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Competitive Intramolecular Aminolysis: Relative Rates of 5- and 6-Membered Lactam Ring Closure

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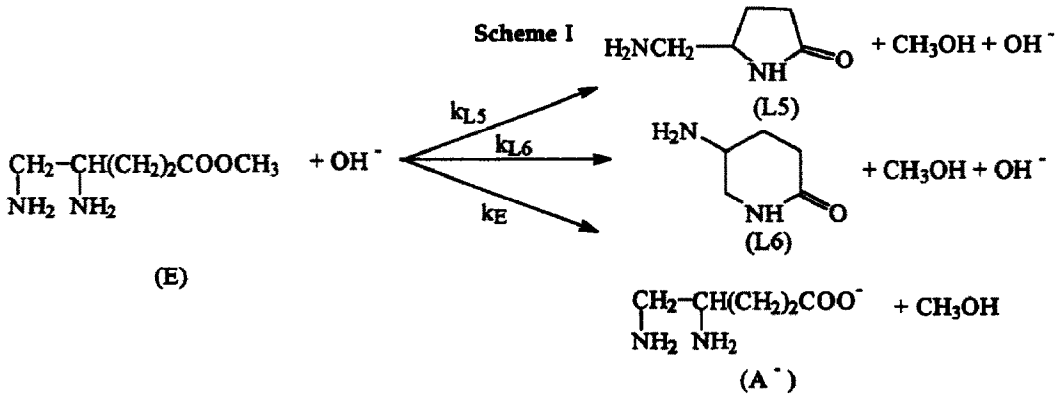
Abstract: Methyl 4,5-diaminopentanoate (4,5-Dape Me) undergoes competitive intramolecular aminolysis to 5-aminomethyl-2-pyrrolidinone (L5) and 5-amino-2-piperidinone (L6) in dilute alkaline aqueous solution at 25°C. Use of this single compound provides an ideal case for assessing the relative rates of 5- and 6-membered lactam ring closure. Assessments are also made using the intramolecular aminolysis of pairs of compounds: methyl 2,4-diaminobutanoate (2,4-Dab Me) and methyl 2,5-diaminopentanoate (2,5-Dape Me); methyl 4-aminobutanoate (4-Ab Me) and methyl 5-aminopentanoate (5-Ape Me).

The alkaline and metal ion catalysed hydrolysis of amino acid esters has been the subject of many investigations,[1] mostly as models for metalloenzymes. It has been reported that the alkaline hydrolysis of some simple monoamino and diamino acid methyl[2] and ethyl[3] esters, and of γ-ethyl glutamate,[4] involves intramolecular aminolysis (lactamisation) in addition to $B_{Ac}2$ hydrolysis. Diamino acid esters can exist in aqueous solution in three forms (E, EH^+, EH_2^{2+}) each of which can undergo $B_{AC}2$ hydrolysis (with second order rate constants, k_E, k_{EH^+}, $k_{EH_2^{2+}}$) to the corresponding amino acid form (A^-, AH, AH_2^+). The three forms in each set are connected by pH dependent pK_a equilibria involving deprotonation of ammonium groups.[5] However, in addition to the $B_{AC}2$ reactions, much faster (but still second order) intramolecular aminolysis pathways are available if a 5- or 6-membered ring lactam can be formed using an unprotonated amino group.

The most complicated case is 4,5-Dape Me. At a given pH, up to six parallel reactions are possible: E undergoing competitive 5- and 6-membered ring lactamisation; EH^+ lactamising; three $B_{AC}2$ reactions. At a sufficiently high pH, only the E form of the ester is present and the reaction scheme simplifies to:

Scheme I



For the E form to be ≥ 99% of the total ester present, the reaction pH must be [6] $\geq pK_a^T(EH^+) + 2.11$, at 25°C and I = mol L^{-1}. This requires approximate minimum reaction pH values as follows: 4,5-Dape Me, 10.8; 2.4-Dab Me, 11.2; 2,5-Dape Me, 10.7; 4-Ab Me 11.9; 5-Ape Me 12.1.

The lactams formed by the five esters are all stable under the reaction conditions and timescales; they can be identified chromatographically, have been isolated and are not formed from the amino acid reaction products which have unprotonated 4- or 5-amino groups (e.g. A^-, Scheme I).

The second order rate constants for the lactamisation of 4,5-Dape Me, 2,4-Dab Me, 2,5-Dape Me, 4-Ab Me and 5-Ape Me were measured over a range of high pH (11.5-12.8) using Stopped Flow at 25°C and I = 0.1 mol L^{-1}. For each ester, the overall reaction was pseudo-first order at constant pH with $k_1/[OH^-]$ being independent of pH. This indicates overall second order kinetics and the absence of any kinetic contribution from EH^+. Results were checked by pH-stat measurements at lower pH, which involved separating out the lactamisation rate constants from those for k_{EH^+} and possibly $k_{EH_2^{2+}}$.[2]

For 4,5-Dape Me, at high pH (Scheme I), the rate equation is:

$$-\frac{d[E]}{dt} = k_{E(tot)}[E][OH^-]$$

$$\text{where } k_{E(tot)} = k_E + k_{L5} + k_{L6}$$

The values of k_E for all of the esters are small and have been estimated (Table 1) from similar compounds involving no lactamisation,[2,7] e.g. 3-Ap Me, k_E = 0.18; 6-Ah Me, k_E = 0.15; estimate k_E for 4-Ab Me as ~0.17 L $mol^{-1}s^{-1}$ at 25°C and I = 0.1 mol L^{-1}.

For 2,4-Dab Me, 2,5-Dape Me, 4-Ab Me and 5-Ape Me, there is only one k_L term so $k_L \sim k_{E(tot)}$, Table 1.

With 4,5-Dape Me, k_{L6}/k_{L5} was assumed to be equal to the ratio of the $t_{\frac{1}{2}}$ concentrations of the two lactams, L6 and L5, as measured by ^{13}C-nmr. This assumes the product concentration ratio is kinetically controlled. There is no evidence for any interconversion of these lactams under the reaction conditions and timescales.

Table 1. Rate Constants: T = 25°C, I = 0.1 mol L^{-1} (all in L mol^{-1} s^{-1})

Ester	$k_{E(tot)}$	k_E	k_{L5}	k_{L6}	k_{L6}/k_{L5}
4,5-Dape Me	440	0.14	80	360	4.5
2,4-Dab Me	422	0.50	422	-	7.2
2,5-Dape Me	3040	0.48	-	3040	
4-Ab Me	27.9	0.17	27.7	-	17.0
5-Ape Me	471	0.16	-	471	

The above k_L rate constants refer to the overall conversion of reactant esters into lactams. How a k_L value is related to the rate constant for the ring closure step depends on the reaction mechanism. This has been the subject of some debate for both intramolecular and intermolecular ester aminolyses.[8] It is now generally accepted, as originally proposed by Martin et al.,[3] that the intramolecular reaction involves essentially two steps; an initial general base catalysed deprotonation of the amino group which

simultaneously subjects the ester carbonyl carbon to intramolecular nucleophilic attack; the resulting tetrahedral intermediate then either forms the product lactam or regenerates the reactants. Which step is rate-determining depends on the ester structure and reaction conditions. (Changes in the rate-determining step have been used as evidence for the tetrahedral intermediate). For our systems, we conclude that the first step, formation of the tetrahedral intermediate (ring closure) is almost certainly rate-determining.

That such a concerted, general base catalysed, step can be rate-limiting has been clearing established for some intermolecular aminolysis reactions.[9] The second step, decomposition of the tetrahedral intermediate, is expected to be very fast under our reaction conditions.[10]

All our observations agree with the Martin et al. mechanism. In addition we have evidence[11] for general based catalysis by the ester itself; OH^- and E become competitive catalysts only for the relatively strongly basic 5-Ape Me under pH-stat conditions at low pH and high [E]. Further support for the mechanism is kinetic and pKa evidence[7] of strong intramolecular hydrogen bonding between the amino and ester carbonyl groups. This will assist the difficult proton abstraction process.

Under our reaction conditions, all the evidence supports a rate determining OH^- catalysed ring closure to a tetrahedral intermediate, i.e. k_{L6}/k_{L5} represents the relative rates of 6- to 5-membered ring closure. It must be emphasised that the rate constants are for a single temperature, 25°C. We are currently completing studies on the effect of temperature on the relative rates of lactam ring closure reactions and the k_{L6}/k_{L5} ratio appears to change dramatically with temperature.

The best case for assessing the relative rates of 5- and 6-membered lactam ring closure is where both reactions occur in a single compound, i.e. 4,5-Dape Me. Such competitive ring closure in two parallel reactions avoids most of the complications of differing electronic, steric and other effects which may be present when comparing two different compounds. The only possible complication is the effect of the non-participating $-NH_2$ group on the $-NH_2$ group involved in ring closure and on the carbonyl carbon. This may be different for the two ring closures. The electronic aspect of this effect is essentially identical: each non-participating $-NH_2$ exerts the same -I effect on the $-NH_2$ involved in ring closure; the difference in the -I effect of a 4-NH_2 and a 5-NH_2 on the carbonyl carbon electron density is negligible because of attenuation by the three or four intervening carbons. Model studies show the steric aspect of the effect should be small. The excellent case of 4,5-Dape Me shows k_{L6}/k_{L5} = 4.5 (Table 1), i.e. at 25°C, 6-membered ring closure is significantly favoured.

A greater preference for 6-membered ring closure is shown in the comparison of different compounds. The diamino acid esters yield k_{L6}/k_{L5} = 7.2 and the monoamino acid esters, k_{L6}/k_{L5} = 17.0 (Table 1). The differences in these figures, and between these figures and that for 4,5-Dape Me, reflects the complications involved in two compound comparisons.

For a given ring size, the relative k_L values (Table 1) can be explained in terms of inductive effects. Larger k_L values are seen for the α, ω-diamino acid esters, than for their monoamino analogues because the -I effect of the additional 2-NH_2 group assists nucleophilic attack by lowering the electron density on the carbonyl carbon. The ratio k_{L5} (2,4-Dab Me): k_{L5} (4-Ab Me) = 15.2 represents the accelerating effect of a 2-NH_2 group on 5-membered ring lactam formation. k_{L6} (2,5-Dape Me): k_{L6} (5-Ape Me) = 6.5 shows the accelerating effect of a 2-NH_2 group on 6-membered ring lactam formation. Removing the 2-NH_2 to the 4-position results in the expected decrease in the accelerating effect on the (k_{L6} (2,5-Dape Me): k_{L6} (4,5-Dape Me) = 8.4). However such simple arguments at a single temperature must be treated with caution because of possible $\Delta S^{\ddagger}$ effects; e.g. the additional 4- or 5-NH_2 of 4,5-Dape Me has an unpredictable effect on the rate of lactamisation (k_{L5} (4,5-Dape Me): k_{L5} (4-Ab Me) = 2.9; (k_{L6} (4,5-Dape Me): k_{L6} (5-Ape Me) = 0.8).

The relative rates of 5- and 6-membered ring closure reactions has been the subject of a few recent studies and reviews.[12] In general, for carbocylic systems, 5-membered ring formation is faster than 6-membered at room temperature. For heterocyclic rings, there is no general preference. Two compound comparisons using the hydroxyl ion catalysed lactamisation of some ω-amino acid ethyl esters at 25°C, has been reported[3] as showing 6-membered ring formation is faster by up to 25 times. Our studies show that such two compound comparisons give an artificially high ratio; in fact the reaction is only slightly tilted in favour of 6-membered lactam ring closure, at 25°C.

Experimental: A Durrum D-110 Stopped-Flow spectrophotometer was used to follow the fast, high pH, reactions at $\lambda \sim 215$ nm. One reservoir syringe contained sodium hydroxide solution at twice the required final concentration; the other syringe contained the ester, enough KCl and HCl to give a final solution concentration of 1.6×10^{-4} mol L^{-1} ester and an ionic strength of 0.1 mol L^{-1}. The pH of the final solution remained constant to ±0.01 pH; temperature was controlled to ±0.05°C. Data was recorded on a Biomation 805 digital waveform recorder. Internal consistency of repeated runs at a given pH was better than ±4%.

The Radiometer pH-stat consisted of a PHM 26c pH meter, 11b titrator, ABU 11 autoburette (2.5 mL burette), G202B glass electrode and K401 calomel electrode. Buffer calibration and temperature control were as described previously.[2] Total ester concentration was 10^{-2} to 10^{-3} mol L^{-1}; 1 mol L^{-1} NaOH was used; 0.1 mol L^{-1} ionic strength was maintained using KCl. Rate constant reproducibility was better than ±2%. These agreed with those obtained by Stopped-Flow to within ±5%.

For quantitative nmr, the ^{13}C spectra were obtained with interrupted decoupling to suppress NOE's. The tip angle was 65°, acquisition time was 0.68 s, with a pulse delay of 1.0 s. When saturation was apparent, the tip angle was reduced to 33° and the pulse delay extended to 4.0 s. The average peak ratio between L6 and L5 was 4.6 ± 0.1.

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