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Alkaline ethanolysis of methyl 4-hydroxybenzoate and hydrolysis of methyl and ethyl 4-hydroxybenzoates in ethanol–water systems

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Summary

Kinetics of the simultaneous hydrolysis and ethanolysis of methyl 4-hydroxybenzoate were studied in 0.5 mol dm^{-3} alkali in ethanol-water mixtures. Rates of hydrolysis of the ethyl ester, an intermediate product, were also evaluated in these solvent systems. Kinetics of the ethanolysis of the methyl ester were further studied in ethanol in the presence and absence of 0.5 mol dm^{-3} alkali. Rates of the aqueous hydrolysis reactions of both esters were also studied in 0.5 mol dm^{-3} alkali. Approximately a 100-fold reduction in the rate of hydrolysis of the methyl ester in 82.43% w/w ethanol occurred compared with water. The majority of this effect was over the solvent range from water to 50% w/w ethanol. Rate changes with solvent composition for ethanolysis of methyl ester were dominated by changes in the ΔH^* values. Larger changes in ΔH^* and ΔS^* values were exhibited for the hydrolysis reactions. These values were, however, compensatory on the reaction rate, a maximum in this compensation occurring at $\cong$ 10% w/w of ethanol. Hence addition of ethanol to an alkaline aqueous solution of methyl 4-hydroxybenzoate resulted in a markedly reduced rate of hydrolysis, and formation of the ethyl ester over the temperature range 25.0–46.1°C studied. This ester subsequently underwent a slower hydrolysis reaction when compared with the methyl ester.

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Introduction

The influence of protic and aprotic solvents on the rate of ester hydrolysis has been discussed in several reviews (Tommila, 1967; Parker, 1969; Engberts, 1979). Protic solvents such as methanol and ethanol, were often added to systems used in hydrolytic studies to increase solubility of the ester. Both of these solvents react with hydroxide ion to produce an alkoxide ion according to the following reaction:

$$OH \ + ROH \rightleftharpoons RO \ + H_2O \qquad (1)$$

This equilibrium reaction has not always been taken into account in studies on the alkaline hydrolysis of esters (Murto, 1971). Addition of monohydric alcohols to water decreases its polarity and dielectric constant. The addition of ethanol has been found to markedly reduce the rate of ethyl benzoate hydrolysis compared with water (Tommila and Savolainen, 1967). This reduced reactivity has been attributed to resonance stabilization in the ground state (Westheimer and Metcalf, 1941).

Laidler and Landskroener (1956) have related the logarithm of the rate constant of such reactions to the reciprocal of the dielectric constant of the medium. Other theories concerned with ion-dipolar molecule interactions (Scatchard, 1932) produce similar relationships. Although some reasonable linear relationships have been reported, they are usually of the opposite slope to that predicted when charge is dispersed in the transition state. This outcome has been rationalized in terms of a transition state that involves a molecule of water to explain the decreased rate as water concentration is decreased (Laidler and Landskroener, 1956). The structural changes that take place on the addition of alcohol to water have been summarized (Arnett et al., 1965). The reaction is exothermic in the high water range, indicative of hydrogen bonding of the solvent or the loss of liberational freedom. In this region the partial molal volume of ethanol and other alcohols goes through a minimum and there is also ultrasonic evidence for increased structure. Extremes in ΔS^* values have been attributed to greatly different solvation characteristics of initial and transition states, as a result of the operation of different mechanisms for interaction with the solvent (Engberts, 1979). The overall behaviour of ΔH^* and ΔS^* is usually in a compensatory manner so as to minimize changes in rate with solvent composition.

Methyl and ethyl 4-hydroxybenzoates are used in the preservation of foods, drugs, cosmetics and beverages. They are often referred to as methyl and ethyl parabens. The increasing use of solvent mixtures in the formulation of pharmaceuticals requires that the influence of these solvents on the stability of such preservatives be better understood. This study expands the understanding of the alkaline degradation of these preservatives in ethanol-water solvent systems.

Materials and Methods

Methyl 4-hydroxybenzoate, ethyl 4-hydroxybenzoate, *n*-propyl 4-hydroxybenzoate and 4-hydroxybenzoic acid were prepared as previously described (Sunderland

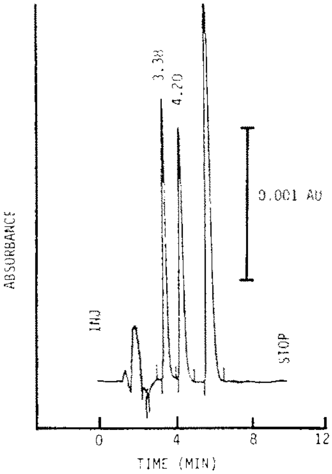


Fig. 1. Data from the HPLC analysis of methyl 4-hydroxybenzoate 2.45×10^{-5} mol dm^{-3} (retention time: 3.38 min) and ethyl 4-hydroxybenzoate 2.55×10^{-5} mol dm^{-3} (retention time: 4.20 min) at 254 nm; *n*-propyl 4-hydroxybenzoate as internal standard 5×10^{-5} mol dm^{-3} (retention time: 5.57 min).

and Watts, 1984). 'Super-dry' ethanol was prepared by a modification of the method of Vogel (1956), and stored under high purity nitrogen and over molecular sieves. Sodium ethoxide was prepared by the addition of clean freshly cut sodium to super-dry ethanol under a stream of high purity nitrogen. Deionized water was distilled from an all-glass still. All other materials were A.R. grade. Kinetic runs in ethanol, or ethanol-water, involved a sampling procedure. Solutions of methyl 4-hydroxybenzoate and alkali were thermostated separately in a water-bath (± 0.05°C). These solutions were then rapidly mixed to give ester and alkali concentrations of 1×10^{-3} mol dm^{-3} and 0.500 mol dm^{-3} respectively. Samples were pipetted at appropriate time intervals into sufficient acetic acid to just quench the reaction. Runs using 'super-dry' ethanol had all operations and samplings performed under dry nitrogen.

The quenched solutions were immediately diluted in ethanol and analyzed by high-performance liquid chromatography (HPLC) using *n*-propyl 4-hydroxybenzoate (5×10^{-5} mol dm^{-3}) as internal standard. A μ-Bondpak C-18 column (Waters Associates) was used with a solvent of 46% acetonitrile-water at a flow rate of 1.5 ml min^{-1} with UV detection at 254 nm. Integrated peak areas were obtained with complete base-line separation and the concentration of each ester was determined relative to the internal standard. Reproducibility was better than $\pm 1\%$ and peak area linearity was confirmed over the concentration range used. A typical analysis trace is shown in Fig. 1.

Methyl 4-hydroxybenzoate (1×10^{-3} mol dm^{-3}) solutions in anhydrous ethanol were also studied without alkali addition. These involved a sampling technique where all manipulations were carried out, and the hard borosilicate glass ampoules used were filled and sealed under high purity dry nitrogen. The ampoules were enclosed in stainless-steel 'bombs' prior to heating in a thermostat (±0.05°C) containing polyethylene glycol. The above HPLC analysis was used without prior quenching.

Aqueous runs were followed directly by UV spectrophotometry and each spectrum was compared with that obtained after $> 10\ t_{1/2}$ of reaction as described previously (Sunderland and Watts, 1984). Data for the dielectric constants of the solvents were interpolated from linear relationships obtained from the data of Akerlof (1932).

Activation data (ΔH^* and ΔS^*) were obtained from normal procedures of plotting ln(k/T) vs I/T for ΔH^* and ΔS^*. ΔG^* was calculated at 298.15 K, by standard thermodynamic methods. Usually four temperatures were employed within the range 25.0–46.1°C. All data were fitted by a least squares procedure and all errors are quoted for 95% confidence limits.

Results and discussion

The nature of the reactions of methyl and ethyl 4-hydroxybenzoates in 0.500 mol dm^{-3} alkali depends upon the solvent. In water, only hydrolysis occurs, whereas in ethanol, ethanolysis is the sole route. In ethanol-water admixtures, both ethanolysis and hydrolysis reactions occur simultaneously. Ethanolysis of the ethyl ester can only be detected by appropriate isotopic labelling. This reaction does not result in any change of ethyl ester concentration and is therefore not considered further in this study. The methyl and ethyl esters in these media exist with the 4-OH group deprotonated, to give 4-carbomethoxyphenolate and 4-carboethoxyphenolate ions respectively.

The significant reaction pathways can be described as follows:

(i) Ethanol

$$\mathrm{ME} \xrightarrow{k_1} \mathrm{EE} + \mathrm{MeO}^- \tag{2}$$

where ME and EE represent the methyl and ethyl esters in the deprotonated forms referred to above, and MeO^- is methoxide ion, and k_1 the rate constant. From 2:

$$-\frac{dc_{ME}}{dt} = k_1 c_{ME} \tag{3}$$

where c is concentration of methyl ester and t is time.

(ii) Water

$$\mathrm{ME} \xrightarrow{k_2} \mathrm{acid} + \mathrm{MeOH} \tag{4}$$

$$\mathrm{EE} \xrightarrow{k_3} \mathrm{acid} + \mathrm{EtOH} \tag{5}$$

where acid is the twice deprotonated form of 4-hydroxybenzoic acid and MeOH and EtOH are methanol and ethanol respectively. The reversible reactions of eqns. 2, 4 and 5 are assumed to be negligible as discussed later.

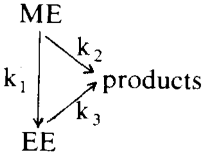
Hence from Eqns. 4 and 5:

$$-\frac{dc_{ME}}{dt} = k_2 c_{ME} \tag{6}$$

and

$$-\frac{dc_{EE}}{dt} = k_3 c_{EE} \tag{7}$$

(iii) Ethanol-water mixtures



(8)

From Eqn. 8:

$$-\frac{dc_{ME}}{dt} = (k_1 + k_2)c_{ME} \tag{9}$$

and

$$-\frac{dc_{EE}}{dt} = k_3 c_{EE} - k_1 c_{ME} \tag{10}$$

Integration of Eqn. 9 gives:

$$c_{ME} = c_{ME_0}\, e^{-(k_1+k_2)t} \tag{11}$$

where c_{ME_0} is the initial concentration. Treatment of the ethyl ester concentration by the secular equation method of Frost and Pearson (1961) gives:

$$c_{EE} = \frac{c_{ME_0} k_1 (e^{-(k_1+k_2)t} - e^{-k_3 t})}{k_3 - k_2 - k_1} \tag{12}$$

Data for the formation and loss of ethyl ester from HPLC measurements were treated using a non-linear, least squares iterative programme with respect to Eqn. 12. The programme minimized the standard deviation of the data, according to this model, to separately solve for k_1, k_2 and k_3 as first-order rate constants. Data (Table 1) obtained by this method gave rate constants within ±3% for k_3, ±5% for

TABLE 1

RATE DATA FOR THE ALKALINE DEGRADATION OF METHYL 4-HYDROXYBENZOATE IN WATER, ETHANOL-WATER MIXTURES AND ETHANOL, AND ETHYL 4-HYDROXYBENZOATE IN WATER AND ALSO THAT FORMED IN SITU IN ETHANOL-WATER MIXTURES

Solvent system	Temperature (°C)	$k_1(s^{-1})$	$k_2(s^{-1})$	$k_3(s^{-1})$
Water	25.0		4.41×10^{-4}	2.18×10^{-4}
	28.0		5.50×10^{-4}	
	32.0			3.68×10^{-4}
	32.3		7.45×10^{-4}	
	36.5		1.03×10^{-3}	
	39.2		1.25×10^{-3}	
	40.0			6.50×10^{-4}
	46.0			9.45×10^{-4}
9.62% w/w Ethanol	24.9	5.97×10^{-5}	3.07×10^{-4}	1.19×10^{-4}
$(\chi_{H_2O} = 0.959)$	31.9	9.87×10^{-5}	4.67×10^{-4}	1.70×10^{-4}
	40.1	1.37×10^{-4}	8.28×10^{-4}	3.00×10^{-4}
27.76% w/w Ethanol	25.0	4.35×10^{-5}	5.15×10^{-5}	2.25×10^{-5}
$(\chi_{H_2O} = 0.866)$	32.0	6.62×10^{-5}	9.82×10^{-5}	3.87×10^{-5}
	39.9	1.11×10^{-4}	2.03×10^{-4}	6.72×10^{-5}
52.64% w/w Ethanol	25.0	1.73×10^{-5}	8.18×10^{-6}	3.97×10^{-6}
$(\chi_{H_2O} = 0.687)$	31.9	2.87×10^{-5}	1.78×10^{-5}	7.57×10^{-5}
	40.0	5.17×10^{-5}	4.68×10^{-5}	1.61×10^{-5}
	46.1	7.38×10^{-5}	8.05×10^{-5}	2.78×10^{-5}
74.66% w/w Ethanol	25.0	1.34×10^{-5}	3.32×10^{-6}	1.61×10^{-6}
$(\chi_{H_2O} = 0.441)$	31.9	2.65×10^{-5}	8.17×10^{-6}	3.02×10^{-6}
	40.0	4.93×10^{-5}	1.68×10^{-5}	7.07×10^{-6}
	46.1	7.77×10^{-5}	3.37×10^{-5}	1.26×10^{-5}
83.43% w/w Ethanol	25.1	1.48×10^{-5}	2.02×10^{-6}	1.01×10^{-6}
$(\chi_{H_2O} = 0.321)$	32.0	2.73×10^{-5}	5.02×10^{-6}	2.17×10^{-6}
	40.0	5.37×10^{-5}	1.35×10^{-5}	4.60×10^{-6}
	46.0	8.58×10^{-5}	2.20×10^{-5}	8.98×10^{-6}
Ethanol	25.0	1.78×10^{-5}		
	30.5	3.16×10^{-5}		
	36.5	5.45×10^{-5}		
	40.0	7.40×10^{-5}		
	42.4	9.65×10^{-5}		

k_1 and ±10% for k_2 for the reaction scheme described by Eqn. 8. In the simpler systems (Eqns. 2, 4 and 5), rate constants were reproducible at better than ±3% (Table 1).

Typical data obtained from the HPLC assay in the ethanol-water systems (Eqn. 8) are found in Fig. 2, which shows the loss of methyl ester described by Eqn. 9; the formation and hydrolysis of the ethyl ester according to Eqn. 12; both of which are described by the lines on the figure, the points being experimental data. The analysis of the data was by application of Eqn. 12 to the ethyl ester data. Other methods of analysis were also applied to the systems. These included a bi-exponential non-linear parameter analysis of the combined Eqns. 10 and 11 for $(k_1 + k_2)$ and k_3 which can also be estimated from the linear terminal portion of the ethyl ester data. Rate

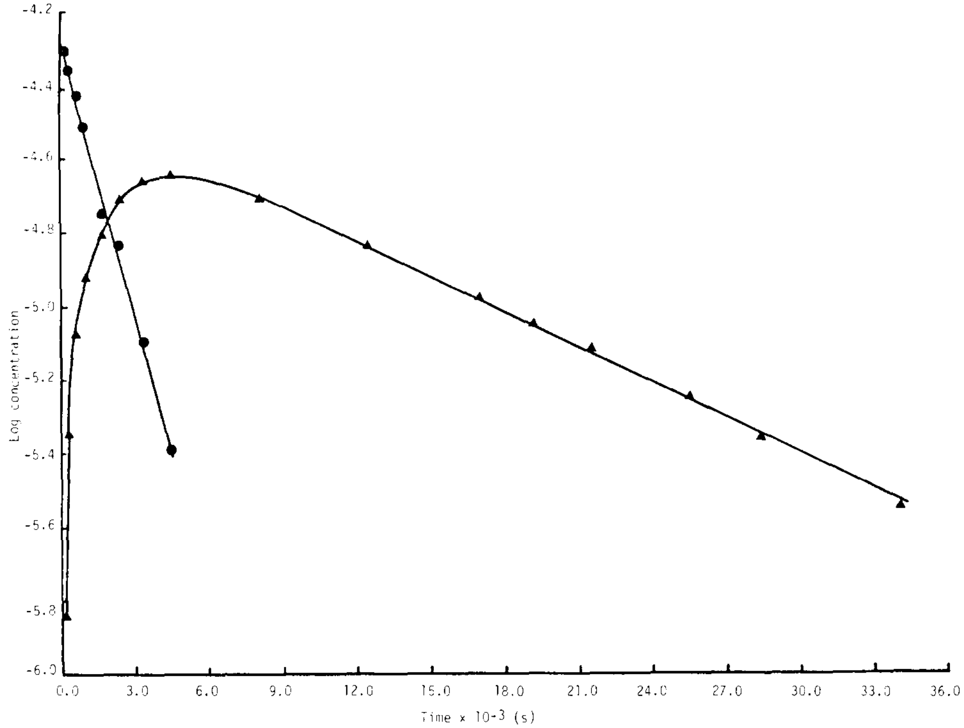


Fig. 2. Hydrolysis and ethanolysis of methyl 4-hydroxybenzoate (●———●) and hence formation and hydrolysis of ethyl 4-hydroxybenzoate (▲———▲) in 52.64% w/w ethanol-water and 0.500 mol dm^{-3} alkali at 31.9°C.

constants well within the experimental errors quoted were obtained from these methods. Some runs were also carried out with methyl 4-hydroxybenzoate in anhydrous ethanol, without alkali addition. A slow ethanolysis reaction resulted. For example, at 120.2°C this reaction was found to have a rate constant of 3.7×10^{-7} s^{-1} ($t_{\frac{1}{2}} \cong 531$ h). Furthermore, no 4-hydroxybenzoic acid could be detected by UV spectrophotometry in any sample, the reaction being followed to approximately 30% completion. These data would appear to exclude any reaction involving a bimolecular basic hydrolysis with alkyl-oxygen fission (BA12) (Ingold, 1969) since 4-hydroxybenzoic acid and methylethyl ether would be the expected products of this reaction.

Second-order rate constants

First-order rate constants are only comparable in this study under constant hydroxide ion or ethoxide ion concentrations (Eqns. 2, 4 and 5), i.e. when either ethanol or water is the solvent. In the first case alkali is in large excess as ethoxide ion and in the latter two, as hydroxide ion. In ethanol-water admixtures (Eqn. 8) the addition of alkali gives rise to the equilibrium reaction:

$$EtOH + OH^- \rightleftharpoons EtO^- + H_2O \qquad (13)$$

involving a proton transfer, which in the time scale of the reactions being studied is instantaneous. This reaction, however, provides pseudo-first-order conditions for both the hydrolysis and ethanolysis reactions when total alkali concentration is in large excess compared with the ester concentration.

The thermodynamic equilibrium constant for Eqn. 13 is:

$$K = \frac{a_{H_2O} \cdot a_{EtO^-}}{a_{EtOH} \cdot a_{OH}} = \frac{a_{H_2O}}{a_{EtOH}} \cdot \frac{c_{EtO^-} \cdot y_{EtO}}{c_{OH} \cdot y_{OH}} \tag{14}$$

where a_{H_2O} and a_{EtOH} are the activities of water and ethanol with respect to pure liquids as standard states, and the activity coefficients y_{EtO} and y_{OH} are unity in infinitely dilute solutions in pure water. This equilibrium has been studied by Caldin and Long (1954). The most practically useful expression of this reaction (Murto, 1971) is:

$$K^1 = \frac{c_{H_2O} \cdot c_{EtO^-}}{c_{EtOH} \cdot c_{OH^-}} = \frac{\chi_{H_2O} \cdot c_{EtO}}{\chi_{EtOH} \cdot c_{OH}} \tag{15}$$

where χ is the mole fraction of substance. In this formulation K^1 has been shown to vary less (Murto, 1971) than does K with solvent composition. Murto (1971) reported the enthalpy of this equilibrium reaction as -14.6 kJmol^{-1}. Values of K^1 in Table 2 were calculated from the data of Caldin and Long (1954) and Murto (1962) with an order of accuracy of ±15%.

The concentrations of hydroxide and ethoxide ions can then be calculated from the mole fractions of ethanol and water present in the solvent admixtures. These have included the effects of increased water produced by hydroxide ion addition according to Eqn. 13. These data permit the rate constants determined under pseudo-first-order conditions (Table 1) to be converted to second-order constants. An example of the influence of solvent on the rate of the reactions studied at 25°C is

TABLE 2

VALUES OF THE EQUILIBRIUM CONSTANT (K^1) FOR ETHOXIDE ION FORMATION

Calculated from the data of Caldin and Long (1954) and Murto (1962).

Temperature (°C)	K^1
24.9	0.65
25.0	0.65
25.1	0.65
31.9	0.57
32.0	0.57
40.0	0.49
40.1	0.49
46.0	0.44
46.1	0.44

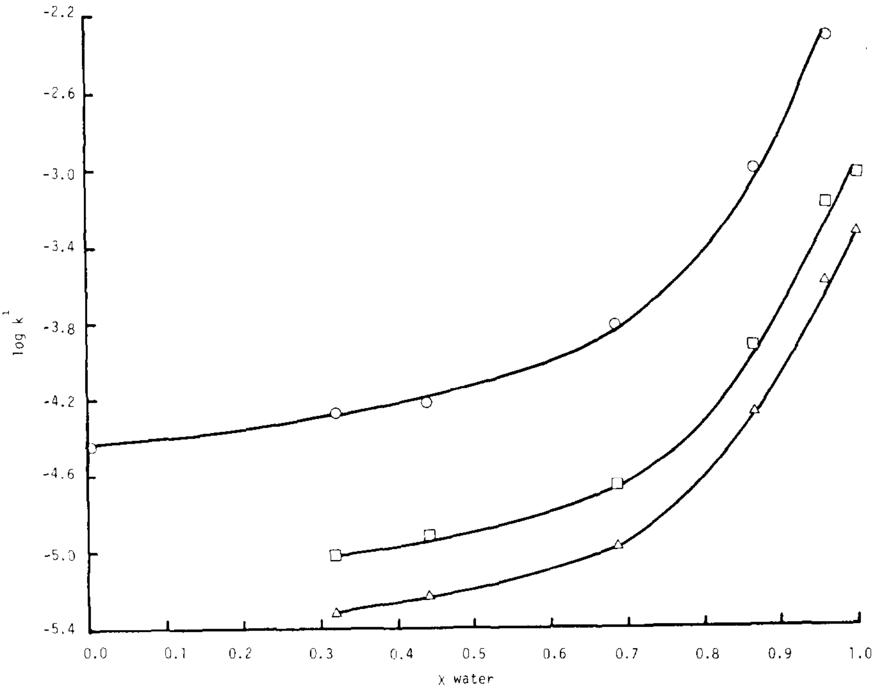
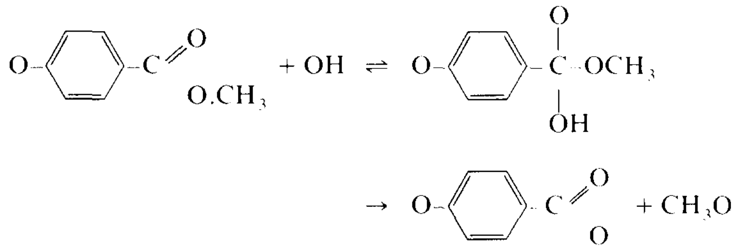


Fig. 3. Effect of solvent composition on the rate of ethanolysis (○———○) and hydrolysis (□———□) of methyl 4-hydroxybenzoate and the hydrolysis (△———△) of ethyl 4-hydroxybenzoate in ethanol-water systems and 0.500 mol dm^{-3} alkali at 25°C.

found in Fig. 3. Values at the other temperatures studied can be calculated using data in Tables 1 and 2. Approximately 100-fold changes in rate occurred for both the ethanolysis and hydrolysis reactions over the solvent compositions studied. Comparisons of rate constants with variation in solvent composition are only valid using second-order rate constants owing to the equilibrium reaction (Eqn. 13). This causes a variation in hydroxide and ethoxide ion concentrations with both temperature and solvent composition, favouring hydroxide ion formation at higher water concentrations.

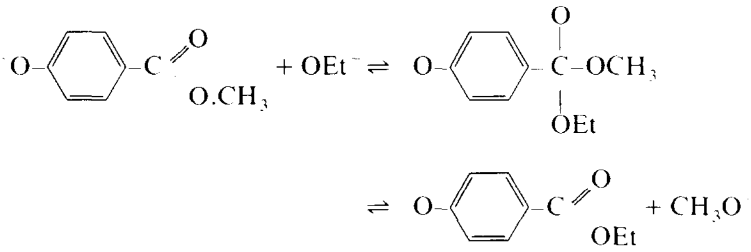
In all solvent admixtures studied, ethanolysis of the methyl ester was faster than its hydrolysis, the difference being reduced when water became a minor component in the solvent. The basicity of the nucleophile is the dominant factor governing the relative reactivities of hydroxide and ethoxide ions when the electrophilic centre of the substrate is carbon of a carbonyl group (Duboc, 1978), i.e., a hard Lewis Acid (Pearson, 1968). Both hydroxide and ethoxide ions are classified as hard Lewis Bases (Pearson, 1968). Thus the rate effects correlate with the greater basicity of ethanol compared with water. In the ethanol water admixtures, two reactions occur together:

hydrolysis:



(16)

and ethanolysis



(17)

The hydrolysis reaction is essentially irreversible; however, transesterification (Eqn. 17) is reversible and the position of the equilibrium depends on the relative concentrations and nucleophilic abilities of ethoxide and methoxide ions. In these studies, since the concentration of methoxide ion is always extremely low compared with ethoxide ion, the reverse reaction can be neglected.

A number of models have been proposed to describe the rate constant as a function of the dielectric constant of solvent. In alkaline ester hydrolysis the rate-controlling step would be that between a negatively charged ion (OH^-) and a dipolar molecule. The Laidler–Eyring Equation (1940) should be applicable to this mechanism.

$$\ln k = \ln k_0 + \frac{Z_A^2 e^2}{2k^+ \epsilon} \cdot \left(\frac{1}{r_A} - \frac{1}{r^*} \right) \tag{18}$$

where ϵ is the dielectric constant, k^+ the Boltzmann constant, $Z_A e$ the charge on the ion A, and r_A and r^* the radii of the ion and activated complex respectively. This equation predicts a linear relationship between ln k and $1/\epsilon$ with a positive slope. Data in Fig. 4, however, appear to give two distinct relationships, both of negative slope. Studies (Nolan and Amis, 1961; Tommila, 1964; Tommila and Savolainen, 1967) involving the addition of less polar solvents to an aqueous medium have frequently shown a marked negative effect on the rate of hydrolysis of esters. Laidler and Landskroener (1956) have resolved this conflict by assuming a transition state in which a molecule of water bridges the attacking hydroxide ion and the leaving group. They explained the increased rate constants with an increased dielectric

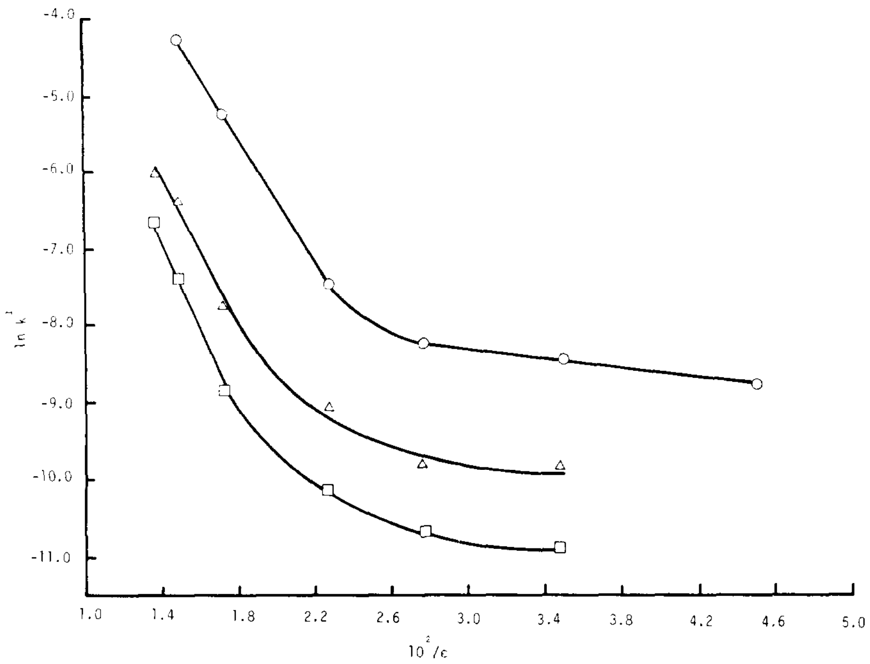


Fig. 4. Dependence of $\ln k^1$ on the reciprocal of the dielectric constant (ϵ^{-1}) of the solvent for the ethanolysis (○———○) and hydrolysis (△———△) of methyl 4-hydroxybenzoate and the hydrolysis (□———□) of ethyl 4-hydroxybenzoate in ethanol-water mixtures at 40.0°C.

constant of the solvent in terms of transition states being more polar than the reactants and hence encouraged in more polar media. It is difficult to reconcile that the transition state is more polar than the ion. Hudson (1966) indicated that a change to a more polar solvent will solvate the ionic transition state more strongly leading to an increased reaction rate. However, any mechanism that includes a molecule of water, in any role, could explain a decreased rate as the water concentration is decreased.

It can be seen in Fig. 4 that when this model is applied to the 3 reactions of this study there is a break in the relationship at a dielectric constant of about 40 which is approximately 50% w/w of ethanol. Where data giving approximately linear relationships for Eqn. 18 have occurred, it has frequently been over a much narrower dielectric constant range than employed in this study. For example, Tommila (1967) reported a similar linear relationship for the alkaline hydrolysis of ethyl acetate in ethanol-water admixtures over a dielectric constant range of 40–80. These data, however, show a sharp divergence from this relationship below a dielectric constant of 35. The most tenable explanation for the sudden decrease in the change of rate when ethanol has become dominant in the solvent composition would be the breaching of the solvation spheres of water molecules by ethanol (Amis and Hinton, 1973). A further explanation of a lack of correlation of rate with the dielectric constant of the medium involves dielectric saturation in the vicinity of the reaction centre (Laidler, 1965).

TABLE 3

ACTIVATION PARAMETERS FOR THE ALKALI CATALYZED DEGRADATION OF METHYL AND ETHYL 4-HYDROXYBENZOATES IN ETHANOL-WATER SYSTEMS

Medium	ΔG^* kJ mol^{-1} [a]	ΔH^* kJ mol^{-1}	ΔS^* JK^{-1} mol^{-1}
k'_1 [b] (ethanolysis methyl ester)			
9.62% w/w Ethanol	83.8	53.7 ± 5	−109 ± 14
27.76% w/w Ethanol	90.4	60.3 ± 5	−101 ± 14
52.64% w/w Ethanol	94.9	63.9 ± 3	−104 ± 8
74.66% w/w Ethanol	97.1	71.8 ± 4	−85 ± 11
82.43% w/w Ethanol	97.5	71.0 ± 1	−89 ± 3
Ethanol	100.0	72.0 ± 3	−94 ± 8
k'_2 (hydrolysis methyl ester)			
Water	92.3	54.4 ± 3	−127 ± 7
9.62% w/w Ethanol	91.2	47.1 ± 4	−148 ± 11
27.76% w/w Ethanol	95.5	68.1 ± 1	−92 ± 3
52.64% w/w Ethanol	99.6	82.0 ± 5	−59 ± 15
74.66% w/w Ethanol	101.1	76.3 ± 5	−83 ± 14
82.43% w/w Ethanol	101.8	82.1 ± 5	−66 ± 14
k'_3 (hydrolysis ethyl ester)			
Water	93.9	52.8 ± 2	−138 ± 5
9.62% w/w Ethanol	93.7	44.5 ± 1	−165 ± 3
27.76% w/w Ethanol	97.4	53.0 ± 1	−165 ± 3
52.64% w/w Ethanol	101.5	67.5 ± 2	−114 ± 5
74.66% w/w Ethanol	102.9	69.2 ± 4	−113 ± 11
82.43% w/w Ethanol	103.3	71.4 ± 3	−107 ± 8

[a] Calculated at 298.15 K.

[b] The prime is to indicate these data are derived from second-order rate constants.

Activation parameters

Temperature-dependence studies were carried out for each solvent admixture. In all cases, the derived second-order rate constants were analyzed for temperature-dependence. Linear relationships for ln(k/T) vs (I/T) were obtained for each solvent composition studied and the activation parameters for each reaction are reported in Table 3. The lines on Fig. 5 depict only the general trends of the activation parameters (shown as points) with solvent composition. These data indicate the increased rate for the ethanolysis reaction in the more aqueous solvents is dominated by ΔH^*. By contrast the hydrolysis reactions exhibit larger reductions in both ΔH^* and ΔS^* values in the more polar solvents. Hence, both of these parameters contribute to a comparable extent to influence reaction rates. The compensation in ΔH^* and ΔS^* values is at a maximum near $\chi_{H_2O} = 0.95$. In all 3 cases a relatively smooth change is seen in ΔG^*. The value of $\chi_{H_2O} = 0.95$ has been termed the 'magic mole fraction' of maximum solvent structural integrity (Engberts, 1979). Mixed aqueous binary solvents continuously change the 3-dimensional hydrogen-bond network of water with increased mole fraction of the organic compound. It has been proposed (Engberts, 1979) that these mutually compensatory changes in ΔH^* and ΔS^* are indicative of water structure effects on reactions. The variation in

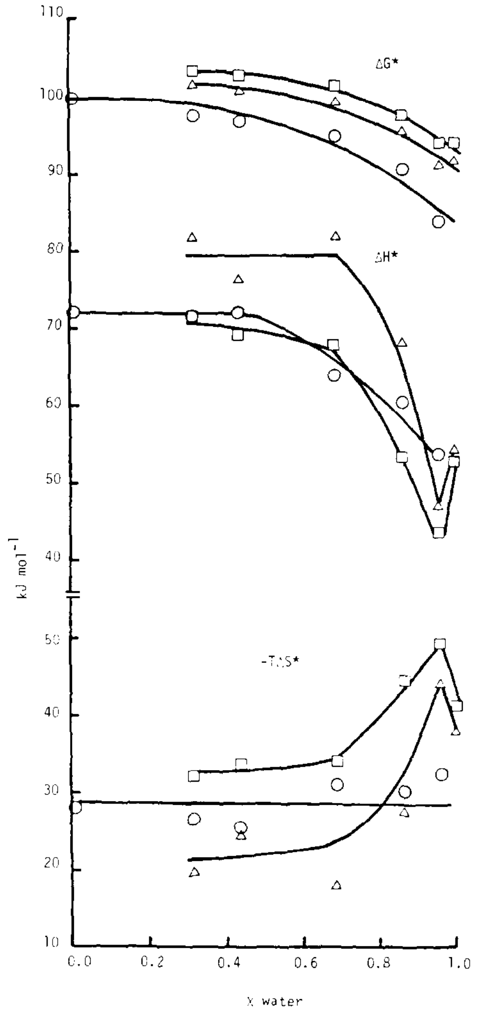


Fig. 5. Dependence of activation parameters on mole fraction of water for the ethanolysis of methyl 4-hydroxybenzoate (○———○) and the hydrolysis of methyl (△———△) and ethyl (□———□) 4-hydroxybenzoates (ΔG^* and $-T\Delta S^*$ at 298.15 K).

these parameters is made up of ground-state and transition-state contributions. It is likely that the substances in each of these states will respond differently with variation of χ_{H_2O}. The lack of a large variation in both ΔH^* and ΔS^* for the ethanolysis reaction could be indicative of the poorer precision of the second-order rate data, since at high water contents the concentration of ethoxide ion is low. However, the solvation of ethoxide ion in the ground state will also be looser than for hydroxide ion, an effect expected to be reflected in ΔS^* values.

This study was carried out to examine the influence of ethanol on the alkaline degradation of methyl 4-hydroxybenzoate. In practical terms (Table 1) the addition of ethanol gives rise to a transesterification of the methyl ester to the ethyl ester and a reduction in the hydrolysis rate. The ethanolysis reaction is less significant at low ethanol concentrations due to the low concentration of ethoxide ion present. For example, at 25°C and 9.62% w/w ethanol, $t_{\frac{1}{2}}$ for ethanolysis of the methyl ester is about 3.2 h, whereas for the hydrolysis of the same compound it is about 0.63 h.

Increasing the ethanol content to 74.66% w/w changes these values to 14.4 and 60.0 h respectively. Hence, increasing the ethanol concentration decreases the rates of both reactions; however, the ethanolysis reaction becomes dominant. These changes occur because the concentration of hydroxide ion in the equilibrium reaction (Eqn. 13) is dominant only at low ethanol concentrations. Ethyl ester resulting from the ethanolysis reaction is approximately twice as resistant to hydrolysis as the methyl ester in the alkaline pH range. The activation parameter data also demonstrate that the hydrolysis reactions are, in general, more affected by temperature change than the ethanolysis reaction.

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