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Kinetics of Oxidation of Atropine by $K_2Cr_2O_7$ in Acidic Aqueous Solutions

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Oxidation of atropine (ATN) by $K_2Cr_2O_7$ has been studied kinetically in aqueous strongly acidic solutions. The kinetics of this reaction was investigated at different temperatures. A constant pH and constant ionic strength were maintained constant throughout all measurements. The concentration of atropine was around an order of magnitude greater than that of $K_2Cr_2O_7$, that is under pseudo first order kinetics. Rate constants were obtained by monitoring change in absorbance of $K_2Cr_2O_7$ with time at its predetermined maximum wavelength. Overall rate constant and the orders of the reaction in terms of concentrations of both atropine and $K_2Cr_2O_7$ were determined. Reaction runs at different temperature allows activation energy of the process to be convoluted from temperature effect on the rate of the reaction. A resonable mechanism for the reaction was proposed in accordance with kinetics results.

Keywords: Kinetics, Atropine, $K_2Cr_2O_7$, H_2CrO_4.

INTRODUCTION

Reaction kinetics of transition metal complexes by various reducing agents has been widely studied. Different methods were employed for kinetics measurements. Methods including: stopped-flow spectrophotometry, chemical analysis of products and the use of radioactive and stable isotope tracers. Details of these methods along with much of data produced are given elsewhere [1]. Of a special interest and relation to the present work, several papers have been published on kinetics study of oxidation by potassium dichromate in its different forms. In particular, kinetics of oxidation of various substrates by chromic acid has been reported [2-12]. Reaction kinetics of oxidation of atropine by alkaline potassium permanganate has been investigated recently [13]. However, detailed mechanistic study of oxidation of atropine by powerful oxidizing reagents including potassium dichromate in appropriate pH's are still limited.

There are several medicinal uses of atropine. In the warfare, atropine in the salt form as atropine sulfate monohydrate (ASM), Fig. 1, mixed with pralidoxime chloride, 2-PAM chloride, is commonly used as an antidote for poisoning by organophosphate insecticides and nerve gases [14].

Chromium(VI) is known to be mutagenic and carcinogenic, hence, posing a serious environmental hazard [15]. It is used for many applications [16-25]. Consequently, it is of crucial importance gaining as much information as possible regarding its various forms and their interaction with organic substrates.

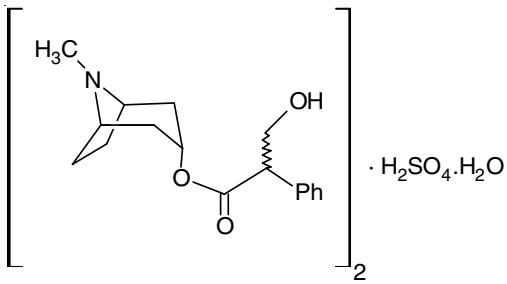

Fig. 1. Atropine sulfate monohydrate

Potassium dichromate in strongly acidic media can be present in the form of chromate ion (CrO_4^{2-}), bichromate ion ($HCrO_4^-$) and chromic acid (H_2CrO_4). Which species presumed present in aqueous media is a function of pH and ionic strength and largely still an open discussion subject [21]. However at the Cr(VI) concentration used herein, the chromate ion is

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absent [22]. It is also demonstrated that the $HCrO_4^-$ species is spectrophotometrically undetectable in the UV-visible region. That will leave chromic acid as the predominant and might be the only detectable species under the highly acidic conditions of this study.

In the present work and as an extension of our previous kinetics studies on biologically important molecules [13], a mechanistic aspect of oxidation reaction of atropine by chromic acid has been investigated. The kinetics of the reaction has been determined spectrophotometrically. Reaction rates have been determined by monitoring the decrease of absorption of Cr(VI) at its absorption maximum, $\lambda_{max} = 350$ nm. It was verified that at this wavelength there are no interferences from either the reactants, products or any other reagent involved. **Scheme-I** represents the overall reactions involved in this study.

EXPERIMENTAL

The following set of preliminary experimental runs was designed to sort out the different reactions taking place under the strongly acidic conditions used herein.

Acidic hydrolysis: Atropine sulfate monohydrate (0.10 M) was treated with concentrated H_2SO_4 (1.0 M) solution for 25 min. Products were then isolated, purified and characterized by various NMR and IR spectroscopic techniques. There is apparently no hydrolysis to any measurable extent under reaction conditions used in this study.

Cr(VI) in strongly acidic medium: A blank run of mixing all ingredients [$K_2Cr_2O_7$ (0.001M), H_2SO_4 0.10M)] except atropine sulfate monohydrate, has shown that the change in absorption by H_2CrO_4 is negligible throughout the measuring period. No spectrophotometrical evidence was obtained for the presence of any other species apart from chromic acid.

Acidic $K_2Cr_2O_7$ oxidation: Approximately 10 folds in excess of atropine sulfate monohydrate solution (0.01 M) was treated with the acidic $K_2Cr_2O_7$ (0.001 M) solution for 25 min. Spectroscopic data of the products have shown the presence of excess atropine and the oxidized product (**Scheme-I**). A radical involvement in this reaction was ruled out based on the tests of adding mercuric chloride or acrylonitrile monomer to the reaction. Neither induced a white precipitate formation or polymerization, respectively [17-19].

As a result, it is presumed that the reaction under investigation is not accompanied by hydrolysis of atropine. No species other than chromic acid has an absorbance at the selected wavelength throughout the course of the reaction.

Kinetics measurements: Different concentrations of atropine sulfate monohydrate and $K_2Cr_2O_7$ were used in this study. In a strongly acidic solution, a condition of this study, atropine sulfate monohydrate is converted to atropine and $K_2Cr_2O_7$ is converted to H_2CrO_4. Diode Array Spectrophotometer model 8453E from HP Agilent Technologies was used. Reactions were monitored by measuring the absorbance of chromic acid with time at its wavelength of maximum absorbance difference, λ_{max}. This wavelength was predetermined from the absorption spectra for chromic acid alone and for its mixture with atropine sulfate monohydrate after completion of the reaction. Fig. 2 shows a scan at different time intervals for reactants and products, from which λ_{max} was determined to be at 350 nm. Absorbance at this wavelength is mainly due to chromic acid. However absorbance at this wavelength of organic compounds, reactant or products is negligible.

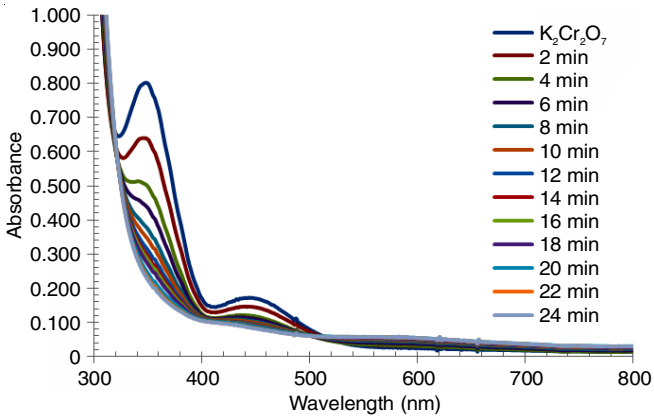
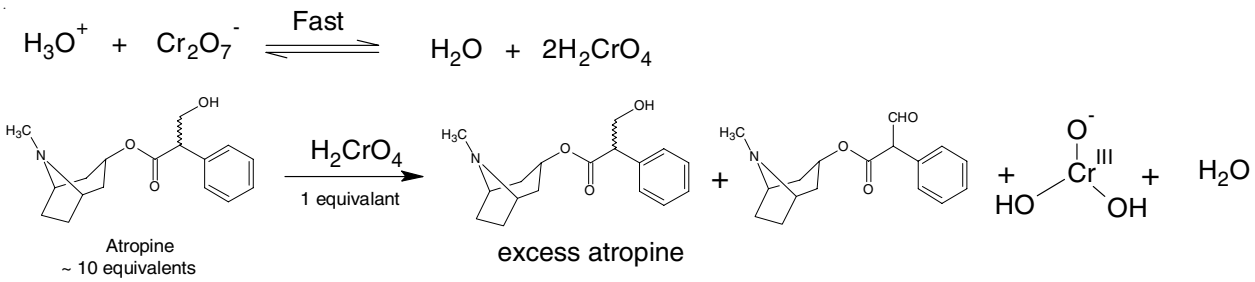


Fig. 2. Absorbance *vs.* λ for $K_2Cr_2O_7$ and for the reaction mixture; λ_{max} = 350 nm [$K_2Cr_2O_7$] = 1.00×10^{-3} M, [ATN] = 1.00×10^{-2} M

Reaction rates were determined under pseudo-first order condition, The concentrations of atropine [10^{-2} to 10^{-1} mol dm^{-3}] were an order of magnitude greater than those of $K_2Cr_2O_7$ [10^{-4} to 10^{-2} mol dm^{-3}]. All runs were done at constant pH and ionic strength (ionic strength was maintained using $NaClO_4$). Rates were also determined at various temperatures. The temperature for each run was thermstatically controlled within ± 0.1 ºC.

RESULTS AND DISCUSSION

Chromium(VI) in strongly acidic medium exists in the form of chromic acid H_2CrO_4 [17]. Atropine on the other hand will exist in the hydrated form. The UV/visible absorption spectrum taken directly after mixing atropine with Cr(VI) in a H_2SO_4/H_2O medium shows an absorbance band at 350 nm and a shoulder at 420–500 nm, characteristic of Cr(VI) in acidic medium (Fig. 2). The absorbencies at 350 nm and 420–470



Scheme-I: Overall reactions involved

nm decay with time, while the absorbance at 570 nm increases. The observation of isosbestic point (centered at λ = 520 nm) indicates that the stoichiometry of the reaction remains unchanged during the chemical reaction and that no competing reactions occur during the considered time range. At the end of the redox reaction, the bands from 520-700 nm indicates the formation of Cr(III) product [20]. It is well-established that both Cr(V) and Cr(IV) species absorb at 350 nm, consequently, Cr(V)/Cr(IV) contributions have to be taken into account when interpreting the absorbance decay [21]. Nevertheless Cr(IV) species are unstable oxidation state throughout the reduction of chromium ion from hexavalent to trivalent states. It implies that the decay rate of Cr(IV), if present, will take place at a much higher rate compared to that of Cr(VI) which will ultimately lead to a little contribution to the absorbance measured at 350 nm.

The involvement of free radicals in this reaction has been ruled out by addition of acrylonitrile or $HgCl_2$ to the reaction mixture with the observations that are consistent with that conclusion.

Kinetics: The rate of oxidation of atropine (ATN) by H_2CrO_4 is given by:

$$\text{Rate} = k\,[ATN]^a[H_2CrO_4]^b \quad (1)$$

where k is the reaction rate constant, a & b are orders of reaction with respect to concentrations of atropine and H_2CrO_4, respectively. The concentration of H^+ was kept constant at 17 M throughout all kinetics measurements. Under pseudo-first order conditions in which [ATN] ⟩⟩ [H_2CrO_4], the concentration of atropine is essentially constant throughout the reaction. The reaction rate is thus given by:

$$\text{Rate} \approx -\frac{d[H_2CrO_4]}{dt} = k_{obs}[H_2CrO_4]^b \quad (2)$$

where k_{obs} is the observed rate of reaction, given by:

$$k_{obs} = k\,[ATN]^a \quad (3)$$

where k is the rate constant of reaction (1).

For a first-order dependence of reaction rate on [H_2CrO_4], *i.e.* b = 1, experimental absorbance-time data pairs were fitted to the exponential function:

$$(A_\infty - A_t) = (A_\infty - A_0)\exp(-k_{obs}\,t)$$

or

$$\ln\left(\frac{(A_\infty - A_t)}{(A_\infty - A_0)}\right) = -k_{obs}t \quad (4)$$

where A_t is the absorbance of the reaction mixture which is mainly due to H_2CrO_4 at a given time (t) through the reaction, A_0 is its initial absorbance (t = 0) and A_∞ is the absorbance of the mixture at the end of the reaction, that is when the absorbance no longer changes with time (t = ∞).

Experimental results showed that a plot of ln [$(A_\infty - A_t)/(A_\infty - A_0)$] *vs.* time gives a straight line. Its slope represents the rate of disappearance of H_2CrO_4, The value of k_{obs} (s^{-1}) was obtained from the slope, according to eqn. 4. Using eqn. 3, a plot of ln k_{obs} *vs.* ln $[ATN]^a$ is a straight line that gives the reaction rate constant, k, in units of $dm^3\ mol^{-1}\ s^{-1}$ (intercept) and the order of the reaction (a) with respect to [ATN] (slope). At specific concentrations of substrate and oxidant, several trials were carried out for each concentration and the average value of the observed rate is reported. Experimental errors in value of rate constant are estimated to be ~ ± 10 %.

The observed rates constant of the reaction (k_{obs}) at various concentrations of $Cr_2O_7^{2-}$ and constant [ATN], with [ATN] ⟩⟩ [$Cr_2O_7^{2-}$] are shown in Table-1.

TABLE-1
KINETICS RESULT FOR THE OXIDATION OF ATROPINE BY $K_2Cr_2O_7$ AT CONSTANT [ATN];
[ATN] = 1.00×10^{-2} M. Average $k_{obs} = (7.54 \pm 0.8) \times 10^{-3}\ s^{-1}$

Run No.	$[Cr_2O_7^{2-}]$ (mol L^{-1})	$k_{obs} \times 10^3$ (s^{-1})
1	2.00×10^{-3}	7.55
2	1.75×10^{-3}	8.27
3	1.50×10^{-3}	6.82
4	1.00×10^{-3}	7.50
5	6.70×10^{-4}	7.54

Table-1 shows that the values of k_{obs} are constant within experimental errors, indicating that the oxidation rate of atropine by $K_2Cr_2O_7$ is first order with respect to [$K_2Cr_2O_7$] according to eqn. 4.

The effect of concentration of atropine on reaction rate was studied. The observed rate of reaction was measured at various concentrations of atropine while keeping the concentration $K_2Cr_2O_7$ constant. Results are shown in Table-2.

TABLE-2
KINETICS RESULT FOR THE OXIDATION OF ATROPINE BY $K_2Cr_2O_7$ AT CONSTANT $[Cr_2O_7^{2-}]$;
$[Cr_2O_7^{2-}] = 1.00 \times 10^{-3}$ M

Run No.	[ATN] (mol L^{-1})	$k_{obs} \times 10^3$ (s^{-1})
1	2.00×10^{-2}	14.9
2	1.75×10^{-2}	13.5
3	1.50×10^{-2}	10.7
4	1.00×10^{-2}	7.50
5	0.75×10^{-2}	5.74
6	0.50×10^{-2}	3.19

The overall rate constant for oxidation of atropine by $K_2Cr_2O_7$, k, and the order of the reaction with respect to [ATN], a, were found from the intercept and the slope, respectively, of a plot of ln (k_{obs}) *versus* ln [ATN] according to eqn. 3. The slope represents the order ($a \approx 1$) and $e^{intercept}$ represent k, equals $(1.04 \pm 0.1) \times 10^{-1} dm^3\ mol^{-1}\ s^{-1}$.

Effect of temperature: Effect of temperature on reaction rate was studied at various temperatures keeping concentrations of atropine and $K_2Cr_2O_7$ constant. As expected, the observed rate and the rate constant of the reaction increase as temperature increases.

Using Arrhenius equation:

$$k = A\,e^{-Ea/RT}$$

or

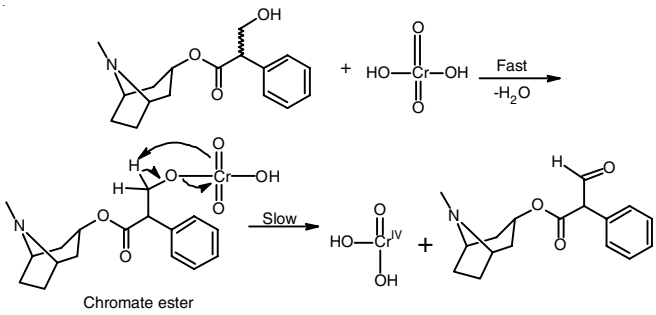
$$\ln k = \ln A - \frac{E_a}{RT} \quad (5)$$

The activation energy (E_a) and the Arrhenius factor (A) were obtained by plotting ln k *versus* (1/T). Results are shown in the Table-3. It was found that E_a = 33. 70 kJ, $A = 8.14 \times 10^5$ $dm^3\ mol^{-1}\ s^{-1}$.

TABLE-3
KINETICS RESULTS FOR THE OXIDATION OF ATROPINE BY $K_2Cr_2O_7$ AT VARIOUS TEMPERATURES; $[Cr_2O_7^{2-}] = 1.00 \times 10^{-3}$ M, [ATN] = 1.00×10^{-2} M

Run No.	Temp. (°C)	k (dm^3 mol^{-1} s^{-1})
1	25.0	1.04
2	40.0	1.84
3	50.0	2.92
4	60.0	4.31

Based on the obtained kinetics results, we propose the following mechanism for the oxidation process of atropine.



Under these reaction conditions, chromic acid reacts with atropine forming chromate ester intermediate in a fast step that is concomitant by loss of water molecule. Chromate ester are well-known intermediates for oxidation of alcohols in acid chromic acid solutions [22]. The formed chromate ester is then decompose quickly to the products that is identified as the corresponding aldehyde of atropine and Cr(IV) species. It is strongly plausible that the reaction does not proceed further to yield the correspond acid due to the limited amount of chromic acid available to react. In addition there is no evidence to show a regeneration mechanism of the oxidizing reagent. Structures of intermediates and complexes are not conclusive. However, identification of the organic product has been established through ^{1}H NMR & ^{13}C NMR, FT-IR and GC-MS techniques.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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