to give, on fractional crystallization from methanol, 0.46 g of the recovered starting compound **24b** and 0.95 g (57%) of tolane **32b**.

C. Attempted Conversion of 29 to an Acetylenic Product.—When benzothiazine **29** was treated with 3 mol equiv of sodium amide in liquid ammonia for 2 hr essentially as described above under A, a black suspension was produced, but, on work up of the reaction mixture, polymeric material was obtained and 40% of the starting compound **29** was recovered.

In an attempt to determine whether the 7-methyl hydrogen of benzothiazine **29** was ionized, 0.005 mol of **29** was treated with 0.0075 mol of potassium amide in liquid ammonia followed, after 1 hr, by 0.0065 mol of benzyl chloride. However, none of the benzyl derivative of **29** was isolated; instead, intractable polymeric material was obtained, and 37% of the **29** was recovered.

Registry No.—Benzonitrile, 100-47-0; **4b**, 18963-14-9; **5b**, 18963-15-0; **6b**, 18963-16-1; **7b**, 18963-17-2; **10a**, 18963-18-3; **10b**, 18963-19-4; **11b**, 18963-20-7; **12a**, 18963-21-8; **12b**, 18963-22-9; **12b HCl**, 18963-23-0; **13a**, 18963-24-1; **13b**, 18963-25-2; **14**, 18963-26-3; **15a**, 18963-27-4; **15b**, 18963-28-5; **21a**, 18963-29-6; **21b**, 18963-30-9; **22a**, 18963-31-0; **22b**, 18963-32-1; **24a**, 18963-33-2; **24b**, 18963-34-3; **27**, 6326-21-2; **28**, 18963-36-5; **29**, 18963-37-6; **32a**, 18963-38-7; **32b**, 18963-39-8.

Catalysis and Inhibition of the Hydrolysis of N-Methylphthalimide by Imidazole[1a]

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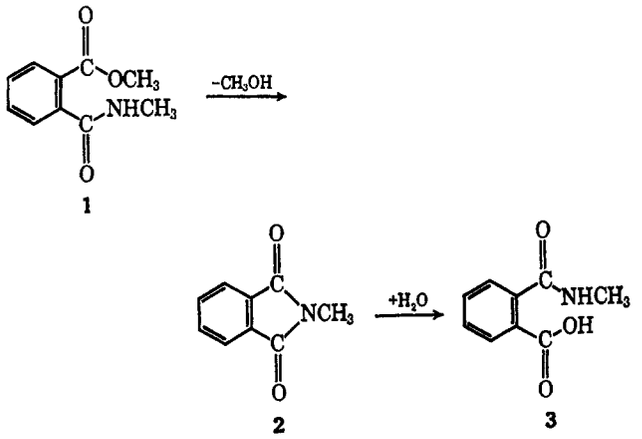
Imidazole was found to catalyze the hydrolysis of N-methylphthalimide (to N-methylphthalamic acid) at pH values of 6.4 and 7.2, and inhibit the hydrolysis of N-methylphthalimide at pH 9.7. While HPO_4^{2-} was observed to catalyze the hydrolysis of N-methylphthalimide, it did not inhibit the hydrolysis of N-methylphthalimide. The second-order rate constants (k_6) for the imidazole and HPO_4^{2-}-catalyzed hydrolysis of N-methylphthalimide were found to be 2×10^{-5} and 1.3×10^{-5} sec^{-1} M^{-1}, respectively. These results are taken as kinetic evidence for the reversible addition of imidazole to N-methylphthalimide to form a tetrahedral addition compound which is relatively unreactive toward hydroxide ion. The dissociation constant for this addition compound estimated from the inhibition of the hydrolysis of N-methylphthalimide by imidazole (1.3 M) was in reasonable agreement with the values estimated from the perturbation of the ultraviolet spectrum of N-methylphthalimide by imidazole (1.5–1.7 M). When deuterium oxide was used in place of water, imidazole and HPO_4^{2-} became less efficient catalysts. Isotope effects of 1.4 and 2.3 were observed for the imidazole and HPO_4^{2-}-catalyzed hydrolysis of N-methylphthalimide. This result and the similar catalytic efficiencies observed for imidazole and HPO_4^{2-} suggest that imidazole and HPO_4^{2-} are general base catalysts for the hydrolysis of N-methylphthalimide.

The neighboring amide group is the only functional group present in hydrolytic enzymes which has also been shown to catalyze substantially the hydrolysis of both alkyl esters and amides in low molecular weight organic compounds.[2] Alkyl esters and amides with neighboring amide groups hydrolyze through an imide intermediate. Very often the catalytic effect of the amide group is reduced, because hydrolysis of the imide intermediate is slow. For example, at 25.9°, the second-order rate constant for the hydroxide ion catalyzed cyclization of ester **1** to N-methylphthalimide (**2**) is 12,400 sec^{-1} M^{-1},[2h] while the second-order rate constant for the hydroxide ion catalyzed hydrolysis of **2** to N-methylphthalamic acid (**3**) is 24 sec^{-1} M^{-1}.[3] Because of the possible involvement of amide groups in enzymically catalyzed reactions, we have investigated the effect of



(1) (a) This study was supported by a grant (AM-09276) from the National Institutes of Health, U. S. Public Health Service; (b) to whom inquiries regarding this work should be made.

(2) For examples of the participation of amide groups in the hydrolysis of esters and amides, see (a) J. E. H. Hancock and R. P. Linstead, *J. Chem. Soc.*, 3490 (1953); (b) E. Sondheimer and R. W. Holley, *J. Amer. Chem. Soc.*, **76**, 2467 (1954); **79**, 3767 (1957); (c) A. R. Battersby and J. C. Robinson, *J. Chem. Soc.*, 259 (1955); (d) B. Vigneron, P. Crooy, F. Kezdy, and A. Bruylants, *Bull. Soc. Chim. Belges*, **69**, 616 (1960); (e) P. Crooy and A. Bruylants, *ibid.*, **73**, 44 (1964); (f) S. A. Bernhard, A. Berger, J. H. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *J. Amer. Chem. Soc.*, **84**, 2421 (1962); (g) A. J. Adler, G. D. Fasman, and E. R. Blout, *ibid.*, **85**, 90 (1963); (h) J. A. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1899 (1963); (i) M. T. Behme and E. H. Cordes, *ibid.*, **29**, 1255 (1964); (j) J. Brown, S. C. K. Su, and J. A. Shafer, *J. Amer. Chem. Soc.*, **88**, 4468 (1966).

(3) (a) Although the rate of hydrolysis of **1** is severely limited by the hydrolysis of **2**, in alkaline solutions ester **1** hydrolyzes much faster than methyl benzoate; M. L. Bender, H. Matsui, R. J. Thomas, and S. W. Tobey [*J. Amer. Chem. Soc.*, **83**, 4193 (1961)] reported a value of 0.0232 sec^{-1} M^{-1} for the hydroxide ion catalyzed hydrolysis of methyl benzoate at 24.8° in 33.3% dioxane–water. (b) The value of 24 sec^{-1} M^{-1} is an average value extrapolated to zero buffer concentration at 25° in the pH range of 6.4–9.7. See Experimental Section.

imidazole on the hydrolysis of N-methylphthalimide (**2**) to N-methylphthalamic acid (**3**).

Experimental Section

Materials.—N-Methylphthalimide was obtained from Eastman Organic Chemicals and recrystallized twice from 95% ethanol, mp 134–135° cor (lit.[4] mp 133–134°).

Imidazole was obtained from the Aldrich Chemical Co., recrystallized three times from benzene and sublimed under reduced pressure, mp 88–89° cor (lit.[5] mp 90.2–90.6°). Deuterium oxide (99.88%) and DCl (20% in D_2O) were obtained from Bio-Rad. The distilled water supplied to the laboratory was run through a demineralizer and redistilled in an all-glass still. All other chemicals used were Mallinckrodt or Baker–Adamson analytical reagents.

Methods.—Measurements of pH and pD were made using a Radiometer Model 4b pH meter which was standardized with a 1:1 phosphate, NBS primary standard solution.[6] The response of the glass electrode was checked with another NBS primary standard solution (either borax or phthalate). Any nonideality in the glass electrode response was corrected with the temperature compensator. This correction never corresponded to more than 1° per pH unit difference between the primary standards. Measurements of pH and pD were made before and after each kinetic run, and the average value of pH was used. The total change in pH or pD during a kinetic run in a buffered solution rarely exceeded 0.02 unit.

Hydrogen ion concentrations were estimated from the pH and the mean activity coefficient of hydrogen chloride in potassium chloride solutions. The mean activity coefficient used (0.71 at $\Gamma/2 = 0.833\ M$) was interpolated from the data listed by Harned and Owen.[7] The hydroxide ion concentration was estimated from the hydrogen ion concentration and the formal dissociation constant for water (K_w'), *i.e.*, $K_w\alpha_{H_2O}/\gamma_{H^+}\gamma_{OH^-}$ which was interpolated from data listed in ref 7. The formal dissociation constant used was $1.76 \times 10^{-14}\ M$ at $\Gamma/2 = 0.833\ M$.[8]

Rate Measurements.—The disappearance of N-methylphthalimide was followed spectrophotometrically (usually at 300 mμ) using a Gilford Model 2000 multiple sample absorbance recorder.

Reactions in buffered solutions were carried out in a cuvette equipped with a ground glass stopper. The absorbance was monitored continuously, and the temperature was controlled (25 ± 0.05°) by circulating water from a thermostated bath through the thermospacers surrounding the cell compartment. The temperature of the reacting solution was determined with a NBS certified thermometer. The approach of the absorbance (A) to its final value (A_∞) was first order. Pseudo-first-order rate constants (k_{obsd}) were determined by the method of Guggenheim[9] or from the slopes of the linear plots of $-\ln(A - A_\infty)$ *vs.* time. The rate constants' independence of the initial concentration of N-methylphthalimide also established that the reaction was first order in N-methylphthalimide.

The hydrolysis of N-methylphthalimide was roughly first order in the hydroxide ion concentration. The absolute value of the second-order rate constant for the hydroxide ion catalyzed hydrolysis of N-methylphthalimide (extrapolated to zero buffer concentration) changed from 20 $sec^{-1}\ M^{-1}$ at pH 7.4 to 28 $sec^{-1}\ M^{-1}$ at pH 9.7.

Below pH values of 7.5, the hydrolysis of N-methylphthalimide to N-methylphthalamic acid does not go to completion,[2i] and the concentration of N-methylphthalimide in equilibrium with N-methylphthamic acid becomes significant. Therefore, below pH values of 7.5, k_{obsd} was determined from the initial rate of disappearance of N-methylphthalimide (R), using the relationship given in eq 1. The initial slope of the absorbance *vs.* time plot

$$R = -(1/E_2)(dA/dt) = k_{obsd}[2°] \quad (1)$$

at 300 mμ is represented by dA/dt, while $[2°]$ is the initial concentration of N-methylphthalimide, and E_2 is the extinction coefficient of N-methylphthalimide. All initial rates were obtained from measurements corresponding to less than 6% decomposition of N-methylphthalimide. For initial rate measurements, full scale on the recorder was set to 0.1 absorbance unit. For other measurements of absorbance, full scale on the recorder was set to 1.0 absorbance unit.

The product of the reaction was characterized by the identity of the ultraviolet spectra taken at the end of the kinetic runs with the spectrum of N-methylphthalamic acid. When the reaction did not go to completion, the final spectrum could be rationalized by assuming a mixture of N-methylphthalimide and N-methylphthalamic acid.[2i] Ultraviolet spectra were determined on a Cary Model 15 recording spectrophotometer.

Results

Qualitative studies of the effect of imidazole and imidazole derivatives on the spectrum of phthalimide and their ability to decrease the rate of hydrolysis of phthalimide have been reported by Champy-Hatem in her studies of the interaction of imidazole and thalidomide.[10] In our studies of the effect of imidazole on the hydrolysis of N-methylphthalimide to N-methylphthalamic acid, imidazole was found to change from a catalyst to an inhibitor as the pH value was increased from 6.4 to 9.7 (Table I). The effect of pH and other buffers on the observed psuedo-first-order rate constant for the hydrolysis of N-methylphthalimide is listed in Table I. Inhibition of the hydrolysis of N-methylphthalimide by imidazole at pH 9.7 is also observed in solutions in which the carbonate buffer is replaced by borate buffer. It is interesting that although phosphate catalyzes the reaction at pH 7.2 it does not inhibit the hydrolysis of N-methylphthalimide at pH 9.7.

Figure 1 illustrates the effect of imidazole on the ultraviolet spectrum of N-methylphthalimide. Assuming that the formation of a 1:1 complex is responsible for the change in the ultraviolet spectrum,[11] the dissociation constant of this complex may be evaluated using the relationship given in eq 2. The absorbance (at 255 mμ)

$$\frac{1}{\Delta A_{255}} = \frac{1}{(E_5 - E_2)[2°]} + \frac{1}{(E_5 - E_2)[2°]}\frac{K_D}{[\text{imidazole}]} \quad (2)$$

of a solution containing N-methylphthalimide (concentration = $[2°]$) and imidazole[12] *vs.* a solution containing the same concentration of N-methylphthalimide with no imidazole is represented by ΔA_{255}, and K_D is the apparent dissociation constant of a 1:1 imidazole–N-methylphthalimide complex. E_2 and E_5 represent the extinction coefficients of N-methylphthalimide and

(4) M. Freund and H. Beck, *Ber.*, **37**, 1942 (1904).

(5) F. Cramer, *Angew. Chem.*, **72**, 236 (1960).

(6) (a) R. G. Bates, "Determination of pH Theory and Practice," John Wiley & Sons, Inc., New York, N. Y., 1964, pp 62–94, 123–130. (b) pD = pH meter reading +0.40; ref 6a. p 220.

(7) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1958, pp 638, 748, and 752.

(8) (a) The effects of 2% acetonitrile on the activity coefficients, the formal dissociation constant of water, and the pH measurement were neglected. Undoubtedly, these effects introduce a small systematic error into the absolute magnitude of the equilibrium constants and the second-order rate constants reported in this work. (b) The effect of KCl on the activity coefficients in water and deuterium oxide were assumed to be equivalent, so that the value (6.5) given by R. W. Kingerly and V. K. La Mer [*J. Amer. Chem. Soc.*, **63**, 3256 (1941)] for the dissociation constant of water relative to the dissociation constant of deuterium oxide could be used to calculate $[OD^-]$.

(9) E. A. Guggenheim, *Phil. Mag.*, [7] **2**, 538 (1926).

(10) (a) S. Champy-Hatem, *Bull. Acad. Natl. Med.* (Paris), **150**, 137 (1966); (b) *ibid.*, **149**, 426 (1965); (c) *ibid.*, **148**, 301 (1964).

(11) Champy-Hatem has previously proposed the formation of an imidazole–phthalimide complex from her spectral studies. See ref 10.

(12) The contribution of free imidazole to the absorbance was subtracted from the absorbance of this solution.

TABLE I

THE EFFECT OF pH AND BUFFERS ON THE HYDROLYSIS OF N-METHYLPHTHALIMIDE[a]

pH	Buffer	Buffer concn,[b] *M*	$10^5 k_{obsd}$, sec^{-1}	$10^5 k_6$,[c] sec^{-1} M^{-1}
6.45	85:15 imidazole·HCl–imidazole	0.0392	1.0	
6.41		0.314	1.5	1.8
6.40		0.392	1.5	
6.39		0.588	1.7	
6.36		0.784	2.0	
7.20	1:1 imidazole·HCl–imidazole	0.0392	4.1	
7.18		0.314	6.3	
7.18		0.392	6.7	2.0
7.16		0.471	7.1	
7.16		0.588	7.4	
7.72[d]	1:1 imidazole·DCl–imidazole[e]	0.0392	3.0	
7.69[d]		0.392	4.4	1.4
7.68[d]		0.588	4.9	
7.17	1:4 KH_2PO_4–Na_2HPO_4	0.0641	4.4	
7.19		0.128	5.3	1.3
7.21		0.192	6.2	
7.25		0.320	7.9	
7.67[d]	1:4 KH_2PO_4–Na_2HPO_4[e]	0.0641	2.8	
7.69[d]		0.128	3.2	0.56
7.71[d]		0.192	3.6	
9.70	129:118 $NaHCO_3$–Na_2CO_3	0.0247	1750	
9.71		0.0594	1780	
9.70	K_2HPO_4[f] in 0.0129 *M* $NaHCO_3$–0.0118 *M* Na_2CO_3	0.111	1820	
9.71		0.166	1880	
9.73		0.224	2090	
9.71	Imidazole[f] in 0.0129 *M* $NaHCO_3$–0.0118 *M* Na_2CO_3	0.196	1600	
9.71		0.392	1370	
9.73		0.588	1270	
9.73		0.784	1150	

[a] In 2% acetonitrile, 25°, $\Gamma/2 = 0.833$ *M* maintained with KCl. [b] Acidic + basic component. [c] For catalysis by HPO_4^{2-}, k_6 was estimated from the slopes of plots of $k_{obsd}/[OH^-]$ *vs.* $[HPO_4^{2-}]/[OH^-]$. For catalysis by imidazole, k_6 was estimated from the slopes of plots of $(k_{obsd}/[OH^-])\{([\mathbf{4a}] + [\mathbf{4b}] + K_D)/K_D\}$ *vs.* $[\mathbf{4a}]/[OH^-]$ and setting $K_D = 1.9$ *M*. [d] pD. [e] D_2O used in place of H_2O. [f] Prepared by adding concentrated stock solutions of imidazole or K_2HPO_4 to a $NaHCO_3$–Na_2CO_3 solution. The concentrated stock solution was adjusted to pH 9.7 with acid or base.

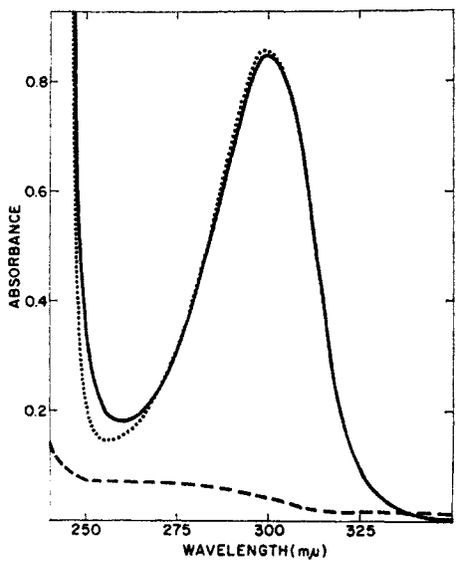


Figure 1.—The effect of imidazole on the ultraviolet spectrum of N-methylphthalimide: spectrum of 3.92×10^{-4} *M* N-methylphthalimide in a 2% acetonitrile solution containing 0.0196 *M* HCl, 0.813 *M* KCl *vs.* a 2% acetonitrile solution containing 0.0196 *M* HCl, 0.813 *M* KCl, ····; spectrum of 3.92×10^{-4} *M* N-methylphthalimide in a 2% acetonitrile solution containing 0.0196 *M* HCl, 0.813 *M* imidazole·HCl *vs.* a 2% acetonitrile solution containing 0.0196 *M* HCl, 0.813 *M* imidazole·HCl, ——; spectrum of 2% acetonitrile solution containing 0.0196 *M* HCl, 0.813 *M* imidazole·HCl *vs.* water, – – –.

the imidazole–N-methylphthalimide complex, respectively. Figure 2 exemplifies the fit of the data to eq 2. The list of the dissociation constants in Table II indicates that both protonated and unprotonated forms of imidazole are capable of complexing with N-methylphthalimide.

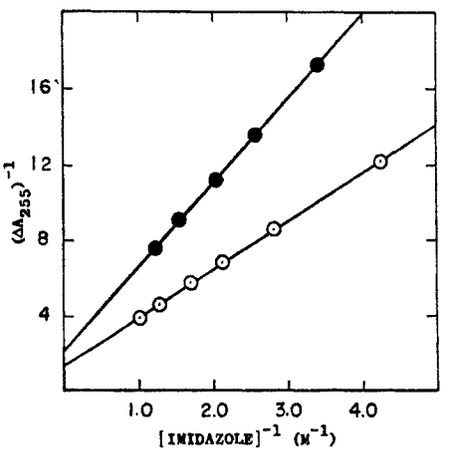
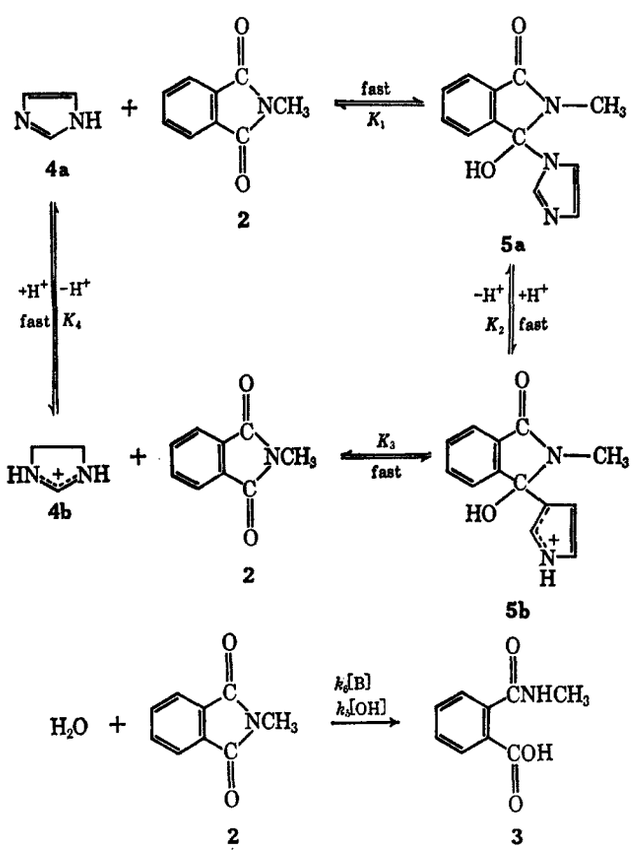


Figure 2.—The effect of the total imidazole concentration on the absorbance of N-methylphthalimide (1.28×10^{-3} *M* in 2% acetonitrile) at 255 mμ: ⊙, 50% neutralized imidazole; ●, imidazole·HCl in 0.0196 *M* HCl ($\Gamma/2$ adjusted to 0.833 *M* by the addition of KCl).

Discussion

In addition to the inhibition of the hydrolysis of phthalimide by imidazole reported by Champy-Hatem,[10] the inhibition of the hydrolysis of methyl *trans*-cinnamate by imidazole has been observed by Connors and Mollica.[13] The inhibition of these hydrolytic reactions by imidazole has been interpreted by assuming that imidazole forms a complex with the reactant,[10,13] which is relatively unreactive toward hydroxide ion. Connors and Mollica[13] obtained a value of 1 *M* for the apparent dissociation constant of the 1:1 imidazole–methyl *trans*-cinnamate complex from solubility measurements. This value was consistent with their kinetic data. The catalytic and inhibitory effects of imidazole reported here seem more complicated; however, they can be rationalized in terms of Scheme I.

SCHEME I



Equation 3 follows from this reaction scheme, assuming that the equilibrium is maintained between imidazole, N-methylphthalimide, **5a**, and **5b**.

$$k_{obsd} = (k_5[OH^-] + k_6[B])\{K_D/([\mathbf{4a}] + [\mathbf{4b}] + K_D)\} \quad (3)$$

The term $k_6[B]$ reflects catalysis of the reaction by bases such as imidazole or phosphate. The apparent dissociation constants (K_D) listed in Table II are related to the individual dissociation constants used in the reaction scheme by eq 4.

$$\{([\mathbf{4a}] + [\mathbf{4b}])[\mathbf{2}]\}/([\mathbf{5a}] + [\mathbf{5b}]) = K_D = K_3\{([H^+] + K_4)/([H^+] + K_2)\} \quad (4)$$

(13) K. A. Connors and J. A. Mollica, Jr., *J. Amer. Chem. Soc.*, **87**, 123 (1965).

TABLE II

APPARENT DISSOCIATION CONSTANTS FOR AN IMIDAZOLE–N-METHYLPHTHALIMIDE 1:1 COMPLEX

Conditions[a]	K_D,[b] *M*
35% neutralized imidazole	1.6
50% neutralized imidazole	1.9
50% neutralized imidazole[c]	1.7
Imidazole·HCl + 0.02 *M* HCl	2.1

[a] In 2% aqueous acetonitrile. The concentration of N-methylphthalimide was 1.28×10^{-3} *M* and $\Gamma/2$ was maintained at 0.833 *M* by the addition of KCl. [b] K_D = [total imidzole][free imide]/[complexed imide]. [c] D_2O used in place of H_2O. The imidazole was neutralized with DCl in D_2O.

Since $K_1 = K_3K_4/K_2$, and $K_4 = 0.94 \times 10^{-7}$ *M* (by titration), values of K_1, K_2, and K_3 may be obtained by applying eq 4 to the values of K_D in Table II. Assuming $K_2 \ll 0.02$ *M*; $K_3 = 2.1$ *M*, $K_2 = 1.1 \times 10^{-7} - 1.3 \times 10^{-7}$ *M*, and $K_1 = 1.5$–1.7 *M*. It is interesting that the basicity of the imidazole residue in **5a** is similar to free imidazole, and that the protonated and unprotonated forms of imidazole have similar affinities for N-methylphthalimide. According to the reaction scheme, as the imidazole concentration is increased a considerable amount of the free imide is converted into tetrahedral addition compounds **5a** and **5b**. Since the concentration of N-methylphthalimide is thereby reduced, the fraction of imide which hydrolyzes *via* direct attack by hydroxide ion is also reduced. Observations of increases or decreases in the rate of reaction with increasing imidazole concentration will depend on whether the increase in the imidazole-catalyzed reaction will compensate for the decrease in the hydroxide ion-catalyzed reaction. Setting [B] = [**4a**], it follows from the first derivative of eq 3 (with respect to the total concentration of imidazole), that when the value of term 5 is positive imidazole will catalyze the reaction,

$$k_6K_D - (k_5K_{w'}/K_4) - k_5[OH^-] \quad (5)$$

and when this term is negative imidazole will inhibit the reaction.

On substituting the value of K_D determined spectrophotometrically into eq 3, k_6 is found to be 2×10^{-5} sec^{-1} M^{-1} [14] (Table I) for the imidizole-catalyzed hydrolysis of N-methylphthalimide in 50% neutralized solutions of imidazole. The data in Table I lead to a value of 1.3×10^{-5} sec^{-1} M^{-1} for the second-order rate constant for the catalysis of the hydrolysis of N-methylphthalimide by HPO_4^{2-}. In general base-catalyzed hydrolyses, imidazole and HPO_4^{2-} have been observed to have similar catalytic efficiencies; however, imidazole has been shown to be a much more potent catalyst in hydrolytic reactions proceeding *via* nucleophilic catalysis.[15] The similarity between the second-order rate constants for the phosphate and imidazole-catalyzed hydrolysis of N-methylphthalimide suggests that in this reaction imidazole is a general base catalyst. In deuterium oxide, both imidazole and HPO_4^{2-} were less efficient in catalyzing the hydrolysis of N-methylphthalimide (Table I). Although the isotope effect observed for imidazole (1.4) is somewhat lower than the

(14) (a) Based on the concentration of unprotonated imidazole. (b) A value of 1.8×10^{-5} sec^{-1} M^{-1} is obtained for k_6 with 85% neutralized imidazole (assuming $K_D = 1.9$ *M*).

(15) W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, **83**, 1743 (1961), and references therein.

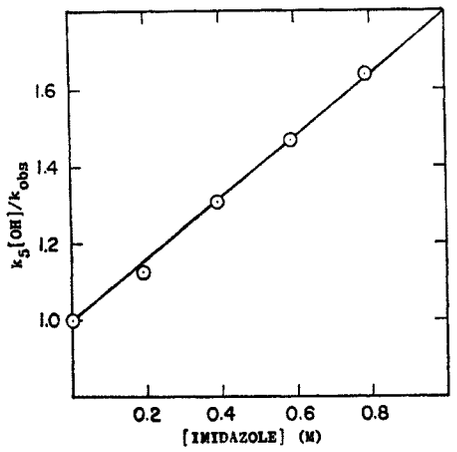


Figure 3.—Inhibition of the hydrolysis of N-methylphthalimide by imidazole at pH 9.7, 25°, $\Gamma/2 = 0.833$ *M*.

isotope effect observed for HPO_4^{2-} (2.3), these isotope effects are also consistent with the assumption that imidazole and HPO_4^{2-} are general base catalysts for the hydrolysis of N-methylphthalimide.

When catalysis by imidazole is insignificant compared to the catalysis by hydroxide ion (at pH 9.7), eq 3 may be put into the form

$$k_5[OH^-]/k_{obsd} = 1 + ([\mathbf{4a}] + [\mathbf{4b}])\ (1/K_D) \qquad (6)$$

From a plot of $k_5[OH^-]/k_{obsd}$ *vs.* the total imidazole concentration (Figure 3), a value of 1.3 *M* is obtained for K_D. Applying the data listed in Table II to eq 4, values of 1.5 and 1.7 *M* are obtained for K_D at pH 9.7. The agreement between the values of the apparent dissociation constant for the 1:1 imidazole–N-methylphthalimide complex determined from spectrophotometric measurements and the kinetics of inhibition is reasonable.

Although the inhibition of the hydroxide ion catalyzed hydrolysis of N-methylphthalimide does not necessitate that the imidazole–N-methylphthalimide complex be tetrahedral intermediates **5a** and **5b**, addition compounds **5a** and **5b** would be expected to be less susceptible than the free imide to hydroxide ion attack at the remaining carbonyl carbon atom.[16] Bruice and Schmir[17] have discussed the difficulty in expelling a poor leaving group from a tetrahedral intermediate containing imidazole as an alternate leaving group. Expulsion of amide anion from **5a** or **5b** to form the acyl imidazole seems unlikely, since the ability of imidazole (by itself) to displace groups from a carbonyl carbon atom decreases sharply as the pK_a of the leaving group becomes larger than 10.[18] Kirsch and Jencks[19] have observed the hydroxide ion catalyzed nucleophilic reactions of imidazole with esters containing poor leaving groups ($pK_a > 10$). It is not surprising, however, that the hydroxide ion catalyzed expulsion of amide anion from **5a** has not been observed, since hydroxide ion catalysis of imidazole catalysis of ester hydrolysis has not been observed with an ester having a leaving group with a pK_a greater than 12.5.[20] No hydroxide ion–imidazole catalysis of the hydrolysis of ethyl acetate was observed (pK_a of ethanol = 16).[19] It may be argued that, if the imidazole addition compound is such a stable intermediate, N-methylphthalimide should be especially susceptible to hydrolysis by the combined action of imidazole and hydroxide ion. This advantage, however, is more than offset by the fact that the leaving amide group remains covalently bound to the product. It should be emphasized that the inhibition of hydroxide ion catalyzed hydrolysis of N-methylphthalimide does not necessitate that the imidazole–N-methylphthalimide complex be tetrahedral intermediates **5a** and **5b**. In fact Menger and Bender[21] have presented convincing arguments for attributing the inhibition by 3,5-dinitrobenzoate of the hydroxide ion and N-butylamine-catalyzed hydrolysis of N-(indole-3-acryloyl)imidazole, *p*-nitrophenyl 3-indoleacrylate, and *p*-nitrophenyl 3-indoleacetate to the formation of charge-transfer complexes between the indole residue and 3,5-dinitrobenzoate. One might therefore propose that imidazole forms a noncovalent complex with N-methylphthalimide which is only susceptible to attack by hydroxide ion when the imidazole is protonated. Although this possibility has not been excluded, it seems unlikely in view of the isotope effects and the similarity between the rate constants for the HPO_4^{2-}- and imidazole-catalyzed reactions.

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(16) The electron density on the remaining carbonyl carbon atom would be expected to be greater because of increased resonance between the nitrogen and the remaining carbonyl group. Also, the leaving nitrogen atom in the tetrahedral addition compounds should be more basic than the amide anion which is the leaving group in the hydroxide ion catalyzed hydrolysis of the free imide.

(17) T. C. Bruice and G. L. Schmir, *J. Amer. Chem. Soc.*, **79**, 1663 (1957).
(18) J. F. Kirsch and W. P. Jencks, *ibid.*, **86**, 837 (1964).
(19) J. F. Kirsch and W. P. Jencks, *ibid.*, **86**, 833 (1964).
(20) The pK_a of the leaving amide group is probably greater than 14, since the pK_a of benzamide has been reported by G. E. K. Branch and J. O. Clayton [*ibid.*, **50**, 1680 (1928)] to be between 14 and 15.
(21) F. M. Menger and M. L. Bender, *ibid.*, **88**, 131 (1968).