# Peroxomonophosphoric Acid Oxidations. VI.[1] Kinetics and Mechanism of Oxidation of 3-Aminopyridine

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The oxidation of 3-aminopyridine to 3,3′-azoxypyridine by peroxomonophosphoric acid (PMPA) is a total second order reaction: first order each in peroxomonophosphoric acid and 3-aminopyridine at constant acidity. The observed pH-rate profile has been rationalized invoking various PMPA species, protonated and unprotonated forms of 3-aminopyridine as the reactive species and their reactivities have been estimated. Interestingly, 2-aminopyridine is not oxidized in the pH-range where the oxidation of 3-aminopyridine is facile.

The oxidation of primary aromatic amines by peroxidic reagents have received considerable attention.[2,3] A general feature of these oxidations is the formation of a tetrahedral intermediate involving nucleophilic attack by the amine lone pair on the electrophilic peroxo bond which undergoes oxidative decomposition to phenylhydroxylamine. Further oxidation of the hydroxylamine derivative leads to nitroso and eventually to the nitro group (Eq. 1).

$$Ar\text{-}NH_2 \rightarrow Ar\text{-}NHOH \rightarrow Ar\text{-}NO \rightarrow Ar\text{-}NO_2 \quad (1)$$

Bimolecular condensation between the products and unreacted amine may also lead to azoxy and azo compounds (Eqs. 2a and 2b).

$$Ar\text{-}NHOH + Ar\text{-}NO \rightarrow Ar\text{-}\overset{\overset{O}{\uparrow}}{N}\text{=}N\text{-}Ar \quad (2a)$$

$$Ar\text{-}N\text{=}O + Ar\text{-}NH_2 \rightarrow Ar\text{-}N\text{=}N\text{-}Ar \quad (2b)$$

We have recently reported that in the oxidation of anthranilic acid,[1] Eq. 2a is the major route leading to 2,2′-azoxybenzenedicarboxylic acid.

In our search for similar systems, we have found that 3-aminopyridine is oxidized to 3,3′-azoxypyridine essentially in quantitative yields.[4] Interestingly 2-aminopyridine did not undergo any oxidation in the pH range where the oxidation of 3-aminopyridine was facile. We wish to report the salient kinetic features of this oxidation.

## Experimental

PMPA was prepared by the acid hydrolysis of $K_4P_2O_8$[5-8] (Eq. 3).

$$H_4P_2O_8 + H_2O \rightarrow H_3PO_5 + H_3PO_4 \quad (3)$$

The rate of hydrolysis Eq. 3 is about two orders of magnitude higher than the hydrolysis of $H_3PO_5$ to $H_2O_2$ (Eq. 4).

$$H_3PO_5 + H_2O \rightarrow H_2O_2 + H_3PO_4 \quad (4)$$

In the entire range of this study, the total amount of $H_2O_2$ was never more than 2% and $H_2O_2$ under our experimental conditions did not oxidize 3-aminopyridine in independent runs.

$NaClO_4$ was used to maintain constant ionic strength. $HClO_4$ (Baker analyzed 60%), $KH_2PO_4$, $Na_2HPO_4$, NaOH, potassium hydrogen phthalate were used to maintain pH which was measured using a Systronics digital pH-meter 335. 3-Aminopyridine (Aldrich 99%) was recrystallized from ethanol mp 157 °C (lit, 158 °C). The kinetics was followed by measuring the rate of disappearance of PMPA which was estimated by iodometry at pH 4—5 with a drop of ammonium molybdate solution.[1] All the reported rate constants, computed by the usual method, are reproducible to within ±5%. $k_{obsd}$ (second order rate constant) is calculated by dividing pseudo-first order rate constant with respect to PMPA disappearance by the substrate concentration. Least squares analysis of the rate laws were done by a DCM Microsystem 1121.

*Stoichiometry.* A clean stoichiometry of 3-aminopyridine: PMPA (1:1.5) was observed at several pH's in the range 0—7. 3,3′-Azoxypyridine has been characterized as the only product of this oxidation and has already been reported.[4]

## Results and Discussion

The oxidation of 3-aminopyridine by peroxomonophosphoric acid (PMPA) in aqueous acid medium at 308 K with different initial concentrations of PMPA and 3-aminopyridine (Table 1) enabled us to write the rate equation at constant acidity;

TABLE 1. PSEUDO FIRST ORDER RATE CONSTANTS AND SECOND ORDER RATE CONSTANTS FOR THE OXIDATION OF 3-AMINOPYRIDINE AT 308 K, $\mu$=0.4 mol dm$^{-3}$ AT pH 1.3

| [PMPA]×10$^4$ / mol dm$^{-3}$ | [3-Aminopyridine]×10$^3$ / mol dm$^{-3}$ | Pseudo first order rate constant×10$^4$ / s$^{-1}$ | $k_{obsd}$×10$^3$ / dm$^3$ mol$^{-1}$ s$^{-1}$ |
|---|---|---|---|
| 4.90 | 2.57 | 0.383 | 14.9 |
| 4.99 | 5.50 | 0.7206 | 13.1 |
| 5.41 | 11.6 | 1.486 | 12.8 |
| 21.40 | 11.1 | 1.376 | 12.4 |
| 49.64 | 11.1 | — | 11.8[a] |
| 96.24 | 11.1 | — | 10.8[a] |
| 4.81 | 25.7 | 3.01 | 11.7 |

a) $k_{obsd}$ calculated directly from second order rate expression.

TABLE 2. EFFECT OF ADDED SUBSTANCES AND ACIDITY ON THE OXIDATION RATE AT 308 K

| pH | [3-Aminopyridine] $\times 10^3$ / mol dm$^{-3}$ | [PMPA] $\times 10^4$ / mol dm$^{-3}$ | $k_{obsd} \times 10^3$ / dm$^3$ mol$^{-1}$ s$^{-1}$ |
|---|---|---|---|
| 0.0 | 10.3 | 4.78 | 56.2 |
| 0.3 | 10.3 | 5.19 | 47.3 |
| 0.7 | 10.7 | 5.21 | 33.4 |
| 1.0 | 10.7 | 4.51 | 25.7 |
| 1.3 | 11.6 | 5.41 | 12.8 |
| 1.73 | 21.2 | 4.78 | 10.15 |
| 2.63 | 21.2 | 5.07 | 2.12 |
| 3.00 | 10.7 | 4.19 | 0.896 |
| 3.20 | 10.7 | 4.01 | 0.908 |
| 3.71 | 23.5 | 4.74 | 1.22 |
| 4.15 | 22.3 | 4.74 | 1.67 |
| 4.46 | 21.2 | 4.86 | 2.21 |
| 4.53 | 22.0 | 4.60 | 2.30 |
| 4.76 | 22.0 | 3.90 | 2.73 |
| 5.01 | 21.2 | 5.01 | 3.90 |
| 5.27 | 22.0 | 4.60 | 4.45 |
| 5.72 | 21.0 | 4.54 | 4.52 |
| 6.04 | 21.0 | 4.84 | 4.95 |
| 6.47 | 21.0 | 4.74 | 3.51 |
| 7.02 | 20.7 | 4.79 | 0.835 |
| 1.3 | 5.31 | 3.91 | 12.8[a] |
| 1.3 | 5.31 | 4.50 | 13.8[b] |
| 1.3 | 22.2 | 4.56 | 11.6[c] |
| 1.3 | 20.8 | 4.70 | 13.6[d] |
| 1.3 | 20.8 | 4.96 | 13.05[e] |

a) $\mu = 0.25$ mol dm$^{-3}$. b) $\mu = 0.8$ mol dm$^{-3}$. c) [Acrylamide] $= 2.31 \times 10^{-2}$ mol dm$^{-3}$. d) [Ag$^+$] $= 4.8 \times 10^{-4}$ mol dm$^{-3}$. e) [Cu$^{2+}$] $= 5.34 \times 10^{-4}$ mol dm$^{-3}$.

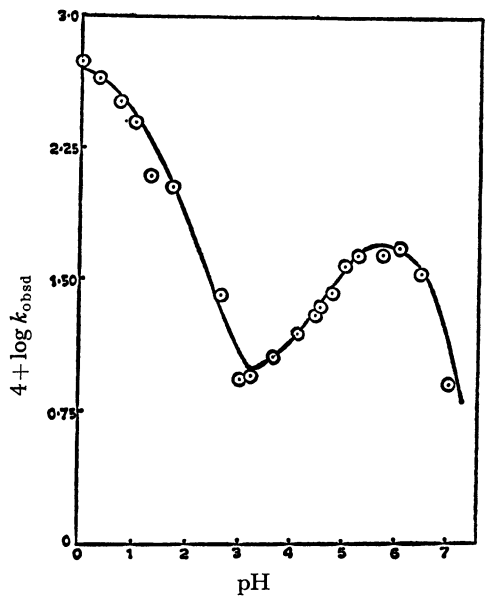



Fig. 1. Plot of log $k_{obsd}$ *vs.* pH.
⊙: Experimental points. —: Theoretical line.

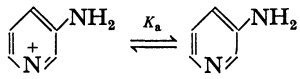
$$\text{Rate} = k_{obsd}[\text{3-Aminopyridine}]_t[\text{PMPA}]_t,$$

where $k_{obsd}$ is the second order rate constant and 't' denotes total concentration.

The influence of acidity on the oxidation rate are presented in Table 2 and shown in Fig. 1 (log $k_{obsd}$ *versus* pH). The pH-rate profile clearly reflects the involvement of various PMPA species and protonated and unprotonated forms of 3-aminopyridine (Eqs. 5, 6, and 7).

$$H_3PO_5 \overset{K_1}{\rightleftharpoons} H_2PO_5^- + H^+, \quad K_1 = 8.0 \times 10^{-2} \qquad (5)^{8)}$$

$$H_2PO_5^- \overset{K_2}{\rightleftharpoons} HPO_5^{2-} + H^+, \quad K_2 = 4.2 \times 10^{-6} \qquad (6)^{8)}$$




(7)[3)]

*Reaction in the pH Range 0—3.* In the pH range 0—3, the rate of oxidation goes on decreasing with the increase in pH *i.e.* with the decreasing electrophilic character of PMPA species.[9)] The p$K_a$ of 3-aminopyridine (5.98) suggests that whole of 3-aminopyridine (B) exists as BH$^+$ and PMPA exists as $H_3PO_5$ and $H_2PO_5^-$ in this pH range. Hence, the steps of the oxidation can be written as

$$BH^+ + H_3PO_5 \xrightarrow{k_1} \text{Products} \qquad (8)$$

$$BH^+ + H_2PO_5^- \xrightarrow{k_2} \text{Products}. \qquad (9)$$

Hence,

$$\text{Rate} = -\frac{d[\text{PMPA}]_t}{dt} = k_1[BH^+][H_3PO_5] + k_2[BH^+][H_2PO_5^-]. \qquad (9a)$$

But

$$[PMPA]_t = [H_3PO_5] + [H_2PO_5^-]. \quad (9b)$$

From Eqs. 9b and 5, we get

$$[H_3PO_5] = \frac{[H^+]}{K_1+[H^+]}[PMPA]_t \quad (9c)$$

and

$$[H_2PO_5^-] = \frac{K_1}{K_1+[H^+]}[PMPA]_t. \quad (9d)$$

Substituting Eqs. 9c and 9d in Eq. 9a, we get

$$-\frac{d[PMPA]_t}{dt} = \frac{k_1[H^+]+k_2K_1}{K_1+[H^+]}[BH^+][PMPA]_t, \quad (9e)$$

where

$$k_{obsd} = \frac{k_1[H^+]+k_2K_1}{K_1+[H^+]}. \quad (10)$$

Least squares analysis of the above equation gave us the values of $k_1$ and $k_2$ which are collected in Table 3. The correspondence between the $k_{obsd}$ and $k_{cald}$ based on the values of $k_1$ and $k_2$ is very good (Fig. 1).

Table 3. Rate constants in $dm^3\ mol^{-1}\ s^{-1} \times 10^2$

| $k_1$ | $k_2$ | $k_3$ | $\left(\frac{k_4K_a}{K_2}+k_5\right)$ | $\approx k_4$ | $k_6$ |
|---|---|---|---|---|---|
| 5.28 | 0.068 | 0.098 | 4.50 | 18 | 0.05 |

*Reaction in the pH Range 3—7.* In this pH region, a bell shaped curve is observed. PMPA exists as $H_2PO_5^-$ and $HPO_5^{2-}$ and 3-aminopyridine exists as $BH^+$ and B.

Therefore, the reaction steps are postulated as

$$BH^+ + H_2PO_5^- \xrightarrow{k_3} \text{Products} \quad (11)$$

$$B + H_2PO_5^- \xrightarrow{k_4} \text{Products} \quad (12)$$

$$BH^+ + HPO_5^{2-} \xrightarrow{k_5} \text{Products} \quad (13)$$

$$B + HPO_5^{2-} \xrightarrow{k_6} \text{Products}. \quad (14)$$

Equations 11—14 lead us to the rate law

$$-\frac{d[PMPA]_t}{dt} = k_3[BH^+][H_2PO_5^-] + k_4[B][H_2PO_5^-] + k_5[BH^+][HPO_5^{2-}] + k_6[B][HPO_5^{2-}]. \quad (14a)$$

But $$[B]_t = [BH^+] + [B]. \quad (14b)$$

From Eqs. 7 and 14b, we get

$$[BH^+] = \frac{[H^+]}{K_a+[H^+]}[B]_t \quad (14c)$$

and

$$[B] = \frac{K_a}{K_a+[H^+]}[B]_t. \quad (14d)$$

Now,

$$[PMPA]_t = [H_2PO_5^-] + [HPO_5^{2-}]. \quad (14e)$$

From Eqs. 6 and 14e, we get

$$[H_2PO_5^-] = \frac{[H^+]}{K_2+[H^+]}[PMPA]_t \quad (14f)$$

and

$$[HPO_5^{2-}] = \frac{K_2}{K_2+[H^+]}[PMPA]_t. \quad (14g)$$

Substituting Eqs. 14c, 14d, 14f, and 14g in 14a, we get

$$-\frac{d[PMPA]_t}{dt} = \frac{k_3[H^+]^2+\left(\frac{k_4K_a}{K_2}+k_5\right)K_2[H^+]+k_6K_aK_2}{(K_a+[H^+])(K_2+[H^+])} \times [B]_t[PMPA]_t, \quad (14h)$$

where

$$k_{obsd} = \frac{k_3[H^+]^2+\left(\frac{k_4K_a}{K_2}+k_5\right)K_2[H^+]+k_6K_aK_2}{(K_a+[H^+])(K_2+[H^+])}. \quad (15)$$

A least squares analysis of Eq. 15 was done and values of $k_3$, $(k_4K_a/K_2+k_5)$ and $k_6$ were obtained (Table 3). These values were used to obtain $k_{calcd}$ which showed excellent agreement with experimental points (Fig. 1).

It is gratifying that the values of $k_2$ (Eq. 9) and $k_3$ (Eq. 11), obtained by two different rate expressions Eq. 10 and Eq. 15 are of the same order of magnitude and provide credence to the steps envisaged.

*Activation Energy and Entropy.* The second order rate constants at 308, 313, 318, and 323 K and at $[H^+]=0.05$ mol $dm^{-3}$ were $1.28\times10^{-2}$, $1.63\times10^{-2}$, $2.18\times10^{-2}$, and $2.73\times10^{-2}$ $dm^3\ mol^{-1}\ s^{-1}$ respectively. The energy of activation from a plot of log $k_{obsd}$ against $1/T$ was 41.8 kJ $mol^{-1}$. $\Delta H^*$ and $\Delta S^*$ were estimated to be 39.5 kJ $mol^{-1}$ and $-153$ J $K^{-1}$ $mol^{-1}$ respectively.

*Mechanism.* That the rate limiting step involves nucleophilic attack of the amino nitrogen on the electrophilic peroxo oxygen is evident from the following facts.

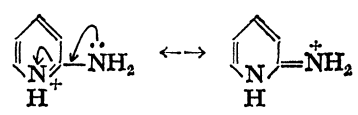
(1) No oxidation is observed above pH 7. The order of decreasing electrophilicity of the various PMPA species is $H_3PO_5 > H_2PO_5^- > HPO_5^{2-} > PO_5^{3-}$. At pH $\approx$7 $HPO_5^{2-}$ is about 90%.

(2) The insensitivity of the rates to added acrylamide, $Cu^{2+}$, $Ag^+$ points to the polar nature of these oxidations without the mediation of free radical intermediates.

(3) The reactivity of $H_3PO_5$ ($k_1$) is about two orders of magnitude higher than that of $H_2PO_5^-$ ($k_2$), Table 3.

(4) The facile oxidation of 3-aminopyridine stands in sharp contrast to the total unreactivity of 2-aminopyridine. The reason most probably lies in the nucleophilicity of the $-NH_2$ nitrogen. The 3-$NH_2$ group is not conjugated with the pyridine nitrogen and thus the nitrogen lone pair is not delocalized into the heterocyclic ring.

Thus the nucleophilicity of the $NH_2$ group in 3-aminopyridine is fully alive. In 2-aminopyridine there are contributing structures like



and this reduces the nucleophilicity of 2-$NH_2$ group to a great extent.[3] In the pH range 0—5 the pyridine nitrogen is protonated which enhances the meso-

meric interaction of the $-NH_2$ group. Above pH 5, we have both B and $BH^+$ and B is decidedly more nucleophilic than $BH^+$. We have seen a very slow oxidation of 2-aminopyridine above pH 5.

In the oxidation of anthranilic acid,[1] it is the unprotonated amine which is the reactive species as the rate decreased at higher acidities. The oxidation of 3-aminopyridine provides altogether a different situation. The $pK_a$ of 3-aminopyridine is 5.98 and this refers to the protonation of the tertiary pyridine nitrogen and the 3-$NH_2$ group is unprotonated. One could in principle protonate it and this obviously requires still higher acidities than presently used in this kinetic study. Our pH-rate profile at still higher acidities could possibly have shown such a decreasing trend which is a reflection of the 3-$NH_2$ protonation. But our attempts to see that presented serious experimental problems in the estimation of PMPA iodometrically.

*Reactivity of Amine and Peroxo Acid.*

1) It is seen that the reactivity of $H_3PO_5$ is two orders of magnitude higher than that of $H_2PO_5^-$ which has been attributed to electrophilicity difference.

2) The peak in the pH region 3—7 is significant which calls for an explanation. In this range, 3-aminopyridine exists as B and $BH^+$. In $BH^+$ the tertiary nitrogen becomes tetrahedral on protonation, the delocalized positive charge experiences a field effect due to the $NH_2$ lone pair which makes the $NH_2$ of $BH^+$ less nucleophilic than that of B.

3) The value of $(k_4K_a/K_2+k_5)$ is of the order of $10^{-2}$, and $k_5$ should be very less than $k_6$ as explained above.

Hence, $(k_4K_a/K_2+k_5) \approx k_4K_a/K_2$.

Using values of $K_a$, $K_2$, a rough estimate of $k_4$ has been obtained (Table 3). Thus it is seen that B is about two orders of magnitude higher in reactivity than $BH^+$.

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