The Kinetics of Aminolysis of Acyl Halides

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The morphinolysis of benzoyl fluoride in various non-hydroxylic solvents exhibits a kinetic form containing both first- and second-order terms in morpholine, a result suggesting that general-base catalysis in the aminolysis of acyl halides may be more common than previously assumed.

For the spontaneous aminolysis of esters [*e.g.* eqn. (1)], in either

$$R^1CO_2R^2 + R^3NH_2 \longrightarrow R^1CONHR^3 + R^2OH \quad (1)$$

hydroxylic or non-hydroxylic solvents, the rate equation usually contains both first- and second-order terms in amine[1-3] [eqn. (2)]. In water other terms arising from species produced

$$-d[\text{Ester}]/dt = \{k_1[\text{amine}] + k_2[\text{amine}]^2\}[\text{Ester}] \quad (2)$$

from ionisation of the solvent can also be present, but for non-hydroxylic solvents eqn. (2) is common. General base catalysis by a second molecule of amine probably underlies the term in k_2. Acyl halides are more powerful acylating agents than esters, and their aminolyses (mostly studied in non-hydroxylic media) are expected to be less in need of catalysis.[2] In keeping with this expectation, no example appears to have been reported of a rate equation of the form of eqn. (2) for the spontaneous aminolysis of an acyl halide [eqn. (3)]: such aminolyses are normally

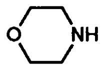
$$R^1COHal + R^2NH_2 \longrightarrow R^1CONHR^2 + HHal \xrightarrow{R^2NH_2} R^1CONHR^2 + R^2NH_3{}^+Hal^- \quad (3)$$

reported to be just first order in each reactant;[1,2,4] indeed, such a kinetic form has often been assumed. Cases[5,6] of catalysis by tertiary bases that could arise from general-base, as well as from nucleophilic catalysis, have however been observed for both acyl chlorides and fluorides, and we considered that rate equations corresponding to eqn. (2) might therefore have gone undetected in the past.

We have now observed a rate equation (4), the analogue of

$$-d[PhCOF]/dt = \{k_1[M] + k_2[M]^2\}[PhCOF] = k_{obs}[PhCOF] \quad (4)$$

M =



eqn. (2), for the morphinolysis of benzoyl fluoride[7] in several non-hydroxylic solvents. Experiments using a range (0.01–0.16 mol dm^{-3}) of morpholine concentrations, and a deficit of the fluoride, led to results such as those in Fig. 1. Typical values for k_1 and k_2 obtained from rectilinear plots of $k_{obs}/[M]$ against [M], or of $k_{obs}/[M]^2$ against 1/[M], are given in Table 1. It is interesting that there seems little obvious correlation between the magnitude of the rate constants and the properties of the solvents. This shows that the curvature in Fig. 1 is unlikely to be due to a 'solvent effect' as [M] is increased, and deliberate additions of the product salt (morpholine hydrofluoride) or of water, produce relatively very small changes in k_{obs}. Added triethylamine, however, produces a catalytic effect similar in magnitude to that due to the second morpholine molecule.

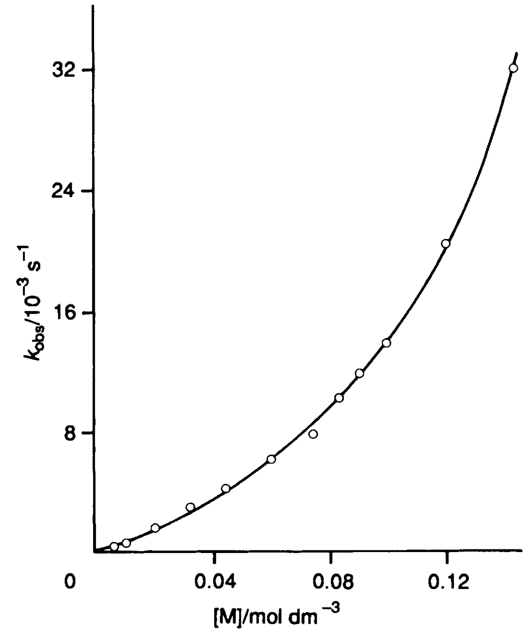


Fig. 1 Dependence of k_{obs} on [M] in diethyl ether at 25.0 °C; $[PhCOF]_{initial}$ *ca.* 5 × 10^{-4} mol dm^{-3}

Table 1 Values of k_1 and k_2 at 25 °C

Solvent	k_1/dm^3 mol^{-1} s^{-1}	k_2/ dm^6 mol^{-2} s^{-1}
Diethyl ether	0.07	0.63
Tetrahydrofuran	0.09	2.1
1,4-Dioxane	0.40	2.5
Chloroform	0.40	2.0
Acetonitrile	0.27	2.8

Acyl fluorides are less powerful acylating agents than the corresponding chlorides although the F/Cl reactivity ratio can approach unity.[4,8] The fluoride will therefore normally be the more likely to exhibit general-base catalysis by a second amine molecule. It now seems probable, however, that such catalysis will also exist for relatively unreactive acyl chlorides, especially when acylating unreactive amines. The common use of second-order conditions, with the assumption of overall second-order kinetics, in studies of acyl chloride aminolysis makes difficult the detection of contributions from kinetic terms second-order in amine. Many of the numerous previous studies[2,4] may have overlooked the type of effect we have now found.

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