Reactions of carbonyl compounds in basic solutions. Part 28.[1] The alkaline hydrolysis of 2-formylbenzonitrile, *N*-(2-formyl and -acetylphenyl)acetamides, *N*-(2-formylphenyl)-substituted benzamides, 4-(2-formylbenzoyl)morpholine, 3-(4-morpholino)- and -(*N*-methylanilino)-phthalides and -naphthalides

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Rate coefficients have been measured for the alkaline hydrolysis of 2-formylbenzonitrile 1, *N*-(2-formyl and -acetylphenyl)acetamides 2, *N*-(2-formylphenyl)-3-substituted benzamides 3,4-(2-formylbenzoyl)morpholine 4, 3-(4-morpholino)- and -(*N*-methylanilino)-phthalides 5 and -naphthalides 6 in 70% (v/v) dioxane–water at various temperatures. The enthalpies and entropies of activation have been evaluated. The hydrolysis of the nitrile is second order in base and that of the amides is first order in base. The relative rates of hydrolysis, activation parameters and substituent effects have been used to suggest the mechanisms of the reactions. Intramolecular catalysis by the neighbouring carbonyl group occurs in the alkaline hydrolysis of 1–4. The alkaline hydrolysis of 5 and 6 is rapid due to their lactone structures.

Comprehensive studies[2,3] have been made of neighbouring group participation by carbonyl groups in ester hydrolysis. Neighbouring group participation, in general, in the hydrolysis of amides[4] and nitriles[5] has not been investigated in such detail as that of esters. However, the alkaline hydrolysis of amides, as well as nitriles, is significantly less facile than that of esters. The mechanism of the alkaline hydrolysis of amides has been investigated in some detail;[6] whereas that of nitriles has received little attention.[7]

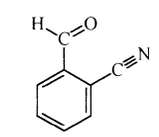
The present study consists of an investigation of the alkaline hydrolysis of 2-formylbenzonitrile **1**, *N*-(2-formyl and -acetylphenyl)acetamides **2** and *N*-(2-formylphenyl)-3-substituted benzamides **3**, as well as 4-(2-formylbenzoyl)morpholine **4** and 3-(4-morpholino)- and -(*N*-methylanilino)-phthalides **5** and -naphthalides **6**. The products of and the effect of substituents on the rates of the reactions have been determined. The latter, as well as the activation parameters, enable a mechanistic pathway to be given.

Results

The product of the alkaline hydrolysis of 2-formylbenzonitrile **1** is 3-hydroxyphthalimidine (2,3-dihydro-3-hydroxy-1*H*-isoindol-1-one) **7**.[8] The reaction is first order in substrate and second order in base. Rate coefficients k_3 for the alkaline hydrolysis of **1** in 70% (v/v) dioxane–water are shown in Table 1, together with those for benzonitrile. For the alkaline hydrolysis of the latter, the primary product is benzamide and the reaction is first order in both substrate and base, *cf.* ref. 7. The activation parameters are shown in Table 2. The alkaline hydrolysis of the *N*-(substituted phenyl)acetamides **2** and *N*-(2-formylphenyl)-3-substituted benzamides **3** results in the formation of the corresponding substituted anilines and carboxylates. The reactions are first order in both substrate and base. However, for the *N*-(2-formylphenyl)-3-chloro- and -nitrobenzamides **3c** and **3d**, ionisation of the relatively acidic amide[9] results in the kinetic form shown in eqn. (1) being observed, in

$$k_1 = k_2[OH^-]/(1 + K_e[OH^-]) \quad (1)$$

which K_e is the equilibrium ionisation constant of the amide,



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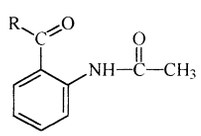
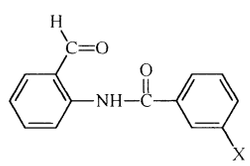
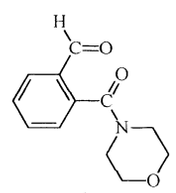


2a R=H
b R=CH_3



3a X=H
b X=CH_3
c X=Cl
d X=NO_2



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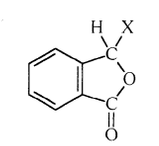
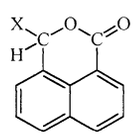
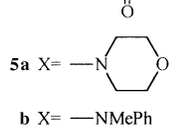
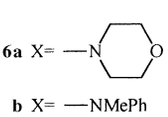






5a X= —N O

b X= —NMePh



6a X= —N O

b X= —NMePh

equal to $[RCON^-R']/[RCONHR'][OH^-]$.[10] Rearrangement of eqn. (1) gives eqn. (2). This allows a plot of $1/k_1$ against $1/[OH^-]$

$$\frac{1}{k_1} = \frac{1}{k_2[OH^-]} + \frac{K_e}{k_2} \quad (2)$$

to give both k_2 and K_e from the slope and intercept. The values of the rate coefficients for the alkaline hydrolysis of the amides k_2, the equilibrium ionisation constant K_e and the activation parameters are shown in Tables 3 and 2, respectively. The alkaline hydrolysis of 4-(2-formylbenzoyl)morpholine **4** and the aminolactones **5** and **6** all result in the formation of the corres-

Table 1 Rate coefficients (k_2 or k_3) for the alkaline hydrolysis of substituted benzonitriles in 70% (v/v) dioxane–water [a]

	$10^{-6}\ k_3$/dm^6 mol^{-2} s^{-1}					
Subst.	at 25.0 °C	at 30.0 °C	at 35.0 °C	at 40.0 °C	at 45.0 °C	λ/nm [b]
2-CHO (**1**)	2.45	3.12	3.84	4.22	5.13	248
	$10^4\ k_2$/dm^3 mol^{-1} s^{-1}					
	at 40.0 °C		at 60.0 °C			
H	0.419		3.75_5			246

[a] The rate coefficients were reproducible to ±3%. [b] Wavelengths used to monitor alkaline hydrolysis.

Table 2 Activation parameters for the alkaline hydrolysis of the amides, benzonitriles and aminolactones in 70% (v/v) dioxane–water at 30.0 °C [a]

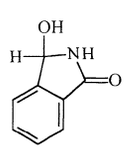
N-Phenylacetamides	$\Delta H^{\ddagger}$/kcal mol^{-1} [b]	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1} [b]
2-Subst.		
CHO (**2a**)	15.9	−22
$C(CH_3)O$ (**2b**)	20.9	−11
N-(2-Formylphenyl)benzamides		
3-Subst.		
H (**3a**)	18.9	−17
CH_3 (**3b**)	20.7	−13
Cl (**3c**)	17.4	−19
NO_2 (**3d**)	16.7	−18
Benzonitrile		
2-Subst.		
CHO (**1**)	6.3	−26
H	19.8	−20
4-(2-Formylbenzoyl)morpholine (**4**)	6.0	−43
3-Morpholinonaphthalide (**6a**)	9.6	−23
3-(*N*-Methylanilino)naphthalide (**6b**)	9.8	−38

[a] Values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are considered accurate to within ±400 cal mol^{-1} and ±1 cal mol^{-1} K^{-1}, respectively. [b] 1 cal = 4.184 J.

Table 3 Rate coefficients (k_2) for the alkaline hydrolysis of *N*-(substituted phenyl) acetamides and *N*-(2-formylphenyl)-3-substituted benzamides in 70% (v/v) dioxane–water [a]

	$10^4\ k_2$/dm^3 mol^{-1} s^{-1}					
N-Phenylacetamides 2-Subst.	at 30.0 °C	at 40.0 °C	at 50.0 °C	at 60.0 °C	at 70.0 °C	λ/nm [b]
CHO (**2a**)	3.18	7.28	16.4	37.8		262
$C(CH_3)O$ (**2b**)		0.530	1.66	4.49	10.9	260
N-(2-Formylphenyl)benzamides 3-Subst.						
H (**3a**)		0.822	2.46	5.47	12.7	247
CH_3 (**3b**)			1.24	3.23	8.48	247
Cl (**3c**)		3.99 (1.44) [c]	9.55 (1.23) [c]	21.2 (1.14) [c]	49.7 (1.00) [c]	247
NO_2 (**3d**)		17.0 (17.7) [c]	40.6 (14.6) [c]	93.4 (13.9) [c]	193 (12.1) [c]	247

[a,b] See Table 1. [c] Equilibrium ionisation constant, K_e (see text).



7

ponding amines and carboxylates. The reactions are first order in both substrate and base. The values of the rate coefficients for the alkaline hydrolysis k_2 and the activation parameters for the amide **4** and aminolactones **5** and **6** are shown in Tables 4 and 2, respectively.

Discussion

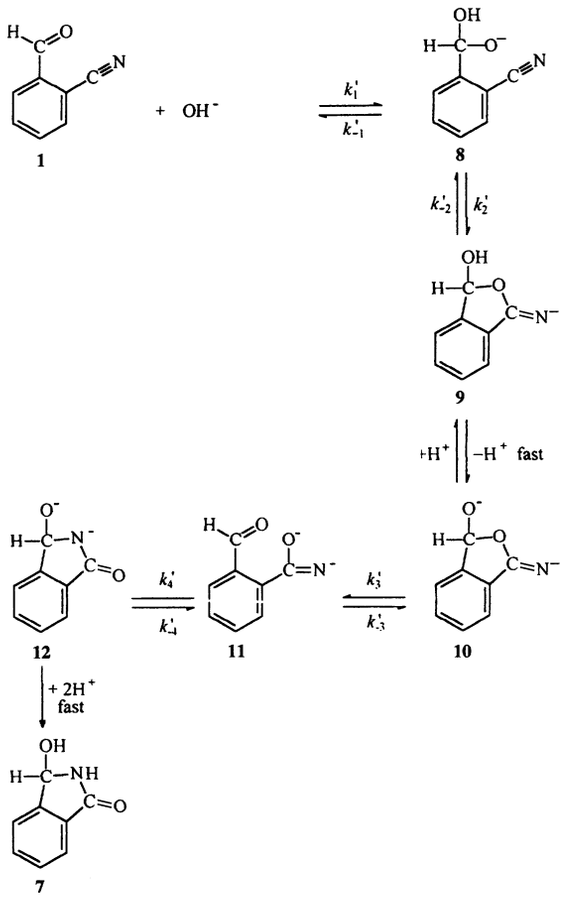
2-Formylbenzonitrile

The rate of alkaline hydrolysis of **1** is very much greater than that of the unsubstituted benzonitrile. It is difficult to compare the rates of the two benzonitriles directly as the kinetic order in base is different. However, for **1** at 40.0 °C and 2×10^{-4} mol dm^{-3} base, $t_{\frac{1}{2}}$ is *ca.* 7 s and for benzonitrile, at 40.0 °C and 8×10^{-2} mol dm^{-3} base, is *ca.* 46 h. The normal polar and steric effect of an *ortho*-formyl group on the latter hydrolysis can be estimated to be rate accelerating; but only by a factor of *ca.* 5.[7,11] The enthalpy of activation for the hydrolysis of **1** is very small compared to that for benzonitrile and is similar to those observed for reactive benzoate esters hydrolysing with intramolecular catalysis from neighbouring carbonyl groups.[2] The stability of the adduct between **1** and hydroxide anion, *i.e.* **8**, can be estimated from literature[12] results for other substituted benzaldehydes. Thus, **8** should be readily formed, but not formed in appreciable amounts at the base concentration used here (see Experimental), *i.e.* at 1×10^{-4} mol dm^{-3} base *ca.* 0.1% of the adduct would be formed using 4-formylbenzonitrile as a

Table 4 Rate coefficients (k_2) for the alkaline hydrolysis of the amide and aminolactones in 70% (v/v) aqueous dioxane[a]

	$10^2\ k_2$/dm^3 mol^{-1} s^{-1}				
	at 30.0 °C	at 40.0 °C	at 50.0 °C	at 60.0 °C	λ/nm[b]
4-(2-Formylbenzoyl)morpholine (**4**)	9.43_5	13.0_5	19.4	24.8	249, 259
	at 25.0 °C	at 30.0 °C	at 35.0 °C	at 40.0 °C	
3-Morpholinonaphthalide (**6a**)	603	803	1090	1360	259
3-(*N*-Methylanilino)naphthalide (**6b**)	115	156	208	268	240
3-Morphlinophthalide (**5a**)	4310				250
3-(*N*-Methylanilino)phthalide (**5b**)	894				300

[a,b] See Table 1.



Scheme 1

model compound.[12] A reaction pathway is shown in Scheme 1 for this exocyclic reaction[11] in which the hydroxide anion adds to the formyl group. This anionic adduct **8** is a very powerful nucleophile which intramolecularly attacks the nitrile group giving the cyclic intermediate **9**. A relatively rapid ionisation gives the dianion **10**, which converts to the open chain tautomer **11**. A second transformation gives the second cyclic tautomer **12**. In weak base, the product **7** results from diprotonation of the dianion. A possible rate determining step is the intramolecular attack process forming **12**, *i.e.* k_4' in Scheme 1. The relative stability of the isolated product **7**, 3-hydroxyphthalimidine, in base apparently arises from the relative stability of the five-membered lactam ring, as well as its acidity. Estimates of the pK_a values of the NH and OH groups in **7** can be made to be 13.0 and 12.7, respectively.[13] At high base concentration, the anionic species formed would be very resistant to alkaline hydrolysis.

N-(2-Formyl and -acetylphenyl)acetamides and *N*-(2-formylphenyl)benzamides

The *N*-(2-formyl and 2-acetylphenyl)acetamides **2a** and **2b** are hydrolysed very much more rapidly than *N*-phenylacetamide (acetanilide) itself. The alkaline hydrolysis of the latter has a kinetic order that is both first and second order in base,[14] so that a direct comparison is not possible. However, for **2a** and **2b**, at 40.0 °C and 2×10^{-2} mol dm^{-3} base, $t_{\frac{1}{2}}$ is *ca.* 19 s and 260 s, respectively; whereas, for acetanilide at 40.0 °C and 0.2 mol dm^{-3} base, $t_{\frac{1}{2}}$ is more than 20 h. The rate ratio for the hydrolysis of the 2-formyl to that of the 2-acetyl substrate is *ca.* 14 at 40.0 °C. This is of the same order as, but somewhat less than, the ratio found for the alkaline hydrolysis of similarly substituted phenyl *trans*-cinnamates.[2] However, the rate of the alkaline hydrolysis of *N*-(2-formylphenyl)acetamide is very much slower than that of 2-formylphenyl acetate.[2] The activation parameters for the acetanilides indicate a bimolecular reaction. However, there is a significantly increased $\Delta H^{\ddagger}$ for the 2-acetyl, compared to that for the 2-formyl substrate; as is found for the alkaline hydrolysis of the comparable methyl benzoates,[2] although the $\Delta H^{\ddagger}$ values for the acetanilides are considerably larger. The *N*-(2-formylphenyl)benzamides **3** are hydrolysed very much more rapidly than comparable *N*-phenylbenzamides, which are very resistant to alkaline hydrolysis.[9] Thus, *N*-(2-nitrophenyl)benzamide is not significantly hydrolysed at 40.0 °C and 0.2 mol dm^{-3} base after 4 h; whereas *N*-(2-formylphenyl)benzamide **3a** has a $t_{\frac{1}{2}}$ of *ca.* 17 s. The rate ratio for the hydrolysis of *N*-(2-formylphenyl)acetamide **2a** to that of the benzamide **3a** is *ca.* 9 at 40.0 °C, which compares favourably with a rate ratio of *ca.* 11 for the alkaline hydrolysis of alkyl acetates to that of alkyl benzoates.[15] The latter arises from the differences in the resonance and steric influences of the methyl and phenyl group when bonded to the carbonyl group suffering attack by hydroxide anion. Furthermore, the Hammett eqn. (3)[16] can be applied to the effects of 3-substitution in the

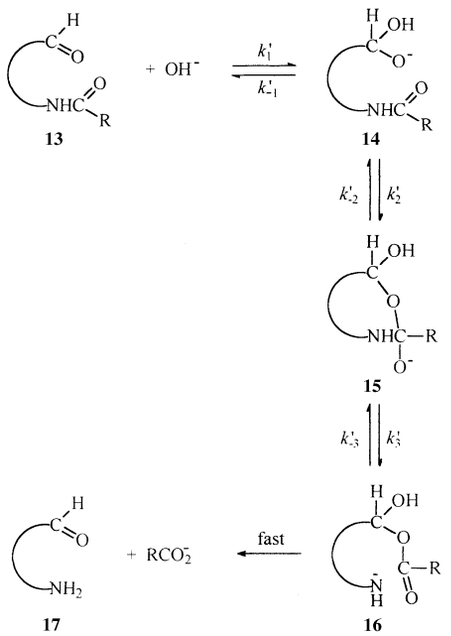
$$\log(k/k_0) = \rho\sigma \qquad (3)$$

benzamides as shown in Table 5. The correlations are very successful and ρ at 50.0 °C is *ca.* 1.84. This can be compared with that of 1.36 for the alkaline hydrolysis of 3-/4-substituted benzamides in 60% aqueous ethanol at 52.8 °C[17] or of 2.38 for the alkaline hydrolysis of methyl 2-benzoyl-4-/5-substituted benzoates in 70% aqueous dioxane at 30.0 °C.[2] A reaction pathway is shown in Scheme 2 for these exocyclic reactions[2] in which the hydroxide anion adds to the formyl group on the substrate **13** to form **14**. This is followed by an intramolecular nucleophilic

Table 5 Hammett reaction constants (ρ) for the alkaline hydrolysis of *N*-(2-formylphenyl)-3-substituted benzamides in 70% (v/v) aqueous dioxane[a]

T/°C	ρ	log k_0	*r*	*s*	*n*
50	1.842	−3.693	0.993	0.152	4
60	1.814	−3.317	0.998	0.082	4
70	1.707	−2.928	0.999	0.044	4

[a] *s* is the standard deviation, *r* the correlation coefficient and *n* the number of substituents studied.

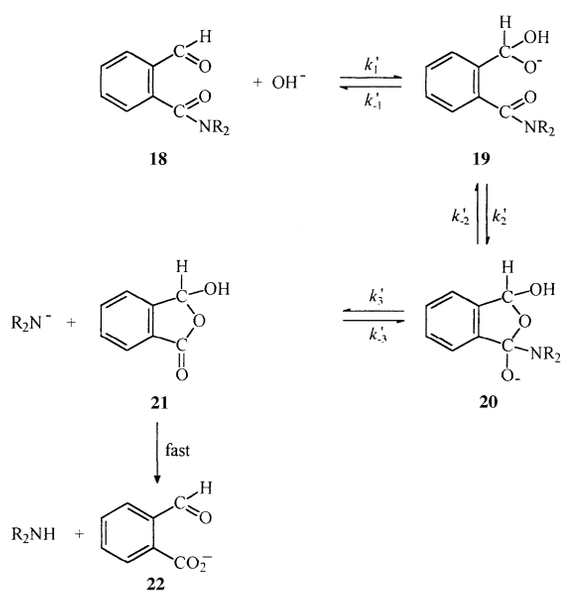


Scheme 2

attack to form **15**, which collapses to the hemi-acetal or -ketal **16**. The latter rapidly decomposes to form the product **17**. The rate-determining step is likely to be the ring fission process, *i.e.* k_3' in Scheme 2.

4-(2-Formylbenzoyl)morpholine and the aminolactones

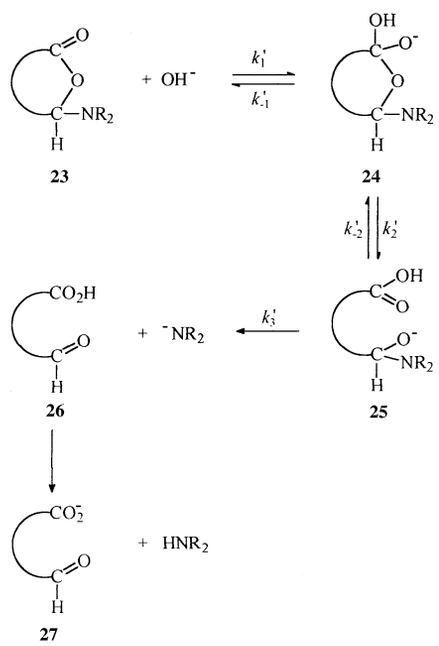
4-(2-Formylbenzoyl)morpholine **4** is hydrolysed very rapidly and *ca.* 10^4 times faster than *N*,*N*-dimethylbenzamide.[18] However, methyl 2-formylbenzoate is hydrolysed *ca.* 4×10^3 faster than **4**.[11] For the hydrolysis of the amide **4**, $\Delta H^{\ddagger}$ is very small and the $\Delta S^{\ddagger}$ is large and negative, as is observed for a number of esters hydrolysing with very favourable intramolecular catalysis from a proximate carbonyl group.[2] A reaction pathway is shown in Scheme 3 for this endocyclic reaction.[2] The amide **18**



Scheme 3

with hydroxide anion forms an adduct **19**, which suffers intramolecular attack to give **20**. Loss of the leaving group gives the cyclic (pseudo) acid **21**, which rapidly gives the final product **22**. The rate-determining step appears to be the formation of **20**, *i.e.* k_2' in Scheme 3.

The aminolactones **5** and **6** are hydrolysed extremely rapidly, as is observed for the closely related cyclic (pseudo) esters.[19–21] Moreover, **5a** is hydrolysed much faster than the corresponding amide **4**. Thus, **5** and **6** are essentially lactones and the five- and six-membered rings have the '*cis*'/*Z* conformation associated with significantly greater reactivity in alkaline hydrolysis than the corresponding esters with the preferred '*trans*'/*E* conformation.[19,21] The order of reactivity for the 3-substituted phthalides is morpholino > *N*-methylanilino > phenoxy > methoxy and for the 3-substituted naphthalides is morpholino > phenoxy > methoxy > *N*-methylanilino.[19,21] The relative reactivities appear to depend on a combination of polar and steric effects. The naphthalides have been shown to be significantly more susceptible to steric 'bulk' effects than phthalides.[21] The 'bulk' effect of the substituents would be methoxy < phenoxy < morpholino < *N*-methylanilino, *cf.* ref. 22. The activation parameters for the hydrolysis of **6** clearly indicate a bimolecular pathway. However, $\Delta H^{\ddagger}$ for the hydrolysis of **6** is less than values for the hydrolysis of 3-methoxy and -phenoxyphthalides. A reaction pathway is shown in Scheme 4 for the



Scheme 4

hydrolysis of the aminolactones in which the hydroxide anion adds to the aminolactone **23** to form the adduct **24**. The latter suffers ring fission to form **25**, followed by loss of the leaving group to give the formyl carboxylic acid **26**. This rapidly forms the final product **27**. The rate-determining attack for the alkaline hydrolysis of the aminolactones would appear to be the same as that for ring esters,[19–21] *i.e.* k_1' in Scheme 4.

In conclusion, it can be seen that suitably positioned proximate carbonyl groups can provide a facile pathway for the alkaline hydrolysis of both nitriles and amides employing an intramolecular catalytic route; whereas, the aminolactones are reactive in their hydrolysis reaction due to their lactonic structure.

Experimental

Materials

2-Formylbenzonitrile, benzonitrile, substituted benzoic acids and 2-aminoacetophenone were obtained commercially and purified as required. 2-Aminobenzaldehyde was prepared by the reduction of 2-nitrobenzaldehyde by $FeSO_4$ in aqueous ammonia solution.[23] The 2-formylbenzanilides and 2-acetylacetanilide were synthesised by the reaction of the corresponding aroyl or acyl chloride with 2-aminobenzaldehyde in the presence of base.[24] Reaction of 2-aminoacetophenone with

Table 6 Physical constants of previously unreported *N*-(2-formylphenyl) substituted benzamides and substituted naphthalides

N-(2-Formylphenyl)benzamides 3-Substituent (formula)	Mp/°C	Elemental analysis Found (%) (Required) C	H	N	Other
CH_3 (**3b**)	71–72[a]	76.1	5.6	6.1	
($C_{15}H_{13}NO_2$)		(75.3)	(5.5)	(5.9)	
Cl (**3c**)	105–106[a]	65.1	3.8	5.3	13.6 (Cl)
($C_{14}H_{10}ClNO_2$)		(64.7)	(3.9)	(5.4)	(13.7) (Cl)
NO_2 (**3d**)	157–158[a]	62.8	3.6	10.5	
($C_{14}H_{10}N_2O_4$)		(62.2)	(3.7)	(10.4)	
Naphthalides 3-Substituent (formula)					
Morpholino (**6a**)	161–162[b]	71.6	5.5	5.1	
($C_{16}H_{15}NO_3$)		(71.4)	(5.6)	(5.2)	
(*N*-Methylanilino) (**6b**)	181–182[b]	79.2	5.1	4.9	
($C_{19}H_{15}NO_2$)		(78.9)	(5.2)	(4.8)	

[a] Recrystallised from aqueous ethanol. [b] Recrystallised from hexane–diethyl ether.

acetic anhydride and sodium acetate gave 2-acetylacetanilide.[25] 3-Hydroxyphthalimidine was prepared by the hydrolysis of 2-formylbenzonitrile.[8] The amide and aminolactones derived from phthalaldehydic or 1,8-naphthaldehydic acid were prepared by the reaction of the appropriate amine with the acid or the corresponding cyclic acid chloride.[26,27] We were unable to prepare the chain (normal) amides of 1,8-naphthaldehydic acid using this method. The mps of the amides or aminolactones, after repeated recrystallization and drying under reduced pressure (P_2O_5) were either in good agreement with the reported[24–28] values or are reported in Table 6. The structures and purity of the amides were monitored by ^{1}H and ^{13}C NMR, IR spectroscopy and mass spectrometry. Solvents were purified as described previously.[11]

Measurements

Rate coefficients for the alkaline hydrolysis of the nitriles, amides and aminolactones were determined spectrophotometrically by use of a Perkin-Elmer lambda 5 or 16 UV–VIS spectrometer. The cell temperature was controlled to within ±0.05 °C by means of a Haake DC3 circulator. The procedure used was that described previously.[29] The reactions were followed at the wavelengths stated in Tables 1 and 3. The substrate concentrations were *ca.* 5×10^{-5} mol dm^{-3} and the base concentrations 1 to 3×10^{-4} (**1**) and 1×10^{-2} to 1×10^{-1} (**2** to **6**) mol dm^{-3}. Good, simple isosbestic points were observed for **1**, **2**, **3a**, **3b** and **4**, as well as for **5** and **6**, between substrate and product. Thus, no appreciable amounts of the adducts **8**, **14** and **19** appear to be formed. The products of the reactions were found to be those stated in the Results section in quantitative yield and were further confirmed spectrophotometrically by comparison of the spectrum of 3-hydroxyphthalimidine or the carboxylic acids and amines in base.

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