Asian Journal of Chemistry Vol. 11, No. 1 (1999), 110–114

Proton Ligand Formation Constant and Chelation Tendency of Pyrazinamide

SARITA SHRIVASTAVA* and PRADEEP KUMAR GUPTA
Chemical Laboratories,
M.V.M., Bhopal-462 003, India

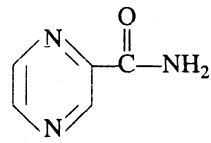
Chelation tendency of pyrazinamide (pyrazine carboxamide) has been worked out and the proton ligand formation constants have been computed using various methods at 30°C and 0.1 M ionic strength.

INTRODUCTION

Metal complexes have been reported to play an important part in the biological activity of drugs.[1,2] A current theory of the drug action enters around the competitive bindings. It was pointed out that antimicrobial agents have chelation tendency[3] and it was also pointed out that many drugs function as metal complexes. Probably with these considerations in the last few years, chelation tendency of various drugs has been worked out.[4] The trace metals present in the body are generally transitional metals. These abnormal metals change the behaviour of enzyme system binding with them and replacing the essential metals of these systems, they also change the structure of the nucleic acid by binding them.

The pyrazinamide drug was developed earlier by Chorine.[5] It is biosisoster of nicotinamide and possesses bacterial action against mycotuberculosis. Since nicotinamide and its derivatives have chelating tendency, it was thought fruitful to work out the avidity of pyrazinamide for chelate formation. It has white needle-like crystals, soluble in hot water. The structure of the molecule clearly indicates its potentiality for complex formation with metals.

Literature survey indicates that practically no work has been done with this compound describing its complex forming potentiality.



*Address for communication Dr. Sarita Shrivastava, 88/10 F, Tulsi Nagar, Bhopal (M.P.), India.

The mechanism of action of pyrazinamide suggested that pyrazinamide may be active as a prodrug. Susceptible organisms produce deaminidase which is responsible for conversion to pyrazinoic acid. Resistant strains of mycotuberculosis do not produce this aminidase enzyme suggesting that the acid form of the drug is the active form. *In vitro* test shows that pyrazinoic acid is 8–16 times less active than pyrazinamide.[6]

Pyrazinamide is an amide of pyrazinoic acid; its pKa value will give an idea about the availability of the chelating species, cation PZA^+ at 6.6 pH, and PZA^- at 7.7 pH.

With this view, in the present note, the proton ligand formation constant log K_n^H of pyrazinamide has been calculated at 30°C and at 0.1 M ionic strength with KNO_3 using Calvin-Bjerrum's pH titration technique[7] as adopted by Irving Rossotti.[8] The stoichiometry of the complexes formed in solution with biologically active metals Mg(II), Co(II), Al(III), Be(II), Ca(II), Ni(II), Cu(II), Fe(II), Fe(III), Zn(II), Cd(II) and Mn(II) was traced using conductometric titrations.

EXPERIMENTAL

All the solutions were prepared by dissolving high purity chemicals. Pyrazinamide was dissolved in hot water, while NaOH solution was prepared in CO_2-free water and standardized against a standard solution of oxalic acid.

The Bjerrum-Calvin pH titration technique was used to determine proton-ligand formation constant of pyrazinamide (PZA).

The three sets of solutions of (a) nitric acid, (b) nitric acid and PZA solution, and (c) nitric acid, PZA and metal solution were prepared such that the total volume was 50 mL and final concentration were 1.0×10^{-2} M HNO_3 and 5×10^{-3} M PZA. In each case the ionic strength was maintained at 0.1 M using KNO_3. The titration was performed with 0.1 M NaOH and Systronics pH meter, with a glass calomel electrode, was used for the titrations. From the titration curves the average number of protons associated with PZA ($\bar{n}A$) was calculated using the relation of Irving-Rossotti.

$$\bar{n}A = \frac{(V_{II} - V_I)(N_0 + E_0)}{(V_0 + V_I)T_{L_0}} + YT_{C_L}$$

where V_I and V_{II} are the volumes of alkali required to react the same pH in the acid and the ligand titration curves respectively, while V_0, T_{L_0}, E_0 and N_0 are the volume of mixture, initial concentration of the ligand, initial concentration of the acid and the concentration of titrant respectively. Y is the number of dissociable protons.

From the value of $\bar{n}A$ at various pH proton-ligand formation constants log K_1^H and log K_2^H were computed by various methods, *e.g.*, half integral point-wise calculation and linear plot methods. The results obtained are recorded in Table-1. The proton-ligand formation curves at 0.1 M ionic strength are shown in Fig. 1 and Fig. 2.

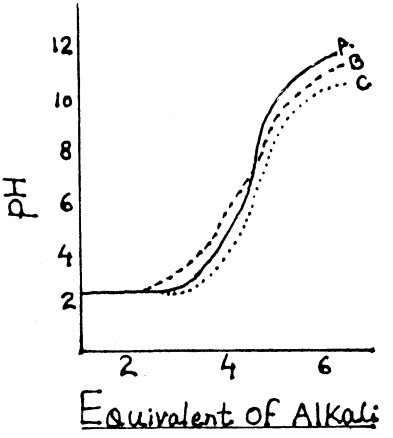


Fig. 1

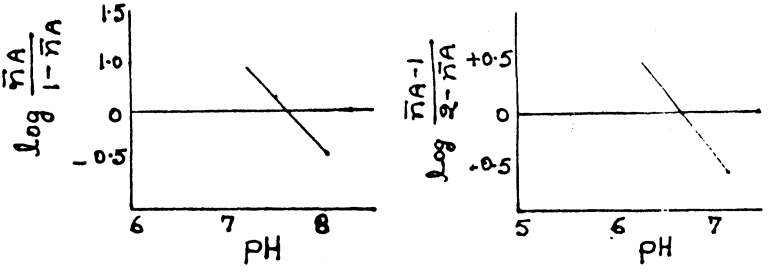


Fig. 2

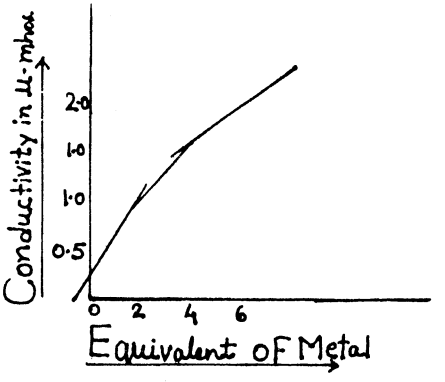


Fig. 3

TABLE-1
PROTON-LIGAND STABILITY CONSTANTS

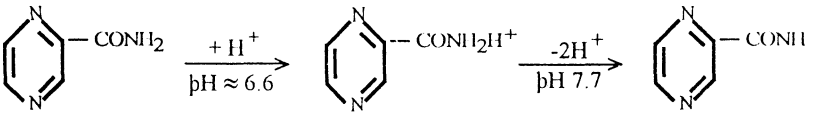
Ionic concentration μ = 0.1 M Temp. = 30°C

S.No.	Method	$\log k_1^H$	$\log k_2^H$	$\log k_n^H$
1.	Half $\bar{n}A$ method	7.70	6.70	14.37
2.	Point wise calculation	7.65	6.60	14.25
3.	Linear plot method	7.70	6.70	14.37
	Average	7.68	6.60	14.33

pH-titration curves in case of the ligand show somewhat unusual as the ligand curve remains behind and above the acid curve and then it goes forward and below the acid curve. The analysis of the curve indicates addition of one proton per mole of the ligand.

In acidic solution this proton may be attached with the amide moiety of the ligand. This protonated species ($^+$HL) ionizes stepwise.

The consumption of one equivalent of alkali indicates neutralisation of one proton in stepwise manner. Thus the ionisation reaction may be represented as follows.

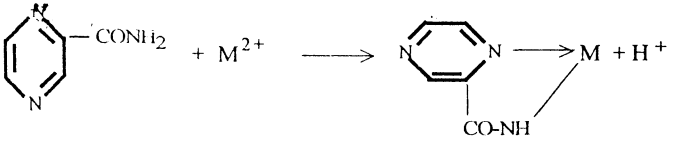


(I) (II) (III)

$$L + H^+ \xrightarrow[pH \approx 6.6]{\log k_1^H} {}^+HL$$

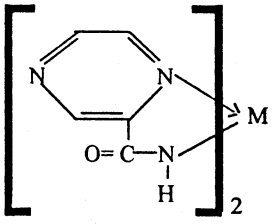
$$^+HL \xrightarrow[pH \approx 7.7]{\log k_2^H} \bar{L} + 2H^+$$

This indicates at the physiological pH (7.7) the species available for the chelation which will react with metal ions with the removal of one proton in the following manner.



I (IV)

This stoichiometric study of the chelates formed with the biologically active metals was done using conductometric titrations applying monovariation method due to Nayer and Pandey[9] which indicated the formation of two complexes ML and ML_2 in stepwise manner. The final product with the divalent metal cation may be proposed to have the following structure:



This clearly indicates that the most expected co-ordiation number, six, for the metal ions is not saturated completely at the physiological pH 7.7. This may favour the attachment of the chelates with the tissue or nucleic acid.

ACKNOWLEDGEMENT

The authors are thankful to the Chemistry Department, M.V.M., Bhopal for providing laboratory facilities.

REFERENCES

1. C.C. Coryell, in: R.N Gurd, Special Problems in the Formation of Metal Complexes in Chemical Specificity in Biological Interaction, Academic Press, New York, pp. 90–160 (1954).
2. H. Sigel, Metal Ions in Biological System, Marcel-Dekker, New York, pp. 10–16 (1980–84).
3. E.D. Weinberg, E.A. Cook and C.A. Winer, *Proc. Soc. Am. Bacteriologists*, **42**, 194 (1956).
4. P.B. Chakrawarti, *J. Scient. Ind. Res.*, **48**, 529 (1989).
5. M.V. Chorine, *Mycobacterium Comp. Rend. Acad. Sci.*, **220**, 150 (1945).
6. L.B. Heifets, *Antimicrob. Agent Chemother.*, **33**, 1252 (1989).
7. A.E. Martell and M. Calvin, Chemistry of Metal Chelate Compounds, Prentice-Hall, N.Y., p. 192 (1953).
8. H.M. Irving and H.S. Rossotti, *J. Chem. Soc.*, 2904 (1954).
9. M.R. Nayer and C.S. Pandey, *Proc. Indian Acad. Sci.*, **27A**, 284 (1948).

(*Received*: 6 July 1998; *Accepted*:30 October 1998) AJC-1576