Proton Transfer from Amides to Hydroxide Ion and Buffers in 70% (v/v) Me_2SO-H_2O

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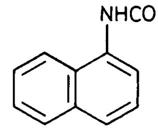
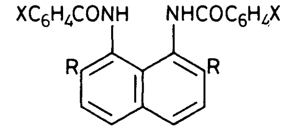
Dissociation of the amide proton from several substituted 1-benzoylaminonaphthalenes has been studied in 70% (v/v) Me_2SO-H_2O in the presence of buffers and hydroxide ion. The acidity varies over 7 p*K* units depending on the substituent. 1,8-Bis(benzoylamino)naphthalene and 1,8-bis(4-nitrobenzoylamino)naphthalene are, respectively, 3 and 5.5 p*K* units more strongly acidic than 1-benzoylaminonaphthalene. The kinetics of the ionisation of 1,8-bis(benzoylamino)naphthalene has been studied in the presence of buffers. Proton removal from the amide by 4-chlorophenolate and 2-bromophenolate ions occurs with rate coefficients of 1.66×10^7 and 0.58×10^7 dm^3 mol^{-1} s^{-1} respectively and in the reverse direction the values of the rate coefficients for protonation of the amide anion by the phenols are 1.27×10^7 and 2.8×10^7 dm^3 mol^{-1} s^{-1}, respectively. The values are lower than those expected for amide ionisation and possible explanations are discussed.

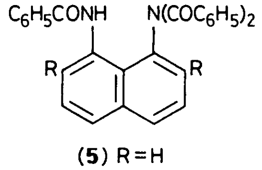
In studies of the hydrolysis of the imide group of 1-benzoylamino-8-dibenzoylaminonaphthalene in 70% (v/v) Me_2SO-H_2O it was found[1] that the kinetics of hydrolysis was influenced by ionisation of the amide proton. The proton of the 1-benzoylamino group was sufficiently acidic to dissociate in the presence of low concentrations of tetramethylammonium hydroxide. There have been few studies of the acidity of amides[2] and we have therefore investigated the ionisation of substituted benzoylaminonaphthalenes more fully. In addition to 1-benzoylamino-8-dibenzoylaminonaphthalene (**5**) and the 2,7-dimethoxy derivative (**6**), we now report studies of the ionisation of the amides (**1**)–(**4**). With 1,8-bis(benzoylamino)naphthalene (**2**) it has also been possible to study the kinetics of ionisation of the amide proton and these results are compared with n.m.r. data[3–5] for the rates of proton exchange of peptides.



(**1**)



(**2**) X=H, R=H
(**3**) X=NO2, R=H
(**4**) X=H, R=OMe



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

Experimental and Results

Materials.—Samples of (**1**), (**2**), and (**4**)–(**6**) were available from a previous study.[1] The preparation of 1,8-bis(4-nitrobenzoylamino)naphthalene (**3**) was achieved by stirring 1,8-diaminonaphthalene (0.16 g) with 4-nitrobenzoyl chloride (0.75 g) and pyridine (0.45 g) in dichloromethane (10 cm^3) at 0 °C for 4 h. The mixture was stirred overnight at ambient temperature and the precipitate was collected and recrystallised from ethanol to give (**3**) (0.11 g, 24% yield) as a brown solid, m.p. 300 °C (decomp.) with δ(360 MHz; [$^2H_6$]Me_2SO) 10.49 (s, 2 H, NH), 7.99 (d, 2 H, $C_{10}H_6$ 2- and 7-H), 7.95 (d, 4 H, C_6H_4 3- and 5-H), 7.90 (d, 4 H, C_6H_4 2- and 6-H), 7.60 (dd, 2 H, $C_{10}H_6$ 3- and 6-H), and 7.53 (d, 2 H, $C_{10}H_6$ 4- and 5-H); (Found: C, 63.2; H, 3.5; N, 12.3. $C_{24}H_{16}N_4O_6$ requires C, 63.2, H, 3.5, N, 12.3%.

Acid Dissociation.—The amides are sparingly soluble in aqueous solution and studies with 1,8-bis(benzoylamino)-2,7-dimethoxynaphthalene (**4**) in 50% (v/v) dioxane–water showed that negligible dissociation of the amide proton occurred in this solvent in the presence of high concentrations of tetramethylammonium hydroxide. The enhanced basicity of Me_2SO-H_2O mixtures is well known[6,7] and preliminary studies with (**4**) in 50%, 70%, and 80% (v/v) Me_2SO-H_2O showed that dissociation of the amide proton occurred at low concentrations of tetramethylammonium hydroxide. At a fixed concentration of tetramethylammonium hydroxide, dissociation increased in the order 50% < 70% < 80% (v/v) Me_2SO-H_2O. Detailed studies were made in 70% (v/v) Me_2SO-H_2O at 15 °C and at an ionic strength of 0.2 mol dm^{-3} maintained by addition of tetramethylammonium chloride. Dissociation of the more weakly acidic amides (**1**), (**4**), and (**6**) was studied in the presence of tetramethylammonium hydroxide but (**2**), (**3**), and (**5**) were fully dissociated at low concentrations of tetramethylammonium hydroxide (0.001 mol dm^{-3}). Since the properties of buffered 70% (v/v) Me_2SO-H_2O are well established,[8–10] the ionisation of (**2**) was studied in 4-chlorophenol and 2-bromophenol buffers and for (**3**) and (**5**), 4-cyanophenol and indazole buffers were used, respectively. Buffer solutions were made up by partial neutralisation of the buffer acid with tetramethylammonium hydroxide.

The equilibria between amide and amide anion, equation (1), with either hydroxide ion or buffer anion as base (B^-)

$$\text{Amide} + B^- \rightleftharpoons \text{Amide anion} + BH \qquad (1)$$

were studied spectrophotometrically. Experiments with (**5**) and (**6**) have been described previously.[1] Dissociation of (**1**)–(**4**) was observed in the presence of varying concentrations of tetra-

Table 1. Acid dissociation of amides.[a]

Amide	K_{OH^-}/dm^3 mol^{-1}	K_{B^-}
(1)	843 ± 55	
(2)	5×10^6 (est)[b]	1.31 ± 0.1 (B^- = 4-chlorophenol)
(2)	7×10^6 (est)[b]	0.21 ± 0.03 (B^- = 2-bromophenol)
(3)	4×10^8 (est)[b]	0.59 ± 0.04 (B^- = 4-cyanophenol)
(4)	357 ± 18	
(5)	2×10^4 (est)[b]	5.6 ± 0.2 (B^- = indazole)
(6)	52.4 ± 7	

[a] 70% (v/v) Me_2SO-H_2O, 15 °C, ionic strength 0.2 mol dm^{-3}. [b] Estimated values, see Discussion.

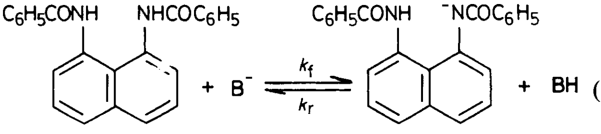
Table 2. Kinetic results for 1,8-bis(benzoylamino)naphthalene.[a]

Buffer	r	gradient/ 10^7 dm^3 mol^{-1} s^{-1}	k_f/ 10^7 dm^3 mol^{-1} s^{-1}	k_r/ 10^7 dm^3 mol^{-1} s^{-1}
4-Chlorophenol	0.67	3.7 ± 0.3	1.73 ± 0.1	1.32 ± 0.1
	0.25	6.4 ± 0.6	1.58 ± 0.2	1.21 ± 0.1
2-Bromophenol	6.0	1.10 ± 0.07	0.62 ± 0.04	3.0 ± 0.2
	2.0	1.82 ± 0.2	0.54 ± 0.05	2.6 ± 0.2

[a] 70% (v/v) Me_2SO-H_2O, 15 °C, ionic strength 0.2 mol dm^{-3}

methylammonium hydroxide or at different buffer ratios by making absorbance measurements at *ca.* 350 nm where the amide anions absorb strongly. The solutions contained low concentrations (*ca.* 3×10^{-5} to 1×10^{-4} mol dm^{-3}) of the amide. Values of the equilibrium constants K_{OH^-} = [amide anion]/[amide][OH^-] for reaction with hydroxide ion and K_{B^-} = [amide anion][BH]/[amide][B^-] for reaction with buffer (B^-) are given in Table 1. Since the equilibrium of **(2)**, **(3)**, and **(4)** with OH^- could not be studied directly, values of K_{OH^-} were estimated from the values of K_{B^-} by use of the acid dissociation constant of the buffer (K_{BH}) and the ionic product of water (K_w). The results are approximate, however, because the values K_{BH} and K_w are known[8] at 20 °C and ionic strength 0.5 mol dm^{-3} in 70% (v/v) Me_2SO-H_2O and K_{B^-} was measured at 15 °C and ionic strength 0.2 mol dm^{-3}. The value of K_w is fairly insensitive to a change in ionic strength.[7] The estimated values of K_{OH^-} for **(2)**, **(3)**, and **(4)** are given in Table 1.

Kinetics.—Kinetic studies of the equilibrium, equation (2), involving 1,8-bis(benzoylamino)naphthalene in 4-chlorophenol and 2-bromophenol buffers were made using the temperature-jump technique. The equilibrium position for a solution of the amide (1×10^{-4} mol dm^{-3}) in 70% (v/v) Me_2SO-H_2O containing buffer, with a total ionic strength of 0.2 mol dm^{-3}, was disturbed by a temperature jump of 2.6 °C. The relaxation to equilibrium at a reaction temperature of 15 °C was observed at 340 nm. Reciprocal relaxation times (τ^{-1}) were measured for each buffer at two buffer ratios over a range of buffer concentrations, typically [B^-] 0.001–0.01 mol dm^{-3}. The dependence of reciprocal relaxation time on buffer concentration was accurately linear and fitted equation (3) in which r is the buffer ratio, r = [B^-]/[BH], and K_{B^-} is the equilibrium constant for the reaction in equation (2). Values of K_{B^-} were used which had been determined in separate equilibrium measurements for each buffer. Values of k_f and k_r were calculated from the gradient at each buffer ratio and the results for 4-chlorophenol and 2-bromophenol buffers are given in Table 2. Attempts to follow the kinetics of the ionisation of the other amides were unsuccessful. Within the shortest timescale of our temperature-jump apparatus no measurable displacement of the equilibrium between the amides and their anions could be observed. This could mean that the reactions of the other amides occur more rapidly than that of 1,8-bis(benzoylamino)naphthalene.



(2)

$$\tau^{-1} = k_f(1 + 1/K_{B^-}r)[B^-] \qquad (3)$$

Discussion

The amides **(1)**–**(6)** are readily dissociated in 70% (v/v) Me_2SO-H_2O in the presence of low concentrations of hydroxide ion. It was not possible to study dissociation in aqueous solution, but approximate pK_a values referring to aqueous solution can be estimated from the acidity function that has been determined for Me_2SO-H_2O mixtures containing tetramethylammonium hydroxide.[6] The acidity function was established for aromatic amines but if it is assumed that the same function applies to the dissociation of amides, values of pK_a *ca.* 16 and 13 are obtained for **(1)** and **(2)** respectively. It is predicted that **(3)** is several pK units more strongly acidic.

The results obtained for the equilibrium constants K_{OH^-} in Table 1 show that the acidities of the amides vary over a range of 7 pK units. The values for **(1)**, **(5)**, and **(6)** are in the ratio 1:24:0.062. This is the order to be expected from the electronic effects of the dibenzoylamino group and the methoxy groups on the stability of the amide anions but the effects are *ca.* four times larger than the effects of the same substituents on the acidity of phenols. Likewise the 4-nitro substituents in **(3)** stabilise the amide anion and lead to a 70-fold increase in acidity of **(3)** compared with **(2)**. The 7 000-fold difference in K_{OH^-} values for **(1)** and **(2)** cannot be attributed to the electron-withdrawing effect of the benzoylamino group. A much more important effect may be stabilisation of the anion of **(2)** by the formation of an intramolecular $N-H \cdots N^-$ hydrogen bond which occurs when one proton is dissociated. Similar effects are responsible for the reduced pK_1 values of dicarboxylic acids.[11] The reduced acidity of **(4)** may mean that the anion derived from **(4)** is unable to form an intramolecular hydrogen bond because the methoxy substituents prevent the anion from adopting the necessary planar conformation.

The kinetics of the equilibration between 1,8-bis(benzoylamino)naphthalene and its anion in 4-chlorophenol and 2-bromophenol buffers was studied by the temperature-jump technique. The average values of the forward and reverse rate coefficients (dm^3 mol^{-1} s^{-1}), equation (2), were k_f $1.66 \pm 0.08 \times 10^7$ and k_r $1.27 \pm 0.06 \times 10^7$ for 4-chlorophenol and k_f $0.58 \pm 0.04 \times 10^7$ and k_r $2.8 \pm 0.2 \times 10^7$ for 2-bromophenol. These results are *ca.* 100-fold below the expected values for normal[12] proton transfer involving a phenol and a nitrogen acid. Previously,[3] n.m.r. data for proton exchange between peptides and hydroxide ion in aqueous solution were explained by assuming that reaction in the thermodynamically favourable direction was diffusion limited with a rate coefficient of *ca.* 1×10^{10} dm^3 mol^{-1} s^{-1}. Proton transfer between *N*-methylacetamide and its anion in Me_2SO occurs[4] with rate coefficients in the forward and reverse directions of *ca.* 2×10^9 dm^3 mol^{-1} s^{-1}. Similarly, rate coefficients for the exchange of protons between a cyclic peptide[5] and hydroxide ion in aqueous solution and in Me_2SO-H_2O mixtures up to 90% (v/v) have values of *ca.* 2×10^9 dm^3 mol^{-1} s^{-1}.

The lower values of k_f and k_r obtained for proton transfer between 1,8-bis(benzoylamino)naphthalene and phenols could arise either because attack of phenol and phenolate ion is sterically hindered or because the amide anion possesses an intramolecular hydrogen bond which must be broken on protonation. The formation of an intramolecular hydrogen bond in the amide anion was suggested as a possible explanation for the 3 pK unit difference in acidity of 1,8-bis(benzoylamino)naphthalene and 1-benzoylaminonaphthalene. In our previous studies of proton transfer with hydrogen-bonded acids,[13] the reactions have involved removal of a hydrogen-bonded proton by base. This has usually been found[13] to occur through a mechanism in which a low concentration of a non-hydrogen-bonded intermediate is in equilibrium with the hydrogen-bonded species and proton removal occurs from the non-hydrogen-bonded species. The value of the rate coefficient for proton transfer is then reduced below the diffusion-limited value by a factor which is equal to the value of the equilibrium constant between the open and closed forms. In the present example, an analogous mechanism consists of a rapid equilibrium between closed and open forms of the amide anion and the open form undergoes protonation by phenol. The depression in rate which results is similar to the difference in acidity between 1-benzoylaminonaphthalene and 1,8-bis(benzoylamino)naphthalene.

Acknowledgements

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