Asian Journal of Chemistry Vol. 20, No. 4 (2008), 2539-2544

Kinetics and Mechanism of Oxidation of 6-[2-Amino-2-(4-hydroxyphenyl)acetylamino]-3,3-dimethyl-7-oxo-4-thiol-1-azabicyclo[3,2,0]heptane-2-carboxylic acid (Amoxicillin Trihydrate) with Bi(V) in $HClO_4$-HCl Mixture

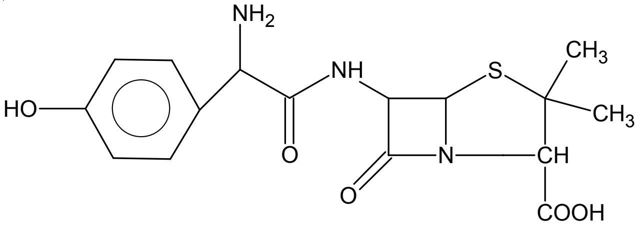
PARASHURAM MISHRA
Department of Chemistry, University of Delhi, Delhi-110 007, India
E-mail: prmmishra@rediffmail.com

Kinetics of oxidation of amoxicillin with Bi(V) complex has been studied in $HClO_4$-HCl mixture. The stoichiometry of Bi(V) with amoxicillin in acidic medium was established in the pH range 2.0-3.0 by iodometric and spectrophotometric methods. The oxidation follows first order kinetics in Bi(V) with [AX] is unity and increases the rate. Oxidation products have been proposed. Dependence of reaction rate on temperature has been studied and Eyring's activation parameters were computed. The mode of electron transfer from the substrate to the oxidant has been explained on the basis of bridged outer sphere mechanisms.

Key Words: Amoxicillin, Antibiotics, Bismuth, Kinetics, Mechanism, Penicillin acid, Oxidation, Stoichiometry.

INTRODUCTION

Amoxicillin is a member of β-lactam antibiotics which is traditionally used for the treatment of common bacterial infections in both human and food producing animals. Amoxicillin is acidic in nature acts by inhibiting the protein synthesis[1] of the bacterial cell wall. The basic nucleus of the amoxicillin is 6-aminopenicillnic acid, which consists of a thiazolidino ring linked to β-lactam ring. The side-chain determines the antibacterial and pharmacological characteristic of this compound[2].



Amoxycillin trihydrate

There is no report in literature on the kinetics of the oxidation of amoxicillin with Bi(V). The solution chemistry of Bi(V) has not been well explored due to inability to get in solution. However, the digestion of sodium bismuthate in a mixture of $HClO_4$ and HCl gives a transparent solution appreciably stable and ambient temperature[2]. The oxidation reaction of amoxicillin trihydrate was undertaken for investigation to elucidate the mode of electron transfer from the substrate (amoxicillin) to the oxidant Bi(V). Hence, as a part of present work on mechanistic studies on Bi(V) oxidation of organic and inorganic substrate in general and medicinal compounds in particular[3-6], we have investigated the stoichiometry and mechanism of oxidation of amoxicillin by Bi(V) in $HClO_4$ and HCl medium.

EXPERIMENTAL

All chemicals used in this study were of analytical grade. Amoxicillin trihydrate ($C_{16}H_{19}N_3O_5S{\cdot}3H_2O$) obtained from CDH Pharmaceutical (India). Sodium bismuthate ($NaBiO_3$) obtained from BDH.

Preparation and standardization of Bi(V) solution: Sodium bismuthate (AR) was used as a source of Bi(V). A known quantity of sodium bismuthate was digested in a known volume of the mixture of HCl (1.5 mol dm^{-3}) and $HClO_4$ (10 mol dm^{-3}) and filtered the undissolved salt. The filtrate gave a transparent solution of Bi(V). The solution of Bi(V) was standardized by modified iodometric method[3]. All the solutions were prepared in double distilled CO_2 free water.

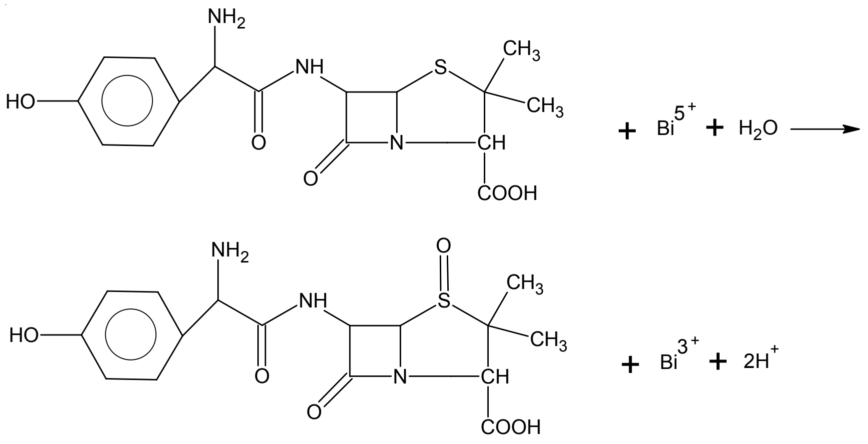
For the kinetic study Shimadzu UV spectrophotometer with 1 cm glass cuvett was used for the absorption measurements at fixed λ_{max} 400 nm for amoxicillin. The reaction mixture were carried out in double wall vessel connected with Julabo thermostat at ambient temperature. $NaClO_4$ has been used to maintain the ionic strength on rate condition. The progress of the reaction was monitored by the iodometric estimation. The course of the reaction was studied over 75 % of the reaction. The rate constants k calculated were reproducible within ± 2 % error, 10^{-3} M < amoxicillin solution was prepared and kept under 4 °C.

RESULTS AND DISCUSSION

The stoichiometry of the reaction between Bi(V) and amoxicillin was investigated under excess oxidant conditions. A known amount of amoxicillin solution was allowed to react completely with excess of Bi(V) at 298 K in the presence of proportional amount of HCl to maintain pH at 3. The excess of Bi(V) was estimated iodometrically. Stoichiometry of the reaction between Bi(V) and amoxicillin was found to be 1:1 (Table-1). The most probable form of the oxidised product[4] is given as

TABLE-1
STOICHIOMETRY RESULTS OF OXIDATION OF [AX] WITH Bi(V) IN $HClO_4$-HCl MIXTURES

[Bi(V)] × 10^3 (mol dm^{-3})	[AX] × 10^3 (mol dm^{-3})	[Bi(V)] × 10^3 (mol dm^{-3}) consumed	$\frac{\Delta Bi(V)}{\Delta [AX]}$
2.10	1.00	1.12	1.12
2.20	1.00	1.13	1.13
2.80	1.50	1.61	1.07
2.40	1.50	1.63	1.09
3.40	2.00	2.30	1.15
3.50	2.00	2.34	1.17
4.50	2.50	2.81	1.12
5.50	2.50	2.80	1.13
5.60	2.50	2.83	1.13



Bi(V) and Amoxicillin dependent

The concentration of Bi(V) and amoxicillin were varied in the range (0.8-2.0) × 10^{-3} mol dm^{-3} and (4.0-20.0) × 10^{-3} mol dm^{-3}, respectively at final concentration of $HClO_4$ (1.0 mol dm^{-3}) and HCl (1.5 mol dm^{-3}). The second order dependence on Bi(V) was indicated, respectively by the linearity passing through origin of log[Bi(V)] *vs.* time plots. The values of second order rate constant k increase in [AX] and a plot of log k_{obs} *vs.* log [AX] showed was two.

Dependence of rate on pH: The pH of the reacting solution was varied between 2.0-3.5 by varying [H^+] at constant Bi(V). The first order reaction rate decreases with increase in pH.

Dependence of rate on ionic strength: The ionic strength was varied in the range 1.0-2.40 by adding requisite quantity of $NaClO_4$ at fixed concentration of [Bi(V) = 1.4×10^{-3} mol dm^{-3}, [HCl] = 1.50 mol dm^{-3} [$HClO_4$] = 1.0 mol dm^{-3}. The rate decreases with the increase in ionic strength indicating reactive species of opposite charge.

Dependence of rate on temperature: The reaction was carried out at 303, 313 and 328 K at constant ionic strength and pH for Bi(V). Arrhenius plot of log k *vs.* 1/T gave a straight-line. From the slope and intercept, the experimental energy of activation E* and frequency factor (A) were found to be 6.13×10^3 JK^{-1} mol^{-1} and 5×10^3 s^{-1}. The Eyring parameters ΔH*, ΔS* and ΔG* which are temperature dependent and can be calculated from

$$\Delta H^* = \Delta E^* - RT,$$

$$\Delta S^* = \frac{2.303 \log\left(\frac{Ah}{kT}\right)}{R}$$

$$\Delta G^* = \Delta H^* - T\Delta S^*$$

where h = Plank's constant; k = Boltzman constant.

At low pH, in the presence of heavy metal ions the penicillinic acid is formed by a complex series arrangement. This acid absorbs strongly in the UV region and this has been used as a method of assay of penicillins[4]. As the reaction on rates are independent of [NaCl] and [HCl] it is obvious that the ultimate chloro species of Bi(V) are involved and as such there appears to be non-involvement of NaCl and HCl in any equilibrium step preceded by the determining step. A detailed information about the chloro species of Bi(V) in $HClO_4$-HCl mixture is lacking and it has been assumed that Bi(V) exist[5] as $BiCl_6^-$ and protonated form $HBiCl_6$. Based on these and other results discussed earlier, as most probable the following mechanism is proposed for the oxidation of amoxicillin by Bi(V). The probable oxidation site is the sulphide moiety of substrate molecules, where S, SH^+, X, Y are the substrate, protonated substrate and the transient intermediated radical cation and the free radical, respectively.

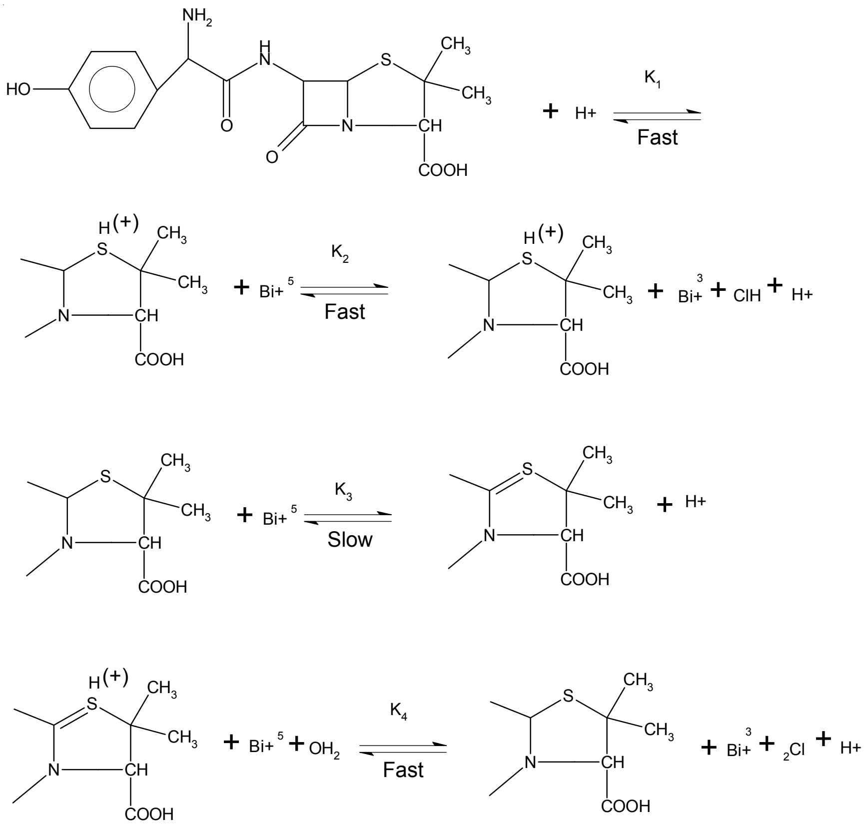
Applying steady state approximation to the intermediate [A],

$$\frac{d[A]}{dt} : K_2[SH^+][Bi(V)] - K_{-2}[A][Bi(V)][H^{-1}] - K_3[A] = 0$$

$$[A] = \frac{K_2[Bi(V)][SH^+]}{K_{-2}[Bi(III)][H^+] + K_3}$$

The rate of oxidation is given by

$$-\frac{d[Bi(V)]}{dt} = K_3[A]$$



$$-\frac{d[Bi(V)]}{dt} = \frac{K_2K_3[Bi(V)][SH^+]}{K_{-2}[Bi(III)][H^+]+K_3}$$

$$K_{obs} = \frac{K_1K_2K_3[S][H^+]}{K_{-2}[Bi(V)][H^+]+K_3}$$

So,

$$\frac{-d[Bi(V)]}{dt} = \frac{K_1K_2[Bi(V)][AX]}{K_2+K_3} = K[Bi(V)][AX]$$

where AX is amoxicillin; K is the first order rate constant (observed).

Plot of k_{obs} *vs.* [AX] was linear passing through the origin (Table-1). Showing the order in [AX] as on. plots of K_{obs} *vs.* [Bi(V)] and $[H^+]$ are also found to be linear. The reactants break down to simpler intermediates and ions during the various stages of oxidation. The kinetics investigations were performed at 30, 40 and 50 °C and the values are first order rate constant.

The thermodynamic parameters were calculated in a conventinal manner. The energy of activation and entropy of activation (ΔS*) calculated to be 6.13×10^3 J K^{-1} m^{-1}, respectively at 30 °C. The low value of ΔE* and negative value of ΔS* suggested that the degree of freedom of intermediate complex is less than that of the reacting molecules and the intermediate complex permits a facile electron transfer from the[7-12] the substrate to Bi(V). The rate of the reaction at 30 °C found to be 4.90×10^5 min^{-1}.

Thus, the values of Eyring parameters were obtained at 303 °K as ΔE* = 5.13×10^3 J K^{-1} mol^{-1}, ΔH = 0.585 kcal mol^{-1}, ΔS = -1.093 J K^{-1} mol^{-1} and ΔG = 325.36 J mol^{-1}.

REFERENCES

1. R.S. Satoskar and S.D. Bandarkar, Pharmacology mcotherapeutics, Vol. 11, 11th Ed. Popular Prakashan, p. 561 (1990).
2. H.P. Rang, M.M. Dale and J.M. Ritter, Pharmacology, Churchill Livingstone Publications, edn. 4, p. 691 (1968).
3. M.A. Zaye and S.M. Abdallah, *Spectrochim. Acta*, **611A**, 2231 (2005).
4. G.T. Burstein and G.A. Wright, *Nature*, **221**, 169 (1969).
5. Y.K. Gupta, K.M. Irani and P.D. Sharma, *J. Indian Chem. Soc.*, **68**, 487 (1991).
6. A.S. Orabi, *J. Solut. Chem.*, **34**, 95 (2005).
7. P. Mishra, *Oxid. Comm.*, **22**, 244 (1999).
8. A. Fernandez-Gonzalez, R. Badia and M.E. Diaz-Garcia, *Anal. Biochem.*, **341**, 113 (2005).
9. S. Tabassum, S. Parveen and F. Arjmand, *Transition Met. Chem.*, **30**, 196 (2005).
10. S. Garcia, L. Ciullo, M.S. Olivera, J.C. Gonzalez, S. Bellu, A. Rockembauer, L. Korecz and L.F. Sala, *Polyhedron*, **25**, 1483 (2006).
11. K.J. Laidler, Chemical Kinetics, Harper Int., edn. 3 (1997).
12. P. Mishra, *J. Saudi Chem. Soc.*, **8**, 377 (2004).

(*Received*: 20 January 2007; *Accepted*: 20 December 2007) AJC-6145