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# Interaction between transition metals and phenylalanine: A combined experimental and computational study

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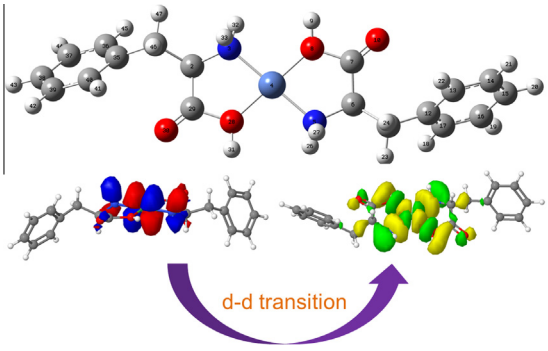
## HIGHLIGHTS

- This study reports a facial synthesis of transition metals complex of phenylalanine.
- DFT confirms square planar geometry of Mn, Co, Ni, Cu and tetrahedral of Zn complex.
- Experimental and computed IR show significant changes in frequencies of $M(Phe)_2$.
- UV–vis and TD-DFT predict characteristic MLCL and d–d transition bands in $M(Phe)_2$.

## GRAPHICAL ABSTRACT

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## ABSTRACT

Some transition metal complexes of phenylalanine of general formula $[M(C_9H_{10}NO_2)_2]$; where M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) are prepared in aqueous medium and characterized by spectroscopic, thermo-gravimetric (TG) and magnetic susceptibility analysis. Density functional theory (DFT) has been employed calculating the equilibrium geometries and vibrational frequencies of those complexes at B3LYP level of theory using 6-31G(d) and SDD basis sets. In addition, frontier molecular orbital and time-dependent density functional theory (TD-DFT) calculations are performed with CAM-B3LYP/6-31+G(d,p) and B3LYP/SDD level of theories. Thermo-gravimetric analysis confirms the composition of the complexes by comparing the experimental and calculated data for C, H, N and metals. Experimental and computed IR results predict a significant change in vibrational frequencies of metal-phenylalanine complexes compared to free ligand. DFT calculation confirms that Mn, Co, Ni and Cu complexes form square planar structure whereas Zn adopts distorted tetrahedral geometry. The metal–oxygen bonds in the optimized geometry of all complexes are shorter compared to the metal–nitrogen bonds which is consistent with a previous study. Cation-binding energy, enthalpy and Gibbs free energy indicates that these complexes are thermodynamically stable. UV–vis and TD-DFT studies reveal that these complexes demonstrate representative metal-to-ligand charge transfer (MLCT) and d–d transitions bands. TG analysis and IR spectra of the metal complexes strongly support the absence of water in crystallization. Magnetic susceptibility data of the complexes exhibits that all except Zn(II) complex are high spin paramagnetic.



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## Introduction

Metals perform pivotal roles including electron transfer, catalysis, structural support, protein folding/unfolding in biological systems by interacting with amino acids [1–6]. Amino acids have diverse functional groups such as amino, carboxyl, phenolic, imidazole, and phenyl which can form chelates with different metals [7]. Although structure and function of many proteins rely on the metal binding sites, the atomic level understanding of metal-amino acid interaction is not fully explored in details [8]. Atomic level understanding of the bonding and interaction of metals with amino acids can provide a wide perspective for catalyst design and protein engineering.

L-Phenylalanine, containing nonpolar phenyl group, is a common aromatic amino acid in living organisms (Fig. 1). Because of the nonpolar group, this amino acid is buried within the hydrophobic core of a protein [9]. The phenyl group in phenylalanine is also intrinsically fluorescent [10]. L-Phenylalanine levels in blood provide a practical and reliable method for the diagnosis and monitoring of metabolic status in patient with phenylketonuria [11].

The importance and applications of transition metal–ligand complexes are widespread from synthetic chemistry to material science and biochemistry. These metals have been used for drug design and delivery [12–17], catalysis [18–21], solar cell applications [22–24], and biological imaging [25,26]. In biological systems, transition metals are involved with very specific structural and cellular functions. Several manganese proteins such as dimanganese catalase, Mn-based ribonucleotide reductase, and tetra Mn-cluster in the photosystem II execute very important catalytic reactions in biological systems [27]. So far eight Ni based enzymes are isolated and these enzymes are actively involved in biological carbon, nitrogen and oxygen cycles [28–30]. Zinc and copper are also the most vital transition metals present in proteins. The common Cu based proteins are Cu–thionein [31], plastocyanin [32], and azurin [33]. Coordination of Zn with two cysteines and histidines in Zinc finger proteins stabilized the self-assembled finger domain [34].

Several studies have been reported on interaction of alkali and alkaline earth metals such as $Na^+$, $K^+$, $Mg^{2+}$, $Ca^{2+}$ with different amino acids [35–39]. Despite the pivotal importance of transition metals in biological functions, very few studies are focused on interaction of these metals with amino acids employing experimental and computational methods. Recently, Remko et al. conducted computational study to understand the effect of some first row transition metals (Ni, Cu and Zn) on aromatic amino acids with water coordination [9]. Metal coordination sties of this study rely on single amino acid binding with carboxylates, amino nitrogen and benzene ring. Ganesan et al. reported the molecular dynamic simulation of Cu–Phenylalanine complex incorporation micro-solvation medium [6]. Ataie et al. showed the Zn coordination with serine and methionine amino acids in order to understand the structure and catalytic features of Zn in *Vibrio proteolyticus* [40]. Details gas phase *ab intio* study on the Cu–π interaction in Phe, Tyr, and Trp confirmed that $Cu^{2+}$-AAA (aromatic amino acids) complex related to the cation–π interaction was not formed. In addition, tridentate complex with $Cu^{2+}$-His was not obtained [41]. Structural properties of peptide–Zn complex are also explored by Niklas et al. which revealed that Zn can form homochiral coordination polymer [42]. Surface enhanced Raman scattering spectroscopy has been employed to unveil the interaction in Ag—Phe and Ag—Tyr complexes [43]. Comprehensive survey was also conducted to compare the metalloprotein structures present in Protein Data Bank (PDB) with small crystal complexes deposited in Cambridge Structural Database (CSD). The comparative study divulged that metal binding pattern in small complexes and metalloproteins are same and validated similar coordination geometry [8]. Guided ion beam tandem mass spectrometry and density functional theory have been employed to investigate the bond energies of $Cs^+$ and $Rb^+$ with Met and aromatic amino acids indicating that bond energies are decreased as the metal cation increases in size [44].

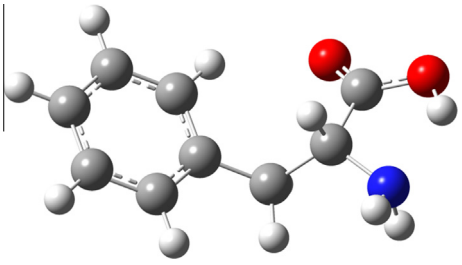

**Fig. 1.** Optimized structure of phenylalanine computed at B3LYP/6-31G(d) level of theory.

Most of the studies limited to structural features related to metal amino acid interaction. Previous investigations only considered the single amino acid binding with metals whereas metals can bind with two amino acids. Photophysical properties of these complexes are not explored in details. In this study, a combined experimental and computational study has been conducted to report the synthesis and characterization of first row transition metals (Mn, Co, Ni, Cu and Zn) complex with two phenylalanine ligands. Structural features, vibrational frequencies, photophysical properties, frontier molecular orbitals, and magnetic properties are also reported as well.

## Experimental

### *Materials and methods*

Analytical grade reagents (BDH and Aldrich) were used in all preparative and analytical works. Micro-analysis for C, H and N were performed on an automatic micro-analyzer in the laboratory of organic structural chemistry (Prof. Shinmyozu lab), Dept. of molecular chemistry, Graduate school of sciences & IMCE, Kyushu University, Japan. Metal content of the complexes were quantitatively determined by complexometric titration. Chloride content of all the complexes were qualitatively tested by $AgNO_3$ solution. The melting point of all the complexes were measured in MELTEMP II Laboratory Devices with a thermometer, USA. Infrared spectra of the complexes were recorded on a calibrated Fourier Transformation Infrared Spectrophotometer (Shimadzu FTIR IR prestige-21 S/N) in the range 500–4500 $cm^{-1}$ as KBr pellets. The electronic spectra of phenylalanine and its complexes were recorded on a Shimadzu UV–visible recording spectrophotometer (UV-160A), in the wavelength 200–1100 nm using Nujol mull technique. The thermo-gravimetric analysis of the complexes was carried out with a computer controlled TA-60WS thermo-gravimetric analyzer and TGA-50H detector (Shimadzu, Japan). The magnetic properties of the complexes were studied at ambient temperature on a Magnetic Susceptibility Balance (Magway MSB Mk1 Sherwood Scientific Ltd, Cambridge, England).

### *Determination of metal-phenylalanine ratio in the complexes in aqueous medium*

The ratio of metal and L-phenylalanine complexes in solution was estimated by continuous variation method using UV–Visible spectrophotometer [45]. A plot of absorbance against % mole of Cu(II) is shown in Fig. 2. It is observed that absorbance increases