The hydrolytic reactivity of β-sultams

Nicholas J. Baxter, Andrew P. Laws, Laurent Rigoreau and Michael I. Page*

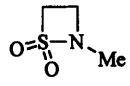
Department of Chemical and Biological Sciences, The University of Huddersfield, Queensgate, Huddersfield, UK HD1 3DH

COMMUNICATION PERKIN 2

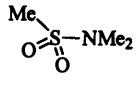
***N*-Methyl β-sultam undergoes acid- and base-catalysed hydrolysis in water at 30 °C and I = 1.0 mol dm^{-3} with k_{H^+} = 2.79 dm^3 mol^{-1} s^{-1} and k_{OH} = 1.38 × 10^{-2} dm^3 mol^{-1} s^{-1}. These second-order rate constants are approximately 10^9 and 10^7, respectively, greater than those for a similar acyclic sulfonamide. The entropy of activation for the acid-catalysed hydrolysis of the β-sultam is −80 J K^{-1} mol^{-1} which may be indicative of unimolecular ring opening, whereas that for the base-catalysed reaction, −184 J K^{-1} mol^{-1}, is consistent with a bimolecular process.**

Sulfonamides are extremely resistant to alkaline and acidic hydrolysis.[1,2] This lack of reactivity makes them potentially attractive as haptens for generating catalytic antibodies by acting as stable tetrahedral intermediate, or transition state, analogues for acyl transfer reactions.[3] Similarly, they have the capacity to act as inhibitors of proteolytic enzymes. Because of our interest in β-lactams[4] we have been exploring the chemistry of β-sultams for both of these purposes.

N-Methyl β-sultam **1** was prepared by literature methods and



1



2

found to undergo facile acid- and base-catalysed hydrolysis to the corresponding amino sulfonic acid,[5] which was confirmed by NMR spectroscopy. The most suitable method for analysis was gas chromatography and the reaction was monitored by measuring the disappearance of *N*-methyl β-sultam on a 5% PEG (20M) on Chromosorb GAWDMCS (100/120 mesh), 1.5 × 4 mm column. With nitrogen as the carrier gas at 210 °C, *N*-methyl β-sultam had a retention time of 2.5 min using a flame ionization detector and tetramethylene sulfone as an internal standard. The rate of hydrolysis in water at 30 °C and I = 1.0 mol dm^{-3} (KCl) is subject to both general-acid- and general-base-catalysis and the pH–rate profile (Fig. 1) was obtained by

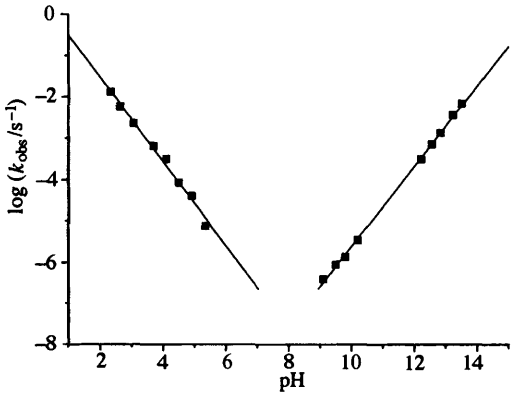
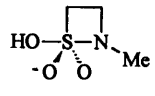


Fig. 1 The observed pseudo-first-order rate constants, extrapolated to zero buffer concentration, as a function of pH for the hydrolysis of *N*-methyl β-sultam, **1**, in water at 30 °C and I = 1.0 mol dm^{-3}

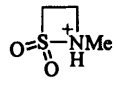
extrapolation of the observed pseudo-first-order rate constants to zero buffer concentration. The second-order rate constant for the acid-catalysed reaction was found to be k_H = 2.79 dm^3 mol^{-1} s^{-1}, whereas that for base was k_{OH} = 1.38 × 10^{-2} dm^3 mol^{-1} s^{-1}. The corresponding rate constants for the analogous acyclic sulfonamide **2** are difficult to obtain. The secondary amine derivative is not only an appropriate model but also removes the problem of decreased reactivity of the sulfonamide in base due to N–H ionisation found with sulfonamides of primary amines. There is less than 7% decomposition of the sulfonamide **2**, as determined by GC analysis, in either 1 M HCl or NaOH in water at 80 °C after 15 days. The maximum rate constant for the acid-catlysed hydrolysis, k_H, of the acyclic sulfonamide **2** at 30 °C is therefore estimated to be < 2 × 10^{-9} dm^3 mol^{-1} s^{-1} and that for alkaline hydrolysis, k_{OH}, is also < 2 × 10^{-9} dm^3 mol^{-1} s^{-1} at 30 °C.

The rate enhancement towards hydrolysis for the four-membered β-sultam, **1**, compared with acyclic sulfonamide, **2**, is thus at least 10^9 for acid-catalysed hydrolysis and at least 10^7 for base-catalysed hydrolysis. This enormous increased reactivity is similar to that shown by β-phospholactams,[6] but contrasts sharply with the similar reactivity of analogous β-lactams and acyclic amides.[4]

Nucleophilic substitution at sulfonyl sulfur is commonly bimolecular although the evidence for a stepwise process occurring through the formation of a trigonal bipyramidal intermediate is not as firm as that for similar reactions at phosphonyl phosphorus.[1] Furthermore, there are examples of sulfonyl transfer occurring by an apparent concerted mechanism.[7] There is no incorporation of D into the methylene α to the sulfonyl centre when the reaction is carried out in D_2O which could have been indicative of an El_cB-type mechanism. Furthermore, such a mechanism is likely to produce an unfavourable 'twisted' sulfene as an intermediate.[8] The entropy of activation for the alkaline hydrolysis of the β-sultam, **1**, is −184 J K^{-1} mol^{-1} (st. st. 1 mol dm^{-3}) and is consistent with a bimolecular process involving hydroxide ion attack on sulfur and, possibly, the formation of a trigonal bipyramidal intermediate, **3**. It has long been known that the alkaline



3



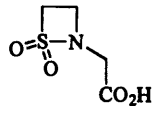
4

hydrolysis of five-membered cyclic sulfate and phosphate esters occurs orders of magnitude faster than that of the corresponding acyclic analogues,[9] although whether this is due to release of strain energy or differences in solvation energy remains controversial.[10] In the four-membered β-sultam, **1**, there is presumably considerable ground state strain, some of which is due to the unfavourable endocyclic bond angle of about 90° around sulfur compared with an ideal tetrahedral geometry of 109°. If nucleophilic substitution at sulfuryl centres occurs through the formation of a trigonal bipyramidal (TBP) intermediate or the transition state resembles this geometry then there may be relief of strain energy.

It seems probable that when pentacoordinate sulfur is contained in a four-membered ring the latter would prefer to be attached apical/equatorial *i.e.* with an approximately 90° endocyclic bond angle around sulfur. Attack by hydroxide ion on sulfur in **1** is therefore accompanied by a large relief in ground-state bond angle strain upon formation of the TBP intermediate, compared with the analogous acyclic derivative. This is in contrast to the β-lactam/amide systems where there is relatively little relief of ground-state bond angle strain around the β-lactam carbonyl carbon upon formation of the tetrahedral intermediate *i.e.* approximately 90° compared with 120° in the ground-state and 90° compared with 109° in the tetrahedral intermediate.

There is convincing evidence that the protonation of sulfonamides occurs on nitrogen[11] and the acid-catalysed hydrolysis of the β-sultam, **1**, could occur by a unimolecular A-1-type process. The evidence for such a mechanism in five-membered sultams is ambiguous, although most of the evidence is consistent with a bimolecular mechanism.[12] The entropy of activation for the acid-catalysed hydrolysis of the β-sultam, **1**, is $-80\ J\ K^{-1}\ mol^{-1}$, which by itself is not strong enough evidence for rate-limiting unimolecular ring opening of the *N*-protonated β-sultam, **4**. This mechanism has been suggested for the acid-catalysed hydrolysis of both β-lactams[13] and β-phospholactams.[14]

The corresponding carboxy derivative **5** is not an inhibitor of



5

any of the β-lactamase enzymes,[15] but the results reported here indicate that the β-sultams may still merit investigation as β-lactam bioisosteres.

Acknowledgements

We thank the EPSRC for financial support.

References

1 H. Maskill, *Chem. Soc. Rev.*, 1989, **18**, 123.
2 S. Searles and S. Nukina, *Chem. Rev.*, 1959, **59**, 1077; P. D. Carpenter and M. Lennon, *J. Chem. Soc., Chem. Commun.*, 1973, 664; R. S. Ryabova, M. I. Vinnik, V. T. Lazareva and R. D. Erlikh, *Zh. Org. Khim.*, 1970, **6**, 797; M. I. Vinnik, R. S. Ryabova and V. T. Lazareva, *Zh. Org. Khim.*, 1970, **6**, 1438; A. J. Buglass and J. G. Tillett, *The Chemistry of Sulphonic Acids, Esters and their Derivatives*, ed. S. Patai and Z. Rappaport, Wiley, Chichester, 1991, ch. 19.
3 W. J. Moree, A. Schouten, J. R. Kroon and R. M. U. Liskamp, *Int. J. Pept. Prot. Res.*, 1995, **45**, 501.
4 M. I. Page, *The Chemistry of β-Lactams*, ed. M. I. Page, Blackie, London, 1992, pp. 79–100; M. I. Page, *Adv. Phys. Org. Chem.*, 1987, **23**, 165.
5 A. Champseix, J. Chanet, A. Etienne, A. Le Berre, J. C. Mason, C. Napierala and R. Vessiere, *Bull. Soc. Chim. Fr.*, 1985, 463; W. Koller, A. Linkies, H. Rehling and D. Reuschling, *Tetrahedron Lett.*, 1983, **24**, 2131.
6 A. P. Laws, J. R. Stone and M. I. Page, *J. Chem. Soc., Chem. Commun.*, 1994, 1223.
7 A. Williams, *Chem. Soc. Rev.*, 1994, 93; N. Bourne, A. Hopkins and A. Williams, *J. Am. Chem. Soc.*, 1985, **107**, 4327; P. Montjoint and M. F. Ruasse, *Bull. Soc. Chim. Fr.*, 1988, 356; T. Okuyama, J. P. Lee and K. Ohnishi, *J. Am. Chem. Soc.*, 1994, **116**, 6480.
8 A. Williams, K. T. Douglas and J. S. Loran, *J. Chem. Soc., Chem. Commun.*, 1974, 689; T. Deacon, A. Steltner and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1778.
9 E. T. Kaiser, *Acc. Chem. Res.*, 1968, **1**, 70; R. Kluger and S. Taylor, *J. Am. Chem. Soc.*, 1990, **112**, 6669; P. C. Haake and F. H. Westheimer, *J. Am. Chem. Soc.*, 1961, **83**, 1102.
10 G. R. J. Thatcher and D. R. Cameron, *J. Chem. Soc., Perkin Trans. 2*, 1996, 767; A. Dejaegere and M. Karplus, *J. Am. Chem. Soc.*, 1993, **115**, 5316; F. H. Westheimer, *Acc. Chem. Res.*, 1968, **1**, 70.
11 R. G. Laughlin, *J. Am. Chem. Soc.*, 1967, **89**, 4268; F. M. Menger and L. Mandell, *J. Am. Chem. Soc.*, 1967, **89**, 4424.
12 Y. Bekdemir, J. G. Tillett and R. I. Zalewski, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1643; D. Klamann and G. Hofbauer, *Liebigs Ann. Chem.*, 1953, **581**, 182; D. Klamann and E. Fabienka, *Chem. Ber.*, 1959, 712; W. F. Erman and H. C. Kretschmar, *J. Am. Chem. Soc.*, 1961, **83**, 4841.
13 P. Proctor, N. P. Gensmantel and M. I. Page, *J. Chem. Soc., Perkin Trans. 2*, 1982, 1185.
14 M. I. Page, A. P. Laws, M. J. Slater and J. R. Stone, *Pure Appl. Chem.*, 1995, **67**, 711.
15 S. G. Waley, *The Chemistry of β-Lactams*, ed. M. I. Page, Blackie, London, 1992, pp. 198–228; R. F. Pratt, *The Chemistry of β-Lactams*, ed. M. I. Page, Blackie, London, 1992, pp. 229–271.

Paper 6/05903A
Received 27*th August* 1996
Accepted 26*th September* 1996