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The first complete pH-rate profile (H_0 -4 ÷ pH 12) for an amide is reported. Hydration of carbonyl moiety is suggested to be the first step of the reaction between H_0 -4 ÷ pH 6.

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Sir:

A reaction mechanism involving preliminary protonation of the amide molecule and the subsequent rate-limiting attack by water appears to be well established in the acid hydrolysis of all the amides examined. The existence of a rate maximum at some high acidity near to the pK_a of the substrate is due to a balance between the increasing concentration of the reactive intermediate and the decreasing activity of water (1). On the other hand, the mechanism of the basic hydrolysis is strongly dependent on the pH and on the structure of the amide: the rate determining step being either the hydroxide ion attack on the carbonyl group or the decomposition of the tetrahedral intermediate (in the monoanionic or in the dianionic form) (2). Neutral hydrolysis have been recorded only for highly activated amides as *N*-acetyl-imidazole (3) and *p*-nitrotrifluoroacetanilide (4). These compounds exhibit a plateau in the pH-rate profile near pH 3. Moreover data obtained in our laboratories show that the last compound exhibits the typical rate maximum

at $H_0 = -2$. On this basis, a complete pH-rate profile for an amide should show the behaviour illustrated in Figure 1A.

We wish to report a kinetic study of the hydrolysis of the highly reactive *N*-trifluoroacetylindole, recently prepared in our laboratories (5), which allowed us to give the first complete pH-rate profile of an amide. The rate of hydrolysis of *N*-trifluoroacetylindole has been measured in water at 25° at H_0 values between -4 and 0 and at pH values between 0 and 12. The pH-rate profile (Figure 1B) shows two regions in which the rate of hydrolysis is quasi-independent of pH; two regions in which it is proportional to the concentration of OH^- ions, with unit slope; one region in which it is proportional to the concentration of H^+ ions with unit slope and with a rate maximum in the H_0 region.

The substantial difference between this profile and that estimated for usual amides prompted us to suppose a substantial different mechanism.

This proposal has been substantiated by experimental

Figure 1

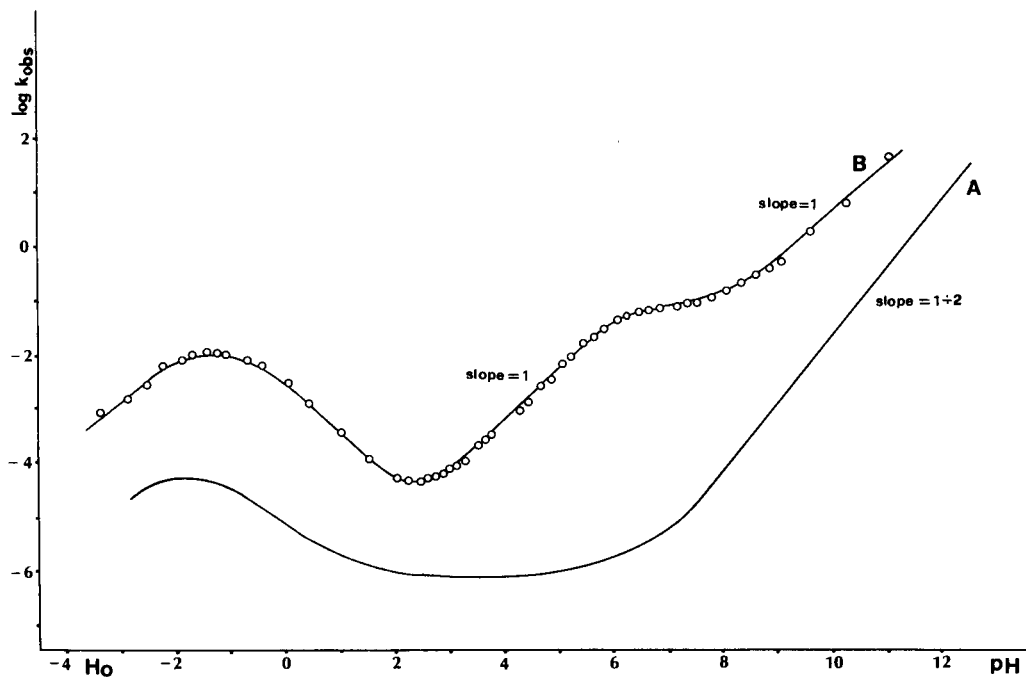


Figure 1A: Estimated pH-rate profile for a simple amide. Figure 1B: Experimental pH-rate profile for *N*-trifluoroacetylindole.

evidence, recently provided, for appreciable hydration of *N*-trifluoroacetylpyrrole in aqueous solution (6). Preliminary data on the pH-rate profile of *N*-trifluoroacetylpyrrole show a close pattern. Although hydration for *N*-trifluoroacetylindole could not be established, probably because the hydration extent is smaller, due to the steric hindrance of the *peri*-hydrogen in the indole nucleus, nevertheless, from the collected data we suggest the first step of the hydrolysis of both compounds to be the hydration of the carbonyl moiety.

Moreover, some reasonable mechanistic conclusions can be drawn: a) between H_0 -4.0 and pH 2.0 the rate determining step (RDST) is the decomposition of T^+ ; b) between pH 2.0-2.8 the breakdown of the neutral hydrate is the RDST; c) between pH 2.8-6.0 the RDST is the decomposition of T^- ; d) the plateau region between pH 6.0-8.0 indicates a drastic change in the RDST; e) between pH 8.0-12.0 the RDST should be the base-catalyzed hydration of the substrate.

We believe that the detection of the hydrate form of *N*-trifluoroacetylpyrrole in a wide range of conditions

(pH 1.0-4.5) might exclude the possibility that formation of T^+ , T^0 , T^- could be the slow step in a), b) and c), although slow proton transfer processes cannot be discarded on the basis of the present data.

Acknowledgement.

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