International Journal of Pharmaceutics, 19 (1984) 1–15
Elsevier

IJP 00636

Research Papers

Kinetics of the degradation of methyl, ethyl and *n*-propyl 4-hydroxybenzoate esters in aqueous solution

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(Received January 18th, 1983)
(Modified version received September 23rd, 1983)
(Accepted October 4th, 1983)

Summary

The kinetics of the hydrolysis of methyl, ethyl and *n*-propyl 4-hydroxybenzoate esters and a subsequent decarboxylation of 4-hydroxybenzoic acid have been studied at pH 1.26–10.59 and the sterilizing temperature of 130.5°C. Enthalpies (ΔH^*) and entropies (ΔS^*) of activation are reported for k_{obs} and the derived rate constants. The decarboxylation reaction showed a maximum rate near the mid-pH region where the esters were more susceptible to hydrolysis. The overall pathway for the degradation of the esters was accounted for by a consecutive reaction sequence:

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

where A represents ester, B, 4-hydroxybenzoic acid and C, phenol. Interference with the spectrophotometric assay by the subsequent oxidation of phenol, made necessary the exhaustive de-oxygenation of solutions for the kinetic runs where phenol was formed. The esters were found to be sufficiently stable to withstand a heat sterilization process within the pH range 3–6. The rate of phenol formation by decarboxylation of the acid was greater in the pH range where the esters are frequently used commercially, as preservatives.

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* This work was carried out at the University of Western Australia as part of a Ph.D. requirement.

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Introduction

Several major reviews (Ingold, 1969; Euranto, 1969; Kirby, 1972) discuss the kinetics and mechanism of ester hydrolysis; however, little emphasis has been placed on studies of the pharmaceutically important esters of 4-hydroxybenzoic acid. These esters are also frequently used alone or in combinations as preservatives in cosmetics and foodstuffs (Barkley, 1959; Gottfried 1962; Buchi et al., 1971a and b) and thus a knowledge of their hydrolytic degradation is of significance in achieving proper use. It is particularly important to understand the rate and nature of the degradation processes at the temperatures associated with normal sterilization procedures.

The current literature on the stabilities of these esters is conflicting. Aalto et al. (1953) found no hydrolysis in solutions heated for 2 h at 100°C, or for 0.5 h at 120°C in pHs between 3 and 6, yet Kamada et al. (1973) report degradation of both the methyl and *n*-propyl esters in acidic media between 40 and 100°C. More recently, Blaug and Grant (1974) have found no detectable hydrolysis of the methyl ester below pH 5.49 and of the ethyl, *n*-propyl and *n*-butyl esters below pH 6.41. Raval and Parrott (1967) report hydrolysis of the methyl ester at $pH = 6-9$ and temperatures from 70–85°C. Benmaman and Sorby (1965) have also isolated phenol as a degradation product of the methyl ester which has not been reported previously in kinetic studies.

A number of reviews of the analogous decarboxylation reactions of aliphatic and aromatic carboxylic acids have been published (Brown, 1951; Long, 1968; Clark, 1969). Decarboxylation of 4-hydroxybenzoic acid was first reported by Cazeneuve (1896) whose qualitative data indicated that the acid was stable in alkaline but unstable in acid solutions. The kinetics of the decarboxylation of this substance in solution has not appeared in the literature.

The present study was aimed at producing data on the kinetics of degradation of these esters in aqueous solution at temperatures appropriate to the normal sterilization cycles applied to products containing these esters.

Materials and Methods

Methyl 4-hydroxybenzoate (B.D.H. L.R.), ethyl 4-hydroxybenzoate (B.D.H. L.R.) and *n*-propyl 4-hydroxybenzoate (Aldrich) were each recrystallized 3 times from aqueous ethanol. 4-Hydroxybenzoic acid (Hopkin and Williams G.P.R.) was recrystallized 3 times from distilled water. Phenol (B.D.H. A.R.) was twice recrystallized from light petroleum. Nitrosomethyl urea was prepared by the method of Arndt (1957b); diazomethane by a modification of Arndt's method (1957a), the deep yellow ether layer was used without distillation. Methyl 4-methoxybenzoate was prepared from anisic acid and methanol using boron trifluoride catalyst after Kadaba et al (1969). The material was recrystallized 3 times from hexane. Water was deionized water distilled from an all-glass still. All other materials were A.R. grade.

Two techniques were used to follow rates. For slower reactions the ester solutions (10^{-2} $mol \cdot dm^{-3}$) in the appropriate buffer, at a total ionic strength of 0.5

(maintained by sodium chloride), were placed in borosilicate glass ampoules. The solutions were bubbled with oxygen-free nitrogen saturated with water vapour for at least 18 h to reduce the oxygen concentration to less than 3×10^{-5} mol · dm^{-3} (measured with a Fieldlab Oxygen Analyzer 10080). Each ampoule was sealed under nitrogen and transferred to a thermostat (±0.05°C) containing polyethylene glycol. At appropriate times samples were removed, chilled, and stored in ice for analysis. Faster reactions in sodium hydroxide solutions were followed in a spectrophotometer cell in an electrically heated cell block ($\pm 0.05°$ at $\leq 80°$C; $\pm 0.07°$ at $\leq 100°$C and $> 80°$C).

In the first technique an aliquot from each ampoule was added to sufficient aqueous sodium hydroxide to give a final hydroxide ion concentration > 0.05 mol · dm^{-3}. The absorbance of these solutions was measured at 350–200 nm on a Varian Techtron 635-D UV-VIS Spectrophotometer. The residual percentage of ester was calculated from standardized extinction data. In each run the hydrogen ion concentration was buffered and pseudo-first-order rate constants for the loss of ester at any given pH were determined from this concentration data.

TABLE 1

THE OBSERVED RATE CONSTANTS FOR THE HYDROLYSIS OF NAMED ESTERS OF 4-HYDROXYBENZOIC ACID AT 130.5°C AND I = 0.500 mol·dm^{-3}

Buffer system	pH	k_{obs} (s^{-1})		
		Methyl pK_a = 7.65 ± 0.10	Ethyl pK_a = 7.68 ± 0.10	*n*-Propyl pK_a = 7.75 ± 0.10
Hydrochloric	1.26	2.82×10^{-4}	2.20×10^{-4}	2.10×10^{-4}
acid	2.26	2.65×10^{-5}	2.30×10^{-5}	2.37×10^{-5}
	2.56	1.24×10^{-5}	1.03×10^{-5}	1.02×10^{-5}
Acetate	3.82	6.53×10^{-7} [b,c]	4.66×10^{-7} [b,c]	6.05×10^{-7} [b,c]
	4.31	5.98×10^{-7} [b,c]	3.07×10^{-7} [b,c]	2.63×10^{-7} [b,c]
	4.74	1.13×10^{-6} [b,c]	5.80×10^{-7} [b,c]	3.49×10^{-7} [b,c]
Phosphate	5.89	8.55×10^{-6}	3.08×10^{-6}	2.61×10^{-6}
	6.58	4.31×10^{-5}	1.60×10^{-5}	1.20×10^{-5}
Borate	7.67	3.68×10^{-4}	–	–
Phosphate	7.75	2.55×10^{-4}	1.13×10^{-4}	1.01×10^{-4}
Borate	7.80	–	1.46×10^{-4}	–
	7.93	4.62×10^{-4}	1.67×10^{-4}	1.42×10^{-4}
	8.06	5.55×10^{-4}	–	–
	8.19	5.87×10^{-4}	–	–
	8.31	–	2.92×10^{-4}	2.55×10^{-4}
	8.60	–	3.27×10^{-4}	2.80×10^{-4}
	8.76	1.06×10^{-3}	6.03×10^{-4}	–
	8.79	–	7.83×10^{-4}	6.93×10^{-4}
Sodium	9.59 [a]	2.84×10^{-3}	1.28×10^{-3}	9.68×10^{-4}
hydroxide	10.29 [a]	1.47×10^{-2}	6.09×10^{-3}	4.68×10^{-3}
	10.59 [a]	3.03×10^{-2}	1.26×10^{-2}	9.27×10^{-3}

[a] Rate constants at these pHs extrapolated from runs at lower temperatures.

[b] Rate constants obtained from data collected over 70–88% of reaction.

[c] Rate constants reproducible to less than ±5%.

For runs carried out in the spectrophotometer, pseudo-first-order rate constants were obtained from a comparison of the absorbance values at various times with that after 10 half-lives (99.9%) of reaction.

Except for the very slow reactions, as recorded in the Tables, data were collected over 5 half-lives of reaction in the determination of rate constants.

Activation data (ΔH^* and ΔS^*) were obtained from normal procedures of plotting ln(k/T) vs (1/T) for ΔH^* and ΔS^*. Except where otherwise stated, in the results all rate constants were reproducible to better than ±3%. All data were fitted by a least-squares procedure and all standard errors are quoted for 95% confidence limits.

Routine pH measurements of buffer solutions were carried out using a Radiometer pH-Meter 22, with glass and calomel electrodes. Temperature dependence studies were on a Radiometer pH-Meter PHM42 fitted with a GK2401 combined electrode. The standard pH values of Bates (1962) were used for calibration. Temperature–pH measurements were carried out from 20 to 80°C at 10°C-intervals in a water bath ±0.05°C). pK_a values for all reactants were determined by UV spectrophotometry following the method of Albert and Serjeant (1962). These determinations were made at 25.0, 40.0, 60.0 and 80.0°C. These values were plotted against (1/T) and fitted to the relationship (Harned and Owen, 1958):

$$pK_a = A/T + B \ln T - C$$

for extrapolation to 130.5°C. The more recent relationship of Ramette (1977) was also used. The extrapolated values obtained are found in Table 1.

Results and Discussion

The pH dependence of the hydrolysis reactions of the esters was determined at a temperature of 130.5°C. The pH of standard solutions of hydrochloric acid and sodium hydroxide at 130.5°C and $I = 0.500\ \text{mol} \cdot \text{dm}^{-3}$ were available from density data of Fabus (1965) and the K_w data of Busey and Mesmer (1978).

Initial experiments on the stability of all esters of 4-hydroxybenzoic acid studied, confirmed that products in addition to those of simple hydrolysis were formed and that the other products were derived from a subsequent process. This subsequent reaction was clearly shown in the loss of isosbestic points at 283 and 236 nm in the spectra of the reactant esters and product acid. In addition, at later times a significant new absorption appeared at 235 nm in addition to absorptions at longer wavelengths. These reactions were not reproducible.

Experiments on the stability of 4-hydroxybenzoic acid in the same buffer solutions showed the same product absorbance at 235 nm and were similarly irreproducible. When the 4-hydroxybenzoic acid concentrations were increased to the preparative level, gas–liquid chromatographic analysis confirmed that phenol (which absorbed at 235 nm) was the only substantial product of the acid degradation. Chromatographic procedures involved treatment of reactant solutions and standard mixtures with diazomethane.

Kinetic runs on the degradation of 4-hydroxybenzoic acid were irreproducible unless the reacting solutions were bubbled with oxygen-free nitrogen for 18 h. After this time the oxygen concentration was $< 5 \times 10^{-5}$ mol · dm^{-3} ($< 5\%$ of reactant concentration). Under these conditions spectrophotometric analysis of a 1×10^{-3} mol · dm^{-3} 4-hydroxybenzoic acid solution after 5.16×10^{5} s at 130.5°C showed that 95% of the acid had reacted and that phenol accounted for 93% of acid loss or 98% of the product. The product spectra under these experimental conditions showed an absence of the previously mentioned absorbances at long wavelengths which were consistent with a range of products (hydroquinone, resorcinol, salicylic acid, pyrocatechol and possibly humic acid) which have been reported in the oxidation of phenol under autoclaving conditions (Repkina, 1970).

The degree to which the second reaction of acid degradation interfered with the study of the primary ester hydrolysis depended on the relative rates of the two processes and thus on the pH. Where the subsequent process could be ignored, analysis of the spectra for ester hydrolysis was carried out at 300 nm, maximizing analytical accuracy. Where phenol formation was significant, analysis was on data at 320 nm where neither the acid nor phenol had significant absorption.

A number of runs, in which the rates of the two reactions were comparable, were analyzed for ester concentration at 320 nm, for the acid at the isosbestic point in the phenol and ester spectra at 249 nm, and for phenol at the isosbestic point in acid and ester spectra at 236.5 nm. The data for one of these runs are shown in Fig. 1.

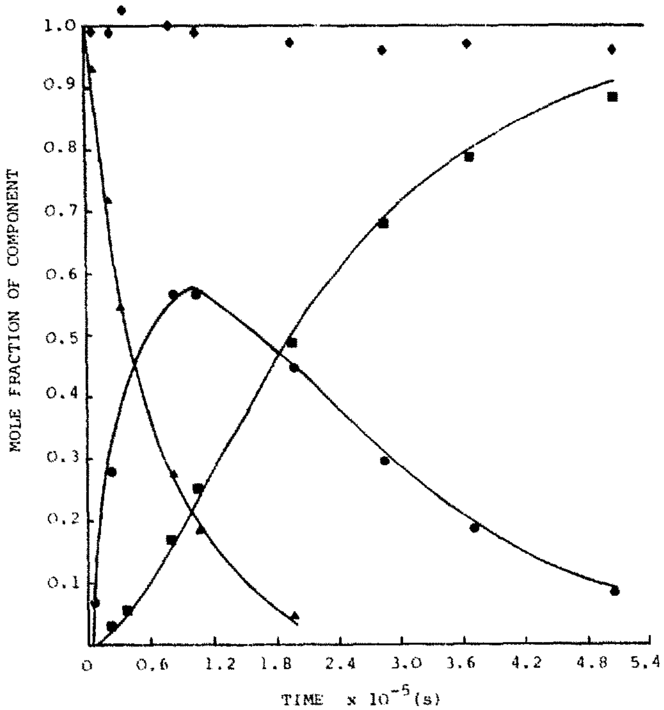

Fig. 1. Plot of mole fractions of: ▲———▲, ethyl 4-hydroxybenzoate; ●———●, 4-hydroxybenzoic acid; and ■———■, phenol obtained from the degradation of ethyl 4-hydroxybenzoate at pH 6.58 and 130.5°C. ◆———◆, sum of the mole fractions.

The lines shown in this figure are derived from the equations:

$$A = A_0 e^{-k_1 t}, \quad B = A_0 k_1 (e^{-k_1 t} - e^{-k_2 t})/(k_2 - k_1), \quad C = A_0 - A - B$$

for the model

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

where A≡ester; B≡4-hydroxybenzoic acid, C≡phenol and k_1 and k_2 (1.60×10^{-5} s^{-1} and 5.50×10^{-6} s^{-1}, respectively) are first-order rate constants. Fig. 1 also shows the sum of the separately determined A, B and C which add up to the initial ester concentration within the experimental error (±4% or ±3 × the experimental error of one concentration determination) at all times.

Hydrolysis of methyl, ethyl and n-propyl 4-hydroxybenzoates

The observed pseudo-first-order rate constants for the hydrolysis of methyl, ethyl and *n*-propyl 4-hydroxybenzoates are presented in Table 1 and consolidated in Fig. 2. The data show 3 distinct regions of linear relationship between k_{obs} and pH with

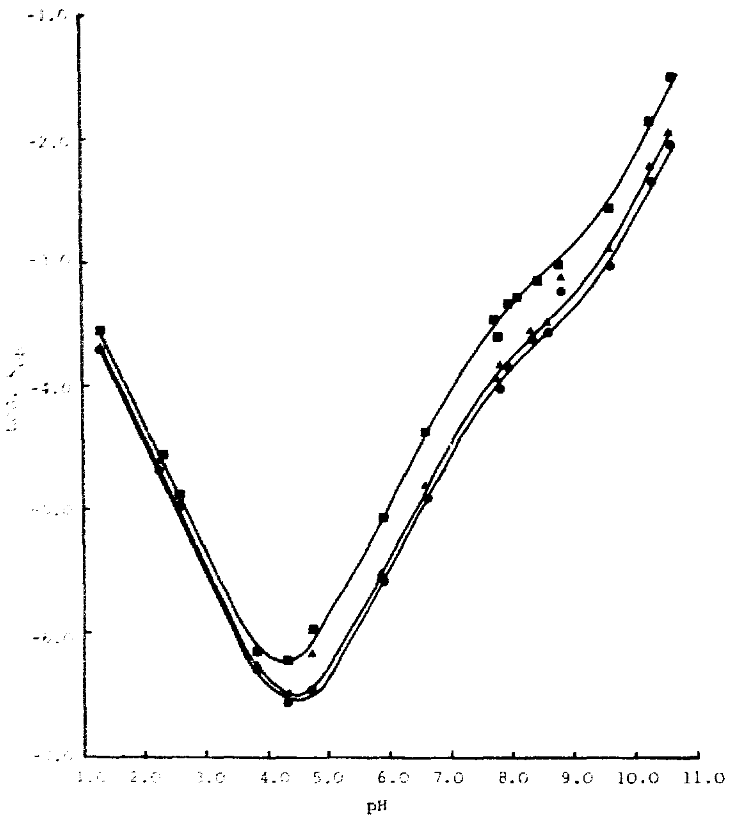

Fig. 2. pH dependence of log k_{obs} for the hydrolysis of: ■———■, methyl; ▲———▲, ethyl; and ●———●, *n*-propyl 4-hydroxybenzoates at 130.5°C.

slopes of -1, $+1$ and $+1$. The section of slope -1 indicates specific H^+ catalysis of ester hydrolysis while the two sections of slope $+1$ indicate two distinct ways in which OH^- catalyzes the hydrolysis; the first being OH^- catalysis of the ester molecule hydrolysis and the second OH^- catalysis of the ester anion reaction. The slightly poorer fit in buffers of high borate ion concentration (pH 8.76) may indicate some specific interference by or complexation of this anion.

These data suggest the following total mechanism for the hydrolysis reaction. In these equations EH = ester, EH_2^+ is the protonated ester and E^- the deprotonated ester, i.e. the ester anion.

$$EH + H_2O \xrightarrow{k_0} \text{Products}$$

$$EH + H^+ \overset{K_b}{\rightleftharpoons} EH_2^+$$

$$EH_2^+ + H_2O \xrightarrow{k_1} \text{Products}$$

$$EH \overset{K_a}{\rightleftharpoons} E^- + H^+$$

$$EH + OH^- \xrightarrow{k_2} \text{Products}$$

$$E^- + OH^- \xrightarrow{k_3} \text{Products}$$

In terms of this mechanism the rate of hydrolysis is given by:

$$\text{Rate} = -\frac{d[\text{total ester}]}{dt} = k_0 c_{EH} + k_1 c_{EH_2^+} + c_{OH^-}(k_2 c_{EH} + k_3 c_{E^-})$$

where the total ester concentration is given by $c_{EH_2^+} + c_{EH} + c_{E^-}$. The observed first-order rate constant for ester loss is given by:

$$k_{obs} = k_0 + k_1 K_b c_{H^+} + \frac{k_2 K_w}{c_{H^+}}\left(\frac{c_{H^+}}{c_{H^+} + K_a}\right) + \frac{k_3 K_w}{c_{H^+}}\left(\frac{K_a}{c_{H^+} + K_a}\right) \quad (1)$$

where K_w and K_a are the ionic product of water and the dissociation constant of the ester on the concentration scale.

This formulation includes simplifications, since at a pH less that 5.0 the rate is dominated by the two terms $k_0 + k_1 K_b c_{H^+}$. These two terms are simplified because only the ester molecule is significant at low pH. Above pH > 5.0 the contribution of these first two terms to the rate becomes insignificant compared to the third and fourth terms. These last two terms are complicated by the presence in significant

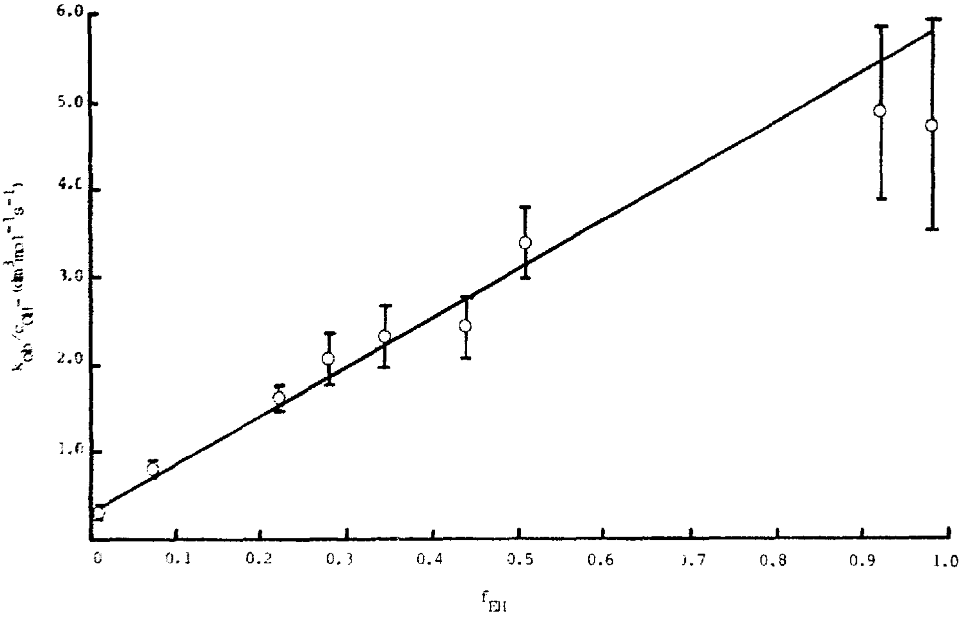

Fig. 3. Plot of k_{obs}/c_{OH} against the fraction of ester molecule of methyl 4-hydroxybenzoate, pH range 5.89–10.29 at 130.5°C.

amounts of both the molecular and anionic forms of the ester. The fractions $c_{H^+}/(c_{H^+} + K_a) = f_{EH}$ and $K_a/(c_{H^+} + K_a) = f_{E^-}$ which appear in the third and fourth terms express the fractions of the ester present as molecule and anion, respectively. These fractions are most important around pH 7.5 because $f_{EH} = f_{E^-}$ when $c_{H^+} = K_a$, at 130.5°C.

The fitting of the log k_{obs} vs pH data (Fig. 2) yields the rate constants recorded in Table 2. An alternative treatment of the results in the pH range 5.89–9.59 in terms

TABLE 2

RATE CONSTANTS FOR THE HYDROLYSIS OF THE NAMED 4-HYDROXYBENZOATE ESTERS AT 130.5°C OBTAINED FROM THE log k_{obs} AND pH DATA[a] AND FROM LINEAR RELATIONSHIPS IN PARENTHESES

Ester	k_0 (s^{-1})	k_1K_b ($dm^6 \cdot mol^{-2} \cdot s^{-1}$)	k_2 ($dm^3 \cdot mol^{-1} \cdot s^{-1}$)	k_3 ($dm^3 \cdot mol^{-1} \cdot s^{-1}$)
Methyl	1×10^{-7}	2.72×10^{-3}	5.90	0.32
		$(2.72 \pm 0.06 \times 10^{-3})$	(5.90 ± 0.60)	(0.29 ± 0.03)
Ethyl	5×10^{-8}	2.28×10^{-3}	1.90	0.12
		$(2.28 \pm 0.04 \times 10^{-3})$	(1.86 ± 0.17)	(0.12 ± 0.01)
n-Propyl	3.5×10^{-8}	2.23×10^{-3}	1.50	0.10
		$(2.23 \pm 0.04 \times 10^{-3})$	(1.50 ± 0.13)	(0.10 ± 0.01)

[a] Data for a_{H^+} have been adjusted to c_{H^+} prior to analysis.

of the second-order rate constant:

$$k_{obs}/c_{OH^-} = \frac{k_{obs}c_{H^+}}{K_w} = (k_2 - k_3)f_{EH} + k_3$$

(Fig. 3) yields the rate constants included in Table 2 which are in acceptable agreement.

Decarboxylation of 4-hydroxybenzoic acid

The pH-dependence of rate constants for the decarboxylation reaction is shown in Fig. 4. The rate is essentially pH-independent below pH 3.82; between pH 3.82 and pH 7.75 the rate increases only to decrease as the pH is further increased. Except for the experiment in 0.1 mol·dm^{-3} NaOH (pH 10.59 at 130.5°C), the reactions were followed for 4–5 half-lives and excellent first-order plots were found for 3–4.5 half-lives. Initially the experiments at high pH gave a white polymeric precipitate which was significantly reduced by the initial addition of 3-*t*-butyl-4-methoxy-phenol. However, addition of this species significantly interfered with the spectrophotometric analysis of the rate experiments.

Exhaustive de-oxygenation (purging with nitrogen passed in turn through BASF catalyst R-311, followed by $CaCl_2$, H_2SO_4, NaOH, $CaCl_2$ and water, followed by solution layering with argon) led to insignificant precipitation and a great improvement in the quality of the analytical results. Under these conditions the amount of phenol produced never differed from the 4-hydroxybenzoic acid lost by more than 2% during the full course of the run. This analysis was carried out at 280 nm (for

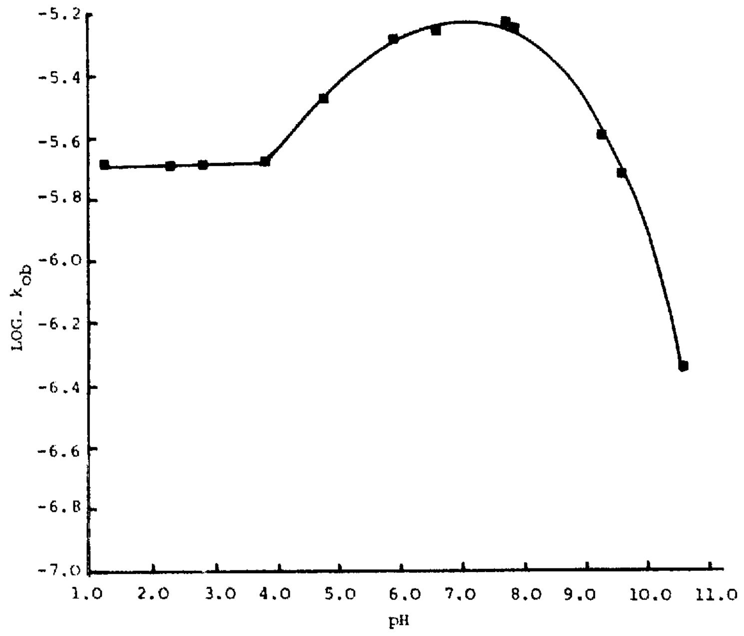

Fig. 4. pH dependence of log k_{obs} for the decarboxylation of 4-hydroxybenzoic acid at 130.5°C.

4-hydroxybenzoic acid) and 235 nm (for phenol) and first-order rate constants calculated from data at these wavelengths agreed within 6%.

Some experiments were attempted in borax buffers, and resulted in the formation of a white precipitate which was shown by flame emission spectrophotometry to contain boron.

The rate of decarboxylation is given by

$$\text{Rate} = -\frac{d[\text{total acid}]}{dt} = k_1 c_{H_2A} + k_2 c_{HA^-} + k_3 c_{A^{2-}}$$

and the experimental first-order rate constants (k_{obs}) were fitted to the relationship

$$k_{obs} = k_1 f_{H_2A} + k_2 f_{HA^-} + k_3 f_{A^{2-}} \tag{2}$$

The fractions of the total acid in each of these forms at any given pH are

$$f_{H_2A} = \left(\frac{1}{1 + K_{a_1} \cdot K_{a_2}/(c_{H^+})^2 + K_{a_2}/c_{H^+}}\right)$$

$$f_{HA^-} = \left(\frac{1}{1 + c_{H^+}/K_{a_1} + K_{a_2}/c_{H^+}}\right)$$

$$f_{A^{2-}} = \left(\frac{1}{1 + (c_{H^+})^2/K_{a_1} \cdot K_{a_2} + c_{H^+}/K_{a_2}}\right),$$

and k_1, k_2 and k_3 are the rate constants shown in the following mechanism for the decarboxylation of the 4-hydroxybenzoic acid (H_2A), and K_{a_1} and K_{a_2} are the successive proton dissociation constants of H_2A.

$$H_2A \xrightarrow{k_1} \text{Products}$$

$$H_2A \overset{K_{a_1}}{\rightleftharpoons} HA^- + H^+$$

$$HA^- \xrightarrow{k_2} \text{Products}$$

$$HA^- \overset{K_{a_2}}{\rightleftharpoons} A^{2-} + H^+$$

$$A^{2-} \xrightarrow{k_3} \text{Products}$$

The calculated values of k_1, k_2 and k_3 at 130.5°C are 1.94×10^{-6} s^{-1}, 5.81×10^{-6}

s^{-1} and 3.00×10^{-7} s^{-1}, respectively, based on $pK_{a_1} = 4.67$ and $pK_{a_2} = 8.84$ at 130.5°C, determined from the experimental values measured at 25, 40, 60 and 80°C. The experimental data closely obeyed the calculated rate constants, over the whole pH range studied.

The simple nature of the dependence of the rate on pH and in particular the constancy of k_2 over such a wide range of pH suggests that rate variation lies only with the state of ionization of the 4-hydroxybenzoic acid and further suggests that a unimolecular heterolytic fission of the C–C bond is the likely mechanism.

Activation parameters

Activation parameters recorded in Table 3 for the hydrolyses of the 3 esters were determined from the temperature-dependence of k_{obs} (Eqn. 1). At pH ~ 1.26 virtually 100% of the reaction occurs through the acid-catalyzed path and thus the values of enthalpies and entropies of activation are combined functions which relate to the temperature-dependence of the product k_1K_b the terms of which cannot be resolved. At pH ~ 6.58 greater than 97% of the reaction occurs through hydroxide ion attack on the ester molecule and the activation parameters are determined from the temperature-dependence of the third term in the rate law which is a complex function:

$$\left(\frac{k_2 K_w}{c_{H^+} + K_a}\right)$$

The temperature-dependence at pH 10.59 is determined by the complex function:

$$\frac{k_3 K_w}{c_{H^+}}\left(\frac{K_a}{c_{H^+} + K_a}\right)$$

since more than 99% of the reaction occurs through hydroxide ion attack on the ester anion. Our separate studies of the temperature-dependence of c_{H^+} and K_a have allowed the resolution of the combined parameters $\Delta H_1^* + \Delta H_b^0$, and $\Delta S_1^* + \Delta S_b^0$ and the separated activation parameters ΔH_2^*, ΔH_3^*, ΔS_2^* and ΔS_3^*, by plotting the functions in the following forms:

$$\ln \frac{k_{obs}}{Tc_{H^+}} = \ln \frac{k}{h} + \frac{\Delta S_1^* + \Delta S_b^0}{R} - \frac{\Delta H_1^* + \Delta H_b^0}{RT} \qquad (3)$$

for pH ~ 1.26,

$$\ln \frac{k_{obs}}{TK_w} \cdot (c_{H^+} + K_a) = \ln \frac{k}{h} + \frac{\Delta S_2^*}{R} - \frac{\Delta H_2^*}{RT} \qquad (4)$$

for pH ~ 6.58 and ~ 8.31, and for pH ~ 10.59

$$\ln \frac{k_{obs} \cdot c_{H^+}}{TK_w} \cdot \frac{a_{H^+} + K_a}{K_a} = \ln \frac{k}{h} + \frac{\Delta S_3^*}{R} - \frac{\Delta H_3^*}{RT} \qquad (5)$$

TABLE 3

ACTIVATION PARAMETERS OF EACH REACTANT IN AQUEOUS BUFFER OF I = 0.500 mol·dm^{-3}

($\Delta H^* = $ kJ·mol^{-1}; $\Delta S^* = $ JK^{-1}·mol^{-1})

Reactant	Temperature range (°C)	pH (approx.)	k_{obs}		$k_1 k_b$		k_2		k_3	
			ΔH^*	ΔS^*	$(\Delta H_1^* + \Delta H_b^0)$	$(\Delta S_1^* + \Delta S_b^0)$	ΔH_2^*	ΔS_2^*	ΔH_3^*	ΔS_3^*
Methyl ester	119.8–139.9	1.26	90.3 ± 4	−92 ± 12	91.2 ± 5	−70 ± 12				
	119.9–139.2	6.58	95.2 ± 3	−94 ± 8			44.6 ± 3	−123 ± 8		
	105.1–139.9	8.10	88.2 ± 4	−91 ± 12			47.4 ± 3	−115 ± 7		
	70.0– 96.0	0.0100 mol·dm^{-3} NaOH	52.8 ± 2	−165 ± 5					52.5 ± 4	−127 ± 11
	50.0– 64.1	0.1000 mol·dm^{-3} NaOH	56.7 ± 3	−134 ± 8					53.2 ± 2	−126 ± 5
Ethyl ester	119.9–139.2	6.58	94.0 ± 3	−106 ± 8			43.8 ± 3	−133 ± 8		
	105.3–139.5	8.31	88.3 ± 3	−96 ± 8			43.5 ± 3	−130 ± 7		
	73.0– 94.0	0.0100 mol·dm^{-3} NaOH	56.7 ± 2	−162 ± 5					54.7 ± 2	−129 ± 6
	60.0– 80.0	0.1000 mol·dm^{-3} NaOH	49.4 ± 3	−163 ± 8					52.3 ± 3	−135 ± 8
n-Propyl ester	119.9–139.2	1.26	90.5 ± 5	−93 ± 12	92.0 ± 5	−70 ± 12				
	119.9–139.2	6.58	97.9 ± 2	−97 ± 6			47.8 ± 2	−124 ± 5		
	110.2–139.1	8.31	82.0 ± 3	−120 ± 6			41.5 ± 4	−137 ± 11		
	73.0– 94.0	0.0100 mol·dm^{-3} NaOH	47.5 ± 4	−189 ± 11					48.8 ± 4	−148 ± 11
	60.0– 84.6	0.1000 mol·dm^{-3} NaOH	49.1 ± 4	−166 ± 13					54.4 ± 2	−140 ± 5
4-Hydroxy-benzoic acid	119.8–140.2	1.26	116.8 ± 4	−67 ± 12						
	119.9–139.2	6.58	110.4 ± 4	−74 ± 12			109.7 ± 2	−76 ± 3		

where k = Boltzmann's constant and h = Planck's constant.

Activation parameters for the decarboxylation of 4-hydroxybenzoic acid have been determined at pH 1.26 and pH 6.58. At a pH = 1.26, k_{obs} (Eqn. 2) is k_1 because $f_{HA} = 1.00$ and the second and third terms are negligible. The temperature-dependence of k_{obs} gives ΔH_1^* and ΔS_1^* directly. At a pH of 6.58 the f_{HA^-} is at least 99% of k_{obs}. Under these conditions a plot of ln k_{obs}/Tf_{HA^-} leads directly to ΔH_2^* and ΔS_2^*.

The combined $\Delta H_1^* + \Delta H_h^0$ parameters for ester hydrolysis at pH ~ 1.26 are higher than the ΔH^* of 82 and 84 $kJ \cdot mol^{-1}$ for the ethyl ester in 60% ethanol–water and 60% acetone–water, respectively, found by Timm and Hinshelwood (1938). Values of 83 and 81 $kJ \cdot mol^{-1}$ for the methyl and *n*-propyl esters in 0.1 $mol \cdot dm^{-3}$ HCl were calculated from the data of Kamada et al. (1973) and are for the temperature-dependence of k_{obs}. With our data it is the separation of c_{H^+} from the effect of temperature on k_{obs} that gives rise to these higher values associated only with $\Delta H_1^* + \Delta H_h^0$. The $\Delta S_1^* + \Delta S_h^0$ values of $-70\ JK^{-1} \cdot mol^{-1}$ are lower than those calculated directly from the k_{obs} data of Kamada et al. (1973); however, both values are higher than that found by Timm and Hinshelwood (1938) of $-107\ JK^{-1} \cdot mol^{-1}$ for the ethyl ester in 60% ethanol–water. The ΔS_h^0 term is probably positive indicating a lower ΔS_1^* value for the rate-limiting step. It is also well-known that different solvents can have significant effects on both ΔH^* and ΔS^* (Amis and Hinton, 1973).

The value of ΔH_2^* for hydroxide ion attack is lower than for the acid-catalyzed path where water is the nucleophile. For the hydroxide ion attack on the ester molecule the activation parameters at both pH ~ 6.58 and ~ 8.31 are in agreement with the activation energies reported by Blaug and Grant (1974) at pH 9.16 where more of the total reaction is through the ester anion pathway. The ΔH_2^* values are generally lower than those reported in aqueous buffers for other benzoic acid esters in aqueous alkali, 60% acetone–water, or 85% ethanol–water. The overall electronic effect of the 4-OH group on the reaction site would be electron donation. Tommila and co-workers (1959) found a ΔH^* for the unsubstituted ethyl benzoate in water of 50.5 $kJ \cdot mol^{-1}$. The 4-OH substituent would be predicted to give a ΔH_2^* slightly above this value. We have found that ΔS_2^* for the 4-OH esters is lower than reported for the unsubstituted ester, this may indicate that the slower rate in the case of the 4-OH substituent is reflected by ΔS_2^*.

Hydroxide ion attack on ester anion is influenced by the 4-O^- substituent which more powerfully donates electrons to the reaction site than 4-OH since both inductive and electromeric effects donate. This results in a slower rate of nucleophilic attack; ΔH_3^* greater than ΔH_2^*. The ΔH_3^* and ΔS_3^* parameters for the esters in this study compare favourably with those found by Tommila and co-workers (1959) for the ionized ethyl 4-hydroxybenzoate ester.

The ΔH_1^* and ΔH_2^* values obtained for the decarboxylation of 4-hydroxybenzoic acid are similar to those found for a number of other substituted benzoic acids in water. The ΔS_1^* value is not sufficiently negative to be associated with a bimolecular reaction and gives support to the unimolecular cleavage of the C–C bond as the likely mechanism. The increased rate of decarboxylation of the anion could be reflected in the marginal lowering of ΔH^* and ΔS^*. Such small changes could not be interpreted as a change in mechanism and provides further evidence for unimolecular cleavage. A compilation of ΔS^* values by Willi (1977) shows considerable overlap in the values obtained from uni- and bimolecular reactions.

The results show that the times taken for a 10% loss of the initial methyl ester concentration at 130.5°C and pHs of 10.59, 8.9 and 6.58 are approximately 4 s, 3 min and 40 min, respectively. This ester is therefore unable to adequately withstand a normal sterilization procedure unless the solution is within a pH range of 3–6 at the sterilization temperature. The other esters show slightly greater stabilities. Decarboxylation of the 4-hydroxybenzoic acid is significant and the rate of phenol production is higher at pHs where the use of these esters is recommended (Wedderburn, 1964). Phenol has a higher toxicity (Gosselin et al., 1977) and is not recommended as an antimicrobial additive to foodstuffs (WHO, 1974). The increased susceptibility of the esters to hydrolysis at alkaline pH may not therefore be widely appreciated.

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