Unusual steric effects in sulfonyl transfer reactions

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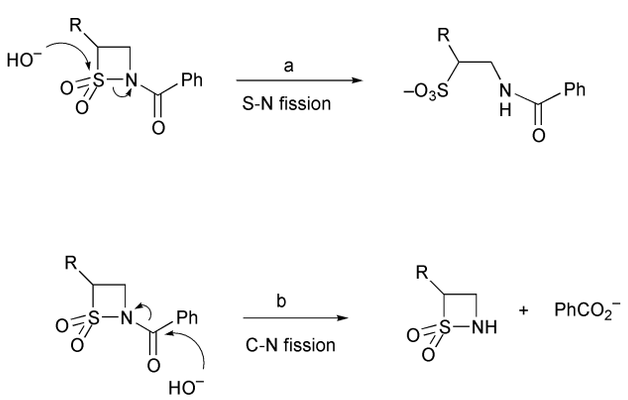
Received (in Cambridge, UK) 5th June 2001, Accepted 18th July 2001
First published as an Advance Article on the web 2nd August 2001

The hydrolysis of *N*-acyl-β-sultams generally occurs with ring opening and S–N fission in contrast to the C–N fission observed in analogous acyclic *N*-acyl sulfonamides. Similar to other β-sultams, the *N*-acyl derivatives are at least 10^6 more reactive than *N*-acylsulfonamides. However, the α-substituted 4-isopropylidene β-sultam is relatively unreactive and undergoes alkaline hydrolysis with C–N fission leaving the strained 4-membered β-sultam ring intact. This reduction in reactivity is shown to be due to steric strain introduced in the transition state for attack at the sulfonyl centre. (*Z*)-4-Ethylidene-β-sultam shows similar behaviour with preferential C–N fission whereas the (*E*)-4-ethylidene isomer and 4-isopropyl-β-sultam revert to hydrolytic ring opening with S–N fission.

Introduction

If a cyclic compound is in equilibrium with its open chain derivative then alkyl substitution thermodynamically favours the cyclic form and kinetically increases the rate of ring closure.[1] A major step forward in separating the contributing factors to this phenomenom was the work of Eberson[2] on measuring the equilibrium constants between substituted dicarboxylic acids and their cyclic anhydrides. Similarly, the rates of ring-opening reactions can be greatly influenced by substituents, such as those observed in the acid catalysed hydrolysis of substituted 1,3-dioxolanes.[3]

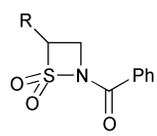
In this paper we describe some unexpected α-alkyl substituent effects upon ring-opening reactions accompanying the alkaline hydrolysis of *N*-acyl-β-sultams, **1**. Depending on the substituent, this hydrolysis may involve either ring opening, arising from nucleophilic attack of hydroxide ion upon the cyclic sulfonamide group as shown in pathway a of Scheme 1,



Scheme 1

or attack of hydroxide ion upon the exocyclic acyl amide group. The latter reaction leads to amide hydrolysis and preservation of the β-sultam ring as shown in pathway b.

In general, acyl transfer reactions in acyclic reactants occur much more readily than analogous sulfonyl transfers.[4] For



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example, the rate of alkaline hydrolysis of acyl derivatives is often about 10^3-fold faster than the equivalent sulfonyl derivative. For *N*-acylsulfonamides, **2**, which incorporate both centres in one molecule, nucleophiles preferentially attack the carbonyl group to displace the sulfonamide anion [eqn. (1)].[5]

$$\underset{\mathbf{2}}{R^1SO_2NHCOR^2} \xrightarrow{NuH} R^1SO_2NH_2 + R^2CONu \quad (1)$$

An additional factor favouring acyl attack in this case is the strong electron-withdrawing character of the sulfonamide group, with the sulfonyl group stabilising the adjacent lone pair on nitrogen by a polarisation effect rather than conjugative d–pπ bonding.[6] This activates the carbonyl group towards nucleophilic attack and, insofar as sulfonamides are stronger acids than amides by about 5 p*K* units, sulfonamide anions are usually better leaving groups than amide anions.

We have recently been studying *N*-acyl-β-sultams as mechanism-based inhibitors of serine proteases[7] and discovered that these compounds generally undergo hydrolysis with S–N fission and displacement of the amide group. The observation that alkyl substituents can redirect reaction to the exocyclic group led us to examine the factors controlling this selectivity by studying the relative hydrolytic reactivity of the 4-alkyl- and 4-alkylidene-β-sultams, **3**–**8**.

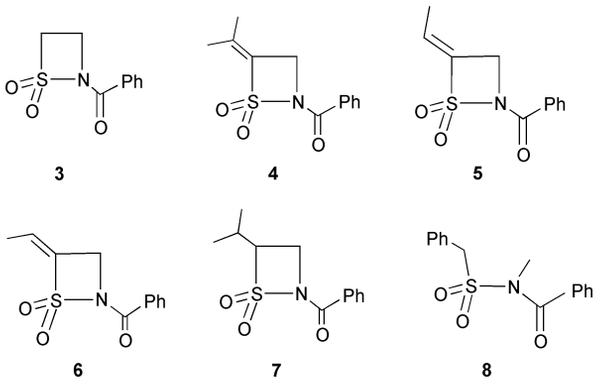
Results and discussion

The alkaline hydrolysis in water of the acyclic *N*-acylsulfonamide, **8**, occurs by *N*-acyl fission as a result of hydroxide ion attack on the carbonyl group followed by displacement of the sulfonamide anion. This is demonstrated by product

DOI: 10.1039/b104923m

Table 1 The second-order rate constants, k_{OH}/dm^3 mol^{-1} s^{-1}, for the alkaline hydrolysis of *N*-benzoyl-β-sultams and -sulfonamides at 30 °C and I = 1.0 M (KCl)

Compound	k_{OH}/dm^3 mol^{-1} s^{-1}
N-Benzoyl-β-sultam, **3**	1.46×10^4
4-Isopropylidene-*N*-benzoyl-β-sultam, **4**	1.18
(*E*)-4-Ethylidene-*N*-benzoyl-β-sultam, **5**	2.54×10^3
(*Z*)-4-Ethylidene-*N*-benzoyl-β-sultam, **6**	1.72
4-Isopropyl-*N*-benzoyl-β-sultam, **7**	3.00×10^2
N-Benzoyl-*N*-methylphenylmethanesulfonamide, **8**	1.30



analysis by UV and ^{1}H NMR spectra as well as ESIMS showing the benzoate anion produced. The second-order rate constant for the alkaline hydrolysis of **8**, k_{OH}, is 1.30 dm^3 mol^{-1} s^{-1} at 30 °C (Table 1), showing the high reactivity of these amide derivatives and the good leaving group ability of the sulfonamide anion. These activated amides show a 10^5 greater reactivity than 'normal' amides and are similar to imides in their susceptibility to attack by hydroxide ion.[8]

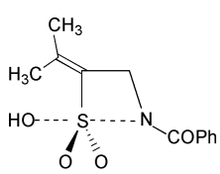
By contrast, the alkaline hydrolysis of the analogous *N*-benzoyl-β-sultam, **3**, occurs exclusively by S–N fission as a result of attack on sulfur and displacement of the carboxamide. This was confirmed by ^{1}H NMR and negative ion ESIMS, with the parent ion m/z = 228 corresponding to the ring-opened β-amidosulfonic acid product. We believe this is the first example of the hydrolysis of an *N*-acylsulfonamide occurring with S–N rather than C–N fission (Scheme 1).

The second-order rate constant, k_{OH}, for the alkaline hydrolysis of the β-sultam **3** is 1.46×10^4 dm^3 mol^{-1} s^{-1} (Table 1). This represents a direct rate enhancement over **8** of 10^4. However, this represents a minimum rate difference for S–N fission because the observed rate constant for the alkaline hydrolysis of the acyclic sulfonamide **8** is that for the reaction occurring by C–N fission and so that by S–N fission must be at least 100-fold less. A more accurate rate enhancement for similar bond breaking processes is therefore at least 10^6. This is of a similar magnitude to that of at least 10^7 previously reported for β-sultams compared with analogous sulfonamides.[9] The slower reaction of nucleophilic attack of hydroxide ion on the four-coordinate tetrahedral acyclic sulfonyl centre of **8** partially reflects the relative introduction of strain into the structure generated as it is converted to a five-coordinate trigonal bipyramidal arrangement in the transition state with an approximate 90° apical–equatorial bond angle around sulfur. Conversely, the β-sultam, **3**, already has this unfavourable bond angle in the reactant state as well as in the transition state. There is, therefore, a relative relief of bond angle strain in the four-membered ring compared with that occurring in the acyclic system, as well as that resulting from any partial opening of the strained four-membered ring in the transition state.

We had synthesised the 4-isopropylidene-β-sultam **4** in the hope that it would prove to be a good inhibitor of elastase based on similar substitution in known potent inhibitors.[7,10] To our surprise, the β-sultam **4** was not only a very poor inhibitor of elastase but showed extremely low chemical reactivity towards alkaline hydrolysis. The 4-isopropylidene derivative **4** is by far the least reactive *N*-acyl-β-sultam we have studied so far, showing a second-order rate constant, k_{OH}, of 1.18 dm^3 mol^{-1} s^{-1} at 30 °C (Table 1). This represents a rate decrease of 1.2×10^4 compared with the unsubstituted *N*-benzoyl-β-sultam, **3** (Table 1). Furthermore, product analysis showed that ring opening was no longer occurring and that hydroxide ion attacks the carbonyl group to give C–N fission to generate the intact β-sultam and benzoic acid! (pathway b, Scheme 1). This was demonstrated by ^{1}H NMR, UV and ESIMS. The product had a pK_a of 4.0 as expected for benzoic acid, but not for the sulfonic acid, and a negative ion ESIMS of the product showed a m/z of 121 corresponding to benzoic acid.

Given the exclusive C–N fission route for **4**, the α-isopropylidene substituent must decrease the unobserved rate of nucleophilic substitution at the sulfonyl centre by at least 10^6 compared with that in **3** which undergoes S–N fission. This is an extraordinarily large factor and may be compared with α-alkenyl substitution at acyl centres, which produces almost identical reactivities of methyl acetate and methyl acrylate towards alkaline hydrolysis.[11]

The transition states for nucleophilic substitution at acyl centres often resemble the tetrahedral intermediates which are commonly formed during such reactions.[12] Conversely, those for sulfonyl transfer reactions are assumed to have a structural resemblance to a trigonal bipyramidal arrangement.[13] Steric substituent effects on the rates of acyl transfer are thus rationalised by differences in their influence on the three-coordinate trigonal planar carbonyl centre in the reactant and on the four-coordinate carbon in the transition state. However, in sulfonyl transfer the less symmetrical trigonal bipyramidal arrangement in the transition state may cause differential effects dependent upon whether the substituents around sulfur occupy an apical or an equatorial position. We assumed that the enormous reduction in reactivity at the sulfonyl centre in **4** was due to the steric hindrance to hydroxide ion attack by the neighbouring isopropylidene residue. In the reactant state the isopropylidene bisects the two sulfonyl oxygens. However, the assumed trigonal bipyramidal arrangement in the transition state, **9**, would be formed by apical attack of hydroxide ion so that the ring S–N bond would also be apical and the two sulfonyl oxygens adopt equatorial positions. The isopropylidene would then eclipse the incipient S–OH bond and furthermore the van der Waals radii of the *syn* methyl would overlap with those of the hydroxy group. Attack at the sulfonyl centre in **4** would thus be accompanied by an enormous increase in strain energy and would considerably increase the activation energy so that it becomes larger than that required for attack at the acyl centre.



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To confirm this explanation, 4-alkylidene and -alkyl substituted β-sultams (**5**–**7**) were synthesised. We were able to separate the two *E*- and *Z*-isomers of the ethylidene derivatives, **5** and **6**, by column chromatography. The *Z*-isomer, **6**, with the methyl substituent *syn* to the sulfonyl centre showed a similar reactivity to the 4-isopropylidene-β-sultam, **4**, and showed a k_{OH} of 1.72 dm^3 mol^{-1} s^{-1} (Table 1). This β-sultam also displayed preferential C–N fission over ring opening and S–N fission.

The (*E*)-4-ethylidene-β-sultam, **5**, with the methyl group *anti* to the sulfonyl centre, however, shows the expected reactivity of

Table 2 Some bond angles/° in the β-sultams as determined by X-ray crystallography

Compound	∠SC4C3	∠C4SN	∠SNC3	∠C3C4C5	∠SC4C5
(*E*)-4-Ethylidene-*N*-benzoyl-β-sultam, **5**	92.0	78.5	96.0	135.8	132.3
(*Z*)-4-Ethylidene-*N*-benzoyl-β-sultam, **6**	91.7	78.8	95.2	138.6	129.5
4-Isopropyl-*N*-benzoyl-β-sultam, **7**	88.5	80.0	95.8	117.8	117.7

an *N*-acyl-β-sultam with a k_{OH} of 2541 $dm^3\ mol^{-1}\ s^{-1}$ (Table 1) and is hydrolysed with S–N fission and ring opening to form the β-amidosulfonic acid. Similarly, the 4-isopropyl-β-sultam **7** undergoes hydrolysis with ring opening and shows an expected reduced reactivity with k_{OH} = 300 $dm^3\ mol^{-1}\ s^{-1}$ (Table 1). The lower rate of hydrolysis is probably attributable to unfavourable steric interactions between the isopropyl residue and the apical hydroxy, *cf*. **9**. However, the isopropyl group can presumably adopt a conformation in which the secondary C–H points towards the incoming OH. Furthermore, the isopropyl eclipses the sulfonyl oxygen in the reactant state and this unfavourable interaction may actually be partially relieved in the transition state as the two sulfonyl oxygens adopt approximately equatorial positions.

Taken all together, there is nothing to indicate from the crystal structures of the reactants that the unusual behaviour between the various β-sultams is due to large differences in their structures (Table 2). Despite the presence at C4 of the unsaturated alkene centre exocyclic to the β-sultam, the internal ∠CCC at C4 remains strained, being 91.80 ± 0.2° for both the *E*- and *Z*-isomers of the 4-ethylidene-β-sultams, **5** and **6**. This may be compared with a value of 88.5° for the corresponding angle in 4-isopropyl-*N*-benzoyl β-sultam, **7**, (Table 2). In general, the internal bond angles remain remarkably similar whether or not the 4-substituent is saturated or unsaturated (Table 2). The internal bond angle around sulfur, as expected, takes most of the strain with an angle of 80° or slightly less. The consequences of the small internal bond angle at the three-coordinate, formally sp^2, carbon at C4 is an expanded exocyclic angle. In both 4-ethylidene isomers the ∠C3C4C5 angle is the largest, approaching 140° in the *Z*-derivative (Table 2). The slightly unexpected observation is that the ∠SC4C5 angle is slightly smaller in the *Z*- than in the *E*-isomer. Of course, although the methyl substituent may appear to "point" towards the sulfonyl group in the *Z*-isomer, it does in fact bisect the two sulfonyl oxygens.

The synthesis and X-ray crystal structures of the β-sultams and their inactivation of serine protease enzymes will be reported elsewhere.

Experimental

Solutions and buffers

Hydrochloric acid and sodium hydroxide solutions were prepared either from commercially available analytical standards or from standardised stock solutions of AnalaR grade reagents. Solutions of deuterium chloride and sodium deuteroxide were prepared by diluting DCl (99+ atom%D, 20% solution in D_2O Sigma) and NaOD (99 atom%D, 40% in D_2O, Goss Scientific Instruments Ltd) with D_2O (99.9 atom%D, Goss Scientific Instruments Ltd) and were titrated against standard bases and acids. AnalaR reagents were used in the preparation of buffers. Glass-distilled water was used throughout and the ionic strength was maintained at 1.0 M with AnalaR grade potassium chloride.

pH Measurements

The pH values of the buffer solutions were measured at the beginning and end of each run to ensure that no significant change had taken place. The electrodes were calibrated using standard buffers at 30 °C prior to use.

The kinetics of hydrolysis of substrates possessing UV chromophores were followed by UV spectrophotometry. With some of the β-sultams there were solubility problems and to ensure a linear photomultiplier response, wavelength scans were recorded with repeated additions of the substrate (5 μl of a 10^{-2} M solution in distilled acetonitrile) to 2.5 ml water pre-incubated at 30 °C. The reactions were normally initiated by adding between 2.5 and 20 μl of the 10^{-2} M substrate solution to 2.5 ml of the reactant solution. The absorbance at the selected wavelength was then monitored as a function of time and, using the Enzfitter programme, the data were fitted to an exponential function to yield the observed first-order rate constant.

Acknowledgements

This work was supported by EPSRC CASE awards with AstraZeneca (JMW) and British Biotech (PSH). We thank Birgitta Stensland of AstraZeneca for the X-ray crystal structures.

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