Oriental Journal of Chemistry Vol. **26**(1), 171-174 (2010)

Synthesis and characterization of 2-mecapto-3-phenyl-4-quinazolinone complexes of copper (I) : Towards new copper radiopharmaceuticals

D.D. DIKSHIT* and S.B. SINGH

Department of Chemistry Jajatpur P.G. College, Jagatpur, Varanasi (India).

(Received: October 30, 2009; Accepted: December 08, 2009)

ABSTRACT

2-Mercapto-3-phenyl-4-quinazolinone complexes of copper is synthesized characterized on the basis of chemical properties, elemental data, magnetic susceptibility and characteristic absorption band in IR and ultra-violet absorption frequencies. The structure of complex underline the ability of Cu (I) centre to exist in distorted tetrahedral environment. The binding mode of the ligand is usual and it coordinates monddently through Sulphur. Electrochemical measurement shows that copper complexes undergo a reversible one electron oxidation-reduction reaction at biologically accessible potential.

Key words: MPQH, Hypoxia, Thiosemicarbazones.

INTRODUCTION

Cupper complexes of bis (thiosemicarbazones) have been investigated for use as anti-cancer chemotherapeutic agents1,2 and as superoxide dismutase-like radical scavengers3. It is however, their use as delivery agents for radioactive copper in new copper based radiopharmaceuticals and the hypoxic selectivity of certain copper bis (thiosemicarbazonato) complexes that has created much recent interest4-10. Hypoxia (Low oxygen concentrations) is often associated with tumours and heart disease and can effect the out come of anti-cancer treatments. This means it is of great clinical utility to develop systems that allow the "non-invasive" imaging of hypoxia with a suitable radiopharmaceutical[11]. Copper radionuclides are of considerable interest in the development of new radiopharmaceuticals as they include isotopes that have both PET imaging and therapeutic potential[12].

The cell uptake and retention characteristics of copper bis (thiosemicarbazonato) complexes have already been studies and it was found that radioactive copper complexes $[Cu^{64} (L)_x]$ shows rapid uptake and washout in normal tissues but it selectively trapped in hypoxic heart and tumour tissue. It is therefore referred as 'hypoxia selective'. In normal oxic cells Cu (I) complex is rapidly oxidized to neutral Cu (II) complex, which is quickly washed out of the cell.

In this paper, we wish to describe the preparation of 2-Mercapto-3-phenyl-4-quinazolinone complexes of copper and it's structural characterization on the basis of elemental and thermal analysis, infrared and electronic spectral studies, conductivity and magnetic susceptibility measurements.

MATERIAL AND METHODS

The ligand 2-mercapto-3-phenyl-4-quinazolinone was synthesized by literature method.13-14It was re-crystallized from ethanolic solution and characterized by sharp melting point and elemental analysis. Sulphur, phosphorus and chlorine were estimated gravimetrically as BaSO4, ammonium phosphomolybdate and AgCl respectively15 while Copper was estimated as [Cu(en)2][HgI4]. Infra-red spectra of the complex in pressed KBr pellets were obtained in the NaCl region with a Perkin-Elmer double beam spectrophotometer Model-13. In KBr region the spectra were obtained on a Perkin-Elmer Model-12 C, while IR spectra of other complexes were measured on a Bruker instrument IFS-88 (Nujolmulls, CsI discs for the range 4000-500 cm-1, polyethylene discs for the range 500-100 cm-1). Ultra-violet absorption spectra were obtained with a Unicam Spectrophotometer Model SP-700 and magnetic susceptibility measurements were made by the Gouy method at room temperature. The tentative structure were discussed on the basis of chemical properties, magnetic susceptibility, IR and U.V-visible spectroscopy.

EXPERIMENTAL

Preparation of [CuCl(MPQH)3].THF

This complex of Cu (I) with title ligand (MPQH) was prepared by substitution of the ligand (MPQH) to an intermediate complex $[CuCl(APh_3)_3]$. THF with replacement of PPh_3 or $AsPh_3$ (A=P or As) with replacement of PPh_3 or $AsPh_3$. It was filtered and added solution of ligand (MPQH) in THF (25 ml. 3 mmol) drop wise, with constant stirring. The resultant mixture was then refluxed for another 30 minutes. It was again filtered and added ethanol to obtain colourless crystals of complex.

All the preparative operations were performed under argon. Purification and drying of solvent was done using standard methods[16].

RESULTS AND DISCUSSION

The micro analytical data as well as sulphur and metal analyses of complexes are in good agreement with stoichiometry. On comparing the stoichiometries of these complexes with similar types of known complexes of Cu(I) with triphenylphosphane, such as [CuCl(PPh3)3],17-18 it appears that in this complex the ligand acting as mono dentate ligand. But the mode of linkage in these complexes was determined on the basis of infrared spectral studies.

Infrared Spectra

Infrared spectrum of the ligand '2-mercapto-3-phenyl-4-quianzolinone' in solid state displays ν(N-H) at 3250cm^{-1} but shows no absorption at 2500cm^{-1} indicating that in the solid state the ligand exist as thione and not as thiol toutomer. The relatively low frequency of ν(N-H) vibration is probably due to hydrogen bonding between >N-H and >C=S group[19] . Compounds containing thioamide group have been studied by several workers and it has been suggested that all such complexes give rise to four thioamide bands in their infrared spectra[20-21]. They are all mixed bands appear around 1540 cm^{-1} (band-I), 1345cm^{-1} (band-II) 980,1000 (band-III) and 770cm-1 (band-IV) and these have contribution from ν (N-H)+ ν (C-H), ν(C=S)+ ν (C-H)+ ν (C=N), ν (C-N)+ ν (C-S) and ν (C=S) respectively. Positions and intensities of these bands shift after complexation. These shifts give us clue to know the mode of bonding.

The ν(N-H) band of the ligand at about 3250 cm^{-1} in the IR spectra of these complexes indicates that ligand is present as neutral species (MPQH) and as the wave number of the ν(N-H) absorption band dose not decrease in these complexes therefore coordination through imino nitrogen is ruled out. Furthermore the thioamide bond I of the ligand remains almost stationary or show very little (±5) blue shift. It indicates the coordination in these complexes occurs through sulphur only, because it has been found that coordination through nitrogen results in blue shift of about 10-30 cm^{-1} in band-I. Similarly the intensity of thioamide band-II, and III, decreases and are shifted to lower wave number. The red-shift of about 50-60 cm^{-1} in band IV also observed. This major red shift in thioamide band- IV also indicates that ligand coordinates to Cu(I) ion only through sulphur,

Electronic Spectra and Magnetic Properties

The magnetic susceptibilities of the complexes determined with the help of a Gouy balance at room temperature Mercury tetra thiocyanato cobalt (II) was used as magnetic susceptibility standard and the magnetic corrections were estimated by the method outlined by Figgis and Lewis22. Complex of Cu(I) is found diamagnetic. The diamagnetism of this complex is in accordance to it's preferred geometry.

The electronic spectrum of complex is taken in DMF. The region from 1000-500 nm was found transparent and thus no band appears. Since Cu (I) is d10 system there is no absorption band due to d-d transition. However the electronic spectra of the ligand (MPQH) taken in DMF exhibits strong peak at 33900 cm-1 and a weak shoulder at 38200 cm-1 which were assigned to $\pi\rightarrow\pi^*$ intraligand (IL) transition23. Another very weak band also observed at lower energy at 26300 cm-1. This band is assigned as $\eta\rightarrow\pi^*$ transition.

The spectrum of complex, $[CuCl(MPQH)_3]$.THF exhibit intense band around 22400 cm^{-1} (395nm) and two medium bands between 37000-32000 cm^{-1}. The band around 22400 cm^{-1} is assigned as charge-transfer band (CT) due to their high intensity while two weak bands are assigned as intra-ligand (IL) bands. It provide an evidence of presence of ligand in distorted tetrahedral environment.

Conductivity measurements:

All the complexes show the residual conductance value 9-14 Ω^{-1} cm² mol^{-1} in solvent DMF. These low value indicates that the complexes behaves as non-electrolytic.24

Description of structure

On the basis of elemental analyses, infrared and electronic spectral studies, magnetic moments, thermal analysis and conductivity measurement, following tentative structures of complexes were proposed (Fig. 1).

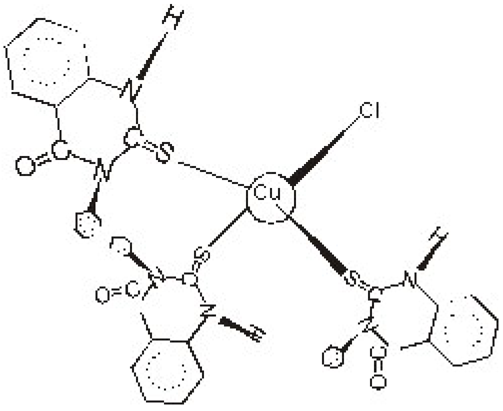

Fig. 1.

REFERENCES

1. D.H. Petening; *Bioinorg. Chem.*, **1:** 255 (1972).
2. D.X. West, A.E. Liberta, S.B. Padhye, R.C. Chikate, P.B. Sonaware, A.S. kumbhar and R.G. Yerande; *Coord. Chem. Rev.*, **123:** 49 (1993).
3. K. Wada, Y. Fujibayashi and A. Yokoyama; *Arch. Biochem. Biophys.*, 310 (1994).
4. Y. Fujibayashi, H. Taniuchi, Y. Yonekura, H.Ohtani, J.Konishi and A.Yokoyama; *J.Nucl. Me*d., **38:** 1155 (1997).
5. J.L.J. Dearling, J.S. Lewis, D.W. Mc Carthy, M.J. Welch and P. J. Blower; *Chem. Commun.,* 2531 (1998).
6. Y. Fujibayansi, C.S. Cutter, C.J. Anderson, D.W. Mc Canthy, L.A. Jones, T.Sharp, Y Yonekura and M.J. Welch; *Nucl. Med: Biol*., **26,** 117 (1999).
7. J.S. Lewis Rlaforest, T.L. Buettner, S.K. Song, Y. Fujibayashi, J.M. Connet and M.J. Welch*; Proc. Natl, Acad Sci-U.S.A*., **98:** 1206 (2001).
8. J.S. Lewis, T. L. Sharp, R. Laforest, Y. Fujibayashi and M.J. Welch; *J. Nucl. Med.*, **42:** 655 (2001).
9. J.L.J. Dearling, J.S. Lewis, G.D. Mullen, M.J. Welch and P.J. Blower; *J. Biol. Inorg. Chem.,* **7:** 249 (2002).
10. A.R. Cowley, J.R. Dilworth, P.S. Donnely, E. Labisbal and A. Sousa; *J. Am. Chem. Soc.*, **124:** 5270 (2002).

11. J.R. Ballinger; *Semin. Nucl. Med.*, XXXI (2001)
12. P.J. Blower, J.S. Lewis and J. Zweit; *Nucl. Med. Biol.*, **23**: 957 (1996).
13. Mehrotra Suman, Barthwal, J.P., Saxena A.K., Bhargawa K.P. and Parmar S.S., *J. heterocyclic Chem.,* **18**: 1157 (1981).
14. Bhargava P.N. and Chaurasia M.R. *J. Med. Chem.* **11**: 405 (1968).
15. Burton J.D. and Riley J.P., *Analyst,* 391 (1955).
16. D. D. Perrin, W. L. F. Arnarego and D. R. Perrin, "Purification of Laboratory Chemicals" 2nd edn. Pergamon Press, Oxford (1980).
17. G. Costa, G. Pellizer and F. Rubessar; *J. Inorg., Chem.,* **26**: 961 (1964).
18. G. Costa and L. Stefani; *J. Inorg. Nucl. Chem.,* **27**: 2581 to 2584, Pergamon press Ltd. (1965).
19. Uber H., Kovae S., Martavon A. and Jezek M., *Chem. Zvesti*, **32**: 486 (1978).
20. Singh B., Rukhaiyar M.M.P. and Sinha J.R., *J. Inorg. Nucl. Chem*., **39:** 29 (1977).
21. Lieder E., Rao C.N., Pillani C.N. and Hites R.D. *Can., J. Chem.*, **39:** 29, (1977).
22. B. N. Figgis and J. Lewis, "Modern Coordination Chemistry", Lewis and R. G. Wilkins; Eds, Interscience Publishers Inc, New York, N. Y. 403 (1960).
23. S. F. Mason; *Q. Rev*., **15**: 287 (1961).
24. Geary W.J., *Coord. Chem. Rev*., **7**: 81 (1971).