Reactivity and Mechanism in the Hydrolysis of β-Sultams

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Reactivity and Mechanism in the Hydrolysis of β-Sultams

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Abstract: β-Sultams show extraordinary rate enhancements of 10^9- and 10^7-fold, respectively, compared with the acid- and base-catalyzed hydrolysis of corresponding acyclic sulfonamides. They are about 10^3-fold more reactive than analogous β-lactams. The alkaline hydrolysis of some β-sultams shows a rate term that is second-order in hydroxide ion concentration, which is indicative of a stepwise mechanism involving a trigonal bipyramidal intermediate (TBPI). The Brønsted β_{lg} value for the alkaline hydrolysis of *N*-aryl-β-sultams is −0.58 and the kinetic solvent isotope effect $k_{OH}^{H_2O}/k_{OD}^{D_2O}$ is 0.60, compatible with rate-limiting formation of the TBPI. Conversely, $k_{OH}^{H_2O}/k_{OD}^{D_2O}$ for *N*-alkyl-β-sultams is 1.55, indicative of rate-limiting breakdown of the TBPI. The acid-catalyzed hydrolysis of β-sultams is strongly retarded by electron-withdrawing groups α to the sulfonyl group, and it is suggested that the mechanism may involve unimolecular ring opening to generate a sulfonylium ion. The Brønsted β_{lg} value for the acid-catalyzed hydrolysis of *N*-benzyl-β-sultams is 0.32. The general-acid-catalyzed hydrolysis of *N*-benzyl-β-sultam by carboxylic acids shows a Brønsted α value of 0.67 and is attributed to a specific acid−nucleophilic mechanism with the formation of a mixed-anhydride intermediate.

Introduction

Sulfonyl transfer reactions involving the displacement of a leaving group by a nucleophile are of interest because of the potential use of sulfonamides as peptide mimics.[1] They are also of interest for comparison with the analogous acyl transfer process. In general, sulfonyl derivatives are less reactive than their acyl counterparts,[2] but herein we report an exception to this generalization.

Stepwise mechanisms involving the formation of unstable intermediates are the norm for acyl transfer[3] whereas the concerted process remains controversial,[4] despite some evidence for its existence.[5] By contrast, sulfonyl transfer is usually discussed in terms of a concerted displacement and it is the evidence for a stepwise process that is questioned.[6,7] In this paper, we present evidence that is indicative of mechanisms in which the bond-making and bond-breaking steps appear to be clearly separated.

Sulfonamides are extremely resistant to alkaline and acid hydrolysis.[8] The NH acidity is greater than that of carboxylic acid amides, and the pK_a values of sulfonamides is typically around 9−10, so that they are ionized in alkaline solution.[9] However, formation of the anion is not the sole reason for the lack of reactivity because sulfonamides of secondary amines are also unreactive.

The basicity of sulfonamides is also of interest relative to that of carboxamides—the former are less basic and have apparent pK_a's (H_0) of about −6[10] and also differ by undergoing protonation on nitrogen.[11] The indications are that the sulfonyl group is more electron withdrawing than an acyl center, but there is little evidence for delocalization of the nitrogen lone pair onto the sulfonyl oxygens in sulfonamides. The S−N bond in sulfonamides is typically 1.65 Å and the nitrogen is pyramidal.[12]

There have been several studies on nucleophilic substitution at sulfonyl centers using reactive derivatives such as sulfonyl halides and aryl esters of sulfonic acids.[6,13] The dissociative, $S_N1(S)$ type, process would generate a sulfonylium ion (Scheme 1) which is then subsequently attacked by a nucleophile. However, the evidence for this mechanism is ambiguous,[4,6] and it appears that sulfonylium ions are much more difficult to generate than acylium ions.[14,15]

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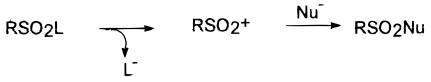
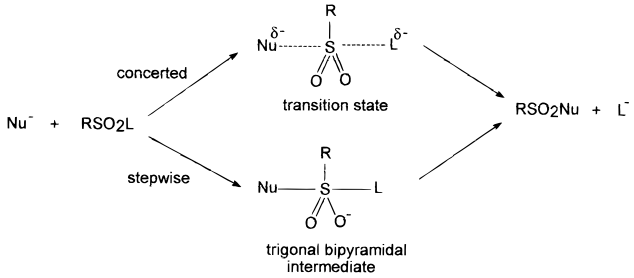
Scheme 1



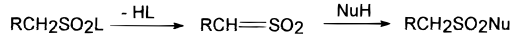
There is considerable controversy concerning the timing of bond making and breaking in the associative mechanism. Attempts to use isotopic exchange experiments to detect addition intermediates[16] in sulfonyl transfer were complicated, compared with reactions involving acyl transfer and tetrahedral intermediates, because of the asymmetry of the trigonal bipyramidal intermediate and the associated requirements for pseudorotation[17] and apical displacement. The use of linear free energy relationships to differentiate stepwise or concerted processes is not free from criticism and has, in fact, been used to support both mechanisms.[6,18] There is no clear evidence for the formation of a trigonal bipyramidal intermediate, and most observations can be interpreted in terms of either a stepwise or a concerted mechanism (Scheme 2), depending on the prejudices of the authors.[19]

Scheme 2



Finally, nucleophilic substitution at sulfonyl centers may sometimes occur by an elimination−addition pathway[6] and the aminolysis of some sulfonyl halides and aryl esters occurs through the intermediate formation of a sulfene (Scheme 3), as demonstrated by deuterium exchange at the adjacent acidic CH_2 and by breaks in linear free energy plots.[20]

Scheme 3



The modification of acyclic compounds to cyclic derivatives often changes their properties and reactivities, and for example, cyclic ethylene sulfate is more than 10^7 more susceptible to alkaline hydrolysis than the corresponding acyclic diethyl sulfate;[21] however, whether this is due to strain energy or solvation effects remains controversial.[22]

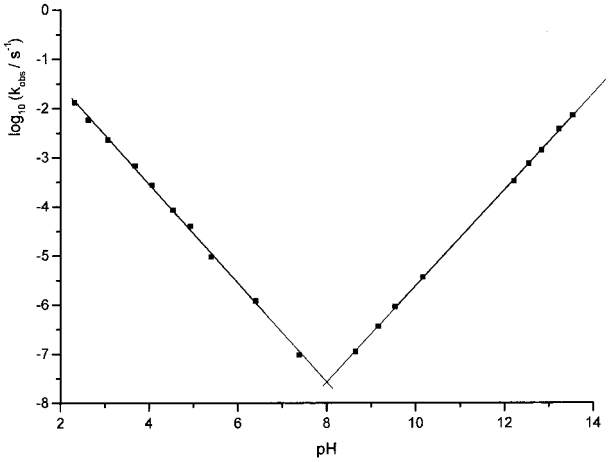


Figure 1. pH−rate profile for the hydrolysis of *N*-methyl-β-sultam at 30 °C and $I = 1.0$ M (KCl).

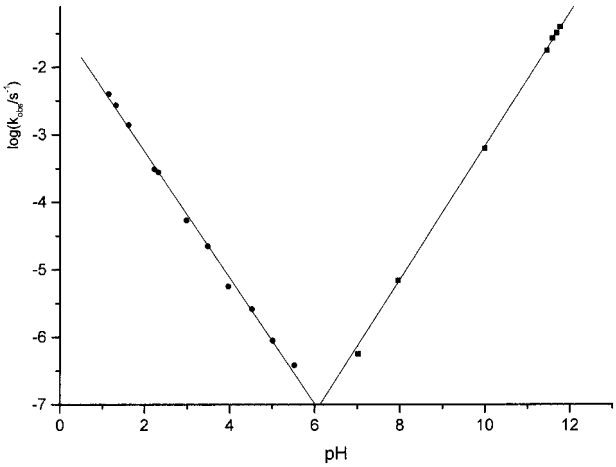
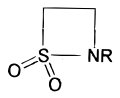
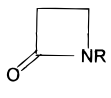


Figure 2. pH−rate profile for the hydrolysis of *N*-phenyl-β-sultam at 30 °C and $I = 1.0$ M (KCl).

Herein, we report kinetic and mechanistic studies of some reactive cyclic sulfonamides—β-sultams, **1**, which are the sulfonyl equivalents of the thoroughly studied[23] β-lactams, **2**.



1



2

Results and Discussion

The hydrolysis of β-sultams occurs with exclusive S−N fission, and for the series reported here, there is no NMR evidence of any reactions involving either C−S or C−N bond breaking. The pH−rate profiles for both *N*-alkyl- and *N*-aryl-β-sultams show only reactions which are first order in either hydronium ion or hydroxide ion concentration. However, for β-sultams activated by electron-withdrawing groups α to the sulfonyl center, there is a term in the rate law that is second order in hydroxide ion, which is discussed later. For all the β-sultams studied, there is no significant pH-independent, spontaneous, hydrolysis.

Reactivity of β-Sultams. Typical pH−rate profiles for the hydrolysis of *N*-alkyl- and *N*-aryl-β-sultams in aqueous solutions of ionic strength 1.0 M (KCl) at 30 °C are shown in Figures 1 and 2, respectively. Two points are noteworthy: first, the high

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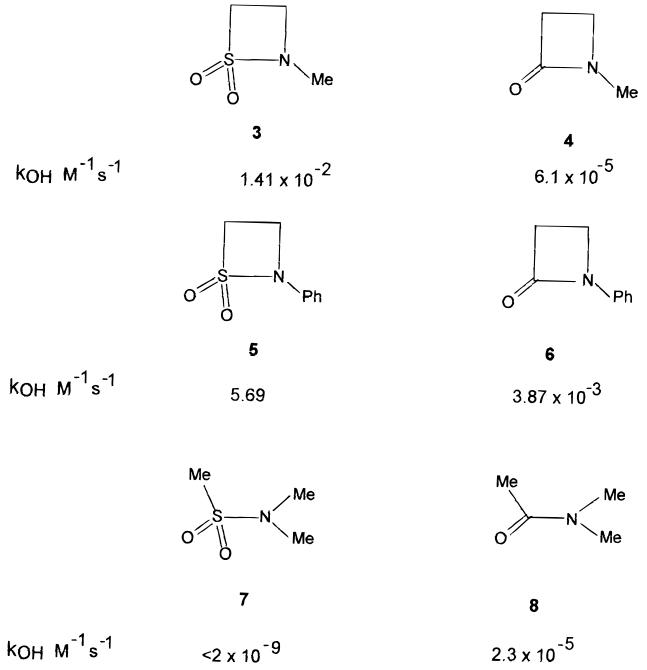
Table 1. Kinetic Parameters for the Alkaline Hydrolysis of N-Substituted β-Sultams in Aqueous Solution at 30 °C and $I = 1.0$ M (KCl)

	N-substituent						
	Me	$PhCH_2$	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$	C_6H_5	*p*-ClC_6H_4	*m*-ClC_6H_4
$k_{OH}/M^{-1}\ s^{-1}$ [a]	1.41×10^{-2}	1.0×10^{-2}	3.30	3.37	5.69	20.4	44.0
$\Delta H^{\ddagger}$/kJ mol^{-1}	34 ± 0.5	37 ± 0.5	37 ± 0.5	45 ± 0.6	47 ± 0.6	42 ± 0.5	
$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	-165 ± 3	-161 ± 3	-114 ± 2	-87 ± 2	-76 ± 2	-84 ± 2	
$k_{OH}^{H_2O}/k_{OD}^{D_2O}$		1.55	0.65	0.57	0.55		

[a] The second-order rate constants are estimated to have an error of ±2%.

Chart 1. Second-Order Rate Constants for the Alkaline Hydrolysis of Comparable β-Sultams and β-Lactams in Aqueous Solution at 30 °C and $I = 1.0$ M (KCl)

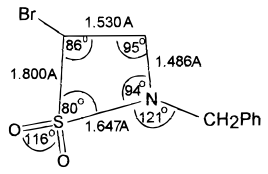


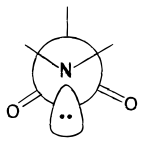
reactivity of the β-sultams toward acid and base hydrolysis and, second, the lack of an apparent pH-independent hydrolytic pathway. The derived second-order rate constants for the alkaline hydrolysis of some *N*-alkyl- and *N*-aryl-β-sultams are given in Table 1.

The second-order rate constants for the hydroxide ion hydrolysis of β-sultams and β-lactams are compared in Chart 1. The β-sultams are 10^2-10^3 times more reactive than their corresponding acyl analogues, the β-lactams. This may be contrasted with the 10^4-fold faster rate of acyl transfer in the simple amide **8** compared with sulfonyl transfer in the corresponding sulfonamide, **7**, or even the 10-fold greater activity, toward hydroxide ion, of the highly reactive benzoyl chloride compared with benzenesulfonyl chloride.[2] Similarly, the second-order rate constant for the alkaline hydrolysis of *p*-nitrophenyl methanesulfonate is 400-fold less than that for the alkaline hydrolysis of *p*-nitrophenyl acetate.[20] β-Sultams are more reactive than the corresponding β-lactams, whereas acyclic sulfonamides are much less reactive than the corresponding amides. This difference in behavior could result from either a relative enhanced rate of hydrolysis for β-sultams or a relative depressed rate for β-lactams, compared with those of their respective acyclic analogues.

Acyclic sulfonamides are so unreactive toward alkaline hydrolysis that it is difficult to measure accurately the second-order rate constants; the value quoted for **7** of 2×10^{-9} M^{-1} s^{-1} is extrapolated from initial rate data obtained at elevated temperatures. Nonetheless, it is clear that β-sultams are enormously reactive compared with their acyclic analogues. The estimated rate enhancement is at least 10^7-fold, which may be contrasted with the almost identical rates of hydrolysis of β-lactams and their acylic amide analogues.[23] It is a surprising fact that the strain energy inherent in the four-membered β-lactam is not even partially released in the transition state to lower the activation energy for reaction.

It has long been known that the alkaline hydrolysis of five-membered cyclic sulfate and phosphate esters occurs orders of magnitude faster than that of the corresponding acyclic analogues although whether this is due to release of strain energy or differences in solvation energy remains controversial.[22] The X-ray crystal structure of *N*-benzyl-4-bromo-β-sultam, **9**, shows an endocyclic CŜN bond angle of 80°, compared with 113° in the acyclic sulfonamide **7**. There is thus considerable ground-state strain present in the four-membered ring. Crystal structures

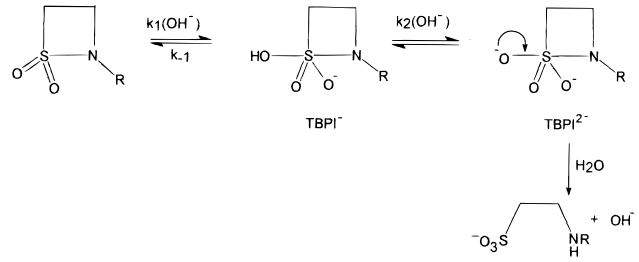




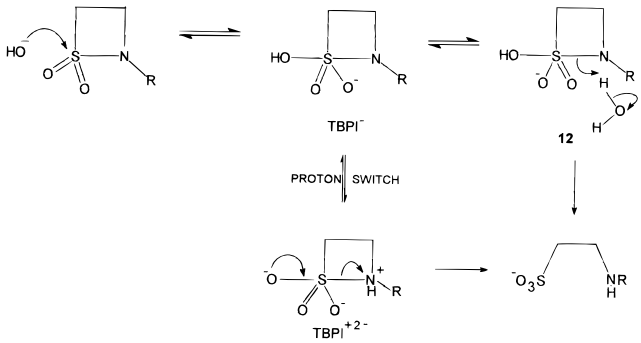
for N,N-disubstituted sulfonamides, available in the Cambridge Crystallographic Database, show variations in the geometry around nitrogen from pyramidal to nearly planar. The majority, however, display a, presumably, tetrahedral arrangement with the nitrogen lone pair bisecting the two sulfonyl oxygens (**10**). It is, therefore, unlikely that there is any additional influence of strain resulting from loss of resonance energy because of the constraint of the nitrogen and the sulfonyl centers within a four-membered ring, and in any case there is little evidence to suggest that sulfonyl groups stabilize adjacent atoms with lone pairs by resonance.

If nucleophilic substitution at sulfuryl centers occurs through the formation of a trigonal bipyramidal intermediate (TBPI) or through a transition state which resembles this geometry (Scheme 2), then there may be relief of strain energy for this step for the reactions of β-sultams. The bond angle around the hypervalent sulfur is expected to be about 90° for *both* cyclic and acyclic sulfonyl derivatives. It seems probable that when pentacoordinate sulfur is contained in a four-membered ring, the latter would prefer to be attached in an apical/equatorial fashion, i.e., with an approximately 90° endocyclic bond angle around sulfur. Attack by a hydroxide ion on sulfur is therefore accompanied by a large relief in ground-state bond angle strain upon formation of the TBPI compared with case of the analogous acyclic derivative. In contrast, in the β-lactam/amide systems, there is less relief of ground-state bond angle strain around the β-lactam carbonyl carbon upon formation of the tetrahedral intermediate; i.e., the angle is approximately 90° compared with 120° in the ground state and 90° compared with 109° in the tetrahedral intermediate.[24]

Scheme 4



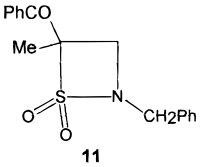
Scheme 5



The stereochemistry of the anionic trigonal bipyramidal intermediate TBPI$^-$ (Schemes 4 and 5) is depicted with both the incoming hydroxyl and the departing amine apical. The relative apicophilicities of nitrogen and carbon make it uncertain whether an arrangement with the ring carbon apical and nitrogen equatorial would not be of similar energy. However, complete or partial protonation of nitrogen is likely to favor the apical position for this atom, and given the difficulty of pseudorotation with the presence of a four-membered ring, it is simplest to describe the reaction pathway as shown.

The Trigonal Bipyramidal Intermediate. Direct substitution at sulfonyl sulfur is thought to occur with an inversion of the configuration.[25] Although this indicates that the displacement probably involves a geometry 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 lifetime.

The pseudo-first-order rate constants (k_{obs}) for the alkaline hydrolysis of the β-sultam **11** are clearly second order in



11

hydroxide ion (Figure 3), and a plot of k_{obs}/[OH$^-$] against [OH$^-$] (Figure 4) shows that this is the dominant term in the rate law, eq 1. The values of k_{OH1} and k_{OH2} are 8.98×10^{-3} dm^3 mol^{-1} s^{-1} and 3.87×10^{-2} dm^6 mol^{-2} s^{-1}, respectively, at 30 °C and $I = 1.0$ M (KCl).

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

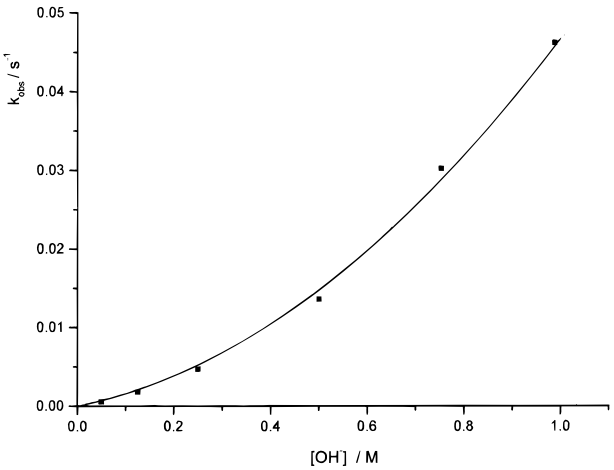


Figure 3. Plot of the observed pseudo-first-order rate constant, k_{obs}, for the hydrolysis of the β-sultam **11** against the hydroxide ion concentration at 30 °C and $I = 1.0$ M (KCl).

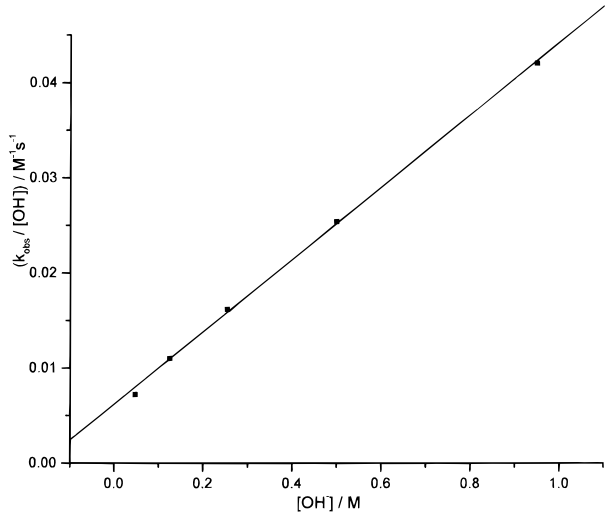


Figure 4. Plot of the apparent second-order rate constant, k_{obs}/[OH$^-$], for the hydrolysis of the β-sultam **11** against the hydroxide ion concentration at 30 °C and $I = 1.0$ M (KCl).

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[26] and acetylpyrroles.[27] 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.[27]

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 a hydroxide ion on the β-sultam **11** generates a monoanionic TBPI$^-$, which requires deprotonation by a second hydroxide ion before the intermediate can collapse to products (Scheme 4). The third-order rate constant k_{OH2} would then be determined by eq 2, with $k_{-1} \gg k_2[OH^-]$.

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$$k_{OH2} = \frac{k_1 k_2 [OH^-]^2}{k_{-1} + k_2 [OH^-]} \quad (2)$$

In addition to observing the rate term that is second order in hydroxide ion for the 4-benzoyl derivative, we also observed it for *N*-benzyl-4-bromo-4-methyl-*β*-sultam. There appears to be a need for an electron-withdrawing substituent at the 4-position to make the observation of the second-order term apparent, and for all other *β*-sultams studied, only a first-order dependence on hydroxide ion was observed.

The rate-limiting step for the alkaline hydrolysis of the *β*-sultam **11** could be (i) diffusion-controlled deprotonation of the monoanionic $TBPI^-$, (ii) the subsequent breakdown of the dianionic $TBPI^{2-}$, or (iii) a concerted process involving both of these steps (Scheme 4).

Solvent Kinetic Isotope Effects. The values for the kinetic solvent isotope effects (SKIE's), $k_{OH}^{H_2O}/k_{OD}^{D_2O}$, indicate that there is a difference in timing for the proton transfer steps and possibly the rate-limiting steps for the hydrolysis of *N*-aryl- and *N*-alkyl-*β*-sultams (Table 1). The values for *N*-aryl derivatives, 0.60 ± 0.05, are consistent with rate-limiting formation of the anionic trigonal bipyramidal intermediate $TBPI^-$. However, the value for the *N*-benzyl derivative, 1.55, suggests that the rate-limiting step is different for the more basic amine leaving group. Possible pathways are outlined in Scheme 5. Formation of $TBPI^-$ can be followed by several possible steps. The situation is complicated by the timing of proton removal from the HO group attached to the incipient sulfonyl center and proton addition to the incipient amine. Breakdown of $TBPI^-$ by S−N fission almost certainly requires protonation of the more basic nitrogen of alkylamines. This could occur through the thermodynamically more stable anionic zwitterionic form of $TBPI^-$, $TBPI^{+2-}$, formed by a proton switch from oxygen to nitrogen, and such a process is kinetically compatible with a reaction pathway that is first-order in hydroxide ion although probably not compatible with the observed SKIE. Fractionation factor analysis[28] for formation of the anionic zwitterionic form $TBPI^{+2-}$ from $TBPI^-$ suggests a solvent kinetic isotope effect, $k_{OH}^{H_2O}/k_{OD}^{D_2O}$, of 0.92, corresponding to an overall effect of 0.46 from the reactants, hydroxide ion, and *β*-sultam. Even in the unlikely event that breakdown of $TBPI^{+2-}$ was rate limiting, this would give an estimated solvent kinetic isotope effect of 0.5.

Ring opening could be facilitated by partial proton transfer from water (**12**), Scheme 5, and this rate-limiting step would generate an SKIE consisting of an equilibrium value of 0.5 for formation of $TBPI^-$ and a primary kinetic effect of 2−3, to give an expected total SKIE of about 1.5 ± 0.3, compared with the observed value of 1.55. This, therefore, seems to be the most likely mechanism for the alkaline hydrolysis of *β*-sultams of alkylamines.

The entropies of activation (Table 1) also indicate different rate-limiting steps for *N*-aryl and *N*-alkyl-*β*-sultams. The more negative values observed for the latter are compatible with the more ordered structure (**12**), involving rate-limiting S−N fission and ring opening.

Rate-limiting ring opening of the strained *β*-sultam appears to be yet another example of the relative difficulty of bond cleavage in four-membered rings despite the release of strain energy. The unexpected phenomenon has been previously observed in azetidine derivatives and has been tentatively linked to the detailed mechanics of ring opening which may occur by bond rotation rather than bond stretching.[29]

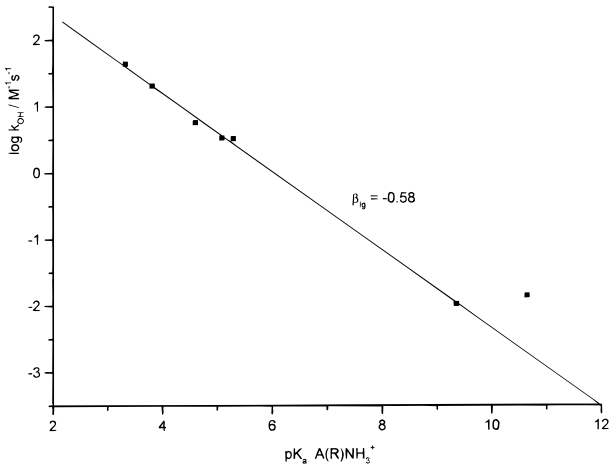

Figure 5. Brønsted plot of the second-order rate constants for the alkaline hydrolysis of *N*-aryl-substituted *β*-sultams against the pK_a's of the corresponding anilinium ions at 30 °C and I = 1.0 M (KCl). Also shown is the extrapolated line for two *N*-alkyl-*β*-sultams.

The solvent kinetic isotope effect for the term second order in hydroxide ion, $k_{OH}^{H_2O}/k_{OD}^{D_2O}$, is 0.35, which 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, then the slow step would probably be the diffusion-controlled encounter of a 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 may be indicative of a stepwise mechanism for the subsequent reaction of $TBPI^-$ rather than a concerted process.

Effects of N-Substituents. Examples of the effects of N-substituents on the alkaline hydrolysis of *β*-sultams are also shown in Table 1. The *β*-sultams of anilines are more reactive than those of alkylamines toward alkaline hydrolysis by more than one 100-fold. A plot of the logarithm of the second-order rate constant against the pK_a of the leaving group amine generates a Brønsted β_{lg} value of −0.58 (Figure 5).

The interpretation of the magnitude of β_{lg} requires a knowledge of the "effective charge"[30] on nitrogen in the *β*-sultam. Unfortunately, this value is not even known for sulfonamides. However, the effective charge on oxygen in sulfonate esters is 0.8+ compared with 0.7+ in carboxylate esters and the value for nitrogen in carboxylic acid amides is also 0.7+.[3,30] It seems reasonable therefore to assume a value of 0.8+ for the effective charge on nitrogen in sulfonamides and *β*-sultams. A rate-limiting step involving anilide anion expulsion would be expected to generate a β_{lg} more negative than −0.8, and although a transition state involving partial protonation of nitrogen by water is compatible with the observed β_{lg}, the solvent kinetic isotope effects are not. Formation of the $TBPI^-$ from the *β*-sultam is expected to correspond to a change in effective charge of −0.8, and the observed Brønsted β_{lg} of −0.58 is therefore consistent with rate-limiting formation of

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Table 2. Kinetic Parameters for the Acid Hydrolysis of N-Substituted β-Sultams in Aqueous Solution at 30 °C and $I = 1.0$ M (KCl)

	N-substituent							
	Me	$PhCH_2$	*p*-HOC_6H_4	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$	C_6H_5	*p*-ClC_6H_4	*m*-ClC_6H_4
$k_H/M^{-1}\ s^{-1}$ [a]	2.64	1.52	1.52×10^{-1}	9.22×10^{-2}	8.79×10^{-2}	5.63×10^{-2}	4.48×10^{-2}	2.30×10^{-2}
$\Delta H^{\ddagger}$/kJ mol^{-1}	64 ± 1	43 ± 0.5	53 ± 0.5	53 ± 0.6	54 ± 0.5	60 ± 0.5	52 ± 0.5	
$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	-30 ± 3	-100 ± 2	-87 ± 2	-90 ± 2	-88 ± 2	-74 ± 2	-99 ± 2	
$k_{OH}^{H_2O}/k_{OD}^{D_2O}$		0.69		0.32	0.44	0.46	0.46	

[a] The second-order rate constants are estimated to have an error of ±2%.

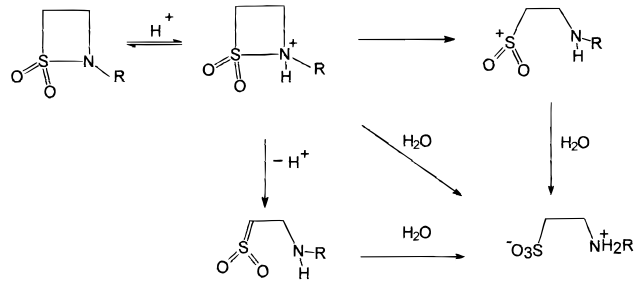
the trigonal bipyramidal intermediate $TBPI^-$, as indicated by the solvent kinetic isotope effects.

Acid Hydrolysis. All of the β-sultams studied undergo an acid-catalyzed hydrolysis (Figures 1 and 2). The degradation products are simply those resulting from hydrolytic S−N fission. There is no evidence of any incorporation of deuterium at C4, which excludes any mechanism involving C−H abstraction, and there are no products resulting from elimination across C4−C3 to give the unsaturated sulfonamide.

The second-order rate constants for the acid-catalyzed hydrolysis of N-substituted β-sultams are given in Table 2 for ionic strength $I = 1.0$ M (KCl) and at 30 °C. In contrast to the case of their alkaline hydrolysis, *N*-alkyl-β-sultams are more reactive than the *N*-aryl derivatives. In general, electron-withdrawing substituents reduce the basicity of the β-sultam nitrogen, resulting in less favorable protonation and a reduced rate of hydrolysis.

Similar to phosphonamides[31,32] and in contrast to carboxylic amides,[33] sulfonamides are believed to undergo N-protonation.[11,34] It seems appropriate to assume N-protonation occurs in the acid-catalyzed reactions of β-sultams. Preequilibrium protonation of the β-sultam nitrogen facilitates S−N bond fission by allowing the amine leaving group to depart as the neutral amine. The combination of this with the relief of ring strain permits the possible involvement of a unimolecular A1 process to be contemplated (Scheme 6). Following the rapid protonation

Scheme 6



of the β-sultam nitrogen, the reaction may involve unimolecular S−N bond fission to form an electron-deficient sulfonylium ion intermediate which could then be trapped by water to form the β-amino sulfonic acid product.

The second-order rate constant for the acid-catalyzed hydrolysis of the β-sultam **11** is 1.90×10^{-3} dm^3 mol^{-1} s^{-1}, which is 1500-fold less than that for the derivative lacking the α-benzoyl group. Similarly, a 4-bromo substituent reduces the rate of hydrolysis, and with the 4-benzoyl group, these 2-electron-withdrawing substituents generate an apparent Hammett ρ_I value for α-substitution of −10. By contrast, the effect of

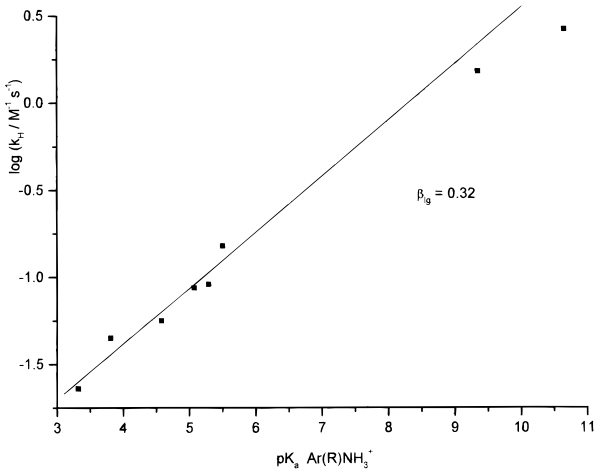


Figure 6. Brønsted plot of the second-order rate constants for the acid-catalyzed hydrolysis of *N*-aryl-substituted β-sultams against the pK_a's of the corresponding anilinium ions at 30 °C and $I = 1.0$ M (KCl). Also shown is the extrapolated line for two *N*-alkyl-β-sultams.

acyl substituents upon the rate of acid-catalyzed hydrolysis of amides is small, with electron-withdrawing substituents producing either a small increase or a small decrease in rate.[35] Although only based on two substituents, this effect indicates a possible 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 β-amino sulfonic acid product (Scheme 6).

Although sulfonylium ions are much more difficult to form than acylium ions[14] and there are no well-established cases for their formation during substitution at sulfonyl centers,[6] the present case is compatible with the similar acylium ion mechanism suggested for the acid-catalyzed hydrolysis of β-lactams[36,37] and the unimolecular ring opening in β-phospholactams.[38] An A1 process has been suggested for the hydrolysis of *N*-nitrobenzenesulfonamides,[39] whereas the evidence for such a mechanism in the hydrolysis of five-membered γ-sultams is ambiguous, although most of the evidence is consistent with a bimolecular mechanism.[40]

The effect of amine basicity on the acid-catalyzed hydrolysis of substituted *N*-aryl β-sultams is shown by the Brønsted-type plot in Figure 6. The points for the acid hydrolysis of the two alkylamine β-sultams, the *N*-benzyl and *N*-methyl derivatives,

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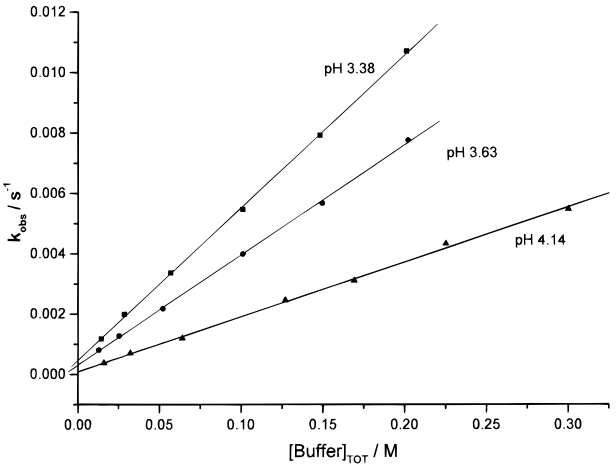


Figure 7. Plot of the observed pseudo-first-order rate constant for the hydrolysis of *N*-benzyl-*β*-sultam as a function of total acetate buffer concentration at the pH indicated at 30 °C and $I = 1.0$ M (KCl).

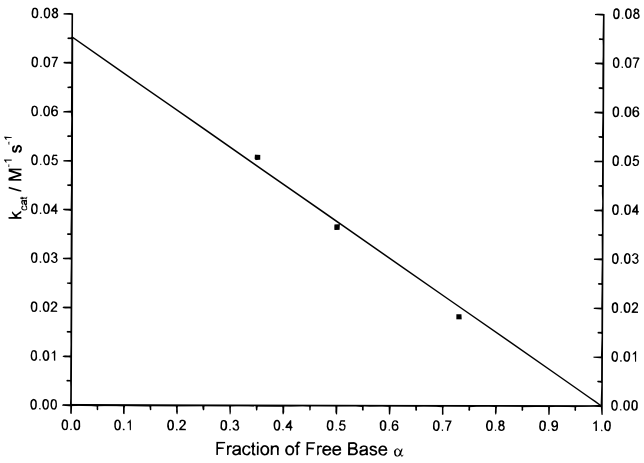


Figure 8. Plot of the catalytic coefficient k_{cat} against the fraction of free base α in the formate/formic acid buffer catalyzed hydrolysis of *N*-benzyl-*β*-sultam at 30 °C and $I = 1.0$ M (KCl).

appear to fit the extrapolation of the line obtained for the *N*-aryl-*β*-sultams. The slope of this line generates a Brønsted β_{lg} of 0.32.

The β_{lg} value of 0.32 is consistent with rate-limiting sulfonylium ion formation with a value of +1.0 for the initial protonation step followed by a value of −0.7 for the formation of the transition state leading to the sulfonylium ion intermediate (Scheme 6). It is, however, also consistent with a bimolecular A2 process in which the S−N bond is partially cleaved.

The entropies of activation are generally about -87 ± 13 J K^{-1} mol^{-1}, except that for the *N*-methyl derivative, which shows a $\Delta S^{\ddagger}$ of -30 J K^{-1} mol^{-1}. These values also include the entropies of the protonation preequilibrium[31,41] and are significantly less negative than those observed in the alkaline hydrolysis of *β*-sultams and may be indicative of an A1 pathway.

Isotopic fractionation factor analysis reveals that the solvent isotope effect of 0.69 observed in the acid hydrolysis of *N*-benzyl-*β*-sultam is consistent with both an A1 process involving rate-limiting attack on the sulfonylium ion by water and either a concerted or stepwise A2 pathway. The somewhat lower solvent isotope effects observed in the hydrolysis of the *N*-aryl derivatives are more consistent with an A1 process with rate-determining S−N bond fission, i.e., formation of the sulfonylium ion.

The second-order rate constants for the acid-catalyzed hydrolysis of *N*-phenyl-*β*-sultam increase slightly with increasing ionic strength. Overall, the second-order rate constant doubles with a 30-fold increase in the ionic strength of the medium. This rate enhancement, though small, is greater than that observed in the alkaline hydrolysis of the same substrate and is probably due to a "secondary salt effect" upon the preequilibrium protonation of the *β*-sultam nitrogen.

General-Acid-Catalyzed Hydrolysis. The rate of hydrolysis of *N*-benzyl-*β*-sultam was measured in a range of carboxylate buffers under pseudo-first-order conditions. At a constant pH and ionic strength ($I = 1.0$ M (KCl)) and at 30 °C, the observed first-order rate constants increase linearly with increasing concentrations of buffer (Figure 7), indicative of buffer catalysis. Plots of k_{obs} against the total buffer concentration yield slopes, k_{cat}, which give the total contribution to the rate law by the concentrations of both the undissociated carboxylic acid and the carboxylate anion. The intercepts of these buffer plots, k_{int}, correspond to the calculated observed first-order rate constants for the specific-acid-catalyzed hydrolyses based on the second-order rate constant, $k_{H^+} = 1.52$ M^{-1} s^{-1}, obtained from reactions studied in solutions of hydrochloric acid. For each series of buffers, a plot of k_{cat} against α, the fraction of the buffer present as the free base, gives intercepts, when $\alpha = 0$ and 1.0, of k_{HA} and k_{A^-}, respectively, the individual second-order rate constants for catalysis by the acidic and basic buffer components (Figure 8). The values of k_{A^-} were indistinguishable from zero. The rate law for the hydrolysis of *N*-benzyl-*β*-sultam in carboxylate buffers is thus given by eq 3.

$$k_{obs} = k_H[H^+] + k_{HA}[HA] \quad (3)$$

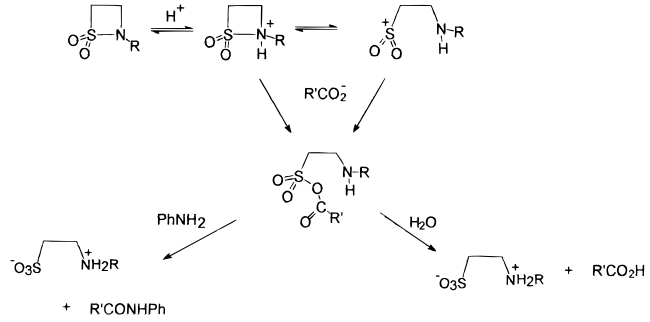
The values of the second-order rate constants k_{HA} are given in Table 3, from which it can be seen that they increase with decreasing pK_a of the carboxylic acid buffer. The observation of general-*acid*-catalyzed hydrolysis is in contrast to the general-*base* catalysis seen with the buffer-catalyzed hydrolysis of *β*-lactams of penicillins.[5] Although catalysis by acidic species other than the protonated solvent is usually referred to as "general-acid catalysis", mechanistically the reaction may proceed via different but kinetically equivalent processes.

Table 3. Second-Order Rate Constants for the Carboxylic Acid Catalyzed Hydrolysis of *N*-Benzyl-*β*-Sultam at 30 °C and $I = 1.0$ M (KCl)

carboxylic acid	pK_a	k_{HA}/M^{-1} s^{-1}	carboxylic acid	pK_a	k_{HA}/M^{-1} s^{-1}
$ClCH_2CO_2H$	2.70	7.61×10^{-2}	HCO_2H	3.67	7.53×10^{-2}
$MeOCH_2CO_2H$	3.38	2.95×10^{-2}	CH_3CO_2H	4.57	4.14×10^{-3}

The probable mechanism of buffer catalysis in this case involves specific acid−nucleophilic catalysis[42] (Scheme 7). The

Scheme 7



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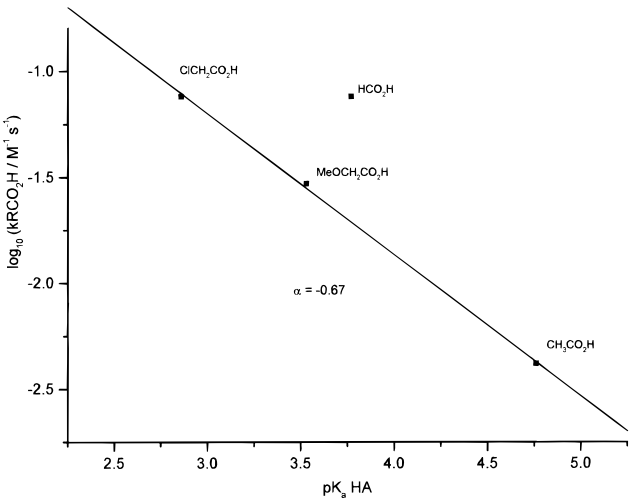


Figure 9. Brønsted plot of the logarithms of the second-order rate constants k_{HA} for the carboxylic acid catalyzed hydrolysis of *N*-benzyl-β-sultam at 30 °C and $I = 1.0$ M (KCl) against the pK_a's of the corresponding carboxylic acids.

β-sultam undergoes reversible protonation, probably on nitrogen, followed by direct nucleophilic attack of the carboxylate anion to form a mixed acid anhydride intermediate which is subsequently hydrolyzed. Nucleophilic catalysis in the carboxylate buffer hydrolysis of β-sultams was confirmed by trapping the mixed acid anhydride intermediate with aniline to give acetanilide, identified by HPLC. In the presence of the β-sultam, a peak with a retention time corresponding to that of acetanilide was observed whereas, in the absence of the β-sultam, no acetanilide was produced. These observations provide the most conclusive evidence that the carboxylate buffer catalyzed hydrolysis of β-sultams is due to specific acid−nucleophilic catalysis. There is convincing evidence that the protonation of sulfonamide occurs on nitrogen,[11,34] and the general-acid-catalyzed hydrolysis of the β-sultam could occur by a unimolecular A1-type process with the carboxylate anion trapping the reversibly formed electron-deficient sulfonylium ion (Scheme 7).

The hydrolysis of *N*-benzyl-β-sultam in acetate buffers showed unusual behavior because the kinetics were biphasic; an initial exponential burst of UV absorbance was followed by a much slower first-order reaction. This was only observed for acetate buffers, and the catalytic rate constants were obtained from the initial rates. The biphasic kinetics observed in the acetate buffer hydrolysis of *N*-benzyl-β-sultam may be attributed to the accumulation, and subsequent hydrolysis of, the anhydride intermediate. The intermediate mixed anhydrides derived from the 2-chloroacetate, 2-methoxyacetate, and formate anions undergo hydrolysis in the forward direction at rates that are greater than those for their formation because of the high nucleofugacity of these anions and so do not accumulate.

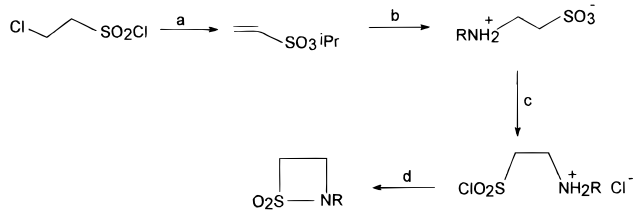
The Brønsted plot (Figure 9) for the carboxylic acid catalyzed hydrolysis of *N*-benzyl-β-sultam gives a good correlation between the values of log k_{HA} and pK_a for 2-chloroacetic, 2-methoxyacetic, and acetic acids with a slope of −0.67. This corresponds to a β_{nuc} value of 0.33 for the specific acid−nucleophilic mechanism, indicative of an early transition state in which there has been a small amount of neutralization of the negative charge on the carboxylate anion. Formic acid shows a positive deviation from this line, which is again indicative of a nucleophilic pathway for catalysis.

The solvent isotope effect k_{H_2O}/k_{D_2O} of 1.57 for the chloroacetate buffer hydrolysis of *N*-benzyl-β-sultam is compatible with the specific acid−nucleophilic process, as is the observed entropy of activation of −148 J K^{-1} mol^{-1} for the chloroacetic acid catalyzed hydrolysis.

Experimental Section

Materials. *N*-Alkyl-β-sultams were prepared according to the general procedure outlined in Scheme 8.[42]

Scheme 8[a]



[a] Conditions: (a) 2 equiv of pyridine, 1 equiv of *i*-PrOH, CH_2Cl_2, −10 °C, (b-i) 1 equiv of RNH_2, MeOH, 0 °C; (b-ii) HCl, 18 h reflux; (c) PCl_5, $POCl_3$, 90 °C; (d) Na_2CO_3, EtOAc, 48 h.

Isopropyl Ethenesulfonate. A mixture of chloro-2-ethanesulfonyl chloride (26 g, 0.16 mol) and 2-propanol (11.8 mL, 0.154 mol) in dichloromethane (70 mL) was cooled to −10 °C (ice−NaCl bath). Pyridine (25.8 mL, 0.319 mol) in dichloromethane (35 mL) was added dropwise to the solution with vigorous agitation, and the mixture was allowed to stand for 2 h, after which it was brought back to room temperature and stirred for $^1/_2$ h. A white precipitate was observed, and an orange coloration developed. The solution was worked up with dilute HCl, water, and brine and dried over magnesium sulfate. The solvent was removed, giving isopropyl ethenesulfonate as a pale yellow oil (18.25 g, 79%). IR (KBr), ν_{max}/cm^{-1}: 3112, 3065, 2988, 2940, 2879, 1468, 1389, 1360, 1174, 1097, 916, 885, 790, 727, 662. ^{1}H NMR ($CDCl_3$), δ: 1.39 (6H, d, J 6.5 Hz, CHCH_3), 4.77 (1H, s, J 6.5 Hz, CHCH$_3$), 6.11 (1H, d, J 10, H_b), 6.37 (1H, d, J 16.5 Hz, H_a), 6.58 (1H, dd, J 10 and 16.5 Hz, H_c). ^{13}C NMR ($CDCl_3$), δ: 22.9, 77.8, 129.3, 133.6. GC−MS, m/z: 150 (M^+), 135, 109, 91, 43.

2-(Methylamino)ethanesulfonic Acid. Isopropyl ethenesulfonate (5 g, 33.3 mmol) in methanol (10 mL) was added dropwise, under agitation and at 0 °C, to a solution of anhydrous methylamine in methanol (2 M, 16.7 mL, 33.4 mmol). After 2 h, HCl gas was passed through the solution until pH 1 was reached. The reaction mixture was then heated at 70 °C for 18 h. The solvent was removed under reduced pressure, yielding an oil which crystallized upon trituration in a cold mixture of 1:1 ethyl acetate/ethanol. The solid obtained was purified by recrystallization in aqueous ethanol (2.3 g, 49.6%). Mp: 236−240 °C dec. IR (KBr), ν_{max}/cm^{-1}: 3457, 3167, 3035, 2970, 2868, 1538, 1468, 1269, 1211, 1180, 1038, 828, 775. ^{1}H NMR (D_2O), δ: 2.79 (s, 3H, *Me*), 3.30 (2H, t, J 6.5 Hz, CH_2N), 3.46 (2H, t, J 6.5 Hz, CH_2SO$_3$).

2-(Methylamino)ethanesulfonyl Chloride Hydrochloride. Finely ground 2-(methylamino)ethanesulfonic acid (2.8 g, 20.1 mmol) was mixed with ground phosphorus pentachloride (5.04 g, 24.2 mmol) at room temperature. A few drops of phosphorus oxychloride were added, and the mixture was heated to 90 °C under agitation. The reaction was stopped when the yellow coloration disappeared and when a gray color started to develop. The residue was triturated with ethyl acetate to give a white precipitate which was collected by filtration (1.5 g, 38%). Mp: 126−128 °C (lit.[43] 124 °C). IR (KBr), ν_{max}/cm^{-1}: 3445, 2931, 2738, 2437, 1478, 1367, 1266, 1171, 1054, 1004, 746.

2-Methyl-1,2-thiazetidine 1,1-Dioxide. 2-(Methylamino)ethanesulfonyl chloride hydrochloride (1.52 g, 7.8 mmol) and sodium carbonate (1.64 g, 15.6 mmol) were ground separately and then suspended in distilled ethyl acetate (500 mL). The suspension was stirred for 48 h, after which it was filtered and the solvent was removed under vacuum to yield a white solid (0.71 g, 75%). Mp: 34−35 °C

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(lit.[43] 36 °C). IR (KBr), ν_{max}/cm^{-1}: 2975, 2900, 2818, 1474, 1454, 1315, 1218, 1185, 1145, 956, 926, 812, 760, 684, 645. ^{1}H NMR ($CDCl_3$), δ: 2.73 (3H, s, *Me*), 3.18 (2H, t, *J* 6.5 Hz, C*H*$_2$N), 4.13 (2H, t, *J* 6.5 Hz, C*H*$_2$SO$_2$). ^{13}C NMR ($CDCl_3$), δ: 32.2, 37.1, 58.0. GC−MS, *m*/*z*: 121 (M^+), 91, 73, 64, 56.

2-Benzyl-1,2-thiazetidine 1,1-Dioxide. 2-(Benzylamino)ethanesulfonyl chloride hydrochloride (2.5 g, 9.3 mmol) and sodium carbonate (1.96 g, 18.5 mol) were ground separately and then suspended in distilled ethyl acetate (500 mL). The suspension was stirred for 48 h, after which it was filtered and the solvent was removed under vacuum to yield a white solid (1.5 g, 82%). Mp: 69−70 °C (lit.[43] 71−72 °C). IR (KBr), ν_{max}/cm^{-1}: 3050, 2990, 2906, 2850, 1458, 1438, 1297, 1245, 1197, 1167, 1146, 1119, 1011, 788, 723, 646. ^{1}H NMR ($CDCl_3$), δ: 3.13 (2H, t, *J* 6.5 Hz, C*H*$_2$N), 4.10 (2H, t, *J* 6.5 Hz, C*H*$_2$SO$_2$), 4.24 (2H, s, C*H*$_2$Ph), 7.34 (5H, m, Ar *H*). GC−MS, *m*/*z*: 198 ($M^+ + 1$), 132, 120, 104, 91, 77, 65.

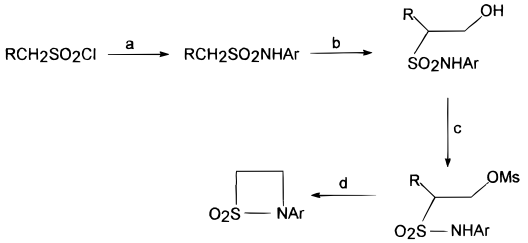
4-Benzoyl-2-methyl-1,2-thiazetidine 1,2-Dioxide. It is possible to abstract the C4 proton from *β*-sultam and react the anion with electrophiles.[44] Butyllithium in hexane (1.6 M, 10.84 mL, 17.35 mmol) was added to a stirred solution of diisopropylamine (2.34 mL, 16.52 mmol) in THF (30 mL) at 0 °C. After 15 min, the solution was cooled to −78 °C and 2-methyl-1,2-thiazetidine 1,2-dioxide (1 g, 8.26 mmol) in THF (40 mL) was added dropwise. The mixture was stirred for 5 min, after which ethyl benzoate (1.2 mL, 16.52 mmol) was added and the resulting mixture was allowed to warm to room temperature. The reaction was quenched with ammonium chloride, after which the mixture was extracted with ethyl acetate (3 × 50 mL) and the extract was washed with water and brine and dried over sodium sulfate. The solvent was removed under vacuum, and the residue was purified by column chromatography (ethyl acetate/hexane; 2:3, R_f 0.35) to give a white solid (0.25 g, 13%). Mp 118−119 °C. IR (KBr), ν_{max}/cm^{-1}: 2986, 2930, 1693, 1596, 1452, 1305, 1227, 1185, 1148, 1066, 907, 824, 735, 713, 686, 637. ^{1}H NMR ($CDCl_3$), δ: 2.72 (3H, s, *Me*), 3.35 (1H, ABX, *J* 6 and 8 Hz, C*H*N), 3.70 (1H, ABX, *J* 6 Hz, C*H*N), 5.89 (1H, ABX, *J* 6 and 8 Hz, C*H*SO$_2$), 7.51 (2H, m, Ar *H*), 7.65 (1H, m, Ar *H*), 8.00 (2H, m, Ar *H*). GC−MS, *m*/*z*: 226 ($M^+ + 1$), 161, 144, 131, 105, 84, 77.

4-Benzoyl-2,4-dimethyl-1,2-thiazetidine 1,2-Dioxide. Butyllithium in hexane (1.71 M, 0.13 mL, 0.22 mmol) was added to a stirred solution of diisopropylamine (0.031 mL, 0.22 mmol) in THF (10 mL) at 0 °C. After 15 min, the solution was cooled to −78 °C, and 4-benzoyl-2-methyl-1,2-thiazetidine 1,2-dioxide (50 mg, 0.22 mmol) in THF (5 mL) was added dropwise. The mixture was stirred for 5 min, after which methyl iodide (0.014 mL, 0.22 mmol) was added and the resulting mixture was allowed to warm to room temperature. The reaction was quenched with ammonium chloride, after which the mixture was extracted with ethyl acetate (3 × 20 mL) and the extract was washed with water and brine and dried over sodium sulfate. The solvent was removed under vacuum, and the residue was purified by column chromatography (ethyl acetate/hexane, 3:7; R_f 0.32) to give a white solid (26 mg, 50%). Mp: 60−61 °C. IR (Nujol), ν_{max}/cm^{-1}: 3068, 1682, 1597, 1309, 1280, 1181, 1145, 1034, 980, 935, 868, 812, 784, 704. ^{1}H NMR ($CDCl_3$), δ: 1.96 (3H, s, *Me*CSO$_2$), 2.67 (3H, s, *Me*N), 3.12 (1H, AB, *J* 6 Hz, C*H*N), 3.66 (1H, AB, *J* 6 Hz, C*H*N), 7.50 (3H, m, Ar *H*), 7.93 (2H, m, Ar *H*).

4-Benzoyl-2-benzyl-1,2-thiazetidine 1,2-Dioxide. Butyllithium in hexane (1.71 M, 2.38 mL, 4.06 mmol) was added to a stirred solution of diisopropylamine (0.57 mL, 4.06 mmol) in THF (40 mL) at 0 °C. After 15 min, the solution was cooled to −78 °C and 2-benzyl-1,2-thiazetidine 1,2-dioxide (0.4 g, 2.03 mmol) in THF (10 mL) was added dropwise. The mixture was stirred for 5 min, after which benzoyl chloride (0.24 mL, 2.03 mmol) was added and the resulting mixture was allowed to warm to room temperature. The reaction was quenched with ammonium chloride, after which the mixture was extracted with ethyl acetate (3 × 30 mL) and the extract was washed with water and brine and dried over sodium sulfate. The solvent was removed under vacuum, and the residue was purified by column chromatography (ethyl acetate/hexane, 3:7; R_f 0.34) to give a white solid (130 mg, 21%). Mp 115−116 °C. IR (Nujol), ν_{max}/cm^{-1}: 3064, 3037, 1692, 1596, 1596, 1320, 1220, 1170, 1156, 1113, 1070, 1020, 918, 763, 734, 707, 700, 688. ^{1}H NMR ($CDCl_3$), δ: 3.28 (1H, ABX, *J* 6 and 8 Hz, CHC*H*$_2$N), 3.70 (1H, ABX, *J* 6 Hz, CHC*H*$_2$N), 3.70 (1H, ABX, *J* 6 and 8 Hz, CHC*H*$_2$N), 4.22 (2H, AB, *J* 14.5 Hz, C*H*$_2$Ph), 5.77 (1H, ABX, *J* 6 and 8 Hz, SO$_2$C*H*CH$_2$N), 7.28 (5H, m. Ar *H*). GC−MS, *m*/*z*: 302 ($1 + M^+$), 236, 220, 160, 132, 105, 91, 65. Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.75; H, 5.00; N, 4.65; S, 10.60. Found: C, 63.95; H, 5.10; N, 4.50; S, 10.10.

N-Aryl-*β*-sultams were prepared according to the general procedure outlined in Scheme 9.[45]

Scheme 9[a]



[a] Conditions: (a) 2 equiv of $ArNH_2$, toluene, 2 h reflux; (b) 3 equiv of BuLi, TMEDA, HCHO, THF; (c) MsCl, Et_3N, $CHCl_3$, 0 °C; (d) 3 equiv K_2CO_3, DMSO, 60 °C, 2 h.

***N*-Phenylmethanesulfonamide.** Aniline (31.8 mL, 0.35 mol) was added to a solution of mesyl chloride (20 g, 0.175 mol) in toluene (150 mL), and the mixture was refluxed for 2 h. The solvent was removed under vacuum to give a solid residue onto which hot water was poured. A solid was recovered after trituration and was recrystallized from ethanol to give a white crystalline solid (14.35 g, 48%). Mp: 101−102 °C. IR (KBr), ν_{max}/cm^{-1}: 3256, 3018, 2932, 1596, 1496, 1472, 1395, 1324, 1151, 757, 694. ^{1}H NMR (DMSO-d_6), δ: 2.98 (3H, s, *Me*SO$_2$), 7.22 (5H, m, Ar *H*), 9.74 (1H, s, N*H*). GC−MS, *m*/*z*: 171 (M^+), 92, 79, 65.

***N*-(4-Chlorophenyl)methanesulfonamide.** Mp: 149−151 °C. IR (KBr), ν_{max}/cm^{-1}: 3288, 3097, 3006, 2928, 1491, 1452, 1387, 1325, 1147, 842, 817. ^{1}H NMR (DMSO-d_6), δ: 3.01 (3H, s, *Me*), 7.22 (2H, d, *J* 8 Hz, Ar *H*), 7.40 (2H, d, *J* 8 Hz, Ar *H*), 9.91 (1H, s, N*H*). GC−MS, *m*/*z*: 205−207 (M^+), 126−128, 99−101, 90, 79, 63.

***N*-4-Toluidinomethanesulfonamide.** Mp: 102−103 °C. IR (KBr), ν_{max}/cm^{-1}: 3292, 3052, 3022, 2932, 2866, 1510, 1331, 1301, 1155, 979, 812. ^{1}H NMR (DMSO-d_6), δ: 2.26 (3H, s, Ar*Me*), 2.92 (3H, s, *Me*SO$_2$), 7.12 (4H, s, Ar *H*), 9.56 (1H, s, N*H*). GC−MS, *m*/*z*: 185 (M^+), 106, 79, 63.

***N*-(3-Chlorophenyl)methanesulfonamide.** Mp: 93−95 °C. IR (KBr), ν_{max}/cm^{-1}: 3252, 3018, 2930, 1594, 1479, 1391, 1317, 1151, 970, 929, 784, 700. ^{1}H NMR (DMSO-d_6), δ: 3.04 (3H, s, *Me*SO$_2$), 7.16 (2H, m, Ar *H*), 7.23 (1H, m, Ar *H*), 7.36 (1H, t, *J* 8 Hz, Ar *H*), 10.02 (1H, s, N*H*). GC−MS, *m*/*z*: 205−207 (M^+), 126−128, 99−101, 91, 73.

***N*-Phenylethanesulfonamide.** Mp: 56−57 °C. IR (KBr), ν_{max}/cm^{-1}: 3218, 3048, 2994, 2942, 1478, 1331, 1304, 1150, 1134, 756, 731, 696. ^{1}H NMR (DMSO-d_6), δ: 1.19 (3H, t, *J* 7.5 Hz, C*H*$_3$CH$_2$), 3.06 (2H, q, *J* 7.5 Hz, CH$_3$C*H*$_2$), 7.21 (5H, m, Ar *H*), 9.79 (1H, s, N*H*). GC−MS, *m*/*z*: 185 (M^+), 157, 130, 106, 93, 65.

***N*-Phenylphenylmethanesulfonamide.** Mp: 98−99 °C. IR (Nujol), ν_{max}/cm^{-1}: 3231, 3088, 3055, 3032, 1482, 1415, 1341, 1155, 918, 782, 754, 695. ^{1}H NMR (DMSO-d_6), δ: 4.45 (2H, s, PhC*H*$_2$); 7.27 (10H, m, Ar *H*), 9.85 (1H, s, N*H*).

***N*-Phenyl-2-hydroxyethanesulfonamide.** *N*-Phenylmethanesulfonamide (2 g, 11.7 mmol) was dissolved in dry THF (30 mL) under a nitrogen atmosphere. Butyllithium in hexane (1.6 M, 22 mL, 35.1 mmol) and TMEDA (5.3 mL, 35.1 mmol) were added to the solution, and the mixture was stirred at room temperature for 2 h. Formaldehyde, generated from pyrolysis of paraformaldehyde, was bubbled through the solution until TLC analysis showed completion of the reaction. The reaction was quenched with ammonium chloride, the mixture was extracted with ethyl acetate (3 × 75 mL), and the extract was washed

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(45) Thompson, M. E. *J. Org. Chem.* **1984**, *49*, 1700.

with water and brine and dried over sodium sulfate. The solvent was removed under vacuum, and the residue was purified by column chromatography (ethyl acetate/hexane, 2:3; R_f 0.17) to yield a pale yellow oil (1.24 g, 53%). IR (KBr), ν_{max}/cm^{-1}: 3386, 2964, 2890, 1495, 1339, 1302, 1145, 1024, 759, 697. ^{1}H NMR (DMSO-d_6), δ: 3.26 (2H, t, *J* 6.5 Hz, CH_2SO$_2$), 3.80 (2H, t, *J* 6.5 Hz, CH_2OH), 4.96 (1H, b s, O*H*), 7.24 (5H, m, Ar *H*), 9.70 (1H, b s, N*H*). GC−MS, *m*/*z*: 201 (M$^+$), 157, 120, 106, 93, 65.

***N*-(4-Chlorophenyl)-2-hydroxyethanesulfonamide.** Mp: 95 °C. IR (KBr), ν_{max}/cm^{-1}: 3422, 3144, 3061, 2935, 2872, 1490, 1326, 1138, 1066, 842, 819, 733, 713. ^{1}H NMR (DMSO-d_6), δ: 3.25 (2H, t, *J* 6.5 Hz, CH_2SO$_2$), 3.75 (2H, t, *J* 6.5 Hz, CH_2OH), 4.94 (1H, br s, O*H*), 7.22 (2H, d, *J* 9 Hz, Ar *H*), 7.38 (2H, d, *J* 9 Hz, Ar *H*); 9.89 (1H, br s, N*H*). GC−MS, *m*/*z*: 235−237 (M$^+$), 140−141, 126, 99−101, 90.

***N*-(4-Methylphenyl)-2-hydroxyethanesulfonamide.** Mp: 165 °C. IR (KBr), ν_{max}/cm^{-1}: 3431, 3193, 2961, 2926, 2882, 1511, 1390, 1329, 1296, 1222, 1162, 1136, 1069, 1009, 950, 918, 815, 717, 703. ^{1}H NMR (DMSO-d_6), δ: 2.26 (3H, s, *Me*); 3.17 (2H, t, *J* 6.5 Hz, CH_2SO$_2$), 3.72 (2H, t, *J* 6.5 Hz, CH_2OH), 4.92 (1H, br s, O*H*), 7.13 (4H, m, Ar *H*), 9.56 (1H, br s, N*H*). GC−MS, *m*/*z*: 215 (M$^+$), 134, 120, 106, 79.

***N*-Phenyl-2-hydroxypropanesulfonamide.** IR (KBr), ν_{max}/cm^{-1}: 3497, 3264, 3087, 2980, 2941, 2890, 1599, 1496, 1416, 1323, 1300, 1220, 1148, 1045, 926, 756, 697. ^{1}H NMR (DMSO-d_6), δ: 1.28 (3H, d, *J* 6.5 Hz, *Me*), 3.15 (1H, m, C*H*SO$_2$), 3.45 (1H, ABX, *J* 8 and 11 Hz, C*H*OH), 3.86 (1H, ABX, *J* 11 and 4.5 Hz, C*H*OH), 5.14 (1H, br s, O*H*), 7.26 (5H, m, Ar *H*), 9.49 (1H, br s, N*H*). GC−MS, *m*/*z*: 215 (M$^+$), 152, 93, 77, 65.

***N*-(3-Chlorophenyl)-2-hydroxyethanesulfonamide.** Mp: 70 °C. IR (KBr), ν_{max}/cm^{-1}: 3417, 3194, 2959, 1596, 1326, 1136, 1066, 949, 789, 723. ^{1}H NMR (DMSO-d_6), δ: 3.28 (2H, t, *J* 6.5 Hz, CH_2SO$_2$), 3.74 (2H, t, *J* 6.5 Hz, CH_2OH), 4.94 (1H, br s, O*H*), 7.23 (4H, m, Ar *H*), 10.00 (1H, br s, N*H*). GC−MS, *m*/*z*: 235−237 (M$^+$), 127−129, 91, 73, 63.

***N*-Phenyl-2-hydroxy-1-phenylethanesulfonamide.** Mp: 106−108 °C. IR (KBr), ν_{max}/cm^{-1}: 3502, 3266, 3064, 2974, 2895, 1599, 1495, 1418, 1339, 1300, 1147, 1058, 928, 754, 696. ^{1}H NMR (DMSO-d_6), δ: 3.99 (1H, ABX, *J* 9 and 11 Hz, C*H*OH); 4.20 (1H, ABX, *J* 4.5 and 11 Hz, C*H*OH), 4.35 (1H, ABX, *J* 4.5 and 9 Hz, C*H*SO$_2$), 5.05 (1H, br s, O*H*), 7.28 (10H, m, Ar *H*), 9.84 (1H, br s, N*H*).

***N*-Phenyl-2-hydroxyethanesulfonamide Mesylate.** *N*-Phenyl-2-hydroxyethanesulfonamide (2.77 g, 13.78 mmol) was dissolved in dry dichloromethane (30 mL) under nitrogen. Mesyl chloride (1.07 mL, 13.78 mmol) and triethylamine (1.92 mL, 13.78 mmol) were added to the solution, and the mixture was stirred at 0 °C for 2 h. The organics were washed with dilute hydrochloric acid, water, and brine and dried over sodium sulfate, and the solvent was removed under vacuum. The residue was purified by trituration from ether to yield a white solid (2.4 g, 62%). Mp: 94−95 °C dec. IR (KBr), ν_{max}/cm^{-1}: 3274, 3024, 2938, 1478, 1416, 1342, 1169, 1152, 1069, 988, 968, 915, 802, 758, 743, 696. ^{1}H NMR (DMSO-d_6), δ: 3.11 (3H, s, *Me*SO$_2$), 3.59 (2H, t, *J* 6 Hz, CH_2SO$_2$), 4.59 (2H, t, *J* 6 Hz, MsOCH_2), 7.19 (5H, m, Ar *H*), 8.82 (1H, br s, N*H*). GC−MS, *m*/*z*: 183 (M$^+$ − MeSO$_3$H), 118, 92, 65.

***N*-(4-Chlorophenyl)-2-hydroxyethanesulfonamide Mesylate.** Mp: 113−114 °C dec. IR (KBr), ν_{max}/cm^{-1}: 3264, 3027, 3017, 2987, 2936, 1492, 1346, 1335, 1177, 1148, 989, 964, 821, 794, 711. ^{1}H NMR (DMSO-d_6), δ: 3.19 (3H, s, *Me*SO$_2$), 3.60 (2H, t, *J* 6 Hz, CH_2SO$_2$), 4.45 (2H, t, *J* 6 Hz, MsOCH_2), 7.22 (2H, m, Ar *H*), 7.42 (2H, m, Ar *H*), 10.17 (1H, br s, N*H*). GC−MS, *m*/*z*: 313−315 (M$^+$), 217−219, 138−140, 126, 99−101, 79.

***N*-(4-Methylphenyl)-2-hydroxyethanesulfonamide Mesylate.** Mp: 84−85 °C dec. IR (KBr), ν_{max}/cm^{-1}: 3269, 3088, 3022, 3014, 2986, 2938, 1513, 1478, 1398, 1335, 1304, 1176, 1148, 981, 964, 916, 883, 814, 794, 729, 704. ^{1}H NMR (DMSO-d_6), δ: 2.26 (3H, s, *Me*Ar), 3.19 (3H, s, *Me*SO$_2$), 3.51 (2H, t, *J* 6 Hz, CH_2SO$_2$), 4.48 (2H, t, *J* 6 Hz, MsOCH_2), 7.13 (4H, s, Ar *H*), 9.86 (1H, br s, N*H*). GC−MS, *m*/*z*: 293 (M$^+$), 197, 133, 120, 106, 91, 79.

***N*-Phenyl-2-hydroxypropanesulfonamide Mesylate:** Mp: 114−115 °C dec. IR (KBr), ν_{max}/cm^{-1}: 3232, 3024, 2937, 2909, 1491, 1423, 1359, 1334, 1288, 1175, 1154, 1097, 979, 961, 948, 929, 840, 762, 696. ^{1}H NMR (DMSO-d_6), δ: 1.33 (3H, d, *J* 6.5 Hz, *Me*CH), 3.19 (3H, s, *Me*SO$_3$), 3.54 (1H, m, C*H*SO$_2$), 4.35 (1H, ABX, *J* 6 and 11 Hz, MsOC*H*), 4.48 (1H, ABX, *J* 5 and 11 Hz, MsOC*H*), 7.24 (5H, m, Ar *H*), 10.06 (1H, br s, N*H*). GC−MS, *m*/*z*: 293 (M$^+$), 197, 132, 104, 93, 79, 65.

***N*-(3-Chlorophenyl)-2-hydroxyethanesulfonamide Mesylate.** Mp 83−84 °C dec. IR (KBr), ν_{max}/cm^{-1}: 3294, 3028, 2939, 1596, 1463, 1340, 1327, 1173, 1154, 969, 941, 904, 804, 783, 742, 681. ^{1}H NMR (DMSO-d_6), δ: 3.18 (3H, s, *Me*SO$_2$), 3.65 (2H, t, *J* 6 Hz, CH_2SO$_2$), 4.49 (2H, t, *J* 6 Hz, MsOCH_2), 7.19 (3H, m, Ar *H*), 7.37 (1H, m, Ar *H*), 10.28 (1H, s, N*H*). GC−MS, *m*/*z*: 313−315 (M$^+$), 217−219, 187−189, 125−127, 99, 79.

***N*-Phenyl-2-hydroxy-1-phenylethanesulfonamide Mesylate.** Mp 139−140 °C dec. IR (KBr), ν_{max}/cm^{-1}: 3278, 3025, 2938, 1598, 1496, 1350, 1175, 1152, 964, 917, 811, 753, 697. ^{1}H NMR (CDCl$_3$), δ: 2.97 (3H, s, *Me*SO$_2$), 4.58 (1H, ABX, *J* 6.5 Hz, C*H*SO$_2$), 4.72 (1H, ABX, *J* 6.5 and 11 Hz, MsOC*H*), 4.97 (1H, ABX, *J* 6.5 and 11 Hz, MsOC*H*), 6.45 (1H, br s, N*H*), 7.26 (10H, m, Ar *H*).

2-Phenyl-1,2-thiazetidine 1,1-Dioxide. *N*-Phenyl-2-hydroxyethanesulfonamide mesylate (1.8 g, 6.45 mmol) was added to a stirred suspension of potassium carbonate (2.67 g, 19.35 mmol) in dry DMSO (30 mL) under nitrogen. The reaction mixture was heated for 1 h at 60 °C, cooled, and poured into water (40 mL). The organics were extracted with ethyl acetate (3 × 75 mL), washed with water and brine, and dried over sodium sulfate, and the solvent was removed under vacuum. The residue was purified by column chromatography (dichloromethane; R_f 0.42) to yield a white solid (0.5 g, 42%). Mp: 128−129 °C (lit.[43] 132 °C). IR (Nujol), ν_{max}/cm^{-1}: 3073, 3057, 3030, 1601, 1499, 1313, 1202, 1179, 1150, 1088, 1038, 962, 774, 760, 695. ^{1}H NMR (CDCl$_3$), δ: 3.66 (2H, t, *J* 6.5 Hz, CH_2N), 4.23 (2H, t, *J* 6.5 Hz, CH_2SO$_2$), 6.90 (2H, d, *J* 8 Hz, Ar *H*), 7.06 (1H, m, Ar *H*), 7.33 (2H, m, Ar *H*). GC−MS, *m*/*z*: 183 (M$^+$), 118, 104, 91, 77, 64. Anal. Calcd for $C_8H_9NO_2S$: C, 52.45; H, 4.95; N, 7.65; S, 17.50. Found: C, 52.40; H, 5.05; N, 7.50; S, 17.50.

***N*-(4-Chlorophenyl)-1,2-thiazetidine 1,1-Dioxide.** Mp: 208 °C. IR (KBr), ν_{max}/cm^{-1}: 3038, 2977, 2911, 1601, 1497, 1422, 1335, 1304, 1205, 1156, 813, 792, 736. ^{1}H NMR (CDCl$_3$), δ: 3.62 (2H, t, *J* 6.5, CH_2N), 4.23 (2H, t, *J* 6.5, CH_2SO$_2$), 6.78 (2H, m, Ar *H*), 7.22 (2H, m, Ar *H*). GC−MS, *m*/*z*: 217−219 (M$^+$), 138−140, 125−127, 111−113, 90, 75, 63. Anal. Calcd for $C_8H_8ClNO_2S$: C, 44.14; H, 3.70; N, 6.43; S, 14.73. Found: C, 44.00; H, 3.65; N, 6.36, S, 14.161.

***N*-(4-Methylphenyl)-1,2-thiazetidine 1,1-Dioxide.** Mp: 143−145 °C. IR (Nujol), ν_{max}/cm^{-1}: 3036, 1515, 1474, 1317, 1296, 1205, 1192, 1152, 1031, 958, 817, 805, 763. ^{1}H NMR (CDCl$_3$), δ: 2.30 (3H, s, *Me*Ar), 3.67 (2H, t, *J* 6.5 Hz, CH_2N), 4.25 (2H, t, *J* 6.5 Hz, CH_2SO$_2$), 6.83 (2H, m, Ar *H*), 7.13 (2H, m, Ar *H*). GC−MS, *m*/*z*: 197 (M$^+$), 149, 130, 118, 105, 91, 77, 65. Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.80; H, 5.60; N, 7.10; S, 16.25. Found: C, 54.60; H, 5.60; N, 7.00; S, 15.90.

***N*-Phenyl-4-methyl-1,2-thiazetidine 1,1-Dioxide.** Mp 124−125 °C. IR (Nujol), ν_{max}/cm^{-1}: 3055, 1600, 1496, 1321, 1310, 1203, 1173, 1146, 1087, 964, 756, 694. ^{1}H NMR (CDCl$_3$), δ: 1.68 (3H, d, *J* 7 Hz, *Me*), 3.23 (1H, t, *J* 5 Hz, CH_2N), 3.86 (1H, dd, *J* 5 and 8 Hz, CH_2N), 4.55 (1H, m, *J* 5, 7, and 8 Hz, C*H*SO$_2$), 6.90 (2H, m, Ar *H*), 7.06 (1H, m, Ar *H*), 7.33 (2H, m, Ar *H*). Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.80; H, 5.60; N, 7.10; S, 16.25. Found: C, 54.80; H, 5.65; N, 7.00; S, 16.10.

***N*-(3-Chlorophenyl)-1,2-thiazetidine 1,1-Dioxide.** Mp: 81−82 °C. IR (Nujol), ν_{max}/cm^{-1}: 3048, 1597, 1481, 1315, 1200, 1152, 1078, 994, 769, 678. ^{1}H NMR (400 MHz, CDCl$_3$), δ: 3.71 (2H, t, *J* 6.5 Hz, CH_2N), 4.30 (2H, t, *J* 6.5 Hz, CH_2SO$_2$), 6.85 (1H, m, Ar *H*), 6.89 (1H, m, Ar *H*), 7.07 (1H, m, Ar *H*), 7.28 (1H, m, Ar *H*). ^{13}C NMR (100 MHz, CDCl$_3$), δ: 33.2, 57.5, 113.4, 115, 123.4, 130.6, 135.4, 139.4. GC−MS, *m*/*z*: 217−219 (M$^+$), 138−140, 125−127, 111−113, 91, 63. Anal. Calcd for $C_8H_8ClNO_2S$: C, 44.15; H, 3.70; N, 6.45; S, 14.75. Found: C, 44.10; H, 3.70; N, 6.35; S, 14.55.

***N*-Phenyl-4-phenyl-1,2-thiazetidine 1,1-Dioxide.** Mp: 155−157 °C. IR (Nujol), ν_{max}/cm^{-1}: 3058, 3038, 1596, 1492, 1472, 1322, 1316, 1301, 1181, 1148, 1087, 1030, 957, 768, 750, 730, 696. ^{1}H NMR (CDCl$_3$), δ: 4.58 (1H, ABX, *J* 7 Hz, C*H*SO$_2$), 4.72 (1H, ABX, *J* 7 and 11 Hz, CH_2N), 4.97 (1H, ABX, *J* 7 and 11 Hz, CH_2N), 7.25 (10H, m, Ar *H*). Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.85; H, 5.05; N, 5.40; S, 12.35. Found: C, 64.70; H, 5.05; N, 5.35; S, 12.30.

***N*-(4-Hydroxyphenyl)-1,2-thiazetidine 1,1-Dioxide.** Mp: 162−165 °C dec. IR (Nujol), ν_{max}/cm^{-1}: 3424, 3155, 3048, 1513, 1319, 1260,

1199, 1174, 1144, 1035, 960, 822, 764, 732. ^{1}H NMR ($CDCl_3$), δ: 3.55 (2H, t, *J* 6.5 Hz, CH_2N), 4.13 (2H, t, *J* 6.5 Hz, CH_2SO_2), 6.75 (4H, s, Ar *H*), 7.61 (1H, br s, O*H*). Anal. Calcd for $C_8H_9NO_3S\cdot0.5H_2O$: C, 46.15; H, 4.84; N, 6.75; S, 15.35. Found: C, 46.00; H, 4.85; N, 6.45; S, 15.10.

***N*-Phenyl-4-phenyl-4-deuterio-1,2-thiazetidine 1,1-Dioxide.** *N*-Phenyl-4-phenyl-*β*-1,2-thiazetidine 1,1-dioxide (0.1 g, 0.386 mmol) was dissolved in THF (20 mL) under a nitrogen atmosphere, and the solution was cooled to 0 °C. LDA (0.58 mmol) in THF (10 mL) was added, and the mixture was allowed to stand for 5 min. The reaction was then quenched with deuterium oxide (2 mL), ammonium chloride (15 mL) was added, the organics were extracted with ethyl acetate (3 × 30 mL), and the extract was washed with brine and dried over sodium sulfate. The solvent was removed under vacuum, and the residue was purified by column chromatography (chloroform; R_f 0.29) to give a white solid (71 mg, 71%). Mp: 158−159 °C. IR (Nujol), ν_{max}/cm^{-1}: 3058, 1594, 1492, 1470, 1308, 1167, 1153, 1087, 1029, 937, 911, 760, 750, 701, 692. ^{1}H NMR ($CDCl_3$), δ: 3.70 (1H, d, *J* 6 Hz, CH_2N), 4.03 (1H, d, *J* 6 Hz, CH_2SO_2), 7.30 (10H, m, Ar *H*). Anal. Calcd for $C_{14}H_{12}DNO_2S\cdot0.2H_2O$: C, 63.95; H, 5.15; N, 5.35; S, 12.15. Found: C, 63.85; H, 5.10; N, 5.15; S, 11.85.

2-Benzyl-4-bromo-1,2-thiazetidine 1,1-Dioxide. Benzylamine (2.3 mL, 21.4 mmol) was added to a solution of 1-bromoethenesulfonyl fluoride (2.03 g, 10.7 mmol) in dried toluene, and the mixture was stirred for 24 h at room temperature. The solvent was removed, and water (50 mL) was added to the residue. The organics were extracted three times with chloroform, and the combined extracts were dried over sodium sulfate and evaporated to yield a brown oil. The residue was purified by column chromatography ($CHCl_3$; R_f 0.44) to give a white crystalline solid, which was recrystallized from ether/petroleum ether (0.33 g, 11%). Mp: 64−65 °C (lit.[43] 41−42 °C). IR (Nujol), ν_{max}/cm^{-1}: 3038, 1446, 1325, 1316, 1211, 1180, 1105, 1072, 1028, 934, 794, 737, 650. ^{1}H NMR ($CDCl_3$), δ: 3.16 (1H, ABX, *J* 4.5 and 7 Hz, CH_2N), 3.67 (1H, ABX, *J* 7 Hz, CH_2N), 4.24 (1H, AB, *J* 14 Hz, CH_2-Ph), 4.30 (1H, AB, *J* 14 Hz, CH_2Ph), 6.65 (1H, ABX, *J* 4.5 and 7 Hz, C*H*Br), 7.34 (5H, m, Ar *H*). ^{13}C NMR ($CDCl_3$), δ: 46.8, 50.6, 60.2, 128.3, 128.6, 128.9, 133.4. Anal. Calcd for $C_9H_{10}BrNO_2S$: C, 39.15; H, 3.65; N, 5.05; S, 11.60. Found: C, 39.15; H, 3.70; N, 5.00; S, 11.50.

2-Benzyl-4-bromo-4-methyl-1,2-thiazetidine 1,1-Dioxide. Butyllithium in hexane (1.63 M, 0.326 mL, 0.2 mmol) was added to a stirred solution of diisopropylamine (0.028 mL, 0.2 mmol) in THF (10 mL) at 0 °C. After 15 min, the solution was cooled to −78 °C and 2-benzyl-4-bromo-1,2-thiazetidine 1,2-dioxide (50 mg, 0.18 mmol) in THF (5 mL) was added dropwise; methyl iodide (0.011 mL, 0.27 mmol) was added after 5 min. The mixture was allowed to warm to room temperature, and the reaction was quenched with ammonium chloride. The resulting mixture was extracted with ethyl acetate (3 × 20 mL), and the extract was washed with water and brine and dried over sodium sulfate. The solvent was removed under vacuum, and the residue was purified by column chromatography (ethyl acetate/hexane, 1:4; R_f 0.23) to give an oil (32 mg, 60%). IR (KBr), ν_{max}/cm^{-1}: 3062, 3028, 2957, 2923, 2854, 1496, 1454, 1320, 1163, 1135, 1096, 1075, 1022, 953, 748. ^{1}H NMR ($CDCl_3$), δ: 2.23 (3H, s, *Me*), 3.31 (1H, AB, *J* 6.5 Hz, CH_2N), 3.41 (1H, AB, *J* 6.5 Hz, CH_2N), 4.25 (2H, AB, *J* 14 Hz, CH_2-Ph), 7.34 (5H, s, Ar *H*).

Kinetic Experimentals. (a) Solutions and Buffers. Hydrochloric acid and sodium hydroxide solutions were prepared either from commercially available analytical standards or from standardized stock solutions of AnalaR grade reagents. Solutions of deuterium chloride and sodium deuterioxide 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.

(b) 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.

(c) Determination of Rate Constants by Gas Chromatography. The kinetics of hydrolysis of *N*-methyl-*β*-sultam were followed by monitoring the decrease in peak area of *N*-methyl-*β*-sultam relative to that of an internal standard (tetramethylene sulfone). The appropriate reactant solution (1.0 mL) was placed in a 1.5 mL polypropylene microcentrifuge tube, which was then suspended in a thermostated water bath to equilibrate to the desired temperature for at least 30 min. The reactions were initiated by injecting 300 *μ*L of a stock solution, comprising 8 × 10^{-2} M *N*-methyl-*β*-sultam and 4 × 10^{-2} M tetramethylene sulfone in distilled acetonitrile, into the reactant solution. Samples (1 *μ*L) were withdrawn at suitable time intervals and injected into a gas chromatograph. The data from the runs were combined to produce a single concentration−time curve, and the pseudo-first-order rate constants were then obtained via an iterative nonlinear least-squares fit of time against concentration data to an exponential function using the Enzfitter software package. The chromatograph employed a 5% PEG (20M) on Chromosorb column at 210 °C, along with a flame ionization detector. The retention times were 2.50 min for *N*-methyl-*β*-sultam and 3.71 min for tetramethylene sulfone.

N,*N*-Dimethylmethanesulfonamide (0.10 g) was dissolved in HCl or NaOH (50.0 mL). Portions (5.0 mL) of this solution were transferred into Pyrex glass test tubes, which were then sealed and thermostated. At selected time intervals, the extent of reaction was determined by mixing the contents of these tubes with a 0.2 M solution of tetramethylene sulfone in 10% acetonitrile (50 *μ*L). Samples (1 *μ*L) were taken and analyzed by gas chromatography using the equipment described in the previous section and a column temperature of 195 °C. The retention times were 2.01 min for *N*,*N*-dimethylmethanesulfonamide and 6.60 min for tetramethylene sulfone.

(d) UV Spectrophotometric Rate Measurements. 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 *μ*L of a 10^{-2} M solution in distilled acetonitrile) to 2.5 mL of water preincubated at 30 °C. The reactions were normally initiated by adding between 2.5 and 20 *μ*L 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 program, the data were fitted to an exponential function to yield the observed first-order rate constant.

(e) Trapping of the Mixed-Anhydride Intermediate. *N*-Benzyl-*β*-sultam (9 mg) was dissolved in 0.2 M pH 4.83 acetate buffer (10 mL) containing 0.05 M aniline and 10% dioxane. Over a 4 h period, alternate samples of this solution and the control without the *β*-sultam were analyzed using HPLC. The acetanilide peak was confirmed by spiking with 5 *μ*L of a 0.16 M solution of acetanilide in dioxane.

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