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INTRAMOLECULAR NUCLEOPHILIC CATALYSIS OF AMIDE HYDROLYSIS BY PYRIMIDINE NITROGEN

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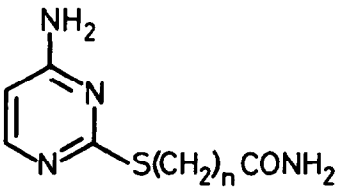
The amide (**1**, n = 1) is rapidly hydrolysed at low pH in a reaction which clearly involves catalysis by pyrimidine nitrogen.[1] Possible mechanisms are intramolecular general acid (**2**) and intramolecular nucleophilic catalysis (Scheme, below). In their original paper[1] Cramer and his co-workers preferred mechanism (**2**), on the grounds that the nucleophilic mechanism should be more favourable for a reaction involving a six-membered cyclic transition state, whereas the propionamide (**1**, n = 2) is actually hydrolysed 25 times more slowly than (**1**, n = 1). This argument is incorrect, and we report evidence that is consistent only with the nucleophilic mechanism.



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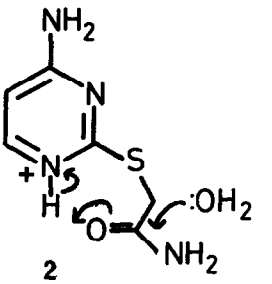

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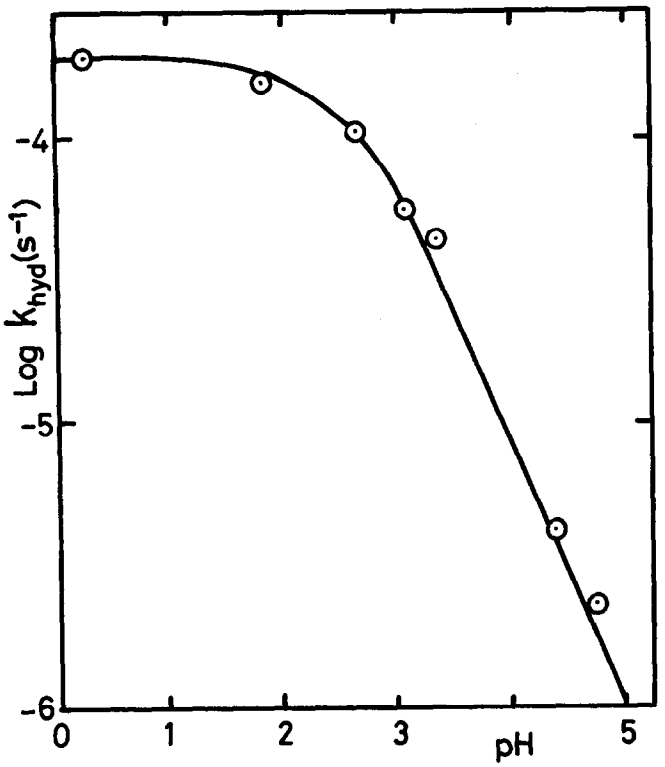
Intramolecular nucleophilic catalysis *via* five-membered ring intermediates is in fact often more efficient than the corresponding reaction involving six-membered rings. Particularly relevant are derivatives of succinic acid, which are geometrically closely similar to the system under discussion, and invariably cyclise more readily than the homologous glutarates.[3] The introduction of a sulphur atom is expected to reinforce this trend, since the strain energies of five-membered rings are significantly smaller than those of the corresponding

cycloalkanes.[4] The observed effects of homologation on the rates of hydrolysis of compounds (**1**) are not therefore inconsistent with the nucleophilic mechanism.

The pH-rate profile (Figure) for the hydrolysis of the N-methylamide (**1a**) shows that the reaction involves the conjugate acid. There is no significant solvent deuterium isotope effect (k_H/k_D = 1.1 ± 0.1 in the region pH 1 - 4), though a substantial effect (k_H/k_D > 2) would be expected for intramolecular general acid catalysis (**2**). The reaction is also catalysed by the acid component of formic acid-formate buffers. This must be catalysis of the intramolecular reaction (general acid catalysis is not observed for the hydrolysis of simple amides[5]) and cannot reasonably be accommodated by mechanism (**2**). It is, however, consistent with nucleophilic catalysis (Scheme, opposite), because proton transfer reactions involving tetrahedral intermediates are an integral part of this mechanism. The pH-rate profile itself provides further evidence that the reaction must involve at least one intermediate: the apparent pK_a (2.70) is clearly not the true pK_a of the pyrimidine (**1**, n = 1, $pK_a \simeq 4.5$), which it should be if mechanism (**2**) were correct.

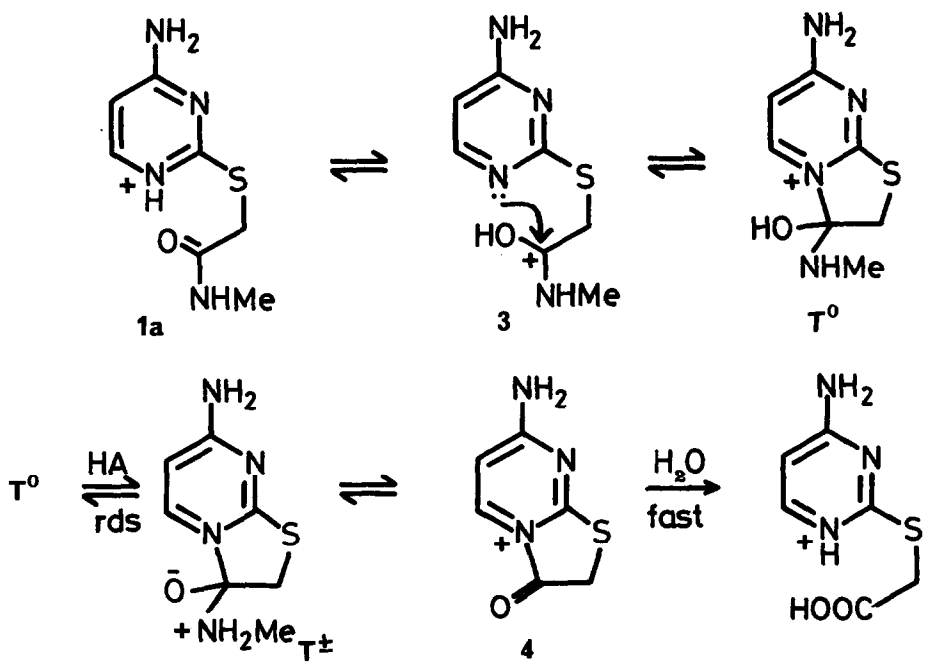
All the available evidence is consistent with the nucleophilic mechanism outlined in the Scheme. This is based on a mechanism proposed to account for intramolecular nucleophilic catalysis of amide hydrolysis by the carboxyl group, which is also a general acid catalysed reaction.[6] Evidently the carboxyl and pyrimidine groups can react in very similar ways. In both cases the conjugate acid of the nucleophile involved is acidic enough (pK_a 4 - 5) for it to coexist with significant concentrations of the form with the amide group protonated (**3**, pK_a ~ 0). Rapid cyclisation of (**3**) gives the neutral tetrahedral intermediate, T^o. This will revert rapidly to starting materials unless it is "trapped" by a proton transfer, in this case from the general acid HA, which catalyses the conversion of T^o to the zwitterion $T^{\pm}$. $T^{\pm}$ can then lose methylamine to generate the acyl pyrimidinium intermediate (**4**). The proton transfers concerned are between O and N centres, and are expected to be diffusion-controlled reactions, accounting for the low deuterium isotope effects observed (k_H/k_D = 1.08 for catalysis by formic acid).

Intramolecular nucleophilic catalysis is potentially far more efficient than intramolecular general acid or general base catalysis,[7] so that pyrimidine nitrogen, in the right situation, is likely to be a very powerful catalyst for reactions of carboxylic acid derivatives. It is also significant that the carboxyl group is a highly effective intramolecular nucleophilic catalyst of the hydrolysis of phosphate and phosphonate esters[8], and our conclusions raise the interesting possibility that pyrimidine nitrogen will behave similarly towards phosphorus centres also.



Figure

pH-rate profile for the hydrolysis of **1a** in H_2O at ionic strength 1.0M (KCl). The points are experimental, and were measured by NMR, at the temperature of the probe (35.5°), by following the appearance of the methyl singlet of methylamine at 2.9 δ (Varian HA 100 instrument locked onto the OH signal). Buffers were HCl (pH 0-3.3) and formate (pH 4-5). The formate points represent extrapolations to zero buffer concentration. The curve is calculated using $pK_{app} = 2.70$, $k_{plateau} = 1.94 \times 10^{-4}\ s^{-1}$.



Scheme

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