ORGANIC LETTERS

2004
Vol. 6, No. 2
201−203

Acyl vs Sulfonyl Transfer in *N*-Acyl *β*-Sultams and 3-Oxo-*β*-sultams

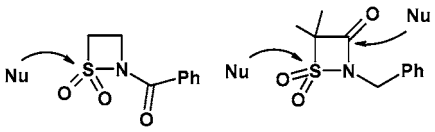
Naveed Ahmed, Wing Y. Tsang, and Michael I. Page*

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

m.i.page@hud.ac.uk

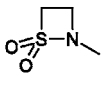
Received October 31, 2003

ABSTRACT

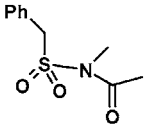


***N*-Acylsulfonamides usually react with nucleophiles by acyl transfer and C–N bond fission. However, the hydrolysis of *N*-acyl *β*-sultams is a sulfonyl transfer reaction that occurs with S–N fission and opening of the four-membered ring. Similar to other *β*-sultams, the *N*-acyl derivatives are at least 10^6-fold more reactive than *N*-acyl sulfonamides. 3-Oxo-*β*-sultams are both *β*-lactams and *β*-sultams but also hydrolyze with preferential S–N bond fission.**

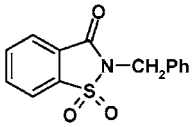
N-Acylsulfonamides **1** are often used to inactivate serine enzymes,[1] and the mechanism invariably involves acylation and C−N bond fission with the serine hydroxyl group attacking the carbonyl group to displace the sulfonamide as the leaving group.[2] In principle, however, nucleophiles could attack the sulfonyl center and expel the amide group, leading to sulfonylation of the nucleophile. We are interested in the role that ring strain plays in controlling reactivity[3] and have been studying the four-membered ring of *β*-sultams **2**.



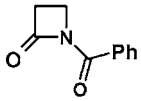
2



5



6



7

In general, acyl transfer reactions in acyclic reactants occur much more readily than analogous sulfonyl transfers. For example, the rates of alkaline hydrolysis of acyl derivatives such as acid chlorides and esters are often about 10^3-fold faster than the equivalent sulfonyl derivative.[4] With *N*-acyl sulfonamides, **1**, which incorporate both centers in one molecule, nucleophiles preferentially attack the carbonyl group to displace the sulfonamide anion (Scheme 1).[5] Acyl attack is favored by an electron-deficient carbonyl center and the strong electron-withdrawing character of the sulfonamide group, with the sulfonyl group stabilizing the adjacent lone pair on nitrogen by a polarization effect rather than conjugative d−p π bonding.[6] This activates the carbonyl group toward nucleophilic attack, and insofar as sulfonamides are

(1) Macdonald, S. J. F.; Dowle, M. D.; Harrison, L. A.; Spooner, J. E.; Shah, P.; Johnson, M. R.; Inglis, G. G. A.; Clarke, G. D. E.; Belton, D. J.; Smith, R. A.; Molloy, C. R.; Dixon, M.; Murkitt, G.; Godward, R. E.; Skarzynski, T.; Singh, O. M. P.; Kumar, K. A.; Hodgson, S. T.; McDonald, E.; Hardy, G. W.; Finch, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 243−6. Macdonald, S. J. F.; Dowle, M. D.; Harrison, L. A.; Shah, P.; Johnson, M. R.; Inglis, G. G. A.; Clarke, G. D. E.; Smith, R. A.; Humphreys, D.; Molloy, C. R.; Amour, A.; Dixon, M.; Murkitt, G.; Godward, R. E.; Padfield, T.; Skarzynski, T.; Singh, O. M. P.; Kumar, K. A.; Fleetwood, G.; Hodgson, S. T.; Hardy, G. W.; Finch, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 895−8.

(2) Sykes, N. O.; McDonald, S. J. F.; Page, M. I. *J. Med. Chem.* **2002**, *45* 2850−2856

(3) Page, M. I. *Chem. Soc. Rev.* **1973**, *2*, 295

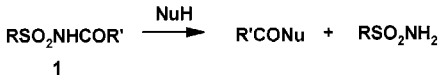
(4) King, J. F.; Rathore, R.; Lam, J. Y. L.; Gao, L. E. R.; Klassen, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 3028. Wood, J. M.; Page, M. I. *Trends Heterocycl. Chem.* **2002**, *8*, 19−34.

(5) Groutas, W. C.; Houser-Archield, N.; Chong, L. S.; Venkateraman, R.; Epp, J. B.; Huang, H.; McClenahan, J. J. *J. Med. Chem.* **1993**, *36*, 3178. Hlasta, D. J.; Bell, M. R.; Boaz, N. W.; Court, J. J.; Desai, R. C.; Franke, C. A.; Mura, A. J.; Subramanyam, D.; Dunlap, R. P. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1801.

(6) Terrier, F.; Kizilian, E.; Gaumont, R.; Faucher, N.; Wakselman, C. *J. Am. Chem. Soc.* **1998**, *120*, 9496.

10.1021/ol0361305 CCC: $27.50
Published on Web 12/25/2003

Scheme 1



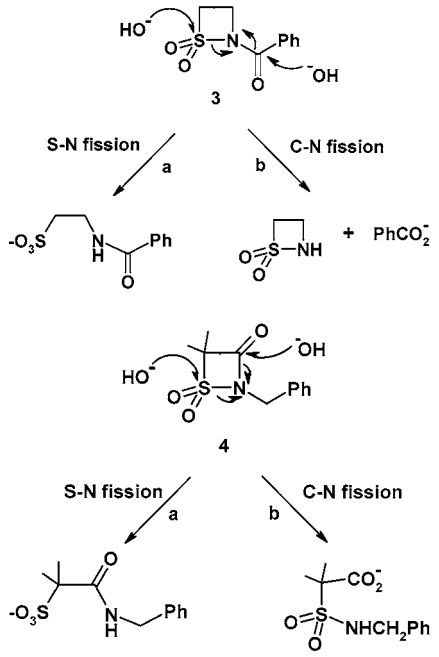
stronger acids than amides by about 5 p*K* units, sulfonamide anions are usually better leaving groups than amide anions.

β-Sultams **2** are the sulfonyl analogues of *β*-lactams and are potential sulfonylating agents of a variety of nucleophiles by displacement of the amine leaving group. As sulfonamides, albeit in cyclic four-membered rings, *β*-sultams are good models for studying the mechanisms of sulfonyl transfer reactions and are also possible inhibitors of proteolytic enzymes.

Acyclic sulfonamides are extremely resistant to alkaline and acid hydrolysis.[7] The difficulty of acid-catalyzed hydrolysis arises from the low basicity of sulfonamides compared with carboxamides, and they also differ from the latter by undergoing protonation on nitrogen.[8] The acid and base-catalyzed hydrolysis of *N*-alkyl and *N*-aryl *β*-sultams occurs with exclusive S−N fission to give the corresponding *β*-aminosulfonic acid.[9] *β*-Sultams show enormously high reactivity compared with sulfonamides and are estimated to be at least 10^7-fold more reactive.[9,10] This is in sharp contrast to the almost identical rate of alkaline hydrolysis of *β*-lactams compared with that of their acylic amide analogues.[11] Although sulfonyl transfer reactions of activated sulfonyl derivatives usually occur 10^2- to 10^4-fold slower than the corresponding acyl transfer process,[4] *β*-sultams are 10^2 to 10^3-fold more reactive than corresponding *β*-lactams, compared with the 10^4-fold slower rate of alkaline hydrolysis of acyclic sulfonamides compared with analogous amides.[9] As *β*-sultams are hydrolyzed faster than the corresponding *β*-lactams, their hydrolysis appears to be the first example of the rate of sulfonyl transfer being greater than that of the corresponding acyl reaction.

The incorporation of an acyl group next to the nitrogen in *β*-sultams may be exo- or endocyclic, giving *N*-acyl *β*-sultams **3** or 3-oxo-*β*-sultams **4**, respectively. Nucleophilic attack on *N*-acyl *β*-sultams **3** may involve either ring-opening, arising from sulfonylation as shown in pathway "**a**" of Scheme 2, or attack upon the exocyclic acyl amide group leading to acylation and preservation of the *β*-sultam ring as shown in pathway "**b**". Nucleophilic attack on 3-oxo-*β*-sultams will result in ring opening but again could involve

Scheme 2



either acylation or sulfonylation. Herein, we report the results of our studies of these reactions.

The alkaline hydrolysis in water of the acyclic *N*-acyl sulfonamide, **5**, occurs by *N*-acyl fission as a result of hydroxide ion attack on the carbonyl group followed by displacement of the sulfonamide anion. This was shown by product analysis using 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 **5**, 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.[11] 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 a *N*-acylsulfonamide occurring with S−N rather than C−N fission (Scheme 2).

The pH−rate profile for the hydrolysis of **3** is shown in Figure 1. It displays a hydroxide-ion catalyzed reaction for which 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). There is also a pH-independent hydrolysis and, at low pH, an acid-catalyzed reaction for which the respective rate constants, k_o and k_H, are given in Table 1.

Although the alkaline hydrolysis of **3** shows an apparent rate enhancement of 10^4 over that for the acyclic analogue **5**, it represents a minimum rate difference for S−N fission because the observed rate for the acyclic sulfonamide **5** is

(7) Kice, J. L. *Adv. Phys. Org. Chem.* **1980**, *17*, 123. Gordon, I. M.; Maskill, H.; Ruasse, M. F. *Chem. Soc. Rev.* **1989**, *18*, 123. King, J. F.; Gill, M. S.; Klassen, D. F. *Pure Appl. Chem.* **1996**, *68*, 825. Kice, J. L. *Progr. Inorg. Chem.* **1972**, *17*, 147. Olah, G. A.; Kobayashi, S.; Nishimura, J. *J. Am. Chem. Soc.* **1973**, *93*, 564.

(8) Laughlin, R. G. *J. Am. Chem. Soc.* **1967**, *89*, 4268. Menger, F. M.; Mandell, L. *J. Am. Chem. Soc.* **1967**, *89*, 4424. Maarsen, P. K.; Cerfontain, H. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1003.

(9) Baxter, N. J.; Laws, A. P.; Rigoreau, L. J. M.; Page, M. I. *J. Am. Chem. Soc.* **2000** *122*, 3375.

(10) Baxter, N. J.; Laws, A. P.; Rigoreau, L.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2245.

(11) Page, M. I. *Adv. Phys. Org. Chem.* **1987**, *23*, 165. Page, M. I. *The Chemistry of β*-Lactams; Page, M. I., Ed.; Blackie: London, 1992; pp 79−100. Page, M. I. *Acc. Chem. Res.* **1984**, *17*, 144−151.

Table 1. Rate Constants for the Hydrolysis of *N*-Acyl Sulfonamides and Amides at 30 °C and an Ionic Strength of 1.0 M (KCl)

compound	k_{OH} (dm^3 mol^{-1} s^{-1})	k_o (s^{-1})	k_H (dm^3 mol^{-1} s^{-1})
N-benzoyl *β*-sultam, **3**	1.46×10^4 [a]	3.11×10^{-6} [a]	5.84×10^{-5} [a]
N-benzyl 4,4-dimethyl-3-oxo-*β*-sultam, **4**	1.83×10^5	2.53×10^{-5}	
N-acetyl *N*-methyl phenylmethyl sulfonamide, **5**	1.30		
N-benzyl saccharin, **6**	4.05		
N-benzoyl *β*-lactam, **7**	11.2	8.77×10^{-7}	3.80×10^{-5}

[a] In 5% acetonitrile−water (v/v).

that for the reaction occurring by C−N fission, and thus that for 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 similar in magnitude to the enhancement of at least 10^7 previously reported for *β*-sultams compared with analogous sulfonamides.[9,10] The *N*-acyl *β*-sultam **3** is also 10^3-fold more reactive than the analogous *N*-acyl *β*-lactam **7**, similar to the difference observed for *N*-alkyl *β*-sultams and *β*-lactams.[9]

The pH−rate profile for the hydrolysis of *N*-benzyl 4,4-dimethyl-3-oxo-*β*-sultam **4** is shown in Figure 1 and displays a base-catalyzed reaction as well as a pH-independent pathway. The associated rate constants for these processes are given in Table 1.

The 3-oxo-*β*-sultam **4** is both a *β*-sultam and a *β*-lactam with a second-order rate constant for alkaline hydrolysis k_{OH} of 1.83×10^5 dm^3 mol^{-1} s^{-1} (Table 1), which is surprisingly only 10-fold greater than the *N*-acyl *β*-sultam **3** with an exocyclic group. Attack by the hydroxide ion at either electrophilic center of **4** involves opening the four-membered ring. However, nucleophilic attack occurs preferentially at the sulfonyl center and expulsion of a carboxamide leaving group, as shown by product analysis. Negative ion ESIMS shows a parent ion $m/z = 256$ corresponding to the ring-opened α-amidosulfonic acid (Scheme 2). ^{1}H,^{13}C HMBC NMR shows a cross-peak between the carbonyl carbon and the hydrogens of the methylene benzyl substituent, demonstrating that the benzyl group remains close to the carbonyl in the product. For comparison *N*-benzyl saccharin **6**, which is a *γ*-lactam *γ*-sultam analogue, undergoes alkaline hydrolysis with exclusive C−N fission and a second-order rate constant of 4.05 dm^3 mol^{-1} s^{-1}, which is about 5×10^4 times smaller than that for **4**.

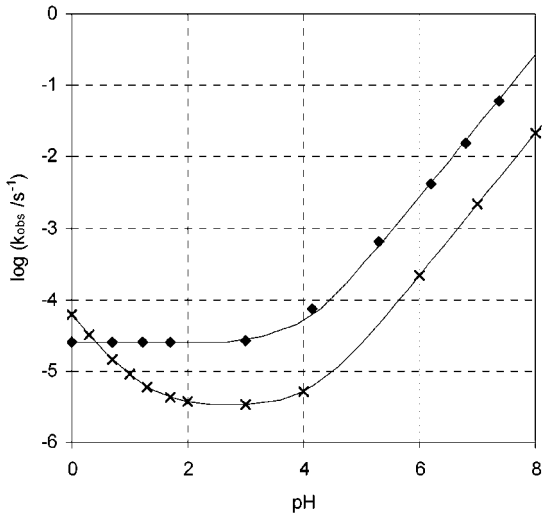


Figure 1. Dependence of the pseudo-first-order rate constant against pH for the hydrolysis of *N*-benzyl 4,4-dimethyl-3-oxo-*β*-sultam **4** (◆) in 1% acetonitrile−water (v/v) and *N*-benzoyl *β*-sultam **3** (×) in 5% acetonitrile−water (v/v) at 30 °C and an ionic strength of 1.0 M.

That hydroxide ion attacks the sulfonyl center in **4** rather than the *β*-lactam carbonyl is consistent with the observation that *β*-sultams are 10^2 to 10^3 times more reactive than *β*-lactams toward alkaline hydrolysis. Attack at the acyl center would expel a better leaving group, the sulfonamide anion, than attack at the sulfonyl center to expel the amide anion. However, based on the similar reactivities of imides and *N*-acylsulfonamides toward alkaline hydrolysis, the nature of the leaving group does not have a large effect. For example, the k_{OH} for *N*-methyl phthalimide[12] is actually 5-fold greater than that for *N*-benzyl saccharin **6**, and that for *N*-methyldiacetamide[13] is very similar to that for the acyclic *N*-acyl sulfonamide **5**. Although oxygen nucleophiles attack the sulfonly center of *N*-acyl *β*-sultams, amines show no reaction in competition with alkaline hydrolysis. In contrast, amines react readily with *β*-lactams[11] and so acyl transfer may become competitive with sulfonyl transfer in the aminolysis of **4** in aqueous solution.

Although the rate of the pH-independent hydrolysis of the 3-oxo-*β*-sultam **4** is also about 10-fold greater than the *β*-sultam **3** with the exocyclic acyl group, there is no acid-catalyzed hydrolysis of **4**. This is consistent with the reduced basicity of *β*-lactams compared with amides,[14] so carbonyl oxygen protonation is more difficult for the *β*-lactam **4** compared with **3**.

Acknowledgment. We thank the University of Huddersfield for financial support.

OL0361305

(12) Eriksson, S. O.; Jakobsson, M. *Acta Pharm. Suecica* **1973**, *10*, 63.
(13) Matsui, S.; Aida, H. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1277.
(14) Proctor, P.; Gensmantel, N. P.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1185. Wan, P.; Modro, T. A.; Yates, K. *Can. J. Chem.* **1980**, *58*, 2423. Cox, R. A.; Yates, K. *Can. J. Chem.* **1981**, *59*, 2853.