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Review

A Review: Synthesis and characterization of metals complexes with paracetamol drug

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Abstract: In this review, previous studies on the synthesis and characterization of the metal Complexes with paracetamol by elemental analysis, thermal analysis, (IR, NMR and UV-Vis (spectroscopy and conductivity. In reviewing these studies, the authors found that paracetamol can be coordinated through the pair of electrons on the hydroxyl O-atom, carbonyl O-atom, and N-atom of the amide group. If the paracetamol was a monodentate ligand, it will be coordinated by one of the following atoms O-hydroxyl, O-carbonyl or N-amide. But if the paracetamol was bidentate, it is coordinated by atoms (O-carbonyl and N-amide), (O-hydroxyl and N-amide) or (O-carbonyl and O-hydroxyl). The authors also found that free paracetamol and its complexes have antimicrobial activity.

Key words: complex, donor atom, paracetamol, analytical and spectral studies

1. Introduction

Paracetamol (N-acetyl-p-aminophenol, acetaminophen, 4-acetamide phenol, or 4-hydroxyacetanilide) (PAPA) is acylated aromatic amide, initially proposed to medicine, which is an analgesic and antipyretic drug adopted to mitigate mild to moderate toxicity pain associated with headache, back pain, arthritis, postoperative pain and fever of bacterial/viral beginning to reduce. PAPA results in serious side effects when over dosed and taken with alcohol or other medications, can cause skin rashes, liver toxicity, kidney damage, liver failure, nephrotoxicity, inflammation of the pancreas and ultimately death[1-5]. In the United States of America, PAPA overdose accounts for approximately (56,000) emergency room visits, (26,000) hospitalizations, and nearly (500) deaths each year.[6]

Fig. 1 Structure PAPA, one of the very common and extensively utilized drugs in the world, has a phenolic structure with a substituent in the PAPA position relative to the hydroxyl group, allowing it to

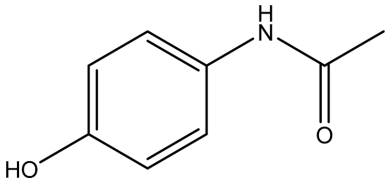

Fig. 1. Structure PAPA.

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react with reactive species.[5-7]

Previous studies showed that some metal(II) complexes of PAPA were active against certain types of microorganisms such as [*Bacillus-cereus*, *Pseudomonas -aeruginosa*, *Klebsiella-oxytoca* and *Escherichia-coli*].[8,9] These complexes also have a different effect against bacteria.[10]

For antioxidants, increasing the intake of PAPA can perform to oxidative stress and kidney damage and cause liver damage.[11,12] But ACPH possesses remarkable antioxidant properties when used in therapeutic doses, with cell-free test systems showing that PAPA at a concentration of (210) μM is able to scavenge reactive oxygen directly.[13] Although not well understood, PAPA cardioprotective effects appear to be related to its antioxidant properties.[14-21]

2. Previous studies on the synthesis and characterization of metal ions complexes with paracetamol

El-Shahawy *et al.* have been synthesized Fe^{2+}, Cu^{2+} and Zn^{2+} complexes of Paracetamol, and characterized by elemental analysis (Atomic absorption NMR and FT-IR) spectra. From the above spectral measurements, it was found that the complexes formed through oxygen-(C=O) atom and nitrogen-N atom see in *Fig.* 2.[22]

Lawal and Obaleye synthesized and characterized Fe^{3+} Co^{2+} and Ni^{2+} complexes with PAPA using infrared, electronic, and 1H-NMR spectra, conductivity measurements, and melting point. Considering all the

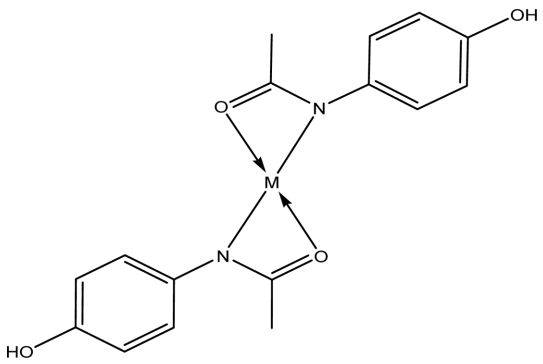


Fig. 2. The structure of $(PAPA)_2$–M(II).

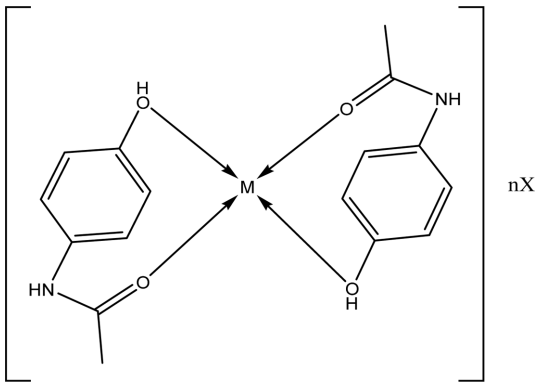


Fig. 3. Proposed structure for $M(PAPA)_2Xn$.
M = Co^{2+}, Ni^{2+}, n = 2, X = Cl
M = Fe^{3+}, n = 3, X = Cl

above analytical and spectroscopic data, PAPA was observed to act as a bidentate-ligand agent coordinated with metal ions via the O-hydroxyl and the O-carbonyl.[23] The tentatively proposed structures for the chelating agents are shown in *Fig.* 3.

Ledeti *et al.* have synthesized and characterized a coordination compound of Zn(II) with PAPA. The chelate was characterized by elemental analysis, TGDTG-HF technique and FTIR-UATR spectroscopy. The data obtained proved that PAPA acts as a bidentate-ligand via the OH-group and the C=O group.

According to the spectroscopic data and the results of the elemental analysis, and to confirm the thermal behavior of the complex, a proposed structure for the metal chelate is shown in *Fig.* 4.[24]

Chandrathilaka, et al. The study binary chelates of Cu^{2+}, Pb^{2+}, Cd^{2+} and Al^{3+} were performed with ascorbic

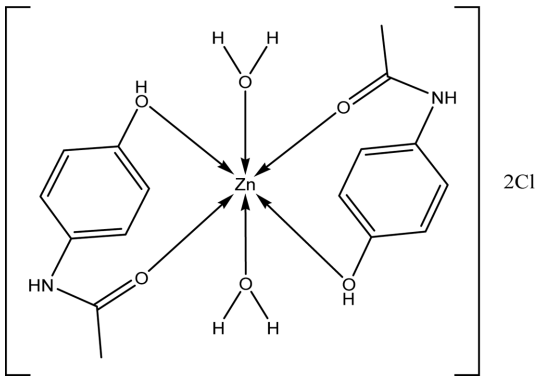


Fig. 4. The proposed structure of $[Zn(ACPH)_2(H_2O)_2]$ 2Cl complex.

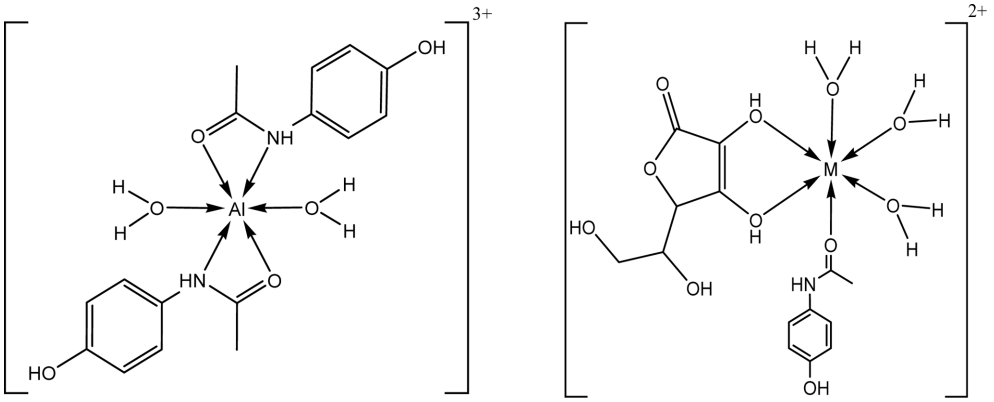


Fig. 5. Structure of $Al(PAPA)_2$ and [M(PAPA)(Asc)] (M = Pb^{2+}, Cd^{2+}, Cu^{2+}).

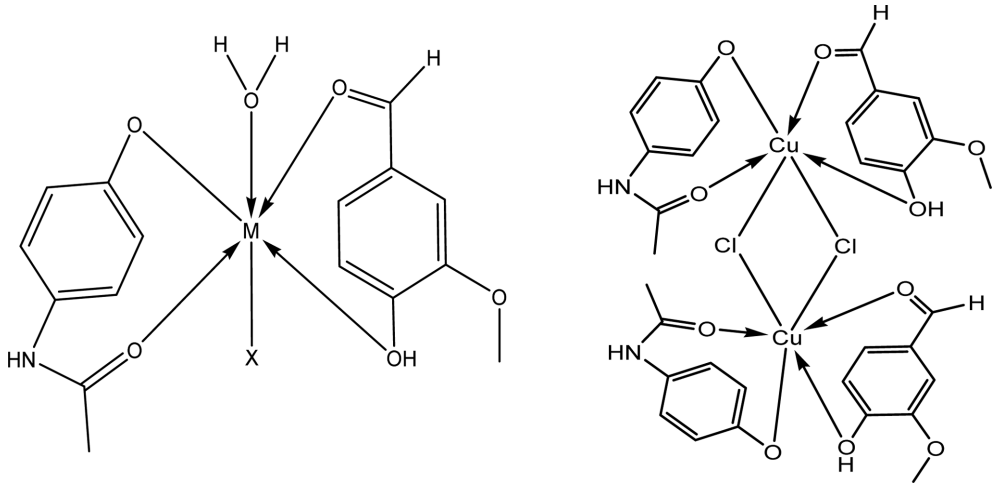


Fig. 6. The structures for Metal(II) complexes.
M : Mn^{2+}, Co^{2+}, Ni^{2+}, and Zn^{2+}
X: Cl, NO_3, CH_3CO_2

acid-(Asc) and PAPA. The stable mixed ligands have been found to chelate; [Cd(PAPA)(Asc)], [Cu(PAPA)(Asc)], and [Pb(PAPA)(Asc)] but Al(III) did not form a chelate that same previous form, it form chelate only with PAPA due to its high stability.[25,26] The following structures can be proposed for the obtained chelating agents *Fig.* 5.[27]

Osowole *et al.* have synthesized chelates of Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} with PAPA and vanillin, and analyzed them by percent metal analysis, magnetic moments, infrared and electronic spectroscopy, melting points, conductivity measurements. From IR spectral data, it was found that the coordination was through the carbonyl oxygen atom of PAPA with metal ions and the structure of all complexes was octahedral geometry *Fig.* 6.[8]

Agbaje *et al.* studied synthesise chelates of Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} with sulfamethoxazole-(Sul) and PAPA and were characterized by melting points, magnetic moments, conductivity measurements, metal percent, electronic and infrared spectroscopy. Infrared spectral data confirmed that coordination occurred via OH and C=O oxygen atoms of PAPA. The complex formula $[Cu(Sul)(PAPA)(NO_3)]_2.H_2O$ has a moment of 0.85 BM, suggesting that antiferromagnetism acts through a copper–copper bond in a dimeric structure[28,29] (*Fig.* 7).

El-Megharbel *et al.* have synthesized Cd^{2+}, Hg^{2+},

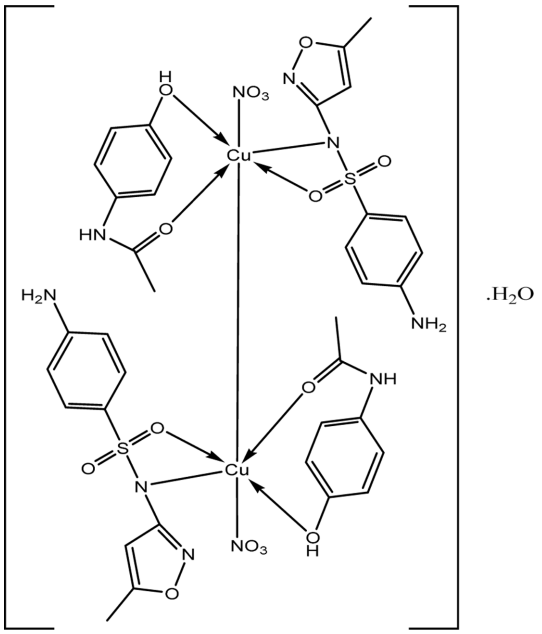


Fig. 7. Structure chelate of Cu(II) with PAPA and sulfamethoxazole.

and Pb^{2+} complexes of the anti-inflammatory drug PAPA. were synthesis and characterized by C.H.N, conductivity, FTIR, 1H-NMR, and UV studies. The oxygen-OH atom is involved in the complexation. These results agree with the results of spectra studies see *Fig.* 8.[30]

Osowole *et al.* studied M(II) = Mn, Fe, Ni, Cu and Zn mixed ligand chelates of PAPA and benzoic acid were synthesized and characterized by melting

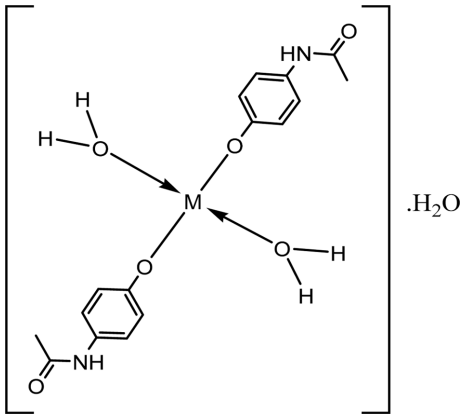


Fig. 8. The structure of chelate $[M(H_2O)_2(PAPA)_2].nH_2O$. M(II) = Cd, Hg and Pb

points, magnetic moments, infrared, and electronic spectroscopy. Molar conductivity measurements in DMSO indicated that metal(II) chelates were covalent. Infrared spectral data confirmed that coordination occurred via carbonyl-O and hydroxyl-O atoms of PAPA.[31] The complexes of the Mn(II) and Cu(II) formula are dimeric (*Fig.* 9), with the Cl atoms bridging the metal centers and each metal center enhancing the overall magnetic susceptibility of the chelate.[32]

Adadey, et al. have made Cu-PAPA chelate. By comparing the IR absorption peaks of the metal coordination complexes with PAPA, it turns out that copper coordinated with PAPA via O-acetyl and N-amide (*Fig.* 10).[33] Copper could chelate with the PAPA on the CH_3 group. This could change the absorption

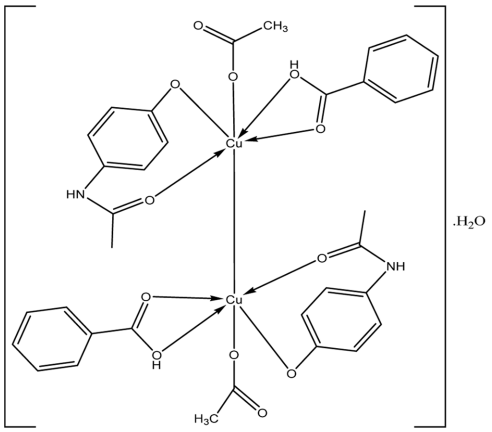
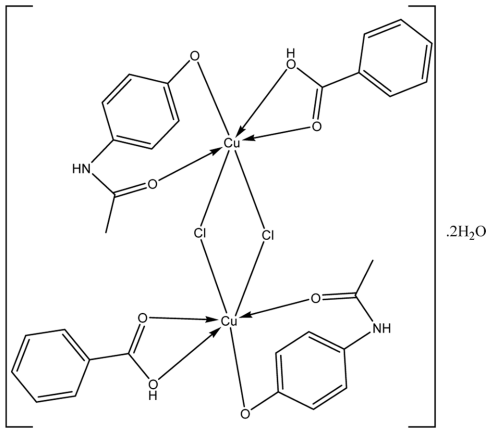


Fig. 9. Propose structures for the Mn^{2+} and Cu^{2+} chelaties.



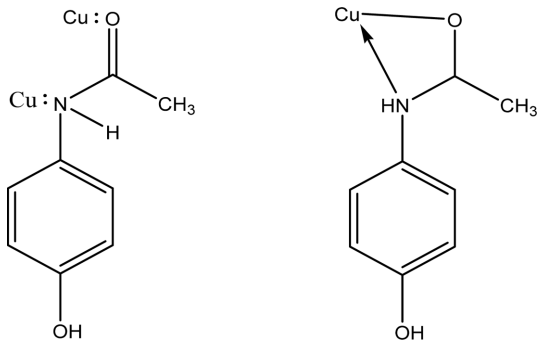


Fig. 10. The possible constituents of (Cu-PAPA).

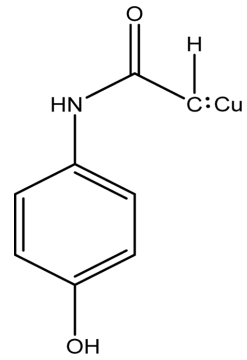


Fig. 11. The (Cu) was able to coordinate with (PAPA) via CH_3-group.

of the CH_3 group in the complex (*Fig.* 11). This implies that the copper forms a chelate with all functional groups and even the benzene ring.[23]

Babamale *et al.* studied mixed metal chelate of PAPA and ascorbic acid-Asc synthesized using $ZnSO_4$, $CuCl_2.2H_2O$, $CoCl_2.6H_2O$, $NiCl_2.6H_2O$ and $FeCl_2.4H_2O$ salts. The chelates were characterized using some physical techniques such as conductivity measurement, melting point, solubility, atomic absorption, UV-Vis and IR spectroscopy. The physical and spectroscopic results show that M is coordinated via the phenol-O and carbonyl-O in PAPA.[34] Through all the spectroscopic and analytical data, the structures for the chelating agents are shown in *Figs.* 12 and 13.

Ayipo *et al*. were obtained from Zn(II), Cu(II), Ni(II), Co(II) and Fe(II) of mixed piperaquine(PQ)-acetylsalicylic acid(AS) and piperaquine(PQ)-PAPA chelates. The chelates were characterized by conductivity measurement, melting point determination, atomic absorption spectroscopy, UV-Vis spectrophotometry, IR spectroscopy, and magnetic susceptibility. It has been suggested that the chelating agents have a 1:1:1 stoichiometric ratio between each metal salt and the PQ-AS or PQ-PAPA of tetrahedral and octahedral geometry. It was found in this study that the complexes of metal ions form with PAPA via (N- and O-phenol) or (N- and O-carbonyl). both octahedral and tetrahedral chelates. See *Figs.* 14 and 15.[35]

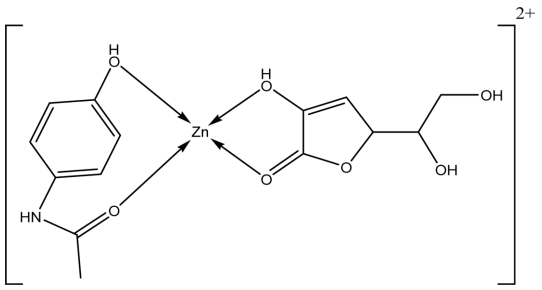


Fig. 12. The structure of PAPA-Asc chelates.
M = Zn(II), Cu(II), Co(II), Ni(II) and Fe(II)

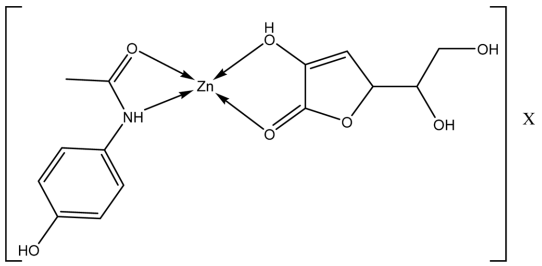


Fig. 13. The structure of PAPA-Asc complex.
M = Cu…… X = Cl_2, M = Zn ……X = SO_4

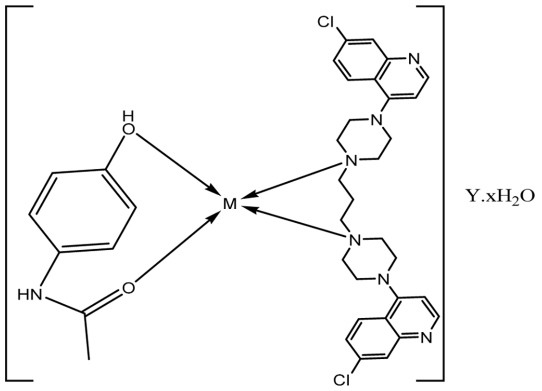


Fig. 14. M-(PQ)(PAPA): Where M(II) = Zn, Cu, Ni, Co and Fe.
Y = Cl_2, $(CH_3COO)_2$, or SO_4

Refat *et al.* The investigated chelating agents of

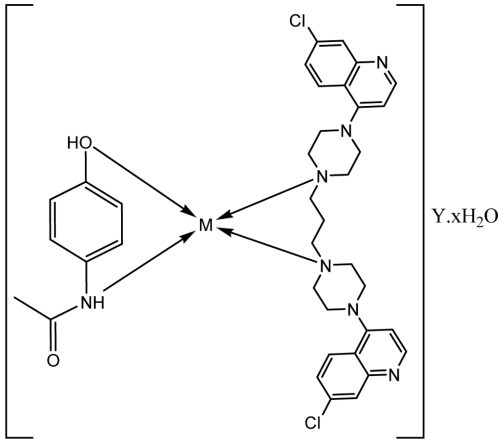


Fig. 15. M-(PQ)(PAPA): Where M(II) = Zn, Cu, Ni, Co, and Fe.
Y = Cl_2, SO_4 or $(CH_3COO)_2$

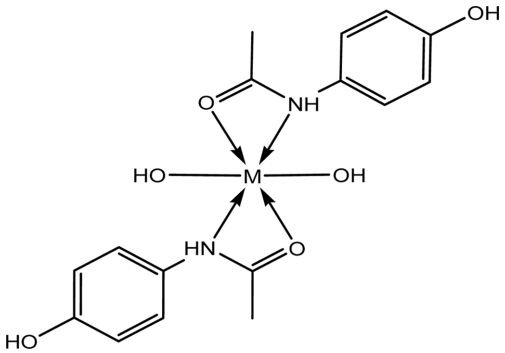


Fig. 16. Structure of (PAPA)-complex.
M = Sr(II), Ba(II), Ca(II), and Mg(II)

the divalent metal ions [Sr, Ba, Ca and Mg] with PAPA were synthesized and characterized by IR and 1H-NMR spectroscopy, conductivity, UV-Vis, elemental analysis and thermal analysis. It was revealed by the IR spectral data that the PAPA behaves as a neutral bidentate ligand coordinated to the metal ions through N and O-(C=O) atoms.[36] As a general conclusion, the examined chelate structures can be given as shown in *Fig.* 16.[37]

Majthoub *et al*. have synthesized a zirconium(IV) complex of PAPA in the form of $[Zr(PAPA)_4(H_2O)_2]$ by elemental analysis, UV-Vis, 1H-NMR, and FT-IR spectra. The FT-IR and 1H-NMR spectra explain that PAPA behaves as a monodentate ligand coordinated to the zirconium(IV) ion via the O-phenol atom of the

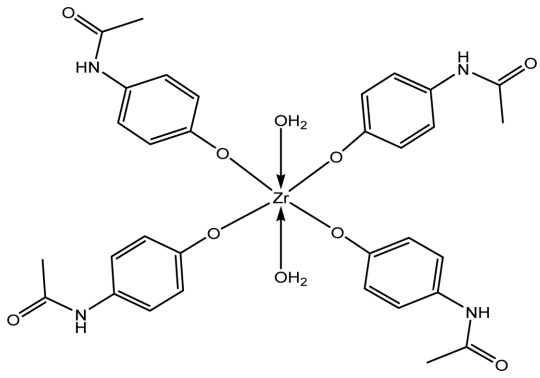


Fig. 17. Structure of $[Zr\ (PAPA)_4(H_2O)_2]$.

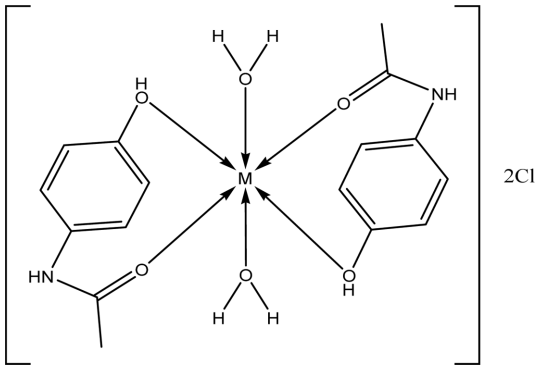


Fig. 18. The structure of M^{2+} complexes.
M= Cu(II) and Zn(II)

phenol group *Fig*. 17.[38]

Faruna *et al.* have synthesized and characterized Zn(II) and Cu(II) using PAPA X-ray diffraction analysis, (UV-Vis, FTIR) spectroscopy, conductivity and melting point measurements. Based on this study, it is established that PAPA acts as a bidentate ligand coordinated to M^{2+} through O-(O-H) and O-(C=O) atoms (*Fig.* 18).[9]

Olagboye *et al.* studied Co^{2+} and Cu^{2+} mixed ligand chelates of prednisolone and PAPA were synthesized and characterized based on their physical properties melting points and spectroscopic studies. FTIR results in this study showed that the metals possibly coordinated with PAPA via the O-hydroxy group.[10]

Subhi *et al.* studied synthesized complexes from PAPA-saccharin (Sac) containing chelating agents with Zn, Cu, Ni, Co, and Mn. These chelating agents are characterized by C.H.N, UV-Vis, molar condu-

ctivity, magnetic susceptibility, IR and 1H-NMR. through these measurements, chelating agents are found to be of the type $[M(Sac)_2(PAPA)_2(H_2O)_2]$; where M is any of the above mentioned elements. In addition, the results of spectroscopic measurements show that the PAPA acts as a monodentate ligand of O-carbonyl *Fig.* 19.[39]

Bhagat has synthesized mixed ligand Cu^{2+} chelates of the type $[Cu(PAPA)(L)].2H_2O$ performed using PAPA and amino acids-(HL) such as L-Valine(Val), L-Threonine(Thr), and L-Serine(Ser). The metal chelates thus synthesized were characterized by elemental analysis, electrical conductivity and spectral analysis UV-Vis and IR. The results of the IR spectroscopic measurements showed that the PAPA acts as a bidentate ligand through O-carbonyl and O-hydroxyl *Fig*. 20.[40]

Ikpeazu *et al.* studied the Zn^{2+} complex with PAPA. The data confirmed that Zn^{2+} and PAPA combine in a 1:1 molar ratio and the free energy and stability constant results indicated that PAPA is good ligand coordination through the O-hydroxyl and O-carbonyl and an active antidote in the treatment of zinc(II) overload or intoxication.[41]

Sultan et al. studied the chelate of Al(III) with PAPA, was synthesized and characterized by IR spectroscopy, UV-Vis and melting point. In this study, the PAPA was found to behave as a tridentate chelating agent by being coordinated through the carboxylate O-atom, the phenol O-atom, and the N-atom. *Fig.* 21.[42]

Obaleye et al. studied chelation through synthesis of complexes of metal ions Co^{2+}, Cu^{2+}, Ni^{2+} and Zn^{2+} with PAPA and diclofenac potassium salt-(Kdc). The

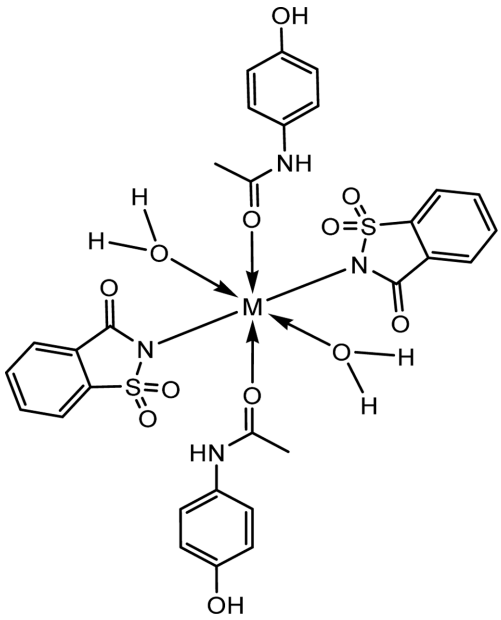


Fig. 19. The structure $[M(Sac)_2(PAPA)_2(H_2O)_2]$ complexes. M=Ni, Co, Mn, Cu, and Zn

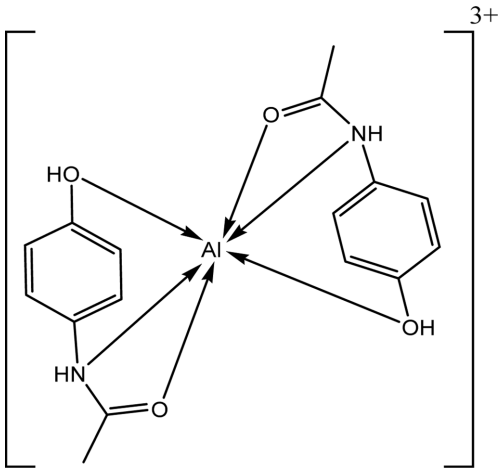
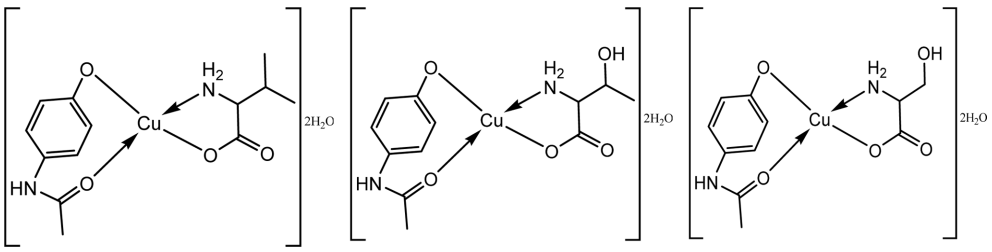


Fig. 21. The structure of Al(III) with PAPA complex.



$[Cu(PAPA)(Val)].2H_2O$ $[Cu(PAPA)(Thr)].2H_2O$ $[Cu(PAPA)(Ser)].2H_2O$

Fig. 20. The structures for the $[Cu(PAPA)(L)].2H_2O$ complexes.

chelates were characterized by conductivity, solubility, elemental analysis, UV-Vis, melting point, FT-IR spectroscopy, X-ray and magnetic susceptibility measurements. The IR spectra showed a bidentate coordination mode. In the case of PAPA, the N- and O-carbonyl atoms were involved.[43]

Aziz *et al.* studied complexes of methyldopa-(Meth) with PAPA synthesized using a basic medium to deprotonate the ligands. These complexe of Mn(II), Fe(II), Co(II), Ni(II) and Cu(II) were characterized using (FTIR, UV-visible) spectra, atomic absorption, magnetic susceptibility, (carbon, hydrogen, nitrogen and sulfur)-(CHNS) analysis and melting point measurements. The PAPA was coordinated via the O-atom of the carboxyl group and the N-atom of the amide group.[44]

Since the PAPA is a bidentate ligand, it forms two bonds with a central atom, so water forms a complexes with these M^{2+} ions, and due to its monodentate nature *Fig.* 22.[45]

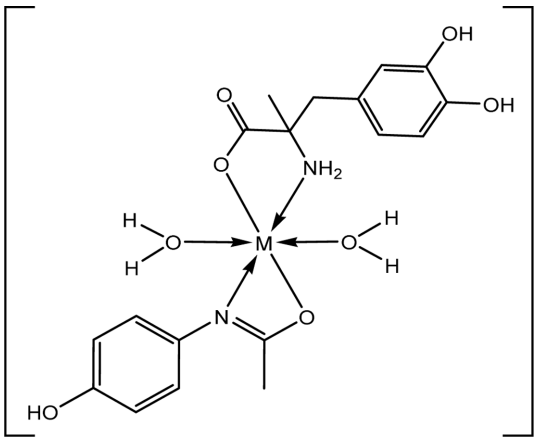


Fig. 22. The structure of $[M(PAPA)(Meth)(H_2O)_2]$ complexes. M=Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+}

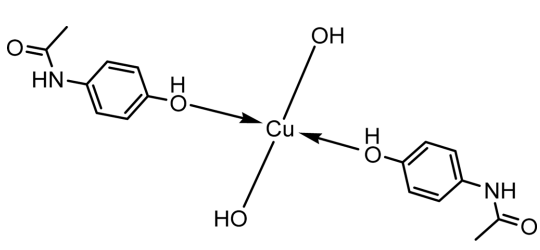


Fig. 23. The structure of Cu-PAPA complex.

Hank *et al.* performed a theoretical study on the synthesis and characterization of copper(II) complexes with PAPA and compared it with the experimental results. The PAPA behaves as a monodentate coordinated ligand for the metal ions through the phenol-O. See *Fig.* 23.[46]

3. Conclusions

Through our review of previous studies on the coordination of paracetamol with some metals. We concluded that paracetamol can be coordinated through the pair of electrons on the hydroxyl O-atom, carbonyl O-atom, or N-atom of the amide group and it can be a monodentate ligand, a bidentate ligand or a tridentate ligand.

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