anion in the third step,[24] then a general acid catalysis behavior which approaches specific oxonium ion catalysis could be exhibited.

The general conclusion based upon the effect of changing mineral acid molarity upon k_{obsd} is that the reaction exhibits general acid catalysis behavior which approaches much more closely the extreme of specific oxonium ion catalysis than it does dependence on the acidity function, h_0. Many points remain unanswered, including the question of which step is rate controlling. It is clear that further studies are in order, including an examination of the kinetics of the reaction in dilute aqueous solution and the determination of deuterium isotope effects. If this reaction can be studied effectively in dilute aqueous solution, it may help to bridge the gap between our knowledge of acid–base catalysis in dilute and non-dilute aqueous acids.

(24) Since the third step is essentially a hydrolysis of a formic acid derivative, it is not unreasonable to expect H_2O to be the only effective base in this step.

GREENCASTLE, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

Electrostatic Catalysis. The Reactivity of an Ester and a Nucleophile of Opposite Charge[1a]

BY MYRON L. BENDER AND YUAN-LANG CHOW[1b]

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Reactions of *o*-nitrophenyl hydrogen oxalate with pyridine, aniline, 2-aminopyridine and 4-aminopyridine occur in buffered aqueous solutions in the region *p*H 3 to 6. The reacting species in the latter cases include both the free aminopyridine and the corresponding monoprotonated species, the aminopyridinium ion. Part of the reaction of the aminopyridines with *o*-nitrophenyl hydrogen oxalate in this *p*H region includes a reaction of a negatively charged substrate and a positively charged nucleophile. There is a difference of thirty in the nucleophilicities of 2-aminopyridinium ion and 2-aminopyridine while there is a difference of fifteen powers of ten in their basicities. The nucleophilicity of 2-aminopyridinium ion is comparable to that of 4-aminopyridinium ion although the basicity of the former is one-tenth as large. The exceptional reactivity of 2-aminopyridinium ion is attributed to the electrostatic stabilization of the quasi cyclic transition state I. This system is considered to be a model reaction for enzymatic processes such as the interaction of acetylcholine and acetylcholinesterase.

Introduction

It is generally believed that the powerful and specific catalysis of the hydrolysis of carboxylic acid derivatives exhibited by proteolytic and hydrolytic enzymes such as chymotrypsin and acetylcholinesterase, respectively, is due to the action of one or more nucleophilic substances on the enzyme, perhaps in conjunction with electrophiles. The source of the nucleophiles is believed to be in the side chain groups of the α-amino acid moieties of the enzymes. For example, the imidazole group (of histidine) and the hydroxymethyl group (of serine) have been implicated in chymotrypsin action.[2–5]

Studies with model systems, involving imidazole or its derivatives alone, have indicated that the enzymatic process is still considerably better than can be accounted for on the basis of a simple nucleophilic attack by an imidazole nitrogen.[6] Attempts have been made to explain the discrepancy between the action of imidazole and the enzyme chymotrypsin. For example, it has been postulated that since enzymatic action proceeds through primary complex formation followed by one or more catalytic steps, enzymatic action may be likened to an intramolecular reaction which would be expected to proceed more readily than the corresponding intermolecular reaction.[7,8] This concept has been amply verified by studies of intramolecular catalysis involving the carboxylate ion,[9] the carboxylic acid group,[10] and the imidazole group[11,12] which has shown impressive similarity to the chymotrypsin system.

While the concept of an intramolecular reaction goes far to explain the enhanced reactivity of enzymes toward carboxylic acid derivatives,[8,12] it does leave unanswered the question of how one obtains the complex between enzyme and substrate that may be considered to lead to an intramolecular process. In the reaction of various substrates with acetylcholinesterase, it has been shown that the "esteratic" site is accompanied by another (anionic) site on the enzyme which interacts electrostatically with a positive site of the substrate, usually the acetylcholine cation. It was therefore conceivable that a system composed of an ester substrate and an amine nucleophile could be constructed in which there would be, adjacent to the reactive centers on each molecule, a second set of centers which would be correctly oriented for electrostatic interaction. It was thought that a considerable rate enhancement might occur under these circumstances and that such a reaction system might provide a better model for enzymatic reaction than

(1) (a) This research was supported by Grant H-2416 of the National Institutes of Health and by a grant from the Upjohn Co. (b) Royal Institute of Technology, Stockholm 70, Sweden.

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models in which simple intermolecular or simple intramolecular processes were operative.

The concept of a bifunctional catalyst or reactant has been demonstrated in a number of instances and has been interpreted in terms of concerted nucleophilic and electrophilic attack on the reactive linkage.[13-16] In the present case, which also can be considered to involve a bifunctional attacking agent, the electrostatic (second) function is *not* involved with the reactive center but rather with a second center in the substrate molecule. That is, the present study involves the reaction of two bifunctional molecules.

An effect which parallels the present study has been found in the quaternization of partially ionized polyvinylpyridine with bromoacetate ion.[17] Here also the electrostatic interaction between two centers of the reacting molecules which do not undergo covalent change (*i.e.*, the carboxylate and protonated pyridine residues of the polymer) enhances the over-all reaction rate by stabilizing the transition state.

Experimental

Materials.—2-Methylquinoline was used as its perchlorate prepared according to the method of Pritchard and Long.[18] Straw-colored crystals were obtained after three recrystallizations from 95% ethanol, m.p. 131–131.5°. 2,6-Lutidine was purified according to the method of Brown.[19] Commercial pyridine was dried over sodium hydroxide pellets and distilled through a column packed with glass helices, b.p. 115°. Aniline was redistilled in a column packed with glass helices, b.p. 182°. 2-Aminopyridine was recrystallized from chloroform–petroleum ether mixture, m.p. 57°. 4-Aminopyridine was recrystallized from benzene, m.p. 158°. Dioxane was purified according to the method of Fieser.[20] *o*-Nitrophenyl acetate was prepared from *o*-nitrophenol, acetic anhydride and sodium hydroxide. The product was recrystallized from benzene–petroleum ether, m.p. 40.5–41°.

o-Nitrophenyl hydrogen oxalate was prepared in the following manner. A solution of sodium acetate trihydrate (2 g.) in 30 ml. of water was added to a solution of 5 g. of bis-*o*-nitrophenyl oxalate in 400 ml. of acetone at room temperature. The mixture was shaken vigorously at room temperature for a few minutes and 5 ml. of 5.8 *N* hydrochloric acid was added after 15 minutes. The acetone was evaporated quickly under vacuum at room temperature. The remaining water solution was extracted with three 50-ml. portions of cold ether. The ethereal solution was dried over anhydrous magnesium sulfate and then the ether was removed in vacuum. The resultant solid contained a trace of water which was removed by drying in a vacuum desiccator. The dried solid was treated with freshly distilled chloroform. The residue of oxalic acid was removed. The chloroform solution was carefully evaporated until a yellow solid separated. Recrystallization of this material from carefully purified chloroform gave yellow needles, m.p. 123–125°.

Anal. Calcd. for $C_8H_5O_6N$: C, 45.55; H, 2.37; N, 6.64. Found: C, 45.60; H, 2.10; N, 6.65.

Ionization Constant.—The pK_I of 2-ammoniumpyridinium ion was determined by the method of Davis and Geissman,[21] using 300 and 257 mμ as the wave lengths for maximal absorption of the protonated and diprotonated forms, respectively. Sulfuric acid solutions, 96% or lower, were titrated with standard base; 100% sulfuric acid was prepared by addition of concd. H_2SO_4 to 15% oleum, the end-point being determined according to Brand.[22] H_0 values were taken from data of Long and Paul.[23]

Product Analysis.—*o*-Nitrophenyl hydrogen oxalate was shaken with 10 ml. of distilled water for several hours. A yellow solution was formed and upon cooling in an ice-bath, yellow needles separated. This material was shown to be identical with authentic *o*-nitrophenol *via* the melting point of a mixture. The colorless filtrate from above was evaporated under vacuum to dryness. The white residue was identified as oxalic acid by its melting point.

Kinetics.—Rate measurements of the reactions of *o*-nitrophenyl hydrogen oxalate were carried out by a determination of the increase of the absorbance of the product, *o*-nitrophenol, at 350 or 370 mμ with time. A Beckman DK2 recording spectrophotometer with a thermostated cell compartment was used. In general the reaction solution minus the ester was equilibrated at the desired temperature. Then about 2–3 mg. of *o*-nitrophenyl hydrogen oxalate, weighed in a dried platinum boat, was added to the thermostated reaction mixture and quickly shaken to achieve solution. The solution then was added to the previously thermostated absorption cells and the optical density of the solution as a function of time was determined.

At *p*H 3 and below, constant *p*H was maintained by the excess hydrochloric acid present in the solution. In reactions with pyridine and aniline, the reactants themselves served as buffers (at *p*H 5.2 and 5.1, respectively). In reactions with 2-aminopyridine and 4-aminopyridine at *p*H 5 and 6, 2-methylquinoline, a hindered buffer was used,[24] which was shown to be unreactive toward *o*-nitrophenyl hydrogen oxalate. In general *p*H measurements were taken before and after each reaction with a Beckman model G *p*H meter to ensure constancy of *p*H during a run. Constant ionic strength was maintained in a set of runs by the addition of the appropriate amount of sodium chloride.

Results and Discussion

Hydrolysis of *o*-Nitrophenyl Hydrogen Oxalate.—It is well known that nitrophenyl esters are easily hydrolyzed,[6] as are oxalate esters.[25] It is therefore not surprising that the principal substrate in this study, *o*-nitrophenyl hydrogen oxalate, hydrolyzed in aqueous solution at a substantial rate. The dependence of the rate of hydrolysis of this substance on the *p*H of the system is illustrated in Table I and Fig. 1. The *p*H behavior from 0.001 to about 1 *M* hydrochloric acid can be explained in terms of the hydrogen ion catalyzed hydrolysis of the ester anion. This hypothesis predicts that the observed rate constant will decrease with decreasing acidity as is observed in this region and further, that a plot of $1/k_{obs}$ *vs.* $1/H^+$ should conform to a linear relationship with intercept equal to $1/k$ and slope equal to K/k. Such a linear relationship does hold over about four powers of ten in the hydrogen ion concentration, although the precision is not high. From the slope of the line, it is calculated that the ionization constant of *o*-nitrophenyl hydrogen oxalate is equal to 3.5×10^{-1}. The rate data at acidities higher than 1 *M* hydrochloric acid are not amenable to simple interpretation. A maximum in the observed rate constant appears at 1.76 *M* hydrochloric acid which at present cannot be explained. Maxima in the acid-catalyzed hy-

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TABLE I

HYDROLYSIS OF *o*-NITROPHENYL HYDROGEN OXALATE[a,b]

HCl, *M*	$k_{obs} \times 10^3$, sec.$^{-1}$
5.85	2.08
4.40	4.55
2.93	5.68
1.76	6.15
1.00	4.79
0.100	1.13
.010	0.13
.001	0.02

[a] In aqueous solution at 25.5 ± 0.2°. For all concentrations of hydrochloric acid of 1.0 *M* or lower the ionic strength was maintained at 1.0 *M* by the addition of sodium chloride. [b] Salmi[25] reports k_2 for the hydrogen ion catalyzed hydrolysis of dimethyl oxalate is 1.60×10^{-4} l./mole sec. at 25°. This corresponds to first-order rates 1/71 to 1/124 times as fast as the last three entries in the table.

drolysis of amides often are observed,[26] but this is due to the fact that amides can be completely protonated at relatively low acidity whereas esters, as in the present instance, ordinarily cannot.

Reaction of *o*-Nitrophenyl Hydrogen Oxalate with Various Nucleophiles.—*o*-Nitrophenyl hydrogen oxalate reacts readily with a number of nucleophiles. In its reactions with pyridine, the experimentally observable reaction to produce *o*-nitrophenol and acylpyridinium ion is followed by attack of a water molecule on the latter compound to give an over-all hydrolytic reaction, similar to the reaction of pyridine with *p*-nitrophenyl acetate.[6,27] The pyridine can be described as a nucleophilic catalyst. In the reaction of aniline with *o*-nitrophenyl hydrogen oxalate, the products of the experimentally observable reaction, *o*-nitrophenol and an anilide, are resistant to attack by water under the reaction conditions. Kinetic comparisons of the formation of *o*-nitrophenol in these diverse systems can be made since the second step in the former case does not affect the rate of the first step. On this basis, the kinetics of a number of reactions of *o*-nitrophenyl hydrogen oxalate with various nucleophiles, including aniline, pyridine, 2-aminopyridine and 4-aminopyridine, were determined, as shown in Table II. For comparative purposes the kinetics of the reactions of *o*-nitrophenyl acetate, an ester not containing a carboxylic acid group, with pyridine and with 2-aminopyridine were determined as shown in Table II.

The second-order rate constants for the reactions of aniline and pyridine with *o*-nitrophenyl hydrogen oxalate and *o*-nitrophenyl acetate were obtained from the slopes of the plots of k_{obs} *vs.* free amine at constant *p*H and constant ionic strength as has been done previously.[6,27]

The nucleophilic reactions of 2-aminopyridine and 4-aminopyridine require a careful analysis. In the *p*H region 3–6, where kinetic measurements were carried out, the concentration of the *o*-nitrophenyl oxalate anion is essentially equal to the stoichiometric ester concentration based on the previous calculation of $K = 3.5 \times 10^{-1}$. The question arises as to the nature of the reactive species of the nucleophile. Both 2-aminopyridine and 4-aminopyridine could function as nucleophiles in either the free base or the monoprotonated form, or in both forms. An analysis of the kinetic data at three *p*H's, 3, 5 and 6 delineates these possibilities. The general equation for the observed first-order rate constant is

$$k_{obs} = k_o + k_B(B) + k_{BH^+}(BH^+) \qquad (1)$$

where k_o is the spontaneous rate constant, k_B is the rate constant of the free base and k_{BH^+} is the rate constant of the monoprotonated base. This equation can be converted to the form

$$(k_{obs} - k_o)/(BH^+) = k_B(B)/(BH^+) + k_{BH^+} \qquad (2)$$

Equation 2 shows that k_B and k_{BH^+} may be calculated, if kinetic data at two or more *p*H values are available. These calculations were carried out both graphically and analytically for the reactions of the aminopyridines and *o*-nitrophenyl hydrogen oxalate. The second-order rate constants for the reactions of these various species with *o*-nitrophenyl hydrogen oxalate are listed in Table III, together with the pK_a's of the various nucleophiles.

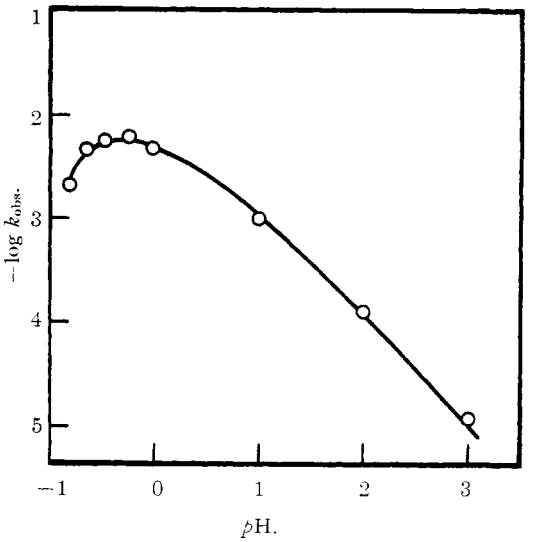

Fig. 1.—Hydrolysis of *o*-nitrophenyl hydrogen oxalate in aqueous hydrochloric acid solutions at 25.5°.

It is of interest to compare the second-order rate constants of the various species in their reactions with *o*-nitrophenyl hydrogen oxalate. A comparison of the nucleophilicity of 2-aminopyridine and 4-aminopyridine in Table III indicates that the latter compound is a considerably better nucleophile as required by its greater basicity. The nucleophilicities of pyridine, aniline and 2-aminopyridine do not greatly differ from one another. It might be predicted that 2-aminopyridine would exhibit the greatest nucleophilicity of this trio since it is the strongest base. However, it exhibits the lowest nucleophilicity of the three, possibly due to the large steric requirements of the *ortho* substituent. It should be pointed out that these comparisons of basicity and nucleophilicity imply the applicability of the Brönsted equation to nucleophilic attack on carboxylic acid derivatives. It has been amply shown that a relationship between the log of the nucleophilic rate constant and the pK_a of the base

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(27) T. C. Bruice and R. Lapinski, THIS JOURNAL, **80**, 2265 (1958).

TABLE II

REACTION OF NUCLEOPHILES WITH VARIOUS ESTERS[a]

pH[f]	Ionic str. μ M	B × 10⁶, M	BH⁺ × 10², M	k_{obs} × 10⁴, sec.⁻¹
2-Aminopyridine and *o*-nitrophenyl hydrogen oxalate				
2.91[b]	0.02	0.6	0.998	1.60
3.01	.02	.4	.505	1.48
3.025	.02	.077	.100	1.41
3.01	.02	.0	.0	1.38
5.08[c]	.058	87.0	.99	0.64
5.10	.060	18.0	.19	.46
5.10	.059	0.0	.0	.42
5.91[c]	.035	560	.94	1.45
5.99	.035	320	.46	1.18
5.99	.035	0.0	.0	0.89
4-Aminopyridine and *o*-nitrophenyl hydrogen oxalate				
3.00[b]	0.02	0.008	0.995	1.81
3.01	.02	.004	.497	1.53
3.01	.02	.001	.107	1.40
3.02	.02	.0	.0	1.38
5.10[c]	.058	.99	.99	17.7
5.10	.057	.50	.50	9.4
5.20	.058	.27	.21	4.4
5.10	.059	.0	.0	0.42
6.02	.035	4.30	.52	64.5
6.03	.035	.82	.097	12.2
6.00	.035	0.0	.0	0.89
Pyridine and *o*-nitrophenyl hydrogen oxalate[d]				
5.20	0.01	2500		10.30
5.20	.01	4900		16.3
5.20	.01	10000		29.1
Aniline and *o*-nitrophenyl hydrogen oxalate[e]				
5.10	0.048	8000		7.65
5.10	0.048	3800		4.35
Pyridine and *o*-nitrophenyl acetate[d]				
5.20	0.01	10000		3.2
5.20	.01	4900		1.67
5.20	.01	2500		0.87
2-Aminopyridine and *o*-nitrophenyl acetate[b]				
3.06	0.0030	2000		0.024
3.10	.0029	980		.024
3.11	.0030	0		.024

[a] 45.5 ± 0.3°. [b] Hydrochloric acid solution; these runs were performed in duplicate. [c] 2-Methylquinoline buffer. [d] Pyridine buffer. [e] Aniline buffer. [f] The pH has an uncertainty of 0.02 pH unit.

does exist.[28,29] But there are various restrictions on the extent to which the Brönsted equation can be applied. For example, pyridines and anilines have Brönsted plots of similar slope but of different intercept.[28] Furthermore, it is reasonable to suppose that 2-substituted pyridines should be considered as as eparate family from 3- and 4-substituted pyridines. These restrictions on the applicability of the Brönsted equation to the present cases require that the comparisons made above be kept on a qualitative level and not on a quantitative level.

A comparison can be made of the nucleophilicity of the aminopyridinium ions in relation to the neutral nucleophiles and to each other. Again it must be said that the aminopyridinium ions belong to a family of positively charged nucleophiles which should be treated separately from neutral nucleophilic species. Acknowledging this restriction, a comparison between 2-aminopyridinium ion and 2-aminopyridine indicates surprisingly that there is a difference of thirty in the nucleophilicities of these two species whereas there is a difference of fifteen powers of ten in their basicities. Likewise, if one compares the nucleophilicities of aniline (or pyridine) with the 2-aminopyridinium ion there is a difference of roughly two orders of magnitude in the nucleophilicities and about thirteen orders of magnitude in the basicities. These observations indicate that 2-aminopyridinium ion has overcome the apparent steric hindrance of 2-aminopyridine mentioned above. Similar comparisons, although not as striking, can be made with 4-aminopyridinium ion.

Finally a comparison between 2-aminopyridinium ion and 4-aminopyridinium ion reveals that the nucleophilicities of these two substances are comparable while the basicity of the former is an order of magnitude less than that of the latter. This comparison should not be given much weight because of the imprecision of the value of the rate constant of 4-aminopyridinium ion due to experimental difficulties caused by the overpowering nucleophilicity of 4-aminopyridine.

TABLE III

SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF VARIOUS NUCLEOPHILES AND ESTERS

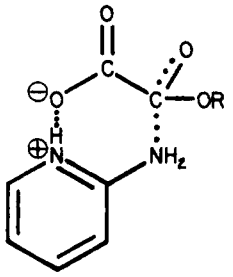
Nucleophile	pK_a of nucleophile	k_2 × 10³, l./mole sec.
o-Nitrophenyl hydrogen oxalate (anionic form)		
Aniline	4.58[a]	95
Pyridine	5.23[b]	248
4-Aminopyridine	9.17[c,d]	1,460,000
4-Aminopyridinium ion	−6.3[e,f,g]	1–3
2-Aminopyridine	7.14[e]	61
2-Aminopyridinium ion	−7.6[e,f,h]	2.1
o-Nitrophenyl acetate		
Pyridine	5.23[b]	31.5
2-Aminopyridinium ion	−7.6	.....

[a] N. F. Hall and M. R. Sprinkle, THIS JOURNAL, **54**, 3469 (1932). [b] A. Gero and J. J. Markham, *J. Org. Chem.*, **16**, 1835 (1951). [c] H. Hirayama and T. Kubota, *J. Pharm. Soc. Japan*, **73**, 140 (1953). [d] A. Albert, R. Goldacre and J. Phillips, *J. Chem. Soc.*, 2240 (1948). [e] The large differences between pK_1 and pK_2 for the 2-amino- and 4-aminopyridines are due to the large resonance stabilizations present in the aminopyridinium ions which are not present in the unprotonated or diprotonated species. This fact indicates that the first proton introduced into these aminopyridines resides on the pyridine nitrogen; see also H. H. Jaffé and G. O. Doak, THIS JOURNAL, **77**, 4441 (1955). [f] T. G. Bonner and J. C. Lockhart, *J. Chem. Soc.*, 364 (1957), indicate that H_0 and H_+ parallel one another over most of the sulfuric acid compositions used in the determinations of these pK_a's. The use of the same calculation for 2-aminopyridinium and 4-aminopyridinium ions results, therefore, in a pair of pK_a values which are relatively, although perhaps not absolutely, correct. [g] A spectrophotometric determination in concentrated sulfuric acid solutions was used, similar to the method employed here for the 2-aminopyridinium ion. The value shown in the table is one calculated from their raw data by the method of Davis and Geissman.[21] The figure quoted in the original paper is −6.55. [h] Calculated by the method of Davis and Geissman.[21]

(28) M. L. Bender and B. W. Turnquest, THIS JOURNAL, **79**, 1656 (1957).

(29) T. C. Bruice and G. L. Schmir, *ibid.*, **79**, 1663 (1957).

The exceptional reactivity of 2-aminopyridinium ion in its reaction with *o*-nitrophenyl oxalate ion, as indicated by the kinetic comparisons above, is attributed to the electrostatic stabilization of the quasi cyclic transition state as shown in I. The



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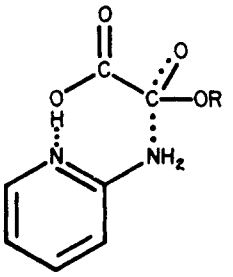

II

similarity of the rate constants for the 2- and 4-aminopyridinium ions indicates that the stabilization of the transition state by long-range coulombic interactions has a relatively low sensitivity to variations in the steric relationships. It is, therefore, possible that a transition state similar to I can be drawn for the 4-aminopyridinium ion.

The kinetic expression for the rate of the reaction involving the anionic form of the ester and the cationic form of 2-aminopyridine (or 4-aminopyridine) is

$$\text{rate} = k_{BH^+}(\text{ester}^-)(BH^+)$$

This rate expression is equivalent to

$$\text{rate} = k'(\text{ester})/(B)$$

where

$$k' = k_{BH^+}(K_{\text{ester}})/(K_{BH^+})$$

Using this relationship for the 2-aminopyridine case, k' is calculated to have a value of 1×10^4 l./mole sec. This large rate constant again can be explained by an interaction between the carboxyl group and the amine nitrogen in the transition state as shown in II.

The conclusion that there is an electrostatic interaction in the reaction of the aminopyridinium ions and *o*-nitrophenyl oxalate ion is confirmed by rate measurements with *o*-nitrophenyl acetate shown in Table II. The second-order rate constants for the reactions of pyridine with *o*-nitrophenyl acetate and with *o*-nitrophenyl hydrogen oxalate differ by a factor of about eight. However, no reaction whatsoever was observed between 2-aminopyridine and *o*-nitrophenyl acetate at *p*H 3.1 whereas an appreciable reaction was observed with 2-aminopyridine and *o*-nitrophenyl hydrogen oxalate under the same conditions. The lack of reaction between *o*-nitrophenyl acetate and 2-aminopyridine can be explained most easily in terms of the lack of the possible interactions described by I or II. The stabilization of the transition state in these systems may approximate the electrostatic interaction that occurs in enzymatic hydrolyses involving acetylcholinesterase.[30]

Acknowledgment.—The comments of Professors T. C. Bruice, H. Morawetz and F. H. Westheimer on this manuscript are gratefully acknowledged.

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CHICAGO 16, ILL.

[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY OF CLARK UNIVERSITY]

Pyridoxine and Pyridoxal Analogs. II.[1,2] Infrared Spectra and Hydrogen Bonding

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Infrared spectra of pyridinecarboxaldehydes, *o*-methoxypyridinecarboxaldehydes and *o*-hydroxypyridinecarboxaldehydes and of the corresponding substituted benzaldehydes are reported for the solid and liquid states and for dilute carbon tetrachloride solutions. Evidence is given that intramolecular hydrogen bonding exists in 3-hydroxy-4-pyridinecarboxaldehyde and 3-hydroxy-2-pyridinecarboxaldehyde in the liquid state and in solution, and the strength of chelation is correlated to the bond order in pyridine. Intermolecular hydrogen bonding is shown to occur in the crystalline 3-hydroxypyridinecarboxaldehydes, 3-pyridol and pyridoxal and a proposal for the structure of these substances is made accordingly. Improved methods are described for the synthesis and the purification of hydroxy- and methoxypyridinecarboxaldehydes.

This paper describes an extension of the work previously reported[3] on the synthesis and study of analogs of pyridoxine and pyridoxal. Specifically, the new compounds under investigation as analogs of pyridoxal (I) are 3-hydroxy-4-pyridinecarboxaldehyde (II), 3-hydroxy-2-pyridinecarboxaldehyde (IV), 3-methoxy-4-pyridinecarboxaldehyde (III) and 3-methoxy-2-pyridinecarboxaldehyde (V). By the measurement of infrared spectra of dilute solutions as well as of the solid and liquid states, it was hoped to obtain information on bond type in these compounds. A knowledge of the character of the carbonyl groups and of hydrogen bonds in these substances was considered desirable as a basis for a subsequent study of their interactions with metal ions and of the catalytic properties of the metal chelates formed.

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(2) Presented at the 134th Meeting of the American Chemical Society in Chicago, Ill., September, 1958.

(3) D. Heinert and A. E. Martell, *Tetrahedron*, **3**, 49 (1958).

Experimental Part

Infrared Spectra.—The spectra were recorded in the region 4000–650 cm.$^{-1}$ with a Perkin–Elmer model 21 double beam spectrometer with sodium chloride optics. The liquid compounds and the methoxypyridinecarboxaldehydes were distilled *in vacuo* immediately before preparation of the solutions. The hydroxypyridinecarboxaldehydes and 2,6-pyridinecarboxaldehyde were purified by fractional sublimation. Solutions in Eastman spectro grade carbon tetra-