Evidence for a trigonal bipyramidal intermediate during nucleophilic substitution at a sulfonyl centre and for a sulfonylium cation in the acid catalysed reaction

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The rate of alkaline hydrolysis of a substituted β-sultam shows a dominant term second-order in hydroxide ion, clearly indicating the reversible formation of a monoanionic trigonal bipyramidal intermediate; substituent effects and kinetic parameters for the acid catalysed hydrolysis are indicative of the formation of a sulfonylium ion intermediate.

Direct substitution at sulfonyl sulfur is thought to occur with inversion of configuration.[1] Although this indicates that the geometry of the displacement probably involves one in which the entering and leaving groups occupy the two apical positions of a trigonal bipyramid, it does not distinguish between an S_N2 type transition state and an intermediate with a real life-time. In fact, unlike substitution at phosphonyl centres[2] there is no real good evidence for the formation of trigonal bipyramidal intermediates for reactions at sulfonyl sulfur.[3]

One of the most convincing pieces of evidence for the formation of tetrahedral intermediates during the hydrolysis of carboxylic acid amides is that terms second order in hydroxide ion have been observed for the hydrolysis of some anilides[4] and acetylpyrroles.[5] Important factors in determining the pathway of breakdown of tetrahedral intermediates are the basicity of the amine nitrogen leaving group and the acidity of the hydroxy group formed from the attacking nucleophilic hydroxide ion.[5]

We have studied the reactivity of β-sultams as potential mimics of the β-lactam antibiotics and shown that they undergo base-catalysed hydrolysis at a rate which is over 10^7-fold faster than that of an analogous acyclic sulfonamide, but by a pathway which is first order in hydroxide ion.[6] We reasoned that β-sultams with electron-withdrawing groups α to the sulfonyl centre may generate a trigonal bipyramidal intermediate which requires a second hydroxide-ion to facilitate its breakdown.

The pseudo-first order rate constants (k_{obs}) for the alkaline hydrolysis of the β-sultam **1** are clearly second-order in hydroxide ion (Fig. 1) and a plot of $k_{obs}/[OH^-]$ against $[OH^-]$ (Fig. 2) shows that this is the dominant term in the rate law, equation (1). The values of k_{OH1} and k_{OH2} are 8.98×10^{-3}

$$k_{obs} = k_{OH1}[OH^-] + k_{OH2}[OH^-]^2 \qquad (1)$$

$dm^3\ mol^{-1}\ s^{-1}$ and $3.87 \times 10^{-2}\ dm^6\ mol^{-2}\ s^{-1}$ respectively at 30 °C and I = 1.0 M (KCl).

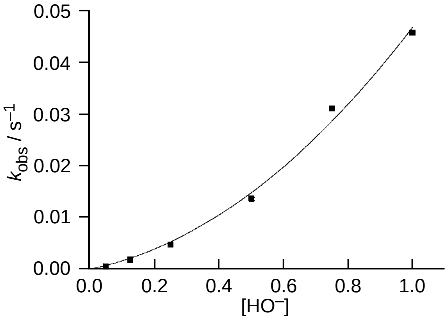
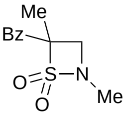


Fig. 1 Plot of the observed pseudo-first order rate constant, k_{obs}, for the hydrolysis of β-sultam, **1**, against the hydroxide ion concentration at 30 °C, I = 1.0 M (KCl)



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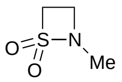


2

The second-order term in hydroxide ion is strong evidence for the formation of a trigonal bipyramidal intermediate (TBPI) with a hypervalent sulfur. Initial but *reversible* attack of hydroxide ion on the β-sultam **1** generates a monoanionic TBPI$^-$, which requires deprotonation by a second hydroxide ion before the intermediate can collapse to products (Scheme 1). The third order rate constant k_{OH2} would then be determined by eqn. (2), with $k_{-1} \gg k_2[OH^-]$.

$$k_{OH2} = (k_1k_2[OH^-]^2)/(k_{-1} + k_2[OH^-]) \qquad (2)$$

Not only is the observation of the term second-order in hydroxide ion evidence for the formation of a TBPI, it

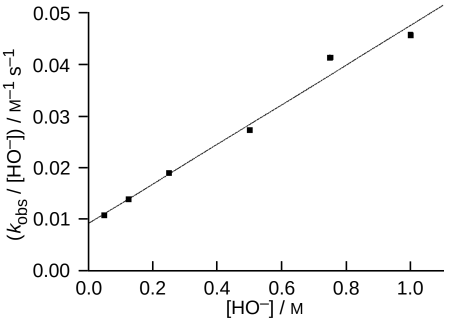
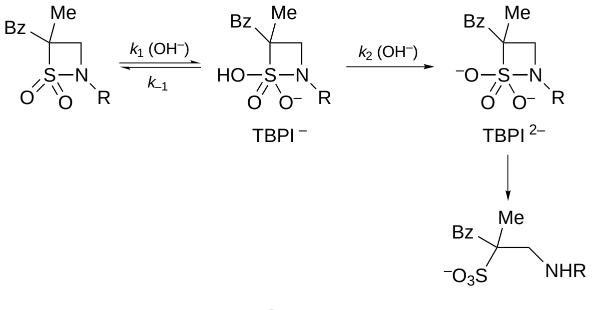
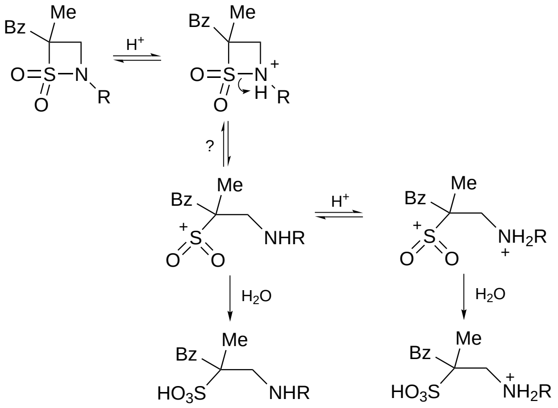


Fig. 2 Plot of the apparent second order rate constants, $k_{obs}/[OH^-]$, for the hydrolysis of the β-sultam, **1**, against hydroxide ion concentration at 30 °C, I = 1.0 M (KCl)



Scheme 1



Scheme 2

demonstrates that k_{-1}, the rate constant for expulsion of hydroxide ion to regenerate starting material, is greater than ring opening of the strained four-membered β-sultam. It is a surprising fact that β-lactams do not undergo ring opening at a rate predicted by the release of strain energy in the four-membered ring.[7] It now appears that this is also the case for β-sultams. The rate limiting step for the alkaline hydrolysis of the β-sultam **1** could be either diffusion controlled deprotonation of the monoanionic TBPI$^-$, the subsequent breakdown of the dianionic TBPI^{2-} or a concerted process involving both these steps. The solvent kinetic isotope effect for the term first order in hydroxide in $k_{OH1}^{H_2O}/k_{OD1}^{D_2O}$ is 0.49 whereas that for the term second order in hydroxide ion $k_{OH2}^{H_2O}/k_{OD2}^{D_2O}$ is 0.35. The latter is consistent with a stepwise process for product formation. For any process involving a proton in flight in the transition state the solvent kinetic isotope effect would be greater than unity. If formation of the dianionic TBPI^{2-} is rate limiting this would be determined by the rate of the diffusion controlled encounter of hydroxide ion with the monoanionic trigonal bipyramidal intermediate TBPI$^-$. Alternatively, breakdown of the dianionic TBPI^{2-} could be rate limiting. The entropy of activation for the third order rate constant k_{OH2} is -131 J K^{-1} mol^{-1} which is similar to that for the second order rate constant, k_{OH1}, of -121 J K^{-1} mol^{-1} and is again indicative of a stepwise mechanism for the subsequent reaction of TBPI$^-$ rather than a concerted process.

The second-order rate constant for the *acid* catalysed hydrolysis of the β-sultam **1** is 1.90×10^{-3} dm^3 mol^{-1} s^{-1} which is 1.5×10^3-fold less than that for the derivative lacking the α-benzoyl group **2**. This enormous rate retardation by electron-withdrawing substituents generates an apparent Hammett ρ_I value for α-substitution of -10. By contrast, the effect of acyl substituents upon the rate of acid catalysed hydrolysis of amides is small, with electron-withdrawing substituents producing either a small increase or decrease in rate.[8] Although only based on a single substituent, this effect indicates a unimolecular A1-type process in which the N-conjugate acid of the β-sultam undergoes rate-limiting ring opening to form an electron-deficient sulfonylium ion which is then trapped by water to give the product β-amino sulfonic acid (Scheme 2).

Although sulfonylium ions are much more difficult to form than acylium ions[9] and there are no well established cases for their formation during substitution at sulfonyl centres,[3] the present case is compatible with the similar acylium ion mechanism suggested for the acid catalysed hydrolysis of β-lactams.[10]

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Footnote and References

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