BOOK OF PROCEEDINGS
(Available at: http://acsnigeria.org/publications/proceedings)

Synthesis and Characterization of Mn (II) Nano Metal Complex of Trimethoprim using Sonicator

Brendan C. Asogwa, Ifeanyi E. Otuokere, Kingsley Nnochirionye
Department of Chemistry, Michael Okpara University of Agriculture Umudike, Abia State.
Corresponding Author's email: chidonwasogwa@gmail.com

ABSTRACT

Trimethoprim, a known antibiotic used in combination with sulfamethoxazole against several strains of bacteria, works by inhibiting the dihydrofolate reductase synthesis in bacteria. This combination therapy of trimethoprim-sulfamethoxazole has achieved outstanding antimicrobial results; however, the clinical misuse of this combination therapy has caused the development of resistant pathogens and unpleasant side effects, springing up the necessity of alternatives for increased mechanisms of antibacterial actions. Metal complexes have been reported to increase the therapeutic efficiency of drugs. Mn (II) nano metal complex of trimethoprim was synthesized by the sonication method. A change in color and reduction in melting point suggested an occurrence of complexation. Spectroscopic analyses indicated the synthesis of a metal complex. The nanosized metal complex was observed to be insoluble in hexane due to an increase in the polarity after complexing with a metal. The crystallite size of 4.04 nm was calculated using Debye-Scherrer's equation. In comparing the FTIR spectra of TMP and the Mn (II) complex, a band shift of the azomethine bond from 1633 cm^{-1} to 1595 cm^{-1} as well as the amine bond from 3317 cm^{-1} in the ligand to 3354 cm^{-1} in the complex was observed. A shift of the methylene protons from 3.533 ppm to a higher field of 1.024 ppm was observed in the proton NMR, and from 32.92 ppm to 18.39 ppm in the carbon-13 spectra indicates a complexation involving the methylene carbon. A diagonal bipyramid structure was proposed for the novel Mn (II) complex. Trimethoprim coordinated as a polydentate ligand to the Mn (II) ion.

KEYWORDS: Trimethoprim, nano metal complexes, Mn (II), sonochemistry.

1. INTRODUCTION

Trimethoprim (TMP) is a therapeutic compound with a strong potential of inhibiting the dihydrofolate reductase in bacteria. This property amplified its use especially in combination therapy with sulfamethoxazole in treatment of several infections (Asogwa *et al.,* 2024; Edozie *et al.,* 2020; Otuokere *et al.,* 2019). TMP as a compound has 1,2,3-trimethoxybenzene and pyrimidine-2,4-diamine in its structure and belonging to diaminopyrimides group of medicines (Ibrahim *et al.,* 2019, Abeer and Moamen, 2024). It has shown to have strong antimicrobial properties against both gram-positive and gram-negative strains of bacteria as well as antifungal effect on different fungi (Masoud *et al.,* 2019) but resistance could be developed by these organisms when trimethoprim is used as a single therapy (Drews, 2000, Otuokere *et al.,* 2024).

The discovery of therapeutic compounds that could inhibit the absoption of the folic acid by the bacteria has greatly increased the success in the treatment of bacterial (Otuokere, *et al.,* 2022, Otuokere *et al.,* 2020). The development of active antimicrobial compounds became one of the most relevant achievements of the twentieth century (Asogwa and Otuokere, 2024). The rampart abuse of these known antimicrobial drugs led to the development of resistant strains of bacteria (Sirajul *et al.,* 2020) making it so necessary for the discovery and administration of more effective therapeutic compounds in the form of novel compounds or structural modified drugs (Otuokere *et al.,* 2017). These modified compounds could be achieved by the coordination of the known therapeutic compounds with metal ions which has been noted in recent researches to have improved the biological effects (Otuokere *et al.,* 2020, Ugochukwu and Otuokere, 2021).

Trimethoprim has shown to be a good ligand leading to formation of several metal complexes with different metals because of the presence of three nitrogen atoms in its structure (Refat *et al.,* 2021) but also known for its poor water solubility (ElShaer *et al.,* 2012). These metal complexes of trimethoprim synthesized have been characterized to give a higher therapeutic activity than the free trimethoprim drug (Ibrahim *et al.,* 2019). This then gave the rationale for the synthesis of different metal complexes

of trimethoprim. To our knowledge, there are no documented instances of sonication methods employed in the production of metal complexes of trimethoprim. Additionally, the Mn (II) nano-sized complex of TMP has not been reported in the literature.

2. MATERIALS AND METHODS

2.1. Compound and solvents used

All the salts used in this synthesis were of analytical grade obtained from Andhra Organics Limited, India.

2.2. Synthesis of the complex

The nanometal complexes were synthesized according to the methodology outlined by Abdel-Rahman *et al.* 2016. Equimolar solutions of the ligand and metal ion were obtained by dissolving 2.9032 g of trimethoprim in 100 ml of ethanol and 1.9791 g of $MnCl.4H_2O$ in 100 ml of water. These equimolar solutions were added together stirred and placed on the probe of an ultrasonic sonicator having a maximum force output of 400 W for a duration of 30 minutes. The obtained mixture obtained was filtered with a Whatman No. 1. filter paper and dried with a desiccator.

2.3. Physical and spectroscopic studies

(a). Melting Point of test compounds

The Melting points of the test compounds were evaluated with Gallenkamp apparatus.

(b). Solubility Test

The solubility profile of test compounds was investigated using solvents of variable polarity namely: hexane, ethanol, water, ethyl acetate, and dimethylsulfoxide by taking 0.1 g of each compound and dissolving in 3 ml of each solvent at 25 °C.

(c). Infrared spectroscopy

FT-IR spectra for the test compounds were obtained with the help of a Perkin Elmer Spectrum BX FT-IR spectrophotometer (4000–600 cm^{-1}).

(d). X-ray Diffraction

The Diffraction pattern for the nanosized complex was obtained with the use of Rigaku D/Max-IIIC X-ray diffractometer. The Debye-Scherrer's equation; $D=K\lambda/(\beta \cos \theta)$ where D is the crystallite size of test compound., K is the Scherrer constant = 0.98, ƛ is wavelength, β is the full width at half maximum (FWHM) was used to determine the crystallite size of the compound.

(e). Nuclear magnetic resonance

The NMR spectra for the nano-sized complex was obtained using a Nanalysis X-685 benchtop NMR which has a frequency of 600 MHz and deuterated DMSO used as solvent.

3. RESULTS AND DISCUSSION

The physical properties are presented in Table 1.

Table 1: Physical parameters

Compounds	Color	Melting Point (°C)	Percentage Yield
Trimethoprim	White	199	-
$[Mn(TMP)(H_2O)_2]$	Green	196	74

TMP and Mn (II) nanometal complex are observed to have a crystalline structure, having non-hygroscopic property and stable in air. A change of color from the white color of the ligand to green pointed to a coordination since transition metal complexes are colored (Trupti *et al.,* 2019).

3.1. Solubility

The solubility profile of the test compounds is presented in Table 2.

Table 2: The solubility profile.

Compounds	Hexane	Ethanol	Distilled water	Ethyl Acetate	DMSO
Trimethoprim	SS	S	IS	S	S
$[Mn(TMP)(H_2O)_2]$	IS	SS	SS	S	S

Key: SS- slightly soluble, IS- insoluble, S-soluble

The synthesized Mn (II) nano metal complex was soluble in ethyl acetate and DMSO and not soluble in hexane. This could be attributed to the fact that DMSO and ethyl acetate are polar aprotic solvents. These are solvents that can dissolve polar as well as non-polar substances and are also very miscible with a wide range of organic solvents and water.
The nano complex was only slightly soluble in ethanol. The solubility profile suggested that the nano metal complexes have considerable higher polarity in comparison with the ligand.

3.2. Infrared Spectroscopy

Some IR peaks of the test compounds are shown in Table 3.

Table 3: Summary of the IR peaks

Compounds	Absorption bands in cm^{-1}					
	NH_2	C-O-C	C=N	M-N	M-C	M-O
TMP	3317	1126	1633	-	-	-
$[Mn(TMP)(H_2O)_2]$	3354	1133	1595	1025	880	-

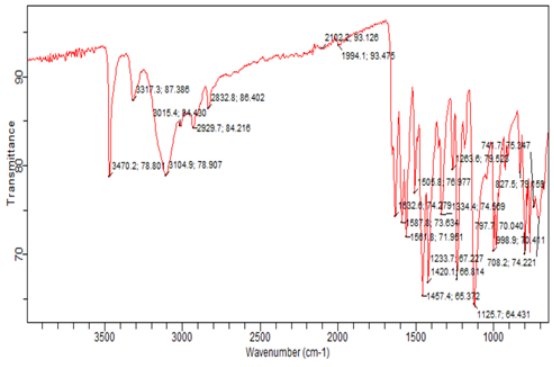

Figure 1a: IR spectrum of Trimethoprim

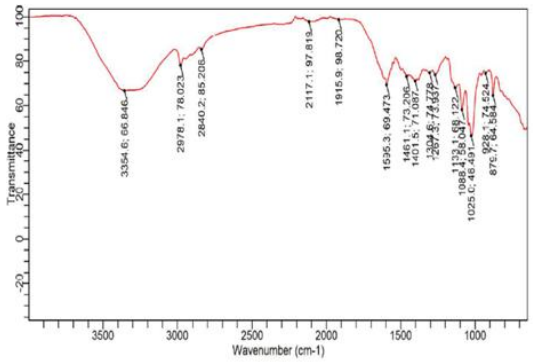

Figure 1b: IR spectrum of $[Mn(TMP)(H_2O)_2]$

The shifting of the azomethine (C=N) vibrations from 1633 cm^{-1} in the spectra of trimethoprim (Asogwa *et al.,* 2024) to 1595 cm^{-1} in the nanometal complex confirmed the coordination of the Mn (II) to the imine nitrogen atom (Aderoju *et al*., 2015). The band at 3317cm^{-1}, in the IR spectrum of trimethorpim, was assigned to NH_2 (Asogwa *et al.,* 2024). This band shifted to 3354cm^{-1} in the spectrum of the nano

metal complex, this indicates that there was coordination of the metal ion to the nitrogen of the amino group without deprotonation (Beyrambadi *et al*., 2011).

3.3. XRD

The X-ray Diffraction data is presented in Table 4.

Table 4: The XRD spectra data of the novel complex

Compound	λ (Å)	2Θ	FWHM	Crystallite size (nm)
$[Mn(TMP)(H_2O)_2]$	1.551	25.169	2.116	4.043

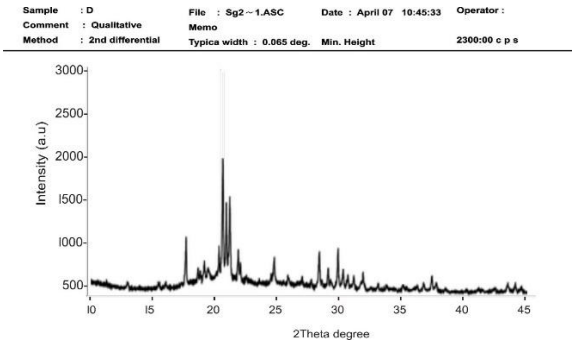

Figure 2: XRD pattern of $[Mn(TMP)(H_2O)_2]$

The XRD pattern showed that the Mn (II) nanocomplex is crystalline with a crystallite size of 4.043 nm, respectively.

3.4 NMR

The ^{1}H and ^{13}C NMR spectral data are summarized in Table 5 and Table 6 respectively .

Table 5: Summary of the ^{1}H NMR bands

Compounds	Chemical shift in ppm				
	Benzyl protons	methoxy protons	methylene protons	pyrimidine protons	H_2O protons
TMP	6.559	3.725, 3.620	3.533	7.529	-
$[Mn(TMP)(H_2O)_2]$	6.627	3.750, 3.591	1.042	7.327	3.242

Table 6: Summary of the ^{13}C NMR bands

Compounds	Chemical shift in ppm			
	CH_2	C-N	C=N	C=C
TMP	32.92	155.00	162 .00	105.00
$[Mn(TMP)(H_2O)_2]$	18.39	155.00	163.00	107.00

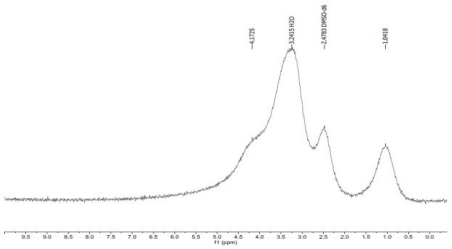

Figure 3a: ^{1}H spectrum of $[Mn(TMP)(H_2O)_2]$

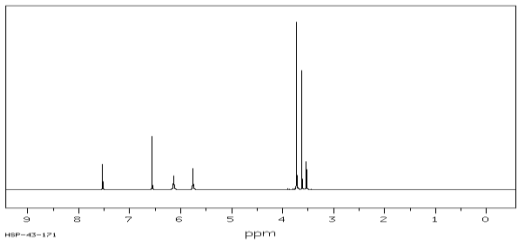

Figure 3b: ^{1}H spectrum of TMP (source: spectra database for organic compounds SDB)

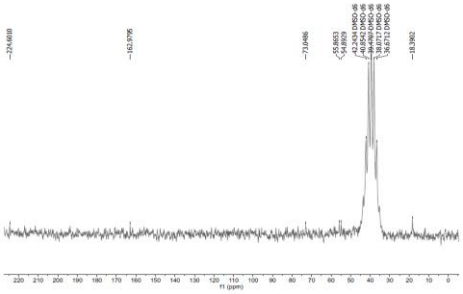

Figure 4a: ^{13}C NMR spectrum of $[Mn(TMP)(H_2O)_2]$

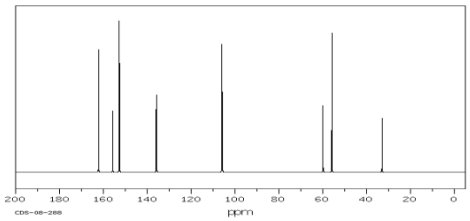

Figure 4b: ^{13}C NMR spectrum of TMP (source: spectra database for organic compounds SDBS)

The proton NMR spectrum of trimethoprim has a singlet peak at 3.533 ppm, attributed to the methylene proton. This was observed at a higher chemical field in the ^{1}H NMR spectrum of the nanometal complexes, showing coordination to a metal atom (Asogwa *et al*., 2024). The protons of the NH_2 group were observed at 6.14 and 5.76 ppm in the ligand spectrum. These peaks shifted upfield in the spectra of the nanometal complexes owing to coordination with the metal ions (Otuokere *et al.,* 2022).
In the ^{13}C NMR, there was a significant shift of the methylene carbon from 32.92 ppm to 18.39 ppm attributed to the withdrawal of electrons from the carbon atom due to the coordination.

Based on the spectroscopic study, the proposed structure for the $[Mn(TMP)(H_2O)_2]$nanocomplex is:

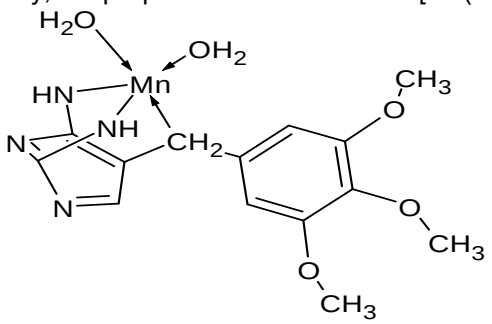

Figure 5: Proposed structure for $[Mn(TMP)(H_2O)_2]$

4. CONCLUSION

Synthesis and characterization of Mn (II) nanocomplex of TMP was achieved. The novel nanometal complex was synthesized by the use of sonication method and characterized utilizing spectroscopic analysis such as FTIR and NMR spectra and physical properties such as melting points and solubility profile. The X-ray Diffraction pattern showed the Mn (II) nanocomplex to be crystalline and having a crystallite size of 4.043 nm. A diagonal bipyramid structure was proposed for the complex showing that TMP behaved as a polydentate ligand towards the Mn (II) ion.

REFERENCES

Asogwa, B. C.; Mac-kalunta, O.M..; Iheanyichukwu, J. I.; Otuokere, I. E. and Nnochirionye, K. Sonochemical synthesis, characterization and ADMET studies of Fe (II) and Cu (II) nano-sized complexes of trimethoprim. Journal of the Nigerian Society of Physical Sciences 2024, 6, 2048.

Edozie, O. I.; Godday, O. J.; Chijioke, A. K.; Uchenna, O. I. and Chigozie, N. F. Synthesis, characterization and molecular docking studies of Co (II) metal complex of sulfathiazole. Bulletin of the Chemical Society of Ethiopia 2020,34, 83.

Otuokere, I. E.; Ohwimu, J. G.; Amadi, K. C.; Alisa, O. C.; Nwadire, F. C.; Igwe, O. U.; Okoyeagu A. A. and Ngwu, C. M. Synthesis, characterization and molecular docking studies of Mn (II) complex of sulfathiazole. Journal of the Nigerian Society of Physical Sciences 2019, 1, 95.

Ibrahim, F.M.; Hammza R. A. and Fadhil D. H. Synthesis and characterization of Trimethoprim metal complexes used as corrosion inhibitors for carbon steel in acid media. International Journal of Corrosion and Scale Inhibition, 2019, 8, 733–742.

Abeer A. and Moamen, S. R. Synthesis, spectroscopic characterizations and biological studies on Gold (III), Ruthenium (III) and Iridium (III) complexes of trimethoprim antibiotic drug. Bulletin of the Chemical Society of Ethiopia 2024, 38, 701.

Masoud, M. S.; Ali, A. E.; Elasala, G. S. and Amer, G. E. Synthesis, Characterization, Biological Activity and Thermal Studies of Trimethoprim Metal Complexes. J. Drug Des Res 2019, 6, 1074.

Drews, J. Drug discovery: a historical perspective. Science 2000, 287, 1960–1964.

Otuokere, I. E.; Asogwa, B. C.; Nwadire, F.C.; Akoh, O. U.; Nwankwo, C. I.; Emole, P. O.; Elemike, E. E. Biological Potentials of Some Schiff Bases and Their Chelates: A Short Review.Intech Open 2024, 1-17.

Otuokere, I. E.; Nwaiwu, K. C.; Nwadire, F. C. and O. U. Akoh. "Synthesis and characterization of Cr (III)-ascorbic acid complex." Journal of Applied Sciences and Environmental Management 2022, 26, 1, 75-80.

Otuokere, I. E.; Anyanwu, J. C. and Igwe, K. K. Synthesis, Characterization and Antibacterial Studies of 4-{[(E)-Phenylmethylidene] amino}-N-(1,3-thiazol-2-yl) benzenesulfonamide and its Mn (II) Complex. Chemsearch journal 2020, 11.

Asogwa, B. C. and Otuokere, I. E. Sonochemical Synthesis and Characterization of Fe (II) and Cu (II) Nano-Sized Complexes of Sulfamethoxazole. Journal of the Nigerian Society of Physical Sciences 2024, 2011–2011.

Sirajul, H.; Dildar, S.; Ali, M. B.; Mezni, A.; Hedfi, A.; Shahzad, M. I.; Shahzad, N. and Shah, A. Antimicrobial and antioxidant properties of biosynthesized of NiO nanoparticles using Raphanussativus (R. sativus) extract. Journal of Inorganic and Organometallic Polymers and Materials2020, 31, 1134–1142.

Otuokere, I. E.; Okorie, D. O.; Asogwa, B. C.; Amadi, O. K.; Ubani L. O. C. and Nwadire, F. C. Spectroscopic and Coordination Behavior of Ascorbic Acid Towards Copper (II) Ion. Research in Analytical and Bioanalytical Chemistry 2017, 1, 1-7.

Refat, M. S.; Al-Humaidi, J. Y.; El-Sayed, M. Y.; Hassan, R. F. In situ methanolic solvent synthesis, spectroscopic and thermogravimetric characterizations of three new transition metal complexes of trimethoprim drug. Polish Journal of Chemical Technology 2021, 23, 60–67.

Ugochukwu O. and Otuokere, I. E. Synthesis, Spectroscopic Characterization and Antibactrial Activities of Co (II) Complex of Ofloxacin Drug Mixed with Ascorbic Acid as a Secondary Ligand. Bio-Scientific Review 2021,3.

ElShaer, A.; Hanson, P.; Worthington, T.; Lambert, P.; Mohammed, A. R. Preparation and characterization of amino Acids-Based trimethoprim salts. Pharmaceutics 2012, 4, 179–196.

Abdel-Rahman, L; Abu-Dief, A.; El-Khatib R. and Abdel-Fatah, M. Sonochemical synthesis, DNA binding, antimicrobial evaluation and in vitro anticancer activity of three new nano-sized Cu (II), Co (II) and Ni (II) chelates on tri-dentate NOO imine ligands as precursors for metal oxides. Journal of Photochemistry & Photobiology, B: Biology 2016, 162, 298-308.

Trupti, P.; Suresh, G.; Khanderao, P.; Shreyas, P. and Rajeshwari, O. A. Review on Bio-Synthesized Co_3O_4 Nanoparticles using Plant Extracts and Their Diverse Applications. Journal of Chemical Reviews 2019, 1, 260-270.

Aderoju, A.; Osowole, S.; Wakil M and Olaoluwa, K. A. Synthesis, Characterization and Antimicrobial Activity of Some Mixed Trimethoprim -Sulfamethoxazole Metal Drug Complexes. World Applied Science Journal, 2015, 33, 336-342.
Beyramabadi, S. A.; Eshtagh-Hosseini, H.; Housaindokht M. R. and Morsali, A. Synthesis, experimental and theoretical characterization of Cu (II) complex of 2-chloropyrimidine. Scientific Research and. Essays 2011, 6, 4341-4346.