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MACROCYCLIC COMPLEXES: POTENT MOLECULES AGAINST DRUG RESISTANT MICROBES

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Abstract

The metal ion chemistry of macrocyclic ligands has now become a major subdivision of inorganic chemistry and is a growing area of research in inorganic and bioinorganic chemistry. The field of macrocylic chemistry of metals is developing very fast because of its applications and importance in the area of coordination chemistry. Macrocyclic ligands and their transition metal complexes have received considerable attention because of their pharmacological properties. Metal ion plays important role in biology which has lead to the development of huge number of metal complexes with diverse therapeutic. Macrocyclic metal complexes are best prepared by 'metal template condensation reactions'. Metals can play an important role in modifying the pharmacological properties of known drugs as chelation causes drastic change in biological properties of ligands. The application of inorganic chemistry to medicine is a rapidly developing field. The novel therapeutic and diagnostic metal complexes are now having an impact on medical practice. Advances in biocoordination chemistry are crucial for improving the design of compounds to reduce toxic side effects and understand their mechanisms of action.The potential for further development of metal-based drugs and treatments as an antimicrobial agent is enormous and also of great importance with the evolution of drug-resistant bacteria and threats from a range of viral diseases. This review tries to summarize the effectiveness of Macrocyclic complexes as antimicrobial agent against microbes.

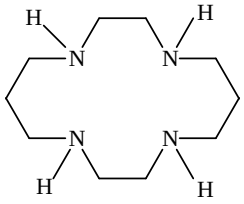
Keywords: Macrocylic, chelation, microbes, template, antimicrobial agent, transition metal,therapeutic, coordination, ligand, complexes.

Introduction

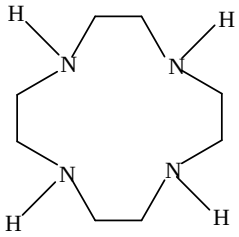
Antibiotics are the natural or synthetic compounds that in, low concentrations, inhibit the growth of or kill microorganisms completely. The intensive use of antibiotics during the past decade has resulted in the rapid development of multiple antibiotic-resistant pathogenic bacteria. Antibiotics are medicinally important molecules used for the treatment of bacterial infections in both human and animals but due to the regular use of antibiotic, resistance has increased substantially in the recent years and is posing an ever increasing therapeutic problem [1]. One of the methods to reduce the resistance towards antibiotics is by using antibiotic resistance inhibitors such as macrocyclic complexes [2]. The studies of macrocycles have undergone tremendous growth in recent years and their complexation chemistry with a wide variety of metal ions has been extensively studied [2]. The chemistry of macrocyclic complexes has been a fascinating area of current research interest to the chemists all over the world. The chemistry of macrocyclic complexes has occupied a central role in the development of coordination chemistry [3] . The metal ion and host guest chemistry of macrocyclic ligands has developed rapidly over recent years and now impinges on wide areas of both chemistry and biochemistry [4]. During the past decade there has been a growing interest in the synthesis of multidentate ligands and their complexes [5].

What is macrocycle?

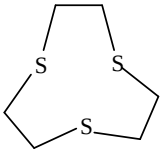
"A **macrocycle is cyclic macromolecule or a macromolecular cyclic portion of a molecule.**"[6] Obviously, a macrocycle is a large cyclic molecule and a macrocyclic ligand should contain donor atoms which may form coordinate bonds with metal centres. In coordination chemistry, **a macrocycle is a cyclic molecule with three or more potential donor atoms in a ring of atleast nine atom**s [2,7]. By this definition, ethylene oxide, 1,4-dithiane, cyclotetradecane, cyclooctatetraene are not macrocycles, whereas molecules such as cyclam, cyclen, 1,4,7-trithiacyclononane and dibenzo-18-crown-6 are macrocycles according to above definition. Fig 1



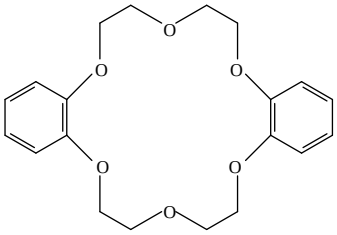
Cyclam



Cyclen



1,4,7-trithiacyclononane



Dibenzo-18-crown-6

Fig 1: Examples of Macrocycles

Characterization of macrocyclic complexes

The important characteristics of the macrocyclic complexes are:

- The complexes with macrocyclic ligands are more stable than those with equivalent open-chain ligands (macrocyclic effect).
- They provide stability to high oxidation states that are not attainable normally.
- They have high thermodynamic stability.
- Metals containing macrocyclic can serve as models for naturally occurring biological systems and have various industrial, analytical and medicinal applications.

Synthesis of macrocyclic complexes

Macrocyclic metal complexes are best prepared by 'metal template condensation reactions'. The term "template" has been widely used since early sixties. The routine use of metal template procedures for obtaining a wide range of macrocyclic systems was developed by Neil F Curtis [8]. In 1963, 'Daryle Hadley Busch' also coined the term template in coordination chemistry [9]. Metal template condensation reactions are simple "one-pot reactions", cheap and high yielding. Macrocyclic complexes are best prepared with the aid of metal ions as templates to direct the condensation reaction which ultimately ends with ring closure [10, 11]. Template schiff base condensation between dicarbonyl compounds and diamines are among the simplest and most popular methods for macrocyclic synthesis [12]. Condensation reactions between carbonyl compounds and primary amines are responsible for a major part of the process leading to the formation of macrocyclic ligands [13]. The macrocyclic complexes of metal ions are also synthesized by the reaction of the required metal ion with the preformed macrocyclic ligands, but there are potential disadvantages in this method. The synthesis of a macrocycle in the free form often results in a low yield of the desired product with side reactions where polymerization is predominating. In order to evade this problem, the ring-closure step in the synthesis may be introduced to restrict rotation in the open-chain precursors thereby facilitating cyclization. Therefore, the effective method for the synthesis of macrocyclic complexes involves an *in situ* approach wherein the presence of a metal ion in the cyclization reaction markedly increases the yield of the cyclic product. The Schiff bases 'an important structural feature of the macrocyclic ligand complexes' [14] having imine or azomethine groups are usually formed by the condensation of an active carbonyl compound and a primary amine as shown in Fig 2 .

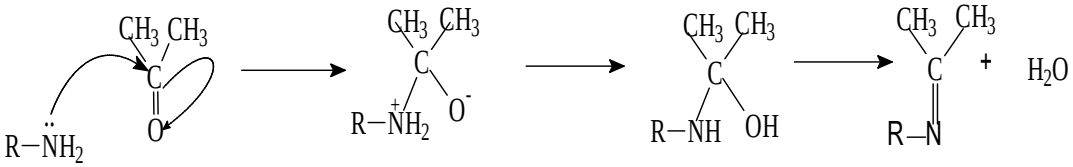
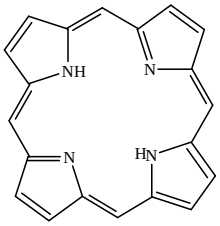


Fig 2 Active carbonyl compound and a primary amine

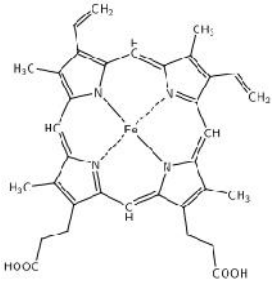
Biological macrocycles occurring in nature

Macrocyclic complexes are widespread in biology and life could not exist in the absence of such molecules. There are few biological macrocycles occurring in nature are as follows:

Heme: Heme, the active site in the hemoglobin (the protein in blood that transports oxygen) is a prosthetic group that consists of an iron atom contained in the center of a large heterocyclic organic ring called **porphyrin [4]**. The intense red or brown colour of the heme proteins is not caused by iron but by porphyrin, a complex cyclic structure [15].



Porphyrin ring



Structure of Heme B

(Porphyrin containing iron)

Fig 3: Porphyrin ring and Porphyrin containing iron

Chlorophyll: Chlorophyll is a green photosynthetic pigment found in green leaves. Chlorophyll contains a **chlorin** ring having magnesium ion in the centre and takes part in the photosynthesis which is the basis for sustaining the life processes of all plants.The chlorin ring of chlorophyll is the actual chromophore, the light absorbing part of molecule. [16]. Since animals and humans obtain their food supply by eating plants, photosynthesis can be said to be the source of our life also [17].

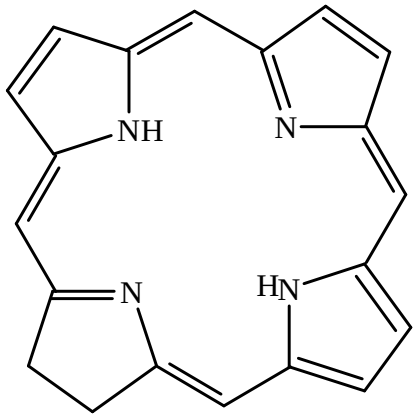


Fig 4: Chlorin ring

Vitamin B_{12}: Vitamin B_{12}, contains cobalt inside the **corrin ring**. Vitamin B_{12} is an important coordination compound in biology. It is an interesting biomolecule in the sense that no other vitamin contains a metal ion. It plays an important role in the metabolism of nucleic acids and in protein synthesis. The term vitamin B_{12} refers to cyanocobalamin Cyanocobalamin is a compound that is metabolized to vitamin, in the B-complex [18].

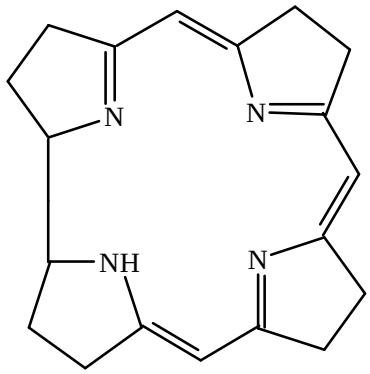


Fig 5: Corrin ring

Nonactin: Nonactin, an antibiotic is known for its ability to form complexes with alkali cations, most notably potassium and sodium selectively and act as a carrier for this ion across the lipid barriers in cell membranes. It is an oxygen donor macrocycles that controls ionic balance within the cells, the transmission of neural impulses [7].

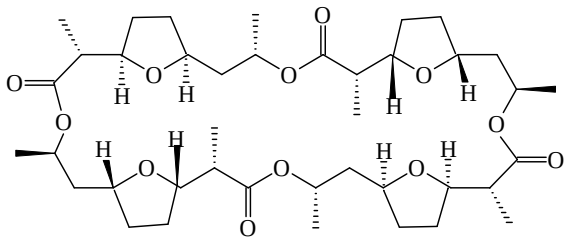


Fig 6: Nonactin

Importance of Macrocyclic complexes as antimicrobial agent

Macrocyclic complexes have also received special attention because of their versatile coordination behaviour and their pharmacological properties, *i.e*., toxicity against bacterial growth [19, 20]. In view of biological importance of macrocyclic complexes, biological screening of the synthetic macrocyclic metal complexes has also been carried out [21]. These macrocyclic complexes have been screened by many research groups for their *in vitro* antibacterial activity to assess their inhibiting potential against some gram positive and gram negative bacteria [22-25]. The coordination chemistry of manganese has achieved remarkable progress in last decade due to the increased recognition of this metal's rate in biological system [26]. Macrocyclic complexes of manganese(II) have been reported to show antifertility, antibacterial and antifungal activities [27]. Some macrocyclic complexes of manganese(II) also show anti-inflammatory approach [28,29]. Several metal complex agents have already been introduced into clinical tumor therapy [30]. Tetraazamacrocyclic copper complex can damage plasmatic membranes and trigger apoptosis [31]. Several macrocyclic complexes of tetraazamacrocyclic ligand such as cyclen, cyclam and bicyclam have been reported to exhibit antitumour activity [32-34] Metal ions are known to bind with nucleic acids and thereby alter their conformation and biological function[35]. Gold(I) and gold(III) complexes, the last isostructural and isoelectronic with platinum(II) complexes, are potentially attractive as anticancer agents [35-37]. Many of the transition metal ions in the living systems work as enzymes or carriers in macrocyclic ligand-field environment. Copper(II) ions play a central role in biological redox metalloenzymes such as plastocyanin, hemocyanin, azurin and galactose oxidase [38].

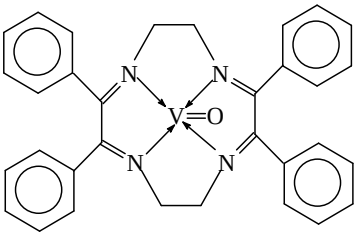
Azomethines constitute one of the most important class of nitrogen donor ligands in coordination chemistry [39]. Azomethines and their transition metal complexes have remarkable potential for inhibiting growth of various pathogenic micro-organisms. Anacona *et al* [40] have reported the antibacterial activities of macrocyclic complexes of manganese (II) and palladium (II) by disc diffusion method. Bhasin *et al* [41] have reported the antimicrobial studies of some alkylene dithiophosphate derivatives of macrocyclic complexes of nicke l(II). Manganese, together with copper and iron exhibits sufficient biological activity, when associated with certain metal protein complexes those are participating in the storage of ions [42]. The antimicrobial screening of 12-membered Schiff base teraazamacrocyclic complexes were registered by Shakir *et al* [43]. Reddy *et al* [44] have reported the antibacterial activity of copper (II) macrocyclic complexes. Sharma *et al* [2] have reported *in vitro* antibacterial activity of tetraazamacrocyclic complexes

against five bacteria i.e. *Streptococcus mutans*, *Escherichia coli, Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*. Siddiqi *et al.* [45] have reported the biological activities of homo-bimetallic complexes. Nishat *et al*. [46] have reported the antimicrobial activities of transition metal complexes. Antimicrobial studies of the tetraazamacrocyclic complexes were reported by Reddy *et al*.[47] P.M.Reddy *et al* have reported that Copper(II) Tetraaza Macrocyclic Complexes are potent against both gram-positive as well as gram-negative bacteria due to the presence of thio group in the coordinated ligands. [47]

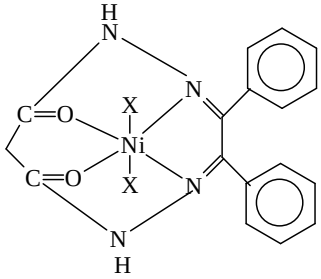
Aghatabay *et al* [48] have reported the antibacterial activity of mixed macrocyclic compounds. Antibacterial activity and DNA interaction of metal complexes have been reported by Shakir *et al* [49]. Roy *et al* [50] have reported the copper (II) and nickel(II) complexes of N,N-*bis* (2-hydroxyethyl) octamethyl-1,4,8,11-tetraazacyclotetradecane showing activity against some pathogenic bacteria and fungi. The tetraazamacrocyclic complexes and their activity against some bacteria like *Staphylococcus aureus*, *Salmonella typhi and Pseudomonas aeruginosa* have been reported by Raman *et al* [51]. Shakir *et al* [52] have reported the antimicrobial screening studies of 14- and 16- membered hexaazamacrocyclic complexes. Nishat and Haq [53] have reported the biological activity of synthesized macrocyclic complexes against some gram positive and gram negative bacteria like *Staphylococcus aureus* and *Escherichia coli*. The antimicrobial activities of biologically potent macrocyclic complexes have been carried out by Singh *et al* [54]. Kumar *et al* evaluated antimicrobial activities of macrocyclic complexes to assess their inhibiting potential [55]. Singh *et al* have investigated *in vitro* antimicrobial activities of macrocyclic complexes against some bacterial strains and yeast [56]. Molecular modelling, spectroscopic characterization and biological studies of new tetraazamacrocyclic metal complexes have been reported by D.P.Singh *et al* [57].

P. Rathi, and D.P. Singh have reported molecular modeling and molecular docking of template engineered biopotent macrocyclic complexes involving furan moiety[58] Synthesis, spectral, thermal and antimicrobial studies of transition metal complexes of 14-membered tetraaza [N4] macrocyclic ligand has been reported by Shankarwar *et al* [59]. Abou-Hussein and W. Linert reported synthesis, spectroscopic studies and inhibitory activity against bacteria and fungi of acyclic and macrocyclic transition metal complexes containing a triamine coumarine Schiff base ligand.[60]. The Transition Metal Macrocyclic complexes are very popular in the medicinal field [2, 61] due to their resistivity towards the gram (-) and gram (+) bacteria, fungal growth and as the virus inhibitors. Few of the drugs such as VL-1, NiL-2 (Fig.7) shows the inhibitor activity towards the microbial growth. D.P Singh *et al* [62] have reported Synthesis, spectroscopic studies and biological screening of 18 membered octaazamacrocyclic complexes derived from acetonylacetone and thiocarbohydrazide. D.P Singh *et al* [63] have also reported *in vitro* antibacterial activities of octaazamacrocyclic complexes derived from carbohydrazide and isatin against Gram-positive(*S. aureus, B. subtilis)* and Gram-negative (*E. coli, P. aeruginosa*) bacteria. So, from this study it was concluded that nickel and zinc macrocyclic complexes were most effective against Gram-positive bacterial strains.

Keeping the importance of the macrocyclic complexes as antibacterial agent, now- a- days macrocyclic chemistry is a growing area of research in inorganic and bioinorganic chemistry.



VL-1



NiL-2

Where X= Cl

Figure 7: Antimicrobial drugs consist of transition metal atoms in the macrocycle.
VL-1, shows antibacterial activities against E.coli(-), S.aureus(+) M.luteus(+) and B.licheniformis (+).
NiL-2, Shows a very good antifungal activity towards Aspergillus flavus and A. niger.

Mode of action

The mode of action of metal complex on living organism is likely to differ from non metals. It shows great diversity in action. [64] The lipophilicity of the drug is increased through the formation of chelates and drug action is increased due to effective permeability of the drug into the site of action. Therefore, activity of the metal chelates can be explained on the basis of chelation theory [65, 66]. Metals can play an important role in modifying the pharmacological properties of known drugs after coordinating to a metal. Chelation causes significant changes in biological properties of ligands and enhance the biochemical potential of bioactive species. Chelation and coordination tend to make metal complexes act as more powerful and potent bactereostatic agents, thus inhibiting the growth of the microorganisms [67]. Because on chelation, the polarity of the metal ion will be reduced due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups [68]. Hence macrocyclic complexes become very stable due to delocalization of π-electrons [69]. It enhances the penetration of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganisms [70]. These complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organisms [71].

It also has been observed that some moieties such as azomethine linkage or heteroaromatic nucleus introduced into such compounds exhibit extensive biological activities that may be responsible for the increase in hydrophobic character and liposolubility of the molecules in crossing the cell membrane of the microorganism and enhance biological utilization ratio and activity of complexes [72,73]. It has also been suggested that the mode of action of the compounds may involve the formation of hydrogen bond through azomethine group with the active center of cell constituents resulting in interference with normal cell process [74]. In the complexes, some uncoordinated donor atoms enhance the activity of the complexes by bonding with trace elements present in microorganism [75]. This may combine with the uncoordinated site and inhibit the growth of microorganisms.

The variation in the effectiveness of different compounds against different organisms depends either on the impermeability of the cells of the microbes or on differences in ribosome of microbial cells [76].

Future in drug development

The advances in the field of chemistry provide better opportunities to use metal complexes as therapeutic agents [77]. Cisplatin, carboplatin and oxaliplatin are the well known metal-based drugs widely used in treatment of cancer [78, 79]. Besides these complexes other metal complexes have shown promising results in the treatment of diseases like diabetes, ulcer, rheumatoid arthritis, inflammatory and cardiovascular diseases etc [80-81]. The macrocyclic complexes demonstrating antibacterial activity could result in the discovery of new chemical classes of antibiotics that could serve as selective agent for the maintenance of animal or human health and provide biochemical tools for the study of infectious diseases [2]. These complexes may be used for formulating novel chemotherapeutic agents and further investigation will be necessary to identify the active principle. These studies may be helpful in solving the rising problems of antimicrobial resistance and these compounds may be utilized for formulating the novel chemotherapeutic agents. Metal complexes offer a platform for the design of novel therapeutic compounds [64]. Activity of the compound can be increased by the formation of complex with different metal ion [78]. In general, metal complexes are more active than the ligands [83]. Metal complexes may serve as a vehicle for activation of ligands as the principle cytotoxic species [84]. It seems that opportunities exist for candidates in the discovery and development of novel therapeutic agents.

Conclusion

A very large number of synthetic, as well as many natural, macrocycles have now been studied in considerable depth. A major thrust of many of these studies has been to investigate the unusual properties frequently associated with cyclic ligand complexes. In particular, the investigation of spectral, electrochemical, structural, kinetic, and thermodynamic aspects of macrocyclic complexes have all received considerable attention. The macrocyclic complexes demonstrating antibacterial activity could result in the discovery of new chemical classes of antibiotics that could serve as selective agent for the maintenance of animal or human health and provide biochemical tools for the study of infectious diseases. It is known that chelation tends to make the ligand to act as more powerful and potent bacterial agent. The encouraging results of preclinical and clinical studies with metal compounds form the basis for further investigations towards the development of metal complexes for better therapeutic profile. Although, metal complexes have some side effects, they are successfully being used in cancer therapy and several other therapies. Therefore, there is a need for new approaches that are required to circumvent these drawbacks and pave a way for better potent drug therapies.

Acknowledgments

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