acetoxy peaks were present in crude aziridine **9**. The yield of **11** was 44%, while that of the insertion products **10** was 11%, based on starting enol acetate, as determined from the vapor phase chromatogram of the hydrolysis product. The oxazoline **12** should not have been formed under these conditions, based on the assumption that this substance is derived from heat treatment of aziridine **9**. Supporting this contention the vpc trace above contained no 18.0-min peak.

Methanol–Sodium Methoxide Treatment of Crude Aziridine 9.—A solution of 142 mg (0.625 mmole) of crude aziridine and 1.5 ml of absolute methanol was treated with 37 mg (0.685 mmole) of sodium methoxide and allowed to stand at 25° for 5.5 hr. The reaction mixture was poured into 4 ml of water and thoroughly extracted with dichloromethane. The extract was dried over sodium sulfate and concentrated, affording 92 mg (79% yield) of a yellow oil. The nmr spectrum of this substance contained no absorption due to acetoxy protons. The spectrum was almost identical with that of ketone **11**, except that the quartet–triplet due to the ethoxy group was slightly broadened and weak absorption appeared at about 3 ppm, attributable to the proton on the carbon bearing the nitrogen atom in the 3- and 4-carbethoxyaminocyclohexanone isomers. The vapor phase chromatogram consisted of minor amounts of material corresponding in retention time to that of solvent together with one symmetrial peak with retention time exactly that of 2-carbethoxyaminocyclohexanone.

Registry No.—**4**, 13640-73-8; **6**, 13640-74-9; **8**, 13640-75-0; **9**, 13640-76-1; **11**, 13640-77-2; ethyl azidoformate, 817-87-8.

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Concerning the Hydrolysis and Aminolysis of Phenyl N-Methylacetimidate[1]

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The pH-rate profiles for hydrolysis and methylaminolysis of phenyl N-methylacetimidate exhibit maxima which cannot be accounted for in terms of ionization of the reactants. In both instances, a transition from rate-determining attack of the nucleophilic reagent on the alkaline side of the pH-rate maximum to rate-determining decomposition of a tetrahedral intermediate on the acid side may account for these observations. Over the pH range from 4 to 13, the hydrolysis and methylaminolysis of phenyl N-methylacetimidate yields phenol (or phenolate) as a product. At room temperature, the thermodynamically stable mixture of the two isomers of phenyl N-methylacetimidate consists of about one-third *syn* and two-thirds *anti*, as was determined from appropriate proton resonance spectra.

Studies of nucleophilic reactions of imido esters have provided considerable information and insight into a central question relevant to such reactions for acyl substrates in general: the problem of the existence, modes of formation, and modes of decomposition of tetrahedral intermediates. Two points are of particular note. In the first place, the hydrolysis of benzimidates,[3] oxazolines,[4] and imino lactones,[5] and the aminolysis of benzimidates[6] occur with rate-determining decomposition of the tetrahedral intermediate under sufficiently acidic conditions but with rate-determining attack of nucleophilic reagent in more basic situations. In the second place, the tetrahedral intermediates formed from these substrates and water or amines may decompose with expulsion of the resident amine moiety and formation of the corresponding oxygen ester or new imidate or, in contrast, with expulsion of alcohol and formation of amides or amidines. The tetrahedral intermediates formed in the course of hydrolysis of imino lactones exhibit more than one mode of decomposition depending on the pH and the nature and concentration of buffers;[5,7] similarly aminolysis of imidates yields either amidines or new imidates depending on reaction conditions.[6,8–12]

In view of the significance of the above results for understanding of nucleophilic reactions at acyl carbon, we were prompted to extend these studies to a novel substrate, phenyl N-methylacetimidate. This substrate is of interest since, in the first place, the phenoxide function is a much better leaving group than the alcoholates of most other substrates studied thus far and the tetrahedral intermediates derived from this substrate may decompose preferentially with its expulsion. Such behavior might provide the basis for an extended study of those factors which influence the modes of decomposition of these intermediates. In the second place, the tetrahedral intermediate generated from this substrate and water is similar to that generated from phenyl acetates and amines. Phenyl acetate aminolysis is a particularly well studied, but not a completely understood, reaction.[13] Examination of the former reaction might shed light on the latter.

Experimental Section

Materials.—Phenyl N-methylacetimidate [bp 79° (5 mm), lit.[14] 65° (1.2 mm)] was prepared by refluxing distilled phenol and acetoxime benzene sulfonate in toluene dried by distillation, according to the procedure of Oxley and Short.[14] Acetoxime benzene sulfonate (mp 52°, lit.[15] mp 53°) was prepared according to the procedure of Kenner, Todd, and Webb,[15] and was dried *in vacuo* for 2 days prior to use.

The position of the C=N stretching frequency of phenyl N-methylacetimidate in the infrared region is 5.88 μ. Table I gives the features of the nuclear magnetic resonance (nmr)

(1) Supported by Grant No. AM 08232 from the National Institutes of Health.

(2) Career Development Awardee of the National Institutes of Health.

(3) R. H. DeWolfe and F. B. Augustine, *J. Org. Chem.*, **30**, 699 (1965).

(4) R. B. Martin and A. Parcell, *J. Am. Chem. Soc.*, **83**, 4835 (1961).

(5) G. L. Schmir and B. A. Cunningham, *ibid.*, **87**, 5692 (1965).

(6) E. S. Hand and W. P. Jencks, *ibid.*, **84**, 3505 (1962).

(7) B. A. Cunningham and G. L. Schmir, *ibid.*, **88**, 551 (1966).

(8) A. Pinner, "Die Imidoather und ihre Derivate," Berlin, 1892.

(9) R. M. Roberts, *J. Am. Chem. Soc.*, **72**, 3603 (1950).

(10) R. M. Roberts and R. H. DeWolfe, *ibid.*, **76**, 2411 (1954).

(11) E. Schmidt, *Ber.*, **47**, 2545 (1914).

(12) R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).

(13) For a thorough review, see T. G. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin Inc., New York, N. Y., 1966, p 27 ff.

(14) P. Oxley and W. F. Short, *J. Chem. Soc.*, 1514 (1948).

(15) G. W. Kenner, A. R. Todd, and R. F. Webb, *ibid.*, 1231 (1956).

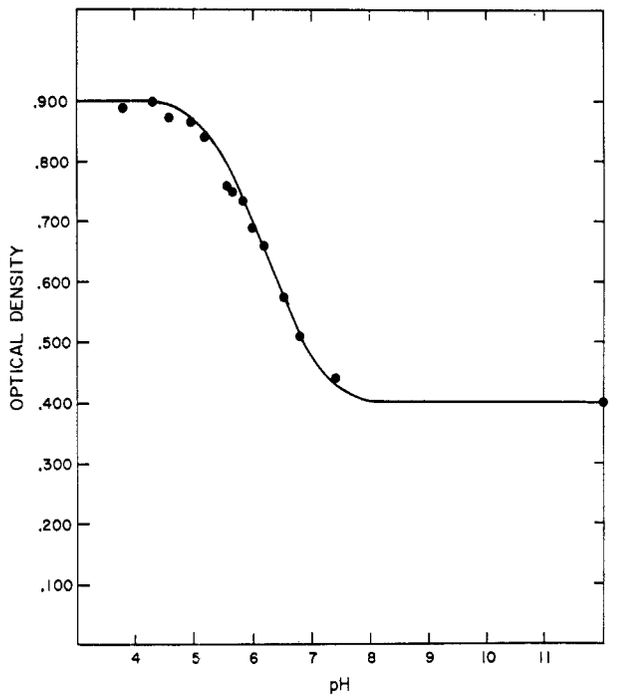


Figure 1.—Spectrophotometric titration of phenyl N-methylacetimidate at 25° and ionic strength 0.5. Optical densities at 247.5 mμ of 2×10^{-3} *M* solutions of substrate are plotted as a function of pH.

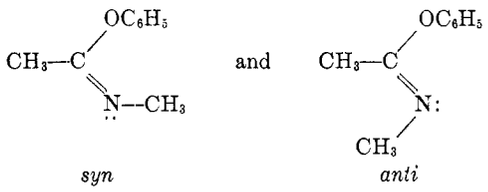
TABLE I

FEATURES OF THE NMR SPECTRUM OF THE THERMODYNAMICALLY STABLE MIXTURE OF THE *syn* AND *anti* ISOMERS OF PHENYL N-METHYLACETIMIDATE[a]

	syn	*anti*
Fraction[b]	1/3	2/3
Chemical shift of C-methyl, δ	1.8	1.95
	1.75[c]	1.9[c]
Chemical shift of N-methyl, δ	3.0	2.85
	2.95[c]	2.8[c]
Coupling constant,[d] cps	1.25	0.25

[a] One molar in carbon tetrachloride unless otherwise noted. [b] Determined from the ratio of peak intensities after heating at 100–110° for 10 min and cooling to room temperature. [c] One molar in carbon disulfide. [d] Determined from a spectrum taken at a sweep width of 100 cps.

spectrum of phenyl N-methylacetimidate, exclusive of the aromatic absorption at low field in carbon tetrachloride. The spectrum consists of four peaks and is symmetrical about a line drawn midway between the central two. Upon further resolution, each peak appears as a quartet. The spectrum may be accounted for on the basis of two slowly interconverting isomers, shown below.



syn *anti*

The quartet farthest upfield is assigned to the *syn* C-methyl; this methyl group is expected to be the most shielded. Since this quartet is coupled to that farthest downfield, and since these two are of equal intensity, it follows that the latter is due to the *syn* N-methyl group. The central quartets are due to the *anti* N- and C-methyl groups, with the former lying farther downfield. The chemical shifts of the various peaks are a function of solvent and of phenyl N-methylacetimidate concentration. The spectrum is symmetrical for 1 *M* imido ester in carbon tetrachloride and in carbon disulfide. The spectrum is not symmetrical for 1 *M* imido ester in *o*-dichlorobenzene, or for higher concentrations of imido ester in carbon tetrachloride. At higher temperatures, the four quartets collapse to two broad singlets. Significant merging was first noted at 70°. At this temperature, the two isomers of phenyl N-methylacetimidate interconvert sufficiently rapidly that the C-methyl groups (and likewise the N-methyl groups) become magnetically equivalent. The nmr spectrum of phenyl N-methylacetimidate shows coupling between the two methyl groups of the imido ester. Coupling between two hydrogens separated by five bonds is rare. However, it has been observed by Weinberger and Greenhalgh for 2-methyl-Δ^2-oxazoline,[16] which is analogous to the present case.

Solutions of phenyl N-methylacetimidate in acetonitrile dried by distillation from phosphorus pentoxide were prepared just prior to use. Buffers were prepared from reagent grade chemicals. Distilled water was used throughout. Methylamine hydrochloride, a commercial product, was purified by recrystallization from ethanol.

Kinetics.—All kinetics were followed spectrophotometrically employing a Zeiss PMQ II spectrophotometer. The temperature was maintained at 25° throughout all runs by circulation of water from a thermostated water bath through the cell compartment. Ionic strength was maintained at 0.50 by the addition of potassium chloride. All runs were carried out in distilled water containing approximately 3% acetonitrile. Values of pH were determined with a glass electrode and a Radiometer PHM 4c pH meter.

Depending on the pH, the rate of appearance of either phenol at 270 mμ or phenolate at 287 mμ was used to measure the rate of the reaction in general. One hydrolysis run was made at pH 4.62, during which the disappearance of protonated imido ester was followed at 247.5 mμ. The rate constant obtained from this run was consistent with the remainder of the data. Infinite time values were obtained by checking all reactions at an estimated ten half-times and at appropriate intervals thereafter until the optical density remained constant over several intervals. In the few cases where the optical density reached a maximum and then decreased, that maximum was taken as the infinite time value.

First-order rate constants were determined from the slopes of semilog plots of the difference in optical density at infinite time and at time *t* *vs.* time *t*. Although most of the plots were not precisely linear through one half-time, the upward curvature was slight, and satisfactory straight lines could be drawn. Those cases are noted in which straight lines could not be drawn and in which the rate constants were obtained from the initial slopes. For the methylaminolysis reactions, first-order rate constants were divided by the concentration of methylamine present as the free base to obtain second-order rate constants.

Determination of pK_a.—The pK_a of the conjugate acid of phenyl N-methylacetimidate was determined by a spectrophotometric titration, using the Zeiss PMQ II spectrophotometer. In acetonitrile, the unprotonated form of the imido ester has an absorption minimum at 247.5 mμ and a maximum of 267.5 mμ. The optical density at 247.5 mμ of solutions containing equal amounts of the imido ester at various values of pH was recorded as a function of time and extrapolated back to zero time. The optical densities at zero time were plotted against pH, and the pK_a was determined from the resulting titration curve (see Results).

Product Analysis.—For the hydrolysis reaction, the product analysis was carried out on a Cary 14 recording spectrophotometer. Ultraviolet spectra were taken after the reactions had proceeded to completion at various values of pH in aqueous solution. Phenol was the only absorbing product above pH 4. At each value of pH examined, production of phenol was essentially quantitative as was judged from the concentration of imidate and the observed extinction at the wavelength of maximum absorption of phenol or phenolate as appropriate. At elevated values of pH, phenol is necessarily the reaction product since, even if phenyl acetate were initially produced, it would be rapidly cleaved under these conditions. In contrast, had phenyl acetate been the reaction product under conditions less basic than pH 8, it would have been stable to hydrolysis over the time period necessary for the reaction to reach completion. In order to ensure that the production of phenol was not the result of aminolysis of initially formed phenyl acetate, reconstruction experiments were performed. At values of pH near 3, 7, and 8, 6.8×10^{-4} *M* phenyl acetate was incubated with an equal concentration of

(16) M. A. Weinberger and R. Greenhalgh, *Can. J. Chem.*, **41**, 1038 (1963).

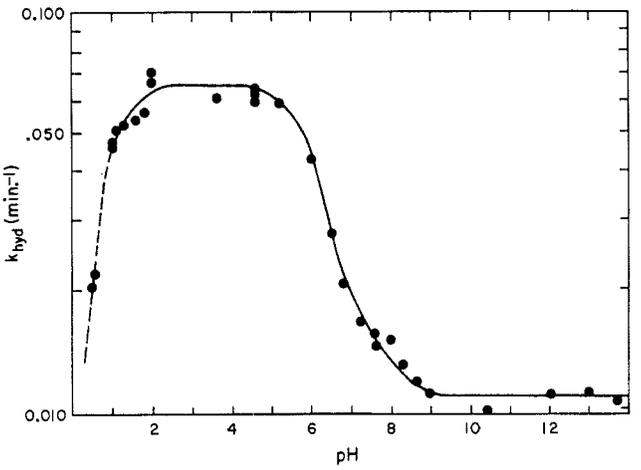


Figure 2.—Plot of first-order rate constants for hydrolysis of phenyl N-methylacetimidate at 25° and ionic strength 0.5 as a function of pH. The dashed line is drawn through those points for which good first-order plots were not obtained.

methylamine. These are the concentrations of these substances that might have been produced at the conclusion of a typical product analysis run had the reaction proceeded appropriately. After incubation for 36 hr at room temperature, the time necessary for completion of the hydrolysis reactions under these conditions, less than 10% of the phenyl acetate was decomposed to phenol in each case. At pH 0.76, a similar experiment resulted in the production of about 50% of the total possible phenol. A subsequent experiment established that this phenol results from hydrolysis, rather than aminolysis, of the phenyl acetate. These experiments clearly establish that phenol is, in fact, the initial product of the hydrolysis of phenyl N-methylacetimidate under these conditions and does not arise from phenyl acetate.

Results

The pK_a of the conjugate acid of phenyl N-methylacetimidate was determined by spectrophotometric titration in aqueous solution at 25°, ionic strength 0.50, as described in the Experimental Section. A plot of zero-time optical densities against pH is shown in Figure 1. From the midpoint of this titration curve, a value for the pK_a of this species of 6.2 was evaluated.

The pH-rate profile for the hydrolysis of phenyl N-methylacetimidate in water at 25° is presented in Figure 2. Acetate, phosphate, borate, and carbonate buffers were employed in appropriate ranges of pH. Rate constants have been extrapolated to zero buffer concentration for those cases in which buffer catalysis was observed. The first-order rate constant is near 1.1×10^{-2} min^{-1} in base, rises to a half-maximum at the pK_a of the conjugate acid of the imido ester, and reaches a maximum of 6.5×10^{-2} min^{-1} under slightly acidic conditions. At a pH of approximately 2, the first-order rate constants fall off. In solutions more acidic than 0.2 M hydrochloric acid, the semilog plots were linear only until one-half to two-thirds of the half time. In these cases, the rate constants were obtained from the initial slopes. Qualitatively, it is clear that these reactions are slow compared with those under less acidic conditions.

Phosphate catalyzes the appearance of phenol from phenyl N-methylacetimidate. Runs were made at several concentrations of total phosphate at pH 6.50 and 6.01 and the rate constants were extrapolated back to zero phosphate concentration. Two points on the hydrolysis pH-rate profile with different percentages

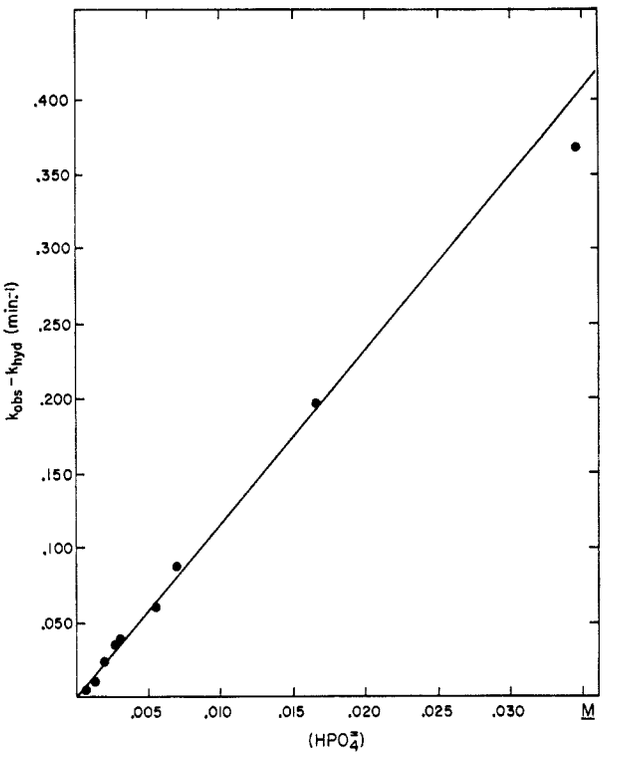


Figure 3.—Plot of first-order rate constants for the phosphate-catalyzed decomposition of phenyl N-methylacetimidate at 25° and ionic strength 0.5 against the concentration of the phosphate dianion.

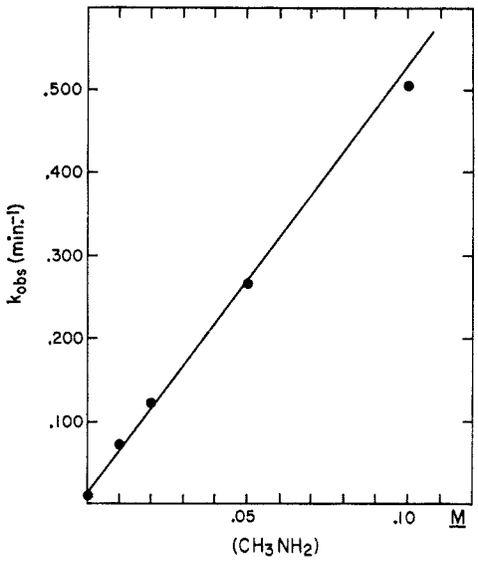


Figure 4.—Plot of first-order rate constants for the appearance of phenol from phenyl N-methylacetimidate as a function of the concentration of methylamine free base at pH 11.1, 25°, and ionic strength 0.50.

of the total buffer as the dianion were obtained in this manner. Qualitatively the phosphate catalysis was observed to be more marked at the more basic pH indicating that the phosphate dianion is the reactive species. Once the shape of the hydrolysis pH-rate profile is known, it is possible to correct for the water reaction and construct the plot shown in Figure 3 which quantitatively shows the dependence of the rate constant on the phosphate dianion concentration. The observed first-order rate constant for the appearance of phenol, corrected for the water reaction, is

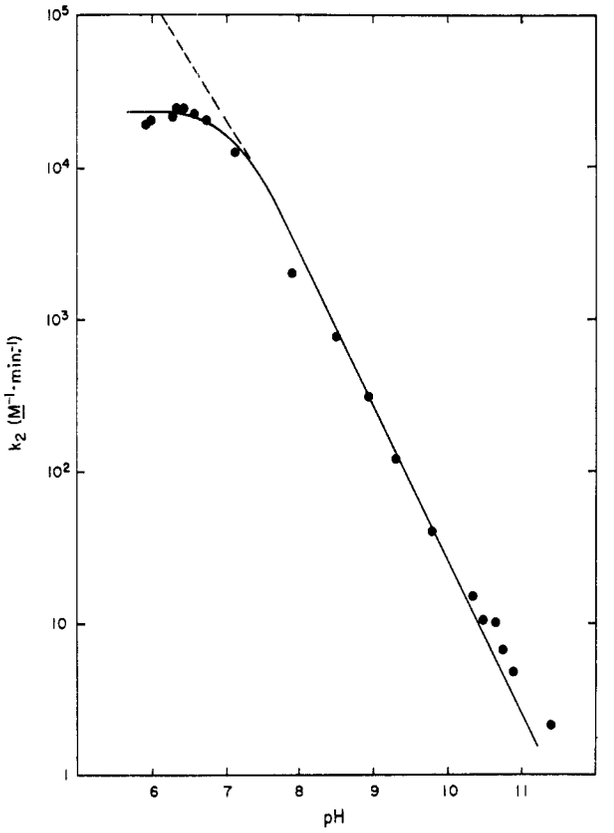


Figure 5.—Plot of second-order rate constants for the methylaminolysis of phenyl N-methylacetimidate at 25° and ionic strength 0.50 as a function of pH. The dashed line is a calculated plot based on the conversion of the substrate to its conjugate acid.

plotted against the concentration of the phosphate dianion. The slope is 11.6 M^{-1} min^{-1}.

The rate of hydrolysis of this substrate is independent of the concentrations of acetate over the range 0.01 to 0.2 M under similar conditions.

In Figure 4, the first-order rate constants for reaction of phenyl N-methylacetimidate with methylamine in water at 25° at pH 11.1 are shown as a function of the concentration of the nucleophilic reagent. This reaction is clearly first-order in methylamine. Pseudo-first- and second-order rate constants for this reaction are summarized as a function of pH in Table II. The second-order rate constants are shown as a function of pH in Figure 5. These rate constants have been corrected for concomitant hydrolysis and for catalysis by phosphate. Above pH 7, the second-order rate constants are first-order in hydrogen ion; under less basic conditions they become substantially independent of this parameter.

Discussion

The pH-rate profile for hydrolysis of phenyl N-methylacetimidate (Figure 2) is qualitatively similar to that for hydrolysis of 2-methyloxazoline.[4,17] The data may be interpreted in a fashion consistent, for the most part, with that proposed to account for the oxazoline data.[4] The reaction scheme is indicated in eq 1. A simple steady-state treatment of this situation

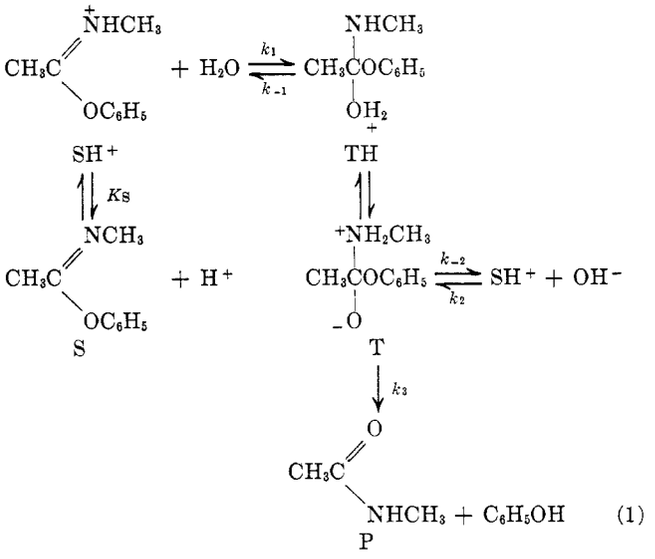
(17) R. Greenhalgh, R. M. Heggie, and M. A. Weinberger, *Can. J. Chem.*, 41, 1662 (1963).

TABLE II

SECOND-ORDER RATE CONSTANTS FOR METHYLAMINOLYSIS OF PHENYL N-METHYLACETIMIDATE AS A FUNCTION OF pH IN AQUEOUS SOLUTION AT 25° AND IONIC STRENGTH 0.50[a]

pH	k_{obsd}, min^{-1}	k_{hyd}, min^{-1}	$k_{obsd} - k_{hyd}$, min^{-1}	(CH_3NH_2),[b] M	k_2,[c] M^{-1} min^{-1}
11.42	0.104	0.011	0.093	4.32×10^{-2}	2.16
10.89	0.166	0.011	0.155	3.25×10^{-2}	4.78
10.73	0.201	0.011	0.190	2.82×10^{-2}	6.73
10.64	0.271	0.011	0.260	2.56×10^{-2}	10.2
10.52	0.245	0.011	0.234	2.21×10^{-2}	10.6
10.36	0.273	0.011	0.262	1.75×10^{-2}	15.0
9.77	0.260	0.011	0.249	6.18×10^{-3}	40.3
9.29	0.282	0.011	0.271	2.23×10^{-3}	121
8.94	0.333	0.011	0.322	1.04×10^{-3}	311
8.51	0.308	0.012	0.296	3.85×10^{-4}	769
7.90	0.208	0.013	0.195	9.65×10^{-5}	2.02×10^3
7.17	0.512	0.018	0.503	3.55×10^{-5}	1.26×10^4
6.86	0.770	0.021	0.749	3.46×10^{-5}	2.06×10^4
6.60	0.262	0.026	0.236	9.55×10^{-6}	2.23×10^4
6.44	0.371	0.029	0.342	1.32×10^{-5}	2.46×10^4
6.36	0.182	0.034	0.148	5.50×10^{-6}	2.45×10^4
6.28	0.248	0.036	0.212	9.14×10^{-6}	2.18×10^4
6.02	0.103	0.044	0.059	2.51×10^{-6}	2.04×10^4
5.95	0.136	0.046	0.090	4.28×10^{-6}	1.96×10^4

[a] Dilute borate and dilute phosphate buffers were used in the appropriate pH ranges. Corrections were made for catalysis by phosphate. [b] As the free base. [c] $(k_{obsd} - k_{hyd})/(CH_3NH_2)$.



(1)

yields expression 2 relating the first-order rate constants to the quantities defined in eq 1 and to (H^+). Under

$$k_{obsd} = \frac{k_3(H^+)}{(H^+) + K_S} \cdot \frac{[k_2(OH^-) + k_1(H_2O)]}{k_3 + k_{-2} + k_{-1}(H^+)} \quad (2)$$

sufficiently basic conditions, this expression reduces to $k_{obsd} = k_2K_w/K_S$, in which the reasonable assumption is made that $k_3 \gg k_{-2}$. Thus, the pH-independent reaction observed under basic conditions is considered to reflect rate-determining attack of hydroxide ion on the protonated imido ester. For several reasons, this alternative seems more likely than the kinetically indistinguishable pathway involving rate-determining attack of water on the unprotonated substrate. In the first place, the pH-independent reaction observed under similar conditions in Schiff-base hydrolysis, a related reaction, is known to proceed with attack of hydroxide

ion on the protonated substrate.[18-22] In the second place, the value of the second-order rate constant for attack of hydroxide ion on the protonated imido ester, k_2, $6.8 \times 10^5\ M^{-1}\ \text{min}^{-1}$, is similar to that obtained for the attack of hydroxide ion on protonated benzylidene-1,1-dimethylethylamines.[19] Finally, the first-order rate constant observed for attack of water on the protonated substrate, discussed below, is only 6.5 times as large as that for the reaction in basic solution. It seems quite unlikely that conversion of the imidoester to its conjugate acid would result in such a modest increase in reactivity toward water, as the assumption of water attack on the unprotonated substrate would require.

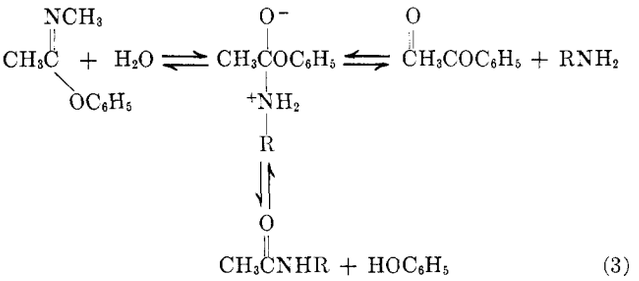
Under more acidic conditions, appreciable protonation of the substrate occurs and reaction of the protonated species with water becomes a kinetically important reaction. Under conditions in which the substrate is completely converted into the conjugate acid, eq 2 reduces to $k_{obsd} = k_1(H_2O)$; that is, attack of water on the protonated substrate is the rate-determining step. Dividing the first-order rate constant observed between pH 2 and 5 by the molar concentration of water, 55, yields the second-order rate constant for attack of water on the protonated substrate: $k_1 = 1.2 \times 10^{-3}\ M^{-1}\ \text{min}^{-1}$. Hence, hydroxide ion is about 5×10^8 times as reactive as water toward the phenyl N-methylacetimidate cation, a reasonable value.

Under still more acidic conditions, the first-order rate constants begin to decrease with increasing (H^+) as predicted by eq 2: $k_{obsd} = k_1k_3(H_2O)/k_{-1}(H^+)$. Although the rate decrease is small, it is certainly real and occurs under conditions in which it is probably not a consequence of decreasing activity of water. Hence, it may reflect a transition in rate-determining step to slow decomposition of the tetrahedral intermediate, T. This conclusion corroborates that of DeWolfe and Augustine made on the basis of substituent effect and activation parameters for the hydrolysis of benzimidates.[3]

That the rate law of eq 2 can account quantitatively for the observed pH-rate profile is indicated by the solid and dotted lines in Figure 2 which are calculated from this equation with $k_1 = 1.2 \times 10^{-3}\ M^{-1}\ \text{min}^{-1}$ and $k_3/k_{-1} = 0.095$. However, the concept of a transition in the rate-determining step for the hydrolysis of phenyl N-methylacetimidate cannot be accepted without reservations, since the rate decrease observed under acidic conditions is rather small and does occur under conditions sufficiently acidic so that the activity coefficients of ionic reactants cannot be assumed constant.

The phosphate-catalyzed hydrolysis of phenyl N-methylacetimidate, Figure 3, almost certainly reflects the nucleophilic attack of phosphate on this substrate. The value for the second-order rate constant for attack of the phosphate dianion on the protonated imido ester, $11.6\ M^{-1}\ \text{min}^{-1}$, together with those for water, $1.2 \times 10^{-3}\ M^{-1}\ \text{min}^{-1}$, and hydroxide ion, $6.8 \times 10^5\ M^{-1}\ \text{min}^{-1}$, suggest a Brønsted β value for this reaction near 0.5.

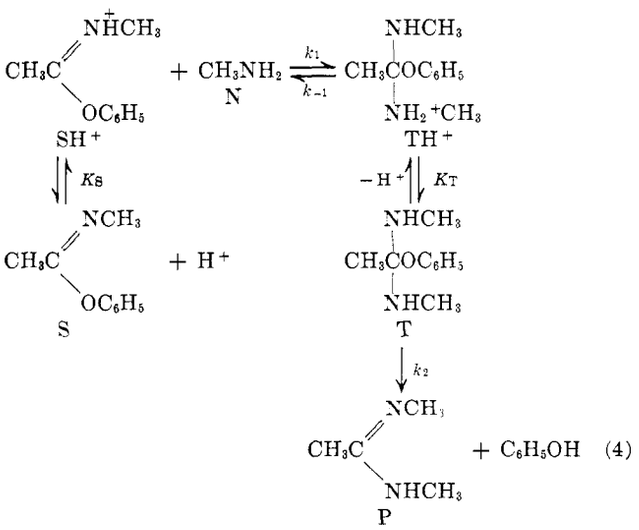
The most significant observation made in this study with respect to phenyl N-methylacetimidate hydrolysis is not the probable transition in rate-determining step as a function of pH but the finding that the product of this reaction is phenol over the pH range above 4.[23] As indicated in the Experimental Section, phenol is the immediate reaction product, below pH 8 at least, and does not arise from phenyl acetate. Thus, decomposition of the tetrahedral intermediate, T in eq 1, proceeds more rapidly with expulsion of phenoxide ion rather than with departure of methylamine. Addition of strongly basic amine to a phenyl acetate yields the same set of tetrahedral intermediates as the addition of hydroxide ion or water to phenyl acetimidates (eq 3). *Thus, the above observation indicates that aminolysis*



(3)

of phenyl acetates with strongly basic amines proceeds with rate-determining attack of amine, not rate-determining decomposition of the tetrahedral intermediate. The latter alternative would require that the amine be expelled from the intermediate more rapidly than phenoxide, in contrast to the observed behavior. This conclusion is of obvious importance for understanding of structure–reactivity correlations, mechanisms for general acid–base catalysis, and susceptibility to general acid–base catalysis for phenyl acetate aminolysis.

The dependence of the second-order rate constants for methylaminolysis of phenyl N-methylacetimidate on pH is qualitatively similar to that observed by Hand and Jencks for the aminolysis of benzimidates and may be explained on the same basis.[6] The reaction sequence is indicated in eq 4. Under basic conditions, attack of



(4)

(18) L. do Amaral, W. A. Sandstrom, and E. H. Cordes, *J. Am. Chem. Soc.*, **88**, 2225 (1966).
(19) E. H. Cordes and W. P. Jencks, *ibid.*, **85**, 2843 (1963).
(20) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 832 (1962).
(21) K. Koehler, W. A. Sandstrom and E. H. Cordes, *ibid.*, **86**, 2413 (1964).
(22) R. L. Reeves, *J. Org. Chem.*, **30**, 3129 (1965).

(23) NOTE ADDED IN PROOF.—Professor William P. Jenks has been kind enough to point out to us that, at values of pH below 4, hydrolysis of phenyl N-methylacetimidate yields appreciable amounts of phenyl acetate although phenol continues to be the major product.

methylamine on the protonated substrate is rate-determining and the second-order rate constants are linear in the concentration of hydrogen ion. As a significant fraction of the imidate is converted into the conjugate acid, these rate constants will tend to become independent of this parameter; the dotted line in Figure 5 exhibits this behavior. The measured second-order rate constants clearly deviate from linearity in a fashion that cannot be explained on the basis of protonation of the substrate. This behavior is interpreted as a transition to rate-determining decomposition of the tetrahedral intermediate. This behavior has been thoroughly treated both qualitatively and quantitatively[6] and need not be reexplained here. Experiments at more acidic conditions would strongly buttress the conclusion of a change in rate-determining step since the deviations from calculated behavior would be magnified. Unfortunately, reliable data are difficult to obtain below pH 6, since the concomitant hydrolysis reaction becomes rapid thus masking the aminolysis.

Registry No.—*syn*-Phenol N-methylacetimidate, 13758-81-1; *anti*-phenyl N-methylacetimidate, 13758-82-2.

Photocyclization of Methyl-*o*-benzyloxyphenylglyoxylate

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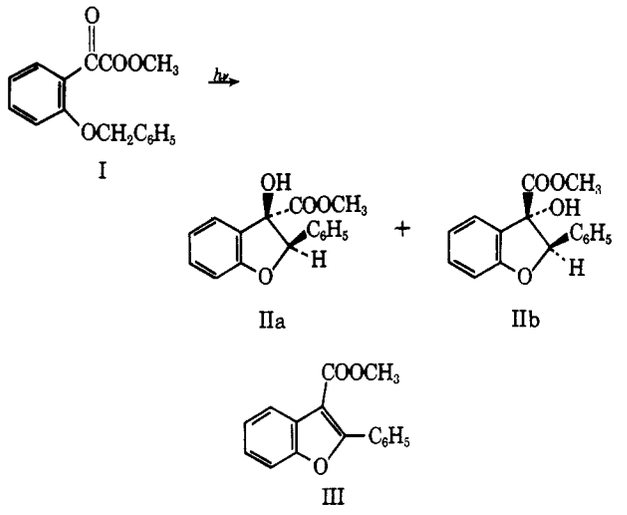
Methyl-*o*-benzyloxyphenylglyoxylate undergoes light-induced, intramolecular cyclization to afford an isomeric mixture of 2-phenyl-3-carboxymethyl-3-hydroxyl-2,3-dihydrobenzofurans in high yield. The stereochemistry of photocyclization is significantly dependent on both solvent and temperature, one of the isomers being formed almost exclusively in nonpolar solvents at low temperature. The results of photosensitization and quenching experiments indicate that reaction occurs predominately *via* the triplet state, suggesting that the stereochemical fate of the triplet is both solvent and temperature dependent. Some implications of the observed stereospecificity are discussed.

Recently, we reported that *o*-benzyloxybenzaldehyde undergoes light-induced cyclization to afford *cis*-2-phenyl-3-hydroxyl-2,3-dihydrobenzofuran and a closely related compound, possibly the corresponding *trans* isomer.[1] Further work has demonstrated that the major product resulting from intramolecular cyclization is the *cis* isomer.[2] While the over-all extent of intramolecular reaction was found to be modest, the resulting stereoselectivity was intriguing particularly since the major product was the less stable isomer. Clearly, studies on the stereospecificity of photocyclization of this system are of interest from both mechanistic and synthetic points of view.

Comprehensive studies on the photochemistry of *o*-benzyloxybenzaldehyde are encumbered, however, primarily because of the resulting complex product mixture, and we have been investigating closely related *o*-alkoxyaromatic carbonyl compounds, as well, with the hope of uncovering a more efficient system. To this end, we were gratified to find that methyl-*o*-benzyloxyphenylglyoxylate (I) undergoes intramolecular photocyclization cleanly to afford isomeric products in greater than 90% yield. Herein we report the effects of solvent and temperature as well as of photosensitization and quenching on the stereochemistry of photocyclization of I.[3]

Results

On solution irradiation, methyl-*o*-benzyloxyphenylglyoxylate (I) is transformed into an isomeric mixture of 2-phenyl-3-hydroxyl-3-carboxymethyl-2,3-dihydrobenzofurans (IIa and IIb). The isomers, separated by careful chromatography on neutral alumina, may be quantitatively dehydrated into 2-phenyl-3-carboxymethylbenzofuran (III).[4]



The relative positions of the carboxymethyl hydrogens in the nmr spectra[5] of the isomers provide compelling evidence for the stereochemical assignments. In addition to aromatic hydrogen resonances, the isomers exhibit two sharp singlets (area ratio 3:1) for the carboxymethyl and benzylic hydrogens, respectively.[6]

(1) S. P. Pappas and J. E. Blackwell, Jr., *Tetrahedron Letters*, 1171 (1966).

(2) Gas chromatography of the product mixture derived from *o*-benzyloxybenzaldehyde after irradiation in acetonitrile at 0° indicated that two major products with similar retention times were produced in the ratio of 2:1 to the extent of about 30%. It was easily demonstrated that the major product was *cis*-2-phenyl-3-hydroxyl-2,3-dihydrobenzofuran by chromatography of the mixture with added pure *cis* material.

(3) Kinetic studies are in progress.

(4) J. N. Chatterjea, *J. Indian Chem. Soc.*, **38**, 175 (1956).

(5) The nmr spectra were obtained in deuteriochloroform solution on a Varian A-60 spectrometer. All resonances are reported in parts per million using TMS as an internal reference.

(6) The isomer IIb exhibits hydroxyl hydrogen resonance, as well, which disappears on the addition of deuterium oxide; in contrast, such resonance has not been observed in the nmr spectrum of either IIa or mixtures of IIa and IIb.