385. *Hydrolysis of Amides and Related Compounds. Part III.** *Methyl Benzimidate in Aqueous Acids.*

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The rate of hydrolysis of methyl benzimidate in aqueous hydrochloric and sulphuric acid decreases sharply with acid concentration after protonation of the base is nearly complete. It is concluded that this hydrolysis may proceed by a mechanism similar to that for the hydrolysis of benzamide.

THE hydrolysis of methyl benzimidate (I; R = Me) in aqueous acids affords chiefly methyl benzoate (V; R = Me) and ammonium ion, but in water small amounts of benzamide (II) and methanol are also formed.[1,2] The kinetics of the reaction were studied extensively by Stieglitz and his co-workers,[1] who showed that with a deficiency of hydrochloric acid the rate was proportional to the concentration of the protonated from (III; R = Me). Since methyl benzimidate is a moderately strong base (pK_a' 5·67),[1] its protonation approaches completion in solutions more acid than about pH 3, and it would be expected that the rate would become constant with increasing acidity. However, in >0·1N-hydrochloric acid the rate began to drop (see Fig. 1).
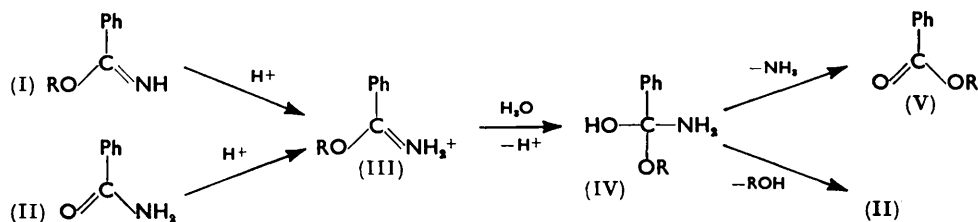
It has been shown [3] that the kinetics of the hydrolysis of benzamide (II) are consistent with a mechanism involving the very similar ion (III; R = H). If the rate-determining step in both hydrolyses is the attack of a water molecule on such an ion (III; R = H or Me) to give the labile intermediate (IV; R = H or Me), it may be predicted that (*a*) the rates of hydrolysis of both compounds should be of the same order when based on the concentration of the ionized species (III; R = H or Me), and (*b*) the decrease in the rate of hydrolysis of methyl benzimidate with increasing concentration of acid should be described by the equation found valid for benzamide.[3] The present paper describes work to test these predictions.

EXPERIMENTAL

Materials.—Methyl benzimidate hydrochloride [4] had m. p. 105—106° (decomp.) after recrystallization from glacial acetic acid–dry ether. On hydrolysis in N-hydrochloric acid at 100° for 4 hr. it afforded 100·1% of the calculated amount of ammonium ion, as estimated by " formol " titration.[5] *Methyl benzimidate hydrogen sulphate,* prepared by adding the calculated quantity of 96% sulphuric acid to methyl benzimidate in dry ether, after three crystallizations as above, melted at 120—121° [Found : C, 41·7; H, 4·7; SO₄ (as BaSO₄), 32·8. $C_8H_{11}O_5NS$ requires C, 41·2; H, 4·7; SO₄, 33·1%]. The imidate salts were kept in a vacuum-desiccator.

Analytical Methods.—The apparent dissociation constant pK_a' of methyl benzimidate hydrochloride was found by potentiometric titration of a 0·14M-solution with 0·1N-sodium hydroxide (glass electrode) to be 5·8. Stieglitz *et al.*[1] reported pK_a' 5·68. On hydrolysis it

* Part II, preceding paper.
  ¹ Stieglitz, *Amer. Chem. J.,* 1908, **39**, 29, 166; Derby, *ibid.,* p. 437; McCracken, *ibid.,* p. 586; Schlesinger, *ibid.,* p. 719.
  ² Mengelberg, *Chem. Ber.,* 1954, **87**, 1425.
  ³ Edward and Meacock, *J.,* 1957, 2004.
  ⁴ Pinner, *Ber.,* 1883, **16**, 352.
  ⁵ Northrop, *J. Gen. Physiol.,* 1926, **9**, 767.

forms ammonium ion (pK_a' 9·2) and methyl benzoate, and possibly a trace of benzamide and methanol; the further hydrolysis of benzamide[3] and methyl benzoate[6] to benzoic acid will be negligible under the conditions of these experiments. Consequently, in the titration of the reaction solution from pH 3·7 to pH 8·0 (glass electrode) (method *a*), 98·5% of the conjugate acid of methyl benzimidate and 5·9% of the ammonium ion will be neutralized. Similarly, the formol titration according to Northrop[5] (method *b*) will in the present instance measure ammonium ion and also the 4·7% of the conjugate acid of methyl benzimidate still unneutralized at pH 7·0. However, while these two methods do not indicate the stoicheiometric concentration either of protonated methyl benzimidate or of ammonium ion, the change in the measurements during the reaction will be proportional to the extent of the reaction, it being assumed that the reaction is of first order with respect to methyl benzimidate in excess of aqueous acid. Reaction rates found by each method were in fair agreement with each other and with the results of Derby,[1] who used a different method (Fig. 1).
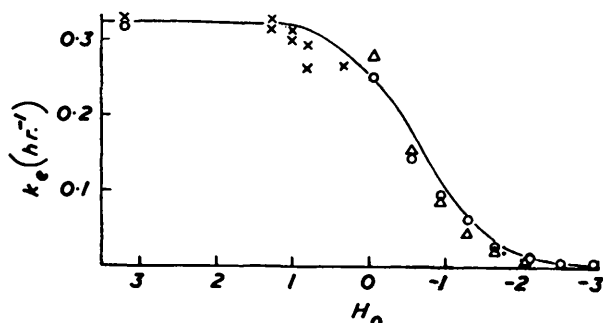

FIG. 1. *Hydrolysis of methyl benzimidate in hydrochloric acid of varying strengths (expressed as the acidity function H_0).*

Sources of experimental points:
× *Derby.*[1] △ *Present work : reaction followed by method (a).* ○ *Present work : reaction followed by method (b).*

Rate Measurements.—A known weight of methyl benzimidate salt, sufficient to give a 0·1—0·2M-solution, was added with shaking at zero time to the acid solution (100·0 ml.), kept at 25·00° ± 0·05°. The salt dissolved in less than 1 min. At intervals aliquot parts (10·0 ml.) were pipetted into a mixture of ice and sufficient 2N-sodium hydroxide to bring the pH to about 3. This solution was then titrated in less than 5 min. Method *a* was used for following hydrolyses of the hydrochloride in 1·00, 2·00, 3·00, 4·00, 5·00, and 6·00M-hydrochloric acid,
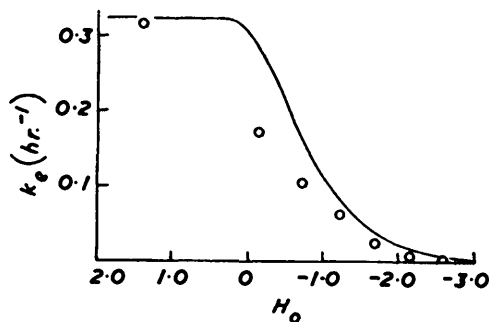

FIG. 2. *Hydrolysis of methyl benzimidate in sulphuric acid of varying strengths.*

Guggenheim's method[7] being used for evaluating rate constants. Method *b* was used for following hydrolyses of the hydrochloride in distilled water (pH of solution 3·2) and in 1·00, 2·00, 3·00, 4·00, 5·00, 6·15, 7·38, and 8·20M-hydrochloric acid; and of the acid sulphate in distilled water (pH of solution 1·4) and in 1·00, 2·00, 3·00, 4·00, 5·00, and 6·00M-sulphuric acid, rate constants being evaluated by the usual graphical method. The results are given in Figs. 1 and 2, the empirical first-order rate constants being plotted against acidity function (H_0) instead of acid concentration.

[6] Chmiel and Long, *J. Amer. Chem. Soc.*, 1956, **78**, 3326.
[7] Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

DISCUSSION

If the hydrolysis of methyl benzimidate has as its rate-determining step the reaction of a molecule of water with the ion (III; R = Me) it would be expected [3] that the empirical first-order rate constant k_e would vary with acid concentration according to the equation

$$k_e = k_2 K_1 [H_3O^+]/(K_1 + h_0)$$

k_2 being a second-order rate constant for the reaction (III; R = Me) + $H_2O \longrightarrow$ (IV), K_1 the equilibrium constant for the reaction (III; R = Me) + $H_2O \rightleftharpoons$ (I; R = Me) + H_3O^+, and h_0 the non-logarithmic acidity function.[8] Since for methyl benzimidate $h_0 \gg K_1$ for the acid concentrations used in our experiments, the equation may be simplified to :

$$k_e = k_3 [H_3O^+]/h_0 \qquad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

This equation gives expression to the fact that the decrease in the rate of hydrolysis with increase of acid concentration is governed by the decreasing concentration of water after complete protonation of the substrate. (The water concentration for kinetic purposes is

FIG. 3. *Hydrolysis of methyl benzimidate* (○) *and of benzamide* (△) *in hydrochloric acid.*
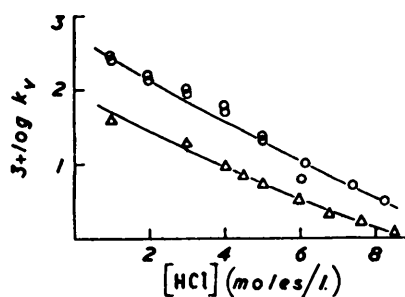
proportional to $[H_3O^+]/h_0$,[3] and *not* to the stoicheiometric water concentration, presumably because of the various effects of the ions in binding water, etc.) The theoretical curves shown in Figs. 1 and 2 have been calculated from this equation, h_0 and the oxonium-ion concentrations for the different acid concentrations being obtained as previously,[3] and k_3 being assigned the value of 0·325 hr.$^{-1}$. The experimental values for hydrolyses in hydrochloric acid (Fig. 1) are in reasonable agreement with the theoretical curve, but in sulphuric acid (Fig. 2) the agreement is less satisfactory.

Although in M-hydrochloric acid the hydrolysis of methyl benzimidate is about 400 times faster than that of benzamide, the difference is due chiefly to the almost complete protonation of the benzimidate as compared with only 1·6% protonation of the benzamide. Account may be taken of this difference by defining a first-order rate constant k_v based on the concentration of the protonated forms (III; R = H or Me) only. This is related to the empirical first-order constant k_e (which is based on the stoicheiometric concentration of amide or imidate) by the equation

$$k_v = k_e([B] + [BH^+])/[BH^+] = k_e(K'_a + h_0)/h_0$$

where B is (I; R = Me) or (II), BH^+ is (III; R = H or Me), and K'_a is the equilibrium constant of the reaction, $BH^+ \rightleftharpoons B + H^+$. It is found (Fig. 3) that in M-hydrochloric acid the value of k_v for methyl benzimidate is only about five times greater than that for benzamide, while in 8M-acid it is only about 2·5 times greater. It would be difficult to predict *a priori* which of the ions (III; R = H) and (III; R = Me) would react more readily with water, but obviously it would be expected that the difference would be small. The present results, while not proving the orthoamide derivative (III; R = H) to be an

[8] Hammett, " Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 271.

intermediate in the hydrolysis of benzamide, show that it would have about the required reactivity.

Some doubt about this mechanism is raised by the failure to observe during hydrolysis any exchange of the oxygen of benzamide with that of water.[9] The intermediate (IV; R = H) might be expected to regenerate some benzamide by the elimination of water, by analogy with the formation of benzamide from methyl benzimidate by the elimination of methanol.[1,2] However, the latter type of reaction has been observed only in solutions of low acidity, and it is possible that the intermediates (IV; R = H or Me) have an overwhelming tendency to eliminate ammonia in moderately acidic solutions. For the moment the precise mechanism of the hydrolysis of amides must be considered unsettled.

[9] Bender and Ginger, *J. Amer. Chem. Soc.*, 1955, **77**, 348.