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RESEARCH ARTICLE

KINETICS AND MECHANISTIC STUDY OF OXIDATION OF NICOTINAMIDE BY BROMAMINE-T IN HYDROCHLORIC ACID MEDIUM CATALYZED BY Ru(III) ION

***[1]Chandrashekar, [2]Radhika R. T., [3]Venkatesha, B. M. and [4]Ananda, S.**

[1]Department of Chemistry, PES College of Engineering Mandya-571401, India
[2]Department of Chemistry Maharani's Science College for Women, Mysore, India
[3]Department of Chemistry, Yuvaraja´s College, University of Mysore, Mysore - 570005, India
[4]Department of Studies in Chemistry, Manasagangothri, University of Mysore-570006, India

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ABSTRACT

Oxidation of nicotinamide by bromamine-T (BAT) have been studied in HCl medium catalyzed by Ru(III) at 303K. The reaction rate shows first order dependence on (oxidant), (Ru(III)), inverse fractional order on (H^+) and fractional order on (nicotinamide). Addition of halide ions and the reduction product of BAT, p-toluenesulphonamide and dielectric constant of the medium do not have any significant effect on the reaction rate. The reaction was studied at different temperatures and activation parameters were evaluated. Mechanisms proposed and the derived rate law is consistent with the observed kinetics.

INTRODUCTION

Nicotinamide is the amide of nicotinic acid (vitamin-B_3). It is a water soluble vitamin and is part of the vitamin B group. Nicotinamide is produced from niacin in human beings. Niacin is converted to nicotinamide when it is taken in amount greater than what is needed by the body. Nicotinamide acts as anti-inflammatory (Niven 2006), anxiolytic (anti-anxiety) agent (Tallman *et al.*, 1980) and also acts as a chemo and radio sensitizing agent by enhancing tumor blood flow, there by reducing tumour hypoxia. Nicotinamide is an activator of sirtuins but it inhibits at higher doses. Nicotinamide and isonicotinamide were oxidized using permanganate ion in acidic medium by Sharma *et al.* (2008). L Avigliano *et al.* (1986) have reported the oxidation of nicotinamide coenzyme dimers by one electron-accepting protein. Mohammed *et al.* (1986) have reported kinetics of the oxidation of reduced nicotinamide adenine dinucleotide by horse radish peroxidase. However a very few kinetic investigation of nicotinamide have been reported. There are no informations available on the oxidation by haloamines. The present studies were undertaken to investigate the kinetic aspects of oxidation of nicotinamide by bromamine-T. Mechanistic studies of the oxidation of diverse organic substrates by these organic haloamines have been reported previously (Venkatesha *et al.*, 1992; Venkatesha *et al.*, 1995; Saldana *et al.*, 2002). We now report a detailed investigation of the kinetics of oxidation of nicotinamide by bromamine-T in acid solution catalysed by Ru(III) at 303K.

Corresponding author: Chandrashekar
Department of Chemistry, PES College of Engineering Mandya-571401, India.

Experimental

Bromamine-T (BAT, p-$CH_3C_6H_4SO_2NBrNa$) was prepared by standard procedure and its purity was checked iodometrically and through UV, IR and ^{13}C NMR spectral data (Nair and Indrasenan 1976; Ahmed *et al.*, 1980). Aqueous solution of BAT was prepared, standardized by the iodometric method and preserved in amber colored bottle. Aqueous solution of nicotinamide was prepared using triply distilled water. All other chemicals were of analytical grade. Triply distilled water was used for preparing aqueous solutions.

Kinetic Measurements

Mixtures containing requisite amounts of substrate, $NaClO_4$, Ru(III) and HCl were equilibrated at 303K. To this was added a measured amount of pre-equilibrated aqueous solution of BAT of known concentration. The progress of the reaction was monitored iodometrically for two half lives by withdrawing aliquots of the reaction mixture at regular time intervals. The pseudo first order rate constants calculated were reproducible with ± 3%. Regression analysis of experimental data was carried out on origin 5.0 HP computer to obtain regression coefficient.

Stoichiometry

Investigations under the conditions [BAT] >> [Substrate] revealed that one mole of BAT was consumed by one mole of substrate. The stoichiometry of oxidation is illustrated as in equation (1)

$$C_6H_6N_2O + ArSO_2NBrNa + H_2O \longrightarrow C_6H_6N_2O_2 + Na^+$$
N.Amide BAT

$$+ Br^- + ArSO_2NH_2 \quad \ldots (1)$$

The presence of 6-hydroxy nicotinamide which is the oxidation product of nicotinamide in the reaction mixture was detected by LCMS mass spectra (Figure 1).

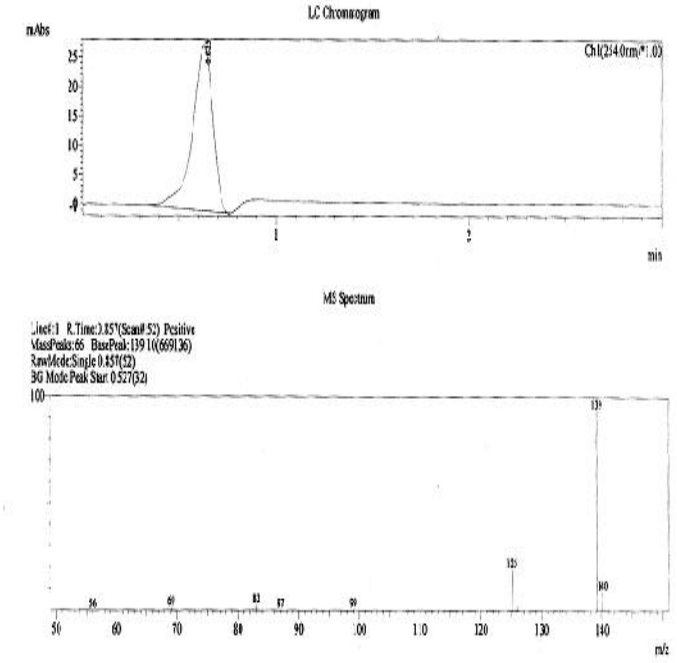


Figure 1. GC-Mass Spectra of 6-hydroxy nicotinamide with molecular peak (133)

Product analysis

The reaction mixture in the stoichiometric ratio in the presence of acid medium catalysis by ruthenium chloride was allowed to progress for 24 hours at 303K. After completion of the reaction (monitored by TLC), the reaction mixture was neutralized and the products were extracted with ether. The organic products were subjected to spot tests and chromatographic analysis (TLC method). The product was 6-hydroxy nicotinamide. For example, the GC-MS data for nicotinamide obtained on a 17A Shimadzu gas chromatograph with LCMS-2010A Shimadzu mass spectrometer showed a molecular ion peak at 133 amu (Figure.1) clearly confirming the formation of 6-hydroxy nicotinamide. The reaction product, toluenesulphonamide ($ArSO_2NH_2$) was detected by paper chromatography **(**Mahadevappa and Gowda 1975**).** Benzyl alcohol saturated with water was used as the solvent with 0.5% vanillin in 1% HCl in ethanol as spray reagent (R_f = 0.905).

RESULTS

Effect of reactant concentration on the rate

Under the conditions [substrate] >> $[BAT]_0$, plots of log [titre value] versus time are linear (r = 0.9943) indicating a first order dependence of rate on [oxidant]. The pseudo first order rate constants k´ are given in Table 1. The values of k´ remain unaffected with a change in [BAT] confirming the first order dependence on [BAT]. The rate increased with increase in [nicotinamide] (Table 1) and plot of log k´ versus log [nicotinamide] was linear with fractional slopes indicating the fractional order dependence of rate on [nicotinamide].

Table 1. Effect of varying reactant concentration on the rate

[HCl] = 24.0 × 10^{-4} mol dm^{-3}, [Ru(III)] = 1.243× 10^{-6} mol dm^{-3}, μ = 0.2 mol dm^{-3}; T = 303K

[BAT] x 10^4 mol dm^{-3}	10^3[Nicotinamide] mol dm^{-3}	10^4k´ (s^{-1})
1.15	2.00	3.93
1.61	2.00	3.79
2.00	2.00	3.30
2.53	2.00	3.40
2.99	2.00	3.42
2.00	1.00	2.42
2.00	1.50	2.81
2.00	2.00	3.32
2.00	3.00	4.08
2.00	4.00	4.78
2.00	5.00	5.30
2.00	6.00	5.75

Effect of [HCl] on the rate

The reaction was studied with varying [HCl] at constant [BAT], [Nicotinamide], [Ru(III)], ionic strength and temperature. The rate of reaction decreased with increase in [HCl] (r = 0.9915). The plot of log k´ versus log [HCl] was linear with negative slope equal to less than unity indicating inverse fractional order in [HCl] Table 2.

Table 2. Effect of varying [HCl] on the rate

$[Nicotinamide]_0$ = 2.0 × 10^{-3} mol dm^{-3}, [BAT] = 2.0 × 10^{-4} mol dm^{-3}, [Ru(III)] = 1.243× 10^{-6} mol dm^{-3}, μ = 0.2 mol dm^{-3}, T = 303K.

[HCl] × 10^4mol dm^{-3}	k´ × $10^4$$sec^{-1}$
5.0	3.61
10.0	2.60
15.0	2.21
20.0	1.90
25.0	1.55
30.0	1.27
40.0	1.14

Effect of [H^+] on the rate

At constant [BAT], [nicotinamide] and [Cl^-], the rate of reaction decreased with increase in [H^+] (r = 0.9966). The plot of log k´ versus log [H^+] was linear with negative slope equal to less than unity (-0.51) indicating an inverse fractional order in [H^+].

Effect of [Ru(III)] ion on the rate

The rate increased with increase in [Ru(III)] and plots of log k´ versus log [Ru(III)] was linear with unit slope indicating a first order dependence of rate on [Ru(III)] (Figure 2).

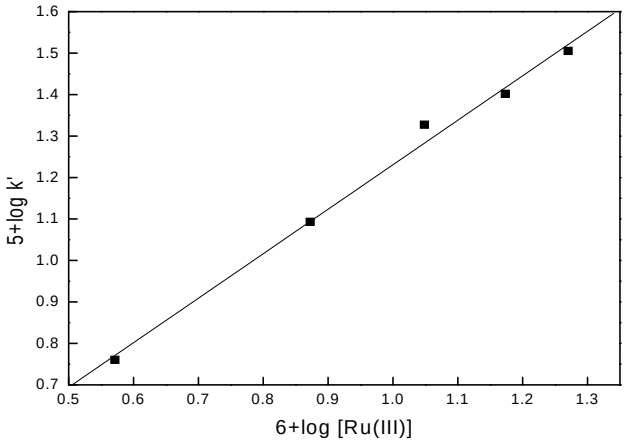


FIG. 2 Plot of log k' versus log [Ru(III)]

$[Nicotinamide]_0 = 2.0 \times 10^{-3}$ mol dm^{-3}, [BAT] = 2.0×10^{-4} mol dm^{-3}, [HCl] = 24.0×10^{-4} mol dm^{-3}, μ = 0.2 mol dm^{-3}, T = 303K.

Effect of halide ions and ionic strength on the rate

Addition of Cl^- ion in the form of NaCl (2.4×10^{-3}–10.4×10^{-3} mol dm^{-3}) and Br^- ion in the form NaBr (5.0×10^{-5} – 18.0×10^{-5} mol dm^{-3}) had no effect on the rate of reaction. Hence, the dependence of the rate on [HCl] reflected the effect of $[H^+]$ only on the reaction.

Effect of toluenesulphonamide and dielectric constant on the rate

Addition of reaction product p-toluenesulphonamide (5.0×10^{-5} – 20.0×10^{-5} mol dm^{-3}) and variation of methanol content (0-20%) in acid medium had no effect on the reaction rate.

Effect of temperature on the rate

The reaction was studied by varying different temperatures in the range 298K to 313K and the values of k´ were determined (Table 3) from the pseudo first order plots. The energy of activation Ea was calculated from the Arrhenius plot of log k´ versus 1/T.

Table 3. Effect of temperature on the rate of reaction and thermodynamic parameters for the Ru(III) catalysed oxidation of nicotinamide by BAT in HCl medium

$[Nicotinamide]_0 = 2.0 \times 10^{-3}$ mol dm^{-3}, [BAT] = 2.0×10^{-4} mol dm^{-3}, [HCl] = 24.0×10^{-4} mol dm^{-3}, [Ru(III)] = 1.243×10^{-6} mol dm^{-3}, μ = 0.2 mol dm^{-3},

Temperature(K)	k´ × 10^4 (sec^{-1})	Thermodynamic parameters
298	2.44	Ea = 56.44 kJ mol^{-1}
303	3.20	$\Delta H^{\neq}$ = 53.88 kJ mol^{-1}
308	5.69	$\Delta S^{\neq}$ = -133.52 JK^{-1} mol^{-1}
313	7.67	$\Delta G^{\neq}$ = 95.01 kJ mol^{-1}
318	9.39	

Test for free radicals

Tests performed for the presence of free radicals by adding the reaction mixture to acrylamide solution were negative. The absence of polymerization shows that the free radical species, *in situ* are not formed in the reaction.

DISCUSSION AND MECHANISM

Pryde and Soper (1926, 1931), Morris *et al*. (1948), Bishop and Jennings (1962) have shown the existence of similar equilibria in acid and alkaline solutions of N-metallo N-haloaryl sulphonamides, bromamine-T ($ArSO_2NBrNa$) which is similar to its chloramine analogues, as chloramine-T behaves as a strong electrolyte in aqueous solutions forming different species as in equation (2 – 6)

$$ArSO_2NBrNa \rightleftharpoons ArSO_2NBr^- + Na^+ \quad \text{... (2)}$$
$$ArSO_2NBr^- + H^+ \rightleftharpoons ArSO_2NHBr \quad \text{… (3)}$$
$$ArSO_2NHBr^- + H_2O \rightleftharpoons ArSO_2NH_2 + HOBr \quad \text{… (4)}$$
$$2ArSO_2NHBr \rightleftharpoons ArSO_2NH_2 + ArSO_2NBr \quad \text{…(5)}$$
$$HOBr + H^+ \rightleftharpoons H_2O^+Br \quad \text{...(6)}$$

In acidic medium the probable oxidizing species are the free acid ($ArSO_2NHBr$), dibromamine-B ($ArSO_2NBr_2$), HOBr or H_2O^+Br. In the present study of nicotinamide oxidation, the reaction shows a first order in $[BAT]_0$, $[RuCl_3]$ and fractional order in [substrate], and fractional order retardation on $[H^+]$. Based on the preceding discussion, a mechanism (Scheme 1) is proposed to account for the experimental observations. Electronic spectral studies of Cady and Connick (1958) and Connick and Fine (1960) reveal that species such as $[RuCl_5(H_2O)]^{2-}$ $[RuCl_4(H_2O)_2]^-$, $[RuCl_3(H_2O)_3]$, $[RuCl_2(H_2O)_4]^+$ and $[RuCl(H_2O)_5]^{2+}$ do not exist in aqueous solutions of $RuCl_3$. A study of oxidation states of ruthenium has shown that Ru((III) exists in the following equilibrium (Back house *et al.*, 1950; Darfokratova 1963; Griffith 1967) in acid medium.

$$[Ru(III)Cl_6]^{3-} + H_2O \rightleftharpoons [Ru(III)Cl_5(H_2O)]^{2-} + Cl^- \quad \text{….. (7)}$$

Singh *et al.* (1984, 1967) employed the above equilibrium in Ru(III) catalyzed BAT oxidation of some primary alcohols in acid medium and in the Ru(III) catalyzed oxidation of diethylgycol and methyl diethyleneglycol by N-bromoacetamide (NBA) in $HClO_4$ medium. However in the present case addition of Cl^- ion in the form of NaCl at fixed (H^+), no effect on the rate indicating that $[Ru(III)Cl_6]^{3-}$ is the most likely catalyzing species. The inverse fractional order in $[H^+]$ indicates that the deprotonation of $ArSO_2N^+H_2Br$ results in the formation of $ArSO_2NHBr$ which is likely to be the active oxidizing species. Based on the preceding discussion, a mechanism (Scheme 1) is proposed to account for the experimental observations.

$$ArSO_2N^+H_2Br \overset{K_1}{\rightleftharpoons} ArSO_2NHBr + H \quad \text{... (i)}$$
$$ArSO_2NHBr + S \overset{K_2}{\rightleftharpoons} X \quad \text{... (ii)}$$

$$X + Ru(III) \xrightarrow{k_3} X' \quad \text{slow} \quad ...(iii)$$

$$X' \longrightarrow X'' + Ru(III) \quad \text{fast} \quad ... (iv)$$

$$X'' \longrightarrow \text{Product} \quad ... (v)$$

Scheme – 1

$$\text{Rate} = -\frac{[BAT]}{dt} = k_3 [X] [Ru(III)] \quad \dots (8)$$

From step (ii)

$$[ArSO_2NHBr] = \frac{[X]}{K_2[S]} \quad \dots (9)$$

From step (i)

$$[ArSO_2N^+H_2Br] = \frac{[ArSO_2NHBr][H^+]}{K_1}$$

$$\therefore [ArSO_2N^+H_2Br] = \frac{[X][H^+]}{K_1 K_2[S]} \quad ...(10)$$

Total effective concentration of $[BAT]_t$

$$[BAT]_t = [ArSO_2N^+H_2Br] + [ArSO_2NHBr] + [X] \quad ... (11)$$

$$[BAT]_t = \frac{[X][H^+]}{K_1 K_2 [S]} + \frac{[X]}{K_2[S]} + [X] \quad ...(12)$$

$$[BAT]_t = [X]\left\{\frac{[H^+]}{K_1 K_2 [S]} + \frac{1}{K_2[S]} + 1\right\}$$

$$= [X]\left\{\frac{[H^+]+K_1+K_1 K_2[S]}{K_1 K_2 [S]}\right\}$$

$$\therefore [X] = \frac{K_1 K_2 [S][BAT]_t}{[H^+]K_1 + K_1 K_2[S]} \quad \dots(13)$$

$$\therefore \text{Rate} = \frac{K_1 K_2 k_3[S][BAT][Ru(III)]}{[H^+]+ K_1 + K_1 K_2 [S]} \quad \dots(14)$$

This is in good agreement with the experimental results. A detailed mechanism of Ru(III) catalyzed oxidation of nicotinamide by BAT in HCl medium is given in Scheme 2. Since rate = k′ under pseudo first order condition of [Nicotinamide] >> [BAT], the rate equation (14) can be transformed into equation

$$k' = \frac{K_1 K_2 k_3 [S][Ru(III)]}{K_1 + [H^+] + K_1 K_2[S]} \quad \dots(15)$$

$$\frac{1}{k'} = \frac{1}{K_2 k_3[S][Ru(III)]} + \frac{[H^+]}{K_1 K_2 k_3 [S][Ru(III)]} + \frac{1}{k_3[Ru(III)]} \quad ...(16)$$

Or

$$\frac{1}{k'} = \frac{1}{[S]K_2 k_3[Ru(III)]}\left\{\frac{K_1 + [H^+]}{K_1}\right\} + \frac{1}{k_3[Ru(III)]} \quad ...(17)$$

Or

$$\frac{1}{k'} = \frac{[H^+]}{K_1 K_2 k_3[S][Ru(III)]} + \left\{\frac{1}{K_2 k_3[S][Ru(III)]} + \frac{1}{k_3[Ru(III)]}\right\} \quad \dots(18)$$

Plots $1/k'$ versus $\frac{1}{[S]}$ at constant $[H^+]$ and [Ru(III)] from equation (17) and $1/k'$ versus $[H^+]$ at constant [S] and [Ru(III)] from equation (18) were found to be linear (Figure 3 and Figure 4). From the intercepts and slopes of the plots, the values of K_1, K_2 and k_3 were evaluated. The protonation constant ($K_P = 1/K_1$) value obtained, 18.40 for the species $ArSO_2NHBr$ is in good agreement with the previously published work (Venkatesha *et al.*, 1993) and (Ananda *et al.*, 1998). This gives indirect evidence for the proposed mechanism of the scheme 1. The thermodynamic parameters Ea, $\Delta H^{\neq}$, $\Delta S^{\neq}$, and $\Delta G^{\neq}$ were calculated as shown in Table 3. The moderate value of enthalpy of activation is supportive for the proposed mechanism in scheme 1. The high negative value of entropy of activation ($\Delta S^{\neq}$) indicates the formation of a rigid transition state by associative process.

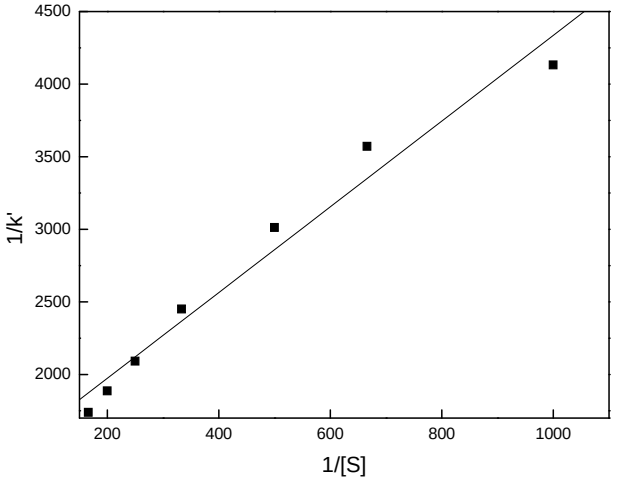


FIG.3 Plot of 1/k' versus 1/[S]

[BAT] = 20.0 × 10^{-5} mol dm^{-3};[HCl] = 24.0 × 10^{-4} mol dm^{-3}; [Ru (III)] = 1.243× 10^{-4} mol dm^{-3}; μ = 0.2 mol dm^{-3}; T = 303K.

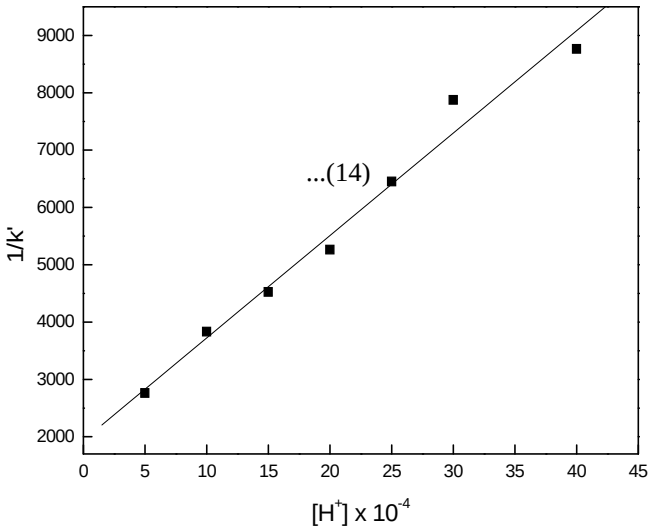
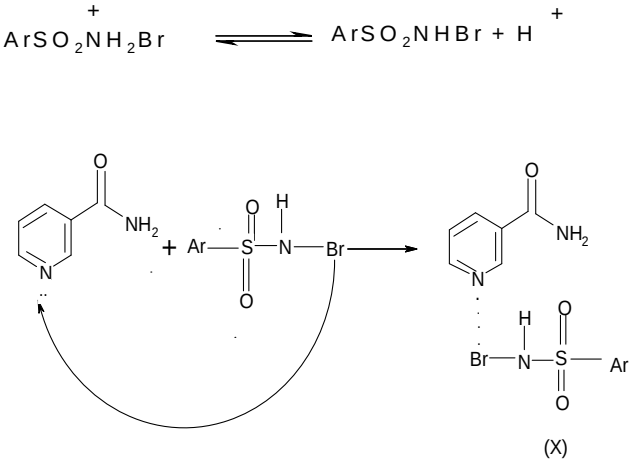
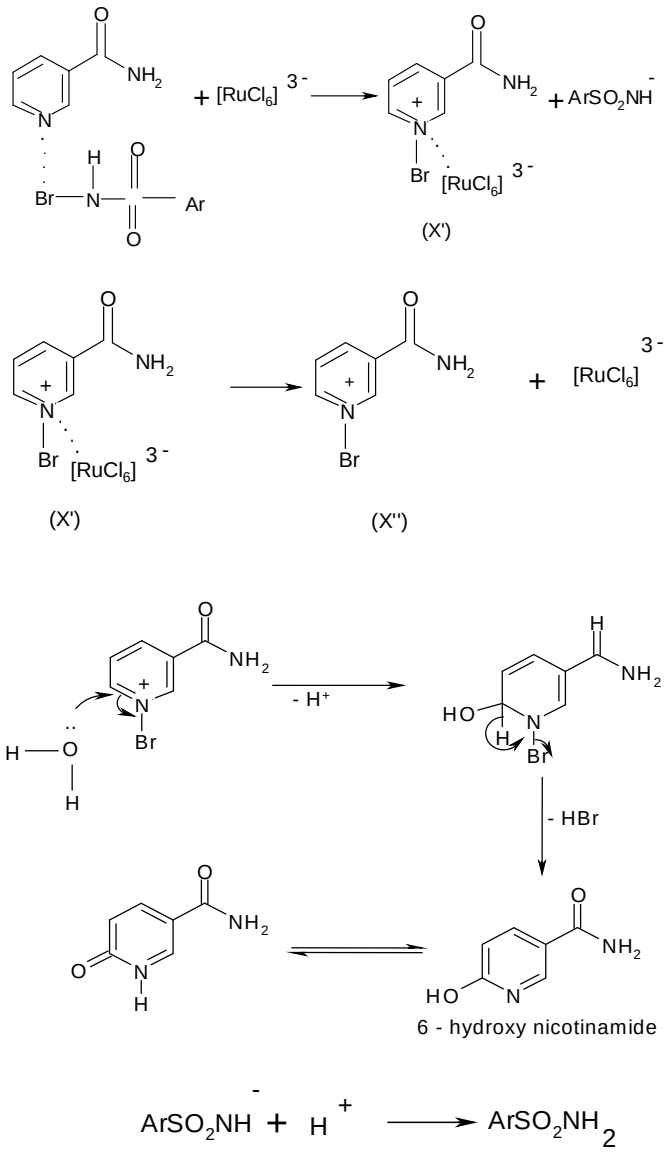


FIG. 4 Plot of 1/k' versus $[H^+]$

$[Nicotinamide]_0$ = 2.0 × 10^{-3} mol dm^{-3}, [BAT] = 2.0 × 10^{-4} mol dm^{-3}, [Ru(III)] = 1.243× 10^{-6} mol dm^{-3}, μ = 0.2 mol dm^{-3}, T = 303K.





Scheme 2. A reaction path for the oxidation of nicotinamide by BAT

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