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Kinetics and Mechanistic Approach to the Chromic Acid Oxidative Degradation of Atropine Drug in Perchlorate Solutions and the Effect of Ruthenium(III) Catalyst

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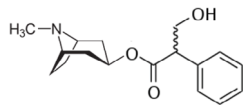
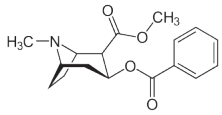
Abstract

The effect of ruthenium(III) catalyst on the kinetics of oxidation of atropine drug (ATR) by chromic acid in perchlorate solutions was studied spectrophotometrically at a fixed ionic strength of 1.0 mol dm^{-3} and at 25°C. Both uncatalyzed and Ru(III)-catalyzed oxidation reactions showed a first order dependence in [Cr(VI)], and less than unit order dependences with respect to both [ATR] and [H^+]. The reaction was first order in [Ru(III)]. The effects of both ionic strength and dielectric constant of the reactions medium were investigated. Addition of Mn(II) was found to decrease the oxidation rate. The rate of Ru(III)-catalyzed oxidation of atropine was found to be about 10-fold higher than that of the uncatalyzed reaction. In both cases, the main oxidation products of atropine were identified as tropine, benzaldehyde, methanol, and carbon dioxide. Plausible mechanisms for both uncatalyzed and Ru(III)-catalyzed oxidations were proposed and the rate-law expressions associated with these mechanisms were derived. The activation parameters related to the second order rate constants were evaluated and discussed.

Keywords: Atropine; Oxidation; Chromic acid; Ruthenium(III); Kinetics; Mechanism

Introduction

Alkaloids have a number of pharmacological activities including antimalarial, antiasthma, anticancer, cholinomimetic, antibacterial, psychotropic and stimulant activities [1-3]. Among the most famous of the alkaloids is tropine alkaloid or atropine (ATR) which is an anticholinergic drug containing two cyclic structures (alicyclic nitrogen-containing alcohol tropine and aromatic tropic acid) joined by an ester linkage [4]. This structure allows for its rapid absorption through the blood-brain barrier. Atropine is structurally similar to cocaine as illustrated below.

Atropine  Cocaine 

Atropine occurs naturally in plants in the nightshade family including deadly nightshade, Jimson weed and mandrake [5]. It is a secondary metabolite of such plants and serves as a drug with a wide variety of effects. Atropine is considered as a core medicine in the World Health Organization (WHO) for a main health care system. Furthermore, it is the most essential drug in the treatment of nerve agent poisoning. Its degradation by microorganisms has been reported by several groups [6] and in the initial stage, the hydrolysis of the ester linkage to give two separate cyclic components takes place. Alkaloids may play an important role in the chemistry of chromium because of its carcinogenic and mutagenic activities [7] which due to chromium(VI) metabolism by various cellular components. Among the various metabolic pathways, generation of chromium(V) intermediate by a variety of biologically active reductants is a prime suspect. Chromium(V) is a putative DNA-damaging agent and has been shown to be a long-lived intermediate in the redox reaction of chromium(VI) [8-10]. Epidemiological and animal studies, as well as *in vitro* mutagenicity assays [11], indicate that chromium(VI) compounds are dangerous for biological systems but chromium(III) compounds are considered as non-toxic [12]. Furthermore, chromium(VI) is considered as one of the most significant oxidants for oxidation of organic compounds [13,14]. On the other hand, some transition metal ions are widely used as homogeneous catalysts for oxidation of organic substrates [15-17]. Kinetic studies on the homogeneous catalyzed oxidation of organic substrates are considered to be an important field of chemistry because of their roles in the biological systems. Although some work on the oxidation of atropine by various oxidants has been performed [18-22], there is a lack of literature on the kinetics of oxidation of this drug by chromic acid in absence or presence of a catalyst. This leads us to study the present reactions. The objectives of this study were to check the reactivity of atropine drug towards chromic acid in perchlorate solutions, to understand the active species of the reactants in such medium, to check the catalytic activity of Ru(III) and to propose the oxidation mechanisms of the drug.

Experimental

Materials

The stock solution of atropine was prepared by dissolving the sample, atropine sulfate monohydrate $(C_{17}H_{23}NO_3)_2.H_2SO_4.H_2O$ (Aldrich), in doubly distilled water. Chromic acid solution was freshly prepared before each experiment and it was standardized spectrophotometrically. Solution of ruthenium(III) chloride was prepared according to the procedure reported earlier [23]. Other chemicals employed in the present investigation were of reagent grade and their solutions were prepared by dissolving the required amounts of the samples in doubly distilled water.

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Kinetic measurements

Kinetic runs were followed under pseudo-first order conditions in an excess of atropine over chromic acid. The courses of the uncatalyzed and Ru(III)-catalyzed oxidation reactions were followed by tracing the decay in chromium(VI) absorbance at λ_{max}=350 nm, its absorption maximum. Absorbance measurements were carried out on Shimadzu UV-VIS-NIR-3600 double-beam spectrophotometer with a temperature controlling system. The observed-first order rate constants of uncatalyzed (k_U) and catalysed (k_C) reactions were calculated as the gradients of ln(absorbance) versus time plots. The rate constants were the main values of at least three kinetic measurements. The rate constants were reproducible to within 3-4%.

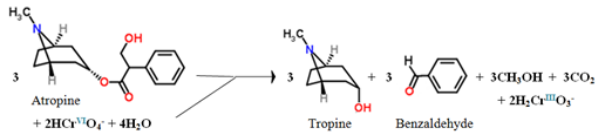
Results

Spectral changes

Spectral changes during the chromic acid oxidations of atropine in the absence and presence of Ru(III) catalyst are shown in Figure 1a and b respectively. In both cases, the recorder spectra indicate gradual decay of Cr(VI) band due to its reduction by atropine drug.

Stoichiometry and product characterization

Reaction mixtures containing various amounts of Cr(VI) and atropine at constant [H$^+$], ionic strength, and temperature were allowed to react for 24 h in closed vessels for completion of the oxidation reactions. The unconsumed [Cr(VI)] was determined spectrophotometrically at 350 nm. The results indicated that two moles of Cr(VI) are consumed by three mole of atropine drug to yield the oxidation products as shown in the following equation:



This equation is consistent with the product characterization. Tropine and benzaldehyde as the main reaction products were identified by spectral analysis as described elsewhere [24-26]. Tropine was also identified by its hydrazone derivative [24]. Methyl alcohol was confirmed by sodium test [24] and carbon dioxide was detected by lime water.

Effect of [chromic acid]

The effect of chromic acid on the oxidation rates of both uncatalyzed and Ru(III)-catalyzed reactions was investigated by varying its concentration in the range of (1.0 - 10.0) × 10^{-4} mol dm^{-3}. Plots of ln(absorbance) versus time were linear up to at least 75% of the reactions completion. Furthermore, increasing the initial oxidant concentration did not significantly affect the rates of the reactions. These observations suggest that the order of reactions with respect to the oxidant is unity.

Effect of [atropine]

The observed-first order rate constants for both paths were evaluated at different [ATR] with other variables constant. The results showed that increasing [ATR] increased the oxidation rates (Table 1). Plots of log k_U and log k_C versus log[ATR] were linear with slopes of 0.51 and 0.57 for uncatalyzed and catalyzed reactions, respectively, (Figure 2) suggesting that the orders of the reactions with respect to atropine concentration were less than unity.

Effect of [perchloric acid]

It was found that increasing [H$^+$] increased the oxidation rates as listed in Table 1 which suggested that the oxidation reactions were acid-catalyzed. Plots of log k_U and log k_C versus log [H$^+$] were found to be linear with positive slopes (Figure 3) confirming the less than unit order kinetics in [H$^+$].

Effect of [Ru(III)]

The effect of ruthenium(III) catalyst was examined by measuring the oxidation rate of atropine at various concentration of Ru(III), namely (2.0-18.0) × 10^{-5} mol dm^{-3}. The oxidation rate increased as [Ru(III)] increased. A plot of log k_C versus log [Ru(III)] was linear with unit slope as shown in Figure 4 indicating that the reaction order with respect to the catalyst concentration was unity.

Effect of manganese(II)

The involvement of Cr(IV) as an intermediate species of chromium during these reactions was examined by addition of different concentrations of Mn(II) to the reaction mixtures up to 0.01 mol dm^{-3}. The rate of the uncatalyzed reaction inhibited with increasing the concentration of Mn(II) as illustrated in Figure 5.

Effect of temperature

The rates of both uncatalyzed and Ru(III)-catalyzed oxidations of

10^4 [Cr(VI)] (mol dm^{-3})	10^2 [ATR] (mol dm^{-3})	[H$^+$] (mol dm^{-3})	10^5 [Ru(III)] (mol dm^{-3})	I(mol dm^{-3})	10^3 k_U (s^{-1})	10^3 k_C (s^{-1})
1.0	1.0	0.5	6.0	1.0	9.7	95.7
3.0	1.0	0.5	6.0	1.0	8.9	94.2
5.0	1.0	0.5	6.0	1.0	9.3	94.6
7.0	1.0	0.5	6.0	1.0	8.8	96.2
10.0	1.0	0.5	6.0	1.0	10.1	94.9
5.0	0.2	0.5	6.0	1.0	3.0	36.8
5.0	0.6	0.5	6.0	1.0	6.7	71.0
5.0	1.0	0.5	6.0	1.0	9.3	94.6
5.0	1.4	0.5	6.0	1.0	11.6	127.3
5.0	1.8	0.5	6.0	1.0	13.7	158.1
5.0	1.0	0.1	6.0	1.0	3.5	30.1
5.0	1.0	0.3	6.0	1.0	6.8	60.7
5.0	1.0	0.5	6.0	1.0	9.3	94.6
5.0	1.0	0.7	6.0	1.0	11.1	123.4
5.0	1.0	0.9	6.0	1.0	12.4	148.3
5.0	1.0	0.5	2.0	1.0	9.3	46.7
5.0	1.0	0.5	6.0	1.0	9.3	94.6
5.0	1.0	0.5	10.0	1.0	9.3	138.0
5.0	1.0	0.5	14.0	1.0	9.3	194.2
5.0	1.0	0.5	18.0	1.0	9.3	257.6
5.0	1.0	0.5	6.0	1.0	9.3	94.6
5.0	1.0	0.5	6.0	1.5	8.9	95.5
5.0	1.0	0.5	6.0	2.0	10.2	96.2
5.0	1.0	0.5	6.0	2.5	9.6	95.7
5.0	1.0	0.5	6.0	3.0	10.7	97.1

Table 1: Effects of variations of [Cr(VI)], [ATR], [H$^+$], [Ru(III)] and ionic strength, I, on the pseudo-first order rate constant values in the uncatalyzed and Ru(III)-catalyzed oxidations of atropine by chromic acid in perchlorate solutions at 25°C.

Reaction	$\Delta S^{\neq}$ (Jmol^{-1}K^{-1})	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta G^{\neq}_{298}$ (kJ mol^{-1})	$E_a^{\neq}$ (kJ mol^{-1})
Uncatalyzed	-103.32	48.02	78.81	46.52
Catalyzed	-84.53	33.47	58.66	35.33

Table 2: Activation parameters for the second order rate constant in the uncatalyzed and Ru(III)-catalyzed oxidations of atropine by chromic acid in perchlorate solutions

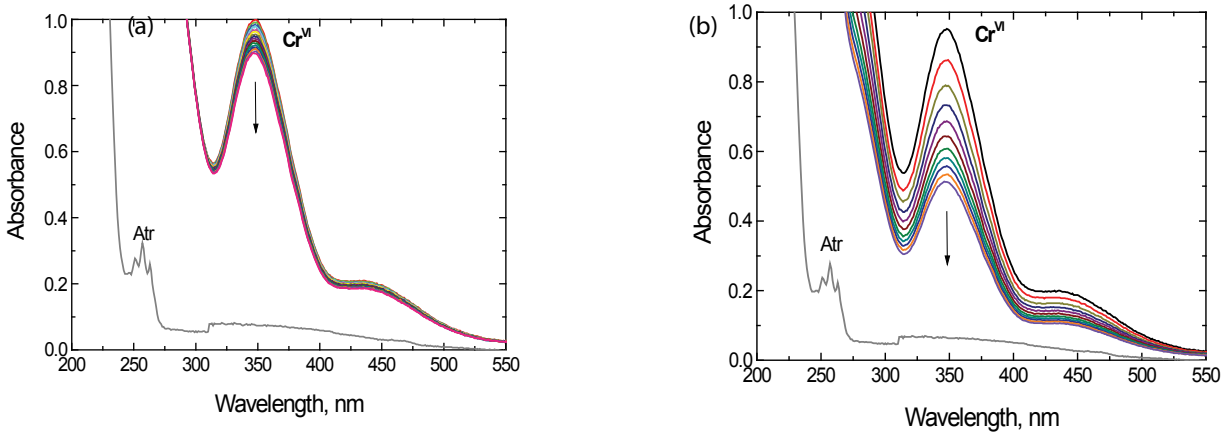


Figure 1: Spectral changes during: (a) uncatalyzed, and (b) Ru(III)-catalyzed oxidations of atropine by chromic acid in perchlorate solutions. [Cr(VI)]=5.0 × 10^{-4}, [ATR]=0.01, [H^+] =0.5 and I=1.0 mol dm^{-3} at 25°C.

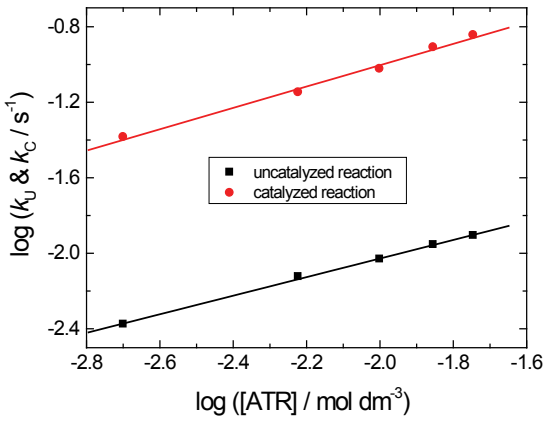


Figure 2: Plots of log k_U and log k_C versus log [ATR] in the: (a) uncatalyzed, and (b) Ru(III)-catalyzed oxidations of atropine by chromic acid in perchlorate solutions. [Cr(VI)]=5.0 × 10^{-4}, [H^+]=0.5 and I=1.0 mol dm^{-3} at 25°C. [Ru(III)]=6.0 × 10^{-5} mol dm^{-3}.

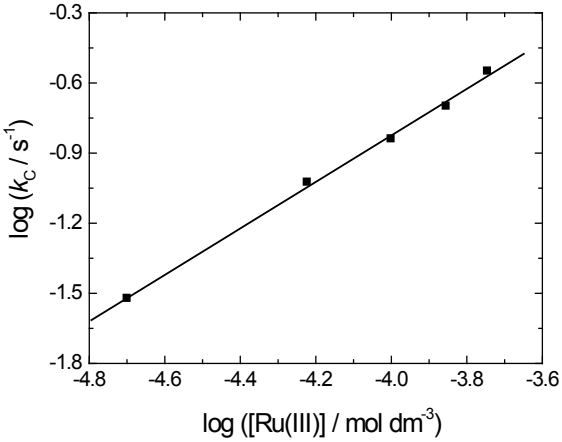


Figure 4: A plot of log k_C versus log [Ru(III)] in the Ru(III)-catalyzed oxidation of atropine by chromic acid in perchlorate solution. [Cr(VI)]=5.0 × 10^{-4}, [ATR]=0.01, [H^+]=0.5 and I=1.0 mol dm^{-3} at 25°C.

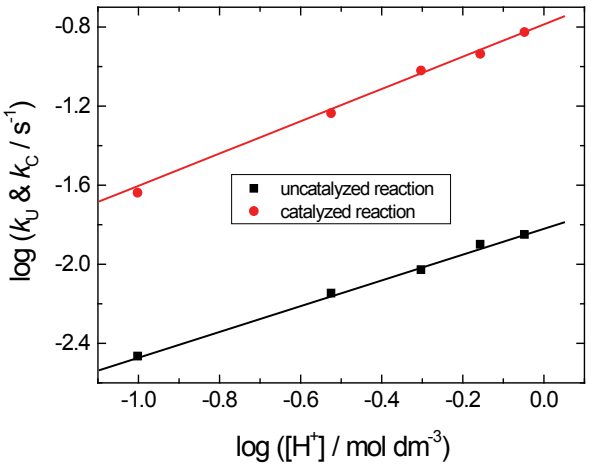


Figure 3: Plots of log k_U and k_C versus log [H^+] in the: (a) uncatalyzed, and (b) Ru(III)-catalyzed oxidations of atropine by chromic acid in perchlorate solutions. [Cr(VI)]=5.0 × 10^{-4}, [ATR] = 0.01 and I=1.0 mol dm^{-3} at 25°C. [Ru(III)]=6.0 × 10^{-5} mol dm^{-3}.

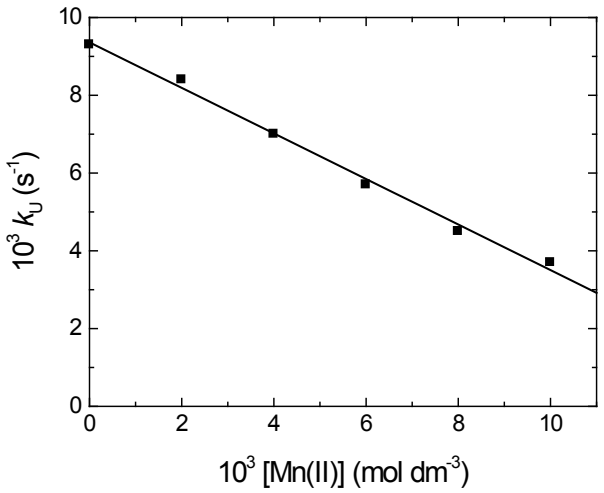


Figure 5: Effect of Mn(II) on the rate of uncatalyzed oxidation of atropine by chromic acid in perchlorate solution. [Cr(VI)]=5.0 × 10^{-4}, [ATR]=0.01, [H^+]=0.5 and I=1.0 moldm^{-3} at 25°C.

atropine were measured at different temperatures between 288 and 308 K, and all other conditions being constant. The values of k_U and k_C were found to increase with raising temperature and the activation parameters of the second order rate constant were determined using Eyring and Arrhenius plots and were listed in Table 2.

Polymerization test for free radical intermediates

The intervention of free radicals in both uncatalyzed and Ru(III)-catalyzed reactions was examined as follows: the mixtures to which known quantities of acrylonitrile had been added, were kept in an inert atmosphere for 6 h at room temperature. On diluting the reaction mixture with methanol, no white precipitates were formed thus confirming the absence of free radicals in the reactions.

Discussion

It is reported [27-31] that aqueous solutions of chromic acid contain ions such as CrO_4^{2-}, $HCrO_4^-$ and $Cr_2O_7^{2-}$, besides other protonated species such as H_2CrO_4, $HCr_2O_7^-$ and $H_2Cr_2O_7$ [32]. Increasing the oxidation rates with increasing $[H^+]$ in the present work suggested [32,33] that the protonated chromate (H_2CrO_4) may be the reactive species of Cr(VI).

Mechanism of uncatalyzed oxidation reaction

The reaction between atropine and chromic acid in perchlorate solutions was found to exhibit a less than unit order dependence on [ATR] suggestion formation of a complex (C_1) between atropine drug and chromic acid which was also proved kinetically by a non-zero intercept of the plot of $1/k_U$ versus 1/[ATR] [34] as shown in Figure 6. The complex formation of chromium(VI) with D-xylose and L-arabinose [35] and with tyrosine [36] in aqueous perchlorate solutions was also reported. The negligible effect of both ionic strength and dielectric constant of the medium is consistent with a reaction between two neutral molecules [37,38], i.e., between ATR and H_2CrO_4. The cleavage of such complex leads to the formation of one of the final oxidation products of atropine (tropine), Cr(IV) intermediate and tropic acid cation. The latter is rapidly hydrolyzed to the remainder oxidation products, benzaldehyde, methyl alcohol and carbon dioxide. This step is followed by a reaction between the second mole of atropine and another mole of chromic acid to give the oxidation products of atropine and another Cr(IV) intermediate. Finally, the third mole of atropine reacts with the formed two Cr(IV) intermediate species leading to the formation of the oxidation products of atropine and Cr(III) as the final oxidation product of chrmioum(VI), satisfying the observed reaction stoichiometry as illustrated in Scheme 1.

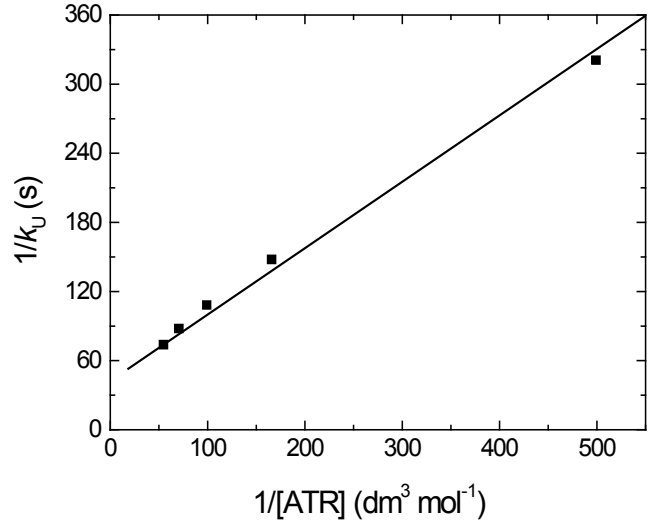


Figure 6: Verification of Eq. (4) in the uncatalyzed oxidation of atropine by chromic acid in perchlorate solutions. [Cr(VI)]=5.0 × 10^{-4}, [H$^+$]=0.5 and I=1.0 mol dm^{-3} at 25°C.

The suggested mechanistic (Scheme 1) leads to the following rate law expression,

$$\text{Rate} = \frac{k_1K_1K_2[HCrO_4^-][ATR][H^+]}{1+K_1[H^+]+K_1K_2[ATR][H^+]} \quad (1)$$

which explains all of the observed kinetic orders of different species.

Under pseudo-first order conditions,

$$\text{Rate} = \frac{-d[HCrO_4^-]}{dt} = k_U[HCrO_4^-] \quad (2)$$

Comparing Eqs. (1) and (2) gives,

$$k_U = \frac{k_1K_1K_2[ATR][H^+]}{1+K_1[H^+]+K_1K_2[ATR][H^+]} \quad (3)$$

Equation (3) can be rearranged into the following forms,

$$\frac{1}{k_U} = \left(\frac{1+K_1[H^+]}{k_1K_1K_2[H^+]}\right)\frac{1}{[ATR]} + \frac{1}{k_1} \quad (4)$$

$$\frac{1}{k_U} = \left(\frac{1}{k_1K_1K_2[ATR]}\right)\frac{1}{[H^+]} + \left(\frac{1}{k_1K_2[ATR]} + \frac{1}{k_1}\right) \quad (5)$$

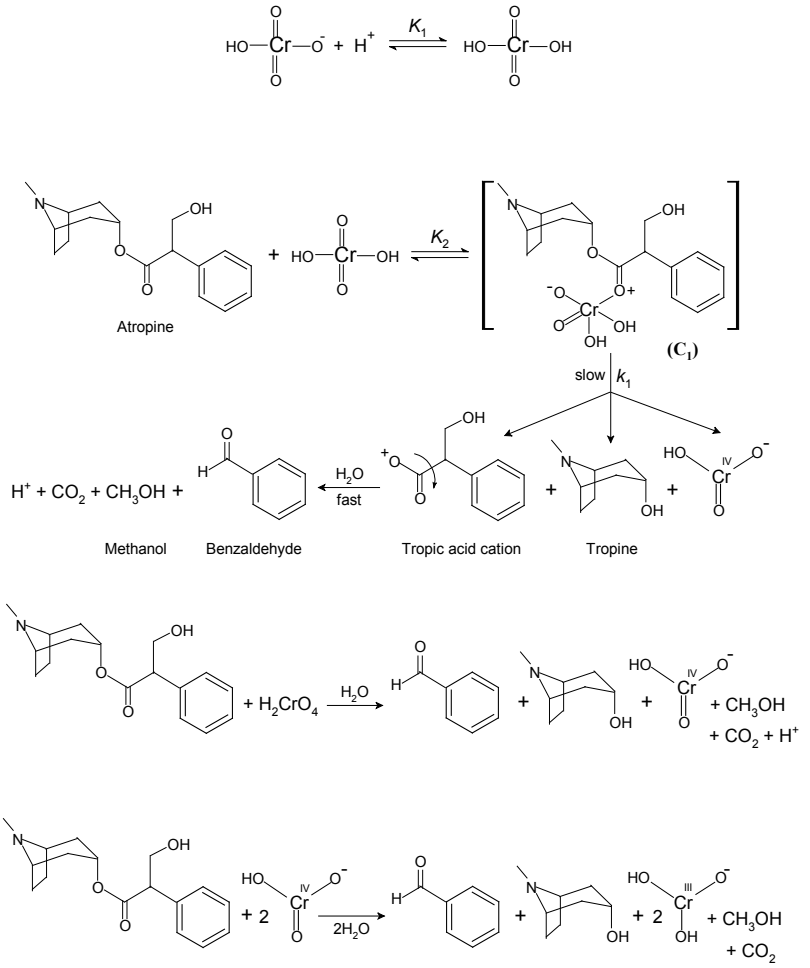
According to Eqs. (4) and (5), a plot of $1/k_U$ versus 1/[ATR] at constant $[H^+]$ should be linear with a positive intercept on $1/k_U$ axis as is observed experimentally (Figure 6) and a plot of $1/k_U$ against $1/[H^+]$ at constant [ATR] also should be a straight line with a positive intercept on $1/k_U$ axis and was found to be so (Figure 7) confirming the validity of the proposed mechanism.

Mechanism of ruthenium(III)-catalyzed oxidation reaction

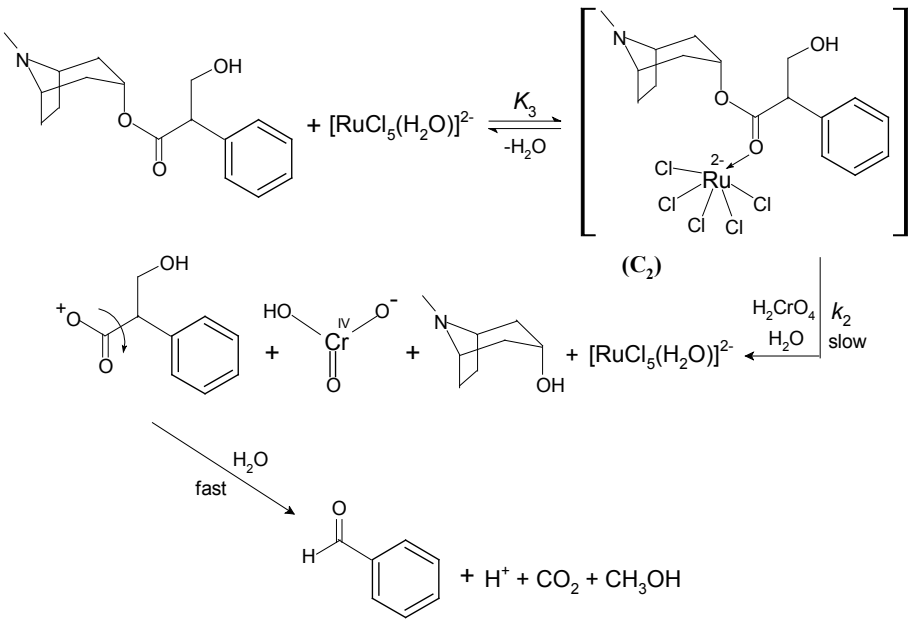
In acid media, the reactive species of Ru(III) chloride is suggested [39-41] to be $[RuCl_5(H_2O)]^{2-}$. The experimental results showed that the oxidation of atropine by chromic acid in the presence of small amounts of Ru(III) is similar to the uncatalyzed oxidation with respect to stoichiometry, reaction orders and effects of both ionic strength and dielectric constant of the reaction medium. The reaction was first order with respect to Ru(III). Therefore, the proposed catalyzed oxidation mechanism (Scheme 2) is likely to be similar, except for the participation of the catalyst. Thus, we propose that atropine forms an intermediate complex with the reactive species of Ru(III) catalyst in a pre-equilibrium step. Kinetic evidence for complex formation was obtained from the non-zero intercept of the plot of $[Ru(III)]/k_C$ versus 1/[ATR] (Figure 8). Such complex between atropine and Ru(III) was reported earlier [19] in the oxidation of atropine by copper(III) periodate complex in aqueous alkaline medium. The formed complex then attached by chromic acid in a slow step resulting in decomposition of the complex with regeneration of the catalyst, as well as formation of the final oxidation product tropine, Cr(IV) intermediate and tropic acid cation. The latter is rapidly hydrolyzed to the remainder oxidation products, benzaldehyde, methyl alcohol and carbon dioxide.

The suggested mechanism leads to the following rate law expression,

$$\text{Rate} = \frac{k_2K_1K_3[HCrO_4^-][ATR][Ru(III)][H^+]}{1+K_1[H^+]+K_1K_3[ATR][H^+]} \quad (6)$$



Scheme 1: Mechanism of the uncatalyzed oxidation of atropine by chromic acid in perchlorate solutions.



Scheme 2: Mechanism of Ru(III)-catalyzed oxidation of atropine by chromic acid in perchlorate solutions.

The rate law (6) is consistent with all observed orders with respect to different species.

Under pseudo-first order conditions,

$$\text{Rate} = \frac{-d[HCrO_4^-]}{dt} = k_C[HCrO_4^-] \quad (7)$$

$$k_C = \frac{k_2K_1K_3[ATR][Ru(III)][H^+]}{1+K_1[H^+]+K_1K_3[ATR][H^+]} \quad (8)$$

and with rearrangement,

$$\frac{[Ru(III)]}{k_C} = \left(\frac{1+K_1[H^+]}{k_2K_1K_3[H^+]}\right)\frac{1}{[ATR]} + \frac{1}{k_2} \quad (9)$$

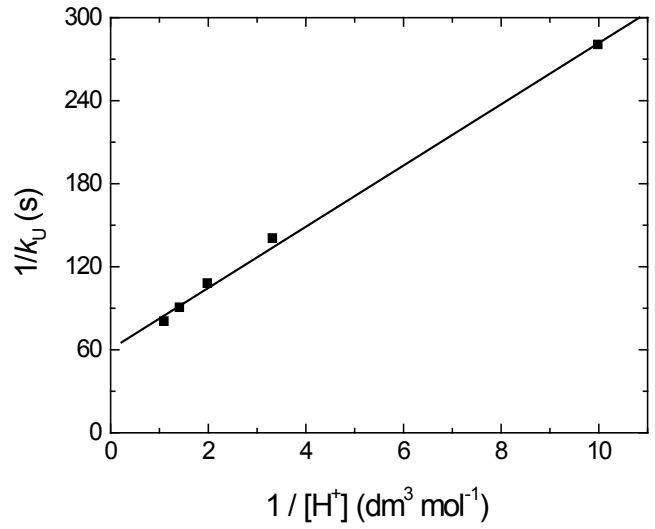


Figure 7: Verification of Eq. (5) in the uncatalyzed oxidation of atropine by chromic acid in perchlorate solutions. [Cr(VI)]=5.0 × 10^{-4}, [ATR]=0.01 and I=1.0 mol dm^{-3} at 25°C.

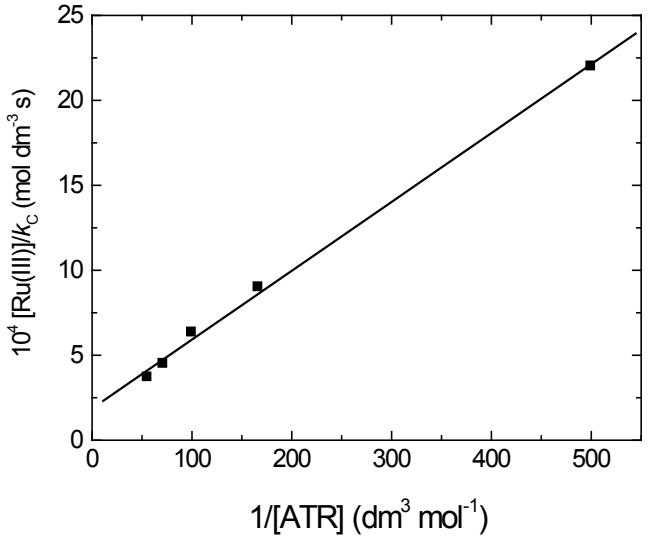


Figure 8: Verification of Eq. (9) in the Ru(III)-catalyzed oxidation of atropine by chromic acid in perchlorate solutions. [Cr(VI)]=5.0 × 10^{-4}, [ATR]=0.01, [Ru(III)]=6.0 × 10^{-5} and I=1.0 mol dm^{-3} at 25°C.

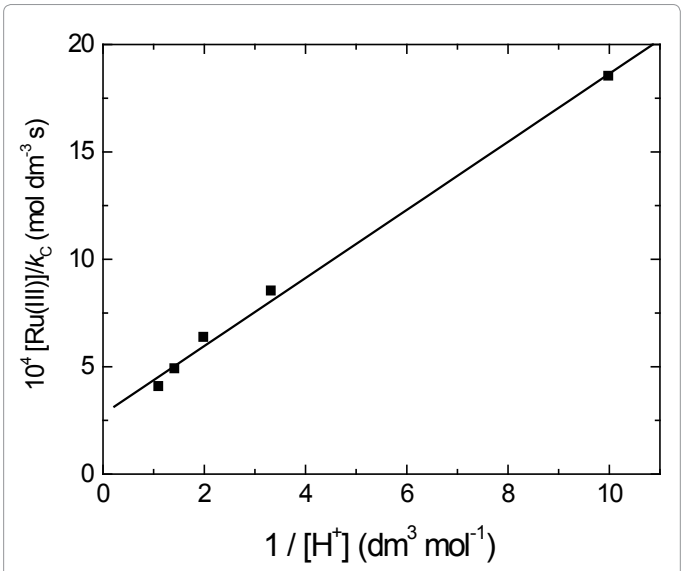


Figure 9: Verification of Eq. (10) in the Ru(III)-catalyzed oxidation of atropine by chromic acid in perchlorate solutions. [Cr(VI)]=5.0 × 10^{-4}, [ATR]=0.01, [Ru(III)]=6.0 × 10^{-5} and I=1.0 moldm^{-3} at 25°C.

$$\frac{Ru(III)}{k_C} = \left(\frac{1}{k_2K_1K_3[ATR]}\right)\frac{1}{[H^+]} + \left(\frac{1}{k_2K_3[ATR]} + \frac{1}{k_2}\right) \quad (10)$$

Equations (9) and (10) suggests that plots of $[Ru(III)]/k_C$ versus $1/[ATR]$ at constant $[H^+]$ and $[Ru(III)]/k_C$ versus $1/[H^+]$ at constant [ATR] should be linear with positive intercepts. The experimental results satisfied these requirements, as shown in Figures 8 and 9 respectively. The determined activation parameters listed in Table 2 showed that the values of entropy of activation ($\Delta S^{\#}$) were negative suggesting formation of compacted intermediate complexes of inner-sphere nature [40]. Also, the values of enthalpy of activation (H^*) and ΔS^* were both favorable for electron transfer processes.

Conclusions

The kinetics of uncatalyzed and Ru(III)-catalyzed oxidations of atropine drug by chromic acid in perchlorate solutions have been studied. Under comparable experimental conditions, the rate of Ru(III)-catalyzed oxidation of atropine was found to be about 10-fold higher than that of the uncatalyzed reaction. In both cases, the main oxidation products of atropine were identified by spectral and chemical analyses as tropine, benzaldehyde, methanol and carbon dioxide.

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