Substituent and solvent isotope effects on the reaction of 2-alkylnaphth[1,8-*de*]-1,3-oxazines to 1-hydroxy-8-acylaminonaphthalenes through reversible formation of a cyclic tetrahedral addition intermediate

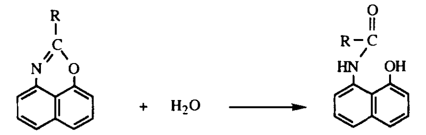
Andrew S. Baynham, Wendy J. Dixon, Frank Hibbert* and Jagvi R. Patel

Department of Chemistry, King's College London, Strand, London, UK WC2R 2LS

The first-order rate coefficient for the addition of water to substituted 2-alkylnaphth[1,8-*de*]-1,3-oxazines to give the corresponding 1-hydroxy-8-acylaminonaphthalenes in aqueous solution at pH 0 to 6 goes through a maximum value with pH. Substituent effects and solvent isotope effects on the rate–pH profile are explained by a mechanism involving reversible addition of water to the protonated naphthoxazine to give a cyclic tetrahedral intermediate and hydronium ion followed by ring-opening of the intermediate to form product. In aqueous alkaline solution and in 50% (v/v) Me_2SO–H_2O containing hydroxide ion the reaction is first-order with respect to hydroxide ion and involves nucleophilic addition of hydroxide ion to the neutral naphthoxazine.

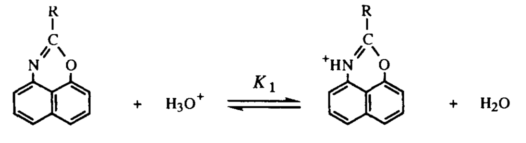
Introduction

The observed[1] maximum in the rate–pH profile for the hydration and ring opening of 2-methylnaphth[1,8-*de*]-1,3-oxazine to give 1-hydroxy-8-acetylaminonaphthalene, reaction (1), has been explained by the mechanism in reactions (2)–(4)

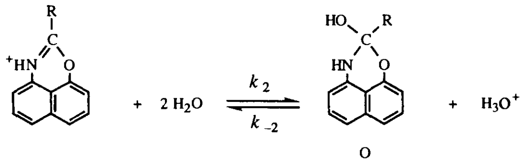


(1)

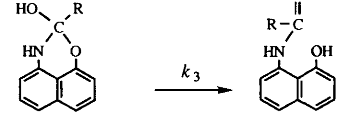
1 R = ClCH$_2$
2 R = CH$_3$
3 R = (CH$_3$)$_2$CH
4 R = (CH$_3$)C



(2)



(3)



(4)

$$k_{obs} = K_1k_2\,[H_3O^+]/(1 + k_{-2}\,[H_3O^+]/k_3)\,(1 + K_1[H_3O^+]) \quad (5)$$

for which the rate expression in eqn. (5) is derived on the assumption that the proton transfer in reaction (2) occurs rapidly and that the tetrahedral addition intermediate is present in low concentration. The rate–pH data were accurately fitted by eqn. (5) but unique values could not be deduced for the individual rate coefficients in the mechanism because the denominator in eqn. (5) is symmetrical with respect to K_1 and k_{-2}/k_3. To resolve this ambiguity we have now compared the results for 2-methylnaphth[1,8-*de*]-1,3-oxazine **2**, R = Me in eqn. (1) with results for naphthoxazines having R = ClCH$_2$ **1**, Pr^i **3** and Bu^t **4**. From the effect of substituents on the rate–pH profile it has been possible to identify the values of K_1 and k_{-2}/k_3 for each naphthoxazine **1**–**4** and to explain the substituent effects and solvent isotope effect in terms of the mechanism in reactions (2)–(4). Substituent effects and the solvent isotope effect on the reaction in alkaline solution have also been investigated.

Experimental

Materials

The preparations of 1-hydroxy-8-acetylaminonaphthalene and 2-methylnaphth[1,8-*de*]-1,3-oxazine **2** have been described previously.[1] Samples of 1-hydroxy-8-(2-methylpropionylamino)naphthalene, 1-hydroxy-8-trimethylacetylaminonaphthalene and 1-hydroxy-8-chloroacetylaminonaphthalene were prepared using similar procedures and recrystallized from ethanol–water (2:1).

1-Hydroxy-8-(2-methylpropionylamino)naphthalene was obtained as a mauve solid (mp 112–113 °C); δ_H(360 MHz, [$^2H_6$]Me$_2$SO) 11.34 (1 H, br s, OH), 11.20 (1 H, s, NH), 8.49–6.88 (6 H, m, Ar-H), 2.61–2.54 (1 H, septet, CH), 1.21–1.19 (6 H, d, CH$_3$)† (Found: C, 73.5; H, 6.5; N, 6.0. $C_{14}H_{15}NO_2$ requires: C, 73.3; H, 6.6; N, 6.1%).

A sample of 1-hydroxy-8-trimethylacetylaminonaphthalene was obtained as a purple solid (mp 171 °C). δ_H(360 MHz, [$^2H_6$]Me$_2$SO) 11.62 (1 H, br s, OH), 11.52 (1 H, br s, NH), 8.59–6.88 (6 H, m, arom.), 1.28 (9 H, s, CH$_3$) (Found: C, 73.7; H, 7.0; N, 5.5. $C_{15}H_{17}NO_2$ requires: C, 74.0; H, 7.0; N, 5.8%).

The sample of 1-hydroxy-8-chloroacetylaminonaphthalene was a brown solid (mp 152–155 °C). δ_H(360 MHz, [$^2H_6$]Me$_2$SO) 11.95 (1 H, br s, OH), 11.50 (1 H, s, NH), 8.53–6.90 (6 H, m, Ar-H), 4.53 (2 H, s, CH$_2$) (Found: C, 61.4; H, 4.3; N, 5.8; Cl, 14.9. $C_{12}H_{10}NClO_2$ requires: C, 61.2; H, 4.3; N, 5.9; Cl, 15.0%).

Sublimation of these samples at *ca.* 150 °C under reduced pressure (2 mmHg) gave the cyclic products. White crystals of 2-isopropylnaphth[1,8-*de*]-1,3-oxazine **3** were obtained, with mp 38 °C, δ_H(360 MHz, [$^2H_6$]Me$_2$SO) 7.49–6.80 (6 H, m, Ar-H), 2.73–2.54 (1 H, septet, CH), 1.26–1.24 (6 H, d, CH$_3$) (Found:

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† *J* Values are given in Hz.

C, 79.7; H, 6.0; N, 6.7. $C_{14}H_{13}NO$ requires: C, 79.6; H, 6.2; N, 6.6%).

The product 2-*tert*-butylnaphth[1,8-*de*]-1,3-oxazine **4** had mp 62 °C. δ_H(360 MHz, [$^2H_6$]Me_2SO) 7.49–6.81 (6 H, m, Ar-H), 1.31 (9 H, s, CH_3) (Found: C, 80.0; H, 6.7; N, 6.2. $C_{15}H_{15}NO$ requires: C, 79.6; H, 6.7; N, 6.1%).

Repeated sublimation of 1-hydroxy-8-chloroacetylaminonaphthalene gave a mixture of 60% 2-chloromethylnaphth[1,8-*de*]-1,3-oxazine **1** and 40% 1-hydroxy-8-chloroacetylaminonaphthalene. The ^1H NMR spectrum of the mixture showed peaks due to 2-chloromethylnaphth[1,8-*de*]-1,3-oxazine **1** at δ_H(360 MHz, [$^2H_6$]Me_2SO) 7.57–6.87 (6 H, m, Ar-H) and 4.47 (2 H, s, CH_2). Despite further sublimation of the mixture a pure sample of **1** could not be obtained and studies were made with this mixture. Microanalysis was not attempted for the oxazine but 1-hydroxy-8-chloroacetylaminonaphthalene gave a satisfactory analysis (see earlier).

Structures for 1-hydroxy-8-chloroacetylaminonaphthalene and 2-chloromethylnaphth[1,8-*de*]-1,3-oxazine were confirmed from mass spectral (EI) results. The MS of 1-hydroxy-8-chloroacetylaminonaphthalene showed *m/z* 235.0 (M^+, 77.5%), 217.0 (M + 1 − OH, 4.8), 159.1 (M + 1 − $ClCH_2CO$, 100) (Found M^+ 235.0374. $C_{12}H_{10}O_2NCl$ requires 235.0348) and for 2-chloro-methylnaphth[1,8-*de*]-1,3-oxazine *m/z* 217.0 (M^+, 100%), 182.1 (M − Cl, 31.1%). (Found 217.0309. $C_{12}H_8ONCl$ requires 217.0324).

Products of reaction and kinetic methods

On introduction of the naphthoxazines **1–4** into acidic aqueous solution a change in the UV–VIS spectrum was observed with time as reaction to the ring-opened species occurred as in reaction (1). Isosbestic points were observed at *ca.* 330 nm. In alkaline solution the spectral changes accompanying the reaction proceeded with isosbestic points at *ca.* 280 and 320 nm. The spectra of the products of reaction under all conditions were identical with the spectra of separately prepared samples of the corresponding 1-hydroxy-8-acylaminonaphthalenes under the same conditions.

Kinetic results in acidic aqueous solution were obtained by following the decrease in absorbance at *ca.* 350 nm corresponding to removal of the oxazines. In some cases the increase in absorbance at *ca.* 300 nm corresponding to the formation of the product was also followed to confirm that the change in absorbance corresponded to reaction (1). In alkaline solution the reactions were followed by observing the increase in absorbance at *ca.* 350 nm or decrease in absorbance at *ca.* 290 nm corresponding to conversion of the oxazines into product. Measurements were made in aqueous solution or in 50% (v/v) Me_2SO–H_2O at 25.0 °C and with an ionic strength maintained at 0.25 mol dm^{-3} by the addition of potassium chloride. Reactions with half-lives of less than *ca.* 10 s were followed using the stopped-flow method (Hi-Tech SF 51) and slower reactions were followed by conventional UV–VIS spectrophotometry. Reactions were accurately of the first-order with respect to the oxazines and were studied typically for two to three half-lives. First-order rate coefficients (k_{obs}) were calculated from the usual logarithmic plots using a measured absorbance value corresponding to complete reaction. In some cases an exponential fit to the data over three half-lives was used to obtain the value of the first-order rate coefficient.

Over the pH range 0.6 to 4.7 the kinetics of the reaction of oxazines **1–4** were measured in aqueous solution in the presence of hydrochloric acid and with buffers of chloroacetic, formic, acetic and trimethylacetic acid at different buffer ratios. Measurements with **2** were also made in phosphate buffers at pH 6.22 and 6.52. At a particular buffer ratio the observed first-order rate coefficient was determined over a range of buffer concentrations. The values of k_{obs} were usually independent of buffer concentration but in some cases a small change in k_{obs} of a few percent was observed. The data were examined closely and it was concluded that the reaction does not show catalysis by the buffer acid or buffer base. The small variation of k_{obs} with buffer concentration probably corresponds to a small salt effect on the reaction as the chloride ion used to maintain constant ionic strength was replaced by the buffer anion.

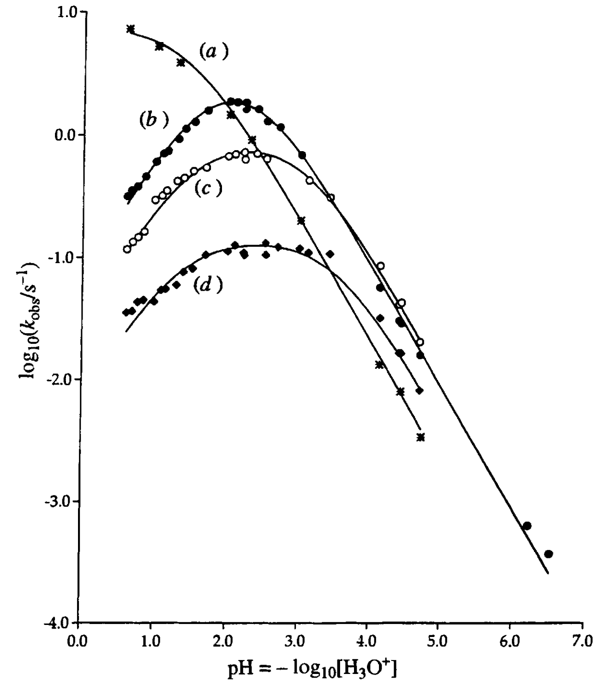


Fig. 1 Variation of observed first-order rate coefficient (k_{obs}) with pH for reaction of 2-alkylnaphth[1,8-*de*]-1,3-oxazines to 1-hydroxy-8-acylaminonaphthalenes; the lines are best-fits of eqn. (5) and the points are experimental values of the rate coefficient for hydrolysis of the oxazines according to reaction (1) with R = CH_2Cl **1** (*a*), CH_3 **2** (*b*), $CH(CH_3)_2$ **3** (*c*) and $C(CH_3)_3$ **4** (*d*)

To investigate the magnitude of the solvent isotope effect on the kinetics of the reaction, rates for **2** were also determined over the pD range 0.6 to 4.9 using DCl and acetate buffer solutions in deuterium oxide as solvent. Studies were also made for **2** and **3** in aqueous solution over a range of hydroxide ion concentrations (0.05 to 0.25 mol dm^{-3}) and for **2** in deuterium oxide containing deuteroxide ion. For **1–4** the reaction with hydroxide ion was also studied in 50% (v/v) Me_2SO–H_2O with hydroxide ion concentrations in the range 0.05 to 0.25 mol dm^{-3}. In this solvent the increased solubility of the oxazines, particularly **4**, allowed larger changes in absorbance to be observed.

Results and discussion

The variation of the first-order rate coefficients with pH for the reaction of oxazines **1–4** is shown in Fig. 1 in which the data points are experimental values of $\log_{10}$ (k_{obs}/s^{-1}). For **2**, **3** and **4** the maximum in the value of k_{obs} is explained by the mechanism in reactions (2)–(4) for which the rate expression in eqn. (5) is derived. Eqn. (5) was fitted to the experimental values of k_{obs} for **2**, **3** and **4** using the methods previously described.[1] The equation was fitted in the form $k_{obs} = a[H_3O^+]/\{(1 + b[H_3O^+])(1 + c[H_3O^+])\}$ and the values of *a*, *b* and *c* were adjusted to give the best fits to the data as shown by the solid lines in Fig. 1. In fitting eqn. (5) to the results a value for $K_1k_2 = a$ is obtained. However, because the equation is symmetrical with respect to k_{-2}/k_3 and K_1 the fits correspond either to $k_{-2}/k_3 = b$ and $K_1 = c$ or $k_{-2}/k_3 = c$ and $K_1 = b$. The best-fit values of K_1k_2, and the two values *b* and *c* which correspond to either k_{-2}/k_3 or K_1 are given in the fourth and fifth columns of Table 1. The ambiguity in the values of k_{-2}/k_3 and K_1 is resolved by considering substituent effects on the reaction (see below).

Table 1 Rate and equilibrium constants obtained by fitting eqn. (5) to the experimental variation of $\log_{10} k_{obs}$ against pH in acidic solution

Oxazine	Substituent	σ*	K_1k_2/ dm^3 mol^{-1} s^{-1}	k_{-2}/k_3 or K_1/dm^3 mol^{-1}	K_1/dm^3 mol^{-1}	k_2/s^{-1}	(k_{-2}/k_3)/dm^3 mol^{-1}
Aqueous solution							
1	$ClCH_2$	0.94	204.0	26.3	0.027[a]	7.6 × 10^3[a]	26.3
2	CH_3	0.0	851.4	63.5 and 180	180	4.7	63.5
3	$(CH_3)_2CH$	−0.19	1050	32 and 1050	1050	1.0	32
4	$(CH_3)_3C$	−0.30	440	20 and 3000	3000	0.147	20
Deuterium oxide							
2	CH_3		1550	155 and 575	575	2.7	155

[a] The value of K_1 0.027 dm^3 mol^{-1} was estimated from a $\sigma^*\rho$ plot of the K_1 values for **2**–**4** (see text) and the value of k_2 was calculated using the estimated value of K_1 and the measured value K_1k_2 204.0 dm^3 mol^{-1} s^{-1}.

For **1**, the values of k_{obs} increase to a limiting value as the hydronium ion concentration is increased and the experimental data are fitted by either of the expressions given in eqns. (6) and (7) which are obtained from the expression in eqn. (5) by

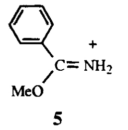
$$k_{obs} = K_1k_2[H_3O^+]/(1 + K_1[H_3O^+]) \quad (6)$$

$$k_{obs} = K_1k_2[H_3O^+]/(1 + k_{-2}[H_3O^+]/k_3) \quad (7)$$

making the assumptions $k_{-2}[H_3O^+] < 1$ or $K_1[H_3O^+] < 1$ respectively. The fit to the experimental data was obtained using $K_1k_2 = 204.0$ dm^3 mol^{-1} s^{-1} and either $k_{-2}/k_3 = 26.3$ dm^3 mol^{-1} or $K_1 = 26.3$ dm^3 mol^{-1}. Identification of the particular values of k_{-2}/k_3 and K_1 for **1**–**4** from the fits is made possible by considering the effect of substituents. The values of the equilibrium constant K_1 = [protonated oxazine]/[oxazine][H_3O^+] are likely to increase along the series $ClCH_2 < CH_3 < (CH_3)_2CH < (CH_3)_3C$. It follows from the two possible values of k_{-2}/k_3 and K_1 in Table 1 that for **3** and **4** respectively 1050 and 3000 dm^3 mol^{-1} correspond to K_1 and 32 and 20 dm^3 mol^{-1} refer to k_{-2}/k_3. Using the results K_1 1050 dm^3 mol^{-1} and 3000 dm^3 mol^{-1} for **3** and **4** respectively and the appropriate values of σ^* (see Table 1), a value of K_1 171 dm^3 mol^{-1} is predicted for **2** and it therefore seems reasonable to assume that of the two possible values 63.5 and 180 dm^3 mol^{-1} for **2** the latter is the more likely for K_1. The separate results for K_1, k_2 and k_{-2}/k_3 for **2**–**4** are given in columns 6, 7 and 8 of Table 1.

The variation of K_1 for **2**, **3** and **4** with σ^* is fitted by the linear free energy relationship $\log_{10} K_1 = \sigma^*\rho + 2.253$ with $\rho = -4.07$ and correlation coefficient 1.00. Extrapolation to σ^* 0.94 gives K_1 0.0268 dm^3 mol^{-1} for **1**. Hence it is unlikely that the value 26.3 dm^3 mol^{-1} estimated from the rate–pH profile for **1** refers to K_1. For hydronium ion concentrations up to 0.25 mol dm^{-3} the value K_1 0.0268 dm^3 mol^{-1} is compatible with the assumption $K_1[H_3O^+] < 1$ which leads to eqn. (7). Hence for **1** $K_1[H_3O^+] < 1$ and k_{-2}/k_3 has the value 26.3 dm^3 mol^{-1}. These results show why the rate–pH profile for **1** differs from the rate–pH profiles for **2**, **3** and **4**. For **1**, $K_1[H_3O^+] < 1$ applies over the whole of the accessible pH range and k_{obs} approaches a limiting value independent of [H_3O^+] because at low pH the term $k_{-2}[H_3O^+]/k_3$ begins to approach and exceed unity at which point the expression in eqn. (7) reduces to $k_{obs} = K_1k_2k_3/k_{-2}$.

The result K_1 180 dm^3 mol^{-1} obtained for **2** corresponds to a pK_a value of *ca.* 2.3. This compares with the result pK_a 5.6 measured[2] for **5**. A value of pK_a *ca.* 0.4 has been estimated[3] for **6** from kinetic results and we have recently estimated[4] pK_a *ca.* 4.6 for the benzoxazine **7**. The value ρ −4.07 obtained for the variation in $\log_{10} K_1$ for **2**, **3** and **4** is of the expected sign and can be compared with the results ρ −1.83 and ρ −2.05 respectively measured[5] for the acid dissociation of protonated primary and secondary amines $RCH_2NH_3^+$ and $(RCH_2)_2NH_2^+$.



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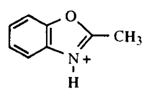

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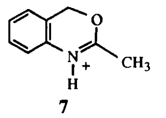

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The result K_1 0.0268 dm^3 mol^{-1} estimated for **1** when combined with the value K_1k_2 204.0 dm^3 mol^{-1} s^{-1} obtained by fitting eqn. (6) to the experimental results leads to the estimate k_2 7.6 × 10^3 s^{-1} for **1**. This result and the k_2 values for **2**, **3** and **4** are well fitted by the relationship $\log_{10} k_2 = \sigma^*\rho + 0.523$ with ρ 3.63 and correlation coefficient 0.99. A positive value of ρ is compatible with the reaction in reaction (3) involving nucleophilic addition of water to the planar sp^2 carbon in the protonated oxazine. The values of k_{-2}/k_3 remain roughly constant along the series **1**–**4** presumably because a decrease in electron-withdrawing ability increases k_{-2} and k_3 by similar extents.

The variation of $\log_{10} k_{obs}$ with pD for the reaction of 2-methylnaphth[1,8-*de*]-1,3-oxazine in deuterium oxide is very similar to the rate–pH profile found for the reaction in aqueous solution although in deuterium oxide the maximum occurs at a lower value of $\log_{10} k_{obs}$ and is shifted to lower acidity. The values of K_1, k_2 and k_{-2}/k_3 for reaction in D_2O obtained by fitting eqn. (5) to the rate–pD profile are given in Table 1 and by comparison with the values for reaction in H_2O deduced from the rate–pH profile, solvent isotope effects on each of these parameters are obtained. The solvent isotope effect on the protonation of the naphthoxazine $K_1(H_2O)/K_1(D_2O)$ 0.313 corresponds to p$K_a(D_2O)$ − p$K_a(H_2O)$ = 0.50 for acid dissociation of the protonated naphthoxazine. This result is well within the range of values normally observed for solvent isotope effects on the dissociation of oxygen and nitrogen acids.[6] The kinetic solvent isotope effect on the addition of water to the protonated oxazine as in eqn. (3) has a value $k_2(H_2O)/k_2(D_2O)$ 1.7. This isotope effect is in the same direction and of similar magnitude to other isotope effects found for other reactions involving nucleophilic addition of water.[7] The isotope effect $[k_{-2}/k_3(H_2O)]/[k_{-2}/k_3(D_2O)]$ 0.41 is likely to be composed of a small kinetic solvent isotope effect on the collapse of the addition intermediate in reaction (4), that is $k_3(H_2O)/k_3(D_2O)$ *ca.* 1.0, and a substantial kinetic isotope effect on the reverse reaction in reaction (3), $k_{-2}(H_2O)/k_{-2}(D_2O)$ *ca.* 0.41. This reverse reaction may involve pre-equilibrium protonation of the hydroxy group in the tetrahedral intermediate followed by rate-limiting elimination of water. The pre-equilibrium protonation is likely[6] to be more favourable in D_2O than in H_2O by a factor of *ca.* 3 to 5 and this, together with a small kinetic isotope effect on the elimination of water will account for the inverse isotope effect $k_{-2}(H_2O)/k_{-2}(D_2O)$ *ca.* 0.41. The value of the equilibrium solvent isotope effect on the reaction in reaction (3) calculated from the ratio $[k_2(H_2O)/k_{-2}(D_2O)]/k_{-2}(H_2O)/k_{-2}(D_2O)]$ *ca.* 4.1 is of the expected size for a reaction involving

Table 2 Second-order rate coefficients for reaction in alkaline solution

Oxazine	Substituent	Solvent	$10^3\ k_{OH}$/dm^3 mol^{-1} s^{-1}
2	CH_3	H_2O	7.9
2	CH_3	D_2O	9.2
3	$(CH_3)_2CH$	H_2O	2.03
1	CH_2Cl	50% (v/v) Me_2SO-H_2O	8064
2	CH_3	50% (v/v) Me_2SO-H_2O	29.7
3	$(CH_3)_2CH$	50% (v/v) Me_2SO-H_2O	7.2
4	$(CH_3)_3C$	50% (v/v) Me_2SO-H_2O	0.95

formation of a hydronium ion. Similar values[6] are observed for the solvent isotope effect associated with acid dissociation of a protonated amine. It follows that the magnitude of the solvent isotope effects can be accounted for in terms of the mechanism in reactions (2)–(4).

In alkaline solution the observed first-order rate coefficient for the reaction of substituted 2-alkylnaphth[1,8-*de*]-1,3-oxazines to 1-hydroxy-8-acylaminonaphthalenes is directly proportional to hydroxide ion concentration over the whole of the concentration range studied (0.05 to 0.25 mol dm^{-3}). The values of the second-order rate coefficients (k_{OH}) calculated for **2** and **3** in aqueous solution and for **1**–**4** in 50% (v/v) Me_2SO–H_2O are given in Table 2. For **2** and **3** the values are 3.8- and 3.5-fold respectively larger in 50% (v/v) Me_2SO–H_2O than in aqueous solution. For the data in 50% (v/v) Me_2SO–H_2O the variation of $\log_{10} k_{OH}$ against σ^* gives a linear correlation with ρ 2.94 and correlation coefficient 0.97. Nucleophilic addition of hydroxide ion at the oxazine carbon is particularly facilitated by the strongly electron-withdrawing chloromethyl substituent and the second-order rate coefficient is 272-fold higher than for 2-methylnaphth[1,8-*de*]-1,3-oxazine. The kinetic solvent isotope effect on the second-order rate coefficient for reaction of **2** with hydroxide ion $k_{OH}(H_2O)/k_{OD}(D_2O)$ 0.86 is compatible with a reaction involving nucleophilic addition of hydroxide ion.[8]

The equilibrium addition of solvent to the protonated oxazine to form an addition intermediate and to liberate a proton in reaction (3) or the addition of a hydroxide ion to the neutral oxazine are equivalent to pseudo-base formation occurring commonly in the chemistry of unsaturated nitrogen heterocycles.[9] In deriving eqn. (5) it has been assumed that the addition intermediate is present in low concentration under all conditions. At low acid concentrations (where $k_{-2}[H_3O^+]/k_3 \ll 1$) addition of water to the protonated naphthoxazine is rate-limiting and the intermediate reaches negligibly low concentrations because collapse to products occurs rapidly. At high acid concentrations (for **1** at $[H_3O^+] > 0.001$ mol dm^{-3} and for **4** at $[H_3O^+] > 0.5$ mol dm^{-3}) the addition intermediate is formed in low equilibrium concentrations and collapse to products is rate-limiting.

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