The Mechanism of the Hydrolysis of Acyl Cyanides

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WE report results of the first quantitative study of the spontaneous and catalysed hydrolysis of acyl cyanides. We have used benzoyl and *p*-chlorobenzoyl cyanides. The overall reaction was (1) and in an excess of water the formation of the benzoic acid (or loss of carbon-bound cyanide) was always an accurately first-order process. The

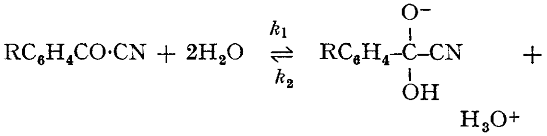
$$RC_6H_4CO{\cdot}CN + H_2O \rightarrow RC_6H_4CO_2H + HCN \quad (1)$$

reaction is *inhibited* by acid and in 5M-$HClO_4$ is very slow. As the pH is raised the rate increases, although the profile (see Figure) contains a region where the rate is largely independent of pH. Studies with buffer solutions show that the reaction is both general base-catalysed and general acid-inhibited. In the absence of effective general acids and bases other than those derivable from water, the first-order rate constant for benzoyl cyanide may be represented by

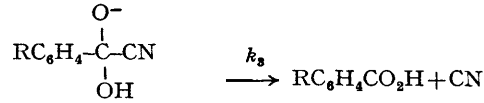
$$k = 1{\cdot}53/(1 + 177[H_3O^+]) + 4{\cdot}3 \times 10^7[OH^-].$$

This expression is plotted as a solid line in the Figure, the points being experimental values. Analogous results are obtained with *p*-chlorobenzoyl cyanide, *k*, however, being about two-fold greater over most of the pH range. The term in $[OH]^-$ begins to be felt at pH = 4·5 and will become dominant at pH > 7.

A very similar pattern of data has been observed recently for the hydrolysis of ethyl trifluorothiolacetate and we agree with Fedor and Bruice[1] that the simplest interpretation is a scheme involving a dominant bimolecular reaction between OH^- and substrate at high pH (here > 7) and a dominant water reaction at lower pH (here < 4·5), this latter reaction being susceptible to general base-catalysis and to inhibition by acid. This acid inhibition, and the absence of significant positive catalysis by acid even at very high acidities, points to the existence of an intermediate whose formation is depressed by acid and the departure of whose leaving group is not assisted by protonation. The water reaction therefore probably involves general base-catalysed addition to the carbonyl group as in (2), followed by a spontaneous loss of CN^- as in (3).



$$RC_6H_4CO{\cdot}CN + 2H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} RC_6H_4\text{-}\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}\text{-}CN + H_3O^+ \quad (2)$$



$$RC_6H_4\text{-}\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}\text{-}CN \xrightarrow{k_3} RC_6H_4CO_2H + CN^- \quad (3)$$

It is difficult to rationalise the data for pH < 4·5 without the assumption of some variety of carbonyl addition.

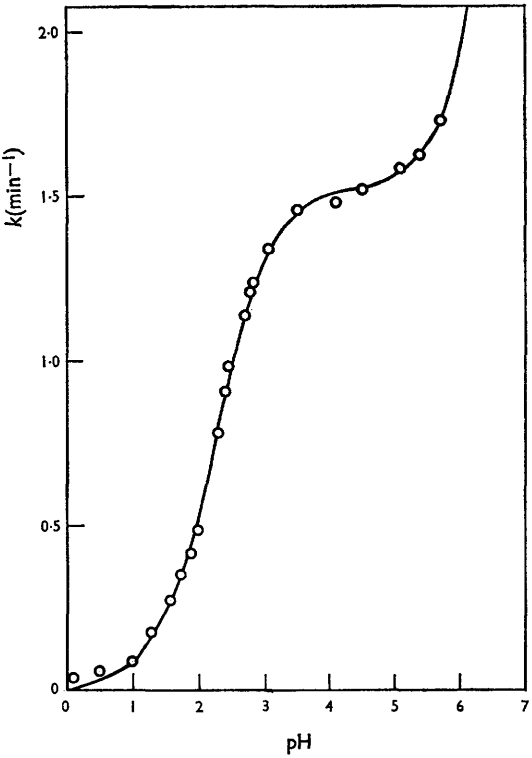


FIGURE: *Plot of* k *against pH for benzoyl cyanide.*

A steady-state treatment of (2) and (3) leads to $k = k_1/(1 + k_2/k_3[H_3O^+])$, so that for benzoyl cyanide $k_1 = 1{\cdot}53$ min.$^{-1}$ and $k_2/k_3 = 177$. For the *p*-chloro-derivative, $k_1 = 2{\cdot}59$ min.$^{-1}$ and $k_2/k_3 = 172$. These results are compatible with the expected substituent effect.

The hydrolytic behaviour of benzoyl cyanides and of trifluoroacetyl thiol esters is clearly very similar. Both types of compound possess (a) electron-withdrawing groups which favour carbonyl addition and (b) leaving groups which do not accept protons readily.

It is the great inhibition of the "normal" hydrolysis of acyl cyanides in strong aqueous acid which permits the hydrolysis of the CN group, which can also occur under such conditions,[2] to become dominant and form a practicable route to α-keto-acids (4).

$$RCO{\cdot}CN + 2H_2O \rightarrow RCO{\cdot}CO_2H + NH_3 \quad (4)$$

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[1] L. R. Fedor and T. C. Bruice, *J. Amer. Chem. Soc.*, 1965, **87**, 4138.

[2] W. J. Hickinbottom, "Reactions of Organic Compounds", Longmans, Green, and Co., London, 1959, p. 381.