Ease of C–N Bond Cleavage in Four-membered Rings

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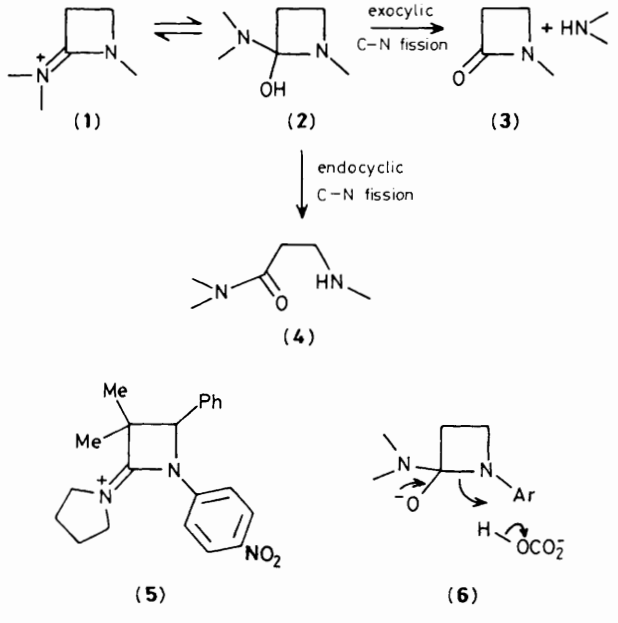
The hydrolysis of an azetidin-2-ylideneammonium salt gives a β-lactam and an aminoamide by competitive endo- and exo-cyclic C–N bond cleavage, the product ratio being pH and buffer dependent; the rate law for hydrolysis shows a third order term which is first order in substrate, hydroxide, and carbonate ions, which is interpreted as kinetically equivalent to general acid catalysed breakdown of the ionised tetrahedral intermediate and as evidence for non-facile C–N bond cleavage in the four-membered ring.

It is commonly thought that one of the major contributions to the antibacterial activity of penicillins and other β-lactam antibiotics is the ease of β-lactam C–N bond cleavage. The release of the strain energy in the four-membered ring would be expected to facilitate this process considerably. However, there are several indications that the C–N bond is not broken easily.[1] In fact, it appears to be an unexplained general phenomenon that four-membered rings are opened and closed slowly whereas the similarly strained three-membered rings open and close readily.[2] Azetidin-2-ylideneammonium salts (**1**) undergo hydrolysis to give either β-lactams (**3**) or aminoamides (**4**),[3] presumably *via* the tetrahedral intermediate (**2**). This system presents an excellent opportunity to study the factors controlling the ease of exocyclic *vs.* endocyclic bond fission. Although endocyclic bond fission is favoured by the release of strain energy the exocyclic process may be accompanied by a favourable entropy change as two product molecules are formed.

The amidinium salt (**5**) undergoes hydrolysis to give a mixture of the expected β-lactam and aminoamide. All three compounds can be detected using reversed phase h.p.l.c. with a non-polar Lichrosorb octadecyl silyl column, with

Table 1. Observed pseudo first order rate constants and the ratio of β-lactam to aminoamide formed in the hydrolysis of the azetidinium ion (**5**) in water at 30 °C, I = 1.0 M (KCl).

[NaOH]/M	$k_{obs.}$/s^{-1}	Molar ratio lactam : amide
1.0	5.74×10^{-1}	0.018
0.5	2.80×10^{-1}	0.021
0.4	2.40×10^{-1}	0.022
0.2	1.15×10^{-1}	0.028
0.1	5.60×10^{-2}	0.030
0.01	4.86×10^{-3}	0.034
pH 11.25, [total carbonate]/M		
0.02	4.15×10^{-4}	—
0.05	4.16×10^{-4}	0.031
0.10	5.19×10^{-4}	—
0.15	5.50×10^{-4}	0.034
0.20	6.01×10^{-4}	0.044
pH 11.00, [total carbonate]/M		
0.02	2.70×10^{-4}	0.049
0.05	3.06×10^{-4}	0.050
0.10	3.68×10^{-4}	0.053
0.20	4.57×10^{-4}	0.061
pH 10.50, [total carbonate]/M		
0.02	6.81×10^{-5}	0.055
0.05	6.97×10^{-5}	0.078
0.10	7.40×10^{-5}	0.148
0.15	7.71×10^{-5}	0.178
0.20	8.20×10^{-5}	0.228
pH 10.00, [total carbonate]/M		
0.02	2.53×10^{-5}	0.168
0.05	2.88×10^{-5}	0.158
0.10	2.92×10^{-5}	0.193
0.15	3.15×10^{-5}	0.228
0.20	3.57×10^{-5}	0.383
pH 9.5, [total carbonate]/M		
0.05	7.10×10^{-6}	0.250
0.10	7.37×10^{-6}	0.375
0.15	7.75×10^{-6}	0.425
0.20	7.95×10^{-6}	0.533



(1) (2) (3) (4) (5) (6)

acetonitrile–0.02 M aqueous acetic acid (50 : 50) as eluant, with 10^{-4} M tetrabutylammonium hydroxide as an ion-pairing reagent, and at a flow rate of 1.0 cm^3 min^{-1}. The rate constants for the disappearance of the amidinium salt (**5**) could also be determined spectrophotometrically. The ratios of β-lactam to aminoamide formed in solutions of sodium hydroxide and in carbonate buffers (Table 1) show that the rates of β-lactam and aminoamide formation have different dependencies upon pH and buffer. The ratio of β-lactam to aminoamide is also decreased 2-fold on changing the solvent from H_2O to D_2O in 0.01 and 0.1 M sodium hydroxide. In carbonate buffers the rate law for the hydrolysis of (**5**) is given by equation (1). The value of the rate constants are k^L_{OH} = 0.015 dm^3 mol^{-1} s^{-1}, k^A_{OH} = 0.144 dm^3 mol^{-1} s^{-1}, k^L_B = 8.0×10^{-5} dm^3 mol^{-1} s^{-1}, and k^A_B = 0.60 dm^6 mol^{-2} s^{-1}, where the superscripts L and A indicate β-lactam and aminoamide formation, respectively.

$$\text{Rate} = k^L_{OH}[OH^-][(5)] + k^A_{OH}[OH^-][(5)] + k^L_B[CO_3^{2-}][(5)] + k^A_B[CO_3^{2-}][OH^-][(5)] \quad (1)$$

The presence of the third order term in the rate law indicates rate limiting breakdown of the tetrahedral intermediate (**2**), the formation of which must be reversible. The simplest explanation is that C–N cleavage occurs by general acid (HCO_3^-) catalysed breakdown of the anion of the tetrahedral intermediate (**6**). The other possibility is that this term represents rate-limiting deprotonation of (**2**) by carbonate. The carbonate catalysed formation of the β-lactam is probably the kinetically equivalent (OH^-)(HCO_3^-) reaction and reflects the protonation of the more basic exocyclic nitrogen of the tetrahedral intermediate (**2**) by HCO_3^-. It has been previously shown that the aminolysis of penicillins and other β-lactams occurs by the microscopically reverse process: general base catalysis.[4] In aqueous sodium hydroxide the ratio of β-lactam to aminoamide decreases with increasing pH because the rate of formation of the aminoamide changes from first to second order and then back to first order in hydroxide ion with increasing pH, whereas the rate of formation of the β-lactam remains first order in hydroxide ion over the whole pH range. This change in kinetic order is evidence for a change in rate limiting step, from breakdown of the tetrahedral intermediate (**2**) below pH 12 to its formation above pH 13.

Opening the four-membered ring by cleavage of the endocyclic C–N bond generates the weakly basic 4-nitroaniline derivative (**4**) but, despite this good leaving group and the accompanying release of strain energy, exocyclic C–N bond fission can be a preferred pathway for breakdown of the tetrahedral intermediate. Opening the four-membered ring by endocyclic C–N bond cleavage is obviously not a facile process and requires protonation of the ring nitrogen by a general acid catalyst.

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