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# Hydrolysis of a sulfonamide by a novel elimination mechanism generated by carbanion formation in the leaving group

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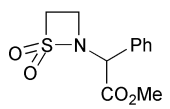
*Received (in Cambridge, UK) 12th December 2001, Accepted 20th February 2002*
*First published as an Advance Article on the web 12th March 2002*

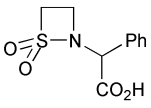
**The alkaline hydrolysis of *N*-α-methoxycarbonyl benzyl-ß-sultam occurs $10^3$ times faster than the corresponding carboxylate and with rapid D-exchange at the α-carbon: the pH rate profile indicates pre-equilibirum CH ionisation and together with formation of benzoyl formate as a product this suggests a novel mechanism for hydrolysis.**

Acyl and sulfonyl transfer reactions which occur by an elimination process are well established for systems with an acidic CH α- to the electrophilic centre.[1] Proton abstraction generates a carbanion which is used to expel the leaving group in the E1cB type process shown in Scheme 1.

In principle, a similar elimination process can occur by generation of a negative charge on a carbon α to the leaving group atom. This is unlikely to occur in acyl transfer reactions because it requires the generation of an acyl carbanion. However, it is a more likely mechanism for sulfonyl transfer because of the variable oxidation states available to sulfur. We report herein the first example of an E1cB type process for the hydrolysis of a sulfonyl centre brought about by an 'acidic' CH α- to the leaving group atom, *i.e.* electron flow is in the opposite direction to that which normally occurs in nucleophilic substitution reactions.

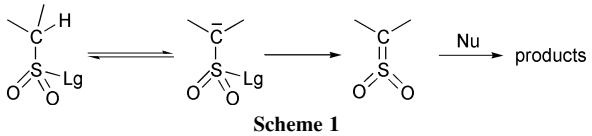



(1)




(2)

The acid catalysed hydrolysis of *N*-α-methoxycarbonylbenzyl-β-sultam (**1**) occurs by N-protonation and subsequent N-fission and ring opening, as established for other ß-sultams.[2] The second order rate constant, $k_H$, for this process is 1.00 $M^{-1}$ $s^{-1}$ at 30 °C, almost identical to that of 0.94 $M^{-1}$ $s^{-1}$ for the corresponding carboxylic acid (**2**). However, several aspects of the alkaline hydrolysis of the two ß-sultams (**1**) and (**2**) are very different. The pseudo first-order rate constants for the hydrolysis of (**1**) were obtained spectrophotometrically by monitoring the absorbance change at 250 nm and the pH-rate profile for the hydrolysis of (**1**) is shown in Fig. 1. The rate shows the expected acid catalysed reaction and a first order dependence on hydroxide ion concentration from pH 7 to 10.5. However, above pH 11 the rate becomes pH independent. The apparent $k_{OH}$ value obtained from the linear region between pH 7 and pH 10.5 is 2.24 $M^{-1}$ $s^{-1}$ at 30 °C. If this value represented hydroxide ion attack at the sulfonyl centre followed by ring opening then there is a significant rate enhancement of greater than $10^3$-fold over the $k_{OH}$ of the corresponding carboxylate derivative *N*-α-carboxybenzyl-β-sultam (**2**), 6.0 × $10^{-4}$ $M^{-1}$ $s^{-1}$. This difference is much larger than the 16-fold greater reactivity of benzyl penicillin methyl ester over its carboxylate analogue.[3] In addition, the change in slope in the pH-rate profile at *ca.* pH 10.5 suggests that a change in rate limiting step or an ionisation has occurred. The CH α- to the sulfonamide nitrogen in (**1**) undergoes D-exchange in deuterated hydrogencarbonate buffer. A reduction in the intensity of the $^1$H NMR CH signal (4.99 ppm) occurred at a faster rate than all other changes. This was followed by a first order reduction in the substrate signals (2H 4.16 ppm, 2H 3.16 ppm, 3H (s) 3.62 ppm) and emergence of product signals (3.00 ppm, 2.41 ppm, (s) 3.23 ppm) for the $CH_3$ and $CH_2$ elements respectively. The aryl-H region gradually became more complex. Doping of the final mixture with methanol led to an increase in intensity of the new $CH_3$ signal at 3.23 ppm. In a separate $^1$H-NMR experiment, benzoyl formate was observed to have identical aryl-H signals for three out of five resonances observed for the hydrolysis product of (**1**). Negative mode ESIMS of the reaction mixture showed *m/z* of 149 corresponding to benzoylformate $PhCOCO_2^-$ and unreacted ß-sultam incorporating one equivalent of deuterium.




**Scheme 1**

The $^1$H-NMR experiment shows that the CH proton was gradually removed in the presence of deuteroxide ion in advance of the emergence of products. Electron withdrawing ester and sulfonamide groups are adjacent to the CH group and, along with a phenyl group, are expected to make this centre quite acidic and it is therefore likely that this proton corresponds to the p$K_a$ of *ca.* 10, indicated by the pH-rate profile (Fig. 1). The emergence of product was accompanied by a change in the methylene resonances, consistent with ring opening, and hydrolysis of the methyl ester. This evidence leads to the proposal of a novel mechanism of β-sultam hydrolysis in the presence of hydroxide ion. Initial reversible deprotonation of the acidic exocyclic methine group α- to the N-'leaving group' leads to formation of a carbanion which then undergoes rate limiting conversion to a ring opened imine species with expulsion of a *sulfinate anion*. The sulfinate anion has been previously described as a leaving group.[4] The imine species and

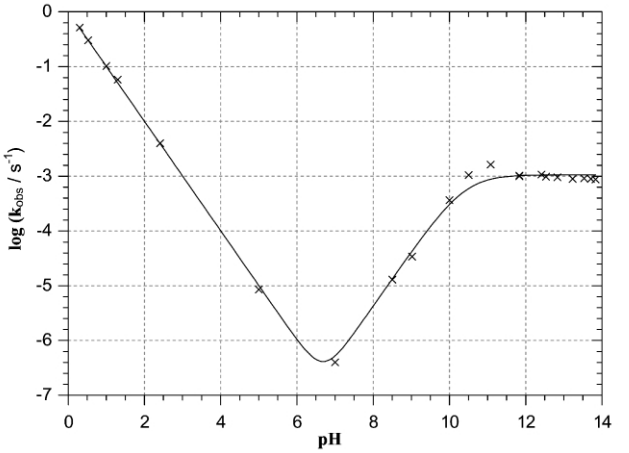



**Fig. 1** pH-Rate profile for the hydrolysis of *N*-α-methoxycarbonylbenzyl-β-sultam (**1**) in aqueous solution at 30 °C, 1% MeCN v/v and $I$ = 1.0 M (KCl).

DOI: 10.1039/b111340m

the methyl ester fragment can then undergo rapid hydrolysis to produce benzoyl formate, the principal reaction product detected by negative mode ESIMS.

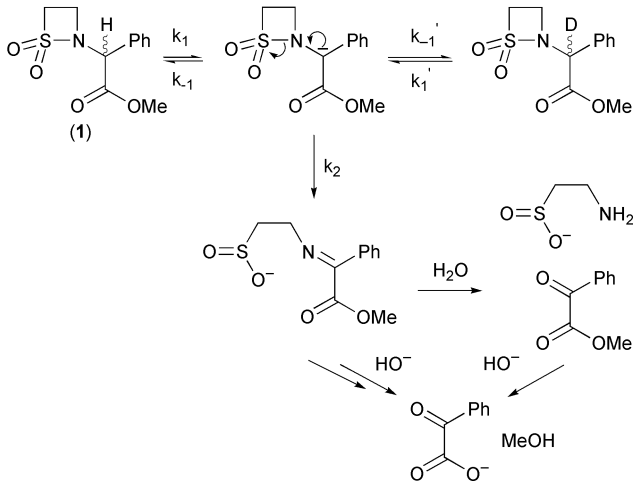
The proposed pathway, outlined in Scheme 2, is essentially similar to an E1cB-type mechanism of elimination. The full pH-rate profile, has been modelled (Scientist) to eqn. (1) based on reversible deprotonation with the rate of reaction, in basic solution, dependent on the fraction of the carbanion present.

$$k_{obs} = k_H[H^+] + k_2(K_a/(K_a + [H^+])) \quad (1)$$

In basic solution, if $[H^+] \gg K_a$, *i.e.* at pHs below the p$K_a$ of the ionisable proton but above pH 7, $k_{obs} = k_2K_a/[H^+]$, and the rate is inversely proportional to the hydrogen ion concentration, as observed. If $[H^+] \ll K_a$, *i.e.* at a pH above the p$K_a$ of the ionisable proton, $k_{obs} = k_2$, and a pH independent rate is observed.

The calculated line in (Fig. 1) represents the fit obtained using the following constants: $k_2 = 1.06 \times 10^{-3}$ s$^{-1}$, $K_a = 4.02 \times 10^{-11}$ M (p$K_a$ = 10.40), $k_H = 1.00$ M$^{-1}$ s$^{-1}$.

The apparent kinetic p$K_a$ of 10.4 for the ionisation of (**1**) indicates an unusually acidic carbon acid for this structure. The p$K_a$ of ethyl acetate in water is 25.6[5] and α-phenyl and α-*N*-acylamino substituents both lower the p$K_a$ of carbon acids by about 4 units each.[6,7] An estimated p$K_a$ of RCON(Me)CH(Ph-)$CO_2$Et is thus about 17, and as $RSO_2NR$- is slightly more electron-withdrawing than RCONR- the p$K_a$ of (**1**) is expected to be about 15. The p$K_a$ of the quaternary ammonium salt of the methyl ester of glycine, $Me_3N^+CH_2CO_2Me$, has recently been reported to be 18.0.[8] The p$K_a$ of 10.4 for (**1**) is thus unexpectedly low. It is clear that C–H ionisation ($k_1$ in Scheme 2) is not rate limiting given the occurrence of rapid D-exchange in the substrate (**1**). Furthermore, the estimated[6] rate constant for the deprotonation of a carbon acid of p$K_a$ 10.4 by hydroxide ion is about $2 \times 10^2$ dm$^3$ mol$^{-1}$ s$^{-1}$ which is about $10^2$ greater than that observed for the reaction of (**1**).




**Scheme 2**

The mechanism outlined in Scheme 2 represents a novel pathway for the hydroxide ion catalysed hydrolysis for a β-sultam and demonstrates electron flow from the 'leaving group' to the electrophilic sulfonyl centre. Based on this mechanism, the apparently enhanced second order rate constant for alkaline hydrolysis, $k_{OH}$, for *N*-α-methoxycarbonylbenzyl-β-sultam (**1**) does not in fact represent hydroxide ion attack at the sulfonyl centre. The rate enhancement for the hydroxide ion hydrolysis of (**1**) over *N*-α-carboxybenzyl-β-sultam (**2**) is the result of a different mechanism of hydrolysis. The fact that the imine species and the methyl ester of benzoyl formate (Scheme 2) cannot be detected by ESIMS suggests that their hydrolysis is rapid.

We thank the EPSRC for CASE studentships to J. M. Wood (AstraZeneca) and P. S. Hinchliffe (British Biotech).

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