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Kinetics and Mechanism of Oxidation of Amoxicillin and 6-Aminopenicillanic Acid by Dichromate in Presence and Absence of Succinic Acid

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In the present studies we report the kinetics of oxidation of organic acids, such as amoxicillin and 6-aminopenicillanic acid by dichromate in acetic acid-water medium in presence and absence of succinic acid. The oxidising reacting species, $HCrO_4^-$ and $Cr_2O_7^{2-}$, participate in the reaction. The effect of varying concentrations of [substrate], [oxidant], $[H^+]$, added neutral salt have been studied. The order of reaction with respect to [oxidant] and [substrate] has been found to be unity from the slope of plots log k *vs.* log [sub]. The rate of reaction increases with increase in pH of perchloric acid. Hammett's acidity function and activity of water have been studied. Effect of temperature has been studied. Activation parameters were computed. The plot of ΔH^* *vs.* ΔS^* is linear. The effect of dielectric constant of the medium indicates the reaction to be ion-dipole. The results of oxidation products have been identified.

Key Words: Kinetics, Oxidation, Amoxicillin, 6-Aminopenicillanic acid, Dichromate, Succinic acid.

INTRODUCTION

Amoxicillin and penicillanic acids are used as antibacterial drugs. The basic nucleus of ampicillin is 6-aminopenicillanic acid, which consists of a thiazolidine ring linked to β-lacton ring. The side chain determines the antibacterial and pharmacological characteristics of this compound[1]. There is no report in literautre on the kinetics of the oxidation of amoxicillin and 6-aminopenicillanic acid with [Cr(VI)]. The oxidation of a number of α-hydroxy acids has been studied with [Cr(VI)][2, 3]. Such oxidation studies may throw some light on the mechanism of the compounds in biological systems. This paper reports the kinetic results on [Cr(VI)] oxidation of amoxicillin and 6-aminopenicillanic acid.

EXPERIMENTAL

Organic materials, amoxicillin and 6-aminopenicillanic acid, were S.D. Fine (AR) grade. Glacial acetic acid (AR) was used as the solvent. All inorganic

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materials including chromic acid and succinic acid (60%) were AR grade. Doubly distilled water was used for preparing different compositions of solvent.

The rate of consumption of [Cr(VI)] was followed colorimetrically by measuring the optical density at 420 nm on a Mac digital photoelectric colorimeter. Requisite volumes of reactants previously equilibrated at 30°C within ±0.01°C were mixed and immediately transferred to the cell. The optical densities were recorded at different time intervals. The ionic strength of the medium was adjusted by adding requisite quantity of sodium chloride. The kinetic runs were carried out under pseudo first order conditions and the first order rate constant was calculated from the slope of the linear plot of log [Cr(VI)] *vs.* time and values reproducible to 2–3%.

RESULTS AND DISCUSSION

Effect of varying [H^+]: In order to study the effect of [H^+], the experiments were carried out at different [$HClO_4$] while keeping the [substrate], [Cr(VI) constant. The results show a proportional dependence on [H^+] ions. It is observed that [H^+] ions are responsible for the increase in rate[4] (Table-1). The plots of log k *vs.* log [H^+] (Fig. 1) are found to be linear in the case of amoxicillin and 6-aminopenicillanic acid where the slopes are significantly nearly one.

TABLE-1

EFFECT OF VARYING [H^+] ON REACTION RATE

[Cr(VI)] = 5×10^4 M, constant μ = 0.3030 M, [HOAc] = 20%, Temperature = 30°C

[H^+] M	log a_w	H_0	6-Aminopenicillanic acid		Amoxicillin	
			$k \times 10^3$	$H_0 + \log k$	$k \times 10^3$	$H_0 + \log k$
0.730	–0.0120	+0.30	6.675	–1.876	12.54	–1.602
0.909	–0.0165	+0.05	8.080	–2.043	14.50	–1.789
1.090	–0.0200	–0.12	10.012	–2.120	17.93	–1.867
1.273	–0.0240	–0.25	11.810	–2.180	21.44	–1.918
1.455	–0.0280	–0.40	14.858	–2.229	23.55	–2.030
1.818	–0.0380	–0.60	19.025	–2.321	27.18	–2.066

Hammetts' acidity function represents the ability of a solvent to donate a proton to neutral base. In dilute solution $H_0 = -\log a_{H^+} = pH$, therefore for pure water $H_0 = pH = 7$ at 25°C. As the acidity of the solution increases, the value of H_0 decreases in order to get a mechanistic interpretation of acid catalysed reactions. The Hammetts' acidity function (H_0) is used. According to Zucker and Hammett[5], involvement of water in the slow step of the reaction mechanism can be formulated.

$$S + H^+ \rightleftharpoons SH^+$$

$$SH^+ \xrightarrow{\text{Slow}} X^+$$

$$X^+ \xrightarrow{\text{Fast}} \text{Product} + H^+$$

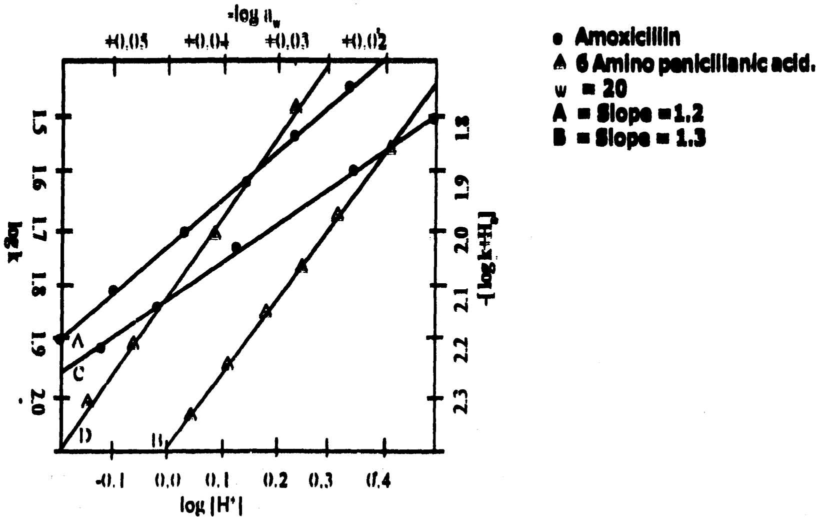


Fig. 1. (A, B) Plot of log k_{obs} *vs.* log $[H^+]$; (C, D) Plot of $-[\log R + H_0]$ *vs.* $-\log a_w$

A linear plot between log k_{obs} *vs.* $-H_0$ for both unimolecular and bimolecular gives unit slopes. This hypothesis is known as Zucker-Hammett hypothesis[6]. Plot of $[\log K + H_0]$ v/s log a_w gives a straight line, positve value of parameter ω (Fig. 1) greater than +3.3, indicates that water behaves as proton transfer agent in the rate controlling step[7].

Effect of varying [oxidant]: The reaction was studied at varying oxidant concentrations and the order with respect to oxidant was found to be one. The first order rate constant showed that rate constant decreases with increasing the initial [Cr(VI)] (Table-2). This suggests that $HCrO_4^-$ is oxidizing reacting species of Cr(VI)[8, 9].

Rate law: $$\frac{-d[Cr(VI)]}{dt} = k[Cr(VI)]\,[\text{Substrate}]$$

The decreasing trend in the rate constant may be due to the hydrolytic equilibrium between $Cr_2O_7^{2-}$ and $HCrO_4^-$. The molecular identity of [Cr(VI)] species present in the solution is given below:

$$Cr_2O_7^{2-} + H_2O \rightleftharpoons 2HCrO_4^-$$

$$HCrO_4^- + H^+ \rightleftharpoons H_2CrO_4$$

$$HCrO_4^- + 2H^+ \rightleftharpoons HCrO_3 + H_2O$$

In addition to the above species there may be other species. Since the reaction has been carried out in acetic acid-water medium, [Cr(VI)] is also expected to exist in the form of an acetyl chromate $AcOCrO_3^-$.

TABLE-2
EFFECT OF VARYING [Cr(VI)] ON REACTION RATE

[Cr(VI)] (10^4 M)	6-Aminopenicillanic acid ($k \times 10^3$ min^{-1})	Amoxicillin acid ($k \times 10^3$ min^{-1})
2.87	7.070	7.402
2.72	7.670	9.322
2.57	9.260	10.966
2.42	10.810	11.515
2.27	13.026	12.337
2.12	14.510	14.579
1.96	15.990	16.458
1.81	17.270	17.565

Effect of varying [substrate]: The rate of oxidation increases with increasing concentration of the substrate. The plots of 1/k *vs.* 1/[sub] are linear and do not pass through the origin but show definite intercepts at $1/k_{obs}$ axis [Fig. 2 and slope = 1.2 and 1.3, of lines (A and B respectively)]. This indicates evidence for complex formation between the oxidant and the substrate[10].

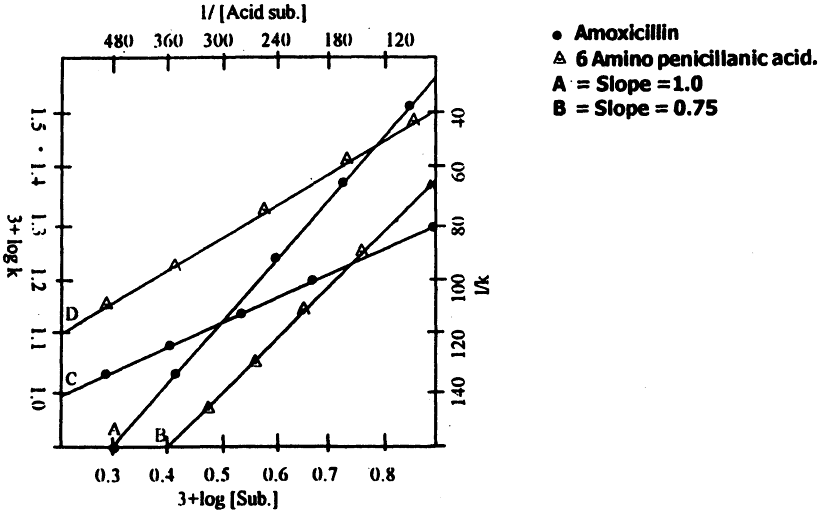


Fig. 2. (A, B) Plot of 3 + log k *vs.* 3 + log [sub], (C, D) Plot of 1/k *vs.* 1/[acid sub]

Effect of varying [ionic strength]: On increasing ionic strength by adding sodium chloride the rate decreases. The plot of [log k – log k_0] *vs.* $\sqrt{\mu}$ indicates that the reaction is between oppositely charged reactants[11]. The acid chromate-dichromate equilibrium constant is a function of the ionic strength. Increase in ionic strength will favour the formation of the dichromate ion and this will decrease the rate of reaction.

Effect of varying [solvent]: It is observed that the rate of oxidation increases with the increasing percentage of actic acid in water. The reaction has been carried out in acetic acid medium. [Cr(VI)] dissolved in high percentage of acetic acid may also exist in the form of an acetyl chromate ion ($AcOCrO_3^-$). Solvent dependence on rate indicates a superior species. The plots of log k v/s 1/D (Fig. 3) are linearly related as expected for ion-dipole reaction[12].

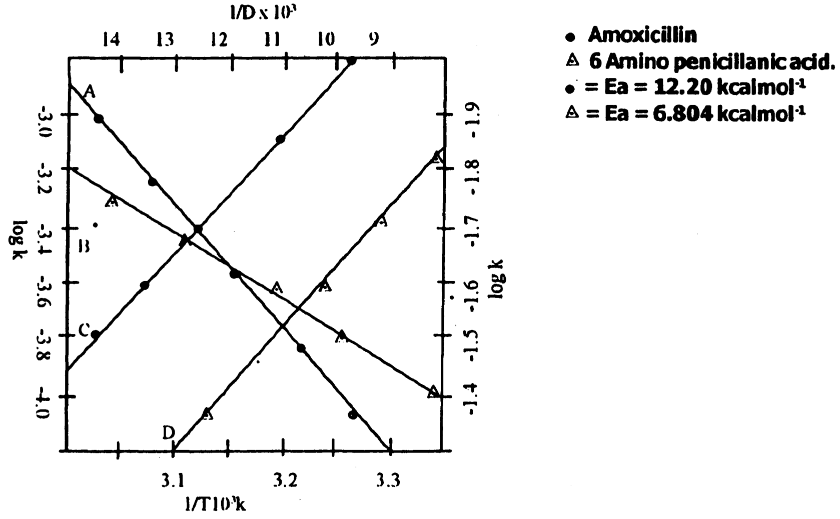


Fig. 3. (A, B) Plot of log *vs.* 1/T *vs.* 10^3 k, (C, D) Plot of log k *vs.* 1/D

Effect of varying temperature: The pseudo first order rate constants of oxidation of amoxicillin and 6-aminopenicillanic acid were determined at different temperatures. The plots of log k v/s 1/T (Fig. 3) are linear and the heat of activation was calculated from these plots. The reactions are as a whole characterized by a wide range of parameters. The activation parameters E_a, ΔH^*, ΔS^*, ΔG^* were evaluated (Table-3).

TABLE-3
ACTIVATION PARAMETERS

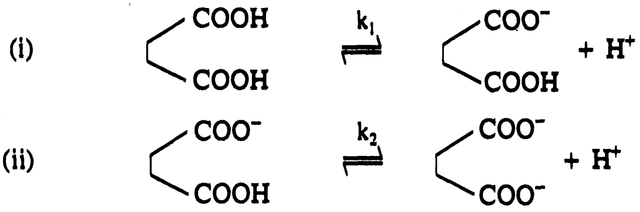
Parameters	Amoxicillin	6-Aminopenicillanic acid
E_a (kcal mol^{-1})	12.20	6.804
ΔH^* (kcal mol^{-1})	11.59	6.262
ΔS^* (eu)	-38.74	-55.911
ΔG (kcal mol^{-1})	23.34	23.202
A (sec^{-1})	5.588×10^4	0.1067×10^2

The positive values of enthalpy of activation ($k\Delta H^*$) indicate that the reactions are endothermic in nature. The activation energy is highest for the slowest reaction suggesting that the oxidation reactions are enthalpy controlled[13]. The negative entropy of activation (kΔS^*) indicates that the oxidation reactions are entropy controlled[13]. The plot of ΔH^* v/s ΔS^* is linear.

In the oxidation of amoxicillin and 6-aminopenicillanic acid by chromic acid, the frequency factor lies in the range of 5.588×10^4 and 0.1067×10^2 respectively. Hence, reactions can be described as normal reactions and suggest that the reactions are not of bimolecular type[14].

In the presence of succinic acid

Effect of varying dibasic acid: The kinetics of oxidation of organic acid in presence of succinic acid ionize into two steps and increase the acidity of the reaction, in order to enhance the reaction.



Hence the increase in concentration of succinic acid increases the rate of reaction because the electron-withdrawing effect of second —COOH group enhances the acidity of the first COOH[15]

Mechanism

The formation of free radical was neither indicated in the initial stage of the reaction not at the later stage by addition of mercuric chloride in the rate-determining step. It is therefore reasonable to assume that the reaction of acid dichromate with amoxicillin and 6-aminopenicillanic acid proceeeds through simple two electron transfer oxidant.

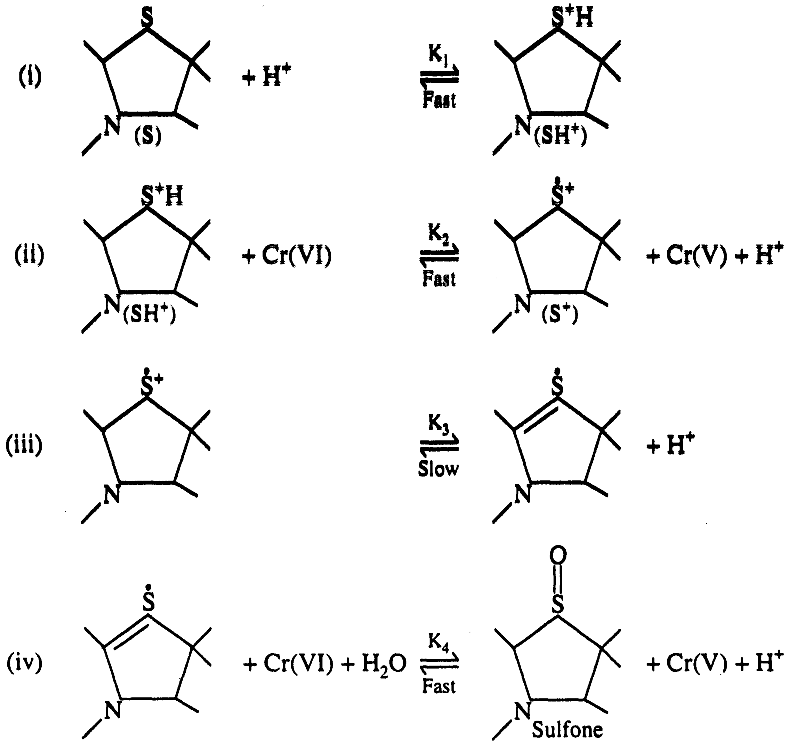
In consideration of the above discussions, the stoichiometry and products formed, and the reaction mechanism between amoxicillin and 6-aminopencicillanic acid with $HCrO_4^-$ can be explained by much simpler mechanism shown in **Scheme-1.**

Scheme-1

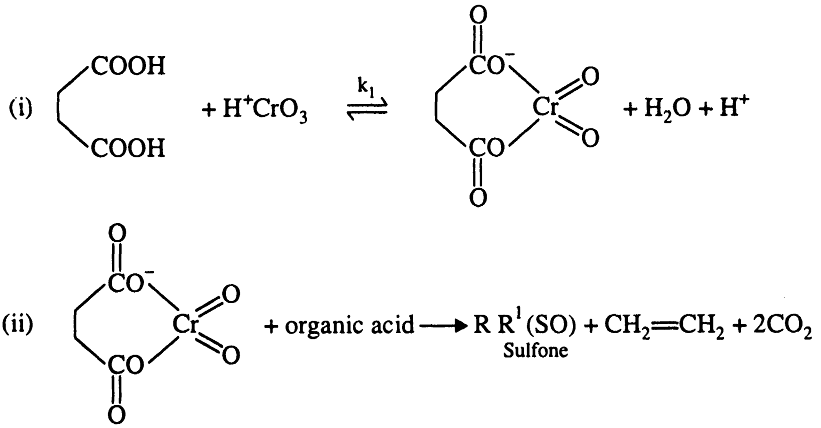
(i) Amoxicillin or 6-aminopenicillanic acid $H^+ + HCrO_4^- \underset{\text{fast}}{\overset{k_1}{\rightleftharpoons}}$ Intermediate complex

(ii) Intermediate complex $\xrightarrow[\text{slow}]{k_2}$ Sulfone + H_2CrO_3

Scheme -2
(In absence of succinic acid)



Scheme-3
(in presence of succinic acid)



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