Kinetics and mechanism of hydrolysis of *N*-amidomethylsulfonamides

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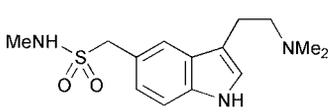
Received (in Cambridge, UK) 20th December 2000, Accepted 14th March 2001
First published as an Advance Article on the web 28th March 2001

The kinetics of the hydrolyses of secondary and tertiary *N*-amidomethylsulfonamides were studied at 50 °C. Both types of *N*-amidomethylsulfonamide hydrolyse through acid- and base-catalysed processes, as indicated by the pH–rate profiles. The order of reactivity for the acid-catalysed pathway implies a mechanism involving protonation of the amide followed by expulsion of a neutral amide and formation of a sulfonyliminium ion. In the base-catalysed region, compound **5c**, which is substituted at both amide and sulfonamide nitrogen atoms, hydrolyses by nucleophilic attack of hydroxide ion at the amide carbonyl carbon atom to form benzoic acid and a sulfonamide. In contrast, compound **5b**, which contains a sulfonamide NH group, hydrolyses to benzamide and sulfonamide products by an $E1cb_{rev}$ mechanism involving ionisation of the sulfonamide. Compound **5a**, which contains an amide NH, also hydrolyses to sulfonamide and amide products, probably by an E2 mechanism.

Although sulfonamides are best known as bacteriostatic agents,[1] there is now a range of drugs, possessing very different pharmacological activities, in which the sulfonamide group is present.[2] Several of these drugs suffer from bioavailability problems or adverse secondary effects. For example, as a result of its low lipophilicity, sumatriptan, **1**, an efficient drug for migraine treatment, has a low oral bioavailability.[3] Similarly, the carbonic anhydrase inhibitor acetazolamide, **2**, used in the treatment of glaucoma, is not absorbed by topical application.[4] The so-called selective COX-2 inhibitor nimesulide, **3**, however, has associated gastrointestinal toxicity[5,6] probably due to residual COX-1 inhibition.



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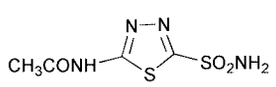

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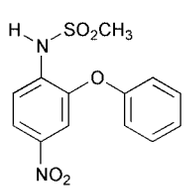

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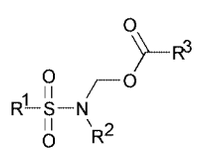

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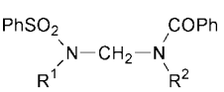
The prodrug strategy[7] has been widely used for solving biopharmaceutical problems of this nature. Although several prodrugs have been specifically developed for sulfonamide agents, only a few have displayed adequate chemical and/or enzymatic activation rates.[8,9] Recently, we reported *N*-acyloxymethylation (to form *e.g.* **4**) as a superior method for derivatisation of secondary sulfonamide drugs.[10] Typically, *N*-acyloxymethylsulfonamide prodrugs display low reactivity in aqueous buffers yet are rapidly activated to the parent sulfonamide by human esterases.[10] The acid-catalysed and spontaneous hydrolyses of these compounds occur *via* an S_N1-type mechanism involving the departure of the carboxylate anion and formation of an *N*-sulfonyliminium ion, while base-catalysed hydrolysis involves direct nucleophilic attack at the carbonyl carbon atom.

Most prodrugs are designed to be enzymatically activated (*e.g.* by plasma esterases). However, such bioactivation pathways are usually subject to biological variability, mainly inter-individual variations. Consequently, it is of obvious interest to develop prodrugs that can be chemically activated and therefore not subject to such individual variability.

Mannich bases have been used as potential prodrugs for sulfonamides, amides and other NH-acidic drugs.[11–14] Typically, in aqueous solution this type of prodrug decomposes rapidly *via* unimolecular N–C bond cleavage in the rate limiting step; half-lives of 0.01–1400 min at pH 7.4 and 37 °C[15] render pharmaceutical formulation a difficult task.

Based on our previous work with *N*-acyloxymethylsulfonamides[10] and *N*-acyloxymethylamides,[16] we anticipated that *N*-amidomethylsulfonamides, *e.g.* **5**, might be more stable Mannich base-type prodrugs, not only for sulfonamide-containing drugs but also for pharmaceutically active amides. The objective of the present study was to determine the broad mechanistic scope of the hydrolysis of this type of derivative. The compounds used in the present study were **5a**–**5c**.



5a R^1 = Me, R^2 = H
b R^1 = H, R^2 = Me
c R^1 = R^2 = Me

Experimental

Melting points were determined using a Kofler camera Bock Monoscop M and are uncorrected. Elemental analyses were performed by either Medac Ltd, Brunel Science Park, Englefield Green, Egham, Surrey, UK or ITQB, Oeiras, Portugal. IR spectra were obtained as Nujol mulls using a Nicolet Impact 400 Spectrophotometer. ^{1}H-NMR spectra were recorded in

$CDCl_3$ solutions at 400 MHz with TMS as internal standard, using a JEOL JNM-EX 400 spectrometer. Chemical shifts are measured in ppm, *J* values in Hz. Mass spectra were recorded using a VG Mass Lab 20-250.

All kinetic measurements were made using either a Shimadzu UV-2100 spectrophotometer equipped with a Shimadzu CPS-260 temperature controller or an HPLC apparatus consisting of a Shimadzu SPD-6AV UV detector, a Shimadzu LC-9A pump with a Rheodine 20 μl injector and a Merck-Hitachi D-2500A integrator.

Reagents for synthesis were used without further purification. Buffer materials for kinetics were of analytical reagent grade. For HPLC, the solvents were Lichrosolve® grade and water was distilled and deionized using a Millipore apparatus.

Synthesis

The amidomethylsulfonamides **5a** and **5c** were synthesised by reacting the appropriate *N*-chloromethylbenzamide[17] with the sodium salt of the *N*-methylsulfonamide. To a solution of the sulfonamide (2.5 mmol) in anhydrous DMF (2 cm^3) was added sodium hydride (2.75 mmol). When liberation of hydrogen was complete (*ca.* 1 h), a solution of *N*-chloromethylbenzamide (2.5 mmol) in DMF (1 cm^3) was added and the mixture was left to react at room temperature. When the reaction was complete the solvent was removed and the residue subjected to column chromatography. Product **5c** was subsequently recrystallized from DCM–Et_2O. For the synthesis of **5b**, a solution of *N*-chloromethyl-*N*-methylbenzamide (2.5 mmol) in THF (2 cm^3) and a suspension of the silver salt of benzenesulfonamide (2.5 mmol) in dry THF (2 cm^3) were simultaneously added to a reaction flask using a Y tube and two syringes. The mixture was stirred at room temperature and when the reaction was complete the solvent was removed and the residue subjected to column chromatography using diethyl ether as eluent. The product was recrystallised from ice-cold MeCN.

Compound 5a. Mp 111–113 °C; ν_{max}/cm^{-1} 3348, 1661, 1349, 1170; δ_H 2.98 (3H, s, N*Me*), 4.93 (2H, d, $J = 6$, NCH_2N), 6.90 (1H, br s, N*H*), 7.42–8.12 (10H, m, 2 × *Ph*); *m*/*z* FAB^+ 305 (MH^+), 184 ($PhSO_2N(CH_2)CH_3^+$), 141 ($PhSO_2^+$), 134 ($PhCONH(CH_2)^+$), 105 ($PhCO^+$). Found: C, 58.9; H, 5.3; N, 9.2%. $C_{15}H_{16}N_2O_3S$ requires: C, 59.2; H, 5.3; N, 9.2%.

Compound 5b. Mp 162–165 °C; ν_{max}/cm^{-1} 3144, 1631, 1341, 1170; δ_H 3.00 (3H, s, N*Me*), 4.70 (2H, d, $J = 6$, NCH_2N), 6.13 (1H, br s, N*H*), 7.23–8.07 (10H, m, 2 × *Ph*); *m*/*z* FAB^+ 169 ($PhSO_2NCH_2^+$), 141 ($PhSO_2^+$), 134 ($PhCONCH_3^+$), 105 ($PhCO^+$), 77 (Ph^+). Found: C, 58.8; H, 5.4; N, 9.3; S, 10.2%. $C_{15}H_{16}N_2O_3S$ requires: C, 59.2; H, 5.3; N, 9.2; S, 10.5%.

Compound 5c. Mp 58–59 °C; ν_{max}/cm^{-1} 1654, 1346, 1190; δ_H 2.83 (3H, s, SO_2NMe), 3.10 (3H, s, CON*Me*), 5.00 (2H, s, NCH_2N), 7.47–8.17 (10H, m, 2 × *Ph*); *m*/*z* FAB^+ 318 (M^+), 184 ($PhSO_2N(CH_2)CH_3^+$), 148 ($PhCON(CH_2)CH_3^+$), 141 ($PhSO_2^+$), 105 ($PhCO^+$). Found: C, 60.9; H, 6.0; N, 9.1; S, 10.0%. $C_{16}H_{18}N_2O_3S$ requires: C, 60.4; H, 5.7; N, 8.8; S, 10.1%.

N-(*N*′-Benzoyl-*N*′-ethoxycarbonylaminomethyl)-*N*-(4-nitro-2-phenoxyphenyl)methanesulfonamide 7

Ethyl *N*-benzoyl-*N*-chloromethylglycinate[17] (1.7 mmol) in THF (1 cm^3) was added to a suspension of the sodium salt of nimesulide (1.25 mmol) in THF (3 cm^3). After stirring at room temperature for 2 h, the solvent was removed, the residue dissolved in DCM (20 cm^3), washed with 5% sodium hydrogen carbonate solution (20 cm^3) and dried ($MgSO_4$). Following removal of the organic solvent, the residue was purified by chromatography on silica gel using diethyl ether–light petroleum (8 : 2). Mp 137–140 °C; ν_{max}/cm^{-1} 1745, 1656, 1347, 1155; δ_H 1.34 (3H, t, $J = 7$, $MeCH_2$), 2.97 (3H, s, $MeSO_2$), 4.19–4.33 (4H, m, $MeCH_2 + NCH_2$), 5.41 (2H, s, NCH_2N), 7.18–7.98 (13H, m, 3 × *Ar*); *m*/*z* 321 {$(M - PhCONCH_2CO_2Et)^+$}, 220 {$(M - MeSO_2NAr)^+$}, 105 ($PhCO^+$), 77. Found: C, 57.2; H, 5.0; N, 7.7%. $C_{25}H_{25}N_3O_8S$ requires: C, 56.9; H, 4.8; N, 8.0%.

Product studies

Characterisation of the products of the hydrolysis of **5a**–**c** under acidic and basic conditions was carried out by HPLC by comparison with authentic samples. In the basic region, hydrolysis of the secondary *N*-amidomethylsulfonamides **5a** and **5b** yields the corresponding sulfonamide and amide. The tertiary substrate **5c**, however, yields benzoic acid and *N*-methylbenzenesulfonamide quantitatively. In the acidic region, hydrolysis of all three compounds quantitatively affords the corresponding amide and sulfonamide. Formaldehyde formation was determined in acidic solutions by conversion into its 2,4-dinitrophenylhydrazone derivative, and in alkaline solutions by the Nash procedure.[18]

Kinetics

Kinetic studies were carried out spectrophotometrically at fixed wavelength by recording the decrease of substrate absorbance in the appropriate buffer solutions (containing 10% dioxane) at 50 °C. The ionic strength was maintained at 0.5 mol dm^{-3} using $NaClO_4$. In a typical run, the reaction was initiated by adding a 15 mm^3 aliquot of a 10^{-2} mol dm^{-3} stock solution of substrate in acetonitrile to a cuvette containing 3 cm^3 of the pre-equilibrated buffer solution at 50 °C. The pseudo-first-order rate constants were obtained from the slopes of plots of $\ln (A_t - A_\infty)$ *vs.* time, where A_t and A_∞ represent the absorbance at time *t* and at infinity, respectively. Rate constants determined by this method were generally reproducible to ± 5%. Alternatively, and mainly for the reactions in acidic solutions, the kinetic studies were carried out using HPLC, following the loss of the substrate. Using this method a 50 mm^3 aliquot of 10^{-3} mol dm^{-3} stock solution of substrate was added to a reaction flask containing 5 cm^3 of the thermostatted buffer solution. At regular intervals, samples of the reaction mixture were analysed using a system comprising a Merck LiChrospher® RP-8 5 μm 125 × 4 mm column and an isochratic mobile phase {acetonitrile–water (35 : 65)} at a flow rate of 1.0 cm^3 min^{-1}. Rate constants determined by this method were generally reproducible to ± 10%.

Results and discussion

pH–Rate profiles

As a result of their low solubility, the hydrolysis of *N*-amidomethylsulfonamides **5a**–**c** was studied in aqueous buffers containing 10% dioxane. The influence of pH on the hydrolysis rate constants for compounds **5a**–**c** is presented in Fig. 1. Below pH *ca.* 3 all three compounds show a specific acid-catalysed pathway. Compound **5a** also exhibits a base-catalysed pathway, but was stable between pH 3 and 9. Compound **5c** is very stable in basic media, and it proved possible to determine an accurate rate constant only at an OH^- concentration of 0.5 mol dm^{-3}. In the pH range employed, the hydrolysis rate constants for compounds **5a** and, presumably, **5c** depend on pH according to eqn. (1), where k_{H^+} is the rate constant for the acid-catalysed

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

pathway and k_{OH^-} is the rate constant for the base-catalysed pathway. For comparison, in the base-catalysed region a line of slope 1 is shown through the point for **5c**.

Compound **5b** behaves somewhat differently, displaying a sigmoid-shaped pH–rate profile in which saturation occurs at

Table 1 Rate constants for the hydrolysis of *N*-amidomethylsulfonamides **5** at 50 °C

Compound	$k_0/10^{-7}$ s^{-1}	$k_{H^+}/10^{-4}$ dm^3 mol^{-1} s^{-1}	k_{OH^-}/dm^3 mol^{-1} s^{-1}	$k_d/10^{-4}$ s^{-1}	pK_a
5a	—	2.34	8.87×10^{-3}	—	—
		3.72[b]	7.29×10^{-3}[b]		
5b	3.88	1.11	2.79[a]	3.26	9.35
	2.07	1.78[b]	6.23[ab]	3.30[b]	9.82[b]
5c	—	7.65	1.48×10^{-5}	—	—
		14.0[b]			

[a] $k_{OH^-} = k_dK_a/K_w$. [b] In D_2O.

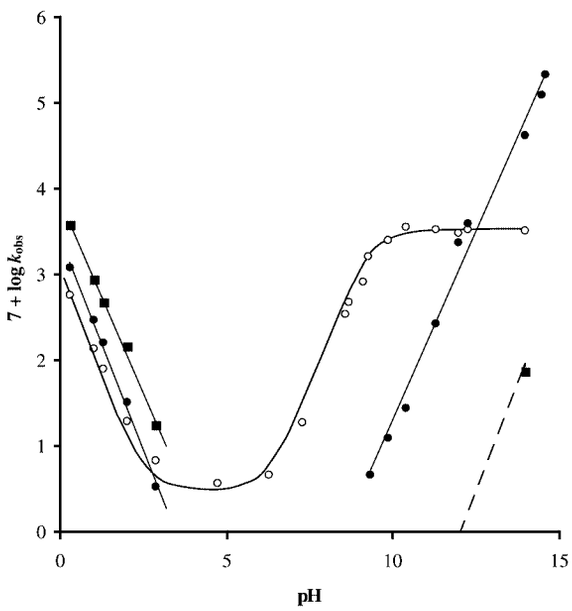


Fig. 1 pH–Rate profiles for the hydrolyses of: ●, **5a**; ○, **5b**; ■, **5c**.

ca. pH 9; this we believe reflects the ionisation of the secondary sulfonamide group to form the sulfonamide anion. The best computer fit (solid line) to the experimental data for **5b** in Fig. 1 was achieved using eqn. (2), where k_0 is the first-order rate con-

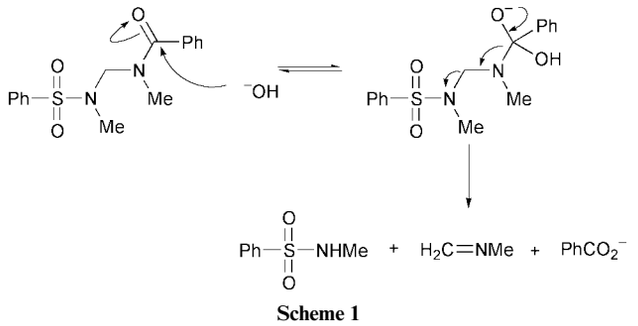
$$k_{obs} = (k_0 + k_H[H^+]) \frac{[H^+]}{K_a + [H^+]} + k_d \frac{K_a}{K_a + [H^+]} \qquad (2)$$

stant for the non-catalysed reaction, K_a is the ionization constant of the sulfonamide NH in **5b**, k_d is the rate constant for the decomposition of the ionised form of the substrate, and $[H^+]/(K_a + [H^+])$ and $K_a/(K_a + [H^+])$ represent, respectively, the fraction of the neutral and ionized forms of **5b**.

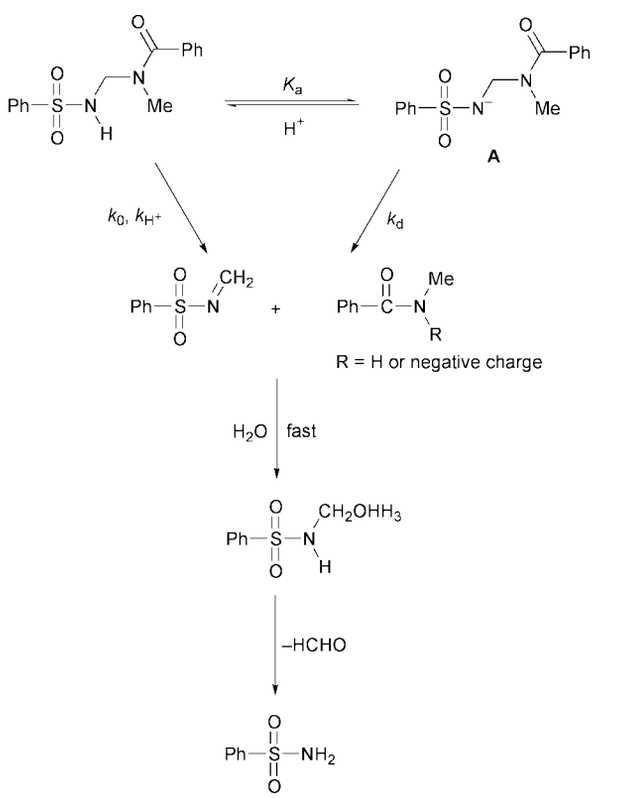
All the derived kinetic data are presented in Table 1, together with the apparent rate constant for the base-catalysed hydrolysis of **5b**, k_{OH^-} ($= k_dK_a/K_w$), calculated using a value of 5.42×10^{-14} for K_w at 50 °C. For compound **5c** k_{OH^-} was derived from $k_{obs}/[OH^-]$.

The base-catalysed pathway

Both secondary (**5a**) and tertiary (**5c**) *N*-amidomethylsulfonamides are hydrolysed by a base-catalysed process, though with vastly different reactivities. As anticipated, in highly alkaline solutions, compound **5c**, which contains no acidic hydrogens, is hydrolysed extremely slowly affording benzoic acid and *N*-methylbenzenesulfonamide. This is consistent with a mechanism involving the nucleophilic attack of OH^- at the amide carbonyl carbon atom (Scheme 1). In contrast, **5b**, which contains a secondary *sulfonamide* group, is hydrolysed to the parent amides, *viz*. *N*-methylbenzamide and benzenesulfonamide. The k_{obs} values for the hydrolysis of compound **5b** increase with pH (from *ca.* pH 6) then become constant, presumably as ionisation of the sulfonamide group is complete. The kinetic pK_a value obtained using eqn. (1) is 9.35, in good agreement with the pK_a value of 9.67 calculated for 25 °C.[19] The apparent bimolecular rate constant ($k_dK_a/K_w = 2.79$ dm^{-3} mol^{-1} s^{-1}) for the attack of hydroxide ion on the neutral substrate is 5 orders of magnitude larger than the k_{OH^-} value for the tertiary compound **5c**. Such a high reactivity ratio is unlikely to be due simply to a substituent effect. More likely, a different mechanism operates in the case of the secondary substrate **5b**, the most reasonable being that an E1cb$_{rev}$ process, involving the formation of an *N*-sulfonylimine, occurs in this case (Scheme 2). The formation



Scheme 1



Scheme 2

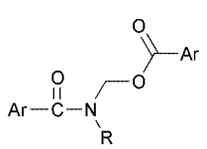
of the sulfonamide anion is the driving force for the unimolecular elimination of the *N*-methylamide anion, which is a poor leaving group[20] (pK_a *ca.* 19).

Table 2 Effect of temperature on the first-order rate constant, k_d, for the base-catalysed hydrolysis of compound **5b** at $[OH^-] = 0.5$ mol dm^{-3}, and on the second-order rate constant, k_{H^+}, for the acid-catalysed hydrolysis of compounds **5a**–**c**

Compound	T/K	$k_d/10^{-4}$ s^{-1}	$k_{H^+}/10^{-4}$ dm^3 mol^{-1} s^{-1}
5a	312	—	0.746
	323	—	2.34
	328	—	5.20
	331	—	8.41
5b	312	—	0.346
	313	0.927	—
	323	3.40	1.11
	328	6.05	2.14
	331	—	3.59
	332	9.69	—
5c	312	—	2.56
	323	—	7.65
	328	—	16.6
	331	—	24.0

Similar differences in reactivity (10^4–10^8) have been reported for aryl *N*-methylaminosulfonates,[21] *N*-acyloxymethylamides,[16] and sulfamoyl chlorides,[22] between compounds where an acidic hydrogen β to a leaving group is replaced by a methyl group. Further evidence supporting the E1cb$_{rev}$ mechanism is given by the temperature effect on the hydrolysis of **5b** in 0.5 mol dm^{-3} HO^- (see Table 2), which gives rise to a $\Delta H^‡$ value of 104 (± 5) kJ mol^{-1} and a $\Delta S^‡$ value of +9.5 (± 3.5) J K^{-1}mol^{-1}. The positive entropy of activation provides confirmation of the dissociative nature of the rate limiting step. Indeed, elimination–addition mechanisms observed for the hydrolysis of aryl *N*-(substituted phenylsulfonyl)carbamates,[23] aryl 3,3-dimethylcarbazates,[24] or 4-nitrophenyl sulfamate,[25] display similar positive entropy values, ranging from 0.8 to 63 J K^{-1} mol^{-1}.

Like compound **5b**, compound **5a**, which contains a secondary *amide* group, also hydrolyses to the parent amides, *viz.* benzamide and *N*-methylbenzenesulfonamide. Unlike **5b**, however, between pH 9 and 14, **5a** displays a linear dependence of k_{obs} on $[OH^-]$. Taken together, the products formed and kinetic dependence imply either E1cb ($K_a \leqslant [H^+]$) or E2 mechanisms. The predicted pK_a value for compound **5a** is *ca.* 13,[19] so we might expect curvature in the pH–rate profile of **5a** at pH *ca.* 12–13 for an E1cb$_{rev}$ mechanism. Although we cannot discount such a pathway, given that the secondary *N*-acyloxymethylbenzamides **6** (R = H) undergo base-catalysed hydrolysis *via* an



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E2 mechanism,[16] it seems likely that **5a** hydrolyses by a similar process.

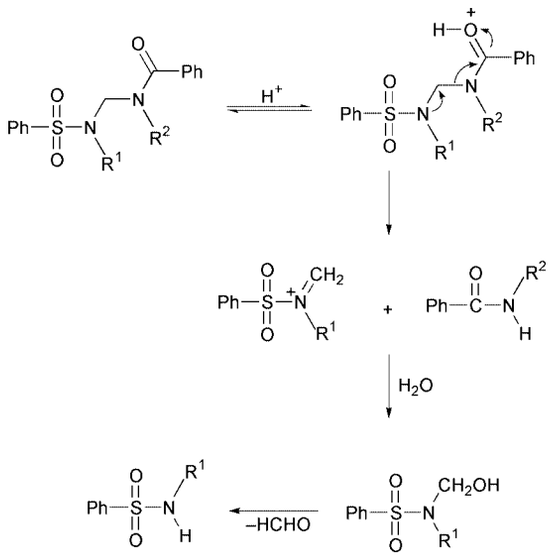
Deuterium solvent isotope effects (Table 1) were also determined for the base-catalysed hydrolyses of **5a** and **5b**. Considering first **5b**, the expected solvent isotope effect for the plateau region associated with an E1cb mechanism, $k_d^{H_2O}/k_d^{D_2O}$, is *ca.* 1,[26] as observed here. However, Pratt and Bruice have suggested that poor leaving groups can lead to substantial solvent participation in the transition state of E1cb mechanisms and therefore to $k_d^{H_2O}/k_d^{D_2O}$ values higher than 1.[27] In the limit, primary solvent isotope effects for the plateau region can be obtained with very poor leaving groups such as R_2N^-.[28] The kinetic solvent isotope effect determined for **5b** thus indicates that the expulsion of the amide anion (pK_a *ca.* 19) from the intermediate **A** (Scheme 2) is not accompanied by transfer of a proton from the solvent to the leaving group. Similar absence of solvent assistance to the departure of an even poorer leaving group has also been reported for the methoxide-catalysed E1cb decomposition of $Ar_2CHSOCH_2SO_2Ar$ in CH_3OH, where the leaving group is $ArSO_2CH_2^-$ (pK_a *ca.* 29).[29] For **5b**, a kinetic pK_a value of 9.83 was determined in D_2O which, taken together with the reported value of K_w of 7.89×10^{-14} for D_2O (50 °C), leads to a kinetic solvent isotope effect for the pre-plateau region, k_{OH^-}/k_{OD^-}, of 0.45. Significantly, this is the value of the solvent isotope effect that can be calculated using fractionation factors for an E1cb$_{rev}$ mechanism in which the decomposition of the conjugate base (plateau region) is not subject to an isotope effect (*i.e.* $k_d^{H_2O}/k_d^{D_2O}$ is *ca.* 1).[30] Thus, we are confident that the hydrolysis mechanism for **5b** in alkaline media depicted in Scheme 2 is correct. The kinetic solvent isotope effect of 0.4 found in the methoxide-catalysed decomposition of $Ar_2CHSOCH_2SO_2Ar$ has been similarly interpreted in terms of an E1cb process.[29] In contrast, the kinetic solvent isotope effect, k_{OH^-}/k_{OD^-}, for the base-catalysed hydrolysis of **5a** is 1.2 (Table 1). This value implies that for this compound the hydrolysis pathway does not involve an E1cb$_{rev}$ mechanism, but more likely proceeds *via* an E2 process.

Table 3 Effect of buffers on the hydrolysis of amidomethylsulfonamides **5** at 50 °C

Compound	Buffer	[Buffer]/ mol dm^{-3}	pH (pD)	$k_{obs}/10^{-7}$ s^{-1}
5a	Chloroacetate	0.05	2.84	4.23
		0.10	2.86	3.38
		0.30	2.82	3.66
5b	Chloroacetate	0.05	2.84	6.34
		0.10	2.86	6.43
		0.30	2.82	5.58
	Acetate	0.2	4.62	4.90
		0.3	4.76	5.48
		0.4	4.80	6.10
		0.1	(5.42)	2.40
		0.2	(5.37)	2.50
		0.3	(5.33)	2.83
5c	Chloroacetate	0.05	2.84	19.2
		0.10	2.86	18.7
		0.30	2.82	20.8

The acid-catalysed pathway

Compounds **5a**–**c** are hydrolysed in acidic media to the corresponding benzenesulfonamide and benzamide and the rate equations have a simple first-order dependence on $[H^+]$. The differences between the k_{H^+} values are much smaller than those observed for k_{OH^-}, suggesting that a different mechanism is operating in the acidic region. From Table 1 it can seen that the order of reactivity is now **5c** > **5a** > **5b**; this presumably reflects the greater electron-donating effect of a methyl group as compared to a hydrogen atom, particularly on the sulfonamide nitrogen atom. This is consistent with a mechanism in which there is positive charge development at this atom in the rate-limiting step. Moreover, the hydrolysis of compounds **5a**–**c** below pH 3 is not subject to chloroactetate buffer catalysis (Table 3), ruling out general acid catalysis. A likely mechanism is the unimolecular dissociation shown in Scheme 3, which involves a pre-equilibrium protonation of the substrate. Indeed, the kinetic solvent isotope effects, k_{H^+}/k_{D^+}, for the acid-catalysed decomposition of compounds **5a**–**c** are 0.62, 0.63 and 0.55, respectively, consistent with such a pre-equilibrium protonation. The most reasonable site of protonation is the amide oxygen; the pK_a for protonation at this site[32] is −1.5 while the pK_a (for protonation of the nitrogen atom) of sulfonamides[33] is



Scheme 3

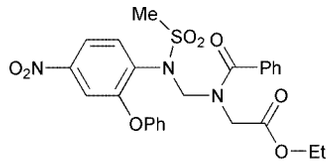
−5.0 to −6.0. Additional support for the unimolecular mechanism depicted in Scheme 3 comes from the temperature dependence for the decomposition of compounds **5a**–**c**, which yields values for $\Delta S^{\ddagger}$ of −9.0 (± 2), +3 (± 1) and −13 (± 5) J K^{-1} mol^{-1}, respectively (Table 2).

A similar reversal of reactivity between the base- and acid-catalysed hydrolysis has been reported for secondary (R = H) and tertiary (R = Me) *N*-benzoyloxymethylbenzamides **6**,[16] for which the tertiary compound was found to be 9-fold more reactive than its secondary counterpart in the acid-catalysed pathway; this compares favourably to the 7-fold difference observed here between **5c** and **5b**.

The pH-independent pathway

Only the hydrolysis of **5b** clearly exhibits a pH-independent pathway; for **5a** and **5c** no hydrolysis reaction was observed between pH 3–9. For compound **5b** the solvent deuterium isotope effect is 1.9 (Table 1). Additionally, at pH *ca.* 4.7 there is a concentration effect for acetate buffers (Table 3). Assuming the basic form of the buffer acts as the catalytic species, and making the appropriate adjustments for temperature and ionic strength effects on pH and pK_a values, the rate constants for the buffer catalysed reactions in H_2O and D_2O are 6.90×10^{-7} and 3.02×10^{-7} dm^3 mol^{-1} s^{-1}, respectively. Thus the solvent isotope effect on the buffer catalysed reaction is 2.3. These data are not consistent with a dissociative unimolecular mechanism such as the uncatalysed equivalent of Scheme 3. Given the greater reactivity of **5b** as compared with the *N*-methylsulfonamide derivates **5a** and **5c**, the hydrolysis mechanism is most likely to be an E2 elimination–addition pathway (Scheme 2, step k_0) that is general-base catalysed.

We have found these data to be consistent with the behaviour of **7**, the ethyl hippurate derivative of the anti-inflammatory agent nimesulide. Compound **7** is an analogue of **5c** and was found to be indefinitely stable in pH 7.4 phosphate buffer. Disappointingly, this compound also proved to be stable in human plasma, thereby making it a poor prodrug of nimesulide. Indeed, our data, especially those for **5b**, imply that the amidomethylsulfonamide functionality would be best deployed as a



7

prodrug system in which a secondary sulfonamide, that has an NH that is readily ionised at pH 7.4, acts as a pro-moiety for the amide drug.

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