Solvent Effect on Activation Parameters for Intramolecular General Base-catalysed Hydrolyses of Salicylate Esters and Hydroxide Ion-catalysed Hydrolysis of Methyl *p*-Hydroxybenzoate

Mohammad Niyaz Khan,* Irene L. Fatope, Kaai I. Isaac, and Mohammad O. Zubair
Department of Chemistry, Bayero University, P.M.B. 3011, Kano, Nigeria

The effects of varying concentrations of methyl alcohol, dimethyl sulphoxide, t-butyl alcohol, and acetonitrile on activation parameters for intramolecular general base-catalysed aqueous cleavages of methyl salicylate and alkaline hydrolysis of methyl *p*-hydroxybenzoate have been studied. The activation parameters for intramolecular general base-catalysed cleavage of phenyl salicylate was studied under varying concentrations of t-butyl alcohol, dimethyl sulphoxide, and acetonitrile. A significant enthalpy–entropy compensation effect is observed in the hydrolyses of these esters with change of t-butyl alcohol content into the reaction medium. The variation of acetonitrile concentration causes an enthalpy–entropy compensation effect only in the alkaline hydrolysis of methyl *p*-hydroxybenzoate. A significantly larger negative value of $\Delta S^{\ddagger}$, observed in the hydrolysis of methyl *p*-hydroxybenzoate at 90% H_2O (v/v), compared with those for hydrolyses of salicylate esters obtained under an essentially similar solvent composition, is attributed to the difference in mechanisms for hydrolysis of these esters.

Although the exact nature of the rate-determining step in the serine protease-catalysed reactions is still under dispute,[1,2] it has been widely accepted that the mechanisms of these reactions involve general base catalysis.[3] It is also generally believed that part of the enzymatic catalysis is possibly due to the removal of solvent molecules from the vicinity of the active site of an enzyme as a result of its binding with the substrate. This belief has created interest among many investigators in the solvent[4] as well as the micellar effect[5] on the so-called enzymatic model reactions. Shaskus and Haake[4] have recently published the results of the effect of the acetonitrile concentration on activation parameters for the imidazole-catalysed hydrolysis of *p*-nitrotrifluoroacetanilide.

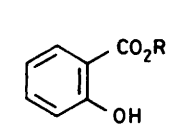
The pH-independent hydrolysis of salicylate esters has been convincingly shown to involve intramolecular general base catalysis[6–8] and hence the hydrolysis of salicylate esters could be considered as an appropriate model for serine protease-catalysed reactions. We therefore decided to study the effect of varying concentration of different organic solvents on activation parameters for pH-independent hydrolysis of salicylate esters. The observed results and their probable explanations are described in this manuscript.

Experimental

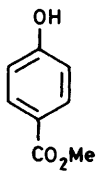
Commercially available reagent grade chemicals such as phenyl salicylate (I) and methyl *p*-hydroxybenzoate (II) were used as received. Methyl salicylate (III) was synthesized as described elsewhere.[9] All other chemicals used were also of reagent grade. Glass-distilled water was used throughout the studies.

Kinetic Measurements.—The rate studies of alkaline hydrolyses of (II) and salicylate esters were studied by monitoring the decrease in their concentrations spectrophotometrically at 320 and 340 nm, respectively. The details of the procedure are described elsewhere.[10] However, because of the possibility of transesterification of (I) in the t-butyl alcohol solvent system, the rates were also studied by monitoring the appearance of products (phenolate ion and salicylate ion) at 280 nm. The observed rate constants, $k_{obs.}$, were calculated from equation (1)

$$A_{obs.} = \varepsilon X_0 [1 - \exp(-k_{obs.}t)] + A_0 \qquad (1)$$



(I) R = Ph
(III) R = Me



(II)

using the non-linear least-squares technique as described elsewhere.[8] The rate constants obtained for a kinetic run carried out at both wavelengths (340 and 280 nm) were almost the same within the limits of the experimental uncertainties. The stock solutions of esters were prepared in the desired solvents of studies and were kept below 0 °C. However, the stock solution of (I) was prepared in MeCN for the kinetic runs carried out at 280 nm within a Bu^{t}OH content range of 5—70% (v/v).

Product Characterization of the Cleavage of (I) *in Aqueous* Bu^{t}OH *Solvent.*—It is known from our earlier studies[8] that piperidine is highly reactive toward (I) ($t_{\frac{1}{2}}$ *ca.* 90 s at 0.1M-piperidine buffer of pH 11) and totally unreactive toward methyl salicylate[8] and ethyl salicylate[11] under essentially similar experimental conditions. On the basis of these observations we assumed that t-butyl salicylate should not show nucleophilic reactivity toward piperidine. Thus the piperidine should selectively react with (I) from an aqueous mixture containing (I) and t-butyl salicylate. Thus a quantitative assay of t-butyl salicylate could be feasible by treating the aqueous mixture of (I) and t-butyl salicylate with piperidine and then measuring the absorbance of the resulting mixture at 340 nm. The extinction coefficients (ε) of ionized forms of (III)[8] and ethyl salicylate[12] are nearly the same at 340 nm (ε *ca.* 4 600 l mol^{-1} cm^{-1}) and hence ionized t-butyl salicylate could also be expected to show strong absorption at 340 nm. For a typical kinetic run, the reaction mixture (total volume of 48.8 cm^3) containing 0.05M-NaOH and 70% Bu^{t}OH (v/v) was equilibrated at 30 °C for a few minutes and then the reaction was initiated by adding 0.2 cm^3 of 0.04M-(I) solution prepared in MeCN. An aliquot portion (2 cm^3) was withdrawn from the mixture at 5 min intervals and was quickly transferred to 1 cm^3 of *ca.* 1M-piperidine solution freshly prepared in water.

Table 1. Effect of solvent on activation parameters for alkaline hydrolyses of (I), (III), and (II)[a]

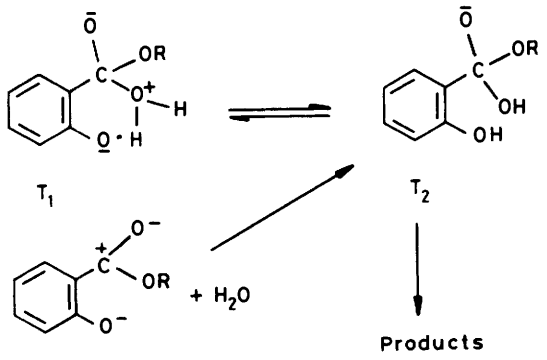
Ester	Solvent	% Solvent (v/v)	$\Delta G^{\ddagger}$/kcal mol^{-1}	$\Delta H^{\ddagger}$/kcal mol^{-1}	$-\Delta S^{\ddagger}$/cal K^{-1} mol^{-1}	Temperature range (°C)	No. of runs
(I)[b]	Bu^{t}OH	5	25.04	15.9 ± 0.5[c]	29.2 ± 1.5[c]	30—55	5
		40	25.35	17.5 ± 0.5	25.0 ± 1.7	30—55	5
		70	25.16	18.5 ± 0.5	21.2 ± 1.7	30—50	4
	CH_3CN	5	25.06	17.6 ± 0.8	23.9 ± 2.3	30—55	5
		40	25.06	18.0 ± 1.7	22.5 ± 5.3	30—55	5
		70	24.84	17.9 ± 0.5	22.2 ± 1.7	30—55	5
	Me_2SO	5	24.94	16.5 ± 0.5	26.9 ± 1.6	30—55	5
		40	24.90	19.6 ± 0.7	17.0 ± 2.1	30—55	5
		80	24.01	19.1 ± 0.8	16.0 ± 2.5	30—55	5
(III)[d]	MeOH	10	25.75	15.8 ± 0.7	31.4 ± 2.2	40—65	5
		40	25.78	16.1 ± 1.1	30.4 ± 3.3	40—65	5
		70	25.79	20.6 ± 1.1	16.8 ± 3.2	40—65	5
	Bu^{t}OH	2	25.82	16.1 ± 1.1	30.9 ± 3.2	40—65	5
		10	25.71	20.3 ± 0.9	17.2 ± 2.8	30—55	5
		40	25.72	23.9 ± 1.4	6.0 ± 4.1	30—55	5
		70	25.69	23.6 ± 1.4	6.6 ± 4.2	30—55	5
	CH_3CN	10	25.77	17.0 ± 0.4	27.8 ± 1.2	40—65	5
		40	25.80	17.2 ± 0.5	27.0 ± 1.5	40—65	5
		70	25.55	17.1 ± 0.7	26.5 ± 2.0	40—65	5
	Me_2SO	10	25.71	16.4 ± 0.4	29.9 ± 1.3	40—65	5
		40	25.81	16.5 ± 1.0	29.2 ± 3.0	40—65	5
		70	26.24	20.2 ± 1.3	18.4 ± 3.8	40—65	5
(II)[e]	MeOH[f]	10	22.44	13.5 ± 0.7	28.7 ± 2.0	40—65	5
		40	23.88	16.7 ± 0.9	22.1 ± 2.8	40—65	5
		60	24.79[g]	16.0 ± 0.4	26.2 ± 1.0	50—65	3
	Bu^{t}OH[h]	10[f]	22.68	10.0 ± 0.8	39.3 ± 2.3	40—65	5
		40[i]	23.94	26.3 ± 3.5	−7.2 ± 10.4	50—65	4
		50[i]	24.12	19.7 ± 1.0	13.1 ± 2.9	50—70	5
	CH_3CN[h,i]	10	22.67	10.5 ± 2.6	37.1 ± 7.7	50—70	5
		40	23.48	14.8 ± 0.4	26.5 ± 1.2	50—70	4
		60	23.84	20.7 ± 2.4	9.2 ± 6.9	50—70	5
	Me_2SO[h,i]	5	22.71	12.4 ± 1.6	31.8 ± 4.8	50—70	5
		30	23.12	12.0 ± 1.3	34.3 ± 4.0	50—70	5

[a] $\Delta G^{\ddagger}$ was calculated from relationship $k' = (K_B T/h)\exp(-\Delta G^{\ddagger}/RT)$ at 40 °C, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated from the non-linear form of the Eyring equation as described in the text. [b] $[(I)]_0$ 1.8 × 10^{-4}M, 0.05M-NaOH, 0.05M ionic strength. [c] Error limits are standard deviations. [d] $[(III)]_0$ 2 × 10^{-4}M; 0.05M-NaOH, 0.05M ionic strength. [e] $[(II)]_0$ 2 × 10^{-4}M. [f] 0.2M ionic strength. [g] At 50 °C. [h] $\Delta G^{\ddagger}$ was obtained at 50 °C. [i] 0.1M ionic strength.

The resulting mixture was then quickly transferred to the cuvette which was put into the cell compartment of the spectrophotometer. The absorbance of the reaction mixture was found to drop from a maximum to a minimum value of 0.10 at 340 nm < 6 min and then it remained constant at 0.10 for a further 220 min. Similar observations were observed for other portions withdrawn at 29, 55, and 174 min. The similarity of the absorbance values (0.10) at 340 nm for all portions withdrawn at different intervals reveals the absence of t-butyl salicylate formation. The product mixtures of 0.1M-piperidine buffer and 1.8 × 10^{-4}M-(I) on 98% H_2O at pH 10.80—11.67 revealed the absorbance values of *ca.* 0.07—0.08 at 340 nm.

The observed extinction coefficients of salicylate ion and phenolate ion at 280 nm are 1 940 and 2 150 l mol^{-1} cm^{-1}, respectively. The observed extinction coefficients of the products of the kinetic runs carried out at 280 nm and under aqueous solvent containing 5, 40, and 70% Bu^{t}OH are 4 050 ± 150, 4 100 ± 200, and 4 000 ± 200 l mol^{-1} cm^{-1}, respectively, within the temperature range 30—55 °C. These values of extinction coefficients are similar to the observed sum of the extinction coefficients (4 100 l mol^{-1} cm^{-1}) of salicylate and phenolate ions at 280 nm. Since the observed rate law obeyed first-order kinetics for more than four half-lives of all the reactions, it is unlikely that both transesterification and hydrolysis might have occurred simultaneously. The reaction of Bu^{t}OH with (I) could have complicated the observed first-order kinetics.

The reaction kinetics for the aqueous cleavage of (I) under varying concentrations of Bu^{t}OH were studied by monitoring both the appearance of products at 280 nm and disappearance of reactant at 340 nm as a function of time. The observed pseudo-first-order rate constants for the same kinetic run monitored at both wavelengths, 280 and 340 nm, turned out to be the same within limits of the experimental uncertainties.



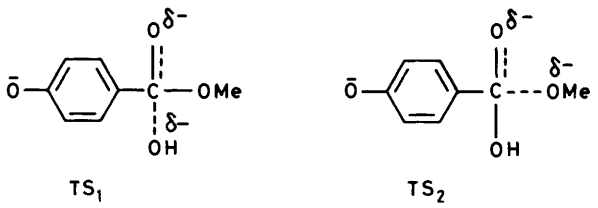
Scheme.

These observations also rule out the possibility of significant t-butyl salicylate formation during the course of the reaction because t-butyl salicylate is expected to hydrolyse much slower than (I) under similar experimental conditions [(III) was found to hydrolyse nearly four times slower than (I) at 30 °C and 0.05M-NaOH].

Results and Discussion

The effects of different organic solvents on activation parameters for aqueous cleavages of (I) and (III) have been studied in 0.05M-NaOH. At a particular solvent composition, the kinetic runs were generally carried out at five different temperatures with a maximum temperature difference of 25 °C. Because of comparatively slow alkaline hydrolysis of (II), the [$\bar{O}H$] was kept constant at 0.1 or 0.2M in the entire kinetic studies of this ester. The organic solvents chosen to study their effects on the rate of hydrolyses of (I)—(III) were dimethyl sulphoxide (DMSO), Bu^{t}OH, and acetonitrile. Methanol was used to study its effect on alkaline hydrolysis of (II) and (III) only. The observed apparent second-order rate constants k' {$k' = k_{obs.}/[\bar{O}H]$ for (II) and $k' = k_{obs.}/[H_2O]$ for (I) and (III)} were found to be well fitted to the Eyring equation and the non-linear least-squares technique was used to calculate ΔH^* and ΔS^*.[9] The results thus obtained at varying concentrations of organic solvents are summarized in Table 1. At a constant temperature, the rate of hydrolysis of each ester was found to decrease with decrease in water concentration.

It has been well established that the pH-independent hydrolyses of salicylate esters involve intramolecular general base catalysis.[6,7,9–13] The pH-independent hydrolysis of salicylamide has been also concluded to involve intramolecular general base catalysis.[14] The exact nature of the rate-determining step involved in the intramolecular general base-catalysed hydrolyses of salicylate esters has not yet been unequivocally ascertained. We, however, considered, though without any convincing evidence, a stepwise mechanism involving intramolecular proton transfer in a thermodynamically favourable direction as the rate-determining step (Scheme).[11] In the Scheme, T_1 and T_2 represent an intramolecular intimate ion pair and monoanionic tetrahedral intermediate, respectively. The presence of organic solvents may be expected to increase the pK_a of salicylate esters as well as decrease the activity of hydroxide ion ($a_{\bar{O}H}$). However these changes are assumed to be not significantly large because a change in ethanol content from 0 to 70% (v/v) in ethanol–water mixed solvent resulted in a change in pK_w from 14.00 to 15.43 at 25 °C.[15] Similarly, the pK_a of phenol was found to change from 10 to 12 with the change of ethanol content from 0.0 to 72.4% (w/w) in ethanol–water.[16] The reaction rates of aqueous cleavages of (I) and (III) have been found to be independent of [$\bar{O}H$] within the [$\bar{O}H$] range



ca. 0.001—*ca.* 0.10M. Also, in an unpublished report we found that the methanolysis of (I) was independent of [$\bar{O}H$] within the [$\bar{O}H$] range 0.01—0.15M in 80% methanol–water. Thus, under the present experimental conditions, we assume that the reacting species were the ionized form of salicylate esters and water. As the proposed mechanism involves water as the reactant, the equilibrium concentration of reactive intermediate T_1 will be decreased with decrease in water concentration. This could be one of the various probable reasons for the decrease in the rate of hydrolysis with decrease in [H_2O].

It is noteworthy that ΔH^* and ΔS^* for alkaline hydrolysis of (III) obtained in the mixed solvents containing 90% water are generally larger by 3—10 kcal mol^{-1} and 1—11 cal K^{-1} mol^{-1}, respectively, compared with those for (II) obtained under essentially similar conditions. This difference in the activation parameters reflects the fact that the hydrolyses of these esters at 0.05M-NaOH follow different mechanisms. The values of ΔS^* observed for alkaline hydrolysis of (II) are comparable with those for alkaline hydrolyses of monomethyl phthalate[17] and di-n-butyl phthalate[18] obtained under similar experimental conditions. These results thus indicate that the reacting species involved in the rate-determining step of alkaline hydrolysis of (II) are probably hydroxide ion and ionized (II). The possibility of involvement of non-ionized form of (II) in its alkaline hydrolysis has been ruled out on a basis described elsewhere.[19]

An increase of acetonitrile content in the reaction medium from 10% to 70% (v/v) was found to cause a decrease in the rate of hydrolyses of salicylate esters and (II) by nearly 2-fold and 3—5-fold, respectively. This decrease for salicylate esters could be attributed to both enthalpy as well as entropy effect for the reason that ΔH^* and ΔS^* were found to be essentially unchanged, within the limits of their standard deviations, with the change of acetonitrile content from 5 to 70% (v/v) (Table 1). However, an inspection of Table 1 reveals that with the change of acetonitrile content from 10 to 60% (v/v) for alkaline hydrolysis of (II), though the increase in ΔG^*_{50} is only *ca.* 1.2 kcal mol^{-1}, ΔH^* and ΔS^* are increased by nearly 10 kcal mol^{-1} and 28 ml mol^{-1} K^{-1}, respectively. This could be attributed to the so-called enthalpy–entropy compensation effect.[17,20] A significantly large negative value of ΔS^* and the decrease in rate with increase of acetonitrile content in the reaction medium indicate that the transition state involved in the alkaline hydrolysis of (II) is more polar than the reactant state. In a separate study on the effect of [$\bar{O}H$] on aqueous cleavage of (II), we concluded that the reacting species are *p*-$\bar{O}C_6H_4CO_2Me$ and $\bar{O}H$.[19] Thus, in the transition state TS_1 (if nucleophilic attack is the rate-determining step) or TS_2 (if expulsion of leaving group is the rate-determining step), the negative charge on phenolic oxygen is apparently more localized compared with that in the reactant state where *p*-CO_2Me is acting as a strong electron-withdrawing group. These activation parameters therefore favour the suggested mechanism.[19]

The increase of methanol content into the reaction medium [from 5 to 70% (v/v)] revealed a more pronounced rate-retarding effect on the aqueous cleavage of (II) and (III) as evident from ΔG^* values (Table 1).

The increase in DMSO concentration into the reaction medium was found to decrease the rate of hydrolysis of both

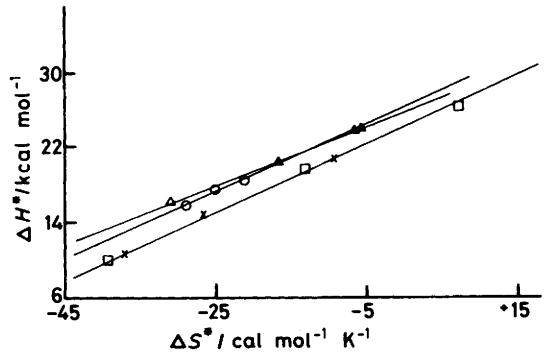


Figure 1. Plots showing the dependence of ΔH^* on ΔS^* for different organic cosolvents. ○ Bu^{t}OH–H_2O for (I) where the activation parameters were derived by linear least-squares techniques using the linear form of the Eyring equation; △ Bu^{t}OH–H_2O for (III); □ t-Bu^{t}OH–H_2O for (II); and × CH_3CN–H_2O for (II)

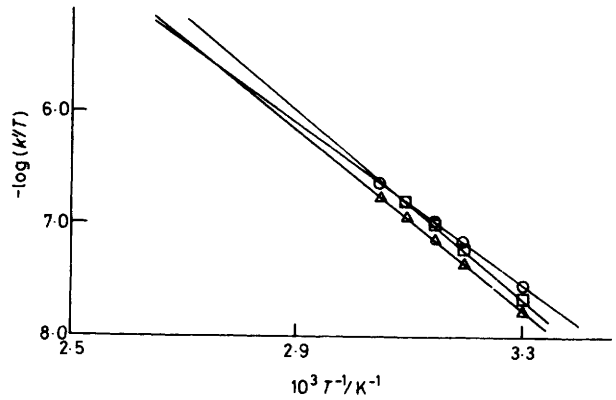


Figure 2. Eyring plots for intramolecular general base-catalysed hydrolysis of (I) in various mixed solvents containing 5% Bu^{t}OH (○), 40% Bu^{t}OH (△), and 70% Bu^{t}OH (□)

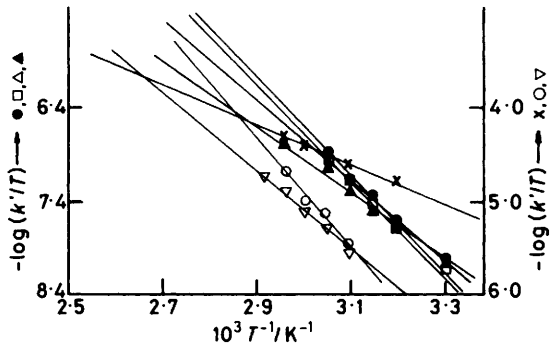


Figure 3. Eyring plots for intramolecular general base-catalysed and hydroxide ion-catalysed hydrolyses of (III) and (II), respectively, in various mixed solvents containing 2% Bu^{t}OH (▲), 10% Bu^{t}OH (△), 40% Bu^{t}OH (□) and 70% Bu^{t}OH (●) for (III) and 10% Bu^{t}OH (×), 40% Bu^{t}OH (○), and 50% Bu^{t}OH (▽) for (II)

salicylate and benzoate esters. However, in the hydrolysis of (I), it was observed that the values of A_∞ at 80% DMSO (v/v) were *ca.* 0.29 at all five different temperatures ranging from 30 to 55 °C. This value of A_∞ of 0.29 is significantly different from the expected value of *ca.* 0.02—0.07. The values of A_∞ of *ca.* 0.02—0.07 were observed in the alkaline hydrolyses of (III) and (I) within the DMSO content range of 10—70% (v/v) and 5—50% (v/v), respectively, at various temperatures ranging from 30 to 65 °C. The values of A_∞ of 0.18 and 0.08 were observed in the hydrolysis of (I) at 70 and 60% DMSO, respectively. Even for 70% of other organic solvents such as CH_3CN and Bu^{t}OH, the values of A_∞ were always found to be <0.07 for alkaline hydrolysis of (I). A sample containing 80% DMSO, 1.8×10^{-4}M-phenol, 1.8×10^{-4}M-salicylic acid, and 0.05M-NaOH gave an absorbance value of 0.23 at 340 nm which could be compared with the corresponding A_∞ values of 0.29 obtained from various kinetic runs carried out under similar experimental conditions at different temperatures. The absorbance value of 0.23 remained constant up to nearly 20 h. Similar samples containing 70 and 10% DMSO gave absorbance values of 0.11 and 0.025, respectively, at 340 nm, which could be compared with the values of A_∞ of 0.18 and 0.03—0.07 obtained from several kinetic runs carried out under similar experimental conditions. An aqueous solution of 1.8×10^{-4}M-phenol in 80% DMSO and 0.05M-NaOH gave absorbance values of 0.005 at 340 nm. These observations indicate that the presence of equal amounts (1.8×10^{-4}M) of salicylate ion and phenolate ion in 80% DMSO–water forms some kind of complex which absorbs significantly at 340 nm. It is also evident from these observations that the presence of both phenolate ion and salicylate ion is essential for the formation of the absorbing species in 80% DMSO–water.

Enthalpy–Entropy Compensation Effect.—The change in Bu^{t}OH content from 5 to 70% (v/v) for alkaline hydrolysis of (I) produced changes of 0.3 kcal mol^{-1}, 2.6 kcal mol^{-1}, and 8 cal mol^{-1} K^{-1} in ΔG^*, ΔH^*, and ΔS^*, respectively (Table 1). Similar changes were also observed with the varying Bu^{t}OH content in the reaction medium for the alkaline hydrolyses of (III) and (II) (Table 1). By using h.p.l.c., Irwin *et al.*[12] recently showed that ethanolysis of (I) is much faster than its hydrolysis, in an alkaline medium. We could not detect this transesterification in our earlier studies[10] simply because the experimental technique used was incapable of detecting it. Bu^{t}OH, however, did not show any detectable nucleophilic reactivity towards (I) under the present experimental conditions which might be attributed to a large steric effect produced by Bu^{t}OH compared with ethanol. This is in agreement with our unpublished observations where we observed *ca.* 15 times larger reactivity of methanol compared with that of ethanol with (I) under similar experimental conditions.

Significantly large changes in ΔH^* and ΔS^* with negligible change in ΔG^*, with varying solvent systems, of a reaction have been normally attributed to the enthalpy–entropy compensation effect.[21] Such a compensation effect generally results in a linear relationship between ΔH^* and ΔS^*. The plots of ΔH^* *versus* ΔS^* as shown in Figure 1 for these esters are also essentially linear. Petersen *et al.*,[22] however, elegantly argued that the linear plots of ΔH^* *versus* ΔS^* could be completely fortuitous for a reason now described. Since both ΔH^* and ΔS^* are derived from the same equation with certain sets of data, therefore the random error in ΔH^* is directly proportional to the random error in ΔS^*. Thus, the measurements involving significant range of errors could lead to a linear relationship between ΔH^* and ΔS^*. Petersen[23] further showed using hypothetical data that a linear relationship of ΔH^* and ΔS^* could be considered due to a compensation effect if the Eyring plots [*i.e.* plot of $\log(k_{obs.}/T)$ *versus* $1/T$] revealed an isokinetic temperature. Such Eyring plots are shown in Figures 2—4 where an isokinetic temperature could not be recognized in the alkaline hydrolysis of any ester of the present study.

The value of ΔH^* increases by 7.4 kcal mol^{-1} upon addition of 70% Bu^{t}OH whereas ΔS^* becomes more positive by *ca.* 24 cal K^{-1} mol^{-1} in the alkaline hydrolysis of (III). These changes in

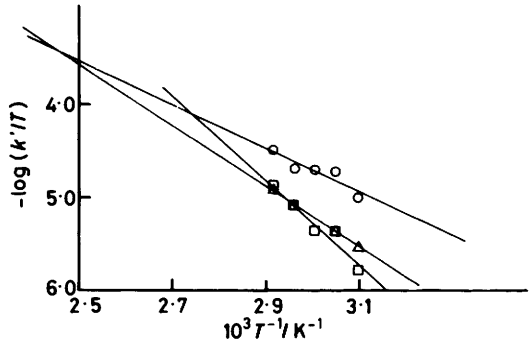


Figure 4. Eyring plots for hydroxide ion-catalysed hydrolysis of (II) in various mixed solvents containing 10% CH_3CN (○), 40% CH_3CN (△), and 60% CH_3CN (□)

ΔH^* and ΔS^* are much larger than the respective maximum standard deviations of these activation parameters. It is therefore difficult to believe that such large changes in ΔH^* and ΔS^* are due to random errors. Furthermore, one wonders why such random errors could not result in significant changes in ΔH^* and ΔS^* upon addition of 70% (v/v) of CH_3CN into the aqueous reaction medium for alkaline hydrolysis of salicylate esters. It is interesting to note that the change in Bu^{t}OH content from 40 to 70% causes insignificant changes in ΔH^* and ΔS^* for the hydrolysis of (III) (Table 1).

Although the changes in ΔH^* and ΔS^* upon changing the Bu^{t}OH content in the reaction medium for alkaline hydrolyses of (I)—(III) do not meet Petersen's empirical criterion, we intuitively believe the occurrence of the enthalpy–enthropy compensation effect. A look at equation (2), where all the

$$\ln(k/T) = \ln(K_B/h) - \frac{\Delta H_0^*}{RT} + \left(\frac{T-\alpha}{T}\right)\frac{\Delta S^*}{R} \quad (2)$$

$$\Delta H^* = \Delta H_0^* + \alpha\Delta S^* \quad (3)$$

$$\ln(k/T) = \ln(K_B/h) - \Delta H_0^*/RT \quad (4)$$

symbols have their usual meanings and which is derived from the Eyring equation and equation (3), reveals that equation (4) could arise under two conditions: (i) at $\alpha = T$, and (ii) at $\Delta S^* = 0$ even if $\alpha \neq T$. The first condition would result in an isokinetic point in the Eyring plots which the Petersen criterion suggests, but when ΔS^* is very close to zero the Eyring plots would tend to be parallel to each other. A close example of the occurrence of the second condition could be seen in the hydrolysis of (III) at 40 and 70% Bu^{t}OH if observed pseudo-first-order rate constants, $k_{obs.}$, rather than apparent second-order rate constants, k', were used in the calculation of ΔH^* and ΔS^*. The linear least-squares-calculated values of ΔH_0^* and α for the reaction which were found to be obeyed by equation (3) are summarized in Table 2. From equation (2), it seems to be apparent that for a system involved with the enthalpy–entropy compensation effect, the Eyring plots will intersect at a single point (isokinetic temperature) provided the random errors in T and α are of similar magnitude and $\Delta S^* \neq 0$. But if random error (σ) in α is larger than that in T then Eyring plots may probably intersect at more than one point within the range of $\geqslant 2\sigma$.

While studying the effect of Bu^{t}OH concentration on aqueous cleavage of ionized (I) we found that the reaction mixture containing 70% Bu^{t}OH remained as a clear solution up to 50 °C and became distinctly turbid at 55 °C. Because of this turbidity we could not conduct kinetic runs containing 70% Bu^{t}OH at 55 °C. In order to check whether this turbidity was a consequence of the presence of 0.05M-NaOH on the changing structure of Bu^{t}OH–H_2O binary solvent due to change of temperature, we carried out a control run in which 50 cm^3 of aqueous solvent containing 70% Bu^{t}OH and 0.05M-NaOH was heated gradually and the optical density of the solvent was measured at 340 nm and at different temperature-ranging from 30 to 80 °C. No turbidity was observed up to 80 °C. This probably indicates that the solubility of phenyl salicylate in aqueous solvents containing 70% Bu^{t}OH and 0.05M-NaOH decreases with increase in temperature.

Table 2. Linear parameters calculated from equation (3) using linear least squares technique

Ester	Solvent	ΔH_0^*/kcal mol^{-1}	α/° K
(I)	Bu^{t}OH–H_2O	25.5 ± 0.9[a]	326 ± 34[a]
(III)	Bu^{t}OH–H_2O	25.7 ± 0.1	311 ± 3
(II)	Bu^{t}OH–H_2O	24.0 ± 0.3	351 ± 13
	CH_3CN–H_2O	24.2 ± 0.5	363 ± 17

[a] Error limits are standard deviations.

Acknowledgements

M. N. K. is grateful to the Research and Higher Degrees Committee of Bayero University for a research grant to purchase a u.v.–visible spectrophotometer.

References

1 J. D. Roberts and K. Kanamori, *Proc. Natl. Acad. Sci. USA*, 1980, **77**, 3095.
2 D. M. Quinn, J. P. Elrod, R. Ardis, P. Friesen, and R. L. Schowen, *J. Am. Chem. Soc.*, 1980, **102**, 5358.
3 J. J. Morris and M. I. Page, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1131; J. Fastrez, *ibid.*, p. 1067.
4 J. Shaskus and P. Haake, *J. Org. Chem.*, 1983, **48**, 2036 and references therein.
5 J. R. E.-Perez and J. H. Fendler, *J. Am. Chem. Soc.*, 1978, **100**, 2234.
6 M. L. Bender, F. J. Kezdy, and B. Zerner, *J. Am. Chem. Soc.*, 1963, **85**, 3017.
7 B. Capon and B. C. Ghosh, *J. Chem. Soc. B*, 1966, 472.
8 M. N. Khan, *J. Org. Chem.*, 1983, **48**, 2046.
9 M. N. Khan and T. O. Olagbemiro, *J. Org. Chem.*, 1982, **47**, 3695.
10 M. N. Khan, T. O. Olagbemiro, and U. Z. Umar, *Tetrahedron*, 1983, **39**, 811.
11 M. N. Khan and S. K. Gambo, *Int. J. Chem. Kinet.*, 1985, **17**, 419.
12 W. J. Irwin, Q. N. Masuda, and A. L.-Wan Po, *Tetrahedron*, 1984, **40**, 5217.
13 T. Maugh, II, and T. C. Bruice, *J. Am. Chem. Soc.*, 1971, **93**, 3237.
14 T. C. Bruice and D. D. Tanner, *J. Org. Chem.*, 1965, **30**, 1668.
15 O. Lukkan, E. Hakoila, and L. Markkola, *Finn. Chem. Lett.*, 1978, **2—3**, 93.
16 C. C. Panichajakul and E. M. Woolley, *Anal. Chem.*, 1975, **47**, 1860.
17 J. Benko and V. Holba, *Collect. Czech. Chem. Commun.*, 1978, **43**, 193.
18 M. N. Khan and A. A. Khan, *Indian J. Chem.*, 1977, **15A**, 220.
19 M. N. Khan and T. O. Olagbemiro, *J. Chem. Res. (S)*, 1985, 166.
20 T. Graafland, A. J. Kirby, and J. B. F. N. Engberts, *J. Org. Chem.*, 1981, **46**, 215.
21 J. E. Leffler and R. A. Hubbard, II, *J. Org. Chem.*, 1954, **19**, 1089; M. G. Alder and J. E. Leffler, *J. Am. Chem. Soc.*, 1954, **76**, 1425; M. D. Cohen, J. E. Leffler, and L. M. Barbato, *ibid.*, p. 4169.
22 R. C. Petersen, J. H. Markgraf, and S. D. Ross, *J. Am. Chem. Soc.*, 1961, **83**, 3819.
23 R. C. Petersen, *J. Org. Chem.*, 1964, **29**, 3133.

Received 28*th January* 1985; *Paper* 5/153