Intramolecular General Base Catalysis in the Hydrolysis of the Ester Group of Benzoylglycolic Acid

By **Antonio Arcelli** and **Carlo Concilio,*** Istituto Chimico ' G. Ciamician ', University of Bologna, Via Selmi 2, 40126 Bologna, Italy

The mechanism of hydrolysis of the ester group of benzoylglycolic acid in buffered aqueous solutions at 80 °C in the range where the rate is independent of pH was studied. The uptake of ^{18}O in benzoic acid during hydrolysis in 20% ^{18}O enriched water, the interpretation of a Brønsted correlation of hydrolysis catalysed by some oxy-anions (β 0.49), and the evaluation of activation entropy brought us to the conclusion that the reaction involves the anion of the substrate, and may be interpreted in terms of intramolecular general base catalysis ($k^{S^-}_{H_2O} \times [H_2O]$ 1.33 × 10^{-6} s^{-1}, $\Delta H^‡$ 22.5 kcal mol^{-1}, $\Delta S^‡$ −22.2 cal mol^{-1} K^{-1}).

In a previous paper [1] we reported the rate of hydrolysis of the ester bond of benzylglycolic acid between pH 1 and 8. The salient feature was the relatively high rate at pH *ca.* 5 and we thought it interesting to investigate the reason for this occurrence. The rate constant for spontaneous hydrolysis of the substrate, reported in Figure 1, is pH independent at pH *ca.* 5.

pH–Rate profiles of protogenic esters can be generally interpreted in terms of acid, neutral, and basic hydrolysis of the acid (SH) and ionized (S^-) substrate. A detailed interpretation of the various parts of a curve of this type has already been given by Edwards [2] for the hydrolysis of aspirin. According to this treatment, the right-hand side of the diagram represents the alkaline hydrolysis of ionized substrate, while the pH-independent region can be essentially identified with the two kinetically indistinguishable processes (1) and (2).

$$\mathrm{PhCOO{\cdot}CH_2{\cdot}COOH + OH \xrightarrow{k^{SH}_{OH}} PhCO_2^- + HO{\cdot}CH_2{\cdot}CO_2 + H^+} \quad (1)$$

$$\mathrm{PhCOO{\cdot}CH_2{\cdot}COO + H_2O \xrightarrow{k^{S^-}_{H_2O}} PhCO_2^- + HO{\cdot}CH_2{\cdot}CO_2 + H^+} \quad (2)$$

The rate constants derived from experiment are: $k^{SH}_{OH^-}$ 3.57 × 10^3 l mol^{-1} s^{-1} and $k^{S^-}_{H_2O} \times [H_2O]$ 1.33 × 10^{-6} s^{-1} at 80 °C (Table 3). These values can be compared with those which can be reasonably estimated as follows. From a Taft type treatment of alkaline hydrolysis of benzoic acid esters $PhCO_2{\cdot}CH_2X$,† when

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† From ref. 1 log $k_{\mu=0} = 0.067 + 4.20\,\sigma_I$, where σ_I is the inductive constant of X.[3]

[1] C. Concilio and A. Arcelli, *Ann. Chim.* (*Italy*), 1968, **58**, 881.

[2] L. J. Edwards, *Trans. Faraday Soc.*, 1950, **46**, 723.

[3] M. Charton, *J. Org. Chem.*, 1964, **29**, 1222.

X = CO_2H we calculate $k^{SH}_{OH^-}$ 28.4 l mol^{-1} s^{-1}. From the nucleophilicity ratio for ester carbonyl hydrolysis

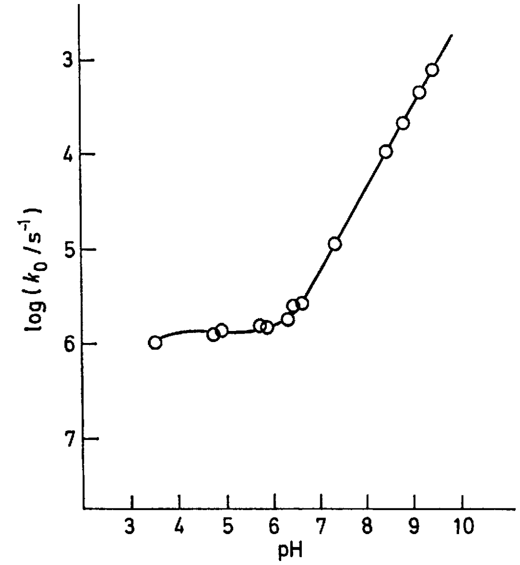
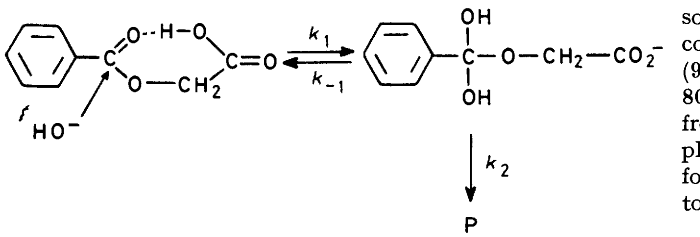
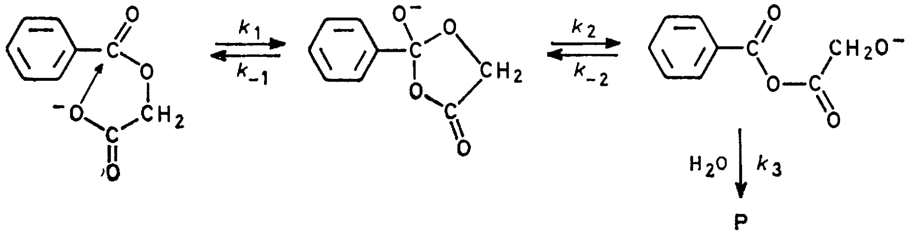


FIGURE 1 pH–Rate profile for spontaneous hydrolysis of benzoylglycolic acid at 80 °C and ionic strength μ = 1 (data from Table 1)

(k_{OH^-}/k_{H_2O} 1.5 × 10^9)[4] and $k^{S^-}_{OH}$ (Table 3), we obtain $k^{S^-}_{H_2O}$ × $[H_2O]$ 3.4 × 10^{-8} s^{-1}.*



SCHEME 1



SCHEME 2

The values derived from experiment are higher than those expected, suggesting that the rate enhancement is due to a catalytic effect. This could be (i) intramolecular general acid catalysis by the un-ionized carboxy-group of the substrate in the reaction with OH^- (Scheme 1), (ii) nucleophilic, or (iii) general base catalysis by the carboxylate group of the ionized substrate in the reaction with water (Scheme 2 or 3).

The participation of an ionized or un-ionized carboxy-group has been postulated for mechanisms of hydrolysis of esters. Invariably the largest rate enhancements are observed in systems where the molecule is more or less rigidly fixed in a favourable conformation.[5]

In this study we investigate the hydrolysis of benzoylglycolic acid and identify the reason for rate enhancement in a system in which the vicinal carboxylate group is present in a flexible structure.

EXPERIMENTAL

Materials and Instruments.—Organic and inorganic reagents (C. Erba AR), 20% [^{18}O] water (D < 10%) (Bio-Rad), and 99.75% D_2O (Merck) were used as purchased. Benzoylglycolic acid was prepared by a known method.[6] Water was distilled twice from $KMnO_4$ before use. pH Determinations were performed at 70—90 °C with a Knick KpH 350 pH meter using a glass electrode standardized with phosphate, phthalate, and borax buffers.[7] Isotopic enrichment was measured with an LKB 9000 mass spectrometer and spectrophotometric determinations were carried out with Optica CF 4 (single beam) and Perkin-Elmer 402 (double beam) instruments.

Methods and Results.—pK_a Values (Table 1) were determined by potentiometric titration[8] at 80 ± 0.2 °C of 0.01M solutions at ionic strength μ = 1 (KCl).† The dissociation constants of benzoylglycolic acid at μ = 1 are 1.02 × 10^{-3} (90 °C), 9.38 × 10^{-4} (80 °C), and 8.85 × 10^{-4} (70 °C). At 80 °C pK_{H_2O} = 14.18 and p$K_{H_3O^+}$ = −1.73; pK_w was taken from ref. 10, $[H_2O]$ from ref. 11; $[H_3O^+]$ was set as −antilog pH; $[OH^-]$ was calculated from pK_w[10] without correction for ionic strength;[12] pD was calculated from pH according to Fife and Bruice.[13]

The rate of hydrolysis of benzoylglycolic acid was measured in buffered solutions with added KCl to keep the ionic strength μ constant at 1. Slow hydrolyses were performed in a sealed glass-ampoules kept in a thermo-

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* This value, divided by 54, fits the Brønsted plot rather well (see below).

† The reproducibility was ±0.03 pK units, though the accuracy is lower than this owing to the liquid junction potential.[9]

[4] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1960, **82**, 1778.

[5] A. J. Kirby and P. W. Lancaster, *J.C.S. Perkin II*, 1972, 1206.

[6] C. Concilio and A. Bongini, *Ann. Chim.* (*Italy*), 1966, **56**, 417.

[7] R. G. Bates, *J. Res. Nat. Bureau Standards A*, 1962, **66**, 179.

[8] A. Albert and E. P. Serjeant, 'Ionization Constants of Acids and Bases,' Methuen, London, 1962, p. 16.

[9] I. Feldman, *Analyt. Chem.*, 1956, **28**, 1859.

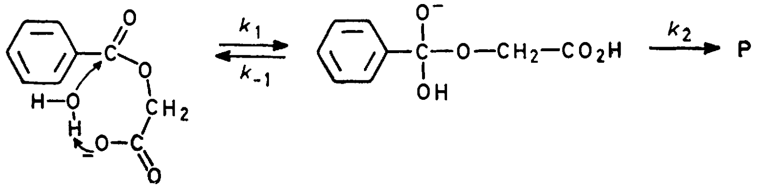
[10] Landolt-Börnstein, 'Physikalisch-Chemische Tabellen,' Berlin, 1923, Hw. II, p. 1164.

[11] 'Handbook of Chemistry and Physics,' ed. R. C. Weast, The Chemical Rubber Co., Cleveland, 1971—1972, pp. F4—F5.

[12] Myung-un Choi and E. R. Thornton, *J. Amer. Chem. Soc.*, 1974, **96**, 1428.

[13] T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, 1961, **65**, 1079.

statted bath (±0.05 °C). At set times ampoules were cooled, the content diluted five times with 0.1M-phosphate buffer (pH 7.68), and the optical density was determined.



SCHEME 3

TABLE 1

Rate constants for buffer catalysis (k_b) and for spontaneous hydrolysis (k_0) of benzoylglycolic acid

Buffer (sodium salt)	t/°C	pK_a [a,b]	pH [b,c]	[Buffer]/M [d]	No. of runs	$10^7 k_b$/ l mol^{-1} s^{-1} [b,e]	$10^6 k_0$/ s^{-1} [b,e]
Acetate	70		4.73	0.1—0.8	4	1.25 ± 0.38	0.489 ± 0.02
Acetate	70		5.76	0.1—0.8	4	1.00 ± 0.04	0.538 ± 0.02
Acetate	80	4.67	4.82	0.1—0.8	4	2.69 ± 0.16	1.35 ± 0.08
Acetate	80	4.67	5.79	0.1—0.8	4	2.15 ± 0.25	1.52 ± 0.02
Acetate in D_2O [f]	80		4.70	0.1—0.8	4	1.43 ± 0.12	0.75 ± 0.07
Acetate	90		4.90	0.1—0.8	4	5.08 ± 0.28	3.19 ± 0.02
Acetate	90		5.82	0.1—0.8	4	4.55 ± 0.43	3.73 ± 0.03
Formate	80	3.99	3.54	0.1—0.8	4	7.63 ± 0.95	1.07 ± 0.05
Formate [g]	80	3.99	4.78	0.08—0.7	4	1.64 ± 0.03	1.26 ± 0.01
Succinate [h]	80	5.41	5.76	0.14—0.54	4	9.24 ± 2.41	1.55 ± 0.08
Phosphate [i]	80	6.61	6.60	0.02—0.20	3	53.9 ± 4.05	2.63 ± 0.05
Imidazole	80	6.57	6.32	0.08—0.29	4	35.0 ± 2.3	1.84 ± 0.07
Sulphite	80	6.90	6.58	0.06—0.20	4	33.1 ± 4.9	2.53 ± 0.77
Borate [j]	80	9.33	8.84—9.18	0.1—0.64	6	838 ± 24	

[a] pK_a of conjugate acid ±0.03. [b] Ionic strength $\mu = 1$ (KCl). [c] ±0.02. [d] Free base; the value of pK_a found at 80 °C is used for acetate buffer at 70 and 90 °C. [e] Standard errors determined by the weighed least squares method. [f] $pD = pH + 0.17 = 4.87$. [g] In 0.025M-acetate carrier buffer. [h] $\mu = 1.9$. [i] HPO_4^{2-}. [j] From the equation $k_{obs}/[\mathrm{Buffer}] = k_b + k^{\mathrm{S}^-}_{\mathrm{OH}^-}[\mathrm{OH}^-]/[\mathrm{Buffer}]$ is also calculated $k^{\mathrm{S}^-}_{\mathrm{OH}^-} = 0.922$, which is in agreement with the value found for phosphate buffer (*cf.* Table 3).

Fast reactions were followed directly in the cell compartment of the spectrophotometer, started by addition of 50 μ l of a stock solution of sodium benzoylglycolate in a thermostatted cuvette containing buffer (3 ml).

The initial concentration of substrate was between 6×10^{-2} and 5×10^{-3}M; the wavelength observed was at 275 nm for imidazole and sulphite buffers,* and 232 nm for other buffers.

The hydrolyses were followed up at least 75% completion; $\mathrm{O.D}_\infty$ values were determined either directly after ten half-lives or after dilution with NaOH. The pseudo-first-order rate constant (k_{obs}) for the disappearance of ester was evaluated from $\ln(\mathrm{O.D}_\infty - \mathrm{O.D}_0)/(\mathrm{O.D}_\infty - \mathrm{O.D}_t)$ *versus* time, using a least-squares method.†

The rate constant for buffer catalysed process (k_b) and for spontaneous hydrolysis (k_0) were obtained from k_{obs} by means of relation (3). The catalytic rate constant k_b for

$$k_{obs} = k_0 + k_b[\mathrm{B}] \qquad (3)$$

borate buffer was evaluated from the equation (3) rearranged in the form: $k_{obs}/[\mathrm{B}] = k_b + k^{\mathrm{S}^-}_{\mathrm{OH}^-} \times [\mathrm{OH}^-]/[\mathrm{B}]$ setting $k_0 = k^{\mathrm{S}^-}_{\mathrm{OH}^-} \times [\mathrm{OH}]$. Both k_0 and k_b were calculated by the least-squares method. Results are shown in Figure 2 and 3 and collected in Table 1.

Hydrolysis in $H_2{}^{18}O$.—(a) *Alkaline*. Sodium (3×10^{-3} g atom) was dissolved in $H_2{}^{18}O$ (2 g) in a nitrogen atmosphere, then added to benzoylglycolic acid (1 mmol). The solution was kept for 1 h at 110 °C, then cooled, lyophilysed to recover $H_2{}^{18}O$, and acidified with HCl. Benzoic acid was separated and sublimed *in vacuo*. The solution was neutralized with NaOH, lyophilysed, and the salts were chromatographed.[15] The fraction containing glycolic acid was treated with diazomethane to obtain the methyl ester.

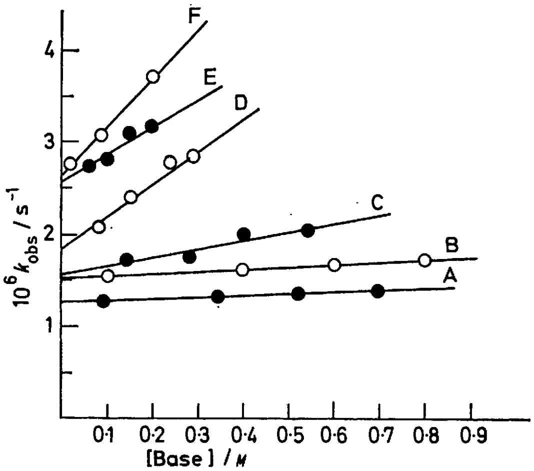


FIGURE 2 Plot of the observed rate constants for hydrolysis of benzoylglycolic acid at 80 °C (in buffered solutions at $\mu = 1$ with KCl) *versus* free base concentration: A, formate pH 4.78; B, acetate pH 5.79; C, succinate; D, imidazole; E, sulphite; F, phosphate (*cf.* Table 1)

(b) *At* pH 5.05. A solution of benzoylglycolic acid (1 mmol), anhydrous sodium acetate (5 mmol), and acetic acid

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* The sulphite buffer did not show any absorption except after some hours in the air it formed $S_2O_5{}^{2-}$.[14]

† CERN computer program E 200 (Geneva).

[14] R. C. Brasted, 'Comprehensive Inorganic Chemistry,' Van Nostrand, New York, 1961, vol. VIII, p. 153.

[15] E. F. Phares, E. H. Mosbach, F. W. Denison, jun., and S. F. Carson, *Analyt. Chem.*, 1952, **24**, 660.

(1 mmol) in $H_2{}^{18}O$ (2 ml) was kept for 200 h at 110 °C, then cooled, neutralized with *ca.* 10N-NaOH (20% ^{18}O), lyophilysed, and treated as above.

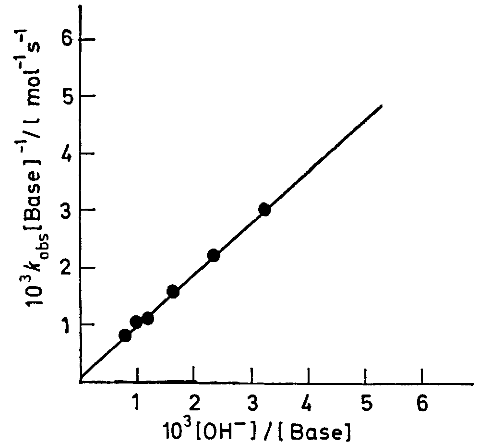

FIGURE 3 Plot of k_{obs}/[Base] *versus* [OH$^-$]/[Base] in the hydrolysis of benzoylglycolic acid at 80 °C in borate buffered solutions

TABLE 2

Percentage ^{18}O uptake of benzoic acid and methyl glycolate after hydrolysis of benzoylglycolic acid in $H_2{}^{18}O$ at 110 °C [a]

	Hydrolysis Alkaline	Hydrolysis pH 5.05 [b]	Control runs [c]	Natural samples
Benzoic acid [d]	19.0	19.5	9.1	0.9
Methyl glycolate [e]	1.0	2.1	1.5	1.1

[a] Mean values over at least five runs in the region of molecular peak approximated to ±0.2 [b] In acetate buffer. [c] Experiment to evaluate uptake after completion of hydrolysis. [d] Direct inlet. [e] G.l.c. inlet.

Procedure (b) was also carried out for benzoic and glycolic acid to ascertain that isotopic exchange was not due to ester hydrolysis. Benzoic acid and methyl glycolate give substantial molecular peaks in the mass spectra, allowing a careful determination of isotopic enrichment[16] (Table 2).

TABLE 3

Rate constants and thermodynamic parameters for water, hydroxide, and acetate ion catalysed hydrolysis of benzoylglycolic acid at ionic strength μ = 1(KCl)

t/°C	$10^7 k^{S^-}_{H_2O}[H_2O]$/s^{-1} [a]	$k^{S^-}_{OH^-}$/l mol^{-1} s^{-1} [b]	10^{-3} $k^{OH^-}_{SH}$/l mol^{-1} s^{-1} [a]	10^7 $k^{S^-}_{AcO^-}$/l mol^{-1} s^{-1} [c]
70	4.82 ± 0.19	0.55 ± 0.02	2.02 ± 0.08	0.971 ± 0.084
80	13.3 ± 0.05	0.933 ± 0.02	3.57 ± 0.13	2.08 ± 0.30
90	31.8 ± 0.02	1.54 ± 0.05	6.10 ± 0.04	4.47 ± 0.53
$\Delta H^\ddagger$/kcal mol^{-1} [d]	22.5 ± 0.4	12.1 ± 0.02	13.0 ± 0.01	18.2 ± 0.3
$\Delta S^\ddagger_{80}$/cal mol^{-1} K^{-1} [e]	−22.2 ± 1.1	−24.9 ± 0.06	−5.9 ± 0.03	−38.0 ± 0.8

[a] Obtained from the values of k_0 (*cf.* Table 1) in acetate buffer averaged over the pH values investigated, after correction at each pH for the contribution of $k^{S^-}_{OH^-}[OH^-]/(1 + [H_3O^+]/K_a)$; the difference between the two figures is at most 5.8%. [b] Obtained in 0.1M-phosphate buffer at pH 8.49 setting $k_{obs} = k^{S^-}_{OH^-}[OH^-]$. In 0.025—0.2M-carbonate buffer at 80 °C (pK_a 9.64), $k^{S^-}_{OH^-}$ 0.927 l mol^{-1} s^{-1} in good agreement with the value found in phosphate and borate buffers. [c] Calculated from the values of k_b (*cf.* Table 1) according to the comments accompanying expression (5). [d] Calculated from the values of the constants at three temperatures with weighed least square method. [e] From $\Delta S^\ddagger = R \ln[A/(kTe/h)]$; standard state 1M at 80 °C.

DISCUSSION

Buffer Catalysed Hydrolysis (k_b).—Catalytic rate constants (k_b in Table 1) establish the existence of the Brønsted relationship (4)* plotted in Figure 4. The

$$\log k_b/q = \log G_b + \beta(\mathrm{p}K_a + \log p/q) \qquad (4)$$

β value calculated by the least-squares method excluding OH^- and H_2O (Table 3) is 0.49 ± 0.02. This value is typical for general base catalysis; nucleophilic catalysis by oxy-anions having a pK_a much smaller than the leaving group † is in fact characterized by β values close to unity.[19]

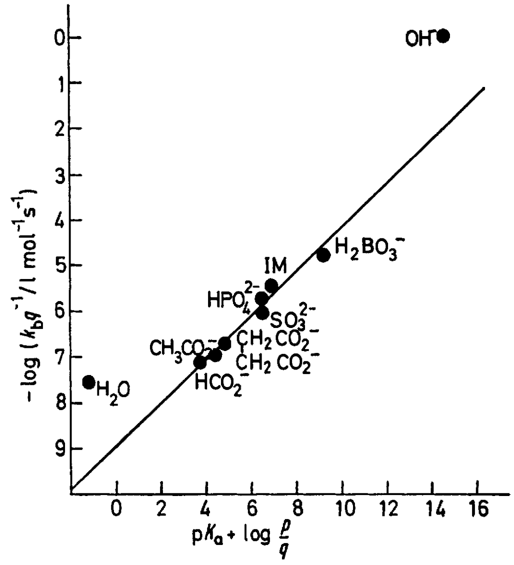

FIGURE 4 Brønsted plot for general base catalysed hydrolysis of benzoylglycolate anion at 80 °C (data from Table 1; acetate pH 5.79, formate pH 4.78). The line of slope 0.49 is the best fit through the rate constants for oxy-anions and imidazole (IM) buffers; $K^{S^-}_{OH^-}$ and $k^{S^-}_{H_2O}$ (1.33 × 10^{-6}/54 l mol^{-1} s^{-1}) are not computed

The positive deviation of about two orders of magnitude from the Brønsted line shown by $k^{S^-}_{OH^-}$, can be attributed to nucleophilic attack by hydroxide ion on the carbonyl carbon, as already reported by other authors.[20]

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* Statistical p and q factors according to Bell and Evans;[17] for imidazole IMH$^+$–IM p = 2 and q = 1.

† We calculate from refs. 3 and 18 for the leaving group RCH$_2$-OH: pK_a 17.1 (R — CO_2^-) and pK_a 13.0 (R — CO_2H) at 25 °C

[16] C. G. Swain, G.-I. Tsuchihaschi, and L. J. Taylor, *Analyt. Chem.*, 1963, **35**, 1415.

[17] R. P. Bell and P. G. Evans, *Proc. Roy. Soc.*, 1966, **A291**, 297.

[18] S. Takahashi, L. A. Cohen, H. K. Miller, and E. G. Peake, *J. Org. Chem.*, 1971, **36**, 1205.

[19] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, **90**, 2622.

[20] Y. Pocker and E. Green, *J. Amer. Chem. Soc.*, 1973, **95**, 113

From the data in Tables 1 and 3 the ratio $k^{\mathrm{S}^-}_{\mathrm{OH}^-}/k_{\mathrm{b}}^{\mathrm{IM}} = 2.7 \times 10^5$ is obtained which lies within the range observed for general base catalysis (10^5—10^6); lower values (10—10^3) are normally observed for nucleophilic catalysis.[21] Similarly, the ratio $k_{\mathrm{b}}^{\mathrm{IM}}/k_{\mathrm{b}}^{\mathrm{HPO_4}^{2-}} = 0.65$ lies in the range observed for general base (0.25—1.9) rather than for nucleophilic catalysis (10^3).

The above evidence substantiates general base catalysis by the buffers. Additional evidence is provided by the results obtained with acetate buffers. (a) Benzoylglycolic acid can participate in hydrolysis both as a free acid (SH) and as an anion (S^-) and the buffer is in principle able to catalyse the reaction both in its acidic (AcOH) and anionic (AcO^-) forms. Therefore k_{b} of equation (3) is given by equation (5) where K_{a}

$$k_{\mathrm{b}} = \frac{k^{\mathrm{SH}}_{\mathrm{AcO}^-}}{(1 + K_{\mathrm{a}}/[\mathrm{H_3O^+}])} + \frac{k^{\mathrm{S}^-}_{\mathrm{AcO}^-}}{(1 + [\mathrm{H_3O^+}]/K_{\mathrm{a}})} + \frac{[\mathrm{AcOH}]}{[\mathrm{AcO}^-]} \left\{ \frac{k^{\mathrm{SH}}_{\mathrm{AcOH}}}{(1 + K_{\mathrm{a}}/[\mathrm{H_3O^+}])} + \frac{k^{\mathrm{S}^-}_{\mathrm{AcOH}}}{(1 + [\mathrm{H_3O^+}]/K_{\mathrm{a}})} \right\} \quad (5)$$

is the dissociation constant of benzoylglycolic acid, $k^{\mathrm{SH}}_{\mathrm{AcO}^-}$ is the catalytic rate constant of the reaction of acetate ion on the acidic substrate. The meaning of other symbols is obvious.

One calculates that on going from pH 5.79 to 4.82, at 80 °C, the $k^{\mathrm{SH}}_{\mathrm{AcOH}}$ term increases by a factor of 85, both kinetically indistinguishable $k^{\mathrm{SH}}_{\mathrm{AcO}^-}$ and $k^{\mathrm{S}^-}_{\mathrm{AcOH}}$ terms increase by a factor 9.2, while the $k^{\mathrm{S}^-}_{\mathrm{AcO}^-}$ term remains essentially unchanged. On the other hand, k_{b} is found to increase by a factor of only 1.25 (Table 1). It is then clear that the $k^{\mathrm{S}^-}_{\mathrm{AcO}^-}$ term makes the most significant contribution to the overall rate. Considering also that intermolecular general acid catalysis occurs only in a very limited number of hydrolyses,[21] it is reasonable to conclude that, at least in the pH range examined, only the first and the second term of equation (5) make significant contributions to k_{b}. One then calculates $k^{\mathrm{S}^-}_{\mathrm{AcO}^-}$ 2.08×10^{-7} and $k^{\mathrm{SH}}_{\mathrm{AcO}^-}$ 4.03×10^{-6} l $\mathrm{mol^{-1}\ s^{-1}}$ and a contribution of the respective terms to the overall rate at pH 5.79 of 96.8 and 3.2%.

Extrapolation of $k^{\mathrm{S}^-}_{\mathrm{AcO}^-}$ (2.08×10^{-7} l $\mathrm{mol^{-1}\ s^{-1}}$) to 109 °C gives 1.6×10^{-6} l $\mathrm{mol^{-1}\ s^{-1}}$ which compares well with the acetate catalysed rate constant for methyl benzoate hydrolysis at the same temperature[22] (1.2×10^{-6} l $\mathrm{mol^{-1}\ s^{-1}}$). (b) The kinetic isotope effect in the presence of acetate buffer ($k_{\mathrm{b}}^{\mathrm{H_2O}}/k_{\mathrm{b}}^{\mathrm{D_2O}}$ 1.88) is consistent with general base catalysis, even though it does not allow a clear cut distinction from nucleophilic catalysis.[21,23,24] (c) The activation entropy has a highly negative value (−38 cal $\mathrm{mol^{-1}\ K^{-1}}$) close to those observed for other hydrolyses catalysed by acetate acting as general base (−30.7 for aspirin,[25] −31.2 and −39 for aryl acetates[26]) whereas less negative values are reported for nucleophile catalysed hydrolysis.[26,27]

In conclusion all evidence on the catalytic effect of acetate ion and other bases is consistent with general base catalysis. This agrees well with the general behaviour of reactions of oxy-anions with esters carrying leaving groups of high basicity.[21,27]

Spontaneous Hydrolysis (k_0).—As reported in the introduction, the spontaneous process at pH *ca.* 5 can be identified with the intramolecularly catalysed reaction either of the acidic substrate with $\mathrm{OH^-}$ (Scheme 1) or of the ionized substrate with water (Schemes 2 or 3).

Taking into account the contribution of alkaline hydrolysis of the ionized substrate (which however contributes only 1.5% to the rate at pH 4.82) k_0 of equation (3) is given by equation (6). The values of the rate constants

$$k_0 = \frac{k^{\mathrm{SH}}_{\mathrm{OH}^-} \times [\mathrm{OH^-}]}{(1 + K_{\mathrm{a}}/[\mathrm{H_3O^+}])} + \frac{k^{\mathrm{S}^-}_{\mathrm{OH}^-} \times [\mathrm{OH^-}]}{(1 + [\mathrm{H_3O^+}]/K_{\mathrm{a}})} \text{ or}$$

$$k_0 \quad \frac{k^{\mathrm{S}^-}_{\mathrm{H_2O}} \times [\mathrm{H_2O}]}{(1 + [\mathrm{H_3O^+}]/K_{\mathrm{a}})} + \frac{k^{\mathrm{S}^-}_{\mathrm{OH}^-} \times [\mathrm{OH^-}]}{(1 + [\mathrm{H_3O^+}]/K_{\mathrm{a}})} \quad (6)$$

$k^{\mathrm{SH}}_{\mathrm{OH}^-}$ and $k^{\mathrm{S}^-}_{\mathrm{H_2O}} \times [\mathrm{H_2O}]$ calculated from k_0 in acetate buffer and $k^{\mathrm{S}^-}_{\mathrm{OH}^-}$ are reported in Table 3.

The following points are indicative in deciding between the mechanisms outlined above. (a) The failure to fit $k^{\mathrm{S}^-}_{\mathrm{H_2O}}$ ($1.33 \times 10^{-6}/54 = 2.46 \times 10^{-8}$ l $\mathrm{mol^{-1}\ s^{-1}}$) into the Brønsted plot (Figure 4) indicates that the hydrolytic reaction cannot be interpreted in terms of simple general base catalysis by water. However, the value interpolated from the plot (3.06×10^{-10} l $\mathrm{mol^{-1}\ s^{-1}}$) agrees rather well with that expected from the nucleophilicity ratio (6.30×10^{-10} l $\mathrm{mol^{-1}\ s^{-1}}$). (b) The kinetic solvent isotope effects calculated from $k_0^{\mathrm{H_2O}}/k_0^{\mathrm{D_2O}} = 1.80$ * are $k^{\mathrm{SH}}_{\mathrm{OH}}/k^{\mathrm{SD}}_{\mathrm{OD}^-}$ 0.52 and $k^{\mathrm{S}^-}_{\mathrm{H_2O}}/k^{\mathrm{S}^-}_{\mathrm{D_2O}}$ 1.76. These values are compatible with either of the mechanisms and they do not permit a choice between them. (c) Hydrolysis in $\mathrm{H_2{}^{18}O}$ gives rise to an uptake of $^{18}\mathrm{O}$ in the benzoic acid moiety only. If the mechanism in Scheme 2 were to operate, an intermediate benzoic glycolic anhydride would be formed, which would be expected to undergo attack by water preferentially at the glycolic carbonyl carbon. This expectation is based on the behaviour of acetic benzoic anhydride (75% of attack occurs on the acetic carbonyl[30]) and on the greater susceptibility to nucleophilic attack of a glycolic with respect to an acetic carbonyl carbon

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* From k_0 in acetate buffer at 80 °C and $K_{\mathrm{a}}^{\mathrm{H_2O}}/K_{\mathrm{a}}^{\mathrm{D_2O}}$ 2.48,[28] $[\mathrm{H_2O}]_4[\mathrm{D_2O}]$ 1,[11] and $pK\mathrm{D_2O}$ 13.43.[29] Terms in $k^{\mathrm{S}^-}_{\mathrm{HO}^-}$ and k^{-}_{SD} are neglected.

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atom.[31] The lack of incorporation of ^{18}O into the glycolate product provides evidence that the anhydride intermediate is not on the reaction path. (d) Valuable information is given by the activation entropies (Table 3). For the reaction of acidic substrate with OH^-, the computed $\Delta S^\ddagger$ is -5.9 cal mol^{-1} K^{-1}, too high for bimolecular alkaline hydrolysis. For such a process a more negative entropy is expected, as is observed for hydrolysis of ethyl benzoate (-25) [32] and of benzoylglycolate anion (-24.9) (Table 3). The mechanism shown in Scheme 1 appears to be unlikely on these grounds.

For reaction with water $\Delta S^\ddagger$ -22.2 cal mol^{-1} K^{-1} is calculated. This value is too negative to be compatible with the mechanism of Scheme 2 since for monomolecular processes values close to zero are generally found.[27,33] This evidence confirms the ^{18}O experiments. The value of $\Delta S^\ddagger$, -22.2 cal mol^{-1} K^{-1}, agrees with the mechanism of Scheme 3 when compared to the value of -38 found for the activation entropy of intermolecular acetate catalysis. A change from an inter- to an intra-molecular reaction corresponds to an increase from 10 to 35 cal mol^{-1} K^{-1}.[30,34]

A similar trend is observed in the hydrolysis of aspirin where the activation entropy is -22.5 for intramolecular base catalysis and -30.7 cal mol^{-1} K^{-1} for intermolecular acetate catalysis.[25]

In conclusion the existence of general base catalysis by oxy-anions, the incorporation of ^{18}O, and the values of activation entropies are all consistent with general base catalysis for intramolecular catalysis by the carboxylate anion. This process makes the most important contribution to hydrolysis of benzoylglycolate anion at pH *ca.* 5.

The effectiveness of intramolecular assistance is indicated by the following. (i) The intramolecular catalytic rate constant at 80 °C is 6.4M times the intermolecular acetate catalysed rate in spite of the higher basicity of latter. (ii) Interpolation on the Brønsted plot of the rate constant for benzoylglycolic acid (pK_a 3.03) shows that an effective concentration of 24.4M of an external anion of that basicity would be required to accomplish the same catalytic effect.

It may be observed that the rather low value of the effective concentration agrees with the 'loose' transition state structure advocated in Scheme 3. Indeed in a 'tight' transition state intramolecular catalysis provides much higher rate enhancements.[35,36]

We are grateful to Professor A. Fava for helpful discussions and to Professor C. Castellari for the least squares CERN computer program.

[6/1975 *Received, 25th October*, 1976]

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