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Mechanistic insight into the oxidation of atropine sulfate monohydrate with aqueous acidic chloramine-T: Design of kinetic modeling

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Atropine sulfate monohydrate (ASM), with the chemical name (RS)-(1R,3r,5S)-3-tropoyloxytropanium sulfate monohydrate, is a prominent anticholinergic drug. The kinetic study of its oxidation is of great significance in understanding the mechanistic chemistry of this drug in redox reactions. For this reason, the kinetics and mechanism of the reaction of ASM with chloramine-T (CAT) in $HClO_4$ medium were investigated at 303 K. The reaction exhibits a first-order dependence of the rate on $[CAT]_o$ and a fractional-order dependence on both $[ASM]_o$ and $[HClO_4]$. The effects of added *p*-toluenesulfonamide and chloride ion, and varying ionic strength and dielectric constant of the medium on the rate of the reaction were studied. The reaction was carried out at different temperatures and activation parameters were determined from the Arrhenius plot. Absence of any polymerization of acrylonitrile added to the reaction mixture indicated a non-radical pathway. The stoichiometry of the reaction gave a mole ratio of 1:1 and the oxidation product was identified as atropine *N*-oxide. The protonated conjugated acid ($CH_3C_6H_4SO_2N^+H_2Cl$) was postulated as the reactive oxidizing species in the acid accelerating step. The mechanistic pathways and kinetic modeling for this redox system were computed.

Keywords: atropine sulfate mo

nohydrate; chloramine-T; oxidation-kinetics; acid medium

INTRODUCTION

The chemical name of atropine sulfate monohydrate (ASM) is (RS)-(1R,3r,5S)-3-tropoyloxytropanium sulfate monohydrate. It is a potent anticholinergic, antispasmodic and antimuscarinic drug [1]. Due to its therapeutical and pharmacological relevance, a lot of attention has been paid on the determination of ASM [2-6], but a very limited number of kinetic and mechanistic investigations on the oxidation of this drug have appeared in the literature. Up to now, ASM has been oxidized by Chimatadar *et al.* [7-9] using a number of oxidizing agents under various experimental conditions. Surprisingly, no such information is available with +1 oxidants. This gave us an interest to investigate the title reaction.

N-haloamines contain a halogen in +1 oxidation state and the chemistry of these compounds is of great significance due to their diverse behavior [10]. Their versatile nature is due to the ability of these compounds to act as sources of halonium cations, hypohalite species, and nitrogen anions, which act both as bases and nucleophiles [10]. The important chlorine compound of this class is chloramine-T (CAT: *p*-$CH_3C_6H_4SO_2NClNa.\ 3H_2O$), which is a well-known oxidizing/ chlorinating reagent. This reagent has been exploited as an oxidant for diverse substrates in both acidic and alkaline media [11-20] and their mechanisms have been kinetically investigated. CAT is commercially available, cost-effective, water-tolerant and relatively non-toxic [21]. Our preliminary kinetic studies revealed that ASM drug oxidation with CAT is most favorable in acidic conditions. It is for these reasons that CAT has been opted as an oxidizing agent in the present redox system.

In view of the above facts, and as a part of our on-going research on the kinetic and mechanistic investigations of oxidation of pharmaceuticals using CAT, we report herein for the first time the results obtained on the kinetics and mechanism of oxidation of ASM with CAT in $HClO_4$ medium. This research program was designed with the following objectives: (i) to accumulate all possible kinetic data, (ii) to formulate the plausible mechanism, (iii) to design the rigorous kinetic rate law, (iv) to deduce thermodynamic parameters, (v) to ascertain the reactive species and, (vi) to identify the reaction stoichiometry and oxidation products.

Further, it is well known that hypochlorous acid (HOCl) is a biologically relevant oxidant. It is also reported that CAT resembles HOCl in its oxidative-mechanistic behavior [10]. Moreover, both CAT and HOCl contain chlorine in +1 oxidation state. Hence, the current research knowledge is very beneficial for kineticists who are working on the kinetics and mechanistic aspects of ASM drug in redox chemistry, as well as in biological processes.

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MATERIALS AND METHODS

Materials

The drug atropine sulfate monohydrate of analytical grade purity was purchased from Rolex Chem. Ind., Mumbai, India and was used as received. An aqueous solution of ASM was freshly prepared whenever required. Chloramine-T was obtained from Merck and was purified by the method of Morris *et al.* [22]. An aqueous solution of CAT was periodically prepared and standardized by the iodometric method. CAT solution was stored in brown bottles to prevent photochemical deterioration. All other chemicals used were of Analar grade. Double distilled water was used throughout the study.

Kinetic procedure

Detailed kinetic runs were performed under pseudo-first-order conditions with a known excess of $[ASM]_o$ over $[CAT]_o$ at 303 K. Detailed kinetic procedure was followed by an iodometric method, which is similar to that reported earlier [16]. The course of the reaction was studied for at least two half-lives. Plots of log [CAT] *vs.* time were made to evaluate the pseudo-first-order rate constants (k/s^{-1}). All kinetic runs were carried out twice and were found to be reproducible within ± 3-6%. The regression coefficients (R^2) of the linear plots were obtained using an fx-100Z scientific calculator.

Reaction stoichiometry

Reaction mixtures containing varying proportions of CAT to ASM in the presence of 0.5×10^{-3} mol dm^{-3} of $HClO_4$ were equilibrated at 303 K for 24 h. Determination of residual CAT by iodometric method showed that one mole of ASM consumed one mole of CAT. The stoichiometry obtained can be formulated as Eq. (1):

Product analysis

The reaction mixture of ASM and CAT in $HClO_4$ solution was stirred for 24 h at 303 K. After completion of the reaction (monitored by TLC), the reaction mixture was neutralized with dilute NaOH and the products were extracted twice with ethyl acetate. The organic products were subjected to spot tests and chromatographic analysis (TLC technique), which revealed the formation of atropine *N*-oxide as the oxidation product of ASM and *p*-toluenesulfonamide as the reduction product of CAT. These products were separated by column chromatography on silica gel (60-120 mesh) using dichloromethane and petroleum ether (3:5 v/v) as the mobile phase. Further, atropine N-oxide was confirmed by GC-MS analysis. The GC-MS data were obtained by an Agilent technologies mass spectrometer. The mass spectrum showed a molecular ion peak at 306 (M+1) amu clearly confirming atropine *N*-oxide. (Figure 1)

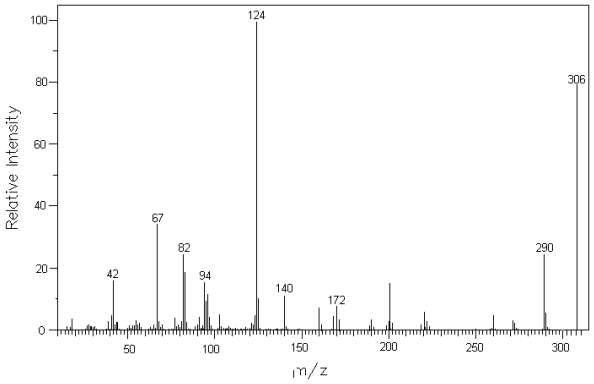
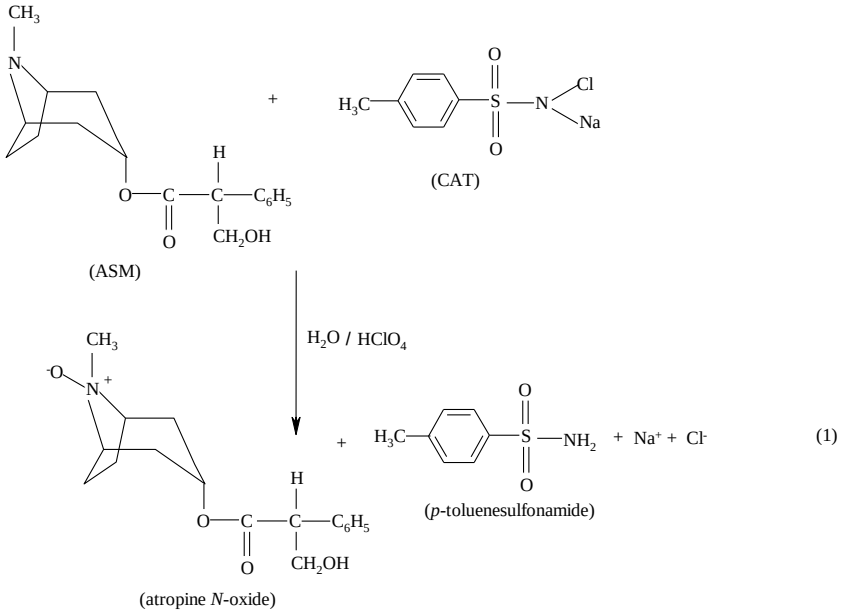


Fig. 1. Mass spectrum of atropine *N*-oxide with its molecular ion peak at m/z 306 (M+1) amu.



(1)

All other peaks observed in GC-MS were interpreted in accordance with the observed structure. It was also observed that there was no further oxidation of these products under the prevailing experimental conditions. *p*-toluenesulfonamide ($TsNH_2$), the reduction product of CAT, was extracted with ethyl acetate and identified by paper chromatography [20]. Benzyl alcohol saturated with water as a solvent with 0.5% vanillin in 1% HCl solution in ethanol was used as a spray reagent (R_f = 0.905). The R_f determined agrees well with the literature value (R_f = 0.905) [20].

RESULTS AND DISCUSSION

The oxidation of atropine sulfate by CAT was kinetically investigated at different initial concentrations of the reactants in $HClO_4$ medium at 303 K. Under pseudo-first-order conditions of $[ASM]_o >> [CAT]_o$ and at constant $[ASM]_o$, $[HClO_4]$ and temperature, plots of log [CAT] *vs*. time are linear ($R^2 > 0.9986$), indicating a first-order dependence of the rate on $[CAT]_o$. The pseudo-first-order rate constants ($k^/ s^{-1}$) are listed in Table 1.

Table 1. Effect of varying oxidant, substrate and acid concentrations on the rate of reaction at 303 K.

10^4 [CAT] (mol dm^{-3})	10^2 [ASM] (mol dm^{-3})	10^3 [$HClO_4$] (mol dm^{-3})	10^4 $k^/$ (s^{-1})
1.0	2.0	0.5	2.70
2.0	2.0	0.5	2.83
4.0	2.0	0.5	2.70
6.0	2.0	0.5	2.68
8.0	2.0	0.5	2.75
4.0	0.5	0.5	1.12
4.0	1.0	0.5	1.91
4.0	2.0	0.5	2.70
4.0	3.0	0.5	3.90
4.0	4.0	0.5	4.94
4.0	2.0	0.1	1.50
4.0	2.0	0.2	2.19
4.0	2.0	0.5	2.70
4.0	2.0	1.0	3.28
4.0	2.0	2.0	4.35

Further, the values of $k^/$ remained unaltered with variation of $[CAT]_o$, confirming the first-order dependence of the rate on $[CAT]_o$. Under the same experimental conditions, an increase in $[ASM]_o$ increased the rate (Table 1). The plot of log $k^/$ *vs*. log [ASM] is linear (R^2 = 0.9959) with a slope of 0.72, indicating a fractional-order dependence of the rate on $[ASM]_o$. Further, the plot of $k^/$ *vs*. $[ASM]_o$ is a straight line (R^2 = 0.9974) with a y-intercept confirming a fractional-order dependence of the rate on $[ASM]_o$. Increase in $[HClO_4]$ increased the reaction rate (Table 1) and the log-log plot of $k^/$ *vs*. $[HClO_4]$ is linear (R^2 = 0.9897) with a slope of 0.35, suggesting a fractional-order dependence of the rate on $[HClO_4]$.

Rate studies were carried out in MeOH-H_2O mixtures of different compositions (0-15% v/v), thereby varying the dielectric constant (D) of the solvent medium. The rate was found to increase with the increase in MeOH content (Table 2). The plot of log $k^/$ *vs*. 1/D was linear (R^2 = 0.9995) with a positive slope. The values of the dielectric constant of MeOH-H_2O mixtures reported in the literature [23] were employed. It was further noticed that no reaction of the dielectric with the oxidant took place under the experimental conditions employed.

Table 2. Effect of varying dielectric constant of the medium on the rate of reaction at 303 K.

% MeOH v/v	D	10^4 $k^/$ (s^{-1})
0	76.73	2.70
5	74.50	3.02
10	72.37	3.39
15	69.75	3.98

Experimental conditions: $[CAT]_o$= 4.0×10^{-4} mol dm^{-3}, $[ASM]_o$ = 2.0×10^{-2} mol dm^{-3}, $[HClO_4]$ = 0.5×10^{-3} mol dm^{-3}.

Addition of 5.0×10^{-4} mol dm^{-3} of *p*-toluenesulfonamide (PTS or $TsNH_2$) to the reaction mixture has no pronounced effect on the reaction rate. This signifies that PTS is not involved in any step prior to the rate-determining step (rds) in the reaction scheme proposed.

The effect of ionic strength of the medium on the reaction rate was studied in presence of 0.2 mol dm^{-3} $NaClO_4$ solution, keeping other experimental conditions constant. It was found that addition of $NaClO_4$ had a negligible effect on the reaction rate, indicating the involvement of non-ionic species in the reaction scheme. Hence, the ionic strength was not a fixed constant for all kinetic runs studied. Addition of NaCl (5.0×10^{-4} mol dm^{-3}) to the reaction mixture had no effect on the rate, suggesting that no free chlorine is formed in the reaction sequence. The reaction rates were determined at 293, 298, 303, 308 and 313 K, keeping the other experimental conditions constant. Based on the Arrhenius plot of log $k^/$ *vs*. 1/T (R^2 = 0.9961) the activation parameters (Ea, $\Delta H^{\neq}$, $\Delta G^{\neq}$, $\Delta S^{\neq}$ and log A) for the overall reaction were computed. These results are summarized in Table 3. Addition of an aqueous solution of acrylamide to the reaction mixture did not initiate polymerization. This suggests non-involvement of free radicals during the oxidation. Appropriate controlled experiments were simultaneously run.

Table 3. Effect of varying temperature on the rate of reaction and activation parameters for the oxidation of ASM with CAT in acid medium.

Temperature (K)	10^4 $k^{/}$ (s^{-1})
293	1.17
298	1.80
303	2.70
308	3.62
313	5.70
E_a(kJ mol^{-1})	59.0
$\Delta H^{\neq}$ (kJ mol^{-1})	56.3
$\Delta G^{\neq}$ (kJ mol^{-1})	95.2
$\Delta S^{\neq}$($JK^{-1}mol^{-1}$)	-122
Log A	9.80

Experimental conditions: $[CAT]_o$= 4.0×10^{-4} mol dm^{-3}, $[ASM]_o$ = 2.0×10^{-2} mol dm^{-3}, $[HClO_4]$ = 0.5×10^{-3} mol dm^{-3}.

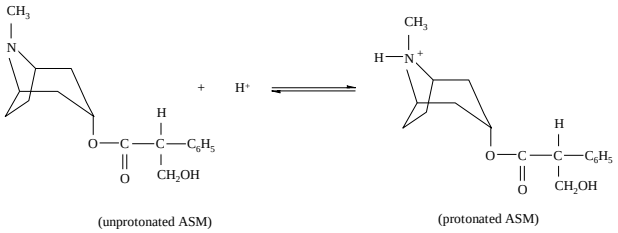
Reactive species of CAT

Chloramine-T acts as a mild oxidant in both acidic and alkaline media, with a two electron change per mole, giving PTS and NaCl [24]. The oxidation potential of the CAT-PTS redox system varies with pH of the medium [25], having values of 1.139V at pH 0.65, 1.778V at pH 7.0 and 0.614V at pH 9.7. It behaves like a strong electrolyte [25] in aqueous solutions, and depending on pH of the medium it furnishes different equilibria in aqueous solutions [10, 25-26].

The possible oxidizing species in acidified CAT solutions are TsNHCl, $TsNCl_2$, HOCl and possibly H_2O^+Cl. From these four possibilities, the reactive species of CAT can be selected based on the observed kinetic results. If $TsNCl_2$ were to be the reactive species, then the rate law would predict a second-order dependence of the rate on $[CAT]_o$, which is contrary to the experimental results. If HOCl were primarily involved, a first-order retardation of the rate by adding PTS or $TsNH_2$ would be expected. Since no such effects were observed, both $TsNCl_2$ and HOCl could be ruled out as the oxidizing species. Hardy and Johnston [26], who have studied the pH dependent relative concentrations of the species present in acidified CAT solutions of comparable molarities, have shown that TsNHCl is the likely oxidizing species in acid medium. Further, formation of doubly protonated species TsN^+H_2Cl in acidic solutions is reported by Narayanan and Rao [27], with a value of 1.02×10^2 at 25°C for the second protonation constant. In the present case, acceleration of the rate by $[H^+]$ indicates that TsN^+H_2Cl is the most active oxidizing species and hence we believe that it is involved in the present reaction.

Reactive species of ASM

Under acidic conditions, the drug ASM may get protonated and exist in the following equilibrium form:



(unprotonated ASM) (protonated ASM)

Unprotonated form of atropine sulfate monohydrate is involved in the present reaction

Reaction Scheme

In the light of the above facts, a detailed mechanism (Scheme 1) is suggested for the oxidation of ASM with CAT in acid medium. In the fast rate accelerating step (step(i)) of Scheme 1, the conjugated acid TsNHCl accepts a proton to give a diprotonated species TsN^+H_2Cl. In the next fast step (step (ii)), TsN^+H_2Cl reacts with the substrate ASM forming an intermediate complex-I with the elimination of $TsNH_2$. In the next slow and rate determining step (step (iii)), complex-I hydrolyses to complex-II with the elimination of a molecule of HCl. Finally, complex-II loses a proton to yield the ultimate product atropine *N*-oxide.

Kinetic rate law

If $[CAT]_t$ is the total effective concentration of CAT, then

$$[CAT]_t = [TsNHCl] + [TsN^+H_2Cl] + [Complex\text{-}I] \quad (2)$$

Finding the values of [TsNHCl] and $[TsN^+H_2Cl]$ from steps (i) and (ii) of Scheme 1, and solving for [Complex-I], we get

$$[Complex\text{-}I] = \frac{K_1K_2[CAT][ASM][H^+]}{1+K_1[H^+] + K_1K_2[ASM][H^+]} \quad (3)$$

From the slow and rds of Scheme 1,

$$Rate = k_3[Complex\text{-}I] \quad (4)$$

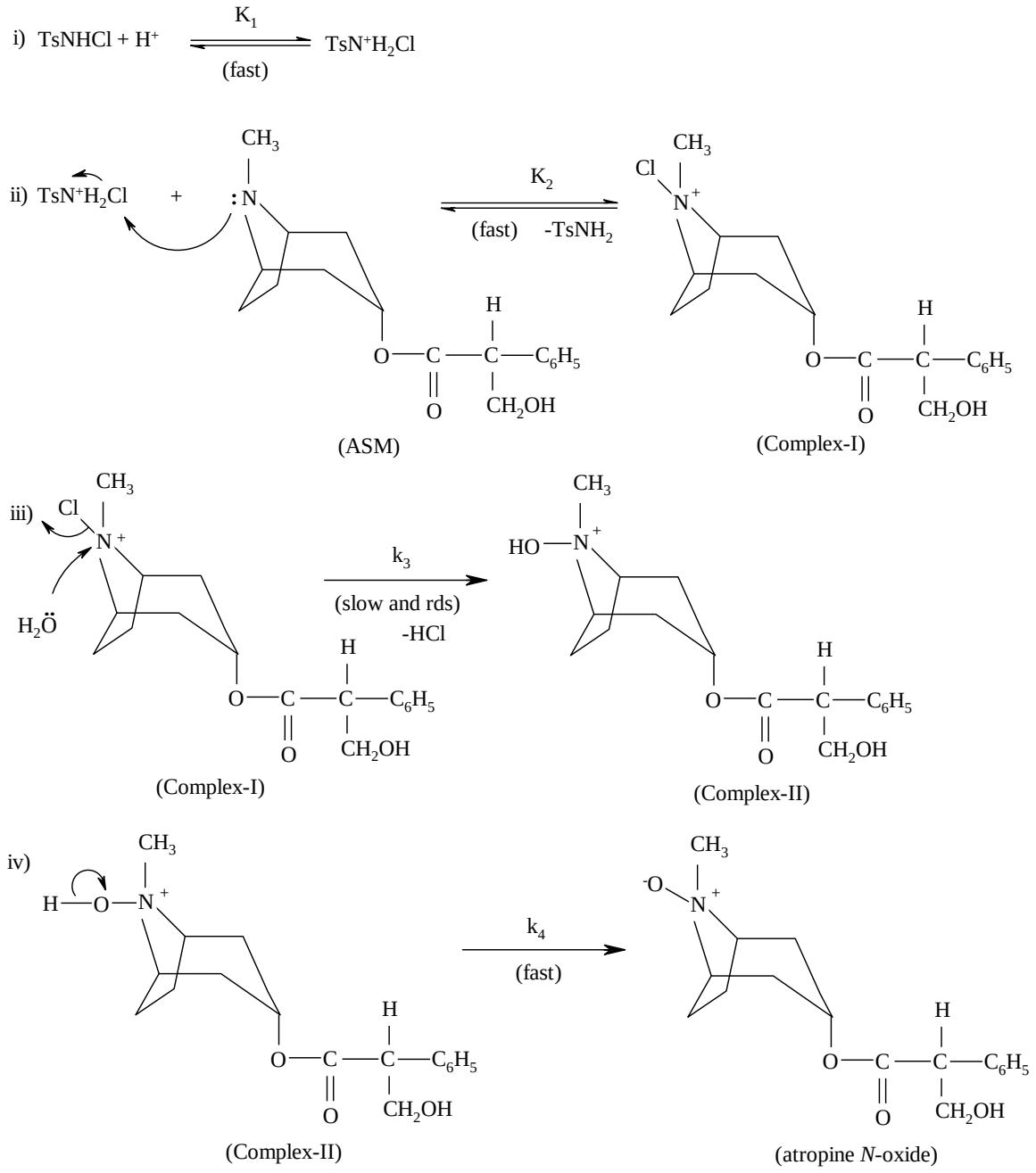
By substituting for [Complex-I] from Eq. (3) into Eq. (4), the following rate law is obtained.

$$Rate = \frac{K_1K_2k_3[CAT][ASM][H^+]}{1+K_1[H^+]+K_1K_2[ASM][H^+]} \quad (5)$$

This rate law is in complete agreement with the experimental results. Since the rate = $k^{/}$ [CAT], under pseudo-first-order conditions of $[CAT]_o$<<$[ASM]_o$,

$$k^{/} = \frac{K_1K_2k_3[ASM][H^+]}{1+K_1[H^+]+K_1K_2[ASM][H^+]} \quad (6)$$

or



Scheme 1. Detailed mechanistic scheme for the oxidation of atropine by CAT in acid medium.

$$\frac{1}{k'} = \frac{1}{K_1K_2k_3[ASM][H^+]} + \frac{1}{K_2k_3[ASM]} + \frac{1}{k_3} \quad (7)$$

or

$$\frac{1}{k'} = \frac{1}{[ASM]}\left\{\frac{1}{K_1K_2k_3[H^+]} + \frac{1}{K_2k_3}\right\} + \frac{1}{k_3} \quad (8)$$

A double reciprocal plot of $1/k'$ *vs.* $1/[H^+]$ from Eq. (7) yields:

$$\text{slope} = \frac{1}{K_1K_2k_3[ASM]} \text{ and an intercept} = \left\{\frac{1}{K_2k_3[ASM]} + \frac{1}{k_3}\right\}$$

Similarly, a double reciprocal plot of $1/k'$ *vs.* $1/[ASM]$ from Eq. (8) gives:

$$\text{slope} = \left\{\frac{1}{K_1K_2k_3[H^+]} + \frac{1}{K_2k_3}\right\} \text{ and an intercept} = \frac{1}{k_3}$$

From the slopes and intercepts of Eqs. (7) and (8), the values of the equilibrium constants K_1 and K_2, and the decomposition constant k_3 were calculated for the standard run. The values obtained are $K_1 = 9.0\times10^5$ dm^3 mol^{-1}, $K_2 = 22.2$ dm^3 mol^{-1} and $k_3 = 1.25\times10^{-3}$ s^{-1}. The proposed reaction scheme and the derived rate law are also evinced by the following experimental findings.

The proposed mechanism is evinced by the observed effect of ionic strength on the rate of the reaction. The primary salt effect on the reaction rate was described by the Brønsted and Bjerrum theory

[28]. According to this concept, the effect of ionic strength on the rate of a reaction involving two ions depends on the charges of the ions. When the ions are of the same charge, an increase in the ionic strength increases the reaction rate because the solvated ions change the dielectric behavior of the solution so that ions of like charge do not repel each other as greatly. If the reacting ions are oppositely charged, raising ionic strength reduces the effective rate constant because the ions are shielded from each other to a greater extent. For the reactions that involve uncharged (neutral) reactants, the rate constant is expected to be independent of the ionic strength of the solution. In the present case, a neutral molecule and a positive ion are involved in the rate-determining step (step (iii) of Scheme 1). Hence, the variation of the ionic strength of the medium does not alter the rate, which clearly confirms the above theory [28].

Several approaches [29-32] have been made to qualitatively explain the effect of dielectric constant of the medium on the reaction rates in solutions. A change in the solvent composition by varying the methanol content in methanol-water affects the reaction rate. For the limiting case of zero angle of approach between two dipoles or an ion-dipole system, Amis [32] has shown that a plot of log $k^{/}$ vs. 1/D gives a straight line, with a negative slope for a reaction between a negative ion and a dipole or between the dipoles, while a positive slope indicates a reaction between a positive ion and a dipole. The positive dielectric effect on the rate of the reaction observed in the present case is in agreement with the positive ion – dipole nature of the rate determining step in the proposed reaction scheme (step (iii) of Scheme 1) and a reaction pathway was suggested to the kinetic results.

The proposed reaction mechanism and the derived rate law are also supported by the moderate value of the energy of activation and other thermodynamic parameters (Table 3). The positive values of free energy and enthalpy of activation indicate that the transition state is highly solvated and enthalpy controlled. The observed large negative entropy of activation may be interpreted in a way that some collisions become more stringent and form a rigid associative activated complex with less degrees of freedom. Hence, decomposition of the activated complex is quite a slow process. The values of the frequency factor (A) specify the frequency of collisions and the orientation of reacting molecules. The negligible effects of PTS and NaCl on the reaction rate also confirm the proposed reaction mechanism and kinetic rate law.

CONCLUSIONS

From the present research, the following conclusions are drawn. The kinetics of oxidation of ASM with CAT in $HClO_4$ medium obeys the rate law: Rate = k $[CAT]^1[ASM]^{0.72}[HClO_4]^{0.35}$. The stoichiometry of the reaction was found to be 1:1 and atropine *N*-oxide was characterized as the oxidation product of ASM by GC-MS analysis. Activation parameters were determined. The protonated conjugated acid ($CH_3C_6H_4SO_2N^+H_2Cl$) is postulated as the reactive oxidizing species in the acid-accelerated step. The observed experimental results were explained by an elegant mechanism and the relevant rate law was formulated.

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МЕХАНИСТИЧЕН ПОГЛЕД ВЪРХУ ОКИСЛЕНИЕТО НА АТРОПИН СУЛФАТ МОНОХИДРАТ С ХЛОРАМИН-Т В КИСЕЛА ВОДНА СРЕДА: ДИЗАЙН И КИНЕТИЧНО МОДЕЛИРАНЕ

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(Резюме)

Химическото съединение (RS)-(1R,3r,5S)-3-тропоил-окситропаниум сулфат монохидрат с търговско наименование атропин сулфат монохидрат (ASM) е разпространено анти-холинергично лекарство. Изследването на кинетиката на окислението му е от голямо значение за механистичното разбиране на редокс-реакциите в които то участва. Изследвани са кинетиката и механизма на реакцията на ASM с хлорамин -T (CAT) в среда на $HClO_4$ при 303 K. Реакцията е от първи порядък по отношение на $[CAT]_o$ и частично от първи порядък по отношение а $[ASM]_o$ и перхлорната киселина. Изучен е и ефекта на добавения *p*-толуенсулфонамид и хлорните йони, йонната сила и диелектричната константа на средата. Реакцията е провеждана при различни температури и активиращата енергия е определена по уравнението на Арениус. Отсъствието на полимеризация при добавянето на акрилонитрил свидетелства за не-радикалов механизъм. Стехиометрията на реакцията дава моларно отношение 1:1, а продуктът окисление е идентифициран като атропин *N*-оксид. Протонираната спрегната киселина ($CH_3C_6H_4SO_2N^+H_2Cl$) е постулирана като реактивно окисляващ компонент в етапа на киселинн ускоряване на реакцията. Направени се изчиления и моделиране на тази редокс-система.