Hydrolysis of aryl *N*-methyl-*N*-arylsulfonylcarbamates

M. Eduarda M. Araújo,[a] Margarida Campelo,[a,b] Jim Iley *[c] and Fátima Norberto *[a,b]

[a] *Departamento de Química e Bioquímica, CECUL, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal*
[b] *CECF, Faculdade de Farmácia, Universidade de Lisboa, Avenida das Forças Armadas, 1649-109 Lisboa, Portugal*
[c] *Chemistry Department, The Open University, Milton Keynes, UK MK7 6AA*

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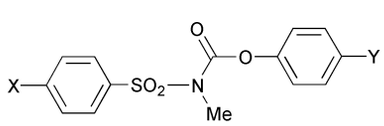
Tertiary sulfonylcarbamates **1** were prepared by reaction of a sulfonamide anion with aryl chloroformates. These previously unreported compounds hydrolyse in aqueous media to the parent sulfonamide and phenol. The pH–rate profile shows both spontaneous and base-catalysed processes. The reaction is also catalysed by buffers. Kinetic data for the hydrolysis of these compounds by HO^- are best interpreted in terms of a mechanism involving rate-limiting formation of a tetrahedral intermediate from nucleophilic attack of hydroxide ion at the carbamate carbonyl carbon atom. For the 4-nitrophenylsulfonyl compound **1h** decomposition of the tetrahedral intermediate appears to be rate-limiting with the sulfonamide anion, rather than the phenoxide, functioning as the leaving group. The buffer-catalysed process is consistent with general base-catalysed attack of water at the carbamate carbonyl carbon atom.

Carbamates have a range of interesting pesticidal and anti-fungal activities,[1] and their chemistry in aqueous media has been well studied.[2] Thus, secondary carbamates hydrolyse *via* an $E1_{cb}$ mechanism whereas the tertiary analogues follow an addition–elimination pathway. Difunctional carbamates, which incorporate an additional functional group at the carbamate nitrogen atom, *e.g.* **1**, are much less well studied, so we have initiated a programme to investigate and exploit such compounds. Recently, secondary sulfonylcarbamates have been reported to act as angiotensin II receptor antagonists,[3] the acidic sulfonylcarbamate moiety acting as an isostere for the tetrazole group in the antihypertensive agent losartan.[4] Surprisingly, there are few studies reported on the chemical reactivity of difunctional carbamates. Secondary phenylsulfonylcarbamates have been shown to hydrolyse *via* an $E1_{cb}$ mechanism to form a sulfonyl isocyanate,[5] whereas phenyl *N*-methyl-*N*-thiobenzoylcarbamate hydrolyses *via* a general base-catalysed pathway.[6] Presently, we have been investigating the previously unreported tertiary *N*-arylsulfonylcarbamates **1** and to aid our studies we have examined the hydrolysis of these compounds in aqueous alkaline media. Herein we present our results.



1a X = Me, Y = Cl
1b X = Me, Y = H
1c X = Me, Y = Me
1d X = Me, Y = OMe
1e X = OMe, Y = Cl
1f X = Cl, Y = Cl
1g X = H, Y = Cl
1h X = NO_2, Y = Cl
1i X = NO_2, Y = H
1j X = NO_2, Y = OMe

Experimental

Melting points were determined using a Kofler camera Bock Monoscop M and are uncorrected. Elemental analyses were performed by Medac Ltd., Brunel Science Park, Englefield Green, Egham, Surrey, UK. IR spectra were obtained using a Nicolet Impact 400 Spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ solutions using a JEOL JNM-LA 300 spectrometer; chemical shifts are reported in ppm relative to TMS as internal standard and coupling constants, *J*, are given in Hz. Mass spectra were recorded using a VG Mass Lab 20-250.

Synthesis of substrates

Compounds **1** were obtained by one of two methods: A or B.

Method A. The appropriate sulfonamide (20 mmol) was dissolved in anhydrous DMF (10 cm^3) and sodium hydride (20 mmol) was added under N_2 with stirring. After 30 min, the corresponding aryl chloroformate (20 mmol) in dry DMF (10 cm^3) was added slowly. The reaction was allowed to proceed for 30 min, then poured into water (100 cm^3) and the solid filtered and purified by column chromatography (diethyl ether–petroleum ether 1 : 1).

Method B. The appropriate sulfonamide (20 mmol) was dissolved in anhydrous THF (20 cm^3). The mixture was stirred and maintained under N_2 at room temperature while butyllithium (10 mmol) was added. After 30 min, the corresponding aryl chloroformate (20 mmol) in dry DMF (10 cm^3) was added slowly. After 1 h the solvent was removed and the residue redissolved in dichloromethane and purified as described in method A.

4-Chlorophenyl *N*-methyl-*N*-(4-tolylsulfonyl)carbamate 1a. Method A, 20%; method B, 30%. Mp 70–72 °C; ν_{max}/cm^{-1} 1743 (C=O), 1360, 1160 (SO_2); δ_H ($CDCl_3$) 2.46 (3H, s, Ar*Me*), 3.51 (3H, s, N*Me*), 6.9 (2H, d, *J* = 9, CO_2Ar), 7.3 (2H, d, *J* = 9, CO_2Ar), 7.33 (2H, d, *J* = 9, $ArSO_2$), 7.86 (2H, d, *J* = 9, $ArSO_2$); *m*/*z* (EI) 339. Found: C, 52.8; H, 4.2; N,4.1%. $C_{15}H_{14}ClNSO_4$ requires: C, 53.0; H, 4.15; N, 4.1%.

Phenyl *N*-methyl-*N*-(4-tolylsulfonyl)carbamate 1b. Method B, 14%. Mp 82–83 °C; ν_{max}/cm^{-1} 1756 (C=O), 1367, 1184 (SO_2); δ_H ($CDCl_3$) 2.45 (3H, s, Ar*Me*), 3.51 (3H, s, N*Me*), 6.96 (2H, d, *J* = 9.2, SO_2Ar), 7.32 (5H, m, CO_2Ar), 7.89 (2H, d, *J* = 9.2, SO_2Ar); *m*/*z* (EI) 306 (M^+). Found: C, 59.0; H, 5.0; N, 4.5%. $C_{15}H_{15}NSO_4$ requires: C, 59.0; H, 4.95; N, 4.6%.

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4-Tolyl *N*-methyl-*N*-(4-tolylsulfonyl)carbamate 1c. Method B, 63%. Mp 90–91 °C; ν_{max}/cm^{-1} 1762 (C=O), 1367, 1150 (SO_2); δ_H ($CDCl_3$) 2.31 (3H, s, Ar*Me*), 2.45 (3H, s, SO_2Ar*Me*), 3.51 (3H, s, N*Me*), 6.83 (2H, d, J = 9.2, SO_2*Ar*), 7.11 (2H, d, J = 6.6, CO_2*Ar*), 7.32 (2H, d, J = 6.6, CO_2*Ar*), 7.89 (2H, d, J = 9.2, SO_2*Ar*); *m*/*z* (EI) 319 (M^+). Found: C, 60.2; H, 5.4; N, 4.4%. $C_{16}H_{17}NSO_4$ requires: C, 60.0; H, 5.4; N, 4.4%.

4-Methoxyphenyl *N*-methyl-*N*-(4-tolylsulfonyl)carbamate 1d. Method A, 10%. Mp 89 °C; ν_{max}/cm^{-1} 1749 (C=O), 1367, 1150 (SO_2); δ_H ($CDCl_3$) 2.45 (3H, s, SO_2Ar*Me*), 3.51 (3H, s, N*Me*), 3.77 (3H, s, O*Me*), 6.84 (4H, m, CO_2*Ar*), 7.31 (2H, d, J = 9, SO_2*Ar*), 7.88 (2H, d, J = 9, SO_2*Ar*); *m*/*z* (FAB^+) 336 (MH^+); (FAB^-) 334 (M^-). Found: C, 57.3; H, 5.1; N, 4.2%. $C_{16}H_{17}NSO_5$ requires: C, 57.4; H, 5.0; N, 4.2%.

4-Chlorophenyl *N*-methyl-*N*-(4-methoxyphenylsulfonyl)carbamate 1e. Method A, 10%. Mp 64 °C; ν_{max}/cm^{-1} 1756 (C=O), 1367, 1167 (SO_2); δ_H ($CDCl_3$) 3.51 (3H, s, N*Me*), 3.88 (3H, s, O*Me*), 6.99 (2H, d, J = 9, SO_2*Ar*), 7.11 (2H, d, J = 9, CO_2*Ar*), 7.31 (2H, d, J = 9, CO_2*Ar*), 7.9 (2H, d, J = 9, SO_2*Ar*); *m*/*z* (EI) 355 (M^+); (FAB^+) 356 (MH^+). Found: C, 50.6; H, 4.0; N, 3.9%. $C_{15}H_{14}ClNSO_5$ requires: C, 50.9; H, 3.9; N, 3.5%.

4-Chlorophenyl *N*-methyl-*N*-(4-chlorophenylsulfonyl)carbamate 1f. Method A, 12%. Mp 95–97 °C; ν_{max}/cm^{-1} 1785(C=O), 1367, 1170 (SO_2); δ_H ($CDCl_3$) 3.51 (3H, s, N*Me*), 6.93 (2H, d, J = 9, CO_2*Ar*), 7.31 (2H, d, J = 9, CO_2*Ar*), 7.51 (2H, d, J = 9, SO_2*Ar*), 7.93 (2H, d, J = 9, SO_2*Ar*); *m*/*z* (EI) 359 (M^+). Found: C, 46.7; H, 3.1; N, 3.9%. $C_{14}H_{11}Cl_2NSO_4$ requires: C, 46.7; H, 3.2; N, 3.9%.

4-Chlorophenyl *N*-methyl-*N*-(phenylsulfonyl)carbamate 1g. Method B, 57%. Mp 77–79 °C; ν_{max}/cm^{-1} 1769 (C=O), 1368, 1163 (SO_2); δ_H ($CDCl_3$) 3.53 (3H, s, N*Me*), 6.89 (2H, d, J = 9, CO_2*Ar*), 7.31 (2H, d, J = 9, CO_2*Ar*), 7.69 (5H, m, SO_2*Ar*); *m*/*z* (EI) 325 (M^+); (FAB^+) 326/328 (MH^+). Found: C, 51.6; H, 3.7; N, 4.3%. $C_{14}H_{12}ClNSO_4$ requires: C, 51.9; H, 3.8; N, 4.3%.

4-Chlorophenyl *N*-methyl-*N*-(4-nitrophenylsulfonyl)carbamate 1h. Method B, 30%. Mp 118–121 °C; ν_{max}/cm^{-1} 1756 (C=O), 1367, 1184 (SO_2); δ_H ($CDCl_3$) 3.57 (3H, s, N*Me*), 6.96 (2H, d, J = 9.2, CO_2*Ar*), 7.32 (2H, d, J = 9.2, CO_2*Ar*), 8.20 (2H, d, J = 9.2, SO_2*Ar*), 8.32 (2H, d, J = 9.2, NO_2*Ar*); *m*/*z* (EI) 372/350 (M^+). Found: C, 45.7; H, 3.1; N, 7.6%. $C_{14}H_{12}ClN_2SO_6$ requires: C, 45.3; H, 3.0; N, 7.6%.

4-Phenyl *N*-methyl-*N*-(4-nitrophenylsulfonyl)carbamate 1i. Method A, 67%. Mp 143–145 °C; ν_{max}/cm^{-1} 1758 (C=O), 1334, 1182 (SO_2); δ_H ($CDCl_3$) 3.57 (3H, s, N*Me*), 6.99 (2H, d, J = 8.6, CO_2*Ph*), 7.26 (1H, m, CO_2*Ph*), 7.36 (2H, d, J = 8.6, CO_2*Ph*), 8.20 (2H, d, J = 8.8, SO_2*Ar*), 8.38 (2H, d, J = 8.8, NO_2*Ar*); *m*/*z* (HRMS) 336.0417 (calc. 336.0416). Found: C, 50.1; H, 4.0; N, 8.4; S, 9.2%. $C_{14}H_{12}N_2SO_6$ requires: C, 50.0; H, 3.6; N, 8.3; 9.5%.

4-Methoxyphenyl *N*-methyl-*N*-(4-nitrophenylsulfonyl)carbamate 1j. Method A, 65%. Mp 119–120 °C; ν_{max}/cm^{-1} 1746 (C=O), 1377, 1179 (SO_2); δ_H ($CDCl_3$) 3.77 (3H, s, N*Me*), 6.84 (2H, d, J = 9.2, CO_2*Ar*), 6.89 (2H, d, J = 9.2, CO_2*Ar*), 8.20 (2H, d, J = 8.8, SO_2*Ar*), 8.37 (2H, d, J = 8.8, NO_2*Ar*); *m*/*z* (HRMS) 366.0504 (calc. 366.0521). Found: C, 49.3; H, 4.3; N, 7.6; S, 8.8%. $C_{15}H_{14}N_2SO_7$ requires: C, 49.2; H, 3.85; N, 7.65; S, 8.75%.

Kinetic studies

All studies in buffer solutions up to pH 10 were monitored following the decomposition of substrate using an HPLC system comprising a Merck RP8 column and an eluant of 50% CH_3CN in 0.01 M pH 7 KH_2PO_4. Studies at higher pH employed UV spectroscopy, also monitoring decomposition of substrate. Thus, an aliquot (30 mm^3) of an acetonitrile solution of the substrate (5 mM) was injected into a thermostatted cuvette containing the buffer solution (substrate concentration *ca*. 0.05 mM). The change in the UV spectrum was monitored at an appropriate wavelength with respect to time and pseudo-first-order rate constants, k_{obs}, were obtained from plots of ln ($A_t - A_\infty$) *versus* time.

Table 1 Pseudo-first-order rate constants, k_{obs}, for the hydrolysis of **1a** in NaOH and NaOD solutions

[NaOH]/10^{-2} M	k_{obs}/10^{-4} s^{-1}	[NaOD]/10^{-2} M	k_{obs}/10^{-4} s^{-1}
0.2	5.94	1.0	45
0.5	16.1	2.4	82
1.0	33.1	3.0	100
2.0	63.0	4.0	140
4.3	128		
10	319		

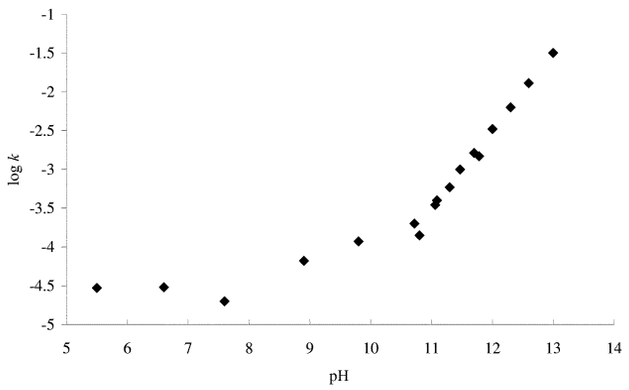


Fig. 1 pH–rate profile for **1a**.

Product analysis

In all experiments the final HPLC chromatograms and/or UV spectra were identical to those of a mixture of the corresponding sulfonamide and phenol. Compound **1a** was studied on a larger scale (20 mg) and hydrolysed both in sodium hydroxide and in piperidine buffer. In both cases, phenol and the corresponding sulfonamide were isolated quantitatively.

Results and discussion

The sulfonylcarbamates **1** hydrolyse to the corresponding sulfonamide and phenol, implying that hydrolysis proceeds by attack at the carbamate carbonyl, rather than at the sulfonyl, group. In buffer solutions, we found no evidence for the formation of an intermediate that could be formed upon nucleophilic attack of the buffer species at the carbamate. Pseudo-first-order rate constants, k_{obs}, for the hydrolysis of **1a** were determined in NaOH solutions (Table 1) and in aqueous buffers (imidazole, phosphate, borate, hydrogen carbonate, *n*-butylamine, piperidine). These data gave rise to the pH–rate profile in Fig. 1, which reveals spontaneous and hydroxide ion-catalysed pathways. As described below, in the HO^--catalysed region the reactions are also buffer-catalysed. Thus, k_{obs} is governed by eqn. (1), in which k_w is the pseudo-first-order rate constant for

$$k_{obs} = k_w + k_{HO}[OH] + k_B[B] \quad (1)$$

pH-independent hydrolysis and k_{HO} and k_B are, respectively, the second-order rate constants for catalysis of hydrolysis by HO^- and by the buffer.

Values of k_{HO} for compounds **1a–j** were determined from plots of k_{obs} *versus* [HO^-] (Table 2). Hydrolysis of compound **1a**

Table 2 Second-order rate constants, k_{OH^-}, for the hydroxide ion-catalysed hydrolysis of **1a–j** at 25 °C

	$k_{OH^-}/M^{-1}\ s^{-1}$
1a	0.318, 0.329,[a] 0.197,[b] 0.312,[c] 0.498,[d], 0.574,[e] 0.952[f]
1b	0.178
1c	0.102
1d	0.135
1e	0.208
1f	0.574
1g	0.422
1h	0.640
1i	0.483
1j	0.873

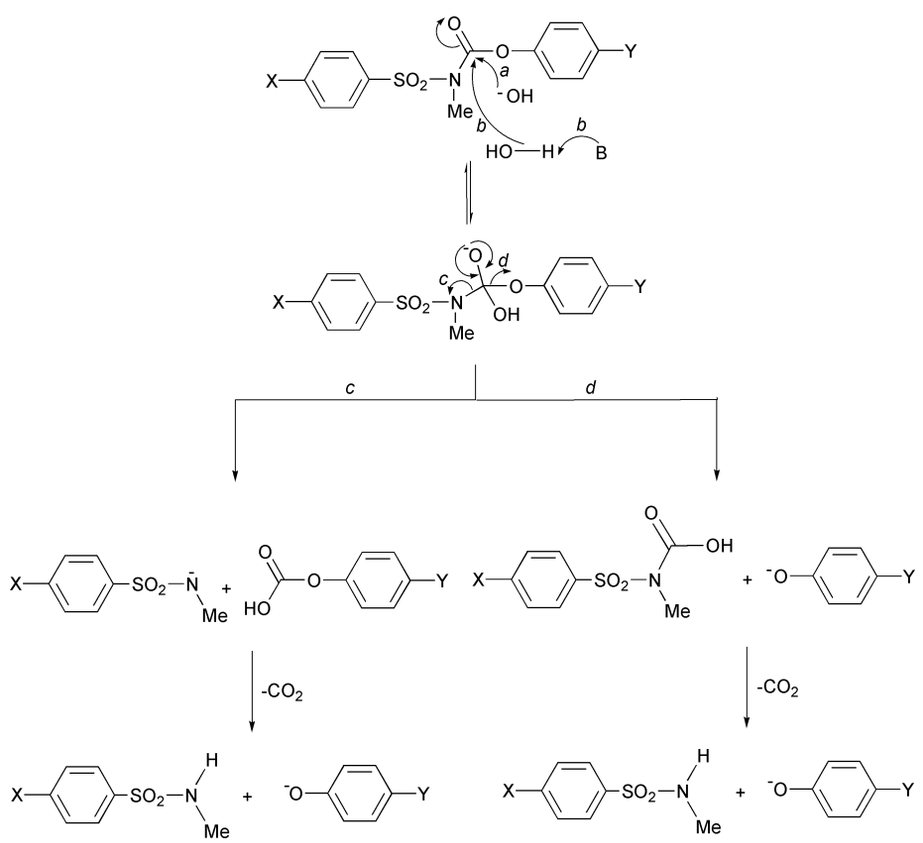
[a] In D_2O. [b] 17 °C. [c] 21 °C. [d] 31 °C. [e] 35 °C. [f] 40 °C.

was also studied in sodium deuteroxide solutions (Tables 1 and 2) enabling a solvent deuterium isotope effect of 0.97 for the hydroxide ion-catalysed reaction to be determined. This is consistent with hydroxide ion acting as a nucleophile rather than a general base. Further, the temperature effect on k_{HO} for **1a** gives rise to values for $\Delta H^{\ddagger}$ of 45 kJ mol^{-1} and $\Delta S^{\ddagger}$ of −104 J K^{-1} mol^{-1}. These values are characteristic of a mechanism involving nucleophilic attack by HO^- at the carbonyl carbon (Scheme 1).[7,8]

Substituents in the aryl carbamate ring (compounds **1a–d**) give rise to a Hammett correlation for k_{HO} that is somewhat better using a σ^- value ($\rho = 1.2$, $r^2 = 0.98$), rather than a σ value ($\rho = 0.83$, $r^2 = 0.88$), for the MeO substituent. The magnitude of ρ is also consistent with rate-limiting nucleophilic attack of the hydroxide ion at the carbamate carbonyl carbon atom (Scheme 1, step *a*).[8,9] Alternative processes, *e.g.* rate-limiting breakdown of a tetrahedral intermediate with expulsion of an aryloxide ion (Scheme 1, step *d*), or direct displacement of the aryloxide ion, are generally characterised by much higher ρ values. For example, $\rho = 2.5$ for rate-limiting breakdown of the intermediate in the reaction of trimethylamine with phenyl acetates,[10] and $\rho \geqslant 2.0$ for reaction of trimethylamine with 2,4-dinitrophenyl quinolinecarboxylates where C–O bond breaking of the leaving phenol is of critical importance in the transition state.[11] Nevertheless, correlation with σ^- is surprising. More commonly, hydrolysis of aryl carbamates is characterised by correlation of the aryl substituents with σ.[2,9,12] Only when there is substantial C–O bond cleavage, and therefore significant increase in negative charge at the carbamate O atom, for example in $E1_{cb}$ mechanisms,[12,13] is there correlation with σ^-. One explanation for this might be that the presence of the strongly electron-withdrawing arylsulfonyl group on the nitrogen atom may increase the extent of electron delocalisation from the carbamate oxygen atom in the ground state of the substrate. On formation of the tetrahedral intermediate such delocalisation is removed, which would result in greater change in the electron density residing on the phenol oxygen for the *N*-arylsulfonyl compounds as compared with simpler carbamates. Whatever the reason, a similar observation has been made for *N*-acylcarbamates.[14]

Clearly, it is not possible to say from the current data whether the sulfonamide anion or the aryloxide anion acts as the leaving group (Scheme 1, steps *c* or *d*). Both paths give rise to the same products. Based on pK_a values one might predict the aryloxide to be the better leaving group; the pK_as of the 4-MeO-, 4-Me-, 4-H- and 4-Cl-phenols are 10.2, 10.19, 9.95 and 9.38, respectively,[15] whereas those of the *N*-methyl 4-MeO-, 4-Me-, 4-H-, 4-Cl- and 4-NO_2-benzenesulfonamides are 11.83,[16] 11.63,[16] 11.43,[17] 11.08[16] and 10.31,[16] respectively. However, in the reaction of aryl carbonates with pyridine nucleophiles the tetrahedral intermediate decomposes with the nitrogen-containing leaving group being some 10^4 times a better leaving group than an aryloxide of the same pK_a[18] (see also below).

The substituent effect in the arenesulfonamide moiety (compounds **1a**, **e–h**) is illustrated in Fig. 2. Compounds **1a**, **e–g** show reasonable linear correlation to yield a ρ value of 0.8, the correlation being with σ. This is unsurprising, as the nitrogen



Scheme 1 Pathways for the hydroxide ion and general base-catalysed hydrolysis of aryl sulfonylcarbamates.

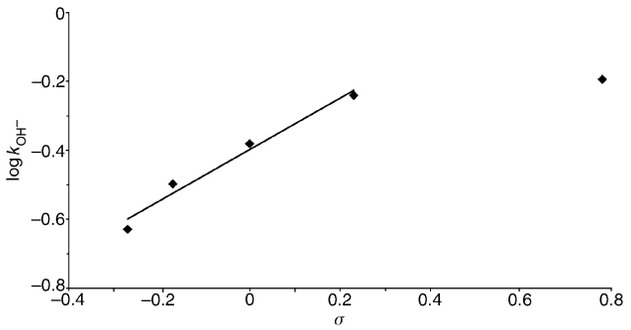


Fig. 2 Hammett plot for the hydrolysis of **1** showing the effect of the substituent in the arylsulfonyl ring.

Table 3 Second-order rate constants, k_B, for the buffer-catalysed hydrolysis of **1a** at 25 °C

Catalytic species	pK_a'	$k_B/M^{-1}\,s^{-1}$
2,2,2-Trifluoroethanol	12.27	0.60
Piperidine	11.36	0.258, 0.180[a]
2,2,6,6-Tetramethylpiperidine	11.23	0.040
n-Butylamine	10.80	0.065

[a] In D_2O.

lone pair does not directly interact with the substituent in the arylsulfonyl ring. However, the sign of ρ indicates that the electron density in the arylsulfonyl moiety increases as the transition state is approached, in contrast with secondary *N*-arylsulfonylcarbamates, which hydrolyse by an $E1_{cb}$ mechanism giving rise to a ρ value for the arylsulfonyl moiety that is negative (−0.66).[5] Again, our data are consistent with a transition from the substrate, in which the nitrogen lone pair is delocalised into a planar carbamate group, to a tetrahedral intermediate, in which delocalisation of the nitrogen lone pair into an adjacent carbonyl is not possible but in which stabilisation is afforded by the arylsulfonyl group. The mechanism shown in Scheme 1 is consistent with these data. However, the 4-nitrophenylsulfonyl compound **1h** appears much less reactive than expected. We interpret this as indicating a change in rate-limiting step with decomposition of the tetrahedral intermediate being rate-limiting for compound **1h** (Scheme 1, steps *c* or *d*). Moreover, we suspect that for the 4-nitrophenylsulfonyl compounds **1h–j** it is the sulfonamide, rather than the phenoxide, anion that functions as the leaving group during decomposition of the intermediate (Scheme 1, path *c*). Thus, k_{HO} values for these compounds reveal little substituent effect in the aryl carbamate ring (indeed, **1j** bearing a 4-MeO substituent is slightly *more* reactive than **1h** bearing 4-Cl). If the phenoxide anion were functioning as the leaving group, as discussed above, one would expect a significant substituent effect with the electron-withdrawing substituents enhancing reactivity. However, for a sulfonamide anion leaving group one would anticipate either a negligible substituent effect in the aryl carbamate group (as the negatively charged oxygen atom in the intermediate should provide the major electron 'push' for the departing leaving group) or one that slightly favours electron-releasing substituents as found here.

Buffer catalysis was examined for **1a** using piperidine, 2,2,6,6-tetramethylpiperidine, butylamine and 2,2,2-trifluoroethanol. Second-order rate coefficients, k_B, for buffer catalysis were determined from the slopes of plots of k_{obs} *versus* the concentration of the basic form of the buffer, and these are contained in Table 3. Comparison of the data for piperidine and 2,2,6,6-tetramethylpiperidine reveals that k_B for the piperidine reaction is only a modest 6-fold greater than that for its sterically hindered analogue . This points to a general base-catalysed process (Scheme 1, path *b*); for general base-catalysed reactions steric hindrance around the basic centre only slightly affects reactivity, whereas for nucleophilic reactions the steric effect is usually larger.[19] For instance, 2-methylpyridine is over 10^3 times less reactive than pyridine in its nucleophilic reaction with 2,4-dinitrophenyl acetate[20] and acetic anhydride,[21] and, for the nucleophile-catalysed hydrolysis of *N*-nitro-*N*-methylacetamide, piperidine was found to be *ca*. 300 times more reactive than 2,2,6,6-tetramethylpiperidine.[22] A further pointer to a general base-catalysed process is the solvent deuterium isotope effect of 1.4 on the piperidine-catalysed reaction (Table 3). This is consistent with the involvement of O–H bond breaking in the rate-limiting step. Further, the values of k_B for piperidine, *n*-butylamine and 2,2,2-trifluoroethanol can be used to define a Brønsted line of slope 0.6 ($r^2 = 0.93$), an observation typical of general base catalysis.[19]

Thus, whereas secondary sulfonylcarbamates, *i.e.* those containing the $-SO_2NH-$ functionality, react *via* an $E1_{cb}$ elimination pathway involving ionisation of the sulfonamide group, the tertiary analogues, for which the $E1_{cb}$ pathway is blocked, undergo hydrolysis either by nucleophilic attack of HO^- or by general base-catalysed attack of water at the carbamate carbonyl. Not surprisingly, the $E1_{cb}$ pathway is the more favoured, the secondary substrates being *ca*. 10^5–10^6 times more reactive than the tertiary analogues reported here.

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