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Kinetics and Mechanisms of the Aqueous Bromination
of 3-Hydroxypyridines

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A Thesis

in

The Department

of

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Presented in Partial Fulfillment of the Requirements
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ABSTRACT

Kinetics and Mechanisms of the Aqueous Bromination

of 3-Hydroxypyridines

Ayuk M. Ako

The kinetics of bromination of 3-hydroxypyridine (1) and a number of its derivatives have been measured in aqueous KBr solutions in the pH range 1-6, at $25 \pm 0.1 \,^{\circ}C$. The results of pH-dependence studies suggest that the reactive neutral form of the 3-hydroxypyridine/zwitterion tautomeric system (1a $\longrightarrow$ 1b) is the zwitterionic species. At high pH, 1 reacts via its anion, and the rate of the reaction is close to the diffusion-controlled limit. Under pseudo-first order conditions no significant polybromination was observed.

The rates of the aqueous bromination of 1 and selected derivatives have been found to be catalysed by carboxylate anions. The results are consistent with the abstraction of the phenolic or azonium proton occuring at the same time as 'ectrophilic attack by molecular bromine.

At high bromide ion concentration, 3-hydroxypyridine (1) reacts with tribromide ion as well as with molecular bromine. However, bromide ion dependence studies do not implicate the possible formation of a long-lived intermediate, in the bromination of 1.

Product studies results are consistent with the established orientation of bromine attack on 1, with substitution occuring in the order C-2 > C-6 > C-4.

Dedicated To My Mother

ACKNOLEDGEMENTS

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I.1 Hydroxypyridines

There are three possible monohydroxypyridines[1]: 2-,3-,and 4-hydroxypyridine, and they behave both as weak acids and weak bases. They may be obtained by several synthetic methods,[2] for example:

1) from aminopyridines via diazotization. The conditions for this reaction are milder for the 2- and 4-aminopyridines;

2) from halopyridines by the action of caustic alkali. This occurs easily with the 2- and 4-halo compounds, but less readily with the 3-compound.

3) by fusing pyridine-3-sulfonic acid derivatives with alkali (eq 1).

$$\text{(1)}$$
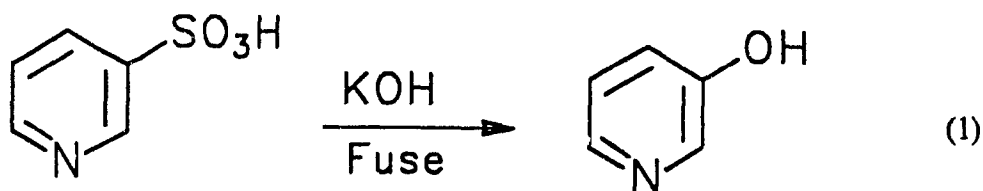
Substituted derivatives of hydroxypyridines occur widely in nature as components of alkaloids, vitamins, and coenzymes. Vitamin B_6 (3-hydroxy-4,5-dihydromethyl-2-methylpyridine) participates in protein, carbohydrate and lipid metabolism. The metabolically active form of B_6, pyridoxal phosphate is a coenzyme of amino acid metabolism and is also the active group of various decarboxylases and other types of enzymes.[3]

Derivatives of hydroxypyridines also occur in a variety of synthetic products which show pharmacodynamic properties.[4] For example, 3-hydroxypyridine and some of its derivatives have been found to show anti-convulsant activities. Some derivatives inhibit mutagenesis induced by drugs such as thiolepa. More recently, substituted derivatives of 3-hydroxypyridine have received study as agricultural chemicals,[4] for example, as plant regulators and herbicidal antidotes. In particular, 6-methyl-3-hydroxypyridine has been used in the preparation of agrochemical fungicides and insecticides.

I.2 Properties and Reactions

The three hydroxypyridines are solids: the 2-, 3-, and 4-compounds have melting points of 107°, 129°, and 148°C, respectively. They are soluble in water, methanol, and ethanol; the 4-compound is sparingly soluble in benzene.

All the hydroxypyridines are more reactive to electrophilic reagents than pyridine itself. Thus, they brominate, sulphonate, and nitrate readily, as we shall see later. At one time these reactions were considered evidence against their "quinonoid" structures, which were expected to undergo addition reactions, but they are not. However, hydroxypyridines do undergo cycloaddition reactions. For example, the 1,3-dipolar character of 3-hydroxypyridines[5a] enable them to undergo some types of addition reactions. Also, thermal electrocyclic reactions 4 + 2 cycloaddition reactions[5b] have also been demonstrated for 2-pyridones.

In general, 3-hydroxypyridine behaves in much the same manner expected for

phenolic compounds, altered somewhat by the presence of the ring nitrogen. Thus, it gives the "ferric chloride" test for phenols (purple color) and also undergoes such reactions as condensation with formaldehyde to give 2-hydroxymethyl-3-hydroxy-pyridine[6] (eq 2).

$$\text{(structure: 3-hydroxypyridine)} + CH_2O \longrightarrow \text{(structure: 2-hydroxymethyl-3-hydroxypyridine)} \qquad (2)$$
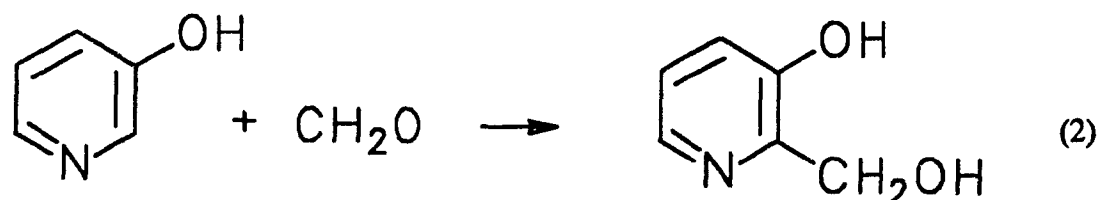
The decreased reactivity of the pyridine ring in 3-hydroxypyridine, as compared to the benzene ring of phenol, is demonstrated in the above reaction with formaldehyde, for although it is extremely difficult to control the reaction of phenol and formaldehyde in order to prevent polymer formation, the reaction with 3-hydroxy-pyridine is readily controllable. 2-Hydroxypridine also shows certain phenol-like properties, as seen in electrophilic substitution, and it gives a positive colour test with ferric chloride, although less strongly than the 3-isomer.

Formerly, colour tests were used to distinguish the three hydroxypyridine isomers.[7] Nowadays, ultraviolet, infrared, NMR, and mass spectral analyses represent the best methods for distinguishing the ß- from the α- and γ-isomers. The structural implications of spectral studies are discussed further in the next section of the introduction.

I.3 Structure and Tautomerism in Aromatic Heterocyclic Systems

Whenever a chemical compound exhibits behaviour consistent with two or more distinct structures differing in the relative positions of at least one atomic nucleus, the phenomenon is known as *tautomerism*,[8] derived from the Greek words meaning "the same part". If the two or more structures differ in the position of attachment of a hydrogen atom, the phenomenon is referred to as *prototropy* or *prototropic tautomerism*.

Keto-enol tautomerism, the coexistence of an equilibrium between the keto and enol tautomeric forms, shown in equation 3, is a well-studied phenomenon.[9]

(3)
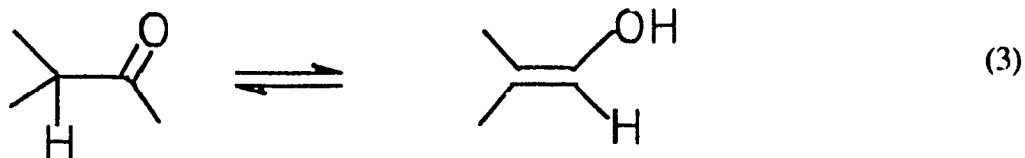
Many pyridine derivatives can exist in two or more tautomeric structures.[10] When the alternative sites for proton attachment are both heteroatoms, the equilibria between the two tautomers are normally established rapidly in solution by inter-molecular proton transfer between nitrogen atom within the ring and a nitrogen, oxygen or sulfur substituent, as shown for 2- and 4-substituted pyridines in equations 4a,b.

(4a)

4

(4b)
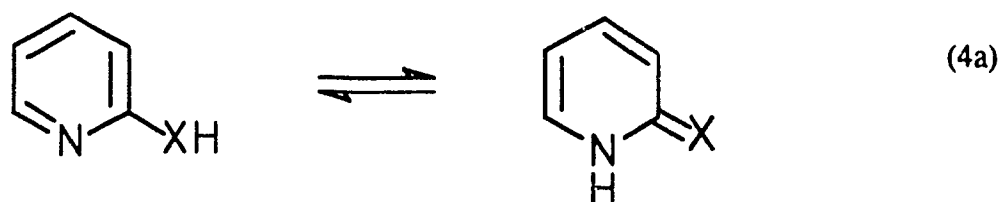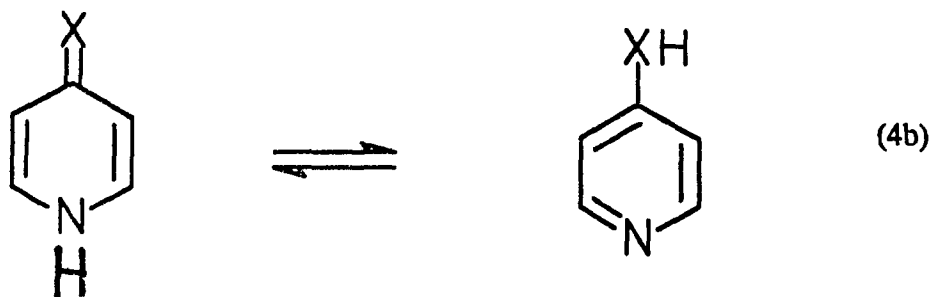
(where **X** = **NR**, **O**, or **S**)

These equilibria are of particular importance in derivatives of pyrimidine and purine,[11] since these heterocycles are incorporated in the structure of nucleic acids. When one tautomer predominates in solution, its structure can usually be assigned by comparing its infrared, ultraviolet, or ^{1}H NMR spectra with those of suitable alkylated derivatives.

A variety of physical evidence[12] indicates that 2- and 4-hydroxypyridines exhibit *Lactim-Lactam* tautomerism.[10] Both derivatives exist in solution in tautomeric equilibrium with 2- and 4-pyridones, respectively. In solution and the solid state, they exist *predominantly* as the pyridones or amide forms. 2-Hydroxypyridine in its "keto" form is not a ketone but an amide and so the amide resonance will stabilize the "keto" form. In the gas phase,[18a] 2-hydroxypyridine predominates over the oxo tautomer by about a 2:1 ratio, and analogously, the 4-hydroxy tautomer is favoured in the vapour phase over the pyridone species.

The infrared spectra of 2- and 4-hydroxypyridines show N-H and C=O stretching vibrations in the solid state and in chloroform solution.[13] Moreover, in

neutral methanol solution the ultraviolet spectrum of 2-hydroxypyridine is almost identical with that of N-methyl-2-pyridone, but it differs considerably from that of 2-ethoxypyridine, a model for the 2-hydroxy tautomer. This concrete evidence suggests that 2-hydroxypyridine exists almost entirely in the lactam form in solution, as shown in equation 5.

$$\text{Lactim} \rightleftharpoons \text{Lactam} \qquad (5)$$

Lactim

1

:

Lactam

10^3
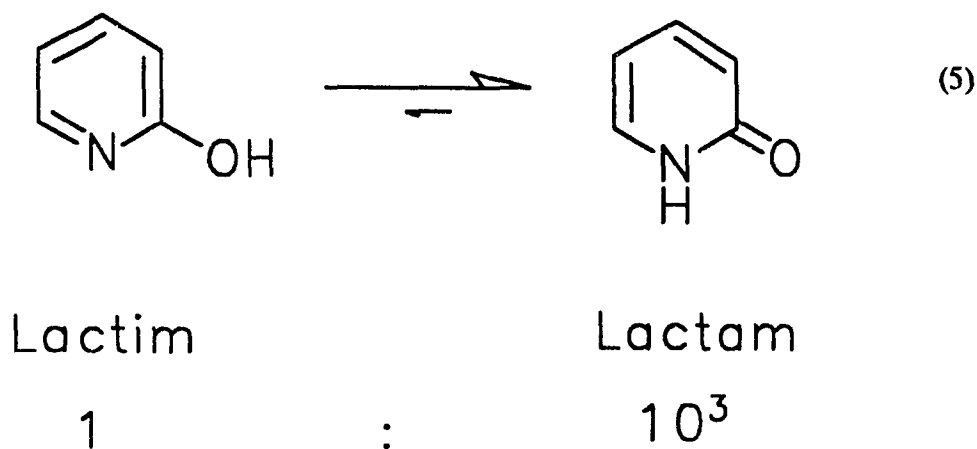
On the other hand, under alkaline conditions,[14] when 4-hydroxypyridine is ionized, its ultra-violet absorption spectrum is very similar to that of 4-methoxy-pyridine, and differs considerably from that of N-methyl-4-pyridone. In summary, the 2- and 4-hydroxypyridines can react in either form (*lactim* or *lactam*), depending on the demands of the attacking reagents and the medium. Spectral evidence, however, confirms that these compounds consist each of two tautomers.

A convincing body of evidence,[14-17] based largely on spectroscopic data has indicated that 3-hydroxypyridine (1) is present in aqueous solution as the neutral molecule (the "phenolic" form) 1a, and the tautomeric dipolar ion 1b (zwitterion[14] or betaine[17]), in approximately equal proportions (eq 6).

$$1a \quad \rightleftharpoons \quad 1b \qquad (6)$$
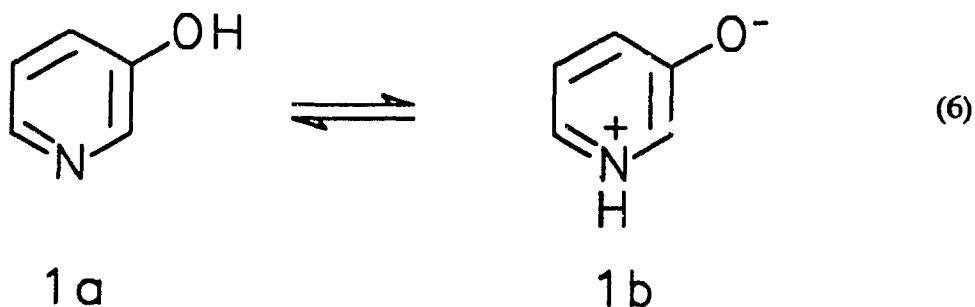
In non-aqueous solvents of low dielectric constant,[14] the position of the equilibrium is **1b** ———→ **1a**, that is, 3-hydroxypyridine exists predominantly in the hydroxy tautomeric form. It can be seen, therefore, that the positions of the prototropic equilibria involving hydroxypyridines are greatly affected by the nature of the medium.[18]

3-Hydroxypyridine cannot exist in a keto or amide form, unlike 2- and 4-hydroxypyridines, because no uncharged lactam structure can be written for this compound. In neutral aqueous solution, Metzler and Snell[15] found that 3-hydroxypyridine exists as a 1:1 mixture of the hydroxy compound **1a** and the corresponding zwitterion **1b**. The uv spectrum of the tautomeric mixture shows one maximum at 277 nm, similar to that of 3-methoxypyridine, and a second maximum at 313 nm, similar to that given by an N-alkylated 3-hydroxypyridine.

The evidence of differences in chemical reactivity is not conclusive in distinguishing between tautomers,[18] although it has frequently pointed to the existence of tautomers. On the basis of evidence from ionization constants, ultraviolet

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and infrared spectra, X-ray crystal analysis, and dipole moments, Albert and Philips[16] reached the conclusion that the hydroxypyridines have properties falling somewhere between those of pure phenols, passing through the isomeric zwitterions, and the cyclic amides. These measurements have shown that whereas the tautomers 1a and 1b of 3-hydroxypyridine are present in comparable amounts, for the 2- and 4-hydroxy-pyridines the amide forms are present in a much larger amount, by a factor $\geq$ 1000 over the phenolic form. The 2- and 4-isomers are, therefore, both less basic and less acidic than the 3-isomer, as shown in the table below.[16]

Hydroxypyridine	pK_a (proton lost)	pK_a (proton gained)
2-	11.62	0.75
3-	8.72	4.86
4-	11.09	3.27

I.4 Electrophilic Substitution of Pyridines

Pyridine is a π-deficient system,[19] due to the electron-withdrawing effects of the nuclear nitrogen, and so it undergoes electrophilic substitution with difficulty. Abramovitch and Saha[20] determined the partial rate factors for pyridine to be about 10^{-6}, similar to nitrobenzene. Gilow and Ridd,[30] estimated the partial rate factor for the bromination of the unsubstituted pyridinium cation at the 3-position to be approximately 6×10^{-13}. Thus, the deactivating effect of the ring nitrogen is even more pronounced when it is protonated, in acidic solution.

Typical benzenoid reactions like electrophilic aromatic substitution in acidic

solution are less common and slow, if they occur at all. In general, halogenation and nitration of pyridinium cations occur at high temperatures. For example, nitration of pyridine with KNO_3 and concentrated H_2SO_4 at 300°C gives a 15% yield of 3-nitro-pyridine.[5b] Sulfonation occurs only in the presence of catalytic amounts of mercuric sulfate.[5b] Good yields of 3-bromopyridine have been obtained by Hertog *et al.*[21] by brominating pyridine at 130°C with bromine in fuming sulfuric acid.

In the electrophilic substitution of pyridine,[2a] the nitrogen atom exerts the dominating orienting influence shown in equation 7.

$$ (7) $$
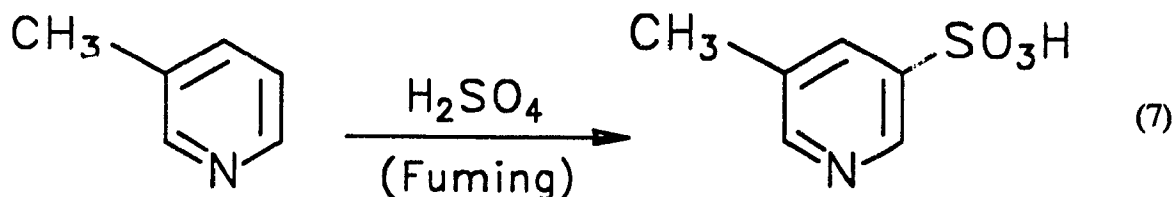
Strongly electron-donating substituents[22] (-OR, -OH, $-NH_2$) facilitate electrophilic substitution. Thus, the pyridinols easily undergo electrophilic substitution, although less readily than phenol. Also, these activating substituents control the site of substitution. For example, a 3-alkoxypyridine gives the 2-nitro compound on nitration (eq 8).

$$ (8) $$
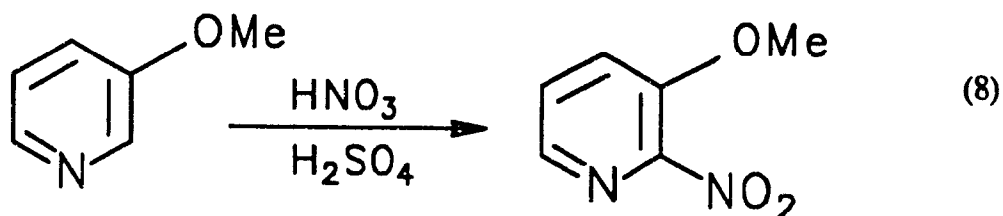
When pyridine is activated by an amino group, halogenation occurs with ease.[1,2b,5b] Fox and Threfall[23] determined that a 2-amino group directs the incoming electrophile predominantly to the 5-position, whereas a 3-amino group leads chiefly to 2-substitution, and a 4-amino group directs attack to the 3-position. Clearly then, an amino group directs the halogen ortho and/or para to itself (eqs 9a,b), as in benzene systems, and overrides the effect of the ring nitrogen. These brominations occur on the free base form of the substrate.[5a]

(9a)

(9b)
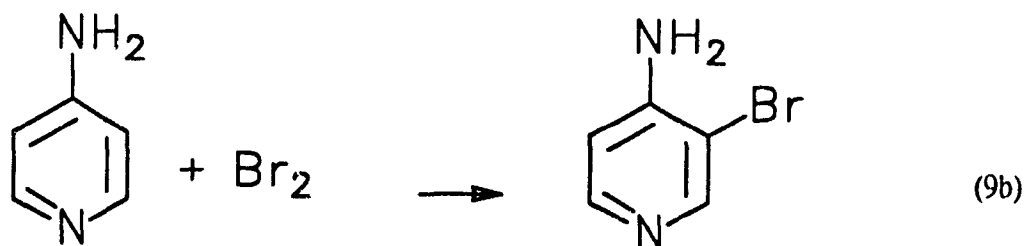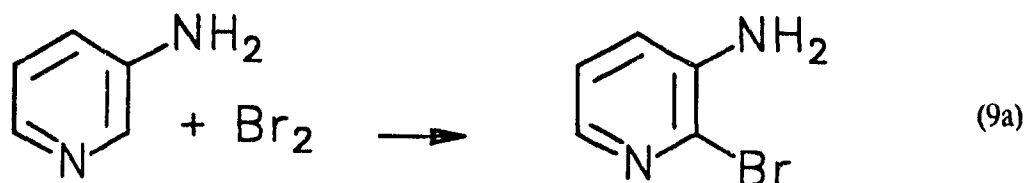
In the case of 3-hydroxypyridine (1), the -OH substituent is sufficiently powerful in its directive influence to dominate matters,[24] as illustrated by bromination of compounds 1 and 6 (eqs 10a,b). Such reactions were carefully studied in the present work, as will be seen later.

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$$\text{1} \quad \xrightarrow{\text{Br}_2 \ / \ 10\% \ \text{NaOH}} \quad \text{(10a)}$$

$$\text{6} \quad \xrightarrow{\text{Br}_2 \ / \ 10\% \ \text{NaOH}} \quad \text{(10b)}$$
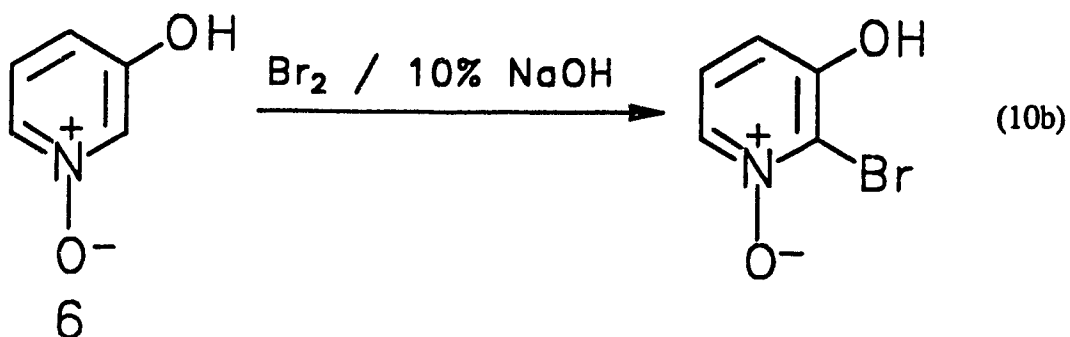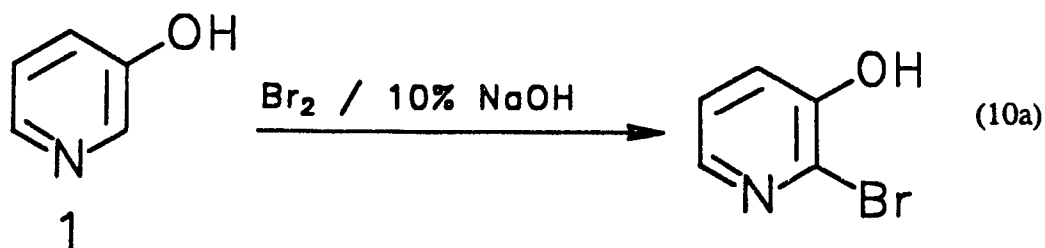
As shown above, 3-pyridinol 1 substitutes first at C-2 position in halogenation.[24] Likewise, nitration of 1 occurs mainly in the ortho rather than the para position.[24] This same orientation is observed when halogenation is carried out with different reagents in various media: bromination with bromine in pyridine solvent,[25a,c] iodination with iodine and Na_2CO_3,[25b] and chlorination with HCl and H_2O_2.[5b]

The literature on sulfonation is sparse, probably owing to the difficulty of the reaction. Sulfonation of 3-pyridinol with 100% sulfuric acid, with vanadium sulfate as a catalyst, gave 2-sulfonic acid as the product.[24] Thus, the nitration, sulfonation, and halogenation of 3-hydroxypyridine all favour o-substitution. Based on H-D exchange studies on 3-hydroxypyridine, Lezina et al. determined that the most reactive site on this ring system was the 2-position whether the reaction was carried

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out in basic[26a] or acidic[26b] solution. Electrophilic substitution for this compound was found to occur in the order of preference: C-2 > C-6 > C-4 > C-5.

As discussed earlier in Section I.3, 2- and 4-hydroxypyridines exist mainly as their pyridone forms in polar solution.[25c] On the other hand, 3-hydroxypyridine exists in aqueous solution as a mixture of the hydroxy and zwitterionic forms in comparable amounts. Any given reaction of these tautomeric systems may, in principle, take place on either tautomer. In the case of 2- and 4-hydroxypyridine previous work in this laboratory it has been shown that the pyridone forms are more reactive towards bromine.[18b,c] However, with 3-hydroxypyridine the situation was unknown, and it was a major object of the present work to find which of the two tautomers is more reactive.

2-Pyridones undergo preferential attack at the 3-position in marked contrast to the behaviour of the related 2-alkoxy derivatives, where 5-substitution is generally observed.[18b] Similarly, nitration of 2-pyridinol gives mainly the 3-nitro product, accompanied by some 3,5-dinitro-, and a trace of the 5-nitro-2-pyridinol.[24] N-Alkyl-2-pyridones, which cannot tautomerize, are likewise substituted at the 3-position.[21b] 4-Pyridones usually undergo substitution in the 3- and 5-positions,[20] and the bromination reaction takes place on the pyridone form.[18c] It should be noted that both 2- and 4-pyridone react with bromine via their anions at higher pH (>6).[18b,c] This possibility also exists for 3-hydroxypyridine.

I. 5 Kinetics of the Bromination of Aromatic compounds

Earlier, de la Mare et al.,[27] and Ridd and co-workers,[28] carried out acid-catalyzed bromination by hypobromous acid of deactivated aromatic compounds in aqueous perchloric acid. In these studies, the formation of the bromoaromatic was monitored spectrophotometrically at suitable wavelengths. They found that at a given pH the rate law for the bromination reaction is given by equation 11.

$$\text{Rate} = k_2 \text{ [ArH][HOBr]} \tag{11}$$

However, the second order rate constant k_2 was found to increase with the concentration of the acid.[27]

Later, Gilow and Ridd[29] performed the same reaction under similar conditions and also found this acidity dependence at low mineral acid concentration so that the rate law for the bromination reaction is given by equation 12:

$$\text{Rate} = k_3 \text{ [ArH][HOBr][H}^+] \tag{12}$$

This observation suggests that the effective electrophile for the reaction is H_2OBr^+, formed in the equilibrium:

$$HOBr + H^+ \rightleftharpoons H_2OBr^+ \tag{13}$$
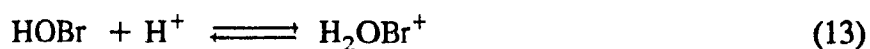
with possibility of attack by the bromine cation Br^+, resulting from the additional equilibrium:

$$H_2OBr^+ \rightleftharpoons Br^+ + H_2O \tag{14}$$
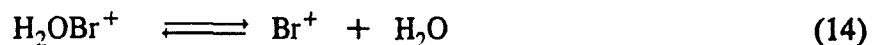
In a subsequent study, Ridd and Gilow[30] studied the rates of bromination of some substituted methylpyridinium cations with hypobromous acid, also in aqueous perchloric acid. They found that the reaction occurs through the corresponding

pyridinium cations and that reaction through the neutral molecule can be neglected.

Tee and Paventi[18b,c] studied the kinetics and mechanism of the aqueous bromination of the 2-pyridone $\rightleftharpoons$ 2-hydroxypyridine and 4-pyridone $\rightleftharpoons$ 4-hydroxypyridine tautomeric systems. Using the stopped-flow technique[32a] they established for both systems that reaction with aqueous bromine occurs via the principal pyridone tautomer at pH < 6, and via the conjugate anion at pH > 6. For the 2-pyridone system, bromine attack on the predominant tautomer occurs preferentially at the 3 position, whereas for the anion attack at the 5 position is preferred. Partial rate factors for bromine attack at these positions have been estimated to be 2.2×10^4 and 4.7×10^4, respectively. In these studies, Tee and Paventi attributed the facile dibromination of the pyridones to the enhanced reactivity of the monobromo products towards bromine, by virtue of their lower pK_as. From these studies the conclusion was reached that 2- and 4-pyridone and their anions behave as substituted phenoxide ions in electrophilic bromination.

In the present study, the bromination of 3-hydroxypyridine (1) and some of its derivatives has been studied in aqueous solution at 25°C, using the stopped-flow technique. Factors which may influence this reaction, for example buffer catalysis and bromide ion concentration, have also been investigated. A preliminary study of the kinetics of bromination of 3-hydroxypyridine had been carried out by Ms. J.M. Bennett. This work is an extension of earlier studies carried out in this laboratory on the bromination of 2-pyridones, 4-pyridones, phenols, and phenoxides.[18b,c,32,33]

I.6 Buffer Catalysis[31]

The importance of acid-base catalysis has been established in many reactions occuring in aqueous solutions.[31a] Most biochemical reactions involve a proton transfer, and in many of these reactions acid-base catalysis facilitates this proton transfer.[31b]

There are four main types of acid-base catalysis: general (acid or base) catalysis and specific (acid or base) catalysis. General acid (or base) catalysis involves catalysis by other acids (or bases) - buffer acid (or anion, water etc). Each of these individual species present in solution can act as a proton donor or acceptor in the rate limiting step and so the overall rate equation includes terms representing these various species.

Scheme 1 illustrates general acid catalysis whereby the rate-limiting step involves a proton transfer.

<u>Scheme 1.</u> General acid catalysis

$$S \; + \; HA \; \longrightarrow \; SH^+ \; + \; A^- \quad (slow)$$

$$SH^+ \; \longrightarrow \; Product \quad (fast)$$
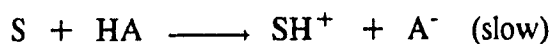
$$Rate \; = \; k_1[S][HA_1] \; + \; k_2[S][HA_2] \; + \; k_3[S][HA_3] \; + \; ...$$

$$= \; [S] \; \Sigma \; k_i[HA_i]$$

where HA_i = HA_1, HA_2, HA_3, etc. are the acids present in solution.

The rate equation usually has a term due to H_3O^+, the buffer acid, and maybe a small term due to H_2O. An example of this type of catalysis is the hydrolysis of

triethyl orthoacetate. This type of catalysis can usual'y be confirmed by studying primary isotope effects, that is, by substituting deuterium for hydrogen in HA. Values of $k_H/k_D > 1$ indicates if the H-A bond is broken in the rate-limiting step. General acid catalysis can also arise from specific acid (see later) + general base catalysis.

In Scheme 2 is illustrated general base catalysis. This is a type of catalysis whereby a reactant transfers a proton to a general base in the rate determining step, followed by rapid conversion of the conjugate base of the reactant into the product. The rate equation usually contains a term due to OH⁻, the buffer anion, and maybe a term for H_2O, also.

Scheme 2. General base catalysis

$$SH + B \longrightarrow S^- + BH^+ \qquad (slow)$$

$$S^- \longrightarrow Products \qquad (fast)$$
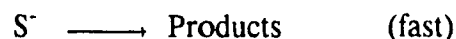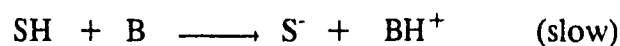
$$Rate = [SH] \Sigma k_j[B_j]$$

Scheme 3 illustrates specific acid catalysis which usually arises from a pre-equilibrium protonation and reaction. One example of this type of catalysis is the acid-catalyzed cleavage of esters.

Scheme 3. Specific acid catalysis

$$S + H^+ \rightleftharpoons SH^+ \longrightarrow Product$$
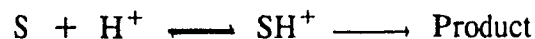
$$Rate = k[SH^+] = k[S][H^+]/K_{SH+}$$

Lastly, there is specific base catalysis which originates from catalysis by the

hydroxide ion alone. This behaviour can arise from OH⁻ acting as a base or as a nucleophile. Specific base catalysis may be due to pre-equilibrium deprotonation, as outlined in Scheme 4.

Scheme 4. Specific base catalysis

$$OH^- + SH \longrightarrow H_2O + S^- \longrightarrow Product$$
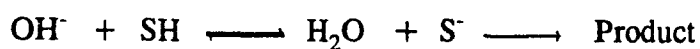
$$Rate = k[S^-] = k[OH^-][SH]/K_wK_a$$

A reaction is said to be buffer catalyzed if the rate of the reaction increases with an increase in the concentration of the buffer when the pH and ionic strength of the medium are held constant. A plot of the slopes of the buffer plots versus the fraction of the free base (f_B) will give an indication as to which buffer component is catalyzing the reaction. From analysis of these plots, the k_A and k_{HA}, the catalytic constants of the basic and acidic components of the buffer, can be deduced.

A number of buffer studies carried out in this laboratory have shown that general acid and base catalysis are important in the bromination of phenols.[33] Firstly, the reaction of bromine on some phenols is catalyzed by carboxylate anion bases, suggesting that the deprotonation of the phenol hydroxyl group by a general base occurs simultaneously with the electrophilic attack by molecular bromine.[33c] Secondly, enolization of the bromocyclohexadienone intermediates is catalyzed by acids and bases.[33b] It should also be noted that phenols react with bromine via their anions, which represents an example of specific base catalysis (Scheme 4).[33c]

Reactions of 3-hydroxypyridine 1 are expected to parallel those of phenol

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because the two compounds are quite similar. For this reason, and because of earlier results obtained with phenols, buffer catalysis in the aqueous bromination of 1 and a number of its derivatives has been studied in the present work.

I.7 Objectives

Studies[15,16,37] on the tautomeric equilibrium of 1 have established that in aqueous solution this compound exists in comparable amounts of the hydroxy species (A_N) and the zwitterionic form (A_Z) (eq 15).

(15)
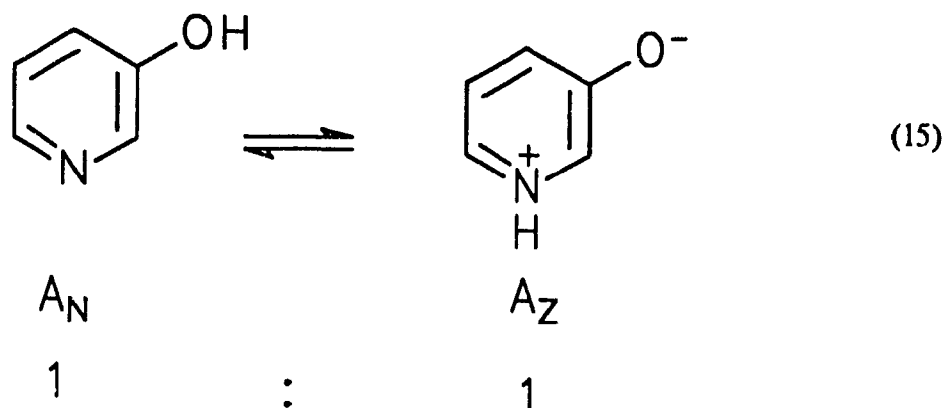
However, such studies provide no insights into the relative reactivities of the two tautomers A_N and A_Z. Therefore, bromination was chosen to study the reactivity of the system towards a simple electrophile and to establish which species is most reactive. The analogy here is to earlier studies of the bromination of pyridones.[18b,c] Tee and Paventi have found that pyridones react with bromine as such, and not as their hydroxy tautomers, at higher pH (>6).[18b,c] The 3-hydroxypyridine tautomeric system was of particular interest because of the greater likelihood of competition of the two principal tautomers, since they exist in equal proportion in aqueous solution.

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Thus, the principal objective of this work was to ascertain the reactive forms of the tautomeric system in 1 over a range of pH. In persuance of this objective, studies on suitable fixed derivatives[36] were also carried out. [By fixed derivative here is meant a model compound in which the prototropic tautomerism is not possible].

Depending on the medium or pH, compound (1) can exist in four different forms: the Cation (A^+), the Anion (A^-), the Neutral molecule (A_N), and the Zwitterion (A_Z).[37,38] It was therefore important to ascertain which of these species is reacting at a given pH range. To this effect, pH dependence studies were carried out, and a comparison made with the rate profiles of N-substituted derivatives.

3-Hydroxypyridine undergoes electrophilic substitution faster than pyridine, but slower than phenol.[22] The enhanced reactivity compared with pyridine is due to the activating effect of the -OH substituent, which directs incoming electrophiles *ortho* or *para* to itself. In an earlier study, Tee and Paventi[18b] have established that bromine attack on 2-pyridone occurs preferentially at the 3-position, and at the 5-position for the anion. In a later study Tee *et al.*[35] found that the monobromination of phenol occurs preferentially at the para position. Another object of this study was therefore to uncover the preferred reactive site on the ring nucleus, under the conditions of aqueous bromination. To this end, product studies were carried out to determine the orientation of bromine attack. Synthetic studies on the bromination of 1 have established that this reaction occurs very easily and could lead to polybromination.[25a] Although the latter problem was minimized by the use of a ten (or more) -fold excess of the substrate on bromine, the kinetics of bromination of 2-

bromo and 2,6-dibromo derivatives of 1 was studied, and product studies were also carried out on a number of substrates, to investigate this potential problem. The analogous problems of the dibromination of pyridones and the tribromination of phenol have been investigated previously.[18b,c,35]

Tee et al.[35] have also found that the phenoxide ion reacts with molecular bromine, and with tribromide ion at high bromide ion concentration. Another objective of the present study was to determine if any reactivity with tribromide ion is involved in the 3-hydroxypyridine (1) system.

Tee and Iyengar[33c] in an earlier study have established that the reaction of bromine with some phenols is general-base catalyzed. Also, the conversion of intermediates is buffer catalyzed.[33b] Therefore, buffer catalysis studies were carried out to ascertain if the bromination reaction with 1 and some of its derivatives is general-base or -acid catalyzed, either in the initial step or some later step.

3-Hydroxypyridine (1) comprises of a tautomeric system (eq 15) in which the two tautomers interconvert rapidly.[38] We have investigated the aqueous bromination of 1, and a number of its derivatives, paying particular attention to the reactivity of the species involved, the possibility of polybromination, and the orientation of the reaction. Some other factors which may influence this reaction, for example, buffer catalysis and tribromide ion concentration, have also been studied.

II.1 pH and Substrate Dependences

The stopped-flow technique was used to monitor the kinetics of the aqueous bromination of 3-hydroxypyridine (1) and a variety of its derivatives (2) - (8) as a function of pH, and the concentration of various species.

The reactions were carried out in aqueous solutions of 0.1 M potassium bromide (KBr) in the range 0 <pH > 6, at 25 ± 0.1 °C. The bromination reactions were monitored as the first order disappearance of bromine in the presence of a large excess of substrate (ten or more -fold). Monitoring the reaction under these pseudo-first order conditions eliminates, or keeps to a minimum, polybromination, one of the problems encountered when following such a reaction under second-order conditions. The kinetic data collected under these conditions showed that the bromination rates of these substrates are second order overall: first order with respect to substrate, and first order with respect to bromine.

COMPOUNDS STUDIED

3-Hydroxypyridine (1) and Its Derivatives
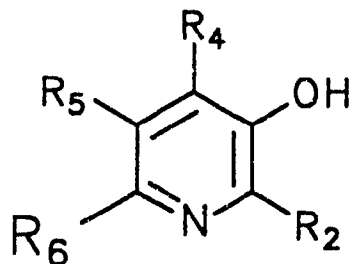
I
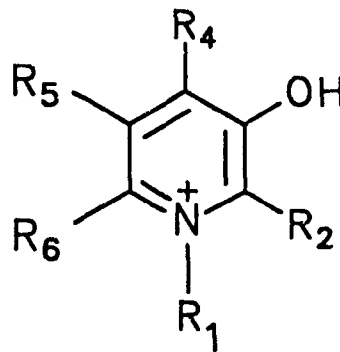
II

I = Compounds 1, 2, 3, 7, 8

II = Compounds 4, 5, 6

(1) 3-Hydroxypyridine, $R_2 = R_4 = R_5 = R_6 = H$

(2) 2-Bromo-3-hydroxypyridine, $R_2 = Br$, $R_4 = R_5 = R_6 = H$

(3) 2,6-Dibromo-3-hydroxypyridine, $R_2 = R_6 = Br$, $R_4 = R_5 = H$

(4) N-Benzyl-3-hydroxypyridinium chloride, $R_1 = PhCH_2$

(5) N-Ethyl-3-hydroxypyridinium bromide, $R_1 = CH_3CH_2$

(6) 3-Hydroxypyridine N-oxide, $R_1 = O$

(7) 6-Methyl-3-hydroxypyridine, $R_2 = R_4 = R_5 = H$, $R_6 = CH_3$

(8) 3-Hydroxypicolinic acid, $R_2 = CO_2H$, $R_4 = R_5 = R_6 = H$

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The observed first-order rate constants (k_1^{obs}) were then converted to second-order constants (k_2^{obs}), taking into account the substrate concentration and the depletion of free bromine due to tribromide ion formation (see Appendix for derivation of equation used in the calculation of k_2^{obs}.

For clarity, the pH-rate profiles of the substrates studied have been illustrated in separate figures. The variations of k_2^{obs} with pH for **1** is given in Table I and plotted in Figure 1, while those for its bromo derivatives **2, 3** are depicted in Table II and Figure 2, respectively. Second-order rate constants for N-substituted 3-hydroxypyridines **4, 5,** are exhibited in Table III and plotted logarithmically against pH in Figure 3. Rate profiles for the acidity dependences of other substituted 3-hydroxypyridines **6, 7,** and **8** are listed in Table IV and plots of log k_2^{obs} against pH for these substrates are shown in Figure 4 respectively. The plots are all linear, with slopes close to unity.

Substrate dependence studies on a number of compounds, **1, 2, 4, 5,** and **7** (Table V, Figures 5a-d) confirmed the overall second order nature of the bromination reaction, as the pseudo-first order rate constants were seen to be linearly dependent on the substrate concentration. Second-order rate constants for these substrate dependence studies, monitored as the first order disappearance of bromine, showed little or no variation with both substrate and bromine concentrations. This provides evidence that the bromination reaction with various substrates is second-order. Bell and Rawlinson,[39] and later Tee *et al.*,[35] have observed the overall second-order behavior in the reaction between phenols and bromine, as well as between

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bromine and the other two hydroxypyridines.[18b,c]

The rate law assumed for the bromination data is:

$$-d[Br_2]/dt = k_{AN} [A_N] [Br_2] + k_{AZ} [A_Z] [Br_2] \qquad (16)$$

where $[A_N]$ and $[A_Z]$ are the concentrations of the hydroxy and the zwitterionic forms of the substrates respectively, and $[Br_2]$ is the concentration of free bromine.

Equation 16 above is, however, the most simplistic approach to the reactivity of the 3-hydroxypyridine system. It can be further complicated by considering other possible reactive forms of 1, which depend on the reaction medium and whether both bromine and tribromide ion are reacting with the various substrate species.

There are in fact four forms of 3-hydroxypyridine in aqueous solution, depending on the pH of the solution:[38] the Cation A^+, the Anion A^-, the neutral species A_N, and the zwitterion A_Z (Scheme 5).[37] In principle, therefore, the bromination of 3-hydroxypyridine could proceed through either of the four possible forms, depending on their relative reactivities.

The more general rate law governing the reactivity of the substrate with bromine would therefore be:

$$Rate = (k_Z[A_Z] + k_A[A^-] + k_C[A^+] + k_N[A_N])[Br_2] \qquad (17)$$

where A_N, A_Z, A^-, A^+ represent the various possible reactive forms as depicted in Scheme V. Obviously, this equation becomes even more complex if each of these species react with tribromide ion (Br_3^-) as well as with Br_2. The relative proportions of the various forms of 3-hydroxypyridine are pH-dependent, and so certain terms in equation 17 vanish in certain pH ranges.

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Scheme V.   Possible Reactive Forms of 3-Hydroxypyridine
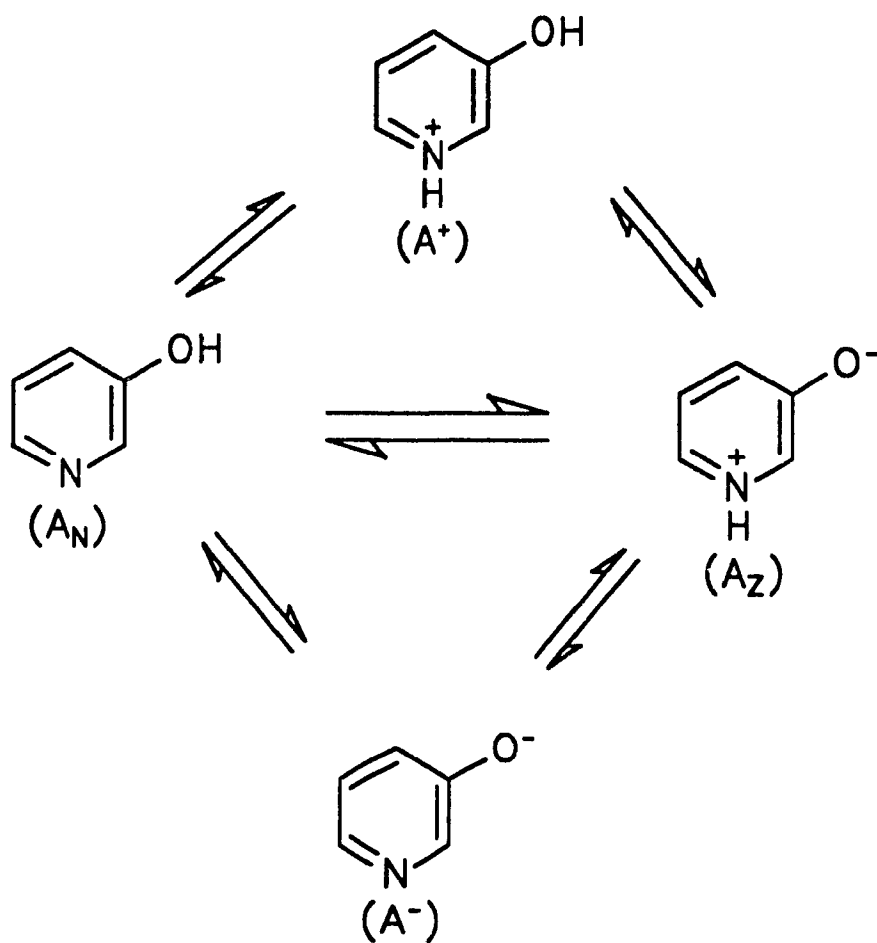
Table I. Rate constants for the Reaction of Bromine with 3-Hydroxypyridine (1)[a]

Substrate	pH	k_1^{obs}, s^{-1}	k_2^{obs}, M^{-1} s^{-1}
1[b]	1.00	0.254	28.8
	1.17		32.2*
	1.82	0.109	124
	1.90	0.163	185
	2.00	0.174	197
	2.12	0.282	320
	2.30	0.414	470
	3.15		1.77×10^3*
	3.52		7.60×10^3*
	3.69		1.16×10^4*
	3.81		1.45×10^4*
	3.90		1.72×10^4*
	4.41		5.62×10^4*
	4.89[c]		1.76×10^5*
	5.38[c]		5.23×10^5*
	5.89[c]		2.06×10^6*

[a] At 25°C, in 0.1M KBr. Values of k_2^{obs} are corrected for the formation of tribromide ion.

[b] [Substrate] = 2.5 mM; [Br$_2$] = 0.25 mM.

[c] [Substrate] = 1.0 mM; [Br$_2$] = 0.10 mM.

* Data collected by Ms. J.M. Bennett.

Figure 1

Rate-profile for the bromination of 3-Hydroxypyridine 1 (Table I).

(slope $= 1.003$; intercept $= 0.345$; $r = 0.999$)
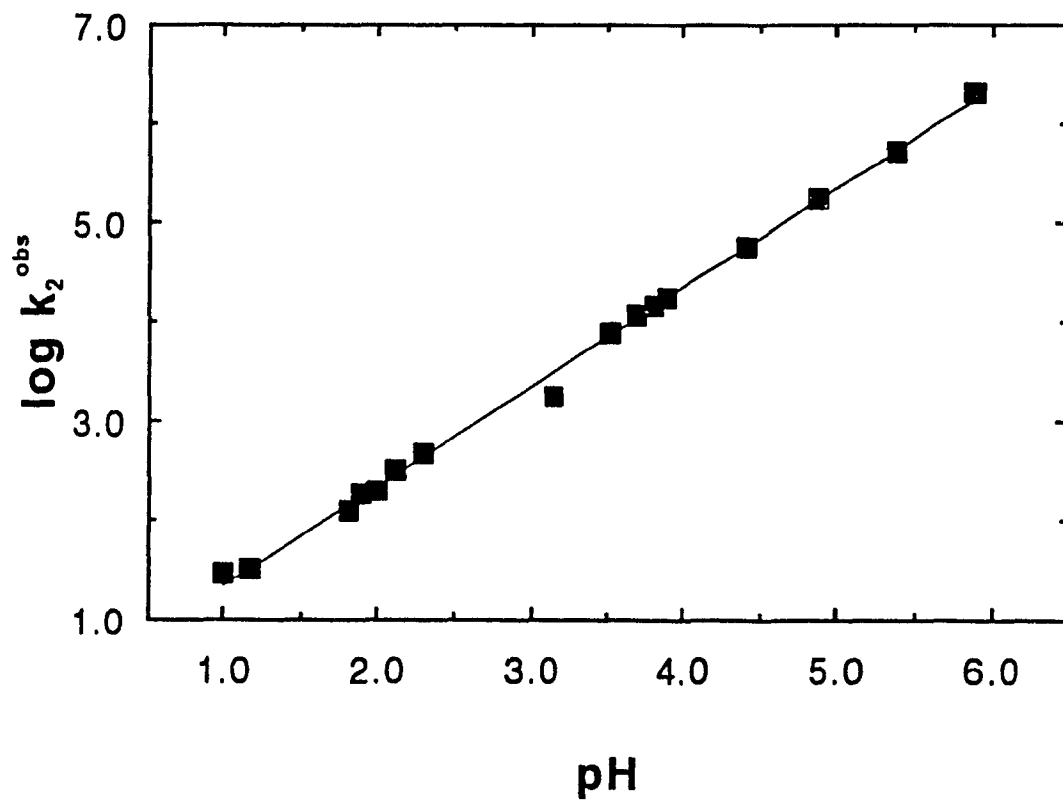
Table II. Rate constants for the Reaction of Bromine with 2-Bromo-3-hydroxy-pyridine(2) and 2,6 dibromo-3-hydroxypyridine (3)[a]

Substrate	pH	k_1^{obs}, s^{-1}	k_2^{obs},M^{-1} s^{-1}
2	1.00	0.0348	102
	1.30	0.0829	243
	2.00	0.552	1.62×10^3
	2.30	1.10	3.22×10^3
	2.65	1.78	5.21×10^3
	2.90	4.17	1.22×10^4
	3.30	11.9	3.48×10^4
	4.05	76.4	2.24×10^5
3	1.00	0.0194	56.8
	1.30	0.0328	95.9
	1.52	0.0501	147
	2.00	0.143	418
	2.30	0.289	846
	2.65	0.536	1.57×10^3
	3.25	2.49	7.28×10^3
	4.10	19.1	5.58×10^4

[a] At 25°C, in 0.1M KBr. Values of k_2^{obs} are corrected for the formation of tribromide ion; [Substrate] = 1.0 mM; [Br_2] = 0.05 mM.

Figure 2

pH-rate profiles for the bromination of 2-bromo-3-hydroxypyridine **2**
(■) (slope = 1.077; intercept = 0.976; r = 0.999), and 2,6-dibromo-3-hydroxy-
pyridine **3** (▲) (slope = 0.970; intercept = 0.709; r = 0.999).
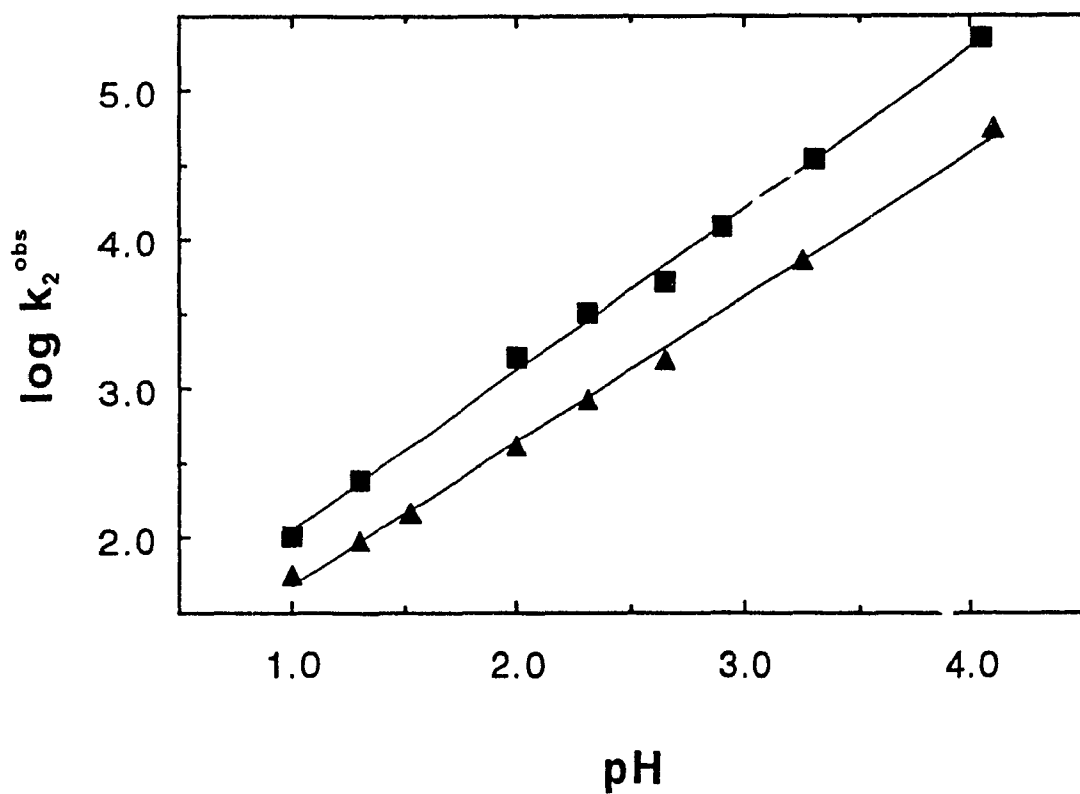
Table III Rate Constants for the Bromination of N-Benzyl-3-hydroxypyridinium chloride (4), and N-Ethyl-3-hydroxypyridinium bromide (5).[a]

Substrate	pH	k_1^{obs}, s^{-1}	k_2^{obs}, M^{-1}s^{-1}
4[b]	0.300	0.0172	21.2
	0.600	0.0351	43.4
	1.00	0.0926	114
	1.12	0.121	149
	1.30	0.181	224
	1.52	0.299	369
	1.70	0.432	534
	1.82	0.562	694
	2.00	0.852	1.05×10^3
	2.30	1.48	1.83×10^3
	2.60	1.20[c]	3.71×10^3
	3.25	3.08[c]	9.52×10^3
	4.05	8.10[c]	2.50×10^4
	5.05	135[c]	4.18×10^5
5[b]	1.00	0.0605	74.8
	1.30	0.123	152
	1.69	0.291	359
	2.00	0.579	715
	2.22	0.929	1150
	2.40	1.29	1590
	2.80	2.98	3.63×10^3
	3.40	7.82	9.66×10^3
	3.95	11.8[d]	3.45×10^4

Table III cont.

Substrate	pH	k_1^{obs}, s^{-1}	k_2^{obs}, M^{-1} s^{-1}
5[b]	4.30	27.4[d]	8.02 x 10^4
	4.85	69.2[d]	2.03 x 10^5

[a] At 25°C, in 0.1M KBr. Values of k_2^{obs} are corrected for the formation of tribromide ion.

[b] [Substrate] = 2.5 mM; [Br$_2$] = 0.25 mM.

[c] [Substrate] = 1.0 mM; [Br$_2$] = 0.10 mM.

[d] [Substrate] = 1.0 mM; [Br$_2$] = 0.05 mM.

Figure 3

pH-rate profiles for the bromination of N-substituted derivatives of 3-hydroxypyridine: (■) N-Benzyl (4) (slope = 0.858; intercept = 1.21; r = 0.995); (▲) N-Ethyl (5) (slope = 0.886; intercept = 1.05; r = 0.999)
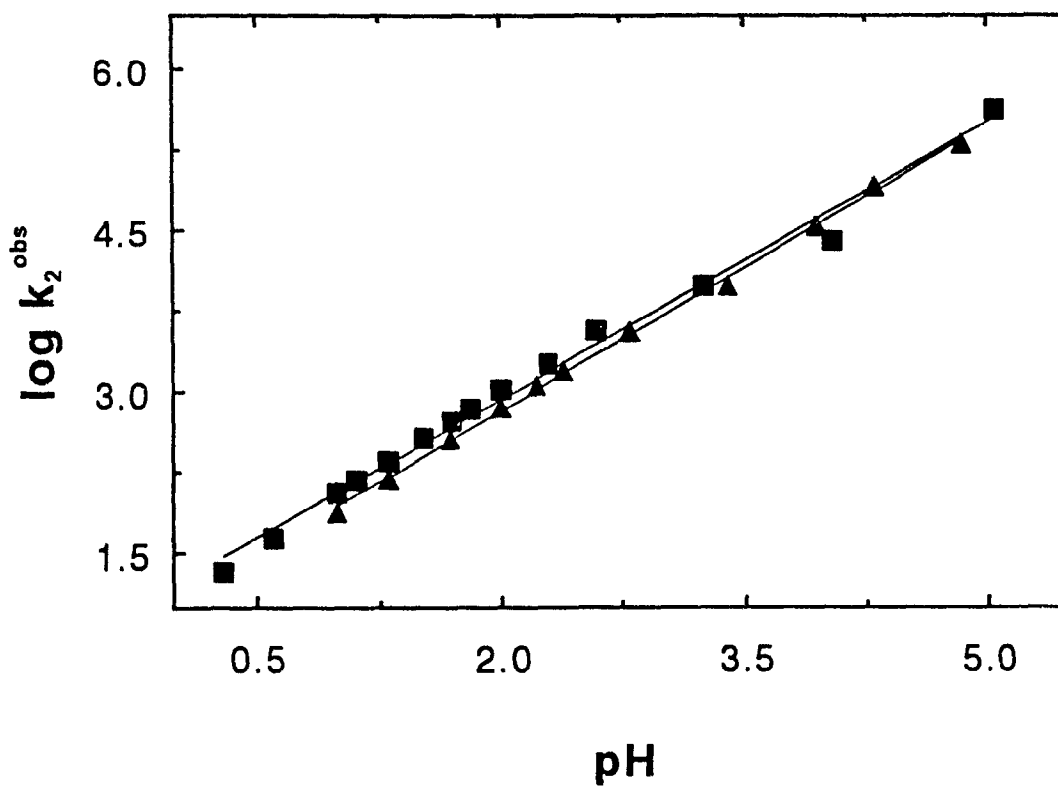
Table IV Rate Constants for the Reaction of Bromine with 3-Hydroxypyridine N -oxide (6), 6-Methyl-3-hydroxypyridine (7), and 3-Hydroxypicolinic acid (8).[a]

Substrate	pH	k_1^{obs}, s^{-1}	k_2^{obs}, M^{-1} s^{-1}
6[b]	1.00	0.146	902
	1.30	0.351	2.17×10^3
	1.69	0.933	5.76×10^3
	2.00	2.05	1.27×10^4
	2.30	3.99	2.46×10^4
	2.60	7.05	4.35×10^4
	2.95	15.5	9.57×10^4
	3.30	41.1	2.54×10^5
7[c]	1.00	0.0399	117
	1.30	0.0799	234
	1.52	0.135	395
	1.82	0.282	825
	2.00	0.425	1.24×10^3
	2.30	0.857	2.51×10^3
	2.80	2.35	6.88×10^3
	2.90	2.56	7.48×10^3
	3.35	7.11	2.08×10^4
	4.00	30.6	8.96×10^4
8	2.204	0.0132[d]	25.3
	2.60	0.0188[e]	36
	2.91	0.0379[e]	72.6
	3.23	0.0841[e]	161
	3.39	0.0954[e]	183

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Table IV cont.

Substrate	pH	k_1^{obs}, s^{-1}	k_2^{obs}, M^{-1} s^{-1}
8	3.47	0.121^c	232
	3.68	0.141^f	430
	3.91	0.213^f	623
	4.09	0.317^f	927
	4.42	0.670^f	1.96×10^3
	4.70	1.10^f	3.22×10^3
	5.03	1.93^f	5.65×10^3
	5.25	3.13^f	9.16×10^3

[a] At 25°C, in 0.1M KBr. Values of k_2^{obs} are corrected for the formation of tribromide ion.

[b] [Substrate] = 0.5mM and $[Br_2]$ = 0.05mM

[c] [Substrate] = 1mM and $[Br_2]$ = 0.05mM

[d] [Substrate] = 2mM and $[Br_2]$ = 0.05mM

[e] [Substrate] = 1.5mM and $[Br_2]$ = 0.05mM

[f] [Substrate] = 1mM and $[Br_2]$ 0.05mM

Figure 4

Rate profiles for the bromination of 3-hydroxypyridine derivatives:

($\blacktriangle$) 3-Hydroxypyridine N-oxide (6) (slope $= 1.035$; intercept $= 1.98$; r $= 0.999$);

($\blacksquare$) 6-Methyl-3-hydroxypyridine (7) (slope $= 0.951$; intercept $= 1.16$; r $= 0.999$);

($\blacklozenge$) 3-Hydroxypicolinic acid (8) (slope $= 0.879$; intercept $= -0.646$; r $= 0.998$)
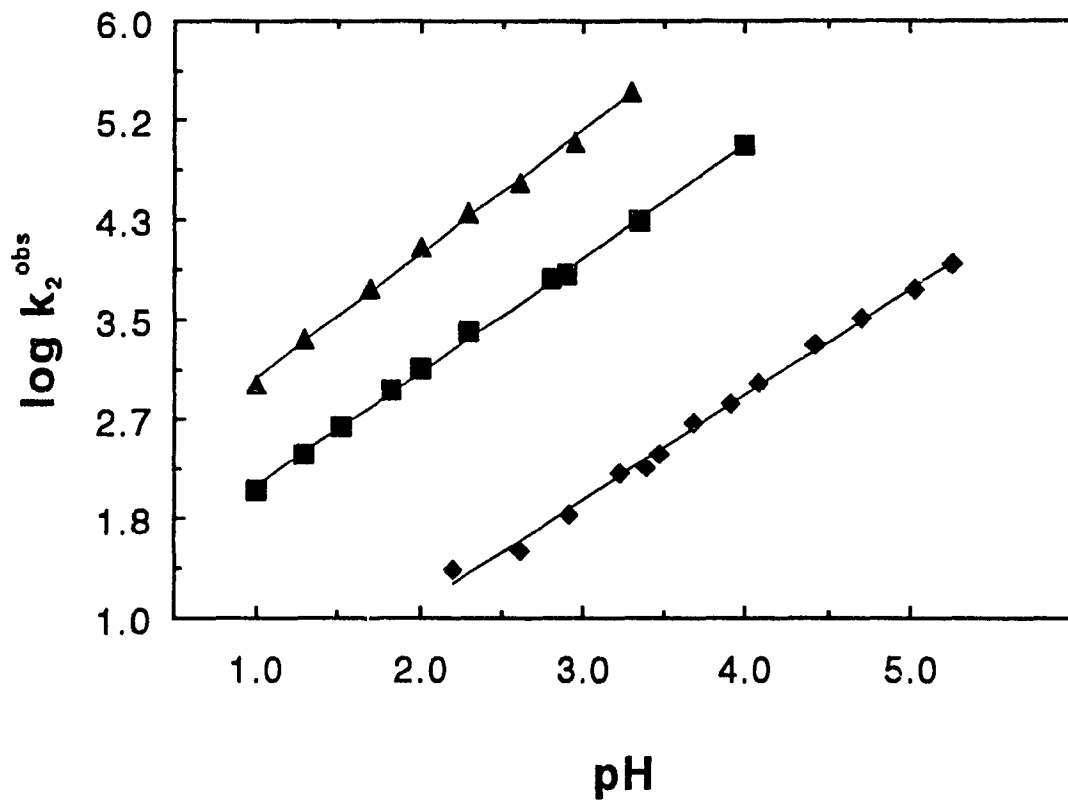
Table V. First and Second-Order Rate Constants for the Bromination of 3-Hydroxypyridine (1) and its Derivatives (2), (4), and (5) in Aqueous Solution.[a]

pH	$[Sub]_o$ mM	$[Br_2]_o$ mM	k_1^{obs} s^{-1}	k_2^{obs} $M^{-1} s^{-1}$
3-Hydroxypyridine (1)				
2.00	2.50	0.05	0.0830	94.2
	2.00	0.05	0.0674	96.06
	1.50	0.05	0.0513	98.3
	1.00	0.05	0.0373	109.0
2-Bromo-3-hydroxypyridine (2)				
2.35	2.00	0.05	1.72	2.45×10^3
	1.50	0.05	1.29	2.47×10^3
	1.00	0.05	0.868	2.54×10^3
	0.500	0.05	0.463	2.86×10^3
2.45	2.00	0.05	2.56	3.65×10^3
	1.50	0.05	2.00	3.84×10^3
	1.00	0.05	1.35	3.95×10^3
	0.500	0.05	0.708	4.37×10^3
N-Benzyl-3-hydroxypyridinium chloride (4)				
2.00	5.00	0.25	1.56	913
	4.00	0.25	1.25	926
	3.00	0.25	0.961	971
	2.00	0.10	0.654	957
	1.00	0.10	0.385	1.19×10^3

Table V cont.

pH	$[Sub]_o$ mM	$[Br_2]_o$ mM	k_1^{obs} s^{-1}	k_2^{obs} $M^{-1} s^{-1}$
N-Ethyl-3-hydroxypyridinium bromide (5)				
2.00	5.00	0.25	1.22	71.4
	4.00	0.25	0.971	71.9
	3.00	0.25	0.735	74.3
	2.00	0.10	0.508	74.3
	1.00	0.10	0.255	78.7
6-Methyl-3-hydroxypyridine (7)				
2.00	2.00	0.05	0.953	1.36×10^3
	1.50	0.05	0.695	1.33×10^3
	1.00	0.05	0.425	1.24×10^3
	0.500	0.05	0.214	1.32×10^3
2.30	2.00	0.050	2.10	2.99×10^3
	1.50	0.050	1.42	2.72×10^3
	1.00	0.050	0.963	2.82×10^3
	0.500	0.050	0.423	2.61×10^3

[a] At 25°C, I = 0.1M KBr

[b] k_2^{obsd} was calcualed from k_1^{obs} by dividing by ($[S]_o - [Br_2]_o$) and multiplying by the correction factor for free bromine, equation 23.

Substrate dependence of the bromination of 3-hydroxypyridine **1**. Notice the linear dependence of first order rate constants on the concentration of the substrate.
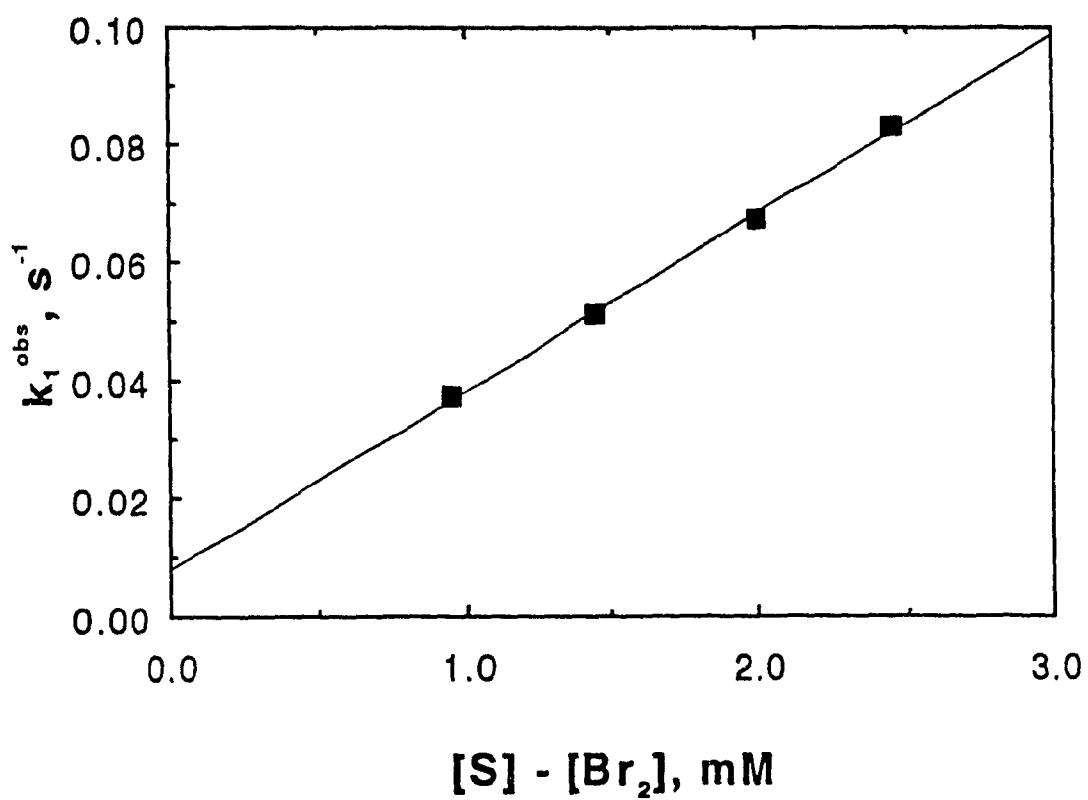
Substrate dependence of the bromination of 2-bromo-3-hydroxypyridine (2) at pH's 2.35 and 2.45.
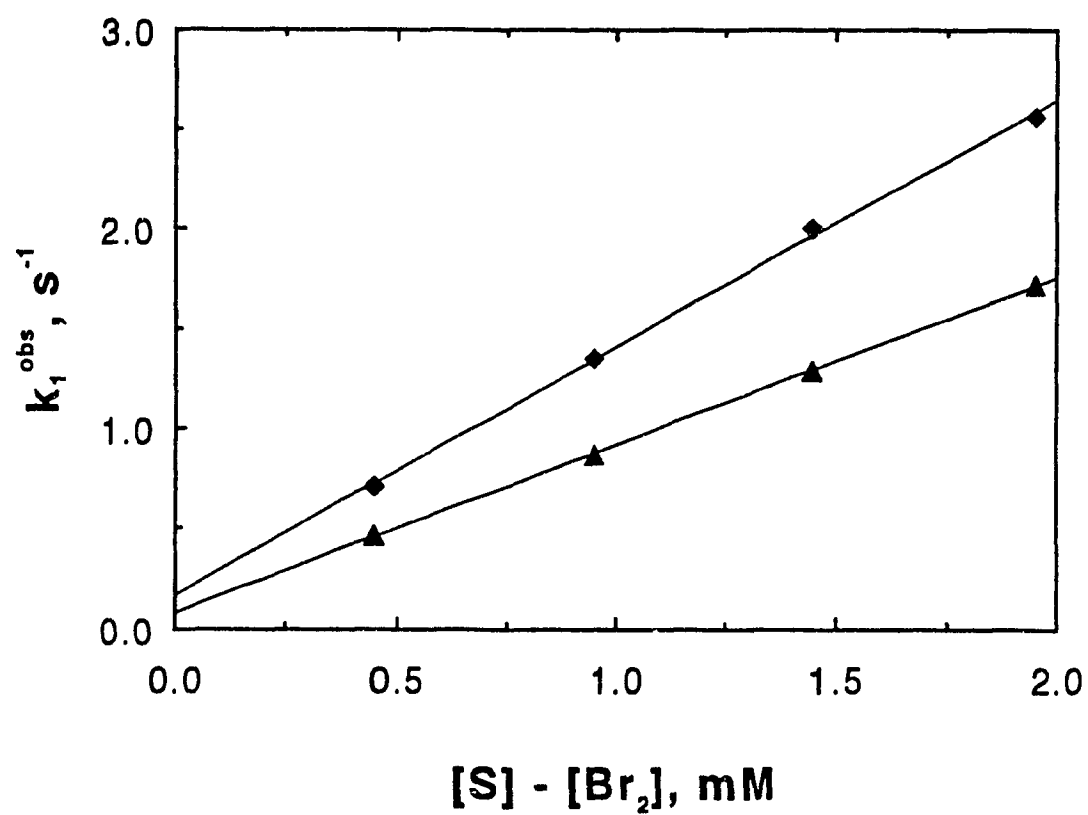
(▲) First order rate constants at pH 2.35

(♦) First order rate constants at pH 2.45

Figure 5c

Substrate dependence of the bromination of N-substituted derivatives of 3-hydroxypyridine at pH 2.0: (♦) N-Ethyl; (▲) N-Benzyl.
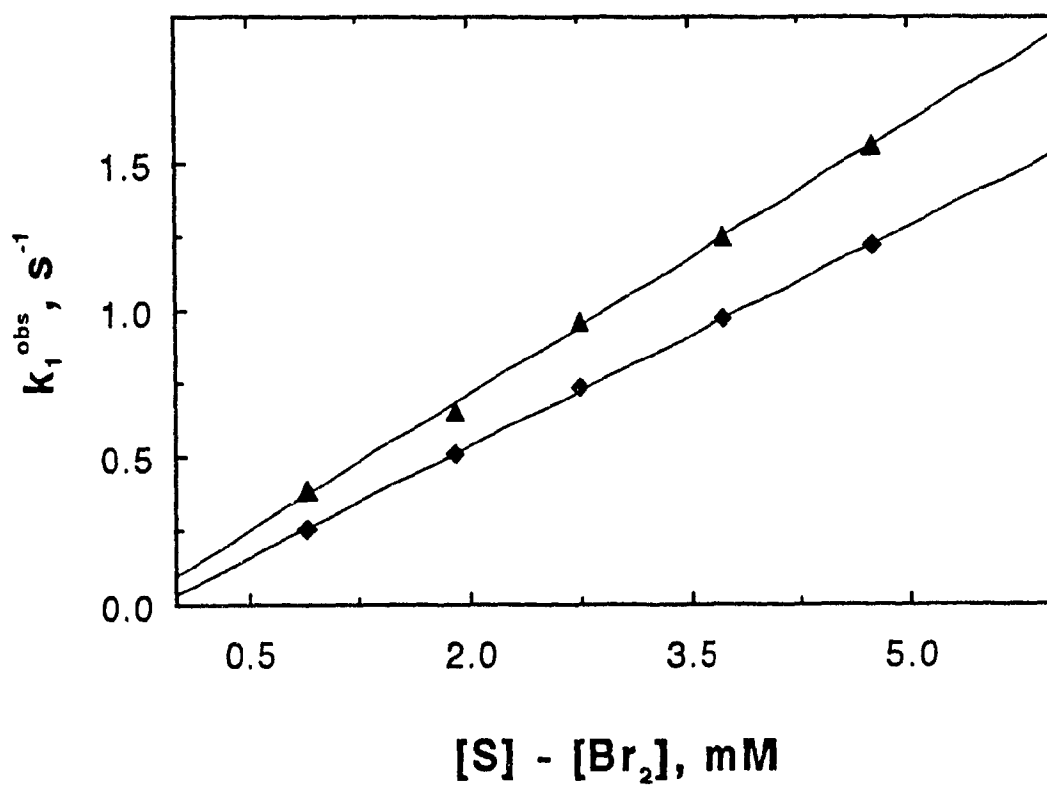
Figure 5d

Substrate dependence of the bromination of 6-methyl-3-hydroxypyridine (7): (■) at pH 2.0; (▲) at pH 2.3.
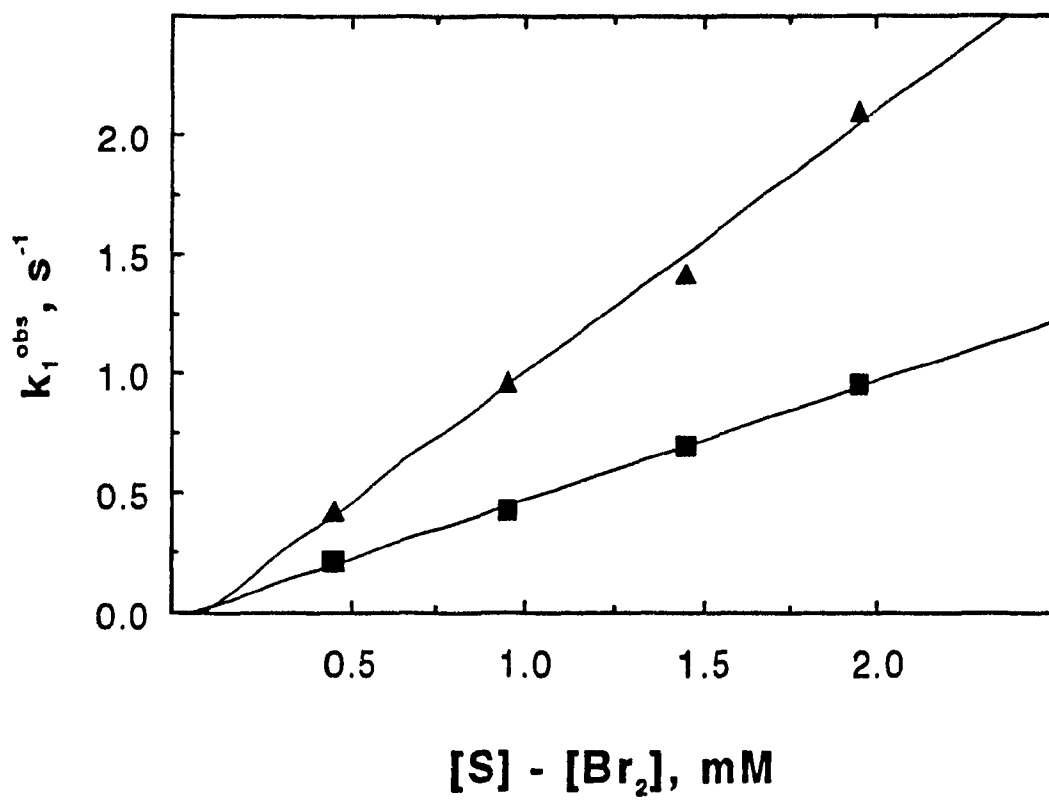
Since pH dependence studies were carried out at relatively low bromide ion concentration (0.1 M KBr), the reaction of tribromide ion with the substrate species may well be neglected. However, a separate study was carried out at high bromide ion concentration to investigate the possible reactivity of this species. This point will be pursued in detail under section II.4.

As stated earlier, the 3-hydroxypyridine tautomeric system exists in aqueous solution as equal proportions of the hydroxy and the zwitterionic species. However, in theory, a pH dependence study of the bromination of the 3-hydroxypyridine system should yield rate profiles which portray the reactivity of the various possible reactive forms. Over the pH range studied, we expect possible reactivity via the neutral and anionic species of the substrates, as shown in equations 18a,b. Reaction upon the cation SH_2^+ is unlikely (and was not observed).

$$SH_2^+ \quad \xrightarrow[\text{H}^+]{\text{K}_1} \quad SH \quad \xrightarrow[\text{Br}_2]{\text{k}_2} \quad P \tag{18a}$$

$$SH \quad \xrightarrow[\text{H}^+]{\text{K}_2} \quad S^- \quad \xrightarrow[\text{Br}_2]{\text{k}_2'} \quad P \tag{18b}$$

In equations 18a,b the species SH_2^+, SH, and S^- are the cationic, neutral, and anionic forms, k_2 is the rate constant for reaction of the neutral species, and k_2' is the rate constant for the reaction via the anion.

Assuming $K_2 << K_1$ and $K_2 << [H^+]$, the form expected for the acidity dependence of the observed rate constant for the systems in equations 18a,b is given

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by:

$$k_{obs} = k_2 K_1/(K_1 + [H^+]) + k_2'K_2/[H^+] \tag{19}$$

where the first term represents reaction via the neutral molecule and the second term is for reaction via the anion which becomes important at higher pH. A rate profile for the bromination of the substrates is therefore expected to show inflections marking a changeover in the form of the reacting species, as illustrated below.
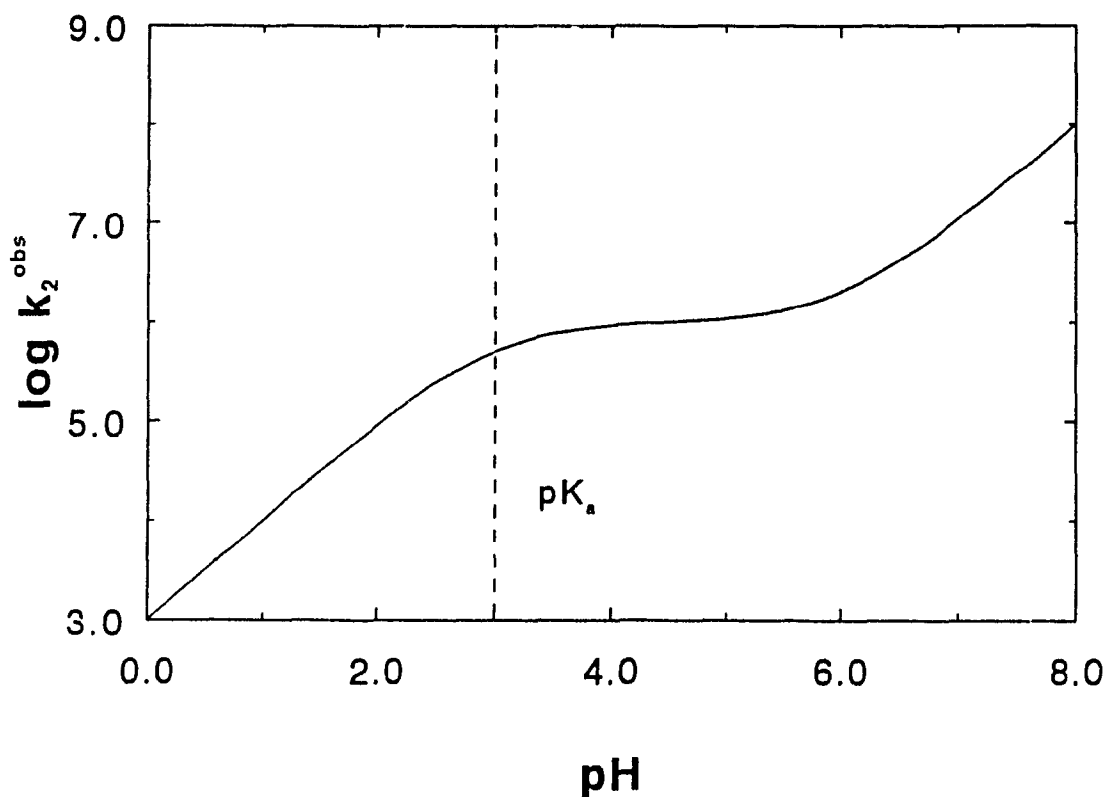
Such pH-rate profiles representing reaction upon the neutral molecule and the anion, at different pH ranges, have been observed in earlier bromination studies with 2- and 4-pyridone.[18b,c]

However, the observed pH-rate profiles displayed in Figs. 1-4 do not show any

inflection near pH $=$ pK$_1$ to implicate a change from reaction via the neutral to reaction of the anion. A possible explanation for the observed behaviour may be that the first and second terms (rising portions) of equation 19, from which the theoretical plot above has been generated, are coincident. For this to be the case,

$$k_2 K_1 \approx k_2' K_2 \tag{20}$$

That is, the difference between k_2 and k_2' is matched by that between K_1 and K_2.

The condition imposed by equation 20 probably explains the origin of the linear plots obtained in the present study. A pH-rate profile generated using the first term at pH $<$ pK$_1$ and the second term when pH $>$ pK$_1$ gives plots with similar slopes which coincide with one another, thus accounting for the absence of the expected inflection which marks reaction via one form or another.

Equation 19 therefore takes the form of:

$$k_2^{obs} = k_2 K_1/[H^+] \qquad \text{when } [H^+] >> K_1 \tag{21a}$$

$$k_2^{obs} = k_2' K_2/[H^+] \qquad \text{when } [H^+] << K_1 \tag{21b}$$

The values of k_2' and k_2 for some of the substrates studied can thus be obtained by using a rearranged form of equation 21b.

$$k_2' = k_2^{obs} [H^+]/K_a \tag{22}$$

where k_2' is the rate constant for reaction upon the anion and K_a is the acid dissociation constant of the substrate.

On the basis of equation 22, the k_2' value for 3-hydroxypyridine has been estimated as follows:

At pH 5.89, $\quad k_2{}^{obs} = 2.06 \times 10^6 \, M^{-1} \, s^{-1}$

Thus, $\quad k_2' = 2.06 \times 10^6 \times 10^{-5.89} \times 10^{8.72}$

$\qquad\qquad = 1.39 \times 10^9 \, M^{-1} \, s^{-1}$

Tee *et al.*[35] determined the second-order rate constant for the reactivity of phenoxide ion to be $1.2 \times 10^9 \, M^{-1} \, s^{-1}$, at the same bromide ion concentration (0.1M KBr). Incidentally, these values are both close to the diffusion-controlled limit. The Smoluchowski and Stokes-Einstein equations,[40] on which the normal model of solute diffusion is based, predicts a rate constant of about $5 \times 10^9 \, M^{-1} \, s^{-1}$ for the encounter of molecules of similar size. The estimated value of k_2' therefore suggests that the anionic species of 3-hydroxpyridine, like the phenoxide ion, reacts with bromine at close to the diffusion-controlled limit.

This interpretation is consistent with the results obtained in the bromination of the 3-nitrophenoxide ion. Bell and Rawlinson[39] had determined the rate coefficient for the bromination of this substrate to be $1.3 \times 10^9 \, M^{-1} \, s^{-1}$ whereas in another study, Tee *et al.*[35] found the rate constant to be $2.7 \times 10^9 \, M^{-1} \, s^{-1}$. Both values are close to that expected for a diffusion-controlled reaction,[40] as are the rate constants for other simple phenoxide ions.[35,39] A comparison is made between 3-hydroxypyridine (1) and 3-nitrophenol because the two substrates have similar reactivity to electrophiles. The ring nitrogen in 1 is roughly equivalent in terms of inductive and mesomeric effects to a nitro group attached at the same site. For example, the Hammett constant at the meta position (σ_{meta}) for -NO$_2$ and =N- substitution in an aromatic ring are 0.74 and

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0.73, respectively.[41]

Diffusion-controlled reactions arise in solution when the chemical reaction within the encounter complexes of the reactants is faster than diffusional separation of the partners.[40] For example, suppose a substrate (S) reacts with an electrophile (X) to form an encounter complex {S.X}, as illustrated below:

$$S + X \overset{k_f}{\underset{k_b}{\rightleftharpoons}} \{S.X\} \xrightarrow{k_{rxn}} P \qquad (23)$$
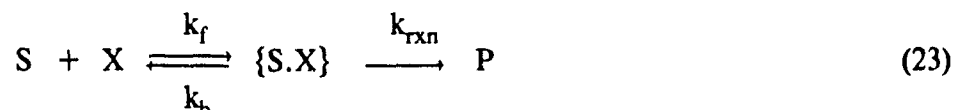
If the chemical reaction is very fast ($k_{rxn} >> k_b \approx 10^{10}$ s^{-1}), then the speed of the reaction is limited by diffusion of S and X together and the effective rate constant for the reaction becomes k_f. In the present case, and like other phenoxides,[35] the {3-hydroxypyridine anion.Br$_2$} encounter complex must react as soon as it is formed and so $k_2' \approx k_f$.

The values of k_2' for the anion of 3-hydroxypyridine N-Oxide 6 (pK$_a$ = 6.40)[44] and the dianion of 3-hydroxy-2-picolinic acid 8 (pK$_a$ = 10.76)[24] have also been estimated, using equation 22, to be 3.2 x 10^8 M^{-1} s^{-1} and 3.0 x 10^9 M^{-1} s^{-1}, respectively. The second value also suggests that the reaction is diffusion-controlled whereas the first is somewhat below the normal limit for small molecules.

The literature value for the pK$_a$ of N-methyl-3-hydroxypyridinium cation is 4.96.[24] Approximately the same value is anticipated for the N-benzyl and N-ethyl cations (4 and 5) because the increase in chain length has little effect on the inductive effect and thus the pK$_a$. On this basis therefore, the pK$_a$'s of 4 and 5 have been assumed to be 4.96 and their k_2 values estimated as above to be 3.0 x 10^5 and

6.5×10^5 M^{-1} s^{-1}, respectively. For the zwitterions derived from the cations **4** and **5** the rate of reaction is considerably less than that for reactivity on encounter. The results obtained for pH dependence studies are summarized in Table VI.

Table VI. Summary of Results obtained for pH-Dependence Studies

Sub.	Int.	Slope	pK_a*	k_2 M^{-1} s^{-1}	k_2' M^{-1} s^{-1}
3-Hydroxypyridine (**1**)	0.335	1.002	8.72	1.9×10^5	1.39×10^9
2-Bromo-3-hydroxy-pyridine (**2**)	0.973	1.08	-	-	-
2,6-Dibromo-3-hydroxy-pyridine (**3**)	0.712	0.970	-	-	-
N-Benzyl-3-hydroxy-pyridinium chloride (**4**)	1.21	0.859	≈4.96	-	$3.03^a \times 10^5$
N-Ethyl-3-hydroxy-pyridinium bromide (**5**)	1.05	0.885	≈4.96	-	$6.5^a \times 10^5$
3-Hydroxypyridine N-oxide (**6**)	1.98	1.032	6.40^b	-	2.39×10^8
6-Methyl-3-hydroxy-pyridine(**7**)	1.16	0.951	-	-	-
3-Hydroxy-2-picolinic acid(**8**)	-0.649	0.88	10.76	-	3.0×10^9

* pK_a's are those for the phenolic -OH and are taken from reference 24.

[a] k_2 values for the reactivity of the zwitterion.

[b] pK_a value taken from reference 44.

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The interpretation given so far to the results obtained in pH dependence studies accommodates our original expectation that bromination of 3-hydroxypyridine (1) occurs via a neutral form (hydroxy or zwitterionic) at low pH and via the anion at higher pH. However, pH-rate profiles for two of the other substrates studied provide evidence which suggests that the zwitterion, rather than the hydroxy species, is the reactive neutral form.

The linear behaviour of the rate profiles for the N-substituted derivatives **4** and **5** seem to suggest that these compounds reacts as their zwitterions (eq 24);

$$\text{(3-OH pyridinium, N-R)} \rightleftharpoons \text{(3-O}^-\text{ pyridinium, N-R)} \xrightarrow[k_2']{Br_2} P \qquad (24)$$
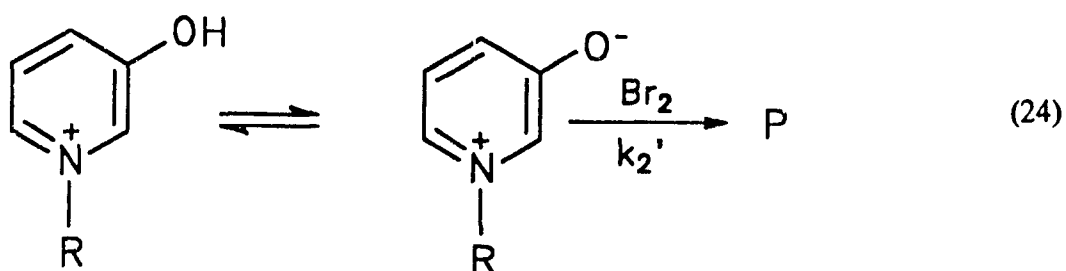
where k_2' is for reaction of the zwitterionic species. Since the pH-rate profile of the parent compound is very similar to those of compounds **4** and **5** (Cf Fig 1 and Fig 3) it is highly likely that the zwitterion of **1** is its reactive neutral form (eq 25):

$$\text{(3-OH pyridine)} \rightleftharpoons \text{(3-O}^-\text{ pyridinium, N-H)} \xrightarrow[k_2]{Br_2} P \qquad (25)$$
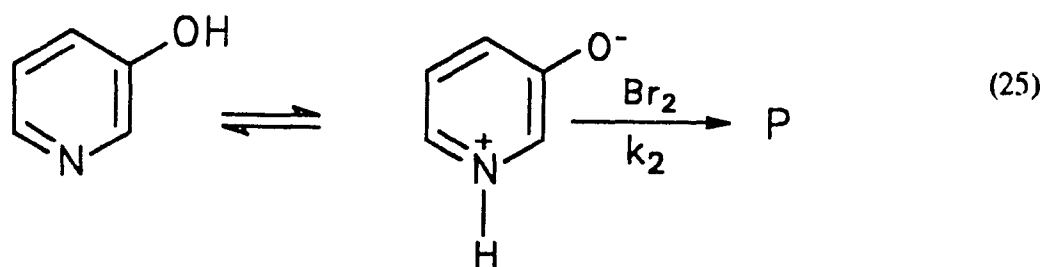
where k_2 is the rate constant for the reactivity of the dipolar neutral form.

In particular, note that k_2 for **1** (1.9×10^5 M^{-1} s^{-1}) is very similar to that for

the values (k_2' = 3.0 x 10^5 and 6.5 x 10^5 M^{-1} s^{-1}) for the N-benzyl and N-ethyl derivatives (Table VI). Tee and Paventi[32a,b] in an earlier study used the similarity in rate profile of a parent compound to those of its model compounds to establish the reactive forms of 2- and 4-pyridone.

Therefore, we hereby propose that at low pH, the reactive neutral form of the 3-hydroxypyridine system is the zwitterion, rather than the hydroxy form, and at higher pH the substrates react via their anions.

Tee and Iyengar[33c] have earlier established that the attack of bromine on

phenol, 4-methylphenol, and 4-bromophenol is catalysed by general bases. In

contrast, the reaction of 2-pyridone did not show buffer catlysis. Since the reactions

of 3-hydroxypyridine 1 seem to parallel those of phenols, it was the objective of this

study to find out if a similar buffer catalysis could be observed in the aqueous

bromination of 1 and some of its derivatives (2, 5, 6). Acetate and chloroacetate

buffers were employed to investigate general base catalysis.

The reactions were monitored as the first-order disappearance of bromine in

the presence of a large excess (ten-fold or more) of substrate at fixed ionic strength,

$I = 0.5$ M KBr. The observed first-order rate constants (k_1^{obs}) were then converted

to second-order constants (k_2^{obs}). The results for these buffer studies are given in

Tables VII-X and plotted in Figures 7-10.

The figures show that the second-order rate constants increase with increasing

buffer concentration, as expected on the basis of equation 26:

$$k_2^{obs} = k_o + k_t [B]_t \tag{26}$$

where k_o represents the reactivity of the substrate in the absence of buffer, k_t is the

weighted sum of the buffer catalysed processes, and $[B]_t$ is the buffer concentration.

Equation 26 requires k_2^{obs} to be a linear function of $[B]_t$, and this is the case. Linear

least-squares analysis of the buffer catalysis results gave slopes (k_t) and intercepts

(k_o) listed in Table XI. Notice that the slopes of the plots increase with pH,

indicating that there is an increase in catalysis as the fraction of the basic component of the buffer increases. This implies that bromine attack on the substrates investigated *is* catalysed by carboxylate anions. It will be noticed, also, that k_o increases with pH. This simply reflects the behaviour already seen in pH-rate profiles.

Analysis of the slopes of the buffer plots in terms of the fractions of carboxylate anion and carboxylic acid should give the basic (k_A) and acidic (k_{HA}) catalytic constants for the buffer catalysis observed. This reasoning is derived from the following equations:

$$k_t [B]_t = k_A[A^-] + k_{HA}[HA] \tag{27}$$

$$k_t = k_A[A^-]/[B]_t + k_{HA}[HA]/[B]_t \tag{28}$$

$$k_t = k_A f_A + k_{HA} f_{HA} \tag{29}$$

where f_A and f_{HA} represent the fractions of the carboxylate anion and carboxylic acid, respectively. These are calculated as outlined in the Appendix.

Origins of Buffer Catalysis

In discussing the origins of buffer catalysis, it is essential to identify the brominating agent. Conceivably, bromine may react with a buffer anion to produce a more reactive electrophile, as shown in equation 30:

$$RCOO^- + Br_2 \rightleftharpoons RCOOBr + Br^- \tag{30}$$
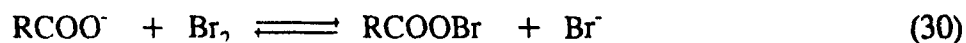
However, this possibility had already been ruled out in an earlier study.[33c] This is because Br-Br is a more reactive brominating agent in aqueous solution than

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RCOOBr because Br⁻ is a better leaving group than RCOO⁻.

The simplest interpretation of the general base catalysis observed is that a carboxylate anion abstracts the phenolic proton of the substrates, just about the same time with the electrophilic attack by bromine (eq 31).

$$\text{(structure)} \quad \longrightarrow \quad \text{Product} \qquad (31)$$
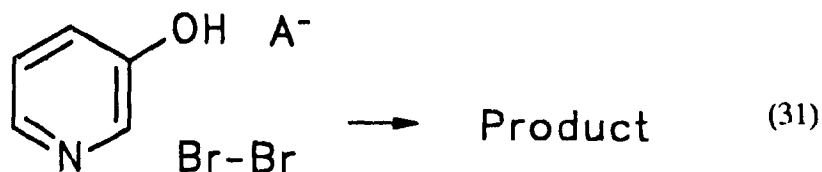
Tee and Iyengar used such an interpretation to explain the anion catalysis which they observed with some phenols.[33c]

Another possibility may be that the general base abstracts the azonium proton ($=^{+}$N$\underline{\text{H}}$-) of the zwitterion (eq 32).

$$\text{(structure)} \quad \longrightarrow \quad \text{Product} \qquad (32)$$
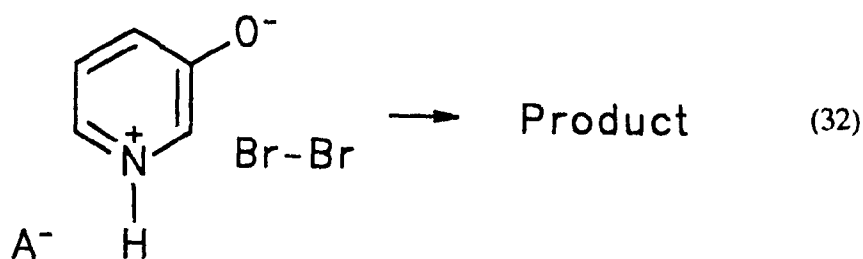
This explanation is quite plausible because the phenolic and azonium protons of the two forms of 3-hydroxypyridine must have very similar acidities ($pK_a = 8.72$). The same interpretation is applicable to the N-oxide where abstraction of the N-hydroxy proton ($=^{+}$N(O$\underline{\text{H}}$)-) possibly accounts for the buffer catalysis observed with this compound. This second scenario is not applicable to the N-ethyl compound 5 because

only its phenolic proton can be abstracted.

The attack of bromine on the 3-hydroxypyridine anion is probably diffusion-controlled, as discussed earlier. This implies that the rate of reaction within the encounter complex $\{Br_2.S^-\}$ is faster than the diffusional separation of Br_2 and S^- (see eq 23). Likewise, reaction within an encounter complex $\{Br_2.S^-.HA\}$ could be very fast. Therefore, a possible explanation for the general base catalysis observed is that reaction occurs through an encounter complex $\{Br_2.SH.A^-\}$. Within this complex, proton transfer from SH to A^- would lead to a highly reactive configuration with Br_2 adjacent to S^- which should react rapidly to give the products (eq 33).

$$Br_2 + SH + A^- \rightleftharpoons \{Br_2.SH\} + A^- \rightleftharpoons \{Br_2.SH.A^-\}$$

$$\{Br_2.SH.A^-\} \longrightarrow \{Br_2.S^-.HA\} \xrightarrow{\text{fast}} \{Br^-.BrS.HA\} \qquad (33)$$
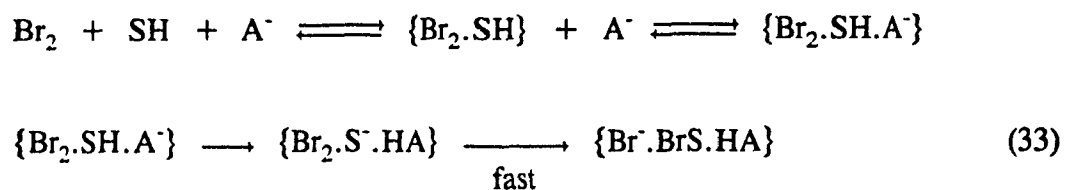
This explanation of the buffer catalysis could apply with either of the two tautomeric forms of 3-hydroxypyridine (eq 31 or 32) since both lead to the same very reactive anion, S^-. There is no easy way to distinguish between these two possibilities.

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Table VII. Effect of Acetate Buffer Concentration on the rate of Bromination of 3-Hydroxypyridine (1).[a]

pH	Buffer Strength mM	k_1^{obs} s^{-1}	k_2^{obsd} $M^{-1} s^{-1}$
4.10[b]	25	1.83	1.91×10^4
	50	2.03	2.11×10^4
	75	2.13	2.22×10^4
	100	2.49	2.59×10^4
4.45[c]	25	1.74	3.83×10^4
	50	2.13	4.68×10^4
	75	2.54	5.59×10^4
	100	2.75	6.05×10^4
4.75[c]	25	3.45	7.58×10^4
	50	4.77	1.05×10^5
	75	5.08	1.12×10^5
	100	5.79	1.27×10^5

[a] At 25°c, in 0.5 M KBr; values of k_2^{obs} are corrected for the formation of tribromide ion. [b] [Substrate] = 1mM and $[Br_2]$ = 0.05mM

[c] [Substrate] = 0.5mM and $[Br_2]$ = 0.05mM

Figure 7. Effect of Acetate Buffer on the Rate of Bromination of **1**. Data taken from Table VII as follows: (■) pH 4.1; (▲) pH 4.45; (♦) pH 4.75. Notice that the slopes of the plots increase with pH.
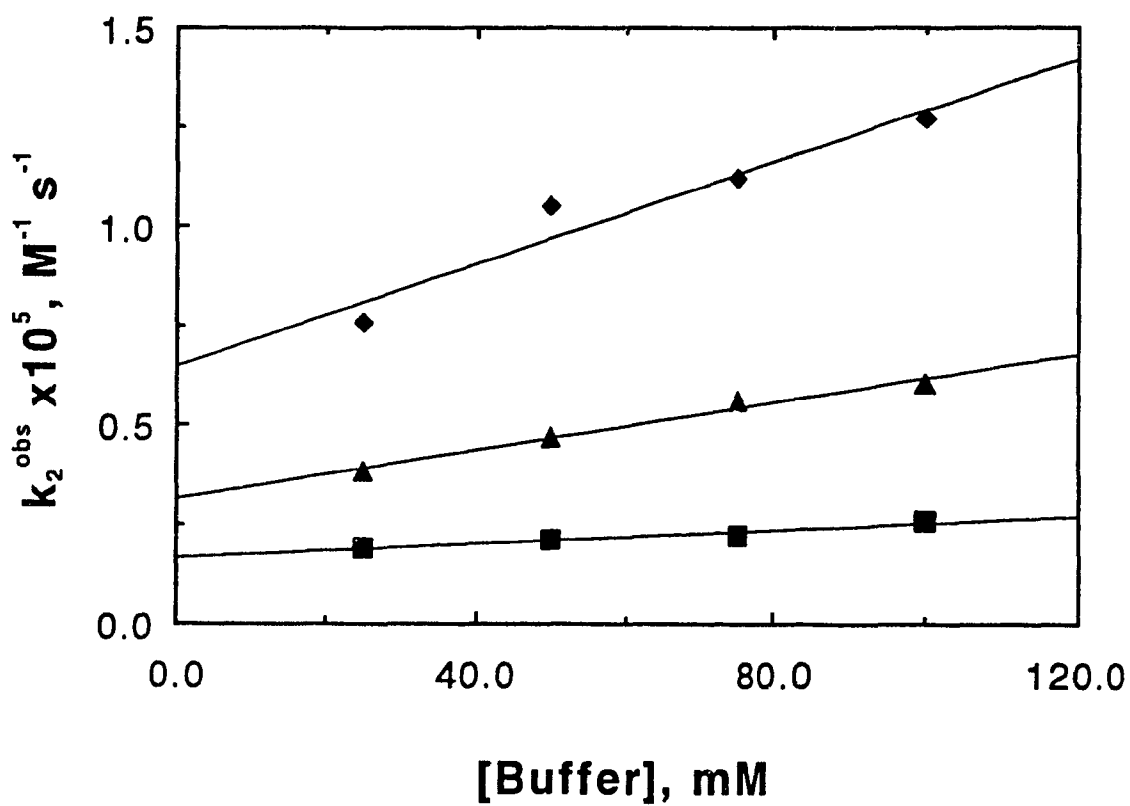
Table VIII. Effect of Chloroacetate Buffer on the Aqueous Bromination of 2-Bromo-3-hydroxy-pyridine (2).[a]

pH	Buffer Strength mM	k^{1obs} s^{-1}	k_2^{obs} $M^{-1} s^{-1}$
2.75	25	0.375	3.91×10^3
	50	0.499	5.19×10^3
	75	0.585	6.09×10^3
	100	0.858	8.94×10^3
3.05	25	1.35	1.41×10^4
	50	1.55	1.61×10^4
	75	1.79	1.86×10^4
	100	2.15	2.24×10^4
3.40	25	2.16	2.25×10^4
	50	2.49	2.59×10^4
	75	2.92	3.04×10^4
	100	3.51	3.65×10^4

[a] At 25°C, in 0.5 M KBr; values of k_2^{obs} are corrected for the formation of tribromide ion; [Substrate] = 1mM and [Br_2] = 0.05mM

Figure 8. Effect of Chloroacetate Buffer on the Rate of Bromination of 2. Data taken from Table 8, as follows: (■) pH 2.75; (▲) pH 3.05; (♦) pH 3.40.
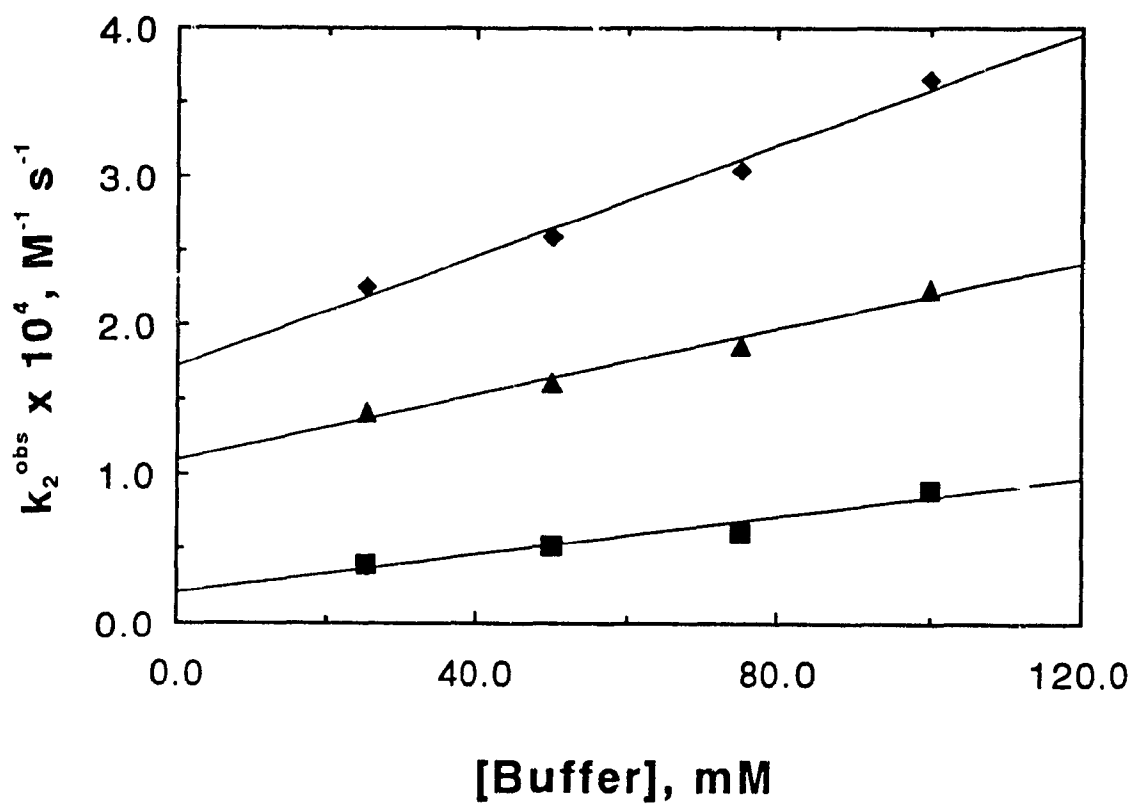
Table IX. Effect of Acetate Buffer on the Aqueous Bromination of N-Ethyl-3-hydroxypyridinium bromide (5).[a]

pH	Buffer strength mM	k_1^{obs} s^{-1}	k_2^{obs} $M^{-1} s^{-1}$
3.95	25	1.48	1.54×10^4
	50	1.68	1.75×10^4
	75	2.29	2.39×10^4
	100	2.86	2.96×10^4
4.40	25	2.56	5.63×10^4
	50	3.10	6.82×10^4
	75	3.49	7.67×10^4
	100	3.89	8.40×10^4
4.80	25	4.49	9.89×10^4
	50	4.91	1.08×10^5
	75	5.47	1.20×10^5
	100	6.10	1.34×10^5

[a] At 25 °C, in 0.5 M KBr; values of k_2^{obs} are corrected for the formation of tribromide ion; [Substrate] = 0.5mM and [Br_2] = 0.05mM

Figure 9. Effect of Acetate Buffer on the Rate of Bromination of 5. Data taken from Table IX, as follows: (■) pH 3.95; (▲) pH 4.40; (♦) pH 4.80.
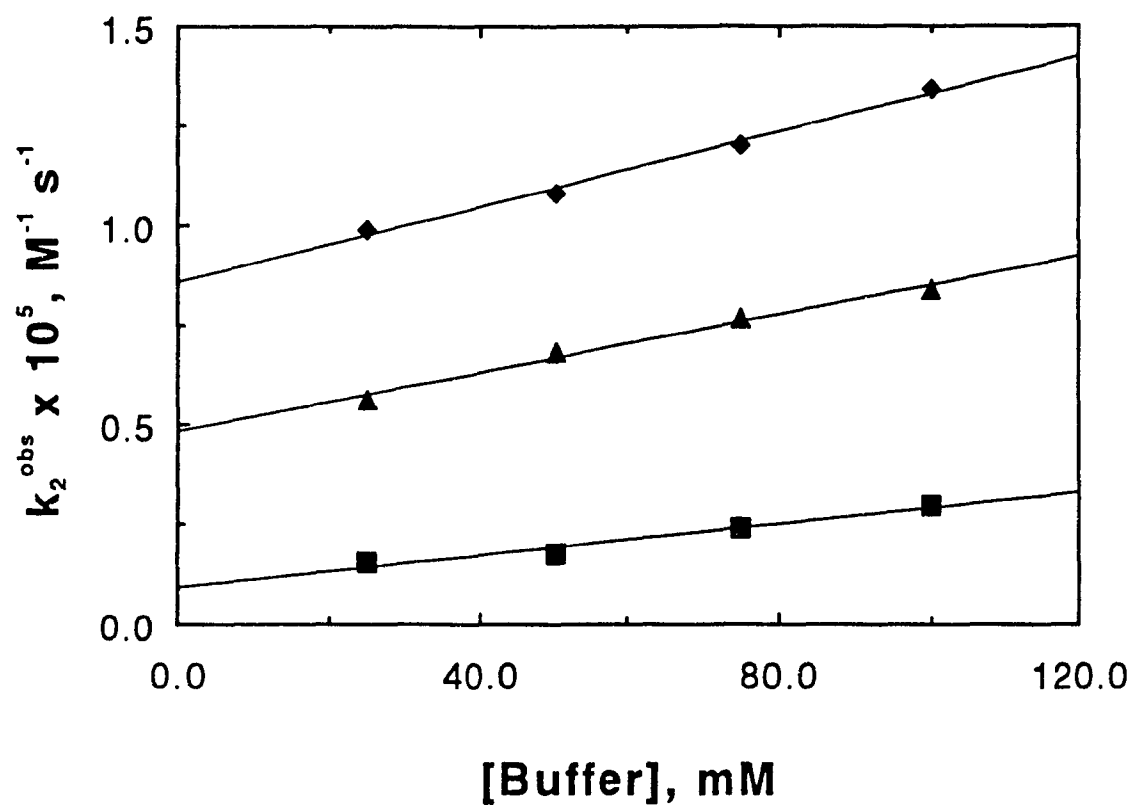
Table X. Effect of Chloroacetate Buffer on the Aqueous Bromination 3-Hydroxypyridine N-Oxide (6).[a]

pH	Buffer Strength mM	k_1^{obs} s^{-1}	k_2^{obs} $M^{-1} s^{-1}$
2.60	25	1.45	3.19×10^4
	50	1.74	3.83×10^4
	75	1.93	4.24×10^4
	100	2.35	5.22×10^4
2.90	25	2.85	6.27×10^4
	50	3.18	6.99×10^4
	75	3.54	7.78×10^4
	100	3.95	8.69×10^4
3.15	25	7.11	1.56×10^5
	50	7.57	1.66×10^5
	75	7.88	1.73×10^5
	100	8.36	1.84×10^5

[a] At 25°C, 0.5 M KBr; Values of k_2^{obs} are corrected for the formation of tribromide ion; [Substrate] = 0.5mM and [Br_2] = 0.05mM

Figure 10. Effect of Chloroacetate Buffer on the Bromination of 6. Data taken from Table X, as follows: (■) pH 2.60; (▲) pH 2.90; (♦) pH 3.15.
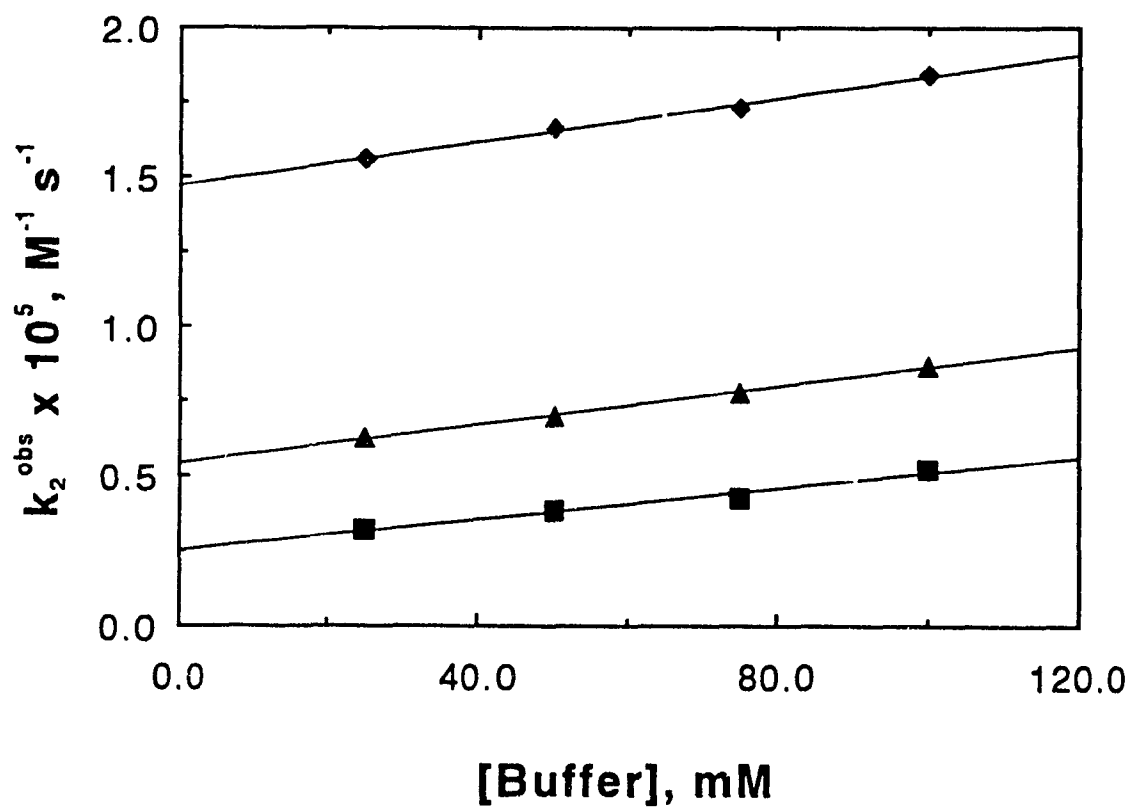
Table XI. Summary of Results Obtained From Buffer Plots for Substrates Studied.[a]

Buffer	pH	f_A	k_o, M^{-1} s^{-1}	k_t, M^{-2} s^{-1}
3-Hydroxypyridine				
Acetate	4.10	0.219	1.67×10^4	8.60×10^4
	4.45	0.386	3.15×10^4	3.03×10^5
	4.75	0.556	6.48×10^4	6.42×10^5
2-Bromo-3-hydroxypyridine				
Chloroacetate	2.75	0.506	2.035×10^3	6.40×10^4
	3.05	0.671	1.095×10^4	1.10×10^5
	3.40	0.821	1.72×10^4	1.86×10^5
N-Ethyl-3-hydroxypyridinium bromide				
Acetate	3.95	0.166	9.35×10^3	1.96×10^5
	4.40	0.359	4.84×10^4	3.66×10^5
	4.80	0.585	8.59×10^4	4.69×10^5
3-Hydroxypyridine N-oxide				
Chloroacetate	2.60	0.420	2.49×10^4	2.60×10^5
	2.90	0.591	5.42×10^4	3.22×10^5
	3.15	0.719	1.47×10^5	3.64×10^5

[a] $f_A + f_{HA} = 1$; see Appendix for the expression used to calculate f_A and f_{HA}.

Tribromide ion (Br_3^-) is generally a weak electrophile towards aromatic substrates, but it has been found that it reacts rapidly with phenoxide ion (8.5×10^8 M^{-1} s^{-1}) at almost the same rate as molecular bromine (1.2×10^9 M^{-1} s^{-1}).[35] The principle behind bromide ion dependence study is that if reaction with Br_3^- is not involved, then values of k_2^{obs}, which are corrected for the conversion of some of the Br_2 to Br_3^-, should be invariant with [Br^-].

In the present work, a bromide ion dependence study was carried out for the bromination of 3-hydroxypyridine (**1**), exclusively. The results are shown in Table XII and plotted in Figure 12. As depicted in the plots, the values of k_2^{obs} increase linearly with [Br^-]. The positive slopes of these plots demonstrate the participation of Br_3^- under the reaction conditions.

Further proof of attack by Br_3^- was obtained by employing solutions with high [Br^-] (1M) and then varying the pH. The results are presented in Table XIII and plotted in Figure 13. Relatively higher values of k_2^{obs} were obtained under these conditions, for example, $k_2^{obs} = 8.03 \times 10^4$ M^{-1} s^{-1} at pH 4.45 for I = 1 M KBr, as compared with $k_2^{obs} = 5.62 \times 10^4$ M^{-1} s^{-1} at pH 4.41 for I = 0.1 M KBr. Figure 14 shows that the pH-rate profile for the bromination of 3-hydroxypyridine in 1.0 M KBr lies well above that for the same reaction in 0.1 M KBr.

Table XII. Bromide Ion Dependence on Bromination Rates of 3-Hydroxypyridine (1)[a]

	[KBr] M	[NaCl] M	k_1^{obs} s^{-1}	k_2^{obs} $M^{-1} s^{-1}$
(a) At pH 3.0				
	0.25	0.75	0.283	1.49×10^3
	0.50	0.50	0.185	1.75×10^3
	0.75	0.25	0.154	2.10×10^3
	1.0	0.0	0.132	2.36×10^3
(b) At pH 3.4				
	0.25	0.75	0.794	4.18×10^3
	0.50	0.50	0.574	5.44×10^3
	0.75	0.25	0.494	6.76×10^3
	1.0	0.0	0.473	8.46×10^3

[a] At 25 °C, I = 1.0 M. Values of k_2^{obs} are corrected for the formation of tribromide ion. [S] = 1.0 mM and [Br_2] = 0.05 mM.

Figure 12.

The linear dependence of k_2^{obs} on the bromide ion concentration for the bromination

of 3-hydroxypyridine: (■) at pH 3.0 (slope $= 1.18 \times 10^3$, intercept $= 1.19 \times 10^3$ and

$r = 0.998$; (♦) at pH 3.4.(slope $= 5.66 \times 10^3$, intercept $= 2.67 \times 10^3$, and $r = 0.997$).
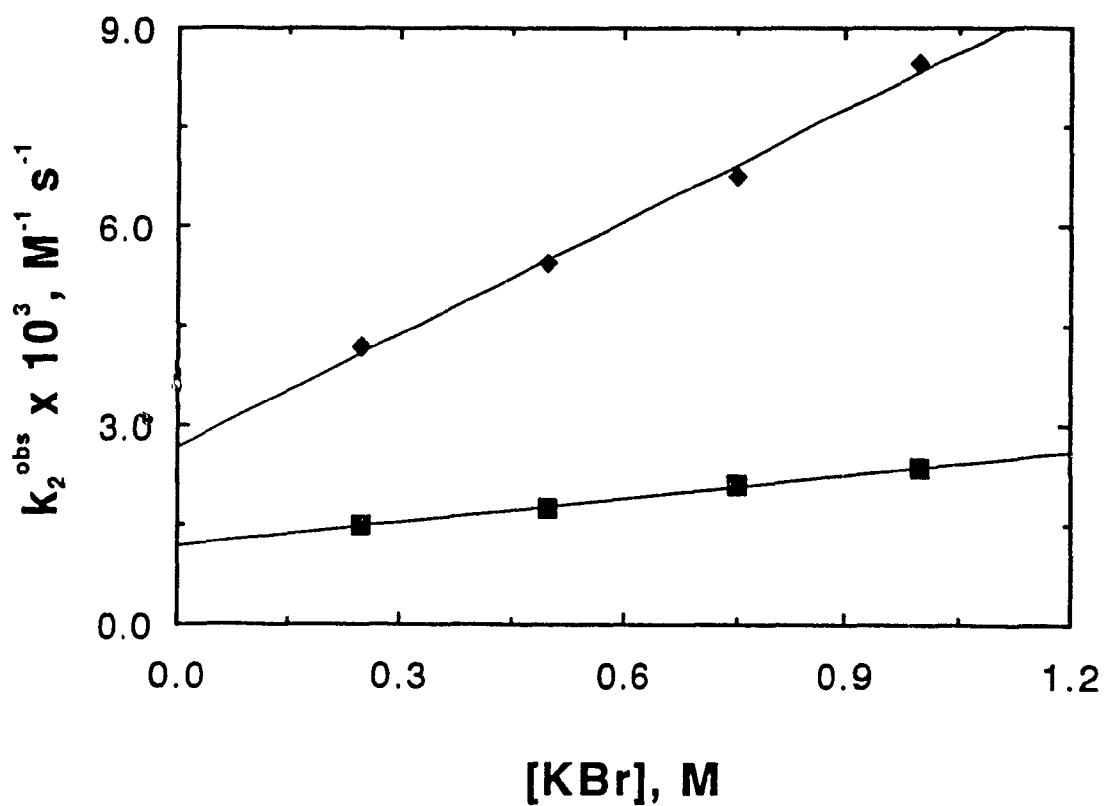
Table XIII. First- and Second-Order Rate Constants for the Bromination of 3-Hydroxypyridine.[a,b]

pH	k_1^{obs}, s^{-1}	k_2^{obs}, M^{-1} s^{-1}
2.55	0.055	980
3.09	0.196	3.50×10^3
3.40	0.473^c	8.46×10^3
4.00	1.63	2.90×10^4
4.45	4.49	8.03×10^4

[a] At 25°C, I = 1.00 M KBr. Values of k_2^{obs} are corrected for the formation of tribromide ion.

[b] [Substrate] = 1.0 mM and [Br_2] = 0.05mM

[c] Taken from Table XII.

Figure 13.

pH-Rate profile for the bromination of 3-hydroxypyridine at 1.0 M KBr,

(slope = 1.007, intercept = 0.443, and r = 0.999).
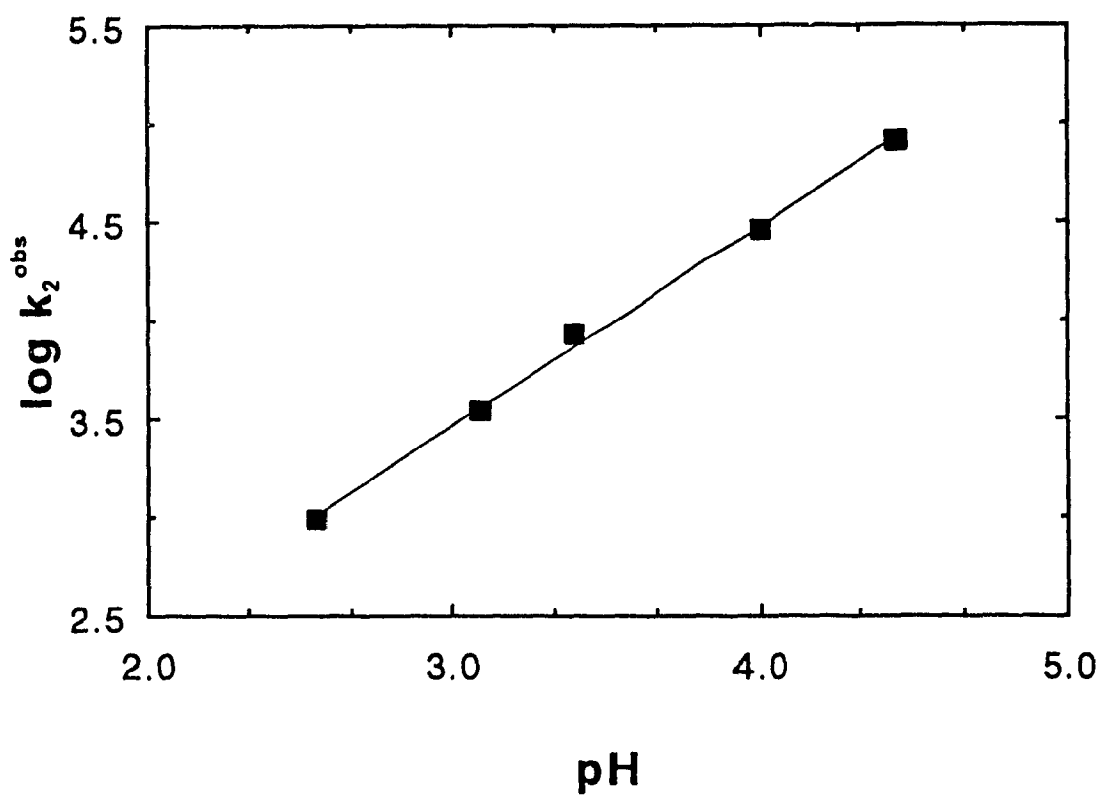
Figure 14.

pH-rate profile for the bromination of 3-hydroxypyridine: (■) at 0.1 M KBr and

(♦) at 1.0 M KBr.
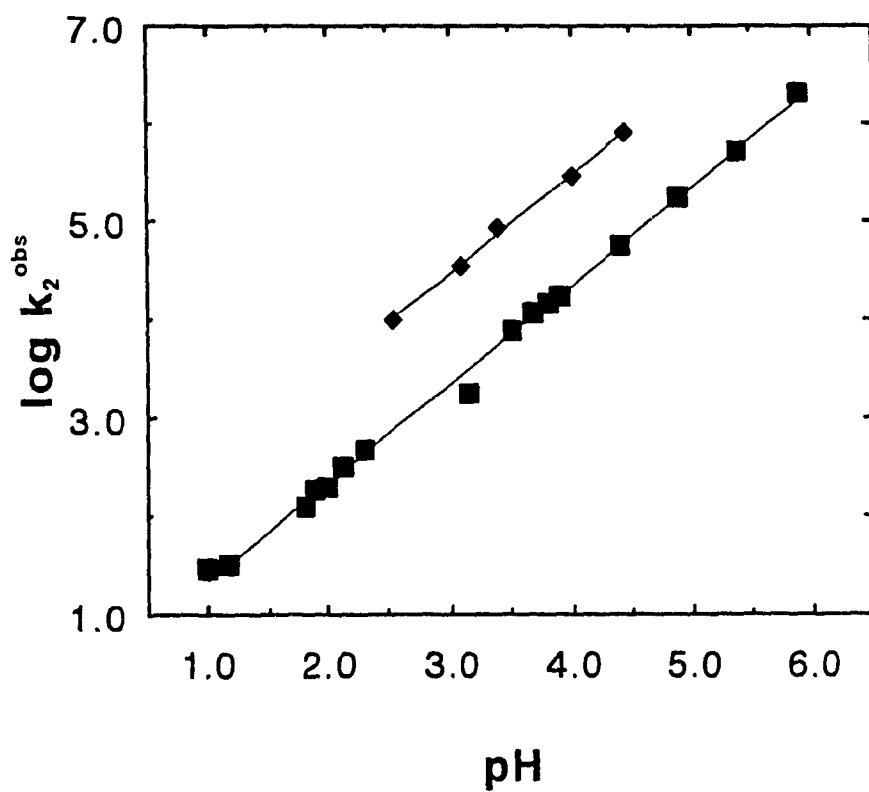
Under the conditions of this study, the apparent second-order rate constant for the reaction of bromine with the substrate is the weighted sum of the two contributions from the reaction with Br_2 (k_B) and Br_3^- (k_T):

$$k_2^{app} = k_B f_B + k_T f_T \qquad (34)$$

where f_B is the fraction of free bromine and f_T is the fraction of bromine in the form of Br_3^-. The "observed" second-order rate constant of the system is given by:

$$k_2^{obs} = k_2^{app}/f_B = k_B + k_T f_T/f_b$$

$$= k_B + k_T[Br^-]/K \qquad (35)$$

since $f_T/f_B = [Br_3^-]/[Br_2] = [Br^-]/K$, from $K = [Br_2][Br^-]/[Br_3^-]$ for the dissociation:

$$Br_3^- \xrightarrow{\quad K \quad} Br_2 + Br^-. \qquad (36)$$

The equation 34 requires k_2^{obs} to vary linearly with bromide ion concentration, and this is the case (Table XII and Figure 12). Least-squares analysis of the data for pH 3.4 gave the following parameters: slope $= 5.66 \times 10^3$ $M^{-2} s^{-1}$, intercept $= 2.67 \times 10^3$ $M^{-1} s^{-1}$. From this slope and intercept, and after correcting for pH, a value of 5.58 $\times 10^8$ $M^{-1} s^{-1}$ has been obtained for the attack of bromine (k_B) on the substrate and 7.39×10^7 $M^{-1} s^{-1}$ for the reaction with tribromide ion (k_T). It seems from these values that Br_3^- is about one eighth as reactive as molecular bromine toward 3-hydroxypyridine. Likewise, Tee et al.,[35] found tribromide ion to be less reactive than bromine towards phenoxide ion.

By substituting $k_B = 5.58 \times 10^8$ $M^{-1} s^{-1}$ for the reactivity of bromine, and $k_T = 7.39 \times 10^7$ $M^{-1} s^{-1}$ for reactivity of tribromide ion into equation 34, and taking the dissociation constant (K) of tribromide ion as 0.0625 M for I $= 1.00$ M KBr,[35] the

apparent second order rate constant for the reaction of bromine with the anion of 3-hydroxypyridine has been determined to be: $5.58 \times 10^8 + (7.39 \times 10^7)(1.0)/0.0625 = 1.74 \times 10^9$ M^{-1} s^{-1}. This value agrees appreciably well with the value of 1.39×10^9 M^{-1} s^{-1} obtained from pH-rate profile in Figure 1, for reaction in 0.1 M KBr.

In an earlier study Kresge and co-workers[42] reported higher values for attack of Br_3^- $(\text{).$ $\times$ 10^9 M^{-1} s^{-1}) and Br_2 (8.3×10^9 M^{-1} s^{-1}) on the anion of malononitrile. They concluded that reactions of the two species with the substrate are diffusion controlled. Such a conclusion cannot be adopted in the present study, as the k_2' value due to the reactivity of Br_3^- is considerably less than that for a diffusion-controlled reaction. But it is evident that the aggregate k_2' value obtained through bromide ion studies is elevated due to the contribution from the reaction of 1 with Br_3^-.

Bromide ion dependence may also be used to probe the rate limiting step of reactions such as those studied in the present work. Consider, for example, a reaction:

$$SH + Br_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} I + H^+ + Br^- \overset{r.l.s}{\underset{k_2}{\longrightarrow}} P \tag{37}$$
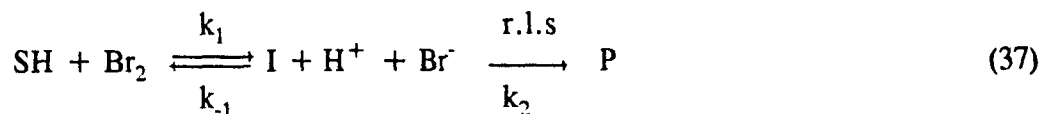
where I is an intermediate. For such a reaction, if the decomposition of the the intermediate is the rate limiting step (r.l.s.), then increasing the concentration of bromide ions ($[Br^-]$), should force the pre-equilibrium to the left. Thus, a bromide ion dependence study should exhibit decreasing k_2^{obs} values with increasing $[Br^-]$, due to a shift in equilibrium. However, results obtained in bromide ion studies show a linear increase in k_2^{obs} with $[Br^-]$, which rules out rate-limiting decomposition of a

reactive intermediate of type shown below.

I
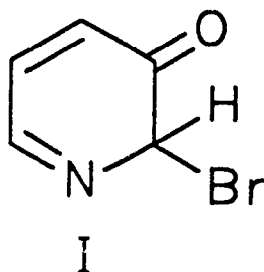
Using a steady state approximation (SSA) the observed second order rate constant for the reaction illustrated above (eq 37) is given by:

$$k_2^{obs} = k_1 k_2/(k_{-1}[H^+][Br^-] + k_2) \tag{38a}$$

But $k_2 << k_{-1}[H^+][Br^-]$. Thus, eq. 38a becomes:

$$k_2^{obs} = k_1 k_2/(k_{-1}[H^+][Br^-]) \tag{38b}$$

Equation 38b is consistent with the linear variation obtained for pH depedences.

Tee and Iyengar[32b] found a totally different scenario when they studied the bromination of phenols. For a reaction:

$$S \xrightarrow[\text{fast}]{Br_2} I \xrightarrow[\text{slow}]{r.l.s.} P \tag{39}$$

they found that they could independently determine the rate of formation of the intermediate, and that for its decomposition. However, as stated earlier, no such intermediate was observed with the 3-hydroxypyridine system. We can therefore conclude that for the present study reaction via molecular bromine is more important, and no long-lived intermediate is involved.

Product studies were carried out under conditions similar to those under which the kinetic data were acquired in order to establish that the monobrominated products were dominant. The studies were performed on a synthetic scale and the r~ ior products were isolated. Particular attention was paid to the question of orientation of bromine attack and the possibility of polybromination.

The isolated products were identified by comparing their spectra with the spectral data of known bromo derivatives of 3-hydroxypyridine, in particular. For these, ^{1}H NMR and mass spectroscopy techniques proved most useful in the analyses of the products. It should be noted that no attempts were made to improve on the yields of the products reported, and the yields given are those of purified products.

Extensive product studies were carried out on the bromination of 3-hydroxy-pyridine (1), in various media: 0.1 M aqueous KBr, glacial acetic acid, an aqueous acetate buffer of pH 4.86, and in alkaline medium (10% aqueous NaOH). In all cases reaction of equimolar quantities of 1 and bromine in these media gave 2-bromo-3-hydroxypyridine (2) as the major product.

TLC analysis, using an authentic sample of 2 (from Aldrich) as a reference, confirmed that the product was compound 2. The ^{1}H NMR spectrum of the product obtained was identical to that of 2 prepared by a literature procedure (reaction in alkaline medium),[50] and to that given in the Aldrich NMR catalogue.[57] However, mass spectra of the products obtained from the acetate buffer (pH 4.86) and acetic

acid media both indicated a trace of 2,6-dibromo-3-hydroxypyridine (3) as a minor product of the reaction, arising from disubstitution.

Nevertheless, the mass spectra confirmed that the principal product of the bromination reaction is 2, as it showed peaks at m/z 173 and 175, attributable to the molecular ion of compound 2 with the ^{79}Br and ^{81}Br isotopes. Another strong peak observed in the mass spectrum was located at m/z 94, which is consistent with the loss of a bromine atom from the molecular ion, giving a fragment ion $C_5H_4NO^+$ (equivalent to 1-H). There is also a large peak at m/z = 93, probably due to $C_5H_3NO^+$. These daughter ions undergo further fragmentation, similar to that seen in the mass spectrum of 3-hydroxypyridine, to give abundant fragments at m/z 65,66, and 67. These may be formulated as the pyrrole-like and furan-like ions, arising from the loss of carbon monoxide and hydrogen cyanide from the ions at m/z = 93 and 94.[43] These fragmentations for compound 2 are outlined in Scheme VII.

Bromination of 2-bromo-3-hydroxypyridine 2 (Aldrich) in an aqueous acetate buffer at pH 4.86 (I = 0.1 M KBr) gave the 2,6-dibromo derivative 3, as did reaction in 10% aqueous sodium hydroxide solution. The melting point and ^{1}H NMR spectrum of the product were consistent with that of 3 given in literature.[50,57] Mass spectral analysis provided conclusive evidence that the only significant product obtained was compound 3. The molecular ion showed three peaks, consistent with the possible isotopic mixtures of the two bromines in 3, corresponding to m/z 251, 253, and 255.

Scheme VII

$$\text{[structure: 2-bromo-3-hydroxypyridine radical cation]} \quad m/z \ 173, \ 175$$

$$\xrightarrow{-Br\cdot} \quad C_5H_4NO^+ \quad m/z = 94 \xrightarrow{-CO} C_4H_4N^+ \quad m/z = 66$$

$$\xrightarrow{-HCN} C_4H_3O^+ \quad m/z = 67$$

$$\xrightarrow{-HBr} \quad C_5H_3NO^{+\cdot} \quad m/z = 93 \xrightarrow{-CO} C_4H_3N^{+\cdot} \quad m/z = 66$$

$$\xrightarrow{-HCN} C_4H_2O^{+\cdot} \quad m/z = 66$$
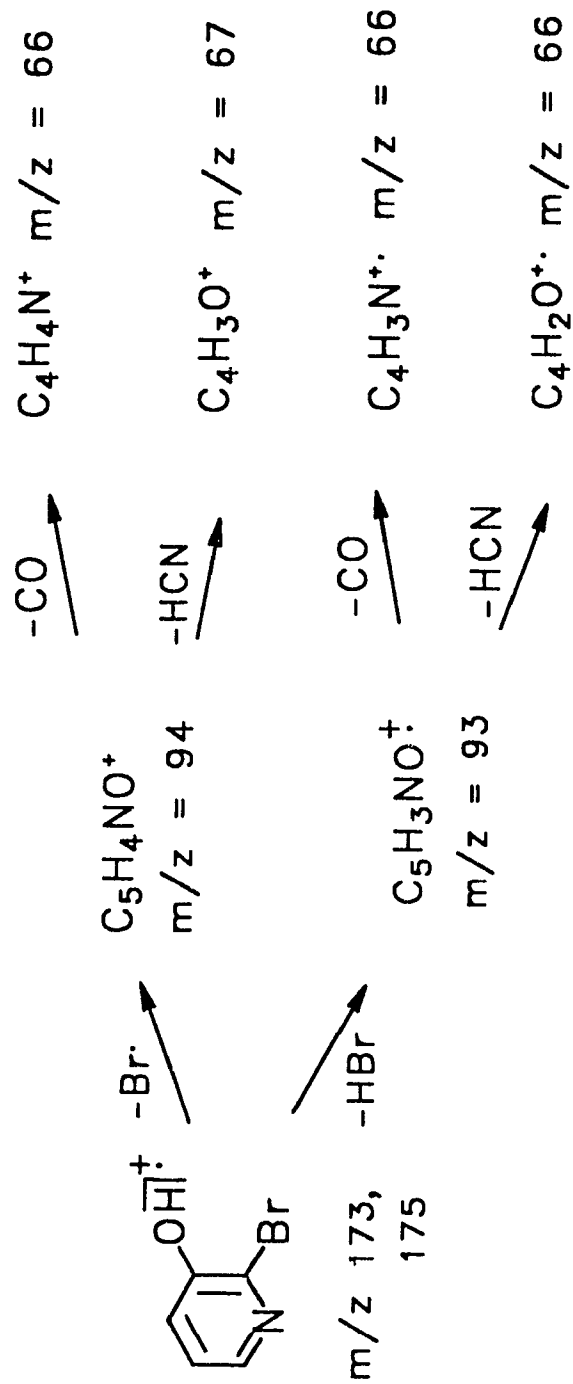
Mass spectral fragmentation pathway of 2-bromo-3-hydroxypyridine

The molecular ions of 3 lose a bromine atom (^{79}Br or ^{81}Br)to give fragment ions of m/z 172 and 174 ($C_5H_3NOBr^+$). The further loss of bromine from these two ions gives a modest peak at m/z = 93. The mass spectrum of 3 also showed peaks corresponding to the pyrrole- and furan-like ions around m/z 65, similar to those seen in the mass spectrum of the monobromo compound, 2. The ^{1}H NMR, and the mass spectral data for compounds 2 and 3 is summarized in Tables XIV and XV, respectively.

Product studies were not carried out for the bromination of 2,6-dibromo-3-hydroxypyridine because the tribromo derivative had been proven to be substituted at the 2,4, and 6 positions.[24] This conclusion was reached when a reaction of 5-bromo-3-hydroxypyridine with excess bromine water gave as product the 2,4,5,6-tetra-bromo derivative. Also a reaction of 3-hydroxypyridine with bromine water at room temperature gives 2,4,6-tribromo product.[5a]

A reaction of equimolar quantities of bromine and 3-hydroxypyridine-N-oxide (6) in aqueous 10% NaOH solution gave exclusively one product whose melting point was close to that of 2-bromo-3-hydroxypyridine-N-oxide (6a) given in literature.[56] Further proof that the product was in fact 6a was obtained by reducing the latter in Fe/CH$_3$COOH to give a product whose melting point and ^{1}H NMR spectrum agreed with those of 2-bromo-3-hydroxypyridine, 2.

Bromination of 3-hydroxy-2-picolinic acid (8), in equimolar quantities, in alkaline solution also gave mainly compound 2. TLC and NMR analyses were consistent with 2 but the mass spectrum of the product did however indicate a trace

Table XIV. ^{1}H NMR spectra of the bromo-3-hydroxy-pyridines.[a]

Compound	Substituent				Chemical Shift[b] (multiplicity)		
	R^2	R^4	R^5	R^6	R^4	R^5	R^6
2	Br	H	H	H	7.2(d)	7.3(d)	7.8(t)
3	Br	H	H	Br	7.32(d)	7.55(d)	

[a] In DMSO-d_6 as solvent. NMR analyses were done by Mr. Liu Zhi and Ms. Ning Qing. Chemical shifts are in p.p.m. d = doublet; t = triplet.

Table XV. Mass spectral data for the fragmentation of 2 and 3[a]

Substrate	Precursor	Fragment Lost	Transition (m/z)
2	C_5H_4NOBr	Br	173 ⟶ 94
	C_5H_4NO	HCN	94 ⟶ 67
		CO	94 ⟶ 66
3	$C_5H_3NOBr_2$	Br	251 ⟶ 172
	C_5H_3NOBr	Br	172 ⟶ 93

[a] Mass spectral analyses were graciously performed by Dr. R. Rye.

of 2,6-dibromo-3-hydroxypyridine (3). In any case, from the major product obtained, it can be concluded that when **8** is brominated in alkaline medium it undergoes bromodecarboxylation (also a form of electrophilic aromatic substitution) to give compound **2**, probably as shown in Scheme VIII.

<u>Scheme VIII</u>. Decarboxylation of 3-hydroxy-2-picolinic acid upon bromination.
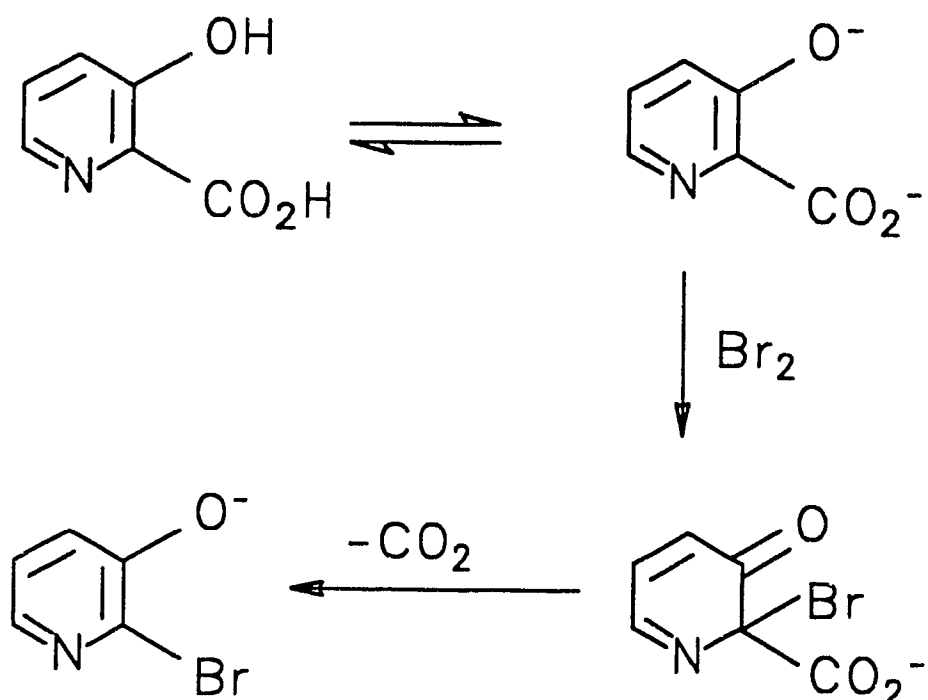
Results from the product studies agree with literature[26,50] that C-2 is the most reactive site on the 3-hydroxypyridine system, followed by C-6 (Scheme IX). Also we can now establish that under the conditions of the present study, the major product from the bromination reaction of equimolar quantities, was the monobrominated product in each case.

Scheme IX. Polybromination of 3-hydroxypyridine.
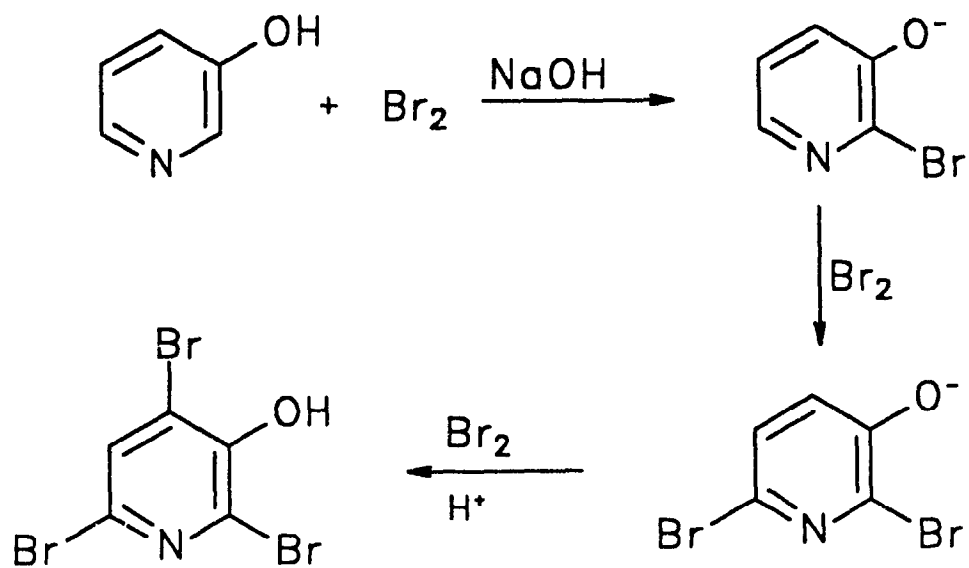
Pyridine undergoes electrophilic substitution only under forcing conditions. For example, bromination of pyridine can only be accomplished in the vapour phase at 200°, where free-radical mechanism may operate.[24] In 3-hydroxypyridine, however, the strongly activating hydroxyl group makes this compound much more reactive than pyridine.

By substituting the hydrogen(s) on the 3-hydroxypyridine ring system with activating or deactivating groups, and also introducing substituents on the ring nitrogen, results consistent with the effects of these groups on an aromatic ring have been obtained, as discussed below. In Table XIV are listed the reactivities of the substrates studied, arranged in increasing order on the basis of the intercepts of plots of log k_2^{obs} vs pH.

3-Hydroxypyridine (1)

The k_2 value for 1 has been calculated to be $1.9 \times 10^5 M^{-1} s^{-1}$ which is of the same order with that of phenol $(4.1 \times 10^5 M^{-1} s^{-1})$.[35] Likewise, the rate coefficient for the reaction of 3-hydroxypyridine anion (k_2') is of the same order $(1.4 \times 10^9 M^{-1} s^{-1})$ as that for the phenoxide ion[35] and the anions of 2- and 4-pyridone,[18b,c] all of which are close to the diffusion-controlled limit. The k_2 values show that phenol is two times more reactive than 3-hydroxypyridine. This modest reduction in reactivity shown by 1 is inconsistent with reaction via the hydroxy tautomer of 1; the

deactivating effect of the ring nitrogen in 3-hydroxypyridine should lead to a reactivity like that of 3-nitrophenol, for which $k_2 \approx 110$ M^{-1} s^{-1}.[35] On the other hand, reaction via the zwitterionic tautomer of 1, which is a phenoxide ion with $=NH^+$- in the ring, could well have the observed reactivity.

Table XIV. Reactivity of substrates based on the intercepts of the pH-rate profiles

Substrate	Intercept
3-Hydroxy-2-picolinic acid (8)	-0.646
3-Hydroxypyridine (1)	0.345
2,6-dibromo-3-hydroxypyridine (3)	0.709
2-Bromo-3-hydroxypyridine (2)	0.976
N-Ethyl-3-hydrcxypyridinium bromide (5)	1.05
6-Methyl-3-hydroxypyridine (7)	1.16
N-Benzyl-3-hydroxypyridinium chloride (4)	1.21
3-Hydroxypyridine N-oxide (6)	1.98

Bromo Derivatives (2 and 3)

The bromo derivatives were found to be more reactive than the parent compound 1. The increased reactivity of these substrates may be attributed to the

expected lowering of the pK_a of the hydroxyl (or NH) group by the negative inductive effect of the bromine atom(s) in 2 and 3. In addition however, the bromo substituent is a weakly deactivating group in electrophilic substitution and is therefore responsible for the relative decreased reactivity of compounds 2 and 3 as compared to the N-substituted derivatives (see later).

6-Methyl-3-hydroxypyridine (7)

Enhanced rate constants were obtained for the bromination of this compound. This is not surprising because the positive inductive effect of the methyl substituent activates the pyridinium ring towards electrophilic substitution. This activating effect seems to override the pK_a raising effect of the methyl substituent which should be quite pronounced at the para position. Evidence for the activating effect of the methyl substituent has been obtained from H-D exchange studies,[26a] where a methyl group on the 3-hydroxypyridine ring system accelerates exchange at the two most reactive sites of the ring (2- and 6-positions).

3-Hydroxy-2-picolinic acid (8)

Compound 8 was found to be the least reactive of the substrates studied. A number of reasons can be put forward to rationalize this observation. Product studies have clearly indicated that C-2 is the most reactive site of the zwitterionic form of 3-hydroxypyridine. Thus, in 8 the carboxyl group at C-2 temporarily blocks the most reactive site of the ring, thus accounting for the reduced rates.

Acidity dependence studies have also established that at higher pH the parent compound (1) reacts via its anion. In compound 8, however, the pK_a of the phenolic OH is exceptionally high (10.76, as compared to 8.72 for 1). This elevation in pK_a arises from intramolecular hydrogen bond formation between the carboxylate group ($pK_a = 5.17$) and the adjacent phenolic hydroxyl group in 8A, similar to the situation in salicylate anions.[33a]

8A
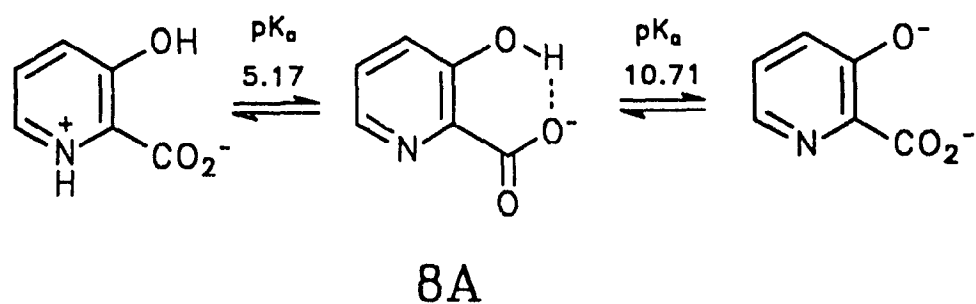
Concerning the parent acid 8, it should be noted that the $-CO_2H$ substituent is a deactivating group which should also decrease the reactivity towards bromine.

N-Ethyl and N-Benzyl Substituted Derivatives (4 and 5)

These substrates showed slightly increased reactivities, compared to compound 1 and the bromo derivatives 2 and 3. The reason for this is most likely due to the inductive effect of the positively charged ring nitrogen which should facilitate ionization of the hydroxy group ($pK_a \approx 4.96$). The rate profiles for the N-alkyl derivatives are virtually superimposable, as shown in Figure 3, reflecting a similar degree of reactivity for both substrates.

3-Hydroxypyridine N-oxide (6)

3-Hydroxypyridine N-oxide was found to be the most reactive of the substrates studied. This enhanced reactivity can be explained by the electronic effects that come into play for this compound. The characteristic $N^+\text{-}O^-$ functionality in pyridine N-oxides can act as both a π-electron donor and a π-electron acceptor, depending on the circumstances:[1,2]
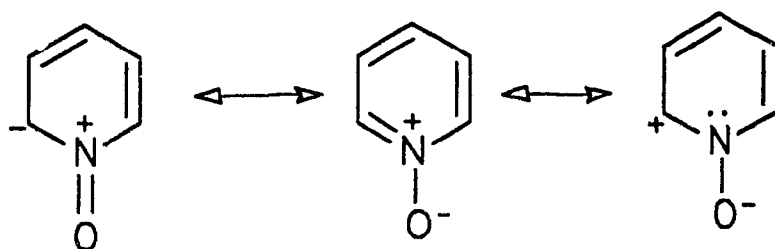
In the case of 6, it seems likely that the oxygen atom donates its π-electrons to the ring thus enhancing the reactivity towards bromine. Furthermore, the positively charged nitrogen of the ring facilitates ionization of the hydroxyl group by an inductive effect. This is reflected in the high acidity of 6 (pK_a = 6.4),[44] as compared to that of 1 (pK_a = 8.72). Therefore, considerably more of the anion of 6 is available, reacting at close to the diffusion-controlled limit (see Table VI, p 47).

83

II.6 Orientation and Polybromination

One of the objectives of this work was to determine the position in 3-hydroxy-pyridine that is most reactive towards bromine, and also to investigate the occurence of polybromination under the kinetic conditions. The hydroxyl group in aromatic systems is a very powerful activating substituent for electrophilic substitution and also a powerful *ortho-para* director. Bearing this in mind, the electrophile has three possible sites of attack of 3-hydroxypyridine: the two ortho positions (2- & 4-) and the para position (6-). Correspondingly, with sufficient bromine, 3-hydroxypyridine **1** undergoes polybromination to yield the 2,4,6-tribromo derivative.[1,2,5b]

In two earlier studies, Lezina *et al.*[26] investigated the acid- and base-catalyzed H-D exchange in 3-hydroxypyridine and some of its analogs at 145°. By monitoring the reactions with ^{1}H NMR spectroscopy, they found that the most reactive site on the 3-hydroxypyridine ring was the 2-position in both cases. Also, as pointed out in the Introduction, other electrophiles preferentially attack the 2-position.

In the present work the results obtained agree with those of earlier studies as far as orientation is concerned, as discussed under product studies. Clark and Deady[50] had earlier used this sequential reactivity of the ring positions to isolate 2-bromo-3-hydroxypyridine **2** and 2,6-dibromo-3-hydroxypyridine **3** which they later used to prepare a variety of other compounds.

The extent of polybromination during the kinetic studies was eliminated or minimized by using a ten fold (or more) excess of substrate over biomine. This was shown to be feasible since pH-dependence studies of the bromination of the 2-bromo

and 2,6-dibromo derivatives (**2** and **3**) ascertained that these compounds are only 4.3 times and 2.3 times, respectively, more reactive than **1** under the reaction conditions. In keeping with these figures, no evidence of the tribromination of **1** was observed in this study, although a small amount of dibromination was found.

Since the existence of the potential reactive forms of the 3-hydroxypyridine system depends on the pH of the medium, product studies were carried out in basic medium, where the anionic form exists exclusively, to test the reactivity-selectivity principle, and also to see if at this high pH polybromination could be observed. Even in this medium, only a trace of the dibromo product was obtained and C-2 was still the most reactive site on the ring. This implies that the rate constants obtained from the kinetic studies were in fact for the monobromination of the substrates studied.

CONCLUSION

The rates of aqueous bromination of 3-hydroxypyridine (1) and a number of its derivatives have been studied. This is an extension of earlier studies carried out in this laboratory on the bromination of the other two hydroxypyridines (2- and 4-hydroxypyridines),[18b,c] and phenols.[35]

The 3-hydroxypyridine/zwitterion tautomeric system (1a ⟶ 1b, p 7) reacts with bromine faster than pyridine, but less so than phenol. From pH-dependence studies it has been established that the reactive neutral form of 3-hydroxypyridine is actually the zwitterionic species. At higher pH the substrate reacts as the anion, with a rate constant of 1.4×10^9, which is close to the diffusion-controlled limit.

The bromination reaction of 1 and a number of its derivatives has also been found to be catalysed by carboxylate anions. This buffer catalysis seem to arise from the abstraction of the phenolic or azonium proton at the same time as electrophilic attack by molecular bromine, similar to the situation with phenol.[33c]

In the present work, the effect of bromide ion concentration on the reaction of bromine and 3-hydroxypyridine (1) was also investigated. At high bromide ion concentration, 1 reacts with tribromide ion as well as with molecular bromine. Bromide ion dependence studies however did eliminate the possible reversible formation of a long-lived intermediate in the reaction of bromine with 1.

Product studies on the bromination of several 3-hydroxypyridines suggest that equimolar quantities of substrate and bromine react to give exclusively the monobrominated product, with substitution occuring in the order C-2 > C-6 > C-4.

The differences in positional react'vities are such that the formation of mixtures of isomers was not observed. These results agree with earlier studies of the reactivities of the various sites of the 3-hydroxypyridine ring system in electrophilic bromination,[50,56] carried out in a different way.

Of the three possible hydroxypyridines (2-, 3-, and 4-hydroxypyridine), results obtained for the reaction of bromine with the 3-isomer seem to parallel that with phenol most closely, especially as regards buffer catalysis. This parallelism occurs even though the hydroxy form of **1** is not the reactive neutral species. It arises because the zwitterionic tautomer **(1b)**, which *is* the reactive form, behaves as a deactivated phenoxide ion.

III.1 Materials

Table XVII. Sources and melting points of compounds studied

Compound	Name	M.Pt., °C[a]
1	3-Hydroxypyridine[b,c]	126-129
2	2-Bromo-3-hydroxypyridine[b,d]	185-188
3	2,6-Dibromo-3-hydroxypyridine[b,d]	162-163
4	N-Benzyl-3-hydroxypyridinium chloride[b,e]	162-164
5	N-Ethyl-3-hydroxypyridinium bromide[b,e]	104-108
6	3-Hydroxypyridine-N-oxide[b,e]	190-192
7	3-Hydroxy-6-methylpyridine[b,e]	168-170
8	3-Hydroxy-2-picolonic acid[b,e]	219-221

[a] Literature values.

[b] Obtained from Aldrich Chemical Company.

[c] Recrystallized from water before use.

[d] Also prepared using literature procedures[50]

[e] Used as received from commercial source.

III.2 Apparatus

The kinetics of bromination were monitored using an Aminco-Morrow Stopped-flow accessory[51,52] attached to an Aminco DW-2 UV-Visible

spectrophotometer, operating in the dual wavelength mode. The chopper speed was set as a function of the half-life of the reaction: normally it was run at 250 Hz, but the kinetic chopper (1 kHz) was used for reactions with half-lives less than one second.

The stopped-flow experiments involved mixing equal volumes of the substrate solution in a selected pH/buffer medium containing KBr (A & C American Chemicals) in syringe #1, with a bromine solution (Aldrich) in aqueous KBr in syringe #2. The two solutions were driven together under nitrogen pressure into a 10 mm long observation cell, maintained at $25.0 \pm 0.1\,^\circ C$ by circulating water from a thermostatted bath.

The progress of the reaction could be observed on an oscilloscope and/or on the computer attached to the spectrophotometer. The latter puts out a voltage proportional to absorbance (2V/abs unit) which was acquired in two different ways. During the initial phases of the project, data acquisition used an Apple II+ microcomputer with a Cyborg Isaac 91a A/D conversion system. Later on, this set-up was superceded by an Olivetti M24 microcomputer with a Metrabyte Dash 16F A/D card. Software for both these systems was written by Dr. O.S. Tee and, more recently, by Mr. T.A. Gadosy.

III.3. Kinetic Solutions

For pH dependence studies of reactions conducted at pH < 2.2, appropriate dilutions of standard 1 M hydrochloric acid (A & C American Chemicals) were used

to prepare substrate solutions. For higher pH's, freshly prepared buffer solutions were made prior to use, following the recipes given by Perrin.[53]

Substrate solutions were prepared by dilution of appropriate aliquots of a stock 0.1 M substrate solution into the desired medium, pH or buffer solutions, all containing 0.1 M aqueous KBr. For the bromo derivatives, which are less soluble in water, stock solutions were prepared in HPLC grade methanol (Fisher) and small volumes of these were diluted with the desired media. Similarly, 0.1 M bromine stock solutions were freshly prepared by weight in aqueous 0.1 M KBr and diluted appropriately.

Both the substrate and reagent (bromine) solution dilutions were made just before the kinetics were performed. For kinetic experiments, these solutions were mixed (1:1) in a stopped flow apparatus (I = 0.1 M KBr). The exact pHs of the substrate solutions were determined using a Corning Digital 110 pH meter calibrated with appropriate standards.

For buffer catalysis studies, stock 200 - 250 mM aqueous buffer solutions were prepared using the Henderson-Hasselbach equation:[54]

$$pH = pK_a + \log [A^-]/[HA] \qquad (35)$$

where pK_a is that of the buffer acid used. From these stock solutions, buffers of lower concentrations (25 - 100 mM) were subsequently prepared in 0.5 M KBr (to maintain a high, fixed ionic strength). At lower pHs, chloroacetate buffers ($pK_a = 2.74$) were used, and acetate buffers ($pK_a = 4.65$) were employed for the higher pH buffer studies. The substrate and bromine concentrations indicated in the tables and

text refer to the final concentrations *after* mixing the reaction solution in the stopped-flow apparatus.

III.4 Kinetic Procedure and Data Acquisition

The rates of reactions were determined by monitoring the disappearance of bromine using an stopped-flow apparatus + Aminco DW-2 spectrophotometer, as outlined earlier. Normally, bromination reactions are monitored at the wavelength maximum of tribromide ion at 265 nm.[55] In this study, the sample monochromator was set between 260 - 267 nm, with the reference monochromator at 310 - 320 nm, where little or no absorbance change occurs.

All reactions were carried out under pseudo first-order conditions, using a ten-fold (or more) excess of substrate over bromine, after 1:1 mixing in the stopped-flow apparatus. The concentration of the reactants were reduced for the fastest reactions. (For specific concentrations, see tables).

The decrease in absorbance exhibited good first order behaviour and from the decay traces, pseudo first-order rate constants (k_1^{obs}) were calculated from least-squares analysis $\ln(A - A_\infty)$ vs time for data covering about 90% reaction (3-4 half-lives), with A_∞ being obtained after 10 half-lives. Good to excellent straight lines $(r \geq 0.999)$ were obtained, and the reported rate constants are the averages of 4 - 6 determinations. First order rate constants (k_1^{obs}) were then converted to second-order rate constants (k_2^{obs}) by correcting for the substrate concentration and the fraction of free bromine in the equilibrium with tribromide ion (see Appendix). For the latter,

the dissociation constant of tribromide ion was taken as 0.0562 (at I = 0.1 M) and 0.0625 (at I = 1.0 M).[35]

III.5 Substrate synthesis

[A] *Synthesis of 2-Bromo-3-hydroxypyridine* (2)[50]

A solution of bromine (8.5g, 0.055 mol) in 50 ml 10% aqueous NaOH (A & C American Chemicals) was added dropwise, with stirring, to a solution of 3-hydroxypyridine (5g, 0.053 mol) in 50ml 10% aqueous NaOH. After the addition was complete, the mixture was cooled and neutralised with conc. HCl. After letting the mixture to stand overnight, the crude precipitate obtained was recrystallized from water to give 2 (2.6g, 28.6%), m.p. 185-187° (*Cf.* lit 184 - 186°,[50] 185 - 186°[56]). The ^{1}H NMR spectrum of the product was consistent with literature, and with that of material from Aldrich.[50,57] Likewise, the mass spectra of these materials were essentially identical. ^{1}H NMR analysis for this sample and others were performed using a Bruker WP-80Sy NMR Spectrometer (80.13 MHz). An LKᴗ 9000 mass spectrometer with solid inlet probe was used for mass spectral analyses of product samples.

[B] *Synthesis of 2,6-Dibromo-3-hydroxypyridine* (3)[50]

An ice-cold solution of bromine (25g, 0.16 mol) in 160 ml 10% aqueous sodium hydroxide was added, with stirring, over 15 minutes, to an ice-cold solution of 3-hydroxypyridine (5g, 0.053 mol) in 55 ml 10% aqueous NaOH. The solution was

stirred at 0° for 30 minutes and then allowed to stand at room temperature for 2 hours. A small amount of white solid was filtered off, the filtrate was cooled to 0°, and conc. HCl was added until the mixture had a pH of 1 (pH paper). The precipitated solid was filtered off, washed with water, dried and recrystallized from carbon tetrachloride (Fisher) to give 3 (3.51g, 26.5%), m.p. 160-162° (*Cf* lit 162-163°[50]). ^{1}H NMR and mass spectra agreed with literature,[57] and with the spectra of commercial material (bought later).

III.6 Product Studies

[A] *Bromination of 3-Hydroxypyridine* (**1**)[58]

(i) In Water

With stirring, bromine (1.58g, 0.0098 mol) in 20 ml 0.1 M KBr was added to 3-hydroxypyridine (1g, 0.01 mol) in 10 ml 0.1 M KBr. The mixture was further stirred for an hour and allowed to stand overnight. The deposited crystals were filtered and recrystallized from water to give (**2**) (0.52g, 28.4%), m.p. 182 - 183 (Cf. lit 184 - 186). ^{1}H NMR spectrum agreed with literature[57] and with that of authentic sample.

(ii) In Acetic Acid

The same quantities as in (i) above were used, but this time the reactants were dissolved in acetic acid. The resulting mixture was stirred for an hour and allowed to stand overnight. The volume of the mixture was reduced considerably and the resulting solution was allowed to stand overnight. The crystals formed were

filtered off and recrystallized from water to give compound (2) 0.3g (16.5%). ^{1}H NMR was consistent with literature, and TLC analysis (dichloromethane solvent system) using reagent grade 2 (Aldrich) as reference, further confirmed that the product obtained was exclusively 2. Commercial grade TLC plates (silica gel G on plastic plates) were employed for analysis.

(iii) In Acetate Buffer, pH 4.86

A solution of 3-hydroxypyridine (2g, 0.02 mol) in 20 ml acetate buffer (I = 0.1 M KBr), pH 4.86 was treated dropwise with stirring, with bromine (3.1g 0.019 mol) in 30 ml acetate buffer (I = 0.1 M KBr). The reaction mixture was stirred for an additional one hour and allowed to stand overnight. The crystals obtained were filtered and recrystallized from water to yield 2-bromo-3-hydroxypyridine 2 (0.45g, 12.3%). ^{1}H NMR and mass spectral data of the product were consistent with the structure of 2.

(iv) In Aqueous Alkaline Solution[56]

A solution of 3-hydroxypyridine (2g, 0.02 mol) in 20 ml 10% aqeous NaOH was treated dropwise with stirring during 30 min. with bromine (3.1g, 0.019 mol) in 20 ml 10% NaOH. The resulting mixture was further stirred for 1 hr and allowed to stand overnight. It was then acidified dropwise under cooling with conc. HCl and allowed to stand for several hours. This afforded a cake of product which was recrystallized from water to give 2 (0.8g, 22.7%). The ^{1}H NMR spectrum of the

product was consistent with literature.[57] The mass spectrum agreed with authentic 2-bromo-3-hydroxypyridine (2), but it also showed a trace of 2,6-dibromo-3-hydroypyridine (3), which is a possible side product.

[B] *Bromination of 2-Bromo-3-hydroxypyridine* (2)[58]

(i) In Acetate Buffer, pH 4.86

A solution of 2-bromo-3-hydroxypyridine (1.75g, 0.01 mol) in acetate buffer (I = 0.1 M KBr), pH 4.86, was treated dropwise, with stirring, with bromine (2.48g, 0.016 mol) in 30 ml acetate buffer (I = 1 M KBr). The reaction mixture was stirred for one hour and allowed to stand overnight. The crystals formed were filtered off and recrystallized from water to give 2,6-dibromo-3-hydroxypyridine (3) 0.35g(13.7%) m.p. 159 - 161°, 160 - 161° after overnight vacuum drying (*Cf* lit 160 - 162[50]). The ^{1}H NMR and mass spectra agreed with those of authentic material.

(ii) In Aqueous Alkaline[56]

2-Bromo-3-hydroxypyridine (1.75g, 0.01 mol) in 20 ml 10% aqueous NaOH was treated dropwise during 30 min. with bromine (2.48g, 0.016 mol) in 20 ml 10% aqueous NaOH. The reaction mixture was stirred for another one hour after which it was left to stand overnight. The mixture was then acidified dropwise under cooling with conc. HCl and allowed to stand for several hours. The crude product obtained was recrystallized from water to yield 3 (1.1g, 43.4%), m.p. 160 - 161°. ^{1}H NMR was consistent with literature.

[C] *Bromination of 3-Hydroxypyridine N-Oxide (6) in Aqueous NaOH*

A solution of 3-hydroxypyridine N-oxide (6) (2g, 0.18 mol) in 20 ml 10%

aqueous NaOH was treated dropwise during 30 min. with bromine (3.1g, 0.019 mol)

in 20ml 10% aqueous NaOH. After stirring for one hour the reaction mixture was

then acidified under cooling with conc. HCl which was added dropwise. The product

obtained was filtered and recrystallized from water to give 2-bromo-3-hydroxypyridine

N-oxide (6a) 1.56g (45.3%), , m.p. 175 - 177 (Cf. lit 178 - 180).[56] Further proof of the

structure of the product was obtained by reducing compound 6a with Fe/AcOH to

2-bromo-3-hydroxypyridine (2) (see below).

[D] *Reduction of "2-Bromo-3-hydroxypyridine N-Oxide " (6a)*[56]

"2-Bromo-3-hydroxypyridine N-oxide" (1g, 0.005 mol), from the previous

experiment, in 20 ml acetic acid was reduced during 1 hr with Fe dust (0.4g, 0.007

mol). The mixture was neutralized to pH 4 with $(NH_4)_2CO_3$ (Aldrich), and then

diluted with 12 ml water. The slurry obtained was filtered under suction to remove

any unreacted Fe dust. The resulting solution was then extracted with several

portions of 10 ml Et_2O (Anachemia). The combined ether extracts was evaporated

and the product obtained recrystallized from water to give 2, 0.31g (33.8%). NMR

analysis was consistent with the structure of 2. Fe dust for this experiment was

obtained from Fisher Scientific.

[E]   *Bromination of 3-Hydroxy-2-picolinic Acid (8) in aq. NaOH*[56]

A solution of 3-hydroxypicolinic acid (**8**) (2.7g, 0.019 mol) in 20 ml of 10%

aqueous NaOH was treated dropwise during 30 min. with bromine (3.1g, 0.019 mol).

The reaction mixture was stirred for an hour then allowed to stand overnight. The

mixture was acidified dropwise under cooling with conc. HCl. The crude product

obtained was recrystallized   from water and the final product (47% yield) was

characterized by TLC, NMR, and its mass spectrum. TLC analysis of the product

obtained gave principally one intense spot which agreed well with a similar spot for

authentic 2-bromo-3-hydroxypyridine (**2**), used as reference. Mass spectral analysis

further confirmed that the product obtained was principally (**2**), although it also

revealed the a trace of 2,6-dibromo-3-hydroxypyridine, arising from disubstitution.

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V.1 Computer Programs

The *NewIst* program (on the Apple II+ or on the Olivetti M24) was used to calculate first order rate constants from the absorbance data. This program treats the data in three different ways, for comparative purposes: Guggenheim, Swinbourne, and Normal methods.[58] The Normal analysis method uses the observed A_∞ (obtained after 10 half-lives) or the value estimated by the Swinbourne method. Wherever possible the observed A_∞ was used. The computer programs were written in Basic by Dr. O.S. Tee.

For the analyses of pH-rate profiles and other k^{obs} - concentration data customized software, written in Pascal by Mr. Bryan Takasaki, was used initially. For the thesis, the commercial software *SlideWrite Plus*™ from Advanced Graphics Software, Inc. was used, and chemical equations and reaction schemes were drawn using *PLT* version 5.0.

V.2 Treatment Of Kinetic Data

First-order rate constants were calculated based on the following approach. For a first order reaction

$$B \longrightarrow P \tag{1}$$

the rate may be represented as

$$d[B]/dt = k_1[B] \tag{2}$$

For an initial concentration b, and reduced concentration $(b - x)$ at time t,

considering that $[P] = x$, integration of equation 2 gives:

$$\ln b/(b - x) = k_1 t \tag{3}$$

where k_1 is the first order rate constant (normal units s^{-1}).

As stated earlier, the aqueous bromination reactions were monitored as pseudo-first-order disappearance of bromine, using a ten-fold or more excess of substrate over the concentration of bromine. The progress of such a reaction can be monitored spectrophotometrically if the Beer-Lambert law is obeyed. This procedure has been employed in previous studies by Tee and co-workers.[33,35,55,58] First order rate constants were evaluated using least-square analysis for data covering 3-4 half lives ($\approx 90\%$ reaction) .

V. 3 Derivation of second order rate constant

$$\text{For the reaction} \quad S + Br_2 \longrightarrow P \tag{4}$$

$$\text{rate} = -d[Br_2]/dt = k_1^{obs} [Br_2]_t \tag{5a}$$

$$= k_2^{obs} [S]_o[Br_2] \tag{5b}$$

$$k_2^{obs} = k_1^{obs} [Br]_t/[S]_o[Br_2] \tag{6}$$

where $[S]_o$ = concentration of substrate; $[Br]_t$ = total bromine concentration.

Under the conditions that the kinetic experiments were carried out (at least a tenfold excess of substrate over bromine), the observed first-order rate constant k_1^{obs} is proportional to $([S]_o-[Br_2]_o)$, the concentration of substrate that remains constant during the reaction.[35,55]

Therefore, equation 6 becomes:

$$k_2^{obs} = k_1^{obs}[Br_2]_t/([S]_o - [Br_2]_o)[Br_2] \tag{7}$$

In aqueous KBr solution the following equilibrium is established:

$$Br_3^- \overset{K}{\rightleftharpoons} Br_2 + Br^- \tag{8}$$

$$K = [Br_2][Br^-]/[Br_3^-]; \quad K/[Br^-] = [Br_2]/[Br_3^-] \tag{9}$$

$$[Br_2]_t = [Br_2] + [Br_3^-] \tag{10}$$

$$f_B = [Br_2]/[Br_2]_t = [Br_2]/([Br_2] + [Br_3^-]) = K/(K + [Br^-]) \tag{11}$$

where f_B is the fraction of free bromine.

Thus,
$$k_2^{obs} = k_1^{obs}/([S]_o - [Br_2]_o)f_B \tag{12a}$$

$$= k_1^{obs} (K + [Br^-])/([S]_o - [Br_2]_o)K \tag{12b}$$

from equation 7 above.

V.4 Derivation of f_A and f_{HA}

For a general buffer acid (HA), the following equilibrium is established in solution.
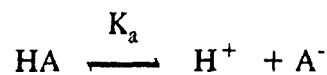
$$HA \overset{K_a}{\longrightarrow} H^+ + A^-$$

where K_a is the dissociation constant of the buffer acid used.

$$[HA]_t = [HA] + [A^-] \tag{13}$$

$[HA]_t$ is the total concentration of the buffer acid.

Dividing eq. 13 by $[A^-]$, gives:

$$[HA]_t/[A^-] = ([HA] + [A^-])/[A^-] = [HA]/[A^-] + 1 \tag{14}$$

But
$$K_a = [H^+][A^-]/[HA]$$

Thus, eq 14 becomes

$$[HA]_t/[A^-] = ([H^+]/K_a + 1) = ([H^+] + K_a)/K_a$$

Thus, $\quad f_A = [A^-]/[HA]_t = K_a/(K_a + [H^+])$ $\qquad$ (15)

and, similarly,

$$f_{HA} = [HA]/[HA]_t = [H^+]/(K_a + [H^+]) \qquad (16)$$

where f_A and f_{HA} are the fractions of the basic and acidic components of the buffer

used, respectively.