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Comparative rate study on the oxidation of nicotinamide and isonicotinamide by permanganate in acidic medium

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Abstract : A comparative rate study on the oxidation of nicotinamide and isonicotinamide by potassium permanganate has been carried out in acidic solutions over an extended $[H^+]$-range (1×10^{-5}–1.0 mol L^{-1}). Under the similar reaction conditions, the oxidation of pyridine is imperceptible. Further, in the absence of acid none of the two amides is oxidized and in both cases, the N-protonated amide species appears to be reactive. For nicotinamide, the results are in agreement with the two-term rate law (A). The oxidation product was corresponding N-oxide.

$$-d[MnO_4^-]/dt = (k_0K + k_1KK_1[H^+])[S]_0[MnO_4^-]_t[H^+]/(1 + K[H^+]) \quad \text{(A)}$$

On the other hand, the oxidation of isonicotinamide follows a simpler rate law (B).

$$-d[MnO_4^-]/dt = k_0K[S]_0[MnO_4^-]_t[H^+]/(1 + K[H^+]) \quad \text{(B)}$$

The values of k_0, K and k_1K_1 for nicotinamide were found to be 5.5×10^{-3} L mol^{-1} s^{-1}, 1.8×10^4 and 1.0×10^{-2} L mol^{-1} s^{-1}, respectively at 35 °C. And for isonicotinamide, the k_0 and K values were 4.4×10^{-3} L mol^{-1} s^{-1} and 5.6×10^3 respectively at 35 °C. The oxidation of nicotinamide is faster than the oxidation of isonicotinamide. It appears that the presence of $-CONH_2$ group at position 3 activates the ring nitrogen more for oxidation than the presence of this group at position 4.

Keywords : Permanganate, nicotinamide, isonicotinamide, oxidation, kinetics, N-protonation.

Introduction

Kinetic studies on the oxidation of pyridine and its derivatives by $KMnO_4$ in particular and by other oxidants in general are scarce. Only recently, some detailed kinetic studies on the oxidation of nicotinamide by permanganate[1] and that of isonicotinate ion by diperiodatocuprate[2] and diperiodatonickelate[3] ions in alkaline media have been reported. For a comparative rate analysis, here we report the oxidation kinetics of nicotinamide and isonicotinamide in acidic medium over an extended hydrogen ion concentration range.

Experimental

Nicotinamide (Sisco), isonicotinamide (Fluka), and their N-oxides (Aldrich) were used. The reactions were studied in a closed Earlenmeyer flask and initiated by adding temperature equilibrated $KMnO_4$ solution of known concentration to the reaction mixture containing the reducing substrate and buffer or $HClO_4$ in required amounts and maintained at the desired temperature (± 0.1 °C). The order of mixing of the reactants was without any effect. The kinetics were followed by estimating the unreacted $KMnO_4$ periodically. The aliquot portions were transferred to a titration flask containing a known amount of ammonium ferrous sulphate solution. The unreacted ferrous sulphate was back-titrated[4] against standard $KMnO_4$.

To avoid the precipitation of MnO_2, the oxidation was studied in the presence of large excess of fluoride ions[5]. The influence of $[H^+]$ has been studied over a wide concentration range. So for study in weakly acidic media, acetate buffer or dilute solution of $HClO_4$ was used. In each case, the initial pH was always measured. In high $[H^+]$ range (0.2–1.0 mol L^{-1}), $HClO_4$ was used and $[H^+]$ was assumed to be equal to the concentration of $HClO_4$ added.

The system displayed high reproducibility and replicate rate measurements were reproducible within ± 5%. All calculations were made using MS-Excel software.

In both cases, the addition of Mn^{II} or a variation in ionic strength with $LiClO_4$ (0.1–2.0 mol L^{-1}) had no effect

on the rate of the reaction. Under the similar reaction conditions, the nicotinamide N-oxide was not oxidized.

Table 1. Pseudo-first order and second order rate constants at I = 1.0 mol L^{-1} and $HClO_4$ = 1.0 mol L^{-1}

10^3 [MnO_4^-] (mol L)	10^2 [Substrate] (mol L)	Temp. (°C)	$10^4 k_{obs}$ (s^{-1})	$10^2 k_2$ (L mol^{-1} s^{-1})
	Nicotinamide			
1.50	3.00	35	5.60	1.87
3.00	3.00	35	5.75	1.92
2.00	3.00	35	5.75	1.92
2.00	2.00	30	2.50	1.25
2.00	2.50	30	2.92	1.17
2.00	3.00	30	3.63	1.21
2.00	3.50	30	4.22	1.20
2.00	4.00	30	4.80	1.20
2.00	4.50	30	5.45	1.21
2.00	5.00	30	5.95	1.19
2.00	2.00	25	1.82	0.91
2.00	2.50	25	2.04	0.82
2.00	3.00	25	2.50	0.83
2.00	3.50	25	2.92	0.83
2.00	4.00	25	3.27	0.82
2.00	4.50	25	3.75	0.83
2.00	5.00	25	4.22	0.84
	Isonicotinamide			
2.00	2.00	30	0.43	0.22
2.00	2.50	30	0.54	0.22
2.00	3.00	30	0.62	0.21
2.00	3.50	30	0.75	0.21
2.00	4.00	30	0.81	0.20
2.00	4.50	30	0.88	0.20
2.00	5.00	30	1.00	0.20
2.00	2.00	40	1.05	0.53
2.00	2.50	40	1.24	0.50
2.00	3.00	40	1.63	0.54
2.00	3.50	40	1.87	0.53
2.00	4.00	40	2.11	0.53
2.00	4.50	40	2.35	0.52
2.00	5.00	40	2.68	0.54
2.00	2.00	45	1.63	0.82
2.00	2.50	45	2.11	0.84
2.00	3.00	45	2.50	0.83
2.00	3.50	45	1.87	0.82
2.00	4.00	45	3.27	0.82
2.00	4.50	45	3.55	0.79
2.00	5.00	45	4.03	0.81

Product analysis :

The attempts to determine the stoichiometry by using an excess of permanganate over reductant concentration failed due to the precipitation of MnO_2, when the reaction mixture was left overnight. A similar behaviour has been noted by Marigangaih *et al.*[6]. Ideally the stoichiometry must be determined under the conditions used for studying kinetics, i.e. reductant concentration must be kept in excess over MnO_4^- concentration. However, the absence of the availability of a suitable method for the determination of either unreacted reductant in the presence of the product and vice versa did not allow the determination of stoichiometry in this way.

Table 2. The values of rate and protonation constants at 35 °C

Substrate	k_0 (L mol^{-1} s^{-1})	k_3 (L mol^{-1} s^{-1})	K (L mol^{-1})	k_1 (L mol^{-1} s^{-1})	Source
Nico-	5.5×10^{-3}	–	1.8×10^4	–	Fig. 1
tinamide	9.5×10^{-3}	1.0×10^{-2}	–	3.3	Fig. 2
	–	–	2.5×10^3 (25 °C)	–	Ref. 10
Isonico-	4.4×10^{-3}	–	5.6×10^3	–	Fig. 1
tinamide		–	4.08×10^3 (25 °C)	–	Ref. 13

Qualitative tests showed manganese(II) to be the reduction product of $KMnO_4$.The test for ammonium was negative showing that the -$CONH_2$ group was not affected. A literature survey revealed that the pyridine ring is resistant to oxidation by $KMnO_4$[7]. Indeed, under the conditions used in this study, we noted no perceptible reaction between pyridine and $KMnO_4$ over a period of two hours. The oxidation of nicotinamide by H_2O_2-urea/phthalic anhydride[8], perbenzoic acid[8] and by UV irradiation and high temperature[9] resulted in the formation of corresponding N -oxide. In the oxidation of isonicotinamide by H_2O_2-urea/phthalic anhydride[8] corresponding N-oxide was the product. Recently, the oxidation products of pyridine derivatives by other oxidants, have been found to be the corresponding N-oxides[1-3]. Thus, in the present study also the N-oxides are likely to be the oxidation products. This possibility was confirmed as follows.

The reaction mixture was prepared in which the ratio [MnO_4^-]/[reductant] was slightly greater than 0.4 and allowed to stand until $KMnO_4$ was completely consumed. Traces of MnO_2 formed were removed by filtration. In case of nicotinamide, for which the corresponding N-oxide could be procured, the UV -visible spectra of filtrate which contained the reaction product, closely matched the UV-visible spectra of the N-oxide. Further, under the experimental conditions of kinetics study, no perceptible oxidation of N-oxide occurred. This observation coupled

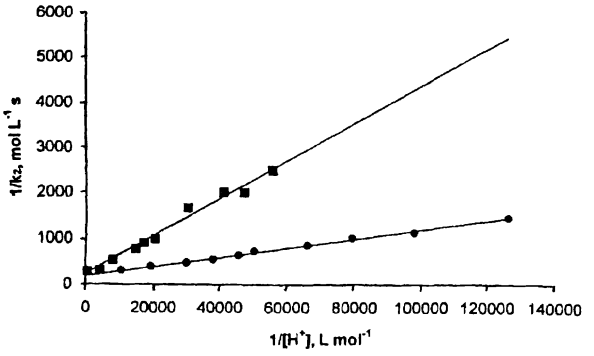


Fig. 1. The plot of $1/k_2$ vs $1/[H^+]$ for the oxidation of nicotinamide (●) and isonicotinamide (■) at I = 1.0 mol L^{-1} and T = 35 °C.

with the fact that the pyridine is also not oxidized under similar reaction conditions suggesting that the oxidation of the amides under study occurs to the stage of N-oxide only, as in other oxidation studies[1-3] and is in agreement with the stoichiometric eq. (1).

$$2\ MnO_4^- + 5\ \text{nicotinamide} \rightarrow 2\ Mn^{2+} + 5\ \text{nicotinamide N-oxide} \quad (1)$$

Results

The kinetics was studied under pseudo-order conditions by keeping the initial concentration of each of the substrates, $[S]_0$, at least ten times in excess over $[MnO_4^-]$. Over the entire $[H^+]$-range, the pseudo-first order plots, obtained by plotting log $[MnO_4^-]$ against time, were linear up to at least 75% reaction, showing first order with respect to $[MnO_4^-]$. The pseudo-first order rate constants, k_{obs}, were found to increase in proportion to initial substrate concentration, $[S]_0$, indicating the first order in $[S]_0$ also (Table 1). Thus, the results at constant $[H^+]$ are in accord with the experimental rate laws (2) and (3).

$$-d[MnO_4^-]/dt = k_2\ [MnO_4^-]_t\ [S]_0 \quad (2)$$

$$k_{obs} = k_2\ [S]_0 \quad (3)$$

where k_2 is second order rate constant, $[MnO_4^-]_t$ is the concentration of permanganate at time t and $[S]_0$ is the initial concentration of amides. The k_2 values determined from eq. (3) are seen to be in excellent agreement with each other (Table 1).

The hydrogen ion concentration dependence was studied in both weakly and strongly acidic solutions. For study in weakly acidic solutions, the selection of pH range was dictated by the value of equilibrium constant of the protonation of the ring nitrogen. The results of $[H^+]$-dependence of nicotinamide oxidation (pH range 3.44–5.27) and that of isonicotinamide (pH range 2.00–4.74) were in agreement with the rate laws(4–5).

$$k_{obs} = k_0 K\ [S]_0\ [H^+]/(1 + K\ [H^+]) \quad (4)$$

$$k_2 = k_0 K\ [H^+]/(1 + K\ [H^+]) \quad (5)$$

where K is the equilibrium constant for N-protonation of amides and k_0 is the rate constant for the oxidation of N-protonated amides by MnO_4^-.

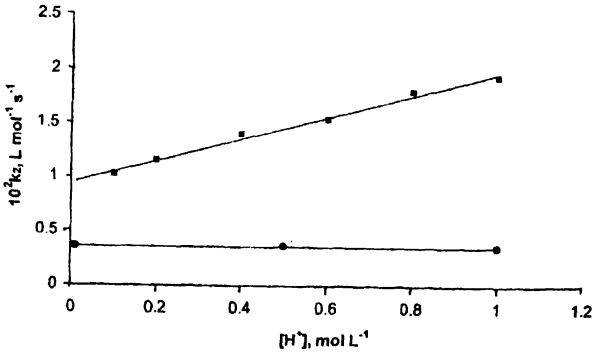


Fig. 2. The variation of k_2 with $[H^+]$ in the high concentration range at 35 °C and at I = 1.0 mol L^{-1}. Nicotianmide (■) and isonicotinamide (●).

In accordance with the rate law (5), the plots of $1/k_2$ vs $1/[H^+]$ were linear (Fig. 1) in case of both the amides. The values of k_0 and K obtained from these plots are given in Table 2. The nature of the rate laws (4-5) require the presence of both the protonated and unprotonated species of the reductant to be present in solution, and that the protonated form should be reactive. To verify this, in some experiments the oxidation of amides was conducted in neutral medium without adding any acid from outside. The reaction was monitored for about 2 h and interestingly no reaction was found to occur. This clearly suggests the unprotonated amides to be unreactive towards oxidation.

The nature of $[H^+]$-dependence in the region of high $[H^+]$ was different in case of the two amides. The rate of the oxidation of isonicotinamide (Fig. 2), when $[H^+]$ was increased from 0.1 to 1.0 M, was independent of $[H^+]$. This is in accordance with the values of K (Table 2) which suggests that when $[H^+]$ is high, the inequality $K[H^+] >> 1$ shall hold and the rate law (5) would reduce to $k_2 = k_0$, and the rate of the reaction would not depend on $[H^+]$. Thus, the kinetics of oxidation of isonicotinamide is defined by rate laws (4–5) over the entire $[H^+]$-range.

On the contrary, in the case of nicotinamide, the rate of oxidation increased continuously with increase in $[H^+]$ in the range 0.1–1.0 M. This suggests the appearance of a new proton-assisted k_3-pathway in addition to k_0-pathway. Thus, the rate in strongly acidic medium is defined by the two-term rate law (6), as discussed later.

$$k_2 = \{k_0 K + k_3 K[H^+]\}\ [H^+]/(1 + K\ [H^+]) \quad (6)$$

where k_3 is a composite rate constant pertaining to the oxidation of N-protonated nicotinamide by $HMnO_4$.

Since in the region of high acid concentration $K[H^+] >> 1$, the rate law (6) reduces to eq. (7).

$$k_2 = k_0 + k_3\ [H^+] \quad (7)$$

It must be pointed out that the k_3-term is important only in the oxidation of nicotinamide and that too only when $[H^+]$ is high. In the region of low acidity this term is not significant. Thus, over the whole range of $[H^+]$, the kinetics of oxidation of nicotinamide is described by the rate law (6), which reduces to rate law (5) at low $[H^+]$ and to rate law (7) at high $[H^+]$. The plot of k_2 vs $[H^+]$ was linear with a non-zero intercept (Fig. 2). The values of k_0 and k_3 are given in Table 2. Interestingly, the value of k_0 determined from rate laws (5) and (6) are in good agreement, as it should be.

The values of the rate constants at different temperatures are given in Table 1. The overall empirical energies of activation were 60 ± 2 (nicotinamide) and 70 ± 2 kJ mol^{-1} (isonicotinamide).

Discussion

Some interesting features of the system under investigation are as follows. Firstly, the oxidation of pyridine in the absence of a substituent in the ring is not perceptible, as reported by others also[7]. Secondly, for oxidation to take place the protonation of the ring nitrogen appears to be *a priori*. The protonation of ring nitrogen in nicotinamide is well known and is quite strong, as is obvious from the K values collected in Table 2. Since the reaction does not occur in the absence of added acid, the N-protonated form must only be reactive. Thirdly, oxidation of nicotinamide is relatively faster than that of isonicotinamide, showing that the presence of the substituent group at position 3 leads to faster rate than the presence of the group at position 4. Fourthly, in case of nicotianamide a new proton-assisted pathway, showing first order dependence in $[H^+]$ also appears, when $[H^+]$ is high.

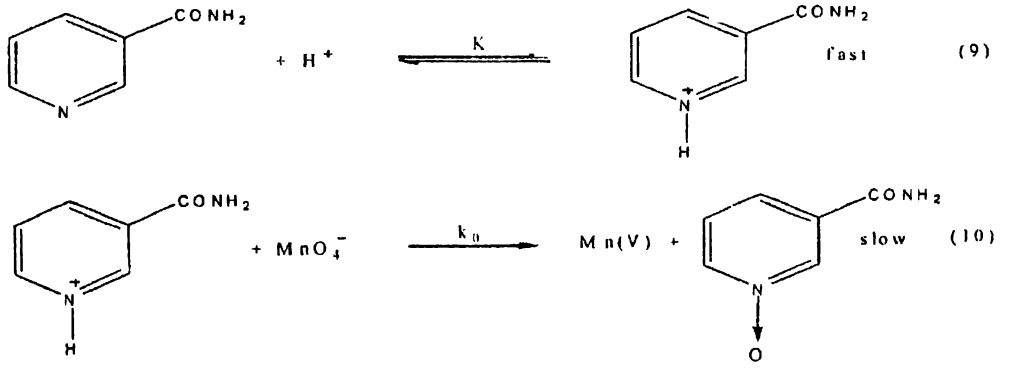
The greater reactivity of nicotinamide as compared to isonicotinamide can be explained as follows. In acidic solutions, the ring nitrogen atom of pyridine and its derivatives gets protonated to form a corresponding pyridinium cation[7]. The positive charge is actually on the ring[1,11,12]. The positive charge greatly intensifies the electronegative properties of ring nitrogen atom because of which the position 3 has relatively high electron density than the positions 2 and 4[11,12]. As a consequence, in the electrophilic substitution reactions the attack of the electrophile is on position 3. This clearly establishes the important link between position 3 and the reactivity of substituted pyridinium cation, for example N-protonated nicotinamide in our case. Likewise, when $-CONH_2$ group is at position 3, as in nicotinamide, the electron density is relatively higher at nitrogen atom than when the $-CONH_2$ group is at positions 4, as in case of isonicotinamide. Probably, for this reason, in the present oxidation study nicotinamide is more reactive than isonicotinamide.

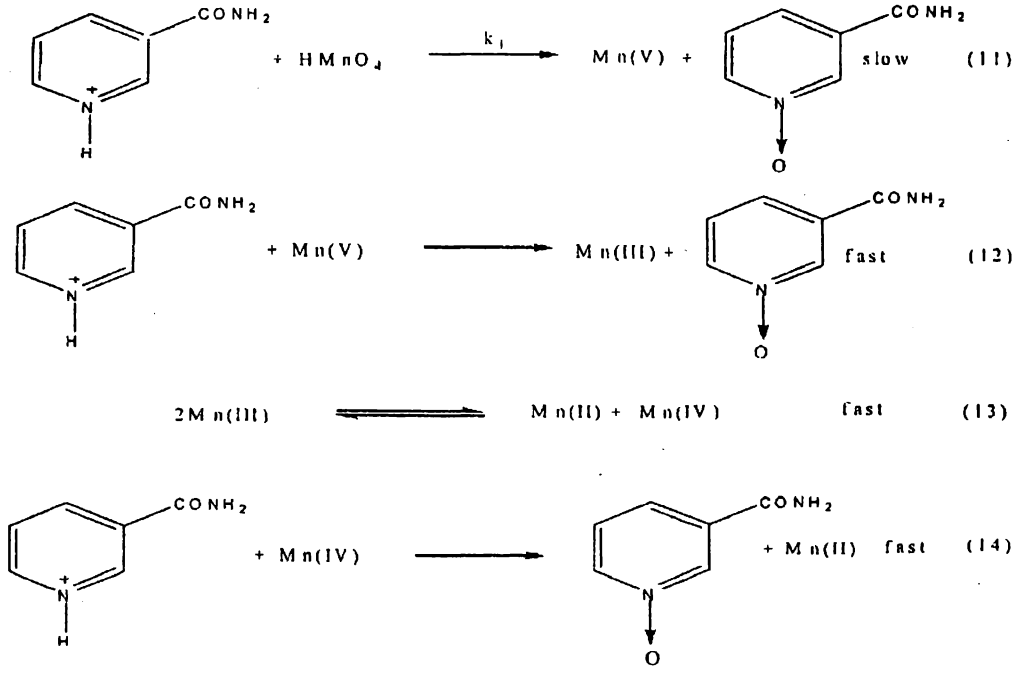
In aqueous acidic solutions, the protonation of MnO_4^- to form $HMnO_4$ with an equilibrium constant, K_1, value of 2.99×10^{-3} is well known[14]. In many instances $HMnO_4$

$$MnO_4^- + H^+ \overset{K_1}{\rightleftharpoons} HMnO_4 \quad (8)$$

has been found to be more reactive than MnO_4^- ion[15,16]. This depends up on the relative reduction potentials of oxidant and the reducing substrate. Actually, in the case of those reductants for which the reduction potential is more positive than that of $MnO_4^- - MnO_4^{2-}$ half cell reaction, the proton-assisted pathway involving $HMnO_4$ as oxidant appears[14–16]. This appears to be the reason for the k_3- term in nicotinamide oxidation.

Based on these arguments, the following mechanism (9–14) is proposed for the oxidation of nicotinamide.





The evidence for Mn^{IV} is provided by precipitation of MnO_2.The mechanistic steps (8–14) lead to the rate law (15).

$$-d[MnO_4^-]/dt = (k_0K + k_1KK_1\,[H^+])\,[S]_0\,[MnO_4^-]_t\,[H^+]/(1 + K\,[H^+]) \quad (15)$$

Due to low value of K_1, in the pH range, 2.00–5.27, the concentration of $HMnO_4$ would be negligible and hence contribution from the step (11) to the overall rate would also be insignificant. Hence, on neglecting the term k_0KK_1 in the rate law (14), it reduces to the observed experimental rate laws (4–5) in the weakly acidic solutions in the reason of low $[H^+]$.

On the other hand, the K value of 1.8×10^4 (Table 2) suggests that in the region of high $[H^+]$ (0.1–1.0 mol L^{-1}), nicotinamide would be fully protonated and hence the inequality, $K[H^+] >> 1$, shall hold and so the rate law (15) would reduce to experimental rate law (7) through $k_3 = k_1K_1$. From the reported K_1 value of 2.99×10^{-3} , the value of k_0 is calculated to be 3.3 $l\,mol^{-1}\,s^{-1}$ at 35 °C.

In case of isonicotinamide, the experimental rate laws (4–5) are applicable over the entire range of $[H^+]$. This clearly shows that for this amide the contribution of the term k_1K_1 in the general rate law (15) is negligible. It is of interest to compare the value of K determined experimentally with those reported in the literature[10,13] (Table 2). Keeping in view the temperature difference and the fact that the values have been determined kinetically by us, the values are seen to be in good agreement with those reported[10,13] (Table 2).

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