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Kinetics and Mechanism of Oxidation of Neomycin and Streptomycin Antibiotics by Alkaline Permanganate

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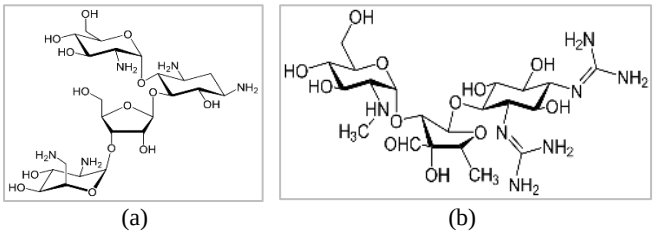
ABSTRACT

The kinetics and mechanistic aspects of oxidation of two aminoglycoside antibiotics, namely, neomycin and streptomycin by permanganate ion (MnO_4^-) in alkaline solutions were examined spectrophotometrically. The stoichiometry of the reactions between the investigated antibiotics and MnO_4^- were set to be 8.0 ± 0.3 mol. The reactions exhibited first order dependence regarding to $[MnO_4^-]$ and less-than unit order dependences with respect to antibiotics and OH^- concentrations. Under the same investigational conditions, the rate of oxidation of streptomycin was found to be about seven times more than that of neomycin. The impact of ionic strength of the reactions medium was explored which revealed that as the ionic strength increases the oxidation rates are also increased. Also, the influence of temperature was studied and the activation parameters were calculated and discussed. The plausible reactions mechanism was proposed and the appropriate rate-law expression consisted with the acquired investigational kinetic results was derived.

1. Introduction

Antibiotics, a kind of pharmaceutical drugs, are composed of synthetic or natural organic compounds employed to cure, treat or prevent human and animal diseases. However, antibiotics are regarded as one of the dangerous pollutants for the environment and human health if they reach to the environment because they contain complex organic compounds in their structures [1]. It was reported [2-10] that antibiotics are greatly susceptible to oxidation which can be a relatively common technique for antibiotics degradation [3,6]. Hence, oxidation of antibiotics is regarded as a presumed way for removal of antibiotics from the environment to care for the human health. During the oxidation process, oxidizing agents convert the polluted substances to less harmful ones that are safe to be discharged into the environment [3,5,7,10]. Furthermore, study of the kinetics of oxidation of antibiotics have significantly help in identifying the mechanism of conversions of such organic compounds in biological systems. A detailed literature review revealed little published studies on the kinetics of oxidative removal of antibiotics in different media [2-5,8-10].



(a) (b)

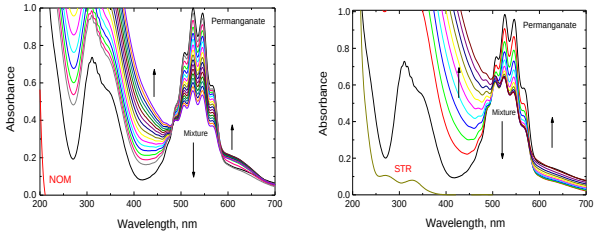
Figure 1: Chemical structures of (a) streptomycin (STR) and (b) neomycin (NOM).

In the light of the above mentioned aspects, this investigation deals with the kinetics and mechanism of oxidation of two aminoglycoside antibiotics, viz. neomycin and streptomycin, (their structures are illustrated in Figure 1) using one of the supreme significant, powerful, cheap and green oxidants, namely, permanganate ion (MnO_4^-) [11-15] in alkaline solutions. This investigation aimed to explore the selectivity of the examined antibiotics towards permanganate ion oxidant and to comprehend the reactive species of both reactants in alkaline solutions. The activation parameters were planned to determine and discuss. Furthermore, the study is extended to propose a plausible reactions mechanism as well as to establish the rate-law expression consistent with the obtained kinetic results.

2. Results and Discussion

2.1. Spectral Changes

Spectral changes during the oxidation of neomycin (NOM) and streptomycin (STP) by permanganate ion are shown in Figure 2 (a) and (b), respectively. These figures showed a continuous decay of MnO_4^- ion band at λ = 526 nm as the reactions advanced. This behavior indicated reduction of permanganate ion as a result of oxidation of such antibiotics. From Figure 2, it can be observed that the rate of oxidation of streptomycin was significantly higher than that of neomycin under the same investigational conditions which may be due to the structural difference between the two antibiotics and presence of two very reactive guanidine groups (–NH=C(NH_2)$_2$) in streptomycin. A careful examination of the spectral scans in case of neomycin antibiotic, shown in Figure 3(a,b), confirmed construction of Mn^{VI} intermediate by detecting the new peak at 606 nm [13]. Also, additional proof of the construction of Mn^{VI} transient species was the continued appearance of the green color as the oxidation reactions proceeded [11,12,15].



(a) (b)

Figure 2: Spectral changes during oxidation of: (a) neomycin (NOM) and (b) streptomycin (STP) by alkaline permanganate. $[MnO_4^-]$ = 4.0 x 10^{-4}, [A] = 5.0 x 10^{-3}, $[OH^-]$ = 5.0 x 10^{-3} and *I* = 0.1 mol dm^{-3} at T = 298 K.

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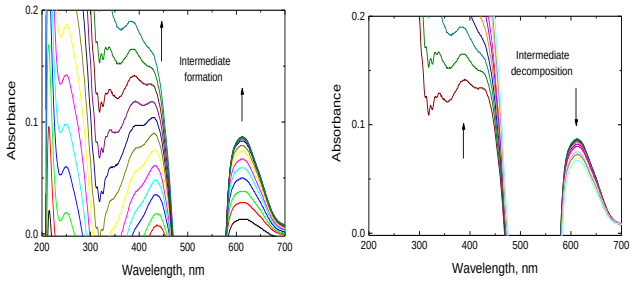


(a) (b)

Figure 3: Spectral changes during: (a) construction, and (b) decay of Mn^{VI} intermediate complex in the oxidation of neomycin by alkaline permanganate. $[MnO_4^-]$ = 4.0 x 10^{-4}, [NOM] = 5.0 x 10^{-3} and I = 0.1 mol dm^{-3} at T = 298 K.

2.2. Reactions Stoichiometry

A set of reaction mixtures containing various ratios of antibiotic, [A] / $[MnO_4^-]$, were equilibrated in a dark place for about 24 h until completion of the reactions in all mixtures at constant $[OH^-]$ and at room temperature. Determination of unreacted $[MnO_4^-]$ spectrophotometrically at λ_{max} = 526 nm indicated that the stoichiometric ratios of ($[MnO_4^-]$ / $[A]_0$), were set to be 8.0 ± 0.3 mol, i.e. each mole of antibiotic was consumed eight moles of permanganate ion.

2.3. Effect of Permanganate Oxidant

The oxidation reactions of both neomycin (NOM) and streptomycin (STR) with permanganate ion in alkaline solutions were investigated at different $[MnO_4^-]_0$, while other reactants concentrations were kept constant. The investigational results showed that the first order rate constant plots were straight lines for more than two half-lives of the reactions completion as illustrated in Figure 4. In addition, change of the initial concentration of the oxidant was set to have no significant effect on the observed first order rate constant values (k_{obs}) as listed in Table 1. These results indicated that such reactions were first order regarding to $[MnO_4^-]$.

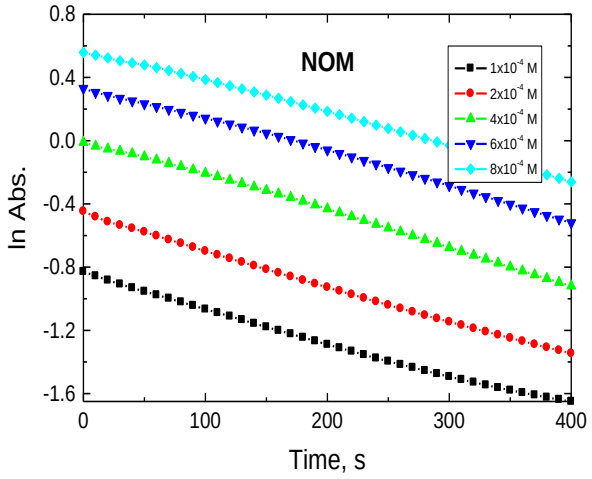


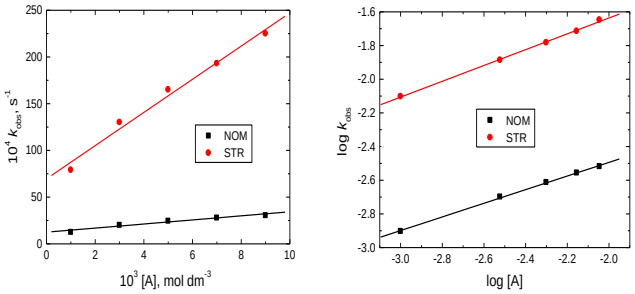
Figure 4: Effect of $[MnO_4^-]$ on the first order plot in the alkaline permanganate oxidation of neomycin (NOM) at [NOM] = 5.0 x 10^{-3}, $[OH^-]$ = 5.0 x 10^{-3}, I = 0.1 mol dm^{-3} and T = 298 K.

2.4. Effect of Antibiotics

In this context, the kinetics experiments were performed at variety of concentrations of the investigated antibiotics, [A], at constant concentrations of MnO_4^- and OH^-, ionic strength and temperature. The values of k_{obs} listed in Table 1 indicated that the reaction rates were set to increase with increasing [A]. The plots of k_{obs} versus [A] were linear with positive intercepts on the k_{obs} axes as shown in Figure 5(a). Also, the plots of log [A] versus log k_{obs} gave good straight lines with slopes of less-than unity as illustrated in Figure 5(b) indicating the fractional-first order credences with respect to [A].

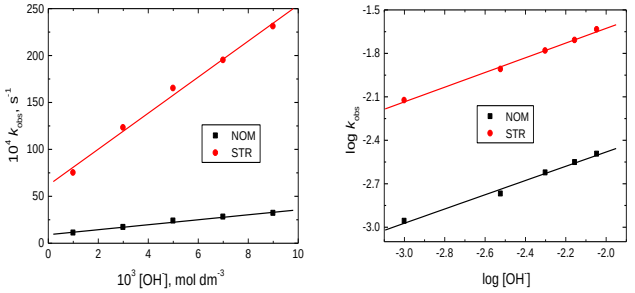
2.5. Effect of $[OH^-]$

To clarify the reactions mechanism, the oxidation rates of the examined antibiotics by alkaline permanganate was measured at various $[OH^-]$. The experimental results indicated that the reaction rates were increased with rising $[OH^-]$ as manifested from the acquired values k_{obs} listed in Table 1. The plots of k_{obs} versus $[OH^-]$ gave straight lines with positive intercepts on the k_{obs} axes as shown in Figure 6(a). Also, the plots of log k_{obs} versus log$[OH^-]$ were set to be straight lines with slopes of 0.894 and 0.883 for neomycin and streptomycin, respectively, as illustrated in Figure 6(b), indicating that these reactions were less-than unit order dependences in $[OH^-]$.



(a) (b)

Figure 5: (a) Plots of k_{obs} vs. [A], and (b) plots of log k_{obs} vs. log [A] in the alkaline permanganate oxidation of antibiotics at $[MnO_4^-]$ = 4.0 x 10^{-4}, $[OH^-]$ = 5.0 x 10^{-3}, I = 0.1 mol dm^{-3} and T = 298 K.



(a) (b)

Figure 6: (a) Plots of k_{obs} vs. $[OH^-]$, and (b) plots of log k_{obs} vs. log $[OH^-]$ in the alkaline permanganate oxidation of antibiotics at [A] = 5.0 x 10^{-4}, $[MnO_4^-]$ = 4.0 x 10^{-4}, I = 0.1 mol dm^{-3} and T = 298 K.

2.6. Effect of Ionic Strength

To explore the nature of the reactive species and, therefore, to the suggested reactions mechanism, kinetic measurements were performed at firm alkali and antibiotic concentrations while the concentration of sodium perchlorate was increased. The results indicated that the rates of the oxidation reactions were increased as the ionic strength (I) of the reactions media increased as observed from the values of k_{obs} listed in Table 1. The Debye-Hückel plots were set to be linear with positive slopes as illustrated in Figure 7. These results suggested that oxidation reactions occurred between ions of similar charges [16].

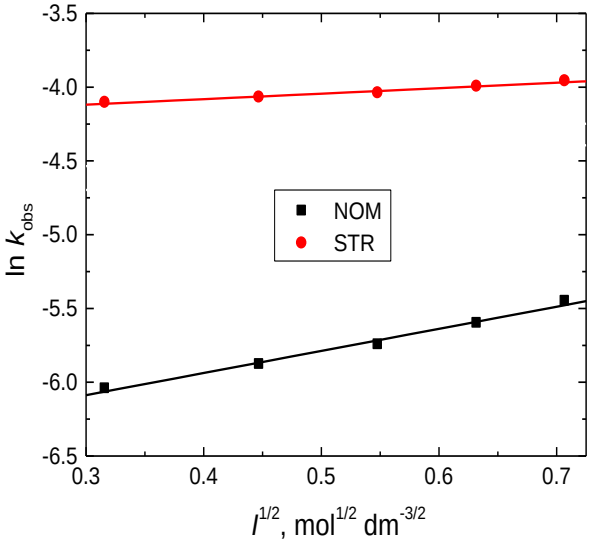


Figure 7: Debye-Hückel plots in the alkaline permanganate oxidation of antibiotics at [A] = 5.0 x 10^{-3}, $[MnO_4^-]$ = 4.0 x 10^{-4}, $[OH^-]$ = 5.0 x 10^{-3} mol dm^{-3} and T = 298 K.

Table 1: Effect of [MnO_4^-], [A], [OH^-] and *I* on the values of k_{obs} in the alkaline permanganate oxidation of antibiotics at T = 298 K.

10^4 [MnO_4^-] (mol dm^{-3})	10^3 [A] (mol dm^{-3})	10^3 [OH-] (mol dm^{-3})	I (mol dm^{-3})	10^4 kobs (s^{-1})	
				NOM	STR
1.0	5.0	5.0	0.1	24.07	161.21
2.0	5.0	5.0	0.1	23.21	162.04
4.0	5.0	5.0	0.1	23.75	160.32
6.0	5.0	5.0	0.1	23.27	161.94
8.0	5.0	5.0	0.1	22.98	159.82
4.0	1.0	5.0	0.1	12.50	79.35
4.0	3.0	5.0	0.1	19.79	129.88
4.0	5.0	5.0	0.1	23.75	160.32
4.0	7.0	5.0	0.1	27.78	193.08
4.0	9.0	5.0	0.1	30.30	221.99
4.0	5.0	1.0	0.1	11.33	75.30
4.0	5.0	3.0	0.1	17.21	123.17
4.0	5.0	5.0	0.1	23.75	160.32
4.0	5.0	7.0	0.1	28.24	194.96
4.0	5.0	9.0	0.1	31.99	231.12
4.0	5.0	5.0	0.1	23.75	160.32
4.0	5.0	5.0	0.2	28.11	171.41
4.0	5.0	5.0	0.3	32.27	176.04
4.0	5.0	5.0	0.4	37.07	184.00
4.0	5.0	5.0	0.5	43.15	191.16

2.7. Effect of Temperature

In order to evaluate the activation parameters, the reactions were conveyed out at different temperatures at firm other variables. The experimental results indicated that the rates of the reactions were set to speed up by rising temperature as listed in Table 2. On the other hand, both Eyring and Arrhenius plots of the second order rate constant values (k_2) were linear as shown in Figures 8(a) and (b), correspondingly. The activation parameters were evaluated from these plots and are inserted in Table 3.

2.8. Polymerization Test

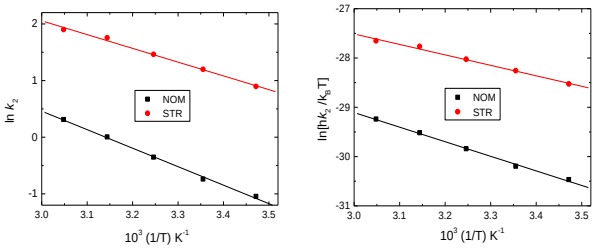
The possibility of formation of free radicals in the existing oxidation reactions was explored by acrylonitrile test. This test was conveyed out by the addition of a definite acrylonitrile quantity to the reaction mixture in an inert atmosphere for about 4 hours. No polymerization appeared in all reaction mixtures (as no white precipitates were formed) indicating that the present oxidation reactions did not proceed via intervention of free radicals.

Table 2: Effect of temperature on the values of k_{obs} in the alkaline permanganate oxidation of antibiotics at [A] = 5.0 x 10^{-3}, [MnO_4^-] = 4.0 x 10^{-4}, [OH^-] = 5.0 x 10^{-3} and *I* = 0.1 mol dm^{-3}.

T (K)	10^4 k_{obs} (s^{-1})	
	NOM	STR
288	17.51	122.07
298	23.75	160.32
308	34.92	215.31
318	49.83	288.14
328	68.06	332.93

Table 3: Activation parameters of k_2 in the alkaline permanganate oxidation of antibiotics at [A] = 5.0 x 10^{-3}, [MnO_4^-] = 4.0 x 10^{-4}, [OH^-] = 5.0 x 10^{-3} and *I* = 0.1 mol dm^{-3}.

Antibiotic	$\Delta S^{\neq}$ J $mol^{-1}K^{-1}$	$\Delta H^{\neq}$ kJ mol^{-1}	$\Delta G^{\neq}_{298}$ kJ mol^{-1}	$E_a^{\neq}$ kJ mol^{-1}
NOM	-169.07	24.61	74.99	27.10
STR	-175.41	18.02	70.29	19.89



(a) (b)

Figure 8: (a) Eyring plots, and (b) Arrhenius plots of k_2 in the alkaline permanganate oxidation of antibiotics at [A] = 5.0 x 10^{-3}, [MnO_4^-] = 4.0 x 10^{-4}, [OH^-] = 5.0 x 10^{-3} and *I* = 0.1 mol dm^{-3}.

2.9. Suggested Reactions Mechanism

In the light of the investigational kinetic outcomes, the appreciable reactions mechanism was suggested and can be discussed as follows. The first step is the rapid deprotonation of antibiotic molecules (A) according to the following equation:

$$A + OH^- \underset{}{\overset{K_1}{\rightleftharpoons}} A^- + H_2O \quad (1)$$

The deprotonated form (A^-) appears to be the reactive species in the rate-controlling stage of the proposed reactions mechanism. This suggested step is based on increasing the oxidation rates upon increasing alkali concentration as well as the structures of the examined antibiotics [17].

The second step of the suggested mechanism is the attack of MnO_4^- on the deprotonated antibiotic to construct a complex, [A - MnO_4]$^{2-}$ (C), Eq. (2):

$$A^- + MnO_4^- \underset{}{\overset{K_2}{\rightleftharpoons}} [A - MnO_4]^{2-} \ (C) \quad (2)$$

Complex construction during the oxidation reactions by MnO_4^- in alkaline solutions was reported earlier [18-21]. Furthermore, such complexation was approved spectrophotometrically by the achieved UV–Vis spectra as shown in Figures 2 and 3, as well as kinetically as the plots of $1/k_{obs}$ vs. 1/[A] were linear with positive slopes [22] as shown in Figure 9(a).

Then, the formed transient complex (C) decomposed in the rate-controlling stage to yield the pr-oxidation products as follows:

$$[A - MnO_4]^{2-} \xrightarrow{k_1} \text{Pre-oxidation products} \quad (3)$$

The latter interacts with other seven MnO_4^- ions in subsequent fast steps to yield the final oxidation products of the antibiotics.

According to the suggested mechanism, the rate law expressing the relationship between the reaction rate and the concentrations of antibiotic, OH^- and oxidant was derive as in Eq. (4):

$$\text{Rate} = \frac{k_1K_1K_2[A][OH^-][MnO_4^-]}{1+K_1[OH^-]+K_1K_2[OH^-][A]} \quad (4)$$

Also, k_{obs} equation was derived, Eq. (5):

$$k_{obs} = \frac{k_1K_1K_2[A][OH^-]}{1+K_1[OH^-]+K_1K_2[OH^-][A]} \quad (5)$$

Rearranging Eq. (5) led to the following two equations:

$$\frac{1}{k_{obs}} = \left(\frac{1+K_1[OH^-]}{k_1K_1K_2[OH^-]}\right)\frac{1}{[A]} + \frac{1}{k_1} \quad (6)$$

$$\frac{1}{k_{obs}} = \left(\frac{1}{k_1K_1K_2[A]}\right)\frac{1}{[OH^-]} + \left(\frac{1}{k_1K_2[A]} + \frac{1}{k_1}\right) \quad (7)$$

Regarding to Eqs. (6) and (7), the plots of $1/k_{obs}$ versus 1/[A] at constant [OH^-] and $1/k_{obs}$ versus 1/[OH^-] at constant [A] must be linear with positive intercepts on the $1/k_{obs}$ axes as were experimentally found to be so as illustrated in Figures 9(a) and (b), respectively. The values of the slow step of the proposed reactions mechanism (k_1) and the equilibrium constants (K_1 and K_2) were calculated from these plots and are inserted in Table ٤.

Table 4: Values of k_1, K_1 and K_2 in the alkaline permanganate oxidation of antibiotics. [A] = 5.0 x 10^{-3}, [MnO_4^-] = 4.0 x 10^{-4}, [OH^-] = 5.0 x 10^{-3}, I = 0.1 mol dm^{-3} at T = 298 K.

Antibiotic	Constant		
	10^2 k_1, s^{-1}	K_1, dm^3 mol^{-1}	10^{-2} K_2, dm^3 mol^{-1}
NOM	0.35	16.4	52.37
STR	2.65	30.00	25.13

2.10. Activation Parameters

The calculated activation parameters listed in Table 3 were found to be in a good accord with the suggested oxidation reactions mechanism. The acquired higher negative values of $\Delta S^{\neq}$ suggested formation of complexes amongst the reacting species. Also, the positive values of both $\Delta H^{\neq}$ and $\Delta G^{\neq}$ indicated that such complexes formation was endothermic and non-spontaneous, respectively [16]. The higher values of $E_a^{\neq}$ proposed that the rate-determining step was the decomposition of the formed complexes.

3. Conclusions

The kinetics of oxidation of neomycin and streptomycin by permanganate ion in alkaline solution were studied. Under the same investigational conditions, the rate of oxidation of streptomycin was found to be about seven times more than that of neomycin. The activation parameters were calculated and discussed. The appreciable reactions mechanism was proposed. The rate-law expression in consistent with the obtained results was derived.

4. Experimental

4.1. Materials and Methods

All employed chemicals were from Merck or Sigma in spectroscopic grade and were used as supplied. Doubly distilled water was utilized to prepare all the solutions. Fresh solutions of neomycin and streptomycin antibiotics were prepared by dissolving their weighted samples in doubly distilled water. Potassium permanganate solution was prepared and standardized as reported earlier [14]. The reactions temperature were equilibrated within ±0.1 ºC.

Kinetic experiments were conveyed out at pseudo-first order conditions where the concentrations of the examined antibiotics were presented in excess higher than that of permanganate concentration at constant ionic strength and temperature. A Shimadzu UV-1800 PC automatic scanning double-beam spectrophotometer was utilized to measuring the absorbance readings of the existing reactions. The reactions were followed by recording the decrease of permanganate ion absorbance at its absorption maximum, λ = 526 nm, with time. All experiments were carried out at least two times and the rate constants were found to be reproducible in the range of ±3 %.

Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Nada Alqarni], [Ahmed Fawzy] and [Metwally Abdallah]. The first draft of the manuscript was written by [Ahmed Fawzy] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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