Anchimeric Assistance in the Specific Acid-catalysed Hydration of Benzonitriles

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2-(Acylamido)benzonitriles react to give exclusively the corresponding 2-(acylamido)benzamides under relatively mild aqueous acid conditions. The kinetics for hydration at 50 °C in aqueous HCl with ionic strength kept at 1 mol dm^{-3} with KCl obey the equation

$$\text{rate} = k_H \times [H^+][\text{nitrile}]$$

at low acid concentrations: at higher concentrations of acid the pseudo first order rate constants show a positive deviation from linearity. The rate constants (k_H) for the substituted benzamidobenzonitriles fit a Hammett relationship.

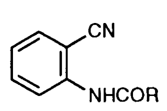
$$\log k_H = -0.36 \pm 0.04\sigma - 3.49 \pm 0.01 \ (r = 0.963)$$

The reactivity due to the *ortho* amido group is more than 25 000 that of the unsubstituted benzonitrile under the same conditions. The mechanism is considered to involve protonation of the nitrile followed by rate limiting intramolecular attack of the amido oxygen to form an intermediate which rapidly breaks down to the acylamidobenzamide.

Although nitriles are employed in many synthetic procedures involving nucleophilic addition their reactivity is much less than that of esters or amides.[1,2,3] The low reactivity of nitriles towards nucleophiles is rationalised by the electron repulsion of the electron cloud making up the triple bond.[4] In most useful syntheses employing nitriles as electrophiles the electron repulsion is alleviated by protonation of the nitrogen atom, by electron sinks such as metal ions or by use of very strong nucleophiles.[5] The Brönsted acid-catalysed hydration of nitriles is nevertheless slow and our fundamental knowledge of the mechanism of solution reactions of the nitrile function is much less than that of its sister amide or ester groups.[6]

Intramolecular catalysis of the hydration of nitriles has been recorded in a number of synthetically useful reactions. Commeyras and co-workers[7] showed that the hydration of α-aminonitriles was accelerated by imine formation with an aldehyde or ketone; acylation of the α-amino function[8] gave an α-amidonitrile which was also susceptible to hydration. Although these studies have provided useful synthetic routes there has been no quantitative estimate of the acceleration of the rates over uncatalysed processes.

It was decided to investigate the kinetics of a relatively straightforward acid-catalysed hydration of the nitriles (**1**) over a range of acid concentrations and substituents in order to assess the acceleration due to a putative neighbouring group affect by the amido function. These nitrile species are useful synthetic precursors of the 2-substituted quinazolin-4-ones (**2**).[9,10]



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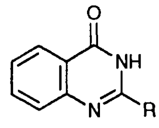

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R = a CH_3; b C_6H_5; c 4-$CH_3OC_6H_4$; d 4-$CH_3OC_6H_4$; e 3-$CH_3OC_6H_4$; f 4-ClC_6H_4; g 3-ClC_6H_4; h 3-$NO_2C_6H_4$; i 4-$NO_2C_6H_4$;

Experimental

Materials.—2-(Acylamido)benzonitriles were prepared from anthranilonitrile by standard procedures. The substituted benzamidobenzonitriles were obtained by refluxing a mixture of anthranilonitrile (0.05 mol), substituted benzoyl chloride (0.05 mol) and K_2CO_3 (0.15 mol) in diethyl ether (100 cm^3) for 2 h. The ether was removed *in vacuo* and the K_2CO_3 dissolved in water (2 x 100 cm^3). The products were recrystallised from methanol–water and obtained in good yield (typically > 95%). 2-Acetamidobenzonitrile was prepared by reaction of acetic anhydride with aq. anthranilonitrile using sodium acetate as base catalyst. The product nitrile, salted from solution with NaCl and recrystallised from toluene, had m.p. 132–133 °C (lit. 132.5 °C).[11]

The purity of the products was checked by TLC on Kieselgel plates using MeOH–benzene eluent, by NMR and by elemental analysis (see Table 1). The identities of the nitriles were checked by comparison of m.p.s with literature values and by NMR spectroscopy. Other materials, such as buffer components, were of analytical reagent grade; water employed in the kinetic studies was double distilled from glass. Plates of aluminium foil coated with silica gel (Merck Kieselgel 60 F254) were obtained from Aldrich.

Methods.—Kinetics were measured in the following way. A stock solution of the benzonitrile in dioxan (50 mm^3; *ca.* 0.1 mmol dm^{-3}) was added on the flattened tip of a glass rod to a solution of HCl (2.5 cm^3) in a silica cell in the thermostatted cell compartment of a Pye-Unicam SP800 spectrophotometer. The progress of the reaction was monitored by repetitive scanning of

Table 1 Physical and analytical data for 2-(substituted benzamido)benzonitriles[a]

		Found (%)[b]				Calculated (%)		
Substituent	M.p./°C	N	C	H	Formula	N	C	H
Parent	157–158[c]	12.5	76.2	4.4	$C_{14}H_{10}N_2O$	12.6	75.7	4.5
4-Methyl	167–168	11.8	76.0	4.9	$C_{15}H_{12}N_2O$	11.9	76.3	5.1
3-Methyl	162–163	11.8	75.8	5.0	$C_{15}H_{12}N_2O$	11.9	76.3	5.1
4-Methoxy	178–179	11.0	71.3	5.0	$C_{15}H_{12}N_2O_2$	11.1	71.4	4.8
4-Chloro	169–170	10.8	65.4	3.3	$C_{14}H_9N_2OCl$	10.9	65.5	3.5
3-Chloro	165–166	10.8	65.6	3.3	$C_{14}H_9N_2OCl$	10.9	65.5	3.5
3-Nitro	188–189	15.4	62.9	3.2	$C_{14}H_9N_3O_3$	15.7	62.9	3.4
4-Nitro	227–228[d]	15.5	63.0	3.1	$C_{14}H_9N_3O_3$	15.7	62.9	3.4

[a] M.p.s determined with a Kofler Thermospan apparatus. [b] Elemental analyses carried out at the Kent Centre for Analysis by Mr. A. J. Fassam with a Carlo Erba Elemental Analyzer. [c] Lit. m.p. = 159–160 °C (F. W. Breukirk, L. H. Krol, P. E. Verkade and B. M. Wepster, *Recl. Trav. Chim. Pays.-Bas.*, 1957, **76**, 40). [d] Lit. m.p. = 229–230 °C (E. C. Taylor, R. J. Knopf and A. L. Borror, *J. Am. Chem. Soc.*, 1960, **82**, 3152).

Table 2 Pseudo first order rate constants for the hydration of 2-(substituted benzamido)benzonitriles[a]

	Substituent							
[HCl]/mol dm^{-3}	3-Cl	3-CH$_3$	4-CH$_3$	4-CH$_3$O	4-Cl	4-NO$_2$	3-NO$_2$	Parent
0.1	0.26	0.35	0.45	0.4	0.34	0.18	0.19	0.4
0.15	0.38		0.60				0.28	
0.2	0.50	0.70	0.75	0.9	0.56	0.37	0.35	0.85
0.25	0.64		1.04				0.48	
0.3	0.74	1.05	1.25	1.3	0.90	0.53	0.58	1.25
0.4	0.99	1.45	1.65	1.8	1.28	0.72	0.77	1.70
0.5	1.31	1.80	2.25	2.24	1.42	0.91	0.97	2.00
0.6	1.55	2.40	2.75	2.85	1.78	1.09	1.24	2.55
0.7		2.85		3.25	2.02	1.24	1.45	2.85
0.8				3.85	2.28	1.45	1.74	3.50
0.9				4.70	2.70	1.68	2.07	4.15
1.0					3.06	1.93	2.28	

[a] Rate constants are quoted as (10^4 s^{-1}) and are for 50 °C, ionic strength made up to 1 mol dm^{-3} with KCl.

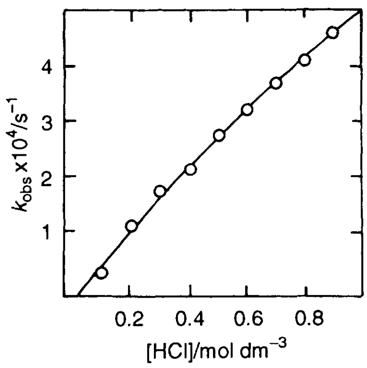


Fig. 1 Hydration of 2-(4-methoxybenzamido)benzonitrile in HCl buffers at 50 °C. Ionic strength is set at 1 mol dm^{-3} with KCl; data are from Table 2 and the line is calculated from parameters in Table 3.

the UV-spectrum and an appropriate wavelength was chosen to study the kinetics of each member of the series. The reactions were studied at single wavelengths between 0.1 and 1 mol dm^{-3} at 50 °C and the ionic strengths were maintained at 1 mol dm^{-3} with added KCl. The optical density (A_t) was recorded as a function of time with a Servoscribe recording potentiometer and pseudo first-order rate constants obtained from plots of ($A_{\text{infinity}} - A_t$) on semi-logarithmic graph paper. The final spectrum for a specimen run for each nitrile was checked against the spectrum of an authentic sample of the 2-acylamidobenzamide. The identities of the products of the reaction of the acylamidobenzonitriles in acid solution were checked by TLC (MeOH–benzene and Kieselgel plates) using known quinazolinones (**2**) and 2-acylamidobenzamides as standards. The former species (**2**) are isomers of the nitriles (**1**) and since they are available by acid and then base treatment of 2-acylamidobenzonitriles[9] it was thought important to check for their presence. The nitrile concentration in the product analysis studies was set at 100 mg per 20 cm^3 of the solvent and the reaction allowed to run at 50 °C for a time period calculated from the kinetic data to ensure completion. The products were extracted with chloroform and then subjected to TLC analysis.

Results

Reaction of the nitriles (**1**) in acid solutions obeyed good pseudo first order kinetics up to greater than 90% of the total progress curves. The pseudo first order rate constants (Table 2) are linearly dependent on acid concentration up to about 0.5 mol dm^{-3} HCl. As the acid concentration is increased further there is an upward curvature of the rate constants from the linear regression. The upward curvature is consistent with the data recorded by Hyland and O'Connor[2] but the increased reactivity enables us to obtain rate constants at lower acid concentrations and temperature. We did not attempt to fit the data to Bunnett or Bunnett–Olsen equations (as reported by Hyland and O'Connor)[2] because these would not yield useful information at the relatively low proton concentrations employed in our study. The slope at zero concentrations of acid was determined from regression of the data to the empirical equation $k_{obs} = k_H[H^+] + b \times [H^+]^2$. The values of b are recorded in Table 3 and their only significance is that they may be used to calculate the rate constants over the given range of acid concentration and give a better value for k_H. Graphical analysis of the data using only the points for low acidity gives slightly higher second order rate constants compared with those from the regression analysis.

Table 3 Kinetic data for the hydration of 2-(substituted benzamido)benzonitriles[a]

Substituent	σ	λ/nm[c]	k_H[b]	b[d]
Parent	0.00	280	3.71 ± 0.22	0.860 ± 0.307
4-Methyl	−0.17	280	3.69 ± 0.16	1.49 ± 0.331
3-Methyl	−0.069	310	3.04 ± 0.17	1.46 ± 0.289
4-Methoxy	−0.26	310	3.85 ± 0.02	1.36 ± 0.278
4-Chloro	0.23	280	2.87 ± 0.14	0.125 ± 0.167
3-Chloro	0.37	280	2.45 ± 0.07	0.239 ± 0.135
3-Nitro	0.72	280	1.69 ± 0.05	0.615 ± 0.059
4-Nitro	0.78	320	1.68 ± 0.05	0.211 ± 0.065

[a] 50 °C; ionic strength maintained at 1 mol dm^{-3} with KCl. [b] Second order rate constant (10^{-4} dm^3 mol^{-1} s^{-1}) deduced from the initial slope of rate constant *versus* concentration. [c] Wavelength for kinetic study. [d] 10^{-4} dm^3 mol^{-2} s^{-1}; the relatively large errors on some of the values of b are due to the small deviation from a linear relationship. The significance of b is only as a fitting parameter to allow a better estimation of the initial slope.

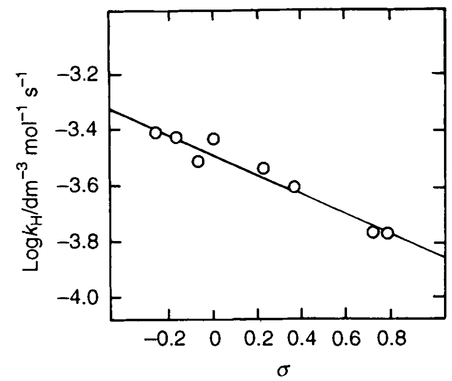


Fig. 2 Hammett dependence for the second order rate constant for hydration of 2-(substituted benzamido)benzonitriles; conditions as for Fig. 1 and the data is from Table 3. Line is drawn from eqn. (1).

The second order rate constants (Table 3) obey a Hammett equation [eqn. (1)].

$$\log k_H = -0.36 \pm 0.04\sigma - 3.49 \pm 0.01 \quad (r = 0.963) \quad (1)$$

Comparison of the UV-spectrum at the end of the reaction with that of the analogous acylamidobenzamide and quinazolinone showed that only the acylamidobenzamide was formed under the acidic conditions. These results were confirmed by TLC studies. Kinetics were not measured for the 2-acetamidobenzonitrile but this substrate was shown by TLC to give only the benzamide under acidic conditions.

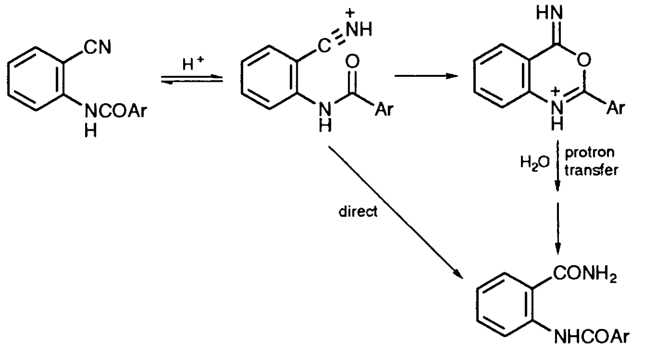
Discussion

The hydration of nitriles catalysed by mineral acids involves equilibrium protonation of the nitrogen followed by rate-limiting attack of water on the carbon centre of the conjugate acid.[2,12] Subsequent proton transfer steps are judged to be kinetically invisible (Scheme 1). The evidence consistent with this mechanism includes an inverse deuterium oxide solvent isotope effect on the acid catalysed hydration and adherence of the kinetics to Bunnett and Bunnett–Olsen relationships.[2]

$$\mathrm{RCN} \overset{H^+}{\rightleftharpoons} \mathrm{RC\overset{+}{N}H} \xrightarrow{H_2O} \mathrm{RC({=}NH)OH_2{}^+} \overset{\text{proton transfer}}{\rightarrow \; \rightarrow \; \rightarrow} \mathrm{RCONH_2}$$

Scheme 1

The acid-catalysed hydration of the 2-acylamidobenzonitriles involves protonation of the nitrile nitrogen as the first step. Protonation on the amido function is thermodynamically more favourable[13] but would not assist nucleophilic attack on the nitrile. Water and the neighbouring amido function will compete for the nitrilium ion species to give respectively amide directly or an isoimide intermediate species (Scheme 2) which subsequently reacts with water to give the amide. The reaction involving direct attack of water on the nitrilium ion should proceed with an overall rate constant (from a neutral ground-state) less than 2.25 × 10^{-8} dm^3 mol^{-1} s^{-1} at 50 °C according to Hyland and O'Connor's data[2] for benzonitrile. This figure is an overestimation because it is extrapolated from the rate constant at 4.42 mol dm^{-3} HCl to low acid concentration and upward curvature is obtained in the plots of rate constant *versus* concentration. Moreover the introduction of an *ortho* substituent should also reduce the rate constant. Since it is not expected that the equilibrium constant for protonation of the nitrile will differ significantly between benzonitrile and the 2-substituted benzonitrile (**1**) the pseudo first order rate constant for attack of bulk water on the nitrilium species is less than 1/25 000 fold as efficient as intramolecular attack by the amido oxygen. The acceleration of nitrile hydration by neighbouring group participation is consistent with the original proposal[2] that water attack on the nitrilium ion is the preferred pathway for acid catalysed hydration of nitriles.



Scheme 2

The proposed mechanism involves rate-limiting attack of the amido-oxygen on the nitrilium ion intermediate. It is inconceivable that the Hammett rho value of −0.36 is due to transmission of substituent effect 'through-bond' to the nitrile because of the large number of intervening atoms between substituent and reaction centre. The observed Hammett selectivity is consistent with the proposed mechanism of Scheme 2; if steps subsequent to the formation of isoimide were rate-limiting then a positive Hammett rho value would result due to water attack at either of the two imido carbon centres. Although the isoimides in question have not been isolated Schmir and Cunningham have studied the hydrolysis of 2-phenyliminotetrahydrofuran (a five membered analogue of the isoimide) over a range of pH;[13] the reactivity of this analogue indicates that it is unlikely that the isoimide would accumulate in our system.

The basicity of nitriles[14] is very much less than that of amides thus the conjugate acid will be a minor component of a tautomeric equilibrium (Scheme 3). An anilide function is expected to hydrolyse much faster than the hydration of the nitrile under similar acid concentrations. Since amide is the observed product of the reaction of the 2-acylamidobenzonitrile the intramolecular process must be sufficiently competitive to divert the reaction flux along the pathway proposed (Scheme 2) away from anilide hydrolysis.

Scheme 3

Because the nitrile group has such a low basicity[2] it is interesting to speculate on the reactivity of the nitrilium ion during the hydration reaction in acid. Assuming a pK_a of -10.45[2] the nitrilium ion should react with water (55.5 mol dm^{-3}) with a rate constant of 11.4 $dm^3\ mol^{-1}\ s^{-1}$ calculated from an overall rate constant of $2.25 \times 10^{-8}\ dm^3\ mol^{-1}\ s^{-1}$ at 50 °C.[2] This rate constant will be a lower limit because the pK_a refers to 25 °C. The diffusion limiting rate constant at 50 °C may be readily calculated to be approximately $1.76 \times 10^{10}\ dm^3\ mol^{-1}\ s^{-1}$ from the Debye equation.[15] The maximum possible acceleration of the rate constant should thus be approximately 1.5×10^9 before diffusion limiting conditions occurred and this is well in excess of the acceleration achieved by the interaction with the neighbouring amido oxygen in the present case.

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