

Anal. Calcd for $C_{38}H_{31}N_2P$: C, 83.49; H, 5.72; N, 5.13; P, 5.67. Found: C, 83.37; H, 5.78; N, 5.11; P, 5.72.

Phosphinimine XVb. A solution of 1 g of sodium carbonate in 10 ml of water was added to a solution of 2 g of salt IXb in 15 ml of methanol. The mixture was extracted with benzene, and the benzene extracts were washed, dried, and evaporated. There was obtained 1.7 g (90%) of crude XVb, mp 168–173°. Recrystallization from benzene–hexane raised the melting point to 178–181°; infrared spectrum ($CHCl_3$): 6.45, 7.50, 9.02 μ ; nmr ($CDCl_3$, τ): multiplet at 2.7, quartet at 3.62, doublet at 4.83 ($J_{P^{31}-H} = 7.0$ cps), singlet at 7.25, peak area ratios 25:4.5:1.1:6.0.

Anal. Calcd for $C_{40}H_{36}N_3P$: C, 81.47; H, 6.15; N, 7.13; P, 5.25. Found: C, 81.27; H, 6.14; N, 7.05; P, 5.20.

Phosphinimine XVc. A solution of 0.5 g of sodium bicarbonate in 10 ml of water was added to a solution of 1 g of phosphonium salt IXc in 10 ml of methanol. The mixture was extracted with benzene and the extracts were washed, dried, and evaporated. There was obtained 0.9 g (95%) of crude XVc, mp 187–189°. Recrystallization from benzene–hexane gave yellow prisms with mp 188–190°; infrared spectrum ($CHCl_3$): 6.50, 7.60, 9.07 μ ; nmr ($CDCl_3$, τ): multiplet at 2.7, doublet at 3.70, doublet at 5.01 ($J_{P^{31}-B} = 6.0$ cps), peak area ratios 27:2.1:1.2.

Anal. Calcd for $C_{38}H_{30}N_3O_2P$: C, 77.14; H, 5.11; N, 7.10; P, 5.24. Found: C, 77.06; H, 5.17; N, 6.97; P, 5.21.

Phosphinimine XVd. A solution of 1.5 g of sodium bicarbonate in 20 ml of water was added to a solution of 3 g of salt IXd in 20 ml of methanol. The mixture was diluted with water and extracted with benzene. There was obtained 2.3 g (82%) of the phosphinimine, mp 143–146°. Recrystallization from benzene–hexane yielded XVd having mp 144–146°; infrared spectrum ($CHCl_3$): 6.43, 7.38, 8.99 μ ; nmr ($CDCl_3$, τ): multiplet at 2.6, doublet at 3.56, quartet at 3.84, doublet at 4.97 ($J_{P^{31}-H} = 7.0$ cps), peak area ratios 26:0.9:1.1:1.0.

Anal. Calcd for $C_{38}H_{29}Cl_2N_2P$: C, 74.15; H, 4.75; Cl, 11.52; N, 4.55. Found: C, 73.98; H, 4.66; Cl, 11.70; N, 4.70.

Treatment of II with Benzoic Acid. A solution of 5.0 g (22 mmoles) of chlorodiphenylacetonitrile in 10 ml of benzene was

added to 5.8 g (22 mmoles) of triphenylphosphine in 30 ml of benzene. The mixture was stirred 15 min and then 2.7 g (22 mmoles) of benzoic acid was added. The mixture was refluxed 15 min and then evaporated. The residue was triturated with pentane. The solid residue was chromatographed on silica gel; there was obtained 4.3 g (100%) of crude diphenylacetonitrile, mp 58–65°. Recrystallization from aqueous methanol raised the melting point to 68–71°, undepressed upon addition of authentic diphenylacetonitrile. There was also obtained 4.9 g (80%) of triphenylphosphine oxide, mp 151–153°; the mixture melting point with authentic material was 152–154°. The pentane tritrate was evaporated to 3.1 g of colorless oil, smelling strongly of benzoyl chloride. The infrared spectrum was almost identical with that of benzoyl chloride; a peak at 5.80 μ indicated the probable presence of benzoic anhydride.

A solution of 5 g of chlorodiphenylacetonitrile in 10 ml of benzene was added to 5.8 g of triphenylphosphine in 30 ml of benzene. After 15 min 3 g of phosphinimine V was added and then after 1 min, 2.7 g of benzoic acid. The mixture was refluxed 15 min and then evaporated. The residue was triturated with pentane. The remaining solid was washed with benzene. There remained 3.1 g of salt XI, mp 177–178°. Recrystallization raised the melting point to 181–184°, undepressed upon admixture of authentic material. The benzene washings were evaporated, and the residue was chromatographed on silica gel and alumina. There was obtained 2.9 g (69%) of diphenylacetonitrile, mp 65–70°, undepressed upon admixture of authentic material. There was also obtained 4.5 g (73%) of triphenylphosphine oxide, mp 139–152°; recrystallization from benzene–hexane raised the melting point to 145–153°, the mixture melting point with authentic material was 150–156°. There was also obtained 0.7 g of phosphinimine V, mp 139–147°, undepressed upon admixture of authentic material. The pentane tritrate was evaporated to 2.8 g of oil having an infrared spectrum essentially identical with that of the benzoyl chloride–benzoic anhydride mixture obtained above.

Isoimides. A Kinetic Study of the Reactions of Nucleophiles with N-Phenylphthalisoimide^{1a,b}

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Abstract: The pH–rate profile of the hydrolysis of N-phenylphthalisoimide (I) has been investigated in the pH range 0–11 (30°) and has been explained in terms of specific acid and specific base catalyzed pathways of hydrolysis, together with a small contribution by an uncatalyzed water reaction. A detailed kinetic study of the reactions of nucleophiles with I has revealed that nucleophilic agents may react with either neutral or protonated isoimide; in the former case, extensive rearrangement to N-phenylphthalimide (II) generally occurs. The reactivity of nine nucleophiles to the carbonyl group of I has been found to parallel closely the reactivity of the same nucleophiles to *p*-nitrophenyl acetate.

Since the initial report² of the isolation of an isoimide in 1893, isoimide intermediates have been proposed to occur in a wide array of reactions. Recent examples include the conversion of amides to nitriles (by means of mixed carboxylic–sulfonic anhydrides,³ arylsulfonyl

chlorides,⁴ or N,N'-dicyclohexylcarbodiimide^{4,5}), the Beckmann rearrangement of an oxime tosylate,⁶ the reaction of amides with acid chlorides,⁷ the photo-oxidation of substituted oxazoles,⁸ and the reaction of the N-ethylbenzoxazolium cation with carboxylate

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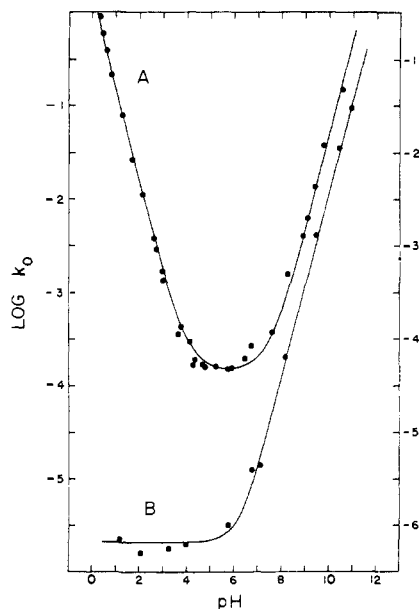


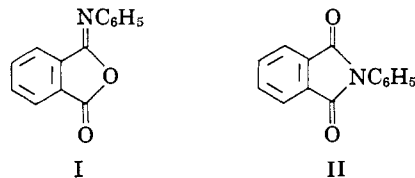
Figure 1. pH-rate profiles for hydrolysis of N-phenylphthalisoimide and N-phenylphthalimide at 30°: (A) isoimide (left ordinate), (B) imide (right ordinate). Rate constants are expressed in units of sec^{-1} . The solid curves are calculated from eq 1 and 2, using the constants given in the text.

ions.⁹ Earlier suggestions of transient isoimides have been summarized by Roderick.¹⁰ In spite of the frequency with which postulated isoimides appear in the literature, the early^{2,11} exploration of isoimide chemistry led to little further experimentation in succeeding decades. Since 1961, however, the isoimide system has received renewed attention.^{10,12-15}

Our interest in this field stems from the conjecture that isoimides may play a role in the amide-catalyzed hydrolysis of carboxylic acid derivatives. The formation of *imides* is a well-recognized consequence of the intramolecular interaction of the amide function with suitably disposed activated acyl groups and has been discussed in connection with the mechanism of enzymatic ester and amide hydrolysis.¹⁶ By contrast, the involvement of isoimide intermediates does not seem to have received serious consideration, although known methods of isoimide synthesis include several^{2,10-13} which most likely require nucleophilic displacement by a neighboring amide group upon an activated carboxyl function.¹⁷

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The present investigation of the behavior of an isoimide in aqueous solution was undertaken to provide quantitative data relevant to future scrutiny of the function of isoimides in amide-catalyzed hydrolytic processes. In this paper, we report the results of a study of the kinetics and mechanism of the reactions of N-phenylphthalisoimide (I) with nucleophilic agents, as well as some observations on nucleophilic catalysis of the isoimide-imide rearrangement.



Results

Kinetic Studies. The pH-rate profile for the hydrolysis of N-phenylphthalisoimide in 10% acetonitrile-water (30°) is presented in Figure 1. Rate data obtained at $\text{pH} > 3$ were extrapolated to zero buffer concentration since all buffers examined increased the rate of disappearance of the isoimide. The hydrolysis of I appears to be subject to uncomplicated acid and base catalysis, and observed first-order rate constants (k_0) depend accurately on the first power of hydronium or hydroxide ion concentration. The data of Figure 1 indicate also the existence of a modest water reaction; the curve drawn in the figure was calculated from eq 1, with $k_{\text{H}_2\text{O}} = 1.53 \times 10^{-4} \text{ sec}^{-1}$, $k_{\text{H}} = 1.55 \text{ M}^{-1} \text{ sec}^{-1}$, and $k_{\text{OH}} = 500 \text{ M}^{-1} \text{ sec}^{-1}$. For comparison, the effect

$$k_0 = k_{\text{H}_2\text{O}} + k_{\text{H}}[\text{H}^+] + k_{\text{OH}}[\text{OH}^-] \quad (1)$$

of pH on the hydrolysis of the isomeric N-phenylphthalimide (II) was similarly determined (Figure 1). With this substance, the rate of hydrolysis is nearly independent of acidity in the range $\text{pH} 1-6$ and becomes directly proportional to hydroxide ion concentration in alkaline medium. The pH-rate profile of the imide is acceptably described by eq 2, with $k_{\text{H}_2\text{O}} = 6.7 \times 10^{-7} \text{ sec}^{-1}$ and $k_{\text{OH}} = 40 \text{ M}^{-1} \text{ sec}^{-1}$. The latter rate constant may be compared to that of $30 \text{ M}^{-1} \text{ sec}^{-1}$ reported for the alkaline hydrolysis of

$$k_0 = k_{\text{H}_2\text{O}} + k_{\text{OH}}[\text{OH}^-] \quad (2)$$

N-methylphthalimide (1% tetrahydrofuran-water and 25°).¹⁸

Owing to the existence of an acid-catalyzed pathway of hydrolysis, the isoimide I is considerably more reactive than its isomer II in moderately acidic solution. While the half-life of isoimide hydrolysis varies from 5 sec at $\text{pH} 1$ to 75 min at $\text{pH} 5.5-6.0$, imide hydrolysis occurs with a half-life of 12 days in the same pH region. At $\text{pH} > 7$, however, the isoimide is only 12 times more reactive than the corresponding imide.

The observation that the rate of isoimide disappearance was markedly enhanced by buffer species led to a detailed investigation of the nature of these effects. Invariably, observed first-order rate constants for isoimide disappearance varied linearly with total buffer concentration at fixed pH and ionic strength. Representative experiments are shown in Figure 2. Apparent second-order rate constants (k_2'), describing

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the reaction of buffer (or other added nucleophile) with the isoimide, are defined by eq 3, where k_w is the con-

$$k_0 = k_w + k_2'[\text{B}_T] \quad (3)$$

tribution of solvent to isoimide hydrolysis at the given pH (cf. eq 1) and B_T is total concentration of buffer (or other nucleophile). The constant k_2' was obtained, for nine nucleophilic agents and at various pH values, from the slopes of plots analogous to those of Figure 2. In the case of very reactive nucleophiles (e.g., azide and mercaptoacetate ions), higher concentrations of less reactive substances (e.g., acetate buffer) were employed to maintain constant pH, and the contribution of the buffer is included in the intercept term k_w . The results of these studies are summarized in Table I.

Table I. Rate Constants for Reaction of Nucleophiles with Isoimide I^a

| Nucleophile | Concn range, M ^b | pH | Mole fraction B ^c | $k_2' \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$ ^d |
|-----------------|-----------------------------|-------|------------------------------|---|
| Formate | 0.02-0.10 | 3.63 | 0.50 | 22.6 |
| | 0.04-0.20 | 4.24 | 0.80 | 10.5 |
| | 0.06-0.40 | 4.68 | 0.90 | 6.1 |
| Azide | 0.0001-0.001 ^e | 3.69 | 0.16 | 19,700 |
| | 0.0001-0.001 ^e | 4.77 | 0.69 | 19,100 |
| Acetate | 0.00005-0.0001 ^f | 5.82 | 0.96 | 19,500 |
| | 0.1-0.6 | 3.72 | 0.09 | 1.31 |
| | 0.1-0.3 | 4.12 | 0.20 | 1.81 |
| | 0.003-0.07 | 4.33 | 0.34 | 2.58 |
| | 0.006-0.17 | 4.78 | 0.58 | 2.97 |
| | 0.01-0.33 | 5.23 | 0.76 | 3.12 |
| | 0.01-0.24 | 5.83 | 0.94 | 3.32 |
| Phosphate | 0.1-0.3 | 6.43 | 0.98 | 3.57 |
| | 0.05-0.25 | 5.75 | 0.10 ^g | 1.58 |
| | 0.05-0.25 | 6.73 | 0.50 ^g | 6.7 |
| Imidazole | 0.05-0.15 | 7.59 | 0.86 ^g | 14.2 |
| | 0.02-0.20 | 6.20 | 0.14 | 2420 |
| | 0.01-0.05 | 6.62 | 0.28 | 4870 |
| Tris | 0.005-0.05 | 7.09 | 0.50 | 8590 |
| | 0.0002-0.002 ^f | 7.59 | 0.75 | 12,900 |
| | 0.02-0.04 | 8.22 | 0.50 | 128 |
| Morpholine | 0.02-0.04 | 8.88 | 0.80 | 242 |
| | 0.01-0.05 | 8.20 | 0.25 | 6940 |
| Borate | 0.005-0.010 | 8.80 | 0.50 | 14,800 |
| | 0.01-0.03 | 9.33 | 0.83 | 23,400 |
| | 0.01-0.03 | 9.10 | 0.35 | 110 |
| Carbonate | 0.02-0.04 | 9.42 | 0.17 ^h | 270 |
| | 0.02-0.04 | 9.77 | 0.34 ^h | 600 |
| | 0.02-0.04 | 10.58 | 0.67 ^h | 950 |
| Mercaptoacetate | 0.0001-0.001 ⁱ | 4.82 | | 590 |
| | 0.0001-0.001 ⁱ | 5.73 | | 640 |

^a In 10% acetonitrile-H₂O, 30°C, $\mu = 0.45$. Isoimide at $0.7-1.6 \times 10^{-4} \text{ M}$. ^b Sum of concentrations of all species. ^c Fraction of total nucleophile present as conjugate base. ^d Apparent second-order rate constants obtained from plots of k_0 vs. total nucleophile concentration (see eq 3). ^e In 0.01 M acetate buffer. ^f In 0.01 M phosphate buffer. ^g Calculated for HPO_4^{2-} . ^h Calculated for CO_3^{2-} . ⁱ In 0.4 M acetate buffer.

Were the reaction of nucleophiles with N-phenylphthalisoimide to involve solely reaction of the conjugate base of the nucleophile with neutral isoimide, then division of the apparent second-order rate constants k_2' by the mole fraction of nucleophile present as its conjugate base should yield a pH-independent intrinsic constant characteristic of each nucleophile. Inspection of Table I (columns 4 and 5) discloses the apparent complexity of the influence of pH on the reactivity of the several nucleophilic agents. With

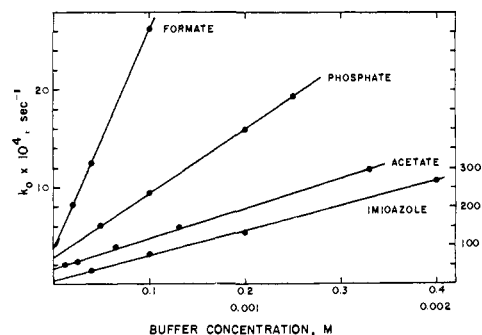


Figure 2. Effect of buffer concentration on rate of isoimide disappearance (formate, pH 3.63; phosphate, pH 6.73; acetate, pH 5.23; imidazole (in 0.01 M phosphate buffer), pH 7.59): imidazole, right ordinate and lower scale on abscissa; all others, left ordinate and upper scale on abscissa.

phosphate, imidazole, Tris, morpholine, and carbonate buffers, the terms k_2' are directly proportional to the mole fraction of nucleophile conjugate base. On the other hand, the reactivities of azide and mercaptoacetate are unaffected by variation in pH, while that of formate buffer appears dependent on the concentration of formic acid rather than of formate ion. For acetate buffers, k_2' increases with increasing pH, but the intrinsic second-order rate constant is greater at lower pH, suggesting the involvement of both acetic acid and acetate ion.

The analysis of the influence of pH on the rates of reaction of the isoimide with nucleophiles was based on the assumption that, in the general case, the conjugate base (B) of the nucleophile may react either with neutral isoimide (I) or with its conjugate acid (IH) (eq 4). Let $\text{I}_T = [\text{I}] + [\text{IH}]$ and $\text{B}_T = [\text{B}] + [\text{BH}]$ and

$$\text{rate} = k_1[\text{IH}][\text{B}] + k_2[\text{I}][\text{B}] \quad (4)$$

define the acid dissociation constants of the protonated isoimide (K_1) and of the nucleophile (K_2) as $K_1 = [\text{I}][\text{H}^+]/[\text{IH}]$ and $K_2 = [\text{B}][\text{H}^+]/[\text{BH}]$. If it is assumed^{19a} that $K_1 \gg [\text{H}^+]$, i.e., that, in the pH region under consideration, the isoimide exists largely as the neutral species, then it may be shown that the total contribution of the nucleophile to the rate of disappearance of the isoimide is given by eq 5, readily transformed to eq 6.

$$k_2'[\text{B}_T] = k_0 - k_w = (k_1K_2/K_1)[\text{BH}] + k_2[\text{B}] \quad (5)$$

$$k_2' = \frac{k_0 - k_w}{[\text{B}_T]} = (k_1K_2/K_1) + \frac{[\text{B}]}{[\text{B}_T]} \left[k_2 - \frac{k_1K_2}{K_1} \right] \quad (6)$$

Although the final expressions are derived from the assumption of reaction with nucleophile conjugate base only (eq 4), the fact that a rate equation containing terms for IH and B is kinetically indistinguishable from one containing terms for I and BH (since $[\text{IH}][\text{B}] = (K_2/K_1)[\text{I}][\text{BH}]$) allows formal expression of the buffer effect in terms of contributions from the conjugate acid and base forms of the buffer (eq 5). Graphical evaluation of the constants k_1K_2/K_1 and k_2 is simplified by use of eq 6, which describes the de-

(19) (a) The linear dependence of rate of hydrolysis on hydronium ion concentration (Figure 1) suggests that the $\text{p}K_a$ of IH is appreciably < 1 . (b) To account for the lack of influence of pH on k_2' for mercaptoacetate at pH 4.8-5.7, it might be suggested that the nucleophile acts *via* its (completely) ionized carboxyl group. This explanation does not readily accommodate the finding that mercaptoacetate ion is nearly 200-fold more reactive than acetate ion.

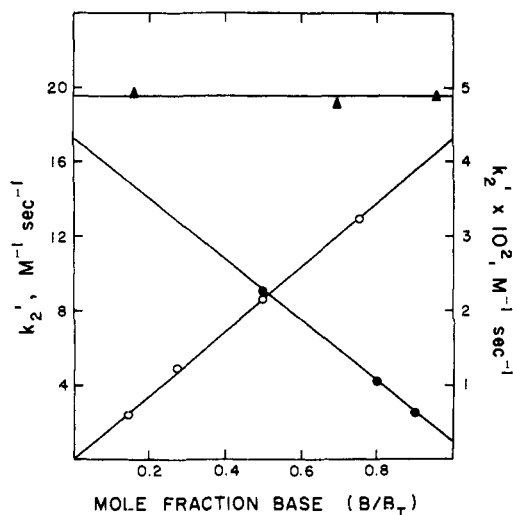


Figure 3. Dependence of apparent second-order rate constants for imidazole, azide, and formate on mole fraction of nucleophile in basic form: \circ , imidazole (left ordinate); \blacktriangle , azide (left ordinate); \bullet , formate (right ordinate).

pendence of k_2' on the mole fraction of nucleophile conjugate base. Once these constants are known, the relative contributions of the two processes of eq 4 to the over-all buffer effect are easily calculated for any pH value from eq 5.

The application of eq 6 for the resolution of the pH dependence of the reaction with nucleophiles into its component terms is illustrated in Figure 3. It is seen that reaction of isoimide with imidazole involves solely the conjugate bases of both reactants, since the plot of k_2' vs. $[B]/[B_T]$ passes through the origin. With azide, the (formal) reactions with hydrazoic acid and azide ions are of equal importance, while in formate buffer, the predominant (although not exclusive) process involves formic acid. The question of deciding which of the kinetically indistinguishable formulations best describes the reaction of neutral isoimide with nucleophile conjugate acids will be considered in the sequel.

The second-order rate constants k_2 and k_1K_2/K_1 determined from plots of eq 6 are listed in Table II. Reactions involving the conjugate acid of the nucleophile were detected only with formate, azide, acetate, and mercaptoacetate. It should be emphasized that the nature of the reaction of isoimide with a given nucleophile is dictated not only by the relative magnitude of the constants (k_1K_2/K_1) and k_2 , but also by the ratio $[B]/[BH]$. Therefore, although reaction with formic acid is favored by a factor of 20 over reaction with formate ion, both processes would be of equal importance at pH 4.95 ($[B]/[BH] = 20$) and at higher pH reaction with formate ion would predominate. Accordingly, the absence of a significant reaction of $-\text{SCH}_2\text{COO}^-$ ($pK_a = 10.3$) with neutral isoimide results probably from the fact that $[B]/[BH] = ca. 10^{-5}$ at the pH values examined.^{19b} It is expected that at higher pH, reaction with thiol anion would become evident.

The hydrolysis of N-phenylphthalimide (II) was also found to be subject to catalysis by buffer species, and the data presented in Figure 1 are extrapolated to zero buffer concentration. Weak catalysis by acetate,

Table II. Rates of Reaction of Nucleophiles with Neutral Isoimide, Protonated Isoimide, and *p*-Nitrophenyl Acetate

| Nucleophile | pK_a | k_2, b, c $M^{-1} \text{ sec}^{-1}$ | $(k_1K_2/K_1), b, d$ $M^{-1} \text{ sec}^{-1}$ | k_2, e $M^{-1} \text{ sec}^{-1}$ |
|--------------------------------|-------------------|--|---|---------------------------------------|
| H ₂ O | -1.7 | 3.1×10^{-6f} | | 1×10^{-8} |
| Formate | 3.65 | 0.0022 | 0.043 | |
| Azide | 4.42 | 19.5 | 19.5 | 0.037 |
| Acetate | 4.73 | 0.0036 | 0.0014 | 8.5×10^{-8} |
| HPO ₄ ²⁻ | 6.83 | 0.016 | | 1.2×10^{-4} |
| Imidazole | 7.04 | 17.2 | | 0.49 ^g |
| Tris ^h | 8.09 | 0.25 | | 0.0012 |
| Morpholine | 8.60 | 28.4 | | 0.69 ⁱ |
| Borate | 9.0 ^j | 0.1 | | |
| Carbonate | 9.97 | 1.6 | | 0.018 |
| Mercaptoacetate | 10.3 ^k | | 0.6 | |
| Hydroxide | 15.7 | 500 ^l | | 14.8 |

^a Dissociation constant of conjugate acid of nucleophile, determined in this study except where indicated. ^b In 10% acetonitrile-water, 30°, $\mu = 0.45$. ^c Second-order rate constant for reaction with neutral isoimide. ^d Apparent second-order rate constant for reaction with protonated isoimides. ^e Second-order rate constants for reaction with *p*-nitrophenyl acetate, in H₂O at 25°; rate constants taken from ref 43b, except where otherwise indicated. ^f Calculated from the value of $1.53 \times 10^{-4} \text{ sec}^{-1}$ for the water reaction (Figure 1) and a water concentration of 49.5 M. ^g In 0.5% acetone-water at 25°: W. P. Jencks, *J. Am. Chem. Soc.*, **80**, 4585 (1958). ^h Tris-(hydroxymethyl)aminomethane. ⁱ In H₂O at 30°: ref 46. ^j In H₂O at 25°, $\mu = 0.1$: N. Ingri, *Acta Chem. Scand.*, **16**, 439 (1962). ^k J. T. Edsall and J. Wyman, "Biophysical Chemistry," Vol. 1, Academic Press Inc., New York, N. Y., 1958, p 465. ^l Calculated from the data of Figure 1, with hydroxide ion activity obtained from the pH readings and $K_w = 10^{-14}$.

Tris, and carbonate buffers (0.02–0.20 M) was seen, while phosphate and imidazole led to greater rate enhancements. These phenomena were not investigated in detail; it was noted, however, that the second-order rate constant k_2 for imidazole catalysis ($1.4 \times 10^{-4} M^{-1} \text{ sec}^{-1}$) was only twice as large as that for phosphate dianion ($0.6 \times 10^{-4} M^{-1} \text{ sec}^{-1}$). In contrast, imidazole is about 1000 times more reactive than HPO₄²⁻ toward the isoimide I (Table II).

The Reaction Products. The long-known conversion of isoimides to amic acids by dilute aqueous acid^{2,11a-c} or alkali²⁰ was verified in the present instance. Ultraviolet spectra of reaction mixtures, taken after hydrolysis of the isoimide in 0.001 N NaOH or 0.01 N HCl, were in accord with quantitative formation of phthalanilic acid. Also, the rate of disappearance of the product of isoimide hydrolysis in 0.01 N HCl was identical with the rate of hydrolysis of authentic phthalanilic acid under these conditions.²¹

In the presence of low concentrations of nucleophilic species, the isoimide I is efficiently rearranged to the imide II, to the detriment of the formation of phthalanilic acid. The extent of rearrangement to N-phenyl-

(20) R. Pummerer and G. Dorfmueller, *Ber.*, **45**, 292 (1912).

(21) Preliminary experiments indicate that the rate of hydrolysis of phthalanilic acid in dilute acid is proportional to the concentration of the neutral species and decreases with increasing pH, as dissociation of the carboxyl group occurs. At pH 1–2, where phthalanilic acid exists predominantly in the neutral form, hydrolysis at 30° (10% acetonitrile-water) takes place with a half-life of about 35 min. The effect of pH on the rate of hydrolysis of phthalanilic acid is analogous to that previously reported^{22,23} for phthalamic and substituted phthalamic and maleamic acids. The pH-rate profile of the hydrolysis of phthalanilic acid in weakly acidic solution has been previously investigated: H. Morawetz and J. Shafer, *J. Am. Chem. Soc.*, **84**, 3783 (1962). Our results are in substantial agreement with those of the earlier study.

(22) M. L. Bender, Y.-L. Chow, and F. Chloupek, *ibid.*, **80**, 5380 (1958).

(23) G. Dahlgren and N. L. Simmerman, *J. Phys. Chem.*, **69**, 3626 (1965).

phthalimide was quantitatively measured by hydroxamic acid assay for the product. In several instances, the identity of the product of reaction with the nucleophile was confirmed by isolation of the imide. The results summarized in Table III (columns 4 and 5) indicate that imidazole, phosphate, Tris, and acetate buffers cause extensive conversion of isoimide to imide, as do 1-methylimidazole and mercaptoacetate ion. Small yields of imide appeared in the presence of formate buffer; with carbonate buffer, the formation of imide remains in doubt. The products formed in the presence of morpholine or borate buffers were not determined.

Table III. Rearrangement of Isoimide to Imide by Nucleophilic Catalysis^a

| Nucleophile | Concn, ^b | | Imide yield, % | | Reaction path | |
|--------------------------------|---------------------|----------|--------------------------|------------------------|-------------------|--------------------|
| | <i>M</i> | pH | Hydroxamate ^c | Iso-lated ^d | Base ^e | Acid/ ^f |
| Imidazole | 0.02 | 6.28 | 93 | | 100 | |
| | 0.01 | 7.08 | 87 | 72 | 100 | |
| | 0.025 | 7.08 | 87 | | 100 | |
| | 0.05 | 7.58 | 93 | | 100 | |
| HPO ₄ ²⁻ | 0.10 | 6.82 | 84 | 59 ^g | 85 | |
| Tris | 0.30 | 8.30 | 95 | 76 | 98 | |
| 1-Methylimidazole | 0.01 | <i>h</i> | | 79 | | |
| Carbonate | 0.30 | 9.38 | <10 | | 86 | |
| Acetate | 0.60 | 3.72 | (64) ⁱ | 59 ^j | 16 | 52 |
| | 0.30 | 4.14 | 62 | | 25 | 40 |
| | 0.03 | 6.45 | 32 | | 36 | 0 |
| | 0.10 | 6.46 | 62 | | 65 | 0.5 |
| Formate | 0.30 | 6.52 | 71 | 64 | 83 | 1 |
| | 0.20 | 4.25 | 12 | 14 ^k | 16 | 76 |
| | 0.40 | 4.67 | 13 | | 29 | 64 |
| Mercaptoacetate | 0.01 ^l | 4.81 | | 70 | | 82 ^m |
| None ⁿ | | 2.03 | 0.0 | | | |

^a 10% acetonitrile-water, 30°, $\mu = 0.45$. Isoimide at 7.5×10^{-5} *M* for colorimetric assay and at 0.001 *M* for isolation experiments.

^b Sum of concentration of all species. ^c Estimated error $\pm 10\%$.

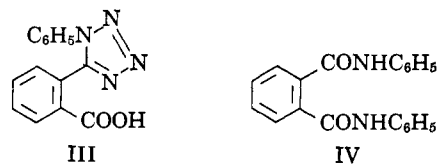
^d For details, see Experimental Section. ^e Per cent of total rate of isoimide disappearance resulting from reactions involving conjugate base of buffer. ^f Per cent of total rate of isoimide disappearance resulting from reactions involving conjugate acid of buffer. ^g Reaction mixture contained 0.2 *M* phosphate, pH 6.8. ^h Half-neutralized with HCl. ⁱ From ultraviolet spectra of reaction mixture. ^j Crude product contaminated with 5–10% phthalanilide. ^k Reaction mixture contained 0.4 *M* formate buffer, pH 4.1. ^l In 0.44 *M* acetate buffer. ^m Does not include contribution of acetate buffer to total rate of isoimide disappearance, which amounts to 17%. ⁿ 0.01 *N* HCl.

The contribution of buffer species to the total rate of isoimide disappearance is shown in Table III (columns 6 and 7) and, where appropriate, has been resolved into terms for the acid and basic forms of the nucleophile. It is seen that imide yields (hydroxamic acid method) parallel closely the extent of nucleophile contribution to the over-all reactions of the isoimide, with two exceptions: in the presence of formate or carbonate, imide yield is much lower than might have been anticipated. It will be noted that the acetate-catalyzed conversion of isoimide to imide is not dependent on the nature of the reactive buffer species (acetic acid or acetate ion). Mechanistic implications of this finding are considered in the Discussion.

A possible objection to the use of hydroxylamine for quantitative assay of imide formation could be that the assay method might not distinguish between imide and other acyl-activated derivatives of phthalanilic acid formed by nucleophilic attack on the isoimide carbonyl

group. With several nucleophiles, however, it is clear that the rate of imide formation is comparable to the rate of isoimide disappearance: (a) in preparative experiments with imidazole buffers, crystallization of imide occurred within 1 min after initiation of reaction; (b) ultraviolet spectra of reaction mixtures containing imidazole, acetate, or mercaptoacetate, taken shortly after complete disappearance of the isoimide, indicated extensive conversion to imide (identified by its characteristic absorption maximum at 300 $m\mu$); (c) yields of isolated imide were frequently in reasonable agreement with yields based on the colorimetric assay.

The products of the reaction of the isoimide with azide buffer were found to vary with the pH of the reaction mixture: the predominant product at pH 6 was the imide II, while at pH 3, the isoimide was largely converted to 1-phenyl-5-(*o*-carboxyphenyl)tetrazole (III). Equal amounts of II and III are formed at pH 4.5. These conclusions are based both on isolation



of the products as well as on spectrophotometric determination of imide yield from absorbance measurements at 300 $m\mu$ (Table IV).

Table IV. Effect of pH on Products of Reaction of Isoimide with Azide^a

| pH | Product yield, % | | | | | |
|------|--------------------------------|------------------------|------------------------|-----------|--------------------------|-----------|
| | Spectral analysis ^b | | Isolation ^c | | Calcd yield ^d | |
| | Imide | Tetrazole ^e | Imide | Tetrazole | Imide | Tetrazole |
| 2.48 | | | 5 | 63 | 5 | 95 |
| 3.29 | 11 | 89 | | | 7 | 93 |
| 4.43 | 51 | 49 | 16 | 44 | 50 | 50 |
| 4.98 | 72 | 28 | | | 78 | 22 |
| 5.74 | 93 | 7 | 58 | 0 | 95 | 5 |

^a Total concentration of azide ion and hydrazoic acid is 0.1 *M*. Isoimide at 7.5×10^{-5} *M* in spectral experiments and ca. 0.009 *M* for isolation. ^b At 300 $m\mu$. ^c For details, see Experimental Section. ^d Based on assumption that reaction of neutral isoimide with azide ion yields imide, and reaction with HN₃ yields tetrazole. ^e 100 – per cent imide yield.

The imide produced by acetate-catalyzed rearrangement of isoimide at pH 3.7 was accompanied by small amounts (5–10%) of a substance whose infrared spectrum was identical with that of the material formed on combination of isoimide with aniline in 50% acetonitrile-water. The by-product, presumably phthalanilide (IV), most likely arises by reaction of isoimide with aniline formed on hydrolysis²¹ of phthalanilic acid during prolonged exposure to acidic medium.²⁴

Discussion

The Rearrangement of Isoimides to Imides. The facile thermal rearrangement of acyclic isoimides to imides was suspected for many years²⁵ and demon-

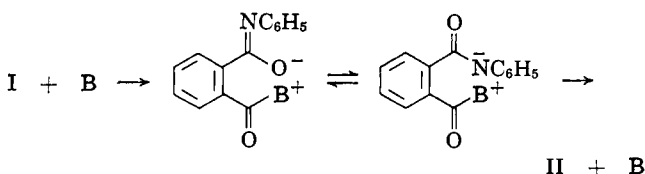
(24) Treatment of the hydrochloride salt of I with aniline has been shown to yield IV.^{11d}

(25) (a) O. Mumm, H. Hesse, and H. Volquartz, *Ber.*, **48**, 379 (1915); (b) J. C. Sheehan and E. J. Corey, *J. Am. Chem. Soc.*, **74**, 4555 (1952); (c) C. L. Stevens and M. E. Munk, *ibid.*, **80**, 4065 (1958); (d) F. Cramer and K. Baer, *Ber.*, **93**, 1231 (1960).

strated recently with the first isolation of acyclic isoimides by Curtin and Miller.¹⁴ The much greater stability of cyclic isoimides derived from phthalic, maleic, and camphoric acid has been ascribed¹⁴ to steric obstacles to the achievement of the required four-membered transition state for rearrangement. On the other hand, the isomerization of cyclic isoimides induced by acetic acid or acetate ion has been widely reported; reaction conditions have included acetic anhydride-sodium acetate at 65–100°,^{12,13,26} benzene-triethylammonium acetate at reflux temperature,¹² dioxane-acetic acid at 65°,²⁶ and refluxing acetic acid.¹⁵ Fusion^{2,11c,e} or prolonged heating in inert solvents^{14,15} (chlorobenzene, dioxane, nitrobenzene, nitromethane, and N,N-dimethylformamide) at elevated temperature (100–250°) convert cyclic isoimides to their imide isomers, but the careful studies of Curtin and Miller^{14,27} suggest that uncatalyzed thermal rearrangement may not yet have been observed. It has been proposed^{12,15} that nucleophilic catalysis of the isoimide-imide transformation may involve attack at the activated carbonyl group of the isoimide to yield an acyl-activated amic acid which undergoes ring closure to the imide.

It is clear from the present study that nucleophilic catalysis of the rearrangement of isoimides to imides is probably a general phenomenon which occurs efficiently at ambient temperature in the presence of dilute aqueous solutions of nucleophiles. In agreement with earlier^{12,15} proposals, the mechanism may be formulated as follows (Scheme I). The results shown in Table III

Scheme I



provide support for the existence of acylimidazole, acylimidazolium ion, acyl phosphate, carboxylic acid anhydride, and thiolester as examples of the intermediate species of Scheme I. The structure of the intermediate formed by reaction with Tris is less certain, since both O- and N-acylations of this nucleophile are known to occur;²⁸ also, both esters and amides of substituted phthalamic acids undergo ready cyclization to imides.^{16b} The failure to detect imide formation in the presence of dilute carbonate solutions is puzzling. Possibly, loss of CO₂ from or hydrolysis of the supposed mixed carboxylic-carbonic anhydride competes with ring closure; alternatively, the carbonate effect on isoimide disappearance represents general base catalysis of water addition, rather than nucleophilic attack, although the reported²⁰ isomerization of I to II in 44% aqueous potassium carbonate weakens the latter argument.

The demonstrated facility with which nucleophiles promote the isoimide-imide conversion further complicates the interpretation of the rearrangement of isoimides on extended heating with or without solvent. Careful exclusion of possible nucleophilic contaminants or indeed of traces of the amic acid²⁹ formed on hy-

(26) W. R. Roderick, *J. Org. Chem.*, **29**, 745 (1964).

(27) L. L. Miller, Ph.D. Thesis, University of Illinois, 1964.

(28) T. C. Bruice and J. L. York, *J. Am. Chem. Soc.*, **83**, 1382 (1961).

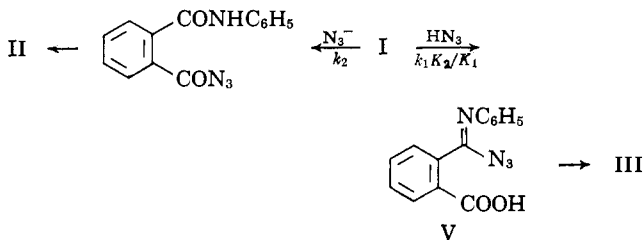
drolysis of the isoimide must precede the evaluation of these data.

The Site of Reaction of Nucleophiles with Isoimides.

The results of the present investigation as well as scattered information in earlier studies are consistent with the hypothesis that, in general, nucleophiles attack the neutral isoimide molecule at the carbonyl function to yield, at least transiently, acyl derivatives of amic acids. Treatment of a substituted maleisoimide with piperidine gave the diamide¹⁰ while several N,N'-biisomaleimides reacted with alcohols to give the derived esters.¹⁵ If the rearrangement of isoimides to imides in the presence of (potential) nucleophiles is accepted as *prima facie* proof of nucleophilic attack on the isoimide molecule, then it is probable that the acetate-catalyzed isomerizations earlier described^{12,13,26} resulted from attack at the carbonyl group. For reaction in aqueous solution, the combination of (a) kinetic evidence for the involvement of the neutral isoimide species, and (b) observation of extensive rearrangement to imide, lead to the conclusion that imidazole, Tris, phosphate dianion, and acetate and azide ions react with neutral isoimide at the carbonyl group. By analogy, it is proposed that morpholine, carbonate, and hydroxide ions react similarly, although no direct evidence is presently available.

The conversion of the isoimide I to mixtures of tetrazole (III) and imide (II) with aqueous azide ion parallels the experience of Behringer and Fischer,³⁰ who obtained the same products on exposure of I to hydrazoic acid in chloroform. Tetrazole formation from I may proceed *via* (but does not require) the iminoazide V (Scheme II); alternatively, closure of the

Scheme II



tetrazole cycle could precede expulsion of carboxylate ion. Efficient cyclization of an iminoazide to the corresponding tetrazole in aqueous solution has been directly observed³¹ and is implied by the reported synthesis of a tetrazole from an imide chloride and sodium azide in buffered aqueous acetone.³² Cycloaddition of azide to the imine function is well known in the chemistry of azlactones³³ and acylantranils.³⁴

Two significant conclusions emerge from the data presented in Table IV: (1) under certain conditions, the isoimide I is susceptible to nucleophilic attack at the imino function; (2) the extent of tetrazole formation

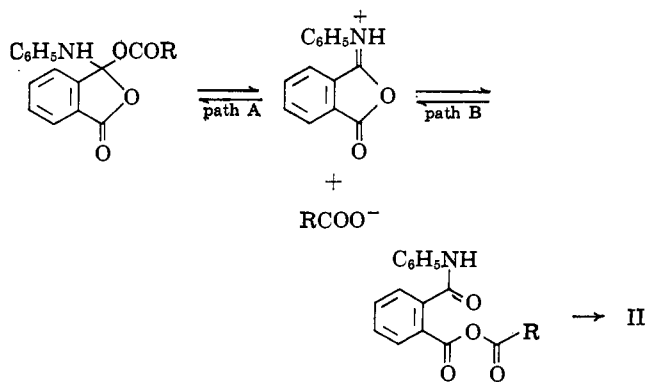
(29) It has been found that phthalanilic acid (0.005–0.02 M) accelerates the disappearance of I in 50% acetonitrile-water (fixed pH and ionic strength). It may be expected that, under appropriate conditions, aqueous solutions of isoimides may be partially transformed to imides in the absence of added nucleophilic agents.

(30) H. Behringer and H. J. Fischer, *Ber.*, **94**, 2562 (1961).(31) R. B. Woodward and R. A. Olofson, *J. Am. Chem. Soc.*, **83**, 1007 (1961).(32) P. A. S. Smith and E. Leon, *ibid.*, **80**, 4647 (1958).(33) (a) R. Filler, *Advan. Heterocyclic Chem.*, **4**, 75 (1965); (b) H. Behringer and W. Grimme, *Ber.*, **92**, 2967 (1959); (c) W. I. Awad, A. F. M. Fahmy, and A. M. A. Sammour, *J. Org. Chem.*, **30**, 2222 (1965).(34) H. Behringer and H. J. Fischer, *Ber.*, **94**, 1572 (1961).

parallels closely the extent to which the isoimide reacts with HN_3 , while imide appearance is directly proportional to that fraction of the isoimide which reacts with azide ion. In view of the previously discussed kinetic ambiguity inherent in the reaction of neutral isoimide with nucleophile conjugate acids, we now propose the following mechanistic explanation for the data of Table IV: (a) reaction of azide ion with neutral isoimide occurs by carbonyl attack, giving the acyl azide precursor of the imide (Scheme II); (b) reaction of azide ion with protonated isoimide takes place by addition to the imino group. The initial addition product is stabilized by eventual formation of a tetrazole. A peculiarity of the isoimide-azide system is the fact that the apparent rate constants for the two processes (k_2 and k_1K_2/K_1) are of equal magnitude. Consequently, the extent to which either pathway occurs depends solely on the mole fractions of the two azide species (eq 5); since each pathway leads to a different product, the yield of imide should parallel exactly the acid dissociation curve of hydrazoic acid, while the dependence of tetrazole yield on pH should be described in a mirror image fashion. At the same time, the total rate of reaction of isoimide with azide buffer remains independent of pH. An interesting kinetic analogy exists between the present work and the recently described³⁵ hydrolysis of propargyl hydrogen phthalate. In the latter study, the rate constant for hydrolysis is independent of pH, owing to the equal reactivity of neighboring carboxylate ion and carboxylic acid; in that case, however, the nature of the products does not vary with pH.

It is not yet clear, either from this investigation or from fragmentary data in the literature, whether the kinetically favored mode of reaction of nucleophiles with protonated isoimides is invariably at the immonium group, as might be expected from the considerations advanced by Hünig³⁶ to explain the reactions of ambident cations. Unlike the reaction with azide ion, nucleophilic attack by acetate ion (Table III) leads to imide formation even when the substrate is largely the protonated isoimide. A plausible interpretation may be that reaction of acetate ion with protonated isoimide occurs initially and reversibly at the immonium site (Scheme III, path A); the thermodynamically favored pathway is that leading to imide *via* the mixed anhydride (Scheme III, path B). In the case of formate

Scheme III

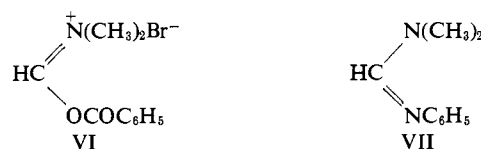


(35) J. W. Thanassi and T. C. Bruice, *J. Am. Chem. Soc.*, **88**, 747 (1966).

(36) S. Hünig, *Angew. Chem. Intern. Ed. Engl.*, **3**, 548 (1964).

ion, imide yields much more nearly approximate that fraction of the isoimide transformations involving neutral isoimide and formate ion. Possibly, the product of path A is stabilized irreversibly by expulsion of the *o*-carboxylate ion; on the other hand, it may be that the mixed anhydride (path B) undergoes largely hydrolysis rather than cyclization. Since imide formation is the predominant result of the reaction with mercaptoacetate ion, the resemblance to the acetate-protonated isoimide system suggests a similar interpretation.

Earlier observations do not lead to a consistent formulation of the reaction of nucleophiles with protonated isoimides. Treatment of isoimide hydrochlorides with methanol affords amic acid esters in some cases (carbonyl attack) and, in others, products of uncertain constitution ("isoesters") most likely derived from alcohol addition to the immonium group.^{14d} The adduct VI formed by combination of benzoyl bromide with *N,N*-dimethylformamide may be considered the



analog of a protonated isoimide; while exposure of VI to aniline in acetonitrile produces benzanilide³⁷ (carbonyl attack), significant yields of the amidine VII are formed in ether or benzene.³⁸ It is known that isoimides are rearranged to imides in the presence of acetic acid,^{15,26} also, reaction of bisoimides with amines in glacial acetic acid gives amides.¹⁵ Although these latter transformation require carbonyl attack by acetic acid or amines, it is not certain whether the other reactant was protonated isoimide.

The kinetics of hydrolysis of the isoimide I to phthalanilic acid implicate nucleophilic attack by hydroxide ion in alkali and (formally) by water or hydronium ion at lower pH. By analogy to other reactions of neutral isoimide, it is suggested that hydroxide ion adds to the carbonyl group; data obtained³⁵ on hydrolysis of *N-n*-butylmaleisoimide in O^{18} -water support this view. The acid-catalyzed hydrolysis of I may well involve water addition to the immonium group since the initially formed carbinolamine could be readily stabilized by conversion to phthalanilic acid. The neutral hydrolysis of I may proceed either by attack of a water molecule on the carbonyl group of neutral isoimide or possibly by addition of hydroxide ion to the immonium center. The latter process seems to represent the course of the pH-independent hydrolysis of Schiff bases³⁹ and other imines⁴⁰ at high pH. It is interesting that neutral hydrolysis of I in O^{18} -water might allow a choice between the two postulated pathways, since the location of O^{18} in the product should reflect the site of nucleophilic attack and, indirectly, the position of the proton in the transition state. With Schiff bases,

(37) H. K. Hall, *J. Am. Chem. Soc.*, **78**, 2717 (1956).

(38) H. Bredereck, R. Gompper, K. Klemm, and H. Rempfer, *Ber.*, **92**, 837 (1959).

(39) (a) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 832 (1962); (b) E. H. Cordes and W. P. Jencks, *ibid.*, **85**, 2843 (1963); (c) K. Koehler, W. Sandstrom, and E. H. Cordes, *ibid.*, **86**, 2413 (1964).

(40) (a) R. B. Martin and A. Parcell, *ibid.*, **83**, 4830 (1961); (b) G. L. Schmir and B. A. Cunningham, *ibid.*, **87**, 5692 (1965).

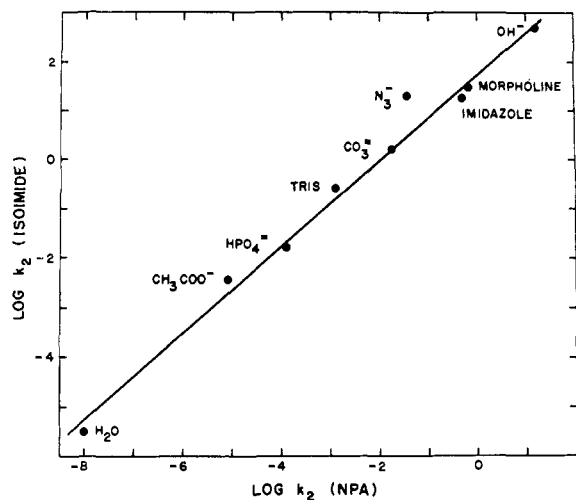


Figure 4. Relative reactivity of nucleophiles to isoimide and to *p*-nitrophenyl acetate. Rate constants are expressed in units of $M^{-1} \text{sec}^{-1}$. Data for *p*-nitrophenyl acetate are listed in Table II, column 5.

selection between the two kinetically indistinguishable mechanisms has been made *via* the study of quaternary derivatives.^{39c}

The azlactone structure is closely similar to the isoimide system and also may suffer nucleophilic attack at two sites. In addition to the well-established reactions of nucleophiles at the acyl carbon,^{33a,41} and the tetrazole synthesis discussed above, the formation of amidines by amine addition to the imino group has been reported.⁴²

The Reactivity of Nucleophiles to the Isoimide Carbonyl Group. Extensive studies of the rates of reaction of nucleophiles toward the acyl carbon of *p*-nitrophenyl acetate have revealed that there exists little correlation between basicity and reactivity for nucleophiles of varied structure.⁴³ It is evident that nucleophilic displacements on the isoimide carbonyl group exhibit a similar lack of correlation (Table II, column 3). It is of interest to compare the relative reactivities of a family of nucleophiles to the isoimide and ester carbonyl function (Figure 4). The only significant deviation from the linear relationship (slope 0.87, calculated by least squares, with omission of the point for azide) is shown by azide ion, which is nearly 10-fold more reactive toward the isoimide than predicted from the reaction rates of the other nucleophiles. The good fit of the point for acetate ion is noteworthy, in view of the fact that acetate clearly acts as a nucleophile to the isoimide carbonyl group, while it may accelerate hydrolysis of *p*-nitrophenyl acetate by general base catalysis.⁴⁴ The plot of Figure 4 suggests that nucleophilicity toward the isoimide increases slightly with decreasing reactivity; however, the deviation of the slope from a value of 1.00 may not be significant, since the isoimide reactions were carried out at 30°, while

the reactions of the ester were studied at 25° for the most part. In general, the behavior of the isoimide relative to *p*-nitrophenyl acetate recalls the findings of Johnson⁴⁵ with *N,N*-dimethylcarbamoylpyridinium chloride; it appears that the various factors which govern the relative reactivity of nucleophiles to *p*-nitrophenyl acetate similarly influence nucleophilic displacement on the isoimide and acylpyridinium systems. On the other hand, it has been shown that the rates of nucleophilic reactions with δ -thiolvalerolactone frequently bear no relationship to similar displacements on *p*-nitrophenyl acetate.⁴⁶

Experimental Section⁴⁷

N-Phenylphthalisoimide.⁴⁸ A solution of 2.5 g (0.012 mole) of *N,N'*-dicyclohexylcarbodiimide in 10 ml of tetrahydrofuran was added dropwise to a stirred solution of 3 g (0.0125 mole) of phthalanilic acid⁴⁹ in 20 ml of tetrahydrofuran. *N,N'*-Dicyclohexylurea began to deposit almost immediately. The reaction mixture was stirred for 2 hr at room temperature and then filtered to remove 2.64 g of the urea. Evaporation of the filtrate *in vacuo* gave 2.3 g (86%) of isoimide, mp 112–116°. Recrystallization of the product from aqueous acetonitrile without application of heat yielded 1.74 g (76%) of yellow crystals, mp 119–120° (lit. mp 112°,¹⁰ 115–117°,^{11c,49} 120–122°^{11e}). The ultraviolet spectrum (acetonitrile) showed: λ_{max} 325 m μ , ϵ_{max} 6800 (lit.²⁷ λ_{max} 326 m μ in dioxane); infrared spectrum (Nujol): 5.60, 5.88 μ (lit.²⁷ 5.58, 5.88 μ for KBr disk); mass spectrum: molecular ion peak at *m/e* 223. *Anal.* Calcd for $C_{14}H_{13}NO_2$ (223.22): C, 75.26; H, 4.07; N, 6.28. Found: C, 75.37; H, 4.10; N, 6.14.

Kinetic Measurements. Acetonitrile and imidazole were purified as previously described.^{40b} *N*-Phenylphthalimide (Eastman Kodak Co.) had mp 209°. Morpholine and mercaptoacetic acid were distilled before use. Other chemicals were of reagent grade and were used without further purification.

All kinetic studies were carried out at 30° in 10% acetonitrile-water, at ionic strength 0.45 (except below pH 1), adjusted with added KCl. For pH below 1, various concentrations of HCl were added to solutions containing 0.45 *M* KCl. Constant pH was maintained in the appropriate ranges with the following buffers: HCl, sodium formate-HCl, sodium acetate-acetic acid, NaH_2PO_4 - Na_2HPO_4 , imidazole-HCl, Tris-HCl, Borax-NaOH, and NaHCO_3 - Na_2CO_3 . Buffer concentrations are shown in Table I and pH was measured with a Radiometer TTT1c pH meter equipped with scale expander.

The rates of reaction of the isoimide I with nucleophiles were determined spectrophotometrically by the decrease in absorbance at 330 m μ , a wavelength where both *N*-phenylphthalimide (II) and phthalanilic acid exhibit negligible absorption. At pH greater than 6, the hydrolysis of the imide II was followed by the increase in absorbance at 270 m μ . At lower pH, the rate of hydrolysis of phthalanilic acid becomes comparable to or faster than imide hydrolysis; in this case, imide disappearance was measured from the absorbance decrease at 237 m μ , an isosbestic point for the spectra of phthalanilic acid and its products of hydrolysis. The equipment employed for determining the rates of slow or fast reactions has been described.^{40b}

Final optical densities were obtained generally after 7–10 half-lives of reaction, and observed first-order rate constants were calculated using the integrated form of the first-order rate equation. In general, nucleophile concentrations far exceeded the concentrations of the isoimide ($1\text{--}2 \times 10^{-4} M$). Even when very low nucleophile concentrations were employed (as with imidazole, azide, and mercaptoacetate), excellent first-order plots were obtained, indicat-

(45) S. L. Johnson and K. A. Rumon, *J. Am. Chem. Soc.*, **87**, 4782 (1965).

(46) T. C. Bruice, J. J. Bruno, and W. S. Chou, *ibid.*, **85**, 1659 (1963).

(47) All melting points are uncorrected. Microanalysis was performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Ultraviolet spectra were determined by means of a Perkin-Elmer Model 350 spectrophotometer and infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer.

(48) The general method employed is that of Cotter, *et al.*,¹² with minor modifications.

(49) M. L. Sherrill, F. L. Schaeffer, and E. P. Shoyer, *J. Am. Chem. Soc.*, **50**, 474 (1928).

(41) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1961, p 823.

(42) (a) M. T. Leplawy, D. S. Jones, G. W. Kenner, and R. C. Sheppard, *Tetrahedron*, **11**, 39 (1960); (b) D. S. Jones, G. W. Kenner, J. Preston, and R. C. Sheppard, *ibid.*, **21**, 3209 (1965).

(43) (a) T. C. Bruice and R. Lapinski, *J. Am. Chem. Soc.*, **80**, 2265 (1958); (b) W. P. Jencks and J. Carriuolo, *ibid.*, **82**, 1778 (1960).

(44) A. R. Butler and V. Gold, *J. Chem. Soc.*, 1334 (1962).

ing the rapid regeneration of the nucleophile as a result of imide formation.

pK Determinations. pK_a values for most of the nucleophiles studied were determined by titration of the conjugate bases with standard HCl, at 30° in 10% acetonitrile–water. Calculated ionic strength at the midpoint of the titration was 0.45. The titration data were analyzed by the method of Reed and Berkson⁵⁰ and the resulting pK_a values are listed in Table II.

Determination of Products. A. Hydroxamic Acid Assay for N-Phenylphthalimide. Reaction mixtures were analyzed for the imide II after complete disappearance of the isoimide (at least 8–10 half-lives of reaction) by means of a modification of the procedure of Lipmann and Tuttle.⁵¹ Immediately prior to use, a solution of neutral hydroxylamine was prepared by mixing equal volumes of 3.5 *N* NaOH and 4 *M* hydroxylamine hydrochloride (recrystallized from 95% ethanol); 1 ml of the mixture was added to a 3-ml sample of the reaction solution. After 10 min at room temperature, 0.5 ml of a 50% solution of FeCl₃ in 5 *N* HCl was added, followed by vigorous shaking. The absorbance of the ferric–hydroxamate complex was measured exactly 10 min later at 540 m μ , using quartz cuvettes with 5-cm path length and a Zeiss PMQ II spectrophotometer. Owing to the insolubility of N-phenylphthalimide at concentrations greater than 0.75×10^{-4} *M*, the maximum optical density change at 540 m μ which could be observed in these experiments was 0.25 unit. Acetonitrile, phthalic acid, and aniline did not interfere with the assay; phthalanilic acid formed a colored complex, whose absorption at 540 m μ was about 15% that of the imide. On the assumption that phthalanilic acid and the imide II accounted for the total isoimide reactant, standard curves were based on the absorbance produced by mixtures of phthalanilic acid and imide, varying from 0 to 100% in each component. Acetate and imidazole buffers did not affect color development; since some influence of carbonate, Tris, and low concentrations of phosphate buffers was noted, standard curves were prepared under the conditions of the reaction mixtures examined. Solutions containing azide ions or high concentrations of phosphate buffer could not be examined by this assay. To prevent possible hydrolysis of imide formed in the presence of carbonate buffer, neutral hydroxylamine was added within 2 min of initiation of reaction; less than 13% hydrolysis of imide would have occurred during that time.

B. Isolation of N-Phenylphthalimide. The rearrangement of I to II in the presence of nucleophilic agents was carried out under conditions identical with those used in the kinetic experiments, with the exception that the isoimide was generally at 0.001 *M*. Experiments were designed so that buffer catalysis would account for most of the rate of isoimide disappearance (Table III, columns 6 and 7) and buffer concentrations used are given in Table III. Under conditions where the half-life of the isoimide was greater than a few seconds (acetate, phosphate, and mercaptoacetate buffers), the isoimide precipitated initially; the heterogeneous reaction mixture was maintained with constant stirring at 30° for 5–12 hr to ensure complete reaction. The imide produced was then collected by filtration. Reactions in solutions containing imidazole, N-methylimidazole, Tris, and formate were sufficiently rapid that the isoimide underwent rearrangement prior to its precipitation from the supersaturated solution. A typical experiment is as follows. To a solution of 12 mg of isoimide in 5 ml of acetonitrile was added, in one portion, 45 ml of an aqueous solution of imidazole (0.011 *M*) adjusted to ionic strength 0.50 with KCl and at pH 6.9. The reaction mixture remained homogeneous for a few seconds, at which time crystallization of the imide began. After a few minutes at room temperature, the reaction vessel was chilled in ice to encourage maximum precipitation of N-phenylphthalimide. The product was collected by filtration, washed with cold water and cold ethanol, and dried *in vacuo* over

P₂O₅, yield 8.5 mg (72%), mp 209°. The infrared spectrum was superimposable on that of authentic imide.

The infrared spectrum of the crude imide (20 mg, 59%) obtained after acetate-catalyzed rearrangement of the isoimide (34 mg) at pH 3.7 indicated contamination by a small amount of by-product. Extraction of the imide with chloroform left an insoluble residue (2 mg). This residue was tentatively identified as phthalanilide (VII) by comparison of its infrared absorption to that of a substance (mp 237° dec)⁵² isolated on reacting equimolar quantities of isoimide and aniline in 50% aqueous acetonitrile at room temperature for 30 min. Addition of petroleum ether (bp 30–60°) to the chloroform extract yielded 10 mg (30%) of pure imide.

C. The Products of the Reaction of I with Azide Buffer. (1) Isolation of Products. The general procedure employed was as follows. To a solution of ca. 50 mg of isoimide in 2.5 ml of acetonitrile was added 22.5 ml of a solution containing 0.11 *M* azide buffer at the appropriate pH and enough KCl so that the final ionic strength was 0.45. The heterogeneous reaction mixture was stirred for 3 hr at room temperature, chilled in an ice bath, and acidified to pH 1.5 with 6 *N* HCl. The precipitate, a mixture of imide II and tetrazole III, was collected by filtration and dried *in vacuo* over P₂O₅. Separation of the two products was achieved by suspension of the precipitate in 2 ml of 0.4 *M* phosphate buffer, pH 7, followed by filtration. Acidification of the filtrate to pH 1.5 with 6 *N* HCl yielded the tetrazole as colorless crystals. The material insoluble in phosphate buffer was dissolved in chloroform. The solution was filtered and the solvent removed *in vacuo*, yielding N-phenylphthalimide. Results of experiments at three different pH values are given in Table IV (columns 4 and 5). The imide and tetrazole were identified by melting point and comparison of infrared spectra to authentic material.⁵⁴

(2) Spectral Analysis. Reaction of the isoimide (7.5×10^{-5} *M*) with 0.1 *M* azide buffer in 10% acetonitrile, $\mu = 0.45$, was allowed to proceed for at least ten half-lives. The final absorbance at 300 m μ of reaction mixtures at four pH values was compared to standard curves based on N-phenylphthalimide under the same conditions (λ_{\max} 300 m μ (ϵ_{\max} 2200)). The tetrazole does not absorb at this wavelength. Both products have the same extinction (1150) at 280 m μ . The absence of phthalanilic acid in the product mixtures was inferred from the constancy of the absorbance at 280 m μ . Since phthalanilic acid exhibits considerably greater absorbance than II or III at 280 m μ , sizeable absorbance increases should accompany decreasing imide yields if the amic acid were the alternate reaction product. Results are shown in Table IV (columns 2 and 3) and are compared (columns 6 and 7) with yields expected on the basis of the mechanism presented in the Discussion.

D. Phthalanilic Acid. Following the hydrolysis of I in 0.001 *N* NaOH, the reaction mixture was acidified to pH 2.0 with 1.1 *N* HCl, and the rate of disappearance of phthalanilic acid was measured at 30° from the absorbance decrease at 250 m μ . The resulting rate constant (0.019 min⁻¹) was similar to that obtained for authentic phthalanilic acid under the same conditions (0.018 min⁻¹). An analogous experiment was performed after hydrolysis of I in 0.01 *N* HCl. The rapid initial reaction ($t_{1/2}$ 45 sec) was followed by a slower disappearance of phthalanilic acid (rate constant 0.018 min⁻¹).

Phthalanilic acid was also identified by examination of ultraviolet spectra of reaction mixtures following hydrolysis of the isoimide at pH 1 or 11 and immediate adjustment to pH 8 with Tris buffer. The spectra were identical with those of authentic material (no λ_{\max} in the range 220–400 m μ ; ϵ_{230} ca. 13,000).

The product of isoimide hydrolysis was isolated from a reaction carried out in 50% acetonitrile–water, pH 1.0. After eight half-lives of reaction, the reaction mixture was adjusted to pH 9 with aqueous NaOH, reduced in volume by two-thirds, chilled, and acidified to pH 1 with concentrated HCl. The crystalline deposit was identified as phthalanilic acid (87% yield) by melting point and infrared spectrum.

(50) W. M. Clark, "Oxidation-Reduction Potentials of Organic Systems," Williams and Wilkins Co., Baltimore, Md., 1960, p 153. It should be noted that eq 27 and 28 of this reference apply to the titration of a proton donor with standard alkali. For the present instance (titration of a proton acceptor), the following modified expressions were used: $pK' - pH_T = -\log C$ and $z = (C + 1)[(z_T - z)10^z / (1 - 10^z)] - Cd$.

(51) F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **159**, 21 (1945).

(52) The melting point of phthalanilide has been variously reported as 230–231°, 237°, 49° and 251–252°^{11d} and seems to be influenced by the rate of heating.^{11e}

(53) R. D. Reynolds and G. L. Anderson, *J. Org. Chem.*, **28**, 3223 (1963).

(54) 1-Phenyl-5-(*o*-carboxyphenyl)tetrazole³⁰ (mp 165–166°) was obtained from Dr. H. Behringer, University of Munich. We are grateful to Dr. Behringer for his kind gift of this substance.