UNSYMMETRIC COMPARTMENTAL LIGANDS FOR METALLOBIOSITE MODELLING: A MINI REVIEW

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ABSTRACT

Studies on bimetallic complexes have received increasing attention recently because of their interesting physico-chemical properties arising from the presence of two dissimilar metal ions in close proximity. Adjacent metal centers with hard-soft combination result co-operative effects that show unique reactivity patterns towards substrate molecules. New dinucleating ligands may be synthesized that feature two distinct binding pockets. These systems proved suitable for the preparation of unsymmetric bimetallic complexes in a controlled and predetermined fashion. This review describes the targeted synthesis, reactivity and structural properties of homo- and heterobinuclear complexes.

Keywords: Bridging ligands, Bimetallic Complexes, Metallobiosites, Metalloenzymes, Dinucleating Ligands, Transition Metals.

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INTRODUCTION

Asymmetry plays an important role in biology because many active centers of metalloenzymes show unique properties due to co-operating unlike metal ions in close proximity. Binuclear sites of dissimilar metal ion combinations appear to control the functioning of enzymes under constraints of protein microenvironment due to their distinct chemical nature. This article describes the design and synthesis of new unsymmetric dinuclear systems that can have, in principle, asymmetric environments of three general types *i.e.* donor atom, coordination number or geometric asymmetry of either homo- or hetero-dinuclear character (Fig.-1).¹

Fig.-1: Metal Coordination Environments present in Metallobiomolecules

Understanding From Biology

Biological problems related to reversible uptake and release of dioxygen in *hemocyanine* or the role of two nickel ions in *urease* catalyzing the hydrolysis of urea to ammonia and carbon dioxide as well as the

Rasayan J. Chem., 13(1), 160-167(2020)

<http://dx.doi.org/10.31788/RJC.2020.1315586>

growing literature on the occurrence of dinuclear metallobiosites² stimulated the interest of bioinorganic modelers to design functional model that simulate the natural site in terms of both structure and function. Synthetic models have been classified as *speculative* or *corroborative*.³ A speculative model is used to reproduce some spectroscopic property of the metallobiomolecule of unknown structure. A corroborative model is designed to replicate the coordination properties of a known structural site. Thus the relationship between coordination chemistry and bioinorganic chemistry may be thought of as synergistic (Fig.-2).⁴ This is an excellent example where biologists learning from chemistry and chemists applying knowledge concerning the structure of metalloprotein to develop new chemistry. To elucidate the latter part, the development of unsymmetric dinucleating ligands is important.

Fig.-2: The Synergism Between Coordination Chemistry and the Chemistry of Metallobiosites (Based on Ref. 4)

Objective

It is becoming increasingly more apparent that asymmetry in coordination environment may have significant role in imparting unique reactivity of metalloenzyme active sites⁵ as the binding and subsequent activation of the substrate by the enzyme necessitates its preferential attachment to one of the available metal centers, a prerequisite normally precluded in binuclear metalloorganic systems with symmetric, identical donor environments. Consequently, binuclear system with unsymmetrically disposed metal ion centers should be viewed as desirable synthetic targets to describe many metalloprotein binuclear active sites⁶. Although many of these model complexes derived unexpectedly from symmetric dinucleating ligands⁷⁻¹¹, polydentate ligands that would generate necessarily unsymmetrical, binuclear complexes remain rare. In fact, only a few systematic approaches with the rational design of ligand frameworks that could induce coordination asymmetry in binuclear complexes have been reported in recent time¹²⁻¹⁸. Homo- and heterobinuclear metal complexes of biological relevance with different transition metal ions such as nickel(II), copper(II) zinc(II) etc. and some other 4d-transition metal ions with unsymmetric dinucleating "end off"¹⁹ compartmental proligands may be synthesized as biomimetic models to understand the biological function of the bimetallic cores in metalloproteins. Furthermore, the perception that the binuclear active sites of many metalloenzyme situate their metal centers in chemically distinct environments has inspired coordination chemists to generate new coordination chemistry with binuclear compounds in unsymmetrical ligand environment. In addition, X-ray crystallography, EPR and electronic spectroscopy magnetic measurement etc. of the synthetic analogs serve to act as a guide to elucidate fundamental aspects pertaining to the metal-containing site.

Research and Development in the Subject

Since 1990 much progress has been made in the synthesis of dinucleating ligands with built-in asymmetric features. A common motif in the design of dinucleating ligands involves an alkoxide/phenoxide or pyrazolate group with pendant polyamino side arms that bridges the two metal

centers, and the remainder of the ligand construct usually requires further coordinating groups to retain the metal atoms and prevent the formation of multinuclear arrays. In the international arena, a few groups of eminent scientists are pursuing this emerging field with much zeal and success. Ōkawa *et al.*²⁰⁻²⁸ focused mainly on phenol based “end-off” compartmental ligands possessing chelating arms attached to the 2 and 6 positions of the phenolic ring (Fig.-3) have often been used for model studies of bimetallic biosites. Recently²⁹, type B ligand is used to obtain heterodinuclear complexes $[M_a M_b (L)(AcO)_2]^+$ (where HL = 2-{N-[2-(dimethylamino)ethyl]iminomethyl}-6-[N,N-di(2-pyridylmethyl)aminomethyl]-4-methylphenol, $M_a = Cu^{II}$ and $M_b = Mn^{II}, Fe^{II}, Co^{II}, Ni^{II}, Zn^{II}$; $M_a = Zn^{II}$ and $M_b = Co^{II}, Ni^{II}$) in one-pot reaction. The site-specificity of metal ions is associated with the ligand L^- providing a five-coordinate geometry for the M_a bound to the bidentate arm and six-coordinate geometry for M_b bound to the tridentate arm.

Fig.-3: Various Unsymmetric “End-Off” Proligands

Krebs and his co-workers^{17,30} employed endogenous alkoxo-bridged ligands to synthesize dinuclear nickel(II) complexes as models for the active site of *urease*. The asymmetric complex¹⁷ in Fig.-4 was prepared in order to mimic the substrate uptake in the dinuclear active site of *ureases*.

Fig.-4: Biomimetic Model for Urease (Reprinted with Permission from Ref. 6f, Copyright ACS)

Latour *et al.* reported mix-valence $Fe^{II}Fe^{III}$ complexes of an asymmetrical phenolate ligand^{12,31,32} that mediates intramolecular hydroxylation of a dangling benzyl residue of the ligand almost quantitatively in the presence of an oxygen donor to give *ortho*-hydroxybenzyl group (Fig.-5). Experimental evidence suggests a oxodiiron(IV) species is presumably the key intermediate. There is no published report of oxo- $Fe^{IV}Fe^{IV}$ compound. This reactivity bears a strong resemblance to the *toluene-2-monooxygenase*³³, which is structurally similar to *methane monooxygenase*.

In contrast to the many dinuclear complexes based on compartmental phenolate or alkoxide ligand matrices, however, examples of unsymmetrical systems of pyrazolate ligands providing additional chelating substituents particularly in the 3- and 5- positions of the heterocycle (Fig.-6) remained relatively rare,³⁴⁻⁴⁸ despite their being attractive targets for controlled synthesis of heterobimetallic complexes. A major reason for this is the lack of readily available functional pyrazole derivatives that might provide a straightforward and high-yielding route for the attachment of various donor side arms. Meyer and his

group have published⁴⁴ a synthetic route opening up access to various unsymmetric pyrazolate-based ligand systems with variable chelating side arms (Scheme-1).

Fig.-5: Intramolecular Aromatic Hydroxylation

Fig.-6: Dinucleating Pyrazolate Ligands with Dissimilar Chelating Side Arms

Recently we prepared heterodinuclear complexes of Cu(II)/Co(II) combinations (Fig.-7) using the dinucleating asymmetric ligands containing N/S donor by a convenient single-pot synthetic procedure (unpublished results).

Fig.-7: μ -Alkoxo- μ -pyrazolato Cu(II)-Co(II) Heterodinuclear Complex

It is an upcoming area in contemporary co-ordination chemistry research and contribution from India is limited.⁴⁹⁻⁵¹

Pyrazolate-Bridge Ligands

The present review focuses on the synthesis of binuclear transition metal complexes of both homo- and heterometal combinations. The phenolate and alkoxide bridges are generally the least challenging as they have been extensively studied. So we have chosen binucleating pyrazolate bridging ligands with different chelating side arms in the 3 and 5 positions of the heterocycle. The negatively charged pyrazolate bridge can form five- or six-membered bimetallic ring systems without significant strain (Fig.-8). Usually, the metal-metal separation in these systems ranges from about 3.5 to 4.0 Å. Binucleating pyrazolate ligands can form either bis- or monopyrazolate systems (Fig.-9). In the latter case, the di-metal ring is completed by the introduction of an exogenous bridging ligand, X. Although the pyrazolate bridge has several attractive features, including its stability, strainless formation of bimetallic complexes, and resemblance

to imidazoles, the synthesis of pyrazole ligands is not an arduous exercise because of the inherent difficulties in the preparation of such ligands. Unsymmetrically substituted pyrazole derivative (**II**) can be prepared by the cycloaddition procedure⁵² (Scheme-1).

Scheme-1 (Adapted from Ref. 44)

The alcohol and ester groups will be manipulated separately to generate unsymmetrical binucleating ligands. Metal ions, viz. Cu(II), Ni(II), Zn(II), V(IV/V), Fe(II/III) and Mn(II/III/IV) can be chosen in various combinations for the synthesis of bimetallic structures with interesting spectroscopic, redox and magnetic properties. Some of the target molecules are expected to have the following combinations of metal centers:

- Synthesis of magnetically coupled binuclear compounds involving Cu(II)-M(II) (M = V(IV), Mn(II), Co(II), Cu(II) etc.) combinations
- Controlled synthesis of homobimetallic mixed-spin complexes.
- Synthetic dizinc complexes to develop a new catalytic process that is beyond the scope of natural enzymes
- Phenol oxidation reactions with dicopper complexes, where often only one of the copper ions is redox-active

Fig.-8: The Bridging Structures Formed without Significant Strain

Fig.-9: Bispirazolate and Monopyrazolate Systems

CONCLUSION

Biological relevance and applications of transition metal complexes are well documented.⁵³⁻⁵⁵ Binuclear complexes have attracted particular interests focused on the modeling of metallobiosites and on the cooperativity of the neighboring metals in promoting reactions.⁵⁶ Cooperative interactions between the two adjacent metal centers are important in bioinorganic model studies, organic synthesis and catalysis and give rise to interesting physicochemical properties.^{49-51,56-67} It is evident that the use of small-molecule model compounds can provide useful information in understanding biological functions and the mechanistic pathway of the bimetallic cores. This is a budding area of coordination chemistry with respect to ligand design and synthesis as well as in the application of the formed dinuclear complexes, as speculative, and to an extent corroborative, a model for binuclear metal centers. Comparison of the physicochemical properties of the asymmetric complexes with those of their symmetric parent complexes can give insight into the fine-tuning available from subtle changes in ligation at binuclear centers.

ACKNOWLEDGMENT

Financial assistance received from UGC MRP No. F. PSW-233/15-16(ERO) dated 21.11.2016, is gratefully acknowledged. Thanks to Professor M. Chaudhury, Retired Senior Professor, IACS, Kolkata for useful discussions.

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[RJC-5586/2019]