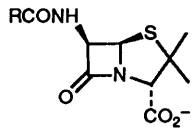
The Hydrolysis of Azetidinyl Amidinium Salts. Part 1. The Unimportance of Strain Release in the Four-membered Ring

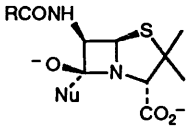
Michael I. Page * and Philip Webster
Department of Chemical Sciences, Huddersfield Polytechnic, Huddersfield HD1 3DH
Leon Ghosez
Laboratoire de Chimie Organique de Synthèse, Université Catholique de Louvain, B-1348 Louvain-La-Neuve, Belgium

The alkaline hydrolysis of azetidin-2-ylideneammonium salts gives a mixture of β-lactams, by exocyclic C–N bond fission, and β-amino amides, by opening the four-membered ring. Despite the anticipated release of strain energy in opening the four-membered ring the β-lactam is usually the major product *i.e.* exocyclic C–N fission is favoured over endocyclic C–N fission. This occurs even when the basicities of the endo- and exo-cyclic nitrogens are similar. The apparent reluctance of the four-membered ring to open is also not the result of entropic or stereoelectronic factors. The kinetics of the reaction indicate the presence of a neutral tetrahedral intermediate because there are two changes in the rate dependence upon hydroxide ion with increasing base concentration. There is also a term in the rate law for the carbonate-catalysed reaction which is both first order in carbonate ion and first order in hydroxide ion. The neutral tetrahedral intermediate must be formed reversibly and undergo deprotonation of its hydroxy group at high pH. By assuming that this deprotonation by hydroxide ion is rate limiting and diffusion controlled, the equilibrium constants for the formation of the neutral tetrahedral intermediate can be calculated. These are reported together with the calculated microscopic rate constants for the formation and breakdown of the intermediate.

A common belief in the development of understanding the molecular basis for the activity of penicillins (**1**) and other β-lactam antibiotics has been the importance of the strain energy in the four-membered ring.[1] It seems logical that the 110 kJ mol^{-1} of strain energy in the β-lactam which is released upon



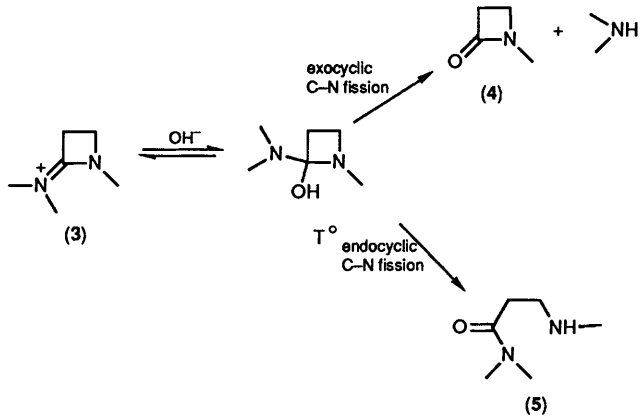
(1)



(2)

ring opening should make a contribution to lowering the activation energy of reactions involving β-lactam C–N bond fission. However, kinetic and mechanistic information indicate that nucleophilic substitution reactions at the β-lactam carbonyl occur with relatively little rate enhancement and that nucleophilic addition to form the tetrahedral intermediate (**2**) is often reversible and the rate-limiting step is the breakdown of this intermediate.[2]

The hydrolysis of azetidin-2-ylideneammonium salts (**3**) can give two products depending on which C–N bond is broken. The alkaline hydrolysis proceeds by formation of the tetrahedral intermediate, T°, which can undergo exocyclic C–N bond fission to give the β-lactam (**4**) and an amine or endocyclic C–N bond fission to give the β-amino amide (**5**) (Scheme 1). This system therefore offers an opportunity to elucidate the factors controlling exocyclic bond fission which leaves the four-membered ring as a product and endocyclic bond fission which results in opening of the four-membered ring. As ring opening is accompanied by the release of strain energy it may be expected to affect the partitioning of the tetrahedral intermediate T°. Exocyclic C–N bond fission of T° generates two molecules which may be favoured entropically.[3]



Scheme 1.

In this paper we present evidence for the formation of the tetrahedral intermediate, and examine the effect of structural changes within the amidinium salt (**3**). In the following paper[4] we report on the effect of buffer catalysis, substituent effects and give a detailed mechanism of the reaction. A preliminary report of this work has been published.[5]

Experimental

Synthesis.—The amidinium salts were prepared by the addition of α-chloroenamines to imines in dry methylene chloride at room temperature. Details of this method have been reported elsewhere,[6] but analytical data for the perchlorate salts are as follows:

3,3-*Dimethyl*-1-(4-*nitrophenyl*)-4-*phenyl*-2-(*pyrrolidinium*-1-*ylidene*)*azetidine perchlorate* (**6**). δ($CDCl_3$) 8.1 (d, 2 H, $ArNO_2$),

7.85 (d, 2 H, $ArNO_2$), 7.3 (s, 5 H, Ph), 5.56 (s, 1 H, H4), 3.66 (m, 4 H, 2 × CH_2N^+), 2.01 (m, 4 H, 2 × CH_2), 1.76 (s, 3 H, Me), and 1.12 (s, 3 H, Me); $\nu_{max}(CH_2Cl_2)$ 1 700 (C=N$^+$), 1 530, 1 350, and 1 100 cm^{-1}.

1,3,3-*Trimethyl*-4-*phenyl*-2-(*pyrrolidinium*-1-*ylidene*)*azetidine perchlorate* (**7**). δ($CDCl_3$) 7.40 (m, 5 H, Ar), 4.85 (s, 1 H, H4), 3.24 (s, 3 H, NMe), 3.55 (m, 4 H, 2 × CH_2N^+), 1.90 (m, 4 H, 2 × CH_2), 1.7 (s, 3 H, Me), and 1.0 (s, 3 H, Me); $\nu_{max}(CH_2Cl_2)$ 1 720 cm^{-1} (C=N$^+$).

2-*Methyl*-8,9-*diphenyl*-2,9-*diazabicyclo*[5.2.0]*non*-1-*en*-2-*ium perchlorate* (**8**). δ($CDCl_3$) 7.41 (m, 10 H, 2 × Ar), 5.2 (d, 1 H, H8), 4.24 (m, 1 H, H3), 3.72 (m, 1 H, H7), 3.34 (m, 1 H, H3), 3.06 (s, 3 H, $^+$NMe), 1.84 (m, 8 H, 4 × CH_2); $\nu_{max}(CH_2Cl_2)$ 1 710 cm^{-1} (C=N$^+$).

2-*Dimethylimino*-1,1-*dimethyl*-1,4,5,9b-*tetrahydro*-2H-*azeto*-[2,1-a]*isoquinoline perchlorate* (**9**). δ[$(CD_3)_2SO$] 7.38 (m, 4 H, Ar), 4.85 (s, 1 H, H4), 4.34 (m, 1 H, H8), 3.46 (s, 3 H, $^+$NMe), 3.30 (s, 3 H, $^+$NMe), 3.04 (m, 3 H, H8, H7), 1.75 (s, 3 H, Me), and 1.10 (s, 3 H, Me); $\nu_{max}(CH_2Cl_2)$ 1 745 cm^{-1} (C=N$^+$).

Product Isolation and Characterisation.—After hydrolysis, the aqueous solution was extracted with dichloromethane and the products were separated chromatographically using silica plates. The products from (**6**) were separated using 25:1 (v/v) methylene chloride–cyclohexane as the eluant: β-lactam R_f 0.35, β-amino amide R_f 0.20. The β-lactam was characterised by IR (C=O 1 760 cm^{-1} in CH_2Cl_2) and ^{1}H NMR spectroscopy δ($CDCl_3$) 8.16 (d, 2 H, $ArNO_2$), 7.34 (m, 7 H, Ph, $ArNO_2$), 4.93 (s, 1 H, H4), 1.56 (s, 3 H, Me), and 0.90 (s, 3 H, Me). The amino amide, 2,2-dimethyl-3-(4-nitrophenylamino)-3-phenyl-*N*-pyrrolidin-1-ylpropionamide was characterised by IR (NH 3 300, C=O 1 600, and NO_2 1 325 cm^{-1} in CH_2Cl_2) and ^{1}H NMR spectroscopy δ($CDCl_3$) 7.86 (d, 2 H, $ArNO_2$), 7.15 (s, 5 H Ph), 7.0 (1 H, NH), 6.63 (d, 2 H, $ArNO_2$) 4.16 (d, 1 H, H3) 2.50 (m, 8 H, pyr, CH_2) 1.53 (s, 3 H, Me), and 1.36 (s, 3 H, Me).

The products from (**7**) were separated using 6:1 (v/v) CH_2Cl_2–MeOH as the eluant: β-lactam R_f 0.80, β-amino amide R_f 0.58. The β-lactam, 1,3,3-trimethyl-4-phenylazetidin-2-one, showed $\nu_{max}(CH_2Cl_2)$ 1 745 cm^{-1} (C=O); δ($CDCl_3$) 7.2 (m, 5 H, Ph), 4.7 (s, 1 H, H4), 3.2 (s, 3 H, NMe), 1.6 (s, 3 H, Me), and 1.0 (s, 3 H, Me). The β-amino amide, 2,2-dimethyl-3-methylamino-3-phenyl-*N*-pyrrolidin-1-ylpropionamide showed $\nu_{max}(CH_2Cl_2)$ 1 630 cm^{-1} (C=O); δ($CDCl_3$) 7.2 (m, 5 H, Ph), 4.75 (s, 1 H, H3), 3.2 (s, 3 H, NMe), 3.75 (m, 4 H, pyr-CH_2), 1.90 (m, 4 H, pyr-CH_2), 1.3 (s, 3 H, Me), and 1.2 (s, 3 H, Me).

The products from (**8**) were separated using 25:2 (v/v) CH_2Cl_2–MeOH as the eluant: β-lactam R_f 0.56, β-amino amide R_f 0.23. The β-lactam, 3-(4-methylaminobutyl)-1,4-diphenylazetidin-2-one, showed $\nu_{max}(CH_2Cl_2)$ 1 740 cm^{-1} (C=O); δ($CDCl_3$) 7.20 (m, 10 H, 2 × Ph), 4.71 (d, 1 H, H4), 3.15–3.0 (m, 3 H, m, NCH_2, H3), 2.8 (s, 3 H, NMe), and 1.75 (m, 7 H, 3 × CH_2 + NH).

The products from (**9**) were separated using 25:1 (v/v) CH_2Cl_2–MeOH as the eluant: β-lactam R_f 0.55, β-amino amide R_f 0.28. The β-lactam, 1,1-dimethyl-1,4,5,9b-tetrahydroazeto-[2,1-*a*]isoquinolin-2-one showed $\nu_{max}(CHCl_2)$ cm^{-1} (C=O); δ($CDCl_3$) 7.06 (m, 4 H, Ar), 4.26 (s, 1 H, H4), 3.95 (m, 1 H, H8), 2.80 (m, 3 H, 2 × H7, H8), 1.56 (s, 3 H, Me), and 0.79 (s, 3 H, Me).

The β-amino amide, *N*,*N*,2-trimethyl-2-(1,2,3,4-tetrahydroisoquinolin-1-yl)propionamide, showed $\nu_{max}(CH_2Cl_2)$ 3 365 (NH) and 1 620 cm^{-1} (C=O); δ($CDCl_3$) 7.1 (m, 4 H, Ar), 4.75 (s, 1 H, 1 cyclohex H), 3.08 (s, 6 H, NMe_2), 2.95 (m, 5 H, 2 × CH_2, NH), 1.32 (s, 3 H, Me), and 1.18 (s, 3 H, Me).

HPLC of Reactants and Products.—All HPLC analyses were performed using a Kontron model 414 pump with a Kontron Uvikon 740 LC UV detector set at 254 nm. The reactants and products could be separated using a reversed-phase column of non-polar Lichrosorb octadecylsilyl RP C18 25 cm × 4 mm column and, as the eluant, aqueous acetonitrile containing 0.02 mol dm^{-3} acetic acid and 3.3 × 10^{-3} mol dm^{-3} tetrabutylammonium hydroxide as an ion-pairing agent. Peak areas were calibrated to concentration for all reactants and products in the range 10^{-6} to 10^{-4} mol dm^{-3}. Using a flow rate of 1 cm^3 min^{-1}, the eluant and retention times (t_R/min) for each derivative were, respectively: amidinium salt (**6**) in CH_3CN–H_2O (50:50) 6.2, β-amino amide 18.2, β-lactam 21.3; amidinium salt (**7**) in CH_3CN–H_2O (35:65) 10.0, β-amino amide 7.0, β-lactam 17.0; amidinium salt (**8**) in CH_3CN–H_2O (50:50) 13.2, β-lactam, 7.5, β-amino amide 18.0; amidinium salt (**9**) in CH_3CN–H_2O (30:70) 5.6, β-lactam 10.4, β-amino amide 17.2.

Kinetics.—AnalaR grade chemicals were used exclusively in the preparation of buffers. Freshly boiled glass-distilled water was used throughout and the ionic strength was maintained at 1.0 mol dm^{-3} with potassium chloride except where otherwise indicated. The eluant required for HPLC analysis was prepared from AnalaR grade glacial acetic acid and Hypersolv HPLC grade acetonitrile.

The pH of buffer solutions was measured with a Philips PW 9409 digital pH meter equipped with a Russel type CEL glass combination electrode, calibrated against standard buffers of known pH at 30 °C. The electrode could be dipped into a reaction cuvette before and after a kinetic run to ensure the pH of the solution had not altered by more than 0.03 of a pH unit.

The reactions were initiated by the addition of 12.5 or 25 mm^3 of a 10^{-2} mol dm^{-3} stock solution of the azetidine iminium salt, dissolved in acetonitrile, to 2.5 cm^3 of aqueous buffer pre-incubated at 30.0 ± 0.05 °C with thorough mixing. The disappearance of the substrate was followed spectrophotometrically using a Gilford 2600 spectrophotometer. The output from the spectrophotometer was fed to either an Apple II Europlus or a BBC microcomputer. The data were processed using a non-linear generalised least-squares program as previously described.[7] The program calculates a first-order rate constant using an iterative non-linear least squares procedure which treats the initial absorbance, final absorbance, and rate constant as adjustable parameters according to the method of Deming and Wentworth.[8]

Results

The products of hydrolysis of the azetidinyl amidinium salts (**3**) are the expected β-lactam (**4**) and the β-amino amide (**5**). Both products were stable under the reaction conditions and during the time period of the investigation there was no interconversion or further hydrolysis of the products. The product ratios were determined by HPLC analysis of the reactant solutions used for the kinetic experiments. These ratios were measured during and at the end of each reaction and found to be invariant. Some kinetic measurements were performed directly from HPLC experiments and gave pseudo-first-order rate constants identical with those determined spectrophotometrically.

The measured pseudo-first-order rate constant for hydrolysis, k_{obs}, is the sum of k_L and k_A, the pseudo-first-order rate constants for β-lactam and amino amide respectively [equation (1)]. In terms of the ratio of β-lactam (L) to amino amide (A)

$$k_{obs} = k_L + k_A \quad (1)$$

formed in the hydrolysis of an azetidinyl amidinium salt, the fraction of β-lactam F_L and amino amide, F_A may be represented by equations (2) and (3), respectively. The pseudo-

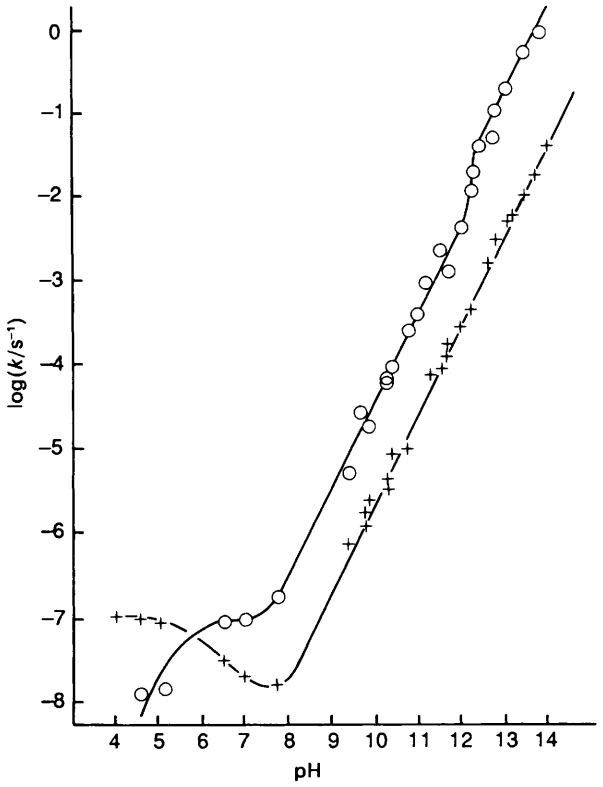


Figure 1. A plot of the pH dependence of the logarithm of the pseudo-first-order rate constants, for β-lactam (+) and β-amino amide formation (○) from the hydrolysis of the 4-nitrophenyl derivative (**6**) at 30 °C. The lines are calculated from the rate constants given in Table 1.

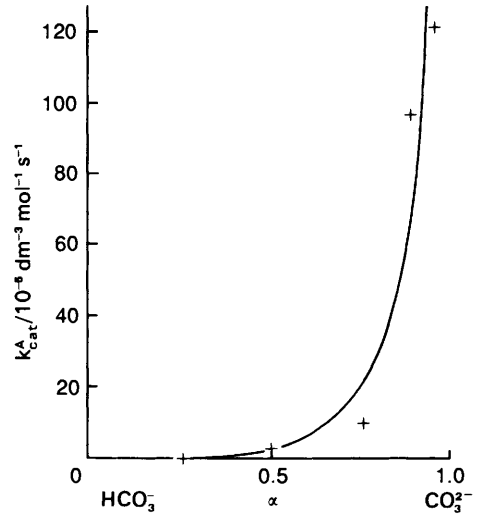


Figure 2. A plot of the catalytic coefficient k_{cat} for the carbonate-buffer-catalysed formation of the β-amino amide from the hydrolysis of the 4-nitrophenyl derivative (**6**) as function of α, the fraction of carbonate ion in buffer.

$$F_L = \frac{L}{A + L} = \frac{L/A}{1 + L/A} \quad (2)$$

$$F_A = \frac{A}{A + L} = \frac{1}{1 + L/A} \quad (3)$$

first-order rate constant k_L for β-lactam formation is then given by equation (4) and that for amino amide formation by equation (5).

$$k_L = k_{obs}F_L \quad (4)$$

$$k_A = k_{obs}F_A \quad (5)$$

The product ratio and kinetics were determined as a function of pH and buffer. Buffer catalysis is observed and the pH-dependent data are those extrapolated to zero buffer concentration. The pH–rate profile for the hydrolysis of the azetidinyl amidinium salt (**6**) is shown in Figure 1. The rate of formation of the β-lactam is first order in hydroxide between pH 8 and 14. However, the rate of formation of β-amino amide shows both a first- and a second-order dependence upon hydroxide-ion concentration. From pH 8 to 12 the rate is first order in hydroxide ion but above pH 12 it changes to second order then back to first order at pH higher than 13. This means that the ratio of β-lactam to β-amino amide formed from (**6**) changes from 1:10 between pH 8 and 12 but increases to about 1:30 above pH 13.

Below pH 7.5 the pseudo-first-order rate constant for hydrolysis of the azetidinyl amidinium salt (**6**) becomes pH independent which is indicative of a water-catalysed reaction. This total rate constant comprises an increase in k_L, the rate constant for β-lactam formation, which reaches a plateau below pH 5 and a decrease in β-amino amide formation (Figure 1). The rate of hydrolysis of the azetidinyl amidinium salt (**6**) is slow at low pH but the β-lactam is the major product in this region. For example, at pH 4.5 the ratio of β-lactam to β-amino amide is 10:1. The change in k_L and k_A with pH is indicative of the ionisation of an intermediate (Figure 1).

The hydrolysis of the azetidinyl amidinium salt (**6**) shows unusual kinetic behaviour in carbonate buffers. Plots of the pseudo-first-order rate constant k_A for the hydrolysis of (**6**) against total carbonate concentration at various pH values are linear, but a plot of the slope of these lines k^A_{cat} against the fraction of free base of carbonate, α, is not linear (Figure 2). The catalytic constant increases rapidly with pH and is indicative of a dependence upon hydroxide-ion concentration. There is therefore an additional third-order term for the formation of the β-amino amide which is first order in carbonate and first order in hydroxide ion. This is similar to the second-order dependence on hydroxide ion seen at high pH. The third-order rate constant for the carbonate–hydroxide term, 6.02×10^{-1} dm^6 mol^{-2} s^{-1}, was obtained from a linear plot of k^A_{cat}/α against hydroxide-ion concentration. There is no such significant third-order term for β-lactam formation which showed a simple first-order dependence on carbonate-ion concentration. The rate law for the hydrolysis of (**6**) in carbonate buffers is given by equation (6)

$$k_{obs} = k_o + k^L_B[CO_3^{2-}] + k^A_B[CO_3^{2-}][OH^-] \quad (6)$$

where k_o is the buffer-independent rate constant. The ratio of β-lactam to β-amino amide thus increases with decreasing pH. At 0.20 mol dm^{-3} total carbonate concentration the ratio increases from 0.044 at pH 11.25 to 0.533 at pH 9.50.

Unlike the *N*-aryl azetidinyl amidinium salts such as (**6**), the rate of formation of *both* β-lactam and β-amino amide from the hydrolysis of *N*-alkyl derivatives show a second-order dependence upon hydroxide-ion concentration. For example, the pH–rate profile for the hydrolysis of the *N*-methyl derivative (**7**) is shown in Figure 3.

The observed pseudo-first-order rate constant for hydrolysis, k_{obs}, is given by equation (7) where k^L and k^A refer to the rate

$$k_{obs} = k^L_{OH}[OH^-] + k^A_{OH}[OH^-] + \frac{[k^L_{OH'}k^L_{OH''}OH^-]^2}{k^L_{OH'} + k^L_{OH''}[OH^-]} + \frac{k^A_{OH'}k^A_{OH''}[OH^-]^2}{k^A_{OH'} + k^A_{OH''}[OH^-]} \quad (7)$$

constants for β-lactam and amino amide formation, respectively.

Table 1. Second- and third-order rate constants for the hydroxide-ion- and carbonate-ion-catalysed hydrolysis of azetidinyl amidinium salts in water at 30 °C and I = 1.0 mol dm^{-3} (KCl).[a]

Salt	k^{L}_{OH}/dm^3 mol^{-1} s^{-1}	k^{A}_{OH}/dm^3 mol^{-1} s^{-1}	$k^{L}_{OH'}$/dm^3 mol^{-1} s^{-1}	$k^{A}_{OH'}$/dm^3 mol^{-1} s^{-1}	$k^{L}_{OH''}$/dm^6 mol^{-2} s^{-1}	$k^{A}_{OH''}$/dm^6 mol^{-2} s^{-1}	$k^{A}_{CO_3,OH}$/dm^6 mol^{-2} s^{-1}
(6)	1.50×10^{-2}	1.44×10^{-1}	—	4.10×10^{-1}	—	73.2	6.02×10^{-1}
(7)	6.49×10^{-4}	5.03×10^{-4}	1.69×10^{-3}	2.54×10^{-3}	7.68×10^{-3}	7.06×10^{-3}	—
(8)	8.76×10^{-2}	4.57×10^{-4}	—	—	—	—	—
(9)	3.44×10^{-3}	2.74×10^{-4}	4.87×10^{-3}	1.45×10^{-3}	2.93×10^{-3}	2.52×10^{-3}	—

[a] The rate constants are defined in equations (6) and (7).

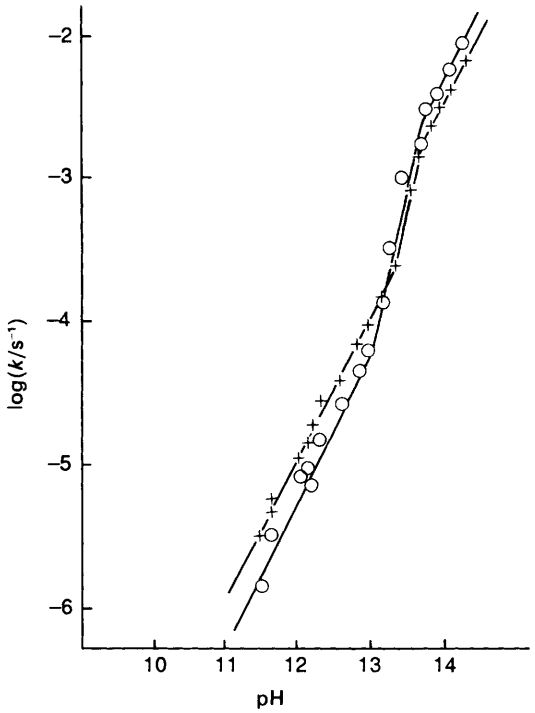
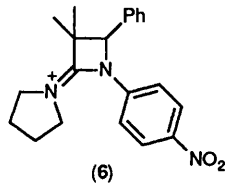
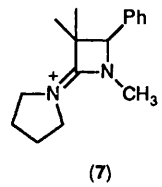


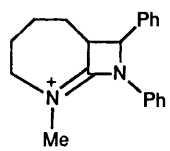
Figure 3. A plot of the pH dependence of the logarithm of the pseudo-first-order rate constants for β-lactam (+) and β-amino amide formation (○) from the hydrolysis of the *N*-methyl derivative (**7**) at 30 °C. The lines are calculated from the rate constants given in Table 1.



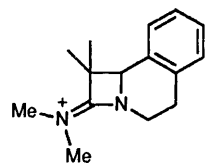
(6)



(7)



(8)



(9)

The subscripts OH and OH′ refer to the second-order rate constants for product formation at low and high pH, respectively. The subscripts OH″ refer to the third-order rate constants which are second order in hydroxide ion. The values of the rate constants for all the azetidinyl amidinium compounds studied are given in Table 1.

Discussion

The azetidinyl amidinium salts which were investigated are given by structures (**6**) to (**9**). All except the 4-nitrophenyl derivative (**6**) undergo preferential exocyclic C–N bond fission and give the β-lactam as the major product. Even with the strongly electron-withdrawing 4-nitrophenyl substituent in (**6**) the hydrolysis products contain a significant amount of the corresponding β-lactam. It is obvious that the 110 kJ mol^{-1} of strain energy of the four-membered ring does not enhance the rate of ring opening of the endocyclic C–N bond compared with that for exocyclic C–N bond fission.

There are several indications that C–N bond fission in β-lactams does not proceed as rapidly as may be expected. The second-order rate constants for the alkaline hydrolysis of β-lactams of basic amines are similar to those for the corresponding *N*-substituted acetamide.[9] The reactivity of penicillin is simply that expected of an activated amide.[2] The aminolysis of penicillin proceeds by rate-limiting steps following reversible formation of the tetrahedral intermediate.[10] The alcoholysis of penicillins occurs with rate-limiting breakdown of the reversibly formed tetrahedral intermediate.[2,11]

The hydrolysis of unsymmetrical amidines and amidinium salts have been shown to give a mixture of products depending on which C–N bond is broken.[12] Some initial studies also attempted to use the preferential cleavage of the tetrahedral intermediate as a test for the theory of stereoelectronic control,[13] however it was later shown that these were ambiguous.[14] It has been suggested that the rate-limiting step in amidinium salt hydrolysis is the addition of hydroxide ion to form the tetrahedral intermediate.[15]

The Tetrahedral Intermediate T°.—The change in the kinetic dependence of the rate of β-amino amide formation from (**6**) upon hydroxide ion (Figure 1) and a similar change observed for *both* β-lactam and β-amino amide formation from *N*-alkyl azetidinyl amidinium salts (Figure 3), indicate a change in rate-limiting step and is evidence of the formation of the tetrahedral intermediate T° (Scheme 1). The appearance of a term in the rate law which is second order in hydroxide means that the formation of the tetrahedral intermediate T° is reversible and that a subsequent step is rate limiting. The observation of the third-order term in carbonate buffers [equation (6)] also indicates the presence of the tetrahedral intermediate. The presence of the rate term which is both first order in hydroxide and first order in carbonate ion cannot sensibly represent a pathway involving rate-limiting termolecular formation of an intermediate. There is thus good evidence from the kinetics that the tetrahedral intermediate T° is formed reversibly and that hydroxide ion is expelled from T° faster than the rate of C–N bond cleavage. A simple mechanistic scheme compatible with the observations is shown in Scheme 2.

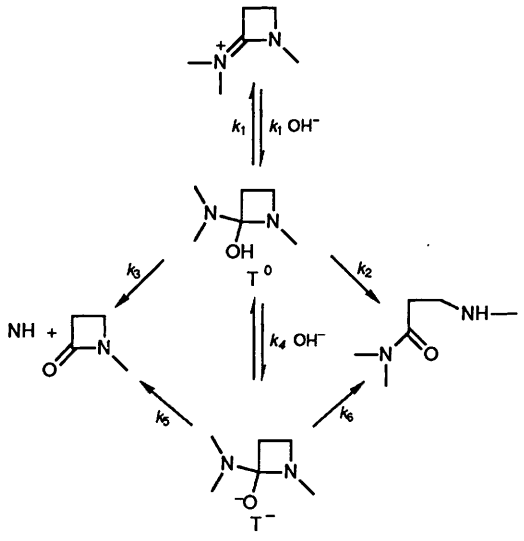
Below pH 12 the hydrolysis rate is first order in hydroxide ion and the rate-limiting step is the breakdown of the neutral tetrahedral intermediate T°, with water acting as a general-acid

Table 2. Observed and calculated microscopic rate and equilibrium constants for the hydrolysis of azetidinyl amidinium salts. The constants are defined in Scheme 2.

Salt	k_1/dm^3 mol^{-1} s^{-1}	k_{-1}/s^{-1}	K_1/dm^3 mol^{-1}	k_2^A/s^{-1}	k_3^L/s^{-1}
(6)	4.10×10^{-1}	5.60×10^{7}	7.32×10^{-9}	1.96×10^{7}	2.05×10^{6}
(7)	2.54×10^{-3} [a]	3.60×10^{9} [a]	7.06×10^{-13} [a]	7.12×10^{8}	8.45×10^{8}
	1.69×10^{-3} [b]	2.20×10^{9} [b]	7.68×10^{-13} [b]		
(9)	1.45×10^{-3} [a]	5.75×10^{9} [a]	2.52×10^{-13} [a]	1.08×10^{9}	1.18×10^{10}
	4.87×10^{-3} [b]	1.66×10^{10} [b]	2.93×10^{-13} [b]		

[a] Calculated from β-amino amide formation. [b] Calculated from β-lactam formation.

catalyst to facilitate both exocyclic, k_3, and endocyclic, k_2, C–N



Scheme 2.

bond fission (Scheme 2). Above pH 12 the neutral tetrahedral intermediate T° is converted into its anion T$^-$ by hydroxide ion removing a proton from the hydroxy group of T°. The rate of this step, k_4, is dependent on hydroxide ion and only becomes competitive with the rate of breakdown of T° *via* k_2 and k_3 at high hydroxide-ion concentration. When the intermediate T$^-$ has a *N*-aryl substituent it breaks down only *via* k_6 to give the β-amino amide because there is no change in the kinetic hydroxide dependence for β-lactam formation. This is consistent with the observation that the rate-limiting step in the aminolysis of β-lactams with good leaving groups is the formation of T$^-$.[10,16]

At even higher concentrations of hydroxide ion there must be a second change in the rate-limiting step when the rate of deprotonation of T° given by k_4[OH$^-$] becomes faster than the rate of expulsion of hydroxide ion from T° by k_{-1}. Consequently above pH 13 the formation of the neutral tetrahedral intermediate T°, k_1, becomes rate limiting for β-amino amide formation from (6) and for the hydrolysis of *N*-alkyl azetidinyl amidinium salts giving both β-lactams and β-amides.

The observed pseudo-first-order rate constant for hydrolysis of the azetidinyl amidinium salt (6) according to Scheme 2 is given by equation (8). It is possible to elucidate these micro-

$$k_{obs} = \frac{k_1k_2(OH^-) + k_1k_3(OH^-) + k_1k_4(OH^-)^2}{k_{-1} + k_2 + k_3 + k_4(OH^-)} \quad (8)$$

scopic rate constants for Scheme 2 if it is assumed that the rate-limiting step in the pathway which is second order in hydroxide ion is k_4 (Scheme 2), the diffusion-controlled encounter of T° and OH$^-$. The rate constant for this process is assumed to be 10^{10} dm^3 mol^{-1} s^{-1}. The observed third-order rate constant for hydrolysis $k_{OH''}$ is then given by equation (9). Hence K_1, the equi-

$$k_{OH''} = k_4K_1 = k_4\frac{k_1}{k_{-1}} \quad (9)$$

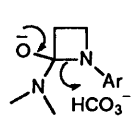
librium constant for formation of the tetrahedral intermediate T°, can be calculated. The observed second-order rate at high pH ($k_{OH'}$) is attributed to rate-limiting formation of the tetrahedral intermediate T° and thus corresponds to the microscopic rate constant k_1 in Scheme 2. Hence, k_{-1}, the rate constant for expulsion of hydroxide ion from T° may also be calculated from equation (8). Finally, according to Scheme 2 the rate-limiting step for the hydroxide-ion-catalysed reactions below pH 12 is given by equations (10) and (11) for β-lactam

$$k_{OH}^L = k_3K_1 \quad (10)$$

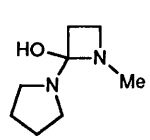
$$k_{OH}^A = k_2K_1 \quad (11)$$

and β-amino amide formation, respectively. All of these calculated microscopic constants are given in Table 2. The calculated equilibrium constant for formation of T° from (6) is relatively high and much more favourable than that reported for other tetrahedral intermediates.[10,17] This may be the result of the favourable conversion of three-co-ordinate carbon in four-membered rings to four-co-ordinate.[3]

The term in the rate law for the hydrolysis of (6) in carbonate buffers which is first order in hydroxide ion and first order in carbonate ion [equation (6)], may also represent the rate-limiting deprotonation of T° to T$^-$ by carbonate ion. Since K_1 is known, the rate constant for this can be calculated from equation (8) and the observed third-order rate constant. The rate constant k_4 is then calculated to be 8.2×10^7 dm^3 mol^{-1} s^{-1}, which is 122 times less than the rate constant for hydroxide-ion deprotonation. The calculated pK_a of T° is 13.4 so deprotonation by carbonate ion should be below the diffusion-controlled limit. It is possible therefore that the carbonate, hydroxide term represents general-acid-catalysed decomposition of T$^-$ by hydrogen carbonate ion (**10**). Below pH 6.5, the



(10)



(11)

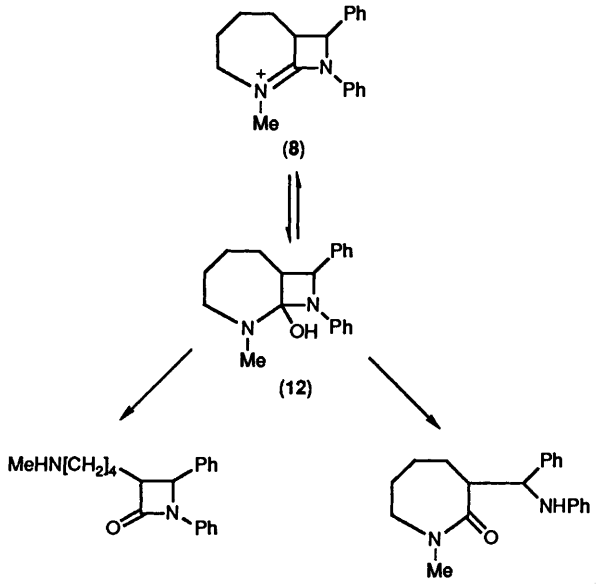
rate of hydrolysis of the amidinium compound (6) becomes pH independent and faster than the calculated rate of formation of T° by the addition of hydroxide ion (k_1 OH$^-$, Scheme 2). The mechanism of hydrolysis at low pH must therefore involve initial attack by water on the amidinium salt.

The hydrolysis of (7). The neutral tetrahedral intermediate (11) generated during the hydrolysis of (7) contains nitrogens of approximately similar basicity. Despite this similarity, the major product is the β-lactam which indicates that *exocyclic*

C–N *bond fission is more favourable than ring opening* via *the endocyclic* C–N *bond even when the nitrogens have similar basicities.* The reluctance of the four-membered ring to open cannot, in this case, be the result of, say, the importance of protonation of the nitrogens in deciding which C–N bond is broken. Interestingly, the rate of hydrolysis of the azetidine iminium salts with endocyclic nitrogen alkyl substituents [(**7**) and (**9**)] show a non-linear dependence on hydroxide ion for both β-lactam and β-amino amide formation (Figure 3). This indicates that the anionic tetrahedral intermediate T^- (Scheme 2) can break down both to the β-amino amide (k_6), and to the β-lactam (k_5). This is in contrast with the behaviour of T^- derived from the *N*-aryl derivative (**6**) which only breaks down by endocyclic C–N fission (k_6) to give the β-amino amide.

The hydrolysis of (**8**). It could be argued that, although β-amino amide formation should be favoured by the release of strain energy during opening of the four-membered ring, β-lactam formation could be favoured entropically because two molecules of product are generated. It is known that in the reverse direction the rate of bimolecular reactions may proceed up to 10^8 mol dm^{-3} more slowly than comparable uni- and intramolecular reactions solely because of the difference in entropy changes between the two systems.[3]

This entropic advantage favouring β-lactam formation is partially removed in the bicyclic system (**8**). The fission of either C–N bond in the tetrahedral intermediate (**12**) (Scheme 3)



Scheme 3.

generates only one molecule. Although β-amino amide formation from cleavage of the seven-membered ring may gain a little more entropy than that from cleavage of the four-membered ring this difference is minimal. The major changes in entropy in bimolecular reactions are associated with translational and rotational freedom.[3]

The major product from the alkaline hydrolysis of (**8**) is, in fact, the β-lactam. The ratio of β-lactam to β-amino amide is nearly 200:1 which is about 20 times greater than the analogous monocyclic system with a phenyl substituent.[4]

It is apparent that entropic factors are also not the cause of the reluctance of the four-membered ring to open.

The hydrolysis of (**9**). The final variation in these structure studies was to cyclise the azetidinyl amidinium salt at the four-membered ring nitrogen as in (**9**). This basic structure is similar to that found in cephalosporins but the most important feature of this bicyclic compound is that the tetrahedral intermediate generated has a relatively rigid structure (**13**). If stereoelectronic factors[18] are operative then hydroxide-ion attack should occur

(**13**)

antiperiplanar to the ring-nitrogen lone pair to generate (**13**). It is conceivable that if the ring-nitrogen lone pair has to be antiperiplanar to the exocyclic C–N to give a β-lactam then the breakdown of (**13**) should favour β-amino amide formation.

In fact, β-lactam formation is again the major product of hydrolysis of (**9**). The ratio of β-lactam to β-amino amide is 13:1 which may be compared with the ratio of 1.3:1 observed for the hydrolysis of the analogous monocyclic compound (**7**).

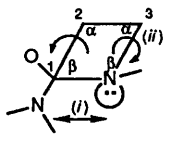
It is clear that stereoelectronic factors do not affect the partitioning of the tetrahedral intermediate T° into β-lactam or β-amino amide.

The Unimportance of Strain Energy.—The major product of the hydrolysis of azetidinyl amidinium salts, except for the derivative (**6**) with the strongly electron withdrawing nitro group, is the β-lactam. Partitioning of the tetrahedral intermediate T° favours exocyclic C–N bond fission rather than four-membered ring opening by endocyclic C–N bond cleavage which would be expected to be facilitated by the release of strain energy. From the compounds studied herein the apparent reluctance of the four-membered ring to open is not the result of differential basicities of the two nitrogens, entropic factors, or stereoelectronic effects.

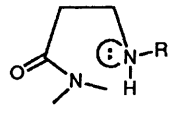
There have been other reports which suggest that the four-membered ring does not open as readily as would be suspected from the strain energy. It is conceivable that either there is an increase in strain energy as four-membered rings open or there is a non-linear relationship between strain energy and bond length so that an early transition state with little bond fission is still highly strained. One problem with this type of explanation is that although four-membered rings are often formed slowly relative to other ring sizes, ring closure is not *exceptionally* slow and is often only about 100 times slower in four-membered rings than in six-membered rings despite a predicted maximum difference of 10^{20} based solely on strain-energy differences.[3,19]

The rate of ring opening of some four-membered rings is sometimes enhanced. For example, the hydrolysis of oxetidinyl and ketals is about 10^5 times faster than that of an analogous acyclic system.[20] However, it has been pointed out that both the rates of ring opening and closure are not exceptional compared with the total strain energy involved.[21] In particular, Stirling has shown that the release of strain energy in four-membered rings is out of phase with the similarly strained three-membered ones.[22] Despite several attempts to rationalise this anomaly with small rings[23] an acceptable theory remains to be developed.

If there is an increase in energy due to strain or other factors as the ring breaks then this should also be manifested in the reverse ring-closure reactions. As the tetrahedral intermediate (**14**) undergoes ring fission the following changes may occur. If C–N bond fission occurs by a stretching motion (*i*) then as the distance between the incipient carbonyl carbon and nitrogen



(**14**)



(**15**)

increases, the bond angles β decrease as those designated α increase. This could increase the strain of the system. In the reverse ring closure reaction this reaction co-ordinate motion would correspond to amine nucleophilic attack on the amide carbonyl carbon in an almost favourable perpendicular direction.[24] If bond fission occurs by an internal rotational mode (*ii*) this also corresponds to a reasonable direction of nucleophilic attack in the reverse direction provided that rotation occurs around both C_1, C_2, and N–C_3 in (**14**) so that the incipient amide becomes roughly coplanar with the ring atoms (**15**). This would not be the normal reaction co-ordinate for the breakdown of tetrahedral intermediates and could offer a possible explanation for the relative rates of exo- and endo-cyclic bond fission.

Acknowledgements

We are grateful to the UK SERC for the award of a research studentship to P. W.

References

1 J. L. Strominger, *Antibiotics*, 1967, **1**, 706.
2 M. I. Page, *Adv. Phys. Org. Chem.*, 1987, **23**, 165; M. I. Page, *Acc. Chem. Res.*, 1984, **17**, 144.
3 M. I. Page, *Chem. Soc. Rev.*, 1973, 295.
4 M. I. Page, P. Webster, and L. Ghosez, *J. Chem. Soc., Perkin Trans. 2*, 1990, accompanying paper.
5 M. I. Page, P. Webster, S. Bogdan, B. Tremerie, and L. Ghosez, *J. Chem. Soc., Chem. Commun.*, 1987, 318.
6 C. Hoornaert, A. M. Hesbain-Frisque, and L. Ghosez, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 569; J. Marchand-Brynaert, M. Portuguez, I. Huber, and L. Ghosez, *J. Chem. Soc., Chem. Commun.*, 1983, 818; M. De Poortere, J. Marchand-Brynaert, and L. Ghosez, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 267.
7 J. J. Morris and M. I. Page, *J. Chem. Soc., Perkin Trans. 2*, 1980, 212.
8 W. E. Deming, 'Statistical Adjustment of Data,' Dover Publications, New York, 1964; W. E. Wentworth, *J. Chem. Educ.*, 1965, **42**, 96 and 162.
9 P. Proctor, N. P. Gensmantel, and M. I. Page, *J. Chem. Soc., Perkin Trans. 2*, 1982, 1185.
10 N. P. Gensmantel and M. I. Page, *J. Chem. Soc., Perkin Trans. 2*, 1979, 137; J. J. Morris and M. I. Page, *ibid.*, 1980, 212 and 220.
11 A. Davis and M. I. Page, unpublished observations.
12 D. R. Robinson and W. P. Jencks, *J. Am. Chem. Soc.*, 1967, **89**, 7088; S. J. Benkovic, W. P. Bullard, and P. A. Benkovic, *ibid.*, 1972, **94**, 7542; A. Cegan, J. Slosar, and M. Vecera, *Collect. Czech. Chem. Commun.*, 1978, **43**, 134; G. Moad and S. J. Benkovic, *J. Am. Chem. Soc.*, 1978, **100**, 5495; B. A. Burdick, P. A. Benkovic, and S. J. Benkovic, *ibid.*, 1977, **99**, 5716.
13 C. L. Perrin and G. M. L. Arrhenius, *J. Am. Chem. Soc.*, 1982, **104**, 2839.
14 C. L. Perrin and O. Nunez, *J. Am. Chem. Soc.*, 1986, **108**, 5997; *ibid.*, 1986, **109**, 522.
15 C. L. Perrin and O. Nunez, *J. Am. Chem. Soc.*, 1986, **108**, 5997.
16 G. M. Blackburn and J. D. Plackett, *J. Chem. Soc., Perkin Trans. 2*, 1973, 981.
17 M. I. Page and P. Proctor, *J. Am. Chem. Soc.*, 1984, **106**, 3820; M. I. Page and W. P. Jencks, *ibid.*, 1972, **94**, 8828.
18 P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon, Oxford 1983; A. J. Kirby, 'The Anomeric Effect and Related Stereoelectronic Effects at Oxygen,' Springer, Berlin, 1983.
19 A. Dr. Markino, C. Galli, P. Gargano, and L. Mandolini, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1345; L. Mandolini, *Adv. Phys. Org. Chem.*, 1986, **22**, 1.
20 R. F. Atkinson and T. C. Bruice, *J. Am. Chem. Soc.*, 1974, **96**, 819.
21 M. A. Casadei, A. di Martino, C. Galli, and L. Mandolini, *Gazz. Chim. Ital.*, 1986, **116**, 659; D. F. De Tar and W. Brooks, *J. Org. Chem.*, 1978, **43**, 2245.
22 H. A. Earl, D. R. Marshall, and C. J. M. Stirling, *J. Chem. Soc., Chem. Commun.*, 1983, 779; H. A. Earl and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1987, 1273; D. J. Young and C. J. M. Stirling, *J. Chem. Soc., Chem. Commun.*, 1987, 552.
23 C. J. M. Stirling, *Tetrahedron*, 1985, **41**, 1613; G. Tonachini, F. Bernardi, N. B. Schlegel, and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1988, 705.
24 H. B. Burgi, J. D. Dunitz, and E. Shefter, *J. Am. Chem. Soc.*, 1973, **95**, 5065; J. D. Dunitz, 'X-Ray Analysis and the Structure of Organic Molecules,' Cornell University Press, Ithaca, 1978.

Paper 9/04763H
Received 6th *November* 1989
Accepted 24th *January* 1990