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Acyloxymethyl as a Drug Protecting Group. Synthesis and Reactivity of N-Acyloxymethylsulfonamide Prodrugs.

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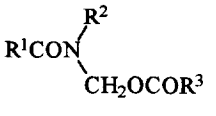
Abstract: Tertiary N-acyloxymethylsulfonamide prodrugs **3**, encompassing penicillin and sulfonamide antibiotics, have been synthesised. The pH-independent hydrolysis of these compounds ocurrs *via* the rate-determining formation of an N-sulfonyl iminium ion. SCF-MO calculations using the PM3 method indicate that iminium ion formation is slightly favoured, when compared with the corresponding amides, by *ca.* 10 $kJmol^{-1}$.

Tertiary N-acyloxymethylamides **1** are of particular interest in drug chemistry because of their potential to be used as prodrugs of both secondary amides and carboxylic acids [1,2]. At physiological pH, compounds **1** undergo hydrolysis *via* a unimolecular mechanism that involves the rate-limiting formation of the N-acyliminium ion **2** [1]. However, when compounds **1** contain a carboxylate leaving group of $pK_a \leq 3$, hydrolysis proceeds very rapidly [2] making pharmaceutical formulation more difficult. Therefore, we rationalized that substituting the more powerful electron withdrawing sulfonamide group for the amide moiety [3] would identify prodrugs able to regenerate a carboxylic acid parent drug at significantly slower hydrolysis rates.



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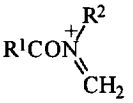

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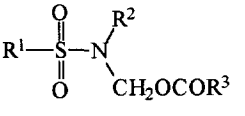

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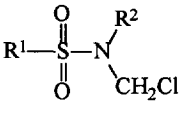

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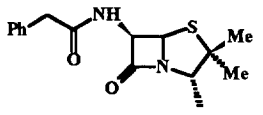
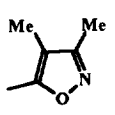
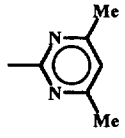
Herein we report the synthesis of the hitherto unknown tertiary N-acyloxymethylsulfonamides **3** and their surprising propensity to generate N-sulfonyliminium ions in aqueous buffers. Compounds **3a-i** were successfully prepared by reacting the appropriate chloromethylsulfonamide **4** with the sodium salt of a carboxylic acid at room temperature and in dry tetrahydrofuran [4]. Interestingly, compounds **4** displayed the same reactivity towards carboxylates as their amide counterparts, *i.e.* the reaction was complete within *ca.* 10 minutes either using benzoic acid (pK_a=4.2) or benzylpenicillin (pK_a=2.8) [2]. Alternatively, compounds **3j-k** were obtained by reacting the sodium salt of the corresponding sulfonamide with the appropriate chloromethyl ester in dimethylformamide as previously described for amides [1]. The rate constants for the solvolysis of compounds **3** were determined by UV (**3a-e**) or HPLC (**3f-k**) [5] usually at 37 °C (Table 1). The pH-rate profiles of esters **3** (an example for **3c** at 25 °C is shown in figure 1A) present a broad U-shape with a pH-independent pathway extending from pH *ca.* 2 to pH *ca.* 9.

Table 1. Pseudo-first order rate constants at 37 °C for the pH-independent solvolysis of acyloxymethylsuphonamides 3. Ionic strength kept constant at 0.5 mol dm^{-3} by addition of $NaClO_4$.

Compound	R^1	R^2	R^3	$10^3k_o/s^{-1}$
3a	4-MeC_6H_4	Me	C_6H_5	6.25; 5.00[a]
3b	4-MeC_6H_4	Et	C_6H_5	15.4
3c	4-MeC_6H_4	Pr	C_6H_5	18.2; 2.69[b]; 1.71[c]; 0.795[d]
3d	4-MeC_6H_4	Pr^i	C_6H_5	44.8
3e	4-MeC_6H_4	Bu	C_6H_5	26.8
3f	4-ClC_6H_4	Me	C_6H_5	1.85; 0.526[b]
3g	4-ClC_6H_4	Me	A	4.29
3h	4-$NO_2C_6H_4$	Me	A	1.64
3i	4-MeC_6H_4	Me	A	>10.0
3j	4-$NH_2C_6H_4$	B	C_6H_5	0.00167
3k	4-$NH_2C_6H_4$	C	CMe_3	0.00205

A: 

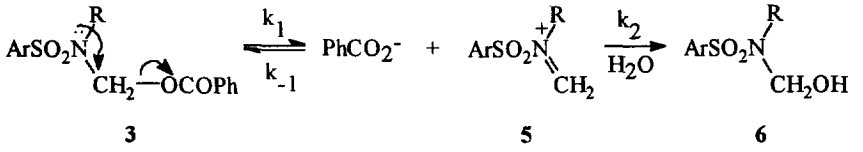
B: 

C: 

a) in D_2O; b) at 25 °C; c) at 20 °C; d) at 15 °C.

The pH-independent pathway is characterized by: *1)* absence of catalysis by acetate (pK_a=4.8), phosphate (pK_a=7.2) and morpholine (pK_a=8.4) buffers over a 10 fold concentration range; *2)* a solvent isotope effect, k_{H_2O}/k_{D_2O}, of 1.25 and *3)* a entropy of activation, $\Delta S^{\neq}$, value of 29±2 J K^{-1} mol^{-1}. Another striking feature is the high susceptibility of the pH-independent pathway to inductive effect of the N-alkyl substituent (Figure 1B). The Taft ρ^* value of -4.5 (r^2=0.98) for compounds **3a-e** (chosen so as to give a reasonable range of chemical reactivity for simple alkyl substituents - compound **3d** was especially included as it could potentially exert a steric influence that might be expected to retard the rate) is comparable to the ρ^* value of -3.5 described for the solvolysis of secondary tosylates, R^1R^2CHOTs in formic acid [6]. Therefore, we propose that the pH-independent pathway for decomposition of acyloxymethylsulfonamides **3** involves the rate-limiting formation of an N-sulfonyliminium ion **5** (Equation). Since the only product detected by HPLC is the corresponding secondary sulfonamide, the iminium ion **5** must be trapped by water to form **6** which, in turn, rapidly loses formaldehyde. With benzylpenicillin prodrugs **3g-i** the values of k_o decrease in the order **3i** > **3g** > **3h**. This result is consistent with the compounds **3g-i** solvolysing by the proposed mechanism rather than by β-lactam ring opening. Indeed, HPLC product analysis reveals the quantitative formation of benzylpenicillin and of the corresponding secondary sulfonamide.

Interestingly, the rate constants for the sulfonamides are very similar to those of the corresponding acyloxymethylamides **1**: at 25 °C the k_o value for **3f** of 5.3×10^{-4} s^{-1} is comparable to the 5.8×10^{-4} s^{-1} for the analogous amide [1], while at 37 °C the value of 4.3×10^{-3} s^{-1} for **3g** compares with 5.8×10^{-3} s^{-1} obtained for its amide analogue [2].



3 5 6

These results are supported by semiempirical SCF-MO calculations performed using the PM3 method[7,8]. The heats of formation for **1** and **3** (for **1** there are *E* and *Z* rotamers) are given in Table 2, together with the differences in enthalpy between **1** and **3** and the derived iminium ion **2** and **5**. These data indicate that iminium ion formation from compounds **3** and **4** is slightly favoured by *ca.* 10 kJmol^{-1} when compared with the amides (row 2; entry 1 with entries 3 and 4, and entry 2 with entries 5 and 6).

Figure 1. A: Dependence of the pseudo first-order hydrolytic rate constants for compound 3c upon pH at 25 °C in aqueous buffers. B: Taft plot for compounds 3a-e showing the relationship between the pH-independent hydrolytic rate constants and the electronic effect of the sulfonamide N-alkyl substituent.

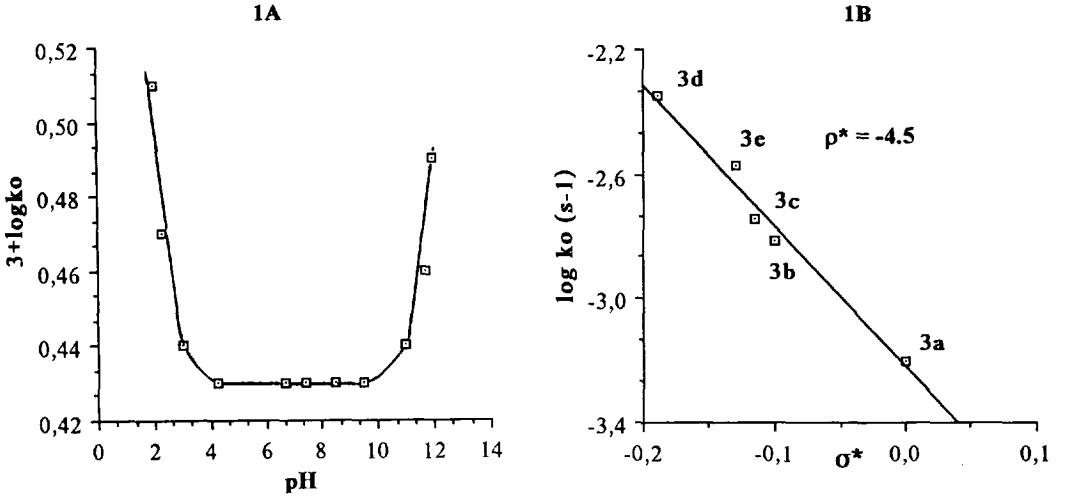


Table 2. Heats of formation calculated by PM3 for acyloxymethylsulfonamides, chloromethylsulfonamides,acyloxymethylamides,chloromethylamides compared with derived iminium ions [a].

Molecule[b]:						
ΔH_f / kJmol^{-1}	-202.9	-525.5	-92.9	-92.5	-419.2	-417.6
$\Delta\Delta H_f$ / kJmol^{-1}[c]	809.2	1131.8	818.8	818.0	1145.2	1143.1

a) Geometric parameters (bond lengths, bond angles and dihedral angles) for all structures fully optimised; b) Entries 3 and 5 relate to the *E*-rotamer of the amide, entries 4 and 6 to the *Z*-rotamer; c) $\Delta\Delta H_f = \Delta H_f$(iminium ion)-$\Delta H_f$(molecule)

In conclusion, tertiary acyloxymethylsulfonamides **3** undergo pH-independent solvolysis *via* rate-limiting formation of an N-sulfonyliminium ion, revealing that compounds **3** are as reactive as their amide counterparts despite the much stronger electron withdrawing effect of the sulfonyl, as compared with the carbonyl, group. Since sulfonamides are more acidic than amides [9], our results contradict the proposal that the ease of iminium ion formation could be related to the pK_a of the parent NH compound [10]. The very low reactivity displayed by prodrugs **3j-k** can be accounted for by the strong electron withdrawing effect of the N-heterocyclic ring.

References and notes

1. Iley,J.; Moreira,R.; Rosa,E.; *J.Chem.Soc. Perkin 2*; **1991**, 563.
2. Moreira,R.; Mendes,E.; Calheiros,T.; Bacelo,M.J.; Iley,J.; *Tetrahedron Lett.*, **1994**, *35*, 7107.
3. The σ^* values for the $PhSO_2$ and PhCO groups are 3.25 and 2.2, respectively.
4. Synthesis of **3h**: a solution of the appropriate compound **4** (1.1 equiv.), prepared as the analogous amides [2], in dry THF (1 ml) was added to a suspension of sodium benzylpenicilloate (5mmol) in THF (5 ml) at room temperature. Upon completion of the reaction, the solvent was evaporated, and the residue treated with ice-water and extracted with ethyl acetate. The organic extracts were washed with ice-water, sodium bicarbonate, brine and dried over magnesium sulfate. Evaporation of the solvent gave the crude **3h** which was purified by column chromatography using ethyl acetate as eluant. ν_{max}: 3332, 1778, 1725, 1633, 1335, 1150 cm^{-1}; δ_H: 1.34(6H, s, C_2-Me), 2.99(3H, s, N-Me), 3.64(2H, s, PhCH_2), 4.16 (1H, s, C_3-H), 5.34(1H, d, J=4 Hz, C_5-H), 5.48(1H, dd, J=11 Hz, NCH_2O), 5.52(1H, dd, J=11 Hz, NCH_2O), 5.59 (1H, dd, J=4 and 9 Hz, C_6-H), 6.09(1H,d, J=9 Hz), 7.25-7.37(5H, m); 7.95-8.42(4H, AA'BB'). FAB-MS, m/z (%): 563(0.5, M+1); 229(100, M-OCOR3). Found: C, 51.1; H, 4.81; N, 9.75. Calc. for $C_{24}H_{26}N_4O_8S_2$: C, 51.2; H, 4.63; N, 9.96.
5. HPLC separation was achieved using a Merck LiChrospher RP-8 5μm column and a mobile phase of methanol (60%) and aqueous 0.04 M tetrabutylammonium phosphate (40%). Pseudo-first order rate constants were determined using peak areas of the prodrug or the parent drug. The upper limit for reproducible pseudo-first order rate constants by this method is *ca.* $5x10^{-3}s^{-1}$ compared to *ca.* $50x10^{-3}s^{-1}$ by the UV method. For compounds **3g-i**, the very small absorbances changes (< 0.01) precluded study by UV.
6. Isaacs, N.S.; *Physical Organic Chemistry*, Longman Scientific, Harlow, 1987, pp.389. In trifluroacetic, which has similar polarity to water, the ρ^* value for the solvolysis of secondary tosylates rises to -7.1.
7. SCF-MO calculations were carried out by using the PM3 procedure from GAMESS [9].
8. Stewart, J.J.P; *J. Computer-Aided Mol. Des.*, **1990**, *4*, 1.
9. The pK_a of $PhSO_2NHMe$ is 11.4 at 20 °C. King, J.F. in *The Chemistry of Sulphonic Acids, Esters and their Derivatives*; Patai, S. and Rappoport, Z.; John Wiley, Chichester, 1991, pp. 249.
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