Formation of a cyclic tetrahedral intermediate by the addition of water to 2-methyl-4H-3,1-benzoxazine followed by ring opening to 2-aminobenzyl acetate and 2-acetylaminobenzyl alcohol; pH-dependence of rate of reaction and product ratio

Wendy J. Dixon and Frank Hibbert

Abstract: Kinetic studies have shown that addition of water to protonated 2-methyl-4H-3,1-benzoxazine occurs to give a cyclic tetrahedral carbonyl addition intermediate. At pH <5, the intermediate is protonated and reacts to 2-aminobenzyl acetate, whereas at pH >7.5, the unprotonated intermediate collapses to give 2-acetylaminobenzyl alcohol. The former reaction is catalysed by buffer base but the latter is uncatalysed. At pH 9–12, reaction of hydroxide ion with protonated 2-methyl-4H-3,1-benzoxazine to give 2-acetylaminobenzyl alcohol becomes important, and at pH >12, the same product is formed by reaction of hydroxide ion with unprotonated 2-methyl-4H-3,1-benzoxazine.

Key words: mechanism, addition, tetrahedral intermediate, hydrolysis, pH profile.

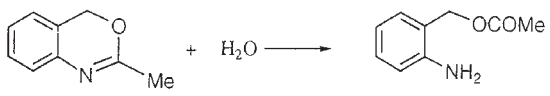
Résumé : Des études cinétiques ont montré que l'addition d'eau à la 2-méthyl-4*H*-3,1-benzoxazine protonée se produit pour donner un intermédiaire d'addition au carbonyle de nature tétraédrique et cyclique. À un pH <5, l'intermédiaire est protoné et réagit vers l'acétate du 2-aminobenzyle alors qu'à pH >7,5, l'intermédiaire non protoné se décompose pour donner l'alcool 2-acétylaminobenzylique. La première réaction est catalysée par une base tampon, mais la dernière n'est pas catalysée. À des pH allant de 9–12, la réaction de l'ion hydroxyde avec la 2-méthyl-4*H*-3,1-benzoxazine protonée conduisant à l'alcool 2-acétylaminobenzylique devient important et à un pH >12, le même produit se forme par réaction de l'ion hydroxyde avec 2-méthyl-4*H*-3,1-benzoxazine non protonée.

Mots clés : mécanisme, addition, intermédiaire tétraédrique, hydrolyse, profil de pH.

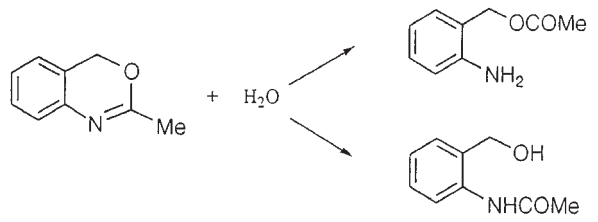
[Traduit par la Rédaction]

Introduction

In the pH range 1–5, 2-methyl-4H-3,1-benzoxazine undergoes addition of water and ring opening to give 2-aminobenzyl acetate, eq. [1] (1). The form of the rate coefficient – pH profile and the observation of rectilinear plots of rate coefficient against the concentration of buffer base have identified the mechanism shown in Scheme 1. The collapse of the cyclic tetrahedral intermediate to product involves uncatalysed and buffer base (B) catalysed pathways, and the variation of the observed first-order rate coefficient with concentration of buffer base is given by eq. [2]. At low buffer concentrations, buffer base catalysed collapse of the tetrahedral intermediate to 2-aminobenzyl acetate is rate-limiting, but at high buffer concentrations, addition of water to protonated 2-methyl-4H-3,1-benzoxazine becomes rate-limiting. In previous studies, measurements were limited to pH <5, under which conditions reaction occurs to give 2-aminobenzyl acetate in greater than ca. 95% yield. At higher pH values, it was noted (1) that increasing amounts of 2-acetylaminobenzyl alcohol were formed, eq. [3]. It was also found that at fixed pH the proportion of 2-aminobenzyl ace-

[1] 

[2] $$k_{obs} = \frac{[H_3O^+]}{K_{SH^+} + [H_3O^+]} \times \frac{k_1(k_2 + k_B[B])}{k_{-1} + k_2 + k_B[B]}$$

[3] 

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This paper is dedicated to Jerry Kresge in recognition of his many achievements in chemistry.

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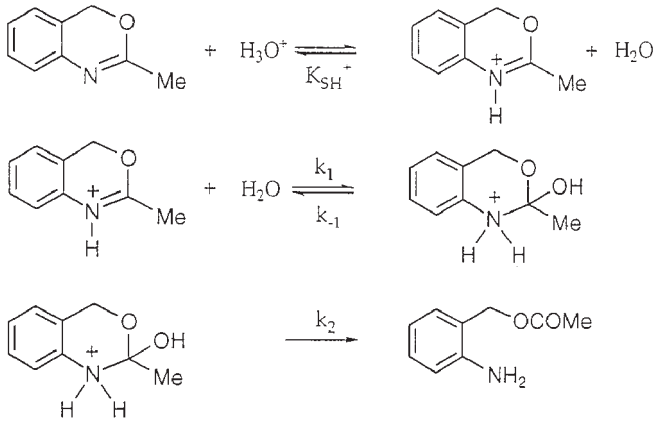
Scheme 1.



tate formed as product compared with 2-acetylaminobenzyl alcohol increased as the concentration of buffer base was increased, implying that reaction to the amide is less susceptible to buffer catalysis than formation of the ester. We have now investigated the factors influencing the formation of ester and amide and the kinetics of the formation of the amide in detail over the whole of the pH range. The reaction of acyclic imidates is known to give amides and esters depending on the reaction conditions and evidence is available to support the participation of tetrahedral carbonyl addition intermediates (2, 3). The tetrahedral carbonyl addition intermediates involved in the present work are cyclic, and their stability relative to reactants and products compared with that of acyclic intermediates is of particular interest.

Experimental

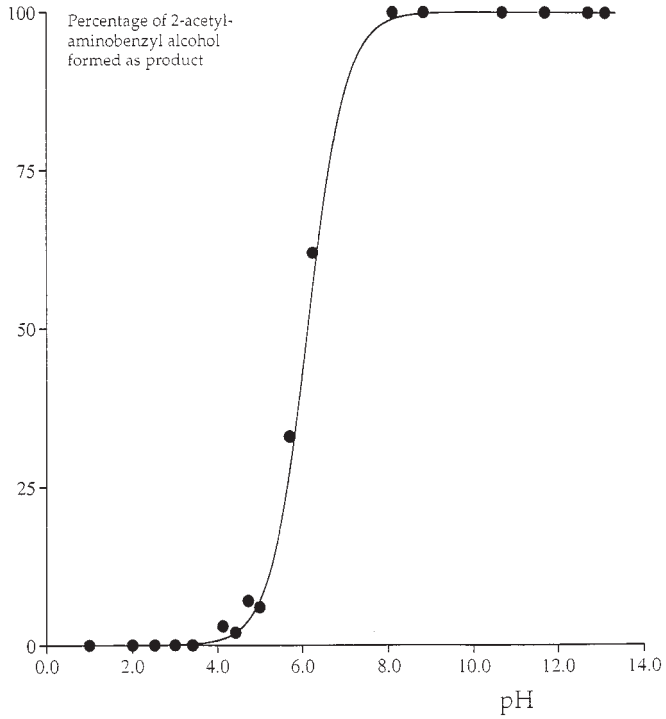
Materials

The preparations of 2-methyl-4H-3,1-benzoxazine, 2-aminobenzyl acetate, and 2-acetylaminobenzyl alcohol have been described previously (1). Carboxylic acid buffer solutions were made up by partial neutralization of a standardized solution of the carboxylic acid with a standard solution of potassium hydroxide. Buffer solutions of dihydrogen orthophosphate monoanion and monohydrogen orthophosphate dianion were made up by partial neutralization of a solution of potassium dihydrogen orthophosphate with a standard solution of potassium hydroxide. Buffer solutions of tris(hydroxymethyl)aminomethane and 2-amino-2-methyl-1,3-propanediol with the corresponding protonated amine were made up by partial neutralization of a standardized solution of the amine with standard hydrochloric acid solution. The ionic strength of all solutions was maintained at 0.25 mol dm^{-3} by addition of a weighed quantity of potassium chloride. Double distilled water was used for the preparation of solutions. Reactions under various conditions were begun by injecting 0.01 cm^3 of a concentrated solution of 2-methyl-4H-3,1-benzoxazine in Me_2SO into the reaction medium (3 cm^3).

Product analysis

The products of hydrolysis of 2-methyl-4H-3,1-benzoxazine were identified from the changes in UV spectrum accompanying the reaction. In the range pH 1–5, the final

Fig. 1. Reaction of 2-methyl-4H-3,1-benzoxazine to 2-acetylaminobenzyl alcohol and 2-aminobenzylacetate; variation with pH of the percentage of 2-acetylaminobenzyl alcohol.

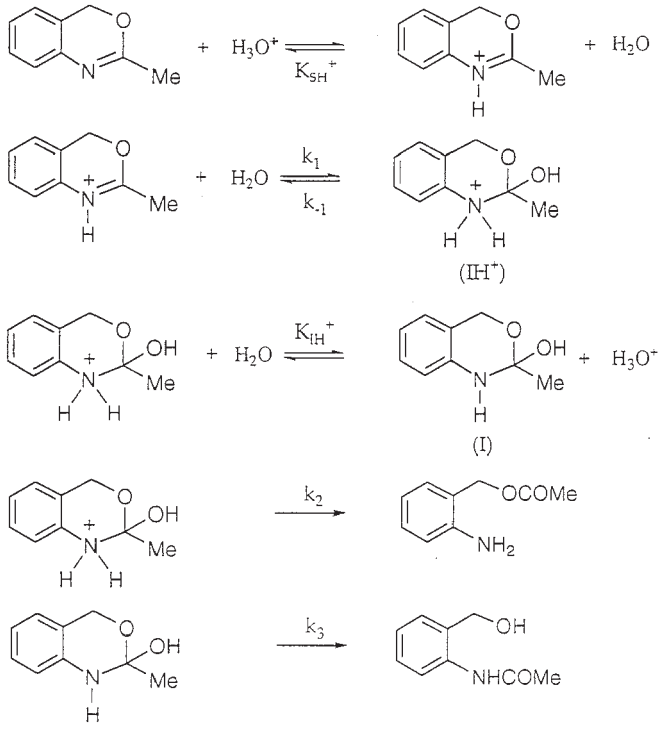


spectrum following reaction was found to be quantitatively identical with the spectrum of an authentic sample of 2-aminobenzyl acetate, and at pH 7.5–13, the spectrum of the product was identical with that of 2-acetylaminobenzyl alcohol. At intermediate pH values of 5–7.5, hydrolysis of 2-methyl-4H-3,1-benzoxazine results in a mixture of 2-aminobenzyl acetate and 2-acetylaminobenzyl alcohol, depending on the pH and buffer concentration. In acetate, pivalate, and phosphate buffers, the exact composition of the product mixture was calculated from the measured absorbance at 284 nm using the known absorbance of 2-aminobenzyl acetate and 2-acetylaminobenzyl alcohol at this wavelength. Results for the variation with pH of the fraction of 2-acetylaminobenzyl alcohol compared with 2-aminobenzyl acetate formed as product are shown in Fig. 1. The results were obtained at a buffer concentration of ca. 0.01 mol dm^{-3} in the basic component of the buffer. The points in Fig. 1 are experimental values, and the solid line is a best fit predicted from the mechanism in Scheme 2 (see below). It was also found that the percentage of 2-aminobenzyl acetate formed increased with buffer base concentration, indicating that reaction to 2-aminobenzyl acetate was more susceptible to catalysis by buffer than reaction to 2-acetylaminobenzyl alcohol. This was confirmed in kinetic studies (see below).

Kinetic measurements

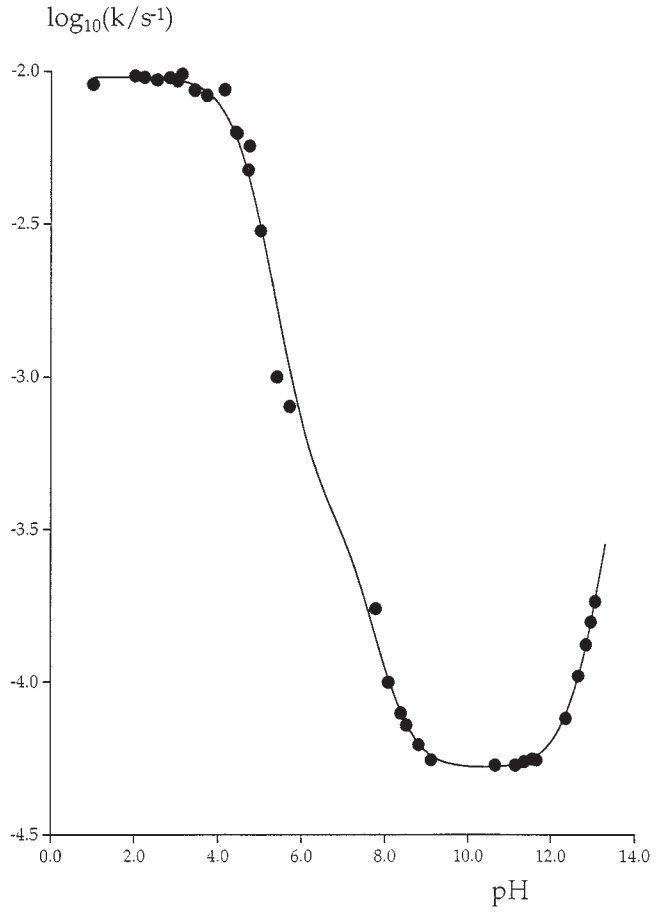
The methods used to study the kinetics of the ring opening of 2-methyl-4H-3,1-benzoxazine to 2-aminobenzyl acetate in the pH range 1–5 have been described previously (1). In the present work, kinetic measurements of the reaction of 2-methyl-4H-3,1-benzoxazine to 2-aminobenzyl acetate and

Scheme 2.



to 2-acetylaminobenzyl alcohol were made at pH values 5–13 at 298.2 K and ionic strength 0.25 mol dm^{-3}. Studies in the range pH 6–9 were made in buffers of orthophosphate monanion and dianion (pK_a 6.52) (4)[2] and of tris(hydroxymethyl)aminomethane (pK_a 8.07) (5)[3] and 2-amino-2-methyl-1,3-propanediol (pK_a 8.80) (5)[3] with the corresponding protonated amines at various buffer ratios. The dependence of the rate of reaction on buffer concentration was also investigated. Solutions of potassium hydroxide with concentrations in the range 0.001–0.25 mol dm^{-3} were used for studies at higher pH. Reactions were begun by injecting a concentrated solution of 2-methyl-4H-3,1-benzoxazine in Me_2SO into the reaction mixture to give an initial concentration of ca. 1.0×10^{-4} mol dm^{-3}. The concentration of 2-methyl-4H-3,1-benzoxazine was always kept in at least 10-fold deficit compared with buffer species or hydronium ion or hydroxide ion. Hydrolysis was followed by observing the UV spectral change with time. In a buffer of tris(hydroxymethyl)aminomethane (buffer ratio 1.0, pH 8.07 at a buffer concentration of 0.25 mol dm^{-3} in each buffer component), the spectral changes with time occurred to give clean isosbestic points at 242 and 308 nm. Reactions were usually followed by measuring the decrease in absorbance at 261 nm and were found to be accurately of first order. The value of the first-order rate coefficient (k_{obs}) was determined from an exponential fit to the variation of absorbance with time over at least three half lives. Reactions were followed for a sufficient time to allow the determination of an absorbance value corresponding to complete reaction except in the case of some of the slowest reactions. Correlation coefficients were typically 0.9999, and standard deviations of the calculated first-order rate coefficients were typically less than 1% The reactions occurred with half-lives in the range ca. 40 – 3.5×10^3 s.

Fig. 2. Dependence on pH of the rate coefficient ($\log_{10}$ k/s^{-1}) for the ring opening of 2-methyl-4H-3,1-benzoxazine in aqueous solution.



Results and discussion

Rate–pH profile

The pH dependence of the rate coefficient (k) for the hydrolysis of 2-methyl-4H-3,1-benzoxazine is shown in Fig. 2. The data were obtained from studies in solutions of hydrochloric acid and potassium hydroxide or in the presence of buffers. The value of the rate coefficient (k) given for hydrolysis in buffer solutions was obtained by extrapolation of the observed rate coefficient (k_{obs}) to zero buffer concentration and hence refers to reaction involving species derived from the solvent (water). In the range pH 1–5 the product of reaction at high buffer concentrations is exclusively 2-aminobenzyl acetate, and at pH 7.5–13, 2-acetylaminobenzyl alcohol is the sole product. In the region 5–7.5, hydrolysis of 2-methyl-4H-3,1-benzoxazine yields a mixture of 2-

[2] The pK_a value (7.20) (ref. 4) for dihydrogen orthophosphate monoanion at infinite dilution was adjusted to ionic strength (I) 0.25 mol dm^{-3} using the Debye–Huckel expression $-\log \gamma_{\pm} = 0.51 Z_i^2 \sqrt{I}/(1 + \sqrt{I})$.

[3] The value of pK_a at infinite dilution (5) was used uncorrected for the present conditions of ionic strength 0.25 mol dm^{-3}.

Table 1. Values of equilibrium constants and rate coefficients for the best fit of eq. [12] to the rate coefficient – pH profile.

K_{SH^+} (mol dm^{-3})	$k_1k_2/(k_{-1} + k_2)$ (s^{-1})	k_1 (s^{-1})	$k_2/k_3K_{1H^+}$ (mol dm^{-3})	k_0 (s^{-1})	k_{OH} (dm^3 mol^{-1} s^{-1})
$2.4 \pm 0.5 \times 10^{-5}$	$9.5 \pm 1 \times 10^{-3}$	0.17	$1.29 \pm 0.1 \times 10^{6}$	$5.1 \pm 0.5 \times 10^{-5}$	$5.3 \pm 0.5 \times 10^{-4}$

aminobenzyl acetate and 2-acetylaminobenzyl alcohol depending on the reaction conditions. The results in each of these pH regions will be considered in turn.

Reaction to 2-aminobenzyl acetate at pH 1–5

Data for hydrolysis in the range pH 1–5 have been published (1). Reaction occurs by addition of water to the protonated form of 2-methyl-4H-3,1-benzoxazine to give a cyclic tetrahedral addition intermediate which collapses to 2-aminobenzyl acetate, Scheme 1. Evidence for the involvement of a tetrahedral addition intermediate on the reaction pathway was provided by the observation of rectilinear plots of the observed rate coefficient against buffer base concentration as described earlier. According to the mechanism in Scheme 1, the rate coefficient for hydrolysis of 2-methyl-4H-3,1-benzoxazine extrapolated to zero buffer concentration is given by eq. [4] in which K_{SH^+} is the acid dissociation

$$[4] \qquad k = k_1k_2[H_3O^+]/(k_{-1} + k_2)(K_{SH^+} + [H_3O^+])$$

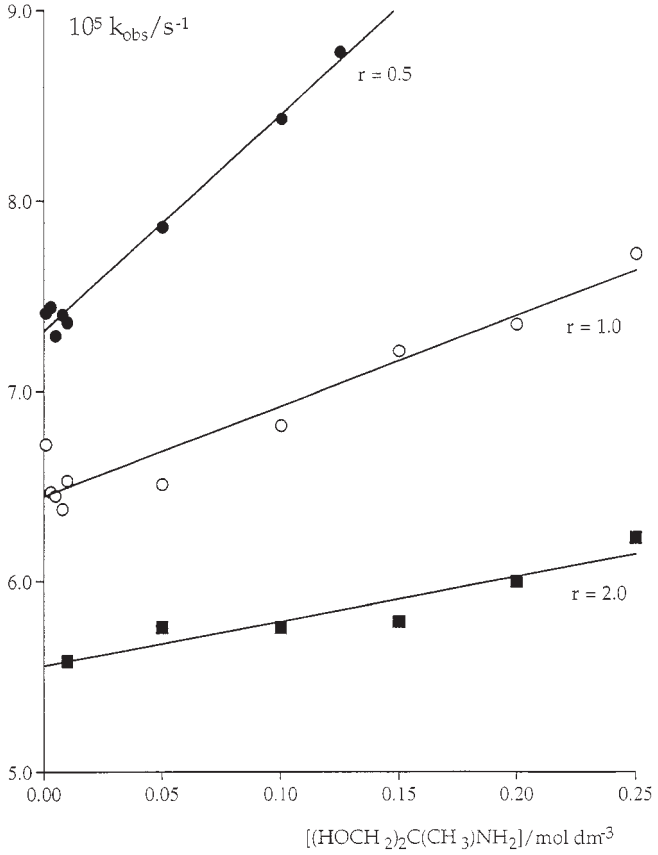
constant of protonated 2-methyl-4H-3,1-benzoxazine and the rate coefficients k_1, k_{-1}, and k_2 refer to the steps in Scheme 1. The solid line in Fig. 2 through the data points in the region pH 1–5 is a best-fit of eq. [4] to the experimental results (1) using the values shown in Table 1 for K_{SH^+}, k_1, and $k_2/(k_{-1} + k_2)$. The observed rectilinear dependence of the first-order rate coefficient (k_{obs}) on buffer concentration, eq. [2], was used to deduce values for the ratio $k_B/(k_{-1} + k_2)$ where k_B is the value of the second-order rate coefficient for catalysis of the collapse of the tetrahedral intermediate to 2-aminobenzyl acetate by chloroacetate, formate, acetate, and pivalate ions. The value of the rate coefficient ratio $k_B/(k_{-1} + k_2)$ was found to increase with increase in base strength of the catalysing buffer, giving a Brønsted plot with a value of β ca. 0.8 for the Brønsted exponent. It was also found that the value of the rate coefficient ratio $k_2/(k_{-1} + k_2)$ for spontaneous collapse of the intermediate with k_2 corrected to a second-order rate coefficient for reaction with water fitted the Brønsted plot for catalysis by buffers. This is compatible with the solvent acting as a base in catalysing the collapse of the tetrahedral intermediate.

Reaction to 2-aminobenzyl acetate and 2-acetylaminobenzyl alcohol at pH 5–9

In the present work, kinetic studies have been extended above pH 5, and the hydrolysis of 2-methyl-4H-3,1-benzoxazine gives a mixture of 2-aminobenzyl acetate and 2-acetylaminobenzyl alcohol, depending on the reaction conditions. Measurements were made in pivalate, phosphate, and in amine buffers.

In buffers of 2-amino-2-methyl-1,3-propanediol and of tris(hydroxymethyl)aminomethane (pH 7.8–9.1) where the reaction occurs to give exclusively 2-acetylaminobenzyl alcohol, there is a shallow dependence of k_{obs} on buffer concentration. Data for the reaction in buffers of 2-amino-2-methyl-1,3-propanediol buffer at different buffer ratios (r = [B]/[BH$^+$]) are shown in Fig. 3. The increase in k_{obs} with buffer concentration up to a concentration of the buffer cation of 0.125 mol dm^{-3} amounts to ca. 10, 8, and 9% at buffer ratios of r = 0.5, 1.0, and 2.0, respectively. Similar effects are observed in buffers of tris(hydroxymethyl)aminomethane. The shallow dependence on buffer concentration could be due to a salt effect as the inert salt (potassium chloride) is replaced by the buffer cation at constant ionic strength. A similar effect was previously observed in the reaction of 2-methylnaphth[1,8-de]-1,3-oxazine to 1-hydroxy-8-acetylaminonaphthalene in acetate buffers and was attributed to a salt effect (6). However, the possibility of weak buffer catalysis cannot be ruled out.

Fig. 3. Variation of the rate coefficient (k_{obs}/s^{-1}) with concentration for buffers of 2-amino-2-methyl-l,3-propanediol at different buffer ratios (r).



In the lower pH range, measurements were made in the presence of buffers of dihydrogen orthophosphate monoanion and monohydrogen orthophosphate dianion at buffer ratios r ($HPO_4^{2-}/H_2PO_4^-$) 0.5, 1.0, and 2.0, corresponding to pH values 6.22, 6.52, and 6.82. The change in k_{obs} with buffer concentration was small. For example, at a buffer ratio r = 1.0, the value of k_{obs} increased from 0.114 to 0.230 s^{-1} as the

buffer base concentration was increased from 0.001 to 0.05 mol dm^{-3}. At buffer ratios of r = 0.5 and 2.0, the values of k_{obs} increased from 0.213 to 0.447 s^{-1} and from 0.0671 to 0.107 s^{-1}, respectively. Extrapolation to zero buffer concentration gave values of k that did not fit the rate–pH profile determined in other buffers. At these pH values, the reaction of 2-methyl-4H-3,1-benzoxazine occurs to give both 2-aminobenzyl acetate and 2-acetylaminobenzyl alcohol. Although the latter reaction is not susceptible to strong catalysis by buffer, the reaction to 2-aminobenzyl acetate is catalysed by buffer. Details of the catalysis of the reaction to 2-aminobenzyl acetate by carboxylic acid buffers can be used to predict the behaviour in orthophosphate buffers. The variation of k_{obs} with buffer concentration for reaction of 2-methyl-4H-3,1-benzoxazine to 2-aminobenzyl acetate is given by eq. [2]. Extrapolation of the Brønsted plot for the variation of the value of $k_B/(k_{-1} + k_2)$ with base strength for carboxylic acid buffers (1) gives the result $k_B/(k_{-1} + k_2)$ = 1.92 × 10^3 dm^3 mol^{-1} for catalysis by monohydrogen orthophosphate dianion. This value can be used to predict that for the reaction of 2-methyl-4H-3,1-benzoxazine to 2-aminobenzyl acetate in a phosphate buffer, catalysis will be close to the upper limiting value of the rectilinear dependence of k_{obs} against buffer concentration for most of the concentrations of monohydrogen orthophosphate dianion studied. At a buffer ratio r = 1.0 and a buffer concentration of 0.001 mol dm^{-3}, catalysis will have reached ca. 66% of the limiting rate. It follows that extrapolation of values of k_{obs} obtained in the range $[HPO_4^{2-}]$ 0.001–0.05 mol dm^{-3} to zero buffer concentration is unreliable, and the results are not included in the rate–pH profile in Fig. 2.

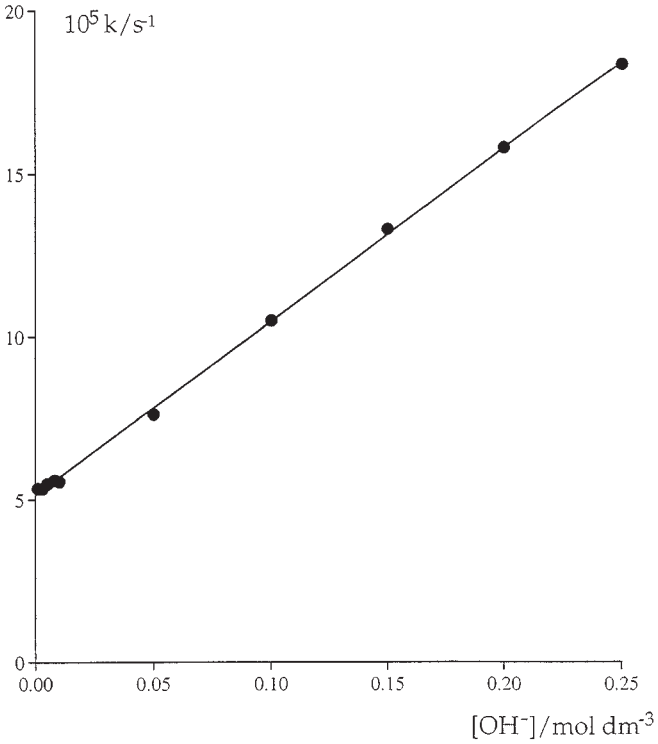
A mechanism that is compatible with the effect of pH on product ratio and with the dependence of the rate coefficient extrapolated to zero buffer concentration on pH in the range 0–9 is shown in Scheme 2. The mechanism differs from that in Scheme 1 used to explain the kinetics and formation of 2-aminobenzyl acetate in acidic solution by the inclusion of a route for collapse of an unprotonated form of the cyclic tetrahedral intermediate to 2-acetylaminobenzyl alcohol. It is assumed that collapse of the intermediate IH^+ to 2-aminobenzyl acetate is catalysed by buffer base but that collapse of the unprotonated intermediate (I) to 2-acetylaminobenzyl alcohol is uncatalysed by buffer species. If the proton transfer steps in Scheme 2 are assumed to occur rapidly and the intermediates IH^+ and I are present in low concentration, the expression in eq. [5] is obtained for the pH dependence of the rate coefficient for disappearance of 2-methyl-4H-3,1-benzoxazine.

$$[5] \qquad k = \frac{k_1[H_2O][H_3O^+](k_2[H_3O^+] + k_3K_{1H^+})}{(K_{SH^+} + [H_3O^+])\{k_3K_{1H^+} + (k_{-1} + k_2)[H_3O^+]\}}$$

$$[6] \qquad \frac{100[A]}{([E] + [A])} = \frac{100k_3K_{1H^+}}{(k_3K_{1H^+} + k_2[H_3O^+])}$$

According to the mechanism in Scheme 2, the percentage of 2-acetylaminobenzyl alcohol (A) formed as product compared with 2-aminobenzyl acetate (E) is given by the expression in eq. [6]. The results obtained for the percentage of 2-acetylaminobenzyl alcohol formed as product compared with 2-aminobenzyl acetate were plotted in the reciprocal form of eq. [6], and linear regression analysis gave a value for $k_2/k_3K_{1H^+}$ of 1.29 × 10^6 mol^{-1} dm^3. This result was used in eq. [6] to calculate the solid line in Fig. 1 for the pH dependence of the percentage of 2-acetylaminobenzyl alcohol formed as product.

Fig. 4. Variation of the rate coefficient (10^5 k/s^{-1}) for ring opening of 2-methyl-4H-3,1-benzoxazine with hydroxide ion concentration.



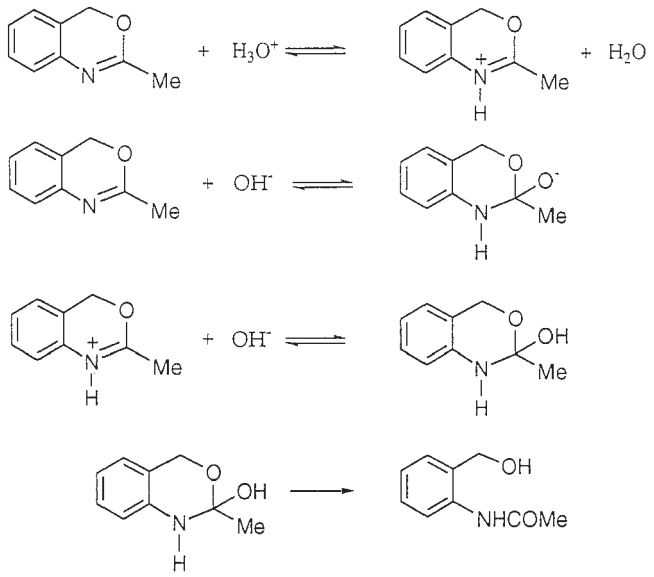
At pH <5 where 2-aminobenzyl acetate is the exclusive product, the terms involving k_3 can be neglected, and eq. [5] reduces to eq. [4]. In the pH region 8–9 where 2-acetylaminobenzyl alcohol is the only product, the terms involving k_2 can be neglected, and eq. [5] reduces to eq. [7]. If it is further assumed that $k_3K_{1H^+} > k_{-1}[H_3O^+]$, eq. [8] is obtained, which further reduces to eq. [9] on the assumption that $K_{SH^+} > [H_3O^+]$. Equation [9] predicts a direct dependence of k against $[H_3O^+]$. The experimental values of k in the range pH 7.8–9.1 were plotted against $[H_3O^+]$. However, a linear plot with gradient 7.1 × 10^3 dm^3 mol^{-1} s^{-1} and intercept 4.9 × 10^{-5} s^{-1} was obtained from linear regression analysis rather than the direct dependence of k against $[H_3O^+]$ predicted by eq. [9]. It was therefore necessary to modify the rate expression to include a pH-independent rate term k_0 as in eq. [10]. Thus, eq. [10] is compatible with the experimental results with values of k_1/K_{SH^+} = 7.1 × 10^3 dm^3 mol^{-1} s^{-1} and k_0 = 4.9 × 10^{-5} s^{-1}.

$$[7] \qquad k = k_1[H_2O][H_3O^+]k_3K_{1H^+}/(K_{SH^+} + [H_3O^+])(k_3K_{1H^+} + k_{-1}[H_3O^+])$$

$$[8] \qquad k = k_1[H_2O][H_3O^+]/(K_{SH^+} + [H_3O^+])$$

$$[9] \qquad k = (k_1/K_{SH^+})[H_2O][H_3O^+]$$

Scheme 3.



$$[10] \quad k = k_0 + (k_1/K_{SH^+})[H_2O][H_3O^+]$$

Reaction to 2-acetylaminobenzyl alcohol at pH 10–13

In the range pH 10–13, the product of reaction is 2-acetylaminobenzyl alcohol. Kinetic studies in this region were made in solutions of potassium hydroxide at concentrations in the range 0.001–0.25 mol dm^{-3}. The dependence of the measured first-order rate coefficient on hydroxide ion concentration is linear as shown in Fig. 4 with linear regression gradient $k_{OH} = 5.3 \times 10^{-4}$ dm^3 mol^{-1} s^{-1} and intercept $k_0 = 5.2 \times 10^{-5}$ s^{-1}. Hence, a pH-independent term and a term that is of first order in hydroxide ion contribute to the rate in this region, eq. [11]. The pH-independent term with a slightly

$$[11] \quad k = k_0 + k_{OH}[OH^-]$$

different value $k_0 = 4.9 \times 10^{-5}$ s^{-1} was also found from the variation of k with $[H_3O^+]$ in the range 7.8–9.1, eq. [10]. The average of these two values leads to k_o 5.1×10^{-5} s^{-1}.

A mechanism that is compatible with the formation of 2-acetylaminobenzyl alcohol as the sole product and with the experimentally observed dependence of k against $[OH^-]$ shown in Fig. 4 involves addition of hydroxide ion to protonated and unprotonated forms of 2-methyl-4H-3,1-benzoxazine to give a tetrahedral intermediate which collapses to product, Scheme 3.

In Scheme 3, it can be assumed that the tetrahedral intermediates are present in low concentration. The pH-independent term and the first-order term in hydroxide ion are explained by reaction of hydroxide ion with the protonated and unprotonated forms of 2-methyl-4H-3,1-benzoxazine, respectively. An alternative mechanism that will explain the pH-independent term involves reaction of the unprotonated form of 2-methyl-4H-3,1-benzoxazine with solvent. The relative importance of these two possibilities for the pH-independent term can be assessed by comparison of the value of the rate coefficient k_0 with the values of the other rate coefficients in the mechanism. If the pH-independent term arises from reaction of hydroxide ion with protonated 2-methyl-4H-3,1-benzoxazine, the result k_0 5.1×10^{-5} s^{-1} corresponds to a second-order rate coefficient for reaction with hydroxide ion of 5.7×10^4 dm^3 mol^{-1} s^{-1} using the values of K_{SH^+} 2.4×10^{-5} mol dm^{-3} for the acid dissociation constant of protonated 2-methyl-4H-3,1-benzoxazine and $K_w = 2.19 \times 10^{-14}$ mol^2 dm^{-6} for the ionic product of water under the reaction conditions. This is to be compared with the value $k_1 = 3.1 \times 10^{-3}$ dm^3 mol^{-1} s^{-1} obtained for the reaction of water with protonated 2-methyl-4H-3,1-benzoxazine. The 1.8×10^7-fold difference seems reasonable in view of the very large difference in nucleophilicity of hydroxide ion and water. If the pH-independent term arises from rate-limiting attack of water on unprotonated 2-methyl-4H-3,1-benzoxazine, the result k_0 5.1×10^{-5} s^{-1} corresponds to a second-order rate coefficient of 9.2×10^{-7} dm^3 mol^{-1} s^{-1} for reaction with water. This is to be compared with the value k_{OH} 5.3×10^{-4} dm^3 mol^{-1} s^{-1} found for reaction of hydroxide ion with unprotonated 2-methyl-4H-3,1-benzoxazine. This 600-fold difference is smaller than would have been anticipated from the very large difference in nucleophilicity of water and hydroxide ion. For this reason, the preferred explanation of the pH-independent term in the rate law, eqs. [10] and [11], is a reaction involving addition of hydroxide ion to protonated 2-methyl-4H-3,1-benzoxazine.

Dependence of *k* in the range pH 0–13

The pH dependence of the rate coefficient (k) for hydrolysis of 2-methyl-4H-3,1-benzoxazine involving species derived from the solvent over the whole of the pH range 0–13 is fitted by eq. [12], which is obtained by combining eq. [5] with eq. [11]. The solid line in Fig. 2 is a plot of eq. [12] using the values of the rate coefficients and equilibrium

$$[12] \quad k = \frac{k_1[H_2O][H_3O^+](k_2[H_3O^+] + k_3K_{1H^+})}{(K_{SH^+} + [H_3O^+])\{k_3K_{1H^+} + (k_{-1} + k_2)[H_3O^+]\}} + k_0 + k_{OH}[OH^-]$$

constants given in Table 1. At low pH, reaction of protonated 2-methyl-4H-3,1-benzoxazine with solvent occurs through a protonated tetrahedral intermediate, leading to 2-aminobenzyl acetate as product. As the pH is raised, reaction of protonated 2-methyl-4H-3,1-benzoxazine leads to 2-acetylaminobenzyl alcohol, since the tetrahedral intermediate that is common to both pathways is present in the unprotonated form. In the protonated form, the intermediate leads to 2-aminobenzyl acetate because departure of an aromatic amine as leaving group is facile. Collapse of the unprotonated intermediate to 2-aminobenzyl acetate would involve departure of an amine anion, and reaction to 2-acetylaminobenzyl alcohol involving an aliphatic alkoxide as leaving group is preferred. The change in pathway that occurs between pH ca. 6 and 7 leads to an inflexion point in the rate coefficient against pH profile. The relative amount of the two products is determined by the fraction of the tetrahedral intermediate that is protonated and the relative rates of collapse of the protonated intermediate to 2-aminobenzyl acetate and the unprotonated intermediate to 2-acetylaminobenzyl alcohol, eq. [6]. At pH 9, reaction of protonated

2-methyl-4H-3,1-benzoxazine with hydroxide ion becomes important, and above pH 12, reaction of unprotonated 2-methyl-4H-3,1-benzoxazine with hydroxide ion predominates. Both of these reactions result in the formation of 2-acetylaminobenzyl alcohol, presumably through the unprotonated form of the tetrahedral intermediate.

It was found that collapse of the protonated intermediate to 2-aminobenzyl acetate is catalysed by buffer base. This presumably occurs by assistance of removal of the hydroxy proton as the carbonyl group of the product is formed. In contrast, collapse of the unprotonated tetrahedral intermediate to 2-acetylaminobenzyl alcohol is not assisted by buffer base. The absence of catalysis in this case could indicate that addition of water to protonated 2-methyl-4H-3,1-benzoxazine is rate-limiting (that is, collapse of the intermediate to product occurs more rapidly than collapse to protonated 2-methyl-4H-3,1-benzoxazine). Alternatively, if the value of the Brønsted exponent for base catalysis of the collapse of the unprotonated tetrahedral intermediate was close to zero, buffer catalysis would be undetectible compared with solvent catalysed collapse.

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