{\cdot}CT(CN)_2 + CH_2Cl{\cdot}CO_2^-$ at 5 °C
$k = 1.99 \times 10^8\, K_1^{0.90}$

(K_1 refers to untritiated compound at 25 °C)

X =	H	4-Cl	4-CN	4-NO_2
pK_1	11.80	11.49	10.96	10.87
10^4k obs.	49	86	270	330
calc.	47	91	270	330

$XC_6H_4{\cdot}CH_2{\cdot}CT(CN)_2 + H_2O$ $k_0 = 3.92 \times 10^4\, K_1^{0.81}$

X =	H	4-Cl	4-CN	4-NO_2
pK_1	11.80	11.49	10.96	10.87
10^4k_0 obs.	27	38	87	91
calc.	25	38	81	92

The picture is different for the reactions of the benzylmalononitriles with carboxylate ions, for which β_1 and β_2 are both unity. This agrees with the finding of Long and his co-workers [23] for β_2, but no systematic study of β_1 has been reported previously. The fact that $\beta_1 = \beta_2 = 1$ implies that the rate of the reverse reaction between carbanions and carboxylic acid molecules is unaffected by substitution in either reactant. This rate is, however, considerably below the diffusion-controlled limit, having an average value of *ca.* 6 × 10^7 dm^3 mol^{-1} s^{-1} for the systems we have studied. As suggested by Long,[23] this may be attributed to the presence of a constant additional activation barrier arising from the necessity to reorganise the solvation shell.

For the reactions of the 3-benzylpentane-2,4-diones with pyridine or water, β_1 is considerably lower than for the corresponding reaction with acetate ion, and is close to β_2 for reaction with carboxylate ions. However, this last comparison is not a legitimate one, since in proton-transfer reactions between two uncharged species the formation of the transition state involves a much greater charge displacement than in a reaction between an uncharged carbon acid and an anion base, with a correspondingly more drastic solvent reorganisation. No information is at present available about the value of β_2 for the reaction of 3-benzylpentane-2,4-dione with a series of uncharged bases.

TABLE 2

Collected values of Brönsted exponents at 25 °C

	β_1	β_2
$PhCH_2{\cdot}CH(COMe){\cdot}CO_2Et + RCO_2^-$		0.44
$XC_6H_4{\cdot}CH_2CH(COMe){\cdot}CO_2Et + MeCO_2^-$	0.76	0.44
$PhCH_2{\cdot}CH(COMe)_2 + RCO_2^-$		
$XC_6H_4{\cdot}CH_2{\cdot}CH(COMe)_2 + MeCO_2^-$	0.58	
$XC_6H_4{\cdot}CH_2{\cdot}CT(COMe)_2 + H_2O$	0.48	
$XC_6H_4{\cdot}CH_2{\cdot}CT(COMe)_2$ + pyridine	0.44	
$PhCH_2{\cdot}CH(CN)_2 + RCO_2^-$		1.00
$XC_6H_4{\cdot}CT(CN)_2 + CH_2Cl{\cdot}CO_2^-$	0.98 *	
$XC_6H_4{\cdot}CT(CN)_2 + H_2O$	0.61	

* Kinetic measurements at 5 °C, corrected to 25 °C as described in the text.

It is surprising that the reaction of benzylmalononitriles with water gives a value of β_1 (0.61) considerably less than unity. The reverse reactions between carbanions and oxonium ions have velocity constants not far below the diffusion-controlled limit (1.3 × 10^9 to 3 × 10^9 dm^3 mol^{-1} s^{-1}) and an exponent close to unity would be expected. No explanation is offered for this behaviour, which merits further study.

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