Effects of inorganic salts and mixed aqueous-organic solvents on the rates of alkaline hydrolysis of aspirin

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The observed pseudo-first order rate constants, $k_{obs}$, for the hydroxide ion-catalyzed hydrolysis of aspirin reveal a nonlinear increase with increase in the concentrations of inorganic salts such as NaCl, Na$_2$CO$_3$, KCl and BaCl$_2$. The observed rate constants, $k_{obs}$, are quite sensitive to the valence state of cations and almost insensitive to the valence state of anions of the salts. These observations are explained in terms of ion-pair formation between the cations and the aspirin anion. An increase in the content of CH$_3$CN in mixed aqueous solvents containing 0.01 mol dm$^{-3}$ MOH (M$^+$ = Li$^+$, Na$^+$ and K$^+$) causes a decrease in $k_{obs}$ until nearly 50%, v/v CH$_3$CN and then an increase in $k_{obs}$ with further increase in the contents of CH$_3$CN. These results are the consequence of the medium and ion-pair formation effects. The values of $k_{obs}$ increase with the increase in the contents of CH$_3$OH until ca. 20%, v/v, in mixed aqueous solvents containing 0.01 and 0.001 mol dm$^{-3}$ NaOH and 2%, v/v, CH$_3$CN. A further increase in the contents of CH$_3$OH beyond ca. 20%, v/v, results in a decrease in $k_{obs}$. These observations are shown to be the consequence of both the medium effect and the fact that $k_{OCH_3} = 58k_{OH}$ where $k_{OCH_3}$ and $k_{OH}$ represent the second order rate constants for $-OCH_3$- and $OH$-catalyzed methanolysis and hydrolysis of aspirin anion, respectively.

Solvent effects on rates of pH-independent hydrolysis of aspirin have been studied by a number of workers. However, such studies on the rates of reactions of OH$^-$ with aspirin anion are almost non-existent. Vera and Rodenas observed that $k_{obs}$ for the reaction of OH$^-$ with aspirin anion increased by nearly 60% due to the increase in [KBr] from 0.0 to 0.5 mol dm$^{-3}$ and these results were correlated to the extended Debye-Huckel law. We initiated the present study to explore the possibility of the occurrence of specific solvation effects on the rates of reaction of OH$^-$ with aspirin anion. Since the specific solvation effects in such reactions appear to be the consequence of the ion-pair formation, we studied the salts of mono- and divalent cations and anions. The results and probable explanations are described in this paper.

Materials and Methods

Reagent grade aspirin was obtained from Merck. All other chemicals used were also of reagent grade and were commercial products. Distilled water was used throughout. The stock solutions of aspirin were frequently prepared in acetonitrile.

Kinetic measurements

Under alkaline pH, aspirin does not absorb strongly at 300 nm (molar extinction coefficient at 300 nm, $\varepsilon$$_{300} = 200 - 300$ mol$^{-1}$ dm$^{-3}$ cm$^{-1}$) while salicylate ion (sal$^-$) absorbs strongly at 300 nm ($\varepsilon$$_{300} = 3200$ mol$^{-1}$ dm$^{-3}$ cm$^{-1}$). Therefore, the reaction rates of alkaline hydrolysis of aspirin were studied spectrophotometrically by monitoring the appearance of the product, the salicylate ion, at 300 nm.

In a typical kinetic run, all reactants, except aspirin, required for a particular experiment (14.7 cm$^3$) were placed in a 50 cm$^3$ reaction vessel and thermally equilibrated for 5-10 minutes at 30°C. The reaction was then initiated by adding 0.3 cm$^3$ of 0.01 mol dm$^{-3}$ aspirin solution prepared in acetonitrile. An aliquot of ca. 2.5 cm$^3$ was quickly withdrawn from the reaction mixture and transferred to a 3 cm$^3$ quartz cuvette kept in the thermostated cell compartment of the spectrophotometer. The increase in absorbance (at 300 nm) with time was monitored by the use of a Shimadzu UV-VIS-NIR spectrophotometer, model UV-3101PC, equipped with an NEC powermate 286 plus microprocessor, NEC multisync 2A monitor, and DXY1100 plotter. Constant temperature
observed pseudo-first order rate constants, $k_{obs}$, are shown graphically as a function of [salt] in Fig. 1. The rate constants revealed a fast increase at low concentration followed by a slow increase at high concentration of each salt. These observed data cannot be explained in terms of Debye-Huckel limiting law because the lowest salt concentration attained in each case was much higher than the limiting concentration (0.01 mol dm$^{-3}$ for salts like NaCl and < 0.01 mol dm$^{-3}$ for salts like BaCl$_2$) above which Debye-Huckel limiting law is no longer valid. The effect of [BaCl$_2$] on $k_{obs}$ is significantly larger than that of [Na$_2$CO$_3$] within the same concentration range. The effect of [Na$_2$CO$_3$], however, is only slightly larger compared to that of [NaCl] under similar conditions.

This shows that the rate of hydrolysis of As$^-$ is more sensitive to the valence state of the cation and almost independent of the valence state of the anion. Such observations may be easily explained in terms of ion-pair formation between cations M$^+$ or M$^{n+}$, of the salt and As$^-$. The major reaction steps involved in the hydroxide ion-catalyzed cleavage of As$^-$ may be given as in Scheme 1.

\[
\text{AS}^- + M^{n+} \rightarrow \text{AS}^- \ldots M^n \quad n = 1 \text{ or } 2
\]
\[
\text{AS}^- + \text{OH}^- \xrightarrow{k_0} \text{Salicylate ion} + \text{acetate ion}
\]
\[
\text{AS}^- \ldots M^{n+} + \text{OH}^- \xrightarrow{k'_s} \text{Salicylate ion} + \text{acetate ion}
\]

In Scheme 1, AS$^- \ldots M^{n+}$ ($n = 1$ or 2) represents the hydrated loose ion-pair, $K_A$ is the association constant for the hydrated loose ion-pair formation, and, $k_0'$ and $k'_s$ are the second-order rate constants for the reaction of OH$^-$ with AS$^-$ and AS$^- \ldots M^{n+}$, respectively. Although the hydrated loose ion-pair formation between M$^{n+}$ ($M = Na$, K and Ba; and $n = 1$ or 2) and X$^-$ ($X = OH^-$, Cl$^-$ and CO$_3^{2-}$, and k = 1 or 2) is not considered in Scheme 1, the existence of such ion-pairs cannot be completely ruled out. However, the effects of these ion-pairs seem to be kinetically unimportant in these and related reactions. It appears that hydrated cations, M$^{n+}$ ($n = 1$ and 2), and hydrated loose ion-pairs, M$^{n+}$ ... X$^-$ ($n = k = 1$ and 2) do not have kinetically detectable different affinities toward the formation of hydrated loose ion-pairs with AS$^-$. Similarly, the nucleophilicity toward AS$^-$ or AS$^- \ldots M^{n+}$ carbonyl carbon, of hydrated

The simple hydrolysis of aspirin under alkaline medium is expected to produce salicylate and acetate ions. The molar extinction coefficients of acetate ion and salicylate ion are nearly zero and 3200 dm$^3$ mol$^{-1}$ cm$^{-1}$, respectively. The observed values of $\varepsilon_{app}$ ($\varepsilon_{app} = \varepsilon_{sal} - \varepsilon_{As}$ where $\varepsilon_{sal}$ and $\varepsilon_{As}$ represent the molar extinction coefficients of salicylate ion and aspirin anion, As$^-$, respectively) at 2%, v/v, CH$_3$CN gave the value of $\varepsilon_{sal}$ as 3500 dm$^3$ mol$^{-1}$ cm$^{-1}$ which is not significantly different from $\varepsilon_{sal}$ (= 3200 dm$^3$ mol$^{-1}$ cm$^{-1}$) obtained using an authentic sample of salicylate ion.

**Results and Discussion**

**Effects of inorganic salts**

A series of kinetic runs was carried out at 0.01 mol dm$^{-3}$ OH$^-$ and at different concentrations of salt such as NaCl, KCl, Na$_2$CO$_3$ and BaCl$_2$. The (30°C) of the cell compartment was controlled by circulating water.

All the kinetic runs were carried out under pseudo-first order kinetic conditions. The observed pseudo-first order rate constants, $k_{obs}$, were calculated from Eq. (1)

\[
A_{obs} = \varepsilon_{app} [X]_0 [1 - \exp(-k_{obs}t)] + A_0 \quad (1)
\]

nonlinear least squares technique considering $\varepsilon_{app}$ (apparent molar extinction coefficient) and $A_0$ (the absorbance at $t = 0$) also as unknown parameters.

In Eq. (1), $A_{obs}$ is the absorbance at any time, and $[X]_0$ is the initial concentration of aspirin. The reactions were carried out for up to 4-9 half lives and the observed data fitted well into Eq. (1).

**Product analysis**

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OH\(^-\) seems to be similar to that of hydrated ion-pair, M\(^{n+}\) ... OH\(^-\). For these reasons, the kinetic terms involving reactions between As\(^-\) and M\(^{n+}\) ... OH\(^-\) and As\(^-\) ... M\(^{n+}\) and M\(^{n+}\) ... OH\(^-\) have been ignored in Scheme 1.

As per Scheme 1, the general rate law for the alkaline hydrolysis of AS\(^-\) under the presence of a salt may be given as:

\[
\text{rate} = (k_0[AS^-] + k_s[AS^- \cdot M^{n+}])[OH^-] \quad \ldots \quad (2)
\]

The observed rate law: rate = \(k_{obs}[AS^-]\), where \([AS^-]' = [AS^-]+[M^{n+} \cdot AS^-]\), and Eq. (2) can lead to Eq. (3)

\[
k_{obs} = \frac{k_0 + k_s K_A[M_kX_n]}{1 + K_A[M_kX_n]} \quad \ldots \quad (3)
\]

where \(k_0 = k_0[OH^-], \quad k_s = k_s[OH^-]\) and \([M_kX_n]\) represents the total concentration of salt.

In the data treatment with Eq. (3), the rate constant, \(k_0\) was obtained experimentally at \([M_kX_n]=0\). The nonlinear least squares technique was used to calculate the unknown parameters, \(k_s\) and \(K_A\) from Eq. (3). These results are summarised in Table 1.

The increase in \([\text{BaCl}_2]\) from 0.0 to 0.03 mol dm\(^{-3}\) increases \(k_{obs}\) from \(16.3 \times 10^{-4}\) to \(27.2 \times 10^{-4}\) s\(^{-1}\) while similar increase in \([\text{Na}_2\text{CO}_3]\) causes the increase in \(k_{obs}\) from \(16.3 \times 10^{-4}\) to \(20.4 \times 10^{-4}\) s\(^{-1}\) under same \([\text{NaOH}] = 0.01\) mol dm\(^{-3}\). Similarly, the increase in \([\text{NaCl}]\) from 0.0 to 0.03 mol dm\(^{-3}\) causes the increase in \(k_{obs}\) from \(16.3 \times 10^{-4}\) to \(18.1 \times 10^{-4}\) s\(^{-1}\) at 0.01 mol dm\(^{-3}\) NaOH. These observations indicate that the rate of alkaline hydrolysis of AS\(^-\) is significantly sensitive to the valence state of the cation and almost insensitive to the valence state of the anion of a salt. Similar observations were obtained in the alkaline hydrolysis of ionized N-hydroxyphthalimide (NHP\(^-\))\(^7\). The insensitivity of the rate to the valence state of anion has been also observed in the alkaline hydrolysis of potassium ethyl malonate\(^6\). Unusually large catalytic effects of divalent cations such as Ba\(^{2+}\) have been observed in many related reactions and these catalytic effects are attributed to the ion-pair formation between cations of the salts and anionic substrates\(^9,10\).

The value of \(K_A (=1.3\pm0.3\text{ dm}^3\text{ mol}^{-1})\) for NaCl is almost similar to \(K_A (=1.2\pm0.2\text{ dm}^3\text{ mol}^{-1})\) for \(\text{Na}_2\text{CO}_3\) obtained on the basis of the use of apparent total concentration of sodium ions. The value of \(K_A\) for \(\text{BaCl}_2\), although associated with significantly high standard deviation, is much larger than \(K_A\) for NaCl, \(\text{Na}_2\text{CO}_3\) and KCl (Table 1). This is conceivable in terms of ion-pair formation as shown in Scheme 1. It is interesting to note that the \(K_A\) values for NaCl, \(\text{Na}_2\text{CO}_3\) and KCl are not significantly different from the corresponding values obtained in the alkaline hydrolysis of NHP\(^-\) under similar experimental conditions\(^7\).

The values of \(k_s\) are nearly 2-3 times larger than \(k_0\) for the salts used in this study (Table 1). The value of \(k_s/k_0 (=2)\) for \(\text{BaCl}_2\) is significantly smaller than \(k_s/k_0 (=14)\) obtained for \(\text{BaCl}_2\) in the alkaline hydrolysis of NHP\(^-\) (ref. 7). The ion-pair formation as shown in I is expected to decrease the rate decreasing effect of \(\sigma\)-CO\(_2\) group in the \(\text{OH}^-\) ion-catalyzed cleavage of AS\(^-\). Thus,

\[
\begin{align*}
\text{O} & \quad \text{O} \quad \text{C} \quad \text{CH}_3 \\
\text{C} & \quad \text{O} \quad \cdot \quad \cdot \quad \cdot \\
\text{N} & \quad \text{H} \\
\text{M}^{n+} & \quad \text{H}
\end{align*}
\]
Effects of [NaOH] on the hydrolytic cleavage of AS⁻ at 76%, v/v, CH₃CN in mixed CH₃CN-H₂O solvents

The rate of hydrolysis of AS⁻ was studied under varying [NaOH] ranging from 0.005 to 0.030 mol dm⁻³ at 76%, v/v, CH₃CN in mixed aqueous solvents. The observed pseudo-first order rate constants, k_{obs}, revealed a linear increase with the increase in [NaOH] and were treated with Eq. (4).

\[ k_{obs} = k_0 + k_{OH}[OH⁻] \]  \( \text{(4)} \)

The linear least-squares calculated values of \( k_0 \) and \( k_{OH} \) turned out to be \( (-3.7 ± 1.0) \times 10^{-4} \) s⁻¹ and \( 0.175 ± 0.005 \) dm³ mol⁻¹ s⁻¹, respectively. The negative values of \( k_0 \) is chemically meaningless and may be considered as the consequence of the insignificant contribution of \( k_0 \) term compared with \( k_{OH}[OH⁻] \) term under the experimental conditions imposed. The reported values of \( k_0 \) are \( 2.56 \times 10^{-6} \) s⁻¹ at 25°C (ref. 12) and \( 1.0 \times 10^{-6} \) s⁻¹ at 39°C (ref. 13). These values of \( k_0 \) indicate the maximum contribution of \( k_0 \) (expected at the lowest \([OH⁻] = 0.005 \) mol dm⁻³) is less than 0.5%. Thus, \( k_0 \) may be neglected compared with \( k_{OH}[OH⁻] \) in Eq. (4). The value of \( k_{OH} \) calculated from the relationship: \( k_{obs} = k_{OH}[OH⁻] \), turned out to be \( 0.145 ± 0.022 \) dm³ mol⁻¹ s⁻¹.

The observed linear increase in \( k_{obs} \) with the increase in \([OH⁻] \), from 0.005 to 0.030 mol dm⁻³ at 76%, v/v, CH₃CN is consistent with Scheme 1 as shown by Eq. (5) for the hydrolytic cleavage of aspirin anion.

Previous studies on related reactions in aqueous medium reveal that the nucleophilic attack by hydroxide ion at the carbonyl carbon involving transition state, II, is the rate-determining step.
Effects of mixed CH$_3$CN-H$_2$O solvents on the hydrolytic cleavage of AS$^-$ at 30°C

The hydrolytic cleavage of aspirin was studied at 0.01 mol dm$^{-3}$ MOH (M$^+$ = Li$^+$, Na$^+$ and K$^+$) and at different contents of CH$_3$CN in mixed H$_2$O-CH$_3$CN solvents. The observed pseudo-first order rate constants, $k_{obs}$, are shown graphically in Fig. 2. The rate constants, $k_{obs}$, decrease with the increase in the contents of CH$_3$CN from 2 to nearly 50%, v/v. A further increase in the contents of CH$_3$CN beyond 50%, v/v, causes an increase in $k_{obs}$. Similar observations were obtained in the alkaline hydrolysis of ionized N-hydroxypthalimide (NHP$^-$) and anionic monomethylphthalate in mixed H$_2$O-CH$_3$CN and H$_2$O-1,4-dioxan solvents, respectively.

According to simple electrostatic theory, the rate of a bimolecular reaction involving anionic reactants should decrease with the decrease in the dielectric constant ($\varepsilon$) of the reaction medium. In the electrostatic treatment of the effects of $\varepsilon$ on reaction rates, the charges on the reactants are presumed to be lying on the reaction site while in the present system, the negative charge on the reactant AS$^-$ is not lying exactly at the specific reaction site. Thus, the use of simple electrostatic theory to predict the effects of $\varepsilon$ on the reaction rates of such reactions is rather hazardous.

The effects of mixed H$_2$O-CH$_3$CN solvents on $k_{obs}$ may be attributed to be combined effects of the following seemingly different reactant-solvent interactions: (i) Differential solvation effects on ground and transition states; (ii) solvation effect on the nucleophilicity of the nucleophile; (iii) decrease in the activity of ionic species with a decrease in the dielectric constant of the reaction medium; (iv) solvation effect on the ion-pair formation; and (v) specific medium effect due to specific solvent-anionic or cationic solute interaction.

The charge density of the transition state (II) is apparently lower than that of the reactant state and hence the increase in the contents of CH$_3$CN (a poorer solvating medium compared to water), in mixed H$_2$O-CH$_3$CN solvents, is expected to destabilize the reactant state more strongly than II and this could lead to an increase in the rate of reaction. However, in the mixed solvents such as H$_2$O-CH$_3$CN, the cations and anions of high charge density are preferentially solvated by only water molecules and therefore the differential solvation effects on reactant and transition states may be realized only at very high contents of the poor solvating solvent component of the mixed aqueous solvents. Acetonitrile is poorer than wa-

ter in solvating ionic solutes and therefore the increase in the contents of CH$_3$CN in mixed aqueous solvents is expected to increase the apparent nucleophilicity of hydroxide ion. This effect is, however, partially or fully counterbalanced or even dominated by the decrease in the activity of hydroxide ion with the decrease in the dielectric constant of the reaction medium. This effect has been ascribed to the increase in the rate of uncatalyzed hydrolysis of monophenylphthalate anion with the increase in the contents of DMSO and 1,4-dioxan in mixed aqueous solvents.

The decrease in the dielectric constant of the reaction medium increases the tendency of stable ion-pair formation the increase in the tendency of stable ion-pair formation between the anion (OH$^-$) and the cation (Li$^+$, Na$^+$ and K$^+$) will decrease the apparent nucleophilicity of the nucleophile (OH$^-$). But the ion-pair formation between the anionic carboxylate group of AS$^-$ and its counterion (Li$^+$, Na$^+$ and K$^+$) will increase the apparent electrophilicity of ester carbonyl carbon. These two opposite effects of ion-pair formation reduce the detectability of the effects of ion-pair formation on the rate of reaction. The specific medium effect which is the consequence of the preferential solvation of specific type of ion (either cation or anion) by the organic cosolvent in mixed aqueous solvent is probably the most effective solvent effect on the rates of reactions described in this paper. Aprotic organic cosolvents (such as acetonitrile and 1,4-dioxan) solvate anionic reactants and transition states poorly compared with protic organic cosolvents (such as methanol and ethanol) in mixed aqueous solvents of similar dielectric constants. The cations are apparently more strongly solvated compared to the anions by the aprotic organic cosolvents (such as acetonitrile and 1,4-dioxan) in mixed aqueous solvents. Such differential solvation effects on cations and anion are expected to either increase the stability of the ion-pair formed between anion and cation or increase the nucleophilicity of the nucleophile if the ion-pair formation is prevented by the geometric constraint of the system.

It is interesting to note that the increase in $k_{obs}$ with the increase in the contents of acetonitrile was observed at $\geq 50\%$, v/v CH$_3$CN in the presence of 0.01 mol dm$^{-3}$ MOH (M$^+$ = Li$^+$, Na$^+$ and K$^+$). Similar observations were obtained in the alkaline hydrolysis of ionized N-hydroxypthalimide. The increase in $k_{obs}$ with the increase in the contents of CH$_3$CN beyond 50%, v/v CH$_3$CN, was attributed to specific medium
effect\(^{18}\). Similar specific medium effect may be ascribed to the observed increase in \(k_{\text{obs}}\) with the increase in contents of CH\(_3\)CN beyond 50%, v/v, in mixed aqueous solvents (Fig. 2). The values of \(k_{\text{obs}}^{80\%}/k_{\text{obs}}^{50\%}\) (where \(k_{\text{obs}}^{80\%}\) and \(k_{\text{obs}}^{50\%}\) represent \(k_{\text{obs}}\) obtained at 80 and 50%, v/v, CH\(_3\)CN, respectively) are 1.5, 1.8 and 1.7 at 0.01 mol dm\(^{-3}\) LiOH, NaOH and KOH, respectively. Similarly, in the alkaline hydrolysis of ionized N-hydroxyphthalimide (NHP\(^{-}\)), the values of \(k_{\text{obs}}^{80\%}/k_{\text{obs}}^{50\%}\) are 7.0, 6.0 and 4.5 at 0.01 mol dm\(^{-3}\) LiOH, NaOH and KOH, respectively\(^{14}\). The larger specific medium effect in the alkaline hydrolysis of NHP\(^{-}\) compared to that of AS\(^{-}\) may be described as follows.

The decrease in apparent nucleophilicity of hydroxide ion due to ion-pair formation between OH\(^{-}\) and M\(^{+}\) (M\(^{+}\) = Li\(^{+}\), Na\(^{+}\) and K\(^{+}\)) is apparently the same in the alkaline hydrolysis of both AS\(^{-}\) and NHP\(^{-}\) under similar experimental conditions. The increase in the apparent electrophilicity of carbonyl carbon due to ion-pair formation between M\(^{+}\) and anionic carboxylate group of AS\(^{-}\) and M\(^{+}\) > N-O\(^{-}\) group of NHP\(^{-}\) is expected to be proportional to the magnitude of \(k_{\text{SH}}^{\text{OH}}/k_{\text{SH}}^{\text{H}}\), where \(k_{\text{SH}}^{\text{OH}}\) and \(k_{\text{SH}}^{\text{H}}\) represent the hydroxide ion-catalyzed second order rate constants for neutral (SH = ASH or NHPH) and anionic (S\(^{-}\) = AS\(^{-}\) or NHP\(^{-}\)) substrate, respectively. Thus, a complete loss of negative charge density on anionic group of the substrate due to tight intimate ion-pair formation may lead to a rate increase up to a maximum of nearly 140-fold for NHP\(^{-}\) and 7-fold for AS\(^{-}\). The 20-fold larger expected maximum specific medium effect on \(k_{\text{obs}}\) for NHP\(^{-}\) compared to that for AS\(^{-}\) is most likely the main reason for the low values of \(k_{\text{obs}}^{80\%}/k_{\text{obs}}^{50\%}\) at 0.01 mol dm\(^{-3}\) MOH for AS\(^{-}\) compared to that for NHP\(^{-}\).

**Effects of mixed CH\(_3\)OH-H\(_2\)O solvents on the hydrolytic cleavage of ASH at 0.01 mol dm\(^{-3}\) NaOH**

A series of kinetic runs was carried out for the hydrolytic cleavage of ASH at 0.01 mol dm\(^{-3}\) NaOH and within the methanol content range of 1-84%, v/v, in mixed aqueous solvents. The observed pseudo-first order rate constants, \(k_{\text{obs}}\) (Fig. 2) showed an increase with the increase in the contents of CH\(_3\)OH until 18%, v/v, and a further increase in the contents of CH\(_3\)OH beyond 18%, v/v, caused a gradual decrease in \(k_{\text{obs}}\). Similar observations were obtained at 0.001 mol dm\(^{-3}\) NaOH. These observations suggest the occurrence of methanolysis of AS\(^{-}\) in mixed CH\(_3\)OH-H\(_2\)O solvents. The increase in the contents of CH\(_3\)OH in mixed CH\(_3\)OH-H\(_2\)O solvents caused the increase in [CH\(_3\)OH] and the decrease in the dielectric constant of the reaction medium. The decrease in the dielectric constant is expected to decrease \(k_{\text{obs}}\) if the rate of cleavage of AS\(^{-}\) involves two anionic reactants (e.g. AS\(^{-}\) and OH\(^{-}\) as well as AS\(^{-}\) and CH\(_3\)O\(^{-}\)).

The plots as shown in Fig. 2 display the combined effects of [CH\(_3\)OH] and the dielectric constant of the reaction medium on the rate of cleavage of AS\(^{-}\).

The \(pH\)-independent rate of hydrolysis of aspirin has been shown to involve intramolecular general base (1GB) catalysis where \(\sigma\)-CO\(^{2-}\) group of AS\(^{-}\) acts as 1GB catalyst for hydrolysis of AS\(^{-}\) (refs 12, 13). The observed pseudo-first order rate constants, \(k_{\text{obs}}\), for the \(pH\)-independent cleavage of aspirin were found to be increased by nearly 10-fold with the increase in the contents of CH\(_3\)OH from 0 to 50%, v/v, in the mixed CH\(_3\)OH-H\(_2\)O solvents\(^{1e}\). These observations may be attributed to the much larger 1GB-catalyzed rate of methanolysis than 1GB-catalyzed rate of hydrolysis of aspirin. We have shown that \(k_{\text{obs}}\) for 1GB-catalyzed methanolysis of ionized phenyl salicylate (PS\(^{-}\)) is nearly 200-fold larger than for 1GB-catalyzed hydrolysis of PS\(^{-}\) (ref. 19). In view of these observations if the rate of methanolysis of aspirin at 0.01 mol dm\(^{-3}\) NaOH involves AS\(^{-}\) and CH\(_3\)OH as the reactants, then the increase in \(k_{\text{obs}}\) with the increase in [CH\(_3\)OH] should be independent of the change in [NaOH] at the low CH\(_3\)OH content. But the significantly larger increase (\(\Delta k\)) in \(k_{\text{obs}}\), at 0.01 mol dm\(^{-3}\) NaOH (\(\Delta k = 13.8 \times 10^{-4}\) s\(^{-1}\)) than at 0.001 mol dm\(^{-3}\) NaOH (\(\Delta k = 0.7 \times 10^{-4}\) s\(^{-1}\)) with the increase in CH\(_3\)OH contents from 2 to 6%, v/v (Fig. 2) indicates that the rate of methanolysis does not involve AS\(^{-}\) and CH\(_3\)OH as the reactants under the experimental conditions of present study. The rate of methanolysis of AS\(^{-}\) presumably involves AS\(^{-}\) and CH\(_3\)O\(^{-}\) as reactants.

The general rate law for the cleavage of AS\(^{-}\) in mixed CH\(_3\)OH-H\(_2\)O solvents containing a constant total [OH\(^{-}\)]\(_{T}\) may be given as

\[
\text{rate} = (k_{\text{OH}}[\text{OH}^-] + k_{\text{OCH}_3}[\text{OCH}_3^-])[\text{AS}^-]_{T} 
\]  \(\text{... (6)}\)
The observed reaction rate is governed by the following reversible reaction:

$$\text{CH}_3\text{OH} + \text{OH}^- \rightleftharpoons \text{OCH}_3^- + \text{H}_2\text{O} \quad \ldots (7)$$

The equilibrium constant, $K$, is equal to $K_{\text{CH}_3\text{OH}}/K_{\text{H}_2\text{O}}$ where $K_{\text{CH}_3\text{OH}}$ and $K_{\text{H}_2\text{O}}$ represents the ionization constant of CH$_3$OH and H$_2$O, respectively. The Eqs (6) and (7) can lead to Eq. (8)

$$\text{rate} = \left( \frac{k_{\text{OH}} + k_{\text{OCH}_3}KY}{1 + KY} \right) [\text{OH}^-]_T [\text{AS}^-]_T \quad \ldots (8)$$

where $Y = [\text{CH}_3\text{OH}]_T/[\text{H}_2\text{O}]_T$, $[\text{OH}^-]_T = [\text{OH}^-] + [\text{OCH}_3^-]$, $[\text{CH}_3\text{OH}]_T = [\text{CH}_3\text{OH}] + [\text{CH}_3\text{O}^-]$ and $[\text{H}_2\text{O}]_T = [\text{H}_2\text{O}] + [\text{OH}^-]$.

But since $[\text{CH}_3\text{OH}] >> [\text{CH}_3\text{O}^-]$ and $[\text{H}_2\text{O}] >> [\text{OH}^-]$ under the experimental conditions imposed, $[\text{CH}_3\text{OH}] = [\text{CH}_3\text{OH}]_T$ and $[\text{H}_2\text{O}] = [\text{H}_2\text{O}]_T$.

The observed rate law: $k_{\text{obs}} = \alpha [\text{OH}^-]_T$ and Eq. (8) yield Eq. (9)

$$k_{\text{obs}}(1 + KY) = k_{\text{OH}}[\text{OH}^-]_T + k_{\text{OCH}_3}K[\text{OH}^-]_T Y \quad \ldots (9)$$

The rate constants, $k_{\text{obs}}$, obtained at 0.01 mol dm$^{-3}$ and 0.001 mol dm$^{-3}$ NaOH and within the CH$_3$OH content range 1 to 8%, v/v, obeyed Eq. (9) with least squares calculated respective values of $k_{\text{OH}}[\text{OH}^-]_T$ and $k_{\text{OCH}_3}K[\text{OH}^-]_T$ as $(16.6 \pm 0.5) \times 10^{-4}$ s$^{-1}$ and $(78.1 \pm 2.0) \times 10^{-3}$ s$^{-1}$ at 0.01 mol dm$^{-3}$ NaOH and $(1.28 \pm 0.14) \times 10^{-4}$ s$^{-1}$ and $(4.53 \pm 0.48) \times 10^{-3}$ s$^{-1}$ at 0.001 mol dm$^{-3}$ NaOH. The known reported values of $K = 1.22$ was obtained from the reported values of $pK_{\text{CH}_3\text{OH}} = 15.7$ and $pK_{\text{H}_2\text{O}} = 15.75$. The calculated values of $k_{\text{OH}}[\text{OH}^-]_T$ and $k_{\text{OCH}_3}K[\text{OH}^-]_T$ at 0.01 mol dm$^{-3}$ are not very reliable because they are derived from only three observed data points. The fitting of the observed data to Eq. (9) is evident from the plots of Fig. 3 where the solid lines are drawn through least-squares calculated points. The observed points at $\geq 10\%$, v/v, CH$_3$OH showed increasing negative deviations from linearity (broken line in Fig. 3) which indicates that under such conditions, the medium effect cannot be neglected compared to the [CH$_3$OH] effect on $k_{\text{obs}}$. The calculated value of $k_{\text{OH}} = 0.169$ dm$^3$ mol$^{-1}$ s$^{-1}$; $k_{\text{OH}} = 16.6 \times 10^{-4}$/([NaOH][[AS$^-$]$_T$]) is comparable with $k_{\text{OH}} = 0.166$ dm$^3$ mol$^{-1}$ s$^{-1}$ obtained under similar experimental conditions with [CH$_3$OH] is zero.

It is of interest to note that the values of $k_{\text{obs}}$ increase with the increase in the contents of CH$_3$CN beyond $\geq 50\%$, v/v, in mixed CH$_3$CN-H$_2$O solvents (Fig. 2). But the values of $k_{\text{obs}}$ decrease with the increase in the contents of CH$_3$OH even until 84%, v/v, CH$_3$OH in mixed CH$_3$OH-H$_2$O solvents. Similar observations were obtained in the hydroxide ion-catalyzed cleavage of ionized N-hydroxyphthalimide. These observations may be attributed to the differential solvation effects on anions and cations at considerably high contents of organic cosolvents in mixed aqueous solvents.

Effects of [NaOH] on rate of methanolation of AS$^-$

A few kinetic runs were carried out at different [NaOH] ranging from 0.010-0.035 mol dm$^{-3}$ at a constant ionic strength of 0.04 mol dm$^{-3}$ (maintained by KCl) and [CH$_3$OH]. The observed pseudo-first order rate constants, $k_{\text{obs}}$, were found to fit to the empirical Eq. (10).

$$k_{\text{obs}} = \alpha [\text{OH}^-]_T \quad \ldots (10)$$

The unknown empirical parameter, $\alpha$, was calculated from Eq. (10) and these calculated values at different [CH$_3$OH] are summarized in Table 2.

Equation (10) is similar to Eq. (9) with

$$\alpha = \frac{k_{\text{OH}} + k_{\text{OCH}_3}KY}{1 + KY} \quad \ldots (11)$$

Equation (11) predicts that the plot of $\alpha (1 + KY)$ versus Y must be linear. Such a plot as shown in Fig. 3 is indeed linear. The least squares calculated
values of intercept ($k_{OH}$) and slope ($Kk_{OH3}$) of this linear plot are $0.172 \pm 0.009$ dm$^3$ mol$^{-1}$ s$^{-1}$ and $11.2 \pm 0.6$ dm$^3$ mol$^{-1}$ s$^{-1}$, respectively. It may be worth to mention that the presence of organic solvents such as methanol may be expected to decrease the activity of hydroxide ion ($a_{OH}$). But Eq. (10) was tested with $k_{obs}$ obtained at different $[OH^-]$, keeping [CH$_3$OH] and ionic strength constant. Under such conditions, the activity coefficients of OH$^-$ and OCH$_3$ remained constant. Hence the empirical constant $\alpha$ includes the activity coefficient term. The $\alpha$ values were obtained within the CH$_3$OH content range of 1-5%, v/v. If the changes in the activity coefficient with change in the content of CH$_3$OH from 1 to 5%, v/v, were kinetically significant, then the $\alpha$ values were not expected to fit Eq. (11). But the reasonably good fit of $\alpha$ values to Eq. (11) and the calculated value of $k_{OH}$ ($=0.172$ dm$^3$ mol$^{-1}$ s$^{-1}$) which is not significantly different from $k_{OH}$ ($=0.166$ dm$^3$ mol$^{-1}$ s$^{-1}$) obtained under similar conditions with (CH$_3$OH) = 0, indicate that the changes in the activity coefficient with change in CH$_3$OH content from 1 to 5%, v/v, were kinetically insignificant.

The calculated value of $k_{OH}$ ($=0.172$ dm$^3$ mol$^{-1}$ s$^{-1}$) may be compared with the reported values of $k_{OH}$ ($0.216$ dm$^3$ mol$^{-1}$ s$^{-1}$ at 25°C and 1.0 mol dm$^{-3}$ ionic strength) and $0.565$ dm$^3$ mol$^{-1}$ s$^{-1}$ at 39°C and 1.0 mol dm$^{-3}$ ionic strength). Interestingly, the value of $k_{OCH3}$ ($=10.0$ dm$^3$ mol$^{-1}$ s$^{-1}$) is nearly 58-fold larger than $k_{OH}$ ($=0.172$ dm$^3$ mol$^{-1}$ s$^{-1}$). Jencks and Gilchrist reported nearly 68-fold larger values of $k_{OCH}$ compared to that of $k_{OH}$ in the cleavage of phenyl acetate. The nearly 58-fold larger reactivity toward AS$^-$ of OCH$_3$ than that of OH$^-$ may be attributed to the difference in the solvation energy of these ions in aqueous solvents.

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**References**