CHAPTER I

ASPECTS OF THE TRANSITION METAL-ION MEDIATED HYDROXYLATION AND THE PURPOSE OF THE PRESENT INVESTIGATION

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Abstract: In this chapter the known chemistry of transition metal mediated hydroxylation with special refernce to aromatic hydroxylation is summerised. The scope and purpose of the present work is delineated.

1.1 INTRODUCTION

The chemistry of the metal-ion mediated hydroxylation reaction has received increasing attention partly because of various biological implications[1] and partly because of their importance in synthetic organic chemistry[2-4]. Oxidation reactions in biological processes are of fundamental importance. At present variety of microbial oxidations of simple hydrocarbons, terpenes and steroids are known[5-9]. Identification of the stereo- and regioselective hydroxylation in biological world draws more attention to the microbial oxygenations. Enzymatic conversions among the microbial oxidations stimulates greater interest since they involve specific transformations catalysed by a single cell-free enzyme and require the stoichiometric presence of any necessary cofactor. Here the metal ions play the key role. The cytochrome P-450 family of enzymes is known for the ability to convert alkanes to alcohols with high regioselectivity and stereospecificity[10-12]. A number of oxygenase associated transition-metal ions are known for wide variety of oxidative transformations. A common reaction catalyzed by monooxygenases is the hydroxylation of aromatic systems i.e. ArH --> ArOH which is a key step in the metabolism of aromatic aminoacids[13].

Phenolase[14], p-hyroxybenzoate hydroxylase;[15] phenylalanine hydroxylase;[16] and cytochrome P-450 are well known examples[17] of oxygenasees which catalyse aromatic hydroxylation. A very significant progress has been made in studying the biological systems[1,18] particularly monooxygenases which are capable of incorporating of oxygen from dioxygen into aromatic molecules.

Nonenzymetic Aromatic Hydroxylation Reactions:

Studies on nonenzymetic hydroxylation reactions that mimic aromatic hydroxylation has started for two reasons

(i) to provide a basis for understanding enzymatic hydroxylation reactions,

(ii) to develop simple catalytic systems those under mild conditions would exhibit selective hydroxylation.

The major problems[19,20] associated with the *in vitro* hydroxylation of aromatic nuclei are as follows.

(i) The low reactivity of aromatic nuclei toward oxidative nuclear substitution.

(ii) The hydroxylated product is more reactive toward oxidation than the precursor aromatic compound.

Work Done:

Biomimetic hydroxylation of aromatic systems have started since 1954. Udenfriend *et al.* used a mixture of Fe(II), EDTA, ascorbic acid and dioxygen at neutral pH to hydroxylate[21] arenes under mild condition. The yield and selectivity is poor. Bracman and Havinga used[22] a mixture of Cu(II), amine and H_2O_2 for hydroxylation of arenes. Hamilton system[23] consists of catechol, Fe(III) and H_2O_2. Most extensively studied system is Fenton's reagent[24] consisting of Fe(II) and H_2O_2. Recently Cu(I)[25], Ni(II)[26] and Pd(II)[27] promoted aromatic hydroxylations have been reported. The hydroxylation of alkanes and arenes by a μ-oxo binuclear iron complex in presence of hexafluroacetylacetone and zinc powder is also reported[28]. Recently palladium(II)-mediated hydroxylation of alkanes and arenes has also been achieved[29,30].

Followings are the main problems in the area of metal mediated aromatic hydroxylation which are to be tackled.

(i) non-availability of smooth reaction conditions

(ii) poor yield

(iii) large number of products i.e. absence of regioselectivity

(iv) isolation of different isomers.

1.2. PURPOSE OF THE PRESENT WORK

The careful consideration of the above problems regarding transition metal-ion mediated aromatic hydroxylation we wish to adopt the following strategy .

1. Metal-ion mediated activation of C-H bond so that the activated bond may act as a potent site for hydroxylation reaction that is otherwise difficult or impossible to achieve.

2. The design of the substrate framework would be made in such a fashion that it would be capable of binding the metal-ions both in its deoxygenated and oxygenated forms.

3. The choice of metal-ion would be kept restricted to those of d^8 electronic configuration.

4. The hydroxylation reaction would be carried out at room temperature (i.e. atmild condition) by careful manipulation of other conditions.

Selective functionalization of hydrocarbons via C-H bond activation[31] especially activation of aromatic C-H bonds by transition metals are of great importance. There is now abundant evidences that the hydroxylation process is stepwise and that C-H bond scission is an event stereochemically discrete from the subsequent formation of the new C-O bond of the product[32]. Our work is based on transition metal mediated oxidation of arenes through a non-radical, electrophilic C-H activation pathway[29,30] i.e. $M^n + R\text{-}H \rightarrow M^n\text{-}R^- + H^+$. The above electrophilic displacement pathway is generally more favourable than the corresponding oxidative reaction $M^n + R\text{-}H \rightarrow M^{n+2}\swarrow^{R}_{H}$.

We have used *ortho*-metallation reaction for the activation of aromatic nuclei. The *ortho*-metallation reactionis an intramolucular organometallic raection of a transition metal ion with a suitable ligand in which a chelate ring is generated *via* a metal-carbon (aryl) σ-bond and a coordinative bond between metal ion and a donor atom of the ligand[33]. Our choice of metal ions has been restricted to palladium (II) (d^8 electronic configuration) for two reasons

(i) palladium(II) is a strong electrophile and a good two-electron oxidant,

(ii) palladium metal is readily oxidised back to

palladium(II) with several cooxidants and it's ability to participate in oxidative reactions (e.g.,the Wacker process[34]) is widely known.

In this thesis we explore aspects of the chemistry of palladium(II) mediated aromatic hydroxylation/ *metaloxylation*[27] (M-C -> M-O-C) reactions. A beginning in this direction has been made[27,35-39] during the last decade. Work done thus far is mainly limited to hydroxylaion of phenyl groups with aromatic peroxy acids. The present work primarily deals with

1. regioselective hydroxylation/ metaloxylation of naphthyl group with iodosylbenzene.

2. regioselective hydroxylation/ metaloxylation of phenyl group with iodosylbenzene.

3. regioselective hydroxylation/ metaloxylation of naphthyl group with aromatic peroxyacids.

4. synthesis and characterisation of hitherto unknoown orthopalladates.

5. studies on the metaloxylation reaction of organometallates containing both σ- and π- type metal-carbon bonds.

6. regiospecific hydroxylation/ metaloxylation of aryl thioethers.

REFERENCES

1. O.Hayashi,Ed., '*Molecular Mechanism of Oxygen Activation* ', Academic Press, New York,1974.
2. R.A.Sheldon and J.K.Kochi, "*Metal-Catalyzed Oxidation of Organic Compounds*", Academic Press, New York, 1981.
3. G.A.Hamilton, "*Molecular Mechanism of Oxygen Activation*", O.Hayashi, Ed.; Academic Press, New York, 1974, p. 405.
4. J.T.Groves, "*Metal Ion Activation of Dioxygen*", T.G.Spiro, Ed.; Wiley Interscience, New York, 1980.
5. G.S.Fonken and R.A.Johnson, "*Chemical Oxidation with Microorganism*", Dekkar, New York, 1972.
6. W.S.Trahanovsky (Ed.), "*Oxidation in Organic Chemistry* ", Academic Press, New York, 1978.
7. K.Kieslich, *Synthesis*, 1969, **120**, 147.
8. K.Keislich, "*Microbial Transformations of Non-Steriod Cyclic Compounds*" Thieme, Stuttgart, 1976.
9. W.Charney and H.L.Herzog, "*Microbial Transformation of Steriods*", Academic Press, New York, 1967.
10. P.R.Orrtiz de Montellano, Ed., "*Cytochrome P-450: Structure, Mechanism, and Biochemistry*", 1986, Plenum, New York.
11. N.R.Orme-Johonson, D.R.Light, R.W.White-Stevens and W.H.Orme-Johonson, *J. Biol. Chem.*, 1979, **254**, 2103.

12. S.Nikajin, M.Shinoda, M.Haniu, J.E.Shievely and P.F.Hall, *J. Biol. Chem.*, 1984, 259, 3971.

13. P.D.Boyer, H.Lardy and K.Myrback, Eds., "*The Enzymes*", Academic Press, 1960.

14. H.S.Mason, W.L.Fowlks, and E.Peterson, *J. Am. Chem. Soc.*, 1955, 77, 2914.

15. S.Yamamoto, Y.Maki, T.Nakazawa, Y.Kajita, H.Takeda, M.Nozaki, and O.Hayashi, *Adv. Chem. Series*, 1968, 77, 177.

16. S.Kaufman, *ibid.*, 1968, 77, 172.

17. R.W.Estabrook, J.Baron, J.Peterson, and Y.Ishimura, *in* "*Biological Hydroxylation Mechanism*", Eds. G.S.Boyd and R.M.S.Smellie. ,Academic Press, New York, 1972.

18. O.Hayashi, *Ann. Rev. Biochem.*, 1963, 38, 21.

19. J.March, "*Advanced Organic Chemistry*", Wiley Eastern Ltd., India, 1987, pp. 576.

20. Norman and Taylor, "Electrophilic Substitution in Benzenoid Compounds", American Elsevier, New York, 1965, pp. 110-116.

21. S.Udenfriend, C.T.Clark, J.Axelord and B.B.Bordie, *J.Biol.Chem.* 1954, 206, 731.

22. W.Brackman and E.Havinga ,*Recl.Trav.Chim.Pays-Bas*, 1955, 74, 1107.

23. G.A.Hamilton and J.P.Friedman, *J. Am. Chem. Soc* ,1963, 85, 1008.

24. C.Walling and R.Johnson, *ibid.*,1975, 97,363.

25. K.D.Karlin, R.W.Cruse, Y.Gultneh, J.C.Hayes, and J.Zubieta *ibid.*,1984, 106, 3372.

26. Y.Kushi, R.Machida and E.Kimura, *J.Chem.Soc., Chem. Commun*, 1985, 216.

27. A.K.Mahapatra, D.Bandyopadhyay, P.Bandyopadhyay and A.Chakravorty, *Inorg. Chem.*, 1986, 25, 2214.

28. N.Kitajima, M.Ito, H.Fukui and Y.Moro-oka, *J.Chem.Soc., Chem. Commun*, 1991, 102.

29. E.Gretz, T.F.Oliver, and A.Sen, *J. Am. Chem. Soc.*, 1987, 109, 8190.

30. L.Kao, A.C.Huston and A.Sen, *J. Am. Chem. Soc.*,1991, 113, 700.

31. A.E.Shilov, "Activation of Saturated Hydrocarbons by Transition Metal Complexes",D.Riedel Dordrecht, 1984.

32. J.T.Groves and P.Viski, J. Am. Chem. Soc., 1989, 111, 8537.

33. I.Omae, Angew. Chem., Int. Ed. Engl., 1982, 230, 1.

34. J.Tsuji, Synthesis, 1984, 369.

35. B.A.Grigor and A.J.Nielson, *J. Organomet. Chem.*, 1977, 129, C17.

36. P.Bandyopadhyay, D.Bandyopadhyay, A.Chakravorty, F.A.Cotton, L.R.Falvello and S.Han, *J. Am. Chem. Soc.*, 1983, **105**, 6321.

37. A.K.Mahapatra, D.Bandyopadhyay, P.Bandyopadhyay and A.Chakravorty, *J. Chem. Soc. Chem. Comm.*, 1984, 999.

38. C.R.Sinha, D.Bandyopadhyay and A.Chakravorty, *J. Chem. Soc. Chem. Comm.*, 1988, 468.

39. C.R.Sinha, D.Bandyopadhyay and A.Chakravorty, *Inorg. Chem.*, 1988, 27, 1173.