Acyloxymethyl as a drug protecting group. Part 5.[1] Kinetics and mechanism of the hydrolysis of tertiary *N*-acyloxymethylsulfonamides

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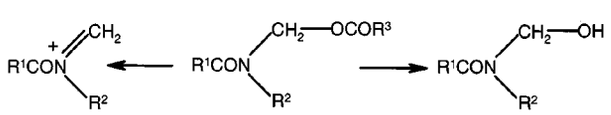
Tertiary acyloxymethylsulfonamides undergo hydrolysis *via* pH-independent and acid- and base-catalysed processes. Reactions are also buffer catalysed for buffer species with pK_a values > *ca.* 10.5. For the pH-independent pathway, hydrolysis takes place *via* formation of an *N*-sulfonyl iminium ion. There is no general-base or nucleophilic catalysis in this region. The mechanism of the acid-catalysed process involves pre-equilibrium protonation of the substrate followed by iminium ion formation. General-acid catalysis is not observed. The base-catalysed pathway involves the normal $B_{Ac}2$ mechanism of ester hydrolysis. The buffer-catalysed reaction gives rise to a curved Brønsted plot, with β values of 1.6 and 0.25 for nucleophiles with pK_a values <12.5 and >13, respectively. This is indicative of nucleophilic catalysis associated with a change in rate-limiting step from formation of the tetrahedral intermediate for buffer species with pK_a > 13 to decomposition of the tetrahedral intermediate for buffer species with pK_a < 12.5.

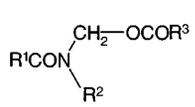
Acyloxymethylsulfonamides have similar reactivity to, and follow similar reaction mechanisms as, the corresponding carboxamide derivatives. Semi-empirical PM3 SCF-MO calculations of the heats of formation, ΔH_f, and atomic charges, q, for acyloxymethyl- and chloromethyl-sulfonamides and amides and their derived iminium ions were performed. These reveal that (1) iminium formation from the sulfonamide series is thermodynamically slightly favoured, and (2) the charge difference at the nitrogen atom, Δq^N, between the neutral molecule and the iminium ion is similar for both sulfonamides and amides.

Tertiary *N*-acyloxymethylamides **1** are of particular interest in drug chemistry because of their potential as prodrugs both of secondary amides and of carboxylic acids.[1–5] These esters display two different modes of decomposition: solvolysis of the ester moiety to generate the corresponding *N*-hydroxymethylamide, which can react further to liberate the secondary amide, and rate-limiting formation of a *N*-acyliminium ion *via* loss of the carboxylate group (Scheme 1). While the first mode



Scheme 1

operates in the HO^--catalysed hydrolysis of **1**, both the H_3O^+-catalysed and pH-independent hydrolysis pathways involve iminium ion formation.[1,4]



1

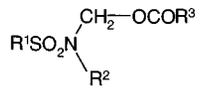
Ester prodrugs **1**, especially those containing electron-donating substituents on nitrogen or carboxylate leaving groups of p$K_a \leq 3$ (*e.g.* benzylpenicillin), hydrolyse very rapidly,[5] making pharmaceutical formulation difficult. We rationalised that replacing the amide moiety by the more powerfully electron-withdrawing sulfonamide group would identify *N*-acyloxymethylsulfonamides, **2**, as prodrugs able to regenerate a carboxylic acid or sulfonamide parent drug at significantly slower hydrolysis rates.

These esters have the potential to act as prodrugs of secondary sulfonamides, especially those that have their therapeutic effectiveness reduced as a result of unfavourable physicochemical properties. For example, sumatriptan **3**, a 5-HT_1 agonist used in the treatment of migraine,[6a] and some non-peptidic inhibitors of human leukocyte elastase, **4**,[6b] exhibit oral absorption problems leading to sub-optimal concentrations of the drugs at their receptor sites.

Unexpectedly, our initial experiments revealed that the rates at which tertiary *N*-acyloxymethyl-*N*-alkylsulfonamides **2** hydrolyse to liberate the carboxylic acid and secondary sulfonamide were similar to the corresponding amide derivatives.[7] Typically, the ratios of the pH-independent rate constants of compounds **1** and **2**, are within the range 1.1–1.3.[7] We now report a more detailed kinetic study of compounds **2a**–**p** that is directed towards clarifying the mechanisms of hydrolysis of tertiary *N*-acyloxymethyl-*N*-alkylsulfonamides. Compounds **2a**–**e** explore the effect of the nitrogen substituent, **2f**–**i** the effect of the arenesulfonyl fragment and **2i**–**p** the effect of the carboxylate group.

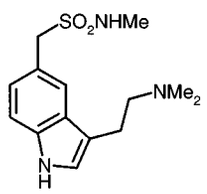
Experimental

Melting points were determined using a Kofler camera Bock-Monoscop M and are uncorrected. IR spectra were recorded using a Nicolet Impact 400 spectrophotometer. UV spectra were recorded using a Shimadzu UV2100 spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ solutions using JEOL JNM-EX 400 and FX90Q spectrometers; chemical shifts are given in ppm relative to Me_4Si and J values are given in Hz. FAB mass spectra were recorded using a VG Mass Lab 25-250 spectrometer. Elemental analyses were obtained from Medac Ltd., Brunel Science Park, Englefield Green, Egham, Surrey, UK, and ITQB, Oeiras, Portugal.



2

	R^1	R^2	R^3		R^1	R^2	R^3
2a	Ph	4-$MeOC_6H_4$	Ph	**2i**	4-$NO_2C_6H_4$	Me	Ph
2b	Ph	4-MeC_6H_4	Ph	**2j**	4-$NO_2C_6H_4$	Me	4-$MeOC_6H_4$
2c	Ph	Ph	Ph	**2k**	4-$NO_2C_6H_4$	Me	4-MeC_6H_4
2d	Ph	4-FC_6H_4	Ph	**2l**	4-$NO_2C_6H_4$	Me	4-$CF_3C_6H_4$
2e	Ph	4-ClC_6H_4	Ph	**2m**	4-$NO_2C_6H_4$	Me	4-CNC_6H_4
2f	4-MeC_6H_4	Me	Ph	**2n**	4-$NO_2C_6H_4$	Me	4- $NO_2C_6H_4$
2g	Ph	Me	Ph	**2o**	4-$NO_2C_6H_4$	Me	4-$ClC_6H_4O(Me)_2C$
2h	4-ClC_6H_4	Me	Ph	**2p**	4-$NO_2C_6H_4$	Me	$CHPr_2$



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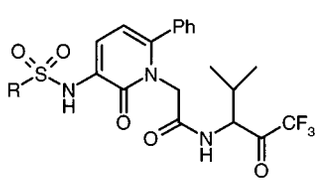


4

Synthesis

N-Aryl-*N*-benzoyloxymethylsulfonamides **2a**–**e** were synthesised by alkylation of the corresponding *N*-arylsulfonamide with chloromethyl benzoate. Typically, sodium hydride (1 mol equiv.) was added to a solution of the appropriate secondary sulfonamide in dry DMF. When liberation of hydrogen was complete this solution was injected slowly into a solution of chloromethyl benzoate (1 mol equiv.) in DMF. When the reaction was complete the solvent was removed under vacuum and the residue was subjected to column chromatography. The synthesis of *N*-alkyl-*N*-benzoyloxymethylsulfonamides **2f**–**p** was achieved by sulfonamidomethylation of the carboxylic acid with the appropriate *N*-alkyl-*N*-chloromethylsulfonamides.[7] The latter were prepared by reacting the corresponding secondary sulfonamide with paraformaldehyde in chlorotrimethylsilane.[8] A solution of the appropriate chloromethylsulfonamide (1.1 mol equiv.) in dry THF was added to a suspension of the sodium carboxylate (1 mol equiv.) in THF at room temperature. Upon completion of the reaction, the solvent was evaporated, and the residue treated with water and extracted with dichloromethane. The organic extracts were washed with water, sodium hydrogen carbonate and dried ($MgSO_4$). Evaporation of the solvent gave the crude ester which was purified by column chromatography.

2a: Mp 71–76 °C; ν_{max}/cm^{-1} 1710, 1365, 1160; δ_H 3.67 (3H, s), 5.82 (2H, s), 6.61–7.74 (14H, m); *m/z* 397 (M^+), 276 ($M - PhCO_2$), 141 ($PhSO_2^+$), 105 ($PhCO^+$). Found: C, 63.1; H, 4.6; N, 3.5%. $C_{21}H_{19}NO_5S$ requires: C, 63.5; H, 4.8; N, 3.5%.

2b: Mp 99–101 °C; ν_{max}/cm^{-1} 1715, 1350, 1160, 930; δ_H 2.29 (3H, s), 5.82 (2H, s), 6.95–7.69 (14H, m); *m/z* 381 (M^+), 260 ($M - PhCO_2$), 141 ($PhSO_2^+$), 105 ($PhCO^+$). Found: C, 66.1; H, 5.0; N, 3.7%. $C_{21}H_{19}NO_4S$ requires: C, 66.1; H, 5.0; N, 3.7%.

2c: Mp 95–98 °C; ν_{max}/cm^{-1} 1725, 1355, 1155; δ_H 5.85 (2H, s), 7.17–7.74 (15H, m); *m/z* 367 (M^+), 246 ($M - PhCO_2$), 141 ($PhSO_2^+$), 105 ($PhCO^+$). Found: C, 65.3; H, 4.7; N, 3.7%. $C_{20}H_{17}NO_4S$ requires: C, 65.4; H, 4.6; N, 3.8%.

2d: Mp 73–76 °C; ν_{max}/cm^{-1} 1718, 1350, 1170; δ_H 5.90 (2H, s), 6.80–7.83 (14H, m); *m/z* 385 (M^+), 264 ($M - PhCO_2$), 141 ($PhSO_2^+$), 105 ($PhCO^+$). Found: C, 62.1; H, 4.3; N, 3.7%. $C_{20}H_{16}FNO_4S$ requires: C, 62.3; H, 4.2; N, 3.6%.

2e: Mp 108–111 °C; ν_{max}/cm^{-1} 1715, 1350, 1160; δ_H 5.77 (2H, s), 7.03–7.66 (14H, m); *m/z* 403/401 (M^+), 282/280 ($M - PhCO_2$), 141 ($PhSO_2^+$), 105 ($PhCO^+$). Found: C, 59.5; H, 4.0; N, 3.5%. $C_{20}H_{16}ClNO_4S$ requires: C, 59.8; H, 4.0; N, 3.5%.

2f: Mp 65–68 °C; ν_{max}/cm^{-1} 1723, 1354, 1170; δ_H 2.37 (3H, s), 2.97 (3H, s), 5.60 (2H, s), 7.07–7.74 (9H, m); *m/z* 198 ($M - PhCO_2$), 155 (4-$MeC_6H_4SO_2^+$), 105 ($PhCO^+$). Found: C, 60.8; H, 5.6; N, 4.4%. $C_{16}H_{17}NO_4S$ requires: C, 60.2; H, 5.3; N, 4.4%.

2g: Mp 69–71 °C; ν_{max}/cm^{-1} 1736, 1345, 1170; δ_H 2.95 (3H, s), 5.60 (2H, s), 7.07–7.88 (10H, m); *m/z* 184 ($M - PhCO_2$), 141 ($PhSO_2^+$), 105 ($PhCO^+$). Found: C, 59.1; H, 5.0; N, 4.6%. $C_{15}H_{15}NO_4S$ requires: C, 59.0; H, 4.9; N, 4.6%.

2h: Mp 89–94 °C; ν_{max}/cm^{-1} 1728, 1350, 1179; δ_H 2.97 (3H, s), 5.57 (2H, s), 7.17–7.77 (9H, m); *m/z* 341/339 (M^+), 220/218 ($M - PhCO_2$), 177/175 (4-$ClC_6H_4SO_2^+$), 105 ($PhCO^+$). Found: C, 52.6; H, 4.3; N, 4.3%. $C_{15}H_{14}ClNO_4S$ requires: C, 53.0; H, 4.1; N, 4.1%.

2i: Mp 162–165 °C; ν_{max}/cm^{-1} 1726, 1354, 1171; δ_H 3.05 (3H, s), 5.62 (2H, s), 7.17–8.12 (9H, m); *m/z* 229 ($M - PhCO_2$), 186 (4-$NO_2C_6H_4SO_2^+$), 105 ($PhCO^+$). Found: C, 52.0; H, 3.9; N, 7.8%. $C_{15}H_{14}N_2O_6S$ requires: C, 51.4; H, 4.0; N, 8.0%.

2j: Mp 144–145 °C; ν_{max}/cm^{-1} 1720, 1360, 1170; δ_H 3.08 (3H, s), 3.85 (3H, s), 5.70 (2H, s), 6.73–7.83 (4H, AA′BB′), 7.93–8.43 (4H, AA′BB′); *m/z* 380 (M^+), 229 (M − 4-$MeOC_6H_4CO_2$), 186 (4-$NO_2C_6H_4SO_2^+$), 135 (4-$MeOC_6H_4CO^+$). Found: C, 50.7; H, 3.8; N, 7.6%. $C_{16}H_{16}N_2O_7S$ requires: C, 50.5; H, 4.2; N, 7.4%.

2k: Mp 137–140 °C; ν_{max}/cm^{-1} 1719, 1349, 1166; δ_H 2.41 (3H, s), 3.10 (3H, s), 5.73 (2H, s), 7.10–7.77 (4H, AA′BB′), 7.97–8.47 (4H, AA′BB′); *m/z* 364 (M^+), 229 (M − 4-$MeC_6H_4CO_2$), 186 (4-$NO_2C_6H_4SO_2^+$), 119 (4-$MeC_6H_4CO^+$). Found: C, 52.7; H, 4.5; N, 7.7%. $C_{16}H_{16}N_2O_6S$ requires: C, 52.7; H, 4.4; N, 7.7%.

2l: Mp 167–170 °C; ν_{max}/cm^{-1} 1727, 1382, 1177; δ_H 3.07 (3H, s), 5.77 (2H, s), 7.60–8.50 (8H, m); *m/z* 399 ($M - F$), 229 (M − 4-$CF_3C_6H_4CO_2$), 186 (4-$NO_2C_6H_4SO_2^+$), 173 (4-$CF_3C_6H_4CO^+$). Found: C, 45.9; H, 2.9; N, 6.7%. $C_{16}H_{13}F_3N_2O_6S$ requires: C, 45.9; H, 3.1; N, 6.7%.

2m: Mp 203–210 °C (decomp.); ν_{max}/cm^{-1} 2219, 1723, 1381, 1177; δ_H (d_6-DMSO) 3.10 (3H, s), 5.73 (2H, s), 7.80–8.47 (8H, m); *m/z* 375 (M^+), 229 (M − 4-$CNC_6H_4CO_2$), 186 (4-$NO_2C_6H_4SO_2^+$). Found: C, 51.2; H, 3.4; N, 11.1%. $C_{16}H_{13}N_3O_6S$ requires: C, 51.2; H, 3.5; N, 11.2%.

2n: Mp 172–173.5 °C; ν_{max}/cm^{-1} 1734, 1382, 1177; δ_H 3.13 (3H, s), 5.80 (2H, s), 7.83–8.53 (8H, m); *m/z* 229 (M − 4-$NO_2C_6H_4CO_2$), 186 (4-$NO_2C_6H_4SO_2^+$), 150 (4-$NO_2C_6H_4CO^+$). Found: C, 45.8; H, 3.3; N, 9.2%. $C_{15}H_{13}N_3O_8S$ requires: C, 45.6; H, 3.3; N, 10.6%.

2o: Mp 121–122 °C; ν_{max}/cm^{-1} 1749, 1361, 1176; δ_H 1.42 (6H, s), 2.84 (3H, s), 5.58 (2H, s), 6.58–7.16 (4H, AA′BB′), 7.95–8.26 (4H, AA′BB′); *m/z* 442 (M^+), 229 (M − 4-$ClC_6H_40OC(Me)_2CO_2$), 186 (4-$NO_2C_6H_4SO_2^+$), 169 (4-$ClC_6H_4OC(Me)_2^+$). Found: C, 48.8; H, 4.3; N, 6.3%. $C_{18}H_{19}Cl\,N_2O_7S$ requires: C, 48.8; H, 4.3; N, 6.3%.

2p: Mp 62–64 °C; ν_{max}/cm^{-1} 1749, 1361, 1177; δ_H 0.79 (6H, t,

$J = 7.5$), 1.09 (4H, sextet, $J = 7.5$), 1.20–1.43 (4H, m), 2.12 (1H, tt, $J = 6.0, 9.0$), 2.95 (3H, s), 5.49 (2H, s), 8.07–8.40 (4H, AA′BB′); *m/z* 372 (M^+), 229 ($M - Pr_2CHCO_2$), 186 ($4\text{-}NO_2C_6H_4SO_2^+$). Found: C, 51.8; H, 7.2; N, 7.5%. $C_{16}H_{24}N_2O_6S$ requires: C, 51.6; H, 6.5; N, 7.5%.

Product analysis

Products were identified by HPLC by comparison with standards. In selected cases, large scale reactions were carried out and the corresponding products isolated and identified by ^{1}H-NMR. In all cases, the products were the secondary sulfonamide and carboxylic acid.

Kinetics

Hydrolyses were monitored using both UV spectroscopy and HPLC. In the UV method, reactions were initiated by addition of a 10–15 mm^3 aliquot of a 10^{-2} mol dm^{-3} stock solution of substrate in acetonitrile to thermostatted UV cuvettes containing 3 cm^3 of the required buffer solution comprising 10% (v/v) of acetonitrile. Ionic strength was maintained at 0.5 mol dm^{-3} with $NaClO_4$. The reactions were monitored at fixed wavelength by following the decrease in absorbance, and the pseudo-first-order rate constants, k_{obs}, were determined from plots of ln $(A_t - A_\infty)$ *versus* time. Alternatively, reactions were monitored using HPLC, following either the loss of substrate or the formation of products. Reactions were initiated by injecting *ca.* 50 mm^3 of the appropriate substrate stock solution (10^{-3} mol dm^{-3}) to 5 cm^3 of the buffer solution. At regular intervals, samples of the reaction mixture were analysed using a system involving a Merck LiChrospher® RP-8 5 μm 125 × 4 mm column, an isochratic mobile phase comprising acetonitrile–0.2 mol dm^{-3} pH 4.0 sodium acetate buffer (varying from 55 : 45 to 70 : 30 depending on the substrate), and a flow rate of 1.0 cm^3 min^{-1}. Quantitation was obtained by comparison with standards analysed under identical conditions. Good agreement (±5%) between the rate constants determined by both UV and HPLC methods was obtained.

SCF-MO calculations

These were carried out using the PM3 procedure from the GAMESS suite of programs.[9] All structures underwent an initial geometry optimization using the MM2 force field program. Complete geometry optimization (bond lengths, bond angles and dihedral angles) was achieved using the Broyden–Fletcher–Goldfarb–Shanno formulation.[10]

Results and discussion

Kinetic data and pH–rate profiles

The influence of pH on the rates of hydrolysis of compounds **2a**, **c**, **g** and **h** is shown in Fig. 1. These pH–rate profiles are marked by a broad U-shape indicative of the presence of acid-catalysed, k_{H^+}, base-catalysed, k_{HO^-}, and pH-independent, k_o, processes, corresponding to eqn. (1). Similar pH–rate profiles

$$k_{obs} = k_o + k_{H^+}[H^+] + k_{OH^-}[OH^-] \quad (1)$$

have been previously described for the closely related tertiary *N*-acyloxymethylbenzamides **1**.[1,4]

The rate constant for the pH-independent process, k_o, was determined from the pH–rate profile, while the catalytic second-order rate constants k_{H^+} and k_{OH^-} were obtained from the plots of k_{obs} *versus* $[H^+]$ (*e.g.* Fig. 2) and $[OH^-]$ (*e.g.* Fig. 3), respectively. The intercepts of these plots were identical to the pH-independent rate constant, k_o, obtained from the pH–rate profile. Values of k_o, k_{H^+} and k_{OH^-} for the esters **2a**–**p** are listed in Table 1.

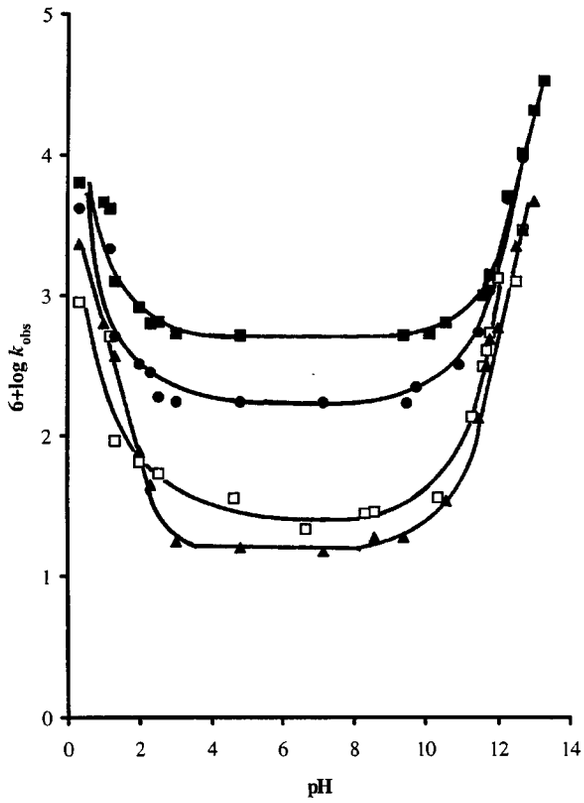


Fig. 1 pH–Rate profiles for compounds **2a** (□), **2c** (▲), **2g** (■) and **2h** (●) at 25 °C, in aqueous buffers containing 10% (v/v) of acetonitrile.

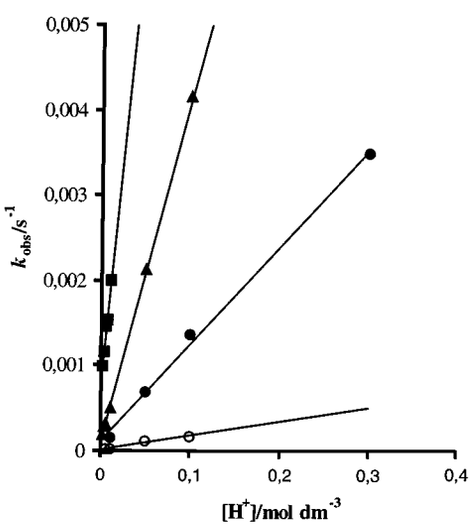


Fig. 2 Variation of pseudo-first-order rate constants, k_{obs}, with $[H^+]$ for compounds **2e** (○), **2f**, (■), **2h** (▲) and **2p** (●) at 25 °C.

The pH-independent pathway

Both the extension of the plateau in the pH–rate profile and the pH-independent pathway rate constant, k_o, are clearly dependent on the polar effect of the nitrogen substituent in compounds **2** (Fig. 1 and Table 1). Thus, the plateau for the *N*-methyl derivative, **2g**, extends over a range of *ca.* 8 pH units, whereas for the *N*-phenyl derivative, **2c**, the plateau extends over a range of *ca.* 6 pH units. This reflects the effect of the *N*-substituent upon the rate of the pH-independent reaction relative to those of the acid- and base-catalysed processes.

The possible pH-independent hydrolysis mechanisms are outlined in structure **A**. Of these, path (*a*) would be expected to be independent of, or slightly retarded by, electron-donating substituents in the arenesulfonamide and *N*-aryl rings, path (*b*) should be enhanced by electron-withdrawing substituents in the

Table 1 Pseudo-first-order rate constants, k_o, for the pH-independent, and second-order rate constants, k_{H^+} and k_{OH^-}, for the acid- and base-catalysed hydrolyses of acyloxymethylsulfonamides **2** at 25 °C

Compound	$k_o/10^{-5}$ s^{-1}	$k_{H^+}/10^{-2}$ dm^3 mol^{-1} s^{-1}	$k_{OH^-}/10^{-2}$ dm^3 mol^{-1} s^{-1}
2a	2.36	0.883	4.44
2b	2.45	1.03	5.53
2c	1.70; 1.61[a] 2.63,[b] 4.85,[c] 7.85,[d] 14.6,[e] 23.5,[f] 77.8[g]	0.455; 0.705[a] 1.13,[b] 1.78,[c], 2.67[d]	6.69; 8.72[a] 11.0,[b] 19.5,[c] 23.0[d]
2d	0.827	0.373	5.92
2e	0.526	0.169	7.66
2f	87.0	11.0	10.3
2g	51.8	7.34	12.2
2h	17.5; 15.4[a]	4.01; 4.32[a]	12.3; 31.3[a]
2i	1.82	0.510	21.2
2j	0.900	0.458	4.50
2k	1.40, 0.73,[h] 2.64,[b] 4.19[c]	0.552, 0.316,[h] 0.927,[b] 2.29[c]	7.33 5.52,[h] 12.7,[b] 17.6[c]
2l	8.68	0.401	133
2m	19.4	0.527	253
2n	24.2	0.479	512
2o	9.72	0.886	29.2
2p	0.118	1.14	0.547

[a] In D_2O. [b] 30 °C. [c] 35 °C. [d] 40 °C. [e] 45 °C. [f] 50 °C. [g] 60 °C. [h] 20 °C.

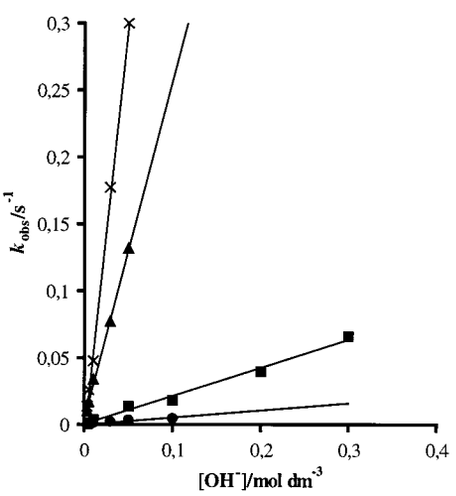
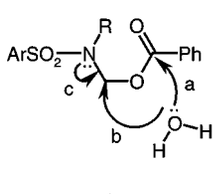


Fig. 3 Variation of pseudo-first-order rate constants, k_{obs}, with [HO$^-$] for compounds **2c** (●), **2i**, (■), **2m** (▲) and **2n** (×) at 25 °C.



A

arenesulfonamide and *N*-aryl rings, and path (*c*) should be enhanced by electron-donating substituents in the arenesulfonamide ring and in the *N*-aryl ring.

For compounds **2f**–**i**, corresponding to a substituent effect in the arenesulfonamide ring, a Hammett plot (Fig. 4) yields a ρ value of −1.80 ($r^2 = 1.0$). For the *N*-aryl derivatives, **2a**–**e**, a Hammett correlation was possible only using the normalised σ° parameters, giving a ρ value of −1.61 ($r^2 = 0.99$) (Fig. 4). These are consistent with path (*c*) above, that is, the mechanism presented in Scheme 2 in which the developing positive charge is stabilised by electron-donating substituents. Interestingly, the ρ value obtained for the arenesulfonamide substituents is of comparable magnitude to that (−1.6) reported for the aroyl substituents in the corresponding reaction of tertiary *N*-aroyloxymethylbenzamides **1**.[4] This would imply that that the sulfonamidomethyl moiety has the same ability to stabilise the incipient carbocation as the amidomethyl moiety (see below).

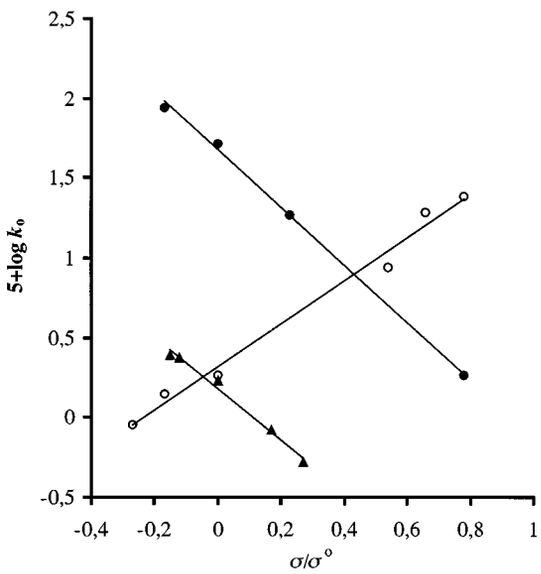
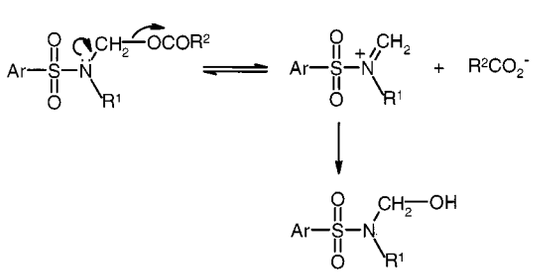


Fig. 4 Hammett plots for the pH-independent hydrolysis of **2a**–**e** (▲), **2f**–**i** (●) and **2i**–**p** (○), at 25 °C.



Scheme 2

Further evidence in support of an S_N1-type mechanism for the pH-independent hydrolysis of acyloxymethylsulfonamides **2** is provided by the following observations. First, the temperature dependence of the solvolysis reaction for compounds **2c** and **2k** (Table 1) yields values of (−43 ± 1) and (−50 ± 2) J K^{-1} mol^{-1}, respectively, for $\Delta S^\ddagger$. These values, though negative, are within the range observed for other unimolecular ionisation reactions studied in aqueous buffers containing organic solvents.[11] S_N2 reactions similar to path (*b*) in **A** above commonly have $\Delta S^\ddagger$ values for mixed aqueous-organic solvents in the

Table 2 Dependence of the pseudo-first-order rate constants, k_{obs}, on the buffer concentration for the hydrolysis of **2a** and **2h** at 25 °C

Compound	Buffer	pH	[Buffer]$_{tot}$/ 10^{-2} mol dm^{-3}	k_{obs}/ 10^{-5} s^{-1}
2a	$MeCO_2H$	4.83	0.10	2.78
			0.20	3.71
			0.50	2.76
	$H_2PO_4^-$	7.15	0.02	2.17
			0.04	3.00
			0.10	2.42
2h	$ClCH_2CO_2H$	2.20	0.05	38.6
			0.10	41.4
			0.30	40.6
			0.50	33.4
	$(CF_3)_2CHOH$	9.45	0.01	24.5
			0.03	22.6
			0.05	22.0
			0.10	21.7
	Pr^nNH_2	10.83	0.01	29.6
			0.03	29.8
			0.05	29.3
			0.10	27.8
	CF_3CH_2OH	11.19	0.01	48.0
			0.03	72.2
			0.05	104
			0.07	155
		11.63	0.01	104
			0.03	200
			0.05	293
			0.07	363
	$HC{\equiv}CCH_2OH$	11.53	0.01	66.7
			0.03	101
			0.05	148
			0.07	237
		11.79	0.01	110
			0.03	268
			0.05	491
			0.07	622

region of -100 J K^{-1} mol^{-1}.[11] Values of $\Delta S^{\ddagger}$ for both S_N1 and S_N2 reactions are more positive in purely aqueous systems[11] and we have previously reported a $\Delta S^{\ddagger}$ of (29 ± 2) J K^{-1} mol^{-1} in aqueous buffers for the corresponding reaction of **2** (R^1 = 4-tol, R^2 = Pr, R^3 = Ph).[7] Second, the solvent isotope effect, k_o^H/k_o^D, of *ca.* 1.1 obtained for **2c** and **2h** (Table 1), is similar to those reported for typical ionisation reactions,[12,13] though it is also consistent with the S_N2 substitution, path (*b*). Third, no general-base or nucleophilic catalysis by the buffer species was observed (Table 2), in contrast to the general-base catalysis normally associated the pH-independent hydrolysis of simple alkyl esters.[14] Fourth, k_o values for the sulfonamidomethyl esters **2i**–**p** (Table 1) display a high dependence on the pK_a of the carboxylate leaving group, with a Brønsted β_{lg} value of -1.33 (r^2 = 0.97) (Fig. 5). Significantly, this correlation includes compounds **2o**,**p** which contain sterically hindered carboxylate groups. A similar β_{lg} value of *ca.* -1 was reported previously the esters **1**, which also included highly hindered carboxylic acid moieties.[1,5] For the pH-independent hydrolysis of RCO_2CH_2OMe, for which a S_N1 mechanism has been suggested,[15] a β_{lg} of *ca.* -0.8 for the carboxylate leaving group can be calculated.

The acid-catalysed pathway

Using the k_{H^+} values in Table 1 the following observations may be made. First, the acid-catalysed pathway is also sensitive to the electronic effects of the substituents in the arenesulfonamide and *N*-aryl rings. Hammett plots (Fig. 6) for the acid-catalysed hydrolysis of esters **2a**–**e** (again using σ°) and **2f**–**i** give rise to ρ values of -1.68 (r^2 = 0.94) and -1.43 (R^2 = 0.99), respectively. These values are similar to those for the pH-independent solvolysis and indicate development of positive charge in the sulfonamide group in the transition state. In contrast, the Hammett plot for the esters **2i**–**n** (Fig. 6) gives rise to a ρ value of almost zero. Second, the solvent isotope effects, k_{H^+}/k_{D^+} for the acid-catalysed decomposition of **2c** and **2h** are 0.6 and 0.9, respectively. Third, the temperature dependence of the reaction for compounds **2c** and **2k** gives rise to values of $\Delta S^{\ddagger}$ of (4 ± 3) and (28 ± 4) J K^{-1} mol^{-1}, respectively. Furthermore, no general-acid-catalysed hydrolysis is observed (Table 2).

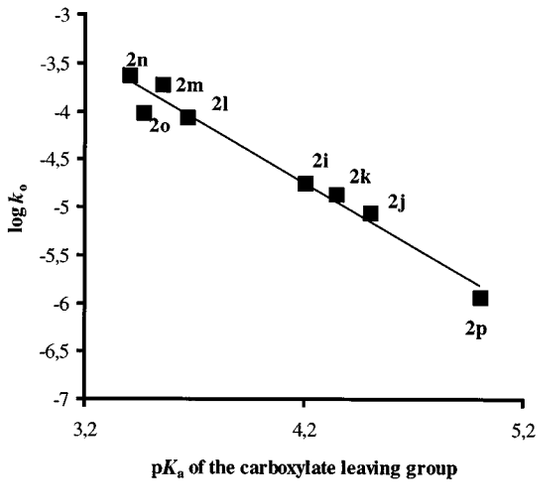


Fig. 5 Brønsted plot for the pH-independent hydrolysis of **2i**–**p** at 25 °C.

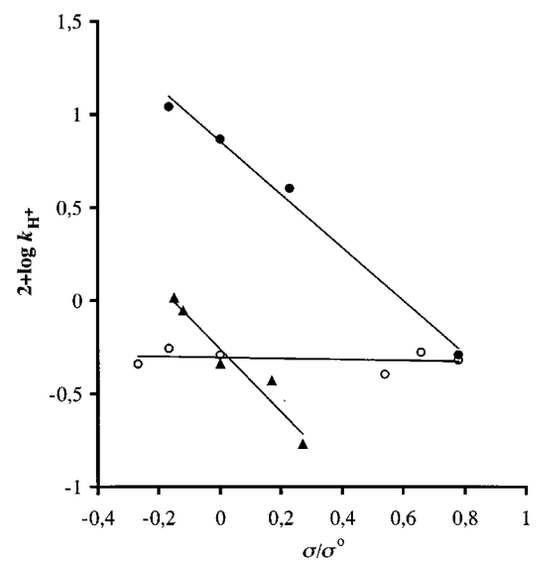
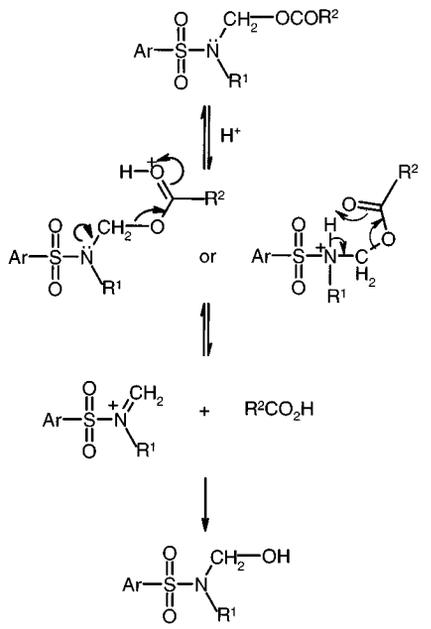


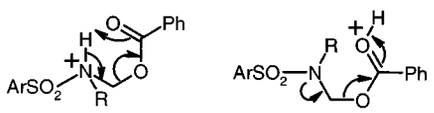
Fig. 6 Hammett plots for the acid-catalysed hydrolysis of **2a**–**e** (▲), **2f**–**i** (●) and **2i**–**p** (○), at 25 °C.

These data provide strong support for a dissociative mechanism for the acid-catalysed hydrolysis of esters **2**, identical to that for the pH-independent pathway, other than an extra step involving protonation of the substrate prior to iminium ion formation (Scheme 3). From our results it is not possible to ascertain the exact site of protonation—the sulfonamide oxygen, the sulfonamide nitrogen or the carbonyl oxygen atom. Sulfonamides are known to be very weak bases, with H_o values at half-neutralisation ranging from -5.0 to -6.0 depending on the measurement procedure.[16] *N*-Arylsulfonamides are much less basic than their *N*-alkyl counterparts, with estimated H_o values $\leqslant 8$.[16] ^{1}H-NMR studies of secondary[17] and tertiary sulfonamides[18] in fluorosulfonic acid point to the most likely site of protonation as the nitrogen, and not the oxygen, atom. Esters are also very weak bases, with pK_a ranging from *ca.* -6.5 to -7.5.[19] Thus, the two possible protonated species derived from **2** are **B** and **C**.

The ρ values for the acid-catalysed pathway are derived from



Scheme 3



B **C**

a combination of the ρ for protonation and that for the decomposition of the protonated species. Protonation of compounds **2** to give the intermediate **B** would be expected to be enhanced by electron-donating substituents in the arenesulfonamide and *N*-aryl groups, whereas decomposition of **B** would not be expected to greatly affected by such substituents since, on going from **B** to the sulfonyliminium ion, a significant proportion of the positive charge would remain on the *N*-atom. Conversely, if hydrolysis were to proceed *via* **C**, then substituents in the arenesulfonamide and *N*-aryl moieties would be expected to have little effect on the protonation and the final ρ value would be expected to reflect the dissociation step. The ρ values of −1.71 and −1.43 observed for **2a**–**e** and **2f**–**i**, respectively, are consistent with either species, though their almost identical values to those for the corresponding pH-independent reaction might suggest **C** as the protonated species (though not unambiguously so). Unfortunately, the substituent effect in the ester group is even less informative. The protonation step leading to **B** would not be expected to be affected by substituents in the ester group, nor would the decomposition of **B** (as one oxygen acts as electron-acceptor and the other acts as electron-donor), resulting in an overall ρ of *ca.* zero, as observed. An identical outcome would be expected for **C**, as ρ values for the protonation and decomposition steps are likely to be of similar magnitude but opposite sign. In contrast, the solvent isotope effect of *ca.* 0.8 is somewhat higher than the value of *ca.* 0.4 usually found for typical fast pre-equilibrium processes,[12] and may be an argument in favour of the formation of species **B**, followed by a rate-limiting intramolecular proton transfer from nitrogen to the carbonyl oxygen. Such rate-limiting proton transfer is likely given that the difference in the pK_a values of the proton donor and acceptor is small.[20] Whichever protonated species is involved we are led to conclude that the acid-catalysed hydrolysis of **2** occurs *via* an $A_{Al}1$ mechanism involving formation of a sulfonyliminium ion (Scheme 3).

Interestingly, the acid-catalysed hydrolysis of aryloxyethyl propanoates[21] (**5**, R^1 = Et, R^2 = Me) and the hydrolysis of aryloxymethyl acetates (**5**, R^1 = Me, R^2 = H) in concentrated

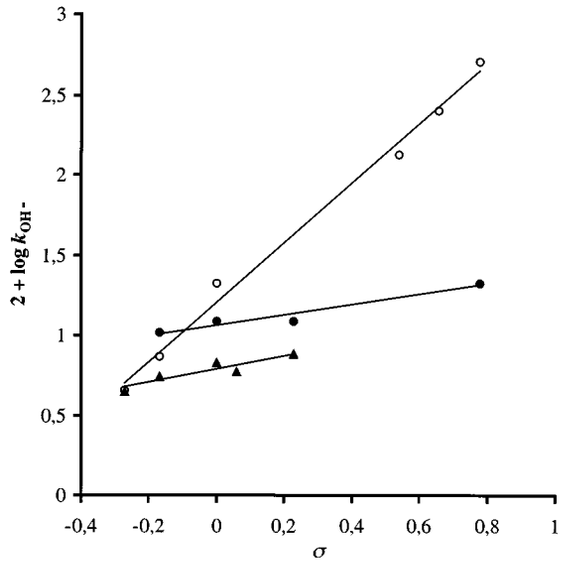
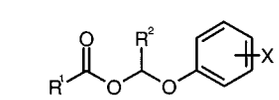
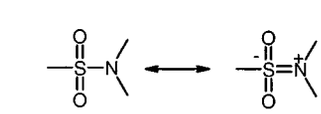


Fig. 7 Hammett plots for the base-catalysed hydrolysis of **2a**–**e** (▲), **2f**–**i** (●) and **2i**–**p** (○), at 25 °C.

sulfuric acid[22] yield Hammett ρ values of −2.07 and −3.06, respectively. These values also are consistent with an $A_{Al}1$ mechanism, involving the formation and subsequent decomposition of a carbonyl oxygen protonated intermediate. The differing magnitudes of the ρ values have been ascribed to the additional inductive stabilisation of the incipient carbocation by the α-methyl, R^2, group in **5**. These values are somewhat more negative than the ρ value of −1.71 obtained here for *N*-aryl substitued compounds **2a**–**e**, which may indicate that, if reaction procedes *via* the protonated form **C**, the nitrogen lone pair in **2** is more efficient in stabilising the incipient carbocation than the phenolic oxygen in **5**, despite the similar pK_a values of the parent *N*-arylsulfonamides and phenols.[16] This would suggest that N→S delocalisation of electrons (*i.e.* **6**↔**7**) for compounds **2** is less important than anticipated.[16]



5



6 **7**

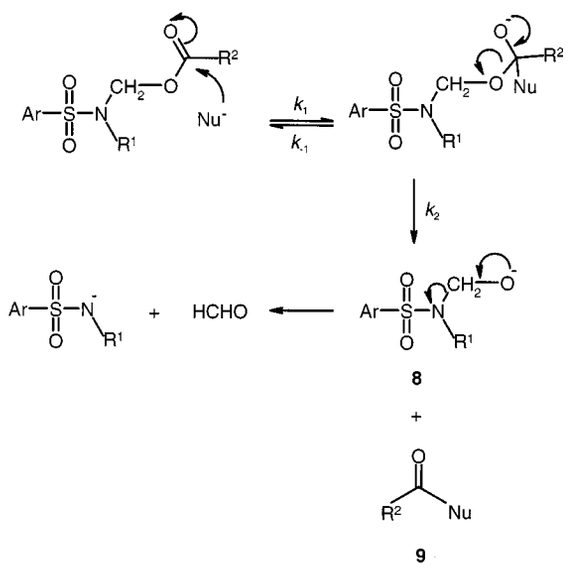
Base- and buffer-catalysed pathways

In the base-catalysed region, the values of k_{OH^-} for series **2a**–**e**, **2f**–**i** and **2i**–**n** (Table 1) define linear Hammett plots with ρ values of 0.42 (r^2 = 0.86), 0.32 (r^2 = 0.95) and 1.86 (r^2 = 0.99), respectively (Fig. 7). Thus, the rate of HO^--promoted hydrolysis increases with the electron-withdrawing ability of the substituents on the arenesulfonamide, *N*-aryl and benzoate groups, indicative of negative charge development in the transition state. The change in sign of the Hammett ρ value for the series **2a**–**e** and **2f**–**i**, as compared with the corresponding ρ values for the acid-catalysed and pH-independent pathways, points to a change in mechanism. The low magnitude of the ρ values for the arenesulfonamide and *N*-aryl groups implies that they are remote from the reaction centre and are consistent with a $B_{Ac}2$ mechanism (Scheme 4, Nu = HO). Similar ρ values (0.36 and 0.42) have been reported for the $B_{Ac}2$-type hydrolysis of compounds **5**.[21,22] In contrast, the ρ value for substituents in the benzoate group is much closer to the value of *ca.* 2.2

Table 3 Second-order rate constants, k_B, for the buffer-catalysed hydrolysis of **2h** at 25 °C

Buffer	pK_a[a]	$k_B/10^{-2}$ dm^3 mol^{-1} s^{-1}
Propylamine	10.69	0
Triethylamine	10.87	0.131
Piperidine	11.28	0.513
Pyrrolidine	11.46	1.58
Trifluoroethanol	12.27	26.0
Propargyl alcohol	13.39	271
Chloroethanol	14.15	446
Hydroxide	15.59	12.3

[a] Corrected for $I = 0.5$ mol dm^{-3}.



Scheme 4

reported for the alkaline hydrolysis of benzoate esters in aqueous acetone and aqueous methanol.[23] For compounds **2c** and **2h**, the solvent isotope effects, k^{OH^-}/k^{OD^-}, are 0.8 and 0.4 (Table 1), respectively, and the $\Delta S^{\ddagger}$ values are (-53 ± 3) and (-72 ± 2) J K^{-1} mol^{-1}, respectively, consistent with the $B_{Ac}2$ mechanism depicted in Scheme 4.

In the pH region where the reactions are HO^--catalysed, buffer catalysis is also observed (Table 2). The pseudo-second-order rate constants, k_B', obtained from plots of k_{obs} *vs.* $[buffer]_t$, where $[buffer]_t$ is the total buffer concentration, are proportional to the fraction of the free base form of the buffer, f_b. Second-order rate constants, k_B, for the buffer-catalysed reaction of **2h** were calculated from the relationship $k_B = k_B'/f_b$ and are contained in Table 3. The Brønsted plot of these data (Fig. 8) is curved. Such plots are characteristic of nucleophilic catalysis of ester hydrolysis involving a change in rate limiting step (Scheme 4).[24] According to this Scheme, the data may be analysed using eqn. (2),[24] where β_1 and β_2 are, respectively, the

$$\log(k_B/k_B^{\circ}) = \beta_2(pK_a - pK_a^{\circ}) - \log\{[1 + 10^{(\beta_2 - \beta_1)(pK_a - pK_a^{\circ})}]/2\} \quad (2)$$

Brønsted exponents of the right- and left-hand branches of the plot, pK_a° is the pK_a of a (theoretical) nucleophile for which $k_{-1} = k_2$ and k_B° is the corresponding rate constant for such a nucleophilic catalyst. The solid line in Fig. 8 is obtained using $\beta_1 = 0.25$, $\beta_2 = 1.6$, $k_B^{\circ} = 1$ dm^3 mol^{-1} s^{-1} and $pK_a^{\circ} = 12.8$.

For nucleophiles on the left-hand branch of the plot $k_{-1} > k_2$ and step k_2 is rate limiting; the value for β of 1.6 is large, but a value of 1.3 has been reported for the nucleophile-catalysed hydrolysis of methyl phenyl carbonate.[25] For nucleophiles on the right-hand branch of the plot $k_{-1} < k_2$ and step k_1 is rate

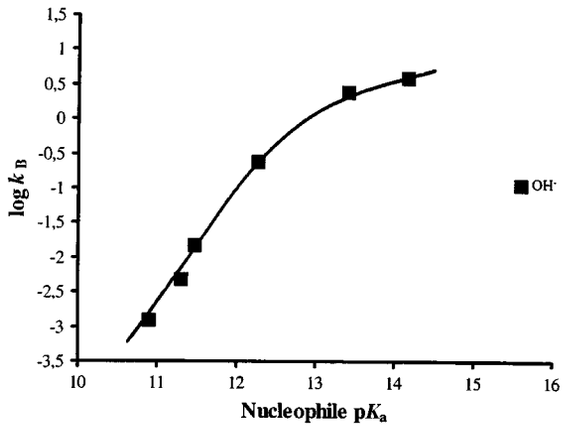


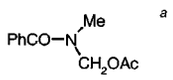
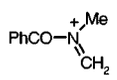
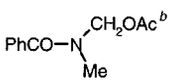
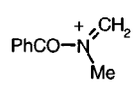
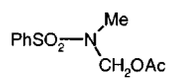
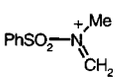
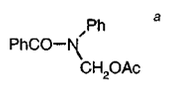
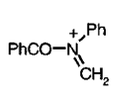
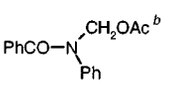
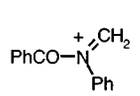
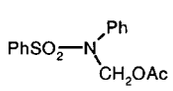
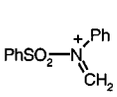
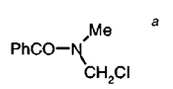
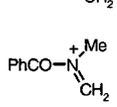
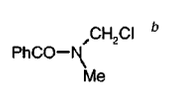
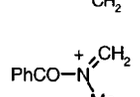
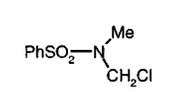
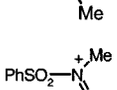
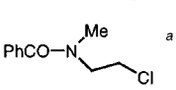
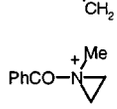
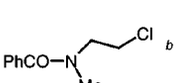
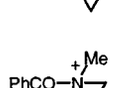
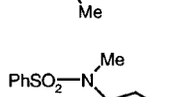
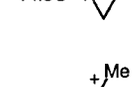
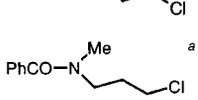
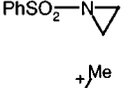
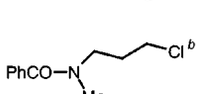
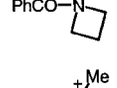
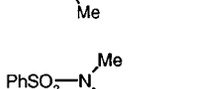
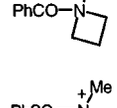
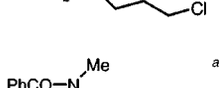
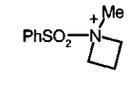
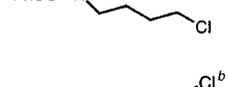
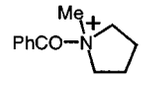
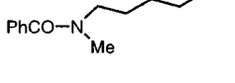
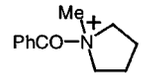
Fig. 8 Brønsted plot for the buffer-catalysed hydrolysis of **2h** at 25 °C.

limiting; the β value of 0.25 is similar to those reported for ester and carbonate hydrolyses.[26] The curvature between the two branches is centred on pK_a°, the pK_a value at which the leaving group ability of the nucleophile and the sulfonamidemethanol, **8**, are equal. The pK_a of **8** can be calculated to be *ca.* 12.9.[27] Similar calculation of the pK_a of $PhCONHCH_2OH$ yields a value of 13.5; this is *ca.* 0.4 units larger than the experimentally observed value of 13.1.[28] Thus, the pK_a of **8** is likely to be in the range 12.5–12.9, in excellent agreement with the pK_a° of 12.8 determined experimentally despite the diverse structures of the nucleophiles employed. It is clear that the value for HO^- lies well away from the Brønsted curve, being much less reactive than anticipated from the other nucleophiles. This effect has been reported previously, for example in the hydrolysis of 4-nitrophenyl acetate.[29]

Molecular orbital calculations

One of the outcomes of the present and previous[4] work is the similar reactivity and susceptibility to substituent effects displayed by the acyloxymethylsulfonamides **2** and their amide counterparts **1**. To gain further insight into these structural effects on reactivity, semi-empirical SCF-MO calculations were carried out using the PM3 program. Atomic charges, q, and heats of formation, ΔH_f, for the fully geometry optimised structures of acyloxymethylsulfonamides, chloromethylsulfonamides, and their amide counterparts, together with the differences, Δq and $\Delta\Delta H_f$, between each molecule and its corresponding iminium ion, are contained in Table 4. For comparison, similar calculations were performed for *N*-(2-chloroethyl)-, *N*-(3-chloropropyl)-, and *N*-(4-chlorobutyl)-sulfonamides, their amide counterparts and their cyclisation products. From these data the following observations are worthy of note. First, iminium ion formation is slightly favoured (lower $\Delta\Delta H_f$) from the sulfonamide derivatives by *ca.* 0.5–10 kJ mol^{-1} as compared with the analogous amides. Second, iminium ion formation from *N*-methyl compounds is favoured compared with the *N*-phenyl compounds, consistent with the pattern of reactivity observed experimentally. Third, the enhanced reactivity of sulfonamides over amides is evident only for the acyloxymethyl and chloromethyl compounds. When the leaving group is more than one carbon atom away from the sulfonamide or amide nitrogen atom amides are predicted to be more reactive than sulfonamides. Fourth, the change in charge density at the *N*-atom (the *N* becomes more positive) upon formation of the iminium ion (from acyloxy- and chloromethyl substrates), as well as the cyclic ammonium ions (from ω-chloroalkyl systems) is almost the same for sulfonamides as for amides. The corresponding changes at the sulfonyl *S*- or carbonyl *C*- atoms are very small. This would imply that a sulfonamide *N*-atom is able to interact with the incipient sp^2 carbocationic centre of the iminium ion (and also the sp^3

Table 4 PM3 SCF-MO calculated heats of formation, ΔH_f, and atomic charges, $q^{S/C}$ and q^N, for acyloxymethylsulfonamides, chloroalkylsulfonamides, acyloxymethylamides, and chloroalkylamides, and $\Delta\Delta H_f$, $\Delta q^{S/C}$ and Δq^N for the formation of the derived cations

Molecule	ΔH_f/kJ mol^{-1}	$q^{S/C}$	q^N	Ion	$\Delta\Delta H_f$/kJ mol^{-1} [c]	$\Delta q^{S/C}$	Δq^N
 [a]	−419.2	0.318	−0.076		1145.2	0.006	0.392
 [b]	−417.6	0.317	−0.099		1143.1	0.002	0.368
	−525.5	2.274	−0.528		1131.8	0.092	0.341
 [a]	−272.9				1155.9		
 [b]	−280.1				1164.4		
	−387.1				1155.4		
 [a]	−92.9	0.314	−0.068		818.8	0.007	0.361
 [b]	−92.5	0.315	−0.067		818.0	0.005	0.359
	−202.9	2.270	−0.515		809.2	0.096	0.328
 [a]	−106.2	0.307	−0.069		881.6	0.011	0.358
 [b]	−106.3	0.306	−0.061		881.7	0.012	0.350
	−217.0	2.250	−0.507		880.4	0.109	0.317
 [a]	−129.6	0.305	−0.066		805.6	−0.010	0.423
 [b]	−131.2	0.307	−0.063		807.3	−0.012	0.420
	−240.6	2.240	−0.498		823.5	0.095	0.382
 [a]	−153.2	0.304	−0.067		754.4	−0.017	0.477
 [b]	−152.3	0.308	−0.064		753.5	−0.021	0.474
	−264.5	2.236	−0.498		778.7	0.092	0.441

[a] *Transoid* rotamer; [b] *Cisoid* rotamer (*cisoid* and *transoid* designate the stereochemical relationship between the carbonyl oxygen and the N–CH_2 group. [c] $\Delta\Delta H_f = \Delta H_f$ (iminium ion) − ΔH_f (molecule).

carbon of the ω-chloroalkyl systems) to the same extent as an amide *N*-atom. Interestingly, a similar conclusion may be made for the ability of the sulfonamide group to interact with the sp^2 centre of an aromatic system through comparison of the Hammett σ_p values[30] for the substituents $N(R^1)SO_2R^2$ and $N(R^1)COR^2$; 0.00 *vs*. 0.03 for $NHCOMe/NHSO_2Me$; −0.07 *vs*. −0.01 for $NHCOPh/NHSO_2Ph$; 0.26 *vs*. 0.24 for $N(Me)COMe/N(Me)SO_2Me$; 0.27 *vs*. 0.39 for $NHCOCF_3/NHSO_2CF_3$; and 0.39 *vs.* 0.44 for $N(Me)COCF_3/N(Me)SO_2CF_3$. Thus, it can be concluded that sulfonamides and amides directly linked to an aromatic ring exert essentially the same electronic effect. This suggests that delocalisation of the sulfonamide nitrogen lone pair to an adjacent sp^2 hybridised carbon is more efficient than N→S delocalisation.

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