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Synthesis and Characterization of Biocidal Studies of Some Hydrazones and Their Metal Chelates

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ABSTRACT: The development of novel compounds, hydrazones and their metal chelates has shown that they possess a wide variety of biological activities viz. antimicrobial, anticonvulsant, antidepressant, anti-inflammatory, analgesic, antiplatelet, antimalarial, anticancer, antifungal, antitubercular, antiviral, cardio protective etc., Hydrazones hydrazones and their metal chelates possess-NHN = CH- and constitute an important class of compounds for new drug development. A number of researchers have synthesized and evaluated the biological activities of hydrazones and their metal chelates . Hydrazones and their metal chelates related to ketones and aldehydes belong to a class of organic compounds with the structure, $R_1R_2C = NNH_2$.These compounds possess diverse biological and pharmacological properties such as antimicrobial, anti-inflammatory, analgesic, antifungal, anti-tubercular, antiviral, anticancer, antiplatelet, antimalarial, anticonvulsant, cardio protective, antihelmintic, antiprotozoal, anti-trypanosomal, antischistosomiasis etc. These compounds contain C = N bond, which is conjugated with a lone pair of electrons of the functional nitrogen atom. The nitrogen atoms of the hydrazones are nucleophilic and the carbon atom has both electrophilic and nucleophilic nature. The α-hydrogen of hydrazones is more potent than that of acidic ketones. The combination of hydrazones and their metal chelates with other functional group leads to compounds with unique physical and chemical character. Owing to their biological and pharmacological properties, they are considered important for the synthesis of heterocyclic compounds.

KEYWORDS: hydrazones, metal chelates, biocidal studies, synthesis, characterization, compounds, applications, future

I. INTRODUCTION

Many organic compounds react with metal ions and form colored precipitates or solutions. Hence, they are extensively used as analytical reagents, even though it is difficult to predict with certainity which organic compound is suitable for the analysis of a particular metal ion. Yoe gave a list of more than twenty ways in which they are used.[1,2] It has been observed that the reactivity of organic reagents with metal ions in the use of the former as analytical reagents requires the presence of certain acidic or basic groupings and coordinating atoms. The aim of research in this field[49,50] is the discovery of compounds possessing a high degree of selectivity and identification of the causes underlying such selectivity. While most of the reagents are not selective, various means are known where by the selectivity of a reagent may be improved. These include adjustment of the pH, [3,4]and the use of masking agents which form complexes with the interfering elements in the determination of the test ion. Within the organic reagent molecule, there is generally a single acidic or basic group, or a combination of these two, which is the key to the reactivity[47,48] of the reagent. Literature survey has revealed that organic compounds capable of forming chelates or inner complex salts give better results than those containing only acidic or basic groupings, in the field of inorganic analysis. [45,46]The element in the organic molecule through which the metal is bonded is generally oxygen or nitrogen, less usually it is sulphur. The oxygen containing groups most often met in organic reagents were -OH, -CHO, -COOH, >CO. The nitrogen containing groups (-NH2, =NH, heterocyclic N) met with in general functional groups are amines (usually aliphatic), heterocyclic rings (usually pyridine), oximes (in which bonding tends to be coordinated to the nitrogen instead of replacement of hydrogen) and azo groupings.[5,6] The aromatic orthohydroxy carbonyl compounds form stable six membered rings with the metal ions. Hydroxy carbonyl compounds derived from benzene and naphthalene, hydroxy quinones of naphthalene and anthracene series have been introduced as analytical reagents. It is observed, that in many cases the formation of a precipitate or a soluble colored product is dependent on the presence of definite atomic groupings.[43,44] Such compounds are therefore designated as metal binding groups with specific or selective action. But, it cannot be over looked that the reaction conditions play a definite role in this direction. Hence, proper choice of solvent and other factors are to be given equal importance. Organic compounds can undergo extensive alteration in their structure as a result of condensation and substitution reactions. These may bring in the useful changes in the reagent to make them better organic reagents. A survey of literature shows, that organic compounds containing a

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phenolic or enolic group and a coordinating group containing nitrogen,[7,8] oxygen or sulphur forms a variety of complexes with different metal ions. It is found that -SH group of an organic compound exhibits a higher acidic character than similarly bound –OH group. Thio-keto group (>C=S) also plays an important role compared to its counterpart, keto group (>C=O) It is observed that aromatic compounds containing nitroso (-N=O) as well as phenolic – OH groups are also useful as analytical reagents. [41,42]It is clear from the above brief review presented, that many organic compounds containing acidic or basic groups, besides the coordinating groups form chelates easily and have been used extensively as analytical reagents. However, these investigations reveal that sensitivity and selectivity of the reagent should be established, even though a few general guidelines are available to predict the potentialities of a reagent for the said purpose. In view of large and varied demand for the new methods to determine the metal ions, under specific conditions, the search for new reagents is a continuous process. This exercise of finding new and novel reagents as well as methods for inorganic analysis has a special significance in these days in view of the alarming and complex problem of environmental pollution. [9,10] Isonicotinoylhydrazones of carbonyl compounds act as good analytical reagents, but they have not been fully exploited. Hence, in the present investigation a detailed study of these reagents has been made with a view to find out their potentialities in inorganic analysis. hydrazones and their metal chelates are usually named after the carbonyl compounds from which they are obtained. Isonicotinoyl hydrazones are the condensation products of isonicotinic acid hydrazide and the carbonyl compounds. [39,40]These isonicotinoyl hydrazones are prepared by refluxing a mixture of isonicotinicacidhydrazide and the desired carbonyl compound for 2-3 h in slightly alkaline medium. The compound usually crystallizes out on cooling. Many of physiologically active hydrazones find application5 in the treatment of diseases like tuberculosis, leprosy and mental disorders. hydrazones and their metal chelates also act as herbicides, insecticides, nematocides, rodenticides and plant growth regulators.[11,12] Isonicotinicacidhydrazide (INH) is an important antitubercular agent and has potential sites for formation of complexes with metal ions. It is also observed, that isonicotinoyl hydrazones and their metal complexes possess higher activity and lower resistivity to tuberculosis bacteria. These reagents, apart from those specified above are also potential analytical reagents for the determination of several metal ions by different physico-chemical techniques, of which the spectrophotometric determination occupies a special place. The analytical applications of hydrazones have reviewed. The latest review was published in this area on 1982. In this, the author reviewed the papers published on analytical potentialities of hydrazones and their metal chelates up to 1980. After 1980 so many researchers have worked on the analytical potentialities of hydrazones and their metal chelates. Hydrazones and their metal chelates have both analytical and biological applications, which attract so many researchers. [13,14]

II. DISCUSSION

Homoleptic and heteroleptic hydrazones and their metal chelates from dehydroacetic acid and 2-furoic acid hydrazide, and 2,2′-bipyridine were synthesized[37,38]. $[Cu(L)_2]$ and $[Cu(L)(bipy)](CH_3COO)$ had the best antibacterial activities, MIC of 31.2 and 61.5 µg/ml against *Staphylococcus aureus* and *Enterococcus faecalis* respectively. Computational studies showed $[Cu(L)(bipy)]\cdot CH_3COO$ had the highest binding energy and interactions with one of the active sites of amino acid residue and possessed low energy gap and ability to donate electrons to electron-accepting species of biological targets.[35,36] Hydrazones and their metal chelates complexes of a hydrazone derived from 3-acetyl-2-hydroxy-6-methyl-4H-pyran-4-one (dehydroacetic acid) and 2-furoic acid hydrazide, and their heteroleptic analogues with 2,2′-bipyridine were synthesized. [15,16]The complexes were characterized by spectroscopic methods (ESI-MS, IR and NMR), elemental analysis, magnetic susceptibility and molar conductance measurements. The homoleptic complexes adopted octahedral geometry, while the heteroleptic analogous had four-coordinate tetrahedral (Co and Cu complexes) and square-planar (Ni complex) geometries. The homoleptic complexes were non-electrolytes, while the heteroleptic complexes were 1:1 electrolytes in DMSO. [33,34]Antimicrobial experiments indicated that $[Cu(L)_2]$ and $[Cu(L)(bipy)](CH_3COO)$ had the best antibacterial activities, with MIC of 31.2 and 61.5 µg/ml against *Staphylococcus aureus ATCC 29213* and *Enterococcus faecalis ATCC 29212*, respectively. Molecular docking determined that $[Cu(L)(bipy)]\cdot CH_3COO$ had the highest binding energy and hydrogen bonding interactions with one of the active sites of amino acid residue (LEU73). Density functional theory (DFT) [17,18] calculations of the complexes revealed that $[Cu(L)(bipy)]\cdot CH_3COO$ possessed low energy gap, suggesting a higher activity and ability to donate electrons to electron-accepting species of biological targets.[31,32]

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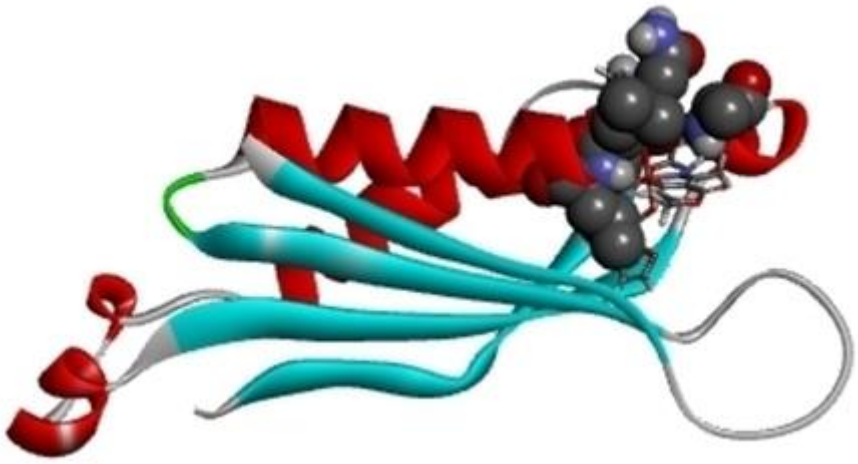

III. RESULTS

Hydrazones and their metal chelates possess an azomethine –NHN=CH group and are considered as derivatives of aldehydes and ketones in which the oxygen atom has been replaced by the NNH2 functional group. These are widely studied molecules owing to their ease of preparation and diverse pharmacological potential. [29,30] This has led researchers to synthesize different heterocyclic compounds bearing Hydrazones and their metal chelates. Medicinal chemists across the world have done immense work on hydrazones and developed agents with better activity and low toxicity profiles. Following different synthetic protocols and through proper SAR studies differently substituted Hydrazones and their metal chelates have been developed and found to be active against different pharmcological targets. They are known to possess different biological activities viz. antimicrobial, antiinflammatory, anticancer, antimalarial etc. These observations have been guiding for the development of new Hydrazones and their metal chelates that possess varied biological activities. [19,20]

Hydrazones and their metal chelates are the basis for various analyses of ketones and aldehydes. For example, dinitrophenylhydrazine coated onto a silica sorbent is the basis of an adsorption cartridge. The hydrazones are then eluted and analyzed by HPLC using a UV detector.

The compound carbonyl cyanide-*p*-trifluoromethoxyphenylhydrazone (abbreviated as FCCP) is used to uncouple ATP synthesis and reduction of oxygen in oxidative phosphorylation in molecular biology.[27,28]

Hydrazones and their metal chelates are the basis of bioconjugation strategies.[6][7] Hydrazone-based coupling methods are used in medical biotechnology to couple drugs to targeted antibodies (see ADC), e.g. antibodies against a certain type of cancer cell. The hydrazone-based bond is stable at neutral pH (in the blood), but is rapidly destroyed in the acidic environment of lysosomes of the cell. The drug is thereby released in the cell, where it exerts its function.[8]

Hydrazones and their metal chelates are susceptible to hydrolysis:

$$R_2C{=}N{-}NR'_2 + H_2O \rightarrow R_2C{=}O + H_2N{-}NR'_2$$

Alkyl hydrazones are 10^2- to 10^3-fold more sensitive to hydrolysis than analogous oximes.[9]

When derived from hydrazine itself, hydrazones condense with a second equivalent of a carbonyl to give azines:[10]

$R_2C{=}N{-}NH_2 + R_2C{=}O \rightarrow R_2C{=}N{-}N{=}CR_2 + H_2O$[21,22]

Hydrazones and their metal chelates are intermediates in the Wolff–Kishner reduction.

Hydrazones and their metal chelates are reactants in hydrazone iodination, the Shapiro reaction, and the Bamford-Stevens reaction to vinyl compounds. Hydrazones can also be synthesized by the Japp–Klingemann reaction[25,26] via β-keto-acids or β-keto-esters and aryl diazonium salts. Hydrazones are converted to azines when used in the preparation of 3,5-disubstituted 1*H*-pyrazoles,[11] a reaction also well known using hydrazine hydrate.[12][13] With a transition metal catalyst, hydrazones can serve as organometallic reagent surrogates to react with various electrophiles.[14]

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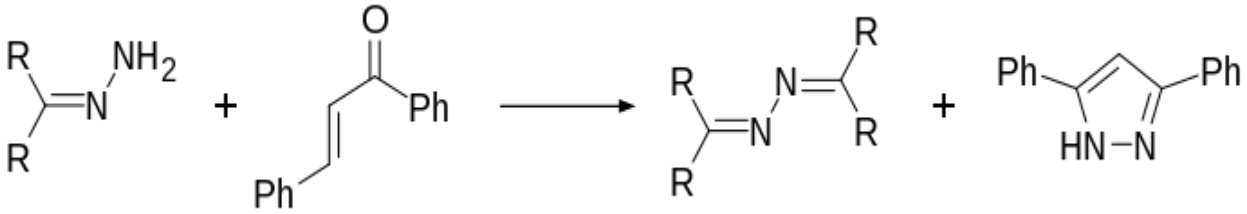
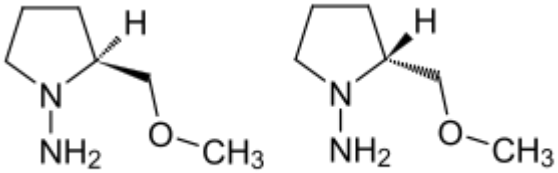


IV. CONCLUSIONS

Hydrazones and their metal chelates [15] the C=N bond can be hydrolysed, oxidised and reduced, the N–N bond can be reduced to the free amine. The carbon atom of the C=N bond can react with organometallic nucleophiles.[23,24]The alpha-hydrogen atom is more acidic by 10 orders of magnitude compared to the ketone and therefore more nucleophilic. Deprotonation with for instance LDA gives an azaenolate which can be alkylated by alkyl halides.[16] Hydrazones and their metal chelates SAMP and RAMP function as chiral auxiliary.[17][18]



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