Nucleophilic Attack by Amine Nitrogen on the Ionised Carboxy Group†

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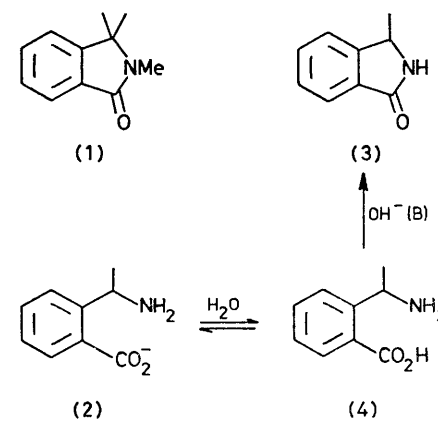
Summary The 2-(1-aminoethyl)benzoate anion cyclises to the lactam (**3**) at high pH, in a reaction which involves intramolecular attack of amine nitrogen on the carboxylate anion.

THE amide bond of the lactam (**1**) is not hydrolysed by alkali, even under vigorous conditions. One possible explanation is that the resulting amino-acid recyclises faster than it is formed, in a reaction that would require the neutral amino-group to react with the carboxylate anion. A reaction of this sort may have been observed recently by Deslongchamps and his co-workers,[1] who found that 2-piperidone is in equilibrium with the open-chain amino-acid anion in alkali at 100 °C. We report a reaction in which a lactam is formed quantitatively in alkali, and kinetic evidence that implicates nucleophilic attack by amine nitrogen on the CO_2^- group.



(1) (3) (2) (4)

† No reprints available.

2-(1-Aminoethyl)benzoate (**2**, prepared by catalytic hydrogenation of the oxime[2] of 2-acetylbenzoic acid) is converted into the lactam (**3**) in a reaction which is pH-independent above the pK_a (9·05) of the amino-group up to 0·1 M NaOH, where a reaction of the first order in hydroxide becomes significant (Figure). Lactam formation below pH 12 is general acid catalysed, but we do not consider this to be a reaction of the anion (**2**), because it can be quantitatively accounted for in terms of the kinetically equivalent general base catalysed reaction of the neutral amino-acid (**4**).‡

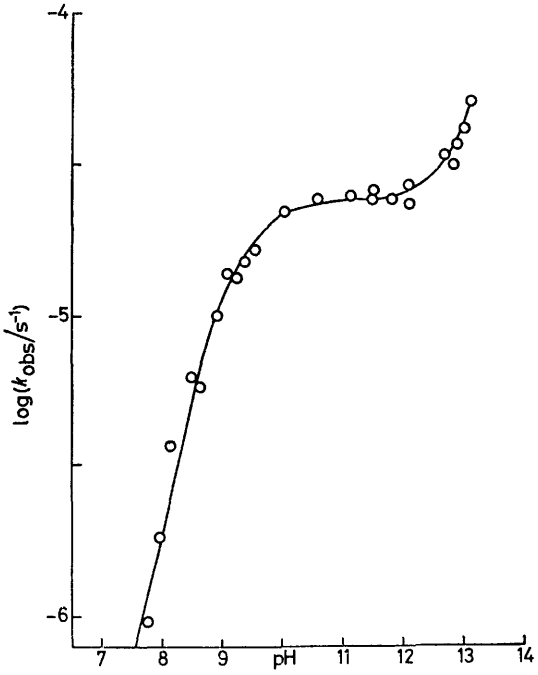
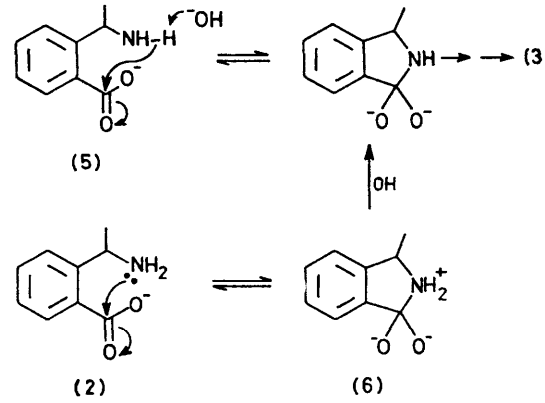


FIGURE. pH–rate profile for the cyclisation of 2-(1-aminoethyl)-benzoate (**2**) to the lactam (**3**) in water at 50 °C and ionic strength 1·0. The points are experimental (and represent extrapolations to zero buffer concentration below pH 11), and the curve calculated, using $pK_a = 9·05$, $k_{plateau} = 2·45 \times 10^{-5}$ s^{-1} and $k_{OH} = 2·75 \times 10^{-5}$ dm^3 mol^{-1} s.$^{-1}$

The hydroxide-catalysed reaction, on the other hand, can only reasonably be interpreted as a reaction of the anion (**2**). The role of hydroxide is clearly to remove the proton from the NH_2 group. This proton transfer could be concerted with cyclisation (**5**), thus avoiding the formation of the highly charged species (**6**), or it could follow it, trapping (**6**) before it can revert to starting materials. Although



the former mechanism has been superseded by the latter for ester aminolysis,[3,4] several factors [*e.g.*, the solvent deuterium isotope effect, $k_{OH}/k_{OD} = 2·44 \pm 0·20$, $\Delta H^{\ddagger} = 15·6$ kcal (65 kJ) mol^{-1}, $\Delta S^{\ddagger} = -31·4$ cal (131 J) K^{-1} mol^{-1}] lead us to prefer the concerted mechanism (**5**) at this stage.

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‡ Although the equilibrium concentration of (**4**) will be very small ($K_{2,4}$ *ca.* 10^{-10}), the rate constant for the hydroxide catalysed cyclisation of (**4**), estimated from data (ref. 3) for the same reaction of methyl 2-aminomethylbenzoate, is high enough to account for the observed rate of the pH-independent reaction.

[1] P. Deslongchamps, U. O. Cheriyan, A. Guida, and R. J. Taillefer, *Nouveau J. de Chim.*, 1977, **1**, 235.
[2] W. Davies and H. G. Poole, *J. Chem. Soc.*, 1927, 2662.
[3] T. H. Fife and B. R. DeMark, *J. Amer. Chem. Soc.*, 1976, **98**, 6978.
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