INTRODUCTION

Atropine sulfate monohydrate (ASM, Fig. 1) is pharmaceutical formulation that is one of the World Health Organization’s list of essential medicines\(^1\). Atropine itself is a naturally occurring tropane alkaloid with chemical structure similar to that of cocaine. Plants of the family Solanaceae that includes Atropa belladonna, Datura stramonium and Mandragora officinarum are the major natural sources of the alkaloid. Atropine serves as a drug with a wide variety of effects\(^2\). It is a competitive antagonist of the muscarinic acetylcholine receptors, hence its major effects are on the parasympathetic nervous system. As an anticholinergic drug (parasympatholytic) it is considered a nonselective muscarinic anticholinergic antagonist. Consequently, its main medical uses are based on these potent biological properties. Since it blocks the action of the vagus nerve, atropine is used in resuscitation procedures\(^3\). Additionally, atropine mixed with pralidoxime chloride (2-PAM chloride) is used as an antidote for poisoning by organophosphate insecticides and nerve gases, such as Tabun (GA), Sarin (GB), Soman (GD) and VX\(^4\). Atropine has also several medical applications that include ophthalmic uses as therapeutic mydriatic and in slowing the progression of myopia in children\(^5,6\).

As much as it is crucially important to understand this kind of physiological activity\(^2\), atropine interactions with common chemical reagents are still lacking. Oxidation of atropine by alkaline copper(III) periodate complex has been recently reported\(^8,9\). Organic oxidation protocols have commonly employed transition metal complexes in their higher oxidation states that can be stabilized by appropriate polydentate ligands\(^10,11\). Atropine oxidation by typical strong oxidizing reagents including potassium dichromate and potassium permanganate in appropriate pH media have never been reported to the best of our knowledge. Understanding the behaviour of atropine when treated with powerful oxidizing agents in aqueous media might shed some light into its interaction with oxidative enzymes such as FAD and NADP\(^12\).

Kinetics of oxidation of organic substrates by alkaline KMnO\(_4\) has been reported in literature and demonstrated to be a powerful mechanism elucidating tool. Examples include oxidation of DL-aspartic acid and sugars\(^13,14\).
It is assumed that, under the reaction conditions and stoio-
methies used herein, oxidation of the aliphatic alcohol of
atropine to a carboxyl group is the predominant reaction\(^\text{15}\) (Scheme-I). Permanganate ion attains its optimum stability
in neutral to slightly alkaline media\(^\text{16}\). However, in strongly
alkaline media, it disproportionates to manganese(V) (hypo-
manganate) or manganese(VI) (manganate). Hence, for oxida-
tion reactions under these conditions it will be difficult to deter-
mine whether a one or two electron process is operating\(^\text{12}\). To
sort out the exact reaction of basic KMnO\(_4\) with atropine a set
of preliminary experiments were done.

In the present work, as an extension of our previous
studies\(^\text{17-20}\) on both kinetics and biological application to widen
our knowledge about the oxidation of biologically important
substances, we report the kinetics of oxidation of atropine by
alkaline KMnO\(_4\). Kinetic results at various temperatures are
presented and a proposed mechanism for the oxidation process
is given and discussed.

**EXPERIMENTAL**

**Alkaline hydrolysis:** Atropine sulfate monohydrate (0.10
M) was treated with KOH (1.0 M) solution for 25 min (optimum
run time frame for reaction monitoring, arbitrary set). Hydrolysis
products were then isolated, purified and characterized by
NMR and IR spectroscopy. Results indicated that hydrolysis
did not proceed to any measurable extent. However, the
addition of MnO\(_2\) greatly enhanced the hydrolysis.

**Alkaline KMnO\(_4\) disproportionation:** A blank run of
mixing all ingredients [KMnO\(_4\) (0.001 M), KOH 0.10 M]
except atropine sulfate monohydrate has shown that the change
in absorption by KMnO\(_4\) is negligible throughout the
measuring period.

**Alkaline KMnO\(_4\) oxidation:** Atropine sulfate monohydrate
solution (0.01 M) (about 10 folds in excess) was treated with
the alkaline KMnO\(_4\) (0.001 M) solution for 25 min. Products
were isolated, purified and thoroughly characterized. The
products were excess atropine, tropine, tropic acid and phenyl-
malonic acid (Scheme-I). Addition of mercuric chloride or
acrylonitrile monomer to the reaction system, directly after
the appearance of the green colour of MnO\(_4^2-\), induced a white
precipitate formation and polymerization, respectively. Conse-
quently, a radical formation throughout the course of the
reaction mechanism cannot be ruled out\(^\text{21,22}\). The reaction was
quenched and the green colour persists.

These results implicated that the major change in the
oxidant concentration (absorbance at its maximum wavelength)
is attributed to the oxidation of atropine primary alcohol.
Hence, kinetic measurements were designed to follow up this
reaction. It is aimed to investigate the mechanism by which
the reaction is taking place.

**Scheme-I:** Main reactions of atropine in presence of KMnO\(_4\) in basic medium
**Kinetics measurements:** Freshly prepared aqueous solutions of desired concentrations of atropine sulfate monohydrate and KMnO₄ were used in the kinetic study. In a strongly basic solution (0.1 M), atropine sulfate monohydrate is converted to atropine. Measurements were carried out using a Diode Array Spectrophotometer model 8453E from HP Agilent Technologies. Reactions were monitored by following the change in absorbance of (MnO₄²⁻) reaction mixture with time at a predetermined wavelength. The wavelength was determined by recording the absorption spectra for KMnO₄ alone and for its mixture with atropine sulfate monohydrate after completion of the reaction. The wavelength of maximum absorbance difference (λ_{max}), preferably in visible region of the spectra, between the absorption of KMnO₄ and the reaction mixture was selected. A λ scan for reactants and products at various time intervals is shown in Fig. 2, from which λ_{max} = 440 nm was selected. At this wavelength absorbance is mainly due to MnO₄²⁻ and absorbance due to all other Mn species is minimal. Also, it should be noted that none of the organic compounds, reactants or products, absorb at this wavelength.

All reactions were studied under pseudo-first order conditions, at which the concentrations of atropine sulfate monohydrate [10⁻² to 10⁻¹ \text{ mol dm}⁻³] were at least an order of magnitude larger than those of KMnO₄ [10⁻⁴ to 10⁻² \text{ mol dm}⁻³]. The pH of the reaction mixture was maintained constant at 13.0 ± 0.1 and its ionic strength was fixed using NaClO₄. Rates were measured at various temperatures and for each measurement it was maintained constant within ± 0.1 °C.

**RESULTS AND DISCUSSION**

The main reactions of oxidation of atropine by KMnO₄ in basic medium are shown in [Scheme-I](image). Since kinetics measurements were run under pseudo first order condition, in which the concentration of atropine is an order of magnitude larger than that for KMnO₄, then, the first stage of the process which involves the oxidation of atropine by alkaline KMnO₄ is given by the following equation:

\[
\text{Rate} = k[\text{ATN}]^a[\text{KMnO}_4]^b
\]

where \(k\) is the reaction rate constant and \(a\) & \(b\) are orders of reaction with respect to concentrations of atropine and KMnO₄, respectively. The concentration of OH⁻ was kept constant at 0.10 M throughout the all kinetics measurements. Under pseudo-first order conditions in which [ATN] >> [KMnO₄], the concentration of atropine is essentially constant throughout the reaction. The reaction rate is thus given by:

\[
\text{Rate} = -\frac{d[\text{KMnO}_4]}{dt} = k_{obs}[\text{KMnO}_4]^b
\]

where \(k_{obs}\) is the observed rate for reaction is given by:

\[
k_{obs} = k[\text{ATN}]^a
\]

where \(k\) is the rate constant for eqn. 1.

For a first-order dependence of reaction rate on [KMnO₄], experimental absorbance-time data pairs were fitted to the exponential function:

\[
\ln \frac{(A_\infty - A_0)}{(A_\infty - A_t)} = -k_{obs}t
\]

where \(A_t\) is the absorbance of the reaction mixture which is mainly due to MnO₄²⁻ at a given time \(t\) through the reaction, \(A_0\) is its initial absorbance \((t = 0)\) and \(A_\infty\) is the absorbance of the mixture at the end of the reaction, that is when the absorbance no longer changes with time \((t = \infty)\).

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 appearance of MnO₄²⁻, which equals the rate of disappearance of MnO₄⁻ (as shown in the suggested mechanism below). 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. \([\text{ATN}]\) is a straight line that gives the reaction rate constant, \(k\), in units of \text{dm}³ \text{ mol}⁻¹ \text{ s}⁻¹ (intercept) and the order of the reaction \(a\) with respect to \([\text{ATN}]\) (slope).

Attach the mechanism diagram here.
In a strongly basic solution, MnO₄⁻ is known to occur in two stages. For the first stage, KMnO₄ is known to occur in two stages. For the first stage, the rate of formation of MnO₄²⁻ is approximately equal to the rate of disappearance of MnO₄²⁻. Oxidation of primary alcohols under strongly alkaline conditions is known to occur in two stages. For the first stage, an aldehyde intermediate is well-established. Further oxidation of the aldehyde to the final product (carboxylic acid) proceeds at a faster rate compared to the first stage.

Fig. 7 depicts the absorbance change over the whole reaction time. Clearly the reaction is governed by two distinctive rates. The reason for two stages is based on the fact that intermediates are reaching their optimum concentration or due to the occurrence of consecutive reactions. At the first stage (steps 1-3) of the reaction, the absorbance increased rapidly with time that indicating that oxidation of atropine to intermediate I which is relatively slow (compared with stage 2 (steps 4 and 5)). The rate limiting step of this stage is represented by step 2 (eqn. 6). However, at certain time when an optimum concentration of intermediate II (then the hydrate form of the aldehyde) is reached, the reaction will be controlled by step 5 (eqn. 9) that is faster than the first limiting step 3. Finally oxidation of intermediate II proceeds cleanly to produce the final products.

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

Step 1

ATN + [MnO₄OH]²⁻ \( \rightarrow \) C

Step 2

C \[ \xrightarrow{k_2} \] MnO₄²⁻ + I + OH⁻ (Slow)

Step 3

MnO₄²⁻ + I \[ \xrightarrow{k_3} \] II + MnO₄⁻ + H₂O

Step 4

Hydrate of II + [MnO₄OH]²⁻ \[ \xrightarrow{k_4} \] D

Step 5

D \[ \xrightarrow{k_5} \] MnO₄²⁻ + product + OH⁻ (Slow)

Step 6

MnO₄²⁻ disproportionates to MnO₂²⁻ where C and D are complexes, I and II are intermediates.

In a strongly basic solution, MnO₄⁻ will be in the form of [MnO₄OH]²⁻. Experimentally, the reaction rate was followed by monitoring the change in absorbance of the reaction mixture with time at λ = 440 nm. At this wavelength, the absorbance (A₀) is mainly due to the formation of MnO₄²⁻ (Fig. 2) and it is increasing with time. Due to regeneration of MnO₄²⁻ from MnO₄⁻ (eqn. 7), then the rate of formation of MnO₄²⁻ is approximately equal to the rate of disappearance of MnO₄⁻.

### TABLE-1

**CONCENTRATION EFFECT ON RATE OF OXIDATION OF ATROPINE BY KMnO₄ IN AQUEOUS BASIC SOLUTIONS, [KOH] = 0.10 M**

| Run | [ATN] M | \( k_{obs} \times 10^3 \) | \( k_{act} \times 10^3 \) |
|-----|---------|--------------------------|--------------------------|
| 1   | 2.00 × 10⁻² | 2.26                     | 5.26                     |
| 2   | 1.75 × 10⁻² | 2.13                     | 5.64                     |
| 3   | 1.50 × 10⁻² | 2.18                     | 5.27                     |
| 4   | 1.00 × 10⁻² | 2.25                     | 5.40                     |

| Run | [ATN] M | \( k_{obs} \times 10^3 \) | \( k_{act} \times 10^3 \) |
|-----|---------|--------------------------|--------------------------|
| 5   | 1.75 × 10⁻² | 2.80                     | 6.51                     |
| 6   | 1.50 × 10⁻² | 2.66                     | 6.30                     |
| 7   | 1.00 × 10⁻² | 2.25                     | 5.40                     |
| 8   | 0.50 × 10⁻² | 1.91                     | 3.79                     |
The change in absorbance with time represents the rate of the reaction according to eqn. 2. From a kinetic point of view, steps 2 and step 5 will be the rate determining steps and steps 1, 3, 4, 6 are fast. Experimentally, two rates were observed. The first reaction rate (rate 1) is due to step 2, consequently, eqn. 1 above can be rewritten as:

\[
\text{Rate 1} = k_1 [\text{ATN}] [\text{MnO}_4^2-]
\]

Here, \( k_1 \) is a constant quantity which represents the first rate of the reaction and will be represented as \( k_{\text{obs1}} \). Then,

\[
\text{Rate 1} = k_{\text{obs1}} [\text{ATN}][\text{MnO}_4^2-]
\]

The second reaction rate (rate 2) is due to step 5, given by:

\[
\text{Rate 2} = k_2 [\text{ATN}] [\text{MnO}_4^2-]a
\]

The concentration of \( \text{MnO}_4^2- \) produced equals to the concentration of reacted \( \text{MnO}_4^- \). The constant quantity \( k_2 \) represent the second rate of the reaction and will be called \( k_{\text{obs2}} \). Then:

\[
\text{Rate 2} = k_{\text{obs2}} [\text{ATN}][\text{MnO}_4^2-]a
\]

A strong reason why a \( \lambda_{\text{max}} \) at 440 nm, which is specific for \( \text{MnO}_4^2- \), was selected is due to the formation of \( \text{MnO}_4^2- \) in both of the slow steps 2 and 5. The disappearance of the distinct peroxidase absorbance band located in the range of wavelengths 490-590 nm and the formation of bands with maxima at 347, 439 and 606 nm (Fig. 2) are characteristic of manganese. MnO4-2, supports this observation. Disproportionation of manganese to form permanganate and manganese dioxide is then follows25. Possible structures of the intermediates and complexes involved are shown in Fig. 8. It is worth mentioning that the proposed structures of these intermediates are not conclusive but highly possible26. The aldehyde-intermediate(II) is logical since it is a common intermediate for similar oxidations (e.g., K2Cr2O7 oxidation)27. Wiberg and Stewart25 demonstrated the free radical mechanism of oxidation of aldehydes by alkaline KMnO4 solution. Formation of permanganate ester of the hydrate of the aldehyde was also implicated. The regenerated permanganate present in the form (\( \text{MnO}_4^2- \)) will react preferentially with intermediate II rather than the excess atropine, since it is known that aldehydes are more reactive compared to primary alcohols toward the permanganate oxidizing reagent. This step involves a second single electron transfer.

\[
\text{Rate 2} = k_{\text{obs2}} [\text{ATN}][\text{MnO}_4^2-]a
\]

The above proposed mechanism is supported by the observation of initial colour change of permanganate from violet to green (manganate). The radical mechanism was invoked due to the precipitation observed when mercuric chloride was added to the system28. When HgCl2 was added after the appearance of the green colour, the colour persists. The reaction was quenched at this stage.

Since the observed overall rate was obtained to be first order with respect to permanganate, eqns. 11 and 12 above will have the following expression

\[
\text{Rate} = k_{\text{obs}} [\text{MnO}_4^-]
\]

And since \( [\text{ATN}] >> [\text{KMnO}_4] \), the observed rate of the reaction, \( k_{\text{obs}} \), is given by:

For step 2:

\[
k_{\text{obs1}} = k_{\text{obs2}} [\text{ATN}]k
\]

For step 5:

\[
k_{\text{obs2}} = k_{\text{obs2}} [\text{ATN}]k
\]

The rates constant \( k_{\text{obs1}} \) and \( k_{\text{obs2}} \) were obtained from plots of \( \ln [\text{ATN}] \) vs. \( \ln [\text{ATN}] \) and \( \ln [\text{ATN}] \) vs. \( \ln [\text{ATN}] \), respectively.

Effect of temperature on rate constant was studied. Results are shown in Table-2. Each value in the table is the average of several runs. Experimental errors in the rate constant are estimated to be ± 10 %. As expected, results show that the rate constant \( k_{\text{obs2}} \) for step 5 is greater than that for step 2 (\( k_{\text{obs1}} \)). The activation energy (Ea) for both steps 2 and 5, were calculated using Arrhenius equation. From plots of \( \ln k \) vs. \( (1/T) \) for both steps (Figs. 9 and 10), Ea’s of 25.64 and 20.69 KJ for steps 2 and 5, respectively. Apparently; the thermodynamics is in

\[
\text{TABLE-2}
\]

| Temp. (°C) | \( k_{\text{obs1}} \) (dm³ mol⁻¹ s⁻¹) | \( k_{\text{obs2}} \) (dm³ mol⁻¹ s⁻¹) |
|-----------|-------------------------------|-------------------------------|
| 10.0      | 6.21 × 10⁻⁷                   | 2.72 × 10⁻⁷                   |
| 15.0      | 7.85 × 10⁻³                   | 3.22 × 10⁻²                   |
| 25.0      | 9.59 × 10⁻³                   | 3.96 × 10⁻²                   |
| 35.0      | 15.90 × 10⁻³                  | 5.70 × 10⁻²                   |
agreement and proportional to the related rate constants determined for these steps.

Conclusion

Reaction and kinetics of the oxidation of the biologically important atropine by alkaline KMnO₄ was studied. Experimental observations show that the reaction proceeds via two stages to give the final products: tropine and phenylmalonic acid. Two rate determining steps with different rates were proposed, which were in agreement with obtained kinetic result. A proposed mechanism for the process is presented. The mechanism suggests the formation of two intermediates in two stages of the reaction with different rates and activation energies.

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