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An Activated Sulfonylating Agent That Undergoes General Base-Catalyzed Hydrolysis by Amines in Preference to Aminolysis

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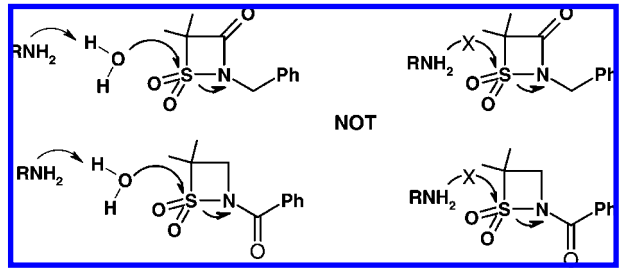

Activated sulfonyl derivatives, similar to acyl ones, usually undergo aminolysis with amines in water as nucleophilic attack by the amine is preferred to hydrolysis. However, despite being active sulfonyl derivatives, four-membered heterocyclic sulfonamides, β-sultams, do not undergo aminolysis in aqueous solution but preferentially react to give hydrolysis products only. The rate of the reaction of β-sultams in buffered solutions of simple primary amines shows a first-order dependence on amine concentrations attributed to general base-catalyzed hydrolysis by the amine. Even *N*-benzyl-4,4-dimethyl-3-oxo-β-sultam, which is both a β-sultam and a β-lactam, undergoes hydrolysis at the sulfonyl center rather than aminolysis at either the sulfonyl or acyl center. The solvent kinetic isotope effects (SKIE, k^{H_2O}/k^{D_2O}) for the amine-catalyzed hydrolyses are 1.4 and 1.9 for the hydrolysis of *N*-benzoyl-β-sultam and *N*-benzyl-4,4-dimethyl-3-oxo-β-sultam, respectively, compatible with a general base-catalyzed mechanism. The amine-catalyzed hydrolysis gives a Bronsted β value of +0.9 for both *N*-benzoyl β-sultam and *N*-benzyl-4,4-dimethyl-3-oxo-β-sultam, indicating that the general base amine is almost fully protonated in the transition state. A general base-catalyzed mechanism for hydrolysis rather than nucleophilic attack was also deduced for the reaction of *N*-benzyl-4,4-dimethyl-3-oxo-β-sultam with carboxylate anions based on a SKIE of 1.7−1.9 and rate constants which fit the Bronsted plot for amines. In contrast to acyl transfer reactions, those for sulfonyl transfer appear to show an inverse reactivity-selectivity relationship—the most active compounds being the most selective. The lack of reactivity of β-sultams toward amine nucleophiles appears to be related to the mechanism of ring opening of β-sultams with a decreased reactivity toward amines relative to hydroxide ion, probably related to the expulsion of the relatively poor leaving group amide anion.

Introduction

The reaction of activated acyl or sulfonyl derivatives with amines in water to give amides and sulfonamides, respectively, is an interesting consequence of the relative rates of aminolysis and hydrolysis. For aminolysis to occur in preference to hydrolysis, not only do relative rates have to be considered, but also absolute reactivity, which historically is encompassed by the reactivity−selectivity principle.[1–3] For acylation, there is generally a decrease in selectivity with increasing reactivity, i.e., the more reactive the acylating agent the less selective and discriminatory it is toward nucleophiles and the ratio k_{OH}/k_{Nu},

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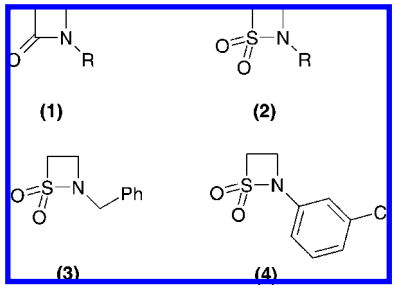
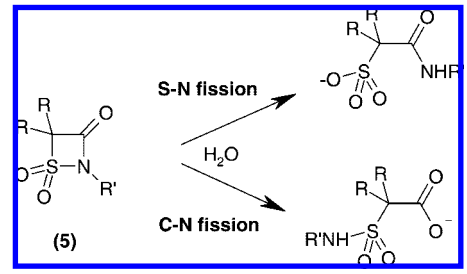
representing the rate constants for the hydroxide ion promoted hydrolysis and aminolysis, respectively, decreases with increasing reactivity.[4] By comparison, nucleophilic substitution reactions at sulfonyl centers are not as well studied or understood as the analogous acyl transfer reactions,[5] although reactive sulfonylating agents such as sulfonyl chlorides, reactive sulfonate esters, and sulfonyl imidazoles do undergo aminolysis rather than hydrolysis with amines in aqueous solution.[6] On the other hand, although β-lactams (**1**) similarly undergo aminolysis with amines in water, the corresponding β-sultams[7] (**2**) appear to prefer hydrolysis under similar conditions.[8] This appears unusual because β-sultams are reactive compounds and, for example, selectively sulfonylate some serine enzymes in preference to hydrolysis.[7] β-Sultams show greater reactivity, as indicated by their rates of alkaline hydrolysis, than their acyl analogues, the β-lactams: *N*-phenyl- and *N*-alkyl-β-sultams are 10^3 times more reactive toward hydroxide than their corresponding β-lactams.[9] However, despite the intrinsic reactivity of β-sultams, there is no increase in the rate of reaction of *N*-benzyl-β-sultam (**3**) in aqueous solutions of sodium hydroxide in the presence of *n*-propylamine or hydrazine or in aqueous buffers of these amines, and the only product is that from hydrolysis of the β-sultam.[8] This is in sharp contrast to *N*-aryl-β-lactams[10] and the β-lactams in penicillins and cephalosporins[11] where aminolysis occurs readily in competition with hydrolysis. Although this may be thought due to relative reactivities of the acylating or sulfonylating agent, the rate of alkaline hydrolysis of *N*-benzyl-β-sultam (**3**) is only about 10-fold less than that of benzyl penicillin. Furthermore, there is no aminolysis or significant change in the rate of hydrolysis of the more reactive *N*-*m*-chlorophenyl-β-sultam (**4**) with increasing concentrations of *n*-propylamine.[8] Why are amine nucleophiles not able to compete with HO^- in attacking *N*-aryl-β-sultams and yet they do with other similarly active sulfonyl and acyl derivatives?

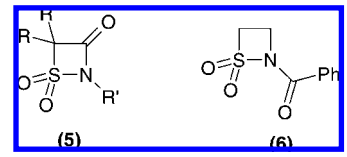


If the second order rate constant for alkaline hydrolysis, k_{OH}, is taken as an indicator of reactivity, *N*-*m*-chlorophenyl-β-sultam (**4**) would appear to be a good sulfonylating agent as it is a reactive compound[8] with a k_{OH} of 46.0 M^{-1} s^{-1} and less reactive acyl systems such as β-lactams react with a variety of nucleophiles in water, showing both alcoholysis and aminolysis.[11,12] The β-sultams do appear to be unusual sulfonyl compounds as other sulfonyl derivatives such as benzenesulfonyl chloride (k_{OH} = 40.4 M^{-1} s^{-1})[13] and tosylimidazole (k_{OH} = 3.16 M^{-1} s^{-1})[14] both undergo aminolysis in water. It is not clear whether this is connected with the intrinsic reactivity of the sulfonyl center and reactivity−selectivity relationships or due to some peculiar aspect of the mechanism of ring opening of β-sultams.

SCHEME 1



Incorporating a carbonyl group within the β-sultam ring gives the 3-oxo-β-sultams (**5**) which are both β-sultams and β-lactams and so nucleophilic attack on them could involve either acylation or sulfonylation resulting from substitution at the carbonyl center and expulsion of the sulfonamide or from substitution at the sulfonyl center and expulsion of the amide, respectively (Scheme 1). We have previously shown that the alkaline hydrolysis of 3-oxo-β-sultams (**5**) occurs by S−N fission and is only 10-fold more reactive than *N*-benzoyl-β-sultam (**6**).[15] However, *N*-benzyl-4,4-dimethyl-3-oxo-β-sultam is 4000-fold more reactive than *N*-*m*-chlorophenyl-β-sultam (**4**) toward hydroxide ion as a result of the amide anion being a better leaving group than the arylamine.[8,15] It is therefore of interest to study if the moderate increase in the reactivity toward alkaline hydrolysis may have an effect on the selectivity of *N*-acyl-β-sultams toward aminolysis rather than hydrolysis.



Results and Discussion

The Reaction of *N*-Benzoyl-β-sultam (6) with Nitrogen Bases. The apparent lack of aminolysis of *N*-benzoyl-β-sultam

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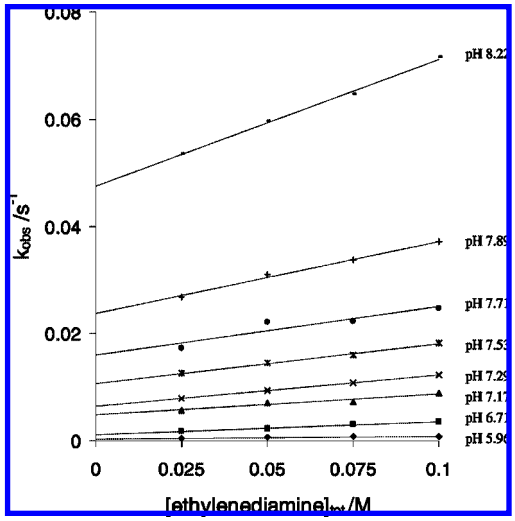


FIGURE 1. The dependence of the observed pseudo-first-order rate constants, k_{obs}, for the reaction of *N*-benzoyl-β-sultam (**6**) with ethylenediamine against total amine concentration with use of the mono- and dication as the buffer at various pH values in 1% acetonitrile at 30 °C with 1.0 M ionic strength (KCl).

(**6**) previously reported[8] with propylamine in aqueous solution is due to the more effective competing hydrolysis by hydroxide ion. To determine whether aminolysis of β-sultams can actually occur in aqueous solution, ethylenediamine was chosen both as a potential nucleophile and a buffer. This is because ethylenediamine has been shown to have enhanced reactivity due to the second amine acting as an intramolecular general base catalyst[11c] and buffered solutions of ethylenediamine mono- and dication are around neutral pH thus reducing the rate of alkaline hydrolysis. The rate of the reaction of *N*-benzoyl-β-sultam (**6**) in aqueous buffers of ethylenediamine was studied by UV-spectrophotometry in 1% acetonitrile−water (v/v) and 1.0 M ionic strength (KCl) at 30 °C. Interestingly, the rate of the reaction of *N*-benzoyl-β-sultam *does* show a small but

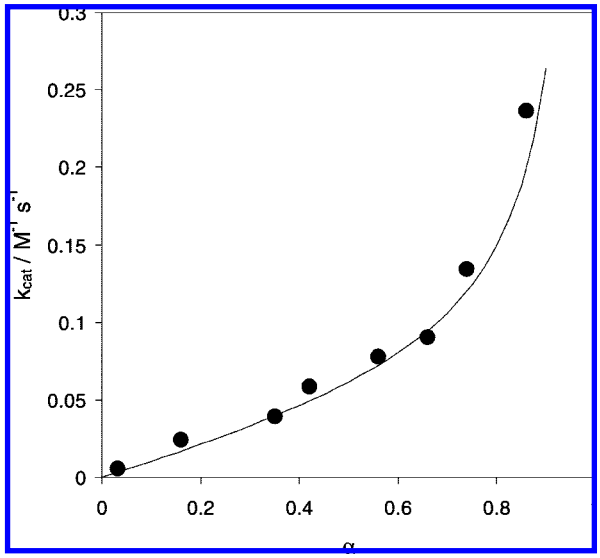


FIGURE 2. The dependence of the second-order rate constant, k_{cat}, on the fraction of free base (the monocation), α, of ethylenediamine in the reaction with *N*-benzoyl-β-sultam (**6**) in 1% acetonitrile at 30 °C with 1.0 M ionic strength (KCl). The theoretical curve was generated by using eq 2 and the rate constant in Table 1.

detectable dependence on the total amine concentration in a buffered solution of ethylenediamine mono- and dication. The reaction shows simple first-order kinetics and the observed pseudo-first-order rate constants, k_{obs}, were plotted against the total concentration of ethylenediamine (Figure 1). Extrapolating the rate constants to zero amine buffer concentration corresponds to that calculated for the background hydrolysis at the given pH and the slopes of these plots give the second-order rate constants, k_{cat}, for the reaction dependent on amine concentration, which when plotted against the fractions of monocationic ethylenediamine α exhibit a sharp upward curvature (Figure 2). The sharp upward curvature indicates that the amine-catalyzed reaction either is hydroxide ion catalyzed or is the result of its kinetic equivalent in the rate law. Since the second-order rate constant, k_{cat}, is indistinguishable from zero as the fraction of the monocation form of ethylenediamine approaches zero, the dication form is not catalytically important. The rate law can thus be described as:

$$\frac{\text{rate}}{[\beta\text{-sultam}]} = k_{obs} = k_o + k_1\alpha[EDAH^+]_{tot} + k_2'\alpha[EDAH^+]_{tot}[OH^-] \quad (1)$$

and the apparent second-order rate constant, k_{cat}, is given by:

$$k_{cat} = \frac{k_{obs} - k_o}{[EDAH^+]_{tot}} = k_1\alpha + k_2'\alpha[OH^-] \quad (2)$$

where k_1 is the second-order rate constant for the amine-catalyzed reaction by the diamine monocation, $EDAH^+$, and k'_2 is the apparent third-order rate constant for the reaction catalyzed by $EDAH^+$ and hydroxide ion. The rate constants k_1 and k'_2 can be obtained from the intercept and slope, respectively, of a plot of k_{cat}/α against hydroxide ion concentration (Figure 3). However, the term in the rate law, $k'_2\alpha[EDAH^+]_{tot}[OH^-]$, is kinetically equivalent to the amine-catalyzed reaction by neutral diamine with a term, $k_2[EDA]$ where

$$k_2 = k_2'\frac{K_w}{K_a} \text{ and } K_a = \frac{[EDA][H^+]}{[EDAH^+]}$$

and k_2 is the second-order rate constant for the amine-catalyzed reaction by neutral ethylenediamine, EDA. The rate law then becomes:

$$\frac{\text{rate}}{[\beta\text{-sultam}]} = k_{obs} = k_o + k_1[EDAH^+] + k_2[EDA] \quad (3)$$

and the values of these rate constants are given in Table 1. However, this kinetic analysis does not distinguish between the amine acting as a nucleophile giving an aminolysis reaction or it being a general base catalyst (**7**) leading to hydrolysis of the β-sultam (**6**). A product analysis with HPLC was undertaken with the reaction of *N*-benzoyl-β-sultam with 1.0 M ethylenediamine at pH 8.03 with 1% acetonitrile−water (v/v). Under the kinetic experimental conditions the background hydrolysis only accounts for 10% and the amine-catalyzed reaction accounts for 90% of the reaction. The HPLC chromatogram of the product reaction mixture is similar to that obtained for the alkaline hydrolysis reaction with the same concentration of *N*-benzoyl-β-sultam. Although the peak area of the signal for the hydrolysis product from the reaction mixture with ethylenediamine is slightly less than that obtained from alkaline

TABLE 1. The Rate Constants for the Reaction of β-Sultams with Nitrogen and Oxygen Bases in Water and Deuterium Oxide

	pK_a	$k^{H_2O}/M^{-1}\ s^{-1}$	$k^{D_2O}/M^{-1}\ s^{-1}$	k^{H_2O}/k^{D_2O}
	N-benzoyl β-sultam (**6**)			
aminoacetonitrile	5.46[a]	1.02×10^{-3}		
ethylenediamine monocation ($EDAH^+$)	7.32[a]	1.02×10^{-1}	5.44×10^{-2}	1.88
ethylenediamine (EDA)	10.1[b]	11.9		
hydroxide-ion	15.6	1.46×10^{4}		
	N-benzyl-4,4-dimethyl-3-oxo-β-sultam (**8**)			
aminoacetonitrile	5.46[a]	3.91×10^{-2}		
trifluoroethylamine	5.65[a]	3.34×10^{-2}	2.39×10^{-2}	1.40
ethylenediamine monocation ($EDAH^+$)	7.32[a]	1.30		
2-cyanoethylamine	7.91[a]	4.90		
taurine	8.85[a]	33.3		
formate	3.58[a]	2.10×10^{-3}		
acetate	4.57[a]	6.95×10^{-3}	4.14×10^{-3}	1.68
hexafluoroacetone	6.38[a]	1.02×10^{-1}	5.33×10^{-2}	1.91
hydroxide-ion	15.6	1.83×10^{5}		
	N-benzyl-3,3-dimethyl-2-oxo-β-lactam (**10**)			
taurine	9.05[b]	7.48×10^{-2}		

[a] ionization constants measured potentiometrically at 30 °C with 1.0 M ionic strength (KCl) in water. [b] ionization constants obtained from ref 11c.

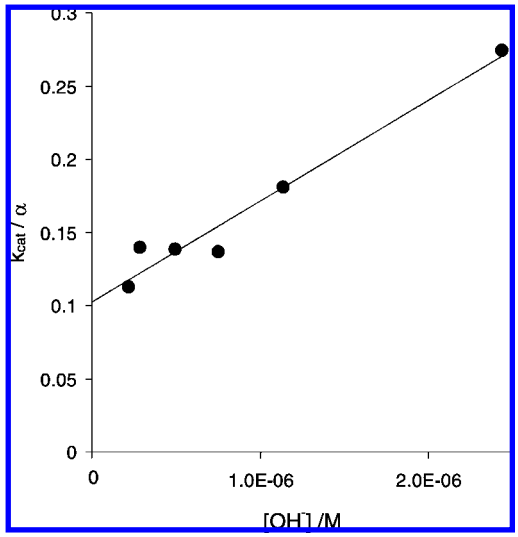
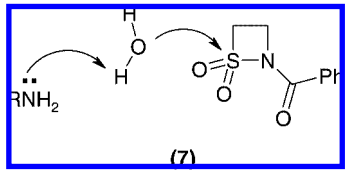


FIGURE 3. The dependence of the second-order rate constants, k_{cat}/α, for the reaction of ethylenediamine monocation with *N*-benzoyl β-sultam (**6**) upon the activity of hydroxide ion. The rate constants were determined in 1% acetonitrile at 30 °C with 1.0 M ionic strength (KCl).

hydrolysis, there are no other peaks observed and it appears that the reaction catalyzed by the amine is a hydrolysis reaction.



(7)

Another experimental distinction between nucleophilic and general base catalysis is their different solvent kinetic isotope effects.[16a] The corresponding rate constants for the reaction of the β-sultam (**6**) with $EDAH^+$ were determined as before but in deuterium oxide. The solvent kinetic isotope effect for $EDAH^+$, $k_1^{H_2O}/k_1^{D_2O}$, is 1.88 (Table 1), which is compatible with general base catalysis as the reaction is slower in deuterium oxide than it is in water.[16a] For comparison, a solvent kinetic isotope effect as high as 4 was determined for the general base-catalyzed hydrolysis of *N*-acetyl-*N*′-methylimidazolium ion by *N*-methylimidazole[17] but solvent kinetic isotope effects as small as 1.1 have been observed in some general base-catalyzed reactions.[18] It is interesting to note that a very large SKIE k_{H_2O}/k_{D_2O} of 4.4 was observed for the pH-independent hydrolysis of the β-sultam (**6**) consistent with rate limiting proton transfer presumably involving general base or acid catalysis by a second molecule of water.[8]

The observation that a reaction due to EDA occurs in buffers of $EDAH^+/EDAH_2^{2+}$ despite its very low concentration indicates the amine-catalyzed reaction must show a large Brønsted β value, i.e., a large dependence of the rate constant on the basicity of the amine. To confirm this, the reaction was also studied in aqueous buffers of the weakly basic amine aminoacetonitrile. Similar to that observed with ethylenediamine, aminoacetonitrile also shows a small, but detectable, catalysis of the hydrolysis reaction at low fractions of free base of the amine, i.e., at low pH. As the fraction of free base of the amine and the pH of the solution increases, catalysis by the amine becomes undetectable, due to the increasing significance of alkaline hydrolysis. The observed pseudo-first-order rate constant, k_{obs}, for the reaction plotted against the total concentrations of aminoacetonitrile and extrapolated to zero amine buffer concentration corresponds to that calculated for the background hydrolysis at the given pH. As before, the slopes of these plots give the second-order rate constants, k_{cat}, which as a function of different fractions of free base, α, of the amine give the contributions to the rate from the protonated and the unprotonated form of the amine. However, unlike that observed with ethylenediamine, a straight line passing through the origin was obtained from the plot of k_{cat} against α, indicating that the reactive form of the amine is the free base form and there is no reaction by the protonated form or catalysis by hydroxide ion. This also supports the interpretation of general base catalysis by the amine rather than hydroxide ion-catalyzed aminolysis, as is commonly observed with reactive acylating agents.[10,11] The rate law that adequately describes the reaction is thus simply:

$$\frac{\text{rate}}{[\beta\text{-sultam}]} = k_{obs} = k_o + k_B\alpha[\text{aminoacetonitrile}]_{tot} = k_o + k_B[\text{aminoacetonitrile}] \quad (4)$$

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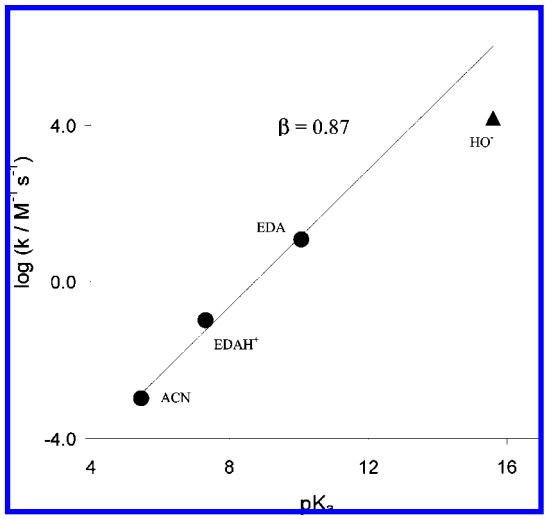


FIGURE 4. The dependence of the second-order rate constant for the reaction of amines with *N*-benzoyl-*β*-sultam (**6**) as a function of the basicity of the amine in 1% acetonitrile at 30 °C with 1.0 M ionic strength (KCl), where ACN = aminoacetonitrile, $EDAH^+$ = ethylenediamine monocation, and EDA = ethylenediamine.

where k_o is the rate constant for the background hydrolysis and k_B is the second-order rate constant for the amine-catalyzed reaction by aminoacetonitrile (Table 1).

The second-order rate constants for the general base-catalyzed hydrolysis of *N*-benzoyl-*β*-sultam (**6**) are correlated with the ionization constants of the conjugate acids of the amines to give a Brønsted β value of +0.87 (Figure 4); although this is based on only three points, the range of basicity covered is nearly 5 pK_a units (a Brønsted β value of +0.80 is obtained with statistical correction). The value of β indicates the degree of charge development of the catalyst in the transition state of the rate-limiting step of the reaction.[16a] The Brønsted β value of +0.87 indicates that the amine, which is acting as a general base in removing a proton from the attacking water molecule (**7**), is almost fully protonated in the transition state. This is an unusually large degree of charge development on the base for a general based-catalyzed reaction. For comparison, the Brønsted β values for the general base-catalyzed hydrolysis of acetylimidazole, acetylimidazolium ion, and ethyl dichloroacetate are +0.55, +0.34, and +0.47, respectively.[19,20] The later transition state for the hydrolysis of the *β*-sultam is indicative of a much greater selectivity on the general base than that observed with acyl transfer.

The Brønsted plot (Figure 4) can also be used to explain why there was no reaction observed in a previous report[8] with propylamine and *N*-benzoyl-*β*-sultam (**6**). From the Brønsted plot, the second-order rate constant for the reaction with propylamine is calculated to be 90 M^{-1} s^{-1} so by using 0.1 M propylamine at pH 11.62 (0.84 fraction of free base), the contribution to the total rate of hydrolysis from the amine catalyzed reaction would be about 8 s^{-1}. The rate of the background hydrolysis at this pH is 80 s^{-1}, which is 10-fold greater than that of the amine-catalyzed reaction, so the detection of this contribution is experimentally difficult.

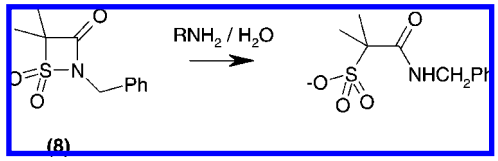
In summary, although a reaction involving amine and the *N*-benzoyl-*β*-sultam (**6**) has now been demonstrated it involves general base-catalyzed hydrolysis and not aminolysis. The aminolysis of reactive acyl and sulfonyl centers in water is well-known.[13,18] It is interesting that *β*-sultams do not undergo aminolysis whereas their acyl analogues, *β*-lactams, react with amines readily in preference to hydrolysis.[10,11,21] It has been shown that, in the nucleophilic-catalyzed hydrolysis of carboxylic acid esters,[22] the mechanism of a nucleophilic displacement reaction depends on the relative nucleophilicity of the nucleophile and the nucleofugacity of the leaving group. With a good leaving group the nucleophilic reaction undergoes an uncatalyzed pathway but it becomes general base or hydroxide ion catalyzed with decreasing nucleofugacity of the leaving group, and no nucleophilic reaction is detected at all for a poor leaving group. The nucleophilicity of the nucleophile and the nucleofugacity of the leaving group in the aminolysis of *N*-aroyl-*β*-sultams and *N*-aroyl-*β*-lactams are the same, and yet only the latter readily undergoes aminolysis in aqueous solution.[21] Sulfonylating agents such as sulfonyl chlorides which are 2 orders of magnitude less reactive toward hydroxide ion compared with *N*-benzoyl-*β*-sultam undergo aminolysis in preference to hydrolysis, so the lack of reactivity of the *β*-sultams toward amine nucleophiles appears not to be related to absolute reactivity or to the fact that the leaving group is an amide.

***N*-Benzyl-4,4-dimethyl-3-oxo-*β*-sultam (8). (i) Reactions with N-Nucleophiles.** Similar to other active acylating agents, *β*-lactams are susceptible to nucleophilic displacement reactions with various nucleophiles, including amines, in water in preference to hydrolysis.[10–12,23] Although *β*-sultams are generally 10^3 more reactive than their acyl analogues, *β*-lactams, toward hydroxide ion, they do not undergo aminolysis in water. 3-Oxo-*β*-sultams (**5**) are both *β*-sultams and *β*-lactams and nucleophilic attack on them could involve either acylation or sulfonylation resulting from substitution at the carbonyl center and expulsion of the sulfonamide or from substitution at the sulfonyl center and expulsion of the amide, respectively (Scheme 1). The alkaline hydrolysis of 3-oxo-*β*-sultams (**5**) occurs by S−N fission as a result of the preferential attack of hydroxide ion on the sulfonyl center,[15] but given the greater susceptibility of *β*-lactams to aminolysis, it is of interest to determine if amines selectively attack the carbonyl center in **5**.

The rate of reaction of *N*-benzyl-4,4-dimethyl-3-oxo-*β*-sultam (**8**) was studied in aqueous amine buffers with 1% acetonitrile-water (v/v) and 1.0 M ionic strength (KCl) at 30 °C. Similar to the amine-catalyzed reaction with *N*-benzoyl *β*-sultam (**6**), a small but measurable increase in rate with increasing amine concentration was observed. The observed pseudo-first-order rate constant, k_{obs}, for the reaction of **8** in aqueous solution buffered with 2-cyanoethylamine is linearly dependent on the total amine concentration and extrapolation to zero amine concentration corresponds to that calculated for the background hydrolysis. The slopes of these plots give the second-order rate constants, k_{cat}, for the reaction by both the protonated and the deprotonated form of the amine and a plot of k_{cat} against α, the fraction of free base, gives a straight line that passes through the origin for all amines studied. This indicates the basic form but not the protonated from of the amines is catalytically active. The second-order rate constants, k_B, for the amine-catalyzed reaction are obtained as the right-hand intercept at $\alpha = 1.0$ and

(19) Jencks, W. P.; Oakenfull, D. G. *J. Am. Chem. Soc.* **1971**, *93*, 178–188.
(20) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1961**, *83*, 1743–1750.
(21) Tsang, W. Y.; Ahmed, N.; Page, M. I. *Org. Biomol. Chem.* **2007**, *5*, 485–493.
(22) (a) Kirsch, J. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1964**, *86*, 833–837. (b) Kirsch, J. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1964**, *86*, 837–846.
(23) Llinas, A.; Vilanova, B.; Page, M. I. *J. Phys. Org. Chem.* **2004**, *17*, 521–528.

SCHEME 2



are given in Table 1. The rate law that adequately describes the reaction is therefore the same as that for the amine-catalyzed hydrolysis of *N*-benzoyl-*β*-sultam with aminoacetonitrile (eq 4) and unlike the aminolysis of *β*-lactams and other active acylating agents shows no second order term in amine- or base-catalyzed aminolysis.[10,11]

A product analysis by HPLC was undertaken with the reaction solution containing *N*-benzyl-4,4-dimethyl-3-oxo-*β*-sultam (0.01 M) and taurine (1.0 M) at pH 8.87 in 5% acetonitrile−water (v/v), as these conditions, based on the kinetic data, correspond to the amine-dependent reaction accounting for 95% of the reaction with the remaining 5% due to the background hydrolysis. The HPLC chromatogram of the product reaction mixture is identical with that obtained from the alkaline hydrolysis reaction with the same concentration of the 3-oxo-*β*-sultam. The fraction was collected and submitted for ESI-MS (negative mode) analysis, which shows an observed mass peak of 256 corresponding to the mass of the hydrolysis product. As the hydrolysis product formed in aqueous amine buffer has the same retention time as that formed in water, it is the *β*-amido sulfonic acid (Scheme 2) as a result of S−N bond fission. Therefore, the amine-catalyzed reaction represents general base-catalyzed hydrolysis, as found for *N*-benzoyl *β*-sultam (**6**).

The second-order rate constants, k_B, for the general base-catalyzed hydrolysis of **8** can be correlated with the ionization constants of the conjugate acids of the amines to give a Brønsted *β* value of +0.90 (Figure 5). The Brønsted *β* value is very

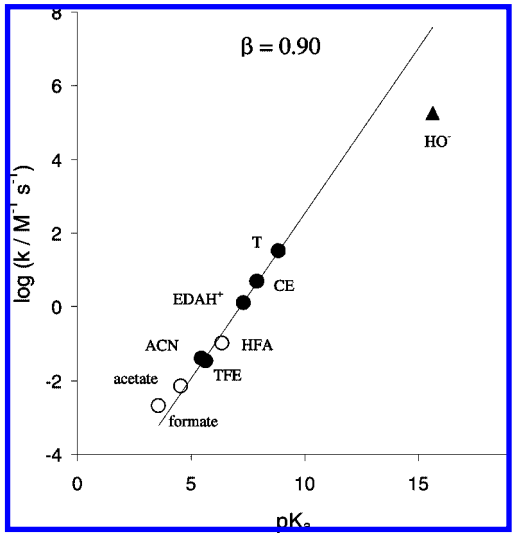
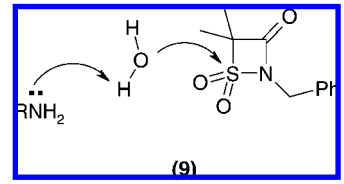


FIGURE 5. The dependence of the second-order rate constants for the reaction of *N*-benzyl-4,4-dimethyl-3-oxo-*β*-sultam (**8**) with amines (●) and carboxylate anions (○) as a function of the pK_a of their conjugate acids. The second-order rate constant for the alkaline hydrolysis of the 3-oxo-*β*-sultam is also shown (▲). The rate constants were determined in 1% acetonitrile at 30 °C with 1.0 M ionic strength (KCl), where ACN = aminoacetonitrile, TFE = trifluoroethylamine, $EDAH^+$ = ethylenediamine monocation, CE = 2-cyanoethylamine, T = taurine, and HFA = hexafluoroacetone.

similar to that of +0.87 for the amine-catalyzed reaction with *N*-benzoyl-*β*-sultam, and is indicative of an almost fully protonated amine in the transition state of the rate-limiting step (**9**). A solvent kinetic isotope effect, $k_B^{H_2O}/k_B^{D_2O}$, of 1.40 was determined for the reaction with trifluoroethylamine (Table 1) which, although low, is compatible with a mechanism involving proton transfer in the transition state of the rate-limiting step (**9**). Further confirmation for amine general base-catalyzed hydrolysis of *N*-benzyl-4,4-dimethyl-3-oxo-*β*-sultam (**8**) comes from the similar magnitude of the rate constants to those for the hydrolysis of *N*-benzoyl-*β*-sultam (**6**) (Table 1) indicative of both reactions involving sulfonyl transfer and opening of the four-membered ring by S−N fission.



The expulsion of the amide anion as a leaving group is presumably facilitated by the energy released in ring-opening and has been previously suggested.[21] For example, the aminolysis of *N*-aroyl-*β*-lactams has a high sensitivity to both the basicity of the attacking amine and that of the amide leaving group. Electron-withdrawing groups in the amide leaving group increase the rate of reaction and the aminolysis of *N*-aroyl-*β*-lactams appears to occur by a concerted pathway in which bond formation and fission occur simultaneously.[21]

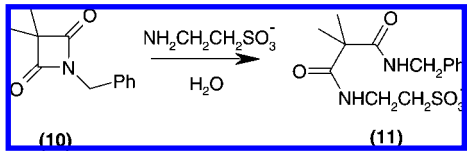
N-Benzyl-4,4-dimethyl-3-oxo-*β*-sultam thus reacts as a *β*-sultam with water preferentially attacking the sulfonyl center resulting in S−N bond fission and expulsion of the amide rather than as a *β*-lactam undergoing amine nucleophilic attack on the acyl center resulting in C−N bond fission and expulsion of the sulfonamide. The poorer susceptibility of the sulfonyl center to N nucleophiles relative to the acyl center has also been observed in the reaction of aniline with acyclic acyl sulfonates.[24]

It was of interest to investigate the site of nucleophilic attack on **8** with amines in a nonaqueous system to determine whether solvent water plays an important role in determining the site of nucleophilic attack. *N*-Benzyl-4,4-dimethyl-3-oxo-*β*-sultam (50 mg, 209 *μ*mol) was left stirring in neat 2-methoxyethylamine (5 mL) and after 2 h the reaction mixture was purified by column chromatography and the main product (20 mg, 64 *μ*mol) was analyzed by NMR and MS. ESI-MS (positive mode) showed mass peaks of 315.0, 337.1, and 354.0 corresponding to those of the aminolysis product complexed with one proton, sodium ion, and potassium ion, respectively. The site of nucleophilic attack was demonstrated by ^{1}H, ^{13}C HMBC NMR spectra which show a coupling between the methylene protons of the attached amine to the carbonyl carbon of the 3-oxo-*β*-sultam. This shows that the amine preferentially attacks the acyl center to form the amide aminolysis product in a nonaqueous system and that solvent water does have a role in determining selectivity.

To estimate the rate constant for amine nucleophilic attack on the *β*-lactam of *N*-benzyl-4,4-dimethyl-3-oxo-*β*-sultam (**8**) the aminolysis of the analogous 2-oxo-*β*-lactam (**10**) was studied. This system may also demonstrate that the lack of

(24) Laird, R. M.; Spence, M. J. *J. Chem. Soc. B* **1971**, 1434.

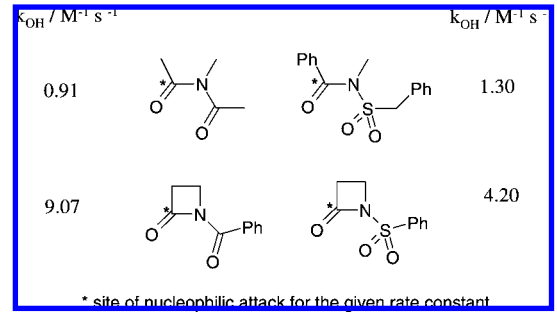
SCHEME 3



aminolysis of 3-oxo-β-sultam is not due to an intrinsic property of the four-membered ring containing two electrophilic centers. The aminolysis of the β-lactam (**10**) was demonstrated by a product analysis, using HPLC with the reaction solution of *N*-benzyl-3,3-dimethyl-2-oxo-β-lactam (0.01M) in taurine (0.2 M) at pH 9.75, 5% acetonitrile−water (v/v). There was no signal corresponding to the hydrolysis product (retention time = 15.7 min) but a new signal at 8.35 min was detected. The fraction was collected and analyzed by ESI-MS (negative mode), which gave a peak of 328 corresponding to the mass of the aminolysis product (**11**) (Scheme 3). The rate of the aminolysis of **10** with taurine was studied by UV spectroscopy in 1% acetonitrile−water (v/v) and 1.0 M ionic strength at 30 °C, using TAPS, CHES, and CAPS as buffers. Similar to the aminolysis of *N*-aroyl-β-lactams,[21] the observed pseudo-first-order rate constants, k_{obs}, are linearly dependent on the total amine concentration from which the second-order rate constant, k_{RNH_2}, was determined to be 7.48×10^{-2} M^{-1} s^{-1} (Table 1). The rate constant for the aminolysis of **10** by taurine is 375-fold slower than that for the general base-catalyzed hydrolysis of the β-sultam of *N*-benzyl-4,4-dimethyl-3-oxo-β-sultam (**8**) by the same amine. Nucleophilic attack at the acyl center of **8** would displace a sulfonamide compared with an amide in **10**, but despite their difference in acidity, sulfonamides and amides appear to behave similarly as leaving groups. For example, the second-order rate constants for alkaline hydrolysis for their displacement from acyl center are similar (Chart 1).[9b,25] Although a weaker nucleophile than hydroxide ion, such as an amine, may have a stronger dependence on the basicity of the leaving group, it seems reasonable to assume that the rate constants for the aminolysis of the acyl centers in **8** and **10** would be similar. It is therefore self-consistent with the observed faster rate of the amine general base-catalyzed hydroylsis of **8** by sulfonyl transfer rather than aminolysis by acyl transfer.

(ii) Reactions with O-Nucleophiles. Having established that hydrolysis of the active sulfonylating β-sultam occurs at a faster rate than aminolysis, it was necessary to demonstrate whether this was simply a preference for sulfonyl transfer to O rather than N, and so the reaction in the presence of O-nucleophiles/bases was studied. The rate of the reaction of *N*-benzyl-4,4-dimethyl-3-oxo-β-sultam (**8**) in the presence of carboxylate buffers was measured by UV-spectrophotometry in 1% acetonitrile−water (v/v) and 1.0 M ionic strength (KCl) at 30 °C. The dependence of the observed pseudo-first-order rate constants, k_{obs}, for the reaction of the 3-oxo-β-sultam (**8**) in aqueous solution buffered with acetate on total buffer concentration is linearly dependent on the total acetate concentration. Extrapolation of the reaction rate to zero buffer concentration corresponds to that calculated for the background hydrolysis. The slopes of these plots give the second-order rate constants, k_{cat}, for the reaction by both

CHART 1



the protonated and the deprotonated form of acetate. Plotting k_{cat} against the fraction of free base, α, gives a straight line that passes through the origin for all carboxylate buffers studied. This indicates the basic form of the carboxylates is catalytically active and there is no reaction with the undissociated acid, as is observed with *N*-benzyl-β-sultam.[9c] The second-order rate constants, k_B, for the reaction with the basic form of carboxylates are obtained as the right intercept at $\alpha = 1.0$ and are given in Table 1.

A solvent kinetic isotope effect, $k_B^{H_2O}/k_B^{D_2O}$, of 1.68 and 1.91 was determined for the reaction of acetate and the anion of hexafluoroacetone hydrate with the 3-oxo-β-sultam (**8**), respectively (Table 1), indicative of a general base-catalyzed reaction. By contrast, the reaction of *N*-benzoyl-β-sultam (**6**) with more basic oxygen anions does, however, appear to involve nucleophilic catalyzed hydrolysis.[8] The second-order rate constants, k_B, for the reaction of the 3-oxo-β-sultam (**8**) with carboxylate anions are correlated with the ionization constant of the carboxylate buffer and are of a similar magnitude to those determined for amines of similar basicity. Although by themselves they would give a lower Brønsted β value, they do give a reasonable fit to the plot generated for the amine general base-catalyzed hydrolysis (Figure 5).

The lack of reactivity of β-sultams toward amine nucleophiles appears to be the intrinsic reactivity of β-sultams and not related to their absolute reactivity as indicated by their rates of alkaline hydrolysis. Presumably this is related to the mechanism of sulfonyl transfer in four-membered rings compared with that in analogous acyclic derivatives. However, a fundamental difference between β-sultams and β-lactams is the enhanced reactivity of greater than 10^6 toward hydroxide ion of the sulfonyl derivative compared with acyclic analogues, whereas β-lactams show little or no enhanced reactivity compared with their acyclic analogues.[7–9]

The difference in behavior between the aminolysis of acyl and acyclic sulfonyl derivatives on one hand and the hydrolysis of β-sultams on the other in aqueous solutions of amines is unlikely to be the result of different reactivity−selectivity relationships. Although sulfonyl transfer reactions do appear to show opposite behavior to acyl transfer, β-sultams show the same unusual pattern. A simple selectivity parameter is the ratio k_{OH}/k_w, representing the rate constants for the hydroxide ion promoted and pH independent water hydrolysis, respectively. We have noticed an inverse selectivity−reactivity relationship with respect to hydrolysis and a plot of log k_{OH}/k_w(selectivity) against log k_{OH}(reactivity) (Figure 6) shows a good correlation but, surprisingly, the more reactive sulfonylating agent is more selective! However, β-sultams show a similar inverse behavior, indicating that this is a general property of all sulfonyl transfer reactions. The structure around the sulfonamide group in

(25) Tsang, W. Y.; Ahmed, N.; Hemming, K.; Page, M. I. *Can. J. Chem.* **2005**, *83*, 1432–1439.

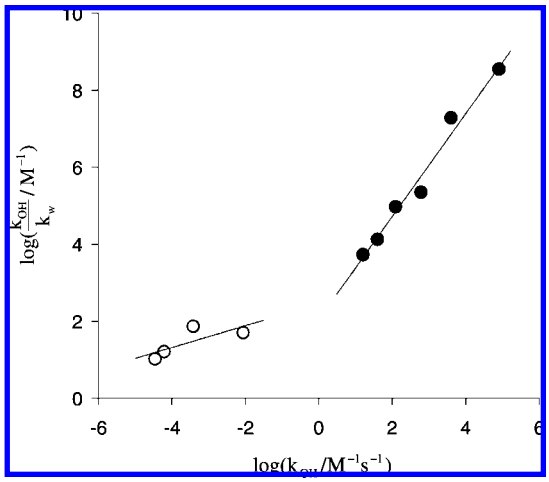


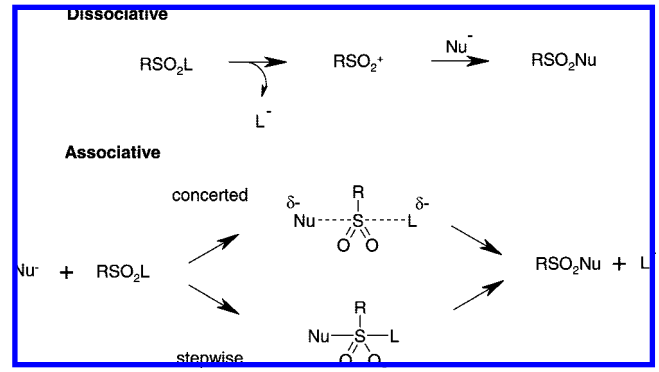
FIGURE 6. The relationship between selectivity (log k_{OH}/k_w) and reactivity (log k_{OH}) for the hydrolysis of sulfonyl derivatives (●) and sulfate esters (o). Data are from: King, J. F.; Rathore, R.; Lam, J. Y. L.; Guo, Z. R.; Klassen, D. F. *J. Am. Chem. Soc*. **1992**, *114*, 3028−3033.

β-sultams is very different from that in acyclic derivatives for which the stability is very dependent on the hybridization of the sulfonamide nitrogen.[26] Furthermore, the mechanism of bond fission in four-membered rings may not be a stretching motion but rather a bond rotational mode that may lead to differences in behavior.[27]

The mechanisms for sulfonyl transfer reactions involving the displacement of a leaving group L by a nucleophile Nu may occur in an associative or dissociative process (Scheme 4).[7] The dissociative $S_N1(S)$ process would generate a sulfonylium ion that is then subsequently attacked by a nucleophile. Although the evidence for this mechanism on sulfonyl transfer is ambiguous,[5] it has been proposed to occur in the acid-catalyzed hydrolysis of β-sultams as a result of the release of ring strain upon ring-opening.[9d] However, in general it appears that sulfonylium ions are more difficult to generate than acylium ions,[28] and this is unlikely to be relevant to the present discussion. Associative, stepwise mechanisms involving formation of unstable intermediates are the norm for acyl transfer whereas the concerted process remains controversial.[16] 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.[29] Most observations can be interpreted in terms of either a stepwise or a concerted mechanism. Although there is no clear evidence for the formation of an intermediate, the transition state and/or the intermediate in the associative mechanism adopt a trigonal bipyramidal geometry and it appears that there are some requirements for pseudorotation[30] and apical displacement of the leaving group by a nucleophile.[9b]

The lack of aminolysis is due to either an enhanced reactivity of β-sultams toward oxygen nucleophiles and hydroxide ion in particular or to a relatively reduced activity of amine nucleophiles to the sulfonyl center. If sulfonyl transfer occurs by a concerted mechanism then aminolysis probably requires general base catalysis to avoid formation of a N-protonated sulfonamide product and proton removal from the attacking amine by base necessitates a termolecular reaction. In a stepwise mechanism this entropically unfavorable step can be avoided. The enhanced reactivity of β-sultams toward hydroxide ion maybe the result of rate-limiting formation of the trigonal bipyramidal intermediate, whereas nucleophilic attack of an amine on the sulfonyl center is reversible and does not lead to reaction unless general base catalysis occurs to remove a proton from the attacking amine and/or the leaving group is expelled in a facile step. In activated acyclic sulfonyl derivatives there is often a good leaving group, whereas in β-sultams it is a poorer one—amide anion or amine—presumably leading to a higher activation energy and a later transition state with significant S−N bond fission.

SCHEME 4



Experimental Section

The methods of preparation for *N*-benzyol-β-sultam (**6**), *N*-benzyl-4,4-dimethyl-3-oxo-β-sultam (**8**), and *N*-benzyl-3,3-dimethyl-2-oxo-β-lactam (**10**) have been given previously.[9a,31,32]

Standard UV spectroscopy was carried out on UV−visible spectrophotometers in double beam mode with cell holders thermostated by using a peltier system. In all experiments temperatures were maintained at 30 °C and ionic strength at 1.0 M with AnalaR grade KCl unless otherwise stated.

The pH of solutions of an amine was controlled by the use of ≤0.2 M buffer solutions of the amine. Buffer sulutions were prepared by partial neutralization of solutions of their neutral form to the required pH. Hydroxide ion concentrations were calculated by using $pK_w(H_2O) = 13.83$ at 30 °C. AnalaR grade reagents and deionized water were used throughout. Organic solvents were glass distilled prior to use and stored under nitrogen.

Reactions studied by UV spectrophotometry were commenced by injections (20 μL) of acetonitrile stock solutions (1×10^{-2} M) of the substrate into the cells containing preincubated buffer (2.0 mL). Final reaction cells contained ≤1% acetonitrile v/v. The pH of the reaction cells was measured before and after each kinetic run at 30 °C, and kinetic runs experiencing a change >0.05 units were rejected. Reactant disappearance or product appearance were followed at absorbance change maxima for individual compounds.

(26) Breneman, C. M.; Weber, L. W. *Can. J. Chem.* **1996**, *74*, 1271–1282.
(27) Page, M. I. *Philos. Trans. R. Soc. London, Ser. B* **1991**, *332*, 149–156.
(28) (a) Bentley, T. W.; Jones, R. O. *J. Phys. Org. Chem.* **2007**, *20*, 1093–1101. (b) Olah, G. A.; Kobayash, S.; Nishimur, J. *J. Am. Chem. Soc.* **1973**, *95*, 564−569. (c) Kice, J. L. *Prog. Inorg. Chem.* **1972**, *17*, 147–206.
(29) (a) Ciuffari, E.; Senatore, L.; Isola, M. *J. Chem. Soc., Perkin Trans. 2* **1972**, 468. (b) Deacon, T.; Farrar, C. R.; Sikkel, B. J.; Williams, A. *J. Am. Chem. Soc.* **1978**, *100*, 2525–2534. (c) Rogne, O. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1486–1490. (d) King, J. F.; Gill, M. S.; Klassen, D. F. *Pure Appl. Chem.* **1996**, *68*, 825–830.
(30) Kaiser, E. T. *Acc. Chem. Res.* **1970**, *3*, 145.
(31) Tsang, W. Y.; Ahmed, N.; Hemming, K.; Page, M. I. *Org. Biomol. Chem.* **2007**, *5*, 3993.
(32) Mulchande, J.; Guedes, R. C.; Tsang, W.-Y.; Page, M. I.; Moreira, R.; Iley, J. *J. Med. Chem.* **2008**, *51*, 1783.

The solubility of compounds was ensured by working within the linear range of absorbance in corresponding Beer−Lambert plots. Reaction concentrations were generally within the range of 2×10^{-5} to 2×10^{-4} M. Pseudo-first-order rate constants from exponential plots of absorbance against time or gradients of initial slopes were obtained by using the Cary Win UV kinetics application (Version 02.00(26)).

Supporting Information Available: Plots of the kinetic data for the reaction of *N*-benzyl-4,4-dimethyl-3-oxo-β-sultam (**8**) with 2-cyanoethylamine and acetate ion. This material is available free of charge via the Internet at http://pubs.acs.org.

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