Alkaline Hydrolysis of Dibenzoylaminonaphthalenes in 70% (v/v) Me_2SO-H_2O and the Effect of a Neighbouring Amide Group

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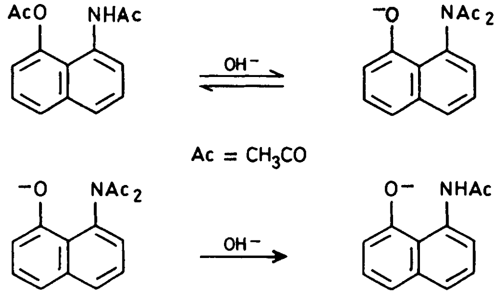
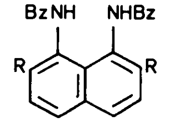
The rate of hydrolysis of 1-benzoylamino-8-dibenzoylaminonapthalene to 1,8-bis(benzoylamino)naphthalene in 70% (v/v) Me_2SO-H_2O is independent of hydroxide ion concentration in the range 0.001–0.2 mol dm^{-3}. For 1-benzoylamino-8-dibenzoylamino-2,7-dimethoxynaphthalene the observed rate coefficients show a curvilinear dependence on hydroxide ion concentration. The order of reaction with respect to hydroxide ion changes from first order to zero order as the concentration is increased. The complex dependence on hydroxide ion concentration is due to ionisation of the 1-benzoylamino groups and equilibrium constants for the ionisation have been determined in separate experiments before appreciable hydrolysis has taken place. The kinetics for both imides can be explained by a mechanism involving reaction of undissociated I-benzoylamino-8-dibenzoylaminonaphthalene with hydroxide ion or by reaction of the dissociated species with solvent. For the latter process the magnitude of the rate coefficient in comparison with that for the spontaneous solvolysis of 1-dibenzoylaminonaphthalene requires that the ionised amide group is involved as an intramolecular base catalyst in assisting the attack of solvent.

Investigations of the mechanisms of intramolecularly catalysed reactions provide information that is relevant to an understanding of the catalytic function of enzymes.[1,2,3] The proximity of groups at the 1- and 8-positions of naphthalene is particularly favourable for the operation of efficient intramolecular catalysis and such catalysis has been demonstrated in a number of cases. For example, cleavage of an acetal at the 1-position is subject to intramolecular acid catalysis by carboxy,[4] ammonium,[5] and hydroxy[6] groups at the 8-position. The aqueous alkaline hydrolysis of 1-acetoxy-8-hydroxynaphthalene involves reaction of the ionised ester with water through a mechanism in which the ionised hydroxy group assists the attack of solvent by intramolecular base catalysis.[7] The alkaline hydrolysis of the ester 1-acetoxy-8-acetylaminonaphthalene occurs by an intramolecular acyl transfer to give 8-diacetylamino-1-hydroxynaphthalene which then undergoes hydrolysis to 8-acetylamino-1-hydroxynaphthalene,[8] Scheme 1. The purpose of the present work was to find out whether a similar mechanism could operate in the hydrolysis of 1,8-bis(benzoylamino)naphthalene (**1**) and the 2,7-dimethoxy derivative (**2**). The intermediate generated by intramolecular acyl transfer would be 1-amino-8-dibenzoylaminonaphthalene which could be expected to undergo rapid hydrolysis to 1-amino-8-benzoylaminonaphthalene. However, as will be shown, 1,8-bis(benzoylamino)naphthalene is unreactive towards alkaline hydrolysis and participation by the neighbouring amide does not occur. In contrast, the imide function in 1-benzoylamino-8-dibenzoylaminonaphthalene (**4**) is susceptible to alkaline hydrolysis and it is found that the reaction does involve participation by the neighbouring amide group. Kinetic results for the hydrolysis of (**3**), (**4**), and (**5**) in 70% (v/v) Me_2SO-H_2O containing hydroxide ion are now reported.

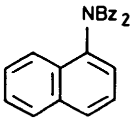


Scheme 1.

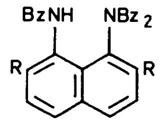
Bz = PhCO



(**1**) R = H
(**2**) R = OMe



(**3**)



(**4**) R = H
(**5**) R = OMe

Experimental and Results

Materials.—The preparation of compounds (**1**)–(**5**) was achieved by reaction of benzoyl chloride with the appropriate amines under various conditions. Samples of 1,8-bis(benzoylamino)naphthalene (**1**)[9] and 1,8-bis(benzoylamino)-2,7-dimethoxynaphthalene (**2**) were prepared by stirring 1,8-diaminonaphthalene and 1,8-diamino-2,7-dimethoxynaphthalene[10] with benzoyl chloride (*ca.* 2.5 molar excess) at 0 °C in dry chloroform containing anhydrous pyridine (threefold molar excess) for 4 h. The precipitated solids were collected and recrystallised from ethanol. 1,8-Bis(benzoylamino)naphthalene was obtained as a white solid[9] (m.p. 310–311 °C) in 61% yield and was identified from its n.m.r. spectrum: δ_H(360 MHz; $[^2H_6]Me_2SO$) 10.32 (s, 2 H, NH), 7.93 (d, 2 H, 2- and 7-H $C_{10}H_6$), 7.72 (d, 4 H, 2- and 6-H Ph), 7.62 (d, 2 H, 4- and 5-H $C_{10}H_6$), 7.56 (dd, 2 H, 3- and 6-H $C_{10}H_6$), 7.39 (dd, 2 H, 4-H Ph), and 7.19 (dd, 4 H, 3- and 5-H Ph). Similarly, 1,8-bis(benzoylamino)-2,7-dimethoxynaphthalene (**2**) was prepared in 56% yield as a white solid, m.p. 286–290 °C; δ_H(360 MHz; $CDCl_3$) 8.07 (s, 2 H, NH), 7.81 (d, 2 H, 4- and 5-H $C_{10}H_4$), 7.66 (d, 4 H, 2-and 6-H Ph), 7.34 (dd, 2 H, 4-H Ph), 7.21

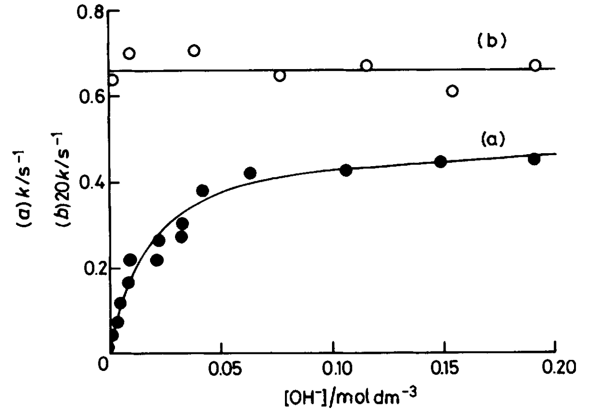


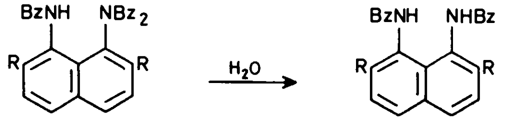
Figure. Rate coefficients for hydrolysis of (a) 1-benzoylamino-8-dibenzoylamino-2,7-dimethoxynaphthalene and (b)-1-benzoylamino-8-dibenzoylaminonaphthalene. The solid lines are fits of equation (1).

(d, 2 H, 3- and 6-H $C_{10}H_4$), 7.16 (d, 4 H, 3- and 5-H Ph), and 3.90 (s, H, CH_3) (Found: C, 73.1; H 5.1; N 6.7. $C_{26}H_{22}N_2O_4$ requires C 73.2; H 5.2; N 6.6%).

The imides (**4**) and (**5**) were prepared by benzoylation of the diaminonaphthalenes under more forcing conditions. In a typical procedure, 1,8-diaminonaphthalene (0.16 g), dry pyridine (0.9 g), and benzoyl chloride (1.14 g) were refluxed for 2 h in dry dichloromethane (25 cm^3) and left to stand overnight. The mixture was filtered and the solid product was collected (0.12 g, 26% yield) and washed with ethanol to give 1-benzoylamino-8-dibenzoylaminonaphthalene (**4**) as a brown solid, m.p. 232–235 °C. The final traces of solvent could not be removed but (**4**) was identified by n.m.r. spectroscopy: δ_H(360 MHz; [$^2H_6$] Me_2SO) 9.48 (s, 1 H, NH) and 7.96–7.17 (m, 21 H, ArH) and by mass spectrometry (chemical ionisation): *m/z* 471 (0.2%, $M^+ + 1$), 367 (5%, $M^+ + 2 - $ PhCO), 349 (23.4%, $M^+ + 2 -$ PhCO $- H_2O$), 287 (1.6%, $M^+ - 1 -$ PhCO $-$ Ph), 244 (30.8%, $M^+ + 2 - 2 \times$ PhCO $- H_2O$), and 105 (100%, PhCO). 1-Benzoylamino-8-dibenzoylamino-2,7-dimethoxynaphthalene was obtained as a pink solid (m.p. 225–228 °C) in 56% yield: δ_H(360 MHz; [$^2H_6$] Me_2SO) 8.98 (s, 1 H, NH), 7.92–7.05 (m, 25 H, ArH), 3.84 (s, 3 H, CH_3), and 3.81 (s, 3 H, CH_3): *m/z* (c.i.) 427 (1.9%, $M^+ + 2 -$ PhCO), 409 (28.7%, $M^+ + 2 -$ PhCO $- H_2O$), 346 (1.1%, $M^+ -$ PhCO $-$ Ph), 305 (77.7%, $M^+ + 1 - 2 \times$ PhCO $- H_2O$), and 105 (100%, PhCO).

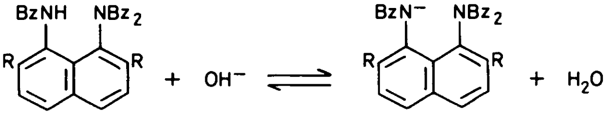
Reaction of benzoyl chloride (1.1 g) with 1-naphthylamine (1.1 g) in aqueous sodium hydroxide (100 cm^3; 10%) for 15 min with shaking gave 1-benzoylaminonaphthalene[11] (0.3 g). The product was recrystallised from ethanol to yield white crystals (m.p. 158–160 °C). When 1-naphthylamine (14 g) was heated with benzoyl chloride (60 g) under reflux for 3 h crude 1-dibenzoylaminonaphthalene[12] (17 g) was obtained as pale yellow crystals (m.p. 198 °C) after recrystallisation from acetic acid.

Kinetics of Hydrolysis.—The hydrolysis of 1-dibenzoylaminonaphthalene (**3**) to 1-benzoylaminonaphthalene and the similar reactions of 1-benzoylamino-8-dibenzoylaminonaphthalene (**4**) and 1-benzoylamino-8-dibenzoylamino-2,7-dimethoxynaphthalene (**5**) (Scheme 2) were followed spectrophotometrically. The increase in the absorbance at 330 nm [which accompanied the hydrolysis of (**3**)] and at 360 nm [for (**4**) and (**5**)] were followed with time for solutions containing initially *ca.* 5×10^{-5} mol dm^{-3} of the imides. The reactions were studied in the presence of varying concentrations of tetramethylammonium hydroxide (0.001–0.20 mol dm^{-3}) in 70% (v/v) Me_2SO–H_2O at 15 °C and at an ionic strength of 0.2 mol dm^{-3} maintained constant by addition of tetramethylammonium chloride. Under these conditions the reactions were accurately first order with respect to imide. For (**3**) and (**4**) the reactions were quite slow, $t_{1/2} > 7$ s, but for (**5**), hydrolysis occurred more rapidly and it was necessary to use the stopped-flow technique (Hi-Tech SFA 51) for measurements in the presence of higher concentrations of hydroxide ion. The spectra after complete reaction were found to be identical with the spectra of solutions made up from separately prepared samples of 1-benzoylaminonaphthalene [for (**3**)] and 1,8-bis(benzoylamino)naphthalene and 1,8-bis(benzoylamino)-2,7-dimethoxynaphthalene [for (**4**) and (**5**) respectively]. The dependence of the first-order rate coefficient (k/s^{-1}) on hydroxide ion concentration for (**4**) and (**5**) is shown in the Figure and is discussed below.



Scheme 2.

The hydrolysis of (**3**) was found to be first order with respect to hydroxide ion, although a slight upward curvature in the plot of k against [OH$^-$] was observed. The departure from linearity is due to an electrolyte effect[13] on the second-order rate coefficient as the electrolyte is changed from tetramethylammonium chloride to tetramethylammonium hydroxide over the range [OH$^-$] 0.001–0.2 mol dm^{-3}. The average value $k_{OH^-} = 0.45 \pm 0.04$ mol dm^{-3} s^{-1} was found for the second-order rate coefficient for the hydrolysis of 1-dibenzoylaminonaphthalene. The intercept of the plot of k against [OH$^-$] was zero within experimental error, showing that the spontaneous solvolysis makes a negligible contribution to the rate in solutions of tetramethylammonium hydroxide. To estimate a value for the rate coefficient (k_{H_2O}) for reaction of 1-dibenzoylaminonaphthalene with solvent, the spectra of 1-dibenzoylaminonaphthalene and the hydrolysis product, 1-benzoylaminonaphthalene, were recorded at periodic intervals in 70% (v/v) Me_2SO–H_2O containing tetramethylammonium chloride (0.2 mol dm^{-3}). The spectra showed negligible change over 20 h and an upper limit of $k_{H_2O} < 4 \times 10^{-7}$ s^{-1} was estimated for the rate coefficient for spontaneous hydrolysis of 1-dibenzoylaminonaphthalene.



Scheme 3.

Dissociation of Amides.—The spectrum taken immediately after having mixed solutions of (**4**) and (**5**) in 70% (v/v) Me_2SO–H_2O with tetramethylammonium hydroxide was found to depend on the concentration of hydroxide ion. This results from dissociation of the amide proton (Scheme 3) and detailed studies of the acid dissociation of (**4**) and (**5**) were carried out in 70% (v/v) Me_2SO–H_2O at 15 °C. The ionic strength was maintained at 0.2 mol dm^{-3} by addition of tetramethylammonium chloride. In order that absorbance readings could be taken before significant hydrolysis had occurred, solutions of (**4**) and (**5**) in 70% (v/v) Me_2SO–H_2O were mixed with a solution of tetramethylammonium hydroxide or buffer in 70% (v/v) Me_2SO–H_2O by means of a rapid mixer (Hi-Tech SFA 11) in a quartz cuvette contained in the thermostatted cell

Table. Analysis of kinetic data for hydrolysis of dibenzoylaminonaphthalenes.[a]

	k_{OH^-}/dm^3 mol^{-1} s^{-1}	k_{H_2O}/s^{-1}
(3)	0.45 ± 0.04	$<4 \times 10^{-7}$
(4)	*ca.* 660[b]	0.033 ± 0.002[c]
(5)	24 ± 3[b]	0.52 ± 0.05[c]

[a] 70% (v/v) Me_2SO–H_2O at 15 °C and ionic strength 0.2 mol dm^{-3}. [b] Calculated from equation (3). [c] Calculated from equation (4).

compartment of a diode array spectrophotometer (Hewlett Packard 8451). Each spectrum was recorded within 0.2 s of mixing. The dissociation of (**5**) was observed by recording the spectrum in the presence of different concentrations of tetramethylammonium hydroxide. The equilibrium constant for the acid dissociation of (**5**), K = [amide anion]/[amide][OH^-], was calculated from absorbance readings at 370 nm where the amide anion absorbs strongly. The absorbance corresponding to complete dissociation was obtained in the presence of tetramethylammonium hydroxide (0.2 mol dm^{-3}) and the spectrum of the undissociated amide was obtained in a benzimidazole buffer in which the concentration of hydroxide ion is low.[14] The result $K = 52.4 \pm 7$ dm^3 mol^{-1} was obtained for the dissociation of (**5**).

For (**4**), dissociation was practically complete in the presence of tetramethylammonium hydroxide (0.001 mol dm^{-3}) and in this case the equilibrium was studied in the presence of indazole buffers.[14] Dissociation was observed at 370 nm with buffer ratios of [indazole]/[indazole anion] from 1.0–9.0. A spectrum corresponding to complete dissociation was obtained in the presence of hydroxide ion (0.1 mol dm^{-3}) and the spectrum of the undissociated species was obtained with HCl (0.1 mol dm^{-3}). A value of the equilibrium constant in the presence of buffer K_{buffer} = [amide anion][indazole]/[amide][indazole anion] = 5.57 ± 0.2 was obtained. To calculate a value for the equilibrium constant for the dissociation of (**4**) in the presence of hydroxide ion from the value of K(buffer), it is necessary to use values for the pK of indazole and the ionic product of water (K_w). The values pK 14.52 for indazole and K_w 7.85×10^{-19} mol^2 dm^{-6} have been measured[14] at 20 °C and ionic strength 0.5 mol dm^{-3} in 70% (v/v) Me_2SO–H_2O. Using these values, the result K [amide anion]/[amide][OH^-] = *ca.* 2×10^4 dm^3 mol^{-1} was obtained for proton removal from (**4**) by hydroxide ion.

Discussion

The dependence of the first-order rate coefficient for the hydrolysis of (**5**) on hydroxide ion concentration can be explained by the mechanism outlined in Scheme 4. On the assumption that ionisation of the proton of the 1-benzoylamino group occurs rapidly the rate expression in equation (1) is obtained. The kinetic results are compatible with reaction of the undissociated form of 1-benzoylamino-8-dibenzoylamino-2,7-dimethoxynaphthalene with hydroxide ion and with spontaneous solvolysis of the ionised species. If either one of these routes predominates, equations (3) and (4) are obtained. A kinetic term corresponding to reaction of the ionised amide with hydroxide ion is not observed. From equation (1), a plot of $1/k$

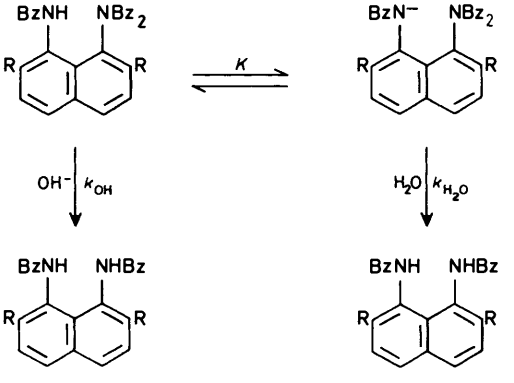
$$k = (Kk_{H_2O} + k_{OH^-})[OH^-]/(1 + K[OH^-]) \quad (1)$$

$$K[OH^-] > 1,\ k = k_{H_2O} + k_{OH^-}/K \quad (2)$$

$$k_{OH^-} > Kk_{H_2O},\ k = k_{OH^-}[OH^-]/(1 + K[OH^-]) \quad (3)$$

$$k_{OH^-} < Kk_{H_2O},\ k = Kk_{H_2O}[OH^-]/(1 + K[OH^-]) \quad (4)$$

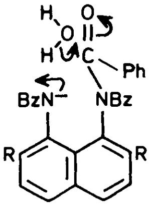
against $1/[OH^-]$ should be linear with gradient $1/(Kk_{H_2O} + k_{OH^-})$ and intercept $K/(Kk_{H_2O} + k_{OH^-})$. The values $K = 46$ dm^3 mol^{-1} and $(Kk_{H_2O} + k_{OH^-}) = 24$ dm^3 mol^{-1} s^{-1} were determined from the linear plot and the line through the data for 1-benzoylamino-8-dibenzoylamino-2,7-dimethoxynaphthalene in the Figure was drawn using these values. The result $K = 46$ dm^3 mol^{-1} is compatible with the independently measured value $K = 52.4 \pm 7$ for dissociation of the proton of the benzoylamino group. The rate coefficient for hydrolysis becomes independent of hydroxide ion concentration at high concentrations when $K[OH^-] > 1$ and equation (1) reduces to (2).



Scheme 4.

For 1-benzoylamino-8-dibenzoylaminonaphthalene (**4**), the observed rate coefficient for hydrolysis (k) is independent of hydroxide ion concentration over the range 0.001–0.2 mol dm^{-3}. The value $K = 2 \times 10^4$ dm^3 mol^{-1} obtained in separate equilibrium measurements means that the amide is almost fully dissociated over this range. The approximation $K[OH^-] > 1$ is satisfied and equation (1) reduces to (2). The line through the data for (**4**) in the Figure is drawn using the value $(k_{H_2O} + k_{OH^-}/K) = 0.033$ s^{-1}.

The kinetic results can be explained by assuming predominant reaction of the undissociated form of (**4**) and (**5**) with hydroxide ion, equation (3), or reaction of the dissociated species with solvent, equation (4), or by a combination of both routes. The values of k_{OH^-} and k_{H_2O} calculated on the assumption that one of the two routes is predominant are shown in the Table in comparison with values for the hydrolysis of 1-dibenzoylaminonaphthalene. The two possibilities are kinetically identical and difficult to distinguish. A similar choice arose in the mechanism of hydrolysis of 8-acetoxy-1-hydroxynaphthalene.[7] Reaction of the ionised form with solvent was preferred to reaction of the unionised species with hydroxide ion although the kinetic evidence, such as the magnitude of kinetic solvent isotope effects, was ambiguous. In the present case it will be argued that reaction of the ionised amides with solvent provides a better explanation of the experimental results. The values of k_{OH^-} for (**4**) and (**5**) obtained by assuming that reaction of the undissociated forms with hydroxide ion predominates are difficult to explain in comparison with the value of k_{OH^-} for (**3**), see Table. The value of k_{OH^-} for (**4**) calculated in this way is over 10^3 times larger than the value measured for (**3**) and this is unlikely to be due to a substituent effect or a steric effect. However the values of k_{H_2O} calculated for (**4**) and (**5**) seem reasonable. The results are much higher than for (**3**) for which the value of k_{H_2O} is too low to be detectable. As in the case of the anion of 8-acetoxy-1-hydroxynaphthalene, attack of solvent on the ionised forms of (**4**) and (**5**) can be assisted by intramolecular base catalysis (Scheme 5). The value of k_{H_2O} for (**5**) is higher than that for (**4**) because the ionised



Scheme 5.

benzoylamino group in (**5**) is a much stronger base, as shown by the values of K for the two groups. The values of k_{H_2O} for (**4**) and (**5**) are higher than the result $k_{H_2O} = 0.0037\ s^{-1}$ obtained[7] for the reaction of the anion of 8-acetoxy-1-hydroxynaphthalene. The carbonyl groups in 1-dibenzoylaminonaphthalene and 1-acetoxynaphthalene are of roughly similar reactivity towards hydroxide ion with second-order rate coefficients $k_{OH^-} = 0.45$ and $1.40\ dm^3\ mol^{-1}\ s^{-1}$ respectively. Hence the higher values of k_{H_2O} for (**4**) and (**5**) compared with 8-acetoxy-1-hydroxynaphthalene probably arise because of the greater basic strength of the intramolecular catalyst in (**4**) and (**5**). The ionised amides are at least four pK units more basic than the naphtholate ion in 8-acetoxy-1-hydroxynaphthalene.

The hydrolysis of 1,8-bis(benzoylamino)naphthalene and 1,8-bis(benzoylamino)-2,7-dimethoxynaphthalene occur negligibly slowly in comparison with the hydrolysis of the corresponding 1-benzoylamino-8-dibenzoylaminonaphthalenes. In the ester hydrolysis of 1-acetoxy-8-acetylaminonaphthalene (Scheme 1), an intramolecular acetyl transfer occurs to give 8-diacetylamino-1-hydroxynaphthalene which then undergoes hydrolysis. If a similar acyl transfer occurred for 1,8-bis(benzoylamino)-naphthalene, the intermediate 1-amino-8-dibenzoylaminonaphthalene would also be expected to be hydrolysed rapidly. Thus the stability of 1,8-bis(benzoylamino)naphthalene in alkaline solution must mean that the benzoyl transfer is unfavourable in this case.

Acknowledgements

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