Rate-determining Proton Transfer in Intramolecular Catalysis of Amide Hydrolysis by the Carboxylic Acid Group

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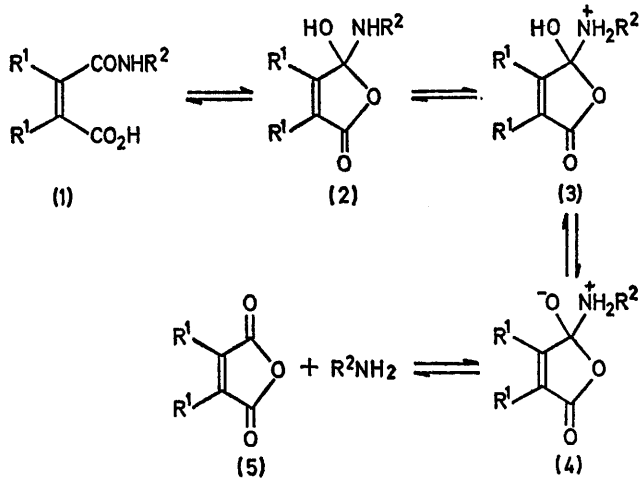
Summary The rate-determining step for the intramolecular carboxy-group-catalysed hydrolysis of a di-isopropylmaleamic acid is a diffusion-controlled proton transfer involving an external general acid–base catalyst.

IN a recent investigation[1] designed to explore the limits of efficiency of intramolecular catalysis of amide hydrolysis by the carboxy-group, we measured rates of hydrolysis for a series of substituted maleamic acids (**1**). Increasing the size of the group R^1 leads to remarkably large increases in reactivity: an amide derived from dimethylmaleamic acid (R^1 = Me), for example, was hydrolysed 23,000 times faster than the compound with R^1 = H. Di-isopropylmaleic acid has recently become available,[2] and we have measured the rate of hydrolysis of the *N*-n-propylamide



(**1**; R^1 = Pr^i, R^2 = Pr^n). Surprisingly, this amide is not hydrolysed significantly faster than the corresponding dimethylmaleamic acid. We report evidence that this is because a different step on the hydrolysis pathway has become rate determining, a step with the kinetic characteristics of a diffusion-controlled proton transfer process.†

The hydrolysis of (**1**; R^1 = H, R^2 = Me) is a typical (unimolecular) intramolecular reaction;[1] the entropy of activation is near zero ($\Delta S^{\ddagger}$ = +2·9 cal K^{-1} mol^{-1}) and there is no significant buffer catalysis. The hydrolysis of (**1**; R^1 = Pr^i, R^2 = Pr^n) is strikingly different; in the pH-independent region between pH 0 and 2 the entropy of activation is moderately large and negative (ΔS = −14 cal K^{-1} mol^{-1}), suggesting that a molecule of water is involved in the rate-determining step, and the reaction is strongly general-acid catalysed.

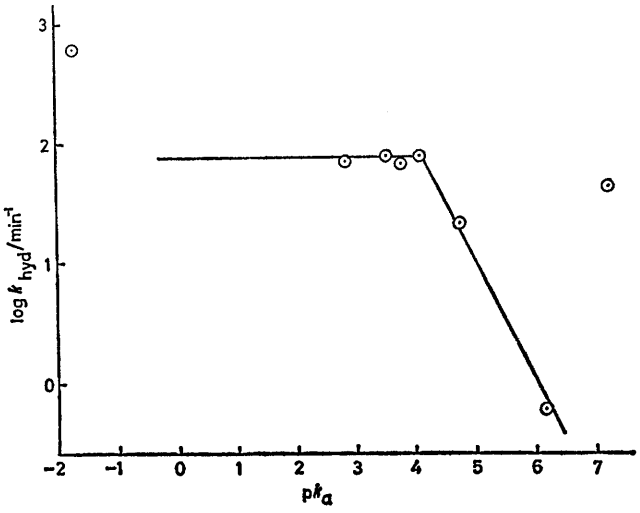


FIGURE. *Brønsted plot for catalysis by general acids of the hydrolysis of di-isopropyl-*N*-n-propylmaleamic acid. Points in order of increasing* pK_a *are for* H_3O^+, *substituted carboxylic acids, 2-(*N*-morpholino)ethanesulphonic acid, and phosphate, respectively, and are based on a* pK_a *of* 4·16 *for the starting material.*

We have shown[1] that the rate-determining step in the hydrolysis of less reactive maleamic acids is the breakdown of the tetrahedral intermediate to the cyclic anhydride (**4**) → (**5**).‡ It is unlikely that the new rate-determining step is the formation of the tetrahedral intermediate (**2**), because it is the increased driving force for cyclisation that makes the dialkylmaleamic acids so reactive.[1] The only other steps involved are proton transfers [(**2**) → (**3**) → (**4**)], and the kinetic properties of the reaction confirm that one of these steps is now rate determining. The evidence is summarised in the Brønsted plot shown. The Brønsted coefficient α changes from *ca.* 0 to unity as the pK_a of the general acid is raised; the catalytic constant for the solvated proton is 24 times greater than that for other general acids, as expected for a diffusion-controlled reaction in water,[3] and a positive deviation is also observed for $H_2PO_4^-$, which can act as a bifunctional acid–base catalyst[3,4] to convert (**2**) into (**4**) directly.

The slowest intermolecular proton transfer of the reaction should be the step in which the tetrahedral intermediate is converted into the zwitterion [(**3**) → (**4**)]. The correspond-

† Methods have been described previously.[1]

‡ The large increases in reactivity associated with the introduction of alkyl substituents R^1 into (**1**) result from a more favourable equilibrium constant for ring-closure [(**1**) ⇌ (**2**)]. The change of rate-determining step observed here with R^1 = Pr^i requires a steric effect of the isopropyl groups on step (**4**) ⇌ (**5**). This further effect need not be large, and we hope to provide independent evidence for its existence.

ing step is also thought to become rate determining in the S to N acetyl-transfer reaction of *S*-acetylmercaptoethanolamine[3] above pH 2·3, and the properties of the two reactions show marked similarities.

This reaction between a carboxy and an amide group is almost certainly a part of a number of enzyme-catalysed reactions. Our result shows that at a point where strain has caused a sufficiently large rate enhancement (some 10^{10}-fold in this system[1]) the rate of the simple intramolecular reaction is determined by the rate of diffusion to the reaction site of a second catalyst molecule. We have thus formally demonstrated a requirement for a second catalytic group already in position if catalysis is to become any more efficient in this or a similar enzymic situation.

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