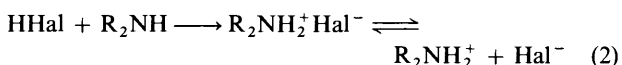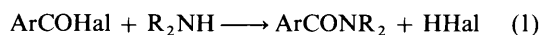# Kinetics of Aminolysis of some Benzoyl Fluorides and Benzoic Anhydrides in Non-hydroxylic Solvents

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The kinetic form of the spontaneous aminolysis of benzoyl fluorides in non-hydroxylic solvents is unlike that reported for the other benzoyl halides, but is similar to that found for the aminolysis of esters. Variations on the mechanisms currently advocated for ester aminolysis are suggested for the benzoyl fluoride reactions. Tetrahedral intermediates are likely, but their rate-determining breakdown to products may involve a simultaneous proton transfer to the leaving fluoride ion. The kinetic behaviour differs from that found for aqueous solutions. The kinetics of the spontaneous aminolysis of benzoic anhydrides by primary amines, and by morpholine, in dioxane solution are first-order in each reagent over a wide amine concentration range, but the aminolysis by imidazoles involves also an important kinetic term second-order in amine. The mechanistic implications are discussed. Again the observations differ from some of those reported for aqueous solutions. For aminolyses of a variety of acylating agents, kinetic observations using non-hydroxylic solvents show that the easier it is for the leaving group to depart, owing to the structure of the acylating agent and/or that of the attacking amine, the less important become paths involving two or more amine molecules, but that such paths are generally more important than they are in hydroxylic solvents.

The aminolysis of aroyl halides by primary or secondary amines in non-hydroxylic solvents can typically be represented by the stoichiometric eqns. (1) and (2). The solubility of the ammonium salt formed will depend upon the particular system involved, and the salt may precipitate if its concentration is not

$$ArCOHal + R_2NH \longrightarrow ArCONR_2 + HHal \quad (1)$$

$$HHal + R_2NH \longrightarrow R_2NH_2^+ Hal^- \rightleftharpoons$$
$$R_2NH_2^+ + Hal^- \quad (2)$$

kept sufficiently low. The kinetics of the aminolysis of aroyl chlorides have been extensively studied, especially by Litvinenko and co-workers.[1-3] The spontaneous and various catalysed reactions have been investigated. The spontaneous aminolyses have always been found to be kinetically first-order in both the acyl chloride and amine [eqn. (3)]. Unlike in ester

$$Rate = k_1 \text{[Amine][ArCOCl]} \quad (3)$$

aminolysis,[4] higher-order terms in amine have never been obtained. The spontaneous reactions possess small-to-moderate positive activation energies, negative $\Delta S^{\ddagger}$ values, negligible hydrogen isotope effects,[5] moderate substituent effects (obeying the Hammett equation) for both reactants, and somewhat variable solvent effects, but with high polarity definitely favouring reaction. The results all point to a bimolecular nucleophilic displacement of some description; sometimes authors include a tetrahedral intermediate, more often they do without. Hinshelwood's early suggestions[2] about the spontaneous reaction are still largely viable. These aminolyses are catalysed by added carboxylic acids, tertiary amines, pyridine N-oxide, and quaternary ammonium salts, and all these types of catalysis have been studied kinetically.[1,2,6]

In contrast to acyl chlorides, the corresponding fluorides, bromides and iodides have been little studied.[2] It is known[7,8] for spontaneous aminolyses that the reactivity sequence is ArCOF ≪ ArCOCl < ArCOBr < ArCOI, and that benzoyl fluoride is much more susceptible to catalysis by acetic acid than is benzoyl chloride,[9] but much less susceptible to (nucleophilic) catalysis by pyridine N-oxide.[10] The spontaneous aminolyses of

these other acyl halides have always been found to be kinetically first order in amine, except that the reaction between benzoyl fluoride and an excess of imidazole in acetonitrile[11] is reported to be of mixed second- and third-order in imidazole, with no first-order term [eqn. (4)]. Equations like (4) have also been found for some ester aminolyses[4,12] and the higher-order terms

$$Rate = (k_2[\text{amine}]^2 + k_3[\text{amine}]^3) \text{ [PhCOF]}$$
$$= k_{obs}[\text{PhCOF}] \quad (4)$$

reflect self-catalysis by the amine. The reactivity of benzoyl fluoride is ca. 2000-fold lower than that of benzoyl chloride,[7] and therefore similar to that of a reactive ester. These facts suggested to us that further study of benzoyl fluoride might reveal other ester-like behaviour patterns. We were thinking in particular of a rate equation analogous to (5), a kinetic form frequently observed in studies of ester aminolysis in non-

$$Rate = (k_1[\text{Amine}] + k_2[\text{Amine}]^2) \text{ [Ester]} \quad (5)$$

hydroxylic solvents.[4] We now report, for a variety of such solvents, the kinetics of aminolysis of benzoyl fluoride and of p-nitrobenzoyl fluoride by several aliphatic amines, including three imidazoles.

Our results with benzoyl fluorides suggested that the aminolysis of carboxylic anhydrides (another class of acylating agent intermediate in reactivity,[13] between acyl chlorides and esters) might also exhibit a kinetic form more ester-like than hitherto observed. Surprisingly little is known from a kinetic viewpoint[14,15] about the aminolysis of anhydrides [e.g. eqn.(6)]

$$(ArCO)_2O + RNH_2 \longrightarrow ArCONHR + ArCO_2H \quad (6)$$

under any circumstances but, like acyl chlorides, bromides and iodides, the spontaneous reactions appear always[16-19] to have been found to possess a rate equation analogous to (3). Depending upon the system, the liberated acid can interact with the unreacted amine, and also lead to auto-catalysis. In non-hydroxylic solvents, as well as powerful catalysis by carboxylic acids,[20] anhydride aminolysis is reported[21] to enjoy weak

general base catalysis by a range of tertiary amines. If this is the case, higher-order terms in amine would be expected for the spontaneous reaction. We now report a study of the aminolysis of three benzoic anhydrides by primary amines, and by imidazole, in dioxane solution.
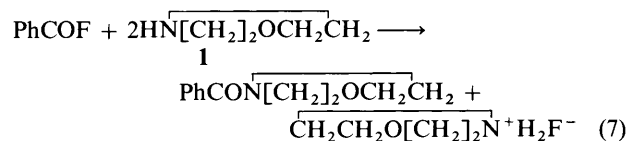
Experimental

Materials.—The benzoyl fluorides and benzoic anhydrides were either commercial samples or were prepared by standard methods.[22] All had m.p. or b.p. in agreement with literature values, and hydrolysed to give an effectively quantitative yield of the corresponding carboxylic acid. The amines were all commercial samples, and were purified by either distillation or recrystallisation. Solvents were of the purest available commercial grade. AnalaR and spectroscopic grades were used without purification, other grades were purified by standard methods. Ethers were dried by distillation from sodium, and (as were most solvents) stored over a molecular sieve before use. Anhydrous morpholine hydrofluoride was prepared by passing hydrogen fluoride into a solution of morpholine in diethyl ether. 2-Methoxyethanol (Aldrich) was used without further purification. Samples of product amides were prepared in separate experiments that simulated, so far as possible, the conditions of the kinetic experiments. All the products had appropriate NMR spectra.

Kinetics.—The acylations were conducted under pseudo-first-order conditions with the amine in a 10- or more-fold excess of the acylating agent; the loss of the latter was followed by UV spectroscopy. Good first-order behaviour over three or more half-lives was found with all the solvents, and the observed first-order rate constant, k_{obs}, was usually reproducible to within ± 5%, and averages of two or more runs were normally taken. No concomitant precipitation of amine salt was observed if the initial concentration of acylating agent was sufficiently low ($\gtrsim 3 \times 10^{-3}$ mol dm⁻³). Stock solutions of the acylating agents in the various solvents were stable over long periods. Reaction with any residual water was negligibly slow compared with the rates of aminolysis. The main restriction on experiments was the limited solubility of the amines in certain solvents. In some experiments the effects of temperature, or of additions of water, 2-methoxyethanol, triethylamine, or amine salt were studied. The initial UV spectra of the acylating agents were negligibly affected by the presence of the amine, so that there was no obvious evidence for rapid complex formation at the carbonyl group.[4,23] The spectra of artificial product mixtures showed, as expected,[1,2,7,9,11] that the kinetic runs produced effectively quantitative yields of the amide product. Typical results for the different systems are collected in Tables 1–3 and Figs. 1–7.

Results

Benzoyl Fluorides.—Spontaneous reaction. Our first experiments extended the work of Bender and Jones[7] who studied the acylation of morpholine (1) by benzoyl fluoride at 25 °C with cyclohexane as solvent [eqn. (7)]. Using pseudo-first-order

$$\text{PhCOF} + 2\overline{\text{HN[CH}_2]_2\text{OCH}_2\text{CH}_2} \longrightarrow$$
$$\mathbf{1}$$
$$\overline{\text{PhCON[CH}_2]_2\text{OCH}_2\text{CH}_2} +$$
$$\overline{\text{CH}_2\text{CH}_2\text{O[CH}_2]_2\text{N}}^+\text{H}_2\text{F}^- \quad (7)$$

conditions similar to ours, Bender and Jones found the aminolysis to be first order in each reactant, but they used only a four-fold morpholine concentration range, and their highest

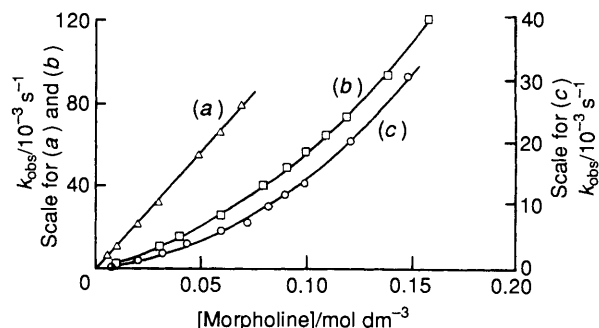$$-\text{d[ArCOF]}/\text{d}t = k_1[\mathbf{1}] \, [\text{ArCOF}] = k_{obs}[\text{ArCOF}] \quad (8)$$

Fig. 1 Reaction of benzoyl fluoride with morpholine at 25 °C. Dependence of k_{obs} on [Morpholine]: [PhCOF]$_{initial}$ = 5 × 10⁻⁴–2 × 10⁻³ mol dm⁻³; (a) cyclohexane; (b) acetonitrile; (c) diethyl ether.

concentration was *ca.* 6 × 10⁻³ mol dm⁻³. We extended the concentration range up to *ca.* 7 × 10⁻² mol dm⁻³, but observed no evidence for second-order terms in morpholine at either of the temperatures studied. The rate equation under the conditions used is therefore (8), the analogue of (3), and our value (Table 1) for the second-order rate constant, k_1, at 25 °C is in excellent agreement with Bender's. We also found simple first-order behaviour at 25 °C using either isooctane or carbon tetrachloride. However, for five other solvents (diethyl ether, dioxane, tetrahydrofuran, chloroform and acetonitrile) with which it was possible to raise the morpholine concentration to $\gtrsim 0.15$ mol dm⁻³, we detected clear departures from eqn. (8) [*e.g.* Figs. 1 and 2]. All the results with these solvents can satisfactorily be fitted by eqn. (9),[*,24] the analogue of (5). Eqn. (9) can be tested by plotting either $k_{obs}/[\mathbf{1}]$ against [1] or

$$-\text{d[ArCOF]}/\text{d}t = \{k_1[\mathbf{1}] + k_2[\mathbf{1}]^2\} \, [\text{ArCOF}]$$
$$= k_{obs} \, [\text{ArCOF}] \quad (9)$$

$k_{obs}/[\mathbf{1}]^2$ against 1/[1]. Typical rectilinear plots are shown in Fig. 3. Agreement between the values of k_1 and k_2 calculated from the alternative plots was normally good, and average values are given in Table 1. Measurements at different temperatures were made for several systems (*e.g.* Fig. 2) and the derived activation parameters are also in Table 1. Since kinetic terms second-order in morpholine are readily detectable in solvents (*e.g.* acetonitrile, chloroform) whose molecules are more polar than morpholine itself, we believe it unlikely that the observed departures from first-order dependence on [1] arise from a general solvent effect on increasing the morpholine concentration. Deliberate additions of polar molecules (*e.g.* acetonitrile) at concentrations > 0.1 mol dm⁻³ have a negligible effect on k_{obs} in dioxane or diethyl ether. The presence of added morpholine hydrofluoride (10⁻³ mol dm⁻³) at the start of an aminolysis produces, if anything, only a small deceleration in rate. The absence of any marked effect on the k_{obs} by the product salt is also attested by the observed excellent first-order loss of benzoyl fluoride. Deliberately added water or 2-methoxyethanol also had only a small effect on k_{obs} (see *e.g.* Fig. 4).

To test the generality of the results obtained with morpholine, we studied also four primary amines [butylamine (2), benzylamine (3), 3-aminopropionitrile (4) and trifluoroethylamine (5)] with benzoyl fluoride; 4 was used with four solvents, 2, 3 and 5 with dioxane only. We also used *p*-nitrobenzoyl fluoride as the acylating agent in some of the systems. In all cases the results were found to be compatible with eqn. (9), and for the *p*-

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* We also detected (results not given) eqn. (9) with 1 in carbon tetrachloride at 15 °C (for which [1]$_{max}$ ≃ 6 × 10⁻² mol dm⁻³). Second-order terms might also be found with cyclohexane and isooctane if higher amine concentrations were possible.

Table 1 Derived rate constants and activation parameters for reactions of morpholine and primary amines with benzoyl fluorides in various solvents

Amine (pK_a)	Acylating agent	Solvent (ε)[a]	T/°C	k_1/dm^3 mol^{-1} s^{-1}	k_2/dm^6 mol^{-2} s^{-1}	$\Delta H_1^{\ddagger}$[b]/kJ mol^{-1}	$\Delta S_1^{\ddagger}$[c]/J K^{-1} mol^{-1}	$\Delta H_2^{\ddagger}$[b]/kJ mol^{-1}	$\Delta S_2^{\ddagger}$[c]/J K^{-1} mol^{-1}	k_{cat}/dm^6 mol^{-2} s^{-1}
$\overline{CH_2CH_2O[CH_2]_2NH}$ (8.3)	PhCOF	Dioxane (2.2)	14.7	0.49	2.8	-11	-290	-12	-277	15
			24.6	0.40	2.5					
			39.7	0.35	2.0					
		Carbon tetrachloride (2.2)	25.1	1.60						
		Cyclohexane (2.3)	14.8	1.23						
			24.8	1.10						
		Isooctane (2.3)	25.0	0.65		-9	-276			
		Diethyl ether (4.3)	25.0	0.065	0.63					1.8
		Chloroform (4.8)	15.3	0.35	2.1	6	-233	6	-219	
			25.1	0.40	2.3					
			39.8	0.45	2.7					
		Tetrahydrofuran (7.6)	25.0	0.090	2.2					0.80
		Acetonitrile (27)	20.0	0.25	3.3	11	-221	-25	-320	
			25.0	0.27	2.8					
			29.0	0.30	2.5					
			40.6	0.36	2.0					
	NO$_2$C$_6$H$_4$COF	Dioxane	25.0	0.46	84	0	-254	-14	-256	
			35.0	0.47	69					
			45.0	0.46	63					
		Acetonitrile	25.0	2.7	509					
NCCH$_2$CH$_2$NH$_2$ (8.0)	PhCOF	Dioxane	25.0	0.032	0.16	-6	-254	-22	-334	0.10
			35.0	0.031	0.12					
			45.0	0.030	0.10					
		Carbon tetrachloride	25.0	8.0 × 10^{-3}	0.10					
		Chloroform		3.0 × 10^{-3}	0.010					
		Acetonitrile		7.0 × 10^{-3}	0.080					
	NO$_2$C$_6$H$_4$COF	Dioxane		7.0 × 10^{-3}	1.8					
BuNH$_2$ (10.7)	PhCOF			1.10	72					
PhCH$_2$NH$_2$ (9.4)				0.23	1.6					
F$_3$CCH$_2$NH$_2$ (5.8)				9.0 × 10^{-5}	4.0 × 10^{-4}					

[a] Relative permittivity. [b] (±2 to ±6) kJ. [c] (±30 to ±40) J.

nitro derivative departures from simple first-order behaviour were found at relatively low amine concentrations. Typical results, and the derived parameters, are given in Figs. 3–5 and in Table 1.

Because of the unexpected rate eqn. (4) obtained by Rogne[11] for the reaction of benzoyl fluoride with imidazole (6) in acetonitrile, we repeated some of his experiments and obtained excellent agreement. We find that eqn. (4) is also obeyed by 2-methylimidazole (7), and by 4-methylimidazole (8), both in acetonitrile and in other solvents, and the same is true when p-nitrobenzoyl fluoride replaces benzoyl fluoride. In testing eqn. (4) we found that plots of $k_{obs}/[\text{imidazole}]^2$ against [imidazole] were rectilinear (e.g. Fig. 6); plots appropriate to eqn. (9) lead to curves for the imidazoles, and we were unable to fit our results to eqn. (10) which produced only negligible, or negative,

$$k_{obs} = k_1[\text{amine}] + k_2[\text{amine}]^2 + k_3[\text{amine}]^3 \quad (10)$$

values for k_1. Values for k_2 and k_3 were obtained from the intercepts and slopes, respectively, of plots such as those in Fig. 6. Our results are collected in Table 2.

Catalysis by triethylamine. For the aminolysis of benzoyl fluoride by morpholine, and by 3-aminopropionitrile, we examined briefly the effect on k_{obs} of added triethylamine. The
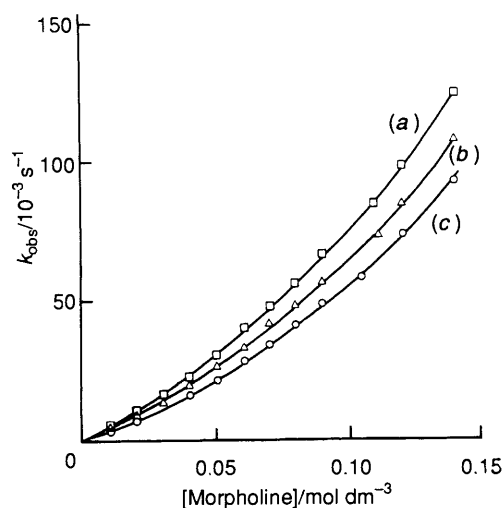
triethylamine concentration was varied from *ca.* 5×10^{-3} to *ca.* 0.1 mol dm^{-3}, at a fixed morpholine or 3-aminopropionitrile concentration, and led to a rectilinear increase in k_{obs}. Additional experiments showed that the overall rate equation for k_{obs} was now (11). Values of k_{cat} obtained from the slopes of the rectilinear plots (not shown) of k_{obs} against [Et$_3$N] are in Table 1.

$$k_{obs} = k_1[\text{amine}] + k_2[\text{amine}]^2 + k_{cat}[\text{amine}][\text{Et}_3\text{N}] \quad (11)$$

Benzoic Anhydrides.—Our results here show that morpholine, and primary amines covering a wide pK_a range, react with benzoic anhydride in dioxane according to the simple rate eqn. (12), the analogue of (3). Table 3 contains our k_1 values

Fig. 2 Reaction of benzoyl fluoride with morpholine in dioxane. Effects of morpholine concentration and temperature: [PhCOF]$_{initial}$ $\simeq$ 1×10^{-3} mol dm^{-3}; (a) 14.7; (b) 24.6; (c) 39.7 °C.
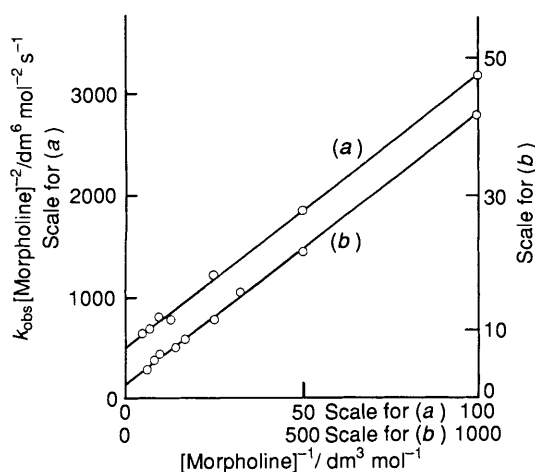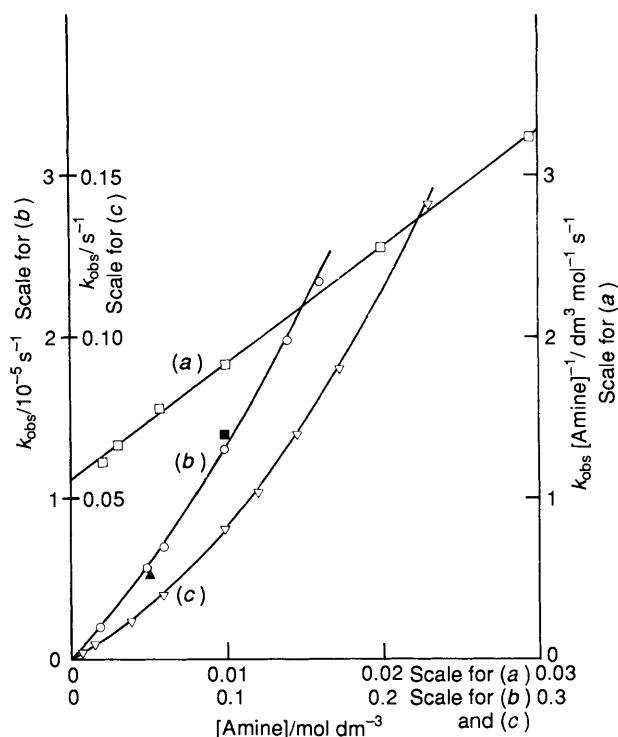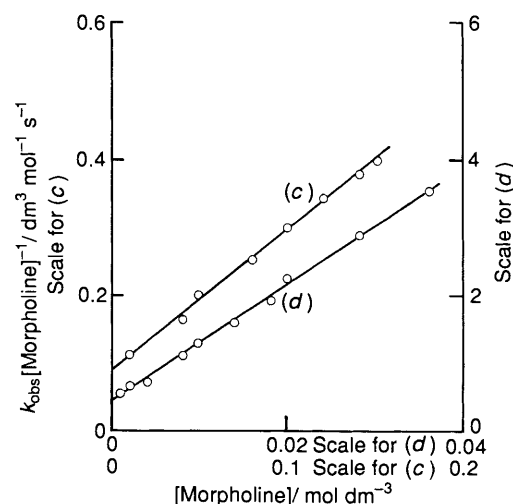

Fig. 4 Reactions of benzoyl fluoride with primary amines at 25 °C: [PhCOF]$_{initial}$ = 1×10^{-4}–1×10^{-3} mol dm^{-3}; (a) butylamine; (b) trifluoroethylamine (▲ [H$_2$O] = 0.02, ■ [2-methoxyethanol] = 0.15 mol dm^{-3}); (c) benzylamine; solvent: dioxane

Fig. 3 Plots of eqn. (9) for reactions of morpholine at 25 °C: [PhCOF]$_{initial}$ $\simeq$ 1×10^{-3} mol dm^{-3}; [NO$_2$C$_6$H$_4$COF]$_{initial}$ $\simeq$ 1×10^{-4} mol dm^{-3}; (a) and (d): p-nitrobenzoyl fluoride in acetonitrile and dioxane, respectively; (b) and (c): benzoyl fluoride in chloroform and tetrahydrofuran, respectively

$-\mathrm{d}[(\mathrm{PhCO})_2\mathrm{O}]/\mathrm{d}t = k_1[\text{amine}][(\mathrm{PhCO})_2\mathrm{O}] =$

$$k_{\text{obs}}[(\mathrm{PhCO})_2\mathrm{O}] \quad (12)$$

obtained from rectilinear plots of k_{obs} against [amine] (from 0.01 up to *ca.* 0.20 mol dm^{-3}). In contrast, imidazoles react with benzoic and substituted-benzoic anhydrides according to eqn. (13), the analogue of (5) and (9) [*e.g.* Fig. 7]. Values of k_1 and k_2

$-\mathrm{d}[\text{anhydride}]/\mathrm{d}t = (k_1[\text{amine}] + k_2[\text{amine}]^2)[\text{anhydride}]$

$$= k_{\text{obs}} [\text{anhydride}] \quad (13)$$

were obtained as for the benzoyl fluoride systems, and are in Table 3; k_1 was found to be relatively small compared with k_2, but terms third-order in amine were not detected. All kinetic experiments with the anhydrides were at 25 °C.

Discussion

Benzoyl Fluorides.—Our results show that, in a variety of non-hydroxylic solvents, the aminolyses both of benzoyl fluoride,
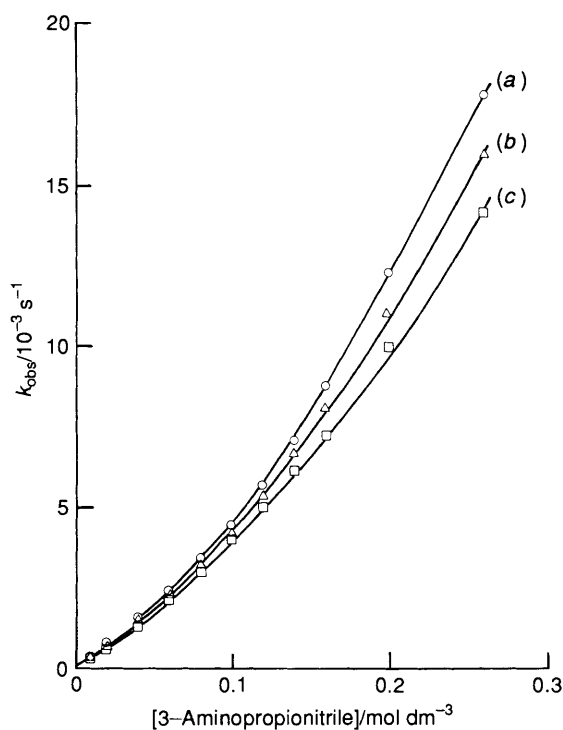
and of *p*-nitrobenzoyl fluoride, by morpholine and by primary amines, obey rate equations of the form of (9), whereas aminolyses by the imidazoles **6–8** obey eqns. like (4). Examination of Tables 1 and 2 and Figs. 1–6 reveals also (i) that the values of k_1 and k_2 from eqn. (9) show no obvious relationship to solvent properties and are, in the main,
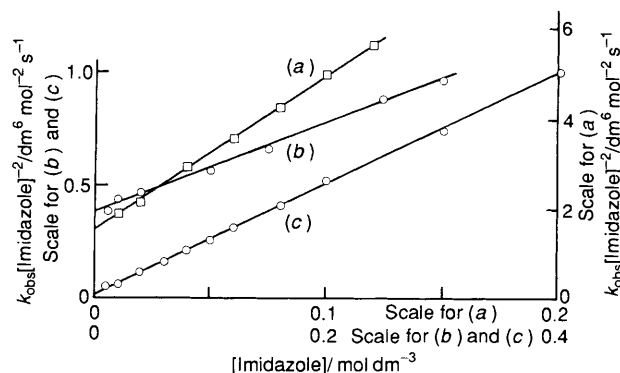

Fig. 6 Plots of eqn. (4) for reaction of benzoyl fluoride with imidazoles in different solvents [PhCOF]$_{\text{initial}}$ $\simeq$ 5 × 10^{-4} mol dm^{-3}; (*a*) imidazole in chloroform at 45 °C; (*b*) 2-methylimidazole in acetonitrile at 25 °C; (*c*) 4-methylimidazole in dioxane at 25 °C
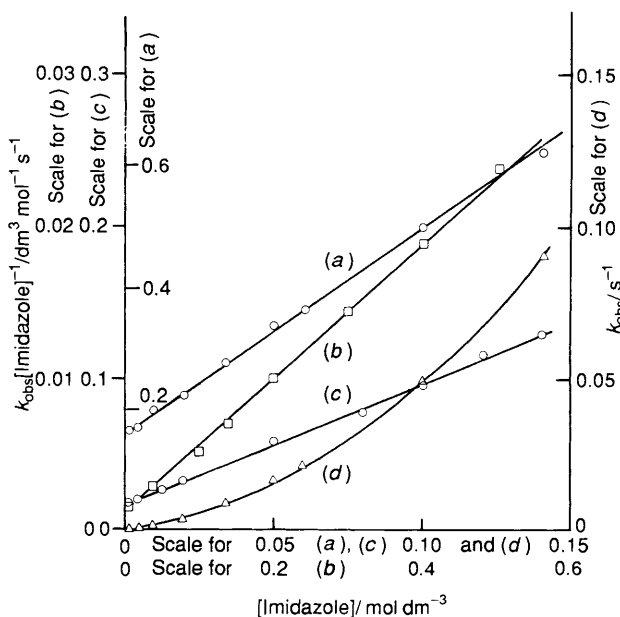

Fig. 5 Reaction of benzoyl fluoride with 3-aminopropionitrile in dioxane. Effects of amine concentration and temperature [PhCOF]$_{\text{initial}}$ $\simeq$ 5 × 10^{-4} mol dm^{-3}; (*a*) 25.0; (*b*) 35.0; (*c*) 45.0 °C.

Fig. 7 Reaction of benzoic anhydrides with imidazole in dioxane at 25 °C: [(*p*-RC$_6$H$_5$CO)$_2$O]$_{\text{initial}}$ $\simeq$ 3 × 10^{-5} mol dm^{-3}; (*a*) and (*d*) R = Cl; (*b*) R = MeO; (*c*) R = H

Table 2 Derived rate constants and activation parameters for reactions of imidazoles with benzoyl fluorides in various solvents

Imidazole (pK_a)	Acylating agent	Solvent	T/°C	$k_2{}^a$	k_3/dm^9 mol^{-3} s^{-1}	$\Delta H_2{}^{\ddagger a}$	$\Delta S_2{}^{\ddagger a}$	$\Delta H_3{}^{\ddagger a}$	$\Delta S_3{}^{\ddagger a}$
Imidazole (7.0)	PhCOF	Dioxane	25.0	0.040	0.85				
		Chloroform	25.0	2.0	19				
			35.0	1.8	23	−13	−281	16	−167
			45.0	1.5	29				
		Acetonitrile	25.0	0.21^b	2.23^b	18^b	−202^b	7^b	−214^b
	NO$_2$C$_6$H$_4$COF			6.0	155				
2-Methylimidazole (7.8)	PhCOF	Chloroform		1.8	6.2				
		Acetonitrile		0.38	2.0				
4-Methylimidazole (7.5)		Dioxane		0.01	2.5				

^{a} As Table 1. ^{b} Ref. 11.

Table 3 Derived rate constants for aminolysis of benzoic anhydrides in dioxane at 25 °C

Amine[a]	R in $(RC_6H_5CO)_2O$	$k_1{}^b$	$k_2{}^b$
$BuNH_2$	H	120	
$PhCH_2NH_2$		26	
$\overline{CH_2CH_2O[CH_2]_2NH}$		40	
$NCCH_2CH_2NH_2$		1.4	
$F_3CCH_2NH_2$		0.026	
Imidazole		0.016	0.81
	Cl	0.16	3.4
	MeO	1.2×10^{-3}	0.44
2-Methylimidazole	H	9.3×10^{-3}	0.21

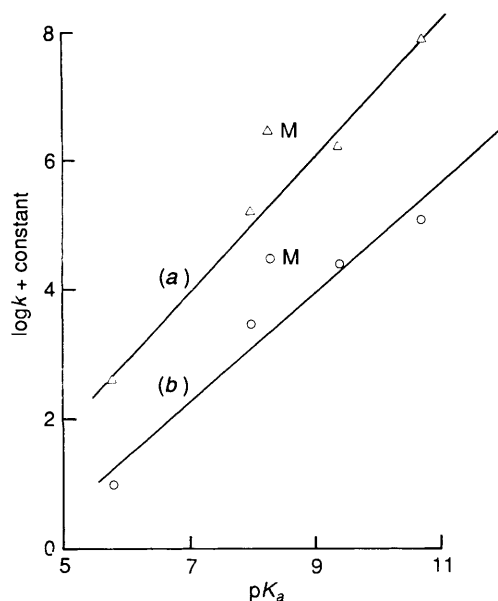[a] For pK_a see Tables 1 and 2. [b] Units as Table 1.

Fig. 8 Plots of $\log k_1$ and $\log k_2$ against pK_a for reactions of benzoyl fluoride with primary amines in dioxane at 25 °C (a) $\log k_2 + 6$; (b) $\log k_1 + 5$; M = morpholine
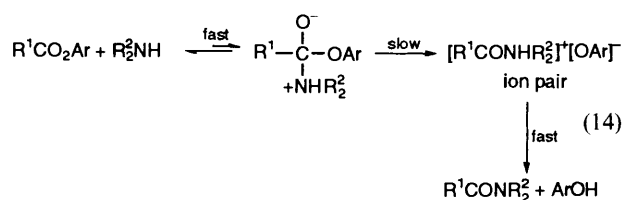
surprisingly independent of the solvent used, (ii) that the values of k_2 and k_3 for the imidazoles [eqn. (4)] are somewhat more solvent-dependent, (iii) that p-nitrobenzoyl fluoride is generally more reactive than is benzoyl fluoride in all the systems studied, and that the rate constants for the higher-order terms in amine are increased significantly more than are those of the first-order terms when the p-nitro derivative is used, (iv) that several systems yield negative $\Delta H^{\ddagger}$ values, and not only for the paths second-order in amine $(\Delta H_2{}^{\ddagger})$ but also for paths first-order in amine $(\Delta H_1{}^{\ddagger})$, (v) that plots of $\log k_1$ and $\log k_2$ against pK_a (in water) for reaction of the primary amines with benzoyl fluoride in dioxane are reasonable straight lines with slopes of ca. 0.85 and 1.0 respectively, with the points for morpholine lying well above the lines (Fig. 8), and (vi) that the catalytic effect of triethylamine on the aminolyses by morpholine and 3-amino-propionitrile is mostly comparable in magnitude to that of the self-catalysis (k_2).

The forms of eqns. (9) and (4) show that spontaneous acylation of amines by benzoyl fluorides is, as we suspected, kinetically much more like that found characteristic of acylation by esters than that characteristic of acylation by acyl chlorides, bromides or iodides. Probably most previous studies with benzoyl fluoride did not detect higher-order terms in amine because of the low amine concentrations they employed, or because of the kinetic procedure used. Some workers still em-
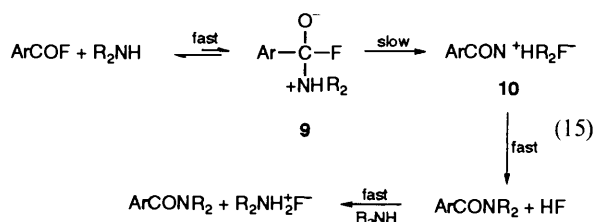
ploy second-order conditions (i.e. comparable concentrations of the two reactants) in kinetic studies, and plot their results using the standard second-order rate equation. In practice it is difficult to detect contributions from higher-order terms using this procedure.[25] Most previous work on the aminolysis of acyl halides suffers from this disadvantage. An extensive and relatively recent study[4] of ester aminolysis (mostly by butylamine) using three types of ester, various non-hydroxylic solvents, and pseudo-first-order conditions, suggests that although a few systems exhibit all the terms on the right hand side of eqn. (10), most show only the first two or the last two, with a small number of esters displaying just the k_1 or the k_2 term. In ester aminolyses as a whole the first order term is usually small or absent unless some feature of the ester, amine or solvent facilitates the departure of the ester's leaving group. Kinetic terms first-order in an imidazole appear particularly rare, although this fact does not appear to have been commented upon previously.[12,26] The similarity between benzoyl fluoride and ester behaviours extends also to other features of the aminolyses. Thus the ester reactions normally display small values of $\Delta H^{\ddagger}$, and in three examples,[4,26,27] small negative values have been found for self-catalytic terms $(\Delta H_2{}^{\ddagger})$. Our results are obviously similar, and not only provide a number of new, negative $\Delta H_2{}^{\ddagger}$ values but (significantly) also cases of negative $\Delta H_1{}^{\ddagger}$ values (Table 1). Most studies of ester aminolysis using non-hydroxylic solvents have not involved much systematic variation of the amine structure (usually none). Nagy's work[4] provides a limited variation: for p-nitrophenyl 3,5-dinitrobenzoate in acetonitrile a plot of $\log k_1$ (called k_2 in Nagy's paper) against pK_a (water) for the primary amines has a slope of ca. 2.5. Our plots (Fig. 8) show that primary and secondary amines probably follow separate lines (as for acyl chlorides);[28] we find slopes < 1 for the primary amines in dioxane. The fact that the slope for k_2 is only a little stepper than that for k_1 suggests that the second amine molecule participates via a feeble acid–base interaction. This result is compatible with the second molecule being involved in proton removal via hydrogen bonding, as suggested for ester aminolysis from studies of the (assumed) general base catalysis by tertiary amines.[4,27,29] However, the small effect of its pK_a could mean that the catalytic molecule is kinetically important both as a proton remover and (perhaps subsequently) as a proton donor.[23] As in the present systems, in ester aminolysis tertiary amines provide a catalytic term of the form of that in eqn. (11). The rather comparable effects of triethylamine (pK_a 10.8) to those of a second molecule of morpholine or 3-aminopropionitrile (Table 1) is another indication of the small effect of the pK_a of the second (catalytic) amine molecule on the rate of the termolecular path. Other similarities between the acyl fluoride and ester aminolyses[4] are the usually small solvent effects for primary and for secondary amines, especially on the k_1 terms, and the much greater effect of a substituent in the acyl group on the k_2 term than on the k_1 term (Table 1). It seems unnecessary to labour the similarities further, and we shall discuss possible mechanisms for the benzoyl fluorides in the light of existing work on ester aminolysis.

Agreement is still far from universal[15] about mechanisms underlying the three terms in eqn. (10). Most authors now believe, however, that for all paths a small amount of a tetrahedral intermediate is formed in a rapid pre-equilibrium, and this intermediate then slowly loses the ester leaving group $(RO^-$ or $ArO^-)$. Eqn. (14) illustrates one version of this type of path for the term controlled by k_1 in eqns. (5) and (10). S_N2-like nucleophilic displacements have not been disproved[30] for any ester aminolysis in a non-hydroxylic solvent, but they are normally ignored, or just paid lip-service to.[4,26] For the k_2 and k_{cat} terms [eqn. (11)] the negative $\Delta H^{\ddagger}$ values sometimes found[4,26,27] certainly indicate a step-wise mechanism, but

do not point unequivocally to a tetrahedral intermediate since some other exothermic pre-equilibrium such as amine hydrogen-bonded self-association,[31] or charge-transfer interaction between amine and carbonyl group,[4] could precede a synchronous displacement of ArO^-. Nevertheless tetrahedral intermediates seem likely for ester aminolyses in hydroxylic media,[15] so we believe that it is reasonable to assume them also in non-hydroxylic solvents since (and this point is rarely stressed) leaving group departure is facilitated by hydrogen bonding in hydroxylic media.[32] In aqueous solution, for paths first-order in amine, the tetrahedral pre-equilibrium is believed to be set up before significant loss of the leaving group with many amines.[15] This may well be even more the case in non-hydroxylic solvents since leaving group departure is there more difficult, and the amine, being less deactivated by hydrogen bonding from the solvent, may be able to attack more easily. Conclusions for aqueous solutions therefore in our view support equations such as (14). Our finding of negative $\Delta H_1^{\ddagger}$ values

$$R^1CO_2Ar + R_2^2NH \xrightleftharpoons{\text{fast}} \underset{\substack{| \\ +NHR_2^2}}{R^1-\overset{\overset{O^-}{|}}{C}-OAr} \xrightarrow{\text{slow}} [R^1CONHR_2^2]^+[OAr]^- \text{ ion pair}$$

$$\downarrow \text{fast} \quad (14)$$

$$R^1CONR_2^2 + ArOH$$

points to a pre-equilibrium in the benzoyl fluoride aminolyses which cannot be amine hydrogen bonded self-association, so that, if charge-transfer interaction is ignored, a tetrahedral route [e.g. eqn. (15)] is indicated.

$$ArCOF + R_2NH \xrightleftharpoons{\text{fast}} \underset{\substack{| \\ +NHR_2}}{Ar-\overset{\overset{O^-}{|}}{C}-F} \xrightarrow{\text{slow}} ArCON^+HR_2F^-$$

9   **10**

$$\downarrow \text{fast} \quad (15)$$

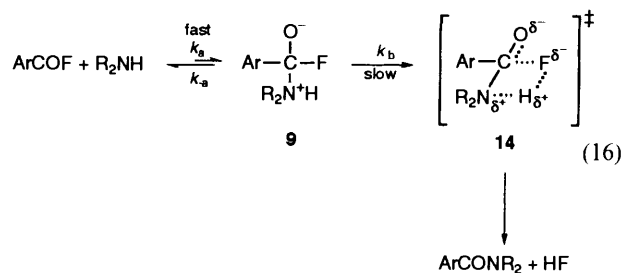$$ArCONR_2 + R_2NH_2^+F^- \xleftarrow[R_2NH]{\text{fast}} ArCONR_2 + HF$$

It is normally considered that for solutions of low relative permittivity mechanisms which minimise charge creation, or separation, will have energetic advantages.[27,33] Cyclic transition states, if feasible, are attractive in this context, and have often been suggested. A circumstance that led one of us to propose[33] such a transition state for the k_1 term of an ester aminolysis in diethyl ether solution was the fact that esters of structure $ArCO_2NR_2$ (**11**) with rather basic leaving groups, do not exhibit higher-order terms in amine, whereas similar esters with superficially much better leaving groups (ArO^-) do exhibit such terms; i.e. catalysis by a second amine molecule is surprisingly unimportant for **11**. Moreover, an increase in solvent polarity actually lowers the rate for **11**. For these esters


12   **13**
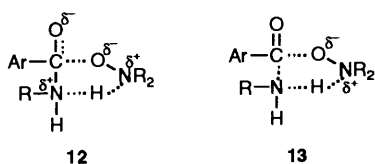
(at least) for which a cycle is convenient, a transition state such as **12**, or even **13**, seems likely. The cyclic proton transfer not only provides charge dispersion: it also helps leaving group departure. This help is likely to be especially important in first-order routes if the solvent cannot assist by hydrogen bonding. In the present aminolyses with benzoyl fluorides the leaving group is a powerful hydrogen bond receptor, and we believe

three facts are compatible with a transition state **14** (analogous to **12**) in the path first-order in amine: (i) the small irregular

$$ArCOF + R_2NH \xrightleftharpoons[k_{-a}]{\overset{\text{fast}}{k_a}} \underset{\substack{| \\ R_2N^+H}}{Ar-\overset{\overset{O^-}{|}}{C}-F} \xrightarrow[\text{slow}]{k_b} \left[\underset{R_2N_{\delta^+}^{\cdots}H_{\delta^+}}{Ar-\overset{\overset{O^{\delta^-}}{\diagup}}{C}^{\cdots}F^{\delta^-}} \right]^{\ddagger}$$

9   **14**   (16)

$$\downarrow$$

$$ArCONR_2 + HF$$

solvent effect on k_1 (k_1 would surely increase in acetonitrile compared to hydrocarbon solvents if the mechanism involved formation of **9** followed by the amide ion pair **10**, whereas **9** moving to neutral products via **14** involves net loss of charge), (ii) the surprisingly negative $\Delta S_1^{\ddagger}$ values (bimolecular substitution in other contexts typically involves $\Delta S^{\ddagger} -120$ to -170 J K^{-1} mol^{-1}), and (iii) the absence of k_1 terms with the imidazoles (these amines, which attack[12,26,34] via their more basic tertiary N-atoms **15**, cannot engage in a cyclic proton transfer for reasons of geometry).

15
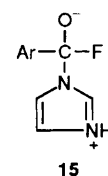
For the mechanism of eqn. (16), $k_1 = (k_a/k_{-a}) \times k_b = Kk_b$. That the p-NO$_2$ group in p-nitrobenzoyl fluoride has relatively little net effect on k_1 (Table 1) implies that, as expected,[2,15] the substituent affects k_b (loss of anion) more than k_{-a} (loss of neutral molecule). Eqn. (16) which involves a Lewis acid–base pre-equilibrium followed by a partial proton transfer, is probably compatible with a slope of 0.85 for the plot of log k_1 against pK_a (Fig. 8) in view of the much larger slope obtained by Nagy. It is interesting that the reactions of primary amines with benzoyl fluorides in water (which only have k_1 terms) lead to lower slopes for such plots.[35] These slopes have been interpreted in terms of an S_N2-like substitution, it being argued that with a leaving group such as F$^-$ any intermediate should be very short-lived. Probably that assumption is sound for aqueous solution since water will greatly facilitate the loss of F$^-$. Acyl chlorides (which have a much better leaving group than fluorides) are often considered by Litvinevko[1] to display S_N2-like mechanisms in their reactions with aryl amines even in non-hydroxylic solvents. The corresponding $\Delta S^{\ddagger}$ values are 80–100 J K^{-1} mol^{-1} more positive than our $\Delta S^{\ddagger}$ values. (And the same is true of Hinshelwood's early values.)[2] Increases in solvent polarity are rather consistently beneficial for acyl chlorides and negative $\Delta H^{\ddagger}$ values have never been observed.[1–3,14] Synchronous or concerted schemes are favoured by a majority of workers for acyl chlorides.[*,1,2] The new features we propose for the mechanism of acyl fluoride aminolysis involving one amine molecule seem therefore compatible with existing knowledge both for esters, and from other work with acyl halides.

The self-catalysis term controlled by k_2 in eqns. (4) and (9) seem very likely to involve some variety of general base catalysis by the second amine molecule. The fact that for both esters and

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* If correct they have important implications for alcoholysis and hydrolysis, the mechanisms of which are still debated.[15]

benzoyl fluoride this catalysis, and also that provided by added tertiary N-bases, is little dependent on the pK_a of the catalyst and, at least for esters,[4,27,29] parallels hydrogen bonding capacity, suggests general base catalysis for both the k_2 and k_{cat} terms *via* an essentially hydrogen bonded interaction, although nucleophilic catalysis by triethylamine is not ruled out in the benzoyl fluoride system. These intimations of hydrogen bonding, together with other current views about the mechanism of ester aminolysis in both hydroxylic and non-hydroxylic solvents,[15,23] suggest for the route reflected by k_2 in the benzoyl fluoride systems, two alternative mechanisms: (17)–(18)

$$2R_2NH \xrightleftharpoons[\overline{K}_{ass}]{fast} R_2NH \cdots NHR_2 \qquad (17)$$

16

(18)
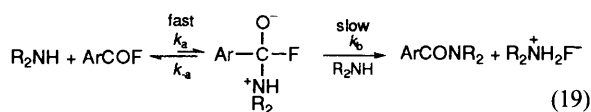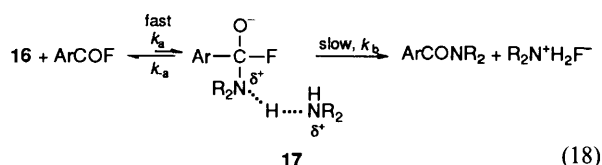
and (19). In route (17)–(18) the extent of proton transfer in **17** is uncertain, but in this mechanism the catalytic molecule assists both nucleophilic attack and leaving group departure. (It helps the latter by decreasing the positive charge on the developing amide N-atom. Perhaps too some electrostatic or hydrogen bond assistance is given to the incipient F^- ion since the product salt is probably stabilised by hydrogen bonding in solution.) In route (19) the proton is not removed until after the nucleophilic attack. This latter type of mechanism is believed[15] to be the most common for ester aminolysis in aqueous solutions, but whether that is true in non-hydroxylic solvents that support significant amounts of amine polymers is to be doubted. The slow steps of the two mechanisms are clearly very similar. Perhaps both routes contribute significantly on occasions. Amine dimers are more numerous for some amines, and for some solvents, than for others.[31] Imidazoles are particularly given to hydrogen-bonded polymerisation.[36]
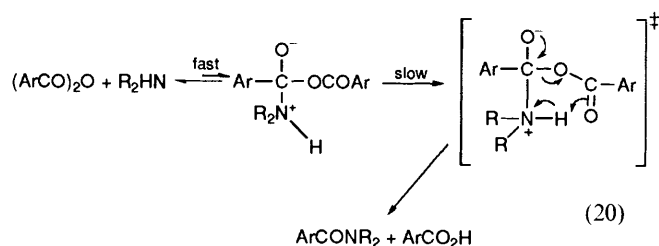
Both mechanisms (17)–(18) and (19) can account qualitatively for the present observations: they are both second-order in amine, involve hydrogen bonding interactions for the catalysis, possess pre-equilibria that can account for the overall small positive, or negative, $\Delta H_2^{\ddagger}$ values, and for the substantial negative $\Delta S_2^{\ddagger}$ values (Table 1). For both the effect of substituting a p-NO$_2$ for a p-H group in the acylating agent should produce a larger increase in k_2 than in k_1 [eqn. (16)]. This is because, for both the self-catalysis mechanisms k_2 [= $K_{ass}(k_a/k_{-a})k_b$ for (17)–(18) and = $(k_a/k_{-a})k_b$ for (19)] will suffer less of a decrease in its k_b component than will k_1. For route (17)–(18) there should also be a notable increase in the ratio k_a/k_{-a} compared to the k_1 route, unless nucleophilic attack by the more basic amine dimer is relatively very sterically hindered compared to that of the monomer.* Nagy's results[4] for secondary amines show that steric hindrance can be important, and ours for 2-methylimidazole also suggest it. A bigger effect certainly seems possible for scheme (17)–(18) than for (19) and, in view of the sometimes large factors found for k_2/k_1 (Table 1), we favour mechanism (17)–(18) as the major route for the self-

catalysis in those cases. Also, as hinted above, this route is favoured for an independent reason with the imidazoles, because of their special capacity for dimerisation.[36]

Suggestions for the mechanisms underlying a kinetic term third order in amine vary from dimer participation in the slow step of a route like (19) for ester aminolysis,[4] to proton transfer from the (rather acidic) N–H group of a third imidazole molecule to the leaving F^- ion, in a route based on[11] (17)–(18). It is difficult to choose between these possibilities. We found (Fig. 4) that an added alcohol with a pK_a as an acid similar to that of imidazole had only a small acceleratory effect on the k_{obs}, but this may be because the alcohol deactivates the amine by hydrogen bonding, as well as helping F^- to depart. Whatever the mechanism, it is rather surprising that we did not find $\Delta S_3^{\ddagger}$ to be significantly more negative than $\Delta S_2^{\ddagger}$ (Table 2). For our imidazole systems perhaps linear trimers participate initially and then break-up again during the slow step, so keeping $\Delta S_3^{\ddagger}$ within bounds.

Benzoic Anhydrides.—The results here show (i) that, in dioxane at 25 °C, benzoic anhydride is considerably more reactive than benzoyl fluoride, and (ii) that our expectation of finding second- or higher-order terms in amine were only partly realised. The simple eqn. (12) holds for the reactions of morpholine, and of the primary amines, with benzoic anhydride up to at least [amine] = 0.2 mol dm^{-3}, but the imidazoles do obey eqn. (13), with the k_2 term particularly important and easily detectable at low imidazole concentrations (Fig. 7). A plot (not shown) of log k_1 from eqn. (12) against pK_a (water) is rectilinear with slope 0.80, but, as for the benzoyl fluoride system, the point for morpholine lies above the line. (A slope of *ca.* 0.84 can be deduced for arylamines reacting with acetic or thioacetic anhydride in benzene.)[16] The three anhydrides studied with imidazole give a straight Hammett plot of log k_1 against σ with a slope ρ *ca.* 4.5; the plot for log k_2 has a slope *ca.* 4 so that the ratio k_2/k_1 is not as much affected by substituent changes as with the benzoyl fluorides (Table 3). A large value of ρ is expected for any nucleophilic attack on symmetrical anhydrides [*e.g.* eqn. (20)] since the effects of the two substituents are likely to be more additive than cancelling. In acylation, when leaving group departure is kinetically important, substituent changes in leaving groups are more likely to have a larger effect than are equivalent changes in the remaining group: in the former the effects on attack and departure are in the same direction (electron-withdrawal helps both) whereas in the latter they are opposed. This is the reason that Menger[30] found large ρ values for substitution in the leaving group in ester aminolysis in aprotic solvents. It is difficult, however, to use substituent effects to support, or exclude, cyclic transition states such as those in eqn. (20) because a substituent effect that draws electrons towards the leaving group, and helps its departure, does not necessarily make a cyclic proton transfer more difficult than in the absence of the substituent. That is because more electron density is available on the leaving group in the transition state, and less is available on the N-atom. This point is not always appreciated.[30] For the present systems, we believe our results are compatible with Litvinenko's conclusion[16,21] (drawn from the relatively feeble effects of solvent polarity and of tertiary base catalysts on the reactions of anhydrides with arylamines in benzene and related solvents) that the path first order in amine proceeds *via* a rate-determining, cyclic elimination of the acid.[37] We formulate this in terms of a tetrahedral intermediate in eqn. (20), making the reaction analogous to eqn. (16), but the anhydride process could be wholly synchronous. It is probably significant that Litvinenko's solvent effects[16] are reminiscent of those we found for benzoyl fluoride. Studies using aliphatic anhydrides and a series of amines in aqueous solvents[17,38] show that, unlike in the present system, a plot of log k_1 against pK_a is

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* k_{-a} must remain significantly larger than k_b if the pre-equilibrium assumption is to hold.

$$(ArCO)_2O + R_2HN \underset{fast}{\rightleftharpoons} Ar-\overset{O^-}{\underset{\underset{H}{R_2N^+}}{\overset{|}{\underset{|}{C}}}}-OCOAr \xrightarrow{slow} \left[\begin{array}{c} Ar-C-O \\ \quad \quad C-Ar \\ R-N-H \quad O \\ R' \end{array} \right]^{\ddagger}$$

$$\downarrow$$

$$ArCONR_2 + ArCO_2H \qquad (20)$$

curved, with the onset of curvature at pK_a 6–8. This result has been interpreted in terms of a tetrahedral intermediate.[38] The comparatively feeble k_1 term (Table 3) for imidazole ($pK_a \sim 7$) compared with that for even trifluoroethylamine ($pK_a \sim 5.8$) could reflect the difficulty (but not now the impossibility) of imidazole using a cycle (eight-membered), although this comparison between primary and tertiary amine reactivity may be misleading. We suggest that the kinetic terms second order in amine in the imidazole reactions with the anhydrides arise from mechanisms similar to those [eqns. (17)–(18) and (19)] proposed for the benzoyl fluoride systems. Why, for the anhydride systems, the ratio k_2/k_1 is less sensitive to substituent changes than it is with the benzoyl fluorides is uncertain; confident predictions are difficult owing to the double substituent effects involved for anhydrides.

Other early suggestions[19,39] about the mechanism of aminolysis of anhydrides in aprotic media were put forward before the importance of leaving group departure, and of auto-catalysis by the product acid, were realised. Experiments such as the present, using an excess of amine, avoid the problems of auto-catalysis since this excess ties up the acid released.

Benzoic anhydride is significantly more reactive than is benzoyl fluoride in the present reactions; the carboxylate ion is therefore the better leaving group. It is to be noted that we found no kinetic terms third order in amine for the imidazole-anhydride systems, in contrast to the findings with the benzoyl fluorides. Results for the aminolysis of acylating agents in non-hydroxylic solvents over the whole field support (although with some exceptions) the expected broad generalisation that, for any system, the better the leaving group in the acylating agent the less is catalysis required.[15] For example, for Nagy's numerous ester systems[4] no terms third-order in amine were obtained when the leaving group was 2,4-dinitrophenylate, and in Menger's systems,[30] only first-order terms were found with the best leaving group. Our results for fluorides establish a similar pattern for the acyl halides, and the results with the anhydrides, when compared to those for fluorides and esters, have a similar flavour. For an acylation in a non-hydroxylic solvent we believe that more catalysis will often be needed than for the same reaction in an aqueous media: the new patterns established in this paper also support this contention, as does the easier detectability of the acid-catalysed hydrolysis of acyl fluorides[40] and anhydrides[41] in dioxane–water mixtures when the dioxane content is increased.

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