Kinetics and mechanism of the addition of water and ring-opening of 2-methyl- and 2-aryl-4*H*-3,1-benzoxazines to 2-aminobenzyl esters in the acidic pH range; change in rate-limiting step with buffer concentration and evidence for a tetrahedral carbonyl addition intermediate

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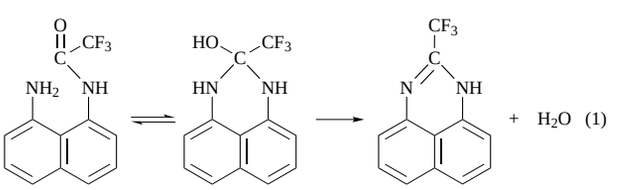
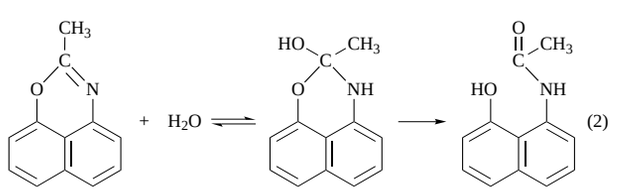
The observed rate coefficients for the reaction of 2-methyl-, 2-phenyl- and 2-(4-nitrophenyl)-4*H*-3,1-benzoxazines to give the corresponding 2-aminobenzyl esters increase as the pH is lowered and reach a constant plateau value at pH 2–4 depending on the substituent. The plateau region corresponds to complete conversion of the benzoxazine to the protonated benzoxazine (SH^+) which is the reactive species. Values of pK_{SH^+} calculated by fitting the appropriate rate expression to the rate–pH profile and the pK_{SH^+} values measured spectrophotometrically before significant reaction to the ester has taken place are in good agreement. For each benzoxazine the observed rate coefficients show a rectilinear dependence on buffer concentration. A mechanism is proposed involving addition of water to the protonated benzoxazine to give a cyclic tetrahedral carbonyl addition intermediate. At low buffer concentrations, buffer catalysed collapse of the intermediate to product is rate-limiting and the reaction is first order in buffer. At high buffer concentrations, collapse of the intermediate to product is rapid and addition of water to the protonated benzoxazine to give the intermediate is rate-limiting.

Introduction

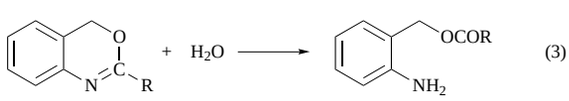
In earlier studies of intramolecular reactions we have found that addition of an amino group to an amide carbonyl will occur when these groups occupy the 1 and 8 positions of naphthalene, as in 1-amino-8-trifluoroacetylaminonaphthalene, eqn. (1). Intramolecular addition gives a tetrahedral intermediate



which eliminates water to form a pyrimidine.[1] If the amino group is replaced by hydroxy, the product of the corresponding intramolecular addition/elimination would be a 2-alkylnaphth-[1,8-*de*]-1,3-oxazine. However we have found that in the case of 2-methylnaphth[1,8-*de*]-1,3-oxazine the thermodynamically preferred direction of reaction is addition of water to the naphthoxazine followed by ring opening to give 1-hydroxy-8-acetylaminonaphthalene, eqn. (2).[2] A possible alternative product of



ring opening of the tetrahedral intermediate is 1-amino-8-acetoxynaphthalene but this product was not detected. These reactions are of particular interest because kinetic evidence for the formation of tetrahedral carbonyl addition intermediates was readily obtained. When the addition intermediate is generated from or leads to a strained cyclic system it may be less unstable with respect to reactant or product than in the case of tetrahedral intermediates generated in intermolecular reactions. The reactions therefore provide a means of studying such intermediates.[3] We have now extended our studies to intramolecular reactions of substituted benzyl substrates with reactive groups at the 2-aromatic position and at the benzylic position. The kinetics and mechanism of the reaction of 2-methyl- and 2-aryl-4*H*-3,1-benzoxazines in aqueous solution have been investigated, eqn. (3), with R = Me, Ph and 4-NO_2-C_6H_4.



Experimental

Materials

Preparation of 2-methyl-4*H*-3,1-benzoxazine. A sample of 2-methyl-4*H*-3,1-benzoxazine has been prepared previously.[4] In our hands a procedure similar to that used for the preparation of 2-methylbenzoxazole[5] was more successful. In this method 2-aminobenzyl alcohol was refluxed for 1 h with acetic anhydride (2 mol equiv.). Distillation under N_2 at reduced pressure gave acetic anhydride and acetic acid as the first fractions and the product was collected as a yellow oil which on further distillation at 2 mmHg and 75 °C (lit.[4] 104–106 °C at 10 mmHg) provided a colourless oil which was stored under N_2. A 20% yield of 2-methyl-4*H*-3,1-benzoxazine was obtained and was identified by ^{1}H NMR, δ[$(CD_3)_2SO$, 360 MHz] 7.26–6.99 (4 H, m, ArH), 5.23 (2 H, s, CH_2), 2.02 (3 H, s, CH_3); ^{13}C NMR, δ[$(CD_3)_2SO$, 90.5 MHz] 160.11 (NCO), 138.73 and 121.93 (quat. arom.), 128.52, 125.97, 124.03 and 123.11 (CH, arom.), 65.10 (CH_2) and 20.80 (CH_3); MS (EI), *m*/*z* 147.07 (M^+, 100%), 132.04 ($M^+ - CH_3$, 22%) and 104.05 ($M^+ - CH_3CO$, 17%); accurate mass, found 147.0688, C_9H_9NO requires 147.0684.

Preparation of 2-phenyl-4*H*-3,1-benzoxazine. A sample of 2-phenyl-4*H*-3,1-benzoxazine was prepared using the published

procedure[6] in which *N*-benzoylation of 2-aminobenzyl alcohol was achieved by stirring with benzoyl chloride in the presence of triethylamine in dichloromethane for one hour. The solution of 2-(benzoylamino)benzyl alcohol in dichloromethane was washed with water followed by aqueous hydrochloric acid and aqueous sodium hydrogen carbonate and dried over magnesium sulfate. Removal of the drying agent and evaporation of the solvent gave the amide which was recrystallised from toluene to give pale yellow needles in 60% yield (mp 94–95.5 °C, lit.[7] 95 °C), identified by ^{1}H NMR, δ[$(CD_3)_2SO$, 360 MHz] 10.17 (1 H, s, NH), 7.98–7.18 (9 H, m, ArH), 5.69–5.66 (1 H, t, OH), 4.65–4.64 (2 H, d, CH_2); ^{13}C NMR, δ[$(CD_3)_2SO$, 90.5 MHz] 164.8 (CO), 136.1, 134.4 and 134.3 (quat. arom.), 131.7, 128.6, 127.5, 127.2, 127.2, 124.7 and 123.6 (CH, arom.), 61.0 (CH_2); MS (EI), *m*/*z* 227.09 (M^+, 57%), 122.06 ($M^+ - PhCO$, 93%), 105.05 ($PhCO^+$, 100%), 76.99 (Ph^+, 91%); accurate mass, found 227.0903, $C_{14}H_{13}NO_2$ requires 227.0946.

Conversion of 2-(benzoylamino)benzyl alcohol into 2-phenyl-4*H*-3,1-benzoxazine was accomplished by warming with conc. H_2SO_4 for 5 min and leaving at room temperature overnight. Addition to crushed ice followed by neutralisation with 15 mol dm^{-3} NaOH at 5 °C and extraction into diethyl ether followed by evaporation of the diethyl ether gave 2-phenyl-4*H*-3,1-benzoxazine which was recrystallised from methanol to give white crystals (mp 92–94 °C, lit.[6] 92 °C) in 10% yield and identified by ^{1}H NMR, δ[$(CD_3)_2SO$, 360 MHz] 8.09–7.15 (9 H, m, ArH), 5.46 (2 H, s, CH_2); ^{13}C NMR, δ[$(CD_3)_2SO$, 90.5 MHz] 156.8 (NCO), 139.0, 131.8, 122.7 (quat. arom.), 131.6, 128.8, 128.4, 127.5, 126.5, 124.2 and 123.9 (CH, arom.), 65.8 (CH_2); MS (EI), *m*/*z* 209.09 (M^+, 100%) 104.99 ($PhCO^+$, 39.5%), 76.91 (Ph^+, 41.5%); accurate mass, found 209.0858, $C_{14}H_{11}NO$ requires 209.0841.

Preparation of 2-(4-nitrophenyl)-4*H*-3,1-benzoxazine. The same procedure was used as for the preparation of 2-phenyl-4*H*-3,1-benzoxazine. A sample of 2-(4-nitrobenzoylamino)-benzyl alcohol was obtained as a pale yellow solid (mp 148–151 °C) in 14% yield and identified by ^{1}H NMR, δ[$(CD_3)_2SO$, 360 MHz] 10.36 (1 H, br s, NH), 8.40–7.23 (8 H, m, ArH), 5.55 (1 H, br s, OH), 4.61 (2 H, s, CH_2); ^{13}C NMR, δ[$(CD_3)_2SO$, 90.5 MHz] 163.4 (CO), 149.2, 140.1, 135.5 and 135.1 (quat. arom.), 128.8, 127.3, 127.1, 125.5, 124.4 and 123.7 (CH, arom.), 60.4 (CH_2); MS (EI), *m*/*z* 272.08 (M^+, 58%), 150.01 ($NO_2C_6H_4CO^+$, 64%), 122.06 ($NO_2C_6H_4^+$, 100%); accurate mass, found 272.0785, $C_{14}H_{12}N_2O$ requires 272.0797. Conversion to 2-(4-nitrophenyl)-4*H*-3,1-benzoxazine by the same procedure used to prepare 2-phenyl-4*H*-3,1-benzoxazine gave a yellow solid (mp 157–159 °C) in 38% yield identified by ^{1}H NMR, δ[$(CD_3)_2SO$, 360 MHz] 8.36–7.17 (8 H, m, ArH), 5.53 (2 H, s, CH_2); ^{13}C NMR, δ[$(CD_3)_2SO$, 90.5 MHz] 155.1 (NCO), 149.0, 138.4, 137.6 and 122.5 (quat. arom.), 128.9, 128.7, 127.4, 124.4, 124.3, 123.6 (CH, arom.), 66.1 (CH_2); MS (EI), *m*/*z* 254.07 (M^+, 100%), 132.00 ($C_6H_4CH_2OCN^+$, 26.4%), 122.26 ($C_6H_4NO_2^+$, 4.6%), 106.04 ($C_6H_4CH_2O^+$, 19.0%); accurate mass, found 254.0679, $C_{14}H_{10}N_2O_3$ requires 254.0691 (Found: C, 66.04; H, 3.75; N, 10.93. $C_{14}H_{10}N_2O_3$ requires C, 66.14; H, 3.76; N, 11.02%).

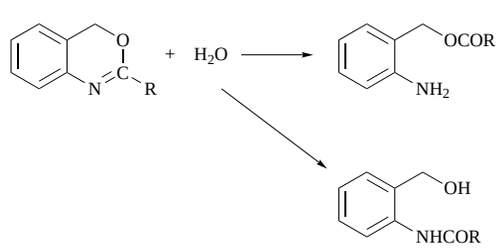
Preparation of 2-aminobenzyl esters. Considerable difficulty was experienced in the preparation of pure samples of the 2-aminobenzyl esters. The preparation of an impure sample of 2-aminobenzylbenzoate was achieved from 2-(benzoylamino)-benzyl alcohol by allowing a pure sample of the amide, prepared as described above, to rearrange in conc. H_2SO_4 at 60 °C for 15 min and at room temperature overnight. The mixture was poured onto crushed ice and extracted with pentane. The aqueous layer was neutralised by addition of 5 mol dm^{-3} NaOH with cooling to keep the temperature below 60 °C. The product was extracted in diethyl ether and after drying, evaporation of the ether gave a yellow oil which crystallised from hexane to give an impure sample of 2-aminobenzyl benzoate as a white solid (mp 67–70 °C) in 14% yield. The product was identified by ^{1}H NMR, δ[$CDCl_3$, 360 MHz] 8.05–6.71 (9 H, m, ArH), 5.35 (2 H, s, CH_2) and 4.04 (2 H, br s, NH_2); ^{13}C NMR, δ[$CDCl_3$, 90.5 MHz] 166.8 (CO), 146.0, 129.9 and 120.2 (quat. arom.), 133.1, 131.5, 130.1, 129.7, 128.4, 118.4 and 116.2 (CH, arom.), 64.8 (CH_2). The purity of the sample as determined from the ^{1}H NMR spectrum was *ca.* 90% with 2-aminobenzyl alcohol present as impurity which could not be removed.

We were unsuccessful in isolating a sample of 2-aminobenzyl acetate. However a solution of the ester was obtained by leaving 2-methyl-4*H*-3,1-benzoxazine in $(CD_3)_2SO$ open to the atmosphere and quantitative conversion to the ester was observed after *ca.* 15 h.[8] The product was identified as 2-aminobenzyl acetate by ^{1}H NMR, δ[$(CD_3)_2SO$, 360 MHz] 7.05–6.52 (4 H, m, ArH), 5.07 (2 H, br s, NH_2), 4.91 (2 H, s, CH_2) and 1.98 (3 H, s, CH_3); ^{13}C NMR, δ[$(CD_3)_2SO$, 90.5 MHz] 171.30 (CO), 146.57 and 118.87 (quat. arom.), 130.31, 129.43, 116.45 and 115.24 (CH, arom.), 63.48 (CH_2) and 20.56 (CH_3). We were unsuccessful in obtaining either a solid sample or a solution of 2-aminobenzyl 4-nitrobenzoate.

Preparation of 2-(acylamino)benzyl alcohols. The preparations of 2-(benzoylamino)- and 2-(4-nitrobenzoylamino)-benzyl alcohols have been described above. The preparation of 2-(acetylamino)benzyl alcohol was achieved by using a procedure[9] in which 2-aminobenzyl alcohol was reacted with acetic anhydride in ethyl acetate. The off-white product (mp 116 °C, lit.[10] 114 °C) was formed in 87% yield and was identified by ^{1}H NMR, δ[$(CD_3)_2SO$, 360 MHz] 9.30 (1 H, s, NH), 7.50–7.11 (4 H, m, ArH), 4.49 (2 H, s, CH_2), 3.28 (1 H, s, OH) and 2.05 (3 H, s, CH_3); ^{13}C NMR, δ[$(CD_3)_2SO$, 90.5 MHz] 168.12 (CO), 135.26 and 134.74 (quat. arom.), 127.11, 126.73, 124.46 and 123.90 (CH arom.), 59.83 (CH_2) and 23.37 (CH_3); MS (EI), *m*/*z* 165.08 (M^+, 97%), 122.06 ($M^+ - CH_3CO$, 94%), 105.07 ($M^+ - CH_3CO - OH$, 100%) and 76.99 (Ph^+, 20.3%); accurate mass, found 165.0804, $C_9H_{11}NO_2$ requires 165.0790.

Products of reaction

The identity of the reactions occurring on introduction of 2-methyl- and 2-phenyl-4*H*-3,1-benzoxazines into acidic aqueous solution was established by following the change in spectrum (200–400 nm) accompanying the reactions. For the reaction of 2-methyl-4*H*-3,1-benzoxazine, quantitative studies were carried out in hydrochloric acid solutions and in chloroacetic acid–chloroacetate, formic acid–formate, acetic acid–acetate and pivalic acid–pivalate buffers over a range of pH and at different buffer concentrations. A concentrated solution of 2-methyl-4*H*-3,1-benzoxazine in Me_2SO was injected into the reaction solution to give an initial concentration of *ca.* 1.0×10^{-4} mol dm^{-3}. The final product spectrum was recorded after sufficient time had elapsed for there to be no further change in the spectrum. In hydrochloric acid solutions and in chloroacetic acid–chloroacetate and formic acid–formate buffers the spectra after complete reaction of 2-methyl-4*H*-3,1-benzoxazine were found to be identical with the spectrum of a solution made up from an authentic sample of 2-aminobenzyl acetate under the same conditions. However in the presence of acetic acid–acetate and pivalic acid–pivalate buffers some slight differences were observed. The differences were greatest at the lowest buffer concentrations and at higher pH. Under these conditions, a small amount of reaction to 2-(acetylamino)benzyl alcohol, eqn. (4),



(4)

was found to occur. In acetic acid–acetate buffers at pH values of 4.12, 4.42 and 4.72 at buffer concentrations above 0.01 mol dm^{-3} it was observed that reaction occurred to the ester to an extent greater than 93% and usually much closer to 100%. In pivalic acid–pivalate buffers at pH 4.99 and buffer concentrations above 0.01 mol dm^{-3}, 2-aminobenzyl acetate was formed in greater than 94% yield. However in pivalic acid–pivalate buffers at pH 5.69 the yield of ester was 67% at a buffer base concentration of 0.01 mol dm^{-3} and 87% at a buffer base concentration of 0.1 mol dm^{-3}. Reaction of 2-methyl-4*H*-3,1-benzoxazine in a dihydrogen orthophosphate–monohydrogen orthophosphate buffer (pH 6.22) gave 84% of 2-aminobenzyl acetate and 16% of 2-(acetylamino)benzyl alcohol at a buffer base concentration of 0.05 mol dm^{-3} but at a buffer base concentration of 0.01 mol dm^{-3} the yields were 38% of ester and 62% of amide. Conditions under which less than 90% of the ester was the product were not used for detailed kinetic studies. Therefore the kinetic results reported in this work almost always refer to conditions where reaction occurs exclusively to the 2-aminobenzyl acetate. The reaction of 2-methyl-4*H*-3,1-benzoxazine to 2-(acetylamino)benzyl alcohol under neutral and alkaline conditions will be the subject of a future publication.[11]

For the reaction of 2-phenyl-4*H*-3,1-benzoxazine, spectra of the final product of reaction were compared with the spectrum of 2-aminobenzyl benzoate under the same conditions. Since a subsequent slow reaction of the ester was found to occur in some cases the reaction solution was not always left for a sufficient time for the reaction to reach 100% completion. In solutions of hydrochloric acid and in buffers of chloroacetic acid–chloroacetate and formic acid–formate the spectrum of the reaction product was identical within experimental error with that of a solution made up to contain the same concentration of 2-aminobenzyl benzoate.

Kinetic measurements

Kinetic measurements of reaction (3) were made in aqueous solution at 298.2 K and at an ionic strength of 0.25 mol dm^{-3}. The pH of the reaction solution was maintained with hydrochloric acid (0.25–0.001 mol dm^{-3}) or with carboxylic acid–carboxylate buffer solutions of chloroacetic, formic, acetic or pivalic acid. Measurements were made at different buffer ratios and at buffer base concentrations in the range 0.001–0.25 mol dm^{-3}. In kinetic runs, the initial concentration of 2-methyl- and 2-phenyl-4*H*-3,1-benzoxazines was 1.0×10^{-4} mol dm^{-3} and the initial concentration of 2-(4-nitrophenyl)-4*H*-3,1-benzoxazine was 3.0×10^{-6} mol dm^{-3} so that the substrates were always in at least ten-fold deficit compared with hydronium ion or buffer. The change in spectrum accompanying the reaction was found to depend on the pH of the solution because the spectrum of the reactants, 2-methyl- and 2-aryl-4*H*-3,1-benzoxazines, and the products, 2-aminobenzyl esters, vary with pH. In unbuffered aqueous solution the reaction of 2-methyl-4*H*-3,1-benzoxazine occurs with a decrease in absorbance at *ca.* 260 nm giving a clean isosbestic point at 242 nm. For the reaction of 2-phenyl- and 2-(4-nitrophenyl)-4*H*-3,1-benzoxazines in hydrochloric acid solutions isosbestic points were observed at 239 and 286 nm respectively. The course of the reactions were followed by measuring the decrease in absorbance accompanying loss of the reactant at wavelengths at which the greatest difference in absorbance between reactant and product was found, typically at 261, 298 and 340 nm for 2-methyl-, 2-phenyl and 2-(4-nitrophenyl)-4*H*-3,1-benzoxazines respectively. In most cases the reactions occurred sufficiently slowly that a conventional Perkin-Elmer λ5 spectrophotometer was used to take absorbance readings. Reactions were then begun by injecting 0.01 cm^3 of a concentrated solution of the benzoxazine in Me_2SO into 3.00 cm^3 of the reaction solution contained in a thermostatted cuvette. Approximately 30 absorbance readings were taken over *ca.* 3 half-lives of the reaction and values of the first-order rate coefficient (k_{obs}) were obtained from a least squares fit to an exponential change in absorbance with time. The reactions were accurately first order with correlation coefficients of better than 0.999. The reaction of 2-(4-nitrophenyl)-4*H*-3,1-benzoxazine occurred more rapidly with $t_{\frac{1}{2}}$ <*ca.* 100 s and the stopped-flow method was used to follow the change in absorbance with time using an Applied Photophysics SX.17MV instrument. In this case the reaction was begun by mixing the reaction solution (hydrochloric acid or carboxylic acid–carboxylate buffer) with an equal volume of an aqueous solution of the benzoxazine.

Equilibrium measurements

The dependence of the first-order rate coefficient for the reaction of the 2-methyl- and 2-aryl-4*H*-3,1-benzoxazines to the corresponding 2-aminobenzyl esters on pH is explained (see later) by reaction through the protonated benzoxazine (SH^+) as the reactive species and a value of pK_{SH^+} was deduced from the rate–pH profile. To provide confirmation, values of pK_{SH^+} for 2-methyl- and 2-phenyl-4*H*-3,1-benzoxazines were determined in separate equilibrium measurements before significant reaction to the 2-aminobenzyl esters had occurred. Partial protonation of 2-methyl-4*H*-3,1-benzoxazine was observed in an acetic acid–acetate buffer solution and under these conditions the reaction to 2-aminobenzyl acetate occurred with $t_{\frac{1}{2}}$ *ca.* 10 s. In order to determine absorbance values corresponding to the equilibrium between 2-methyl-4*H*-3,1-benzoxazine and its protonated form, it was necessary to use the stopped-flow method (Applied Photophysics SX.17MV). An aqueous solution of 2-methyl-4*H*-3,1-benzoxazine in the presence of a low concentration of a 2-amino-2-methylpropane-1,3-diol buffer to prevent significant hydrolysis was mixed with an acetic acid–acetate buffer solution and the change in absorbance over the first 100 ms was measured and extrapolated back to zero time after mixing. Absorbance readings (A) were taken at 260 nm for solutions of 2-methyl-4*H*-3,1-benzoxazine (1.0×10^{-4} mol dm^{-3}) in acetic acid–acetate buffer solutions at buffer ratios $r = [B^-]/[BH]$ of 4.0–0.25 at 298.2 K and an ionic strength of 0.25 mol dm^{-3}. An absorbance reading (A_{SH^+}) corresponding to fully protonated 2-methyl-4*H*-3,1-benzoxazine was obtained in the presence of 0.05 mol dm^{-3} hydrochloric acid and an absorbance reading (A_S) corresponding to unprotonated 2-methyl-4*H*-3,1-benzoxazine was obtained in the presence of a buffer of 2-amino-2-methylpropane-1,3-diol and the protonated amine ($r = 1.0$, pH = 8.80). Values of the equilibrium constant $K = [SH^+][AcO^-]/[S][AcOH]$ were calculated from the expression $K = (A - A_S) \times r/(A_{SH^+} - A)$ and the average of measurements at six buffer ratios gave $K = 1.37 \pm 0.28$ mol dm^{-3}, corresponding to pK_{SH^+} 4.56 ± 0.1 at 298.2 K and ionic strength 0.25 mol dm^{-3}. For the dissociation of 2-phenyl-4*H*-3,1-benzoxazine similar measurements in formic acid–formate buffers gave pK_{SH^+} 3.48 ± 0.1. The limited solubility of 2-(4-nitrophenyl)-4*H*-3,1-benzoxazine did not permit measurement of pK_{SH^+} in this case.

Results and discussion

Rate–pH profile

The variation of the observed first-order rate coefficient (k_{obs}) with pH for the reactions of 2-methyl-, 2-phenyl- and 2-(4-nitrophenyl)-4*H*-3,1-benzoxazines to the corresponding 2-aminobenzyl esters, eqn. (3), in solutions of hydrochloric acid are shown as the open data points in Fig. 1. Also shown (as the solid data points) are the values of k_{obs} extrapolated to zero buffer concentration from measurements over a range of buffer concentrations at different buffer ratios. The variation of k_{obs} with pH is compatible with reaction through the protonated benzoxazine as the reactive species.

Buffer catalysis

The reactions of 2-methyl-, 2-phenyl- and 2-(4-nitrophenyl)-

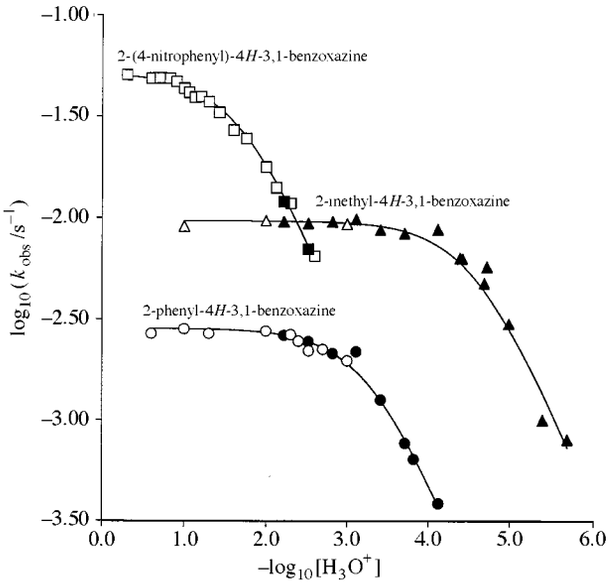


Fig. 1 Rate–pH profile for the hydrolysis of substituted 2-methyl- and 2-aryl-4*H*-3,1-benzoxazines in aqueous acidic solution

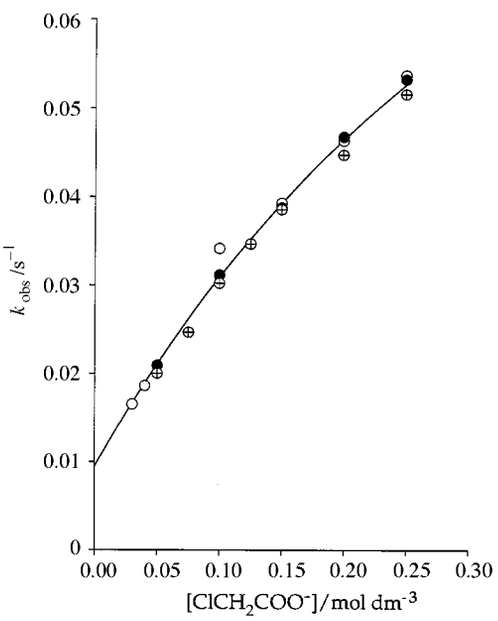


Fig. 2 Variation of observed rate coefficient for the hydrolysis of 2-methyl-4*H*-3,1-benzoxazine with buffer concentration in chloroacetic acid–chloroacetate buffers at buffer ratios $r = 0.5$ (●), 1.0 (⊕), 2.0 (○)

4*H*-3,1-benzoxazines to the corresponding 2-aminobenzyl esters, eqn. (3), were studied in carboxylic acid–carboxylate buffer solutions. The buffers were present in at least ten-fold excess compared with the benzoxazine and, for each buffer, the reaction was studied at several buffer ratios. Values of k_{obs} were determined at different buffer concentrations in the range 0.001–0.25 mol dm^{-3}. The variations of k_{obs} with buffer base concentration for the reaction of 2-methyl-4*H*-3,1-benzoxazine in chloroacetic acid–chloroacetate buffers and in pivalic acid–pivalate buffers are shown in Figs. 2 and 3 respectively. The change in order of reaction with respect to buffer base from first order at low buffer concentrations to zero order at high buffer concentrations implies a change in rate-limiting step with buffer concentration. Also, the kinetic behaviour varies in going from the most acidic chloroacetic acid–chloroacetate buffers to the least acidic pivalic acid–pivalate buffers. In chloroacetic acid–chloroacetate buffers the plots of k_{obs} against buffer base concentration show less pronounced curvature than those observed for pivalic acid–pivalate buffers and the data at three

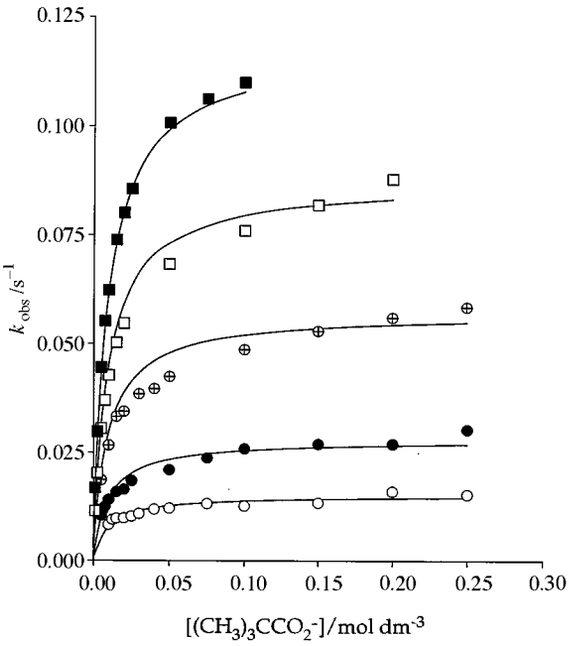
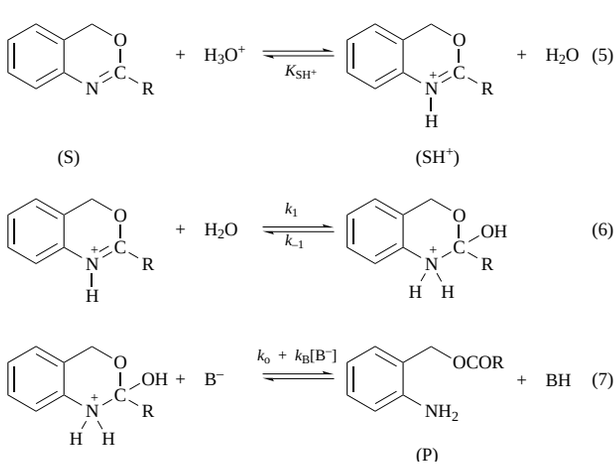


Fig. 3 Variation of observed rate coefficient for the hydrolysis of 2-methyl-4*H*-3,1-benzoxazine with buffer concentration in pivalic acid–pivalate buffers at buffer ratios $r = 0.5$ (■), 1.0 (□), 2.0 (⊕), 5.0 (●) and 10 (○)

ratios fall on the same plot of k_{obs} against buffer concentration. In chloroacetic acid–chloroacetate buffers the value of the intercept at zero buffer concentration is the same for each buffer ratio. For the reaction of 2-methyl-4*H*-3,1-benzoxazine in pivalic acid–pivalate buffers, the values of the intercepts at zero buffer concentration vary with buffer ratio and curved plots of k_{obs} against buffer base concentration observed at each buffer ratio are not superimposable.

Mechanism of reaction

The mechanism shown in eqns. (5)–(7) provides a satisfactory



explanation for all the kinetic data. If it is assumed that protonation of the benzoxazine occurs rapidly and that the tetrahedral carbonyl addition intermediate is present in low concentration the expressions in eqns. (9) and (10) are derived for this

$$-\mathrm{d}([S] + [SH^+])/\mathrm{d}t = \mathrm{d}[P]/\mathrm{d}t = k_{obs}([S] + [SH^+]) \quad (8)$$

$$k_{obs} = \frac{[H_3O^+]}{K_{SH^+} + [H_3O^+]} \times \frac{k_1(k_0 + k_B[B^-])}{k_{-1} + k_0 + k_B[B^-]} \quad (9)$$

$$\text{If } [B^-] = 0,\ k_{obs} = \frac{[H_3O^+]}{K_{SH^+} + [H_3O^+]} \times \frac{k_1 k_0}{k_{-1} + k_0} \quad (10)$$

Table 1 Spontaneous reaction of 2-methyl- and 2-aryl-4*H*-3,1-benzoxazines to 2-aminobenzyl esters

	pK_{SH^+} (meas.)[a]	pK_{SH^+} (fitted)[b]	$k_1k_0/(k_{-1} + k_0)/s^{-1}$	Av. dev.[c] (%)
R = Me	4.56 ± 0.1	4.62 ± 0.1[d]	9.54×10^{-3}	7.8
		4.52 ± 0.1[e]		
		4.64 ± 0.1[f]		
R = Ph	3.48 ± 0.1	3.30 ± 0.1[d]	2.85×10^{-3}	4.9
		3.31 ± 0.1[g]		
		3.30 ± 0.1[e]		
R = 4-$NO_2C_6H_4$	n.a.	1.73 ± 0.1[d]	5.20×10^{-2}	3.6

[a] Determined directly from rapid spectrophotometric equilibrium measurements. [b] Obtained by fitting eqn. (10) or eqn. (15) to the kinetic results. [c] Average deviation of the experimental values from values calculated from eqn. (10) using the best-fit values of K_{SH^+} and $k_1k_0/(k_{-1} + k_0)$. [d] Obtained from fits to the rate–pH profile. [e] Obtained from fits in acetic acid–acetate buffers. [f] Obtained from fits in pivalic acid–pivalate buffers. [g] Obtained from fits in formic acid–formate buffers.

scheme. In eqn. (5) the equilibrium constant (K_{SH^+}) is defined as the acid dissociation constant of the protonated substrate (SH^+) and is given by the expression $K_{SH^+} = [S][H_3O^+]/[SH^+]$. The term $[H_3O^+]/(K_{SH^+} + [H_3O^+])$ in expressions (9) and (10) is the fraction of the benzoxazine present in the reactive protonated form at a particular concentration of hydronium ion. In eqn. (6), the rate coefficient for the addition of water (k_1) is written as a first-order rate coefficient. The tetrahedral intermediate collapses to product in a spontaneous reaction and in a buffer-base-catalysed reaction with first-order rate coefficients of k_0 and $k_B[B^-]$ respectively.

The values of the observed first-order rate coefficients for reaction in the presence of hydrochloric acid and the values of k_{obs} extrapolated to zero buffer concentration from plots of k_{obs} against buffer base concentration are given by the expression in eqn. (10). The experimental values of k_{obs} at different hydronium ion concentrations were plotted in the form $1/k_{obs}$ against $1/[H_3O^+]$ and linear regression analysis gave values for $K_{SH^+}(k_{-1} + k_0)/k_1k_0$ and $(k_{-1} + k_0)/k_1k_0$ as gradient and intercept respectively. The best-fit values of K_{SH^+} and $k_1k_0/(k_{-1} + k_0)$ are given in Table 1. The solid lines in Fig. 1 drawn using these values of K_{SH^+} and $k_1k_0/(k_{-1} + k_0)$ provide good fits to the experimental results as shown by the average deviations of the experimental values from the fitted curve given in Table 1.

The dependence of k_{obs} on buffer base concentration at different buffer ratios in a range of buffers is explained by the expression in eqn. (9). At low buffer concentrations for which $k_B[B^-] < k_{-1}$ the expression in eqn. (9) reduces to the expression in eqn. (11) which predicts that the reaction is first order with

$$k_{obs} = \frac{[H_3O^+]}{K_{SH^+} + [H_3O^+]} \times \frac{k_1(k_0 + k_B[B^-])}{k_{-1} + k_0} \qquad (11)$$

respect to buffer concentration with an intercept at zero buffer concentration given by the expression in eqn. (10).

At high buffer concentrations for which the approximation $k_B[B^-] > k_{-1}$ is valid, the expression in eqn. (9) reduces to that in eqn. (12) which predicts that k_{obs} is independent of buffer

$$k_{obs} = \frac{[H_3O^+]}{K_{SH^+} + [H_3O^+]} \times k_1 \qquad (12)$$

concentration and reaches a limiting value at high buffer concentrations of $k_1[H_3O^+]/(K_{SH^+} + [H_3O^+])$. The condition $k_B[B^-] < k_{-1}$ corresponds to rate-limiting buffer-base-catalysed collapse of the tetrahedral intermediate to product by the reaction in eqn. (7). The condition $k_B[B^-] > k_{-1}$ corresponds to rate-limiting nucleophilic addition of H_2O to the protonated benzoxazine to form the tetrahedral intermediate, as in eqn. (6), and the reaction does not then show catalysis by buffer.

Eqn. (9), which is derived for the mechanism in eqns. (5)–(7), can be rearranged to give the expressions in eqns. (13) and (14).

$$(k_{obs} - I)/[B^-] = -k_{obs} \times \frac{k_B}{(k_{-1} + k_0)} + \frac{k_1k_B}{(k_{-1} + k_0)} \times \frac{[H_3O^+]}{K_{SH^+} + [H_3O^+]} \qquad (13)$$

$$k_{obs} = \frac{[H_3O^+]}{K_{SH^+} + [H_3O^+]} \times \frac{\{k_1k_0/(k_{-1} + k_0)\} + \{k_1k_B/(k_{-1} + k_0)\}[B^-]}{1 + \{k_B/(k_{-1} + k_0)\}[B^-]} \qquad (14)$$

The results for the variation of k_{obs} at different buffer concentrations for the reaction of 2-methyl-4*H*-3,1-benzoxazine in chloroacetic acid–chloroacetate, formic acid–formate, acetic acid–acetate and pivalic acid–pivalate buffers, for the reaction of 2-phenyl-4*H*-3,1-benzoxazine in chloroacetic acid–chloroacetate, formic acid–formate and acetic acid–acetate buffers and for the reaction of 2-(4-nitrophenyl)-4*H*-3,1-benzoxazine in chloroacetic acid–chloroacetate buffers were plotted in the form of eqn. (13) in which I is the intercept of plots of k_{obs} against $[B^-]$ at $[B^-] = 0$. Straight line graphs of the left hand side of eqn. (13) against k_{obs} were treated by linear regression analysis to give best-fit values of $k_B/(k_{-1} + k_0)$ as gradient and $\{k_1k_B/(k_{-1} + k_0)\} \times [H_3O^+]/(K_{SH^+} + [H_3O^+])$ as intercept. In some cases the value of I obtained by extrapolation of k_{obs} against $[B^-]$ to $[B^-] = 0$ involved high uncertainty. In these cases the value of I was treated as an adjustable parameter to improve the linearity of plots of eqn. (13). The value of I used was always within experimental error of the value of I obtained by extrapolation of the plots of k_{obs} against $[B^-]$ to $[B^-] = 0$. For each substrate in each buffer the average of the values of $k_B/(k_{-1} + k_0)$ at each buffer ratio was taken and the results are given in Table 2. The ratio of the gradient/intercept of the plot in eqn. (13) is given by the expression in eqn. (15) in which r is

$$\text{gradient/intercept} = (1/k_1) \times (K_{SH^+} + [H_3O^+])/[H_3O^+] = (1/k_1)(rK_{SH^+}/K_{BH} + 1) \qquad (15)$$

the buffer ratio ($r = [B^-]/[BH]$) and K_{BH} is the acid dissociation constant of the buffer. For each buffer, plots of eqn. (15) were used to determine values for k_1 and for the ratio K_{SH^+}/K_{BH}. By combining this latter value with the known value of the acid dissociation constant of the buffer, values for K_{SH^+} were obtained. These procedures were used to obtain values for $k_B/(k_{-1} + k_0)$, k_1 and K_{SH^+} for the reaction of 2-methyl-4*H*-3,1-benzoxazine in acetic acid–acetate and in pivalic acid–pivalate buffers and for the reaction of 2-phenyl-4*H*-3,1-benzoxazine in formic acid–formate and acetic acid–acetate buffers and the values are given in Tables 1 and 2. For the reactions of each substrate in chloroacetic acid–chloroacetate buffers and for the reaction of 2-methyl-4*H*-3,1-benzoxazine in formic acid–formate buffers the data did not vary sufficiently with buffer ratio to allow this detailed analysis. In these cases the values of $k_B/(k_{-1} + k_0)$ were obtained as the gradients of plots of eqn. (13) at each buffer ratio and the value of k_1 was calculated from the intercept using the value of $k_B/(k_{-1} + k_0)$ and the value of pK_{SH^+} obtained from the rate–pH profile.

The values of k_1 and $k_B/(k_{-1} + k_0)$ and pK_{SH^+} used to fit the kinetic results in buffer solutions are given in Tables 1 and 2 together with the average deviation of the experimental values of k_{obs} from the results predicted from eqn. (14). The fits to the

Table 2 Analysis of data for buffer catalysis

Buffer (B)	pK_{BH}[a]	r ([B$^-$]/[BH])	k_1/s^{-1}	$k_B/(k_{-1} + k_0)$/ dm^3 mol^{-1}	Av. dev. (%)
2-Methyl-4*H*-3,1-benzoxazine					
H_2O	−1.74			0.000 847[b]	
$ClCH_2COO^-$	2.52	0.5, 1.0, 2.0	0.143	1.92	1.9
$HCOO^-$	3.41	0.5	0.235	5.7	1.1
		1.0			4.7
		2.0			2.5
CH_3COO^-	4.42	0.5	0.247	39.2	3.8
		1.0			3.1
		2.0			5.5
Me_3CCOO^-	4.69	0.5	0.185	99.2	1.6
		1.0			4.3
		2.0			7.7
		5.0			5.5
		10.0			5.7
2-Phenyl-4*H*-3,1-benzoxazine					
H_2O	−1.74			0.004 93[b]	
$ClCH_2COO^-$	2.52	0.5	0.011 2	10.5	2.4
		1.0			2.8
		2.0			2.4
$HCOO^-$	3.41	0.5	0.011 2	36.4	2.9
		1.0			3.6
		2.0			2.7
CH_3COO^-	4.42	0.25	0.009 62	374.7	2.2
		0.5			4.4
2-(4-Nitrophenyl)-4*H*-3,1-benzoxazine					
H_2O	−1.74			0.007 68[b]	
$ClCH_2COO^-$	2.52	0.5	0.122	4.64	1.5
		1.0			1.6

[a] Buffer pK_{BH} values refer to the acid dissociation constant of the buffer acid at 298.2 K and ionic strength 0.25 mol dm^{-3} and were corrected from values[14] at infinite dilution using the Debye–Hückel approximation.[15] [b] For participation by solvent this value refers to $k_0/(k_{-1} + k_0)$ and has been converted to units of dm^3 mol^{-1} by division by 55.5.

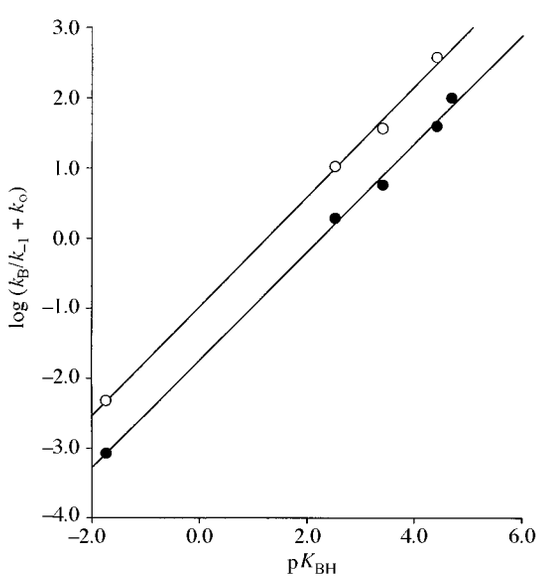


Fig. 4 Brønsted plot for base catalysis in the reactions of 2-methyl-4*H*-3,1-benzoxazine (●) and 2-phenyl-4*H*-3,1-benzoxazine (○)

experimental results for the reaction of 2-methyl-4*H*-3,1-benzoxazine in chloroacetic acid–chloroacetate buffers and in pivalic acid–pivalate buffers are shown in Figs. 2 and 3 respectively.

Because the protonation in eqn. (5) occurs rapidly compared with the subsequent steps in the reaction it was possible to study the equilibrium in eqn. (5) before significant reaction to the 2-aminobenzyl esters had taken place. This experiment was carried out for 2-methyl- and 2-phenyl-4*H*-3,1-benzoxazines but was not possible for the 2-(4-nitrophenyl) derivative because of limited solubility and a smaller change in spectrum on protonation. The values of the equilibrium constants (K_{SH^+}) determined in this way were in good agreement with the values obtained by fitting eqns. (10) and (15) to the kinetic results and are given in Table 1.

The values of $k_1k_0/(k_{-1} + k_0)$ for each benzoxazine determined by fitting eqn. (10) to the rate–pH profile were combined with the average values of k_1 for each benzoxazine to give values for $k_0/(k_{-1} + k_0)$ and these are shown in Table 2 for comparison with the values of $k_B/(k_{-1} + k_0)$. The rate coefficients k_B and k_0 respectively refer to base catalysed and spontaneous decomposition of the tetrahedral intermediate to product and the rate coefficient k_{-1} refers to collapse of the tetrahedral intermediate to the protonated benzoxazine. Hence k_{-1} and k_0 are expected to be independent of the particular buffer and it follows that the value of $k_B/(k_{-1} + k_0)$ will reflect the dependence of k_B on the basicity of the catalysing base as measured by the acid dissociation constant of its conjugate acid (pK_{BH}). The values of $k_B/(k_{-1} + k_0)$ for the reactions of 2-methyl- and 2-phenyl-4*H*-3,1-benzoxazines increase with an increase in pK_{BH} for three base catalysts. This is illustrated in the Brønsted plots in Fig. 4 which also include a point for the rate coefficient $k_0/(k_{-1} + k_0)$ for the spontaneous reactions. Since this latter point fits on the Brønsted plot for general base catalysis it is likely that the solvent functions as a general base in catalysing the decomposition of the tetrahedral intermediate. Values for the Brønsted exponent β of *ca.* 0.8 were obtained for the reactions of 2-methyl- and 2-phenyl-4*H*-3,1-benzoxazines.

Rate-limiting step

At low buffer concentrations the rate-limiting step in the buffer catalysed reaction is the decomposition of the tetrahedral intermediate to the 2-aminobenzyl esters. At high buffer concentrations the observed rate coefficient reaches a limiting value and the rate-limiting step is the hydration of the protonated benzoxazine. For the spontaneous uncatalysed reaction the

values of $k_0/(k_{-1} + k_0)$ can be used to calculate the values of the ratio of rate coefficients k_0/k_{-1} for collapse of the tetrahedral intermediates in the spontaneous reaction. The values obtained are k_0/k_{-1} 0.049, 0.38 and 0.74 for 2-methyl-, 2-phenyl- and 2-(4-nitrophenyl)-4*H*-3,1-benzoxazines respectively and it follows that both the dehydration and the decomposition of the tetrahedral intermediate to 2-aminobenzyl esters contribute to the overall rate coefficient for the spontaneous reaction.

Substituent effects

The values of pK_{SH^+} determined by direct measurement or deduced from kinetic data for the substituted benzoxazines increase with substituent R in the order R = Me > Ph > 4-$NO_2C_6H_4$. This is the order expected for increasing destabilisation of the protonated benzoxazine with increasing electron-withdrawing ability of the substituent. The effect of substituents on the value of the rate coefficient k_1 for addition of water to the benzoxazine ring is in the order Me > 4-$NO_2C_6H_4$ > Ph and can be explained by a combination of two substituent effects. Electron-withdrawing groups will destabilise the protonated benzoxazine and to a lesser extent the transition state for its conversion into the carbonyl addition intermediate. This effect alone would lead to an increase in the value of k_1 for more strongly electron-withdrawing substituents. In addition however there will be a steric effect associated with the change from a planar configuration around the reactive carbon to the tetrahedral geometry in the sterically more crowded transition state. This latter effect accounts for the higher value of k_1 found for 2-methyl-4*H*-3,1-benzoxazine than for the 2-aryl-4*H*-3,1-benzoxazines. The electronic effect explains the higher value of k_1 found for 2-(4-nitrophenyl)-4*H*-3,1-benzoxazine than for 2-phenyl-4*H*-3,1-benzoxazine since the steric effect will be similar in these cases. The values of $k_0/(k_{-1} + k_0)$ and $k_B/(k_{-1} + k_0)$ for each benzoxazine shown in Table 2 can be used to calculate values of k_0/k_{-1} and k_B/k_{-1}. The values of k_0/k_{-1} for R = Me, Ph and 4-$NO_2C_6H_4$ are 0.049, 0.38 and 0.74 respectively and increase in the order Me < Ph < 4-$NO_2C_6H_4$. The values of k_B/k_{-1} for catalysis by chloroacetate ion for R = Me, Ph and 4-$NO_2C_6H_4$ are 2.0, 14.5 and 8.1 $dm^3\ mol^{-1}$ and increase in the order Me < 4-$NO_2C_6H_4$ < Ph. The rate coefficients k_0, k_B and k_{-1} refer to strongly thermodynamically favourable reaction steps in which the transition states will resemble the reactants and small substituent effects are expected. Electron-withdrawing substituents are likely to increase the values of k_0 and k_B since this reaction occurs with loss of positive charge on the group attached to the carbon on which the substituent is located. The value of k_{-1} is likely to decrease with an increase in electron-withdrawing effect but there will also be steric effects which will be different for the reaction of 2-methyl-4*H*-3,1-benzoxazine compared with the reactions of the 2-aryl-4*H*-3,1-benzoxazines.

Comparison with related reactions

The mechanism of hydrolysis of 2-methyl-4*H*-3,1-benzoxazine to give 2-aminobenzyl acetate, eqn. (3), and the mechanism of hydrolysis of 2-methylnaphth[1,8-*de*]-1,3-oxazine under acidic conditions to give 1-hydroxy-8-acetylaminonaphthalene, eqn. (2), are closely related. Both reactions occur through the formation of a cyclic tetrahedral carbonyl addition intermediate by addition of water to the protonated oxazine. However the product of hydrolysis of 2-methyl-4*H*-3,1-benzoxazine in hydrochloric acid and in carboxylic acid buffers is the ester rather than the amide, 2-(acetylamino)benzyl alcohol, eqn. (4). This is explained because under the present reaction conditions the tetrahedral intermediate in eqns. (5)–(7) is protonated and formation of the ester by collapse of the intermediate involves departure of an aromatic amino group whereas formation of the amide, 2-(acetylamino)benzyl alcohol, would involve departure of a much poorer aliphatic alkoxide ion leaving group. In the hydrolysis of 2-methylnaphth[1,8-*de*]-1,3-oxazine, eqn. (2), formation of the observed amide product, 1-hydroxy-8-acetylaminonaphthalene, is less unfavourable than it would be in the case of the corresponding reaction of 2-methyl-4*H*-3,1-benzoxazine because departure of a naphthoxide ion as leaving group from a tetrahedral intermediate is involved rather than departure of an alkoxide ion.

A further difference in the hydrolyses of 2-methyl-4*H*-3,1-benzoxazine and 2-methylnaphth[1,8-*de*]-1,3-oxazine is also found. In the hydrolysis of 2-methylnaphth[1,8-*de*]-1,3-oxazine, buffer catalysis was not detected.[2] Addition of water to the protonated naphthoxazine is rate-limiting because collapse of the tetrahedral intermediate to product occurs more rapidly than collapse to the protonated naphthoxazine. In comparison in the hydrolysis of 2-methyl-4*H*-3,1-benzoxazine, buffer catalysis is observed. At low buffer concentrations collapse of the intermediate to the protonated benzoxazine occurs more rapidly than collapse to 2-aminobenzyl acetate. This latter step is therefore rate-limiting and is catalysed by buffer base. At high buffer concentrations collapse of the intermediate to 2-aminobenzyl acetate occurs more rapidly than collapse to the protonated benzoxazine and addition of water to the protonated benzoxazine is rate-limiting. The overall reaction is then of zero order in buffer.

In the hydrolysis of acyclic imidates an amine and an ester are formed at low pH and an amide and alcohol are formed at high pH.[12] Buffer catalysis of the collapse of a tetrahedral intermediate to reactant or product or to a second intermediate has been observed in different cases.[13]

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