

383. *Hydrolysis of Amides and Related Compounds. Part I.
Some Benzamides in Strong Aqueous Acid.*

By J. T. EDWARD and S. C. R. MEACOCK.

The rate of hydrolysis at 25° of the following amides reaches a maximum in approximately the acid strengths shown: benzamide, in 4.5M-hydrochloric acid or 3.5M-sulphuric acid; *p*-methoxybenzamide, in 3.0M-sulphuric acid; *p*-nitrobenzamide, in 4.5M-sulphuric acid. It is shown that these are the acid concentrations in which maximum rates are to be expected if account is taken of the ionization of the amides.

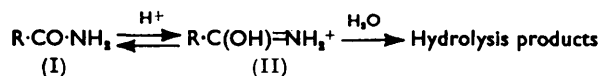
THE rates of the acid-catalysed hydrolysis of several amides go through a maximum as the concentration of acid is increased.¹⁻³ The concentrations for maximum rate depend on both the amide and the acid: for formamide, acetamide, and propionamide in sulphuric acid they are 4.75M, 2.5M, and 2.4M respectively.² These results may be explained in terms of the generally accepted mechanism for the hydrolysis of amides (I), in which the

¹ Euler and Ölander, *Z. phys. Chem.*, 1927, **131**, 107; Taylor, *J.*, 1930, 2741; Rabinovitch and Winkler, *Canad. J. Res.*, 1942, **20**, B, 73.

² Krieble and Holst, *J. Amer. Chem. Soc.*, 1938, **60**, 2976.

³ Edward, Hutchison, and Meacock, *J.*, 1955, 2520.

rate-determining step is the attack of a water molecule on the conjugate acid (II) of the amide.⁴ (The possibility that the *N*- rather than *O*-protonated form of the amide is the intermediate⁵⁻⁷ is considered below.)



Amides are strong enough bases to be appreciably protonated in 3–6*M*-mineral acid.⁸ Below the concentration for maximum rate, the effect of increasing acid strength is chiefly to increase the concentration of the protonated intermediate; above the concentration for maximum rate, the effect is chiefly to decrease the concentration or activity of the water.²

The purpose of the present work was to see whether this hypothesis accounts quantitatively for the changes in rate of hydrolysis with acid concentration. We studied the hydrolysis of benzamide, *p*-methoxybenzamide, and *p*-nitrobenzamide, since it seemed probable that their ionization in acid could be determined by well-established spectrophotometric methods.^{9, 10}

EXPERIMENTAL

Benzamide, *p*-methoxybenzamide, *p*-nitrobenzoic acid, and *p*-nitrobenzamide were recrystallized from water or aqueous ethanol to constant m. p. Aqueous acid solutions were made by dilution of reagent-grade acids with distilled water. They were standardized by titration against standard sodium hydroxide solution, except for concentrations of sulphuric acid above 80% which were determined by measurements of density.

Ionization Constants of p-Methoxybenzamide and of Benzamide.—The ultraviolet absorption of *p*-methoxybenzamide dissolved in water and in 17 different concentrations of aqueous sulphuric acid was measured in a 1 cm. quartz cell in a Beckman DU spectrophotometer. A selection of absorption curves is shown in Fig. 1. Absorption at 253 μ is due mainly to the free amide (B) and at 280 μ to its conjugate acid (BH⁺). The difference ($\Delta\epsilon = \epsilon_{280} - \epsilon_{253}$) between the extinction coefficients at these two wavelengths varied with acid concentration ($C_{\text{H}_2\text{SO}_4}$) as follows:

Temp. 18° ± 3°.

$C_{\text{H}_2\text{SO}_4}$ (% w/w) ...	0.00	0.56	2.41	4.51	9.31	13.9
$\Delta\epsilon$	-12,200	-12,100	-11,400	-11,500	-9520	-8580
$C_{\text{H}_2\text{SO}_4}$ (% w/w) ...	20.7	25.0	28.9	33.0	37.5	41.4
$\Delta\epsilon$	-6340	-3910	-1370	+1410	3420	6630
$C_{\text{H}_2\text{SO}_4}$ (% w/w) ...	44.3	48.5	51.1	53.1	56.0	97.0
$\Delta\epsilon$	8240	8500	9200	10,600	11,000	9800

In Fig. 3 $\Delta\epsilon$ is plotted against the acidity function H_0 following the method used by Davis and Geissman¹⁰ for determining *pK* values. The values of the acidity function for different concentrations of acid were found by reference to a large scale plot of Hammett and Deyrup's results.^{11, 12} It is evident that in the complete conversion of the amide into its protonated form, $\Delta\epsilon$ changes by approximately +23,100. Hence, any purely solvent effect of the changing acid concentration on absorption⁹ being ignored, the extent of ionization at any acidity should be measured by:

$$[\text{BH}^+]/([\text{B}] + [\text{BH}^+]) = \Delta\epsilon/23,100$$

Since

$$[\text{B}]/[\text{BH}^+] = K/h_0$$

⁴ Hantzsch, *Ber.*, 1931, **64**, 661; Taylor and Baker, "Sidgwick's Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1945, p. 144; Pauling, "The Nature of the Chemical Bond," Cornell University, Press, Ithaca, 1948, p. 208.

⁵ Hammett, "Physical Organic Chemistry," McGraw Hill, New York, 1940, p. 365.

⁶ Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, London, 1953, p. 786.

⁷ Meloche and Laidler, *J. Amer. Chem. Soc.*, 1951, **73**, 1712.

⁸ Hall, *J. Amer. Chem. Soc.*, 1930, **52**, 5115, and references cited there.

⁹ Flexser, Hammett, and Dingwall, *ibid.*, 1935, **57**, 2103.

¹⁰ Davis and Geissman, *ibid.*, 1954, **76**, 3507.

¹¹ Hammett and Deyrup, *ibid.*, 1932, **54**, 2721.

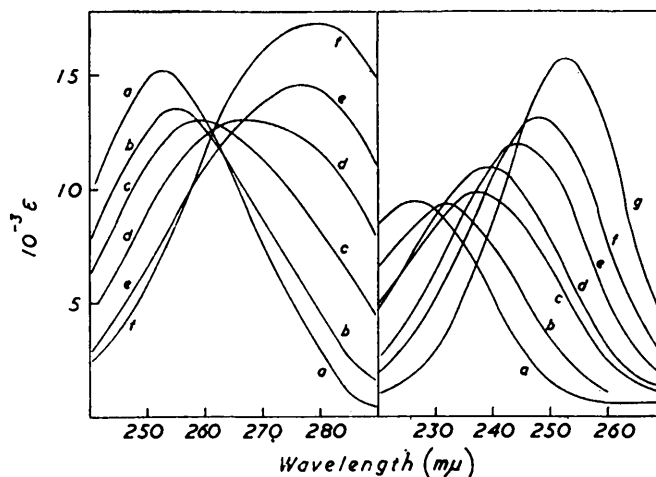
¹² Hammett and Paul, *ibid.*, 1934, **56**, 827.

where K is the ionization constant for the equilibrium $\text{BH}^+ \rightleftharpoons \text{B} + \text{H}^+$, and h_0 ($= -\text{antilog } H_0$) is Hammett's non-logarithmic acidity function,¹³ the equation may be written:

$$h_0/(K + h_0) = \Delta\epsilon/23,100$$

The theoretical curve corresponding to this equation, with $K = 40$ ($\text{p}K = -1.60$) is shown in Fig. 3, and is in reasonable agreement with the experimental values. The systematic deviations from the curve are probably to be attributed to solvent effects.^{9, 11}

FIGS. 1 & 2. Absorption spectra of *p*-methoxybenzamide (Fig. 1) and of benzamide (Fig. 2) in sulphuric acid.



	Curve	a	b	c	d	e	f	g
Fig. 1	Acid, %	0.0	13.9	25.0	33.0	41.4	97.0	—
Fig. 2	„	0.0	27.3	38.3	41.4	58.1	73.2	97.0

In the same way the absorption of benzamide dissolved in water and in 20 different concentrations of sulphuric acid was determined. A selection of curves is given in Fig. 2. Absorption at 225 $\text{m}\mu$ is evidently due mainly to the free amide, and at 240 $\text{m}\mu$ to its conjugate acid. The difference ($\Delta\epsilon = \epsilon_{240} - \epsilon_{225}$) between the extinction coefficients at these two wavelengths varied with acid concentration as follows:

Temp. $18^\circ \pm 3^\circ$.

$c_{\text{H}_2\text{SO}_4}$ (% w/w) ...	0.00	0.56	2.19	4.51	9.31	13.9	21.7	27.3
	-3920	-4050	-3920	-3860	-3340	-2920	-1830	-420
$c_{\text{H}_2\text{SO}_4}$ (% w/w)	33.0	38.3	41.4	47.3	53.1	55.3	58.1	59.9
	+1500	3130	4100	5510	6790	6950	6940	6970
$c_{\text{H}_2\text{SO}_4}$ (% w/w) ...	62.3	66.2	73.2	86.2	97.0			
	7900	7610	7550	8230	7290			

These results fit best the theoretical curve for $K = 71$ ($\text{p}K = -1.85$) (Fig. 3). The increase in ϵ and the shift of λ_{max} to longer wavelengths in acid concentrations above 62.3% (Fig. 2) are then to be ascribed wholly to the solvent effect of the sulphuric acid, which is known to be greatest in the range 60—85% acid.¹¹ Shifts of similar or greater magnitude have been noted with other compounds.^{10, 14}

The analysis of the spectral results by the original procedures of Flexser *et al.*⁹ rather than that of Davis and Geissman led to substantially the same $\text{p}K$ values.

The ionization constant of *p*-nitrobenzamide could not be determined by spectroscopic methods because the change in absorption on ionization was too small: in water, λ_{max} , 265 $\text{m}\mu$, $\log \epsilon_{\text{max}}$, 4.06; in 47.3% sulphuric acid, λ_{max} , 265.5 $\text{m}\mu$, $\log \epsilon_{\text{max}}$, 4.09; in 97% sulphuric acid, λ_{max} , 266.5 $\text{m}\mu$, $\log \epsilon_{\text{max}}$, 4.18.

¹³ Ref. 5, p. 271.

¹⁴ Brand, *J.*, 1950, 997.

Rate Measurements for the Hydrolysis of Benzamide and p-Methoxybenzamide.—These were carried out according to the procedure described previously,³ the reaction being followed by "formol" titration¹⁵ of the ammonium ion formed. In the excess of acid used the hydrolyses were of the first order with respect to the amide, as shown by the linearity of plots of $\log [\text{NH}_4^+]$ against time. The apparent first-order constants (k_e), found by multiplying the slope of these curves by 2.303, are shown in Fig. 4. The constants for benzamide in 1N- (6.8×10^{-4} hr.⁻¹)

FIG. 3. Variation of $\Delta\epsilon$ for benzamide (a) and *p*-methoxybenzamide (b) with acidity function (H_0) of aqueous sulphuric acid.

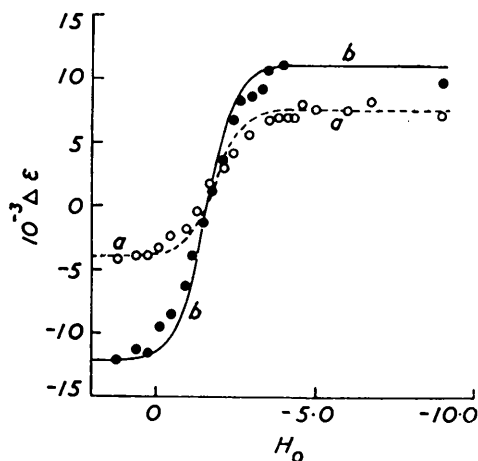
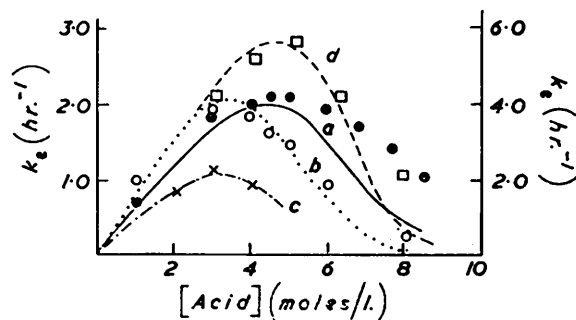


FIG. 4. Variation in first-order constants with acid concentration.



	Theor.	Exper.
Left-hand scale { Benzamide in HCl	a	●
Benzamide in H ₂ SO ₄	b	○
<i>p</i> -Methoxybenzamide in H ₂ SO ₄	c	×
Right-hand scale <i>p</i> -Nitrobenzamide in H ₂ SO ₄	d	□

and 4N-hydrochloric acid (2.00×10^{-3} hr.⁻¹) proved to be in good agreement with values (6.9×10^{-4} and 2.00×10^{-3} hr.⁻¹, respectively) calculated for this temperature by interpolation of Arrhenius plots of Rabinovitch and Winkler's results;¹ these investigators used a different method for estimating the ammonia formed.

Rate Measurements for the Hydrolysis of p-Nitrobenzamide.—The solubility of *p*-nitrobenzamide was too small in sulphuric or hydrochloric acid weaker than about 6M for the formol titration to be used. However, the reaction could be followed spectrophotometrically since the absorption spectra of *p*-nitrobenzamide and of *p*-nitrobenzoic acid are appreciably different in sodium carbonate solution (Fig. 5) although almost identical in aqueous acid. Aliquot parts (2 ml.) of a solution of *p*-nitrobenzamide (*ca.* 40 mg., accurately weighed) in aqueous sulphuric acid (100 ml.), kept at $25.00^\circ \pm 0.05^\circ$ in a shaded bottle in a thermostat, were withdrawn at intervals and diluted to 100 ml. with 0.202N-sodium carbonate (for runs in 3.08M-sulphuric acid)

¹⁵ Northrop, *J. Gen. Physiol.*, 1926, 9, 767.

or 0.298N-sodium carbonate (for runs in 4.15M-, 5.22M-, and 6.24M-sulphuric acid). The absorption was measured in the region 245—300 $m\mu$ inclusive. Hydrolysis could be followed only to about 40% completion, after which *p*-nitrobenzoic acid began to crystallize from the solution.

In a modification of this method the sodium carbonate solution was extracted with an equal volume of ethyl acetate before the spectroscopic examination; this had been shown to remove $91.5 \pm 0.1\%$ of the *p*-nitrobenzamide but none of the *p*-nitrobenzoate ion. The partition coefficient for *p*-nitrobenzamide was shown to be independent of concentration in the ranges studied. The effect of the extraction was to increase the total change in optical density during a run; readings were made in the range 285—300 $m\mu$, in which ethyl acetate is transparent. The results agreed well with those obtained by the first method. The first-order constants shown on Fig. 4 are the average of at least three values found by following the reaction at different wave-lengths according to the first method, and three by the second method.

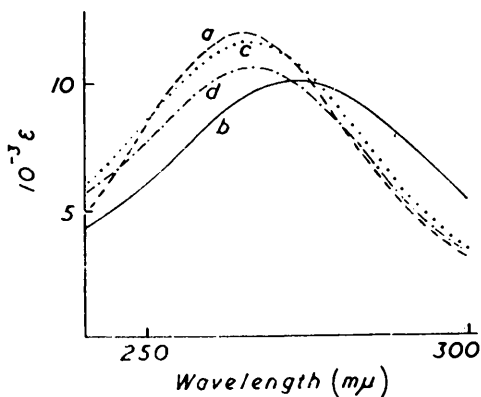
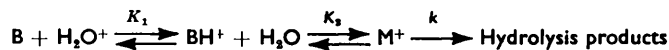


FIG. 5. Absorption spectra of *p*-nitrobenzoic acid in 2M-sulphuric acid (a) and in 0.089N-sodium carbonate (b); of *p*-nitrobenzamide in water (c) and in 0.089N-sodium carbonate (d).

DISCUSSION

While ionization frequently leads to large spectral changes, it does not invariably do so.⁹ In the present instance, we have found the ultraviolet absorption of *p*-nitrobenzamide to be almost the same in 97% sulphuric acid as in water, although in the former solvent it should be completely protonated, like the weaker base *p*-nitrobenzoic acid.¹⁶ However, although the ionization constant of the amide cannot be determined by absorption measurements, a rough estimate of it may be obtained from the application of Hammett's equation,¹⁷ $pK_0 - pK = \rho\sigma$, pK_0 in this case being the ionization constant of benzamide, pK the ionization constant of a *para*- or *meta*-substituted benzamide, ρ a constant characteristic of the ionization of benzamides, and σ a constant characteristic of the *meta*- or *para*-substituent. When Hammett's σ values of -0.268 for the *p*-methoxy- and $+0.778$ for the *p*-nitro-group are used, it follows that σ is $+0.933$, and hence for *p*-nitrobenzamide the pK is -2.58 and K is 380.

The amides and their conjugate acids are involved in the equilibria :



where K_1 and K_2 are equilibrium constants, M^+ is the transition complex for the hydrolysis, and k is a velocity constant. The Brønsted¹⁸ equation for the rate v of the hydrolysis is :

$$v = k[M^+] = kK_2[B][H_3O^+]f_{BH^+}/(f_M + K_1) \quad \dots \quad (1)$$

the quantities in brackets being concentrations and the f 's activity coefficients. The

¹⁶ Hantzsch, *Z. phys. Chem.*, 1908, **61**, 257; **65**, 41.

¹⁷ Ref. 5, p. 186.

¹⁸ Brønsted, *Z. phys. Chem.*, 1922, **102**, 169; ref. 6, p. 48.

term ($f_B/f_{H_3O^+}/f_M$) is approximately constant,¹⁹ and may be merged with the other constants into a second-order rate constant k_2 , giving :

$$v = k_2[B][H_3O^+]$$

However, the experimental first-order constants k_e , giving the rate of the reaction in different concentrations of excess acid, are based on the change in stoichiometric concentration of amide, ionized and un-ionized :

$$\begin{aligned} v &= k_e([B] + [BH^+]) \\ &= k_e[B](K + h_0)/K \end{aligned}$$

Hence

$$k_e = k_2K[H_3O^+]/(K + h_0) \dots \dots \dots (2)$$

For very weak bases such as esters, $K \gg h_0$ in the range of acid concentrations being considered here, and so equation (2) simplifies to :

$$k_e = k_2[H_3O^+]$$

This gives the linear dependence of experimental first-order constants on the concentration of oxonium ion¹⁹ which has been found for the hydrolysis of esters,²⁰ lactones,²¹ and alkyl phosphates.²² However, when $K \ll h_0$, equation (2) simplifies to :

$$k_e = k_2K[H_3O^+]/h_0$$

Since h_0 increases with concentration much more rapidly than $[H_3O^+]$ when mineral acid concentrations exceed about 2M,^{11, 12} k_e will decrease in high acid concentrations. {When

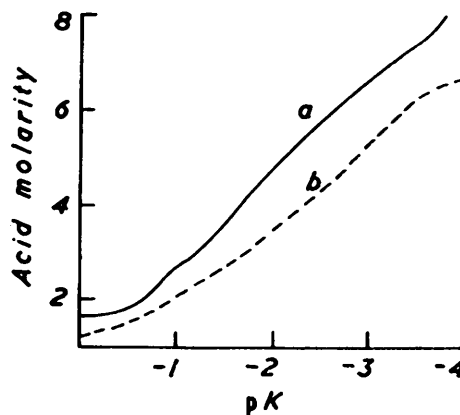


FIG. 6. Effect of basicity of substrate on the concentration of hydrochloric (a) or sulphuric acid (b) in which the first-order rate constant of hydrolysis is maximal.

$K \ll h_0$, ionization to BH^+ is substantially complete; the decrease in rate of hydrolysis can be regarded as due to the decreasing availability of water, since $[H_2O] = K_w[H_3O^+]/h_0$, where K_w is the equilibrium constant for the reaction $H_3O^+ \rightleftharpoons H_2O + H^+$.} At a certain acid concentration, which depends on the ionization constant K of the substrate, and on the variation with concentration of $[H_3O^+]$ and of h_0 for the acid concerned, k_e will reach a maximum. The variation of these concentrations for maximal rate with the pK ($= -\log K$) of the substrate, in either hydrochloric or sulphuric acid, is shown in Fig. 6. In calculating these curves, the concentration of oxonium ion in aqueous hydrochloric acid has been assumed to be identical with the stoichiometric acid concentration in the range studied;²³ the concentration in aqueous sulphuric acid has been estimated from Young's results²⁴ from Raman spectral studies. The acidity functions for different

¹⁹ Ref. 5, p. 276.

²⁰ Bell, Dowding, and Noble, *J.*, 1955, 3106.

²¹ Long, McDevit, and Dunkle, *J. Phys. Colloid Chem.*, 1951, 55, 829.

²² Barnard, Bunton, Llewellyn, Oldham, Silver, and Vernon, *Chem. and Ind.*, 1955, 760.

²³ Robinson and Stokes, "Electrolyte Solutions," Butterworths, London, 1955, pp. 362, 370 *et seq.*

²⁴ Young, *Rec. Chem. Progr.*, 1951, 12, 81; Dr. V. Gold, personal communication.

concentrations of hydrochloric^{12, 20, 25} and sulphuric acid^{11, 12} have been determined from large-scale plots of data in the literature.

In the Table the pK 's of various amides, as predicted (according to Fig. 6) from the acid concentrations for maximal rates, are compared with experimental values. The agreement is reasonably good. In the latest study of the ionization of acetamide,²⁶ two ionization constants, $pK_1 = +0.37$ and $pK_2 = -1.40$, have been reported. The latter value is in good agreement with the predicted value. It is possible that the first ionization constant refers to the formation of a cation (B_2H^+) made up of two molecules of amide and one proton. Stable salts of such cations are well known.²⁷ However, it is unlikely that such a cation is an important intermediate in the hydrolysis of acetamide, since it would necessitate the reaction rate's being of second order with respect to acetamide. The reaction appears to be of first order even in dilute acid solution,¹⁻³ in which the formation of B_2H^+ relative to BH^+ should be favoured.

Relation between pK 's of amides and the acid concentrations (c_M , in moles/l.) in which rates of hydrolysis are maximal at 25°.

Amide	Acid	c_M	pK	
			Predicted	Found
Formamide ²	HCl	6	-2.60	—
	H ₂ SO ₄	4.75	-2.75	—
Acetamide ³	HCl	3.25	-1.33	-0.5; ⁸ -0.04 ^a
	H ₂ SO ₄	2.5	-1.35	-1.40 ²⁶
Propionamide ²	HCl	3.20	-1.30	—
	H ₂ SO ₄	2.40	-1.30	—
Benzamide	HCl	4.5	-1.90	-1.85 (18° ± 3°)
	H ₂ SO ₄	3.5	-2.01	—
<i>p</i> -Methoxybenzamide	H ₂ SO ₄	3.0	-1.70	-1.60 (18° ± 3°)
	H ₂ SO ₄	4.5	-2.60	-2.58 (18° ± 3°)

^a Lemaire and Lucas, *J. Amer. Chem. Soc.*, 1951, **73**, 5198.

The pK values predicted for formamide and propionamide seem plausible, since they have the same qualitative relation to the pK of acetamide that the pK 's²⁸ of formic (3.75) and propionic acid (4.87) have to that of acetic acid (4.76) in water at 25°.

Equation (2) also covers the variation in rate with acid concentration reasonably well. This is shown in Fig. 4, in which the theoretical curves have been calculated by using the following arbitrary values of k_2 : benzamide, 6.4×10^{-2} ; *p*-methoxybenzamide, 3.8×10^{-2} ; *p*-nitrobenzamide, 11.5×10^{-2} hr.⁻¹ mole⁻¹; and assuming the pK values of the base to be the same at 25° as at 18° ± 3°. Agreement is reasonably satisfactory at lower acid concentrations, but at higher concentrations the experimental values tend to be higher than predicted. However, deviations in this direction have been noted in the hydrolysis of esters²⁰ and in many other acid-catalysed reactions.²⁹ They may perhaps be attributed to a systematic variation in the term ($f_{BH_3O^+}/f_{M^+}$) as the concentration of acid is increased.³⁰

(III) While the foregoing argument shows that the rates of hydrolysis in acid of different strengths may be explained by assuming as intermediate the *O*-protonated

²⁵ Braude, *J.*, 1948, 1971; Paul, *J. Amer. Chem. Soc.*, 1954, **76**, 3236.

²⁶ Goldfarb, Mele, and Gutstein, *ibid.*, 1955, **77**, 6194.

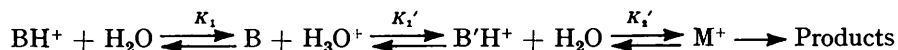
²⁷ Werner, *Ber.*, 1903, **38**, 154; Walden, *Bull. Acad. St. Pétersbourg*, 1911, 1055; *Chem. Zentr.*, 1912, **16**, I, 122; White, *J. Amer. Chem. Soc.*, 1955, **77**, 6215.

²⁸ Ref. 23, p. 496.

²⁹ Long and Purchase, *J. Amer. Chem. Soc.*, 1950, **72**, 3267; Paul, *ibid.*, 1952, **74**, 141; McIntyre and Long, *ibid.*, 1954, **56**, 3240; Bell and Brown, *J.*, 1954, 774; Gold and Hilton, *J.*, 1955, 843; Gold and Satchell, *J.*, 1955, 3622.

³⁰ Long and McIntyre, *J. Amer. Chem. Soc.*, 1954, **76**, 3243.

form (BH⁺; II) it does not exclude the *N*-protonated form (B'H⁺; III). The latter will be a very much less powerful base,⁴ *i.e.* $K_1' \gg K_1$ for the equilibria :



However, it will be correspondingly more reactive (*i.e.*, $K_2' \gg K_2$). It is obvious that the postulation of this mechanism leads to an equation differing from (1) only in having K_1' and K_2' in place of K_1 and K_2 . The two mechanisms are accordingly kinetically indistinguishable.³¹

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CHEMICAL LABORATORY, TRINITY COLLEGE, DUBLIN.

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³¹ Frost and Pearson, "Kinetics and Mechanism," Wiley, New York, 1953, p. 264.
