Proc. Indian Acad. Sci. (Chem. Sci.), Vol. 108, No. 3, June 1996, pp. 251–256.
© Printed in India.

Dicopper complexes of relevance to tyrosinase modelling: An overview

DEBALINA GHOSH, TAPAN KUMAR LAL and RABINDRANATH MUKHERJEE*

Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India

Abstract. A number of dicopper(II) complexes containing binucleating, primarily nitrogen donor ligands having *m*-xylyl spacers between the coordination units of relevance to tyrosinase activity and a brief account of the recent results obtained using a new non-Schiff base binucleating ligand providing only two-nitrogen coordination at each copper centre are described in this paper. This new system exhibits tyrosinase activity. A dihydroxo-bridged copper(II) complex has also been obtained with a novel ligand assembly formed as an impurity during our desired ligand synthesis. A brief review has been presented in this field emphasising the nature of the ligand systems and the reaction conditions.

Keywords. Dicopper(II) complexes; tyrosinase modelling

1. Introduction

Tyrosinase is a monooxygenase that catalyses *o*-hydroxylation of monophenols and the oxidation of *o*-diphenols to *o*-quinones (Solomon and Lowery 1993; Kitajima and Moro-oka 1994). The structure of tyrosinase is not known to date but it is well-documented that its dioxygen adduct (oxytyrosinase) is closely related to that of oxyhemocyanin. Hemocyanin is a ubiquitous dioxygen carrier in invertebrates, containing a dinuclear copper active site to which dioxygen is bound as peroxide. X-ray structures of the deoxy- and oxy-forms of hemocyanin reveal that each copper centre is surrounded by three histidyl nitrogen atoms from the protein chains. Interestingly, in one form of deoxy- and in oxy-hemocyanin, one of the histidyl nitrogens is bound more weakly.

Tailor-made binucleating ligands having *m*-xylyl spacers between the coordination units have been widely used in synthetic studies to mimic tyrosinase activity outside protein environment. Most noteworthy of them and the first synthetic model was that of Karlin *et al* (1981). During the past 10 years several modified xylyl systems have appeared in the literature (Karlin and Gultneh 1987; Tyeklar and Karlin 1989; Sorrell 1989; Kitajima 1992; Karlin and Tyeklar 1993).

Recently we have initiated a systematic programme to model tyrosinase activity using a newly designed ligand system, a,a′-*bis*[(N-methyl-2-pyridyl)ethylamino]-*m*-xylene (L). Here we provide a brief account of our findings and a brief review on the present status of our understanding of this fascinating chemistry. A report on this work has already been communicated (Ghosh *et al* 1996).

*For correspondence

2. Results and discussion

2.1 *Synthetic strategies*

Generally, the synthetic reaction sequence follows the following order. First, the reaction of the properly designed binucleating ligand with copper(I) salts in a suitable solvent to generate or isolate two- or three-coordinate copper(I) complexes. The two copper centres should be in close proximity. The second stage involves the reaction between the dinuclear copper(I) complexes and molecular oxygen, in a dry proton-free solvent preferably at low temperature.

Reacting the ligand L with $[Cu(CH_3CN)_4]ClO_4$ (mole ratio 1:2) in dichloromethane at ambient temperature, we generated supposedly a dinuclear copper(I) complex. Subsequent exposure to dioxygen resulted in a colour change from yellow to deep green and the formation of a substantial amount of bluish-grey precipitate. On evaporation, the dark green solution gave a green precipitate. Recrystallisation of this solid from acetonitrile afforded two complexes: a green complex and a few light-blue crystals. A deep blue solution still remained (Ghosh *et al* 1996).

2.2 *X-ray structures of the copper(II) complex*

Single-crystal X-ray analysis of the green product revealed that the structure consists of a discrete dicationic complex with two separated perchlorate anions. A schematic presentation of the coordination environment of the copper(II) centres is in figure 1. It clearly demonstrates the incorporation of two oxygen atoms in the complex: one into the aryl-hydrogen bond and the other into the hydroxo bridge. Key structural parameters for this compound are given below.

Average Cu–O(phenoxo) 1·961(5) Å Cu–Cu 2·999(2) Å
Average Cu–O(hydroxo) 1·912(5) Å
Average Cu–N(aliphatic) 2·016(5) Å
Average Cu–N(pyridine) 2·002(5) Å

The Cu_2O_2 unit is almost planar. Other structural features are normal amongst this class of compounds.

X-ray analysis of the light blue crystal revealed a novel dihydroxy bridged copper(II) complex wrapped up by an unprecedented ligand assembly L′ formed under our experimental conditions during the synthesis of ligand L (Ghosh *et al* 1996). The structure of this

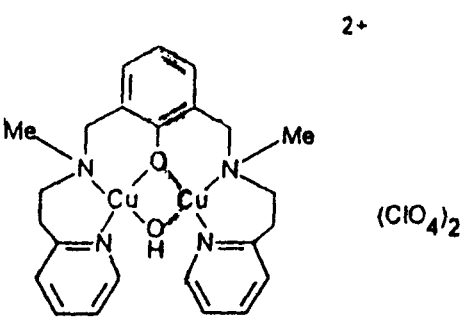


Figure 1. Schematic representation of the coordination environment of the copper(II) centres.

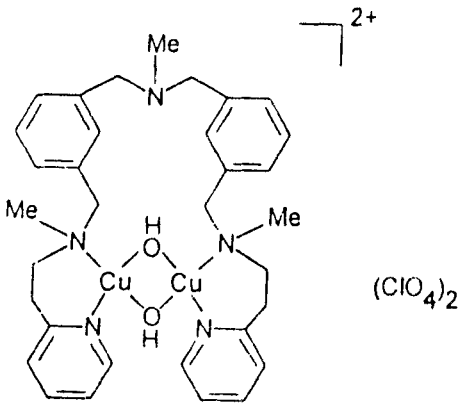


Figure 2. Schematic representation of the novel dihydroxybridged copper(II) complex.

complex also revealed discrete discationic complex and two separated perchlorate anions. A schematic presentation of this complex is in figure 2. Key structural parameters for this compound are given below.

Average Cu–O(hydroxo) 1·924(5) Å Cu–Cu 3·004(2) Å

Average Cu–N(aliphatic) 2·045(8) Å

Average Cu–N(pyridine) 1·997(8) Å

The Cu_2O_2 unit is again almost planar. Other structural features are normal amongst this class of compounds.

2.3 *Comments on the nature of product(s) of model systems*

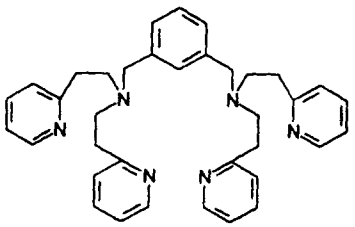
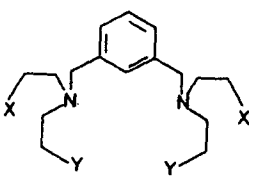
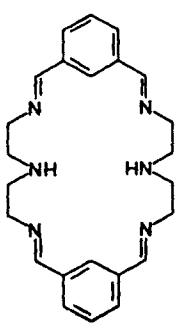
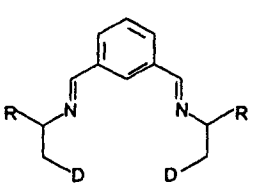
Systematic variations on xylyl ligand systems and reaction conditions have been done. Thus, it will be appropriate here to compare the results of the present work with those of very closely related reported systems.

A scrutiny of the nature of the dicopper(II) complexes obtained from such oxygenation studies on many binuclear copper(I) complexes reveals that the main products are either of the two: the hydroxylated phenoxo- and hydroxo-doubly bridged dicopper(II) complex and *bis*(hydroxo) copper(II) dimers (table 1).

Karlin *et al* (1981) utilised the binucleating ligand that provides two tridentate *bis*[2-(2-pyridylethyl)amine] to each copper ion and demonstrated aromatic ring hydroxylation. Interestingly when 1-pyrazolyl or 2-imidazolyl donor groups fully or partially replace the 2-pyridyl ligands, hydroxylation does not occur. However, when Schiff base ligands providing three or even only two nitrogen donors at each copper centre are used, hydroxylation takes place. In order to complete the missing link between Schiff base and non-Schiff base families, we used the present ligand L. It is worth mentioning here that the present ligand was so designed as to replace one of the ethylpyridine units in each arm of Karlin's ligand by a methyl group, to pinpoint the number of donor atoms necessary to bring about aromatic hydroxylation keeping the basic ligand structure fixed.

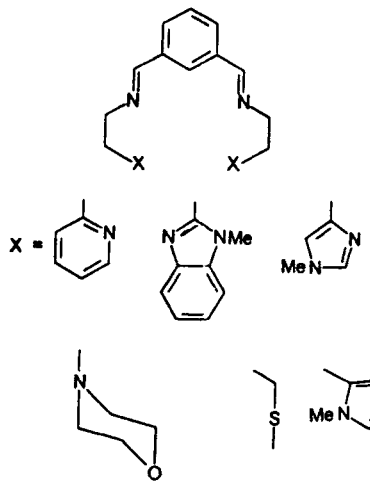
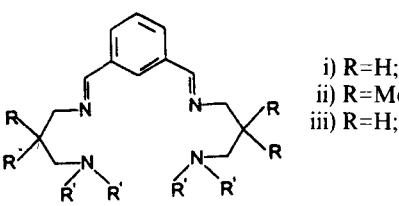
It is worth noting here that proper placement of the xylyl group is a prerequisite for aromatic ring hydroxylation and it is nicely demonstrated here for the ligand L′ which

Table 1. Known *m*-xylyl ligand systems used to model tyrosinase with nature of the resulting dicopper(II) complexes and references.

Ligand systems	Comments	References
	a	Karlin *et al* (1984)
 *X = Y = Pz; X = Y = Melm; X = Y = 3,5-dimethyl pyrazole; X = Py, Y = Pz; X = Py, Y = Melm; X = Pz, Y = 3,5-dimethyl pyrazole	b	Sorrell and Garrity (1991)
	a	Menif *et al* (1990)
 D = 4-imidazolyl or 1-methyl-4-imidazolyl R = H or $COOCH_3$	a	Casella *et al* (1988)

(*Continued*)

Table 1. (*Continued*)

Ligand systems	Comments*	References
	b	Gelling *et al* (1988); Casella *et al* (1991); Sorrell *et al* (1991)
 i) R=H; R'=Me ii) R=Me; R'=Me iii) R=H; R'=$CH_2CH{=}CH_2$	b	Drew *et al* (1989)

[a]Aromatic hydroxylation (phenoxo-/hydroxo-bridged dicopper(II) complex)
[b]Dihydroxo-bridged dicopper(II) complex

does not give aromatic hydroxylation but gives dihydroxy bridged structure. However, the ligand L gives rise to aromatic hydroxylation.

2.4 *Criteria for achieving a good model system*

From the available results obtained from systematic model studies, a viable model system of a binuclear copper centre expected to bind dioxygen and activate it for further oxygenation chemistry can be designed. It appears that the model should fulfil the following properties. (i) The environment for the binding of dioxygen should be proton-free, so as to suppress the displacement of the bound O_2 ligand as protonated superoxide or peroxide. Thus, a hydrophobic environment is sought for the dioxygen binding centre. (ii) The copper centres should be isolated in order to prevent further attack (and reduction) of the Cu_2 (O_2^{2-}) unit by additional Cu(I) in solution. Reaction between dicopper(I) complex and dioxygen at low temperatures seems to work to

minimise the irreversible reduction reactions in some cases. (iii) The binucleating ligands should provide two or three coordinated copper(I) centres in close proximity, coordinated by unsaturated nitrogen donors.

3. Concluding remarks

The results presented here neatly demonstrate the aromatic ring hydroxylation (tyrosinase activity) using a new dinucleating non-Schiff base ligand system providing only two nitrogen coordination at each copper centre. The synthesis of a dihydroxy bridged copper(II) complex with a novel ligand assembly, having some similarity with the ligand used for aromatic hydroxylation, emphasises the importance of correct placement of the xylyl group for aromatic hydroxylation.

Acknowledgements

Financial assistance received from the Council of Scientific and Industrial Research, and the Department of Science and Technology, New Delhi, is gratefully acknowledged.

References

Casella L, Gullotti M, Pallanza G and Rigoni L 1988 *J. Am. Chem. Soc.* **110** 4221
Casella L, Gullotti M, Bartosek M, Pallanza G and Laurenti E 1991 *J. Chem. Soc., Chem. Commun.* 1235
Drew M G B, Trocha-Grimshaw J and McKillop K P 1989 *Polyhedron* **8** 2513
Gelling O J, van Bolhuis F, Meetsma A and Feringa B L 1988 *J. Chem. Soc., Chem. Commun.* 552
Ghosh D, Lal T K, Ghosh S and Mukherjee R N 1996 *J. Chem. Soc., Chem. Commun.* 13
Karlin K D and Gultneh Y 1987 *Prog. Inorg. Chem.* **35** 219
Karlin K D and Tyeklar Z 1993 *Adv. Inorg. Biochem.* **9** 123
Karlin K D, Dahlstrom P L, Cozzette S N, Scensny P M and Jubieta J 1981 *J. Chem. Soc., Chem. Commun.* 881
Karlin K D, Hates J C, Gultneh Y, Cruse R W, McKnow J W, Hutchinson J P and Zubieta J 1984 *J. Am. Chem. Soc.* **106** 2121
Kitajima N 1992 *Adv. Inorg. Chem.* **39** 1
Kitajima N and Moro-oka Y 1994 *Chem. Rev.* **94** 737
Menif R, Martell A E, Squattrito P J and Clearfield A 1990 *Inorg. Chem.* **29** 4723
Solomon E I and Lowery M D 1993 *Science* **259** 1575
Sorrell T N 1989 *Tetrahedron* **45** 3
Sorrell T N and Garrity M L 1991 *Inorg. Chem.* **30** 207
Sorrell T N, Vankai V A and Garrity M L 1991 *Inorg. Chem.* **30** 210
Tyeklar Z and Karlin K D 1989 *Acc. Chem. Res.* **22** 241