



Schiff Bases and their Transition Metal Complexes: The Drugs for the Next Generation

BAYERO UNIVERSITY KANO
PROFESSORIAL INAUGURAL LECTURE
NO. 30

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Thursday, 21st June, 2018

Published 2018 by:
Bayero University Press,
Main Library Building,
Bayero University Kano,
New Site, Gwarzo Road,
P.M.B. 3011.
Kano.

Website: www.buk.edu.ng
E-mail: info.bukpress@buk.edu.ng

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ISBN 978 - 978 - 54517 - 3 - 3

PRINTED BY BAYERO UNIVERSITY PRESS KANO, NIGERIA.



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WORK EXPERIENCE

- i) National Youth service Corps: Gov. Sec. School Azare, Bauchi State (1982 -1983)
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PROFESSIONAL MEMBERSHIP

- i) Fellow, Institute of Chartered Chemists of Nigeria
- ii) Member, Chemical Society of Nigeria

Professor Habu Nuhu Aliyu acquired his BSc. Chemistry degree in 1982, from Bayero University, Kano. He obtained his Master of Science degree in 1987 and his Doctor of Philosophy degree in Inorganic Chemistry in 1996 also from the same university. Professor Habu Nuhu Aliyu began his teaching profession during his National Youth Service at Government Secondary School Azare, Bauchi State in 1982. After his National Youth Service, he was appointed Assistant Lecturer at Katsina Polytechnic. While there, he taught Chemistry and Mathematics from 1983 to

1991 and he rose from Assistant Lecturer to Senior Lecturer. At the end of 1991, he moved to Bayero University, as a Lecturer II and rose through the ranks to become a professor of Inorganic Chemistry. Professor Habu Nuhu Aliyu is perhaps best known for his studies on synthesis and characterization of transition metal Schiff base complexes.

Since his appointment, he has supervised over 230 undergraduate projects, 37 postgraduate Diploma Long Essays, 40 Master Dissertations and 4 Doctor of Philosophy Theses. He has published over 83 papers in reputable Journals; 13 published conference proceedings and 11 unpublished conference proceedings. He is the author of *Essential Chemistry* and *The Chemistry of the Main Group Elements*, he also co-authored *Exam Focus – Chemistry for UME/PCE* published by University Press Plc, Ibadan. Furthermore, he attended a number of international and local conferences among which were: Annual International Inorganic Chemistry Conference, University of Bristol, United Kingdom on 16th December, 1993; International Conference on Cluster Compounds, University of Reading, United Kingdom on 9th February, 1994; International Inorganic Conference at University of Wales College of Swansea, United Kingdom on 25th July, 1994.

He has served in various capacities in the University: Level Coordinator at undergraduate (Departmental Coordinator (1997 – 2009); Faculty Postgraduate Coordinator (1998 – 2010), Examination Supervision for Faculty Courses (1992 – Date); Chairman, UME/DE Admission Committee (2005 -2006) and Editorial Board Member of BAJOPAS (2012 – Date); Acting Head of Department, Head of Inorganic Chemistry Unit (2006 – 2010); Member Guest House Committee (1996 – 2000); Member, Vehicle Rehabilitation Committee (1996 – 2000); Hall Adviser (1996 – 1998); Chairman, UME Screening Committee of Chemistry Candidates (2006); Strategic Committee, Instrument Committee, Student Reconciliation Committee (2001 – 2003), Patron, Chemical Students Society (2005 – 2007) etc..

Professor Habu Nuhu Aliyu also held responsibilities outside the University among which are; External Examiner, Federal University, Dutse, Jigawa State, (2012 – 2016); Sabbatical, Federal University, Dutsin-Ma, Katsina State (2014); External Examiner for Oral Examination, Umaru Musa Yar’adua University, Katsina State (2014); Team Leader (Chemistry) for West African Examinations Council (1987 – 1991); Item Writer for Joint Admissions and Matriculation Board for UME (1995 – 2011); Member, Accreditation Panel of Federal Polytechnic, Ofa, Kwara State (2001); Member, Accreditation Panel of Women’s Technical College of Education, Gusau ((2003); Member, Accreditation Panel of Technical College of Education Bichi

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In the Name of Allah, The Beneficent The Merciful....

“You alone do we worship and from you alone do we seek help”

- Suratul Fatiha, verse 4

*The Vice Chancellor,
Deputy Vice Chancellor (Academic),
Deputy Vice Chancellor (Administration),
Registrar,
Deans and Directors,
Heads of Department and Administrative Units,
Distinguished Alumni and Alumnae here present,
Distinguished Professors,
Distinguished Colleagues,
Ladies and Gentlemen,*

I am sincerely deeply touched to have this august assembly - an array of dignitaries gathered to listen to me, deliver my inaugural lecture. My appreciation goes to my Vice Chancellor, Prof. Mohammed Yahuza Bello, for giving me approval to deliver this inaugural lecture and for chairing the occasion.

Preamble

I feel greatly honoured to stand before you to present my professorial lecture, which provides me the opportunity to inform my colleagues, the university community and the general public of my work to date, including current research and future plans. The area of my research interest is ***Schiff bases and their transition metal complexes***. The cohesive aspects of certain advances are shown by bringing together researches published in different journals, including, in a few cases, journals of limited circulation. Therefore, this should aid historical studies and give the feeling of the general nature of research on Schiff bases and the potential of their transition metal complexes for use as drugs.

Introduction

The field of knowledge concerned with the application of coordination compounds to therapy or diagnosis of disease is still considered a rather young discipline by many.

However, this is contrary to the historically proven use of metals in pharmaceutical potions, which traces back to the ancient civilizations of Egypt and China (Jakupec *et al.*, 2008; Sigel *et al.*, 2012). Metals have been used in medicinal applications for centuries (Yamada, 1999; Singh *et al.*, 2009; Sadler, 1991). For example, the Egyptians used copper to sterilize water, gold was used in a variety of medicines in Arabia and China, and various iron remedies were used in Egypt around 1500 BC. About the same time, zinc was discovered to promote the healing of wounds. In the renaissance era, mercury chloride was used as diuretic and the nutritional essentiality of iron was discovered. However, in the last 100 years, the medicinal activity of inorganic compounds has been developed in a rational manner. Thus, in the early 1900s, potassium dicyanoaurate (I), $K[Au(CN)_2]$ was used for treating tuberculosis. In addition, the antibacterial activity of various gold salts and arsenic compounds were used for treating various diseases (Williams, 2009).

In the twentieth century, a highly therapeutic activity of metal complexes were discovered, namely their application for the treatment of cancer. Rosenberg's fortunate discovery of the anticancer action of cis-diaminedichloroplatinum(II), cis- $[Pt(NH_3)_2Cl_2]$ in the 1960s precipitated a widespread search for related complexes with similar or better activity e.g. palladium(II) dithiocarbamates have emerged as really promising candidates. These complexes have been observed to suppress cell division, as a result, and over the years, has become the Food and Drug Administration (FDA)-approved drugs of choice for cancer treatment, especially ovarian and testicular cancers. Unfortunately, these metal complexes have serious unwanted side-effects, e.g., kidney and nerve damage, nausea and vomiting, and hearing loss that have restricted their widespread clinical use (Rosenberg and Camp, 1970).

Consequently, many research groups throughout the world have been searching for suitable alternative metal complexes for the treatment of cancer, tuberculosis and other various diseases. And to this, Schiff bases and their transition metal complexes provide the answer.

Schiff Bases and their Transition Metal Complexes

Over the last few decades, the research field of medicinal inorganic chemistry has experienced continuous growth in the synthesis of nitrogen containing heterocyclic derivatives because of their utility in various applications. Schiff bases are the compounds containing an imine or azomethine group, $(-N=CH-)$. They are condensation products of ketones (or) aldehydes with primary amines and were first

reported by Hugo Schiff in 1864 (Khuba *et al.*; 2009; Worku *et al.*; 2002 and Zhang *et al.*; 2006).

Schiff bases are studied widely due to their synthetic flexibility, selectivity and sensitivity towards the central metal atom; structural similarities with natural biological compounds and also due to presence of azomethine (-N=CH-) active pharmacophore, which play major roles in their significant bio-activities (Gao and Zheng, 2002; Balsells *et al.*, 1998). Schiff bases having oxygen, nitrogen etc. donors have been reported to possess a wide remarkable biological activities, including **antibacterial** (Amin *et al.*, 2012; Neelakantan *et al.*, 2010), **antifungal** (Bharti *et al.*, 2010; Fioravanti *et al.*, 1995; Pandeya *et al.*, 1999), **antiviral** (Kumar *et al.*, 2010; Pignatello *et al.*, 1994), **antiulcer** (Mohammed *et al.*, 2012; Parashar *et al.*, 1989), **anticancer** (Babasaheb *et al.*, 2010; Zhang *et al.*, 2012; Jakupec *et al.*, 2008; Křikavová *et al.*, 2016), **antimalarial** (Shane *et al.*, 2006; Badwaik *et al.*, 2009), **antiproliferative** (Song *et al.*, 2013), **anti-inflammatory** (Salgm *et al.*, 2007), **antitubercular** (Shiradkar *et al.*, 2007), rifampicin and clofazimine for leprosy treatment and many others.

The azomethine nitrogen in Schiff base, not only provides binding site for metal ions but also makes attachment with various substrates of bio-molecules like proteins and amino acids in biological systems and that of diseases-causing germs. Through the metabolic activities, our body generates Schiff base complexes that show activities against various microbes. Schiff bases in the form of enzymes catalyse many metabolic reactions. Schiff base ligands easily form complexes with almost all metal ions in various oxidation states (Losada *et al.*, 2001; Santos *et al.*, 2001). Various researches in the field of Schiff bases indicated that their transition metal complexes have additional and improved bio-functions, that they have enhanced antibacterial, antifungal, antiviral, antiulcer, anticancer, antimalarial, antiproliferative, anti-inflammatory e.t.c activities depending upon the transition metal ions present in the Schiff bases (Gupta *et al.*, 1998).

Despite the enormous number of studies reported on antimicrobial activities of Schiff base transition metal complexes, just a few are cited in this report. For example, metal complexes of Schiff base derived from 2-thiophene carboxaldehyde and 2-aminobenzoic acid (HL) and Fe(III) or Co(II) or Ni(II) or UO₂(II) showed a good antibacterial activity against *E. coli*, *P. aeruginosa* and *S. pyogenes*. 2-Aminomethylthiophenyl-4-bromosalicylaldehyde Schiff base and its metal complexes have been screened for their antibacterial activities using the disc diffusion method against bacteria, the results showed that the metal complexes showed enhanced

inhibitory activity compared to the parent ligand under experimental conditions (El-Sherif and Eldebss, 2011). The *in vitro* antibacterial activity of the Schiff base ligands (L' , L'' and L''') and their metal(II) complexes have been carried out using disc diffusion method in DMF. The diameter of inhibition zone (mm) including the disc diameter was measured for each treatment. *Kleb* was found to be resistant to all the Schiff base ligands at all concentrations, *E. coli* was resistant to Schiff bases L' and L'' but active against L''' . The result for *Proteus sp.* showed minimal activity against the organism at all concentrations. The cobalt(II) complexes of the Schiff base ligands (L' , L'' and L'''), showed strong activity on the isolates, while Ni (II) and Cu (II) complexes showed no activity on all the isolates, however, Fe (II) and Mn (II) complexes showed some activity on *Proteous sp* and *Salmonella sp.* each with no activity on *E. coli* and *Kleb*. All the Schiff bases and their complexes reportedly showed activity below the standard drug, *Augmentin* (Aliyu and Umar, 2010). Four Platinum(II) Schiff bases complexes containing of salicylaldehyde and 2-furaldehyde with o- and p-phenylenediamine were reported as antibacterial against *E. coli*, *B. subtilis*, *P. aeruginosa*, *S. aureus*. The activity data showed that the Platinum(II) complexes are more potent antimicrobials than the parent Schiff base ligands against one or more microorganisms (Gaballa *et al.*, 2007). Metal complexes of a novel Schiff base derived from condensation of sulphametrole and varelaldehyde were screened against bacterial species (*E. coli* and *S. aureus*). The newly prepared Schiff base and its metal complexes showed a higher effect on *E. coli* (Gram-negative bacteria) and *S. aureus* (Gram-positive bacteria) (Mohammed *et al.*, 2010).

The antifungal experimental results of the Cr(III), Mn(III), and Fe(III) complexes of the Schiff base ligand derived from 1,4-dicarbonyl-phenyl-dihydrazide and chromene-2,3-dione, showed that all the metal complexes exhibited greater antifungal activity against *Aspergillus sp.* However, they showed slightly lesser activity against *Rhizoctonia sp.* than the standard drug Miconazole. The Cr(III) and Fe(III) complexes are more effective against *Penicillium sp.* than the standard drug at the same concentration. From the data, it has also been observed that the activity depends upon the type of metal ion and varies in the following order of the metal ion: Cr > Fe > Mn (Kumar *et al.*, 2012). Sensitivity of fungal isolates to Schiff base ligands and their metal (II) complexes has been determined. The results, showed that Schiff base L' is active at the highest concentration on both isolates while L'' is active on *Mucor sp.* at all concentrations and L''' active on both isolates at all concentrations. The complex $[MnL']$, was active on *Rhizopus sp.* at 1000 μ g and 2000 μ g while $[FeL']$ and $[CoL']$ were active at all concentrations on both *Rhizopus sp* and *Mucur sp.* while $[NiL']$ and $[CuL']$ complexes were inactive on the isolates. Similar results were obtained in the

metal complexes with L^{''} with increase in activity in the case of [FeL^{''}] with activity recorded in the case of [NiL^{''}] and [CuL^{''}]. The results indicated that the complexes showed more activity than the Schiff base ligands under similar experimental conditions (Aliyu *et al.*, 2011).

Semicarbazones and thiosemicarbazones complexes of Ni(II) ion showed antifungal activities against 11 pathogenic fungi. The complexes were moderately active against all pathogenic fungi and much lower than those of standard fungicide *Nistatin* (Chandra and Gupta, 2005). The antifungal activity against N-(2-hydroxy-1-naphthalidene) phenylglycine and its transition metal complexes was investigated. From the antifungal screening data, it was concluded that the activity of the ligand has increased upon complexation. Cu(II), Ni(II) and Co(II) complexes have shown better antifungal activity compared to the ligand and the corresponding metal salts (Gudasi *et al.*, 2006).

Copper(II) complexes containing Schiff bases derived from S-benzylthiocarbamate and saccharinate showed anticancer properties. The complexes were highly active against the leukemic cell line (HL-60) but only [Cu(NNS)(sac)] was found to exhibit strong cytotoxicity against the ovarian cancer cell line (Caov- 3). The activities being higher than the standard anticancer drug Doxorubicin (Jovanovski *et al.*, 1995).

Dapsone is well known, was synthesized and reported by Fromm *et al.*, (1908), and has been used for treatment of leprosy since 1947 (Cochrane *et al.*, 1949; Lowe, 1950). However, exhausted literature search on Dapsone revealed paucity of information, and that the current standard treatment for multibacillary leprosy is a multi-drug treatment (MDT) which consists of *dapsone*, *rifampicin* and *clofazimine*. The advantage of using multibacillary treatment is that it has shortened the recommended duration of treatment of multibacillary leprosy from two years to one year. Since dapsone is an amine, it was reacted with an aldehyde (2-hydroxybenzaldehyde) and a ketone (2, 4-pentanedione) separately, each forming a Schiff base (Aliyu and Ozoro, 2017). The two Schiff bases were each reacted with a number of transition metal (II) ions to give Schiff base metal(II) complexes. But it is well known that Schiff bases are active against bacteria and fungi and that their metal complexes exhibit higher activities than the parent Schiff bases. Therefore, the Schiff bases and their metal(II) complexes synthesized, were tested against a number of bacterial and fungal isolates except that bacterium responsible for leprosy, called *Mycobacterium leprae*. This is because *Mycobacterium leprae* cannot be isolated and cultured in the laboratory and so much is unknown about the infectious dose, incubation and transmission of the disease (Wheeler, 2003; Scollard *et al.*, 2006). For

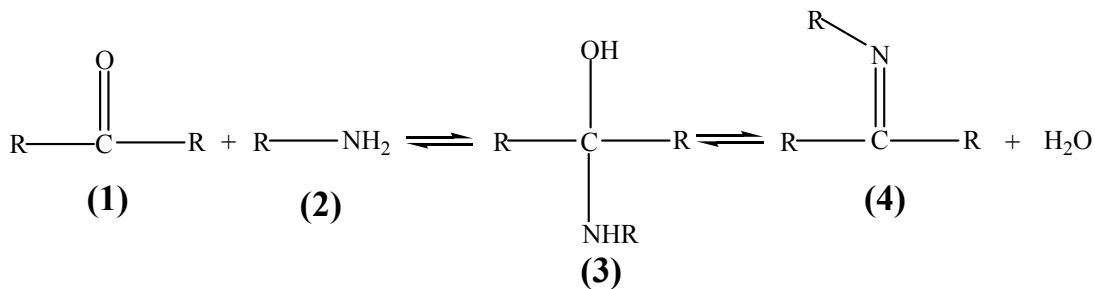
this reason, direct *in vitro* testing using *Mycobacterium leprae* isolate was not feasible in the laboratory. Moreover, rifampicin and clofazimine were separately reacted with a number of transition metal(II) ions each forming respective metal(II) complexes. The antibacterial activity tests of the synthesized compounds were carried out against three bacterial isolates; *E. coli*, *S. aureus* and *S. typhi* while the antifungal activity tests were carried out also using three fungal strains: *A. flavus*, *A. niger* and *A. fumigatos*. Dapsone, rifampicin and clofazimine were used as controls, respectively.

From the results obtained for the Schiff base ligand derived from dapsone and 2, 4-pentanedione and its metal(II) complexes, the Schiff base ligand showed more activity than the control (dapsone) and that some of its metal(II) complexes showed even higher activity than the Schiff base ligand, especially those of Co(II), Ni(II) and Zn(II). The results obtained from the Schiff base ligand derived from dapsone and 2-hydroxybenzylaldehyde and its metal(II) complexes, also showed that the Schiff base ligand exhibits higher antibacterial activity than the standard (dapsone), while the Co(II), Ni(II) and Zn(II) complexes, clearly showed higher antibacterial activities compared to the Schiff base ligand.

On the other hand, the antibacterial activities of the rifampicin metal(II) complexes investigated exhibited higher activity than the standard, rifampicin especially those of Fe(II), Co(II) and Cu(II). A similar trend was observed for clofazimine metal(II) complexes, particularly those of Fe(II), Co(II) and Zn(II), showing remarkably higher activity than the standard, clofazimine. Investigation into the antifungal activity of the compounds under study also showed similar trend to that of antibacterial tests (Aliyu and Ozoro, 2017).

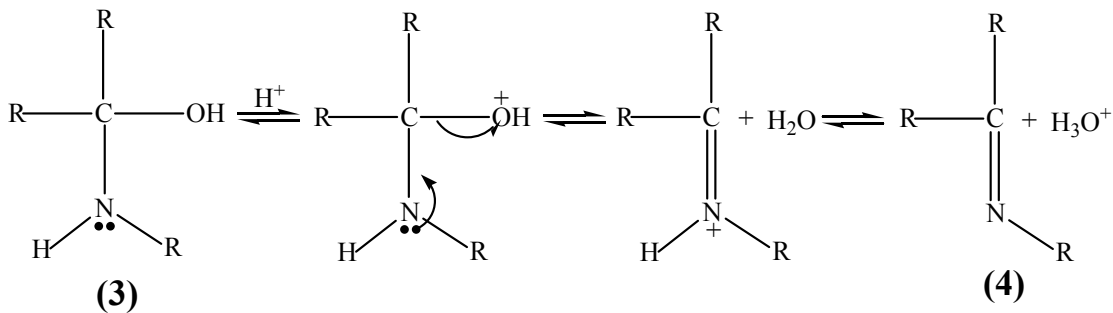
Preparation of Schiff Bases

The preparation of Schiff bases involves a variety of conditions and is brought about by mixing carbonyl compounds (**1**) and primary amines (**2**) in various proportions and employing a range of solvents (**Scheme 1**).



Scheme 1: *General synthesis of Schiff bases*

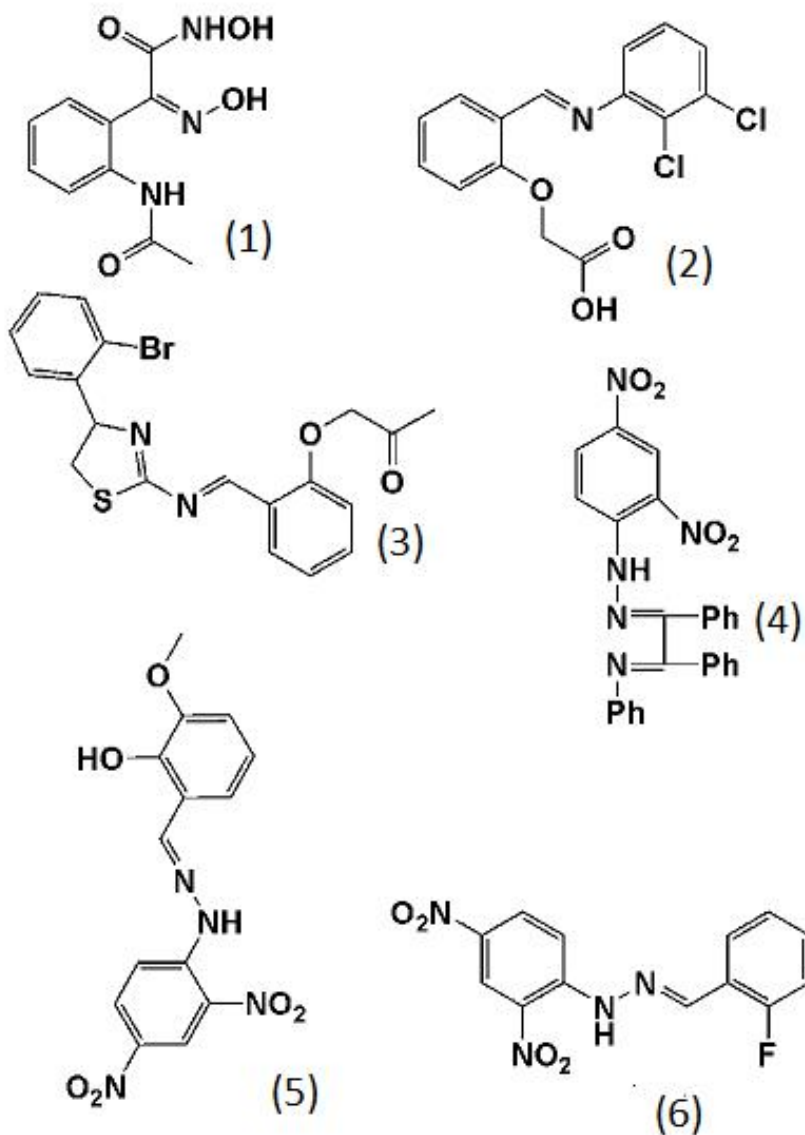
The formation of Schiff bases **(4)** is generally favoured by making use of dehydrating agents. A great care should be taken for the purification of Schiff bases as they are degradable. The acid/base catalysis or heating is employed for the synthesis of Schiff bases as their reactions are mostly reversible. The Schiff bases are formed by the reaction of amines with carbonyl compounds but it does not follow simple nucleophilic addition, but gives an unstable addition compound called carbinolamine **(3)**. The compound thus obtained is unstable and loses water molecule. The dehydration step during formation of Schiff base is actually the rate determining step and the reaction shown in scheme is catalysed by acid (**Scheme 2**).

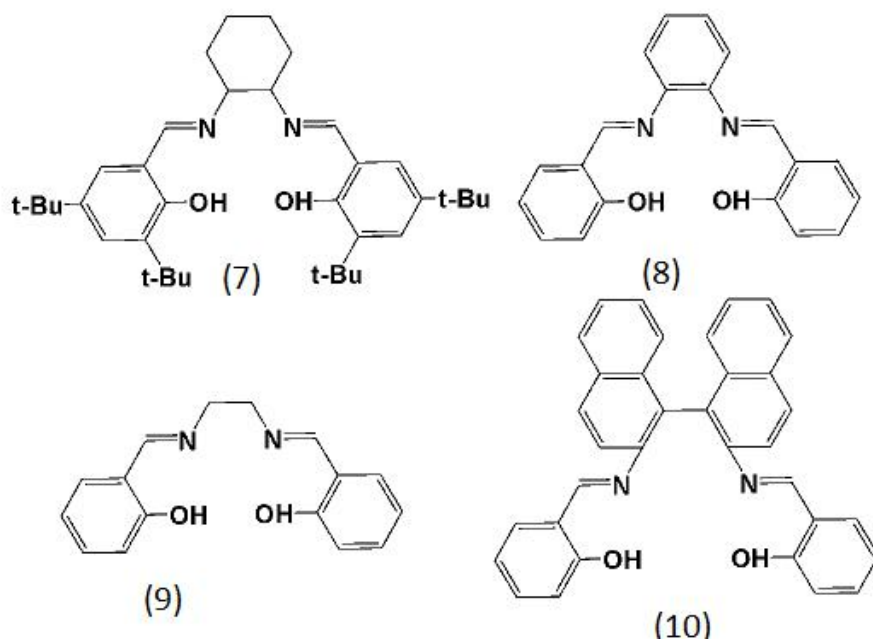


Scheme 2: *The mechanism for dehydrogenation for formation of Schiff base*

The removal of product or separation of water from the reaction mixture assists the formation of product. The aqueous acids or bases may hydrolyse Schiff bases towards their respective aldehydes or ketones and primary amines as well. In this regard, high concentration of acid is not needed due to basic character of amines. The formation of carbinolamine cannot occur and equilibrium is shifted towards left side because

protonated amine does not act as nucleophile. This is the reason that mildly acidic pH is quite good for the formation of Schiff bases (Abdul *et al.*, 2016).



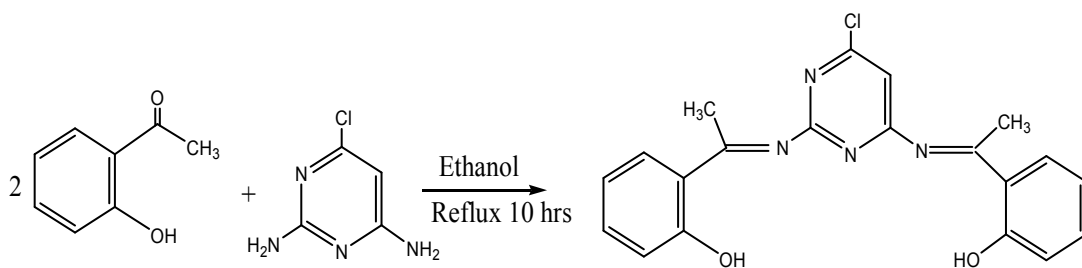


Scheme 4: Schiff bases having one or more donor atom(s)

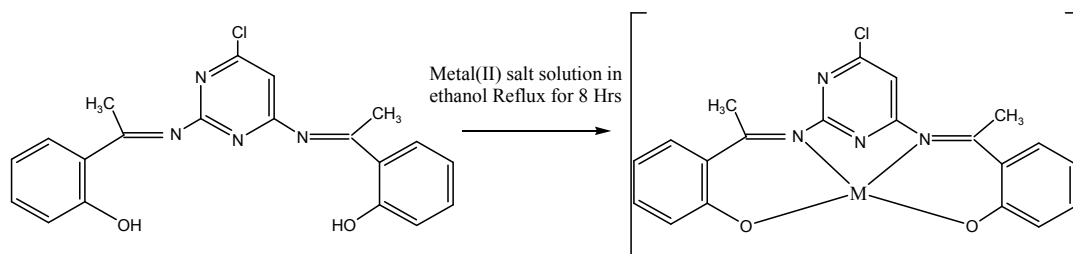
Preparation Methods of Schiff Base Complexes: (By Direct Interaction of the Schiff Base with the Metal Salts)

The Schiff base can be synthesised without using the metal ion and then followed by addition of the metal ion as salt solution for complex formation (Itrata *et al.*, 2013). This can be easily described by the following two steps;

Step One: Preparation of the Schiff Base



Step Two: Preparation of the Metal(II) Schiff Base Complex



Scheme 5: Preparation of Schiff base complex by direct method

A variety of Schiff bases can be obtained by changing aldehydes or amines. Thus, synthesis of large number of Schiff bases with diverse structural features could be possible with ease. They can have additional donor groups like oxygen, sulphur, phosphorus etc. which makes them good candidates for metal ion complexation and for mimicking biological systems. They can be functionalised by the insertion of appropriate groups in the aliphatic or aromatic chains.

Conclusion

Schiff bases are considered as a very important class of organic compounds because of their ability to form complexes with transition metal ions and of their pharmacological properties. Transition metal complexes containing Schiff bases have been of much interest over the last years, largely because of their various applications in biological processes and potential applications in designing new therapeutic agents. But still there is need to explore the biological properties of these already synthesized transition metal complexes and to synthesise new complexes with more properties.

ACKNOWLEDGEMENTS

This professorial inaugural lecture would not have been possible without the existence of Bayero University, Kano, where I enrolled for my first degree (B.Sc Chemistry 1979-1982), second degree (MSc Inorganic Chemistry 1985-1987), and Doctorate degree (PhD Inorganic Chemistry 1993-1996). I am especially indebted to Professor M. A. Quaraish, the third Head of Chemistry Department and also my B.Sc Chemistry research supervisor, As my teacher and mentor, he had taught me more than I could ever give him credit for here. He showed me, by his example, what a good Inorganic Chemist should be. Dr Joseph Mbadcam, my MSc Inorganic Chemistry research supervisor (1986-1987), Professor K. S. Patel, my PhD Inorganic research supervisor (1993-1996) and R. D. Gillard (University of Wales College of Cardiff, United Kingdom) – my PhD research co-supervisor, who had been supportive of my career goals and who worked actively to provide me with what it is required to be an Inorganic chemist.

I wish to acknowledge the help provided by Bayero University for nominating me for Federal Government Acquired World Bank loan (1993) for my bench work in the Department of Inorganic Chemistry, University of Wales College of Cardiff (UWCC), UK for a period of twelve months. I would like to express my deep gratitude to the Vice Chancellor, Professor Mohammad Yahuza Bello, who is also the Chairman Inaugural Lecture, for organising and supporting this professorial inaugural lecture. I would like to offer my special thanks to the Registrar, Hajiya Fatima Binta Mohammed and the University Librarian, Dr Musa Auyo, who was a colleague at Government Secondary School Hadejia and Bayero University, Kano, and currently my neighbour.

Nobody has been more important to me in the pursuit of my academic career than the members of my family. I would like to thank my late parents, whose love and guidance are with me in whatever I pursue. They are the ultimate role models. Most importantly, I wish to thank my loving and supportive wife, Hajiya Maryama, and my wonderful children, Jamila, Asiya, Zubaida, Ibrahim, Mohammed, Aliyu, Abdullahi, Imran, Saudat, and Baba Ali, who provide unending inspiration.

My special thanks are extended to Professor Junaidu Na'aliya, Dr Haruna Musa (Head of Department of Pure and Industrial Chemistry), Professor M. S. Gumel, Professor W. L. O. Jimoh, Professor A. A. Audu, Professor S. Y. Mudi, Professor M. B. Ibrahim, Professor M. I. Mohammad, Professor A. A. Salisu, Professor M. D. Said, Professor U. M. Adoum and many others, for having provided insight, constructive criticism and expertise that greatly assisted the production of this inaugural lecture document.

Thank you all for listening.

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