Tetrahedron Vol. 40, No. 24, pp. 5217 to 5223, 1984
Printed in the U.S.A.

0040-4020/84 $3.00 + .00

TRANSESTERIFICATION KINETICS OF PHENYL SALICYLATE

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(*Received in UK 8 December 1983*)

Abstract—The degradation of phenyl salicylate in alkaline aqueous ethanol is shown to proceed via competing transesterification and hydrolysis processes. The transesterified product, ethyl salicylate, also undergoes hydrolysis, but at a slower rate and a kinetic model is presented which allows the simultaneous determination of all three rate constants. These results are contrasted with those of an earlier literature study and show the necessity for specific assay systems in kinetic analysis.

Salicylate esters are widely used in topical preparations in pharmacy and medicine. The polarity of the molecule is mediated by the nature of the ester substituent and this controls the use profile. Short chain esters such as methyl salicylate are rapidly absorbed through the skin and are used as topical analgesics whereas bulkier groups such as the menthyl ester show more substantivity and are used in suntan preparations. These compounds are susceptible to hydrolysis and much work has appeared on the mechanisms involved.[1-8] Recently, the alkaline hydrolysis of phenyl salicylate has been described.[9] Experiments were undertaken in aqueous ethanol to overcome solubility problems and the kinetics were followed by the reduction of UV absorbance of the solution at 340 nm. We here present evidence that these conditions lead to a competitive transesterification, forming the ethyl ester, in addition to hydrolysis (Scheme 1) and that the analytical methodology was incapable of revealing this effect.

EXPERIMENTAL

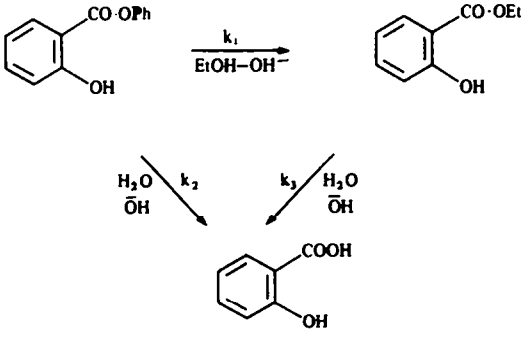
Materials and methods. Phenyl salicylate and ethyl salicylate were supplied by Graesser Salicylates Ltd, HPLC solvents and EtOH were obtained from Fisons. Distilled water was double distilled in glass and all other chemicals were of reagent grade.

Apparatus. Analyses were performed using a high-performance liquid chromatograph constructed from an Altex 100A dual-reciprocating, constant-flow, solvent-metering pump, a Rheodyne 7120 injection valve fitted with a 20 μl loop and a Pye LC3 variable wavelength ultraviolet monitor, equipped with an 8 μl flow cell and operated at a wavelength of 235 nm with a sensitivity of 0.08–0.016 AUFS. Chromatography was performed using a Shandon 10 cm × 4.6 mm ID stainless steel column packed with ODS-Hypersil (5 μm) reversed phase material. The pre-filtered mobile phase (0.45 μm), consisting of acetonitrile : water : phosphoric acid (60 : 40 : 2) with a pH of 2.33, was delivered at a flow rate of 1 ml min^{-1}. Ultraviolet spectra were determined in ethanol solution using a Pye-Unicam SP8000 ultraviolet spectrophotometer or a Beckman Acta V spectrophotometer. pH measurements were obtained using a Radiometer PHM 64 Research pH meter with a 4.5 digit, 3 decimal place display of pH, fitted with a combined glass electrode with a silver–silver chloride reference system. Calculations were undertaken using the BASIC programs: LIN-REG (calibration data, first-order and Arrhenius kinetics), IONSTREN (ionic strength calculations for weak electrolytes) and NONREG (non-linear least squares regression analysis). A FORTRAN version of NONLIN was also used for non-linear regression analysis.

Kinetic analyses. All components of the reaction media, with the exception of phenyl salicylate, were buretted directly into a 50 ml stoppered flask and the mixture was allowed to reach thermal equilibrium at the required temp. Reactions were initiated by the addition of a freshly prepared soln of phenyl salicylate in EtOH (3.1 mM) followed by rapid agitation. Aliquots (2 ml) were withdrawn immediately and at appropriate time intervals (1–60 min) over a period of 15 min to 8 hr. Samples were quenched by addition to the chilled internal standard (2 ml) consisting of butyl paraben (2 mg) in HCl (100 ml) sufficient to neutralise the alkali in the test soln (0.01–0.7 M) and were analyzed by high-performance liquid chromatography (20 μl).

Concentrations of reactants and products were calculated by interpolation onto a calibration line prepared from freshly prepared calibration solns containing 0.0124–0.124 mM of ethyl salicylate, phenyl salicylate and salicylic acid which were similarly treated with internal standard. To reduce sample-solvent problems,[10] the proportion of EtOH in the calibration and sample solns were made equivalent.

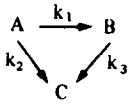
The effect of hydroxide ion concentration on the stability of phenyl salicylate (0.124 mM) was observed at 35° over the range 0.01–0.7 M NaOH in 4% EtOH with a constant ionic strength of 2 M, adjusted by the addition of KCl. The effect of temp was followed in 0.05 M NaOH at 25–50° in 4% EtOH with a constant ionic strength of 2 M, adjusted by the addition of KCl. The effect of EtOH concentration on phenyl salicylate (0.124 mM) was monitored over the range 10–80% at 25° with 0.05 M NaOH and an ionic strength of 0.1 M and at 35° with 0.01 M NaOH.



Scheme 1. Transesterification of phenyl salicylate in alkaline aqueous ethanol.

THEORETICAL

The reactions in Scheme 1 may be represented by:



where A, B and C represent phenyl salicylate, ethyl salicylate and salicylic acid, k_1 is the first order rate constant for transesterification and k_2 and k_3 are the first order hydrolysis rate constants.

The instantaneous rates of change of these species are given by:

$$\frac{dA}{dt} = -k_1A - k_2A = -A(k_1 + k_2) \quad (1)$$

$$\frac{dB}{dt} = k_1A - k_3B \quad (2)$$

$$\frac{dC}{dt} = k_2A + k_3B. \quad (3)$$

Integration of these equations between time zero and the current time t enables expressions for the instantaneous concentrations of each species to be obtained.

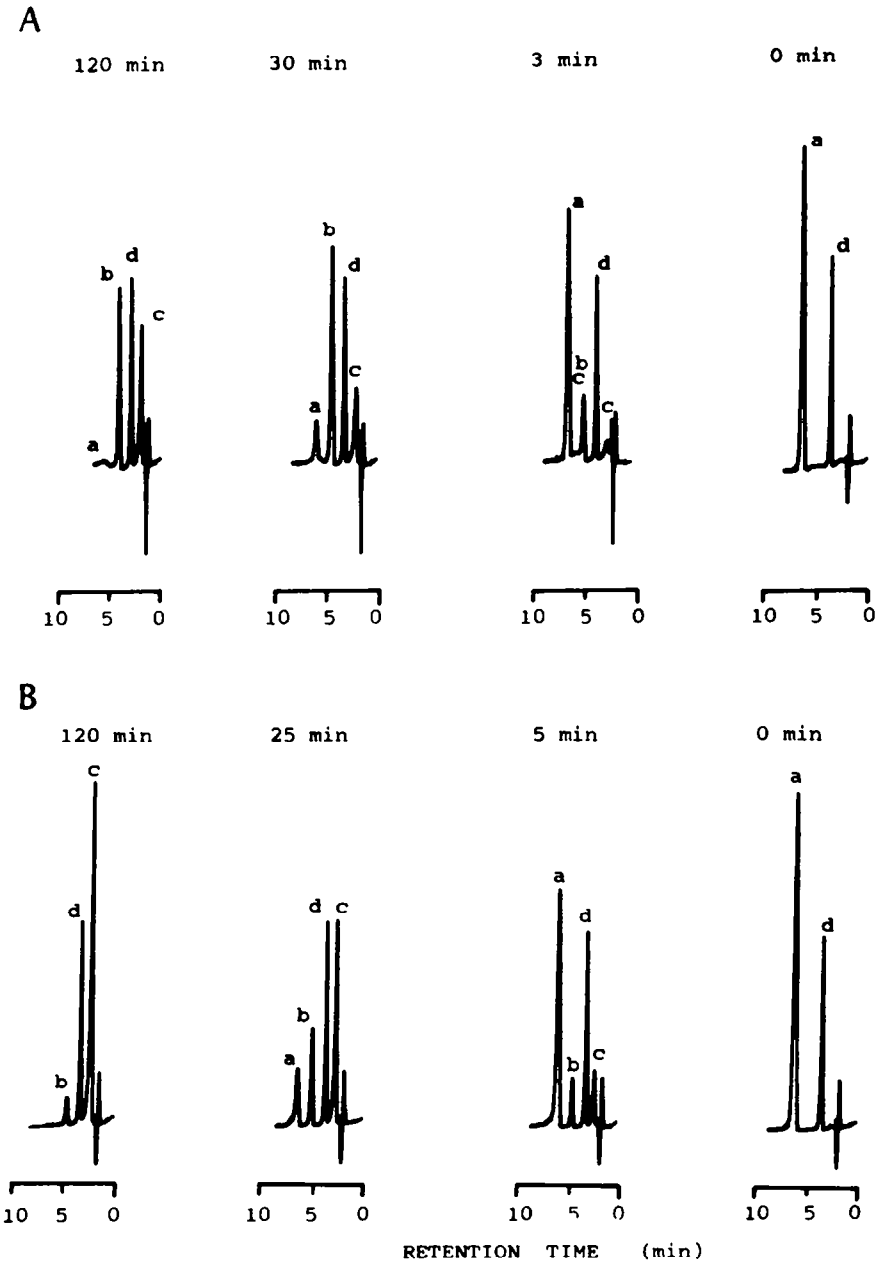


Fig. 1. High performance liquid chromatography of phenyl salicylate in alkaline aqueous ethanol. (A, 20% ethanol, 0.05 M NaOH, 35°; B, 4% ethanol, 0.05 M NaOH, 35°.) Components are: a, phenyl salicylate; b, ethyl salicylate; c, salicylic acid; d, internal standard: butyl 4-hydroxybenzoate.

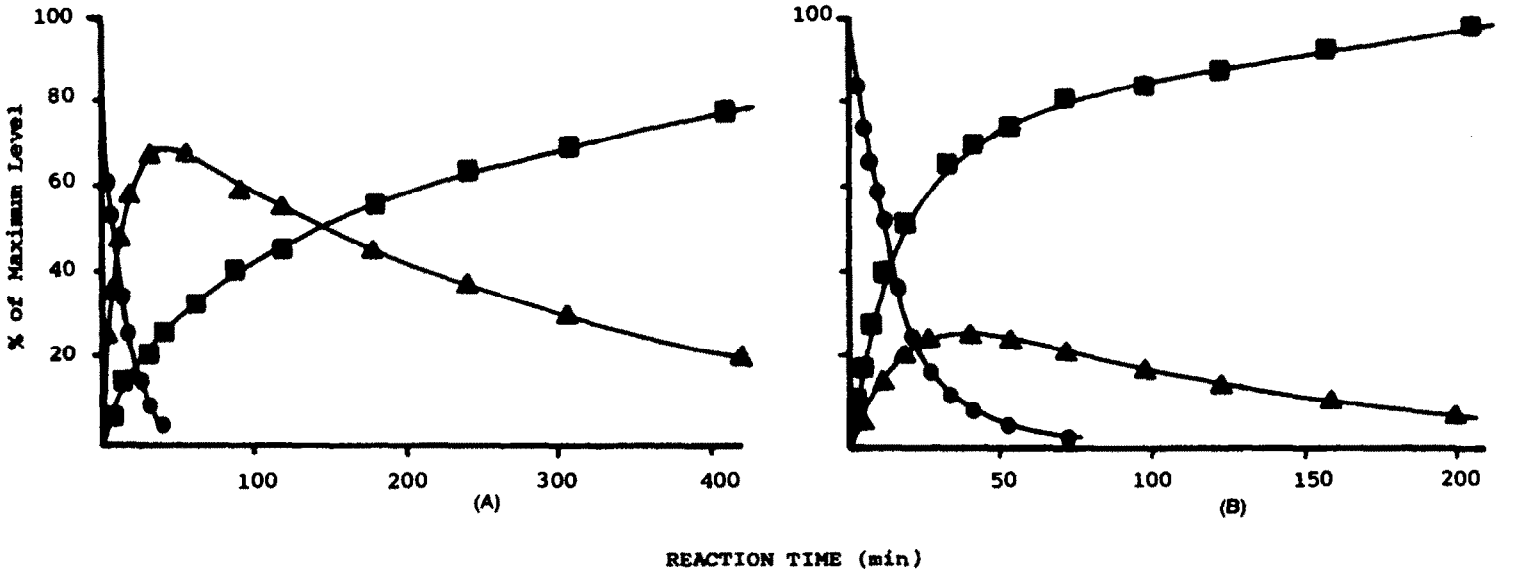


Fig. 2. Concentration–time profile for the degradation of phenyl salicylate in aqueous ethanol (●, phenyl salicylate; ▲, ethyl salicylate; ■, salicylic acid. A, 20% ethanol, 0.05 M NaOH, 35°, $k_1 = 0.127\ min^{-1}$, $k_2 = 0.0561\ min^{-1}$, $k_3 = 0.0134\ min^{-1}$; B, 4% ethanol, 0.05 M NaOH 35°; $k_1 = 0.0242\ min^{-1}$, $k_2 = 0.0494\ min^{-1}$, $k_3 = 0.00787\ min^{-1}$).

Thus

$$At = Ao \cdot e^{-(k_1 + k_2)t} \quad (4)$$

$$Bt = Ao \cdot k_1 \cdot \left[\frac{e^{-k_3 t}}{(k_1 + k_2 - k_3)} + \frac{e^{-(k_1 + k_2)t}}{(k_3 - k_1 - k_2)} \right] \quad (5)$$

$$Ct = A_0 \cdot \left[1 - \frac{k_1 \cdot e^{-k_3 t} + (k_2 - k_3) \cdot e^{-(k_1 + k_2)t}}{(k_1 + k_2 - k_3)} \right]. \quad (6)$$

Equations (4)–(6) were fitted to the measured profiles by non-linear least squares regression techniques, using NONREG and NONLIN, to evaluate the rate constants. Preliminary estimates were chosen so that the sum $(k_1 + k_2)$ equalled the slope of the logarithmic first-order plot from eqn (4).

RESULTS AND DISCUSSION

Figure 1(a) illustrates the HPLC separation of phenyl salicylate and reaction products in 20% ethanol with 0.05 M NaOH at 35°. At zero time only phenyl salicylate and internal standard are present. After 3 min a large decrease in phenyl salicylate has occurred and two new peaks are present. The early one is salicylic acid, the hydrolysis product, and the later, intense peak has been identified as ethyl salicylate by retention time behaviour and by isolation.[1] After 30 min virtually no phenyl ester remains although ethyl salicylate is still the major component.

Figure 2 plots the fate of each component and reveals the rapid disappearance of phenyl salicylate, essentially via transesterification to yield ethyl salicylate which undergoes a slow hydrolysis to salicylic acid. When 4% aqueous ethanol is used as the solvent (Fig. 1b), transesterification of the reactive phenyl ester still competes effectively with the hydrolysis reaction (Scheme 1). In an earlier report of this reaction[9] it was claimed that hydrolysis was the only degradation pathway and the kinetics, proposed to follow the simple first-order case, were followed by the measurement of the ultraviolet absorbance at 340 nm. At this wavelength the phenyl salicylate ion has an extinction of 6200 l cm mol^{-1} whereas the ethyl ester anion exhibits an extinction of 4600 l cm mol^{-1}.

The significant contribution of ethyl salicylate to the absorbance at 340 nm ensures that the degradation of phenyl salicylate cannot be adequately monitored in a system where transesterification is evident. Indeed, due to the rapid removal of phenyl salicylate, the absorption at 340 nm effectively monitors the degradation of ethyl salicylate in the later stages of the reaction. In contrast, ethanol levels of 1% such as those used by Capon and Ghosh,[4] which also involved more weakly alkaline conditions, traces only of the ethyl ester were observed. It should also be noted that stock solutions of phenyl salicylate (3.1 mM) in 96% aqueous ethanol, as described by Khan *et al.*,[9] undergo slow transesterification and 25% conversion to the ethyl ester is observed after 3 weeks storage.

The individual rate constants (Scheme 1) may be estimated from the time profiles of the salicylate components (Fig. 2) by a non-linear least squares regression analysis using eqns (4)–(6) as the theoretical model. All analyses showed good agreement between the measured and predicted data with the value $(k_1 + k_2)$ equivalent to the negative slope of first-order plot describing the disappearance of phenyl salicylate. As expected from the reactivity of the leaving group, phenyl salicylate hydrolysis was significantly faster than that of ethyl salicylate for both systems in Fig. 2. The transesterification rate, however, depended upon the proportion of ethanol in the solvent. The effect of ethanol concentration on each process is displayed in Fig. 3. This reveals a dramatic and almost linear ($k = 4.731 \times 10^{-3}$ (EtOH%) + 0.01877; $r = 0.994$, $n = 9$) dependence upon the percentage ethanol in the solvent up to a level of 80%. In contrast, both hydrolysis rates are suppressed with increasing alcohol and although, these, too, appear linearly related to solvent composition in the figure the plots are better described by a shallow curve. Indeed, using the equation:

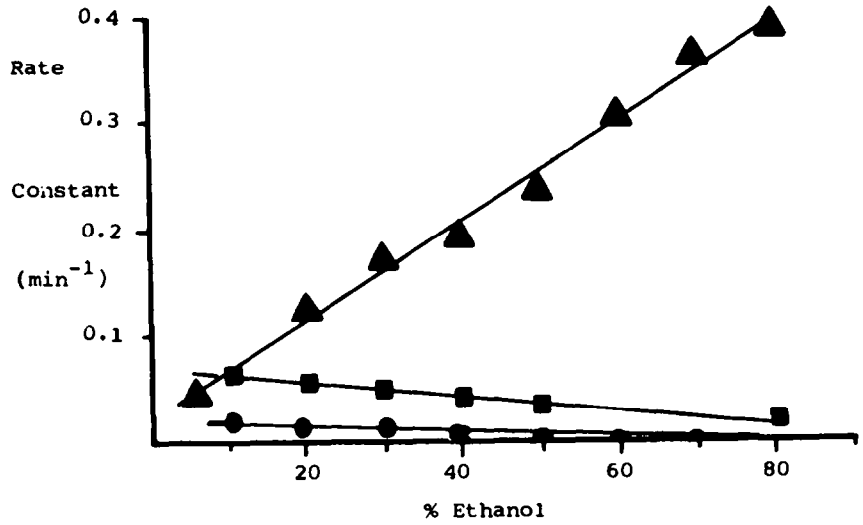


Fig. 3. Effect of ethanol concentration on degradation of phenyl salicylate (▲, k_1; ■, k_2; ●, k_3; 0.01 M NaOH, 35°).

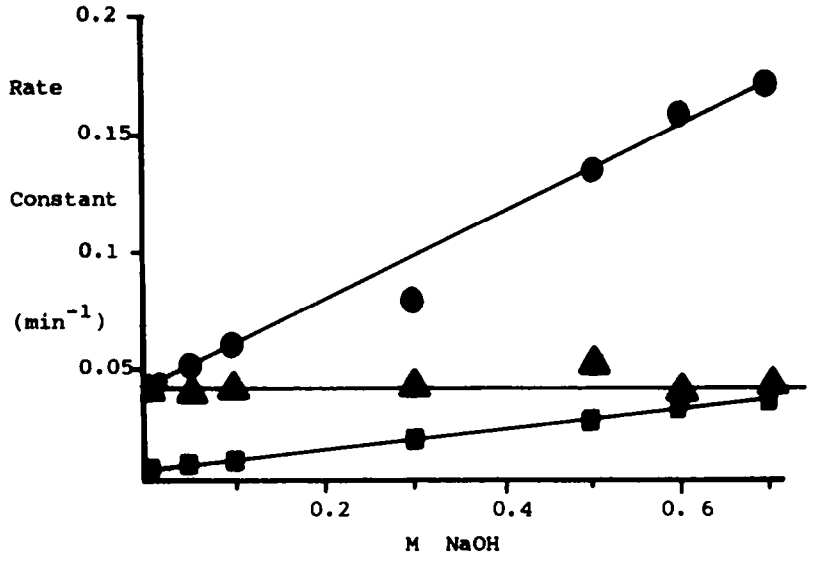


Fig. 4. Effect of sodium hydroxide concentration on phenyl salicylate degradation (▲, k_1; ●, k_2; ■, k_3; 4% ethanol, 35°).

$$\ln k = \ln k_{\epsilon=0} - \frac{KZ_AZ_B}{\epsilon} \quad (7)$$

where k is the measured degradation rate constant, ϵ is the dielectric constant of the medium, $k_{\epsilon=0}$ is the rate constant in a medium of infinite dielectric constant, Z_A and Z_B are the charges on the reacting species and K is a nominal constant holding Avogadro's number (N), electrical charge (e), the interionic distance within the activated complex (r) and temperature (T) such that

$$K = \frac{Ne^2}{RTr}$$

the variation of degradation rate constant follows closely the change in dielectric constant caused by solvent change:

Phenyl salicylate hydrolysis

$$\ln k = -0.175 - \frac{208}{\epsilon} \quad r = -0.998, \; n = 6. \quad (8)$$

Ethyl salicylate hydrolysis

(i) low alcohol

$$\ln k = 1.632 - \frac{454}{\epsilon} \quad r = -0.995, \; n = 5 \quad (9)$$

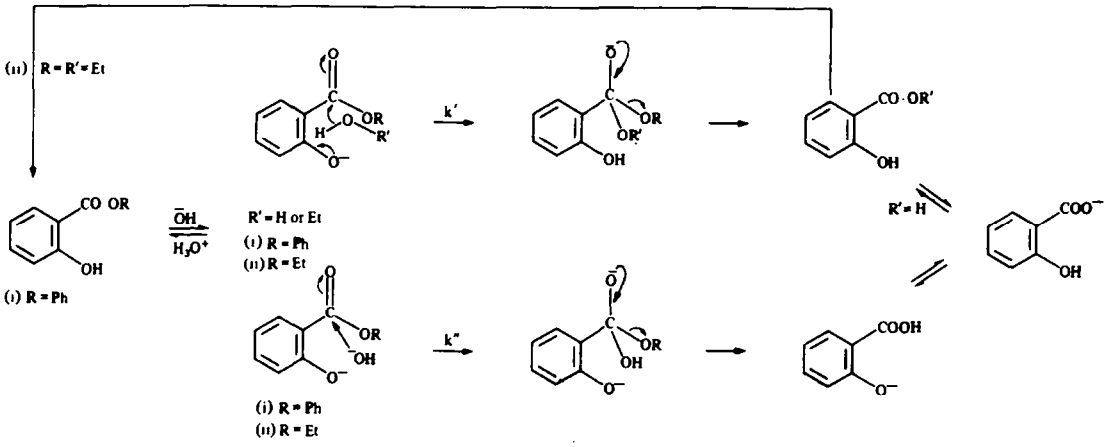
(ii) high alcohol

$$\ln k = -3.019 - \frac{139}{\epsilon} \quad r = -0.997, \; n = 4. \quad (10)$$

The plot for ethyl salicylate shows a change in slope at 50% ethanol and both lines are reported

Table 1. Arrhenius parameters for degradation of phenyl salicylate in 4% ethanol with 0.05 M NaOH (μ = 2.0 M)

Temperature	Rate constant (min^{-1})		
(°C)	k_1	k_2	k_3
35	0.02416	0.04939	0.007865
45	0.05746	0.1003	0.02549
50	0.06254	0.1343	0.03561
55	0.08736	0.2101	0.05466
Eact (kJmol^{-1})	52.91	59.66	81.47
A (min^{-1})	2.34×10^7	6.13×10^8	5.17×10^{11}
r	-0.981	-0.997	-0.995
ΔG^* (kJ mol^{-1})	85.62	83.78	88.51



Scheme 2. Mechanism of phenyl salicylate degradation in alkaline aqueous ethanol.

individually. This effect parallels that observed when the hydrolysis of ethyl salicylate in aqueous ethanol is followed.[1] The effect of dielectric canstant on the transesterification rate cannot readily be identified from these data as reactant concentration is simultaneously altered but it is clear that the use of ethanol to model dielectric effects in this system cannot provide useful estimates. The ethanol concentrations used by Khan *et al.*[9] appear to cover the range 5–95% and hence transesterification is probably the most important reaction of phenyl salicylate under these conditions. It is likely that the measured rate constants are largely those of ethyl salicylate hydrolysis.

The effect of sodium hydroxide concentration on each process is shown in Fig. 4 which covers only part of the range used earlier[9] due to the very rapid degradation of phenyl salicylate at higher hydroxide concentrations. At the level of ethanol used here (4%) the hydrolysis of phenyl salicylate is more rapid than the transesterification reaction (see Fig. 2). Comparison with earlier data,[9] reveals that the UV assay procedure underestimates this true hydrolysis rate due to the slower removal of the absorbing ethyl salicylate product. As an example, Fig. 1 shows the hydrolysis of phenyl salicylate monitored over a period of 20 hr with an apparent halving of the absorbance in some 40 min ($t_{\frac{1}{2}}$ calculated = 39.8 min). The true half-life for the *hydrolysis* process under these conditions should be 14 min and the overall loss of phenyl salicylate has a $t_{\frac{1}{2}} = 9.42$ min. In contrast, the ethyl salicylate half-life under these conditions is 88.1 min. The extraction of thermodynamic parameters is similarly compromised. Table 1 shows the Arrhenius data for the individual rate constants determined at 35, 45, 50 and 55°. These confirm the facile nature of both degradation pathways available to phenyl salicylate compared to ethyl salicylate hydrolysis and constrast markedly with the earlier values of 69.22 kJ mol^{-1} (Eact) and 1.55×10^{-6} min^{-1} (A).

It has been proposed that the hydrolysis of salicylates under strongly alkaline conditions follows Scheme 2 with a concerted reaction involving solvent and the salicylate anion competing with direct hydroxide attack. The observed rate constant (k) has been shown to depend upon both processes:

$$k = \frac{k'Ki'[H_2O][O\bar{H}] + k''Ki'[O\bar{H}]^2}{1 + Ki'[O\bar{H}]} \text{ where}$$

$$Ki' = \frac{Ka}{Kw}. \qquad (11)$$

For phenols, pka ~ 9–10, $Ki'[O\bar{H}] \gg 1$ at the levels of hydroxide used and equation 11 may be simplified to give the linear relationship:

$$k = k'[H_2O] + k''[O\bar{H}]. \qquad (12)$$

Using this equation to model the variation of degradation rate with hydroxide concentration (Fig. 4) the contribution of each mode of attack may be

Table 2. Partial rate constants for the decomposition of phenyl salicylate in 4% ethanol

Degradation Process	Rate constants for degradation via: (min^{-1}) Solvent attack (k^1 [solvent])	Anion attack (k'')	
Phenyl salicylate transesterification (k_1)	0.0251		(-)
Phenyl salicylate hydrolysis (k_2)	0.0384	0.185	(0.976)
Ethyl salicylate hydrolysis (k_3)	5.178×10^{-3}	0.0415	(0.980)

isolated for each of the three reactions involved. These are displayed in Table 2 and suggest that (i) transesterification is independent of hydroxide concentration in this region and involves the anchimeric attack of alcohol at the ester function of the salicylate anion; (ii) the hydrolysis reactions involve anchimeric attack of water and also the direct attack of hydroxide ion at the ester function of the salicylate anion which is presumably responsible for the observed dependence upon dielectric constant. Phenyl salicylate is significantly less stable in both modes of degradation due to the phenoxide ion being an effective leaving group.

This work reveals that reactions may occur as a result of solvent choice and a specific assay method should be used to confirm degradation pathways before kinetic analysis. When such processes are observed, the development of the appropriate kinetic model enables a full study of the reaction to be undertaken.

Acknowledgement—We are grateful for the award of a Commonwealth Research Scholarship to Q. N. Masuda.

REFERENCES

[1]W. J. Irwin, Q. N. Masuda and A. Li Wan Po, *Int. J. Pharmaceutics*, in press.
[2]L. Pekkarinen and E. Tommila, *Acta Chem. Scand.* **13**, 1019 (1959).
[3]M. L. Bender, F. J. Kezdy and B. Zerner, *J. Am. Chem. Soc.* **85**, 3017 (1963).
[4]B. Capon and B. C. Ghosh, *J. Chem. Soc.* (B) 472 (1966).
[5]S. K. Pal, S. C. Lahiri and S. Aditya, *Z. Phys. Chem.* Leipzig **255**, 226 (1974).
[6]I. G. C. Coutts, M. Edwards and D. J. Richards, *Synthesis* **6**, 487 (1981).
[7]M. N. Khan and T. O. Olagbemiro, *J. Org. Chem.* **47**, 3695 (1982).
[8]M. N. Khan, *J. Org. Chem.* **47**, 2046 (1983)
[9]M. N. Khan, T. O. Olagbemiro and U. Z. Umar, *Tetrahedron* **39**, 811 (1983).
[10]K. J. Williams, A. Li Wan Po and W. J. Irwin, *J. Chromatogr.* **194**, 217 (1980).