Acyloxymethyl as a Drug Protecting Group. Kinetics and Mechanism of the Hydrolysis of *N*-Acyloxymethylbenzamides

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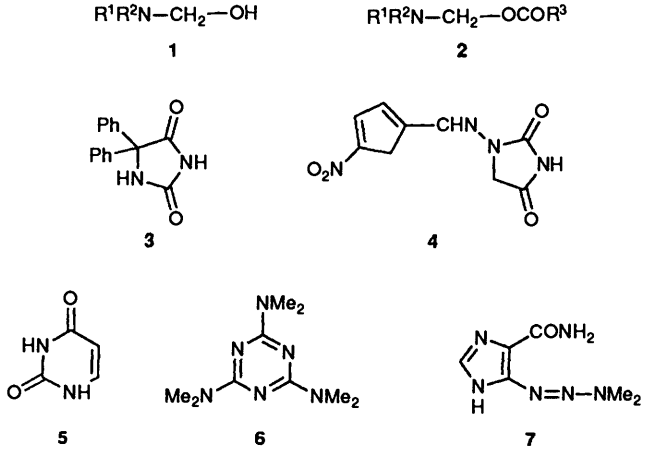
Acyloxymethyl derivatives of secondary and tertiary amides undergo hydrolysis *via* acid-catalysed, base-catalysed and pH-independent processes. The pH-independent pathway involves rate-limiting iminium ion formation and is characterised by the following: a Hammett ρ value for the substituent in the benzamide moiety of *ca.* −1.2 for both types of substrate; the absence of general-base or nucleophilic catalysis; a common benzoate ion effect; a solvent deuterium isotope effect, $k_{obs}^{H_2O}/k_{obs}^{D_2O}$, of *ca.* 1.6; $\Delta S^{\ddagger}$ values of −4 and −12 J K^{-1} mol^{-1} for secondary and tertiary substrates respectively; and higher reactivity of the tertiary amides over their secondary counterparts. The acid-catalysed process involves protonation of the substrate followed by iminium ion formation, and is characterised by the following: a Hammett ρ value of *ca.* −1.5 for the substituent effect of the benzamide moiety; a solvent deuterium isotope effect of *ca.* 0.4; a monotonic rise in the pseudo-first-order rate constant k_{obs} with increasing [H_2SO_4]; $\Delta S^{\ddagger}$ values >0 J K^{-1} mol^{-1}; higher reactivity of the tertiary substrates over their secondary counterparts; and a value of 0.85 for the Brønsted coefficient, β_{lg}, for the carboxylate nucleofuge. The base-catalysed hydrolysis of tertiary substrates involves normal ester hydrolysis *via* acyl–oxygen bond cleavage, and is characterised by a Hammett ρ value of +0.38, a solvent deuterium isotope effect, k^{OH^-}/k^{OD^-}, of 0.85, and a $\Delta S^{\ddagger}$ value of −96 J K^{-1} mol^{-1}. The corresponding base-catalysed process for the secondary substrates involves imine formation *via* an E2 elimination reaction. The secondary acyloxymethylamides are some 7 × 10^4 times more reactive than their tertiary counterparts in the base-catalysed region. Hammett ρ values of +1.1 and +0.6 are obtained for the substituents in the ester and amide moieties, respectively. Buffer catalysis is observed, and the value of *ca.* 0.5 for the Brønsted β coefficient identifies the amide proton as approximately 50% transferred to the buffer species in the transition state.

Heats of formation, ΔH_f, calculated using the AM1 SCF MO package reveal that iminium ion formation is thermodynamically equi-energetic for cyclic and acyclic systems. Iminium ion formation from tertiary substrates is favoured by *ca.* 25 kJ mol^{-1} over the corresponding secondary analogues.

Carbinolamines **1** and their acyl esters **2** are of particular interest in drug chemistry.[1] For example, the *N*-hydroxymethyl derivatives of phenytoin **3**,[2] nitrofurantoin **4**[3] and uracil **5**[4] have been developed as pro-drugs for the parent compounds, and several cancer chemotherapeutic drugs, *e.g.* hexamethylmelamine **6**,[5] and DTIC **7**,[5] exert their cytoxic effect by first



undergoing oxidative metabolism to the corresponding carbinolamine. The mode of action of these drugs appears to be a fine balance between loss of formaldehyde to generate the parent N–H compound and loss of OH^- to form an iminium ion [eqn. (1)]. For some, *e.g.* uracil, loss of formaldehyde from

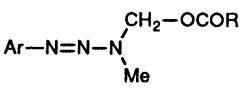
$$R^1R^2\overset{+}{N}{=}CH_2 \xleftarrow{-OH^-} R^1R^2\text{-N-}CH_2OH \xrightarrow{-HCHO} R^1R^2\text{-N-H} \quad (1)$$

the carbinolamine generates the active drug,[4] whereas for others, *e.g.* hexamethylmelamine, iminium ion formation appears to be important.[5] Indeed, for DTIC there is some debate as to which mechanism is important.[5,6]

Esters of carbinolamines also have been developed as pro-drugs.[1] In some cases it is the amine moiety which acts as the drug, *e.g.* the triazene esters **8**[7] and 5-fluorouracil derivatives **9**,[8] in others it is the ester moiety which is biologically active *e.g.* the penicillin derivatives **10**.[9]

Such esters also have the possibility of undergoing decomposition by two modes; solvolysis of the ester moiety to generate a hydroxymethyl derivative which can liberate the parent N–H compound, or iminium ion formation *via* loss of the carboxylate group [eqn. (2)]. The use of carbinolamine esters as pro-drugs generally relies on the former pathway.[1]

$$R^1R^2\overset{+}{N}{=}CH_2\ R^3CO_2^- \longleftarrow R^1R^2\text{-N-}CH_2OCOR^3 \longrightarrow R^1R^2\text{-N-}CH_2OH \quad (2)$$



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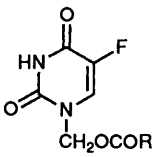

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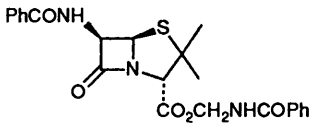

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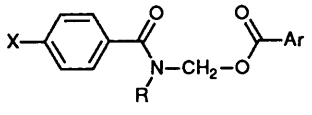
Although the iminium ion is capable of reacting with water, providing an alternative route to the carbinolamine, it is also able to react with other nucleophilic species [eqn. (3)] thus

$$R^1R^2\text{-}\overset{+}{N}\text{=}CH_2 + NuH \xrightarrow{-H^+} R^1R^2N\text{-}CH_2\text{-}Nu \quad (3)$$

diverting the drug into pathways which might interfere with their therapeutic efficacy and might potentially give rise to toxic side effects. Thus an understanding of the factors which influence the ways in which both carbinolamines and their ester derivatives react is of central importance to the rational design of pro-drugs.

Recently, we studied the triazene derivatives **8** and found them to undergo solvolysis *via* the iminium ion pathway.[10] We, and others, have shown that this iminium ion is capable of reacting with various nucleophiles other than water *e.g.* RCO_2^-,[10] ROH,[7,11] N_3^-[12] and RSH.[11,13,14] Clearly, compounds of structure **2** in which the amino moiety is more nucleophilic than a triazene will undergo a similar pattern of decomposition. We have therefore turned our attention to compounds which contain an amino moiety that is less basic than a triazene *viz.* the benzamides **11**. While we were carrying out this investigation, Bundgaard *et al.* reported a similar study and proposed that, for the NH compounds, decomposition proceeded *via* an E2 elimination to generate an imine, and that, when NH is replaced by an *N*-alkyl group, such a process is precluded and the resulting compounds are stable.[15] However, our preliminary results were inconsistent with this interpretation and we now present evidence which identifies iminium ions as intermediates in the solvolysis of both secondary and tertiary acyloxymethylamides. The compounds used for the current work are **11a–m**.



11	X	R	Ar
a	MeO	H	Ph
b	H	H	Ph
c	4-Cl	H	Ph
d	4-CF_3	H	Ph
e	4-NO_2	H	Ph
f	H	Me	Ph
g	4-Cl	Me	Ph
h	4-NO_2	Me	Ph
i	4-MeO	Me	Ph
j	4-Cl	H	4-$MeOC_6H_4$
k	4-Cl	H	4-ClC_6H_4
l	4-Cl	H	4-$CF_3C_6H_4$
m	4-Cl	H	4-$NO_2C_6H_4$

Experimental

Synthesis of Substrates.—The benzoyloxymethylbenzamides **11a–e** and **j–m** were synthesised from the corresponding *N*-hydroxymethyl compounds[16] with benzoyl chloride in pyridine. After 1 h, the reaction mixture was poured over ice-water and the resulting precipitate or oil was separated and purified by flash chromatography. The *N*-methyl compounds **11f–i** could not be prepared in this way because the corresponding *N*-hydroxymethyl derivatives are unstable. We were able to synthesise them in modest yield, however, by the following procedure. Sodium hydride (1.5 mol equiv.) was added to a solution of the appropriate *N*-methylbenzamide in dry DMF. When the liberation of H_2 was complete this solution was syringed slowly into a solution of chloromethyl benzoate[17] (1 mol equiv.) in DMF. The reaction was monitored by TLC and upon completion the solvent was evaporated under vacuum. The residue was then subjected to flash chromatography. New compounds are as follows (those quoted without melting points are oils).

11a: M.p. 86–87 °C; ν_{max}/cm^{-1} 3290, 1730, 1660 and 1555; $\delta_H(CDCl_3)$ 3.82 (3 H, s) 5.67–5.75 (2 H, d) and 6.85–8.10 (9 H, m) (Found: C, 67.0; H, 5.3; N, 4.8. Calc. for $C_{16}H_{15}NO_4$: C, 67.4; H, 5.26; N, 4.91%).

11c: M.p. 115–117 °C; ν_{max}/cm^{-1} 3300, 1725 and 1655; $\delta_H(CDCl_3)$ 5.66–5.75 (2 H, d) and 7.35–8.11 (9 H, m) (Found: C, 61.8; H, 4.1; N, 4.7. Calc. for $C_{15}H_{12}ClNO_3$: C, 62.2; H, 4.15; N, 4.83%).

11d: M.p. 112–114 °C; ν_{max}/cm^{-1} 3335, 1720 and 1650; $\delta_H(CDCl_3)$ 5.65–5.75 (2 H, d) and 7.20–8.22 (9 H, m) (Found: C, 59.4; H, 3.8; N, 4.3. Calc. for $C_{16}H_{12}F_3NO_3$: C, 59.4; H, 3.71; N, 4.33%).

11e: M.p. 139–140 °C; ν_{max}/cm^{-1} 3335, 1725 and 1640; $\delta_H(CDCl_3)$ 5.68–5.76 (2 H, d) and 7.32–8.33 (9 H, m) (Found: C, 59.3; H, 4.0; N, 9.2. Calc. for $C_{15}H_{12}N_2O_5$: C, 60.0; H, 4.00; N, 9.33%).

11f: ν_{max}/cm^{-1} 3060, 1725 and 1650; $\delta_H(CDCl_3)$ 3.2 (3 H, s), 5.57 (2 H, s) and 7.4–8.1 (10 H, m) (Found: C, 71.5; H, 5.6; N, 5.3. Calc. for $C_{16}H_{15}NO_3$: C, 71.4; H, 5.6; N, 5.2%).

11g: ν_{max}/cm^{-1} 3080, 1725 and 1660; $\delta_H(CDCl_3)$ 3.20 (3 H, s), 5.60 (2 H, s) and 7.45–8.20 (9 H, m) (Found: C, 63.3; H, 4.6; N, 4.6. Calc. for $C_{16}H_{14}ClNO_3$: C, 63.3; H, 4.61; N, 4.61%).

11h: M.p. 75–76 °C; ν_{max}/cm^{-1} 3080, 1730 and 1640; $\delta_H(CDCl_3)$ 3.18 (3 H, s), 5.45 (2 H, s) and 7.30–8.15 (9 H, m) (Found: C, 61.1; H, 4.4; N, 9.0. Calc. for $C_{16}H_{14}N_2O_5$: C, 61.1; H, 4.45; N, 8.92%).

11i: ν_{max}/cm^{-1} 3055, 1720 and 1590; $\delta_H(CDCl_3)$ 3.20 (3 H, s), 3.75 (3 H, s), 5.60 (2 H, s) and 6.78–8.10 (9 H, m) (Found: C, 68.2; H, 5.5; N, 4.6. Calc. for $C_{17}H_{17}NO_4$: C, 68.2; H, 5.7; N, 4.7%).

11j: M.p. 97–100 °C; ν_{max}/cm^{-1} 3305, 1720 and 1620; $\delta_H(CDCl_3)$ 3.80 (3 H, s), 5.65–5.75 (2 H, d) and 6.95–8.20 (8 H, m) (Found: C, 60.0; H, 4.3; N, 4.4. Calc. for $C_{16}H_{14}ClNO_4$: C, 60.1; H, 4.38; N, 4.38%).

11k: M.p. 122–123 °C; ν_{max}/cm^{-1} 3300, 1725 and 1643; $\delta_H(CDCl_3)$ 5.70–5.82 (2 H, d) and 7.37–8.25 (8 H, m) (Found: C, 55.0; H, 3.4; N, 4.3. Calc. for $C_{15}H_{11}Cl_2NO_3$: C, 55.6; H, 3.39; N, 4.32%).

11l: M.p. 142–144 °C; ν_{max}/cm^{-1} 3360, 1720 and 1655; $\delta_H(CDCl_3)$ 5.65–5.77 (2 H, d) and 7.30–8.32 (8 H, m) (Found: C, 54.0; H, 3.1; N, 3.9. Calc. for $C_{16}H_{11}ClF_3NO_3$: C, 53.7; H, 3.08; N, 3.92%).

11m: M.p. 124–126 °C; ν_{max}/cm^{-1} 3350, 1730 and 1645; $\delta_H(CDCl_3)$ 5.67–5.78 (2 H, d) and 7.35–8.32 (8 H, m) (Found: C, 53.2; H, 3.3; N, 8.4. Calc. for $C_{15}H_{11}ClN_2O_5$: C, 53.8; H, 3.29; N, 8.37%).

Product Analysis.—Products were identified by both isolation and HPLC analysis. For the secondary amide substrates, the products at pH < *ca.* 8 are the *N*-hydroxymethylbenzamide

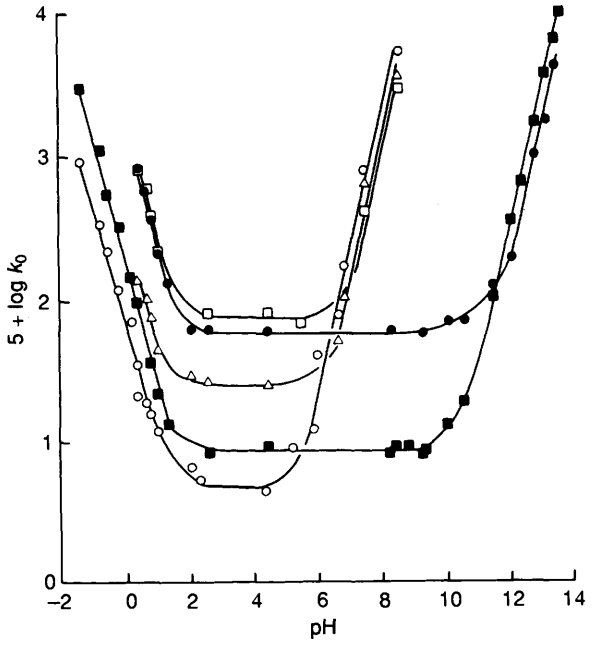


Fig. 1 pH profiles for the hydrolysis of compounds **11a** (□), **11c** (△), **11e** (○), **11g** (●) and **11h** (■)

Table 1 Pseudo-first-order rate constants, k_o, for the pH-independent hydrolysis of compounds **11a**–i at 25 °C and μ = 0.5 mol dm^{-3}

Compound	$k_o/10^{-4}$ s^{-1}
11a	7.87
11b	2.58
11c	2.53
	1.50[a]
11d	1.22
11e	0.451
11f	9.90
11g	5.93
	3.62[a]
11h	0.836
11i	50.1

[a] In D_2O.

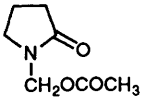
and the corresponding benzoic acid. At pH > 9, the amidic product is the primary benzamide. For the tertiary amide substrates the amidic product is the *N*-methylbenzamide at all pH values.

Kinetics.—A small aliquot (10–20 mm^3) of a solution of the benzoyloxymethylamide (7.5 × 10^{-3} mol dm^{-3}) in acetonitrile was injected into a thermostatted cuvette containing the required buffer solution. The final concentration of **11** was *ca* 5 × 10^{-5} mol dm^{-3}. The change in UV spectrum was monitored at an appropriate wavelength with respect to time, and pseudo-first-order rate constants, k_0, were obtained from plots of $\ln(A_t - A_\infty)$ *versus* time. Rate constants were reproducible to within ±5% using this procedure. Alternatively, reactions were monitored using HPLC to follow either the loss of substrate or the formation of products. The HPLC system employed a Merck LiChrospher® 100 RP8 5 μm 125 × 4 mm column and an acetonitrile–water (1:1) eluent flowing at 1.5 cm^3 min^{-1}. Values of rate constants obtained by the HPLC method were concordant with those obtained spectrophotometrically for the tertiary substrates at all pH values and for the secondary substrates at pH values <8. At pH >8.5, the solvolysis of the secondary substrates is instantaneous and the observed pseudo-first-order rate constants obtained spectrophotometrically at these pH values were found to be identical with those obtained for the corresponding *N*-hydroxymethyl derivatives.[18]

MO Calculations.—These were carried out using the AM1 procedure from the MOPAC4 suite of programs.[19] All structures underwent complete geometry optimization using the Broyden–Fletcher–Goldfarb–Shanno formulation.[20]

Results and Discussion

pH Profiles.—Both secondary, *e.g.*, **11a**, **c**, **e** and tertiary, *e.g.*, **11g**, **h**, amides undergo hydrolysis in a pH-dependent manner (Fig. 1). The pH dependence for both types of compound is largely similar, exhibiting both acid and base catalysis as well as a pH-independent region. However, for tertiary substrates the pH-independent pathway extends to pH *ca.* 9, whereas for secondary substrates incursion of the base-catalysed process occurs at *ca.* pH 5. This is in contradistinction to the work of Bundgaard who studied the cyclic tertiary amide derivative **12** and found it to be stable.[15] We shall discuss each of these regions in turn.



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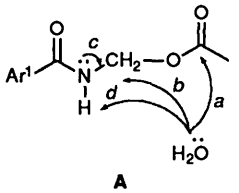
The pH-independent Region.—Solvolysis of compounds **11a**–**e** in this region is subject to the electronic effect of the substituents in the benzamide ring (Table 1). This effect is most diagnostic of the mechanism of solvolysis. Thus, of the four potential mechanisms that could be operating, illustrated in **A**, path *a* should be largely independent of the substituent in Ar^1, paths *b* and *d* should be enhanced by electron-withdrawing substituents in Ar^1, and path *c* should be retarded by electron-withdrawing substituents in Ar^1. The Hammett ρ value is −1.1 (r = 0.97) which points to path *c*, iminium ion formation, as the



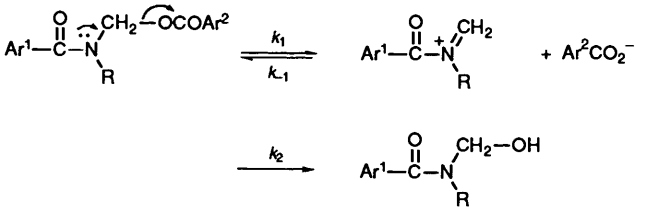
A

hydrolysis pathway followed. Path *d* is, of course, not available to the corresponding *N*-methyl compounds **11f–i**. Nonetheless, the values of k_0 for these compounds define a Hammett plot at slope *ca.* −1.6 (r = 0.99). Thus, both the amides **11** (R = H) and **11** (R = Me) apparently undergo a similar hydrolytic mechanism in the pH-independent region. The lack of any general-base or nucleophilic catalysis by acetate, trichloroacetate or pyridine (Table 2) is further evidence against the involvement of path *d*.

Several other lines of argument confirm path *c* as the mechanism of the pH-independent solvolysis. First, iminium ion formation followed by trapping of the ion by solvent water, as in Scheme 1, should be subject to a common-ion effect. The data presented in Table 3 for **11a** indicate that this is so. A plot of $1/k_o$ *versus* [$PhCO_2^-$] for these data results in a value for the $k^{PhCO_2^-}/k^{H_2O}$ ratio of 1.08 × 10^4. That is, benzoate ion is some ten thousand times more effective at trapping the iminium ion than water. Secondly, the temperature dependence of the reaction (Table 4) for compounds **11a** and **11h** yields values for $\Delta H^\ddagger$ of 89.5 and 93.0 kJ mol^{-1} and for $\Delta S^\ddagger$ of −4 and −12 J K^{-1}, respectively. The values of $\Delta S^\ddagger$, though negative, are small and

Table 2 Effect of buffer concentration on the observed pseudo-first-order rate coefficient, k_o, for the hydrolysis of acyloxymethylbenzamides at 25 °C, μ = 0.5 mol dm^{-3}, in the pH-independent region

Compound	Buffer	[Buffer]/ 10^{-2} mol dm^{-3}	pH	$k_o/10^{-4}$ s^{-1}
11a	CH_2ClCO_2H	1.0	2.66	7.71
		5.0	2.45	7.94
		10.0	2.57	7.96
	Pyridine	0.2	5.45	6.88
		0.4	5.44	6.89
		1.0	5.43	6.68
11b	AcOH	2.0	4.40	2.62
		10.0	4.40	2.59
		40.0	4.43	2.65
		1.2	5.23	2.49
		2.4	5.22	2.54
		6.0	5.20	2.59
11c	CH_2ClCO_2H	1.0	2.66	2.37
		5.0	2.45	2.82
		10.0	2.57	2.41
11g	AcOH	2.0	4.40	6.00
		4.0	4.28	5.78
		10.0	4.40	6.07
		20.0	4.42	5.86
11h	CH_2ClCO_2H	1.0	2.66	0.814
		5.0	2.45	0.870
		10.0	2.57	0.823
	Morpholine	0.07	8.44	0.937
		0.21	8.44	0.925
		0.35	8.45	0.895
		0.56	8.41	0.912



Scheme 1 Mechanism of the pH-independent hydrolysis of acyloxymethylbenzamides

Table 3 Effect of added benzoate ion on the pseudo-first-order rate constant, k_o, for the hydrolysis of **11a** at pH 4.49, 25 °C and μ = 0.5 mol dm^{-3}

$[PhCO_2^-]/10^{-3}$ mol dm^{-3}	$k_o/10^{-4}$ s^{-1}
0.0	7.30
1.0	5.92
2.0	4.93
3.0	4.60

well within the range observed for a unimolecular ionisation, reaction.[21] Thirdly, ionisation reactions, such as that represented by step k_1 of Scheme 1, are associated with a solvent deuterium isotope effect k^{H_2O}/k^{D_2O} of *ca.* 1.2.[22] Solvent isotope effects observed for compounds **11c** and **11g** are 1.7 and 1.6, respectively (Table 1).

The greater reactivity of the NMe, as compared with the NH compounds, may be ascribed to the inductive stabilisation afforded to the iminium ion by the *N*-methyl group. Paths *a* and *b* in **A** might be expected to show a reversed order of reactivity due to the greater steric effect of the *N*-methyl group. Moreover, the mechanism should be dependent on the nucleofugacity of the carboxylate group. Bundgaard and Nielsen elsewhere have shown that the Brønsted value for the leaving group, β_{lg}, is −0.85 for the pH-independent process.[15]

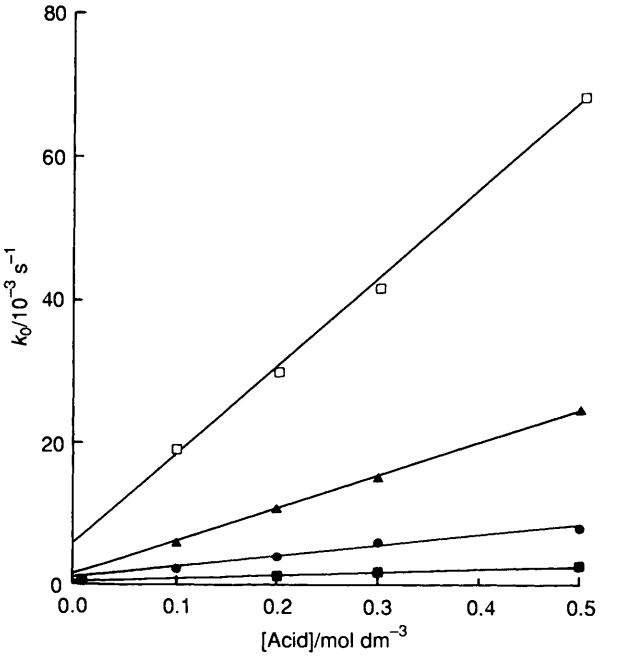


Fig. 2 Variation of the pseudo-first-order rate constants, k_o, with acid concentration for compounds **11a** (●), **11b** (■), **11f** (▲) and **11i** (□)

The Acid-catalysed Pathway.—All of the acyloxymethylamides **11a–m** exhibit an acid-catalysed region similar to those shown in Fig. 1. Second-order rate constants for this acid-catalysed process, k^{H^+}, are obtained from the slope of the linear plots of k_o *versus* hydrochloric acid concentration (Fig. 2). These plots exhibit a small positive intercept that corresponds to the rate constant for the pH-independent process. The intercept values obtained from such plots are consistent with those obtained from buffer solutions in the pH-independent region. Collected values for k^{H^+} are contained in Table 5, from which the following observations may be made. First, compounds **11a–e** define a Hammett ρ value of −1.3, a value similar to that obtained for the pH-independent region. Secondly, the k^{H^+} values for the corresponding *N*-methyl compounds, **11f–i**, yield a Hammett ρ value of −1.7. Thirdly, the deuterium solvent isotope effects k^{H^+}/k^{D^+} found for the acid-catalysed decomposition of compounds **11c** and **11g** are 0.45 and 0.33, respectively. Fourthly, compounds **11c**, **j–m** yield a Hammett ρ value for the substituent in the benzoate moiety of 0.85. Thus, it appears that both the NH and NMe compounds decompose by a similar mechanism, and for both compounds this involves pre-equilibrium protonation of the substrate. Confirmation of this comes from the decomposition of compounds **11b**, **e**, **h** in sulphuric acid solutions. These show (Fig. 3) that there is a monotonic increase in k_o with $[H_2SO_4]$. No maximum is observed at higher acidities, and such observations are most consistent with an A1 mechanism. Furthermore, the temperature dependence of the reaction for compounds **11a**, **b**, **h** reveal values for $\Delta S^{\ddagger}$ (in J K^{-1} mol^{-1}) of −1.0 for **11a**, 11 and 49 for **11b** and 44 for **11h** (Table 6).

Thus, it is reasonable to propose that the acid-catalysed decomposition of acyloxymethylamides follows a mechanism similar to that for the pH-dependent pathway, except that there

Table 4 Effect of temperature on the pH-independent hydrolysis of compounds **11a** and **11h**

Compound	T/K	$k_o/10^{-4}$ s^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}
11a	293	4.37	89.5 ±5	−4 ±10
	298	7.87		
	303	13.6		
	308	49.7		
11h	292	0.269	93.0 ±5	−12 ±10
	298	0.836		
	304	1.45		
	308	2.56		
	312	3.87		
	318	7.76		
	323	12.3		

Table 5 Second-order rate constants, k^{H^+}, for the acid-catalysed hydrolysis of acyloxymethylamides at 25 °C, μ = 0.5 mol dm^{-3}

Compound	$k^{H^+}/10^{-4}$ dm^3 mol^{-1} s^{-1}
11a	148
11b	50.7
11c	22.7
	50.6[a]
11d	9.48
11e	5.65
11f	468
11g	161
	492[a]
11h	18.5
11i	1246
11j	12.2
11k	50.0
11l	65.5
11m	106

[a] In D_2O.

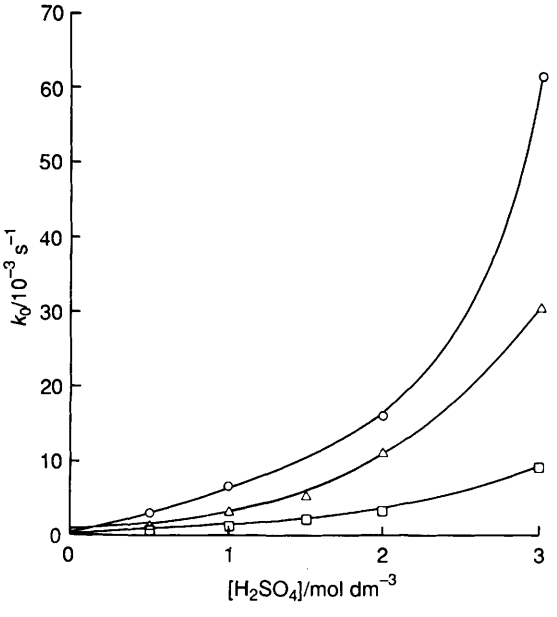
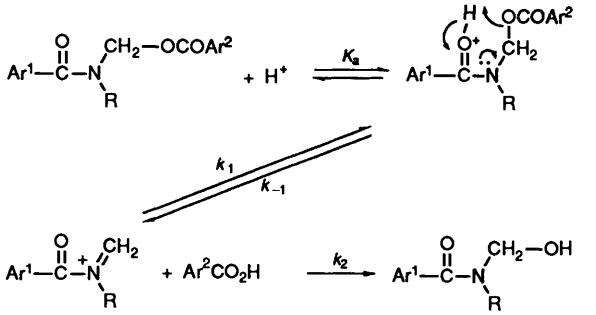


Fig. 3 Variation of k_o with sulphuric acid concentration for compounds **11b** (○), **11e** (□) and **11h** (△)

is an extra equilibrium step for the protonation of the substrate prior to iminium ion formation (Scheme 2). It is difficult to ascertain precisely the position of protonation. However, the known differences in the pK_a values of aryl amides and aryl



Scheme 2 Mechanism of the acid-catalysed hydrolysis of acyloxymethylbenzamides

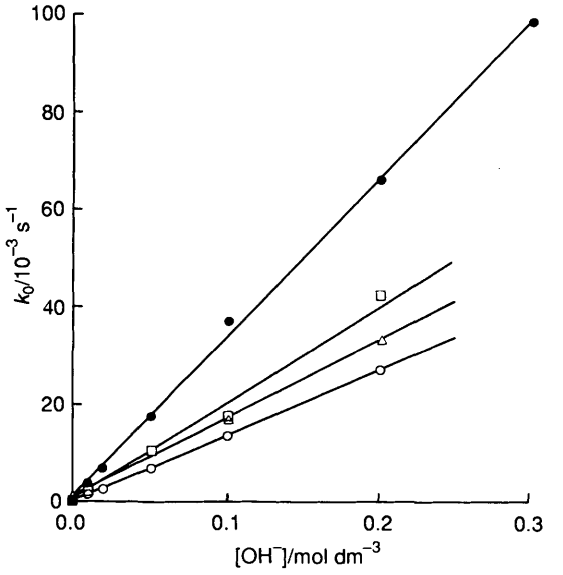


Fig. 4 Variation of k_o with hydroxide-ion concentration for compounds **11f** (△), **11g** (□), **11h** (■) and **11i** (○)

esters,[23] together with the incursion of the acid-catalysed process at pH *ca.* 2, strongly suggests that initial protonation occurs at the amide group as shown in Scheme 2.

The Base-catalysed Process for Tertiary Substrates.—The *N*-methylated acyloxymethylamides **11f–i** undergo base-catalysed hydrolysis to the parent *N*-methylbenzamide. The pseudo-first-order rate constants, k_o, are linear with respect to the concentration of OH^-, and second-order rate constants for base catalysis, k^{OH^-}, are obtained from the slopes of the plots in Fig. 4. Values of k^{OH^-} for **11f–i** (Table 7) define a Hammett plot of slope ρ = +0.38 (r = 0.995). The solvent deuterium isotope effect (Table 7), k^{OH^-}/k^{OD^-}, for the base-catalysed reaction is 0.85, and the value of $\Delta S^{\ddagger}$ is −96 J K^{-1} mol^{-1}. Taken together, these values are consistent with normal base-catalysed ester hydrolysis (Scheme 3) in which nucleophilic attack at the ester carbonyl group, step k_1, is rate-limiting. Certainly, the change in sign of the Hammett ρ value for this OH^--catalysed process, as compared with the corresponding ρ values for the acid-catalysed and pH-independent pathways, is indicative of a change in mechanism, and the low magnitude of the ρ value implies that the benzamide group is remote, or insulated from, the site of attack. Subsequent decomposition of the so-formed tetrahedral intermediate may involve either stepwise formation initially of the carbinolamide followed by the *N*-methylamide or a concerted loss of formaldehyde to form the *N*-methylamide directly. Since these steps are rapid compared with initial OH^- attack at the carbonyl group, neither mechanism is precluded.

The Base-catalysed Process for Secondary Substrates.—The

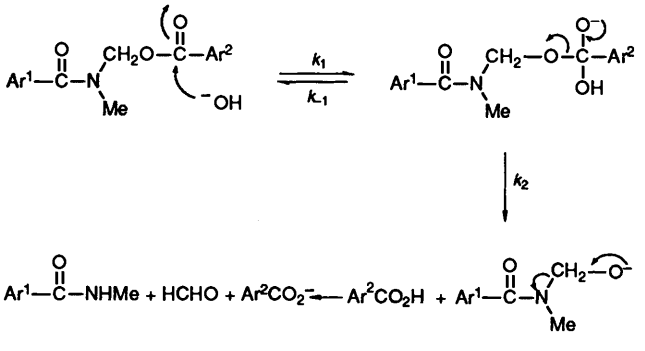
Table 6 Temperature dependence of the pseudo-first-order rate constants, k_o, or the second-order rate constants, k^{H^+}, for the acid-catalysed solvolysis of compounds **11a, b, h**

Compound	Medium	T/K	$k_o/10^{-2}$ s^{-1}	$k^{H^+}/10^{-2}$ dm^3 mol^{-1} s^{-1}	$\Delta H^‡$/kJ mol^{-1}	$\Delta S^‡$/J K^{-1} mol^{-1}
11a	HCl	20		0.779	84	−1.0
		25		1.48		
		30		2.06		
		35		3.71		
		40		7.29		
11b	H_2SO_4 (0.5 mol dm^{-3})	15	0.0674		91	11
		20	0.131			
		25	0.296			
		30	0.412			
		35	0.843			
	H_2SO_4 (3 mol dm^{-3})	10	0.783		94	49
		15	1.67			
		20	2.75			
		25	6.11			
11h	HCl	20		0.094	102	44
		25		0.185		
		30		0.395		
		35		0.797		
		40		1.34		

Table 7 Second-order rate constants, k^{OH^-}, of the hydroxide-ion-catalysed hydrolysis of **11f–i** at 25 °C and μ = 0.5 mol dm^{-3}

Compound	T/K	$k^{OH^-}/10^{-1}$ dm^3 mol^{-1} s^{-1}
11f	298	1.60
11g	298	2.10
11h	293	2.47[a]
	298	3.26[a]
		3.85[b]
	304	4.82[a]
	308	6.43[a]
11i	298	1.29

[a] $\Delta H^‡$ = 47 ± 5 kJ mol^{-1}; $\Delta S^‡$ = −96 (± 10) J K^{-1} mol^{-1}. [b] In D_2O.



Scheme 3 Mechanism of the base-catalysed hydrolysis of *N*-acyloxymethyl-*N*-methylbenzamides

secondary acyloxymethylamides **11a–e, k–m** also suffer a base-catalysed hydrolysis reaction (Fig. 1). However, unlike the tertiary substrates which experience base catalysis only at pH values >9, incursion of the base-catalysed process is observed at pH values *ca.* 5–6, depending on the substituent in the benzamide moiety (Fig. 1). Moreover, at pH 5.83 in pyridine buffers, the decomposition of compound **11a** occurs via the pH-independent pathway (Fig. 1) and there is no observable buffer

Table 8 Effect of pyridine buffer concentration on k_o for compound **11e**; μ = 0.5 mol dm^{-3}, T = 25 °C

[Pyridine]/10^{-4} mol dm^{-3}	$k_o/10^{-4}$ s^{-1}
0.88	1.43
1.76	1.69
3.66	2.07
5.86	3.32

Table 9 Rate constants, k^B for the buffer-catalysed hydrolysis of secondary acyloxymethylamides at 25 °C

		k^B/dm^3 mol^{-1} s^{-1}						
Buffer	pK_a[a]	**11a**	**11b**	**11c**	**11e**	**11k**	**11l**	**11m**
Pyridine	5.40	—	—	—	0.233			
HPO_4^{2-}	6.70	0.0946	0.158	0.29	0.456			
Imidazole	7.11	0.246	0.403	0.515[b]	1.23[b]			
				0.53[c]	1.18[c]			
Morpholine	8.70	1.63	2.73	3.45	15.7	7.12	13.0	27.4
OH^-	15.75	10 800	11 000	12 800	20 400			

[a] Corrected for μ = 0.50 mol dm^{-3}. [b] pH = 6.82. [c] pH 6.62.

catalysis (Table 2), whereas compound **11e** decomposes by both the pH-independent and base-catalysed pathways as well as undergoing a buffer-catalysed process (Table 8). All the secondary substrates were subject to buffer catalysis in the OH^--catalysed region of hydrolysis. The observed pseudo-first-order rate constants, k_o, were found to have a linear dependence on the concentration of the buffer species, and the second-order rate constants for buffer catalysis, k^B, were obtained from the slopes of the plots of k_o *versus* buffer concentration and these values are given in Table 9. The catalytic rate constants for OH^- catalysis contained in Table 9 could not be obtained from simple plots of k_o *versus* [OH^-] because the reactions were too fast to monitor. Instead, the intercepts, k_{int}, obtained from the plots of k_o *versus* [buffer] at a variety of different pH values were

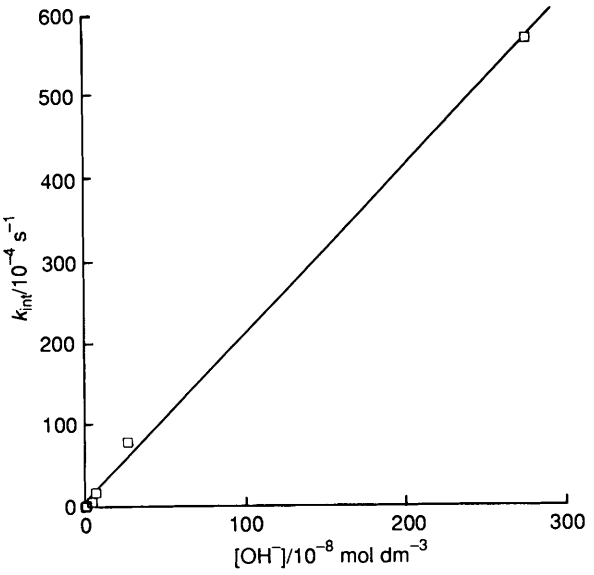
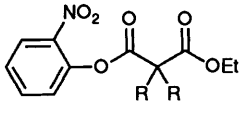


Fig. 5 Variation of k_{int} with hydroxide-ion concentration for **11e**

themselves plotted against the corresponding value of [OH^-] (Fig. 5), the slopes of which give k^{OH^-}.

A comparison of the k^{OH^-} values for the secondary substrates **11a–c, e** (Table 9) with their tertiary counterparts (Table 7) demonstrates that the secondary compounds are *ca.* 7×10^4 more reactive under base catalysis. This order of reactivity is the reverse of that identified for the acid- and pH-independent processes, and implies a change in the mechanism for the hydrolysis reaction. It cannot be attributable to the greater steric influence of a methyl group. Similar differences in reactivity, 7×10^3–10^6, have been reported for analogous groups of compounds, *e.g.* **13–15**, in which a hydrogen atom in a position β to a leaving group is replaced by a methyl group.[24]



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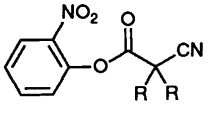

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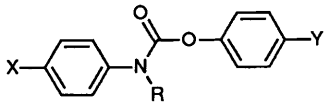

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For each of the compounds **11a–c, e** it is possible to construct a Brønsted plot of log k^B *versus* the pK_a of the buffer material, and the following relationships are found.

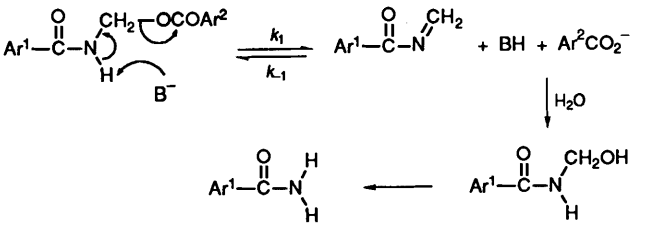
11a $\log k^B = 0.55\ pK_a - 4.58$ ($r = 0.999$)

11b $\log k^B = 0.52\ pK_a - 4.18$ ($r = 0.999$)

11c $\log k^B = 0.51\ pK_a - 3.92$ ($r = 0.999$)

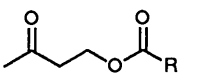
11e $\log k^B = 0.49\ pK_a - 3.34$ ($r = 0.995$)

Thus, it would appear that secondary acyloxymethylamides undergo hydrolysis by a mechanism that is different from that suffered by their tertiary counterparts. The most likely mechanism, which is shown in Scheme 4, involves a base-catalysed E2 elimination of a benzenecarboxylic acid. The Brønsted correlations identified above imply that the amidic proton is *ca.* 50%



Scheme 4 Mechanism of the OH^-- and buffer-catalysed hydrolysis of secondary acyloxymethylbenzamides

transferred to the abstracting base in the transition state. Similar values of the Brønsted β coefficient have been reported for β-elimination reactions involving compounds **13** (R = H), **16** (R = Me or Ph) and **17**.[25]



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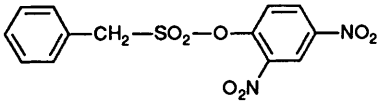

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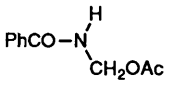
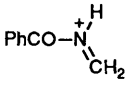
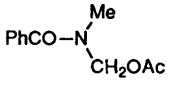
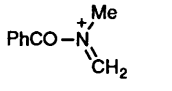
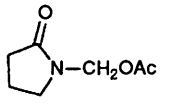
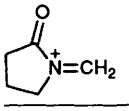
Further evidence that the buffer species act as general-base catalysts is provided by the pH-independence of the catalytic rate constant, k_B, for imidazole catalysis (Table 9) and also the inability to detect any *N*-acylimidazole or *N*-acylmorpholine, both of which would have been observable products if the buffer species acted as nucleophilic catalysts.

The data for the morpholine-catalysed hydrolysis of **11c, k–m** enable the effect of the leaving group on the reaction to be identified; a Hammett ρ value of +1.1 is obtained, which suggests that the C–O bond is extensively broken in the transition state. The data in Table 9 also show that, as expected, electron-withdrawing substituents in the amide ring enhance the reactivity of the substrate. For morpholine, imidazole and phosphate, Hammett ρ values of *ca.* 0.6 (±0.5) are obtained, though for OH^- the corresponding value is 0.3. We are unable to account for this lower value for OH^-, though it is clear from plots such as those in Fig. 5 that the values for k^{OH^-} are less accurate than those for k^B.

Molecular-orbital Calculations.—Our experimental findings clearly demonstrate that acyloxymethylamides **11f–i** undergo spontaneous expulsion of the carboxylate group to form an iminium ion. Since Bundgaard and Nielsen have reported that the cyclic compound **12** does not undergo such a spontaneous reaction,[15] we carried out semiempirical SCF MO calculations using the AM1 program. Table 10 contains heats of formation for secondary, acyclic tertiary and cyclic tertiary amides. For the acyclic compounds both *cisoid* and *transoid* rotamers are included. The ΔH_f values for the iminium ions derived from these compounds are also contained in Table 10. From the data in Table 10 the following observations may be made. First, on thermodynamic grounds, iminium ion formation is equally likely from both *cisoid* and *transoid* rotamers. This observation is important since the cyclic tertiary amide can only adopt a *cisoid* conformation. Secondly, iminium ion formation from tertiary, as opposed to secondary, substrates is favoured by *ca.* 25 kJ mol^{-1}, which is consistent with their greater reactivity. Thirdly, there appears to be no difference energetically between iminium ion formation from acyclic and cyclic tertiary amides. Thus, the reason for the apparent unreactivity of **12** must be sought elsewhere.

Relevance to Pro-drug Chemistry.—In aqueous buffer solutions at physiologically relevant pHs it is clear that *both* acyclic secondary and tertiary acyloxyalkylamides undergo a spontaneous decomposition reaction. The relative facility of this reaction depends on at least three factors: (*i*) the nucleophilicity of the

Table 10 Heats of formation for acyloxyamides and derived iminium ions calculated by AM1

Molecule or ion	ΔH_f/kJ mol^{-1} *cisoid*	ΔH_f/kJ mol^{-1} *transoid*	$\Delta\Delta H_f$/kJ mol^{-1} *cisoid*	$\Delta\Delta H_f$/kJ mol^{-1} *transoid*
	−422.8	−414.0		
			1161.2	1162.0
	738.4	748.0		
	−381.8	−380.9		
			1136.1	1135.6
	754.3	754.7		
	−522.0	−		
			1134.4	—
	612.4	−		

amide moiety, (*ii*) the nucleofugacity of the carboxylate leaving group, and (*iii*) the electronic effect of the nitrogen substituent. It is probable that the nature of the alkyl part of the acyloxyalkyl group also determines the rate of the pH-independent hydrolysis,[1] but we did not examine this here. Enhanced stability is conferred to the parent acyloxyalkyl substrate by including one or more of the following: (*i*) a weakly nucleophilic amide, (*ii*) a carboxylate group with a relatively high pK_a and (*iii*) a nitrogen substituent that is weakly electron donating (or, probably even better, electron withdrawing). If the amide moiety is fixed, since that is the drug of study, then the carboxylate group may be varied to provide the appropriate stability. Conversely, if the carboxylate group must be fixed then the other two factors may be varied appropriately.

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