

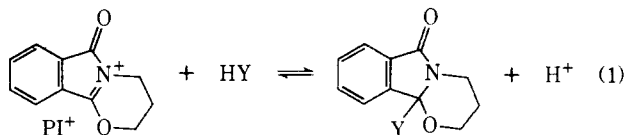
Mechanism of Hydrolysis of a Phthalimidium Cation. Direct Observation and Trapping of the Tetrahedral Addition Intermediate and the Effect of Strong Acid on Rate and Equilibrium Constants of the Reversible Reaction¹

Norman Gravitz and William P. Jencks*

Contribution No. 925 from the Graduate Department of Biochemistry,
Brandeis University, Waltham, Massachusetts 02154. Received June 19, 1973

Abstract: The formation and breakdown of the tetrahedral addition intermediate have been observed directly during the hydrolysis of *N,O*-trimethylenephthalimidium cation in weakly acidic solutions. Formation of the intermediate above pH 0 follows the rate law $k_b (\text{sec}^{-1}) = 56 + 4.6 \times 10^6 a_{\text{OH}^-} + k_b' [\text{B}]$ and breakdown follows the rate law $k_d (\text{sec}^{-1}) = 1.84 + 10.6 a_{\text{H}^+} + 5.2 \times 10^9 a_{\text{OH}^-} + k_d [\text{B}]$. Brønsted β values are 0.25 for the attack and 0.57 for the breakdown steps. In the presence of alcohols a portion of the phthalimidium is trapped as the alcohol addition compound. Substitution of an alkyl group for the proton of the water addition compound decreases the rate of pH-independent breakdown by a factor of *ca.* 10^8 . The water and buffer catalyzed reactions are formulated as general acid catalysis of the departure of alcohol from the anion of the tetrahedral intermediate (general base catalysis of ROH attack in the reverse direction) and it is suggested that this mechanism is general for reactions of carbonyl compounds. In strong acid solutions the hydrolysis reaction is reversible and the rate constant for hydrolysis is markedly decreased; $\log K_{\text{eq}}$ and $\log k_b$ follow the H_0 function with slopes of 0.94 and 0.82, respectively. The rate constant for dehydration of the phthalimide (the reverse reaction) shows a much smaller dependence on acidity, with a slope of <0.2 for $\log k$, against $-H_0$. It is suggested that these results are mainly a consequence of the large hydration requirement for the proton in the transition state and product.

There is strong, but indirect, evidence that many acyl transfer reactions proceed in a stepwise manner through tetrahedral addition intermediates. The elucidation of the mechanism of catalysis of such reactions requires a knowledge of whether the formation or breakdown of the tetrahedral intermediate is rate determining and an understanding of the mechanism of the rate-determining step. There are now many examples of stable tetrahedral addition compounds,² but there are only a few cases in which such compounds have been observed directly as reaction intermediates and even fewer in which their formation and breakdown have been studied quantitatively.³ In this series of papers we report an examination of the kinetics, equilibria, and structure-reactivity correlations for the trapping, formation, and breakdown of tetrahedral addition compounds of the *N,O*-trimethylenephthalimidium cation PI^+ (eq 1). The results lead to conclusions



regarding the mechanism and mechanism of catalysis of the individual steps that should be applicable to corresponding steps in other reactions of acyl com-

pounds. The imidate PI^+ has been prepared by Hünig and Geldern⁴ and shown to form stable addition compounds with alcoholate ions and secondary amines, which give adducts with no labile proton on the atom that adds to the phthalimide nucleus. For simplicity we will generally refer to the *N,O*-trimethylenephthalimidium ion as the "phthalimidium ion" and to the hydrolysis product, *N*-(3-hydroxypropyl)phthalimide, as the "phthalimide" in this series of papers.

Experimental Section

Materials. *N,O*-Trimethylenephthalimidium perchlorate, mp 172–173° dec, was synthesized by the procedure of Hünig and Geldern.⁴ Scrupulous care was taken to maintain anhydrous conditions, including oven drying of glassware, distillation of diethyl ether from sodium, drying of nitromethane with calcium sulfate followed by distillation over phosphorus pentoxide, and carrying out of procedures in a glove bag under dry nitrogen. The product was stable for a year at room temperature over drying agents.

Reagent grade salts and acids were used without further purification, except that chloroacetic and cyanoacetic acids were recrystallized and methoxyacetic acid was redistilled at reduced pressure. Acetonitrile was dried by stirring with Linde 4A molecular sieves followed by stirring with calcium hydroxide and distillation from fresh calcium hydride. It was stored under dry nitrogen in serum-stoppered bottles, taking care to avoid contact of the acetonitrile with the stopper.

Kinetics. Fast reactions were followed using a spring-loaded rapid-injection syringe⁶ or a stopped-flow apparatus^{6,7} with a cuvette or viewing chamber inserted into the thermostated cell compartment of a Gilford spectrophotometer. The changes in absorbance were recorded with a storage oscilloscope or chart recorder. Pseudo-first-order rate constants were determined in the usual manner from semilogarithmic plots of absorbance change against time or directly from the oscilloscope trace by measurement of half-lives, if 3 successive half-lives were in agreement with

(1) Supported by grants from the National Science Foundation (GB 5648) and the National Institute of Child Health and Human Development of the National Institutes of Health (HD 01247). N. G. was a Predoctoral Fellow of the National Institutes of Health (GM 212).

(2) See, for example, S. Hünig, *Angew. Chem., Int. Ed. Engl.*, **3**, 548 (1964), and references therein; G. V. Boyd and A. J. H. Summers, *Chem. Commun.*, 549 (1968); S. Cerrini, W. Fedeli, and F. Mazza, *ibid.*, 1607 (1971); G. Lucente and A. Romeo, *ibid.*, 1605 (1971).

(3) D. R. Robinson, *J. Amer. Chem. Soc.*, **92**, 3138 (1970); M. Rothe and R. Steinberger, *Tetrahedron Lett.*, 2467 (1970); M. Rothe, T. Toth, and D. Jacob, *Angew. Chem., Int. Ed. Engl.*, **10**, 128 (1971); D. A. Buckingham, J. Dekkers, A. M. Sargeson, and M. Wein, *J. Amer. Chem. Soc.*, **94**, 4032 (1972); see also M. I. Vinnik and Y. V. Moiseyev, *Tetrahedron*, **19**, 1441 (1963).

(4) S. Hünig and L. Geldern, *J. Prakt. Chem.*, **24**, 246 (1964).

(5) B. Perlmutter-Hayman and M. A. Wolff, *Isr. J. Chem.*, **3**, 155 (1965).

(6) R. E. Barnett and W. P. Jencks, *J. Amer. Chem. Soc.*, **91**, 6758 (1969).

(7) R. E. Barnett, Ph.D. Thesis, Brandeis University, 1968.

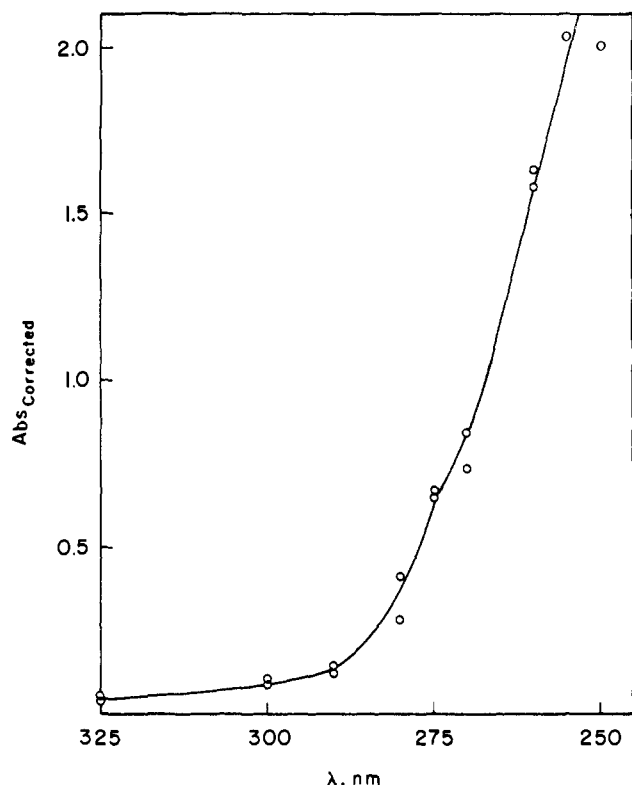


Figure 1. Absorption spectrum of the water addition intermediate formed during the hydrolysis of phthalimidium cation in 0.04 *M* chloroacetate buffer solutions at pH 2.61, 25°, and ionic strength 1.0 (KCl). Phthalimidium cation was generated from the acid-catalyzed breakdown of the piperidine adduct (4.6×10^{-4} *M*).

each other. Solutions were generally degassed with a water aspirator while on a vortex mixer for about 5 min, followed by temperature equilibration at 25°.

Breakdown of the water addition intermediate in the hydrolysis of the phthalimidium cation was followed by measuring the appearance at 300 nm of the phthalimide product at 25° utilizing the rapid-injection syringe. The reaction was initiated by the injection of 0.1 ml of 0.01 *M* phthalimidium perchlorate in dry acetonitrile to 2.4 ml of solution. The formation and breakdown of the addition intermediate were also followed in the stopped-flow apparatus by generating the phthalimidium cation from the acid-catalyzed breakdown of the morpholine adduct,^{4,8} which is fast relative to the subsequent reactions at low pH. The hydration reaction was followed by the decrease in the absorbance of phthalimidium cation at 350 nm in hydrochloric acid solutions at ionic strength 1.0, maintained with potassium chloride, or in concentrated sodium perchlorate solutions. A slightly basic solution of morpholine adduct and salt in one syringe was mixed with hydrochloric acid-salt solution in the other syringe, which had been adjusted to the same refractive index. The concentration of morpholine adduct was generally approximately 10^{-3} *M*. Attempts to measure the rate of formation of the addition compound at an ionic strength of 1.0, maintained with potassium chloride, were unsuccessful using the rapid-injection syringe because of mixing artifacts. Experiments using the rapid-injection syringe and 5 *M* sodium perchlorate solutions containing <0.1 *M* hydrochloric acid gave a rapid disappearance of most of the phthalimidium absorbance that was attributed to exclusion of the inhibitory salt from the acetonitrile-water interface, with a consequent rapid hydrolysis of phthalimidium ion before complete mixing took place. Qualitative evidence was obtained that hydroxide ion is also excluded during the mixing process, although morpholine is not.

The rate constant for the acid-catalyzed breakdown of the water addition intermediate was obtained from the slope of a plot of observed rate constants, extrapolated to zero buffer concentration or in dilute hydrochloric acid, against hydrogen ion activity.

The rate constant for hydroxide ion catalyzed breakdown was determined similarly from the slope of a plot against hydroxide ion activity of observed rate constants, extrapolated to zero buffer concentration, or corrected for buffer catalysis using the known catalytic constants. Hydroxide ion activity was determined from the pH of the solution and from $K_w = a_{H^+} \cdot a_{OH^-} = 10^{-14}$. The rate constant of the pH-independent "water" reaction was obtained from the intercepts of these plots at zero hydronium and hydroxide ion concentration. Rate constants for catalysis by buffers, k_B , were obtained from the slopes of plots of pseudo-first-order rate constants against buffer concentration and were corrected for the fraction free base of the buffer. Measurements of pH were obtained at the end of the kinetic runs.

The kinetics of phthalimidium cation hydrolysis and approach to equilibrium were followed in concentrated perchloric acid solutions at 300 and 325 nm, the absorbance maxima of phthalimide and phthalimidium cation, respectively. The reactions were initiated by the addition of 0.03 ml of 0.024 *M* phthalimidium perchlorate in acetonitrile or of 0.024 *M* phthalimide in water to 3 ml of perchloric acid solution. Values for the activity of water were taken from Robinson and Stokes⁹ and were calculated from the osmotic coefficients given by the same authors. Values of H_0 were taken from Yates and Wai.¹⁰

The apparent equilibrium constants, K_{eq}' , for phthalimidium ion hydrolysis were determined from the absorbance of phthalimidium ion at 350 nm in a series of perchloric acid solutions in the range 8–10 *M*; the absorbance of phthalimide is negligible at this wavelength. The equilibrium constant was obtained from eq 2 in

$$K_{eq}' = \frac{[I]}{[PI^+]} = \frac{A_{obsd}}{A_{max} - A_{obsd}} \quad (2)$$

which PI^+ is phthalimidium ion, I is phthalimide, A_{obsd} is the observed absorbance, and A_{max} is the absorbance for complete conversion to phthalimidium ion. The value of $1/A_{max}$ was obtained from the ordinate intercept of a plot of $1/A_{obsd}$ against $1/[HClO_4]$.

The spectrum of the water addition intermediate was obtained from the initial absorbance at a series of wavelengths after the injection of a constant amount of piperidine adduct into 0.04 *M* chloroacetate buffer, 44% free base. Cleavage of the adduct and hydration of the phthalimidium ion are fast under these conditions. A correction (less than 15% of the observed absorbance) was made for traces of phthalimide present in the initial reaction mixture and formed from hydrolysis at the time of the initial readings. The initial concentration of phthalimide was obtained by measuring the absorbance change at 300 nm upon alkaline hydrolysis to phthalamate anion. Correction for phthalimide formed during hydrolysis was made from the known concentrations of adduct and rates of phthalimide formation. A similar spectrum was obtained from the initial change in absorbance, before a significant amount of phthalimide is formed, upon the addition of 0.01 ml of water to a solution of phthalimidium ion in 3 ml of dry acetonitrile.

Results

The addition of phthalimidium perchlorate to water results in the rapid and complete disappearance of the absorption of the phthalimidium ion, followed by the slower (but still rapid) appearance of the absorption of the phthalimide product. The same result is obtained by generating the phthalimidium ion *in situ* by adding the piperidine or morpholine adduct of the phthalimidium ion to an acidic solution in which the acid-catalyzed expulsion of amine is faster than the hydration reaction. The spectrum of the water addition intermediate, which is similar to that of alcohol adducts, was obtained by measuring the absorption of a constant amount of phthalimidium ion at a series of different wavelengths immediately after completion of the hydration reaction (Figure 1). Thus, the overall reaction can be formulated according to eq 3, with $k_h > k_d$ and $k_h > k_{-h}$ in dilute acid solutions.

(9) R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," Butterworths, London, 1955.

(10) K. Yates and H. Wai, *J. Amer. Chem. Soc.*, **86**, 5408 (1964).

(8) N. Gravitz and W. P. Jencks, *J. Amer. Chem. Soc.*, **96**, 499 (1974).

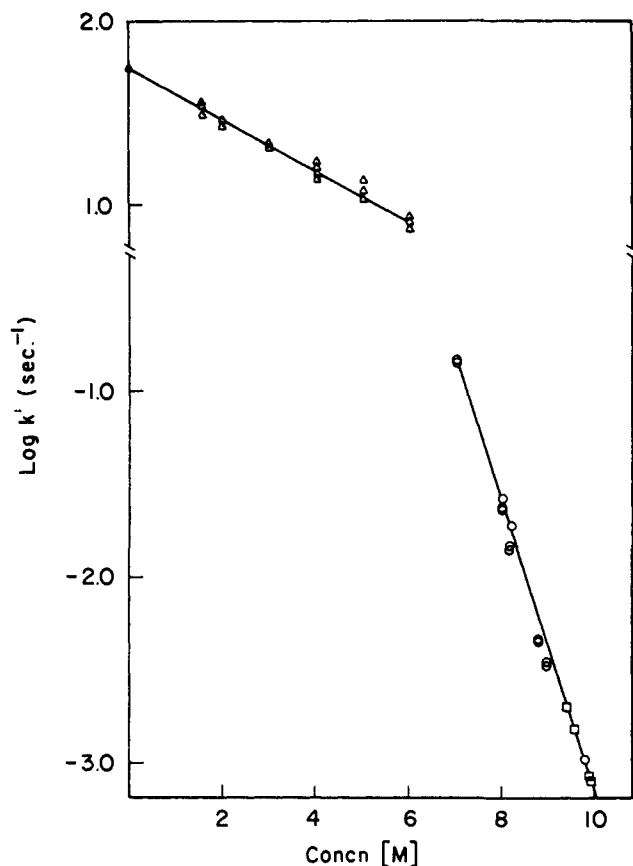
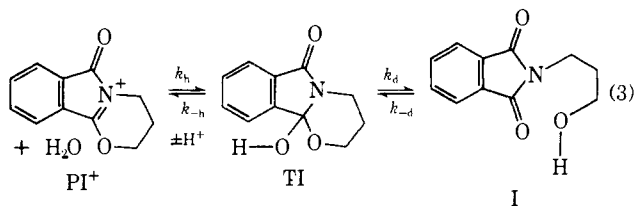


Figure 2. Inhibition of the attack of water on phthalimidium cation by sodium perchlorate (Δ) and by perchloric acid at 25° . The rate constants in perchloric acid were calculated from the observed rate for approach to equilibrium from phthalimide (\square), and from phthalimidium perchlorate (\circ).



The Hydration Reaction. The rate of water addition to the phthalimidium cation, generated from the morpholine adduct in the stopped-flow apparatus, was found to follow first-order kinetics with a rate constant of $56 \pm 6 \text{ sec}^{-1}$ at 25° in 0.02 and 0.05 M hydrochloric acid solutions brought to ionic strength 1.0 with potassium chloride. The rate of breakdown of the morpholine adduct was estimated to be >100 times faster than the rate of the hydration reaction under these conditions.

The reaction was also followed with the rapid injection syringe in 1.5–6.0 M sodium perchlorate containing hydrochloric acid at concentrations between 1.0 M (dilute salt solutions) and 0.2 M (concentrated solutions). The rate in 6 M sodium perchlorate solutions was found to be independent of hydrochloric acid concentration between 0.2 and 2.0 M . A plot of the logarithms of the observed rate constants against sodium perchlorate concentration is linear (slope -0.14 , Figure 2) and gives an extrapolated rate constant at zero sodium perchlorate concentration of 56 sec^{-1} . Since the reactions were carried out in the

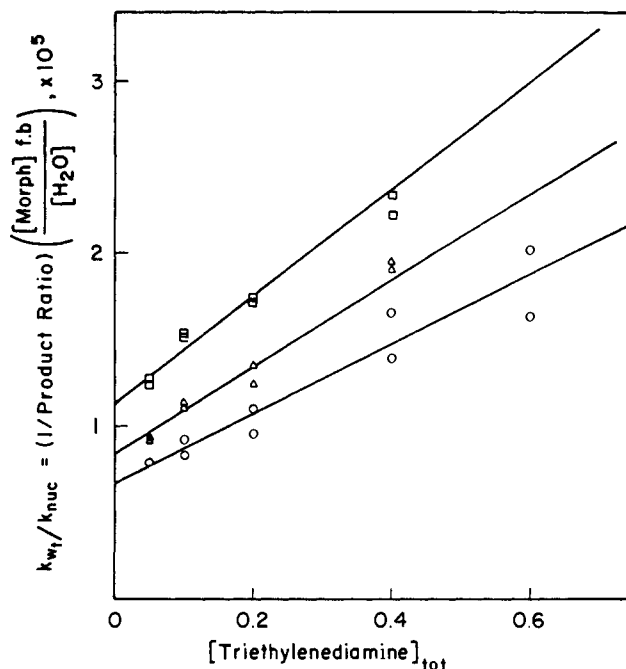


Figure 3. The effect of triethylenediamine buffers on k_{wt}/k_{nuc} (*i.e.*, $1/\text{product ratio}$) $([\text{morpholine}]_{f.b.}/[\text{H}_2\text{O}])$, for the morpholine/solvent competition reaction⁸ at 25° and an ionic strength of 1.0 maintained with tetramethylammonium chloride. The buffers are 0.50 (\circ), 0.65 (Δ), and 0.80 (\square) fraction free base. Phthalimidium ion was generated from the imidazole adduct.

presence of 1.0 M hydrochloric acid at the lower sodium perchlorate concentrations, this result is in good agreement with the rate constant obtained with the stopped-flow apparatus at an ionic strength maintained at 1.0 with potassium chloride. Rate constants obtained by the direct addition of the phthalimidium perchlorate in acetonitrile to 4.0–7.0 M solutions of sodium perchlorate containing hydrochloric acid, using the rapid injection syringe, gave rate constants identical with those obtained from experiments in which the phthalimidium ion was generated from the morpholine adduct in the stopped-flow apparatus. However, at acid concentrations of $<0.1 M$ mixing artifacts with the syringe technique prevented the determination of reliable rate constants (see Experimental Section).

Buffer catalysis of the hydration reaction could not be studied directly because of the requirement for acid to generate phthalimidium ion rapidly from the amine adducts. However, catalysis by triethylenediamine buffers was demonstrated by showing that the attack of water on phthalimidium ion is increased relative to that of morpholine with increasing buffer concentration (Figure 3). Since the breakdown and, hence, the formation of amine adducts are not subject to buffer catalysis and the rate constant for water addition in the absence of buffer is known, the rate constants for buffer catalysis of water addition may be calculated.⁸ The catalytic constants for the buffers at each buffer ratio were plotted against the fraction free base of the buffer to give a rate constant of $8.0 M^{-2} \text{ sec}^{-1}$ for catalysis by triethylenediamine as the free base and a zero intercept for catalysis by the acidic form of the buffer.

At intermediate pH values, at which the alcohol

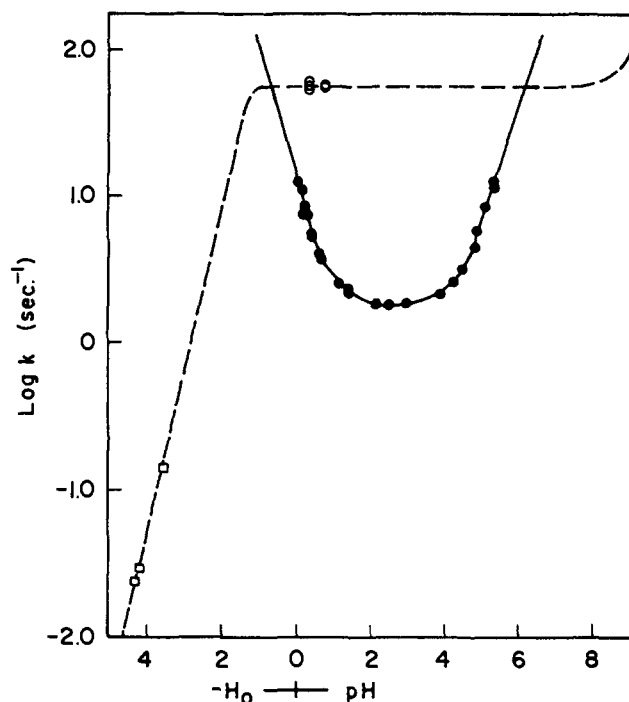


Figure 4. Dependence on acidity of the logarithms of pseudo-first-order rate constants for the formation and breakdown of the water addition intermediate in the hydrolysis of phthalimidium cation at 25°. The rate constants for breakdown of the water addition intermediate follow eq 4, as shown by the solid line. The dashed line describes the rate of the acid-inhibited (\square), pH-independent (\circ), and base-catalyzed formation of the intermediate. The ionic strength was maintained at 1.0 (KCl) except in concentrated acid.

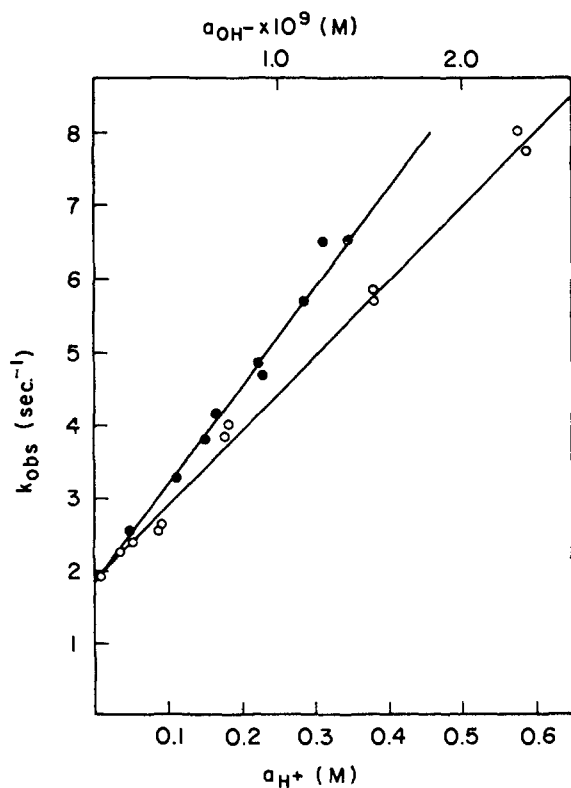


Figure 5. Dependence of the observed first-order rate constants for the breakdown of the water addition intermediate on the activity of hydronium (\circ) and hydroxide (\bullet) ions at 25°, ionic strength 1.0 (KCl). The rate constants were obtained from experiments in hydrochloric acid solutions or were extrapolated to zero buffer concentration.

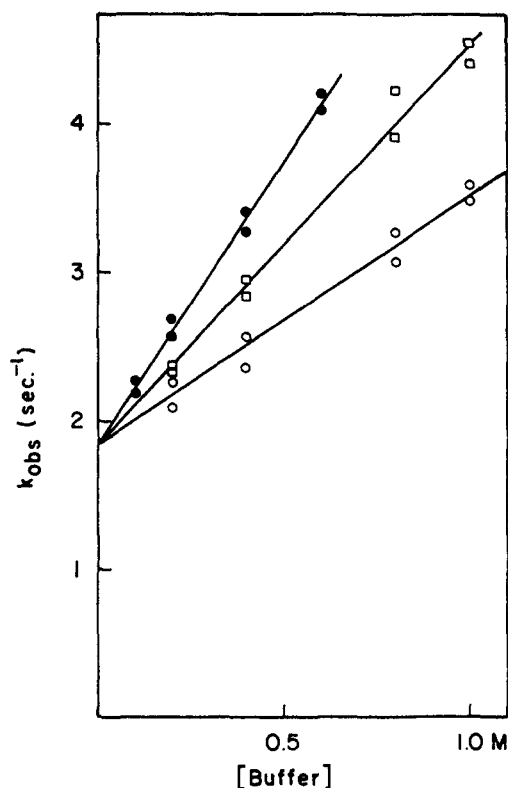


Figure 6. Dependence of the observed first-order rate constants for breakdown of the water addition intermediate on cyanoacetate buffer concentration at 25°, ionic strength 1.0 (KCl). The buffers were: 0.30 (\circ), 0.50 (\square), and 0.70 (\bullet) fraction free base.

adducts are stable, phthalimidium ion that is added directly or generated from an amine adduct in the presence of aqueous methanol or ethanol reacts with the alcohol to form a stable addition compound, as well as with water to give the hydrate that rapidly breaks down to phthalimide. For example, in the presence of 2 and 4 M methanol the phthalimidium ion gave 15 and 28% alcohol adduct as product. The ratio of alcohol adduct to hydrolysis products increases linearly with increasing ratio of alcohol to water concentration and indicates that on a molar basis methanol is 5.3 and ethanol is 3.7 times more reactive than water as nucleophilic reagents toward the phthalimidium ion. The alcohol addition reaction is described in more detail elsewhere.¹¹

Breakdown of the Water Addition Intermediate. The dependence on pH of the pseudo-first-order rate constants, extrapolated to zero buffer concentration, for breakdown of the water addition intermediate is shown in Figure 4 (solid line). The rate constants for the acid and base catalyzed and pH-independent reactions were obtained from the slopes and intercepts of plots of the rate constants against hydrogen and hydroxide ion activity (Figure 5). The rate of breakdown of the intermediate in the absence of buffer is described by eq 4 and the solid line in Figure 4 is based on these rate constants.

$$k_d (\text{sec}^{-1}) = 10.6a_{\text{H}^+} + 1.84 + 6.2 \times 10^9 a_{\text{OH}^-} \quad (4)$$

The breakdown is also catalyzed by the basic species of buffers (Figure 6); no general acid catalysis was

(11) N. Gravitz and W. P. Jencks, *J. Amer. Chem. Soc.*, **96**, 507 (1974).

detected. The rate constants k_B for general base catalysis and the experimental conditions for their determination are summarized in Table I.

Table I. Base-Catalyzed Breakdown of the Water Addition Intermediate Formed during Phthalimidium Cation Hydrolysis at 25° and Ionic Strength 1.0 (KCl)

Base	Total buffer concn, M	Fraction free base	No. of runs	$k_B, M^{-1} \text{sec}^{-1}$
Hydroxide Acetate	0.02–0.10	0.50	5	5.2×10^9
	0.02–0.20	0.30	8	
	0.02–0.20	0.15	6	
Methoxyacetate	0.05–0.20	0.70	6	1.1×10^9
	0.10–0.60	0.30	8	
Chloroacetate	0.10–0.80	0.70	6	3.2×10^1
	0.20–0.80	0.30	8	
Cyanoacetate	0.10–0.60	0.70	8	1.1×10^1
	0.20–1.0	0.50	8	
	0.20–1.0	0.30	8	
Water				5.7 $3.3 \times 10^{-2} \text{ }^a$

^a Calculated from the rate constant for the pH-independent reaction divided by the water concentration (55.5 M).

Hydrolysis and Formation of Phthalimidium Ion in Concentrated Acid Solutions. In 8–10 M perchloric acid solutions the hydrolysis of the phthalimidium cation to phthalimide is reversible and the equilibrium as well as the rate constants in both directions may be measured. Apparent equilibrium constants K_{eq}' for phthalimidium ion hydrolysis were determined from absorbance measurements at 350 nm, as described in the Experimental Section, and are summarized in Table II along with some observed pseudo-first-order rate

Table II. Equilibrium and Approach to Equilibrium for Phthalimidium Perchlorate and Phthalimide in Concentrated Perchloric Acid Solutions at 25°

HClO_4 , M	$-H_0$	$K_{eq}'^a$	k_{obsd}^b , sec^{-1}	k_f^c , sec^{-1}	$k_r \times 10^4$, sec^{-1}
8.05	4.26	155	1.95×10^{-2}	1.95×10^{-2}	1.25 ^e
8.50	4.68	54	9.2×10^{-3}	9.03×10^{-3}	1.67
9.03	5.18	24	3.7×10^{-3}	3.55×10^{-3}	1.5
9.37	5.51	8.9	2.04×10^{-3}	1.89×10^{-3}	2.13
9.61	5.74	6.6	1.35×10^{-3}	1.17×10^{-3}	1.8
9.80	5.93	4.21	1.04×10^{-3}	8.5×10^{-4}	1.9
10.02	6.15	2.40	7.66×10^{-4}	5.2×10^{-4}	2.26

^a Apparent equilibrium constant $K_{eq}' = [I]/[PI^+]$. ^b Observed rate constant for approach to equilibrium. ^c Pseudo-first-order rate constant for phthalimidium cation hydrolysis. ^d Pseudo-first-order rate constant for phthalimidium formation from phthalimide (see text). ^e Calculated from k_f , k_{eq}' , and k_{obsd} .

constants for approach to equilibrium and rate constants for the forward and reverse reactions, calculated from the equations $K_{eq}' = k_f/k_r$ and $k_{obsd} = k_f + k_r$ at each acid concentration. The effect of perchloric acid on k_f is also shown in Figures 2 and 4.

An equilibrium mixture formed from phthalimide in 70% perchloric acid was quenched in 80% aqueous ethanol. The rate constants for hydrolysis of aliquots of the product (70–80% yield) in buffered aqueous solutions were found to be the same as for hydrolysis of the ethanol adduct prepared from phthalimidium

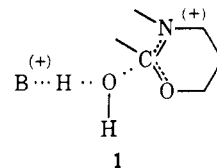
perchlorate,¹¹ thereby confirming the identity of the phthalimidium ion that had been observed spectrophotometrically in concentrated perchloric acid. Spectra taken during the approach to equilibrium from both directions in 9.4 M perchloric acid exhibited isosbestic points at 239, 245–246, 258, and 305 nm; no evidence was obtained for the accumulation of significant amounts of the addition intermediate under these conditions.

Discussion

Formation of the Tetrahedral Addition Intermediate.

The addition of water to N,O -trimethylenephthalimidium ion to form the tetrahedral addition compound and the breakdown of this intermediate to phthalimide (eq 3) were observed directly as a rapid disappearance of the absorbance of the starting material followed by a slower appearance of the absorbance of the product at low pH values. The rate of hydration is independent of acidity in dilute acid solutions, but is inhibited by strong acid. Although the rate of attack of hydroxide ion could not be measured directly, the ratio of the rate constants for the attack of water and hydroxide ion was obtained from the dependence on pH of the ratio of water to amine attack on the phthalimidium ion.⁸ A rate constant of $4.6 \times 10^6 M^{-1} \text{sec}^{-1}$ was calculated from this ratio and the observed rate constant for water attack of 56 sec^{-1} . This defines the complete pH profile for the hydration step, which is shown as the dashed line in Figure 4. Hydroxide ion attack becomes significant at approximately pH 8.

General base catalysis of the hydration step was demonstrated from the effect of buffers on the ratio of water to morpholine attack at constant pH (Figure 3). A two-point Brønsted plot based on the rate constants for catalysis of water addition by triethylenediamine and by water gives a β value of 0.25, in good agreement with the β value of 0.26 for the analogous addition of ethanol.¹¹ The reaction of hydroxide ion is formulated as a direct nucleophilic attack because no significant free energy advantage is expected from general base catalysis of water addition by hydroxide ion.¹² The rate constant for hydroxide ion addition is some 500-fold faster than predicted from the two point Brønsted plot for general base catalysis, in accord with this formulation. The hydration of other imidates and of a carbonium ion, malachite green, is known to be subject to general base catalysis.^{13–15} The mechanism of the catalyzed hydration-dehydration step may be formulated as 1; this mechanism is considered in greater detail elsewhere.¹¹



The product-determining step of the solvolysis reaction is the attack of solvent on phthalimidium cation

- (12) W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 4731 (1972).
 (13) E. S. Hand and W. P. Jencks, *J. Amer. Chem. Soc.*, **84**, 3505 (1962).
 (14) G. L. Schmir and B. A. Cunningham, *J. Amer. Chem. Soc.*, **87**, 5692 (1965).
 (15) C. D. Ritchie, *J. Amer. Chem. Soc.*, **94**, 3275 (1972).

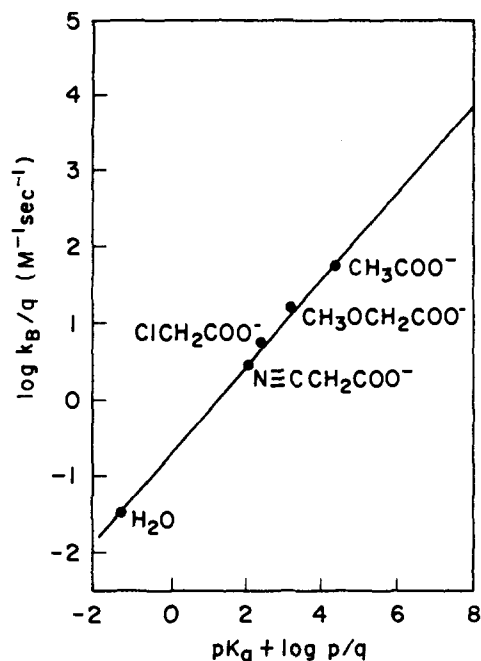


Figure 7. Brønsted plot for general base catalysis of the breakdown of the water addition intermediate formed during phthalimidium cation hydrolysis. Statistical corrections were made according to Bell and Evans.^{21b} The line of slope 0.57 is the best fit through the rate constants for carboxylate buffers.

over the entire pH range, with the possible exception of a region below pH 2, in spite of the fact that there is a cross-over of the rate constants for the hydration and dehydration steps between pH 0 and 6 (Figure 4). The rate constant k_{-1} for the back reaction, the dehydration of the water addition compound to phthalimidium ion, was not measured directly, but should be of a magnitude similar to that for the expulsion of ethanol from the ethanol adduct. The rate constant for the pH-independent expulsion of ethoxide ion¹¹ is $3.3 \times 10^{-8} \text{ sec}^{-1}$, which is negligible compared to the pH-independent rate constant of 1.84 sec^{-1} for breakdown of the water addition compound to phthalimide, so that at neutral and alkaline pH values any water addition compound that is formed will go on to products faster than it reverts to starting materials.

The fact that alcohol trapping experiments can be used to demonstrate the comparable molar reactivities of water and alcohols toward phthalimidium ion confirms that the attack step is product determining under the conditions of these experiments. If addition compound formation were reversible, the fast formation and breakdown of the water addition compound would rapidly drain away all of the phthalimidium ion and only the hydrolysis product (phthalimide) would be observed. It has been shown by kinetic criteria that the addition of water is the rate-determining step in the hydrolysis of other imidates, with rare exceptions at low pH values.^{14, 16-19}

Breakdown of the Tetrahedral Addition Intermediate.

(16) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968).

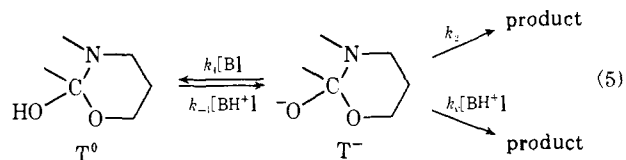
(17) G. M. Blackburn and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 2638 (1968).

(18) T. C. Pletcher, S. Koehler, and E. A. Cordes, *J. Amer. Chem. Soc.*, **90**, 7072 (1968).

(19) B. A. W. Collier, F. W. Eastwood, L. Y. Foo, and N. C. G. H. Y. Ho, *Chem. Commun.*, 900 (1970).

The key factor in the breakdown of the water addition intermediate to phthalimide above pH 2 is the ability of this intermediate to lose a proton from its hydroxyl group. If an alcohol instead of a water molecule adds to the phthalimidium ion at neutral or alkaline pH the tetrahedral intermediate is trapped in the form of the stable alcohol adduct (the pH-independent rate constant for the breakdown of the ethanol adduct is $3.3 \times 10^{-8} \text{ sec}^{-1}$); the intermediate formed from water addition breaks down to product some 10^8 more rapidly at pH 2-3 and even faster above pH 4, as the base-catalyzed breakdown becomes significant ($k (\text{sec}^{-1}) = 1.84 + 5.2 \times 10^9 a_{\text{OH}^-}$).

The rate constant of $5.2 \times 10^9 \text{ M}^{-1} \text{ sec}^{-1}$ for hydroxide ion catalysis is in the range expected for a diffusion-controlled reaction, so that one might propose that the reaction involves breakdown of the hydrate on each encounter with a hydroxide ion. However, this value of the rate constant is fortuitous and the observed hydroxide ion reaction proceeds by a mechanism of specific base catalysis in which the intermediate anion T^- is formed in a rapid equilibrium step and the rate-determining step is the breakdown of this intermediate, so that $k_{\text{OH}^-} = k_1 k_2 / k_{-1}$ (eq 5). The pK_a of



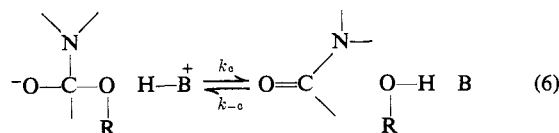
the intermediate T^0 is on the order of 7.5, based on the strong electron-withdrawing effect of the phthalimide nucleus of some 8.4 units for amine adducts⁸ and a pK_a of 15.9 for ethanol.²⁰ With a pK_a of this magnitude, the rate of formation of T^- by proton transfer from T^0 to water or buffer bases is much larger than $k_{\text{OH}^-} a_{\text{OH}^-}$ under the conditions of the experiments, so that T^- is at equilibrium with T^0 and the formation of T^- cannot be rate determining. For example, assuming diffusion-controlled rates of proton transfer^{21a} from hydronium ion and carboxylic acids to T^- , the rate of proton removal from T^0 is approximately 10^5 sec^{-1} by 0.01 M acetate, $6 \times 10^3 \text{ sec}^{-1}$ by 0.06 M chloroacetate, 300 sec^{-1} by water, and only 4 sec^{-1} by hydroxide ion at pH 4.6. The rate of formation of T^- is also much larger than the observed reaction rate in the presence of buffers so that proton removal is not rate determining in the buffer-catalyzed reaction; furthermore, a thermodynamically unfavorable rate-determining proton transfer should give a Brønsted slope of 1.0 rather than the observed slope of 0.57^{21a} (Figure 7). The rate constant k_2 for the unassisted breakdown of T^- , calculated from k_{OH^-} and the dissociation constant of T^0 , is ca. $1.6 \times 10^3 \text{ sec}^{-1}$. Because of the relatively slow breakdown and the rapid rate of proton transfer catalyzed by buffer and solvent, there is no advantage to a "one-encounter" mechanism in which the same molecule of catalyst removes a proton and donates it to the leaving group.

The mechanism of the buffer-catalyzed reaction may be assigned with considerable confidence to general acid

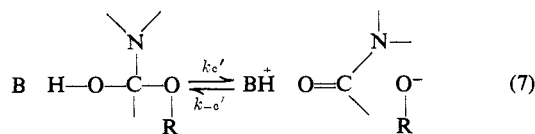
(20) S. Takahashi, L. A. Cohen, H. K. Miller, and E. G. Peake, *J. Org. Chem.*, **36**, 1205 (1971).

(21) (a) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964); (b) R. P. Bell and P. G. Evans, *Proc. Roy. Soc., Ser. A*, **291**, 297 (1966).

catalysis of the breakdown of the anionic intermediate (eq 6) rather than to the kinetically equivalent general



base catalysis according to eq 7 and 8. Encounter of



$$k_{a'} = k_a K_{\text{BH}^+} / K_{\text{T}^0} \quad (8)$$

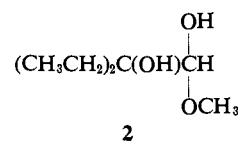
the neutral hydrate with a buffer base of $\text{p}K > 7.5$ would result simply in a rapid, thermodynamically favorable proton transfer to form the anion T^- which would break down in a subsequent step; thermodynamically unfavorable reprotonation followed by a concerted proton transfer and carbon-oxygen cleavage would clearly be a less favorable mechanism, in accord with a recently proposed rule.¹² Catalysis by acetate ion ($\text{p}K = 4.6$) would provide only a small additional advantage, certainly much less than could be gained from proton transfer from acetic acid to a developing alkoxide ion in the mechanism of eq 6. The situation may be represented diagrammatically by three-dimensional reaction-coordinate diagrams with separate axes for the proton transfer and carbon-oxygen bond breaking processes;²² the mechanism of eq 7 must proceed by a stepwise path along the borders of such a diagram for bases of $\text{p}K > 7.5$. In view of the considerable stability of T^- ($\text{p}K \text{ ca. } 7.5$, $k_2 = 1.6 \times 10^3 \text{ sec}^{-1}$), the same stepwise path would surely be favored for proton removal from T^0 by a base of $\text{p}K = 4.6$ and, since breakdown of T^- (k_2) is much slower than its formation from T^0 (k_1), general base catalysis of the reaction would not be observed. In the corresponding diagram for the mechanism of eq 6 a much larger advantage may be gained by avoiding the formation of the two unstable intermediates at the corners of the diagram that would be required for a stepwise reaction: alkoxide ion and the zwitterion that is fully protonated on the leaving oxygen atom, so that a more or less concerted pathway through the central region of the diagram is feasible. Such a mechanism is supported by the observed Brønsted slope of $\beta = 0.57$ (Figure 7), which is equivalent to a value of $\alpha = 1 - \beta = 0.43$ for catalysis by BH^+ ; a stepwise mechanism with a rate-determining thermodynamically unfavorable proton transfer would give an α value approaching 1.0.^{21a}

The α value of 0.43 for general acid catalysis of the expulsion of alcohol from T^- may be compared to the α value of $1 - 0.25 = 0.75$ for general acid catalysis of the expulsion of water or unsubstituted alcohols¹¹ from T^0 . The smaller α value for the former reaction suggests that there has been a smaller amount of proton transfer to the leaving oxygen atom; *i.e.*, less proton transfer is required for the reaction of T^- , with its large driving force for alcohol expulsion arising from the negative charge of the oxyanion. Conversely, in the reverse reactions the larger β value of 0.57 for

(22) W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).

general base catalysis of the attack of ROH on an uncharged amide than for attack on a cationic amide or imidate ($\beta = 0.25$) suggests a larger amount of proton removal in the former, more difficult, reaction. These conclusions are in accord with the predictions that were made from inspection of three-dimensional energy contour diagrams for reactions of this type.²² However, no prediction can be made regarding the relative amounts of carbon-oxygen bond formation or cleavage in these two reactions.

The fact that the point for water fits on the Brønsted plot of Figure 7 suggests that the mechanism of the "water reaction" is the same as that for the other catalysts on the plot. According to the mechanism of eq 6, this reaction represents hydronium ion catalysis of the breakdown of T^- . The fact that the pH-independent breakdown of the water addition compound is some 10^8 faster than that of the alcohol adduct is consistent with the mechanism of eq 6, since proton removal to form the intermediate T^- is impossible for the alcohol adduct. This mechanism is reasonable for catalysis by the hydronium ion, as well as by weaker acids, because of the strongly electron-withdrawing character of the phthalimide nucleus. The resulting low basicity of the leaving oxygen atom of T^- makes protonation thermodynamically unfavorable even by the solvated proton so that "concerted" catalysis, which avoids both the unstable protonated ether oxygen atom and the basic alkoxide ion product, is energetically feasible. This mechanism is also supported by the relative rate constants for the pH-independent breakdown of T^0 and the simple hemiacetal **2**.²³ The rate constant of $7 \text{ M}^{-1} \text{ sec}^{-1}$ for the acid-



catalyzed breakdown of **2** is similar to that of $10.6 \text{ M}^{-1} \text{ sec}^{-1}$ for T^0 , but the pH-independent reaction of T^0 ($k = 1.84 \text{ sec}^{-1}$) is nearly 10^4 faster than that of **2** ($k = 4.8 \times 10^{-4} \text{ sec}^{-1}$). This difference is difficult to explain if T^0 and **2** break down directly, but is reasonable for a mechanism that proceeds through the corresponding anions because formation of the anion will be greatly favored by the electron-withdrawing nucleus of T^0 .

On the other hand, there is little or no thermodynamic advantage to proton transfer from water to the leaving alkoxide ion, so that the k_2 term of eq 5 presumably does not involve general acid catalysis by water. The rate constant k_{OH^-} that corresponds to this term falls some 20 times above the extrapolated Brønsted line of Figure 7.

These considerations support several generalizations. First, the reverse reaction of eq 6 corresponds to the attack of alcohol or water on an amide and, since the same transition state must be reached in both directions, the mechanism of catalysis of this attack must involve proton removal from the attacking nucleophile by water or other general base catalysts. A similar mechanism was proposed to account for part of the "water" reaction and general base catalyzed hydrolysis

(23) A. L. Mori, M. A. Porzio, and L. L. Schaleger, *J. Amer. Chem. Soc.*, **94**, 5934 (1972).

of acetylimidazole, although the rate-determining step of this reaction has not been conclusively established.²⁴ However, the observed general base catalysis of the hydrolysis of most amides involves breakdown of the tetrahedral intermediate with amine expulsion.²⁵

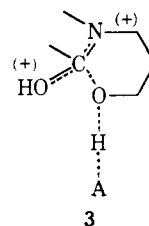
Second, the mechanism of eq 6, rather than that of eq 7, may be assigned to the observed general base catalysis of alcohol expulsion during the breakdown of the tetrahedral addition intermediate in the aminolysis of esters with unsubstituted alkyl leaving groups.¹⁷ The more general conclusion appears to be warranted that the mechanism of eq 6 will be preferred to that of eq 7 for general acid–base catalysis of the departure or addition of water or unsubstituted aliphatic alcohols in all reactions of amides and other carbonyl compounds. The electron-withdrawing substituents in a tetrahedral addition intermediate will always make the hydroxyl group of the intermediate more acidic than that of water or the alcohol. Consequently, avoiding the formation of the alkoxide or hydroxide ion by the mechanism of eq 6 will provide a larger saving in free energy than avoiding the formation of the anion of the addition compound through the mechanism of eq 7. A similar situation holds for the dehydration of a 3-hydroxyenol, which may be regarded as the vinylogous dehydration of a hydrated carbonyl group.²⁶ The Brønsted α value for addition to simple carbonyl compounds decreases progressively with increasing basicity of the attacking reagent and no general acid catalysis is detectable ($\alpha = 0$) for strong, basic nucleophiles,²⁷ in accord with this generalization.

Third, the existence of a labile proton on the hydroxyl group of a tetrahedral intermediate is of primary importance in determining the mechanism and rate-determining step of many acyl transfer reactions. Thus, the facile removal of a proton from the tetrahedral intermediate and the advantage gained from catalysis according to the mechanism of eq 6 provide an explanation for the fact that water addition is the rate-determining step in the hydrolysis of imidates at neutral and alkaline pH;^{14,16–19} in the case of phthalimidium ion hydrolysis the advantage is apparent in the factor of about 10^8 favoring breakdown to products by this mechanism rather than regeneration of starting materials by expulsion of the attacking group. Partial cleavage of the oxygen–hydrogen bond appears to be important even in acid-catalyzed reactions, since the acid-catalyzed breakdown of **2** has been estimated to be 500 times faster than that of the corresponding dimethyl acetal.²³

Fourth, the rate of breakdown of T^- supports the conclusion that the lifetime of certain ionic species of tetrahedral addition intermediates is so short that they cannot reach equilibrium with respect to proton transfer and may not even exist at all.^{22,28} The rate constant for breakdown of T^- catalyzed by the solvated proton is $5.9 \times 10^7 M^{-1} \text{sec}^{-1}$ (eq 8). The driving force for alcohol expulsion comes from the oxygen anion and

from nitrogen, but the basicity and electron-donating ability of the nitrogen atom are small because its free electron pair is largely delocalized by resonance into the amide carbonyl group of the starting material. Consequently, a more ordinary tetrahedral intermediate, with a more basic oxygen atom, an unencumbered nitrogen atom, and significant development of the resonance stabilization of the amide product in the transition state, would be expected to break down with a rate constant that is much larger than that for T^- ; *i.e.*, the breakdown would become diffusion controlled.

The mechanism of acid-catalyzed breakdown of T^0 certainly involves protonation of the leaving alcohol and probably involves general acid catalysis, by analogy with the mechanism of breakdown of the alcohol adduct¹¹ and because of the great instability of the O-protonated hydrate. The strong electron-withdrawing influence of the phthalimide nucleus will lower the pK of this intermediate some 8.4 units below that of a protonated ether. As in the case of ortho ester hydrolysis,²⁹ the rate constant for the protonation of this intermediate is similar to or less than the observed rate constant for the overall reaction, depending on the assumption one makes regarding the acidity dependence of ether protonation and assuming a diffusion-controlled proton transfer from the protonated intermediate to water.³⁰ Again, general acid catalysis serves to avoid the formation of this unstable intermediate as well as the alternative alkoxide ion as discrete entities by bringing about proton donation to the leaving group in a more or less concerted manner. The proposed mechanism, **3**, is similar to that for the general base catalyzed



reaction (eq 6) and is essentially the mirror image of that for the hydration reaction (1). In contrast to the pH-independent breakdown, which is 10^8 faster for the water than for the alcohol addition compound, the acid-catalyzed (endocyclic) breakdown of the water addition compound ($k_H^+ = 10.6 M^{-1} \text{sec}^{-1}$) occurs at about the same rate as the exocyclic breakdown of the ethanol adduct ($k_H^+ = 24.6 M^{-1} \text{sec}^{-1}$).

Effects of Strong Acid on Rate and Equilibrium Constants. Hydrolysis of the phthalimidium ion is of particular interest in that it is significantly reversible in the presence of concentrated perchloric acid, so that the effect of acidity upon the equilibrium as well as the rate

(29) C. A. Bunton and R. H. De Wolfe, *J. Org. Chem.*, **30**, 1371 (1965); T. Pletcher and E. A. Cordes, *ibid.*, **32**, 2294 (1967).

(30) If a simple ether has the same basicity as water, the pK_a of the protonated hydrate is approximately $-1.7 - 8.4 = -10.1$ and, assuming a rate constant of $10^{10} M^{-1} \text{sec}^{-1}$ for the protonation of water by this species, the rate constant for protonation of the hydrate is $40 M^{-1} \text{sec}^{-1}$, comparable to the observed rate constant of $10.6 M^{-1} \text{sec}^{-1}$. Alternatively,²⁹ the observed rate constant would require a rate constant for the deprotonation of the protonated hydrate of $>10^{11} \text{sec}^{-1}$ if this species is at equilibrium and its breakdown is rate determining. In fact, simple ethers are half-protonated only at $H_0 = -6.4$, although the ratio $\log ([BH^+]/[B])$ gives a slope of only 0.32–0.35 when plotted against $-H_0$: D. G. Lee and R. Cameron, *Can. J. Chem.*, **50**, 445 (1972).

(24) R. Wolfenden and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 4390 (1961).

(25) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 523.

(26) D. J. Hupc, M. C. R. Kendall, G. T. Sinner, and T. A. Spencer, *J. Amer. Chem. Soc.*, **95**, 2260 (1973).

(27) Reference 25, p 198.

(28) R. E. Barnett and W. P. Jencks, *J. Amer. Chem. Soc.*, **91**, 6758 (1969).

constants in both directions can be determined. The reversible ring closure has some similarities to both the reversible synthesis of γ -butyrolactone³¹ and the equilibrium dehydration of alcohols to carbonium ions, as measured by the H_R function,^{9,32} but there are significant differences with respect to both of these reactions. The experimental fact that is most surprising, at least upon initial inspection, is that the effect of acid on the equilibrium closely parallels a strongly inhibitory effect of acid on the rate of phthalimidium hydrolysis (a 38-fold decrease between 8 and 10 M perchloric acid), whereas the acid-catalyzed dehydration of the phthalimide shows a very much smaller dependence on acidity (Table II). The rate and equilibrium constants are plotted as a function of $-H_0$ in Figure 8.

The inhibition of the rate of phthalimidium hydrolysis by acid follows the H_0 function with a slope of 0.82 for $\log k$ against H_0 ; the corresponding Bunnett and Olsen³³ slope ϕ against $H_0 + \log [\text{HClO}_4]$ is very similar, 0.87. These slopes are similar to those for acid inhibition³⁴ of the hydrolysis of other protonated or cationic imidates.^{33,35-38} There are three general explanations for such inhibition. (1) Inhibition reflects a stabilization of the phthalimidium ion relative to the transition state through a salt effect; *i.e.*, the acid increases f_{\pm}/f_{PT^+} .³⁹ (2) Inhibition reflects a decrease in the availability of several water molecules that are required for proton transfer and hydrolysis in a strongly solvated transition state.^{33,36-38,40} (3) There is acid inhibition of the reaction because of a change to a rate-determining step with an uncharged, unprotonated transition state in the strong acid solution.⁴¹ We will show that explanation 3 is untenable, explanation 1 may contribute, and explanation 2 provides the principal basis for the acid inhibition.

The acid inhibition is not caused by a change to a rate-determining step with an uncharged transition state because (a) both steps of the reaction (*i.e.*, both the formation and the breakdown of the tetrahedral intermediate) have been shown directly to proceed through cationic transition states containing a proton; the attack of water on the phthalimidium ion must correspond to acid-catalyzed dehydration of T^0 in the reverse direction according to the principle of microscopic reversibility. (b) The reverse, ring closure reaction is acid catalyzed so that the forward reaction must also contain a proton in the transition state, in spite of the observed acid inhibition, under the same experimental conditions. Thus, there is no step in the reaction that proceeds through an uncharged,

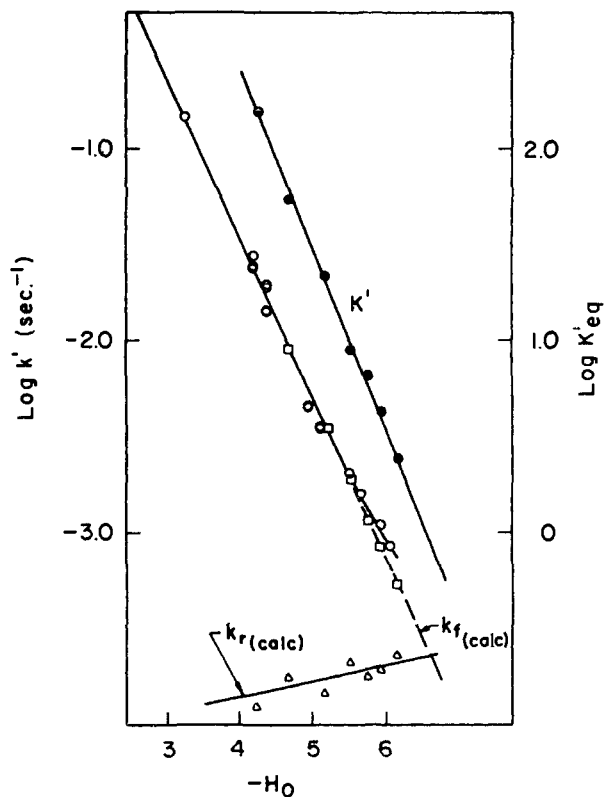


Figure 8. The dependence on the H_0 function for: the apparent equilibrium constants K_{eq}' (\bullet), the observed pseudo-first-order rate constants for the approach to equilibrium k_{obsd} (\circ), and the calculated pseudo-first-order rate constants for the forward direction k_f (\square) and the reverse direction k_r (Δ) of the approach to equilibrium for phthalimidium perchlorate hydrolysis in 7–10 M perchloric acid at 25°.

unprotonated transition state.⁴² It has been shown previously that the inhibition of the hydrolysis of a morpholine imidate by hydrochloric acid is abolished if the experiment is carried out at a constant ionic strength maintained with lithium chloride;¹⁷ *i.e.*, the inhibition represents a salt effect rather than an acid-dependent decrease in the concentration of an unprotonated transition state. Explanation 3 does apply, however, to the acid inhibition of the hydrolysis of thioimidates and 1,2-dimethylbenzoxazolium ion.^{36,41b,44}

Inhibition by salt (explanation 1) is observed with sodium perchlorate, which gives a Setschenow slope k_s of $\log k$ against $[\text{NaClO}_4]$ of -0.14 (Figure 2). The rate is not inhibited significantly by dilute hydrochloric acid, up to 2 M, in the presence of sodium perchlorate. A specific effect of perchlorate ion of the sort found for the stabilization of carbonium ions⁴⁵ is suggested for

(42) Expulsion of amide from the tetrahedral addition intermediate to give a nine-membered ring intermediate is possible in principle but is unlikely to represent the main reaction path since ring closure must occur again to give the phthalimide product and formation of such large ring compounds is not favored in the phthalimide series.⁴³ The observed rate of acid-catalyzed breakdown of the intermediate is similar to that for breakdown of the alcohol adduct to phthalimidium ion, as would be expected if the former reaction also involved alcohol expulsion. In any case, breakdown of the intermediate has been shown directly to be acid catalyzed and amide expulsion would not be expected to give rise to an obligatory step proceeding through a neutral transition state.

(43) S. Wolfe and S. K. Hasan, *Can. J. Chem.*, **48**, 3572 (1970).

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

(45) C. A. Bunton and S. K. Huang, *J. Amer. Chem. Soc.*, **94**, 3536 (1972); C. A. Bunton, J. H. Crabtree, and L. Robinson, *ibid.*, **90**, 1258 (1968).

(31) F. A. Long, W. F. McDevit, and F. B. Dunkle, *J. Phys. Chem.*, **55**, 813 (1951); F. A. Long, F. B. Dunkle, and W. F. McDevit, *ibid.*, **55**, 829 (1951).

(32) B. J. Huckings and M. D. Johnson, *J. Chem. Soc.*, 5371 (1964).

(33) J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1899, 1917 (1966).

(34) J. Stieglitz, *Amer. Chem. J.*, **39**, 29 (1908); I. H. Derby, *ibid.*, **39**, 437 (1908).

(35) J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2009 (1957).

(36) R. B. Martin, R. I. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 3197 (1964).

(37) R. H. De Wolfe, *J. Org. Chem.*, **36**, 162 (1971).

(38) R. Greenhalgh, R. M. Heggie, and M. A. Weinberger, *Can. J. Chem.*, **41**, 1662 (1963).

(39) F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 935 (1957).

(40) J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4973 (1961).

(41) (a) R. B. Martin and A. Parcell, *J. Amer. Chem. Soc.*, **83**, 4835 (1961); (b) P. F. Jackson, K. J. Morgan, and A. M. Turner, *J. Chem. Soc., Perkin Trans. 2*, 1582 (1972).

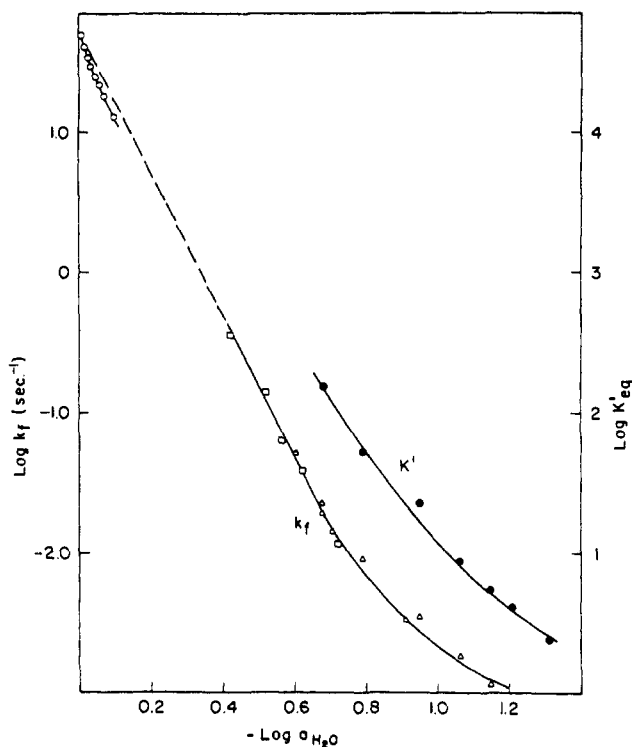


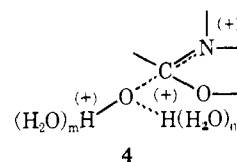
Figure 9. The dependence on the negative logarithm of water activity of: (a) the apparent equilibrium constants for phthalimidium cation hydrolysis (●), (b) the calculated rate constants, k_f , for phthalimidium cation hydrolysis in concentrated perchloric acid based on the approach to equilibrium starting with phthalimidium perchlorate (□, 350 nm), or phthalimide (Δ, 300 nm), (c) the observed first-order rate constants for the attack of water on phthalimidium cation in sodium perchlorate solutions (○). The slope of the dashed line is 4.8.

the phthalimidium ion by the fact that the observed hydrolysis rate is 13- and 34-fold faster in sulfuric and hydrochloric acids, respectively, than in perchloric acid at the same H_0 value. Similar, rather small differences have been observed for acid inhibition of the hydrolysis of other imidates and the initial slopes of plots of $\log k$ against $\log a_{H_2O}$ of >10 for ethyl *N*-phenylformimidate and ≥ 15 for 2-methyloxazoline hydrolysis at low acid concentrations are hard to account for other than as a salt effect.^{35,37}

The importance of explanation 2, a larger hydration requirement for the transition state than for the phthalimidium ion, is suggested by the fact that the inhibition by sodium perchlorate ($k_s = -0.14$, Figure 2) is much less than by perchloric acid ($k_s = -0.78$), although the two compounds show comparable behavior in a plot of $\log k$ against a_{H_2O} (Figure 9). The slope of the dashed line in Figure 9 is -4.8 and a limiting interpretation of the Bunnett-Olsen parameter $\varphi = 0.87$ corresponds to a requirement of 3.9 additional molecules of water of hydration to reach the transition state.³³ Extrapolation along the dashed line of Figure 9 to $a_{H_2O} = 1.0$ gives a rate constant of $50 \pm 15 \text{ sec}^{-1}$, in agreement with the observed rate constant of 56 sec^{-1} , in agreement with the observed rate constant of 56 sec^{-1} for the attack of water on the phthalimidium ion in dilute acid solution.

Mechanistically, this increase in hydration may be ascribed to a requirement for several water molecules to solvate the proton that is released concurrently with

the attack of water on the phthalimidium ion in a transition state such as 4. It is expected that several water



molecules are required to serve as proton acceptors in the optimal transition state for a concerted reaction of this kind and it is of interest that the fully solvated proton, presumably $H_9O_4^+$, falls on the Brønsted plots for the loss of $-OR$ from the alcohol addition intermediates.¹¹ In strong acid solutions of low water activity in which the proton exists in a less hydrated form such as H_3O^+ it would be expected that the reaction would proceed at a slower rate through a less favorable reaction path involving a smaller number of water molecules in the transition state; this may account for the leveling off of the plot of $\log k$ against $\log a_{H_2O}$. General acid-base catalysis of proton transfer involving electronegative atoms probably proceeds preferentially through transition states involving more water molecules than in the case of carbon.⁴⁶

The logarithm of the equilibrium constant for the dehydration of the phthalimide to the phthalimidium ion exhibits a strong dependence on H_0 with a slope of -0.94 ; the corresponding Bunnett-Olsen slope φ of a plot of $[\log (1/K_{eq}') + H_0]$ against $(H_0 + \log [H^+])$ is $+0.04$. Thus, the dependence on acidity of this equilibrium, which involves the net uptake of a proton and the release of a molecule of water, is almost the same as that for the protonation of a Hammett base; it is much less than for the dehydration of an alcohol to a carbonium ion, which follows the H_R function and gives a Bunnett-Olsen slope of about -1.3 . The dependence on H_0 is similar to that for the equilibrium dehydration of γ -hydroxybutyric acid to butyrolactone,³¹ but the reactions differ in that the lactone equilibrium does not involve the uptake of a proton. The large effect of perchloric acid on the lactone equilibrium may be ascribed to a salting-in of the lactone by perchlorate ion³¹ and to hydration of the hydroxy acid.³³

Three factors contribute to the smaller dependence on acidity of phthalimide than of alcohol dehydration. (a) The very strong dependence of the equilibrium for alcohol dehydration on perchloric acid concentration, as measured by the H_R function, is caused in part by stabilization of the carbonium ion product by perchlorate ion.⁴⁵ Although there may be some stabilization of the phthalimidium ion by perchlorate ion, any such stabilization appears to be considerably smaller than for carbonium ions, since the inhibition of the hydration of PI^+ by sodium perchlorate ($k_s = -0.14$) is smaller than that of the hydration of trianisylmethylcarbonium ion ($k_s = -0.37$).⁴⁵ (b) Perchlorate salts are known to decrease the activity coefficient of the amide group,⁴⁷ and are therefore expected to salt in the phthalimide. (c) Partial protonation of the hy-

(46) D. M. Goodall and F. A. Long, *J. Amer. Chem. Soc.*, **90**, 238 (1968); M. M. Kreevoy and J. M. Williams, Jr., *ibid.*, **90**, 6809 (1968).

(47) D. R. Robinson and W. P. Jencks, *J. Amer. Chem. Soc.*, **87**, 2470 (1965).

droxyl group of the phthalimide reduces the dependence of the observed equilibrium constants on acidity. Although the spectrophotometric evidence suggests that the phthalimide does not undergo protonation on a carbonyl group, direct physical measurements indicate that simple alcohols are partially protonated in the range of acid strengths examined; in more dilute acid solutions there is a significant decrease in the activity coefficient of alcohols, as measured by distribution techniques for example, presumably because the alcohol is involved in solvation of the proton.⁴⁸⁻⁵⁰ The degree of alcohol protonation shows a relatively shallow dependence on acid strength so that the phthalimide is expected to undergo only a small increase in degree of protonation in the range 8-10 *M* perchloric acid, from 0.30 to 0.49 by analogy with the protonation of ethanol.⁴⁹ Thus, dehydration to the phthalimidium ion results in the uptake of less than 1.0 mol of acid and curvature in the H_0 plots as a consequence of this degree of ionization would be difficult to detect over the range of acid concentrations examined.⁵¹

The rate of the reverse, ring closure reaction shows a

(48) R. E. Weston, Jr., S. Ehrenson, and K. Heinzinger, *J. Amer. Chem. Soc.*, **89**, 481 (1967); E. M. Arnett, R. P. Quirk, and J. J. Burke, *ibid.*, **92**, 1260 (1970).

(49) D. G. Lee and R. Cameron, *J. Amer. Chem. Soc.*, **93**, 4724 (1971).

(50) L. S. Levitt and B. W. Levitt, *Tetrahedron*, **27**, 3777 (1971), and references therein.

(51) In the absence of experimental data for the protonation of the hydroxyl group of the phthalimide in perchloric acid it seems preferable to include its solvation and protonation in an overall activity coefficient, as is usually done in analogous systems in which water is a reactant, rather than attempting to correct for its degree of protonation.

much smaller dependence on acidity, with a slope of $\log k_r$ against $-H_0$ of approximately 0.11 (Figure 8); a plot of $\log k$ against $\log [\text{HClO}_4]$ in the range 8-10 *M* has a slope of approximately 2.7. A plot of $(\log k_r + H_0)$ against $(H_0 + \log \text{H}^+)$ gives a slope of $\varphi = 0.91$. Even allowing for partial protonation of the alcohol, this dependence on H_0 is much smaller than that for butyrolactone formation³¹ or the dehydration of alcohols to carbonium ions,⁵² which follow H_0 ; however, it is similar to that for amide hydrolysis.^{33, 39, 40, 53} Evidently, the intramolecular attack of the hydroxyl group of an alcohol is not grossly different from the intermolecular attack of the hydroxyl group of water on an amide; in both cases the activity of the attacking hydroxyl group is decreased by solvation and protonation, and additional water molecules are required for proton transfer and solvation of the transition state. A strongly hydrated transition state with the characteristics of **4** for the ring closure reaction is consistent with the results; similar transition states containing a total of three water molecules have been suggested for amide hydrolysis from the dependence on water activity of the rate of reaction of the protonated amide.⁵⁴

Acknowledgment. We are grateful to Professor J. Bunnett for his advice on the utilization of the φ function.

(52) C. H. Rochester, "Acidity Functions," Academic Press, New York, N. Y., 1970, p 162.

(53) H. H. G. Jellinek and J. R. Urwin, *J. Phys. Chem.*, **57**, 900 (1953); H. H. G. Jellinek and A. Gordon, *ibid.*, **53**, 996 (1949).

(54) R. B. Moodie, P. D. Wale, and T. J. Whaite, *J. Chem. Soc.*, 4273 (1963); K. Yates and J. B. Stevens, *Can. J. Chem.*, **43**, 529 (1965).

The Mechanism of Formation and Breakdown of Amine Tetrahedral Addition Compounds of a Phthalimidium Cation. The Relative Leaving Group Abilities of Amines and Alkoxide Ions¹

Norman Gravitz and William P. Jencks*

Contribution No. 926 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02154. Received June 19, 1973

Abstract: The breakdown of amine addition compounds formed from *N,O*-trimethylenephthalimidium cation shows no buffer catalysis and apparently proceeds by a stepwise mechanism of specific acid catalysis; the reverse reaction involves the uncatalyzed attack of the free amine. A negative deviation from structure-reactivity correlations for the reaction of protonated *N,N'*-dimethylhydrazine adduct may reflect a change to rate-determining protonation of this weakly basic adduct. Rate constants for acid-catalyzed breakdown and for amine attack show only a small dependence on amine basicity ($\beta_{1g} = 0.1$ and $\beta_{\text{unc}} = 0.1$) and the equilibrium constants for formation of the uncharged adducts are independent of amine basicity. Rate constants for breakdown of the protonated adducts are highly sensitive to amine basicity ($\beta = -0.9$), indicating a late transition state. Direct comparison of the rate constants for expulsion of amines to those for expulsion of alkoxide ions shows that for a given basicity the amines are better leaving groups by a factor of *ca.* 10^5 . This suggests that alkoxide departure will ordinarily be rate determining in the uncatalyzed aminolysis of esters. Imidazole is an abnormally poor leaving group.

In this paper we report the results of our studies on the rate and equilibrium constants and on the

(1) Supported by grants from the National Science Foundation (GB 5648) and the National Institute of Child Health and Human Development of the National Institutes of Health (HD 01247). N. G. was a Predoctoral Fellow of the National Institutes of Health (GM 212).

mechanism for the breakdown and formation of amine tetrahedral addition compounds of a phthalimidium cation (eq 1). We also describe a comparison of the leaving group abilities of amines and alkoxide ions of a given basicity that is relevant to the question of