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The Kinetics and Mechanism of the Hydrolysis of o-Carboxyphthalimide[1]

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The kinetics of hydrolysis of phthalimide and of o-carboxyphthalimide have been investigated at 100°, the latter both in water and in deuterium oxide. The phthalimide hydrolysis exhibits normal acid- and base-catalyzed reactions. Below pH 1 and above pH 5, o-carboxyphthalimide also exhibits normal acid- and base-catalyzed reactions of comparable magnitude to those of phthalimide. However, in the region from pH 1 to 4, the o-carboxyphthalimide pH–rate profile exhibits a hump (not found in the phthalimide hydrolysis) which indicates the direct participation of the o-carboxy group and a mechanism which is dependent on two protonic equilibria, one of which occurs after the formation of the first tetrahedral intermediate. Three possible mechanisms are suggested and labeled pathways I, II, III: pathway I involves intramolecular *nucleophilic* catalysis by o-carboxylate ion, pathway II involves intramolecular *general basic* catalysis by o-carboxylate ion and pathway III involves intramolecular *general acid* catalysis by the protonated o-carboxyl group. The considerable diminution in the rate of hydrolysis in deuterium oxide (k_{obs}^H/k_{obs}^D = 2.6 at pH 3) can be analyzed satisfactorily only in terms of either pathway II or III. Thus steric constraint can transform an intramolecular nucleophilic catalysis (in the hydrolysis of phthalamic acid) into an intramolecular general basic or acidic catalysis (in this system) by prohibition of perpendicular attack at the carbonyl carbon atom.

Introduction

Three geometries of the transition state for the attack of a nucleophile at the carbonyl carbon of a carboxylic acid derivative have been postulated[3]: one in which the attacking nucleophile approaches the compound along a line perpendicular to the plane of the –C(O)R group leading to a maximum overlap of the bonding orbital of the nucleophile and the π-electron cloud of the carbonyl carbon atom (hereafter called perpendicular attack) and two others in which the nucleophile approaches the reaction center from the back side with respect either to the leaving group, or to the carbonyl group.

The postulate of attack from the back side with respect to the carbonyl group derived from consideration of the stereochemical effects observed in the reaction between α-N-carboxyamino acid anhydrides and substituted glycine dimethylamides.[4] When both R_2 and R_3 are bulky substituents, there is a considerable diminution in the rate (factors of 10^{-3} to *ca.* 10^{-7} as compared with $R_2 = R_3 = H$).
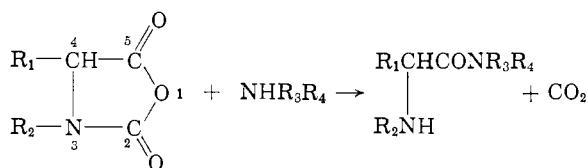

R_2 = H, Me, i-Pr; R_3 = H, Me, i-Pr; R_4 = –CH₂CONMe₂

This effect was interpreted in terms of approach of the nucleophile to C_5 along a path slightly inclined to the plane of the ring and passing over (or under) the nitrogen atom.

A similar explanation[5] has been invoked to account for the difference in reactivity between 6-oxabicyclo[3.2.1]octan-7-one (I) and 2-oxabicyclo-

[2.2.2]octan-3-one (II) as compared with 5- and 6-membered-ring lactones and their acyclic analogs.
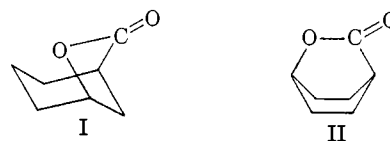
Compound	$k_2^{OH^-}$, l./mole-sec.[a]	Ref.[b]
I	0.36	5
II	.027	
γ-Butyrolactone	.83	d
δ-Valerolactone	18.3	
Ethyl propionate	8.81 × 10⁻³ᶜ	
Ethyl butyrate	6.59 × 10⁻³ᶜ	e

[a] In water at 25° unless otherwise specified. [b] Letters refer to references in footnote. [c] In *ca.* 56% w./w. acetone-water at 24.8°. [d] H. C. Brown, J. H. Brewster and H. Schecter, *ibid.*, **76**, 467 (1954); see also R. Huisgen and H. Ott, *Tetrahedron*, **6**, 253 (1959). [e] G. Davies and D. P. Evans, *J. Chem. Soc.*, 339 (1940).

The decrease in rate of II compared with δ-valerolactone was explained on the grounds that rearward attack is not possible in this case, whereas it is for I, which reacts at a rate comparable with other 5-membered-ring lactones.

Both sets of data may be interpreted in terms of the perpendicular model of the transition state. Severe steric repulsions are present in this model for the attack of the bulky amines on the highly-substituted N-carboxyanhydrides. The importance of perpendicular attack is brought out by the rate of reaction of II. This compound with backside attack completely blocked nevertheless hydrolyzes faster than its open chain analog. In terms of the perpendicular model the decrease in the rate of II as compared with δ-valerolactone can be reasonably interpreted in terms of steric repulsion toward the incoming nucleophile by the methylene hydrogens in close proximity to the carbonyl group, this effect being much smaller for δ-valerolactone. Further, the intramolecular step of phthalamic acid hydrolysis[6] offers convincing evidence for perpendicular attack. In this case

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(3) M. L. Bender, *Chem. Revs.*, **60**, 60 (1960).

(4) D. G. H. Ballard and C. H. Bamford, *J. Chem. Soc.*, 355 (1958).

(5) H. K. Hall, Jr., M. K. Brandt and R. M. Mason, *J. Am. Chem. Soc.*, **80**, 6420 (1958).

(6) M. L. Bender, *ibid.*, **79**, 1258 (1957); M. L. Bender, Y. L. Chow and F. Chloupek, *ibid.*, **80**, 5380 (1958).

the rearward attack of o-carboxylate ion on the protonated amide is impossible since both groups cannot lie in the plane of the benzene ring. π-Orbital attack, however, is easy as is shown in III, and the reaction is extremely facile.
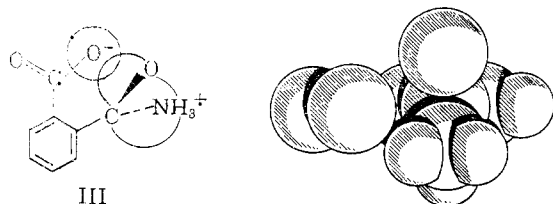
III

With a view to examining the hypothesis of perpendicular attack from a different standpoint, we have investigated the hydrolysis of o-carboxyphthalimide. In this molecule, the carbonyl groups are constrained to lie in the plane of the benzene ring; perpendicular approach by o-carboxylate ion therefore should not be possible and intramolecular catalysis, of extreme importance in the phthalamic acid hydrolysis, should not occur in the hydrolysis of o-carboxyphthalimide.

Experimental

Materials.—Benzene-1,2,3-tricarboxylic acid (Aldrich Chemical Co.) was recrystallized twice from water; m.p. 190° dec., resolidification, m.p. 196° (lit.[7] m.p. 190°; the acid is converted into the anhydride above the melting point). Benzene-1,2,3-tricarboxylic acid anhydride was prepared by heating the acid at 210° for 30 min.; m.p. 198-198.5° (lit.[7] 196°). o-Carboxyphthalimide was prepared in virtually quantitative yield from the reaction of benzene-1,2,3-tricarboxylic acid anhydride with urea; the reagents in stoichiometric proportions were heated at 250° for 30 minutes. The product was recrystallized three times from water; m.p. 246.5-247° (lit.[7] m.p. 247°). The same product was shown to result from the reaction of the anhydride with concentrated aqueous ammonia.[7] Phthalimide (Matheson Co.), twice recrystallized from ethanol with decolorizing charcoal, had m.p. 235°. A monoamide of benzene-1,2,3-tricarboxylic acid was made from the reaction of the anhydride (1.19 g.) with concentrated aqueous ammonia (3.3 ml.)[8] and subsequent treatment of the ammonium salt of the amic acid with cold 1 N nitric acid. The product was washed 6 times with cold 1 N nitric acid and 3 times with distilled water; m.p. 146-151°; this is possibly a mixture of isomers. Attempts to recrystallize the product always resulted in conversion to benzene-1,2,3-tricarboxylic acid, m.p. 190° dec. Supporting evidence that the compound is, in fact, an amic acid was obtained by heating it above its melting point to form the corresponding imide. It resolidified above 180° and finally melted at 244° (o-carboxyphthalimide, m.p. 247°). o-Phthalic acid (Eastman Kodak Co.) was recrystallized twice from water; m.p. 211-211.5°.

Acetate buffers (0.1 M in total acetate) were prepared from glacial acetic acid (Baker and Adamson, reagent grade) and anhydrous sodium acetate (Baker reagent grade). Phosphate buffers (Sörensen,[9] 1/15 M) were prepared from Mallinckrodt reagent grade potassium hydrogen phosphate and sodium dihydrogen phosphate. Glycine buffers (Sörensen,[11] 0.1 N HCl with 0.1 N glycine in 0.1 N NaCl) were prepared from Eastman Kodak Co., "ammonia-free" glycine. Hydrochloric acid solutions were prepared from reagent grade product (Baker and Adamson) and were standardized against borax (Baker reagent grade, twice recrystallized from water) which was prepared and stored as recommended by Vogel.[10] A stock solution of DCl in D$_2$O

(ca. 0.68 N) was made by absorbing hydrogen chloride (dried with H$_2$SO$_4$) in D$_2$O (General Dynamics Corp., >99.5%). Calculation of the dilution showed the D content of the stock solution to be 99% (very nearly). Other DCl solutions were made up from this by quantitative dilution with D$_2$O. An approximately 0.1 N deuterio-acetic acid solution was prepared by the addition of 0.58 ml. of glacial acetic acid to enough D$_2$O to make 100 ml. (D content of solution ~99%). Acetate buffers (0.1 M in total acetate) were made using this solution and anhydrous sodium acetate dried at 150° for 6 hours.

Kinetic Measurements.—The kinetics of hydrolysis of o-carboxyphthalimide (λ_{max} 301 mμ, ϵ 1570, in 0.01 N HCl) and phthalimide (λ_{max} 298.5 mμ, ϵ 2430, in 0.01 N HCl) at constant pH were followed with a Beckman DU spectrophotometer at 278 mμ (where suitable) and 301 mμ, and 298.5 mμ, respectively. The solutions were prepared by weighing the compound into a 50-ml. or 100-ml. volumetric flask, filling to the mark with the required buffer, and shaking mechanically until the compound was in solution. The initial concentrations of the compounds varied from 4.0-6.0 × 10^{-4} M for o-carboxyphthalimide and from 4.0-5.0 × 10^{-4} M for phthalimide. Pyrex ampoules were used for each sample and the reactions were carried out in a boiling-water-bath, the temperature of which was 99.8 ± 0.2° checked against an N.B.S. certificated thermometer. The reaction was quenched by vigorously shaking the ampoule in an ice-water slurry. At least two infinity samples were always measured. The first-order plots of log ($A_t - A_\infty$) vs. time were strictly linear to 80% completion of reaction, except in the region of poorly controlled pH (pH ca. 3; see Fig. 1, curve B). When measurements were made at two wave lengths (e.g., for o-carboxyphthalimide the appearance of benzene-1,2,3-tricarboxylic acid at 278 mμ and the disappearance of imide at 301 mμ) the rate constants agreed to better than 2%. The spectrum of an infinity sample was always taken (Beckman DK-2 spectrophotometer) and checked quantitatively against authentic samples of the product acids under the same conditions. These results agreed to ±5%; considering the small amount of material weighed out, this agreement is satisfactory.

The kinetics of hydrolysis of o-carboxyphthalimide were also followed in D$_2$O solutions (over a more restricted pD range) by exactly the same procedure as described for the water runs.

pH (pD) Control and Measurement.—Each run was carried out at constant pH; in acid solutions (pH ca. 0 to 3), the pH was controlled by excess of hydrochloric acid, and at higher values of pH, acetate and phosphate buffers were used. The pH was shown to be accurately constant throughout a run (±0.01 pH unit), except in the weakly controlling acid solutions at ca. pH 3, where the variation at complete reaction was 0.15 unit; in these solutions the pH was measured at each point of the reaction and the pH measured at the half-life (variation <0.1 pH unit) was that used in calculations. These runs showed slight curvature at 75% reaction (see Fig. 1, curve B). To obtain the pH at 100°, no correction was applied to the value as measured at room temperature for the acid solutions or phosphate buffers[11a] and 0.22 unit was added to the measured pH of the acetate buffers; this difference was calculated using K_{HOAc} at 100° = 11.1 × 10^{-6} (vide infra[11b]).

A conventional pH meter (Radiometer pH meter, model 4b, precision ±0.002 pH unit) was used to obtain the value of pD in the D$_2$O solutions. Lumry, et al.,[12a] have reported that the glass electrode yields a higher value of [D$_3$O$^+$] than actually exists in solution by 0.4 pH unit; i.e., pD = "meter pH" + 0.4. This result confirmed that obtained by Hart,[12b] but is at variance with an earlier report.[12c] The above relationship has therefore been checked in the region of major experimental significance.[13]

(7) C. Graebe and M. Leonhardt, Ann., 290, 228 (1896).

(8) E. Chapman and H. Stephen, Trans. Chem. Soc., 127, 1791 (1925).

(9) I. M. Kolthoff and C. Rosenblum, "Acid-Base Indicators," Macmillan Co., New York, N. Y., 1937, pp. 247-249.

(10) A. I. Vogel, "A Textbook of Quantitative Inorganic Analysis," 2nd ed., Longmans, Green and Co., London, 1951, pp. 231-232.
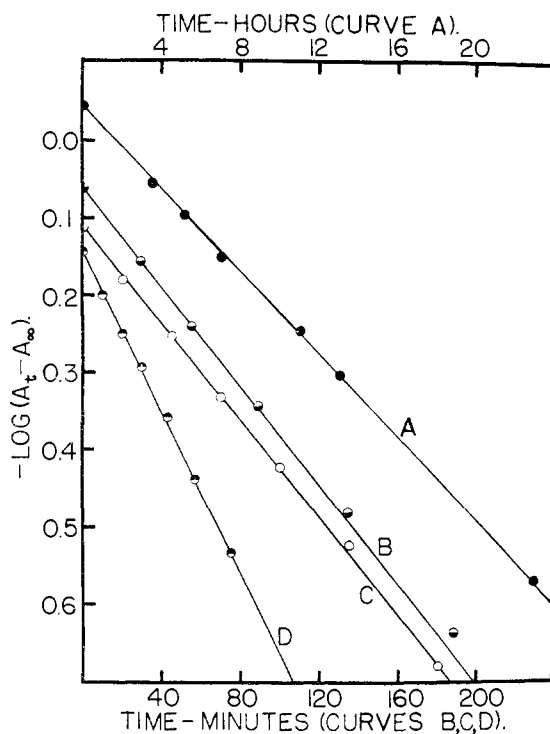
(11) (a) S. Stene, Rec. trav. chim., 49, 1133 (1930); (b) A. A. Noyes, J. Am. Chem. Soc., 30, 335 (1908).

(12) (a) R. Lumry, E. L. Smith and R. R. Glantz, ibid., 73, 4330 (1951); (b) R. G. Hart, Nat. Res. Council, Canada, CRE 423, June, 1949; (c) R. B. Fischer and R. A. Potter, A.E.C. document NODC-715, Sept. 12, 1945; C. A., 46, 2887 (1952).

(13) After this work was completed the results of more extensive studies (P. K. Glasoe and F. A. Long, J. Phys. Chem., 64, 188 (1960); K. Mikkelsen and S. O. Nielsen, ibid., 64, 632 (1960)) were published and the results are in excellent accord with those obtained in the present work.

Fig. 1.—Kinetics of hydrolysis of phthalimide and o-carboxyphthalimide at 100.0 $\pm$ 0.2°: A, phthalimide, pH 1.06; B, D, o-carboxyphthalimide in water, pH 2.96, 5.28, respectively; C, o-carboxyphthalimide in deuterium oxide, pD 0.17.

Roughly identical acetate buffers were made up accurately in H_2O and D_2O, by weight, using anhydrous sodium acetate and glacial acetic acid. The acetate buffer in D_2O contained 99.3% D. Using K_{HOAc} = 1.84 $\times$ 10^{-5} and K_{DOAc} = 0.55_5 $\times$ 10^{-5}, [14a,b,d] the calculated difference for the two (setting the activity coefficients ratio equal to unity) was $pD - pH = 0.54_0$. The pH of the buffer in water was 4.76_4, while the buffer in D_2O yielded a "pH" of 4.88_6, both at 25°. Thus, pD = "meter pH" + $(0.54_0 - 0.12_2)$ = "meter pH" + 0.41_8. It should be noted that if K_H/K_D = 3.21^{14c} (K_{DOAc} = 0.58 $\times$ 10^{-5}), as used by Lumry, then this correction becomes 0.39_3, in good agreement with his result. Similar experiments with HCl at pH ca. 2 and 3 yielded correction terms of 0.39_4 and 0.39_7 (D content of solutions in D_2O > 99.3%). Therefore, over the pH range investigated, pD = "meter pH" + 0.40 ($\pm 0.01_5$).

To obtain the pD of the solutions in D_2O at 100°, no correction was added to the pD as determined above for the DCl solutions. However, the acetate buffers necessitated measurements at 100°. These were made on a Beckman model H2 meter, employing electrodes designed for use at 100°. The response of the glass electrode was checked (using HCl, DCl solutions) and the relationship previously measured at room temperature appears to hold. The precision of the measurements was, however, poor (± 0.1 pH unit). The acetate buffers in H_2O and D_2O were also measured and within the limits of the poor precision, K_{HOAc}/K_{DOAc} does not alter with temperature; the pH (pD) of the buffers increased by $\sim$0.2 unit. In the absence of more reliable data, therefore, the pD as determined at 25° was corrected by 0.22 unit.[15]

(14) (a) S. Korman and V. K. LaMer, J. Am. Chem. Soc., 58, 1396 (1936); (b) V. K. LaMer and J. P. Chittum, ibid., 58, 1642 (1936); (c) V. K. LaMer, Chem. Revs., 19, 363 (1936); (d) C. K. Rule and V. K. LaMer, J. Am. Chem. Soc., 60, 1974 (1938).

(15) It is appreciated that this assumption is not strictly valid. However, calculations from available data and measurements herein suggest the error in the pD so estimated may be 0.1 unit on the high side. An error of this magnitude does not affect the conclusions drawn; cf. F. Brescia and V. K. LaMer, ibid., 62, 614, 617 (1940).
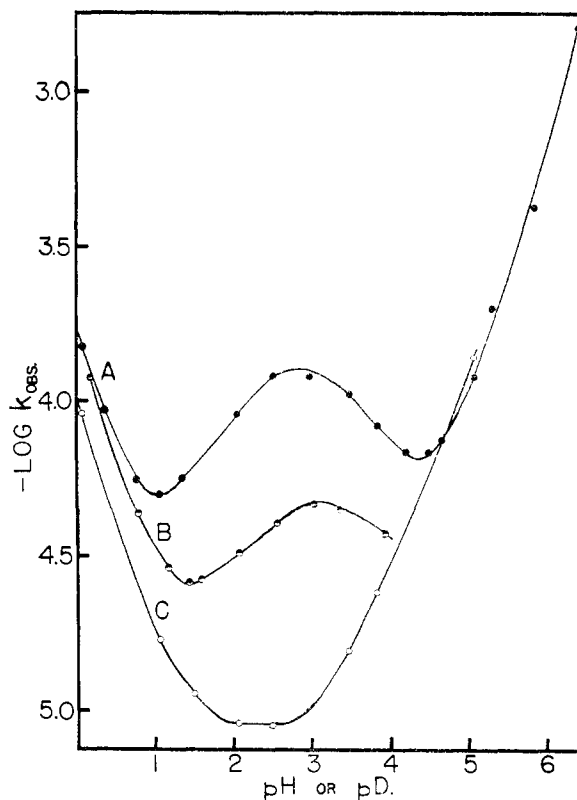

Fig. 2.—pH (pD)–rate profiles at 100°: A, o-carboxyphthalimide in water; B, o-carboxyphthalimide in deuterium oxide; C, phthalimide in water.

pK_a' of o-Carboxyphthalimide.—The pK_a' at 100° of the carboxyl group of o-carboxyphthalimide was needed for the treatment of the kinetic data. It was determined from pH measurements on accurately partially neutralized solutions of the imide (5.0 $\times$ 10^{-3} M in total imide) and by potentiometric titrations of solutions of the imide with standard sodium hydroxide solution. In the latter procedure, the pH read at half-theoretical neutralization was taken as the pK_a'. Both procedures assume 100% purity of the imide and measurements made on independently prepared and purified samples were consistent. The break in the titration curve could not be utilized owing to rapid hydrolysis above pH ca. 4.5, and variable amounts of hydrolysis occurred during the titration: pK_a' = 3.65 $\pm$ 0.15, based on 6 determinations at 100°. The pK_a' was determined similarly in D_2O by titration with sodium deuteroxide solution: pK_a' in D_2O = 4.05 $\pm$ 0.15.[16] It will be seen subsequently that analysis of the kinetic data required the pK_a' to be 3.90 in water and 4.30 in D_2O. The agreement can at best be considered fair, and indicates that the precision gives a false estimate of the accuracy of the determinations.

Results and Discussion

Typical plots of the experimental data used to calculate the first-order rate constants, k_{obs}, are shown in Fig. 1. A plot of log k_{obs} vs. pH for each of the compounds is given in Fig. 2. In the region below pH 1, both the phthalimide and o-carboxyphthalimide hydrolyses conform to reactions catalyzed by hydronium ion. Above pH 3, phthalimide reacts by a simple base-catalysed process, as does o-carboxyphthalimide above pH 5. In both hydronium ion- and hydroxide ion-catalyzed reac-

(16) For the effect of D_2O on K_a, see ref. 14; also P. Ballinger and F. A. Long, ibid., 81, 1050 (1959); 82, 795 (1960); E. Högfeldt and J. Bigeleisen, ibid., 82, 15 (1960); R. P. Bell, "The Proton in Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1959, p. 188.

tions, the absolute rates of hydrolysis of the two compounds are similar, indicating that the o-carboxy group exerts only a small substituent effect on both of these reactions. The catalytic constants for the two compounds are given in Table I. However, in the region between pH 1 and 4, the phthalimide and o-carboxyphthalimide hydrolyses differ markedly from one another in their pH–rate profiles. The phthalimide hydrolysis pH–rate profile is seen to exhibit just a continuation of hydronium ion- and hydroxide ion-catalyzed reactions in this region, falling to a flat minimum at about pH 2.5. The data support the existence of a slight "water" reaction in the region pH 2 to 2.5, given by k_0 (see Table I) in the equation[17] but most of the reaction is due to acid- or base-catalyzed processes. On the other hand, the

$$k_{obs} = k_0 + k_{H^+}[H^+] + k_{OH^-} \cdot K_w/[H^+]$$

pH–rate profile of the o-carboxyphthalimide hydrolysis exhibits a hump (sometimes called a bell-shaped curve) in the region between pH 1 and 4, with a maximum at about pH 2.9. This phenomenon is characteristic of a reaction which depends on two ionization equilibria.[18]

TABLE I

RATE CONSTANTS FOR ACID- AND BASE-CATALYZED REACTIONS AT 100°

	Phthalimide	o-Carboxyphthalimide
$10^5 k_{H^+}$	9.83[a]	17.0[a]
$10^3 k_{OH^-}$	4.08[a]	1.18[a]
$10^6 k_{H_2O}$	8.98[b]	....

[a] Units of l./mole sec.   [b] Units of sec.$^{-1}$.

In order to investigate the possibility that the hump might be related to the ionization constants of the amic acid, the initial product of hydrolysis, the amic acid prepared from the imide was hydrolyzed at 50° and pH 2.5. The reaction was complete in about 75 minutes, much faster than the hydrolysis of the imide. Further, the spectrum of the amic acid resembles that of the final product, benzene-1,2,3-tricarboxylic acid, which has no maximum at 301 mμ. The conversion of the amic acid to the final product, therefore, must be a fast step at 100° and the kinetics of hydrolysis must correspond to the conversion of o-carboxyphthalimide to the amic acid, B (B$^-$). Qualitatively, the hump in the pH–rate profile is quite different from that found in the phthalamic acid hydrolysis,[6] although the reactants are in some sense similar.

The fact that an additional hydrolytic pathway occurs in the o-carboxyphthalimide hydrolysis, but not in the phthalimide hydrolysis, points to the implication of the o-carboxy group in the former reaction. This conclusion suggests an error in the original hypothesis concerning the impossibility of direct interaction of the o-carboxy group and the sterically constrained imide carbonyl atom. However, there are three possibilities that can explain

(17) R. P. Bell, "Acid–Base Catalysis," Oxford University Press, London, 1941, p. 7.

(18) Cf. H. Morawetz and I. Oreskes, J. Am. Chem. Soc., 80, 2591 (1958); R. B. Martin, S. Lowey, E. L. Elson and J. T. Edsall, ibid., 81, 5089 (1959); H. Hansson, Acta Chem. Scand., 13, 1309 (1959); L. A. Cohen and W. M. Jones, J. Am. Chem. Soc., 82, 1907 (1960).

the pH–rate profile, each involving the o-carboxylate ion. One mechanism postulates intramolecular nucleophilic catalysis by o-carboxylate ion (pathway I), which was originally predicted as unlikely on steric grounds. The other mechanisms involve intramolecular general basic catalysis by o-carboxylate ion (pathway II) and intramolecular general acid catalysis by the protonated o-carboxyl group (pathway III). These are not prohibited by the steric constraint of the imide ring.

The first of these possibilities may be formulated

Pathway I
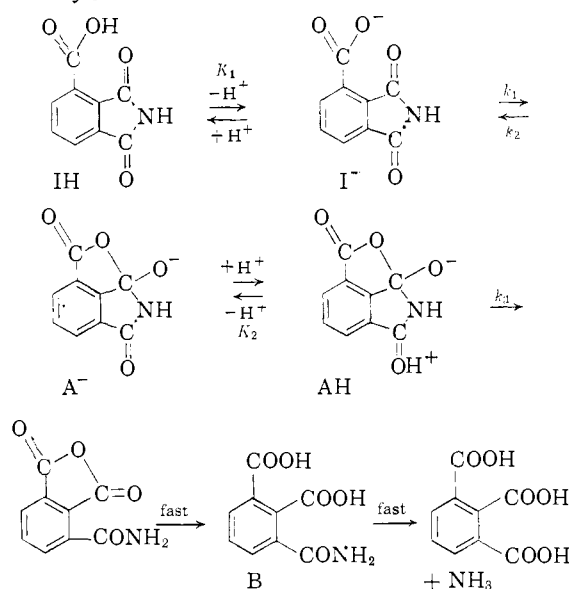
From the experimental data

rate $= k_{obs}([IH] + [I^-]) = k_{obs}[IH](1 + K_1/[H^+])$ (1)

From the above scheme

$$d[B]/dt = k_3[AH] \quad (2)$$

Applying the steady-state approximation that

$$d([AH] + [A^-])/dt = 0 \quad (3)$$

one can derive the expression

$$d[B]/dt = \frac{k_1 k_3 K_1[IH]}{K_2(k_2 + k_3[H^+]/K_2)} \quad (4)$$

From eq. 1 and 4

$$k_{obs} = \frac{k_1 k_3 K_1}{K_2(k_2 + k_3[H^+]/K_2)(1 + K_1/[H^+])} \quad (5)$$

From the dependence of eq. (5) on [H$^+$], it is clear that this expression (qualitatively at least) accounts for the hump. However, the k_1 step, the formation of the anhydride-like intermediate, A$^-$, appears unlikely owing to the constraint of the fused "imide" ring.

Another mechanism which also conforms to the pH-rate profile in the region of pH 1 to 4, involves intramolecular general basic catalysis. The essential requirement of this mechanism is that the general base carboxylate ion abstracts a proton from the incoming water molecule as it forms the tetrahedral intermediate, C$^-$, in a slow step.[19]

(19) If water merely adds in an equilibrium step, it readily can be shown that $k_{obs} = k_2 K_1/K_2 K_3 (1 + K_1[H^+])$, where $K_3 = k_2/k_1$; this mechanism does not satisfy the requirements of the rate profile.
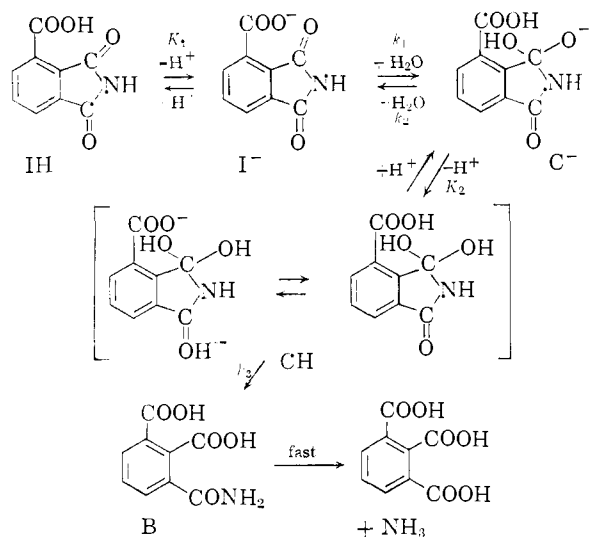
Pathway II

C⁻ then *adds* a proton to give the zwitterionic form of the neutral species CH as the intermediate which decomposes to form the product. Using arguments similar to those already presented, it can be shown for pathway II that

$$k_{obs} = \frac{k_1 k_3 K_1}{K_2(k_2 + k_3[H^+]/K_2)(1 + K_1/[H^+])} \quad (6)$$

which has exactly the same form as eq. 5. Differentiation of k_{obs} with respect to $[H^+]$, followed by setting the derivative to zero, leads to expression (7) for $[H^+]$ at the maximum of the hump

$$[H^+]_{max} = (k_2 K_1 K_2/k_3)^{1/2} \quad (7)$$

Equation 6 may be rearranged to give

$$1/k_{obs} = 1/k_1\{1 + k_2 K_2/k_3 K_1 + ([H^+]/K_1 + k_2 K_2/k_3[H^+])\} \quad (8)$$

A plot of $1/k_{obs}$ vs. $([H^+]/K_1 + k_2 k_2/k_3[H^+])$ should therefore give a straight line of slope $1/k_1$ and intercept $1/k_1(1 + k_2 K_2/k_3 K_1)$. Thus, using K_1 and eq. 6 and 7, it is possible to determine the rate constant, k_1.

Pathway III is an alternative scheme involving intramolecular general acid catalysis. In this formulation, the k_1' step involves addition of water to the zwitterionic form of the neutral species IH in a slow step to form the intermediate CH, which then *loses* a proton to give C⁻, the intermediate which decomposes to form the product.

A treatment similar to that already given for pathways I and II leads to eq. 9 for pathway III

$$k_{obs} = \frac{k_1' k_3'}{(k_2'[H^+]/K_2 + k_3')(1 + K_1/[H^+])} \quad (9)$$

where the primed rate constants are numbered to correspond to the unprimed constants in eq. 8. Also, a plot of $1/k_{obs}$ vs. $(K_1/[H^+] + k_2'[H^+]/k_3'K_2)$ should be linear, with slope $1/k_1'$ and intercept $1/k_1'(1 + k_2'K_1/k_3'K_2)$. Thus it is again possible to determine the value of k_1'.

The series of runs in D₂O was made in an attempt to distinguish between pathway I (intramolecular nucleophilic catalysis) and pathways II and III (intramolecular general base or acid catalysis), since D₂O might be expected to produce a significant effect on $k_1(k_1')$, if the reaction goes *via*

Pathway III
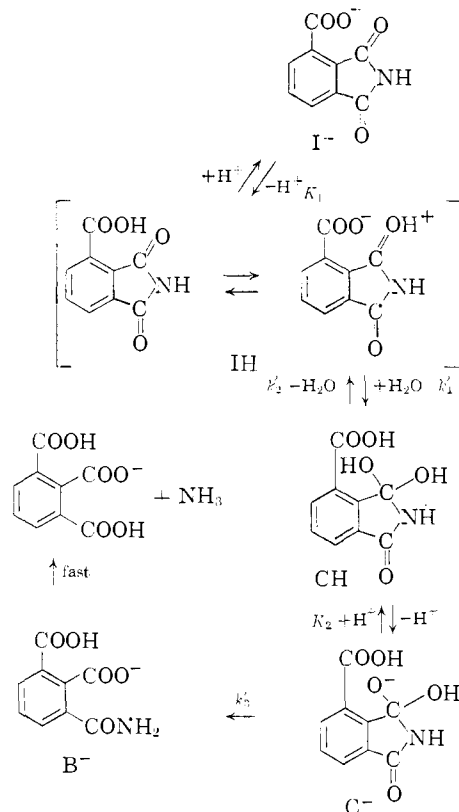
general base or acid catalysis (pathway II or III), while the value of k_1 should be scarcely altered if nucleophilic catalysis (pathway I) is favored.

Figure 3 shows the plots based on eq. 6 and 9 for the runs in water and deuterium oxide. Table II
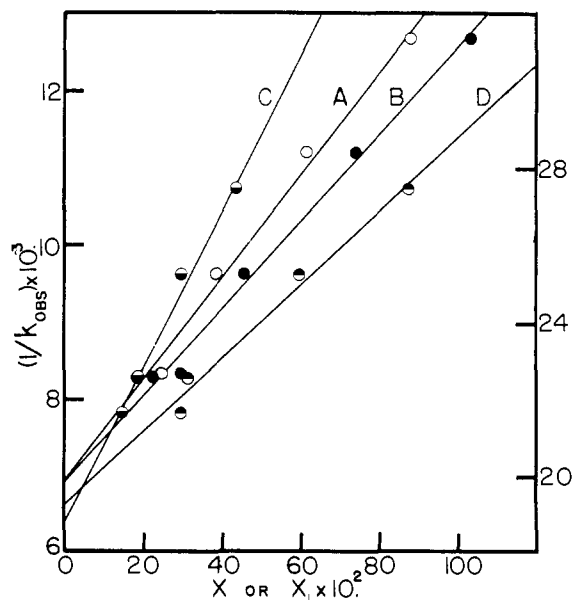

Fig. 3.—Evaluation of rate constants k_1 and k_1' in water and in deuterium oxide for the hydrolysis of o-carboxyphthalimide: A, B (water); C, D (deuterium oxide), right-hand scale. For B, D (pathway II), $X = [H^+]/K_1 + k_2 K_2/k_3[H^+]$; for A, C (pathway III), $X_1 = K_1/[H^+] + k_2'[H^+]/k_3'K_2$.

records the data used (pK_1 and pH_{max}) and also the values of the constants obtained from the plots. In making the plots, k_{obs} was corrected for the contribution from the acid- or base-catalyzed reaction[20] and the values of pH_{max} and pK_1 were adjusted to give the best least-squares plot, such that k_1 obtained from the slope was consistent with that obtained from the intercept (pathway I or II); the same values then were used to obtain the values of k_1' from the least-squares plot based on eq. 9. In addition to the ratios, $k_1^H/k_1^D = 1.69$ and $(k_1')_H/(k_1')_D = 2.87$, it is possible to derive further information from the data in Table II by assuming a reasonable value for K_2. If K_2 varies between 10^{-2} and 10^{-5}, K_2^H/K_2^D may be expected to vary from about 2.5 to 3.5.[14,16] A value of 3 for this ratio is used in the following calculations. In de-

TABLE II

EFFECT OF DEUTERIUM OXIDE ON SOME PARAMETERS OF EQ. 6 AND 9

	Pathway	In H_2O	In D_2O
pH_{max}		2.86	3.15
pK_1		3.90	4.30
k_1 (slope)[a]	I or II	1.77×10^{-2}	1.04×10^{-2}
k_1 (intercept)	I or II	1.75×10^{-2}	1.04×10^{-2}
k_1' (slope)	III	1.51×10^{-4}	4.95×10^{-5}
k_1' (intercept)	III	1.45×10^{-4}	5.34×10^{-5}
$k_2 K_2/k_3$	I or II	1.51×10^{-2}	1.00×10^{-2}
$k_3' K_2/k_2'$	III	1.51×10^{-2}	1.00×10^{-2}

[a] Units of rate constants are sec.$^{-1}$.

termining the values of the other ratios, equilibria involved must be considered. While $k_1^H/k_1^D = 1.69$ is not dependent on any implicit equilibria involving I^-, the k_1' step of pathway III includes
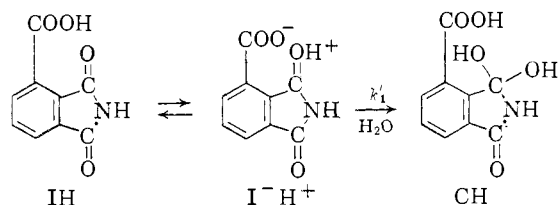
two dissociation constants. As an example of the type of calculation involved, consider the k_1' step. Now it may be shown readily if $I^- H^+$ is the only reactive species, that

$$k_1' = k_{I^-H^+}' \cdot K_{IH}/K_{I^-H^+}$$

where $k_{I^-H^+}'$ is the separate rate constant for the reaction of I^-H^+, and K_{IH}, $K_{I^-H^+}$ are the dissociation constants of the species IH and I^-H^+, respectively. A reasonable value for K_{IH}/K_{ID} is about 3, and a reasonable value for $K_{I^-H^+}/$

$K_{I^-D^+}$ is about $2^{14.16}$ (IH is a normal carboxylic acid, while I^-H^+ is in the nature of a protonated amide). Thus

$$(k_{I^-H^+}')_H/(k_{I^-H^+}')_D = 2.87 \times 2/3 = 1.9^{23}$$

Using similar treatments for other equilibria, with reasonable ratios of the dissociation constants in H_2O and D_2O, the ratios in Table III have been derived. The structure of the assumed reactive species is also presented with the relevant ratio.
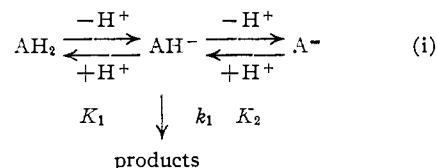
It is seen from Table III that the isotope effects (in favor of H) on the $k_1(k_1')$ step may be estimated to vary from about 1.7 to 2.9. Similarly, the effects (in favor of H) on the $k_3'(k_3)$ step may be estimated to vary from about 0.7 to 3.0.

From the very careful measurements of Robertson and Laughton[24] on the effect of deuterium oxide on the solvolytic constants of extensive series of esters and organic halides, a k_H/k_D ratio of 1.7 is clearly too large to be attributed to a solvent effect. Further, since the difference in zero point energies is the main factor causing isotopic discrimination,[25] one should expect to find a reduced effect at 100°. This is borne out by the available experimental data.[24,26] It follows that pathway I can be safely rejected, for had the reaction occurred via this pathway, the values of both k_1 and k_3 should have been little affected in going from water to deuterium oxide.[27-30]

This leaves pathways II and III open to consideration. The effect of deuterium oxide on the $k_1(k_1')$ step and $k_3(k_3')$ step does not allow an unequivocal assessment of the more likely scheme, partly since the estimated effects may be accommodated by either one, and partly on account of the approximate nature of the estimations. However, the original premise of this work is borne out, namely, that steric constraint can in fact transform an intramolecular nucleophilic catalysis into an intramolecular general basic or acidic catalysis by prohibition of perpendicular attack at the carbonyl carbon atom.

Bell-shaped Curves.—The dependence of the reaction on the equilibrium constant K_2, in addition to dependence on o-carboxylate ion (as part of a zwitterionic system), warrants a more general discussion of bell-shaped rate-profiles.

The "simple" bell-shaped curve arises from the following kinetic scheme where AH^- is the only

(20) In the absence of a value for the ionic product of deuterium oxide at 100°, the correction for the base-catalyzed reaction in this solvent was made by assuming that $k_{OD^-} \approx k_{OH^-}$ and that the ionic product of deuterium oxide at 100° is 8.7×10^{-14}. This value assumes a constant ratio for the ionic products of the two solvents and was calculated from the known ionic products of water at 25° and 100°[21] and the ionic product of deuterium oxide at 25°.[22] The corrections were of the order of 3%, so that the exact validity of the above assumptions is not critical.

(21) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed., Reinhold Publishing Corp., New York, N. Y., 1958, p. 645.

(22) R. W. Kingerly and V. K. LaMer, *J. Am. Chem. Soc.*, **63**, 3256 (1941).

(23) In the following treatment, the relevant ratios will be starred to indicate correction for equilibrium processes: thus $k_{I^-H^+}' = k_1'^*$.

(24) P. M. Laughton and R. E. Robertson, *Can. J. Chem.*, **34**, 1714 (1956); **35**, 1319 (1957); **37**, 1491 (1959).

(25) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p. 187.

(26) P. E. Yankwich and A. E. Veazie, *J. Am. Chem. Soc.*, **80**, 1835 (1958).
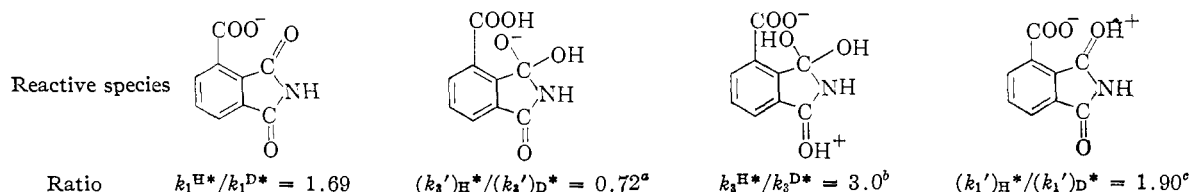
(27) A. R. Butler and V. Gold, *Proc. Chem. Soc.*, 15 (1960).

(28) Y. Pocker, *ibid.*, 17 (1960).

(29) M. L. Bender and M. C. Neveu, unpublished observations.

(30) F. A. Long and J. Bigeleisen, *Trans. Faraday Soc.*, **55**, 2077 (1959).

TABLE III

RATIOS OF "SPECIES" RATE CONSTANTS IN H_2O AND D_2O

Reactive species

| Ratio | $k_1^{H*}/k_1^{D*} = 1.69$ | $(k_3')_H*/(k_3')_D* = 0.72^a$ | $k_3^{H*}/k_3^{D*} = 3.0^b$ | $(k_1')_H*/(k_1')_D* = 1.90^c$ |

^{a} $(k_2')_H*/(k_2')_D*$ was taken as 1.90, since there is no implicit equilibrium in the back reaction; the ratio so obtained was further corrected by 3/4 for equilibria involving C^-, the ratio of the dissociation constants in H_2O and D_2O for the reactive species being taken as 4. The equations summarize the calculations:

$$(k_2')_H/(k_2')_D \times (k_3')_D/(k_3')_H \times K_2^D/K_2^H = 0.66 \text{ (from Table III)}$$

$$1.90 \times [(k_3')_D*/(k_3')_H* \times 3/4] \times 1/3 = 0.66; \text{ whence } (k_3')_H*/(k_3')_D* = 0.72$$

^{b} k_2^H/k_2^D was taken as 2.25 after correcting for equilibria involving C^- (1.69 × 4/3). The ratio so obtained (4.5) was further corrected by 2/3 for equilibria involving CH; these effects tend to cancel. The equations summarize the calculations

$$k_2^H/k_2^D \times K_2^H/K_2^D \times k_3^D/k_3^H = 1.51 \text{ (from Table III)}$$

$$(4/3 \times 1.69) \times 3 \times (k_3^{D*}/k_3^{H*} \times 2/3) = 1.51, \text{ whence } k_1^{H*}/k_3^{D*} = 3.0$$

^{c} An alternative formulation of pathway III is possible, namely
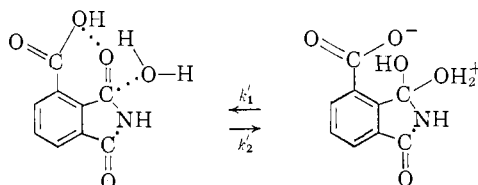
for which $(k_1')_H*/(k_1')_D* = 2.87$, since no equilibria corrections are here involved.

species which reacts to form products and K_1, K_2 are the successive ionization constants of AH_2.[31] It may be shown readily that the observed first-order rate constant k_{obs} is given by

$$k_{obs} = \frac{k_1 K_1 (H^+)}{(H^+)^2 + K_1(H^+) + K_1 K_2} \quad (10)$$
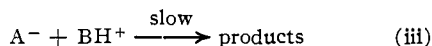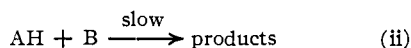
Other conclusions are

(a) pH for maximum observed rate $= \frac{1}{2}(pK_1 + pK_2)$

$$\quad (11)$$

and

(b) $(k_{obs})_{max} = \dfrac{k_1}{1 + 2\sqrt{K_2/K_1}}$ (12)[32]

From eq. 12, k_{obs} will be within 1% of k_1 if $pK_2 - pK_1 = 4.6$.

In like manner, the following kinetic schemes lead to bell-shaped curves

$$AH + B \xrightarrow{slow} products \quad (ii)$$

$$A^- + BH^+ \xrightarrow{slow} products \quad (iii)$$

where AH is a general acid and B is a general base. It should be noted that schemes ii and iii are kinetically indistinguishable.[33] Nor is there any restriction on whether AH and B are different molecules or are groups on the same molecule involved in an intramolecular reaction. That is, if a molecule AH . . . BH undergoes reaction only in the half-ionized form, A^- . . . BH or AH . . . B^-, it is im-

possible kinetically to distinguish which is the reactive species.[33] This type of rate-profile is exemplified by the hydrolysis of o-carboxyphenyl hydrogen succinate.[34]

However, in the event that the pK's of AH and BH are widely separated, chemical intuition may give an *indication* of which species is reactive.

A general conclusion (but one of more particular importance in enzyme systems where the pK's may not be widely separated) which follows directly, appears too frequently to have been overlooked. This is, that if one has a reaction proceeding in two directions (with or without the formation of an intermediate) and if the forward reaction involves a general acid–base catalysis, then the principle of microscopic reversibility requires that the reverse reaction be catalyzed by the *conjugate* general base–acid system. As an example consider the hydration of fumaric acid catalyzed by fumarase.[35] The generalized reaction may be written

$$E + F \rightleftarrows EF \rightleftarrows EM \rightleftarrows E + M^{36}$$
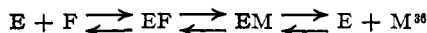
In the forward reaction of the step EF $\rightleftarrows$ EM, a general base B' abstracts a proton from the water molecule attacking carbon atom 2, as a general acid BH^+ donates a proton to carbon atom 3. In the reverse of the step EF $\rightleftarrows$ EM, the conjugate species $B'H^+$ and B perform the catalysis by donating a proton to the hydroxyl group on carbon atom 2 and removing a proton from carbon atom 3.

(31) For a good example of such a rate-profile, see C. A. Bunton, D. R. Llewellyn, K. G. Oldham and C. A. Vernon, *J. Chem. Soc.*, 3574 (1958).

(32) *Cf.* R. A. Alberty and V. Massey, *Biochem. Biophys. Acta*, 13, 347 (1954).

(33) For an excellent discussion of the relevant arguments, see M. Dixon and E. C. Webb, "The Enzymes," Academic Press, Inc., N. Y., 1958, p. 123 *et seq.*
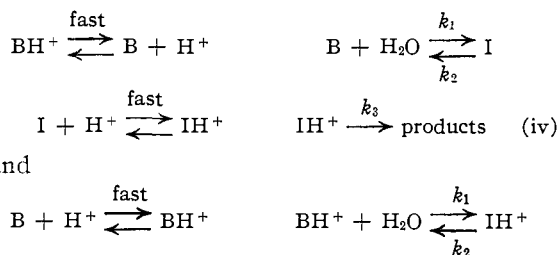
(34) H. Morawetz and I. Oreskes, *J. Am. Chem. Soc.*, 80, 2591 (1958).

(35) R. A. Alberty in "Molecular Structure and Biological Specificity," pub. No. 2, American Institute of Biological Sciences, 1957, p. 155, and references therein; O. Gawron and T. P. Fondy, *J. Am. Chem. Soc.*, 81, 6333 (1959).

(36) E. enzyme (fumarase); F, fumarate; M, malate.

In addition to the families of reactions exemplified by eq. i, ii and iii, pathways II and III of the o-carboxyphthalimide hydrolysis are but special cases of two more families of reactions not previously recognized as leading to bell-shaped rate profiles.[37]

These can be written schematically

$$BH^+ \underset{}{\overset{fast}{\rightleftarrows}} B + H^+ \qquad B + H_2O \underset{k_2}{\overset{k_1}{\rightleftarrows}} I$$

$$I + H^+ \underset{}{\overset{fast}{\rightleftarrows}} IH^+ \qquad IH^+ \overset{k_3}{\longrightarrow} products \qquad (iv)$$

and

$$B + H^+ \underset{}{\overset{fast}{\rightleftarrows}} BH^+ \qquad BH^+ + H_2O \underset{k_2}{\overset{k_1}{\rightleftarrows}} IH^+$$

(37) In reported work[38] on the hydrolysis of 2-methyl-Δ^2-thiazoline (q.v.), no account was taken of the second protonic equilibrium of scheme v, so that the rate constants k_3, k_5 (in the authors' terminology) contain this equilibrium constant. This interpretation invalidates some of the conclusions drawn. With this exception, however, the mechanism postulated is that of scheme v.

$$IH^+ \underset{}{\overset{fast}{\rightleftarrows}} I + H^+ \qquad I \overset{k_3}{\longrightarrow} products \qquad (v)$$

Again, it should be noted that the schemes iv and v are "conjugates" of each other.

The prevalent bell-shaped curves in the pH–rate profiles of enzymatic processes have often been interpreted in terms of eq. i. It is a consequence of the above discussion that such curves can be interpreted in terms of any of the eq. i through v. It should be particularly noted that as yet no enzymatic process has been treated according to eq. iv or v. Of course, in the identification of such pH–rate profiles with specific groups on the enzyme, the admonitions previously given for the application of apparent pKa's should be kept in mind.[39]

Acknowledgments.—The authors wish to acknowledge very valuable discussion with Dr. G. A. Hamilton and Dr. K. A. Connors.

(38) R. B. Martin, S. Lowey, E. L. Elson and J. T. Edsall, J. Am. Chem. Soc., 81, 5089 (1959).

(39) T. C. Bruice and G. L. Schmir, ibid., 81, 4552 (1959).

Acid-catalyzed Decomposition of Ferrocenylphenylcarbinyl Azide

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The decomposition of ferrocenylphenylcarbinyl azide has been studied in various acidic media. In concentrated sulfuric acid–chloroform solution the products obtained are nitrogen, ferrocenecarboxaldehyde, aniline, the two diastereoisomeric forms of 1,2-diferrocenyl-1,2-diphenylethane, benzoylferrocene, ferrocenylphenylcarbinol, resinous material, and an unidentified iron salt in solution. When the decomposition is carried out in a less strongly acidic medium, namely, sulfuric acid–acetic acid, the amount of ferrocenecarboxaldehyde produced is lowered significantly, and an appreciable quantity of benzylferrocene is formed in addition to the other products cited above. On the basis of the products obtained, it is thought that the Schmidt rearrangement reaction takes place only with a doubly protonated conjugate acid of ferrocenylphenylcarbinyl azide. Decomposition of the azide in sulfuric acid–chloroform solution containing a variety of additives gives rise to products which appear to be formed by radical reactions. For example, decomposition of the azide in the presence of benzaldehyde gives N-benzoylferrocenylphenylcarbinylamine and benzylferrocene in addition to the other products noted previously. Also, decomposition of ferrocenylphenylcarbinyl azide in the presence of benzaldehyde and benzhydryl azide affords 1,1,2,2-tetraphenylethane and diphenylmethane in addition to the usual products.

Benzhydryl azide is known to undergo sulfuric acid-catalyzed decomposition to give nitrogen and the conjugate acid of benzalaniline. A substituted benzhydryl azide gives nitrogen and a mixture of the conjugate acids of two isomeric Schiff bases, the predominant isomer being the one predicted on the basis of analogy with other similar rearrangement reactions.[1] Inasmuch as ferrocene is more reactive than benzene in electrophilic substitution reactions,[2] and since the ferrocenyl group has been reported to undergo exclusive migration in the pinacol–pinacolone rearrangement of 1,2-diferrocenyl-1,2-diphenylethylene glycol, catalyzed by a trace of hydrogen chloride,[3] it was anticipated that the ferrocenyl group would undergo preferential migration in the sulfuric acid-catalyzed rearrangement of ferrocenylphenylcarbinyl azide. Actually, we have found that a

complex reaction occurs and that, insofar as the Schmidt rearrangement takes place, there is an apparently exclusive migration of the phenyl group.

Ferrocenylphenylcarbinyl azide (I) was prepared by treatment of ferrocenylphenylcarbinol with hydrogen azide in benzene solution in the presence of trichloroacetic acid as catalyst. After isolation by chromatography on alumina and crystallization from Skelly B solvent, the azide had a melting point of 49–50°. Reaction of the azide with concentrated sulfuric acid in chloroform solution afforded nitrogen and a complex mixture of organic products. After hydrolysis of the mixture there was obtained a deep yellow chloroform phase and a deep blue aqueous phase. The following products were isolated from the organic layer by chromatography on an alumina column: the two diastereoisomeric forms of 1,2-diferrocenyl-1,2-diphenylethane (II)[4] and ferrocenecarboxaldehyde. The material in the blue aqueous phase was reduced by treatment with zinc dust and,

(1) R. F. Tietz and W. E. McEwen, J. Am. Chem. Soc., 77, 4007 (1955).

(2) G. D. Broadhead, J. M. Osgerby and P. L. Pauson, J. Chem. Soc., 650 (1958).

(3) N. Weliky and E. S. Gould, J. Am. Chem. Soc., 79, 2742 (1957). It is still an open question whether the proof of structure of the pinacolone offered by these authors is conclusive.

(4) K. L. Rinehart, Jr., C. J. Michejda and P. A. Kittle, Angew. Chem., 72, 38 (1960).