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General acid catalysed hydrolysis of β-sultams involves nucleophilic catalysis

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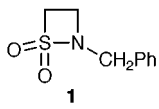
The hydrolysis of the four-membered ring sulfonamide *N*-benzyl β-sultam is catalysed by carboxylic acids, which is attributed to specific acid–nucleophilic catalysis with the intermediate formation of a mixed anhydride which can be trapped with aniline.

Contrary to intuition, the four-membered monocyclic β-lactams are not significantly more reactive than their acyclic amide analogues. For example, the second-order rate constant for the alkaline hydrolysis of *N*,*N*-dimethylacetamide is only three times greater than that of *N*-methyl β-lactam.[1] By contrast, β-sultams undergo alkaline hydrolysis at least 10^8-fold faster than an analogous acyclic sulfonamide.[2] It is normally difficult to study the mechanism of reactions of sulfonamides because of their intrinsic stability,[3] despite their inherent interest as potential therapeutic agents.[4] The four-membered β-sultams therefore offer the opportunity to readily investigate sulfonyl transfer reactions.



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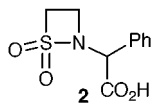

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The rate of hydrolysis of *N*-benzyl β-sultam **1** was measured by monitoring changes in its UV spectrum at 225–235 nm in a range of carboxylate buffers under pseudo-first-order conditions. At a constant pH, ionic strength [I = 1.0 M (KCl)] and at 30 °C, the observed first-order rate constants increase linearly with increasing concentrations of buffer, 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 both the concentration of 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 catalysed hydrolysis 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 α = 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. 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 eqn. (1).

$$k_{obs} = k_H[H^+] + k_{HA}[HA] \quad (1)$$

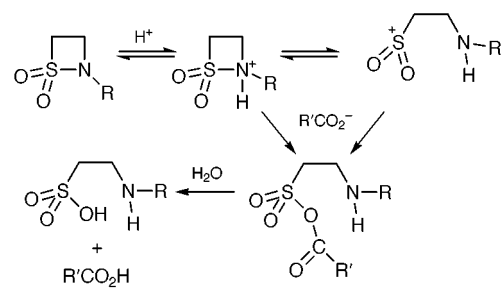
The values of the second-order rate constants k_{HA} are given in Table 1, from which it can be seen that they increase with decreasing pK_a of the carboxylic acid buffer. The observation of general acid catalysed hydrolysis is in contrast to the general base catalysis seen with the buffer catalysed 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. Mechanistic general acid catalysed hydrolysis could involve nucleophilic attack by water which is concerted with the protonation of the β-sultam by the undissociated carboxylic acid. Interestingly, there is no evidence of intramolecular general acid catalysis in the hydrolysis of *N*-carboxy(phenyl)-methyl β-sultam **2**. Alternatively, a specific acid–general based catalysed pathway could involve pre-equilibrium protonation of the β-sultam nitrogen, followed by the general base catalysed attack by water, the nucleophilicity of which is enhanced as a result of proton abstraction by the carboxylate anion.

Table 1 Second-order rate constants for the carboxylic acid catalysed hydrolysis of *N*-benzyl β-sultam at 30 °C [I = 1.0 M (KCl)]

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

The third and probable mechanism of buffer catalysis involved specific acid–nucleophilic catalysis (Scheme 1). The 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 hydrolysed. Nucleophilic catalysis in the carboxylate buffer hydrolysis of β-sultams was confirmed by trapping the mixed acid anhydride intermediate with aniline to give acetanilide. A series of high performance liquid chromatograms were obtained by injecting samples of acetate buffer (0.2 M, pH 4.83) containing aniline (0.50 M) with and without added *N*-benzyl β-sultam. 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 is produced. These observations provide the most conclusive evidence that the carboxylate buffer catalysed hydrolysis of β-sultams is due to specific acid–nucleophilic catalysis.

The hydrolysis of *N*-benzyl β-sultam in acetate buffers showed unusual behaviour because the kinetics showed biphasic behaviour; 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 rate of decomposition of the intermediates derived from the 2-chloroacetate, 2-methoxyacetate and formate anions are greater than those for their formation because of the high nucleofugacity of these anions.



Scheme 1

As a result, the intermediates decompose faster than they are formed and normal first-order kinetics are observed.

There is convincing evidence that the protonation of sulfonamide occurs on nitrogen[6] and the general acid-catalysed hydrolysis of the β-sultam could occur by a unimolecular A-1 type process with the carboxylate anion trapping the reversibly formed electron-deficient sulfonylium ion (Scheme 1). The evidence for such a mechanism in the hydrolysis of five-membered γ-sultams is ambiguous, although most of it is consistent with a bimolecular mechanism.[7] Unimolecular ring opening has been suggested for the acid-catalysed hydrolysis of both β-lactams[8] and β-phospholactams.[9]

The Brønsted plot (not shown) for the carboxylic acid catalysed hydrolysis of *N*-benzyl β-sultam gives a good correlation between the values of log k_{HA} and the pK_a for 2-chloroacetic, 2-methoxyacetic and acetic acids with a slope of −0.67. This corresponds to a β_{nuc} of 0.33 for the specific acid–nucleophilic mechanism, indicative of an early transition state in which there has been a small amount of neutralisation of the negative charge on the carboxylate anion. Formic acid shows a positive derivation 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 catalysed hydrolysis.

Notes and references

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